Online Supplementary Content


eMethods
eTable 1. Characteristics of a Woman’s First Pregnancy in the Study Period Resulting in Live Birth or Stillbirth, Denmark, 1978-2012 (Unless Otherwise Specified) for Women Lost to Follow-up (due to Emigration or "Missing" Designation in the Civil Registration System)
eTable 2. Hazard Ratios for Cardiomyopathy >5 Months After First Delivery by History of Hypertensive Disorder of Pregnancy, With and Without Additional Adjustment for Smoking, Denmark, 1991-2012
eTable 3. Hazard Ratios for Cardiomyopathy >5 Months After First Delivery by History of Hypertensive Disorders of Pregnancy in a Woman’s First Pregnancy, Denmark, 1978 to 2012
eTable 4. Hazard Ratios for Cardiomyopathy >5 Months After First Delivery by History of Hypertensive Disorders of Pregnancy, Denmark, 1978 to 2005
eTable 5. Hazard Ratios for Heart Failure by History of Hypertensive Disorder of Pregnancy, Denmark, 1978-2012
eFigure. Follow-up Time (Dotted Line) for Women in the Study Cohort
eReferences

This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods

Data Sources
Since 1968, the Danish Civil Registration System has assigned a unique personal identification number to all Danish residents and continuously updates demographic, vital status and kinship information.\(^1,2\) Patient contacts with the national healthcare system are registered using the personal identification number, which permits the conduct of record-linkage studies based on Danish health register data with very little loss to follow-up. The National Patient Register contains information on all hospital discharge diagnoses assigned since 1977 and all outpatient diagnoses assigned since 1995.\(^3\) Diagnoses are coded in accordance with the International Classification of Diseases (ICD) 8th revision (ICD-8) from 1978-1993 and 10th revision (ICD-10) from 1994 onwards.\(^3\) The Causes of Death Register has recorded death certificate information, including underlying and contributing causes of death, since 1970.\(^4\) The Medical Birth Register contains detailed information on all live births and stillbirths in Denmark since 1973, with gestational length at delivery in completed weeks from 1978.\(^5\) The Register of Medicinal Product Statistics contains individual-level data on all prescriptions filled in Denmark since 1994.\(^6\) Registered information includes the amount and dose of dispensed medication and the product’s Anatomic Therapeutic Chemical (ATC) code, linked to the personal identification number recorded on the prescription.

International Classification of Diseases (ICD) and Anatomic Therapeutic Chemical (ATC) Codes Used to Define Pre-Pregnancy Exclusion Diagnoses, Hypertensive Disorders of Pregnancy, Cardiomyopathy and Heart Failure

Pre-pregnancy exclusion diagnoses (National Patient Register)
Cardiovascular disease, any: ICD-8: 390.00-458.99, 782.49; ICD-10: 100.0-99.9*
Diabetes mellitus: ICD-8: 249.00-250.09; ICD-10: E10.0-14.9

*Exclusions from the main cohort due to pre-gestational hypertension were based only on registered hypertension diagnoses, as medication data were only available from 1994 onwards. Additional analyses were conducted based on a sub-cohort with data on use of anti-hypertensive medications (see eMethods: Covariate Definitions and Mediation Analyses).

Hypertensive disorders of pregnancy (HDP) (National Patient Register)
Severe preeclampsia, including eclampsia\(^\dagger\) and HELLP\(^\dagger\) syndrome:
ICD-8 codes 637.04, 637.19, 762.19, 762.29, or 762.39,
ICD-10 codes O14.1, O14.2, or O15.0-15.9

Mild/moderate preeclampsia:
ICD-8 codes 637.03, 637.09 or 637.99,
ICD-10 codes O14.0 or O14.9

Gestational hypertension:
ICD-8 codes 637.00
ICD-10 codes O13 or O16

\(^\dagger\)We included eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome diagnoses under severe preeclampsia because these conditions are rare in Denmark and there were too few affected women to allow for separate groups.

HDP diagnosis, and its coding in the National Patient Register, follow guidelines set out by the Danish Society for Obstetrics and Gynecology (DSOG), which have evolved over time. The most recent guidelines, from 2012, are consistent with the ACOG (2002)\(^7\) NICE/RCOG (2010) guidelines\(^8\) and define hypertensive disorders of pregnancy as follows (online, in Danish\(^9\)):

Moderate preeclampsia:
Blood pressure: systolic ≥140 mmHg or diastolic ≥90 mmHg, accompanied by
Proteinuria: >300mg/24 hours or ≥1+ urine dipstick
Onset after gestational week 20

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Severe preeclampsia:
Fulfills the criteria for moderate preeclampsia, with the addition of either blood pressure in excess of an even greater threshold or symptoms/laboratory findings of organ involvement:

Blood pressure:
- Systolic blood pressure >160 mmHg or diastolic blood pressure ≥110 mmHg

Symptoms:
- CNS: headache, vision abnormalities, seizures (eclampsia)
- Circulatory: dyspnea, chest pressure (pulmonary edema)
- Liver: epigastric pain, vomiting

Laboratory findings:
- Liver: Elevated liver enzymes (alanine aminotransferase/aspartate aminotransferase >70 U/L), elevated serum bilirubin
- Kidney: Oliguria (<400 mL/24 hours), severe proteinuria (>3 g/24 hours), serum uric acid >0.45 mmol/L, serum creatinine >110 µmol/L = >1.24 mg/dL
- Coagulation: platelet count <100 x 10^9/L, disseminated intravascular coagulation (activated partial thromboplastin time >1.5 x baseline value, antithrombin <70 U/dL), hemolysis (lactate dehydrogenase >600 U/L and/or haptoglobin <30 mg/dL = < 3 µmol/L)

The DSOG defines HELLP syndrome as hemolysis (as above), elevated liver enzymes (alanine aminotransferase/aspartate aminotransferase >100U/L), and low platelets (<100 x 10^9/L).

Gestational hypertension:
Blood pressure: systolic ≥140 or diastolic ≥90 mmHg in the absence of proteinuria
Onset after 20 weeks gestation

Outcome diagnoses (National Patient Register and Causes of Death Register)
Registered from 5 months after first registered pregnancy, excluding the period from 1 month before delivery to 5 months after delivery in any subsequent pregnancy.
Cardiomyopathy:
ICD-8, 425.99; ICD-10, I42.0-43.8, O90.3
Dilated cardiomyopathy:
ICD-10 code O14.0
Heart failure:

Handling of HDP Status as a Time-Dependent Variable
A woman whose first registered pregnancy was not complicated by an HDP contributed normotensive person-time to the study until she experienced a pregnancy complicated by preeclampsia or gestational hypertension, if ever. She then contributed person-time according to the most severe HDP registered during that affected pregnancy. According to our definition, a woman could only change exposure status if a given pregnancy was more complicated (in terms of HDP) than a previous pregnancy, i.e. she could only become more severely affected. In other words, she could contribute person-time first to the gestational hypertension group and then to a preeclampsia group if a preeclamptic pregnancy followed a gestational hypertension pregnancy, or first to the moderate preeclampsia group and then the severe preeclampsia group, if a pregnancy with severe preeclampsia followed a moderately preeclamptic pregnancy. However, she could not contribute person-time to the normotensive or gestational hypertension groups if a normotensive or gestational hypertension pregnancy followed a pregnancy complicated by preeclampsia; in this case, she was considered to have a history of preeclampsia from that pregnancy until follow-up ended.

Covariate Definitions
We obtained information on maternal birth year and age from the Civil Registration System and information on parity, multiple pregnancy, stillbirth and smoking status from the Medical Birth Register. Information on diabetes and ischemic heart disease with debut after the first registered pregnancy was obtained from the National Patient Register, with a woman considered to have the condition from the first time she was registered with: diabetes, ICD-8 codes 249.00-250.09, ICD-10 codes E10.0-14.9; ischemic heart disease, ICD-8 codes 410.09-414.99, ICD-10 codes I20.0-25.9. We identified women initiating use of anti-hypertensive medications (ATC codes C02, C03, C07, C08, C09) at any time after their first registered pregnancy using the

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Register of Medicinal Product Statistics. Initiation of medication use was defined as registration of two filled prescriptions for an anti-hypertensive medication within a 6-month period, without previous use of the medication. Time-limited use of anti-hypertensive medications during pregnancy or in the first 3 months postpartum (i.e. in connection with an HDP diagnosis) was not considered when determining whether, and when, medication use was initiated.

With the exception of smoking status and anti-hypertensive medication use, information on potential confounders was available from 1978 onward. Smoking status early in pregnancy and anti-hypertensive medication use data became available in 1991 and 1994, respectively; consequently, adjustment for smoking and the mediation analyses (hypertension) occurred only in sub-cohorts. Parity, multiple pregnancy, stillbirth, diabetes and hypertension were treated as time-dependent variables, whereas smoking status was handled as a time-independent variable based on smoking status in the first pregnancy registered in or after 1991. Women with filled prescriptions registered in 1994 were considered prevalent (current) users of anti-hypertensive medications and excluded from the mediation analyses.

Mediation Analyses
To determine the degree to which the observed association between HDP and cardiomyopathy after the peripartum period was potentially mediated by the development of post-gestational hypertension (for which we used anti-hypertensive medication use as a proxy), we performed mediation analyses to estimate the natural direct effect and the natural indirect effect of HDP (note that in this context, everything that is not due to the indirect effect of hypertension is termed a direct effect of HDP). To emphasize that these estimates are based on observations, we term the two estimates the direct association and indirect association (through post-gestational hypertension), respectively. The mediation analysis was performed based on the principles underlying the approach of Lange et al., a marginal structural model approach based on a model for the mediator and a model for the outcome. In addition to the traditional assumption of no confounding of the association between exposure and outcome, the mediation analysis is based on the assumption of no confounding of the associations between exposure and mediator and between mediator and outcome.

Outcome Model
The inclusion criteria and follow-up for the mediation analyses were the same as in the main analyses, except that follow-up started later (1995) and women with anti-hypertensive medication use registered before 1995 or before their first pregnancy, if this occurred after 1995, were excluded. To approximate the Cox regression used in the main analyses, the outcome model in the mediation analyses was based on a log-linear Poisson model. The model was applied to an aggregated dataset with information on observation time and number of cardiomyopathy events during follow-up for each combination of history of hypertension, attained maternal age, maternal birth year, attained parity, history of multiple pregnancy and history of stillbirth. The dataset was duplicated before the analyses and two variables were created to estimate direct and indirect associations with a history of HDP, with one variable being equal to the (binary) exposure and the other variable being equal to the exposure in the first part and to the opposite value of the exposure in the second part, as described in the paper by Lange et al. The log-linear Poisson model included number of cardiomyopathy events as the outcome and the two variables used to estimate the direct and indirect associations with HDP as the main variables, with adjustment for age (5-year categories, with lower and upper categories 12-19 years and ≥74 years), maternal birth year, parity, multiple pregnancy and stillbirth; the logarithm of the observation time was used as the offset and weights were calculated from the mediator model (see below). The ratio between the direct association and the total association (defined as the sum of the direct and indirect association) was estimated on the log(hazard ratio) scale. Confidence intervals were estimated by a bootstrap approach using the 2.5% and 97.5% percentiles in a bootstrap sample with 1,000 replications.

Mediator Model
The mediator model was used to estimate the likelihood of having hypertension at time of entry into a new data cell in the outcome analyses i.e. the likelihood of having hypertension for each combination of the covariates in the outcome model. These likelihoods were used to calculate weights for the outcome model, as described in Lange et al. The mediator model was a logistic regression model with the events being the number of women in a given data cell with a history of hypertension, the “trials” being the total number of women contributing to the data cell, history of HDP (binary variable) serving as the main exposure, and adjustment for age (5-years categories with lower and upper categories 12-19 years and ≥74 years), maternal birth year, parity, multiple pregnancy and stillbirth.

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Sub-Cohort with Known or Possible Pre-Gestational Hypertension

Sensitivity analyses estimating the association between HDP and cardiomyopathy among women with known or suspected pre-gestational hypertension were based on women excluded from the mediation analyses i.e. women who would have been included in the mediation analyses had they not had anti-hypertensive medication use registered before 1995 or before their first pregnancy, if this occurred after 1995. To be conservative, women with first pregnancies pre-dating the start of follow-up (January 1, 1995) and anti-hypertensive medication use registered in 1994 (the year the Register of Medicinal Product Statistics began operating) were classified as having (possible) pre-gestational hypertension, as we had no way of knowing whether their medication use pre- or post-dated their first pregnancy.

eResults

Mediation Analysis Results

1,049,625 women were included in the mediation analyses. We observed a significant direct association of HDP with the later risk of cardiomyopathy of 1.40 (95% confidence interval [CI] 1.16-1.67) and a significant indirect association of 1.43 (95% CI 1.39-1.48). Consequently, the direct association represented 49% (95% CI 29%-59%) of the total association (on a log-scale).

Since the weights estimated from the mediation model are based on cross-sectional data, the effects of HDP on hypertension and of hypertension on HDP (in second or later births) could not be disentangled. To evaluate the degree to which this might have affected our results, we performed an additional mediation analysis including only women’s risk-time while primiparous. Here, the direct association was 1.32, the indirect association was 1.43, and the direct association represented 44% of the total association, a proportion similar to that observed in the main analysis.

There was no indication that the pure direct association (1.46) and the total direct association (1.38) differed (ratio= 1.38/1.46 = 0.95 [95% CI 0.86-1.04]). Therefore, our data do not support a dependence of the direct effect on the natural level of the mediator. When we approximated the estimation of the direct effect by simply adjusting the exposure for history of hypertension (a time-dependent variable), the direct association represented 47% of the total association.
eTable1. Characteristics of a Woman’s First Pregnancy in the Study Period Resulting in Live Birth or Stillbirth, Denmark, 1978-2012 (Unless Otherwise Specified) for Women Lost to Follow-up (due to Emigration or “Missing” Designation in the Civil Registration System)

<table>
<thead>
<tr>
<th></th>
<th>Normotensive N (%)</th>
<th>GH&lt;sup&gt;a&lt;/sup&gt; N (%)</th>
<th>Moderate PE&lt;sup&gt;b&lt;/sup&gt; N (%)</th>
<th>Severe PE&lt;sup&gt;c&lt;/sup&gt; N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>24,457</td>
<td>142</td>
<td>477</td>
<td>167</td>
<td>25,243</td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>1,082 (4.42)</td>
<td>1 (0.7)</td>
<td>26 (5.45)</td>
<td>4 (2.40)</td>
<td>1,113 (4.41)</td>
</tr>
<tr>
<td>20-24 years</td>
<td>5,771 (23.6)</td>
<td>30 (21.1)</td>
<td>122 (25.6)</td>
<td>50 (29.9)</td>
<td>5,973 (23.7)</td>
</tr>
<tr>
<td>25-29 years</td>
<td>9,378 (38.3)</td>
<td>49 (34.5)</td>
<td>180 (37.7)</td>
<td>59 (35.3)</td>
<td>9,666 (38.3)</td>
</tr>
<tr>
<td>30-34 years</td>
<td>5,968 (24.4)</td>
<td>45 (31.7)</td>
<td>100 (21.0)</td>
<td>40 (24.0)</td>
<td>6,153 (24.4)</td>
</tr>
<tr>
<td>≥35 years</td>
<td>2,258 (9.23)</td>
<td>17 (12.0)</td>
<td>49 (10.3)</td>
<td>14 (8.38)</td>
<td>2,338 (9.26)</td>
</tr>
<tr>
<td><strong>Multiple pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>315 (1.29)</td>
<td>2 (1.41)</td>
<td>22 (4.61)</td>
<td>8 (4.79)</td>
<td>347 (1.37)</td>
</tr>
<tr>
<td>No</td>
<td>24,142 (98.7)</td>
<td>140 (98.6)</td>
<td>455 (95.4)</td>
<td>159 (95.2)</td>
<td>24,896 (98.6)</td>
</tr>
<tr>
<td><strong>Stillbirth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>117 (0.48)</td>
<td>0 (0)</td>
<td>3 (0.63)</td>
<td>2 (1.20)</td>
<td>122 (0.48)</td>
</tr>
<tr>
<td>No</td>
<td>24,340 (99.5)</td>
<td>142 (100)</td>
<td>474 (99.4)</td>
<td>165 (98.8)</td>
<td>25,121 (99.5)</td>
</tr>
<tr>
<td><strong>Smoking status (1991-2012)&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2,178 (13.4)</td>
<td>10 (10.9)</td>
<td>30 (10.9)</td>
<td>3 (2.75)</td>
<td>2,221 (13.3)</td>
</tr>
<tr>
<td>No</td>
<td>14,077 (86.6)</td>
<td>82 (89.1)</td>
<td>245 (89.1)</td>
<td>106 (97.3)</td>
<td>14,510 (86.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16,255</td>
<td>92</td>
<td>275</td>
<td>109</td>
<td>16,731</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (2004-2012)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>345 (5.99)</td>
<td>2 (4.65)</td>
<td>1 (1.05)</td>
<td>1 (2.70)</td>
<td>349 (5.88)</td>
</tr>
<tr>
<td>18.5-24</td>
<td>4,135 (71.8)</td>
<td>27 (62.8)</td>
<td>47 (49.5)</td>
<td>28 (75.7)</td>
<td>4,237 (71.4)</td>
</tr>
<tr>
<td>25-29</td>
<td>931 (16.2)</td>
<td>6 (14.0)</td>
<td>30 (31.6)</td>
<td>5 (13.5)</td>
<td>972 (16.4)</td>
</tr>
<tr>
<td>30-34</td>
<td>267 (4.63)</td>
<td>4 (9.30)</td>
<td>13 (13.7)</td>
<td>1 (2.70)</td>
<td>285 (4.80)</td>
</tr>
<tr>
<td>≥35</td>
<td>84 (1.46)</td>
<td>4 (9.30)</td>
<td>4 (4.21)</td>
<td>2 (5.41)</td>
<td>94 (1.58)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5,762</td>
<td>43</td>
<td>95</td>
<td>37</td>
<td>5,937</td>
</tr>
</tbody>
</table>

a. Gestational hypertension. ICD-8 code 637.00, ICD-10 codes O13.0-O13.9 or O16.0-O16.9
b. Moderate preeclampsia. ICD-8 codes 637.03, 637.09 or 637.99, ICD-10 codes O14.0 or O14.9
c. Severe preeclampsia. ICD-8 codes 637.04, 637.19, 762.19, 762.29 or 762.39, ICD-10 codes O14.1, O14.2 or O15.0-15.9
d. Smoking status in the first trimester (yes: smoking during some or all of the first trimester) in a woman’s first pregnancy resulting in live birth or stillbirth between 1991 and 2012
eTable2. Hazard Ratios for Cardiomyopathy >5 Months After First Delivery by History of Hypertensive Disorder of Pregnancy, With and Without Additional Adjustment for Smoking, Denmark, 1991-2012

<table>
<thead>
<tr>
<th>Condition</th>
<th>Person-years (x10^3)</th>
<th>Events</th>
<th>Events per 100,000 person-years (95% CI)</th>
<th>Hazard ratio (95% CI) Unadjusted for smoking</th>
<th>Hazard ratio (95% CI) Adjusted for smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia(^d)</td>
<td>102</td>
<td>15</td>
<td>14.7 (8.85, 24.3)</td>
<td>2.86 (1.71, 4.80)</td>
<td>2.98 (1.77, 5.01)</td>
</tr>
<tr>
<td>Moderate preeclampsia(^e)</td>
<td>313</td>
<td>40</td>
<td>12.8 (9.37, 17.4)</td>
<td>2.35 (1.70, 3.27)</td>
<td>2.38 (1.71, 3.31)</td>
</tr>
<tr>
<td>Gestational hypertension(^f)</td>
<td>99</td>
<td>12</td>
<td>12.1 (6.88, 21.3)</td>
<td>2.07 (1.16, 3.70)</td>
<td>2.17 (1.21, 3.87)</td>
</tr>
<tr>
<td>Normotensive pregnancies(^g)</td>
<td>7,921</td>
<td>396</td>
<td>5.00 (4.53, 5.52)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

CI: confidence interval

These analyses included 723,507 women, of whom 9,747 contributed person-time to the severe preeclampsia group, 27,220 contributed person-time to the moderate preeclampsia group, 10,520 contributed person-time to the gestational hypertension group and 684,624 contributed person-time to the normotensive group. These numbers of women sum to more than the total number of women included in the analyses because women with more than one pregnancy could contribute person-time to more than one exposure category.

\(^a\) Adjusted for maternal age, maternal birth year, parity, multiple pregnancy and stillbirth.

\(^b\) Registration of a cardiomyopathy code (ICD-8 code 425.99, ICD-10 codes I42.0-43.8 or O90.3) in the National Patient Register >5 months after a woman’s first delivery in the study period. For women with more than one delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until 1) cardiomyopathy diagnosis; 2) death; 3) emigration; 4) designated “missing”; or 5) 31 December 2012 (see Figure 2). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered.

\(^c\) Smoking status at the beginning of the first pregnancy in or after 1991.

\(^d\) ICD-8 codes 637.04, 637.19, 762.29 and 762.39, ICD-10 codes O14.1, O14.2 and O15.0-15.9.

\(^e\) ICD-8 codes 637.03, 637.09 and 637.99, ICD-10 codes O14.0 and O14.9.

\(^f\) ICD-8 code 637.00, ICD-10 codes O13.0-13.9 and O16.0-16.9.

\(^g\) Women not registered with any of the above (\(^d\)-\(^f\) codes) during pregnancy.
eTable 3. Hazard Ratios<sup>a</sup> for Cardiomyopathy >5 Months After First Delivery<sup>b</sup> by History of Hypertensive Disorders of Pregnancy in a Woman’s First Pregnancy, Denmark, 1978 to 2012

<table>
<thead>
<tr>
<th></th>
<th>Person-years (x10&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>Events</th>
<th>Events per 100,000 person-years (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>136</td>
<td>19</td>
<td>14.0 (8.91, 21.9)</td>
<td>2.02 (1.28, 3.18)</td>
</tr>
<tr>
<td>Moderate preeclampsia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>568</td>
<td>84</td>
<td>14.8 (11.9, 18.3)</td>
<td>1.91 (1.53, 2.38)</td>
</tr>
<tr>
<td>Gestation hypertension&lt;sup&gt;e&lt;/sup&gt;</td>
<td>186</td>
<td>29</td>
<td>15.6 (10.8, 22.4)</td>
<td>1.83 (1.27, 2.65)</td>
</tr>
<tr>
<td>Normotensive pregnancies&lt;sup&gt;f&lt;/sup&gt;</td>
<td>18,423</td>
<td>1,445</td>
<td>7.84 (7.45, 8.26)</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

CI: confidence interval

These analyses included 1,075,763 women, of whom 9,469 contributed person-time to the severe preeclampsia group, 31,366 contributed person-time to the moderate preeclampsia group, 11,137 contributed person-time to the gestational hypertension group and 1,023,771 contributed person-time to the normotensive group.

<sup>a</sup> Adjusted for maternal age, maternal birth year, parity, multiple pregnancy and stillbirth.

<sup>b</sup> Registration of a cardiomyopathy code (ICD-8 code 425.99, ICD-10 codes I42.0-43.8 or O90.3) in the National Patient Register >5 months after a woman’s first delivery in the study period. For women with more than one delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until 1) cardiomyopathy diagnosis; 2) death; 3) emigration; 4) designated “missing”; or 5) 31 December 2012 (see Figure 2). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered.

<sup>c</sup> ICD-8 codes 637.04, 637.19, 762.29 and 762.39, ICD-10 codes O14.1, O14.2 and O15.0-15.9.

<sup>d</sup> ICD-8 codes 637.03, 637.09 and 637.99, ICD-10 codes O14.0 and O14.9.

<sup>e</sup> ICD-8 code 637.00, ICD-10 codes O13.0-13.9 and O16.0-16.9.

<sup>f</sup> Women not registered with any of the above (c-e) codes during pregnancy.
eTable 4. Hazard Ratios\(^a\) for Cardiomyopathy >5 Months After First Delivery\(^b\) by History of Hypertensive Disorders of Pregnancy, Denmark, 1978 to 2005

<table>
<thead>
<tr>
<th>Person-years (x10(^3))</th>
<th>Events</th>
<th>Events per 100,000 person-years (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia(^c)</td>
<td>102</td>
<td>9</td>
<td>8.81 (4.58, 16.9)</td>
</tr>
<tr>
<td>Moderate preeclampsia(^d)</td>
<td>457</td>
<td>49</td>
<td>10.7 (8.11, 14.2)</td>
</tr>
<tr>
<td>Gestational hypertension(^e)</td>
<td>149</td>
<td>17</td>
<td>11.4 (7.11, 18.4)</td>
</tr>
<tr>
<td>Normotensive pregnancies(^f)</td>
<td>12,102</td>
<td>599</td>
<td>4.95 (4.57, 5.36)</td>
</tr>
</tbody>
</table>

CI: confidence interval

These analyses included 887,813 women, of whom 8,958 contributed person-time to the severe preeclampsia group, 32,978 contributed person-time to the moderate preeclampsia group, 11,245 contributed person-time to the gestational hypertension group and 846,536 contributed person-time to the normotensive group. These numbers of women sum to more than the total number of women included in the analyses because women with more than one pregnancy could contribute person-time to more than one exposure category.

\(^a\) Adjusted for maternal age, maternal birth year, parity, multiple pregnancy and stillbirth.

\(^b\) Registration of a cardiomyopathy code (ICD-8 code 425.99, ICD-10 codes I42.0-43.8 or O90.3) in the National Patient Register >5 months after a woman’s first delivery in the study period. For women with more than one delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until 1) cardiomyopathy diagnosis; 2) death; 3) emigration; 4) designated “missing”; or 5) 31 December 2005 (see Figure 2). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered.

\(^c\) ICD-8 codes 637.04, 637.19, 762.29 and 762.39, ICD-10 codes O14.1, O14.2 and O15.0-15.9.

\(^d\) ICD-8 codes 637.03, 637.09 and 637.99, ICD-10 codes O14.0 and O14.9.

\(^e\) ICD-8 code 637.00, ICD-10 codes O13.0-13.9 and O16.0-16.9.

\(^f\) Women not registered with any of the above (c-e) codes during pregnancy.
### eTable5. Hazard Ratios\(^a\) for Heart Failure\(^b\) by History of Hypertensive Disorder of Pregnancy, Denmark, 1978-2012

<table>
<thead>
<tr>
<th></th>
<th>Person-years (x10(^3))</th>
<th>Events</th>
<th>Events per 100,000 person-years (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia(^c)</td>
<td>173</td>
<td>60</td>
<td>34.8 (27.0, 44.8)</td>
<td>2.23 (1.73, 2.89)</td>
</tr>
<tr>
<td>Moderate preeclampsia(^d)</td>
<td>697</td>
<td>245</td>
<td>35.2 (31.0, 39.9)</td>
<td>1.86 (1.63, 2.12)</td>
</tr>
<tr>
<td>Gestational hypertension(^e)</td>
<td>231</td>
<td>103</td>
<td>44.6 (36.8, 54.1)</td>
<td>2.07 (1.70, 2.52)</td>
</tr>
<tr>
<td>Normotensive pregnancies(^f)</td>
<td>18,200</td>
<td>3,478</td>
<td>19.1 (18.5, 19.8)</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

CI: confidence interval

These analyses included 1,075,751 women, of whom 12,280 contributed person-time to the severe preeclampsia group, 40,261 contributed person-time to the moderate preeclampsia group, 15,324 contributed person-time to the gestational hypertension group and 1,023,760 contributed person-time to the normotensive group. These numbers of women sum to more than the total number of women included in the analyses because women with more than one pregnancy could contribute person-time to more than one exposure category.

\(^a\) Adjusted for maternal age, maternal birth year, parity, multiple pregnancy and stillbirth.

\(^b\) Registration of a cardiomyopathy code (ICD-8 codes 427.09-427.19, 427.99, 428.99 and 782.49, ICD-10 codes I50.0-I50.9) in the National Patient Register >5 months after a woman’s first delivery in the study period. For women with more than one delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until 1) cardiomyopathy diagnosis; 2) death; 3) emigration; 4) designated “missing”; or 5) 31 December 2012 (see Figure 2). Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered.

\(^c\) ICD-8 codes 637.04, 637.19, 762.29 and 762.39, ICD-10 codes O14.1, O14.2 and O15.0-15.9.

\(^d\) ICD-8 codes 637.03, 637.09 and 637.99, ICD-10 codes O14.0 and O14.9.

\(^e\) ICD-8 code 637.00, ICD-10 codes O13.0-13.9 and O16.0-16.9.

\(^f\) Women not registered with any of the above (c-e) codes during pregnancy.
The peripartum period for each delivery X is denoted by the box around that delivery. Pregnancies affected by gestational hypertension, moderate preeclampsia and severe preeclampsia are marked in yellow, orange and red, respectively. For each woman, follow-up began 5 months after her first delivery in the study period (ie, after the peripartum period associated with the first delivery). For women with more than 1 delivery in the study period, follow-up extended from 5 months after the first delivery, through subsequent pregnancies, until December 31, 2012 (women #1, #2 and #5), cardiomyopathy (CM) diagnosis (woman #3) or censoring due to peripartum cardiomyopathy (PPCM) (woman #4), death, emigration or a “missing” designation. Peripartum time associated with all pregnancies after the first was excluded from the person-time included in the analyses. For women who developed peripartum cardiomyopathy in connection with a second or later pregnancy, follow-up stopped at the time the peripartum cardiomyopathy diagnosis was registered (woman #4). A woman could contribute person-time to several exposure groups, changing her exposure status if a given pregnancy was more complicated (in terms of HDP) than a previous pregnancy (women #2 and #5) but not if the pregnancy was less complicated (woman #3).
eReferences