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Is the risk of cardiovascular disease in women with pre-eclampsia modified by very low or very high offspring birth weight? A nationwide cohort study in Norway

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ABSTRACT

Objectives To examine whether the risk of cardiovascular disease (CVD) in women with pre-eclampsia is modified by very low or very high offspring birth weight. Further, we studied whether diabetes in pregnancy modified this risk.

Design Nationwide cohort study.

Setting Norwegian population registries.

Participants 618 644 women who gave birth to their first child during 1980–2009.

Methods The women were followed from delivery until the development of CVD or censoring, by linkage of the Medical Birth Registry of Norway to the Cardiovascular Disease in Norway project, and the Norwegian Cause of Death Registry.

Primary outcome measure: CVD.

Results Compared with normotensive women with normal offspring birth weight, women with pre-eclampsia had increased risk of CVD (HR 2.16; 95% CI 2.05 to 2.26). The CVD risk was even higher when pre-eclampsia was accompanied with a large for gestational age offspring (LGA, z-score >2.0) (HR 2.57; 95% CI 2.08 to 3.18). Women with pre-eclampsia and a small for gestational age offspring (SGA, z-score <−2.0) had an HR of 1.54 (95% CI 1.23 to 1.93) compared with normotensive women with normal offspring birth weight.

Also, women with diabetes had increased CVD risk, but no additional risk associated with an LGA or SGA offspring.

Conclusions Women with pre-eclampsia and an LGA offspring had higher risk of CVD than pre-eclamptic women with a normal weight (z-score −2.0 to 2.0) or SGA offspring. These findings suggest that factors causing pre-eclampsia and an LGA offspring are also linked to development of CVD.

Strengths and limitations of this study

- Large nationwide cohort study of 618 644 Norwegian women.
- Detailed follow-up information of both non-fatal and fatal cardiovascular disease over a period of up to 29 years.
- A unique person identification number allowed linkage of data from several national data sources with compulsory reporting, thus enabling follow-up of almost all women who had given birth in Norway.
- No information about smoking or body mass index was available, since such information was not included in the nationwide health registries in our study period.

INTRODUCTION

Pre-eclampsia, defined as hypertension and proteinuria in pregnancy, affects 2%–8% of all pregnancies,[1] and is an important cause of maternal and offspring morbidity and mortality.[2 3] Several studies have shown that pre-eclampsia increases the risk of subsequent cardiovascular disease (CVD) in women.[4 5] Also offspring birth weight is a risk marker for subsequent CVD, and both low[6–8] and high birth weight[9–11] have been associated with increased risk. However, the reported associations of high offspring birth weight with CVD have been inconsistent.[9 12 13] Women with diabetes in pregnancy are at increased risk of giving birth to an offspring with high birth weight, and their risk of pre-eclampsia is also increased.[14 15] Improved understanding of the relations of pre-eclampsia and high birth weight with CVD will also improve our understanding of the causes of these conditions.

To our knowledge, no previous study has examined the combined effect of pre-eclampsia and giving birth to a large for gestational age (LGA) offspring on the risk of developing CVD. Therefore, we aimed to compare the associations of high and low offspring birth weight with the risk of developing CVD in women who had pre-eclampsia

in her first pregnancy. Further, we studied whether diabetes in pregnancy modified this association.

METHODS

Design

Our study is a historical cohort study, in which women with a singleton first pregnancy during the years 1980–2009 were followed from the date of delivery until the development of CVD, death, or end of the follow-up period (31 December 2009).

Data sources

Women were identified in the Medical Birth Registry of Norway (MBRN), established in 1967. This registry is based on compulsory notification of all live births and stillbirths in Norway. The registry includes all pregnancies lasting beyond 16 weeks, and has information about maternal characteristic, maternal medical history and pregnancy complications.[16] Information about the development of CVD was obtained by linking individual data in the MBRN to the Cardiovascular Disease in Norway (CVDNOR) project (http://cvdnor.w.uib.no). CVDNOR contains information about all persons who were discharged from any somatic hospital in Norway with a CVD or a diabetes diagnosis during the years 1994–2009.[17] Information on cause and date of death (1980–2009), sociodemographic status and date of emigration was obtained by linkage to the Norwegian Cause of Death Registry and Statistics Norway.

Study population

A total of 708 614 women (aged 16–49 years) had a first delivery recorded in the MBRN, during the years 1980–2009. Of these, 29 657 (4.2%) had emigrated from Norway during the study period and were not included in the study. We further excluded women with (1) presence of CVD prior to pregnancy ((International Classification of Diseases (ICD), 10th revision: I00–I99 and corresponding codes for ICD-9) (n=6385)), (2) delivery of an offspring with outlying birth weight ((z-scores below −4 or above +4 (n=858)), (3) missing information on birth weight or gestational age of the offspring at delivery (n=38 259), (4) multiple pregnancy (n=9553), (5) delivery before 20 weeks of gestation (n=3), (6) missing information on educational level (n=5249) and (7) erroneously negative follow-up time (n=6). The study sample thus included 618 644 women with a first singleton pregnancy during the years 1980–2009.

Outcome measure

The outcome, CVD, was defined as a hospitalisation with ICD-9 codes 390–459 or ICD-10 codes I00-I99 as primary or secondary diagnosis or as the underlying cause of death.

Exposures

Pre-eclampsia was defined as maternal blood pressure of at least 140 mm of mercury (mm Hg) systolic or 90 mm Hg diastolic after gestational week 20, or an increase of >15 mm Hg in systolic blood pressure measured during pregnancy, in combination with proteinuria (protein in the urine >0.3 g per 24 hours or >+1 on dipstick).[18] The validity of the pre-eclampsia diagnosis in the MBRN is reported to be high.[18] Offspring birth weight was calculated as z-scores, using means and SD of birth weight at each combination of gender and gestational week in the current study sample.[19] Normal offspring birth weight was defined as birth weight z-score −2.0 to 2.0. An LGA offspring was defined as an offspring with birthweight z-score >2.0 (corresponding to the 97th percentile), and a small for gestational age (SGA) offspring was defined as an offspring with birthweight z-score <−2.0 (corresponding to the second percentile). Diabetes was defined as any diabetes in pregnancy (type 1 diabetes, type 2 diabetes, gestational diabetes, unspecified diabetes or use of glucose-lowering medications during pregnancy). Maternal diabetes is reported to the MBRN as type 1 diabetes, type 2 diabetes, or gestational diabetes. Type 1 and type 2 diabetes are in most cases present prior to the pregnancy. Women with gestational diabetes were identified by testing for presence of glucose in the urine at routine antenatal clinical examination. Such testing is as a part of the public antenatal healthcare programme in Norway. For women with glycosuria, the WHO criteria defined gestational diabetes, and for most of our study period the criteria was: fasting blood glucose level ≥7.0 mmol/L and/or a oral glucose tolerance test with 75 g 2-hour level of blood glucose ≥7.8 mmol/L. and <11 mmol/L.[20]

Statistical methods

Descriptive characteristics of the study sample are reported as means with SD and as proportions (%). The follow-up time from the delivery until any CVD diagnosis or end of follow-up (31 December 2009), was calculated as the difference between the woman's age at the date of discharge from hospital with first CVD diagnosis, death, or end of follow-up (31 December 2009) and her age at delivery.

The following exposure variable with mutually exclusive categories was created: (1) no pre-eclampsia, gestational hypertension, LGA or SGA offspring (reference), (2) pre-eclampsia without SGA or LGA offspring, (3) LGA offspring, (4) SGA offspring, (5) pre-eclampsia +LGA offspring and (6) pre-eclampsia +SGA offspring.

We applied Cox proportional hazard regression models to estimate HRs with 95% CIs for the risk of developing CVD for women with pre-eclampsia with or without LGA or SGA offspring (using the categorical variable defined above). The proportional hazard assumption for applying Cox proportional hazard models was examined by inspecting log-(log) survival plots for each exposure variable.

We estimated both crude and adjusted HR's, and the following variables were included as potential confounding factors in the multivariable analyses; highest

achieved educational level at the end of follow-up (basic, secondary or tertiary education), marital status (married/cohabitant or other), year and age at delivery.

For each of the exposure categories above, we calculated the crude incidence of CVD (cases per 1000 person years) with 95% CI. We studied all women, and we also repeated the above analyses among women with and women without diabetes. Finally, we studied the association of birth weight with CVD, by including birthweight z-score as a continuous variable in the Cox regression analyses. We made separate analyses for women with and women without pre-eclampsia. Likelihood ratio tests comparing models with and without penalised splines suggested that the association of birth weight z-score with CVD was not linear (p<0.001). Therefore, we included birth weight z-score as a continuous variable with penalised splines in the analyses. Predicted values of the associations were obtained by multiplying the obtained regression coefficients for the spline-terms with birth weight z-scores, and the results are presented graphically as exponentiated predicted values (partial hazard) according to birthweight z-score. We also tested for possible interaction between birthweight z-score and pre-eclampsia on the risk of CVD by including an interaction term between the continuous birth weight variable and the binary pre-eclampsia variable in a Cox model.

The level of significance was defined as p<0.05 in all analyses (two sided). All statistical analyses were conducted by using STATA V.16 and R.

Patient and public involvement

No patient involved.

RESULTS

Characteristics of the study sample

Among the 618 644 women in our study, 17 298 (2.8%) gave birth to an LGA offspring, while 11 903 (1.9%) gave birth to an SGA offspring (table 1). Compared with women without pre-eclampsia, women with pre-eclampsia gave birth to a higher proportion of LGA offspring (3.8% vs 2.7%). Among women with an LGA offspring, women with pre-eclampsia were more likely to have diabetes than non-pre-eclamptic women (12.1% vs 4.1%).

In total, 21 705 (3.5%) women developed CVD during the follow-up period. Mean age at the end of the follow-up was 40.7 years, and the mean follow-up time was 14.4 years (SD 8.6 years).

Pre-eclampsia, offspring birth weight and subsequent CVD

Women with pre-eclampsia and normal offspring birth weight (not SGA or LGA) had a twofold increased risk of developing CVD (adjusted HR 2.16; 95% CI 2.05 to 2.26), compared with normotensive women with normal offspring birth weight (reference category) (table 2). Women with pre-eclampsia and an LGA offspring had the highest risk of CVD (HR 2.57; 95% CI 2.08 to 3.18), and this risk was higher than for women with pre-eclampsia and an SGA offspring (HR 1.54; 95% CI 1.23 to 1.93) (p=0.001). The CVD risk was also increased in normotensive women who gave birth to an SGA offspring (HR 1.24; 95% CI 1.14 to 1.35). In normotensive women with an LGA infant the HR of CVD was 1.08 (95% CI 0.99 to 1.18).

The absolute risk of CVD, presented as number of CVD cases per 1000 person-years (incidence), was highest

Table 1 Sociodemographic characteristics of 618 644 Norwegian women with a first delivery during 1980–2009

	Pre-eclampsia (n=29 448)			No pre-eclampsia (n=589 196)		
	Normal birth weight (Z-score ≥−2.0 to ≤2.0)	SGA (z-score <−2.0)	LGA (z-score >2.0)	Normal birth weight (z-score ≥−2.0 to≤2.0)	SGA (z-score <−2.0)	LGA (z-score >2.0)
No (%)	27 051 (91.9)	1272 (4.3)	1125 (3.8)	562 392 (95.5)	10 631 (1.8)	16 173 (2.7)
Mother's age at first delivery, mean years (SD)	26.5 (4.9)	26.2 (5.0)	26.6 (4.8)	26.3 (4.8)	26.1 (5.1)	26.4 (4.8)
Educational level						
Basic education, n (%)	7304 (27.0)	444 (34.9)	320 (28.4)	150 613 (26.8)	4188 (39.4)	3944 (24.4)
Secondary education, n (%)	8490 (31.4)	388 (30.5)	353 (31.4)	168 748 (30.0)	3160 (29.7)	5143 (31.8)
Tertiary education, n (%)	11 257 (41.6)	440 (34.6)	452 (40.2)	243 031 (43.2)	3283 (30.9)	7086 (43.8)
Marital status						
Married/cohabitant, n (%)	23 167 (85.6)	1039 (81.7)	969 (86.1)	472 244 (84.0)	8251 (77.6)	13 760 (85.1)
Other, n (%)	3884 (14.4)	233 (18.3)	156 (13.9)	90 148 (16.0)	2380 (22.4)	2413 (14.9)
Any diabetes in pregnancy, n (%)*	644 (2.4)	12 (0.9)	136 (12.1)	4304 (0.8)	48 (0.5)	657 (4.1)
Infant characteristics						
Mean birth weight, grams (SD)	3117.7 (794.8)	2222.5 (387.5)	4516.2 (371.8)	3457.2 (522.8)	2407.8 (334.7)	4528.0 (399.6)
Preterm delivery, n (%)	5765 (21.3)	143 (11.2)	130 (11.6)	31 005 (5.5)	415 (3.9)	1806 (11.2)
Total cardiovascular disease (morbidity and mortality), n (%)	1760 (6.5)	76 (6.0)	85 (7.6)	18 668 (3.3)	572 (5.4)	544 (3.4)

*Diabetes in pregnancy includes type 1 diabetes, type 2 diabetes, unspecified diabetes, gestational diabetes or use of glucose-lowering medications during pregnancy. The table is made by the authors and all permits are obtained.
LGA, large for gestational age (birthweight z-score >2.0); preterm delivery, <37 week of gestation; SGA, small for gestational age (birthweight z-score <−2.0).

Table 2 HRs with 95% CIs for the association between PE in the first pregnancy, offspring birth weight and future risk of cardiovascular disease (CVD) in 618 644 Norwegian women.

	Total no/no with CVD	No with CVD per 1000 person years (95% CI)	Crude HR (95% CI)	Adjusted* HR (95% CI)
Without PE, GH, LGA or SGA	551 593/17 974	2.27 (2.23 to 2.99)	1 (ref.)	1 (ref.)
PE only	27 051/1760	4.87 (4.65 to 5.10)	2.21 (2.11 to 2.32)	2.16 (2.05 to 2.26)
LGA only	15 739/524	2.37 (2.18 to 2.58)	1.09 (1.00 to 1.18)	1.08 (0.99 to 1.18)
SGA only	10 254/530	3.11 (2.85 to 3.38)	1.31 (1.20 to 1.42)	1.24 (1.14 to 1.35)
PE +LGA	1125/85	5.74 (4.64 to 7.10)	2.72 (2.20 to 3.36)	2.57 (2.08 to 3.18)
PE +SGA	1272/76	3.70 (2.96 to 4.64)	1.60 (1.27 to 2.00)	1.54 (1.23 to 1.93)

The table is made by the authors and all permits are obtained.
*Adjustments made for year of delivery, marital status and maternal educational level.
GH, gestational hypertension; LGA, large for gestational age (offspring birthweight z-score >2.0); PE, pre-eclampsia; SGA, small for gestational age (offspring birthweight z-score <−2.0).

among women with pre-eclampsia and an LGA offspring (table 2).

Birth weight used as a continuous variable

The association between z-score and risk of subsequent CVD appeared different among women with and without pre-eclampsia (figure 1A). In women without pre-eclampsia, the association between offspring birth weight and CVD risk was U-shaped, with increased risk both for high and low birthweight z-scores (figure 1B). The likelihood ratio test, comparing a model without and a model with interaction between birthweight z-score and pre-eclampsia, was significant (p<0.001), indicating a significant difference in the association between birthweight z-scores and CVD among women with and women without pre-eclampsia.

Diabetes in pregnancy

A total of 2651 (0.43%) women had diabetes prior to their first pregnancy, while 5801 (0.94%) had any diabetes in the pregnancy. In total, 365 (6.6%) developed CVD. The incidences of CVD indicate higher overall risk among women with diabetes compared with women without diabetes for all combinations of pre-eclampsia, SGA, and LGA (table 3). Among women without pre-eclampsia and normal offspring birth weight, women with diabetes had higher risk of CVD compared with women without diabetes (HR 2.89 (95% CI 2.54 to 3.28) (numbers not

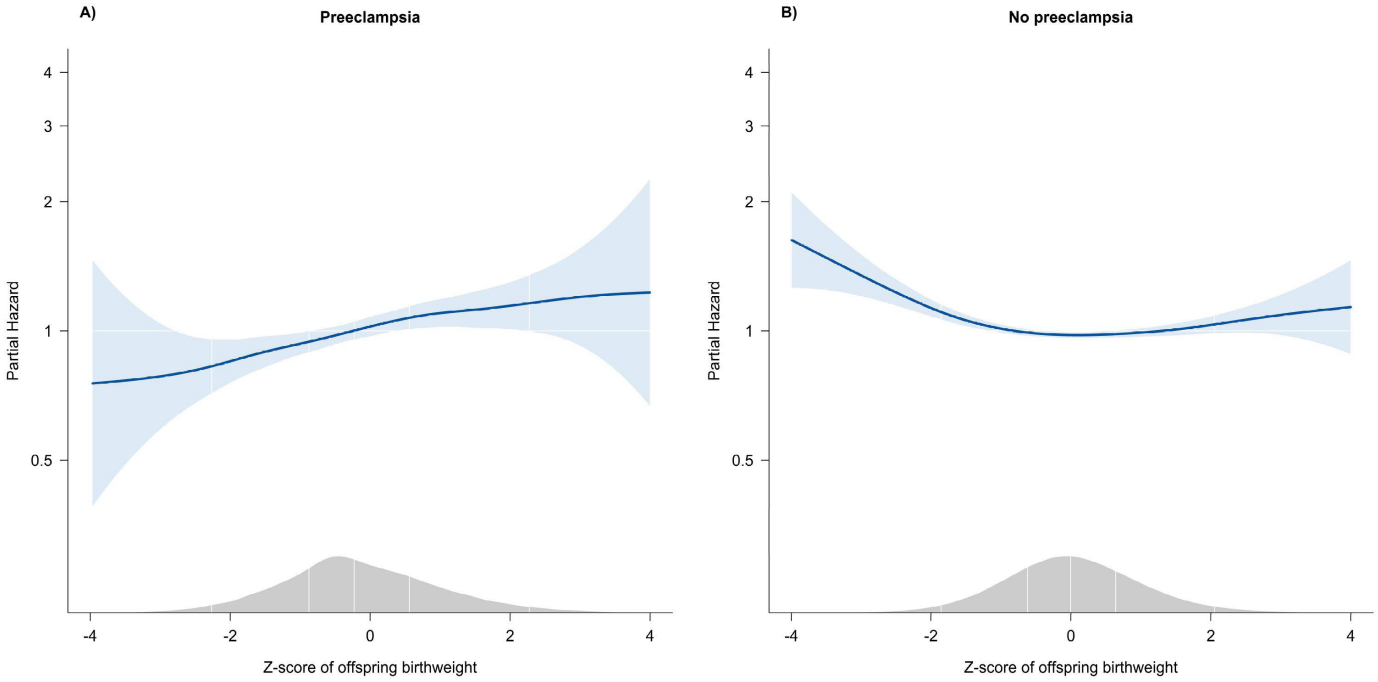

Figure 1 Z-score of offspring birth weight is used as a continuous variable with penalised splines in Cox regression analyses. The figure is made by the authors and all permits are obtained. The risk of CVD (partial Hazards) is presented graphically as exponentiated predicted values versus z-score. All analyses are adjusted for year of delivery, marital status and maternal educational level. Diabetes includes type 1 diabetes, type 2 diabetes, unspecified diabetes, gestational diabetes or use of glucose-lowering medications during pregnancy. CVD, cardiovascular disease.

Table 3 HRs with 95% CIs for the association between PE in the first pregnancy, offspring birth weight and future risk of cardiovascular disease (CVD) in 618 644 Norwegian women

	Total no/no with CVD	No with CVD per 1000 person years (95% CI)	Crude HR (95% CI)	Adjusted* HR (95% CI)
Women without diabetes				
Without PE, GH, LGA, SGA	547 477/17 737	2.25 (2.21 to 2.28)	1 (ref.)	1 (ref.)
PE only	26 407/1675	4.71 (4.49 to 4.95)	2.16 (2.05 to 2.27)	2.11 (2.00 to 2.21)
LGA only	15102/499	2.32 (2.13 to 2.54)	1.07 (0.98 to 1.17)	1.07 (0.98 to 1.17)
SGA only	10 209/523	3.08 (2.83 to 3.35)	1.31 (1.20 to 1.42)	1.24 (1.13 to 1.35)
PE+LGA	989/76	5.64 (4.50 to 7.06)	2.66 (2.12 to 3.33)	2.53 (2.02 to 3.17)
PE+SGA	1260/74	3.64 (2.89 to 4.57)	1.58 (1.26 to 2.00)	1.52 (1.21 to 1.92)
Women with diabetes				
Without PE, GH, LGA, SGA	4116/237	6.07 (5.35 to 6.90)	1 (ref.)	1 (ref.)
PE only	644/85	14.02 (11.33 to 17.34)	2.44 (1.91 to 3.13)	2.45 (1.91 to 3.14)
LGA only	637/25	4.04 (2.73 to 5.98)	0.72 (0.48 to 1.09)	0.73 (0.48 to 1.10)
SGA only	45/7	10.95 (5.22 to 22.98)	1.38 (0.65 to 2.92)	1.40 (0.66 to 2.96)
PE+LGA	136/9	6.75 (3.51 to 12.97)	1.29 (0.66 to 2.50)	1.30 (0.67 to 2.53)
PE+SGA	12/2	12.10 (3.03 to 48.38)	1.90 (0.47 to 7.64)	1.74 (0.43 to 7.02)

Diabetes includes type 1 diabetes, type 2 diabetes, unspecified diabetes, gestational diabetes or use of glucose-lowering medications during pregnancy.
Other combinations, that is, GH+LGA or SGA, not shown (n=11 610).
The table is made by the authors and all permits are obtained.
Separate analyses are made for women with and without diabetes in pregnancy.
*Adjustment made for year of delivery, marital status and maternal educational level.
GH, gestational hypertension; LGA, large for gestational age (offspring birthweight z-score >2.0); PE, pre-eclampsia; SGA, small for gestational age (offspring birthweight z-score <−2.0).

shown in table). We found no association of LGA or SGA with CVD risk in women with diabetes, independent of their pre-eclampsia status (table 3). The increased risk of CVD in women with pre-eclampsia and an LGA offspring was confined to women without diabetes. When testing for interaction between the six-category exposure variable and diabetes to investigate possible effect modification by diabetes the overall likelihood ratio test for the interaction term was not significant (p=0.08).

DISCUSSION

In this large nationwide follow-up study of more than 600 000 women, we found that women with pre-eclampsia and high offspring birth weight in her first pregnancy had higher risk of subsequent CVD than pre-eclamptic women with a normal birth weight or SGA offspring. Also women with diabetes had increased CVD risk, but they had no additional risk associated with an LGA or SGA offspring.

Comparison with previous studies

The association between pre-eclampsia and subsequent CVD in the mother is well known.[4 5 21 22] We are not aware of any previous studies comparing the association of high and low birth weight with CVD in women with pre-eclampsia. A few studies have reported high CVD risk in mothers with high offspring birth weight independent of their pre-eclampsia status. A study in Denmark of 782 287 women, found that women who delivered an offspring with high birth weight (≥2 SD above the median), had increased risk of future hypertension.[10] The study also found positive associations of high offspring birth weight with later ischaemic heart disease, stroke and thrombosis, but the effects were weak. Also, a study of 37 718 women in Jerusalem reported that giving birth to an offspring with high birth weight (>4000 g) increased the risk of death from CVD.[11] A Norwegian study reported that particularly women who gave birth preterm to a large offspring (birthweight z-score >2.5), were at increased risk of CVD death.[9] On the contrary, a Swedish study of more than 900 000 women[7] and a Norwegian study of almost 100 000 women [23] found no association between high offspring birth weight and CVD. Inconsistencies in findings across studies may be related to different definitions of high birth weight.[9]

Increased risk of CVD in women with an SGA offspring has previously been reported in women with[4 24] and in women without pre-eclampsia.[6–8] In our study, however, we found that pre-eclamptic women, with an SGA offspring had a lower CVD risk than for women with offspring with birthweight appropriate for gestational age.

Interpretation of findings

We found increased risk of developing CVD in women with pre-eclampsia during pregnancy, and the risk was

particularly increased if the offspring was LGA. The association of pre-eclampsia and LGA offspring with CVD was present in women without diabetes only. The association between high offspring birth weight and CVD is not easy to explain, but adverse maternal metabolic factors, such as obesity and high levels of fatty lipids, may be underlying causes. Adverse metabolic factors increase the risk of pre-eclampsia, high offspring birth weight and CVD.[25 26] Adverse metabolic factors are often seen in women with high body mass index (BMI), and high BMI increases the risk of both pre-eclampsia and an LGA offspring.[27–29] Unfortunately, we had no information about BMI or other metabolic factors in the current study.

As in previous studies,[4 24 30] we found that pre-eclamptic women with an SGA offspring had increased risk of CVD compared with normotensive women with a normal weight offspring. Their risk, however, was lower than in pre-eclamptic women with a normal weight or LGA offspring. Pre-eclampsia, and particularly pre-eclampsia with an SGA offspring, is closely linked to fetoplacental hypoxia and an imbalance in maternal angiogenic factors.[31 32] Also in pregnancies without pre-eclampsia, but an SGA offspring, imbalance in maternal angiogenic factors is present.[32] In pregnancy, development of new vessels (angiogenesis), is necessary for placental development and for the provision of oxygen to the feto-placental unit. Thus, the imbalance in angiogenic factors in pre-eclampsia with or without an SGA offspring may be a sign of impaired angiogenesis.

Our findings could therefore suggest at least two different pathways to CVD. One pathway may be linked to high BMI and adverse metabolic factors, such as diabetes and the other pathway may be linked to suboptimal ability to develop new vessels. A normal pregnancy requires a well-functioning cardiovascular system. The development of pre-eclampsia and abnormal offspring birth weight may therefore be a 'stress-test' for the cardiovascular function system, and also indicate underlying pathways for the development of CVD.[33]

In women with diabetes in pregnancy, we found no association between offspring birth weight and CVD. However, women with diabetes had higher absolute risk of pre-eclampsia and CVD. Diabetes in pregnancy is most often gestational diabetes or diabetes type 2, and these conditions are closely linked to high BMI and adverse metabolic factors.[34 35] Thus, the increased CVD risk in women with diabetes may have similar causal pathways to CVD as non-diabetic women with an LGA offspring. The lack of association between birth weight and CVD in diabetic women may be due lack of statistical power to detect true differences between groups. Our findings are however in line with other studies. Known risk factors do not seem to explain the mechanisms of CVD among individuals with diabetes.[36]

Clinical implications

Since pregnancy outcomes seem to be indicators of future CVD risk, pregnancy and the postpartum period may represent an opportunity for CVD prevention. Our study suggests that particularly women with concomitant pre-eclampsia and an LGA offspring may benefit from CVD preventive interventions. Also women with diabetes in pregnancy may benefit from CVD preventive interventions. However, trials should be performed to estimate the effects of CVD prevention after pregnancy.

Strengths and limitations

Strengths of the current study include inclusion of a large nationwide cohort of 618 644 women with detailed follow-up information of both non-fatal and fatal CVD over a period of up to 29 years. A unique person identification number allowed linkage of data from several national data sources with compulsory reporting, thus enabling follow-up of almost all women who had given birth in Norway.

Some limitations need to be addressed. First, in our study we had no information about smoking, or BMI, since such information was not included in the nationwide health registries in our study period. We can therefore not exclude the possibility that these factors may play a role in the association between pre-eclampsia, offspring birth weight and CVD. Second, few women in our study had diabetes in pregnancy. Diabetes may have been underdiagnosed or under-reported to the MBRN. However, it is likely that the women diagnosed, actually had diabetes.[37] Subclassification of type of diabetes (type 1, type 2, gestational diabetes or unspecified diabetes) was available from 1999 and onwards in the MBRN, and lacking for the majority of our study participants. Due to limited statistical power, the risk estimates among women with diabetes must be interpreted with caution, and we cannot rule out that the risk differs by type of diabetes. Third, the CVD endpoints in our study were based on discharge diagnoses from hospitals in Norway or death certificates (either with a primary or secondary CVD diagnosis). This definition does not include women with CVD diagnosed in primary healthcare only, or not diagnosed at all. Thus, we may have failed to identify some of the less severe cases of CVD and this may have caused an underestimate of the true incidence of CVD after pregnancy. Fourth, women who had pre-eclampsia in pregnancy may have been followed-up at the hospital after pregnancy more often than women without pre-eclampsia, and thereby more likely to be diagnosed with CVD. If that is true, our findings may be biased by differential misclassification. However, in most of our study period, the association of pre-eclampsia with CVD was not well known, and no guidelines for clinical follow-up after pre-eclampsia excised. It is also unlikely, that a possible misclassification of CVD according to pre-eclampsia status would be differential according to offspring size. Thus, we do not believe that misclassification of the outcome has caused any substantial bias. Lastly, the diagnostic criteria for pre-eclampsia and for gestational diabetes in pregnancy have changed in Norway after our study period. Also, the guidelines for follow-up in and after pregnancy have

changed. Differences in diagnostic criteria and follow-up may influence the likelihood of being diagnosed, and possibly also the estimates for the associations between exposure and outcome in observational studies.

CONCLUSION

Women with pre-eclampsia and high offspring birth weight in her first pregnancy had higher risk of subsequent CVD than pre-eclamptic women with a normal weight or SGA offspring. Also, women with diabetes had increased CVD risk, but they had no additional risk associated with an LGA or SGA offspring. It is possible that underlying metabolic factors cause pre-eclampsia, LGA offspring and also the development of CVD.

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Contributors HKRR researched data and wrote the manuscript. JI acquired and facilitated data, researched data and reviewed/edited the manuscript. GS reviewed/edited the manuscript. MMI reviewed/edited the manuscript. MG reviewed/edited the manuscript. AE had the research idea and reviewed/edited the manuscript. GST acquired and facilitated data and reviewed/edited the manuscript. AKD reviewed/edited the manuscript and applied for funding to merge the data. HKRR is the guarantor of this work and takes the responsibility for the accuracy of the data analyses.

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Competing interests This study used data from the Medical Birth Registry of Norway and the Norwegian Cause of Death Registry. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Medical Birth Registry of Norway or the Norwegian Cause of Death Registry is intended, nor should be inferred.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Regional Committee for Medical and Health Research Ethics approved the study (Reference number 2014/1047).

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REFERENCES

1 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.
2 Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011;25:391–403.
3 Khan KS, Wojdyla D, Say L, *et al*. Who analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–74.
4 Riise HKR, Sulo G, Tell GS, *et al*. Incident coronary heart disease after preeclampsia: role of reduced fetal growth, preterm delivery, and parity. *J Am Heart Assoc* 2017;6. doi:10.1161/JAHA.116.004158. [Epub ahead of print: 06 Mar 2017].
5 Pittara T, Vyrides A, Lamnisos D, *et al*. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. *BJOG* 2021;128:1421–30.
6 Davey Smith G, Hyppönen E, Power C, *et al*. Offspring birth weight and parental mortality: prospective observational study and meta-analysis. *Am J Epidemiol* 2007;166:160–9.
7 Bonamy A-KE, Parikh NI, Cnattingius S, *et al*. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation* 2011;124:2839–46.
8 Bukowski R, Davis KE, Wilson PWF. Delivery of a small for gestational age infant and greater maternal risk of ischemic heart disease. *PLoS One* 2012;7:e33047.
9 Morken N-H, Halland F, DeRoo LA, *et al*. Offspring birthweight by gestational age and parental cardiovascular mortality: a population-based cohort study. *BJOG* 2018;125:336–41.
10 Lykke JA, Paidas MJ, Triche EW, *et al*. Fetal growth and later maternal death, cardiovascular disease and diabetes. *Acta Obstet Gynecol Scand* 2012;91:503–10.
11 Friedlander Y, Paltiel O, Manor O, *et al*. Birthweight of offspring and mortality of parents: the Jerusalem perinatal study cohort. *Ann Epidemiol* 2007;17:914–22.
12 Davey Smith G, Hart C, Ferrell C, *et al*. Birth weight of offspring and mortality in the renfrew and paisley study: prospective observational study. *BMJ* 1997;315:1189–93.
13 Smith GD, Whitley E, Gissler M, *et al*. Birth dimensions of offspring, premature birth, and the mortality of mothers. *Lancet* 2000;356:2066–7.
14 Dypvik J, Strøm-Roum EM, Haavaldsen C, *et al*. Preeclampsia in pregnancies with and without diabetes: the associations with placental weight. A population study of 655 842 pregnancies. *Acta Obstet Gynecol Scand* 2016;95:217–24.
15 Matheus ASdeM, Tannus LRM, Cobas RA, *et al*. Impact of diabetes on cardiovascular disease: an update. *Int J Hypertens* 2013;2013:653789.
16 Irgens LM. The medical birth registry of Norway. epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;79:435–9.
17 Sulo G, Igland J, Vollset SE. Cardiovascular disease and diabetes mellitus in Norway during 1994-2009 CVDNOR. *Norsk Epidemiologi*2013;23 https://www.ntnu.no/ojs/index.php/norepid/article/view/1609
18 Thomsen LCV, Klungsøyr K, Roten LT, *et al*. Validity of the diagnosis of pre-eclampsia in the medical birth registry of Norway. *Acta Obstet Gynecol Scand* 2013;92:943–50.
19 Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440–9.
20 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a who consultation. *Diabet Med* 1998;15:539–53.
21 Riise HKR, Sulo G, Tell GS, *et al*. Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors. *Int J Cardiol* 2019;282:81–7.
22 Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort. *Circulation* 2015;132:1234–42.
23 Egeland GM, Skurtveit S, Staff AC, *et al*. 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. *J Am Heart Assoc* 2018;7. doi:10.1161/JAHA.117.008318. [Epub ahead of print: 13 05 2018].
24 Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;357:2002–6.
25 Gaudet L, Ferraro ZM, Wen SW, *et al*. Maternal obesity and occurrence of fetal macrosomia: a systematic review and meta-analysis. *Biomed Res Int* 2014;2014:1–22.
26 Misra VK, Trudeau S, Perni U. Maternal serum lipids during pregnancy and infant birth weight: the influence of prepregnancy BMI. *Obesity* 2011;19:1476–81.
27 Berntorp K, Anderberg E, Claesson R, *et al*. The relative importance of maternal body mass index and glucose levels for prediction of large-for-gestational-age births. *BMC Pregnancy Childbirth* 2015;15:280.
28 Yu Z, Han S, Zhu J, *et al*. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS One* 2013;8:e61627.
29 O'Brien TE, Ray JG, Chan W-S. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology* 2003;14:368–74.
30 Lykke JA, Langhoff-Roos J, Sibai BM, *et al*. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53:944–51.
31 Vatten LJ, Åsvold BO, Eskild A. Angiogenic factors in maternal circulation and preeclampsia with or without fetal growth restriction. *Acta Obstet Gynecol Scand* 2012;91:1388–94.
32 Åsvold BO, Vatten LJ, Romundstad PR, *et al*. Angiogenic factors in maternal circulation and the risk of severe fetal growth restriction. *Am J Epidemiol* 2011;173:630–9.
33 Eskild A, Strøm-Roum EM, Haavaldsen C. Does the biological response to fetal hypoxia involve angiogenesis, placental enlargement and preeclampsia? *Paediatr Perinat Epidemiol* 2016;30:305–9.
34 Scott-Pillai R, Spence D, Cardwell CR, *et al*. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. *BJOG* 2013;120:932–9.
35 Chu SY, Callaghan WM, Kim SY, *et al*. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care* 2007;30:2070–6.
36 Norhammar A. Diabetes and cardiovascular mortality: the impact of sex. *Lancet Diabetes Endocrinol* 2018;6:517–9.
37 Stene LC, Eidem I, Vangen S. The validity of the diabetes mellitus diagnosis in the medical birth registry of Norway. *Norsk Epidemiologi* 2007;17:9.