Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors

Running headline: Heart disease after pregnancy

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Abstract

Background and aim: Hypertensive pregnancy disorders are associated with subsequent cardiovascular disease (CVD), but the extent to which this association is explained by shared risk factors is unknown. We aimed to evaluate whether hypertensive pregnancy disorder in first pregnancy is associated with increased subsequent risk of maternal CVD after adjustment for established CVD risk factors measured after pregnancy.

Methods and results: A total of 20,075 women with a first delivery registered in the Medical Birth Registry of Norway (1980-2003) participated in Cohort of Norway (CONOR) health surveys a mean (SD) of 10.7 (5.5) years after delivery. They were then followed (median 11.4 years) for an incident fatal or non-fatal CVD event through linkage to the Cardiovascular Disease in Norway (CVDNOR) database and the Norwegian Cause of Death Registry. Hypertensive pregnancy disorders were associated with an increased risk of CVD [Hazard ratio (HR) 2.3; 95% confidence interval (CI) 1.9-2.8], which remained significant after adjustment for established CVD risk factors including body mass index, smoking, hypertension, diabetes, serum glucose and lipid levels (HR 1.5; 95% CI 1.2-1.8). The population attributable fraction of CVD due to hypertensive pregnancy disorder was 4.3% (95% CI 1.9-6.6) after multivariable adjustment.

Conclusion: The association between hypertensive pregnancy disorders and CVD risk was mediated in part by related CVD risk factors measured 10 years following delivery. These results underline the importance of post-pregnancy follow-up of women with hypertensive pregnancy disorders focusing on modifiable, lifestyle related risk factors to prevent future CVD.

Key words: Hypertensive pregnancy disorder; Cardiovascular disease; pregnancy; women`s cardiovascular Health; cohort study; cardiovascular risk factors

Introduction

Hypertensive disorders (preeclampsia and gestational hypertension) affect 5-10% of pregnancies worldwide [1] and contribute significantly to the global burden of maternal and perinatal morbidity and mortality [2]. Studies have found that hypertensive pregnancy disorders associate with increased risk of short- and long-term maternal cardiovascular disease (CVD) [3-8]. We have recently found an increased risk for CVD associated with preeclampsia [9] and gestational hypertension [10], with the risk tending to be higher when the hypertensive pregnancy disorder occurred simultaneously with a small for gestational age (SGA) infant and/or preterm delivery. Whether pregnancy complications unmask an already existing CVD risk or whether the hypertensive pregnancy disorder is causally related to maternal risk of CVD remains uncertain. The first hypothesis is supported by the fact that established risk factors such age, smoking, elevated body mass index (BMI), low density lipoprotein (LDL) cholesterol, diabetes mellitus and a family history of coronary heart disease (CHD) are shared between hypertensive pregnancy disorders and CVD [11, 12], and that endothelial dysfunction is central to the development of both disorders [13, 14]. Alternatively, the proatherogenic stress of pregnancy could contribute to an arterial wall inflammation that is not resolved after delivery [15], and may lead to further increased risk of CVD. The two hypotheses are not mutually exclusive.

Although the overall CVD mortality rates have declined over the past decades in western countries [16], in the United States, mortality from coronary heart disease has plateaued among young women <55 years since the year 2000 [17] and in Norway, the overall falling incidence and recurrences of acute myocardial infarction over the past decades do not encompass younger women [18, 19].

In general, 80% of CVD development may be explained by established risk factors [20-22]. Existing knowledge of risk factors for future CVD is, however, limited in young women [23, 24]. While an association between hypertensive pregnancy disorders and later CVD has been repeatedly reported, the possible impact of established risk factors on this association is not known. An attenuation of risk estimates is observed when adjusting for established CVD risk factors, but hypertensive pregnancy disorders seem to remain persistent and significant predictors of later CVD [5, 6, 25-27]. The existing studies are limited by missing or inadequate data risk factors (e.g. lipids, blood pressure, height and weight) [5, 25-27], parity [6], gestational hypertension [6, 26] and by survival bias [6]. Furthermore, Cain et al. (2016) found higher risk of CVD after preeclampsia, but not after gestational hypertension, when accounting for established risk factors [5].

This study aimed to explore the extent to which established CVD risk factors explain the association between hypertensive pregnancy disorders in first pregnancy and subsequent risk of maternal CVD.

Methods

Data material

By use of the national identification number unique to each Norwegian resident, we linked data from the Medical Birth Registry of Norway (MBRN) to Cohort of Norway (CONOR) health surveys, the Cardiovascular Disease in Norway 1994–2009 (CVDNOR) database and the Norwegian Cause of Death Registry (1980-2009).

MBRN is a national registry established in 1967 based on compulsory notification of live and still births. The registry contains information on all pregnancies beyond 16 weeks of gestation, including maternal characteristics and medical history, as well as pregnancy complications [28].

CONOR is a collaboration between regional health surveys in Norway and consists of questionnaire data, physical measurements and biological samples gathered through attendance in short health examinations carried out in several Norwegian counties from 1994 through 2003 [29]. Questions included education, presence of specific diseases and general health status, use of blood pressure medications, physical activity, smoking, alcohol consumption, and family history of myocardial infarction (MI) prior to age 60. Blood pressure, height, weight, as well as waist and hip circumferences were measured. A non-fasting blood sample was collected for serum lipid and glucose analyses. The overall participation rate was 58%.

The CVDNOR database (https://cvdnor.w.uib.no) was established as a collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health services (now included in the Norwegian Institute of Public Health) [30, 31]. Information on all hospital stays with a cardiovascular or diabetes-related diagnoses was retrieved from the electronic patient administrative systems of Norwegian hospitals from 1994 through 2009. Information included patient`s age, sex, date of admission and discharge, main and secondary discharge diagnoses and information on diagnostic and/or treatment procedures performed during a given hospital stay.

The Norwegian Cause of Death Registry covers all deaths in Norway, including Norwegians who die abroad [32]. The official cause of death statistics are based on death certificates filled out by doctors and are prepared in accordance with the International Classification of Diseases (ICD). Norway implemented the 10th revision of ICD in 1996.

Further linkages to Statistics Norway and the National Registry provided us with information on educational level and date of emigration.

Ethical considerations

The study was approved by The Regional Committee for Medical and Health Research Ethics (2014/1047). All CONOR participants signed a written informed consent for research and linkage of health registries.

Study population

A total of 23,369 women (age 16-49 with parity ≤5) registered with a first delivery in the MBRN (1980 through 2003) subsequently participated in one or more regional CONOR surveys between 1994 and 2003. For women who had participated in more than one health survey after the first pregnancy (n=510), information from the last survey was used. Date of CONOR participation served as baseline for the follow-up evaluation of CVD events and we excluded women who were pregnant at that time (n=825). Women with a recorded diagnosis of CVD (ICD-9 codes 390-459; ICD–10 codes I00-I99, except 455/I84 (hemorrhoids)) in the MBRN/CVDNOR before baseline (CONOR) were excluded (n=469). Using information from the first pregnancy in the MBRN, we further excluded women with a delivery before 20 weeks of gestation and women with infants born with a weight-for-gestational age and sex zscore more extreme than -4/+4 (n=63); those with multiple-birth pregnancies (n=277); and missing information on SGA and/or preterm delivery (defined below) (n=1,415). In addition, we excluded women with missing CONOR information on age, blood pressure, total serum cholesterol (total- C), high-density lipoproteins cholesterol (HDL-C), triglycerides, daily smoking, BMI or a family history of MI (n=207). Lastly, women with missing information on education were excluded (n=38). The final cohort included 20,075 women (Figure 1).

Exposures

The main exposures for the current study was gestational hypertension or preeclampsia in the first pregnancy. Gestational hypertension was defined as hypertension identified after 20 weeks of gestation (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or an increase >15 mm Hg from blood pressure measured before gestational week 20). According to the definition in the MBRN, the preeclampsia diagnosis required the additional presence of proteinuria (≥0.3 g in 24 hour urine or ≥1 point increase on dip-stick), and also included eclampsia and the HELLP syndrome. SGA offspring was defined as fetal growth below the 10^{th} percentile based on Norwegian sex-specific birthweight curves [33] and preterm delivery was defined as delivery before 37 weeks of gestation.

Endpoints

The primary endpoint was the first episode of CVD (ICD-9 codes 390-459; ICD-10 codes I00-I99; either non-fatal or fatal (except 455 and I84)) identified through CVDNOR or the Cause of Death Registry. The most frequent CVD diagnosis was hypertensive disease (ICD-9 401-405; ICD-10 I10-I15) (Supplementary table 1), accounting for one third of the cases. Secondary endpoints included coronary heart disease (CHD) (ICD-9 410-414; ICD-10 I20-25), and the combined endpoint of acute myocardial infarction (AMI) or acute cerebral stroke.

The endpoint AMI or acute cerebral stroke was defined as the first occurrence of hospitalization with AMI (ICD-9 410; ICD-10 I21-22) or death from CHD (ICD-9 410-414; ICD-10 I20-25), and hospitalization or death with acute cerebral stroke (ICD-9 43; ICD-10 I60-61, I63-64 (except I63.6)).

Statistical analyses

All potential CVD risk factors available were evaluated for statistical associations with the exposure (hypertensive disorders of pregnancy) and the outcomes (CVD). From the MBRN we used mother's age at first delivery. From CONOR we first evaluated the following parameters separately: age at baseline (CONOR), blood pressure reading in the hypertensive range [hereafter referred to as hypertension [defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive drugs (yes or no)], diabetes mellitus (yes (type 1, type 2, unspecified) or no), daily smoking (yes or no), family history of MI before the age of 60 (yes or no), low HDL-C (yes (≤1.3 mmol/L) or no)), total-C (mmol/L), triglycerides (mmol/L), glucose (mmol/L) alcohol consumption (never/seldom, monthly, weekly), vigorous physical activity (hours per week: none, less than 1, 1-2, 3 or more) and BMI (kg/m^2) (model 1). Information on serum glucose, alcohol consumption and physical vigorous activity was missing for 13.1%, 4.7% and 8.7% of the women, respectively, and were therefore not included in the main analyses. Secondly, risk associations were explored using Cox proportional hazard regression and results were reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The proportional hazards assumption was checked by inspecting log-(log) survival plots for all relevant variables. Follow-up time was calculated as time from participation in CONOR until hospital admission, death, emigration or December 31, 2009 (whichever occurred first).

Hypertensive pregnancy disorders were stratified into gestational hypertension and preeclampsia and term and preterm deliveries to study potential subgroup differences. We also tested for significant interactions between hypertensive pregnancy disorders and each of the CVD risk factors. No interactions were significant and therefore not included in further analyses.

In additional analyses, we excluded women who had their first delivery within six months before CONOR and women who had a subsequent delivery within six months before or nine months after CONOR since these women may have risk factor alterations due to pregnancy itself. Further, we also included all established CVD risk factors in the fully adjusted model independent of missing values to study potential changes in estimates; women with missing values on one or more covariates were excluded from these analyses (complete case analysis).

The level of significance was defined as P <0.05 in all analyses. Stata 15 and ***R*** were used in the analyses.

Risk prediction

We investigated the potential value of including hypertensive pregnancy disorders in CVD risk prediction by comparing two models. Model 1 included age at baseline, age at first delivery, hypertension, diabetes mellitus, daily smoking, family history of MI before the age of 60, low HDL-C, total-C, triglycerides and BMI. Model 2 additionally included hypertensive pregnancy disorder. All continuous variables were mean centered to get a reasonable baseline level for estimation of baseline survival. The predicted 10-year risk was calculated for both model 1 and model 2 as

$$1 - \hat{S}(10)^{\exp(Z*\beta)}$$

where $\hat{S}(10)$ is the predicted baseline survival at 10 years of follow-up, Z is the vector of covariates and β is the vector of regression coefficients.

The models` ability to distinguish between those who do and do not develop the disease of interest (discrimination) was evaluated with Harrell's C-statistics [34] obtained using the STATA package somersd. Akaike information criterion (AIC) and Bayes information criterion (BIC) were reported as measures of improvement of model fit. Studies have shown that the C-statistic is insensitive in evaluating risk prediction models [35]. Thus, we calculated net reclassification improvement (NRI) and integrated discrimination improvement (IDI) using the "survIDINRI" package in ***R*** [36-38]. Only women with the possibility of at least 10 years follow-up for CVD were included in the risk prediction analyzes (n=12,389, events=688).

Attributable risk

The attributable fraction can be interpreted as the burden of CVD attributable to hypertensive pregnancy disorders. The attributable fraction was calculated by the STATA package *punafcc* and presented as percentages [39, 40].

Results

Characteristics of the study population

Baseline demographic characteristics stratified by hypertensive pregnancy disorder are presented in Table 1. The mean (SD) for the time between first delivery and participating in CONOR was 10.7 (5.5) years. Mean (SD) age of women at first delivery was 26.0 (4.6) years. A total of 1246 (6.2%) women were diagnosed with a hypertensive pregnancy disorder in their first pregnancy. Women with a hypertensive pregnancy disorder had a greater prevalence of preterm (P <0.001), SGA (P <0.001) and stillbirth deliveries (P =0.001) compared to women without a hypertensive pregnancy disorder. In the subsequent CONOR health survey, women with a hypertensive pregnancy disorder had higher prevalence of diabetes mellitus and systolic and diastolic blood pressure, BMI, total-C and triglycerides, but lower HDL-C, as well as less smoking and alcohol consumption compared to women with no hypertensive pregnancy disorder (all P <0.001).

Figure 2 presents age-adjusted HR`s for CVD events for each CVD risk factor examined. Vigorous physical activity reported at CONOR baseline was associated with a decreased risk of CVD (HR 0.8; 95% CI 0.7-0.9). All other factors analyzed predicted an increased risk of CVD; e.g. women with hypertension and women with BMI ≥30 had HR`s of 3.5 (95% CI 3.1-4.0) and 3.2 (2.7-3.7), respectively, for the risk of CVD.

The importance of CVD risk factors in the association between hypertensive pregnancy disorder and later CVD

Associations of hypertensive pregnancy disorder with subsequent maternal CVD are presented in Table 2. The median duration of follow-up from CONOR participation was 11.4 years (Q1-Q3: 8.7-13.6). In the unadjusted analyses, hypertensive pregnancy disorder in first pregnancy increased the risk of subsequent maternal CVD 2.3 times (95% CI 1.9-2.8). After adjustment for non-modifiable and modifiable risk factors, the HR was partially attenuated but remained an independent risk factor for maternal CVD (HR 1.5; 95% CI 1.2-1.8). Corresponding HR for the combined endpoint AMI/acute cerebral stroke was 1.8 (95 % CI 1.1-2.9) and for CHD it was 1.5 (95% CI 0.9-2.6). These associations were evident for both preeclampsia and gestational hypertension (Table 2). In analyses also adjusting for non-fasting serum glucose, vigorous physical activity and alcohol consumption, comparable results were found (data not shown).

Women with hypertensive pregnancy disorder combined with preterm delivery had increased risk of CVD relative to women without hypertensive pregnancy disorder and term delivery; HR 1.9 (95% CI 1.3-2.9) for hypertensive pregnancy disorder, HR 3.6 (95% CI 1.7-7.6) for gestational hypertension and HR 1.6 (95% CI 1.0-2.7) for preeclampsia (Table 3).

In additional analyses where we excluded women with deliveries around CONOR participation (six months before - nine months after) no notable changes in risk estimates were found (data not shown).

The value of including hypertensive pregnancy disorders in risk prediction

Based on established CVD risk factors registered at baseline (CONOR) (model 1), women with a history of hypertensive pregnancy disorder had a significantly higher predicted 10-year mean absolute risk of CVD compared to women with no hypertensive pregnancy disorder (0.06% vs 0.04%, P < 0.001). The 10-year risk of CVD for women with a history of hypertensive pregnancy disorder was further increased when hypertensive pregnancy disorder was included in the 10-year risk prediction model (model 2); 0.09% vs. 0.04%, P <0.001 (data not shown).

Table 4 shows that the predictive value of the survival model increased from 0.69 to 0.70 when hypertensive pregnancy disorders was included. Both AIC and BIC decreased in model 2, indicating an improvement of model fit. NRI and IDI showed no significant improvement in the risk prediction model by including hypertensive pregnancy disorder in the model.

Population attributable risk

A total of 7.3% (95% CI 5.1-9.5) of the risk of CVD could be attributed to hypertensive pregnancy disorder that occurred an average of 21.9 years earlier. After adjustment for CVD risk factors, measured an average of 10.7 years after delivery, the attributable fraction decreased to 4.3 (95% CI 1.9-6.6) (data not shown).

Discussion

After accounting for a number of established modifiable and non-modifiable CVD risk factors assessed on average 10 years after pregnancy, a 50% increased risk of maternal CVD after hypertensive pregnancy disorder in the woman`s first pregnancy persisted. This suggests that the association between the disorders is a result of both shared CVD risk factors and pregnancy specific components.

Hypertensive pregnancy disorder and risk of CVD

This study identified a strong and persistent risk of CVD after hypertensive pregnancy disorders when accounting for established CVD risk factors. Similar associations were found for CHD and the combined endpoint AMI/stroke.

Only one other large cohort study [6] with access to data on blood measures (i.e. lipids) and physical examinations (i.e. blood pressure, height and weight (BMI)) have identified an impact of hypertensive pregnancy disorders on the risk of future hypertension and CVD after adjustment for such parameters, but with somewhat smaller risk estimates. Ray et al. 2005 found an increased risk of CVD subsequent to experiencing maternal placental syndrome after controlling for CVD risk factors measured after the index delivery [25]. Cain et al. 2016 found similar overall results, but the risk of CVD following gestational hypertension did not remain significant when accounting for risk factors [5]. This is in contrast to our study where an increased risk of future CVD was found for both preeclampsia and gestational hypertension after adjustment. Timpka et al. 2017 and Egeland et al. 2018 reported a higher risk of chronic hypertension after hypertensive pregnancy after accounting for several CVD risk factors [26, 27]. In the latter study, the association remained in a sensitivity analysis restricted to women with a normal pre-pregnancy BMI (kg/m^2) [27].

This study contributes important knowledge by showing an independent association between hypertensive pregnancy disorders and subsequent CVD, after taking into account the effects of several established CVD risk factors. Vascular damage associated with hypertensive pregnancy disorders is suggested as a mechanism for increasing women's susceptibility to CVD later in life [41]. A link between pregnancy-related complications and CVD risk is biologically plausible and supported by the profound effects of pregnancy on the maternal cardio-metabolic system [42]. Our uncovering of a dependent and independent risk factor component in the association between hypertensive pregnancy disorder and later CVD, is suggestive that the underlying aetiology probably is a combination of both shared predispositions (familial/genetic and lifestyle) and a direct causal connection between the consequences of hypertensive pregnancy disorders and CVD [14, 43, 44].

The value of including hypertensive pregnancy disorders in risk prediction

The negligible improvement of the 10-year risk prediction model after including hypertensive pregnancy disorder as a variable may be partly explained by the relatively short follow-up time in this study and the women`s young age. Women in the age group included here have a low absolute risk of CVD and few women met the 5 or 10% criteria that are recommended for intervention for prevention of CVD. Lower thresholds for interventions in young women and men are recommended since CVD risk factors over many years may cause irreversible vascular damage [45]. A downside with the established risk prediction models is that new variables need to be strongly related to the outcome in order to show statistically significant improvement [46, 47]. NRI and IDI are widely used methods based on risk stratification, but the translation into clinical practice is questioned [48], and we found no improvement when incorporating hypertensive pregnancy disorder in the 10-year risk prediction model. Our findings substantiate larger studies with longer follow-up to determine whether hypertensive pregnancy disorders could be a valuable addition to maternal CVD prediction scores. Monitoring of women with hypertensive pregnancy disorders is needed as they are at higher risk for future CVD. These women should be considered for lifestyle rehabilitation aiming at reducing smoking and overweight and improving diet and physical activity, and, when indicated, targeted for pharmacological treatment of important mediators, such as hypertension and diabetes mellitus.

Population attributable fraction

About 4.3% of the cardiovascular events, occurring an average of 21.9 years after delivery, could be attributed to a history of hypertensive pregnancy disorder after adjusting for risk factors measured an average of 10.7 years after delivery. In contrast, a recent Norwegian study found that 25.3% of pharmacologically treated hypertension within 10 years of delivery was attributed to preeclampsia/gestational hypertension after adjusting for 10 important pre-pregnancy and 6-months post-partum covariates [27]. The sizable differences in the attributable fractions between the current and aforementioned study, likely relate to the length of follow-up and the differences in the outcomes assessed. Successful identification and treatment of hypertension, a major determinant of CVD and a key mediator between hypertensive pregnancy disorders and subsequent CVD, would be expected to result in a low attributable fraction percentage associated with hypertensive pregnancy disorders in the current study. Nonetheless, the current findings further support that a history of hypertensive pregnancy disorders could identify women at risk not identifiable through established CVD risk factors.

Strengths and limitations

The major strengths of our study are the large national cohort with follow-up of incident non-fatal and fatal CVD. We investigated women in a relatively homogeneous low-risk population with low loss to follow-up (<5%), and detailed information on a large number of shared risk factors for hypertensive pregnancy disorders and CVD was available. However, several limitations need to be addressed. Our data are based on a single measurement of risk factors after the woman's first delivery, and cannot account for changes in risk factors over time. Information on diet, genetic, and other risk factors were not available. Residual confounding may also have occurred due to inappropriate or imprecise measurements of the CVD risk factors. The diagnostic validity for preeclampsia in the MBRN is high [49, 50], but gestational hypertension may be less reliable due to underreporting of the less severe cases [51] and misdiagnosed chronic hypertension [52]. The positive predictive value for gestational hypertension is 68% [53]. Inclusions of deliveries from 1980-1993 gave up to 14 years without morbidity follow-up, but the number of CVD events before 1994 is expected to be very low due to the women`s young age. This limitation has been described in details in a previous publication [9].

Conclusion

The association between hypertensive pregnancy disorder and maternal CVD is partially explained by established CVD risk factors such as, smoking, elevated BMI, diabetes and dyslipidemia, but there remains an increased risk of CVD associated with hypertensive pregnancy disorder after taking these risk factors into account, pointing to a separate pregnancy specific contribution. Even among young women a healthy lifestyle plays an important role in prevention of CVD, and targeted follow-up programs should be initiated to assess prevention of CVD at an early stage.

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Disclosures

The authors declare that they have no conflict of interest.

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Figure title and legends

Figure 1

Title: Flow chart of the study population of 20,075 Norwegian women

Legend: CVD indicates cardiocascular disease; CONOR, Cohort of Norway; SGA, small for gestational age; preterm delivery, <37 weeks of gestation; BMI, body mass index; MI, myocardial infarction; HDL-C, high-density lipoproteins cholesterol

Figure 2

Title: Lifestyle and cardiovascular risk factors and their associations with subsequent maternal cardiovascular disease (I00-99) among 20,075 young Norwegian women (mean age CONOR 37.1 years)

Legend: CONOR indicates Cohort of Norway 1994-2003; HR, age-adjusted hazard ratio (all variables except mother`s age at first delivery are adjusted for age at participation in CONOR); CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hypertension defined as SBP ≥140 or DPB ≥90 or currently on antihypertensive drugs; MI, myocardial infarction; Glucose; Diabetes, type 1, type 2 or unspecified diagnosed before baseline: HDL-C, low high-density lipoproteins cholesterol; Daily smoking, daily smoker versus not daily smoker; Alcohol consumption, drinking weekly compared to never/seldom; BMI, body mass index (categorical(<25 reference)); Vigorous physical activity, less than 1 hour a week versus 1 or more hours a week

Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors

- Tables and figures

Table 1 Characteristics of 20,075 Norwegian women with or without a hypertensive pregnancy disorder who subsequently participated in Cohort of Norway (CONOR, 1993-2004)

	No hypertensive pregnancy disorder (18,829 (93.8 %))	Hypertensive pregnancy disorder (1246 (6.2 %))
Mother`s age at first delivery, mean (SD)	26.0 (4.6)	26.2 (4.8)
Infant characteristics		
Preterm delivery, n (%)	902 (4.8)	196 (15.7)**
Small for gestational age, n (%)	2500 (13.3)	316 (25.4)**
Stillbirth, n (%)	123 (0.7)	18 (1.4)*
Parity at baseline, mean (SD)	2.0 (0.8)	2.0 (0.8)*
Mother`s age at CONOR, mean (SD)	37.2 (6.5)	37.1 (6.7)*
Education level		*
Basic education, n (%)	5824 (31.0)	424 (34.1)
Secondary education, n (%)	4900 (26.0)	363 (29.1)
Tertiary education, n (%)	8105 (43.0)	459 (36.8)
Marital status		
Married/cohabitants, n (%)	14,621 (77.7)	993 (79.7)
Other, n (%)	4208 (22.3)	253 (20.3)

Systolic blood pressure, mean (SD)	118.8 (12.6)	127.8 (15.1)**
Diastolic blood pressure, mean (SD)	70.1 (9.3)	75.9 (10.2)**
Hypertension §		**
No, n (%)	17,391 (92.4)	936 (75.1)
Yes, n (%)	1438 (7.6)	310 (24.9)
Current use of antihypertensive drugs, n (%)	221 (1.2)	75 (6.02)**
Family history of MI		**
One family member, n (%)	2294 (12.2)	174 (14.0)
Two or more family members, n (%)	148 (0.8)	13 (1.0)
Glucose, n (%)	5.0 (0.9)	5.2 (1.5)**
Diabetes mellitus †, n (%)	160 (0.9)	30 (2.4)**
Elevated total cholesterol (> 5.0 mmol/L), n (%)	9839 (53.3)	719 (57.7)**
Low HDL (< 1.3 mmol/L), n (%)	6688 (35.5)	535 (43.0)**
Elevated triglycerides (≥ 1.7 mmol/L) ‡, n (%)	3165 (16.8)	329 (26.4)**
Current daily smoking		**
No, n (%)	12,909 (68.6)	942 (75.6)
Yes, n (%)	5920 (31.4)	304 (24.4)
Alcohol		**
Never/seldom, n (%)	5916 (31.4)	452 (36.3)

Monthly, n (%)	7549 (40.1)	526 (42.2)
Weekly, n (%)	4479 23.8)	209 (16.8)
Missing, n (%)	885 (4.7)	59 (4.7)
BMI units (kg/m2)		**
< 25.0, n (%)	11,671 (62.0)	515 (41.3)
25.0-29.9, n (%)	5282 (28.1)	441 (35.4)
≥30.0, n (%)	1876 (10.0)	290 (23.3)
Vigorous physical activity		
Less than 1 hour peer week, n (%)	10,821 (57.5)	711 (57.1)
1 or more hours per week, n (%)	6390 (33.9)	415 (33.3)
Missing, n (%)	1618 (8.6)	120 (9.6)

Hypertensive pregnancy disorders indicate gestational hypertension or preeclampsia; preterm delivery, <37 weeks of gestation; small for gestational age, <10th percentile; stillbirth, ≥20 weeks of gestation.

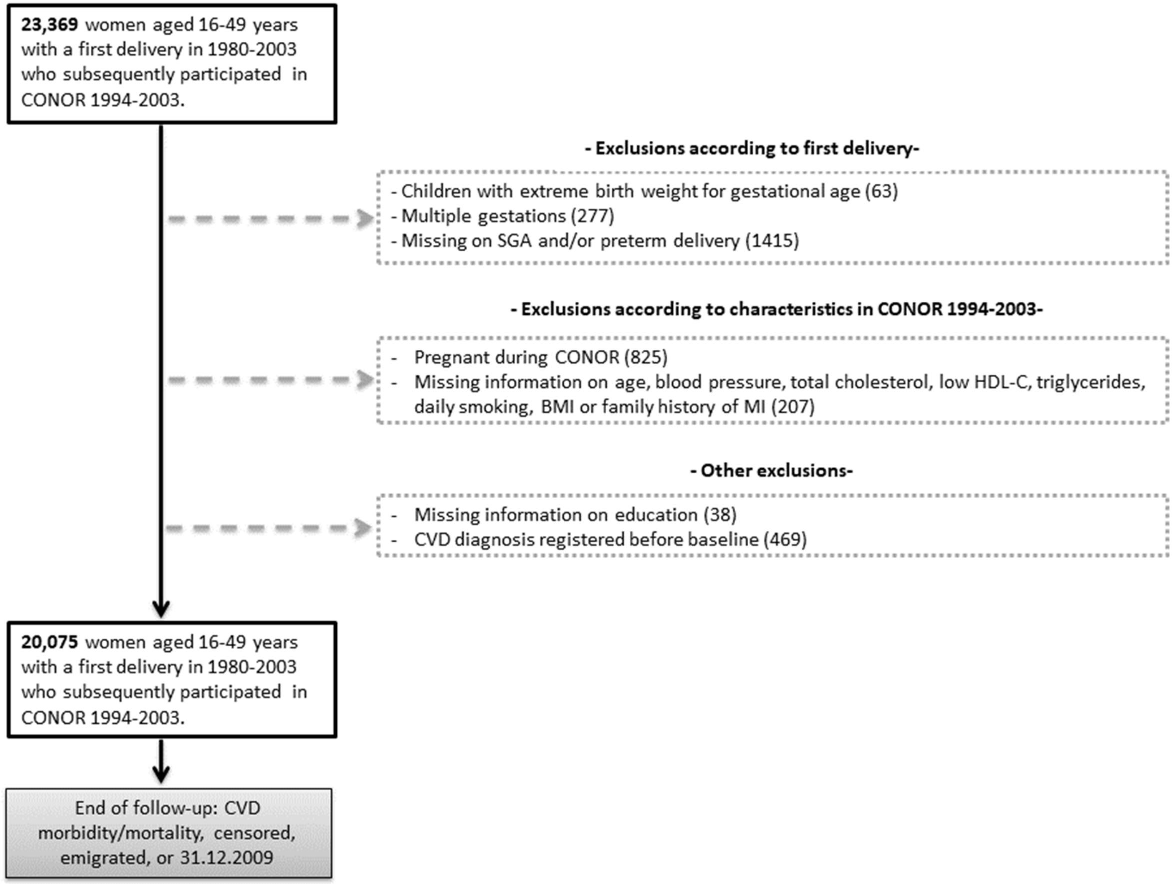
*indicates P <0.05 and **indicates P <0.001 for comparisons of women with and without hypertensive pregnancy disorder. Chi-square test for categorical data and t-test for continuous data.

† Diabetes mellitus (defined as type 1, type 2, or unspecified) diagnosed before the first pregnancy and/or in CONOR.

‡ A non-fasting blood sample was collected for serum lipid and glucose analyses.

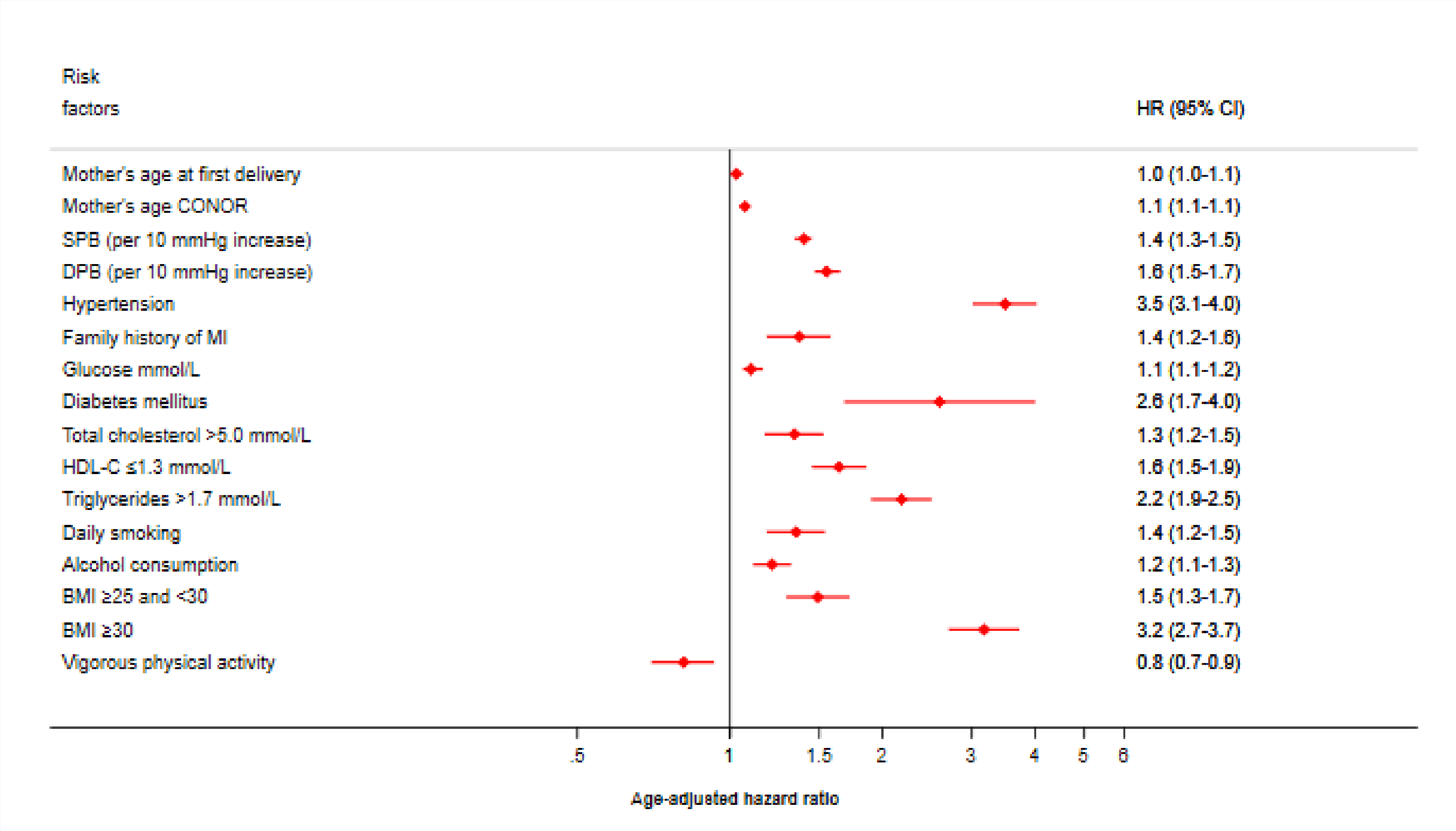
§ Hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 or use of antihypertensive drugs.

Figure 1 Flow chart of the study population of 20,075 Norwegian women



CVD indicates cardiocascular disease; CONOR, Cohort of Norway; SGA, small for gestational age; preterm delivery, <37 weeks of gestation; BMI, body mass index; MI, myocardial infarction; HDL-C, high-density lipoproteins cholesterol.

Figure 2 Lifestyle and cardiovascular risk factors and their associations with subsequent maternal cardiovascular disease (I00-99) among 20,075 young Norwegian women (mean age CONOR 37.1 years)



CONOR indicates Cohort of Norway 1993-2004; HR, age-adjusted hazard ratio (all variables except mother`s age at first delivery are adjusted for age at participation in CONOR); CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hypertension defined as SBP ≥140 or DPB ≥90 or currently on antihypertensive drugs; MI, myocardial infarction; Glucose; Diabetes, type 1, type 2 or unspecified diagnosed before baseline: HDL-C, low high-density lipoproteins cholesterol; Daily smoking, daily smoker versus not daily smoker; Alcohol consumption, drinking weekly compared to never/seldom; BMI, body mass index (categorical(<25 reference)); Vigorous physical activity, less than 1 hour a week versus 1 or more hours a week.

Table 2 Risk of cardiovascular disease according to hypertensive disorder (HPD) in first pregnancy (1980-2009) among 20,075 Norwegian women

	No./Events	Unadjusted HR (95% CI)	Model A HR (95% CI)*	Model B HR (95% CI)†
Total CVD				
No HPD‡	18,829/840	1 (ref.)	1 (ref.)	1 (ref.)
HPD	1246/125	2.3 (1.9-2.8)	2.3 (1.9-2.7)	1.5 (1.2-1.8)
Preeclampsia	884/83	2.1 (1.7-2.7)	2.2 (1.7-2.7)	1.5 (1.2-1.9)
Gestational hypertension	362/42	2.7 (2.0-3.6)	2.5 (1.8-3.4)	1.5 (1.1-2.0)
AMI/acute cerebral stroke				
No HPD ‡	18,829/128	1 (ref.)	1 (ref.)	1 (ref.)
HPD	1246/19	2.2 (1.4-3.6)	2.2 (1.4-3.6)	1.8 (1.1-2.9)
Preeclampsia	884/13	2.2 (1.2-3.8)	2.2 (1.3-3.9)	1.8 (1.0-3.3)
Gestational hypertension	362/6	2.4 (1.1-5.5)	2.2 (1.0-5.1)	1.8 (0.8-4.1)
CHD				
No HPD ‡	18,829/116	1 (ref.)	1 (ref.)	1 (ref.)

HPD	1246/16	2.2 (1.2-3.5)	1.9 (1.1-3.2)	1.5 (0.9-2.6)
Preeclampsia	884/10	1.8 (1.0-3.5)	1.8 (0.9-3.4)	1.4 (0.7-2.7)
Gestational hypertension	362/6	2.7 (1.2-6.1)	2.2 (1.0-5.1)	1.7 (0.7-4.0)

CVD indicates cardiovascular disease; AMI, acute myocardial infarction; CHD, coronary heart disease; HPD, hypertensive pregnancy disorder; HR, hazard ratio; CI, confidence interval.

* Adjusted for non-modifiable risk factors: age at baseline (yrs.), age at first delivery (yrs.), education (primary, high school/vocational, any college/university) and a family history of MI prior to age 60.

† Adjusted for non-modifiable and modifiable risk factors: age at baseline (yrs.), age at first delivery (yrs.), education (primary, high school/vocational, any college/university), hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 or currently on antihypertensive drugs), total serum cholesterol (mmol/L), low high-density lipoproteins cholesterol (<1.3 mmol/L), triglycerides (mmol/L), daily smoking, body mass index (kg/m2), diabetes mellitus and family history of MI prior to age 60.

‡ No preeclampsia or gestational hypertension in first pregnancy.

Table 3 Risk of cardiovascular disease among 20,145 Norwegian women, stratified by hypertensive disorders (HPD) and term/preterm delivery

	Term delivery		Preterm delivery	
Total CVD	**No./Events**	**Adjusted HR (95% CI)**	**No./Events**	**Adjusted HR (95% CI)**
No HPD†	17,927/798	1 (ref.)	902/42	1.1 (0.8-1.5)
HPD	1050/102	1.4 (1.1-1.8)	196/23	1.9 (1.3-2.9)
Gestational hypertension	334/35	1.3 (0.9-1.9)	28/7	3.6 (1.7-7.6)
Preeclampsia	716/67	1.5 (1.1-1.9)	168/16	1.6 (1.0-2.7)

CVD indicates cardiovascular disease; HPD, hypertensive pregnancy disorder; HR, hazard ratio; CI, confidence interval; preterm delivery, <37 weeks of gestation.

*Adjusted for non-modifiable and modifiable risk factors: age at baseline (yrs.), age at first delivery (yrs.), education (primary, high school/vocational, any college/university), hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 or currently on antihypertensive drugs), total serum cholesterol (mmol/L), low high-density lipoproteins cholesterol (<1.3 mmol/L), triglycerides (mmol/L), daily smoking, body mass index (kg/m2), diabetes mellitus and family history of MI prior to age 60.

†No preeclampsia or gestational hypertension in first pregnancy

Table 4 Comparison of two different risk prediction models for 10-year risk of cardiovascular disease

Total CVD	C Statistics*	95% CI	P -value	AIC	BIC	NRI (p-value)§	IDI (p-value)§
Prediction model 1†	0.69	0.67-0.72	< 0.001	12445.68	12527.35		
Prediction model 2‡	0.70	0.68-0.72	< 0.001	12436.25	12525.35	0.055 (0.066)	0.001 (0.133)

CVD indicates cardiovascular disease; HR, hazard ratio; CI, confidence interval; AIC, akaike information criteria: BIC, Bayesian information criteria; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

*The Harrell`s C statistics were obtained by use of the "somersd" package in STATA 15. Only women with the possibility of at least 10 years of follow-up were included (n=12,389).

†Prediction model 1 includes age at baseline (yrs.), age at first delivery (yrs.), educational level (primary, high school/vocational, any college/university), hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 or currently on antihypertensive drugs), total serum cholesterol (mmol/L), low high-density lipoproteins cholesterol (<1.3 mmol/L), triglycerides (mmol/L), daily smoking, body mass index (kg/m2), diabetes mellitus and family history of MI prior to age 60.

‡ Prediction model 2 includes the variables in prediction model 1 in addition to hypertensive pregnancy disorder (preeclampsia, gestational hypertension).

§Result of continuous NRI and IDI using the "survIDINRI" package in ***R***.