

Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension and Preeclampsia

Cohort Norway Study

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Abstract—Preconception predictors of gestational hypertension and preeclampsia may identify opportunities for early detection and improve our understanding of the pathogenesis and life course epidemiology of these conditions. Female participants in community-based Cohort Norway health surveys, 1994 to 2003, were prospectively followed through 2012 via record linkages to Medical Birth Registry of Norway. Analyses included 13 217 singleton pregnancies (average of 1.59 births to 8321 women) without preexisting hypertension. Outcomes were gestational hypertension without proteinuria (n=237) and preeclampsia (n=429). Mean age (SD) at baseline was 27.9 years (4.5), and median follow-up was 4.8 years (interquartile range 2.6–7.8). Gestational hypertension and preeclampsia shared several baseline risk factors: family history of diabetes mellitus, pregravid diabetes mellitus, a high total cholesterol/high-density lipoprotein cholesterol ratio (>5), overweight and obesity, and elevated blood pressure status. For preeclampsia, a family history of myocardial infarction before 60 years of age and elevated triglyceride levels (≥ 1.7 mmol/L) also predicted risk while physical activity was protective. Preterm preeclampsia was predicted by past-year binge drinking (≥ 5 drinks on one occasion) with an adjusted odds ratio of 3.7 (95% confidence interval 1.3–10.8) and by past-year physical activity of ≥ 3 hours per week with an adjusted odds ratio of 0.5 (95% confidence interval 0.3–0.8). The results suggest similarities and important differences between gestational hypertension, preeclampsia, and preterm preeclampsia. Modifiable risk factors could be targeted for improving pregnancy outcomes and the short- and long-term sequelae for mothers and offspring. (*Hypertension*. 2016;67:1173-1180. DOI: 10.1161/HYPERTENSIONAHA.116.07099.) • [Online Data Supplement](#)

Key Words: alcohol consumption ■ behavior ■ hypertension ■ lipids ■ obesity ■ preeclampsia

Hypertensive disorders of pregnancy are prevalent complications and include preexisting chronic hypertension, gestational hypertension and preeclampsia, and preeclampsia superimposed on chronic hypertension.¹ Among these conditions, preeclampsia associates with the most significant immediate risks to offspring and mother,^{1,2} increases women's long-term risk of end-stage renal disease,³ and cardiovascular morbidity and mortality.⁴⁻⁸ Preeclampsia is conceptualized into 2 primary stages: the first being altered placental perfusion as a result of abnormal early trophoblast growth and differentiation, poor placentation, or other pathologies and the second involving maternal responses to placental factors excreted because of a dysfunctional placenta.⁹⁻¹⁷ Further, the pathophysiology of preterm and late-onset preeclampsia may differ with poor placentation being more important for preterm than term preeclampsia.¹⁸

Preexisting cardiovascular risk factors may identify women at risk for de novo hypertensive disorders of pregnancy, where pregnancy acts as a metabolic and vascular stress test for women with underlying acquired or genetic predispositions.¹⁹ Gestational hypertension and preeclampsia and term and preterm preeclampsia may have important etiologic differences, but no study to date has compared the preconception risk factor differences between these outcomes. We, therefore, evaluated the extent of differences and similarities in the pregravid cardiovascular risk factors associated with gestational hypertension, preeclampsia, and preterm preeclampsia using a prospective study design linking regional health surveys with subsequent pregnancies identified in the Norwegian Medical Birth Registry.

We are aware of only 2 earlier studies, of substantially smaller sample sizes, that evaluated preconception risk factors

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for their ability to predict preeclampsia.^{20,21} As these studies had discrepant findings, perhaps owing to the smaller sample sizes, the current analyses provide a more robust evaluation of preconception risk factors. Also, the current study provides novel preconception risk factor information regarding physical activity and binge drinking and is unique in the literature for its evaluation of preconception differences and similarities in risk factors for gestational hypertension and preeclampsia.

Methods

Participants in Cohort Norway (CONOR) health surveys (1994–2003) were linked, using a national identification number, to the Medical Birth Registry of Norway for births subsequent to CONOR participation (through to December 31, 2012). The Materials and Methods in the online-only Data Supplement provides additional details and the study design figure. The reproductive-aged women from CONOR health surveys²² came from 3 regions (24.2% from Oslo, 49.9% from Nord-Trøndelag, and 21.3% from Troms). An earlier study evaluated pregravid risk factors in 3494 women in Nord-Trøndelag; a subset of the current analyses.²¹ The majority of CONOR participants were ethnic Norwegians, but only 61.9% of women of reproductive age in Oslo surveys were born in Norway, given an immigrant survey component, in contrast to 97.5% in Nord-Trøndelag and 95.0% in Troms.

Record linkages identified 17320 births with a mother that participated in CONOR before delivery (Figure S1 in the online-only Data Supplement). Exclusions included preexisting hypertension, nonviable births, mother pregnant during or delivered <1 year before CONOR participation, and multiple birth pregnancies, resulting in 13217 singleton births for analyses (representing 8321 women; 1.59 births/woman).

CONOR Assessments

Assessments included height and weight, past-year leisure-time light and vigorous physical activity,²³ alcohol consumption frequency and binge drinking,²⁴ blood pressure, nonfasting lipids,²² and a family history of diabetes mellitus, stroke, or myocardial infarction before 60 years of age in first-degree relatives. Analyses used the average of the last 2 of 3 systolic and diastolic blood pressure readings taken by an automatic device (DINAMAP, Criticon, Tampa, FL). Binge drinking was defined as ≥ 5 drinks/d at least once in the past year. Those who reported drinking alcohol but who did not answer the binge drinking question were assigned to a nonresponse category. Binge drinking frequency was also evaluated (none, 1–5, and ≥ 6 binges in past year). Binge drinking was not assessed in Nord-Trøndelag; otherwise, missing data were low (<0.1%) for the majority of parameters, with the exception of physical activity (7%) and smoking (5%).

Definition of Outcomes

Gestational hypertension was defined as hypertension diagnosis after 20 weeks of gestation (systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg, or both). Preeclampsia diagnosis required the additional presence of proteinuria (≥ 0.3 g in 24 hour urine or ≥ 1 point increase on a urinary dipstick).²⁵ Term and preterm preeclampsia were defined based on gestational age at delivery (≥ 37 or <37 weeks or when gestational age was missing ($n=287/13217$), having a birth weight ≥ 2500 g or <2500 g. Gestational age was determined by ultrasound for 80.0%, last menstrual period for 17.8%, and birth weight for remaining 2.2% of pregnancies.

Statistical Methods

Descriptive characteristics are reported as mean (SD) and percent. Multivariable multinomial logistic regression analyses provided odds ratios (OR) and 95% confidence intervals (CI) of characteristics for their prediction of gestational hypertension and preeclampsia and in a separate analyses of term and preterm preeclampsia. Multivariable models included parity (0, 1, or 2+), length of follow-up, baseline age (years), daily smoking (yes versus no), pregravid diabetes mellitus, and a history of gestational hypertension or preeclampsia in a prior

pregnancy (obtained via record linkages to pre-CONOR pregnancies), educational level (≤ 12 , 13–16, ≥ 17 years), marital status (married/common law partner versus other), and region of survey (Oslo versus other). Mother's pseudo-ID was entered as a cluster variable. When lipids were evaluated, oral contraceptive use was added to the multivariable model.

Each potential additional risk factor was evaluated separately with the above mentioned parameters. Risk factors evaluated included physical activity (≥ 3 hours per week of light or vigorous activity on average in the past year), body mass index classifications (<25, 25–29.9, and ≥ 30 kg/m²), oral contraceptive use (yes versus no), alcohol consumption frequency (≥ 1 /week, 1–3 times/month, and <1/month which included abstainers), binge drinking, a high total cholesterol/high-density lipoprotein (HDL) cholesterol ratio (≥ 5 versus lower), a high triglyceride level (≥ 1.7 mmol/L versus lower), and blood pressure status (normal: systolic BP <130 mmHg and diastolic BP <85 mmHg; elevated: systolic BP 130–139 mmHg or diastolic BP 85–89 mmHg; hypertensive: systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). Family history of chronic diseases was evaluated in unadjusted analyses. Selected postestimation tests were conducted to evaluate whether differences in regression coefficients between outcome groups were statistically significant. Stata 12 (StataCorp LP, College Station, TX) was used in analyses; significance was determined by $P < 0.05$.

Sensitivity Analyses

Three sensitivity analyses were conducted: (1) restricted to those with a follow-up <7.2 years (approximately the 70th percentile); (2) restricted to nulliparous women; and (3) for preterm preeclampsia, restricted to preterm births.

Results

Average age (SD) at the time of the baseline CONOR assessment was 27.9 years (4.5). At baseline, 24.1% patients had a higher education, 21.3% were married or had a common law partner, and 55.9% engaged in physical activity of ≥ 3 hours per week (Table 1). The median follow-up was 4.8 years (interquartile range 2.6–7.8; maximum 17.5 years). A total of 666 (5.0%) pregnancies were affected by either gestational hypertension (without proteinuria) or preeclampsia, of whom 114 were preterm and 315 term preeclampsia. Only 23 of 237 gestational hypertensive pregnancies resulted in preterm deliveries. The percent small-for-gestational age by sex (<10th percentile) was 16.5%, 36.8%, and 14.0% for gestational hypertension, preterm, and term preeclampsia groups, respectively, and the percent very small-for-gestational age (<2.5th percentile) was 5.9%, 14.9%, and 3.8%, for the 3 groups, respectively.

A family history of diabetes mellitus and women's pregravid diabetes mellitus predicted both gestational hypertension and preeclampsia, whereas a family history of myocardial infarction before 60 years of age predicted preeclampsia, but not gestational hypertension (postestimation test for differences in coefficients, $P=0.053$; Table 2). A family history of stroke predicted the combined outcome of gestational hypertension or preeclampsia (OR 1.5; 95% CI: 1.02–2.10), with similar but nonsignificant ORs noted for the 2 outcomes separately evaluated (Table 2).

Physical activity was protective for preeclampsia (OR 0.8; 95% CI 0.61–0.97) and particularly for preterm preeclampsia (OR 0.5; 95% CI 0.32–0.76), but not for gestational hypertension (Table 3). Body mass index classifications and baseline hypertensive status predicted both outcomes, albeit with

Table 1. Preconception Baseline Demographic and Cardiovascular Risk Factors: Cohort Norway and Medical Birth Registry of Norway (N=13217)*

Baseline Characteristics:	Mean (SD) or %
Age, y	27.9 (4.5)
Current daily smoking, %	27.1
Education %	
≤12 y	46.1
13–16 y	29.8
≥17 y	24.1
Married, %	21.3
BMI, kg/m ²	23.9 (3.8)
Systolic blood pressure, mm Hg	118.9 (10.9)
Diastolic blood pressure, mm Hg	68.9 (8.4)
Total cholesterol, mmol/L	4.90 (0.92)
HDL cholesterol, mmol/L	1.54 (0.36)
Triglyceride, mmol/L	1.14 (0.68)
Physical activity (≥3 h/wk in past year), %	55.9
Weekly past-year alcohol consumption, %	22.2
Binge drinkers (≥5 drinks/d at least once in past year), %†	63.6

BMI indicates body mass index; and HDL, high-density-lipoprotein.

*A total of 8321 women with an average of 1.59 births per woman.

†Excluding Nord-Trøndelag because of lack of inclusion of this question in that region.

stronger effects noted for gestational hypertension than for preeclampsia (postestimation tests, $P < 0.05$). Further, the Oslo region had a greater risk of gestational hypertension (OR 1.9; 95% CI 1.38–2.67) than the other regions, but no regional differences in preeclampsia were noted. Baseline educational attainment, marital status, smoking, and oral contraceptive use were not significantly related to gestational hypertension or preeclampsia (Table 3). A high total cholesterol/HDL cholesterol ratio predicted both gestational hypertension and preeclampsia. In contrast, an elevated triglyceride level only predicted preeclampsia.

Weekly alcohol consumption relative to none or less than once a month was associated with lower risk of preeclampsia (OR 0.7; 95% CI 0.48–0.95) and term preeclampsia (OR 0.7; 95% CI 0.47–0.99; Table 3). In the analyses limited to the subcohort with available binge drinking data, weekly alcohol consumption (adjusted for binge drinking and other covariates) was associated with an OR for preeclampsia of 0.5 (95% CI 0.27–0.78) with a stronger protective effect noted for preterm preeclampsia (Table 4). Binge drinking (adjusted for alcohol consumption frequency and other covariates) was associated with increased risk of preeclampsia (OR 1.8; 95% CI 1.16–2.92) with an especially strong association noted for preterm preeclampsia (OR 3.7; 95% CI 1.25–10.78). However, there was no evidence for a binge frequency dose-response effect given that the OR associated with 1 to 5 binges was the same as that associated with ≥6 binges in the past year (Table 4).

Sensitivity Analyses

The adverse effects of binge drinking for preterm preeclampsia remained significant when analyses were restricted to preterm births ($n=703$; OR 3.2; 95% CI 1.07–9.57), restricted to pregnancies occurring within 7.2 years of follow-up ($n=9419$; OR 3.8; 95% CI 1.11–12.81), and when restricted to nulliparous women ($n=3975$; OR 4.5; 95% CI 1.15–17.30).

In contrast, the protective effect of weekly alcohol consumption was not consistently observed in the sensitivity analyses (ie, a protective association was noted when restricting analyses to within 7.2 years of follow-up, but not when restricting analyses to nulliparous women or to preterm deliveries).

The protective effect of physical activity for preterm preeclampsia, however, persisted in analyses limited to nulliparous pregnancies (OR 0.5; 95% CI 0.28–0.85); to those with a follow-up within 7.2 years (OR 0.5; 95% CI 0.33–0.89); and to preterm deliveries (OR 0.5; 95% CI 0.30–0.81). Further, the majority of all results reported remained unaltered in the sensitivity analyses with the exception that in nulliparous pregnancies, a history of oral contraceptive use predicted gestational hypertension (OR 1.9; 95% CI 1.16–3.01).

Discussion

The results presented provide evidence of similarities and potentially important differences in predisposing factors for gestational hypertension and preeclampsia and preterm preeclampsia. Gestational hypertension and preeclampsia shared several baseline risk factors: a family history of diabetes mellitus, pregravid diabetes mellitus, baseline blood pressure status, obesity, a high total cholesterol/HDL cholesterol ratio, and a nonsignificant tendency to have a family history of stroke. Preeclampsia, however, was also predicted by a family history of myocardial infarction before 60 years of age, physical inactivity, an elevated triglyceride level, and binge drinking.

The notable adverse association of binge drinking with preterm preeclampsia in the current study mirrors the deleterious cardiovascular disease effects of heavy or binge drinking noted in the literature.^{24,26–28} Biologically plausible mechanisms for the observed association between binge drinking and increased risk of preterm preeclampsia, but not gestational hypertension or term preeclampsia, likely relate to alcohol's impairment of placentation and utero-placental growth and function through a variety of mechanisms.^{29–32}

There are only a few studies that report on alcohol consumption's association with preeclampsia. In the Screening for Pregnancy End points study of 5628 participants, early pregnancy alcohol consumption including binge drinking was not associated with preeclampsia or any other adverse outcome.³³ In a large study of over 1 million singleton birth in Missouri, binge drinking was not assessed, but 1 to 2 drinks per week was associated with a lower multivariable adjusted OR for preeclampsia (OR 0.82; 95% CI, 0.74–0.90).³⁴ Further, in an evaluation of blood pressure in pregnancy, those reporting light alcohol drinking during pregnancy were reported to have significantly lower blood pressure.³⁵ Although our study found reduced risk of preeclampsia associated with preconception weekly alcohol consumption, the results were not

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for Gestational Hypertension and Preeclampsia by Family History of Disease and Prepregnancy Diabetes Mellitus: Cohort Norway and Medical Birth Registry of Norway (N=13217)*

	N	G. Hypertension† (n=237)		Preeclampsia‡ (n=429)	
		Cases	OR (95% CI)§	Cases	OR(95% CI)§
Family history in first-degree relatives					
Diabetes mellitus					
No	12 386	209	1.0	389	1.0
Yes	831	28	2.1 (1.39–3.09)	40	1.6 (1.12–2.25)
Cerebrovascular stroke					
No	12 666	223	1.0	404	1.0
Yes	551	14	1.5 (0.85–2.55)	25	1.5 (0.95–2.24)
Myocardial infarction before 60 y					
No	12 099	216	1.0	370	1.0
Yes	1118	21	1.1 (0.69–1.70)	59	1.8 (1.31–2.39)
Women's prepregnancy diabetes mellitus¶					
No	13 138	233	1.0	422	1.0
Yes	79	4	3.2 (1.14–8.68)	7	3.1 (1.43–6.49)

*A total of 8321 women with an average of 1.59 births per woman.

†Gestational hypertension without proteinuria.

‡Gestational hypertension with proteinuria.

§Multinomial logistic regression model in which mother was entered as a cluster variable.

|| $P < 0.10$, postestimation test for differences in coefficients between gestational hypertension and preeclampsia.

¶Identified in the Norwegian Medical Birth Registry (type 1, type 2, or unspecified) and identified in the Cohort Norway baseline assessment.

consistent in our sensitivity analyses. In contrast, our findings that preconception past-year binge drinking was associated with increased risk of preterm preeclampsia were consistently observed in all subsequent sensitivity analyses. We did not, however, observe a dose–response effect related to past-year binge drinking frequency. We speculate that there may have been reluctance to report the frequency of binge drinking in the current study or that binge drinking is a marker for other risk factors not measured.

The protective association of physical activity with preterm preeclampsia may reflect several protective underlying mechanisms beyond weight management, such as reduced inflammation and oxidative stress and improved endothelial function and placental growth and vascular development.³⁶ The preponderance of evidence suggests physical activity is protective of preeclampsia with a few notable exceptions.³⁷

Our lipid results indicate that nonfasting lipid levels are useful in predicting preeclampsia and gestational hypertension and note that nonfasting lipid levels have been successfully used in cardiovascular research.^{38,39} In the previous prospective study in Norway, which forms a subset of our current study, cholesterol, low-density lipoprotein cholesterol and nonHDL cholesterol were positively related to preeclampsia but trends associated with serum triglyceride quintiles were nonsignificant.²¹ In Finland, triglycerides were associated with increased risk of preeclampsia but not cholesterol, low-density lipoprotein cholesterol, or HDL cholesterol.²⁰ Our lipid results corroborate the preponderance of existing evidence that elevated triglyceride levels is a risk factor for preeclampsia⁴⁰ and identified that a high total cholesterol/HDL cholesterol ratio

was a shared risk factor for gestational hypertension and preeclampsia. Nonfasting triglyceride levels reflect exposures to atherogenic remnant lipoproteins³⁹ and elevated triglyceride levels associate with small, dense low-density lipoprotein cholesterol,^{41,42} which is readily oxidized. Of relevance to preeclampsia is that oxidized low-density lipoprotein inhibits the fetal trophoblast invasion of the uterus.⁴³ Thus, further investigation of the role of derangements in lipid metabolism in preeclampsia is warranted.

Obesity was an important risk factor for gestational hypertension and preeclampsia as expected. However, our postestimation test for equality in coefficients identified that obesity was a significantly stronger predictor of gestational hypertension than preeclampsia, highlighting that for preeclampsia, there are other factors that increase risk.

Strengths and Weaknesses

Strengths of the current study include the large population-based cohort with uniformly assessed preconception risk factors and complete linkage to the Medical Birth Registry: strengths which contribute to the generalizability of the study. Further, the national healthcare system in Norway and our multivariate adjustment for educational and marital status and region are strengths of the study in that they minimize the possibility for disparities in the adequacy of prenatal care to influence results. Also, self-reported alcohol consumption data were obtained before pregnancy and would, therefore, not be influenced by under-reporting associated with the stigma of drinking during pregnancy. However, we recognize that under-reporting of alcohol consumption is also

Table 3. Preconception Risk Factors for Gestational Hypertension and Preeclampsia: Cohort Norway and Medical Birth Registry of Norway (N=13 217)*

	N	G. Hypertension† (n=237)		Preeclampsia‡ (n=429)		Preterm Preeclampsia§ (n=114)		Term Preeclampsia (n=315)	
		Cases	OR (95% CI)¶	Cases	OR (95% CI)¶	Cases	OR (95% CI)¶	Cases	OR (95% CI)¶
Physical activity (past year)									
Not active	5425	92	1.0	190	1.0	62	1.0	128	1.0
Active (≥3 h/wk)	6869	131	1.1 (0.8–1.40)	209	0.8 (0.61–0.97)	45	0.5 (0.32–0.76)#	164	0.9 (0.70–1.19)
BMI classifications, kg/m²									
<25	9266	120	1.0	248	1.0	71	1.0	177	1.0
25–29.9	3037	69	1.8 (1.31–2.56)	127	1.7 (1.32–2.18)	25	1.2 (0.69–1.92)	102	1.9 (1.46–2.52)
≥30	869	46	4.2 (2.86–6.21)	50	2.0 (1.35–3.02)**	16	2.2 (1.13–4.09)	34	2.0 (1.21–3.14)
Education									
≤12 y	6019	105	1.0	189	1.0	51	1.0	138	1.0
13–16 y	3882	56	0.7 (0.47–0.99)	128	0.9 (0.66–1.14)	30	0.7 (0.43–1.24)	98	0.9 (0.68–1.24)
≥17 y	3149	72	0.9 (0.66–1.42)	102	0.8 (0.56–1.09)	29	0.8 (0.45–1.39)	73	0.8 (0.53–1.14)
Smoking daily									
No	9194	173	1.0	305	1.0	80	1.0	225	1.0
Yes	3415	50	0.8 (0.56–1.08)	95	0.8 (0.56–1.08)	29	0.8 (0.46–1.27)	66	0.8 (0.58–1.02)
Marital status									
Single, divorced	10 348	181	1.0	352	1.0	88	1.0	264	1.0
Married	2799	56	1.3 (0.90–1.95)	74	1.0 (0.70–1.32)	24	1.0 (0.59–1.68)	50	1.0 (0.67–1.38)
Region									
Other	10 023	148	1.0	311	1.0	78	1.0	233	1.0
Oslo	3194	89	1.9 (1.38–2.67)	118	1.1 (0.80–1.38)	36	1.3 (0.81 – 2.13)	82	1.0 (0.70 – 1.33)
Blood pressure status††									
Normotensive	10 977	140	1.0	287	1.0	78	1.0	209	1.0
Elevated	1577	50	2.7 (1.90–3.90)	87	2.1 (1.57–2.87)	19	1.6 (0.91–2.93)	68	2.3 (1.66–3.23)
Hypertensive	615	46	7.1 (4.84–10.44)	54	3.5 (2.48–4.97)#	17	3.8 (2.04–7.08)	37	3.4 (2.32–5.01)#
Triglyceride**									
<1.7 mmol/L	9014	172	1.0	263	1.0	72	1.0	191	1.0
≥1.7 mmol/L	1388	33	1.3 (0.84–2.03)	86	2.4 (1.71–3.30)	22	2.3 (1.29–4.07)	64	2.4 (1.65–3.52)
Chol/HDL ratio**									
<5.0	12 417	214	1.0	382	1.0	97	1.0	285	1.0
≥5.0	769	23	1.9 (1.11–3.10)	44	1.8 (1.17–2.84)	15	2.4 (1.24–4.65)	29	1.6 (0.94–2.85)
Oral contraceptive use									
No	7610	137	1.0	250	1.0	63	1.0	187	1.0
Yes	4061	73	1.1 (0.77–1.45)	136	1.0 (0.75–1.26)	35	1.1 (0.71–1.81)	101	0.9 (0.69 – 1.25)
Alcohol frequency									
Less than monthly	3306	59	1.0	110	1.0	27	1.0	83	1.0
Occasional	6800	120	1.0 (0.68–1.36)	230	0.9 (0.70–1.17)	67	1.2 (0.73–1.90)	163	0.8 (0.61–1.10)
Weekly	2880	55	0.9 (0.48–1.39)	85	0.7 (0.48–0.95)	18	0.7 (0.32–1.36)	67	0.7 (0.47–0.99)

BMI indicates body mass index; CI, confidence interval; Chol, cholesterol; and HDL, high-density-lipoprotein.

*A total of 8321 women with an average of 1.59 births per woman.

†Gestational hypertension without proteinuria.

‡Gestational hypertension with proteinuria.

§Delivery <37-wk gestation or when missing gestational age (n=287), with a birth weight <2500 g.

|| Delivery 37-wk gestation or later or when missing gestational age (n=287), with birth weight ≥2500 g.

¶Multinomial logistic regression model included covariates: baseline age (years), daily smoking (yes vs no), parity (0, 1, ≥2), pregravid diabetes mellitus, pre-CONOR history of gestational hypertension or preeclampsia, marital status (married/common law partner vs other), region of survey (Oslo vs other), education (≤12, 13–16, ≥17 y), and time between CONOR and delivery (months); mother was entered as a cluster variable.

#P<0.05, postestimation test for differences in coefficients between the designated category and gestational hypertension.

**Also adjusted for oral contraceptive use.

††Baseline blood pressure status was categorized as normal (systolic BP <130 mm Hg and diastolic BP <85 mm Hg), elevated (systolic BP 130–139 mm Hg or diastolic BP 85–89 mm Hg), or hypertensive (systolic BP ≥140 or diastolic BP ≥90 mm Hg).

Table 4. Subcohort Preconception Past-Year Alcohol Consumption Frequency and Binge Drinking in Gestational Hypertension and Preeclampsia: CONOR and Medical Birth Registry of Norway (N=6488)*

	N	G. Hypertension† (n=133)		Preeclampsia‡ (n=211)		Preterm Preeclampsia§ (n=56)		Term Preeclampsia (n=155)	
		Cases	OR (95% CI)¶	Cases	OR (95% CI)¶	Cases	OR (95% CI)¶	Cases	OR (95% CI)¶
Alcohol Frequency									
Less than monthly	1748	36	1.0	53	1.0	15	1.0	38	1.0
Occasional	2871	60	0.9 (0.51–1.57)	106	0.8 (0.55–1.28)	31	0.9 (0.32–2.27)	75	0.8 (0.53–1.30)
Weekly	1869	37	0.8 (0.40–1.42)	52	0.5 (0.27–0.78)	10	0.3 (0.09–0.92)	42	0.5 (0.30–0.96)
Binge drinking#									
None	1297	27	1.0	28	1.0	5	1.0	23	1.0
Yes	4125	87	1.0 (0.60–1.78)	152	1.8 (1.16–2.92)	41	3.7 (1.25–10.78)**	111	1.5 (0.89–2.45)
Nonresponders	1066	19	0.7 (0.32–1.32)	31	1.5 (0.86–2.71)	10	2.8 (0.78–10.06)	21	1.2 (0.63–2.37)
Binge drinking frequency††									
None	1297	27	1.0	28	1.0	5	1.0	23	1.0
1–5 times past year	1173	27	0.9 (0.45–1.64)	45	1.8 (1.06–3.12)	14	3.7 (1.09–12.36)**	31	1.5 (0.83–2.71)
≥6 times past year	2952	60	1.2 (0.65–2.12)	107	1.8 (1.09–2.94)	27	3.7 (1.22–11.02)	80	1.5 (0.85–2.53)

*A total of 4349 women with an average of 1.49 births per woman.

†Gestational hypertension without proteinuria.

‡Gestational hypertension with proteinuria.

§Occurring <37-wk gestation or when missing gestational age when birth weight was <2500.

|| Occurring 37-wk gestation or later or when missing gestational age when birth weight was ≥2500 g.

¶Multinomial logistic regression model included covariates: baseline age, daily smoking, parity (0, 1, ≥2), pregravid diabetes mellitus, and a pre-CONOR history of gestational hypertension or preeclampsia, marital status (married/common law partner vs other), region of survey (Oslo vs other), education (≤12, 13–16, ≥17 y), and time between CONOR and delivery (months); mother's ID was entered as a cluster variable. For the subcohort analyses, alcohol frequency was also adjusted for binge drinking, and binge drinking was adjusted for alcohol frequency.

#Reporting ≥5 drinks/d at least once in past year, those reporting past year alcohol consumption, but missing binge drinking response were coded as nonresponders. Participants of surveys which did not include binge drinking assessment were excluded from analyses.

** $P < 0.05$, postestimation test for differences in coefficients between designated category and gestational hypertension.

††Model replaced binge drinking with frequency of binge drinking; otherwise, all covariates listed above were included in model.

possible in nonpregnant study populations. Limitations of the study include the lack of information of fasting glucose or HbA1C, apolipoproteins, urine samples, and family history of hypertension. Other limitations include the largely ethnic Norwegian study population and inability to generalize to more ethnically diverse populations. Further, changes in risk factors over time could not be assessed. In our study, smoking had a nonsignificant association with a lower risk of preeclampsia in multivariable analyses, with the observed OR of 0.8 being greater than the anticipated OR of 0.5.⁴⁴ However, because of the sharp decline in smoking in women in Norway over the past decade, the attenuated smoking association may result from misclassification, where smokers identified in CONOR would be less likely to be smokers at the time of their subsequent pregnancy.

Perspectives

The study suggests similarities and some potentially important differences between risk factors for gestational hypertension and preeclampsia and between preterm and term preeclampsia. The results are intriguing given the lifetime increased risk of cardiovascular morbidity and mortality observed in women with a history of preeclampsia.^{4–8} Further, although the majority of prospective studies of long-term consequences have focused on preeclampsia, an 18-year follow-up of mothers found that women with a history of gestational hypertension

had similar predicted 10-year cardiovascular disease risk based on the Framingham score as women with a history of preeclampsia.⁴⁵ Our findings support the hypotheses that pregnancy unmasks predisposing familial and modifiable cardio-metabolic risk. However, in the current study, a greater number of risk factors predicted preeclampsia than gestational hypertension. The presence of risk factors in women of reproductive age could help clinicians identify women needing greater clinical monitoring and lifestyle changes. Promoting better lifestyles in women of reproductive age would be advantageous for preventing the short- and long-term outcomes associated with hypertension disorders of pregnancy.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Preeclampsia, but not gestational hypertension, was predicted by a family history of myocardial infarction before 60 years of age, binge drinking, physical inactivity, and an elevated triglyceride level.
- Gestational hypertension and preeclampsia shared many pregravid risk factors, including a high total cholesterol/high-density lipoprotein cholesterol ratio, family history of diabetes mellitus, pregravid diabetes mellitus, overweight and obesity, and baseline blood pressure status.

What Is Relevant?

- The majority of risk factors were modifiable.

Summary

Physical activity, avoidance of binge drinking, weight management, blood pressure, and glucose monitoring and control for women of reproductive age may reduce hypertensive disorders of pregnancy and its short- and long-term sequelae.

Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension and Preeclampsia: Cohort Norway Study

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ONLINE SUPPLEMENT

Preconception cardiovascular risk factor differences between gestational hypertension and preeclampsia: Cohort Norway Study

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Materials and Methods

Linkages

Women provided written informed consent and Regional Ethics Committees approved the health surveys and record linkages (REK 2010/260, REK Southeast). The Medical Birth Registry involves compulsory recording of medical characteristics of births of gestational age 16 weeks or greater.¹ Linkages between the health surveys participating in Cohort Norway (CONOR) and the Medical Birth Registry of Norway enabled review of births prior to CONOR participation for determining the presence of a history of either gestational hypertension or preeclampsia prior to CONOR participation. Further, the linkages to births after CONOR participation enabled the prospective evaluation of CONOR risk factors as predictors of subsequent gestational hypertension or preeclampsia.

Exclusions

Exclusions included preexisting hypertension (antihypertensive medications reported in CONOR, n=275; or pregravid hypertension noted in the Medical Birth Registry, n=133); nonviable births (i.e., gestational age < 22 weeks, n=65, or a birth weight < 500 g if gestational age was missing, n=7);² mother pregnant during or delivered less than one year prior to CONOR participation (n=3,100); and multiple birth pregnancies (n=661). With minor overlap, a total of 4,103 were excluded, resulting in 13,217 singleton births for analyses (representing 8,321 women and 1.59 births/woman) (Figure S1).

Preexisting history of gestational hypertension or preeclampsia

Of 13,217 singleton births, 4,764 (36%) had a sibling born prior to mother's CONOR participation; 5.8 % had either gestational hypertension or preeclampsia noted in the Medical Birth Registry prior to CONOR participation.

Determination of Preterm and Term Deliveries

Some misclassification of term and preterm deliveries always exists. Of the 287 pregnancies where gestational age was missing, 14 were preterm based on their birthweight (11 preterm of 275 normotensive pregnancies, and 3 preterm preeclampsia pregnancies). Further, the extent of misclassification of term and preterm deliveries was evaluated in a subset of the study population which had both ultrasound and last menstrual period date available and was found to be negligible.

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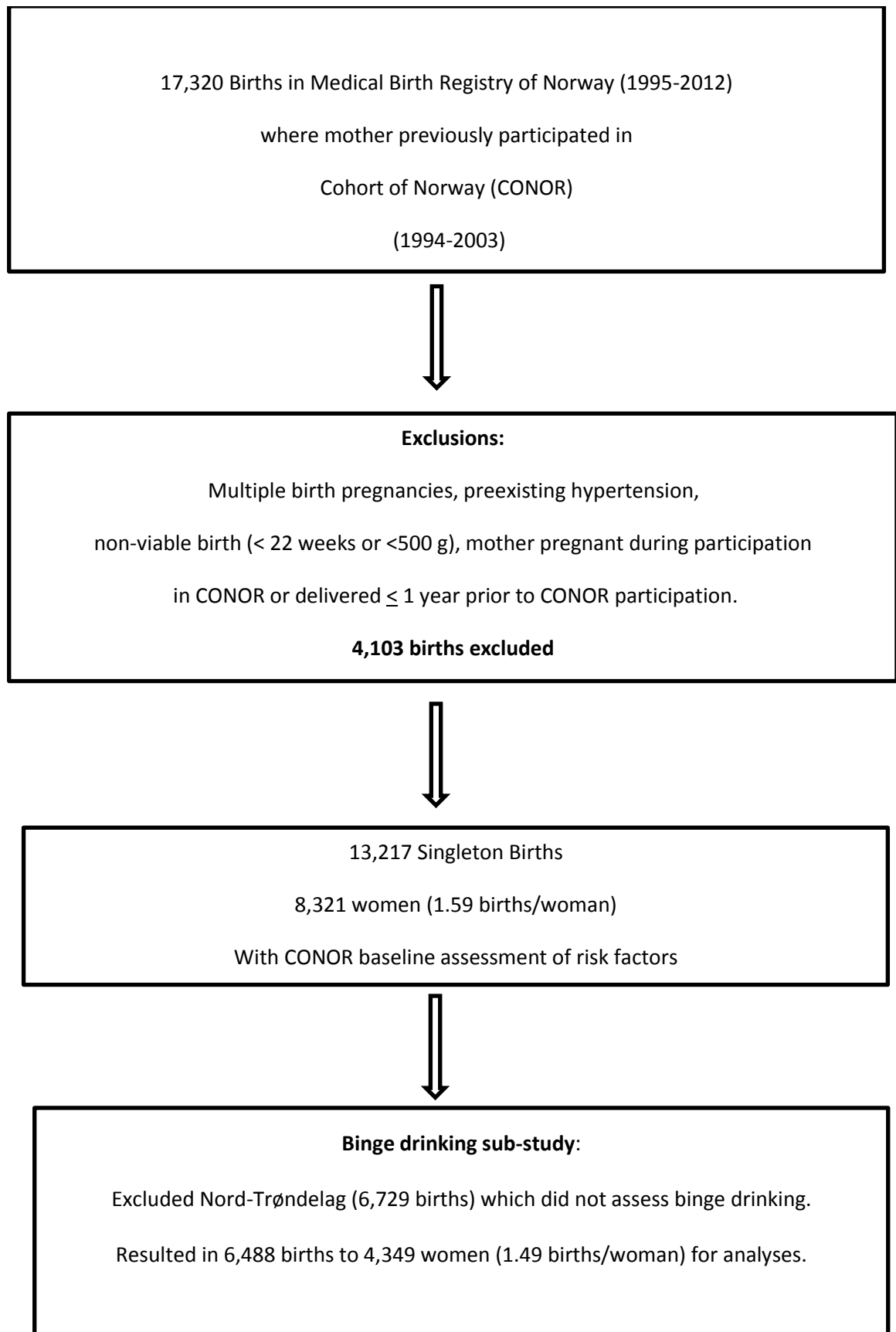


Figure S1. Flow diagram of participants in the current study.