No Midpregnancy Fall in Diastolic Blood Pressure in Women With a Low Educational Level

The Generation R Study

Lindsay M. Silva, Eric A.P. Steegers, Alex Burdorf, Vincent W.V. Jaddoe, Lidia R. Arends, Albert Hofman, Johan P. Mackenbach, Hein Raat

Abstract—Low socioeconomic status has been associated with preeclampsia. The underlying mechanism, however, is unknown. Preeclampsia is associated with relatively high blood pressure levels in early pregnancy and with an absent midpregnancy fall in blood pressure. At present, little is known about the associations among socioeconomic status, blood pressure level in early pregnancy, blood pressure change during pregnancy, and preeclampsia. We studied these associations in 3142 pregnant women participating in a population-based cohort study. Maternal educational level (high, midhigh, midlow, and low) was used as an indicator of socioeconomic status. Systolic and diastolic blood pressure was measured in early, mid-, and late pregnancy. Relative to women with high education, those with low and midlow education had higher mean systolic and diastolic blood pressure levels in early pregnancy; this was explained largely by a higher prepregnancy body mass index. Although women with high, midhigh, and midlow education had a significant midpregnancy fall in diastolic blood pressure, those with low education did not (change from early to midpregnancy: −0.38 mm Hg; 95% CI: −1.33 to 0.58). The latter could not be explained by prepregnancy body mass index, smoking, or alcohol consumption during pregnancy. The absence of a midpregnancy fall also tended to be related to the development of preeclampsia, especially among women with a low educational level (OR: 3.8; 95% CI: 0.80 to 18.19). The absence of a midpregnancy fall in diastolic blood pressure in women with a low education level may be a sign of endothelial dysfunction that is manifested during pregnancy. This might partly explain these women’s susceptibility to preeclampsia. (Hypertension. 2008;52:645-651.)

Key Words: blood pressure ■ education ■ hypertension ■ preeclampsia ■ pregnancy ■ socioeconomic factors

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

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

Although the exact etiology of preeclampsia is unknown, it is known that an important role in its pathophysiology is played by endothelial cell dysfunction.10,11 It has been suggested that this endothelial dysfunction is initiated by factors from the placenta that are released in response to reduced trophoblastic perfusion. In women who develop preeclampsia, endothelial cell injury is believed to lead to intravascular coagulation, loss of fluid from the intravascular space, and increased sensitivity to vasoressors.11 The latter results in an abnormal cardiovascular adaptation to pregnancy, which is reflected in an abnormal pattern of blood pressure change during pregnancy.10,12 In pregnant women who are clinically healthy, blood pressure, most notably diastolic blood pressure, falls steadily until the middle of gestation and then rises again until delivery.12 In women who develop preeclampsia, this midpregnancy fall in blood pressure does not occur; instead, blood pressure tends to remain stable during the first half of pregnancy and then rise continuously until delivery.12
It is also the case that, even before preeclampsia manifests itself, these women have higher blood pressure levels in early pregnancy than pregnant women who remain normotensive. At present, little is known about the association of SES with blood pressure level or with the pattern of blood pressure change during pregnancy. There are 2 reasons we would benefit from studying these associations. First, it would improve our knowledge of the magnitude of socioeconomic differences in blood pressure level during pregnancy. Second, it would indicate whether endothelial function in young pregnant women may be affected by SES and whether any such effects may be involved in the association of SES with preeclampsia and later cardiovascular disease.

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

Methods

The Generation R Study
This study was embedded within the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood that has previously been described in detail. Briefly, the cohort comprises 9778 (response 61%) mothers of various ethnicities and their children living in Rotterdam, The Netherlands. All children were born between April 2002 and January 2006. Assessments in pregnancy took place in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18 to 25 weeks), and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam. Written consent was obtained from all participating parents.

Study Population
Ninety-one percent (n=8880) out of a total of 9778 women were enrolled during pregnancy. Because socioeconomic inequalities in blood pressure may differ between ethnic groups, the present study was restricted to women with a Dutch ethnicity (n=4057). A woman was classified as Dutch if both her parents were born in The Netherlands. For several reasons, 915 women were excluded from analysis (see Figure S1, available in the online data supplement at http://hyper.ahajournals.org), which made 3142 women eligible for the primary analyses.

Additional analyses were performed in a subgroup of 2441 women on whom blood pressure measurements in both early and mid pregnancy were available as well as information about diagnosis of preeclampsia (see Figure S1).

Educational Level
On the basis of a questionnaire used at enrollment, we established the highest education each mother had achieved. This was categorized into 4 levels: high (university or higher), midhigh (higher vocational training), midlow (>3 years of general secondary school, intermediate vocational training completed, or first year of higher vocational training), and low education (no education, primary school, lower vocational training, intermediate general school, or ≤3 years of general secondary school).

Blood Pressure
At the research centers, the validated Omron 907 automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, The Netherlands) was used to measure systolic (SBP) and diastolic blood pressure (DBP) in early, mid-, and late pregnancy; participants were seated in an examination room in a chair with back support and were asked to relax. Blood pressure measurement started after 5 to 10 minutes of rest. A cuff was placed around the nondominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation. If the circumference of the upper arm exceeded 33 cm, a larger cuff was used. Per participant, the mean value of 2 blood pressure readings over a 60-second interval was documented.

Preeclampsia
The data collection regarding the development of preeclampsia in our study population has been described elsewhere. Briefly, the presence of doctor-diagnosed preeclampsia was retrieved from hospital charts and was determined on the basis of the criteria described by the International Society for the Study of Hypertension in Pregnancy (Table S1).

Potential Mediators and Confounders
Maternal educational level cannot affect blood pressure directly but is likely to act through other more proximal determinants of blood pressure. We considered prepregnancy BMI, smoking, and alcohol consumption during pregnancy to be potential mediators in the pathway between maternal education and blood pressure (see Figure S2); these factors are known to contribute substantially to socioeconomic inequalities in blood pressure in the general population. Prepregnancy BMI was calculated on the basis of height and prepregnancy weight (weight/height2); height was measured at enrollment in one of the research centers, and prepregnancy weight was established at enrollment through a questionnaire. Maternal smoking and alcohol consumption (yes, no) were established using questionnaires in early, mid-, and late pregnancy.

Maternal age, parity, and twin pregnancy were treated as potential confounders in this study (see Figure S2), because they could not be considered indisputable mediators. Maternal age was established at enrollment. Parity (para 0, para ≥1) was obtained by questioning at enrollment. The presence of twin pregnancy was determined by fetal ultrasound.

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

To calculate the overall effect of education on blood pressure, we started with a linear mixed model that included the potential confounders (basic model). Next, the potential mediators were added to the basic model, first separately and then simultaneously (full model).
For each confounder and mediator, an interaction term with pregnancy period was tested for significance. If the test was significant, these interactions were retained in the model. Missing data on smoking and alcohol consumption were included as separate categories.

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

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

Results

Maternal and birth characteristics of the study population are described in Table 1. Compared with women with a high educational level, those with a low level were younger, shorter, and heavier. During pregnancy, they were more likely to smoke but less likely to consume alcohol (P for all <0.05, Table 1). Preeclampsia was more common in women with a low educational level than in those with a high level (P for trend: 0.004). Gestational age at delivery and birth weight of the newborn were inversely associated with educational level (P<0.001).

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

Figures 1 and 2 show that throughout pregnancy, women with a low and midlow educational level had higher mean SBP and DBP levels than women with a high educational level. These differences were statistically significant, except for the difference in mean DBP in early pregnancy between

![Figure 1](http://hyper.ahajournals.org/)

Figure 1. Mean SBP in early, mid-, and late pregnancy stratified by educational level. All values are adjusted for gestational age at time of blood pressure measurement. *Mean blood pressure significantly different from that in subgroup of women with high educational level (P<0.001).
women with a low educational level and those with a high educational level.

Educational Level and Blood Pressure in Early Pregnancy

Table 2 shows the educational differences in blood pressure level in early pregnancy as calculated on the basis of the linear mixed models. After adjustment for confounders, mean SBP in early pregnancy in women with low and midlow education were, respectively, 2.67 mm Hg higher (95% CI: 1.27 to 4.07) and 3.02 mm Hg higher (95% CI: 1.83 to 4.21) than in women with high education (basic model, Table 2). Additional adjustment for maternal prepregnancy BMI, smoking, and alcohol consumption (full model) attenuated these differences to 0.63 mm Hg (95% CI: −0.78 to 2.04) and 1.51 mm Hg (95% CI: 0.35 to 2.67), respectively. This attenuation was due mainly to the adjustment for prepregnancy BMI.

In the basic model, mean DBP in early pregnancy was 1.49 mm Hg higher (95% CI: 0.55 to 2.44) in women with a midlow education than in women with a high education (Table 2). Additional adjustment for prepregnancy BMI, smoking, and alcohol consumption during pregnancy (full model) attenuated this difference to 0.41 mm Hg (95% CI: −0.49 to 1.31). Again, this attenuation was due mainly to the adjustment for prepregnancy BMI.

Educational Level and Blood Pressure Change During Pregnancy

Mean SBP increased as pregnancy progressed in all educational subgroups (Figure 1). The magnitude of increase did not differ between educational levels (P≥0.05).

In all educational subgroups except one, mean DBP decreased from early to midpregnancy followed by an increase from mid- to late pregnancy (Figure 2). In the basic model, the change in mean DBP from early to midpregnancy was −1.82 mm Hg (95% CI: −2.58 to −1.05) in women with a high education, −2.07 mm Hg (95% CI: −2.91 to −1.24) in women with a midhigh education, and −1.60 mm Hg (95% CI: −2.43 to −0.77) in women with a midlow education (Table 2). The exception was the subgroup of women with low education in whom there was no significant fall in DBP (change: −0.38 mm Hg; 95% CI: −1.33 to 0.58). In this subgroup, the change in DBP from early to midpregnancy was also significantly different from that in women with a high education (P<0.01). After additional adjustment for prepregnancy BMI, smoking, and alcohol consumption (full model), the change in women with a low education was −0.61 mm Hg (95% CI: −1.66 to 0.43) and was still significantly different from that in women with a high education (P<0.05).

There were no educational differences in the change in mean DBP from mid- to late pregnancy (P≥0.05).

Additional logistic regression analyses (n=3441) showed that, relative to women who had a midpregnancy fall (n=1280 [52.4%]), those in whom there was no fall (n=1161...
The presence of systematical bias, however, is unlikely, association between educational level and blood pressure. Random measurement error, which may have weakened the measurements. These limitations probably introduced some because our study did not include ambulatory blood pressure monitoring of a large number of women early in pregnancy.14

Discussion

This population-based prospective cohort study produces 2 major findings. First, relative to women with a high education, those with a low and a midlow education had higher mean SBP and DBP levels from early pregnancy onward. These differences were due largely to a higher prepregnancy BMI in women with a lower educational level. Second, even after adjusting for prepregnancy BMI, smoking, and alcohol consumption during pregnancy, the fall in DBP one would normally expect in midpregnancy was not found in women with a low education. This absence of midpregnancy fall tended to be related to the development of preeclampsia, particularly in the subgroup of women with a low educational level.

Methodological Considerations

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

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

First, although the OMRON 907 device has been validated according to the Association for the Advancement of Medical Instrumentation Standard23 as well as the preliminary criteria of the International Protocol,18 further validation studies using the final International Protocol criteria are needed to make definite statements about the accuracy of the device. Furthermore, during the day, blood pressure varies according to a circadian rhythm.24 We were unable to account for this, because our study did not include ambulatory blood pressure measurements. These limitations probably introduced some random measurement error, which may have weakened the association between educational level and blood pressure. The presence of systematical bias, however, is unlikely, because we do not assume that inaccurate measurements or the influence of the circadian rhythm on blood pressure change differed systematically by educational level.

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

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

Educational Level and Blood Pressure in Early Pregnancy

Previous studies in the general, nonpregnant population have described socioeconomic inequalities in blood pressure and essential hypertension.2,3 A review by Colhoun et al2 showed that most studies conducted in developed countries found age-adjusted differences of approximately 2 to 3 mm Hg in mean SBP between the highest and lowest socioeconomic groups. This is in line with our results. In our study, educational differences in blood pressure levels in early pregnancy were explained largely by educational differences in prepregnancy BMI. This indicates that the well-known socioeconomic gradient in overweight among women26 is an important pathway through which educational inequalities in blood pressure during pregnancy arise.

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

Remarkably, blood pressure in early pregnancy was higher in women with a midlow education than in those with a low education. However, this does not imply that the latter are

<table>
<thead>
<tr>
<th>Educational Level</th>
<th>Basic Model†</th>
<th>Basic Model† + BMI</th>
<th>Basic Model† + Smoking</th>
<th>Basic Model† + Alcohol</th>
<th>Full Model‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>High education</td>
<td>−1.82 (−2.58 to −1.05)</td>
<td>−1.82 (−2.59 to −1.05)</td>
<td>−1.95 (−2.72 to −1.17)</td>
<td>−1.93 (−2.70 to −1.16)</td>
<td>−1.98 (−2.76 to −1.12)</td>
</tr>
<tr>
<td>Midhigh education</td>
<td>−2.07 (−2.91 to −1.24)</td>
<td>−2.04 (−2.88 to −1.21)</td>
<td>−2.26 (−3.11 to −1.40)</td>
<td>−2.21 (−3.05 to −1.37)</td>
<td>−2.26 (−3.11 to −1.41)</td>
</tr>
<tr>
<td>Midlow education</td>
<td>−1.60 (−2.43 to −0.77)</td>
<td>−1.59 (−2.42 to −0.76)</td>
<td>−1.80 (−2.66 to −0.93)</td>
<td>−1.76 (−2.59 to −0.92)</td>
<td>−1.83 (−2.70 to −0.96)</td>
</tr>
<tr>
<td>Low education</td>
<td>−0.38 (−1.33 to 0.58)</td>
<td>−0.34 (−1.30 to 0.61)</td>
<td>−0.61 (−1.66 to 0.44)</td>
<td>−0.51 (−1.47 to 0.45)</td>
<td>−0.61 (−1.66 to 0.43)</td>
</tr>
</tbody>
</table>

*Data are derived from linear mixed models fitted on DBP.
†Basic model: adjusted for gestational age, maternal age, parity, and twin pregnancy.
‡Full model: basic model + prepregnancy BMI, smoking, and alcohol consumption at time of blood pressure measurement.
§Significantly different from change in DBP in subgroup with high educational level (P<0.05).
||Significantly different from change in DBP in subgroup with high educational level (P<0.01).
better off than the former; in early pregnancy, women with a low education had the highest pulse pressure (ie, the difference between SBP and DBP; data not shown). An elevated pulse pressure is an indicator of poor arterial compliance and is an additional risk indicator both for preeclampsia and for cardiovascular disease.27,28

**Educational Level and Diastolic Blood Pressure Change During Pregnancy**

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

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

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

**Perspectives**

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

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

**Acknowledgments**

The Generation R Study is conducted by the Erasmus MC, University Medical Centre Rotterdam in close collaboration with the Erasmus University Rotterdam, School of Law and Faculty of Social Sciences, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation, and the Stichting Trombosdienst & Arsenenlaboratorium Rijnmond (STAR), Rotterdam.

**Sources of Funding**

This study was supported by the Erasmus MC, University Medical Center Rotterdam, Erasmus University Rotterdam, The Netherlands Organization for Health Research and Development (ZonMw), and The Netherlands Organization for Scientific Research (NWO, grant No 017.002.107).

**Disclosures**

None.

**References**


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*Hypertension*. 2008;52:645-651; originally published online August 25, 2008; doi: 10.1161/HYPERTENSIONAHA.108.116632

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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http://hyper.ahajournals.org/content/52/4/645

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NO MID-PREGNANCY FALL IN DIASTOLIC BLOOD PRESSURE IN WOMEN WITH A LOW EDUCATIONAL LEVEL.

THE GENERATION R STUDY.

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Short title: Educational level and pregnancy blood pressure

Supplemental tables: 1

Supplemental figures: 2

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SUPPLEMENTAL REFERENCE

Table S1. Applied criteria for the diagnosis of preeclampsia\textsuperscript{1}.

<table>
<thead>
<tr>
<th>Criteria preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) New onset hypertension</td>
</tr>
<tr>
<td>(i.e. SBP $\geq$140 mmHg and/or a DBP $\geq$90 mmHg after 20 weeks of gestation in a previously normotensive woman)</td>
</tr>
<tr>
<td>and</td>
</tr>
<tr>
<td>2) Proteinuria</td>
</tr>
<tr>
<td>(i.e. two or more dipstick readings of 2+ or greater, one catheter sample reading of 1+ or greater, or a 24–hour urine collection containing at least 300 mg of protein)</td>
</tr>
</tbody>
</table>
N=9778
Generation R cohort

N=8880
Participants enrolled during pregnancy

N=4057
Participants with a Dutch ethnicity

Excluded: data on 2nd (n=332) or 3rd (n=5) pregnancy of the same participant, induced abortions (n=14), fetal death <20 weeks gestation (n=7), lost to follow-up (n=3), chronic hypertension (n=40)

N=3656

Excluded due to missing information on:
- educational level (n=21)
- parity (n=7)
- height (n=3)
- pre-pregnancy weight (n=480)
- blood pressure during pregnancy (n=3)

N=3142
Women eligible for primary analysis

N=2441
Complete data on blood pressure in both early and mid pregnancy, and on preeclampsia.

Figure S1. Flow chart participants
Figure S2. Simplified conceptual framework for the association between maternal educational level and blood pressure in pregnancy.

**Educational level**

**Blood pressure in pregnancy**

**Mediators**
- Pre-pregnancy body mass index
- Smoking
- Alcohol consumption

**Confounders**
- Age
- Parity
- Twin pregnancy