Prenatal exposure to preeclampsia is associated with accelerated height gain in early childhood

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Abstract

Background
Preeclampsia is associated with low birth weight, both because of increased risks of preterm and of small-for-gestational-age (SGA) births. Low birth weight is associated with accelerated childhood height gain and cardiovascular diseases later in life. The aim was to investigate if prenatal exposure to preeclampsia is associated with accelerated childhood height gain, also after adjustments for SGA-status and gestational age at birth.

Methods
In a cohort of children prenatally exposed to preeclampsia (n = 865) or unexposed (n = 22,898) we estimated height gain between birth and five years of age. The mean difference in height gain between exposed and unexposed children was calculated and adjustments were done with linear regression models.

Results
Children exposed to preeclampsia were on average born shorter than unexposed. Exposed children grew on average two cm more than unexposed from birth to five years of age. After adjustments for maternal characteristics including socioeconomic factors, height, body mass index (BMI) and diabetes, as well as for parents smoking habits, infant’s breastfeeding and childhood obesity, the difference was 1.6 cm (95% CI 1.3–1.9 cm). Further adjustment for SGA birth only slightly attenuated this estimate, but adjustment for gestational age at birth decreased the estimate to 0.5 cm (95% CI 0.1–0.7 cm).

Conclusion
Prenatal exposure to preeclampsia is associated with accelerated height gain in early childhood. The association seemed independent on SGA-status, but partly related to shorter gestational age at birth.
Introduction

Cardiovascular disease is a leading cause of death and imposes a substantial burden on the health care system.[1] According to the Developmental Origins of Health and Disease concept, early life environment induces changes in the development of both a fetus and a child, which may impact future risks of diseases.[2] More than 20 years ago an association between low birth weight and cardiovascular disease was first reported.[3] Recently, the question was raised if also prenatal exposure to preeclampsia is associated with future adverse cardiovascular health in the offspring.[4] Prenatal exposure to preeclampsia is associated with increased risk of hypertension in young adults, [5] also in offspring born with normal birth weight.[4]

Accelerated height gain in children is associated with hypertension in adulthood,[6, 7] and in infants born short, accelerated height gain during childhood is also associated with cardiovascular disease.[8] Accelerated growth in infancy is often seen in children born with low birth weight.[9, 10] Preeclampsia is strongly associated with low birth weight, both because of preterm birth and birth of small-for-gestational-age (SGA) infants.[11, 12] However, it is uncertain if exposure to preeclampsia is associated with accelerated growth in offspring born with normal birth weight.

We hypothesized that exposure to preeclampsia is associated with accelerated height gain during early childhood, also after adjustments for SGA-status and gestational age at birth. We investigated the association between exposure to preeclampsia and growth in height during the first five years of life in a population-based cohort of more than 23,000 children.

Methods

Data sources

Uppsala County mother and child database was created by linkage between the Swedish Medical Birth Register, the Uppsala County Child Health Register, the Register of Total Population, and the Register of Education. Individual record linkage was enabled through the personal identity number, uniquely assigned to each Swedish resident at birth or at immigration.

The Swedish Medical Birth Register includes information collected at antenatal visits, during and after delivery until discharge from the hospital. At the first antenatal visit the mother is interviewed about her reproductive history and smoking habits. The mother’s weight is measured and recorded, while maternal height is generally self-reported. After delivery, the mother’s age, the infant’s anthropometric measurements and complications during pregnancy and delivery (according to the International Classification of Diseases (ICD) codes) are recorded.

The Uppsala County Child Health Register includes information collected from visits to child health care units, starting at 1 week of age and ending at six years. Attendance to child health care in Uppsala County is high, where 97% of children have at least six registered visits. [13] Parents are interviewed about breastfeeding that is registered as exclusive, partial and no breastfeeding. The child’s height and weight are measured at 18 months, 3, 4, and 5 years. The height is registered as whole centimeters whereas weight is registered in grams. Anthropometric measurements are not recorded in the Register if the appointments are more than 2 months earlier or later than the planned according to age of the child. Length of newborns and 18 month children (measured in a supine position) will be referred to as height throughout the article.

From the Registers of Total Population and Education, held by Statistics Sweden, we retrieved information on mother’s country of birth and years of formal education, respectively.
Study population

The study population was children born in Uppsala County 2000–2007 with registered height at five years of age. During this period 31,951 children were born in Uppsala County. We excluded 445 infants exposed to gestational hypertension (ICD-10 code O13), since we suspect that there may be some misclassification between preeclampsia and gestational hypertension. The final population included children with a registered height at 5 years, a total of 23,763 children. Electronic registration of height at child health care started in 2005, and children born before 2003 therefore have incomplete series of height measurements. (Table 1)

Exposure

The exposure variable was preeclampsia that was defined through the ICD-10 diagnostic codes O14-O15. Severe preeclampsia was defined by O14.1 (severe preeclampsia), O14.2 (HELLP-syndrome) or O15 (eclampsia) whereas mild preeclampsia was defined by O14.0 and O14.9. According to Swedish guidelines the clinical definition of preeclampsia during the study period was a rise in blood pressure (≥140/90 mm Hg measured on at least two subsequent occasions) combined with significant proteinuria (≥0.3 g/24 hours or +1 on at least two subsequent occasions or +2 on dipstick). The quality of the diagnosis of preeclampsia in the Birth Register has been validated previously: of 148 pregnancies coded as preeclampsia according to ICD-9 standards in the Birth Register, 137 (93%) had the disease according to the individual records.[14] Number of children exposed to preeclampsia was 865 (3.6%).

Outcome

The main outcome was height gain (cm) during childhood, defined as the growth in height from birth to five years of age. Height gain was estimated by subtracting height at birth from the height at 5 years of age. We also calculated Z-scores of height and weight at birth, 18 months, 3, 4 and 5 years using population means and standard deviations in each age group according to Swedish standardized growth curves.[15, 16]

Covariates

Maternal parity, age, body mass index (BMI) in early pregnancy, height, smoking habits in early pregnancy, mothers’ country of birth and level of education, maternal diabetes and infant’s sex, paternal smoking four weeks after birth of the child, exclusive or partial breastfeeding at 6 months and childhood obesity at 5 years were used as covariates. Maternal diabetes was defined as pre-gestational or gestational diabetes and identified through ICD-10 codes (O24.0, O24.1, O24.3, O24.4, O24.9, E10-11 and E13-14). Pre-gestational diabetes was also defined by a check-box in the Birth Register. Childhood obesity was defined as BMI ≥19.3 in boys and ≥19.2 in girls, which is more than 2 standard deviations (SD) over population average according to Swedish reference for 5 year old children.[17]

Statistical analyses

Demographic and clinical variables were compared between pregnancies exposed to severe and mild preeclampsia and unexposed by one-way ANOVA with Tukey post hoc test for continuous covariates and qui square test for categorized covariates.

Children’s pattern of height gain was compared longitudinally with Z-scores. Height measurements at birth, 18 months, 3, 4 and 5 years were standardized to population growth curves in boys and girls separately. [15, 16] Population mean in each age group was subtracted from the observed value, which was then divided by the population standard deviation. The Z-score
at birth was further standardized by gestational age in weeks. Mean Z-scores of height with 95% CI were calculated at each time point in children exposed to mild and severe preeclampsia and unexposed to create line graph. Because of the partly missing data at 18 months, 3 and 4 years of age in children born 2000–2003 (see Table 1) we re-analyzed the z scores in a population of children born 2003–2007 but this did not change the results.

Height gain (cm) during the first five years of life was calculated and the difference in mean height gain between exposed and unexposed was estimated with linear regression. Adjustments were made in three steps. Step one (model 1) included parity, maternal age, early pregnancy BMI, height, maternal smoking habit in early pregnancy, mothers’ country of birth, level of education, diabetes, and infant’s sex, breastfeeding at 6 months, paternal smoking habit four week after birth and childhood obesity. In the attempt to estimate if the effect of preeclampsia was mediated through decreased birth weight, step two and three were introduced. In step two (model 2) the standardized birth weight for gestational age was added into the model categorized to small, appropriate, and large for gestational age infants, defined by the 10th and 90th percentiles according to the Swedish sex-specific fetal growth curve. [15] Finally, in step three (model 3) the gestational age in days at birth was further added into the model. Maternal BMI and height were used as continuous variables whereas other variables were categorized according to Tables 2 and 3. To minimize the risk of a remaining effect modification by birth weight for gestational age, the regression was repeated in a population restricted to children appropriate for gestational age (AGA), with adjustments to all the covariates in model 1 and gestational age in days.

SPSS software (version 22) was used for the analysis.

The study was approved by the Regional Ethical Review Board in Uppsala (2013–351).

Results

In pregnancies complicated with preeclampsia (severe and mild), mothers had higher mean BMI than in pregnancies without preeclampsia whereas maternal height was similar in women with and without preeclampsia. (Table 2) Further, mothers with mild preeclampsia were more often born in Nordic countries and had slightly shorter education than those without preeclampsia. Lastly, mothers with severe and mild preeclampsia had more often pre-gestational or gestational diabetes than mothers without preeclampsia.

Children exposed to preeclampsia were more often their mother’s first born child and were less often breastfed at the age of six months than unexposed. (Table 3) Further, children exposed to preeclampsia were more often born SGA than unexposed, especially those exposed to severe preeclampsia. Among children exposed to severe preeclampsia, 63.1% were born pre-term and they were on average shorter at birth (45.6 cm) than unexposed (50.8 cm) children. Although children exposed to severe preeclampsia grew more than unexposed from birth to 5 years, they were shorter at the age of five than unexposed and with an average height below the

### Table 1. Number of children with height registered at different age by year of birth.

| Year of birth | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---------------|------|------|------|------|------|------|------|------|
| 18 months     | 251  | 315  | 389  | 1447 | 2795 | 2722 | 2950 | 2873 |
| 3 years       | 263  | 355  | 2479 | 2615 | 2835 | 2818 | 3005 | 2892 |
| 4 years       | 322  | 2323 | 2561 | 2710 | 2924 | 2829 | 3005 | 2958 |
| 5 years       | 2544 | 2652 | 2844 | 2986 | 3161 | 3106 | 3313 | 3153 |

* The cursive numbers represents measurements from before 2005, the year of electronic recording to the Child Health Register.

Bold numbers represents our study population in the analysis of height gain.

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Among children exposed to mild preeclampsia, only 12.1% were born preterm and they were only slightly shorter at birth than unexposed. However, children exposed to mild preeclampsia were taller than unexposed and above the population mean at the age of five. Obesity at the age of five did not differ between groups.

After adjustments for maternal parity, age, BMI, height, country of birth, smoking, level of education and diabetes, paternal smoking, child’s sex, infant’s breastfeeding and childhood obesity, the difference in mean height gain between exposed and unexposed was slightly attenuated from 1.9 cm (95% CI 1.6–2.1 cm) to 1.6 cm (95% CI 1.3–1.9 cm) (Table 4). This analysis was also repeated with stratification by sex, and the result did not imply an effect modification by sex (not shown in table). With further adjustments for birth weight for gestational age the population mean. (Fig 1) Among children exposed to mild preeclampsia, only 12.1% were born preterm and they were only slightly shorter at birth than unexposed. However, children exposed to mild preeclampsia were taller than unexposed and above the population mean at the age of five. Obesity at the age of five did not differ between groups.

Table 2. Maternal characteristics in pregnancies complicated with severe and mild preeclampsia and women without preeclampsia.

|                          | Severe preeclampsia (N = 179) | Mild preeclampsia (N = 686) | No preeclampsia (N = 22,898) |
|--------------------------|-------------------------------|----------------------------|----------------------------|
| Age (years)              |                               |                            |                            |
| < 25 years               | 21                            | 85                         | 2737                       |
| 25–29 years              | 57                            | 235                        | 6954                       |
| 30–34 years              | 56                            | 227                        | 8475                       |
| ≥ 35 years               | 35                            | 139                        | 4732                       |
| BMI in early pregnancy   |                               |                            |                            |
| Mean (kg/m²)             | * 26.0 (4.9)                  | * 26.8 (5.5)               | 19,501 24.5 (4.3)          |
| Missing                  | 28                            | 103                        | 3397                       |
| Height                   |                               |                            |                            |
| Mean (cm)                | * 166.0 (5.8)                 | * 166.6 (6.3)              | 22,120 166.7 (6.3)         |
| Missing                  | 5                             | 27                         | 778                        |
| Mothers country of birth |                               |                            |                            |
| Nordic counties          | * 86.6%                       | * 92.6%                    | 19,985 87.3%               |
| European other           | 7                             | 14                         | 768                        |
| Asian countries          | 9                             | 23                         | 1521                       |
| Other                    | 8                             | 14                         | 623                        |
| Parental smoking         |                               |                            |                            |
| Maternal                 | * 5.6%                        | 51                         | 1594                       |
| Missing                  | 9                             | 25                         | 725                        |
| Paternal                 | * 8.2%                        | 50                         | 1793                       |
| Missing                  | 13                            | 14                         | 623                        |
| Education (years)        |                               |                            |                            |
| ≤9                       | 24                            | 102                        | 3594                       |
| 10–14                    | 120                           | 480                        | 14,351 62.7%               |
| ≥15                      | 30                            | 86                         | 4032                       |
| Missing                  | 5                             | 18                         | 921                        |
| Diabetes                 | * 6.7%                        | 32                         | 311                        |

P values calculated with one-way ANOVA with Tukey post hoc test and chi square test.

*p < 0.001 compared to unexposed.

*p > 0.05 compared to unexposed.

† Maternal smoking daily in early pregnancy and paternal smoking one month after the birth of the child.

§ Pre-gestational or gestational diabetes.

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estimates were similar, but adjustment for gestational age in days substantially decreased the estimates, 0.5 cm (95% CI 0.1–0.7 cm). When the population was restricted to children with birth weight appropriate for gestational age (10th–90th percentile according to the Swedish sex-specific fetal growth curve) [15], the fully adjusted estimate of height gain was 0.5 cm (95% CI 0.1–0.8 cm) larger in exposed than unexposed (adjusted for covariates in model 1 and gestational age in days, result not shown in table).

### Discussion

In this population-based prospective study we could show that exposure to preeclampsia was associated with accelerated height gain during early childhood. The association seemed stronger in children exposed to severe than mild preeclampsia. The association was not confined to children born SGA, but the difference in early childhood height gain between exposed and unexposed may partly be explained by shorter gestational age at birth.
Strengths and limitations

The major strength of the study was the large number of included children that made it possible to estimate the association between preeclampsia and childhood height gain. The exposure data was collected before measurement of the outcome which precludes recall bias, and the population-based design makes the results generalizable. Further, we had available

Fig 1. Mean Z scores of height with 95% confidence intervals at different ages in children exposed to mild and severe preeclampsia and unexposed to preeclampsia.

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Table 4. The mean difference in height gain between children exposed and unexposed to preeclampsia.

|                  | Crude  | Adjusted 1 * | Adjusted 2 † | Adjusted 3 ‡ |
|------------------|--------|--------------|--------------|--------------|
| Preeclampsia total | 1.9 (1.6–2.2) | 1.6 (1.3–1.9) | 1.5 (1.2–1.9) | 0.5 (0.1–0.7) |
| Mild preeclampsia | 1.3 (1.0–1.6) | 1.0 (0.6–1.4) | 0.9 (0.6–1.3) | 0.4 (0.0–0.7) |
| Severe preeclampsia | 4.4 (3.7–5.0) | 4.3 (3.6–5.0) | 4.2 (3.4–4.9) | 1.0 (0.3–1.7) |

Height gain defined as length at birth subtracted from the height at 5 years of age.

* Model 1: Adjusted for maternal parity, age, early pregnancy BMI, height, country of birth, smoking in early pregnancy, level of education and diabetes, paternal smoking at 4 weeks after birth, child’s sex, infant’s breastfeeding at 6 months and child’s obesity at 5 years of age.[17]

† Model 2: Adjusted as model 1 with the addition of being born small, average or large for gestational age.[15]

‡ Model 3: Adjusted as model 2 with the addition of gestational age at birth in days.

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information on many possible confounding factors, including maternal parity, height and smoking.[18] Information was also available on several covariates related to the metabolic syndrome, including maternal BMI, maternal diabetes,[19] breastfeeding,[18] and children's obesity.[20] However, we lacked information on maternal gestational weight gain and the family diet, factors that may have affected the association.[18] Further, we lack information on paternal height that seems to be associated with children's height gain, especially between the age of two and five years.[21] Residual confounding by paternal covariates such as height or weight cannot be excluded. The height measurements were registered as whole numbers and therefore a bias related to rounding cannot be excluded. When we studied the gain in height from birth to five years in children exposed and unexposed to preeclampsia, we chose to adjust for gestational age at birth. This seemed reasonable since preeclampsia is strongly associated with preterm birth and therefore shortness at birth. However, the severity of preeclampsia disorder may be reflected by low gestational age and therefore some over adjustment may have occurred.

**Comparisons to earlier studies**

A pattern of accelerated post-natal growth (height and weight gain) is previously described in children born SGA.[9, 10] The majority of children born SGA catch-up in size with their same age peers within the first two years of life, but those who do not catch-up have increased risk of short adult stature.[9] The final height in people exposed to preeclampsia has in a previous study not shown to differ from unexposed,[22] whereas gestational age at birth is associated with the final height.[23] In two previous studies height gain in children exposed to preeclampsia is described.[24, 25] Catch-up growth is described in a cohort of 135 preterm SGA infants born to mothers with preeclampsia.[24] Our results of increasing Z-scores in children exposed to severe preeclampsia indicates a pattern of catch-up growth, and one third of those children were born SGA and more than half of them were born preterm. Therefore, our results seem in concert with previous findings of catch-up growth in children born SGA.[26] However, our results suggest that the association is not confined to children born SGA but also seen in children born AGA. Further, children exposed to mild preeclampsia were taller than unexposed children at the age of five. This interesting finding is also observed recently by Byberg *et al* [25] but in their study the finding was confined to boys. In our study sex did not seem to modify the mean difference in height gain between exposed and unexposed. This difference in results may be explained by different methods used for comparing growth in height in our study (increased height in cm from birth to five years) and Byberg study (modelling of Z scores).

**Potential explanation of the association**

More than 20 years ago Barker hypothesized that an intrauterine environment of restricted nutrition might alter the physiology or metabolism in the fetal tissue to optimize the growth of key organs.[27] Further, this adaptation could become unfavorable in a high nutritional post-natal environment.[20, 28] Our results indicate that not only children born growth restricted but also those exposed to preeclampsia, may have different physiology or metabolism compared with unexposed children. A common imbalance in growth factor signaling may explain the shown association between prenatal exposure to preeclampsia and childhood height gain.[29, 30] Insulin-like growth factors (IGFs) are found to correlate with both intrauterine [30] and post-natal growth [29], but the evidence that prenatal preeclampsia induces epigenetic changes in IGFs is limited to small case-control studies at present time.[31, 32]

Alternatively, the shown association may be related to a maternal inheritable trait (genetic or environmental) that predisposes the mother to preeclampsia and the child to an accelerated
growth pattern. The metabolic syndrome may be a predisposing trait that confounds the association between prenatal preeclampsia and childhood height gain.\cite{20, 33, 34} Adjustments for factors associated with the metabolic syndrome as well as childhood obesity only had a minor impact on the association in our study. Therefore we find it unlikely that confounding by the metabolic syndrome explains the accelerated height gain in childhood seen after prenatal exposure to preeclampsia. However, unknown genetic confounding may explain the association, i.e. that the same sets of genes influence preeclampsia development in mothers and growth in height of their children.

**Conclusion**

Our data implies that early childhood growth trajectories are associated with prenatal exposure to preeclampsia, particularly to severe disease. The association was not confined to children born SGA, but was attenuated after adjustment for gestational age at birth. The observation is mostly interesting on the basis of a possible pathophysiological difference between exposed and unexposed, but the clinical relevance of the observation is uncertain.

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