



HAL
open science

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

Lindsay M Silva, Pauline W Jansen, Eric Ap Steegers, Vincent Wv Jaddoe, Lidia R Arends, Henning Tiemeier, Frank C Verhulst

► **To cite this version:**

Lindsay M Silva, Pauline W Jansen, Eric Ap Steegers, Vincent Wv Jaddoe, Lidia R Arends, et al.. Mother's educational level and foetal growth; the genesis of health inequalities. *International Journal of Epidemiology*, 2010, 10.1093/ije/DYQ069 . hal-00593431

HAL Id: hal-00593431

<https://hal.science/hal-00593431>

Submitted on 16 May 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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



| | |
|-------------------------------|---|
| Journal: | <i>International Journal of Epidemiology</i> |
| Manuscript ID: | IJE-2009-03-0189.R2 |
| Manuscript Type: | Original Article |
| Date Submitted by the Author: | 12-Feb-2010 |
| Complete List of Authors: | <p>Silva, Lindsay; Erasmus MC, University Medical Centre Rotterdam, The Generation R Study Group/Department of Public Health</p> <p>Jansen, Pauline; Erasmus MC, University Medical Centre Rotterdam, The Generation R Study Group; Erasmus MC, University Medical Centre Rotterdam, Department of Public Health; Erasmus MC, University Medical Centre Rotterdam, Department of Child and Adolescent Psychiatry</p> <p>Stegers, Eric; Erasmus MC, University Medical Centre Rotterdam, Department of Obstetrics and Gynaecology</p> <p>Jaddoe, Vincent; Erasmus MC, University Medical Centre Rotterdam, The Generation R Study Group; Erasmus MC, University Medical Centre Rotterdam, Department of Paediatrics; Erasmus MC, University Medical Centre Rotterdam, Department of Epidemiology</p> <p>Arends, Lidia; Erasmus MC, University Medical Centre Rotterdam, Department of Biostatistics; Erasmus University Rotterdam, Institute of Psychology</p> <p>Tiemeier, Henning; Erasmus MC, University Medical Centre Rotterdam, Department of Child and Adolescent Psychiatry;</p> <p>Erasmus MC, University Medical Centre Rotterdam, Department of Epidemiology</p> <p>Verhulst, Frank; Erasmus MC, University Medical Centre Rotterdam, Department of Child and Adolescent Psychiatry</p> |
| Key Words: | socioeconomic status, education, pregnancy, foetal, intrauterine , growth |
| | |

1
2
3 **Mother's educational level and foetal growth;**
4
5 **the genesis of health inequalities**
6
7
8
9

10
11 LM Silva^{1,2}, PW Jansen^{1,2,3}, EAP Steegers⁴, VWV Jaddoe^{1,5,6}, LR Arends^{7,8},
12
13 H Tiemeier^{3,6}, FC Verhulst³, HA Moll⁵, A Hofman⁶, JP Mackenbach², H Raat²
14
15

16
17
18 From ¹The Generation R Study Group; ² Department of Public Health; ³ Department of
19
20 Child and Adolescent Psychiatry; ⁴ Department of Obstetrics and Gynaecology, Division
21
22 of Obstetrics and Prenatal Medicine; ⁵ Department of Paediatrics; ⁶ Department of
23
24 Epidemiology; ⁷ Department of Biostatistics, Erasmus MC, University Medical Centre
25
26 Rotterdam and ⁸ Institute of Psychology, Erasmus University Rotterdam, the
27
28 Netherlands.
29
30

31
32
33 Word count abstract: 249
34

35 Word count main text: 3723
36
37

38
39 **Corresponding author:** Lindsay M Silva, MD
40

41 The Generation R Study Group, Erasmus MC, University Medical Centre Rotterdam.
42

43 Dr. Molewaterplein 50, 3015 GE, Rotterdam.
44

45 PO BOX 2040, 3000 CA Rotterdam, The Netherlands.
46

47 Telephone: (+31) 10 704 3405; fax: (+31) 10 704 4645; e-mail: l.silva@erasmusmc.nl.
48
49
50
51
52
53
54
55
56
57
58
59
60

SUMMARY

Background: Women of low socioeconomic status (SES) give birth to lighter babies. It is unknown from which moment during pregnancy socioeconomic differences in foetal weight can be observed, whether low SES equally affects different foetal-growth components, nor what the effect of low SES is after taking into account mediating factors.

Methods: In 3545 pregnant women participating in the Generation R Study, we studied the association of maternal educational level (high, mid-high, mid-low and low) as a measure of SES with foetal weight, head circumference, abdominal circumference and femur length. We did this before and after adjusting for potential mediators, including maternal height, pre-pregnancy BMI, and smoking.

Results: In foetuses of low-educated women relative to those of high-educated women, foetal growth was slower, leading to a lower foetal weight that was observable from late pregnancy onwards. In these foetuses, growth of the head (-0.16 mm/week; 95% CI: -0.25,-0.07; p=0.0004), abdomen (-0.10 mm/week; 95% CI: -0.21,0.01; p=0.08) and femur (-0.03 mm/week; 95% CI: -0.05,-0.006; p=0.01) were all slower; from mid-pregnancy onwards, head circumference was smaller, and from late pregnancy onwards, femur length was also smaller. The negative effect of low education was greatest for head circumference (difference in standard-deviation score in late pregnancy: -0.26; 95% CI: -0.36,-0.15; p<0.0001). This effect persevered even after adjustment for the potential mediators (adjusted difference: -0.14; 95% CI: -0.25,-0.03; p=0.01).

Conclusions: Low maternal education is associated with a slower foetal growth and this effect appears stronger for growth of the head than for other body parts.

Keywords: socioeconomic status, education, pregnancy, foetal, intrauterine, growth

INTRODUCTION

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

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

Therefore, among pregnant women participating in a population-based cohort study, we studied level of maternal education as an indicator of socioeconomic status and its association with foetal weight, head circumference, abdominal circumference, and femur length, measured in different periods of pregnancy. We also studied the

1
2
3 extent to which the association of maternal education with these foetal-growth
4 characteristics is explained by known mediating factors. Educational level was selected
5 as main indicator of socioeconomic status because it has been shown to be the best
6 socioeconomic predictor of pregnancy outcomes **9,11**. Assuming that a low maternal
7 education is associated with a slower foetal growth, we expected that educational
8 differences in foetal size can be observed from late pregnancy onwards, since in that
9 period inter-individual variability in foetal size is highest **12**. Because available data
10 suggest that socioeconomic status does not affect proportionality at birth **13**, we
11 hypothesized head circumference, abdominal circumference, and femur length to be
12 equally affected by low maternal education.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 **METHODS**

30 **The Generation R Study**

31
32
33
34
35
36 The present study was embedded within the Generation R Study, a population-
37 based prospective cohort study from foetal life until young adulthood. The Generation R
38 Study has previously been described in detail **14**. Briefly, all mothers with an expected
39 delivery date between April 2002 and January 2006 and living in Rotterdam, the
40 Netherlands, were eligible for participation in the study. While enrolment ideally took
41 place in early pregnancy, it was possible until after the birth of the child. In total, 9778
42 mothers of various ethnicities and their children were included and followed-up
43 (participation rate 61%) **14**.
44
45
46
47
48
49
50
51
52

53 Assessments during pregnancy took place in early pregnancy (gestational age
54 <18 weeks), mid pregnancy (gestational age 18-25 weeks) and late pregnancy
55 (gestational age \geq 25 weeks). The study was conducted in accordance with the
56
57
58
59
60

1
2
3 guidelines proposed in the World Medical Association Declaration of Helsinki, and has
4
5 been approved by the Medical Ethical Committee at the Erasmus University Medical
6
7 Centre Rotterdam. Written consent was obtained from all participating parents.
8
9

10 11 12 **Study population**

13
14 Of the 9778 women, 91% (n=8880) were enrolled during pregnancy **14**. Because
15
16 prevalences of risk factors for adverse pregnancy outcomes, as well as the effects of
17
18 these risk factors on pregnancy outcomes may vary by ethnicity **15,16,17**, and because
19
20 preliminary results showed that educational inequalities in foetal weight varied by
21
22 ethnicity, we restricted the present analyses to women with a Dutch ethnicity (n=4057). A
23
24 woman was classified as Dutch if she reported that both her parents had been born in
25
26 the Netherlands **18**. For several reasons, 512 women were excluded from analysis
27
28 (figure 1), leaving a study population of 3545 women.
29
30
31
32

33 34 **Educational level**

35
36 At enrolment, we used a questionnaire to establish the highest education
37
38 achieved by each mother. This was categorized into four levels: 1.) high (university
39
40 degree), 2.) mid-high (higher vocational training), 3.) mid-low (>3 years general
41
42 secondary school, intermediate vocational training), and 4.) low (no education, primary
43
44 school, lower vocational training, intermediate general school, or ≤3 years at general
45
46 secondary school) **19**.
47
48
49
50

51 52 **Foetal ultrasound measurements and birth weight**

53
54 Trained sonographers carried out foetal ultrasound measurements in early, mid
55
56 and late pregnancy, which were used to establish gestational age and to measure foetal-
57
58 growth characteristics **20**. For the analyses presented below, we used the
59
60

1
2
3 measurements in mid and late pregnancy of head circumference, abdominal
4
5 circumference and femur length, as measurements in early pregnancy were intended
6
7 primarily for pregnancy dating. All growth characteristics were measured to the nearest
8
9 millimetre using standardized procedures **21**. The estimated foetal weight was calculated
10
11 on the basis of head circumference, abdominal circumference and femur length **22**. For
12
13 the models for estimated foetal weight, we also used information on birth weight and
14
15 gestational age at birth, which was obtained from midwife and hospital registries.
16
17 Longitudinal growth curves and gestational-age adjusted standard-deviation (SD) scores
18
19 were constructed for all growth measurements **20**.

24 25 **Covariates**

26
27 Any effect of educational level on foetal growth is probably an indirect one, acting
28
29 through other more proximal determinants of foetal growth, so-called mediators **23**. The
30
31 factors listed below were included in this study as potential mediators, because these
32
33 factors have been shown to contribute to explaining socioeconomic inequalities in size at
34
35 birth **8**.

36
37
38
39
40 Maternal anthropometrics Maternal height was measured in the research centres.
41
42 Pre-pregnancy weight was established at enrolment through questionnaire. On the basis
43
44 of height and pre-pregnancy weight (weight/height²) we calculated pre-pregnancy body
45
46 mass index (BMI).
47

48
49
50 Smoking Through questionnaires in early, mid and late pregnancy, we obtained
51
52 information on smoking during pregnancy (no, until pregnancy was known, continued in
53
54 pregnancy).
55
56
57
58
59
60

1
2
3 Psychosocial and material factors Using questionnaires during pregnancy we
4 established marital status (married/cohabiting, single motherhood), whether the
5 pregnancy was planned (yes, no), and the presence of financial difficulties (yes, no).
6
7
8
9

10
11 All models were adjusted for maternal age and parity. We treated maternal age and
12 parity as potential confounders, since they cannot be considered indisputable mediators
13
14 **23.** Maternal age was established at enrolment in the study. Parity, which in this study
15 was defined as the number of previous live births ($0, \geq 1$), was obtained through a
16 questionnaire at enrolment. Foetal gender, which was obtained from midwife and
17 hospital registries, was not included as confounder, since it had no association with
18 maternal education (see table 1).
19
20
21
22
23
24
25
26
27
28

29 **Statistical analyses**

30
31 We started by evaluating the effect of educational level on overall foetal growth,
32 after which we separately analysed the associations of educational level and of the
33 potential mediators with head circumference, abdominal circumference and femur
34 length. These associations were examined using longitudinal multilevel analysis, as this
35 type of analysis takes account of the correlation between repeated measures on the
36 same subject and allows for incomplete outcome data **24.** The best fitting model to
37 predict each growth characteristic as a function of gestational age was built using
38 fractional polynomials **25.** To these models we added educational level as a main
39 determinant (reference: high education), and an interaction term of educational level with
40 gestational age. The best-fitting model structures are presented in box 1. These models
41 were based on 10387 observations for foetal weight and birth weight, 6845 for head
42 circumference, 6876 for abdominal circumference, and 6882 for femur length.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Using the same strategy, additional models were constructed for the SD scores
4 for each growth characteristic (box 1). To evaluate educational differences in foetal size,
5 SD scores were compared between educational subgroups at specific time-points in
6 pregnancy, i.e. at 20, 30 and 40 weeks for estimated foetal weight, and at 20 and 30
7 weeks for head circumference, abdominal circumference, femur length.
8
9

10
11 For each growth characteristic, we started with a complete unadjusted model
12 (crude model), followed by a model that included the confounders (basic model). Next,
13 this model was additionally adjusted for the potential mediators, separately and
14 simultaneously (fully adjusted model), to establish to what extent educational differences
15 in foetal growth or size could be explained by these factors.
16
17

18 For each covariate, an interaction term with gestational age was added to the
19 model, and retained only when the p-value was below 0.10. To handle missing values in
20 the covariates (all $\leq 13\%$, see table 1) we applied multiple imputation based on five
21 imputed data sets ('PROC MI' procedure in SAS 9.1.3) **26,27**. Imputations were based
22 on the relationships between all covariates included in this study.
23
24

25 Statistical analyses were performed using Statistical Package of Social Sciences
26 version 15.0 for Windows (SPSS Inc, Chicago, IL, USA) and the Statistical Analysis
27 System (SAS) for Windows (SAS Institute Inc, USA), version 9.1.3.
28
29

30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45 *Box 1 here*
46
47

48 **RESULTS**

49
50 Table 1 shows a description of the study population. Of the 3545 women in this
51 study, 17.9% were in the lowest educational level and 31.3% in the highest. Compared
52
53
54
55
56
57
58
59
60

1
2
3 with women with a high education, those with a low education were younger, shorter,
4
5 heavier before pregnancy, less likely to be nulliparous, and gave birth to lighter babies;
6
7 they were also more likely to smoke during pregnancy (p for trend for all <0.05).
8
9

10 Compared with participants with complete data, those with missing data on one
11
12 or more of the covariates were more often low educated (14.4% versus 28%, $p<0.0001$),
13
14 younger (31.3 versus 30.7 years, $p=0.003$), shorter (170 cm versus 171 cm, $p<0.0001$),
15
16 were more likely to smoke during pregnancy (16.4% versus 25.7%, $p<0.0001$), more
17
18 likely to be a single mother, (7.3% versus 10.6%, $p=0.002$), more often considered their
19
20 pregnancy unplanned (17.5% versus 25%, $p<0.0001$), and gave birth to lighter babies
21
22 (3496 versus 3398 grams, $p<0.0001$).
23
24

25
26
27 Table 1 here.
28
29
30
31
32

33 **Educational level and estimated foetal weight**

34
35
36 Relative to foetuses of women in the highest educational subgroup, those of
37
38 women with mid-high, mid-low and low education had a slower foetal growth (figures 2a
39
40 and 2b). Foetal growth rate was lowest in foetuses of women with a low educational
41
42 level, and the difference in foetal growth rate increased as pregnancy progressed.

43
44 According to the basic models, women with a low educational level had smaller foetuses
45
46 from 30 weeks onwards (difference at 30 weeks: -0.16 SD; 95% CI: -0.25,-0.08;
47
48 $p=0.0001$; table 2). This difference became larger towards term (difference at 40 weeks:
49
50 -0.35 SD; 95% CI: -0.46,-0.24; $p<0.0001$). After adjustment for the potential mediators,
51
52 the educational differences in estimated foetal weight attenuated, but at 40 weeks the
53
54 difference did not disappear (-0.18 SD; 95% CI: -0.29,-0.07; $p=0.002$).
55
56
57
58
59
60

1
2
3
4
5
6 Table 2 here.
7

8
9 **Educational level and head circumference, abdominal circumference and femur**
10 **length**

11
12 Table 3 shows the association of educational level with head, abdominal and
13 femur growth, and supplemental table 2 shows the associations of each potential
14 mediator with head, abdominal and femur growth. Relative to foetuses of women with a
15 high educational level, in foetuses of women with a low educational level growth of the
16 head was on average 0.16 mm/week slower (95% CI: -0.25,-0.07; p=0.0004), growth of
17 the abdomen 0.10 mm/week slower (95% CI: -0.21, 0.01; p=0.08) and that of the femur
18 0.03 mm/week slower (95% CI: -0.05,-0.006; p=0.01) after adjustment for the
19 confounders. Adjustment for the potential mediators attenuated the difference in head
20 growth and that in femur growth, but not the difference in abdominal growth. Even after
21 full adjustment, foetuses of women with a low educational level still had a slower head
22 growth compared with those of women with a high level (table 3).
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 Table 3 here.
40
41
42

43 Table 4 presents the educational differences in size of the foetal head, abdomen
44 and femur at 20 and 30 weeks gestation, expressed in SD-scores. Compared with
45 foetuses of women with a high educational level, those of women with a low educational
46 level had a smaller head circumference from 20 weeks onwards; femur length was
47 smaller from 30 weeks onwards (basic models). Although abdominal circumference was
48 also smaller in these foetuses, the difference did not reach statistical significance.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Remarkably, at 20 weeks gestation a mid-low educational level was associated with a
4
5 greater femur length compared with a high educational level.
6

7
8 The effect of low education was larger for head circumference than for femur
9
10 length or abdominal circumference. Even after adjustment for the potential mediators,
11
12 head circumference at 30 weeks gestation was smaller in fetuses of women with low
13
14 educational level than those of women with a high level.
15

16
17 The largest attenuations were due to the adjustment for smoking, followed by
18
19 maternal height (see supplemental table 3). We additionally tested for interaction
20
21 between educational level, smoking and gestational age; this 3-way interaction was not
22
23 statistically significant in any of the models (p values > 0.30 , data not shown).
24
25
26
27
28

29 Table 4 here.
30
31

32 33 **DISCUSSION** 34 35 36 37

38 The present study is the first to present a longitudinal assessment of the effect of
39
40 an individual-level indicator of socioeconomic status on foetal growth. We demonstrated
41
42 that a low maternal educational level is associated with a progressively slower foetal
43
44 growth, causing differences in foetal weight that are observable from late pregnancy
45
46 onwards. This study also suggests that low maternal educational level predominantly
47
48 affects growth of the foetal head, followed by growth of the foetal femur and abdomen.
49
50
51
52
53
54
55
56
57
58
59
60

Methodological considerations

The main strength of this study lies in its population-based prospective design, with enrolment of a large number of women early in pregnancy, and extensive measurements during pregnancy **14**.

Although there are other measures of socioeconomic status, including income level and occupational class **28**, we selected maternal educational level as a main indicator of socioeconomic status for two reasons: first educational level not only partly reflects material resources because it structures occupation and income, it also reflects non-economic social characteristics, such as general and health-related knowledge, literacy, problem-solving skills and prestige **28,29**; second, educational level has been shown to be the best socioeconomic predictor of pregnancy outcomes **9,11**.

Furthermore, when we repeated the analyses using household income level as determinant, we found comparable results, although the effect estimates were smaller and income-related differences in foetal head circumference were observable from 30 weeks gestation onwards.

For this study, we conceptualized maternal age and parity to be confounders in the association between educational level and foetal growth, because age, for example, partly determines the maximum educational level that can theoretically have been achieved. It could be argued though, that age and parity might also have mediating effects. Whatever the choice, it has no implications for the results in the fully adjusted model. Furthermore, height was conceptualized as a mediator in our study, because it is a determinant of growth in utero and birth weight **30**, and since evidence shows that adult height is influenced not only by genetic factors, but also significantly by social and environmental influences earlier in life **31,32**. Therefore, we hypothesized that the

1
2
3 contribution of maternal height to socioeconomic inequalities in foetal growth may partly
4 represent transgenerational effects of adverse environmental exposures accumulated
5 over maternal life course. Treating height as a confounder would lead to an
6
7
8 underestimation of social influences on foetal growth **31**.
9
10

11 When interpreting the results of this study, one should take account of a number
12 of limitations.
13
14

15 First, our study was conducted in a Dutch, urban population, which limits
16 generalizability of our results to non-Dutch or rural populations. Furthermore, although
17 the participation rate was relatively high (68% among the Dutch women) **14**, there was
18 some selection towards a study population that was relatively highly educated and more
19 healthy **33**.
20
21
22
23
24
25
26

27 Second, while foetal ultrasound examinations are a more reliable basis than the
28 last menstrual period for establishing gestational age **34**, it also has a disadvantage: the
29 growth variation before the first measurement of the foetal characteristics that were used
30 for pregnancy dating, i.e. crown-rump length and biparietal diameter, was set to zero **20**.
31 Since these characteristics are correlated throughout pregnancy with head
32 circumference, abdominal circumference and femur length, our study may have
33 underestimated the variation in the latter three growth characteristics, resulting in an
34 underestimation of our effect estimates. An additional limitation to the foetal ultrasound
35 equipment is that it will be equally precise to detect absolute differences in foetal size
36 throughout pregnancy, and therefore less likely to detect differences in foetal size early
37 in pregnancy than later in pregnancy. This might explain the lack of significant
38 educational differences in many of the studied growth characteristics at 20 weeks
39 gestation.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

55 Third, our study may have been vulnerable to misclassification, because many
56 covariates were measured using questionnaires. In particular, smoking behaviour and
57
58
59
60

1
2
3 pre-pregnancy weight may have been underreported. The effect on our results of this
4
5 misclassification is difficult to predict, since we cannot be certain whether this
6
7 misclassification was random or not.
8

9
10 Finally, since we did not include a variable indicating the number of cigarettes
11
12 smoked during pregnancy, we could not account for the dose-related effect of smoking
13
14 on foetal growth **35**, nor the contribution of this dose-related effect to the explanation of
15
16 socioeconomic inequalities in foetal growth.
17

22 **Maternal educational level and foetal growth**

23
24
25
26 In contrast with our expectations the effect of low maternal education was not
27
28 equal for the various body segments of the foetus. Relative to growth of the foetal femur
29
30 and abdomen, the adverse effect of a low educational level seemed greatest for growth
31
32 of the foetal head.
33

34
35
36 Clear educational differences in foetal head circumference were detectable
37
38 already at 20 weeks gestation. By 30 weeks, educational differences in femur length
39
40 could also be detected, but not in abdominal circumference, although there was a clear
41
42 trend towards a smaller abdominal circumference in foetuses of lower educated women.
43
44 The timing of the emergence of educational differences in head, femur and abdomen
45
46 might be explained by the inability of the ultrasound instrument to detect small
47
48 differences, or by the different growth patterns of the various foetal-growth components.
49
50 Peak growth velocity for head circumference is steeper and occurs earlier (around 18
51
52 weeks) than that for femur length (around 20 weeks) and abdomen (around 22 weeks)
53
54
55 **12,36.**
56
57
58
59
60

1
2
3 One should also take account of the fact that, in our study, only 2.5% of these
4
5 measurements took place after the 32nd week of gestation. For physiological
6
7 pregnancies, it has been shown that the difference in abdominal circumference between
8
9 smaller and larger babies increases with increasing gestational age **36**. Therefore, the
10
11 observed educational differences in abdominal circumference might have been larger if
12
13 we had had availability to more growth measurements near term. It is thus important that
14
15 our results are confirmed in future studies with more comprehensive foetal-growth data
16
17 and with information on proportionality at birth.
18
19

20
21
22
23
24 One possible explanation for low maternal education being more strongly
25
26 associated with foetal head circumference is that the factors that mediate the effect of
27
28 maternal education affect foetal head growth more than growth of the foetal femur and
29
30 abdomen. However, smoking in pregnancy, the strongest mediator in this study, has
31
32 been found to cause a more general, symmetrical growth restriction **37,38**. Some studies
33
34 even suggest that smoking affects the lower extremities more than the head or abdomen
35
36 **39,40**. On the other hand, the contribution of maternal height to the education-related
37
38 inequalities, is more in line with the above explanation; shorter mothers tend to give birth
39
40 to babies that are shorter and have smaller heads for their weight **13**. This corresponds
41
42 with the type of growth impairment associated with low maternal education.
43
44
45
46
47

48 The potential mediators included in this study explained only about half the
49
50 educational differences in foetal head circumference at 30 weeks gestation. This may be
51
52 explained by measurement error in the mediating variables. The remaining effect may
53
54 also be due to other factors, such as nutritional factors or genetic factors **7,41**. Since
55
56 head circumference is associated with academic achievements **3,42** and maternal head
57
58
59
60

1
2
3 circumference is a strong predictor of neonatal head circumference **43**, there may be
4
5 genetic factors linking head circumference of the mother, her educational achievement
6
7 and head growth of her offspring. However, given the results from Genome Wide
8
9 Association Studies, suggesting that individual genes explain little of the variances in
10
11 diseases and traits **44**, the contribution of genes to the remaining association between
12
13 educational level and foetal head circumference may be small. Furthermore, we could
14
15 not explain why, only at 20 weeks gestation, the second lowest educational subgroup
16
17 had a larger femur length compared with the highest educational subgroup. It is possible
18
19 that other unmeasured factors that specifically determine femur growth explain this
20
21 unexpected finding. This merits further investigation.
22
23
24
25
26

27
28 In conclusion, this unique study demonstrates that, relative to a high maternal
29
30 educational level, a low educational level is associated with a slower foetal growth, in
31
32 particular growth of the head. Important mediators such as smoking explained only part
33
34 of this association. Future research should aim at additional determinants of foetal
35
36 growth, such as nutritional, psychosocial or genetic factors to further disentangle the
37
38 pathway between SES and foetal growth.
39

40
41 The socioeconomic inequalities in foetal growth as demonstrated here may
42
43 represent the genesis of socioeconomic health inequalities in infancy, childhood and
44
45 adulthood. In particular, since foetal head growth is associated with future cognitive
46
47 functioning and academic achievement **3,42**, the observed socioeconomic inequalities in
48
49 foetal head growth might have consequences for later cognitive ability, educational
50
51 attainment and job performance for the offspring of low-educated mothers. Taking
52
53 measures to narrow inequalities in foetal growth should be an important public health
54
55 issue. Smoking during pregnancy being the most important modifiable factor explaining
56
57 these inequalities, such measures should primarily be aimed at reducing smoking rates
58
59
60

1
2
3 among pregnant women of low socioeconomic status. Further research is needed to
4
5 provide other entry points for interventions and to study the short and long term
6
7 consequences of socioeconomic inequalities in intra-uterine growth.
8
9

10 11 12 **FUNDING**

13
14 This work was supported by Erasmus MC, University Medical Centre Rotterdam,
15
16 Erasmus University Rotterdam, the Netherlands Organization for Health Research and
17
18 Development (ZonMw), and the Netherlands Organization for Scientific Research
19
20 (NWO) (017.002.107 to L.M.S.)
21
22
23

24 25 **ACKNOWLEDGEMENTS**

26
27 The Generation R Study is conducted by the Erasmus MC, University Medical
28
29 Centre Rotterdam in close collaboration with the Erasmus University Rotterdam, School
30
31 of Law and Faculty of Social Sciences, the Municipal Health Service Rotterdam area, the
32
33 Rotterdam Homecare Foundation, and the Stichting Trombosedienst &
34
35 Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the
36
37 contribution of participating mothers, general practitioners, hospitals, midwives and
38
39 pharmacies in Rotterdam.
40
41
42
43

44
45 **Duality of interest:** The authors declare that there is no duality of interest for this study.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Key Messages

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

REFERENCES

1. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. *Pediatrics* 2003;111(1):e61-6.
2. Barker DJ. Fetal origins of coronary heart disease. *Bmj* 1995;311(6998):171-4.
3. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S. Birth characteristics and risk of low intellectual performance in early adulthood: are the associations confounded by socioeconomic factors in adolescence or familial effects? *Pediatrics* 2006;117(3):714-21.
4. Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, et al. Respiratory symptoms in the first 7 years of life and birth weight at term: the PIAMA Birth Cohort. *Am J Respir Crit Care Med* 2007;175(10):1078-85.
5. Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease:

- 1
2
3 cohort study of 15 000 Swedish men and women born 1915-29. *Bmj*
4
5 1998;317(7153):241-5.
6
7
8 6. Hediger ML, Overpeck MD, Maurer KR, Kuczmarski RJ, McGlynn A, Davis WW.
9
10 Growth of infants and young children born small or large for gestational age:
11 findings from the Third National Health and Nutrition Examination Survey. *Arch*
12
13 *Pediatr Adolesc Med* 1998;152(12):1225-31.
14
15
16 7. Lunde A, Melve KK, Gjessing HK, Skjaerven R, Irgens LM. Genetic and
17
18 environmental influences on birth weight, birth length, head circumference, and
19
20 gestational age by use of population-based parent-offspring data. *Am J*
21
22 *Epidemiol* 2007;165(7):734-41.
23
24
25 8. Jansen PW, Tiemeier H, Looman CWN, Jaddoe VWV, Hofman A, Moll HA, et al.
26
27 Explaining educational inequalities in birthweight. The Generation R Study.
28
29 *Paediatr Perinat Epidemiol* 2009;23(3):216-228.
30
31
32 9. Mortensen LH, Diderichsen F, Arntzen A, Gissler M, Cnattingius S, Schnor O, et al.
33
34 Social inequality in fetal growth: a comparative study of Denmark, Finland,
35
36 Norway and Sweden in the period 1981-2000. *J Epidemiol Community Health*
37
38 2008;62(4):325-31.
39
40
41 10. Hansen CA, Barnett AG, Pritchard G. The effect of ambient air pollution during early
42
43 pregnancy on fetal ultrasonic measurements during mid-pregnancy. *Environ*
44
45 *Health Perspect* 2008;116(3):362-9.
46
47
48 11. Parker JD, Schoendorf KC, Kiely JL. Associations between measures of
49
50 socioeconomic status and low birth weight, small for gestational age, and
51
52 premature delivery in the United States. *Ann Epidemiol* 1994;4(4):271-8.
53
54
55 12. Di Battista E, Bertino E, Benso L, Fabris C, Aicardi G, Pagliano M, et al. Longitudinal
56
57 distance standards of fetal growth. Intrauterine and Infant Longitudinal Growth
58
59 Study: IILGS. *Acta Obstet Gynecol Scand* 2000;79(3):165-73.
60

- 1
2
3 13. Kramer MS, Olivier M, McLean FH, Dougherty GE, Willis DM, Usher RH.
4
5 Determinants of fetal growth and body proportionality. *Pediatrics* 1990;86(1):18-
6
7 26.
8
9
- 10 14. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, et al.
11
12 The Generation R Study: Design and cohort profile. *Eur J Epidemiol*
13
14 2006;21(6):475-84.
15
- 16 15. Knuist M, Bonsel GJ, Zondervan HA, Treffers PE. Risk factors for preeclampsia in
17
18 nulliparous women in distinct ethnic groups: a prospective cohort study. *Obstet*
19
20 *Gynecol* 1998;92(2):174-8.
21
- 22 16. Troe EJ, Raat H, Jaddoe VW, Hofman A, Looman CW, Moll HA, et al. Explaining
23
24 differences in birthweight between ethnic populations. The Generation R Study.
25
26 *Bjog* 2007;114(12):1557-65.
27
- 28 17. Savitz DA, Kaufman JS, Dole N, Siega-Riz AM, Thorp JM, Jr., Kaczor DT. Poverty,
29
30 education, race, and pregnancy outcome. *Ethn Dis* 2004;14(3):322-9.
31
- 32 18. Statistics Netherlands. Allochtonen in Nederland 2004. Voorburg/Heerlen; 2004.
33
- 34 19. Statistics Netherlands. Standaard Onderwijsindeling 2003. Voorburg/Heerlen; 2004.
35
- 36 20. Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, et al. New
37
38 charts for ultrasound dating of pregnancy and assessment of fetal growth:
39
40 longitudinal data from a population-based cohort study. *Ultrasound Obstet*
41
42 *Gynecol* 2008;31(4):388-96.
43
44
- 45 21. Royal College of Obstetricians and Gynaecologists. Routine ultrasound screening in
46
47 pregnancy: protocol, standards and training. London RCOG Press, 2000.
48
- 49 22. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation
50
51 of fetal weight. The value of femur length in addition to head and abdomen
52
53 measurements. *Radiology* 1984;150(2):535-40.
54
55
56
57
58
59
60

- 1
2
3 23. McNamee R. Confounding and confounders. *Occup Environ Med* 2003;60(3):227-
4 34; quiz 164, 234.
5
6
7 24. Goldstein H. *Multilevel Statistical Models*. 3rd ed. London: Arnold, 2003.
8
9
10 25. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model
11 continuous risk variables in epidemiology. *Int J Epidemiol* 1999;28(5):964-74.
12
13 26. SAS institute. *The MI procedure*. <http://support.sas.com/rnd/app/papers/miv802.pdf>.
14
15
16 27. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple
17 imputation for missing data in epidemiological and clinical research: potential and
18 pitfalls. *Bmj* 2009;338:b2393.
19
20
21 28. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of
22 socioeconomic position (part 1). *J Epidemiol Community Health* 2006;60(1):7-12.
23
24
25 29. Braveman PA, Cubbin C, Egerter S, Chideya S, Marchi KS, Metzler M, et al.
26 Socioeconomic status in health research: one size does not fit all. *Jama*
27 2005;294(22):2879-88.
28
29
30 30. Ay L, Kruithof CJ, Bakker R, Steegers EA, Witteman JC, Moll HA, et al. Maternal
31 anthropometrics are associated with fetal size in different periods of pregnancy
32 and at birth. The Generation R Study. *Bjog* 2009;116(7):953-63.
33
34
35 31. Spencer NJ, Logan S. The treatment of parental height as a biological factor in
36 studies of birth weight and childhood growth. *Arch Dis Child* 2002;87(3):184-7.
37
38
39 32. Whincup PH, Cook DG, Shaper AG. Social class and height. *Bmj*
40 1988;297(6654):980-1.
41
42
43 33. Center for Research and Statistics, Rotterdam (COS); <http://www.cos.rotterdam.nl>;
44 2005.
45
46
47 34. Tunon K, Eik-Nes SH, Grottum P. A comparison between ultrasound and a reliable
48 last menstrual period as predictors of the day of delivery in 15,000 examinations.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 35. Pringle PJ, Geary MP, Rodeck CH, Kingdom JC, Kayamba-Kay's S, Hindmarsh PC.
4
5 The influence of cigarette smoking on antenatal growth, birth size, and the
6
7 insulin-like growth factor axis. *J Clin Endocrinol Metab* 2005;90(5):2556-62.
8
9
10 36. Milani S, Bossi A, Bertino E, di Battista E, Coscia A, Aicardi G, et al. Differences in
11
12 size at birth are determined by differences in growth velocity during early prenatal
13
14 life. *Pediatr Res* 2005;57(2):205-10.
15
16
17 37. Lindley AA, Gray RH, Herman AA, Becker S. Maternal cigarette smoking during
18
19 pregnancy and infant ponderal index at birth in the Swedish Medical Birth
20
21 Register, 1991-1992. *Am J Public Health* 2000;90(3):420-3.
22
23
24 38. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of
25
26 women who smoked in pregnancy. *Early Hum Dev* 1996;45(3):245-55.
27
28
29 39. Jaddoe VW, Verburg BO, de Ridder MA, Hofman A, Mackenbach JP, Moll HA, et al.
30
31 Maternal smoking and fetal growth characteristics in different periods of
32
33 pregnancy: the generation R study. *Am J Epidemiol* 2007;165(10):1207-15.
34
35
36 40. Lindsay CA, Thomas AJ, Catalano PM. The effect of smoking tobacco on neonatal
37
38 body composition. *Am J Obstet Gynecol* 1997;177(5):1124-8.
39
40
41 41. Godfrey K, Robinson S, Barker DJ, Osmond C, Cox V. Maternal nutrition in early and
42
43 late pregnancy in relation to placental and fetal growth. *Bmj* 1996;312(7028):410-
44
45 4.
46
47 42. Silva A, Metha Z, O'Callaghan F J. The relative effect of size at birth, postnatal
48
49 growth and social factors on cognitive function in late childhood. *Ann Epidemiol*
50
51 2006;16(6):469-76.
52
53
54 43. Leary S, Fall C, Osmond C, Lovel H, Campbell D, Eriksson J, et al. Geographical
55
56 variation in relationships between parental body size and offspring phenotype at
57
58 birth. *Acta Obstet Gynecol Scand* 2006;85(9):1066-79.
59
60

1
2
3 44. Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, et al.
4

5 Genome-wide association analysis identifies 20 loci that influence adult height.
6

7
8 *Nat Genet* 2008;40(5):575-83.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Review Only

Table 1. General characteristics in the total study population and by maternal educational level (n=3545)*.

| | Maternal education | | | | | P for trend† |
|--|---------------------|---------------------|---------------------|---------------------|---------------------|--------------|
| | Total (n=3545) | High (n=1109) | Mid-high (n=877) | Mid-low (n=925) | Low (n=634) | |
| Pregnancy characteristics | | | | | | |
| Maternal age (years) | 31.1 (4.6) | 32.9 (3.2) | 31.9 (3.8) | 30.0 (4.8) | 28.6 (5.6) | <0.001 |
| Parity (% nullipara) | 65.0 | 64.3 | 68.1 | 68.1 | 57.3 | 0.049 |
| Infant gender (% girls) | 49.6 | 49.6 | 49.6 | 50.7 | 47.8 | 0.71 |
| Gestational age at birth (median in weeks, 95% range) | 40.3 (35.7,42.4) | 40.3 (35.9,42.4) | 40.3 (36.3,42.4) | 40.1 (35.9,42.3) | 39.9 (34.3,42.3) | <0.001 |
| Birth weight (grams) | 3470.5 (561.6) | 3538.6 (538.9) | 3509.5 (547.8) | 3448.5 (563.8) | 3329.0 (589.3) | <0.001 |
| Maternal anthropometrics | | | | | | |
| Height (cm) | 170.7 (6.4) | 171.4 (6.0) | 171.3 (6.3) | 170.5 (6.4) | 168.8 (6.7) | <0.001 |
| Pre-pregnancy weight (kg)‡ | 67.8 (12.4) | 66.4 (9.7) | 66.9 (11.3) | 69.2 (13.3) | 69.8 (15.9) | <0.001 |
| Pre-pregnancy BMI (kg/m ²)‡ | 23.3 (4.0) | 22.5 (2.9) | 22.7 (3.5) | 23.8 (4.4) | 24.4 (5.3) | <0.001 |

Table 1. (continued)

| | Maternal education | | | | | P for trend† |
|--|--------------------|------------------|---------------------|--------------------|----------------|--------------|
| | Total (n=3545) | High (n=1109) | Mid-high (n=877) | Mid-low (n=925) | Low (n=634) | |
| Smoking | | | | | | |
| No (%) | 68.7 | 80.4 | 74.3 | 65.3 | 45.6 | |
| Until pregnancy known (%) | 8.0 | 7.8 | 9.0 | 8.8 | 6.0 | |
| Continued during pregnancy (%) | 17.3 | 5.1 | 10.7 | 20.1 | 43.5 | <0.001 |
| Missing (%) | 6.0 | 6.7 | 5.9 | 5.8 | 4.9 | |
| Psychosocial and material factors | | | | | | |
| Pregnancy was planned | | | | | | |
| No (%) | 18.1 | 9.4 | 14.7 | 21.5 | 33.0 | <0.001 |
| Missing (%) | 5.4 | 5.5 | 6.3 | 4.4 | 5.2 | |
| Marital status (% single) | 8.2 | 3.5 | 4.6 | 8.8 | 20.3 | <0.001 |
| Financial difficulties | | | | | | |
| Yes (%) | 10.7 | 4.1 | 8.3 | 12.5 | 22.7 | <0.001 |
| Missing (%) | 11.8 | 5.9 | 5.8 | 13.4 | 27.9 | |
| Ultrasound participation rate | | | | | | |
| Mid pregnancy | 97.0 | 97.7 | 97.7 | 96.3 | 95.3 | 0.002 |
| Late pregnancy | 98.2 | 98.8 | 98.9 | 98.1 | 96.5 | 0.001 |

BMI: body mass index

* Values are means (with standard deviations) for continuous factors (except for gestational age), or percentages for categorical factors.

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

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

Table 2. Associations between maternal educational level and standard deviation scores for estimated foetal weight at 20, 30 and 40 weeks gestation (n=3545).

| Difference in standard deviation score for | | | |
|--|---------------------------------|---------------------------------|------------------------------|
| estimated foetal weight at 20 weeks gestation (with 95% CI and P values) | | | |
| | Crude model | Basic model* | Fully adjusted† |
| Maternal education | | | |
| High | Reference | Reference | Reference |
| Mid-high | 0.02 (-0.07,0.11) p=0.73) | 0.02 (-0.07,0.11) p=0.61 | 0.02 (-0.07,0.12) p=0.59) |
| Mid-low | 0.06 (-0.03,0.14) p=0.21 | 0.08 (-0.01,0.17) p=0.10 | 0.07 (-0.02,0.17) p=0.14) |
| Low | -0.01 (-0.11,0.089) p=0.82 | 0.02 (-0.09,0.13) p=0.70) | 0.05 (-0.07,0.17) p=0.44) |
| Difference in standard deviation score for | | | |
| estimated foetal weight at 30 weeks gestation (with 95% CI and P values) | | | |
| | Crude model | Basic model* | Fully adjusted† |
| Maternal education | | | |
| High | Reference | Reference | Reference |
| Mid-high | -0.02 (-0.09,0.05) p=0.61 | -0.009 (-0.08,0.06) p=0.80 | 0.002 (-0.07,0.07) p=0.96 |
| Mid-low | -0.04 (-0.11,0.03) p=0.29 | -0.03 (-0.10,0.05) p=0.48 | -0.01 (-0.09,0.06) p=0.72 |
| Low | -0.16 (-0.24,-0.08) p=0.0001 | -0.16 (-0.25,-0.08) p=0.0001 | -0.07 (-0.16,0.02) p=0.15 |

Table 2. (Continued)

| | Difference in standard deviation score for estimated birth weight at 40 weeks gestation (with 95% CI and P values) | | |
|--------------------|---|---------------------------------|--------------------------------|
| | Crude model | Basic model* | Fully adjusted† |
| Maternal education | | | |
| High | Reference | Reference | Reference |
| Mid-high | -0.05 (-0.14,0.04) p=0.25 | -0.04 (-0.13,0.05) p=0.35 | -0.02 (-0.11,0.06) p=0.62) |
| Mid-low | -0.13 (-0.22,-0.04) p=0.003 | -0.13 (-0.22,-0.04) p=0.005 | -0.10 (-0.19,-0.008) p=0.03 |
| Low | -0.30 (-0.40,-0.20); p<0.0001 | -0.35 (-0.46,-0.24) p<0.0001 | -0.18 (-0.29,-0.07) p=0.002 |

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

Table 3. Associations between maternal educational level and growth of the foetal head, abdomen and femur (n=3545).

| Differences in foetal head circumference growth (mm/week) | | | |
|--|---------------------------------|---------------------------------|--------------------------------|
| (with 95% CI and P values) | | | |
| | Crude model | Basic model* | Fully adjusted† |
| Educational level | | | |
| High | Reference | Reference | Reference |
| Mid-high | -0.03 (-0.22,0.05) p=0.42 | -0.03 (-0.11,0.05) p=0.46 | -0.02 (-0.09,0.06) p=0.63 |
| Mid-low | -0.10 (-0.17,-0.02) p=0.02 | -0.09 (-0.17,-0.02) p=0.02 | -0.08 (-0.15,-0.003) p=0.04 |
| Low | -0.15 (-0.24,-0.06) p=0.0007 | -0.16 (-0.25,-0.07) p=0.0004 | -0.10 (-0.18,-0.01) p=0.04 |
| Differences in foetal abdominal circumference growth (mm/week) (with 95% CI and P values) | | | |
| | Crude model | Basic model* | Fully adjusted† |
| Maternal education | | | |
| High | Reference | Reference | Reference |
| Mid-high | 0.01 (-0.09,0.11) p=0.78 | 0.02 (-0.09,0.12) p=0.73 | 0.02 (-0.08,0.12) p=0.67 |
| Mid-low | -0.02 (-0.12,0.08) p=0.75 | -0.01 (-0.11,0.09) p=0.80 | -0.03 (-0.14,0.07) p=0.50 |
| Low | -0.09 (-0.20,0.03) p=0.13 | -0.10 (-0.21,0.01) p=0.08 | -0.10 (-0.22,0.02) p=0.11 |

Table 3. (continued)

| | Differences in foetal femur length growth (mm/week) | | |
|--------------------|---|--------------------------------|-------------------------------|
| | (with 95% CI and P values) | | |
| | Crude model | Basic model* | Fully adjusted† |
| Maternal education | | | |
| High | Reference | Reference | Reference |
| Mid-high | -0.004 (-0.02,0.01) p=0.66 | -0.003 (-0.02,0.02) p=0.72 | 0.001 (-0.02,0.02) p=0.92 |
| Mid-low | -0.01 (-0.03,0.004) p=0.66 | -0.01 (-0.03,0.004) p=0.14 | -0.003 (-0.02,0.01) p=0.71 |
| Low | -0.025 (-0.046,-0.004) p=0.02 | -0.03 (-0.05,-0.006) p=0.01 | 0.0004 (-0.02,0.02) p=0.96 |

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

Table 4. Associations between maternal educational level and foetal head circumference, abdominal circumference and femur length (in standard deviation scores) at 20 and 30 weeks gestation (n=3545).

| <u>20 weeks gestation</u> | | High education | Mid-high education | Mid-low education | Low education | |
|---------------------------|-----------------|-----------------|--------------------------------|--------------------------------|--------------------------------|-------------------------------|
| HC (SD score) | Crude model | Reference | -0.09 (-0.19,0.002); p=0.06 | -0.11 (-0.21,-0.02); p=0.02 | -0.17 (-0.28,-0.06) p=0.002 | |
| | | Basic Model* | Reference | -0.09 (-0.19,0.005) p=0.06 | -0.10 (-0.20,0.00) p=0.05 | -0.14 (-0.25,-0.03) p=0.01 |
| | Fully adjusted† | Reference | -0.09 (-0.19,0.007) p=0.07 | -0.09 (-0.19,0.01) p=0.07 | -0.10 (-0.22,0.03) p=0.13 | |
| | AC (SD score) | Crude model | Reference | -0.01 (-0.10,0.08); p=0.81 | -0.05 (-0.14,0.04) p=0.28 | -0.09 (-0.19,0.01) p=0.09 |
| | | | Basic Model* | Reference | 0.005 (-0.09,0.10) p=0.92 | -0.006 (-0.10,0.09) p=0.90 |
| | | Fully adjusted† | Reference | 0.005 (-0.09,0.10) p=0.88 | -0.001 (-0.10,0.10) p=0.98 | 0.01 (-0.11,0.13) p=0.87 |
| FL (SD score) | Crude model | Reference | 0.02 (-0.07,0.11) p=0.68 | 0.13 (0.04,0.22) p=0.005 | 0.05 (-0.05,0.16) p=0.30 | |
| | | Basic Model* | Reference | 0.01 (-0.08,0.11) p=0.77 | 0.12 (0.02,0.21) p=0.02 | 0.02 (-0.08,0.13) p=0.67 |
| | Fully adjusted† | Reference | 0.02 (-0.08,0.11) p=0.73 | 0.10 (0.008,0.20) p=0.03 | 0.04 (-0.08,0.16) p=0.48 | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 4. (continued)

| <u>30 weeks gestation</u> | | High education | Mid-high education | Mid-low education | Low education |
|---------------------------|-----------------|----------------|-------------------------------|---------------------------------|---|
| HC (SD score) | Crude model | Reference | -0.08 (-0.17,0.007) p=0.07 | -0.17 (-0.25,-0.08) p=0.0002 | -0.28 (-0.37,-0.18) p<0.0001 |
| | Basic Model* | Reference | -0.07 (-0.16,0.01) p=0.10 | -0.15 (-0.24,-0.06) p=0.001 | -0.26 (-0.36,-0.15) p<0.0001 |
| | Fully adjusted† | Reference | -0.06 (-0.15,0.03) p=0.17 | -0.12 (-0.21,-0.03) p=0.01 | -0.14 (-0.25,-0.03) p=0.01 |
| AC (SD score) | Crude model | Reference | 0.0014 (-0.09,0.0); p=0.97 | -0.04 (-0.13,0.04) p=0.30 | -0.14 (-0.24,-0.04) p=0.005 |
| | Basic Model* | Reference | 0.02 (-0.07,0.11) p=0.66 | 0.001 (-0.09,0.09) p=0.99 | -0.08 (-0.19,0.02) p=0.10 |
| | Fully adjusted† | Reference | 0.03 (-0.06,0.11) p=0.56 | -0.008 (-0.10,0.08) p=0.86 | -0.04 (-0.15,0.07) p=0.44 |
| FL (SD score) | Crude model | Reference | -0.01 (-0.10,0.07) p=0.73 | 0.03 (-0.05,0.11) p=0.49 | -0.09 (-0.18,0.006) p=0.07 |
| | Basic Model* | Reference | -0.02 (-0.10,0.07) p=0.69 | 0.02 (-0.07,0.10) p=0.70 | -0.13 (-0.22,-0.02) p=0.01 |
| | Fully adjusted† | Reference | -0.001 (-0.08,0.08) p=0.99 | 0.05 (-0.04,0.13) p=0.31 | -0.006 (-0.11,0.10) p=0.92 |

1
2
3
4
5 Values are based on multilevel models and represent differences in head circumference, abdominal circumference and femur length (expressed in standard-
6 deviation scores, with associated 95% CI and P values) relative to foetuses of women with high educational level. HC: head circumference; AC: abdominal
7 circumference; FL: femur length; SD-score: standard deviation score. * Basic model: adjusted for maternal age and parity. † Fully adjusted: adjusted for maternal
8 age and parity, maternal height, pre-pregnancy BMI, smoking during pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties.
9 The following covariate*gestational age interactions were also included: for head-circumference model: parity*gestational age, height*gestational age, BMI*
10 gestational age, smoking*gestational age; for abdominal-circumference model: parity*gestational age, BMI* gestational age, smoking*gestational age; for femur-
11 length model: parity*gestational age, height*gestational age, smoking*gestational age.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

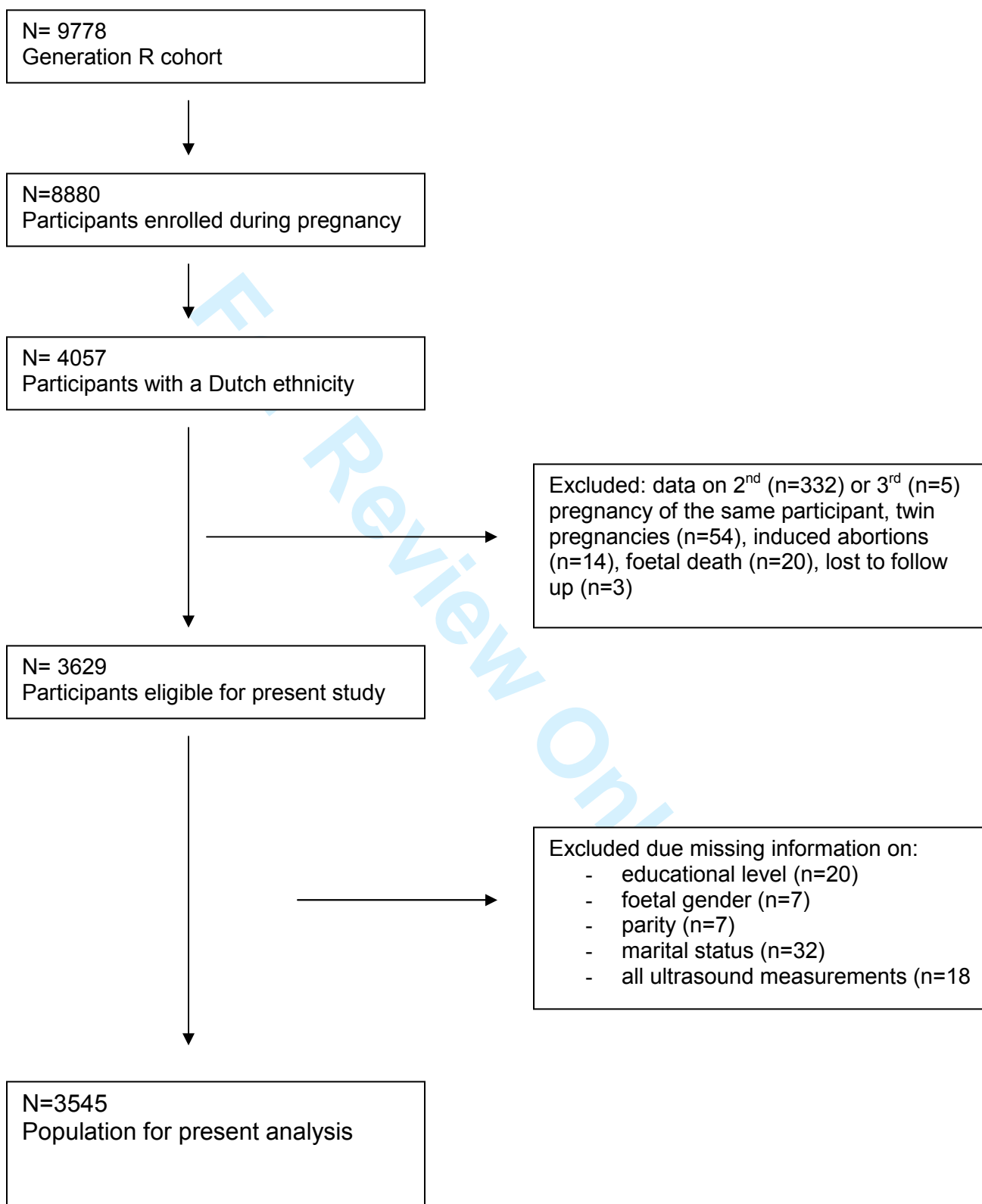
For Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Box 1.

| |
|---|
| Model structures for analyses with estimated foetal weight, head circumference, abdominal circumference, and femur length |
| Estimated foetal weight = $\beta_0 + \beta_1 \cdot \text{educational level} + \beta_2 \cdot \text{gestational age} + \beta_3 \cdot \ln(\text{gestational age}) + \beta_4 \cdot \text{gestational age} \cdot \ln(\text{gestational age}) + \beta_5 \cdot \text{educational level} \cdot \text{gestational age} + \beta_6 \cdot \text{educational level} \cdot \ln(\text{gestational age})$. |
| Head circumference = $\beta_0 + \beta_1 \cdot \text{educational level} + \beta_2 \cdot \text{gestational age} + \beta_3 \cdot \text{gestational age}^2 + \beta_4 \cdot \text{gestational age}^2 \cdot \ln(\text{gestational age}) + \beta_5 \cdot \text{educational level} \cdot \text{gestational age}$. |
| Abdominal circumference = $\beta_0 + \beta_1 \cdot \text{educational level} + \beta_2 \cdot \text{gestational age} + \beta_3 \cdot \text{gestational age}^2 + \beta_4 \cdot \text{gestational age}^2 \cdot \ln(\text{gestational age}) + \beta_5 \cdot \text{educational level} \cdot \text{gestational age}$. |
| Femur length = $\beta_0 + \beta_1 \cdot \text{educational level} + \beta_2 \cdot \text{gestational age} + \beta_3 \cdot \text{gestational age}^3 + \beta_4 \cdot \text{educational level} \cdot \text{gestational age}$. |
| Best-fitting model for analyses with standard-deviation (SD) scores for estimated foetal weight, head circumference, abdominal circumference, and femur length |
| SD score = $\beta_0 + \beta_1 \cdot \text{educational level} + \beta_2 \cdot \text{gestational age} + \beta_3 \cdot \text{educational level} \cdot \text{gestational age}$. |

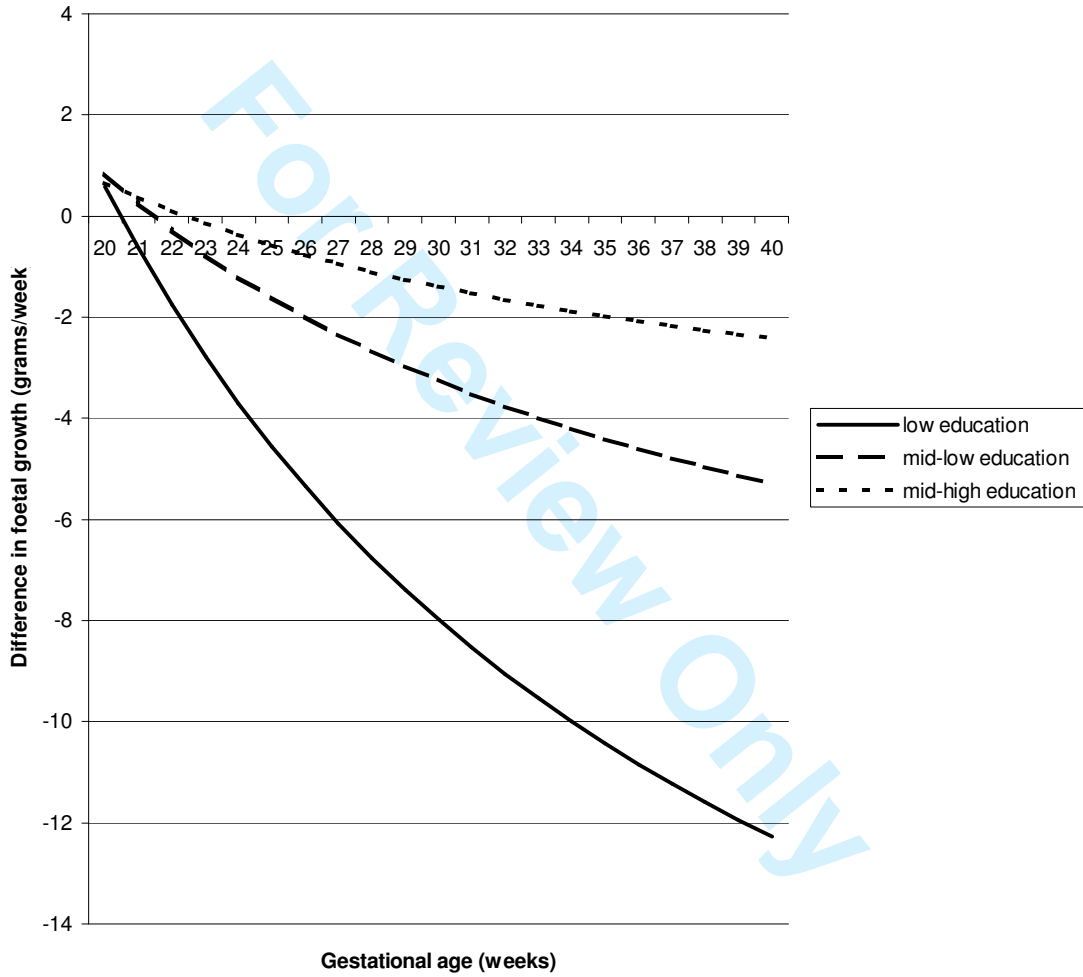
Figure 1. Flow chart participants



Created by LM Silva

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

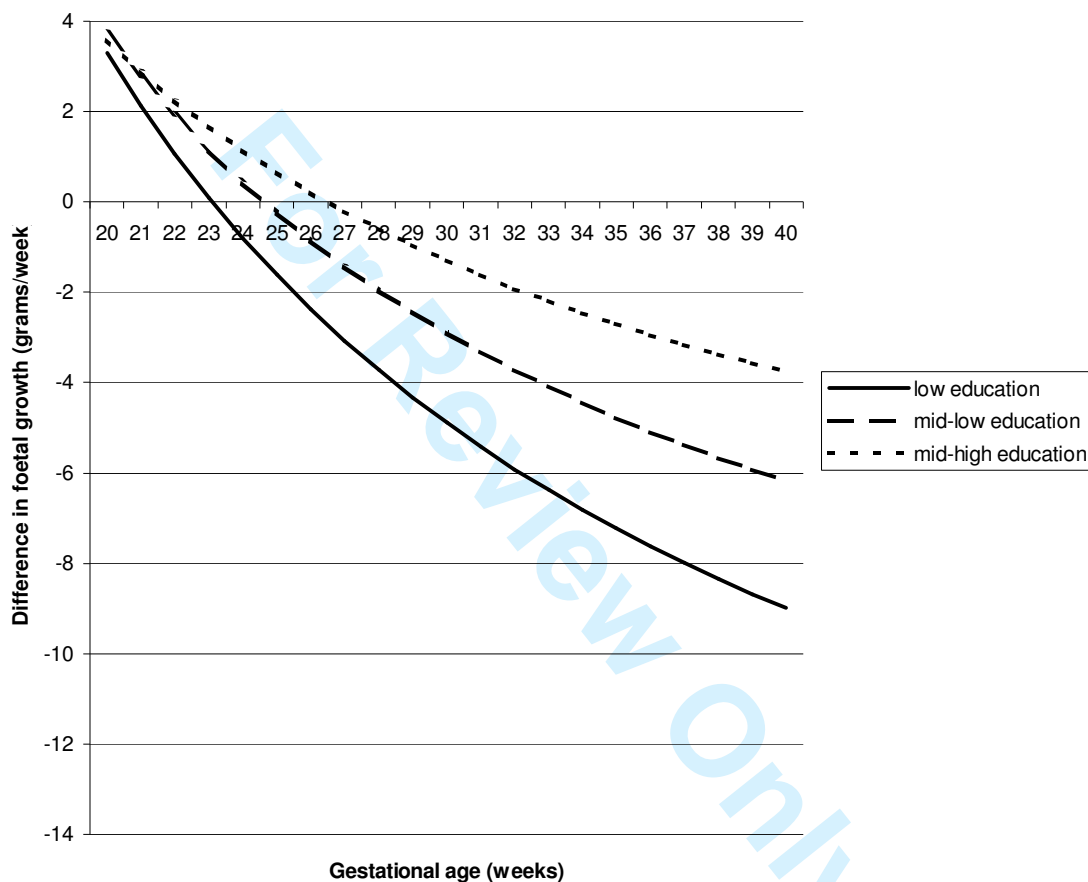
Figure 2a. Estimated differences in foetal growth rate (grams/week) for foetuses of women with low, mid-low and mid-high education relative to foetuses of women with high education (n=3545)*.



* Values are based on multilevel models and represent the differences in foetal growth rate for foetuses of women with low, mid-low and mid-high education relative to those of women with high education. All values are adjusted for maternal age and parity. The following covariate*gestational age interactions were also included: age*gestational age, parity*gestational age.

Created by LM Silva

Figure 2b. Estimated differences in foetal growth rate (grams/week) for foetuses of women with low, mid-low and mid-high education relative to foetuses of women with high education, fully adjusted (n=3545)*.



* Values are based on multilevel models and represent the differences in foetal growth rate for foetuses of women with low, mid-low and mid-high education relative to those of women with high education. All values are adjusted for maternal age and parity, maternal height, pre-pregnancy BMI, smoking during pregnancy, single motherhood, whether the pregnancy was planned and financial difficulties. The following covariate*gestational age interactions were also included: age*gestational age, parity*gestational age, height*gestational age, BMI* gestational age, smoking*gestational age, financial difficulties*gestational age.

Created by LM Silva

Supplementary table 1. Estimated foetal weight, head circumference, abdominal circumference and femur length at median gestational age in mid and late pregnancy in the total study population.

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

Values are means (with standard deviations)

For Review Only

Supplementary table 2. Crude associations between potential mediators and growth of the foetal head, abdomen and femur.

| | Head circumference growth (mm/week, with 95% and p-value | Abdominal circumference growth (mm/week, with 95% and p- value) | Femur length growth (mm/week, with 95% and p-value) |
|---|--|---|---|
| Maternal height (per cm increase) | 0.015 (0.01,0.02) p<0.0001 | 0.0028 (-0.003,0.009) p=0.3622 | 0.0039 (0.0028,0.005) p<0.0001 |
| Maternal pre-pregnancy BMI (per kg/m ² increase) | 0.011 (0.003,0.019) p=0.0050 | 0.04 (0.03,0.05) p<0.0001 | 0.00098 (- 0.00089,0.0029) p=0.3054 |
| Smoking | | | |
| No | Reference | Reference | Reference |
| Until pregnancy known | 0.007 (-0.10,0.12) p=0.9049 | 0.05 (-0.09,0.19) p=0.4964 | -0.015 (-0.04,0.01) p=0.2509) |
| Continued during pregnancy | -0.22 (-0.30,-0.14) p<0.0001 | -0.25 (-0.35,-0.15) p<0.001 | -0.05 (-0.07,-0.03) p<0.0001 |
| Pregnancy was planned | | | |
| Yes | Reference | Reference | Reference |
| No | -0.07 (-0.15,0.006) p=0.07 | -0.09 (-0.19,0.005) p=0.0624 | -0.02 (-0.04,-0.002) p=0.0259 |
| Marital status | | | |
| Married/cohabiting | Reference | Reference | Reference |
| Single | -0.13 (-0.24,-0.02) p=0.0197 | -0.21 (-0.35,-0.07) p=0.0027 | -0.03 (-0.06,-0.006) p=0.0148 |
| Financial difficulties | | | |
| No | Reference | Reference | Reference |
| Yes | -0.13 (-0.22,-0.03) p=0.009 | -0.13 (-0.25,-0.009) p=0.035 | -0.028 (-0.051,-0.003) p=0.0239 |

Values are based on multilevel models. The effect estimates represent the difference in growth rate in mm/week per unit increase in case of continuous variables, or relative to the reference category in case of categorical variables. CI: confidence interval.

Supplementary table 3. Associations between maternal educational level and standard-deviation scores for foetal head circumference, abdominal circumference and femur length at 30 weeks gestation, after individual adjustment for the potential mediators.

| HC (SD-score) at 30 weeks gestation (with 95% CI) | | | | |
|---|-----------|---------------------|----------------------|----------------------|
| Educational level | High | Mid-high | Mid-low | Low |
| Basic model* | Reference | -0.07 (-0.16,0.01) | -0.15 (-0.24,-0.06) | -0.26 (-0.36,-0.15) |
| Basic model + maternal height | Reference | -0.07 (-0.16,0.02) | -0.13 (-0.22,-0.04) | -0.20 (-0.30, -0.10) |
| Basic model + Pre-pregnancy BMI | Reference | -0.08 (-0.16,0.01) | -0.18 (-0.27, -0.09) | -0.30 (-0.40,-0.190) |
| Basic model + Smoking during pregnancy | Reference | -0.06 (-0.15, 0.03) | -0.11 (-0.20, -0.02) | -0.17 (-0.28, -0.06) |
| Basic model + Single motherhood | Reference | -0.07 (-0.16,0.01) | -0.14 (-0.23,-0.05) | -0.23 (-0.33,-0.13) |
| Basic model + Whether pregnancy planned | Reference | -0.07 (-0.16,0.02) | -0.14 (-0.23,-0.06) | -0.25 (-0.35,-0.14) |
| Basic model + Financial difficulties | Reference | -0.07 (-0.16,0.02) | -0.14 (-0.23,-0.05) | -0.24 (-0.34,-0.13) |
| AC (SD-score) 30 weeks gestation (with 95% CI) | | | | |
| Educational level | High | Mid-high | Mid-low | Low |
| Basic model* | Reference | 0.02 (-0.07,0.11) | 0.001 (-0.09,-0.09) | -0.09 (-0.19,-0.02) |
| Basic model + maternal height | Reference | 0.02 (-0.07,0.11) | 0.01 (-0.08,0.10) | -0.06 (-0.16,0.05) |
| Basic model + Pre-pregnancy BMI | Reference | 0.01 (-0.07,0.10) | -0.05 (-0.14,0.04) | -0.16 (-0.26,-0.06) |
| Basic model + Smoking during pregnancy | Reference | 0.03 (-0.06,0.12) | 0.031 (-0.06,0.12) | -0.002 (-0.11,0.11) |
| Basic model + Single motherhood | Reference | 0.02 (-0.07,0.11) | 0.007 (-0.08,0.10) | -0.06 (-0.17,0.04) |

| | | | | |
|------------------------------|-----------|-------------------|--------------------|--------------------|
| Basic model + | Reference | 0.02 (-0.06,0.11) | 0.007 (-0.08,0.10) | -0.07 (-0.17,0.03) |
| Whether pregnancy planned | | | | |
| Basic model + | Reference | 0.02 (-0.07,0.11) | 0.006 (-0.08,0.09) | -0.07 (-0.17,0.03) |
| Financial difficulties | | | | |

FL (SD-score) 30 weeks (with 95% CI)

| Educational level | High | Mid-high | Mid-low | Low |
|---|-------------|--------------------|--------------------|---------------------|
| Basic model* | Reference | -0.02 (-0.10,0.07) | 0.02 (-0.07,0.10) | -0.13 (-0.22,-0.02) |
| Basic model + maternal height | Reference | -0.01 (-0.10,0.07) | 0.04 (-0.05, 0.12) | -0.06 (-0.15,0.05) |
| Basic model + Pre-pregnancy BMI | Reference | -0.02 (-0.11,0.06) | -0.05 (-0.11,0.07) | -0.19 (-0.29,-0.09) |
| Basic model + Smoking during pregnancy | Reference | 0.001 (-0.08,0.09) | 0.07 (-0.02,0.15) | 0.002(-0.10,0.11) |
| Basic model + Single motherhood | Reference | -0.02 (-0.10,0.07) | 0.02 (-0.07,0.11) | -0.11 (-0.21,-0.01) |
| Basic model + Whether pregnancy planned | Reference | -0.02 (-0.10,0.07) | 0.01 (-0.07,0.11) | -0.12 (-0.22,-0.01) |
| Basic model + Financial difficulties | Reference | -0.02 (-0.10,0.07) | 0.02 (-0.07,0.11) | -0.12 (-0.22,-0.01) |

Values are based on multilevel models and represent differences in head circumference, abdominal circumference and femur length (expressed in standard-deviation scores) relative to fetuses of women with high educational level. HC: head circumference; AC: abdominal circumference; FL: femur length; SD-score: standard deviation score. * Basic model: adjusted for maternal age and parity.