ORIGINAL RESEARCH

Pregnancy-Related Risk Factors Are Associated With a Significant Burden of Treated Hypertension Within 10 Years of Delivery: Findings From a Population-Based Norwegian Cohort

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Background—The association between pregnancy complications and women's later cardiovascular disease has, primarily, been evaluated in studies lacking information on important covariates. This report evaluates the prospective associations between pregnancy-related risk factors (preeclampsia/eclampsia, gestational hypertension, pregestational and gestational diabetes mellitus, preterm delivery, and fetal growth restriction) and pharmacologically treated hypertension within 10 years after pregnancy, while adjusting for a wide range of covariates.

Methods and Results—Prepregnancy normotensive women participating in the MoBa (Norwegian Mother and Child Cohort Study) from January 2004 through July 2009 were linked to the Norwegian Prescription Database to identify women with pharmacologically treated hypertension beyond the postpartum period of 3 months. The burden of hypertension associated with pregnancy-related risk factors was evaluated using an attributable fraction method. A total of 1480 women developed pharmacologically treated hypertension within the follow-up among 60 027 women (rate of hypertension, 3.6/1000 person-years). The proportion of hypertension associated with a history of preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational diabetes mellitus was 28.6% (95% confidence interval, 25.5%–31.6%) on the basis of multivariable analyses adjusting for numerous covariates. The proportion was similar for women with a healthy prepregnancy body mass index (18.5-24.9 kg/m^2; attributable fraction (AF)% 25.9%; 95% confidence interval, 21.3%-30.3%), but considerably higher for nulliparous women at baseline within the first 5 years of follow-up. Small-for-gestational age, however, did not increase subsequent hypertension risk in multivariable analyses.

Conclusions—A structured postpartum follow-up of high-risk women identified through pregnancy-related risk factors would facilitate personalized preventive strategies to postpone or avoid onset of premature cardiovascular events. **(*J Am Heart Assoc*. 2018;7:e008318. DOI: 10.1161/JAHA.117.008318.)**

Key Words: cardiovascular disease • fetal growth restriction • gestational hypertension • Norwegian Mother and Child Cohort Study • prediction statistics • preeclampsia/pregnancy • pregnancy • preterm delivery

Hypertension is an important early detectable and modifiable risk factor for cardiovascular disease (CVD), and blood pressure–related disease is a major contributor to the global burden of disability-adjusted life years.[1] De novo hypertensive disorders of pregnancy and gestational diabetes mellitus (GDM) are recognized as risk factors for premature maternal CVD.[2] Evidence has also been accumulating on maternal CVD associated with other pregnancy-related complications and outcomes,[3] such as preterm delivery,[4–11] fetal growth restriction[5,7,10,12] placental abruption,[13] and pregnancy losses.[5,14–16]

Most studies evaluating pregnancy-related outcomes for their prediction of long-term maternal morbidity and mortality have relied on large registry-based data sources that lack

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Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/7/10/e008318/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Consideration of a wide range of covariates did not appreciably alter the association of pregnancy-related risk factors with risk of subsequent hypertension.
- A high population burden of hypertension (28.6%) was attributed to pregnancy-related risk factors, including preeclampsia/eclampsia, gestational hypertension, preterm delivery, and pregestational or gestational diabetes mellitus.
- Findings were similar when limited to women with a normal prepregnancy body mass index and stronger when limited to nulliparous women at baseline with a follow-up limited to the first 5 years.

What Are the Clinical Implications?

- Pregnancy-related complications can help identify women early in the disease trajectory and help target monitoring and interventions to women at risk.

important information of risk factors that could contribute to both adverse pregnancy-related outcomes and increased lifetime risk of CVD. Preconception CVD risk factors, for example, predicted preeclampsia/eclampsia (PE) and gestational hypertension (GH) in a prospective cohort,[17] and prepregnancy obesity is a known antecedent of many pregnancy-related complications.[18] Furthermore, prepregnancy maternal body mass index (BMI; kg/m^2), blood pressure, and lipid measurements accounted for a large percentage of the postpregnancy differences in these risk factors between women with and without PE/GH.[19] Several recent studies, however, have evaluated multiple relevant covariates in analyses of the association between pregnancy-related events and future maternal CVD end points.[11,15,20–22] The multivariable adjustment for numerous covariates has resulted in attenuation in the measures of association with CVD outcomes. However, there were persistent and significant predictions of later CVD outcomes for PE,[20] small-for-gestational age (SGA) infants,[20] preterm delivery,[11,20] pregnancy losses,[15] and placental insufficiency disorders combined.[21]

Given the high percentage of women experiencing ≥1 adverse pregnancy events associated with maternal CVD, and given that CVD remains a leading cause of morbidity and mortality among women, better understanding of the importance of pregnancy events within context of a wide range of other CVD risk factors is needed.

Therefore, the aim of the current study was to evaluate pregnancy-related events for their association with subsequent maternal hypertension development within 10 years after delivery in analyses adjusting for numerous prepregnancy and 6-month postpartum risk factors for hypertension. Furthermore, the proportion of risk of subsequent hypertension identified by PE, GH, pregestational diabetes mellitus (DM) and GDM, preterm delivery, and fetal growth restriction was evaluated.

Methods

Data related to the current study are not available to third parties unless the data request meets the needs of specific guidelines (E-mail: datatilgang@fhi.no for more information). However, any details about methods or materials used to conduct the research, not provided herein, are available on request to the corresponding author.

Women from the MoBa (Norwegian Mother and Child Cohort Study) were included in the current analyses. The study is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health.[23] The current project was approved by the Regional Ethics Committee (Region West: 2013/740), and all participants gave informed consent. Details of the study subset used in the current analyses are reported elsewhere.[24] In brief, pregnant women were recruited from all regions in Norway, from 1999 to 2008, which included deliveries in 2009. Participation rate was 41%, providing a sample size of 95 200 pregnant women.

Outcome

The outcome was pharmacologically treated hypertension in mothers identified through the Norwegian Prescription Database (2004–2013), hereafter referred to as subsequent hypertension. Because the prescription database was established in 2004,[25] MoBa deliveries before 2004 were excluded for the current analyses. Hypertension is defined as ≥140/90 mm Hg measured at ≥2 physician visits.[26,27] Antihypertensive medications are recommended after a total evaluation of blood pressure and concurrent disease and indicated if systolic blood pressure is >160 mm Hg or diastolic blood pressure is >100 mm Hg. Hypertension was considered present if hypertension was listed as the underlying indication for treatment for ≥1 of the Anatomical Therapeutic Chemical (ATC) classification system dispensed prescriptions: antihypertensives (ATC code: C02), diuretics (ATC code: C03), β blockers (ATC code: C07), calcium channel blockers (ATC code: CO8), and renin-angiotensin system medications (ATC code: C09).[28] If medication was used only during the immediate postpartum period (<90 days from date of delivery), women were coded as nonhypertensive for analyses.

Covariates

The baseline lifestyle-related risk factors evaluated came primarily from the first MoBa questionnaire administered in

the second trimester (15–17 weeks) of pregnancy. The maternal prepregnancy lifestyle-related factors included education, daily smoking, physical activity, and alcohol consumption frequency in the past 3 months before pregnancy, and prepregnancy height and weight for determining BMI. The baseline questionnaire also included questions of oral contraceptive use and duration of use. At 6 months after delivery, another questionnaire ascertained breastfeeding, changes in weight from prepregnancy weight, and smoking status. Dietary intake was obtained from a semiquantitative food frequency questionnaire developed specifically for the MoBa, and administered in the 22nd week of pregnancy.[29] The MoBa food frequency questionnaire has been validated in substudies using a 4-day weighted food diary, motion sensors, and biological markers.[30,31] A poor diet quality indicator variable was created on the basis of having a high sodium/potassium ratio (top quartile, ≥0.88) or a low dietary calcium or low magnesium intake (<736 or <310 mg/d, respectively) given the available evidence of their importance in hypertension.[32–34] Low intake of calcium and magnesium and a high ratio of sodium/potassium associated with hypertension development in the current cohort of women.[24] The extent of missing data was low for most parameters (0%–3.2%), with the exception of the 6-month postpartum data on weight gain (17.9%), breastfeeding (14.3%), and smoking (20%).

The Medical Birth Registry of Norway (MBRN)[35] was used to identify PE (new-onset hypertension and proteinuria at >20 gestational weeks, as in the previous American College of Obstetricians and Gynecologists' criteria),[36,37] GH (new-onset hypertension diagnosed at >20 gestational weeks without proteinuria), preterm delivery (<37 weeks), very preterm delivery (<32 weeks), DM, GDM, birth weight for gestational age and sex,[38] multiple birth pregnancies, parity (0, 1, and ≥2), and maternal age at time of delivery. Given the small numbers with DM and GDM, these 2 conditions were combined (DM/GDM).

A total of 62 746 mothers were identified who delivered from January 2004 through July 2009, of whom 21% participated in MoBa for >1 pregnancy. Women who had hypertension before pregnancy or who had an early fetal loss (<22 weeks) (n=1414), or women who reported unrealistically high (>4400 kcal/d) or low (<1070 kcal/d) energy intakes, were excluded (n=1305),[29] leaving 60 027 women for the analyses. If women participated more than once in MoBa, only information from the last pregnancy was used in the current analyses. By using the last pregnancy in MoBa, we avoided methodological problems associated with changing status over time in exclusion criteria and in important covariates, such as BMI, physical activity, and smoking.

Statistical Analyses

Descriptive statistics provide the mean, SD, count, percentage, and confidence interval (CI). Prepregnancy, pregnancy, and 6-month postpregnancy characteristics were evaluated for their association with time to subsequent hypertension using hazard ratios (HRs) and 95% CIs obtained from Cox proportional hazard analyses. Two models were used in the evaluation of pregnancy-related risk factors for their association with subsequent hypertension. Model 1 adjusted for maternal age (years) at delivery. Model 2 adjusted for maternal age and prepregnancy risk factors, including the following: BMI (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 and ≥3 times/wk), daily smoking (yes versus no), alcohol consumption frequency (less than monthly, monthly, or weekly), and duration of lifetime oral contraceptive use (none, <4 years, and ≥4 years). Other risk factors that were adjusted for included midpregnancy poor diet quality (yes versus no) and total energy intake (kcal/d) and multiple birth pregnancies at delivery.

We evaluated the possibility of effect modification between PE/GH (yes versus no) and gestational age (very preterm, <32 weeks; moderately preterm, 32–36 weeks; and term) and between PE/GH and weight-for-gestational age and sex categories (very small, <2.5%; moderate, 2.5%–9.9%; and average, ≥10%) in age-adjusted analyses (Table S1). No significant interactions were noted. The presence of a PE/GH with a very preterm delivery (gestational week, <32) was associated with the highest age-adjusted HR for subsequent hypertension when compared with term deliveries without PE/GH (Table S1). The small sample size with this combination resulted in overlapping 95% CIs with other risk groups and a nonsignificant (PE/GH×preterm) interaction term. There was no evidence of interaction between PE/GH and SGA (Table S1) or between SGA and preterm delivery (data not shown). Also, there was no interaction between PE/GH and large for gestational age (LGA; data not shown).

Given that PE/GH associates with the other pregnancy-related events, PE/GH was added as a covariate to model 2 when evaluating DM/GDM, preterm delivery, and weight-for-gestational age categories for their prediction of subsequent hypertension.

For the analyses of the subgroup with available data measured at 6 months postpartum, the follow-up time and case counting started immediately at 6 months after delivery, as opposed to 3 months after delivery. Models 1 and 2 were repeated in the subgroup. An additional model was conducted that included model 2 covariates plus daily breastfeeding (yes versus no) and a high weight gain (≥7 versus <7 kg) at 6 months postpartum. The results of the analyses (models 1 and 2) in the subgroup with available 6 months postpartum data were similar to the results based on the entire study population. Furthermore, model 3 results were similar to model 2 results. Therefore, results of the additional analyses are not presented.

Smoking at 6 months postpartum was also evaluated for its association with subsequent hypertension in analyses substituting it for the prepregnancy smoking variable and in analyses evaluating combinations of prepregnancy and postpregnancy smoking and missing smoking data. Because prepregnancy smoking and educational level were strongly predictive of smoking at 6 months postpartum, additional consideration of the postpartum smoking information did not modify results.

The burden of hypertension detectable through pregnancy-related events was estimated using the attributable fraction (AF) method in STATA.[39,40] The STATA *punafcc* calculates the unattributable fraction, which, in the case of survival analyses, represents the between-scenario HR where 2 scenarios are possible: a theoretical counterfactual scenario where no one has the risk factor in the population and the real-world scenario where a percentage of the population has the risk factor in question. The unattributable fraction is subtracted from 1 to estimate the AF×100% (AF%) interpreted as the burden of hypertension related to the unfavorable conditions identified in pregnancy or at delivery.

Because pregnancy-related events are, to some degree, interrelated, we also evaluated the cumulative percentage at risk by sequentially adding pregnancy-related events, one at a time, to the at-risk group. We then estimated the sequential age- and multivariable-adjusted cumulative AF% on the basis of the total percentage having ≥1 of the risk factors versus none of the risk factors.[41]

We also conducted 3 sensitivity analyses to evaluate consistencies in results: (1) restricted to women with a healthy prepregnancy BMI (18.5–24.9 kg/m^2); (2) restricted to nulliparous women at baseline, with a follow-up limited to the first 5 years after delivery; and (3) by age groups (<30, 30–34, 35–39, and with too few ≥40 years for analyses; n=1382). Finally, we also evaluated the extent to which HRs varied with sequentially greater lengths of follow-up given that the Schoenfeld test indicated deviations in proportionality of HR for some, but not all, of the pregnancy-related characteristics.[42] Statistical significance was determined by $P \leq 0.05$. Stata 14 (Stata Corp LP, College Station, TX) was used in the analyses.

Results

The mean (SD) age of participants at childbirth was 30.5 (4.6) years, and the mean length of follow-up was 7.1 (1.6) years, with a maximum follow-up of 10 years. Before pregnancy, 21.7% were overweight and 9.5% were obese; 16.5% smoked daily, with a mean (SD) of 11 (5.9) cigarettes/d; and 47.9% engaged in leisure-time physical activity ≥3 times per week (Table 1). On the basis of questions about mothers' parents' native language, 9% of the study participants had either a mother or father who was not ethnic Norwegian. At 6 months postpartum, 80% reported daily breastfeeding, and 10% reported a weight gain of ≥7 kg compared with prepregnancy weight. The mean (SD) weight gain was 1.16 (4.6) kg.

Table 1. Baseline Prepregnancy and 6 Months Postpartum Characteristics: MoBa Cohort Study (60 027 Women With Deliveries in 2004–2009 in Norway)

Characteristics	Values
Maternal age at delivery, mean (SD), y	30.5 (4.6)
Norwegian ethnicity, %	91.1
Prepregnancy body mass index, mean (SD), kg/m^2	24.0 (4.3)
Prepregnant overweight (25.0–29.9 kg/m^2), %	21.7
Prepregnant obese (≥30 kg/m^2), %	9.5
Any college/university, %	28.1
Weekly alcohol consumption, %	28.2
Daily smoking, %	16.5
Physical activity ≥3 times/wk, %	47.9
Poor diet quality, %*	42.7
Oral contraceptive use history ≥4 y, %	53.3
Weight gain >7 kg, %†	10.0
Breastfeeding daily, %‡	80.3

MoBa indicates Norwegian Mother and Child Cohort Study.
*A high sodium/potassium ratio in the top quartile (≥0.88) or a low dietary calcium or magnesium intake (<736 or <310 mg/d, respectively).
†At 6 months postpartum relative to prepregnancy weight.
‡At 6 months postpartum.

A total of 1480 women developed pharmacologically treated hypertension within the follow-up among the 60 027 women who contributed 412 518 total person-years of observation (ie, rate of subsequent hypertension, 3.6/1000 person-years). The estimated median duration of antihypertensive use based on number of dispensed medication episodes was 24 months (interquartile range, 9–48 months), with increasing duration of use noted with increasing years of follow-up.

In maternal age-adjusted analyses (model 1), a greater risk of subsequent hypertension was predicted by an overweight and obese prepregnancy BMI, prepregnancy daily smoking, low educational level (primary or secondary), poor diet quality, low physical activity level, and high weight retention at 6 months postpartum relative to the respective comparison groups (data not shown). Occasional and weekly alcohol consumption, a greater duration of oral contraceptive use before index pregnancy, and breastfeeding daily at 6 months associated with reduced risk of hypertension compared with their respective comparison groups. A parity of ≥2 before the MoBa registered pregnancy was associated with a maternal age-adjusted HR (95% CI) for subsequent hypertension of 1.45 (1.26–1.66), whereas a parity of 1 was not significantly

Table 2. HRs (95% CIs) of Pharmacologically Treated Hypertension Within 10 Years After Delivery With Respect to Pregnancy-Related Risk Factors: MoBa Cohort Study (60 027 Women With Deliveries in 2004–2009 in Norway)

Risk Factors	N	Cases*	Model 1†	Model 2‡
De novo hypertensive disorders of pregnancy				
None	56 646	1039	1.00 (Reference)	1.00 (Reference)
PE	2146	266	7.67 (6.69–8.80)	6.00 (5.15–6.99)
GH	1235	175	8.93 (7.61–10.49)	7.13 (5.93–8.58)
DM/GDM§				
No	59 100	1391	1.00 (Reference)	1.00 (Reference)
Yes	927	89	4.08 (3.29–5.06)	2.43 (1.91–3.10)
Preterm delivery§				
No	56 466	1301	1.00 (Reference)	1.00 (Reference)
Yes (<37 wk)	3298	170	2.25 (1.92–2.64)	1.45 (1.19–1.76)
<32 wk	447	36	3.58 (2.55–5.03)	2.10 (1.44–3.06)
32–36 wk	2851	134	2.04 (1.70–2.44)	1.35 (1.09–1.66)
Weight-for-gestational age§,‖				
All small (<10%)	4232	111	1.15 (0.95–1.40)	1.12 (0.90–1.39)
<2.5%	854	30	1.50 (1.05–2.16)	0.81 (0.53–1.24)
2.5%–9.9%	3378	81	1.06 (0.84–1.33)	1.07 (0.84–1.38)
Average (10%–90%)	48 875	1146	1.00 (Reference)	1.00 (Reference)
Large (>90%)	6624	214	1.29 (1.12–1.49)	0.94 (0.81–1.11)

CI indicates confidence interval; DM/GDM, pregestational and gestational diabetes mellitus or type not specified; GH, gestational hypertension; HR, hazard ratio; MoBa, Norwegian Mother and Child Cohort Study; and PE, preeclampsia/eclampsia.

*Identified through antihypertensive medications dispensed after pregnancy, where hypertension is listed as indication for treatment. When medication dispensed only during the postpartum period of <3 months, individuals were coded normotensive.

†Adjusted for maternal age (years).

‡Adjusted for maternal age (years), prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 and ≥3 times/wk), daily smoking (yes vs no), alcohol consumption frequency (less than monthly, monthly, or weekly), duration of prepregnancy oral contraceptive use (never, <4 years, or ≥4 years), poor diet quality (yes vs no), energy intake (kcal/d), and multiple birth pregnancy.

§Additional adjustment for PE/GH included in model 2.

‖Using national birth weight by gestational age and sex growth curves.[38]

associated with risk (HR, 1.07; 95% CI, 0.94–1.21) relative to nulliparity at baseline (data not shown).

During pregnancy, a total of 3381 women developed either PE or GH, of whom 1235 had GH, 1642 had term PE, and 504 had preterm PE (defined as a PE delivery before gestational week 37). There were 46 women with eclampsia in the PE group.

In age-adjusted analyses (model 1), PE (HR, 7.67; 95% CI, 6.69–8.80) and GH (HR, 8.93; 95% CI, 7.61–10.49) had similar HRs for subsequent hypertension averaged over the entire follow-up (Table 2). In age-adjusted analyses, DM/GDM, preterm delivery, particularly early preterm delivery, very SGA (<2.5 birth weight percentile), and LGA (>90 birth weight percentile) were also significantly associated with increased risk of subsequent hypertension (Table 2).

In evaluation of combinations of pregnancy-related complications, the presence of a PE/GH with a very preterm delivery (gestational week <32) was associated with the highest HR for subsequent hypertension (age-adjusted HR of 14.33; 95% CI, 9.03–22.70) when compared with term deliveries without PE/GH (Table S1). However, the small sample size with this combination resulted in overlapping 95% CIs with other risk groups and a nonsignificant (PE/GH×preterm) interaction term. There was no evidence of interaction between PE/GH and SGA (Table S1) or between SGA and preterm delivery (data not shown). Also, there was no interaction between PE/GH and LGA (data not shown).

In model 2 analyses, there was only a modest attenuation in the HRs associated with PE and GH (Table 2). Also, DM/GDM and preterm delivery persisted as being significantly associated with subsequent hypertension, although there was a marked attenuation in the multivariable-adjusted HRs observed. In contrast, SGA, including very SGA, and LGA were no longer significantly associated with increased risk of subsequent hypertension in multivariable models.

Table 3. AFs and Cumulative AFs (95% CIs) for Pharmacologically Treated Hypertension by Pregnancy-Related Risk Factors: MoBa Cohort (60 027 Women With Deliveries in 2004–2009 in Norway)*

Risk Factor	% at Risk	Age-Adjusted AF% (95% CI)	% Cumulative at Risk†	Model 1 AF% (95% CI)‡	Model 2 AF% (95% CI)§
Total study sample (1480 cases among 60 027 women)					
PE	3.6	15.3 (13.3–17.3)	3.6	15.3 (13.3–17.3)	14.7 (12.5–16.9)
GH	2.1	10.2 (8.5–11.9)	5.6	26.1 (23.7–28.5)	25.3 (22.6–27.9)
DM/GDM	1.5	4.5 (3.3–5.8)	7.0	28.8 (26.3–31.3)	27.5 (24.7–30.3)
Preterm delivery	5.5	6.5 (4.7–8.2)	11.4	30.4 (27.6–33.1)	28.6 (25.5–31.6)
Normal body mass index (≥18.5 to < 25) (549 cases among 38 559 women)‖					
PE	2.7	11.9 (8.9–14.8)	2.7	11.9 (8.9–14.8)	12.8 (9.6–16.0)
GH	1.6	10.8 (8.0–13.5)	4.3	23.2 (19.3–26.9)	23.8 (19.7–27.7)
DM/GDM	0.9	2.6 (1.0–4.1)	5.1	24.0 (20.0–27.8)	24.5 (20.3–28.7)
Preterm delivery	5.2	5.1 (2.4–7.7)	9.4	25.0 (20.6–29.0)	25.9 (21.3–30.3)
Follow-up <5 y for nulliparous women at baseline (327 cases among 26 023 women)					
PE	5.2	29.2 (23.7–34.3)	5.2	29.2 (23.7–34.3)	28.4 (22.4–33.9)
GH	2.7	11.0 (7.1–14.7)	7.9	41.7 (35.6–47.2)	41.0 (34.4–47.0)
DM/GDM	1.5	5.8 (2.9–8.6)	9.3	45.8 (39.6–51.5)	44.6 (37.8–50.7)
Preterm delivery	6.7	11.4 (6.9–15.7)	14.4	47.5 (40.9–53.4)	46.4 (39.1–52.7)

AF indicates attributable fraction; CI, confidence interval; DM/GDM, pregestational and gestational diabetes mellitus or type not specified; GH, gestational hypertension; MoBa, Norwegian Mother and Child Cohort Study; and PE, preeclampsia/eclampsia.

*Identified through antihypertensive medications dispensed after pregnancy, where hypertension was listed as indication for treatment. When medication dispensed only during the postpartum period of <3 months, individuals were coded normotensive.

†Because risk factors are interrelated, the cumulative percentage at risk does not equal the addition of the individual percentage with each risk factor.

‡Cumulative age-adjusted AFs based on sequential population AFs using method described elsewhere.[40]

§Cumulative AFs adjusted for maternal age (years), prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 and ≥3 times/wk), daily smoking (yes vs no), alcohol consumption frequency (less than monthly, monthly, or weekly), duration of prepregnancy oral contraceptive use (never, <4 years, or ≥4 years), poor diet quality (yes vs no), energy intake (kcal/d), and multiple birth pregnancy.

‖Pregnancy body mass index (kg/m^2) removed from model 2.

Sensitivity Analyses

In the analyses restricted to women with a healthy prepregnancy BMI (18.5–24.9 kg/m^2), slightly greater HRs were observed for the pregnancy-related risk factors than those observed in the primary analyses (Table S2). Furthermore, greater HRs were associated with the pregnancy-related risk factors in the analyses restricted to nulliparous women within the first 5 years of follow-up than in the primary analyses (Table S3). In contrast, SGA and LGA were not associated with subsequent hypertension risk in the 2 sensitivity analyses, similar to the overall findings (Tables S2 and S3). Finally, in age-stratified analyses, we found homogeneous HRs and overlapping 95% CIs for all pregnancy-related risk factors by age group examined and, because results were comparable to those presented in Table 2, they are not separately presented.

HRs by Length of Follow-Up

The HRs for subsequent hypertension associated with having PE/GH and preterm delivery decreased over greater lengths of follow-up, whereas the HRs associated with having DM/GDM remained stable over time (Table S4).

Burden of Hypertension Assessed Via AFs

In age-adjusted analyses, the AF%s associated individually with PE (15.3%), GH (10.2%), DM/GDM (4.5%), and preterm delivery (6.5%) provided a cumulative percentage at risk of 11.4%, corresponding to a combined at-risk group HR of 5.0 (95% CI, 4.5–5.6). This resulted in a cumulative AF% of 30.3% (95% CI, 27.6%–33.1%) (Table 3). In analyses adjusting for model 2 covariates, the cumulative AF% was only modestly reduced to 28.6% (95% CI, 25.5%–31.6%). In the sensitivity analyses restricted to women with a normal prepregnancy BMI (18.5–25.9 kg/m^2), we observed similar results, where 9.4% had ≥1 risk factor that contributed to a cumulative multivariable-adjusted AF% of 25.9% (95% CI, 21.3%–30.3%). For nulliparous women, 14.4% had ≥1 pregnancy-related risk factors, with a combined at-risk group HR of 7.3 (95% CI, 5.9–9.1), which corresponded to a cumulative multivariable-adjusted AF% of 46.4% (95% CI, 39.1%–52.7%) in analyses restricted to the first 5 years of follow-up. A large proportion

of the cumulative AF%s was attributed to the effect associated with PE/GH. However, in analyses of nulliparous women restricted to the first 5 years after delivery, DM/GDM and preterm delivery contributed more to the cumulative AF% than in the other analyses.

Discussion

We found persistent excess risk of hypertension after pregnancy within 10 years after PE/GH, DM/GDM, and preterm delivery after adjusting for numerous covariates. However, we found no evidence that SGA or very SGA associated with increased hypertension risk independent of PE/GH. Furthermore, the AF% provides another quantitative perspective of the value of pregnancy events beyond that of the HR, indicating the proportion of at-risk hypertensive women who would be identified by women's reproductive histories early in the disease trajectory. Hypertension is an important and modifiable intermediary between pregnancy-related events and future cardiovascular morbidity and mortality. Although there are common antecedents between pregnancy complications and CVD, our analyses indicated that, after adjustment for numerous prepregnancy and 6-month postpartum risk factors, the increased risk for subsequent hypertension within 10 years after a pregnancy complicated by PE/GH, DM/GDM, and/or preterm delivery persisted.

Furthermore, in analyses restricted to women with a healthy prepregnancy BMI, we found a similar magnitude in the HRs and the AF%s as those observed for the total study population. The results provide further evidence that pregnancy is a "stress test" for long-term maternal health and disease,[43] even in low-risk women with a healthy prepregnancy weight.

For preterm delivery, we observed an attenuation in the age-adjusted HR for subsequent hypertension of 2.0 to 1.45 after adjustment for multiple covariates. The results of the current study are similar to findings from a study evaluating preterm delivery and subsequent CVD in the NHS (Nurses' Health Study), where a multivariable-adjusted HR of 1.4 was identified for preterm delivery.[11] We also observed a high HR associated with having PE/GH and a very preterm delivery (<32 weeks' gestation), findings that corroborate several previous studies that lacked adjustment for many of the covariates included in the current study.

The observed age-adjusted association between having delivered an LGA infant and subsequent hypertension became nonsignificant in multivariable analyses. For associations between high birth weights and future maternal CVD risk, maternal obesity and issues related to glycemic control are likely important mediators of long-term risks.[7,44]

An important finding of our study is the lack of an association between SGA and very SGA and subsequent hypertension independent of PE/GH or preterm delivery, and lack of evidence of interaction between SGA and preterm delivery or between SGA and PE/GH. SGA deliveries represent diverse situations, including constitutionally small but healthy births to constitutionally small but healthy mothers as well as placental dysfunction, with various underlying causes, including smoking (the latter associating with lower rates of PE). Therefore, the implications of SGA may vary between diverse study populations and by the ability to adjust for important covariates, such as smoking or mother's BMI. Another inherent problem about the use of birth-weight-by-gestational age and sex percentiles, particularly for low gestational ages, is the bias introduced by not being able to account for the fetal weights of unborn fetuses that continue to mature until delivery, resulting in SGA infants that are preterm likely being more growth restricted than their birth weight percentiles indicate. Although we did observe a 50% elevated risk of subsequent hypertension among women who delivered a very SGA infant in age-adjusted analyses, the excess risk did not persist in multivariable analyses. Several studies indicate that an SGA or low birth weight associated with higher subsequent maternal blood pressure[20,44] or CVD.[7,45,46] In a predominantly Swedish study population, with only 10.3% immigrants from non-Nordic countries, very SGA (<2 SDs) was associated with a 60% greater CVD risk compared with a birth weight percentile within $\pm$1 SDs in analyses adjusting for smoking, socioeconomic status, and other covariates.[7] Also, the Swedish study observed significant associations between very SGA and early preterm deliveries with CVD.[7] However, in our analyses including additional covariates, we found no evidence that SGA or very SGA predicted subsequent hypertension independent of PE/GH or preterm delivery. In 6000 women in the National Health and Nutrition Examination Survey, preterm SGA was a significant predictor of hypertension only in non-Hispanic blacks.[47] It is postulated that the more severe the placental dysfunction, the higher the risk for maternal premature CVD.[48] Our SGA results may relate, in part, to having more healthy study participants than the general population; our rates of SGA and very SGA were lower than anticipated (7.1% and 1.4% versus the expected 10% and 2.5%, respectively).

Because risk factors can change over time and because the first pregnancy may represent the optimal stress test for future maternal health, we conducted sensitivity analyses limited to nulliparous women within the first 5 years of follow-up, in which we observed stronger associations between PE/GH, DM/GDM, and preterm delivery with subsequent hypertension.

In a previous study based on record linkages in Norway, HRs for hypertension associated with PE decreased as the

duration of follow-up increased.[49] Also, a meta-analysis identified greater HRs for heart failure, stroke, and CVD deaths during the first 10 years after a pregnancy affected by PE compared with that beyond 10 years.[50] Our higher HRs for subsequent hypertension associated with PE/GH than those observed in the prevailing literature of long-term CVD outcomes may be attributed to hypertension being a modifiable intermediary of CVD and to our shorter length of follow-up in a young population. With increasing age, there is an increasing hypertension and CVD occurrence in women without a history of pregnancy-related events.

In the Netherlands component of the EPIC (European Prospective Investigation Into Cancer and Nutrition), hypertension and type 2 DM fully accounted for the association between self-reported hypertension in a prior pregnancy and later-life CVD.[22] The excess risk of future CVD associated with pregnancy-related events could, theoretically, be mitigated by early detection, preventive action, and pharmacological treatment.

Strengths and Limitations

Strengths of the current study involve the availability of a wide range of important prepregnancy risk factors and weight gain and breastfeeding status at 6 months postpartum. Furthermore, the sample size of >60 000 women enabled us to conduct sensitivity analyses limited to relevant subgroups. Limitations include the lack of information about family history of disease and maternal hyperlipidemia before or after pregnancy. The ethnically homogeneous study population prevents generalizability to more ethnically diverse populations. Also, because of the small number of women ≥40 years of age in the current study, the results may not be generalizable to older women. Another limitation is a likely underascertainment of GDM in the MBRN. Therefore, our ability to evaluate the implications of GDM for future hypertension risk is limited in the current research material. GDM, however, is already an established precursor to DM, which, in turn, is an established risk factor for CVD.[51] Another limitation is that we anticipate some underreporting of milder PE/GH in the MBRN, and this would result in an underascertainment of the true burden of subsequent hypertension associated with PE/GH. Furthermore, we were not able to evaluate participants' entire reproductive histories in the current analyses. Nonetheless, the magnitude of the HRs observed in the current report is similar to many studies on this topic in which a full reproductive history has been available. Finally, the low participation rate in MoBa (41%) raises questions of generalizability. However, in an evaluation of the potential for selection bias in the MoBa, no differences were noted in 8 exposure-outcome associations comparing results obtained from the MoBa study population with that obtained from the MBRN.[52] Furthermore, in all births registered in the MBRN (2004–2009), we observed similar percentages of births affected by PE (3.6%), GH (1.9%), DM/GDM (2.0%), and preterm delivery (6.3%) (http://www.fhi.no) as in our selected MoBa cohort of women who were normotensive before index pregnancy. The similar prevalence in these events in the MoBa and the national population-based register suggests that the AF%s derived from the MoBa cohort are likely reasonable estimates of the AF%s for the general population.

Summary

Our finding of several pregnancy complications predicting development of premature hypertension, particularly after the first pregnancy, suggests the first postpartum assessment of women[46] would be an ideal time for triaging for high premature maternal CVD risk. A 6- to 12-week postpartum assessment, routinely offered in many high-income countries, could be an ideal time for physicians to identify and offer high-risk women at a young age enhanced monitoring and interventions. Pregnancy histories can optimize maternal cardiovascular health and reduce the burden of premature CVD disease for women.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios (95% CI) of pharmacologically-treated hypertension[*] by preeclampsia/eclampsia and gestational hypertension stratified by gestational age and weight-for-gestational age categories: MoBa Cohort Study (60,027 women with deliveries 2004-2009 in Norway).

	Preeclampsia/eclampsia or gestational hypertension							
	Yes				No			
Risk Factor	**N**	**Cases**	**Model 1[†]**	**Model 2[‡]**	**N**	**Cases**	**Model 1[†]**	**Model 2[‡]**
Gestational age (weeks)								
< 32	106	22	14.33 (9.03-22.70)	12.68 (7.70-20.89)	341	14	2.27 (1.33-3.85)	2.15 (1.24- 3.74)
32 – 36	490	72	9.25 (7.22-11.86)	7.94 (5.97-10.56)	2,361	62	1.45 (1.12-1.87)	1.42 (1.07-1.88)
≥ 37	2,766	345	8.01 (7.08-9.06)	6.19 (5.38-7.13)	53,700	956	1.00 (reference)	1.00 (reference)
Weight-for-gestational age categories[§]								
< 2.5%	159	18	6.69 (4.19-10.70)	5.26 (3.03-9.13)	695	12	0.93 (0.53-1.63)	0.80 (0.41-1.55)
2.5 – 9.9%	392	45	6.91 (5.11-9.37)	6.14 (4.42-8.52)	2,986	36	0.68 (0.48-0.94)	0.67 (0.46-0.98)
≥ 10%	2,811	376	8.24 (7.31-9.29)	6.38 (5.56-7.31)	52,688	984	1.00 (reference)	1.00 (reference)

CI indicates confidence interval.

* Identified through antihypertensive medications dispensed following pregnancy where hypertension listed as indication for treatment. When medication dispensed only during the post-partum period of < 3 months individuals were coded normotensive.

†Adjusted for maternal age (yrs).

‡Adjusted for maternal age (yrs), prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 times, and 3 or more times/week), daily smoking (yes v. no), alcohol consumption frequency (less than monthly, monthly, weekly), duration of prepregnancy oral contraceptive use (never, < 4 years, 4 or more years), poor diet quality (yes *v.* no), energy intake (Kcal/d), and multiple birth pregnancy.

§Using national birth weight by gestational age and sex growth curves (very small, < 2.5%, moderate small 2.5-9.9%, and not small $\geq$ 10%).[1]

Table S2. Pregnancy-related events hazard ratios (95% CI) for pharmacologically-treated hypertension[*] within 10 years following delivery among women with a healthy prepregnancy body mass index: MoBa Cohort Study (38,559 women with deliveries 2004-2009 in Norway).

	Women with prepregnant body mass index 18.5 – 24.9 kg/m^2			
Risk Factor	**N**	**Cases[*]**	**Model 1[†]**	**Model 2[‡]**
De novo hypertensive disorders of pregnancy				
None	36,908	406	1.00 (reference)	1.00 (reference)
PE	1,037	77	7.61 (5.95-9.74)	8.40 (6.49-10.88)
GH	614	66	11.55 (8.90-14.98)	12.07 (9.09-16.03)
DM/GDM				
No	38,200	530	1.00 (reference)	1.00 (reference)
Yes	359	19	3.89 (2.47-6.15)	3.36 (2.05-5.51)
Preterm delivery				
No	36,410	490	1.00 (reference)	1.00 (reference)
Yes (<37 weeks)	1,983	55	2.05 (1.55-2.71)	2.19 (1.59-3.02)
< 32 weeks	263	9	2.49 (1.28-4.83)	2.64 (1.28-5.47)
32-36 weeks	1,720	46	2.00 (1.48-2.71)	2.15 (1.53-3.01)
Weight-for-gestational age and sex[§]				
All small (<10%)	2,902	44	1.14 (0.83-1.55)	0.70 (0.48-1.00)
<2.5%	569	14	1.82 (1.07-3.09)	0.92 (0.50-1.66)
2.5-9.9%	2,333	30	0.97 (0.67-1.40)	0.62 (0.40-0.95)
Average (10-90%)	32,078	440	1.00 (reference)	1.00 (reference)
Large (>90[%])	3,392	61	1.24 (0.95-1.62)	1.01 (0.74-1.37)

CI indicates confidence interval; PE, preeclampsia/eclampsia; GH, gestational hypertension; DM/GDM, pregestational and gestational diabetes mellitus or type not specified.

[*]Identified through antihypertensive medications dispensed following pregnancy where hypertension listed as indication for treatment. When medication dispensed only during the post-partum period of < 3 months individuals were coded normotensive.

[†]Adjusted for maternal age.

[‡]Adjusted for maternal age, prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 times, and 3 or more times/week), daily smoking (yes v. no), alcohol consumption frequency (less than monthly, monthly, weekly), duration of prepregnancy oral contraceptive use (never, < 4 years, 4 or more years), and a low dietary intake of minerals (yes v. no), energy intake (Kcal/d), and multiple birth pregnancy. For all non-hypertensive pregnancy risk factors, adjusts for hypertensive disorders of pregnancy.

[§]Using national birth weight by gestational age and sex growth curves.[1]

Table S3. Pregnancy-related event hazard ratios (95% CI) for pharmacologically-treated hypertension[*] within 5 years following delivery in nulliparous women at baseline: MoBa Cohort Study (26,023 women with deliveries 2004-2009 in Norway).

	Follow-up ≤ 5 years for nulliparous women at baseline			
Risk Factor	**N**	**Cases[*]**	**Model 1[†]**	**Model 2[‡]**
De novo hypertensive disorders of pregnancy				
None	23,964	176	1.00 (reference)	1.00 (reference)
PE	1,346	107	9.31 (7.39-11.72)	6.97 (5.31-9.14)
GH	713	44	5.50 (4.01-7.55)	4.31 (3.05-6.08)
DM/GDM				
No	25,625	303	1.00 (reference)	1.00 (reference)
Yes	398	24	4.87 (3.22-7.38)	3.22 (2.07-5.02)
Preterm delivery				
No	24,152	268	1.00 (reference)	1.00 (reference)
Yes (all <37 weeks)	1,726	57	2.93 (2.20-3.91)	1.88 (1.35-2.63)
< 32 weeks	265	15	5.03 (2.97-8.52)	2.62 (1.45-4.73)
32-36 weeks	1,461	42	2.55 (1.84-3.54)	1.73 (1.19-2.52)
Weight-for-gestational age and sex[§]				
All small (< 10%)	2,644	42	1.26 (0.91-1.74)	0.92 (0.65-1.29)
<2.5%	548	12	1.71 (0.96-3.04)	0.89 (0.48-1.67)
2.5 – 9.9%	2,096	30	1.14 (0.78-1.66)	0.93 (0.67-1.37)
Average (10-90%)	21,507	263	1.00 (reference)	1.00 (reference)
Large (>90%)	1,714	20	0.97 (0.61-1.52)	0.60 (0.35-1.01)

CI indicates confidence interval; PE, preeclampsia/eclampsia; GH, gestational hypertension; DM/GDM, pregestational and gestational diabetes mellitus or type not specified.

[*]Identified through antihypertensive medications dispensed following pregnancy where hypertension listed as indication for treatment. When medication dispensed only during the post-partum period of < 3 months individuals were coded normotensive.

[†]Adjusted for maternal age.

[‡]Adjusted for maternal age, prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 times, and 3 or more times/week), daily smoking (yes v. no), alcohol consumption frequency (less than monthly, monthly, weekly), duration of prepregnancy oral contraceptive use (never, < 4 years, 4 or more years), and a low dietary intake of minerals (yes v. no), energy intake (kilocalories/d), and multiple birth pregnancy. For all non-hypertensive pregnancy risk factors, adjusts for hypertensive disorders of pregnancy.

[§]Using national birth weight by gestational age and sex growth curves.[1]

Table S4. Hazard ratios (95% CI) of pharmacologically-treated hypertension[*] with respect to pregnancy-related risk factors by sequentially longer lengths of follow-up: MoBa Cohort (60,027 women with deliveries 2004-2009 in Norway).

	Length of follow-up			
Risk Factors	**4 yrs**	**6 yrs**	**8 yrs**	**10 yrs**
PE/GH combined				
Model 1[†]	11.39 (9.88-13.13)	9.26 (8.17-10.49)	8.38 (7.47-9.41)	8.13 (7.27-9.09)
Model 2[‡]	9.40 (8.00-11.04)	7.45 (6.46-8.58)	6.62 (5.80-7.55)	6.38 (5.62-7.26)
DM/GDM				
Model 1[†]	4.34 (3.29-5.74)	4.23 (3.32-5.39)	4.22 (3.39-5.26)	4.08 (3.29-5.06)
Model 2[‡,§]	2.45 (1.82-3.31)	2.43 (1.86-3.16)	2.44 (1.90-3.12)	2.43 (1.91-3.10)
Preterm delivery[‖]				
Model 1[†]	3.14 (2.59-3.81)	2.55 (2.13-3.04)	2.39 (2.03-2.81)	2.25 (1.92-2.64)
Model 2[‡,§]	1.89 (1.51-2.36)	1.60 (1.30-1.97)	1.56 (1.29-1.90)	1.45 (1.19-1.76)
Combined group[#]				
Model 1[†]	6.88 (5.99-7.91)	5.68 (5.04-6.40)	5.23 (4.69-5.83)	5.02 (4.52-5.57)
Model 2[‡]	5.94 (5.08-6.95)	4.77 (4.16-5.46)	4.36 (3.85-4.93)	4.17 (3.70-4.70)

CI indicates confidence interval; PE, preeclampsia/eclampsia; GH, gestational hypertension; DM/GDM, pregestational and gestational diabetes mellitus or type not specified.

[*]Identified through antihypertensive medications dispensed following pregnancy where hypertension listed as indication for treatment. When medication dispensed only during the post-partum period of < 3 months individuals were coded normotensive.

[†]Adjusted for maternal age (yrs).

[‡]Adjusted for maternal age, prepregnancy body mass index (kg/m^2), educational level (primary, secondary/vocational, and any college/university), physical activity (<3 times, and 3 or more times/week), daily smoking (yes v. no), alcohol consumption frequency (less than monthly, monthly, weekly), duration of prepregnancy oral contraceptive use (never, < 4 years, 4 or more years), poor diet quality (yes *v*. no), energy intake (kilocalories/d), and multiple birth pregnancy.

[§]Additional adjustment for PE/GH.

[‖] Less than 37 weeks gestational age.

[#]Having one or more of the following: PE/GH, DM/GDM, or preterm delivery.

Supplemental Reference:

1. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand.* 2000;79:440-9.