Cardiovascular Risk Factors in Children and Young Adults Born to Preeclamptic Pregnancies: A Systematic Review

abstract

BACKGROUND AND OBJECTIVE: Preeclampsia is an independent cardiovascular risk factor for the mother, and recent studies reveal that offspring of affected pregnancies also may have an increased cardiovascular risk. Our objective was to examine evidence for increased cardiovascular risk factors in children exposed to preeclampsia in utero.

METHODS: We performed a systematic review and meta-analysis on studies reporting traditional cardiovascular risk factors in those exposed to preeclampsia compared to controls. Information was extracted on the classic cardiovascular risk factors, including blood pressure, lipid profile, glucose metabolism, and BMI from articles published between 1948 and August 2011 in Medline and Embase.

RESULTS: Eighteen studies provided cumulated data on 45,249 individuals. In utero exposure to preeclampsia was associated with a 2.39 mm Hg (95% confidence interval: 1.74–3.05; P < .0001) higher systolic and a 1.35 mm Hg (95% confidence interval: 0.90–1.80; P < .00001) higher diastolic blood pressure during childhood and young adulthood. BMI was increased by 0.62 kg/m² (P < .00001). Associations were similar in children and adolescents, for different genders, and with variation in birth weight. There was insufficient evidence to identify consistent variation in lipid profile or glucose metabolism.

CONCLUSIONS: Young offspring of pregnancies complicated by preeclampsia already have increased blood pressure and BMI, a finding that may need to be considered in future primary prevention strategies for cardiovascular disease. Pediatrics 2012;129:e1552–e1561

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preeclampsia, offspring, cardiovascular risk, systematic review

ABBREVIATION
CI—confidence interval

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Women who develop preeclampsia have an increased risk of later cardiovascular disease,1,2 so guidelines propose that a history of preeclampsia is an integral part of preventive cardiology assessments in women.3 It has now emerged that there also may be cardiovascular health implications for offspring of affected pregnancies. Authors of a long-term follow-up study found that these offspring had almost double the risk of stroke in adulthood,4 and subsequent meta-analysis of early studies of blood pressure variation found they had a 2.3 mm Hg higher systolic and a 1.7 mm Hg higher diastolic blood pressure.5 Because preeclampsia affects 2% to 5% of pregnancies,6,7 these findings are potentially relevant to the cardiovascular health of >300 million people worldwide. We investigated whether an increased cardiovascular risk profile was already evident in childhood, which may warrant early prevention advice, and the characteristic features of this risk profile. We performed a systematic review of all studies that reported variation in cardiovascular risk factors, including blood pressure, BMI, lipid profile, and glucose metabolism in children and young adults exposed to preeclampsia in utero. Furthermore, we determined whether associations vary between genders, with age, or in the presence of intrauterine growth restriction.

METHODS

Search Strategy
All studies describing the effect of preeclampsia on offspring cardiovascular risks in childhood and young adulthood were sought by computerized Ovid search of Medline (1948–August 2011) and Embase (1980–August 2011). The search strategy is described in Supplemental Fig 6. Review was undertaken with reference to the PRISMA and the MOOSE Group guidelines8,9 (Supplemental Fig 7). Case-control studies, cohort studies, and clinical trials were included. References of identified studies were searched, and all identified studies were sifted by abstract for relevance by 2 authors (E.F.D. and M.L.). Eligibility was assessed without reference to results, author, or journal. Discrepancies were resolved by discussion. Data were extracted from eligible studies by 1 author (E.F.D.) and cross-checked for accuracy by a second author (A.J.L.). When required data could not be extracted, authors of the relevant studies were contacted.

Inclusion Criteria
Studies were selected if they compared cardiovascular risk factors in children exposed to preeclampsia in utero with controls. In addition to diagnosis of a risk factor, outcome measures included were blood pressure, BMI, lipid levels, insulin sensitivity, and glucose or glucose metabolism. The primary summary measure for continuous outcome variables was difference in means. Studies reporting only relative risk of an outcome such as hypertension, obesity, or diabetes, rather than mean values in the study population, were excluded. Preeclampsia was defined by using the current International Society for the Study of Hypertension in Pregnancy research definition10; however, as diagnostic criteria have varied historically, studies in which preeclampsia was diagnosed by de novo onset of hypertension and proteinuria also were included. When the same cohort was reported in multiple publications at similar ages, the most recent publication was included. Studies in which distinction between gestational hypertension and preeclampsia was impossible and studies comparing offspring to another potential risk group were excluded. All studies were published in peer-reviewed journals, undertaken in human participants, and published in English or French.

Analysis
From each included study, definition of preeclampsia, age of offspring at follow-up, number of cases and controls, birth weight, and the gestational age of cases and controls were collected. Outcome measures were documented and, for each, the mean and SD were recorded. Funnel plots were examined for evidence of bias (Supplemental Fig 8).

Comparative review of outcome measures was undertaken, and consideration was given to whether results varied between genders, with age, or in the presence of intrauterine growth restriction. When informative, meta-analysis was performed by using Cochrane Collaborations RevMan software (Review Manager (RevMan) Version 5.1.1, The Nordic Cochrane Centre: The Cochrane Collaboration, Copenhagen)11 based on an inverse variance method. The mean difference between outcome measures and 95% confidence interval (CI) was calculated by using a fixed-effect model, which reflects only the random error within each study and is less affected by publication bias, which is a greater issue in observational studies compared with randomized controlled trials.12–14 To ensure our conclusions were not unduly influenced by choice of model, we also repeated the analysis with a random effects model, but no differences in outcome were identified (data not shown). Statistical assessment of heterogeneity was undertaken.11

RESULTS

Study Identification
Of the 2484 articles identified by the search 83 were eligible for review (Fig 1). Of these 18 studies were included providing data on 45 249 individuals (Table 1). Of the 65 studies excluded, 30 were without relevant outcome measures, and reasons for exclusion of the other studies were inability to distinguish gestational hypertension and
preeclampsia (17 studies); repeat publication of data (4 studies); inability to exclude hypertension before pregnancy (12 studies); and studies reporting relative risk of a diagnosis rather than mean values in the study population (2 studies).

**Blood Pressure**

Blood pressure data on 44,293 individuals, 1,241 of whom were exposed to preeclampsia, was available from 10 studies (Table 1).15–24 Authors of 1 additional study reported only relative risk of hypertension in adult offspring 60 to 70 years after a preeclamptic pregnancy, and the study was not included in the analysis.4 Persons who had been included were aged from 4 to 30 years, with all but 1 study reporting only on those aged <20 years. Five studies reported increased systolic blood pressure in those exposed to preeclampsia (range: 1.8024–6.70 mm Hg22), and 6 studies reported increased diastolic blood pressure (range: 1.718–6.0 mm Hg22).16–20,22 None reported significant decreases. Quantitative summary measures obtained by meta-analysis indicated that in childhood, offspring of preeclamptic women have a 2.39 mm Hg (P < .0001) greater systolic (Fig 2) and a 1.35 mm Hg (P < .00001) greater diastolic blood pressure (Fig 3).

Two studies reported increased systolic blood pressure in male individuals only16,17; for diastolic blood pressure, 2 studies reported increases in female individuals,17,19 and 1 reported increases in male individuals.18 Meta-analysis of studies in which data were reported in genders separately demonstrated a 2.41 mm Hg (P < .0001) increase in systolic blood pressure in those who were female, similar to the 2.48 mm Hg (P < .0001) increase in those who were male. For diastolic blood pressure, however; female individuals had a 1.69 mm Hg (95% CI: 0.89–2.50; P < .0001) increase, and male individuals had a nonsignificant 0.67 mm Hg (95% CI: −0.312 to 1.45; P = .1) difference. When we then studied whether the blood pressure difference varied with age of follow-up. Studies of younger children, aged <10 years at the time of follow-up, had a mean increase of 2.91 mm Hg in systolic blood pressure (95% CI: 1.55–4.27; P < .00001), similar to the 2.24 mm Hg increase (95% CI: 1.49–2.98; P < .00001) in those aged ≥10 years. Because birth weight25 and gestational age26 associate with later blood pressure, we also analyzed 4 studies that reported findings in term-born offspring and in which those born to pregnancies complicated by preeclampsia had a mean birth weight ≥2.5 kg, similar to the level in controls. In these studies, preeclampsia still was associated with a 2.26 mm Hg (95% CI: 1.35–3.16; P < .00001) higher systolic and a 1.48 mm Hg (95% CI: 0.82–2.14; P < .0001) higher diastolic blood pressure (Fig 4).

**BMI**

Eight studies compared BMI with data on 39,611 participants.15,17–21,27 In 5 studies, BMI was greater in exposed individuals, but this finding was significant only in 2, and then only in girls in 1 study17 and boys in the other study.27 In 1 study of adolescents living at altitude, BMI was reduced significantly15; however, meta-analysis identified a significant increase of 0.57 (P < .00001) in the children of preeclamptic women. Heterogeneity was significant (heterogeneity: χ² = 23.40, degrees of freedom = 9 [P = .005]; I² = 62%), and appeared to be driven by the study of offspring living at altitude.15 Because the authors of some works have suggested that living at high altitude is associated with a lower BMI, this factor was considered a plausible explanation for the observed heterogeneity.28 When this study was removed, an increase in BMI without significant heterogeneity was noted (0.62; 95% CI: 0.41–0.84; P < .0001; Fig 5). Significant increases in BMI were seen both when female individuals were considered alone (0.69; 95% CI: 0.35–1.03; P < .0001) and in studies considering male individuals alone (0.83; 95% CI: 0.48–1.18; P < .006); however, no difference was evident in studies that included only children aged <10 years (0.15; 95% CI: −0.34 to 0.64; P < .55), whereas there was a significant increase.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Definition of Preeclampsia</th>
<th>Definition of Proteinuria</th>
<th>No. Exposed to Preeclampsia/Control</th>
<th>Birth wt, Cases/Controls, g</th>
<th>Gestational Age, Cases/Controls, wk</th>
<th>Follow-Up, y</th>
<th>Outcome Measure Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiller et al, 2007</td>
<td>CS</td>
<td>DBP &gt;10 mm Hg or 2× DBP &gt;80 mm Hg</td>
<td>300 mg/24 h or 2× 2+ proteinuria</td>
<td>10/78a</td>
<td>—</td>
<td>—</td>
<td>4–7</td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Jayet et al, 2010</td>
<td>CC</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>≥1+ on ≥2 samples</td>
<td>48/90</td>
<td>2843/5244</td>
<td>&gt;37 and &lt;42</td>
<td>14</td>
<td>SBP/DBP, BMI</td>
</tr>
<tr>
<td>Kvehaugen et al, 2010</td>
<td>CC</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>≥1+ on ≥2 samples</td>
<td>25/17</td>
<td>1740/526</td>
<td>2+</td>
<td>32.3/38.6</td>
<td>5–8</td>
</tr>
<tr>
<td>Lawlor et al, 2011</td>
<td>CS</td>
<td>&gt;139/≥89</td>
<td>1+</td>
<td>145/5367</td>
<td>3042/5445</td>
<td>37.6/39.5</td>
<td>9–10</td>
<td>SBP/DBP, BMI, lipids</td>
</tr>
<tr>
<td>Ladam et al, 2010</td>
<td>CC</td>
<td>&gt;140/90</td>
<td>2+</td>
<td>16/58</td>
<td>1325/7</td>
<td>30.95/37</td>
<td>20–30</td>
<td>SBP/DBP, BMI, lipids, glucose/insulin</td>
</tr>
<tr>
<td>Ogland et al, 2009</td>
<td>CC</td>
<td>&gt; in DBP to &gt;90</td>
<td>1+</td>
<td>181/536</td>
<td>—</td>
<td>33/26</td>
<td>37.6/40.1</td>
<td>10–12</td>
</tr>
<tr>
<td>Palti et al, 1989</td>
<td>CC</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>Edema and proteinuria</td>
<td>94/94</td>
<td>12.7% low birth wt cases/4.2% low birth wt control subjects</td>
<td>—</td>
<td>6</td>
<td>SBP/DBP</td>
</tr>
<tr>
<td>Tenhola et al, 2003</td>
<td>CC</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>&gt;300 mg/24 h</td>
<td>60/60</td>
<td>2622/2886</td>
<td>36.8/36.7</td>
<td>12</td>
<td>SBP/DBP, BMI, lipids, glucose/insulin</td>
</tr>
<tr>
<td>Vatten et al, 2003</td>
<td>CS</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>&gt;300 mg/24 h</td>
<td>220/3553</td>
<td>3421/3485</td>
<td>40.5/40.6</td>
<td>15–19</td>
<td>SBP/DBP, BMI</td>
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<td>Other outcome factors</td>
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<td></td>
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<tr>
<td>Akcakus et al, 2010</td>
<td>CC</td>
<td>&gt;140/90</td>
<td>300 mg/24 h</td>
<td>3050/30</td>
<td>1817/1899</td>
<td>32.4/32.4</td>
<td>0</td>
<td>Lipids</td>
</tr>
<tr>
<td>Catarino et al, 2008</td>
<td>CC</td>
<td>ISSHP definition</td>
<td>Severe &gt;160/110</td>
<td>46/42</td>
<td>2600/3400</td>
<td>37/38.5</td>
<td>0</td>
<td>Lipids</td>
</tr>
<tr>
<td>Howlader et al, 2009</td>
<td>CC</td>
<td>&gt;140/90 or rise &gt;30/15</td>
<td>3000 mg/24 h</td>
<td>15/20</td>
<td>1750/2370</td>
<td>33.2/36.9</td>
<td>0</td>
<td>Lipids</td>
</tr>
<tr>
<td>Kvehaugen et al, 2011</td>
<td>CC</td>
<td>&gt;140/90 on ≥2 occasions</td>
<td>≥1+ on ≥2 midstream urine</td>
<td>26/15</td>
<td>—</td>
<td>—</td>
<td>6</td>
<td>Lipids</td>
</tr>
<tr>
<td>Ogland et al, 2009</td>
<td>CC</td>
<td>&gt; in DBP to &gt;90</td>
<td>1+</td>
<td>F: 91/194</td>
<td>M: 92/186</td>
<td>37.5/39.7</td>
<td>10–12</td>
<td>BMI</td>
</tr>
<tr>
<td>Ophir et al, 2009</td>
<td>CC</td>
<td>&gt;140/90</td>
<td>&gt;300 mg/24 h</td>
<td>36/33</td>
<td>2863/3274</td>
<td>37.7/38.8</td>
<td>0</td>
<td>Lipids</td>
</tr>
<tr>
<td>Rodie et al, 2004</td>
<td>CC</td>
<td>ISSHP definition</td>
<td>—</td>
<td>14/41</td>
<td>2510/3770</td>
<td>36.6/40</td>
<td>0</td>
<td>Lipids</td>
</tr>
<tr>
<td>Yavuz et al, 2008</td>
<td>CC</td>
<td>&gt;140/90</td>
<td>&gt;300 mg/24 h</td>
<td>14/30</td>
<td>2640/3500</td>
<td>36.3/39</td>
<td>0</td>
<td>Lipids</td>
</tr>
</tbody>
</table>

CC, case-control study; CS, cohort study; DBP, diastolic blood pressure; F, females; ISSHP, International Society for the Study of Hypertension in Pregnancy; M, males; SBP, systolic blood pressure.

a Includes only those children whose mothers did not receive calcium.

b Cases whose mothers were defined as having severe preeclampsia.
in those ≥10 years (0.69; 95% CI: 0.35–1.03; P < .0001). When studies which reported findings in term born offspring and in which those born to pregnancies complicated by pre-eclampsia had a mean birth weight greater than 2.5 kg were considered, a significant increase in BMI was seen (0.67; 95% CI: 0.35–0.99; P < .0001).

Cholesterol

Ten studies considered lipid levels, representing data on 6164 individuals, of whom 423 were exposed to pre-eclampsia18,20,23,29–35 (Table 2). Uniquely, 6 of the studies, comprising 366 participants, reported levels at birth in cord blood.30–35 Because these studies reflect the unique postdelivery biological situation, we considered the studies separately. Five reported changes in lipid profile; 4 reported an increase in triglycerides;30–32,34; 2 reported an increase in low-density lipoprotein;32,33 and 3 reported a decrease in high-density lipoprotein.30–32 In studies in later life (considering children and young adults aged 9–30), 1 was performed on nonfasted samples.23 Two of the fasting studies found increased total cholesterol, with 1 reporting an increase in low-density lipoprotein cholesterol.20,29 No other differences were demonstrated. These studies included only 208 subjects, and in view of the small number of participants, meta-analysis was not performed.

Glucose Metabolism

Only 2 studies have considered fasting glucose, representing only 174 participants.18,20 At age 12, there was no difference in serum insulin, glucose, or glucose-to-insulin ratio.18 In young adulthood, preterm offspring of pre-eclamptic mothers had increased fasting glucose (5.04 vs 4.57 mmol/L; P = .0001).20 In view of the limited number of studies, no meta-analysis was performed.

DISCUSSION

This study generates the first comprehensive analysis of the cardiovascular phenotype of children and young adults whose mothers had preeclampsia. The results are based on published data, on
multiple outcomes, on ~45,000 individuals. In childhood and early adult life, these offspring have higher blood pressure and a small increase in BMI. Differences are evident in both male individuals and female individuals and in those with normal birth weight. Based on current reports, there are insufficient studies to allow an appreciation of the long-term effects, if any, of preeclampsia on the glucose metabolism or lipid levels of offspring, except for probable acute changes in perinatal lipid profiles.

If the 2.4 mm Hg difference in systolic blood pressure tracks into adulthood, this difference would be associated with an ~8% increased risk of mortality from ischemic heart disease and a 12% increased risk from stroke. The only long-term mortality follow-up study reported so far showed a 1.9-fold increased risk of stroke mortality in the offspring of preeclamptic pregnancies. Together, these data suggest that this population of children may be one in which intensive monitoring and early primary prevention advice may be warranted. Current data are limited almost exclusively to young cohorts, and it is possible the blood pressure difference increases with age to explain the greater observed stroke risk. We found no evidence that the observed increase in blood pressure varies between childhood and young adulthood, however, and it is possible that preeclampsia exposure is associated with other biological variations that alter risk. Some studies found gender-specific variation in associations between preeclampsia and offspring blood pressure; however, our combined analysis indicates gender is unlikely to be a further significant factor, certainly for systolic blood pressure, although there was some evidence for differences in diastolic pressure that may warrant investigation.

Preeclampsia is a recognized cause of fetal growth restriction, which is itself associated with increased blood pressure in adult life. We therefore performed an analysis restricted to

### Table A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Preeclamptic Pregnancy</th>
<th>Normotensive Pregnancy</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Lawlor (23), 9-10 yrs</td>
<td>107</td>
<td>11</td>
<td>114</td>
<td>104</td>
</tr>
<tr>
<td>Oglænd (24), 10-12 yrs</td>
<td>115.3</td>
<td>8.9</td>
<td>191</td>
<td>113.5</td>
</tr>
<tr>
<td>Vatten (19), 13-19 yrs</td>
<td>127.4</td>
<td>10.6</td>
<td>220</td>
<td>119.5</td>
</tr>
<tr>
<td>Juel (15), 14 yrs</td>
<td>108</td>
<td>9</td>
<td>107</td>
<td>110</td>
</tr>
</tbody>
</table>

Total (95% CI) 592 10292 100.0% 2.26 [1.35, 3.16]

Heterogeneity: $\chi^2 = 7.65$, df = 3 ($P = 0.05$), $\phi^2 = 81$
Test for overall effect: $Z = 4.87$ ($P < 0.00001$)

### Table B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Preeclamptic Pregnancy</th>
<th>Normotensive Pregnancy</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Lawlor (23), 9-10 yrs</td>
<td>62</td>
<td>8</td>
<td>143</td>
<td>60</td>
</tr>
<tr>
<td>Oglænd (24), 10-12 yrs</td>
<td>68.4</td>
<td>6.8</td>
<td>151</td>
<td>65.3</td>
</tr>
<tr>
<td>Vatten (19), 13-19 yrs</td>
<td>85.3</td>
<td>7.57</td>
<td>220</td>
<td>63.8</td>
</tr>
<tr>
<td>Juel (15), 14 yrs</td>
<td>73</td>
<td>7</td>
<td>100</td>
<td>73</td>
</tr>
</tbody>
</table>

Total (95% CI) 592 10292 100.0% 1.48 [0.82, 2.14]

Heterogeneity: $\chi^2 = 2.53$, df = 3 ($P = 0.47$), $\phi^2 = 0$
Test for overall effect: $Z = 4.41$ ($P < 0.00001$)

### Figure 4

A. Mean difference in systolic blood pressure in term-born infants of normal birth weight. B. Mean difference in diastolic blood pressure in term-born infants of normal birth weight.

### Figure 5

Mean difference in BMI between those who were exposed to preeclampsia in utero and controls.
Studies of individuals who were born at term, and in which the mean birth weight of the cases was >2.5 kg. These offspring still had a 2.26 mm Hg higher systolic and a 1.48 mm Hg higher diastolic blood pressure and a 0.67 increase in BMI. Currently available data do not allow for more detailed analysis of the effects of various degrees of growth restriction. Interestingly, some evidence suggests that very low birth weight individuals born preterm have higher blood pressure regardless of whether the mother had preeclampsia, however, the underlying mechanistic link with later blood pressure may vary, depending on the blood pressure of the mother. More focused studies will provide interesting insight into the potential highly complex interaction of growth restriction and exposure to preeclampsia in modulating offspring cardiovascular phenotype.

Rapid postnatal growth also may impact blood pressure, and offspring of mothers with affected pregnancies appear to have a consistently higher BMI of ~0.6. It remains unlikely that this increase alone accounts for the variation in blood pressure, because based on previous reports, at least a 1 to 2 difference in BMI would be needed to explain the >2 mm Hg difference.

Alternatively, because raised maternal BMI is a risk for both preeclampsia and offspring obesity, shared environmental influences may be important in this association.

The data available on lipid, glucose, and insulin levels were more limited, so the available publications are insufficient to allow definitive conclusions on the effect, if any, of preeclampsia on offspring glucose metabolism or lipids. There did appear to be changes in lipid profile in cord blood. These samples likely reflect acute conditions at delivery in a mother with increased circulating oxidative and inflammatory stimuli. Samples from later in life suggest that, if preeclampsia exposure has a long-term impact on childhood cholesterol levels, it is likely to account for up to 1 mmol/L variation in total cholesterol. Further data will be useful to refine this estimate.

There are several potential limitations to our analysis. Our study cannot provide insight into mechanisms underlying this phenotype. It seems probable that there are links with the etiology and

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**TABLE 2 Lipid Studies in Offspring of Preeclamptic Pregnancies**

<table>
<thead>
<tr>
<th>Studies on cord blood</th>
<th>Total Cholesterol</th>
<th>HDL</th>
<th>LDL</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akbas et al, 2010(29,</td>
<td>No difference: 73.3</td>
<td>Decreased: 17.3 vs 27.9; $P = .002$</td>
<td>No difference: 48.2 vs 49.9; $P = .82$</td>
<td>Increased: 39.2 vs 14.9; $P = .039$</td>
</tr>
<tr>
<td>mg/dL</td>
<td>vs 80.5;</td>
<td>Decreased: 32 vs 53; $P &lt; .001$</td>
<td>No difference: 34 vs 32;</td>
<td>Increased: 49 vs 39; $P = .049$</td>
</tr>
<tr>
<td>Catarino et al, 2008(30,</td>
<td>No difference: 73</td>
<td>Decreased: 10.3 vs 13.3; $P &lt; .001$</td>
<td>Increased: 65.6 vs 28.0; $P &lt; .001$</td>
<td>Increased: 52.4 vs 31.6; $P &lt; .01$</td>
</tr>
<tr>
<td>mg/dL</td>
<td>vs 86;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howlander et al,</td>
<td>Increased: 70.9 vs 13.5; $P &lt; .001$</td>
<td>Increased: 42 vs 36.8; $P &lt; .01$</td>
<td>No difference: 46.5 vs 45.0;</td>
<td></td>
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<tr>
<td>2009(32,</td>
<td>mg/dL</td>
<td></td>
<td></td>
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<tr>
<td>Ophir et al, 2006(33,</td>
<td>No difference: 70.6</td>
<td>Not reported: —</td>
<td>Increased: 42 vs 36.8;</td>
<td></td>
</tr>
<tr>
<td>mg/dL</td>
<td>vs 82.0;</td>
<td></td>
<td>$P &lt; .001$</td>
<td></td>
</tr>
<tr>
<td>Rodie et al, 2004(34,</td>
<td>Increased: 0.36</td>
<td>No difference: —</td>
<td>Not reported:</td>
<td></td>
</tr>
<tr>
<td>log mmol/L</td>
<td>vs 0.11;</td>
<td></td>
<td></td>
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<tr>
<td>Yavuz et al, 2008(35,</td>
<td>No difference: 65 vs 56; $P = NS$</td>
<td>No difference: 28.3 vs 25.2; $P = NS$</td>
<td>No difference: 30.4 vs 25.5; $P = NS$</td>
<td>No difference: 30.6 vs 32.6; $P = NS$</td>
</tr>
<tr>
<td>mg/dL</td>
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</table>

| Studies in children and young adults | | | | |
| Kvehaugen et al, 2011(36, | Increased: 5.01 vs 5.16; $P = .617$ | No difference: 1.60 vs 1.41; $P = .1$ | No difference: 1.61 vs 1.53; $P = .3$ | No difference: 6.0 vs 5.8; $P = .8$ |
| mmol/L | vs 8.54; | | | |
| Lazdam et al, 2010(37, | Increased: 4.7 vs 1.46; $P = .001$ | No difference: 1.6 vs 2.0; $P = .0001$ | No difference: 2.65 vs 2.09; $P = .34$ | No difference: 0.99 vs 0.89; $P = .44$ |
| mg/dL | vs 3.87; | | | |
| Lawlor et al, 2012(38, | Not reported: 1.37 vs 1.40; $P = .21$ | No difference: 2.87 vs 2.87; $P = .76$ | No difference: 2.87 vs 2.87; $P = .76$ | No difference: 0.99 vs 1.03; $P = .78$ |
| mmol/L | | | | |
| Tenhola et al, 2003(39, | No difference: 4.54 vs 1.35; $P = .48$ | No difference: 3.1 vs 2.75; $P = .342$ | No difference: 2.62 vs 2.75; $P = .34$ | No difference: 0.90 vs 0.86; $P = .517$ |
| mg/dL | vs 4.50; | | | |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

* Raw data not published.
pathogenesis of maternal preeclampsia. Disturbed placentation is thought to be a key factor in preeclampsia, with relative placental ischemia and decreased uterine and placental flow. There is extensive literature on developmental programming of offspring in response to placental insufficiency and in utero exposure to preeclampsia. For example, maternal smoking reduces the risk of preeclampsia by up to 50%, but it increases offspring blood pressure in adult life. Interpretation of our findings also needs to take into account the fact that observational studies are more prone to publication bias than randomized clinical trials; however, funnel plots for considered outcome measures were grossly symmetrical. Meta-analysis of continuous outcome variables also can be affected significantly by heterogeneity, and without source data, it can be difficult to explore subgroup variation. Nevertheless, our review did not highlight heterogeneity. It did highlight a striking paucity of end-point data in this research area. In this situation, meta-analysis of continuous outcome variables previously has been used effectively to provide clinically interpretable assessment of effects. The studies also had been published during a period when preeclampsia definitions varied, and we cannot exclude the possibility that studies misidentified cases or included individuals who would not meet current diagnostic criteria. We did not include studies examining gestational hypertension, because it may have a different pathophysiology. Nevertheless, offspring of hypertensive pregnancies have been noted to have an increased blood pressure, and this literature warrants review. We also identified increasing reports of variation in other biological measures in offspring of preeclamptic pregnancies, but these reports were excluded because they did not report established prognostic markers of cardiovascular disease. Finally, nearly all studies were of infants born close to term, presumably to mothers with less severe preeclampsia. The one study that considered the risk of hypertension found this risk to be greater in those born to mothers with more severe preeclampsia, and there was some evidence that the blood pressure differences may be greater in those born preterm. The impact on the offspring of maternal disease severity needs further exploration.

**CONCLUSIONS**

Children and young adults born to pregnancies complicated by preeclampsia have adverse changes in cardiovascular risk factors present from early life. The predominant phenotype that is now evident in multiple studies is of changes in blood pressure and BMI. Greater mechanistic understanding of these differences in blood pressure may provide useful insights into why some people are predisposed to hypertension and preeclampsia. From a public health perspective, children born to a pregnancy complicated by preeclampsia appear to have a unique, lifetime cardiovascular risk profile that is present from early life, and so may constitute a population that may benefit from risk profile monitoring and early implementation of primary prevention strategies.

**REFERENCES**


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Cardiovascular Risk Factors in Children and Young Adults Born to Preeclamptic Pregnancies: A Systematic Review
Esther Frances Davis, Merzaka Lazdam, Adam James Lewandowski, Stephanie Anne Worton, Brenda Kelly, Yvonne Kenworthy, Satish Adwani, Andrew R. Wilkinson, Kenny McCormick, Ian Sargent, Christopher Redman and Paul Leeson
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The online version of this article, along with updated information and services, is located on the World Wide Web at: /content/129/6/e1552.full.html