Height and risk of severe pre-eclampsia. A study within the Danish National Birth Cohort

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Background Pre-eclampsia shares a number of risk factors with cardiovascular disease (CVD). Women with recurrent pre-eclampsia or pre-eclampsia early in pregnancy reportedly have an increased long-term risk of CVD. Short stature is a risk factor for CVD but has rarely been examined in relation to pre-eclampsia.

Methods We used data from 59,968 singleton live births in the Danish National Birth Cohort born between 1998 and 2001 to assess risk of severe pre-eclampsia/eclampsia (296 cases) in relation to self-reported height. We examined the association in multiple logistic regressions stratified by parity.

Results Among primiparas there was a weak association (compared with women ≥165 cm, women ≥172 cm had an OR of 0.79, 95% CI: 0.55, 1.14). Among multiparas, the tallest women had an adjusted OR of 0.42 (95% CI: 0.20, 0.87) of developing severe pre-eclampsia compared with women <165 cm. The OR per centimetre was 0.94 (95% CI: 0.91, 0.97). Self-reported pre-existing hypertension did not explain this association, which also persisted when the analysis was restricted to non-overweight women.

Conclusions Short stature was associated with a higher risk of severe pre-eclampsia in multiparas participating in the Danish National Birth Cohort.

Keywords Height, pregnancy complications, pre-eclampsia (severe), cohort study

Pre-eclampsia is a serious and poorly understood complication of pregnancy, which can progress to eclampsia and maternal death, but that typically resolves quickly upon termination of pregnancy. Pre-eclampsia shares a number of risk factors with cardiovascular disease (CVD), especially atherosclerosis, but also obesity, diabetes, endothelial disease, and pre-existing hypertension, and it is believed that women who are at high risk of CVD are more prone to developing pre-eclampsia. There is evidence that pre-eclampsia is associated with CVD later in life, especially in the case of early-onset and/or recurrent severe pre-eclampsia or eclampsia. Chesley et al. followed up 267 women after an episode of eclampsia. While the overall group of women who had eclampsia as primiparas did not have an increased risk of hypertension later in life, those with eclampsia as multiparas had a higher than expected morbidity and mortality associated with hypertension. Sibai et al. reported an increased risk of hypertension among all women who had had severe pre-eclampsia/eclampsia in the first pregnancy. Within this group, however, those with a pre-eclamptic pregnancy following the index pregnancy were at the highest risk, and risk was also elevated among women with early onset pre-eclampsia, compared with women in whom the disease had started later. A subsequent study on eclampsia showed a similar pattern. A recent study reported that women with pre-eclampsia who had given birth preterm had an eightfold risk of later dying of CVD compared with women without pre-eclampsia who had given birth at term. There is thus increasing evidence that pre-eclampsia may be a single syndrome resulting from heterogeneous causes, which may differ on average between primiparas and multiparas.

There is some evidence that short stature is associated with CVD, although two reports disagree. If short stature is a marker of risk for CVD, it may also be a marker of risk for pre-eclampsia. Only a few studies have, to our knowledge, examined the association between height and risk of pre-eclampsia, and the findings were inconsistent. It is of both scientific and clinical interest to assess whether short women are at a higher risk of pre-eclampsia. Stature could...
be an additional marker for identifying high-risk women, and may help provide new clues to the aetiology of this disease. We analysed data from women participating in the Danish National Birth Cohort to explore the association between short stature and risk of severe pre-eclampsia.

**Methods**

The Danish National Birth Cohort is a nationwide longitudinal project where women are recruited early in pregnancy and are interviewed four times by telephone, twice during pregnancy and twice after delivery. Approximately 60% of all eligible women across Denmark are informed about the study (depending on the collaboration level of the general practitioners), and about 60% of the informed women participate. This study makes use of data from the first interview combined with hospital and birth records obtained from the Danish National Board of Health.

We linked the 64,167 responses to the first interview to 62,122 births from the Danish Medical Birth Registry, which was updated through 31 December 2001. In addition, we identified 778 births that took place in 2002, and 345 live births for which, at present, no record could be found in the Birth Registry, despite the information from the Central Person Registry that these babies had been born alive. The delivery would not appear in the birth record if it had taken place in the home or abroad. Errors in the mother's personal identification number may also cause failures in the matching. For a further 922 interviews, we found no record of a birth in either source, suggesting that these were likely fetal deaths occurring after the first interview had taken place. We limited this analysis to singleton live births recorded in the Danish Medical Birth Registry with a gestational age of ≥24 completed weeks (60,525 records).

We further excluded 117 records because of missing values in parity, mother's height, or smoking. Of the remaining 60,408 births, however, 1,884 women had more than one pregnancy in the study. When these were the first and a second (or later) birth (n = 1444) we kept them, as primiparas and multiparas were analysed separately. In the case of 440 women, however, both births were beyond the first and we kept the earliest. The 59,968 interviews in this study were completed between April 1998 and February 2001. Median week of interview was the 16th and 95% of the women had been interviewed by week 24.

We limited our analysis to severe pre-eclampsia for two reasons: (1) the evidence suggesting an association with hypertension later in life was mainly obtained from women with severe pre-eclampsia or eclampsia, and (2) because, although rare, the severe form is likely to be diagnosed correctly more frequently than the mild form. The latter is important because lack of specificity affects more profoundly relative measures of risk than does lack of sensitivity. To define cases we used the International Classification of Diseases, Tenth Revision (ICD-10) codes for severe pre-eclampsia (O141) and eclampsia (O150–O159) from the hospital records. The current Danish guidelines for defining severe pre-eclampsia include the presence of a diastolic blood pressure of ≥110 mmHg or a systolic blood pressure of ≥180 mm Hg, proteinuria (>3 g/l/24 h), and/or other signs or symptoms involving one or more organ systems. However, we do not have specific information other than the record that there was a clinical diagnosis.

We included diagnoses of severe pre-eclampsia from the 20th week of gestation. There were 296 cases of severe pre-eclampsia, with a frequency of 0.8% among primiparas and of 0.3% among multiparas.

We examined the effect of mother's height by dividing height into quartiles (<165 cm, 165–168 cm, 169–172 cm, and ≥173 cm), and we estimated odds ratios (OR) and 95% CI using multiple logistic regression models stratified by parity (primiparas versus multiparas), because pre-eclampsia in primiparas and multiparas are considered to be somewhat distinct syndromes. Although we were most interested in the risk of the shortest women compared with the tallest, we used as reference category women <165 cm, because the tallest category had fewer cases, which would affect the confidence limits. We adjusted all analyses for mother's age at delivery, pre-pregnancy body mass index (BMI), smoking in pregnancy, and mother's social status.

We also explored the exposure–response for height on pre-eclampsia by fitting a quadratic spline, allowing separate curves for the two categories of parity. The overall fit, however, was not improved over that of a linear model so we present the estimate for continuous height linearly.

Height, parity, and all covariates except age (based on the civil registration number) were self-reported. The variables used in the models were categorized as in Table 1. Decisions on confounders were made on the basis of the known predictors of pre-eclampsia for which we had information.

There were 3730 (6.2%) births with a missing value in either social status (N = 2836), BMI (N = 836), or both (N = 58). Missing values were included in the model as a separate category for each variable. Social status was based upon the job title of the woman's current or most recent job (held within the last 6 months). The partner's occupation was not considered. Job titles had been categorized according to Statistics Denmark’s job classification. If participants were in school, even if working part time, the social status was based on the type of ongoing education. Our category for high social status included all women in management and having jobs requiring higher education (≥4 years beyond the compulsory level of 9 years). Office workers, service workers, skilled manual workers, and women in the military constituted the middle category, and unskilled workers were classified in the lowest social class.

Analyses were performed with and without women who had reported in the interview that they had had hypertension (not restricted to a pregnancy). We also carried out analyses with and without women with a BMI ≥25, even though we saw no interaction between height and BMI in relation to severe pre-eclampsia, to assess whether the association differed by BMI.

In Denmark the threshold for defining a stillbirth as opposed to a late spontaneous abortion is currently 28 weeks. It is possible that missing stillbirths might have biased our results, therefore we re-analysed the data including only women giving birth from the 28th week onwards but including stillbirths to see whether the estimates changed.

**Results**

Table 1 shows the characteristics of the births according to whether the mother had had a diagnosis of severe pre-eclampsia. Women with severe pre-eclampsia were more likely to have a BMI >20 and, especially, >30. Primiparas who...
smoked during pregnancy were less likely to have a diagnosis of severe pre-eclampsia, but we did not see this relationship in multiparas. A low social status, on the other hand, was associated with severe pre-eclampsia among multiparas, but not primiparas. Women with pre-eclampsia had, as expected, smaller babies and a much higher frequency of preterm deliveries compared with the women without pre-eclampsia. The frequency of caesarean (C) section, especially emergency C-section, was much higher among cases. Mean height was lower among women with severe pre-eclampsia, but especially so among multiparas. The overall risk of pre-eclampsia was 0.8% among primiparas and 0.3% among multiparas. Women shorter than 165 cm had a risk of 0.9% in primiparas and 0.3% in multiparas, while women taller than 172 cm had a risk of 0.7% and 0.1% in primiparas and multiparas, respectively.

In Table 2 we report the adjusted OR of severe pre-eclampsia as a function of mother’s height. Among primiparas, height showed a weak negative association with severe pre-eclampsia when it was examined as a continuous variable. Among multiparas, however, the tallest women had an estimated risk of severe pre-eclampsia less than half compared with women with a height below the median, and each centimetre of increased height was associated with a 6% decrease in risk. After excluding women who had reported previous hypertension not restricted to a previous pregnancy, the association between short height and pre-eclampsia was virtually unchanged among primiparas and slightly steepened among multiparas (Table 2).

Women who reported smoking at the time of interview were, on average, 0.6 cm shorter than women who reported having never smoked in pregnancy. Restricting the analysis to non-smokers resulted in a slightly stronger association between quartiles of height and pre-eclampsia (data not shown) and virtually the same estimates per centimetre of height: 0.97 (95% CI: 0.94, 0.99) in primiparas and 0.93 (95% CI: 0.89, 0.97) in multiparas.
Table 2  Estimated effect of height (in quartiles and linear) on severe pre-eclampsia, by parity. Logistic regression models

<table>
<thead>
<tr>
<th>Mother's height (cm)</th>
<th>All women</th>
<th>Did not report hypertension$^a$</th>
<th>Did not report hypertension$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Cases</td>
<td>Crude estimates</td>
<td>Adjusted estimates$^b$</td>
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<tr>
<td></td>
<td>OR$^d$ (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
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<td></td>
<td>N  Cases</td>
<td>Adjusted estimates$^b$</td>
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<td></td>
<td>OR (95% CI)</td>
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<td></td>
<td>N  Cases</td>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
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</tr>
<tr>
<td>Primiparas</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;165</td>
<td>6395</td>
<td>60</td>
<td>1.00</td>
</tr>
<tr>
<td>165–168</td>
<td>6853</td>
<td>47</td>
<td>0.73 (0.50, 1.07)</td>
</tr>
<tr>
<td>169–172</td>
<td>6798</td>
<td>51</td>
<td>0.80 (0.55, 1.16)</td>
</tr>
<tr>
<td>173–176$^c$</td>
<td>7537</td>
<td>55</td>
<td>0.78 (0.54, 1.12)</td>
</tr>
<tr>
<td>Per cm (linear)</td>
<td>0.97 (0.95, 1.00)</td>
<td></td>
<td>0.97 (0.95, 1.00)</td>
</tr>
<tr>
<td>Multiparas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;165</td>
<td>7875</td>
<td>25</td>
<td>1.00</td>
</tr>
<tr>
<td>165–168</td>
<td>8517</td>
<td>31</td>
<td>1.15 (0.68, 1.94)</td>
</tr>
<tr>
<td>169–172</td>
<td>7998</td>
<td>17</td>
<td>0.67 (0.36, 1.24)</td>
</tr>
<tr>
<td>173–176$^f$</td>
<td>7995</td>
<td>10</td>
<td>0.39 (0.19, 0.82)</td>
</tr>
<tr>
<td>Per cm (linear)</td>
<td>0.94 (0.90, 0.97)</td>
<td></td>
<td>0.94 (0.91, 0.97)</td>
</tr>
</tbody>
</table>

$^a$ Analysis restricted to women who did not report hypertension outside pregnancy (women reporting pregnancy hypertension are included).
$^b$ Variables in the model: mother’s age, pre-pregnancy BMI, smoking, social status (categorized as in Table 1).
$^c$ Number of women with severe pre-eclampsia.
$^d$ Odds ratio.
$^f$ Tests for trend over the four quartiles in primiparas: crude = 1.29 (P = 0.256); adjusted = 1.06 (P = 0.303); excluding hypertension = 0.726 (P = 0.394).

Discussion

In this study elevated height was associated with a reduced risk of severe pre-eclampsia in multiparas. Among primiparas the association was weak, but in the same direction. Compared with those with a height >172 cm, multiparas <165 cm had a 2.5-fold risk of developing severe pre-eclampsia (95% CI: 1.2, 5.3). The association persisted when women who reported having had hypertension not restricted to pregnancy were excluded and when the analysis was restricted to non-overweight women, although the number of cases was then small.

Pre-eclampsia might result from heterogeneous pathological pathways that are differently distributed between primiparas and multiparas. In primiparas pre-eclampsia may be primarily the result of placental hypoperfusion, while in multiparas it might to a large extent reflect pre-existing sub-clinical maternal disease and this might explain the stronger association between short stature and severe pre-eclampsia seen in multiparas, if short stature is in fact a marker of CVD. Previous reports showed that the long-term risk of adverse health outcomes in women who had pre-eclampsia was higher if pre-eclampsia was recurrent, had early onset, or appeared in a pregnancy other than the first. In a study from Norway it was found that women who had had pre-eclampsia were at a significantly increased risk of later death by CVD only if they had given birth preterm.

Short maternal height has not, to the best of our knowledge, been previously reported as a risk indicator for pre-eclampsia. Although data on height are probably available to researchers studying pre-eclampsia, since it is used to calculate the BMI, height is not usually reported among the results. Whether this is because no association is found or because height is not examined per se we do not know. We were able to identify three papers where information on pre-eclampsia in relation to categories of maternal height was presented. A lack of association was noted in two: a study of Latin American women and a study of teenage pregnancies. The third, a case-control study of mild and severe pre-eclampsia in Zimbabwean women, reported a higher risk of pre-eclampsia in tall women.

Pre-eclampsia in our study was diagnosed through hospital records, and we restricted the analysis to severe pre-eclampsia, which is a serious condition, unlikely to be missed and less likely than mild pre-eclampsia to be erroneously diagnosed. If some non-cases had mistakenly been included among the cases, this would presumably have biased our estimates towards null values. If we missed some cases, this would have little effect because of the rarity of this condition, unless tall cases were more likely to be missed than short cases, which seems unlikely. In our data, cases of severe pre-eclampsia had a high incidence of preterm delivery and C-section, compatible with severe pregnancy complications.

Our overall estimated incidence of severe pre-eclampsia (0.5%) was similar to that of 0.4% reported by a British study, but lower than that of 1.7% reported in a Canadian study. In the latter study, however, the authors pointed out...
that the sample was hospital-based and thus markedly influenced by referrals.

Another issue involves potential misclassification of stature. It is generally accepted that self-reported height and weight are often inaccurate.\textsuperscript{21–24} In particular, height tends to be overstated, especially by shorter people. The relationship we observed is unlikely to be an artifact of such errors because they are likely to occur similarly among women with and without pre-eclamptic pregnancies, especially since the height data were, in most cases, collected before diagnosis of pre-eclampsia.

The women in the cohort represent about one-third of eligible pregnant women in Denmark, which may lead to lack of representativeness, since participation is probably associated with social factors, and some areas are less represented because of lack of participation among the general practitioners.\textsuperscript{17} However, unless tall women who would have developed severe pre-eclampsia were systematically under-represented (or short women who would have developed severe pre-eclampsia over-represented), it is unlikely that this artifactually produced our findings, considering the longitudinal nature of this study.

We did not have information on the origin or nationality of the participants, and it is possible that women with a shorter stature were more frequently immigrants, since Danish women are rather tall. We do not think that this is likely to have produced our results, however, since in a random sample of births from 1980 to 1994 a larger proportion of births were recorded with pre-eclampsia among women with Danish citizenship compared with women of foreign nationality.\textsuperscript{25}

We conducted this study on live births only, and missing stillbirths might have biased our results if tall women with pre-eclampsia had more stillbirths. However, we conducted an additional analysis including stillbirths but, since in Denmark stillbirths are registered from the 28th week of gestation, we restricted this analysis to all births from the 28th week. There was no change in the estimated results in this subgroup of births.

Short stature has been reported to be related to increased risk of cardiovascular disease (CVD).\textsuperscript{7–11} and women who have had pre-eclampsia are at elevated risk of developing CVD.\textsuperscript{2–4,6} Our findings show that short stature and risk of pre-eclampsia are also related. The two conditions, CVD and pre-eclampsia, share several other risk factors, including a high BMI and high blood pressure, but short stature was related to pre-eclampsia even after controlling for these two factors. Other possible shared mechanisms could not be controlled for in our analysis, such as lipid levels and homocysteine status.

There are also other possible explanations for the association of short stature with pre-eclampsia. Haig has suggested that pre-eclampsia can arise when fetal demands overwhelm maternal resources,\textsuperscript{26} and this may be more common for short women and a reason for this association. However, we would expect this to be especially likely for short women with tall partners because the foetus would then be predisposed to a larger size.\textsuperscript{27–30} However, when we looked at risk of severe pre-eclampsia in short women with tall partners compared with short women with short partners, we found no difference, and father’s height was not associated with severe pre-eclampsia in our data (data not shown), thus providing little support to this hypothesis. On the other hand, short stature may be a marker for suboptimal prenatal and postnatal development that results in phenotypes that could predispose to pre-eclampsia.

Our study, if corroborated, adds a new piece to the puzzle of the aetiology of pre-eclampsia. An easily measured risk factor such as height may also be useful in identifying women at increased risk.

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**References**