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ORIGINAL RESEARCH ARTICLE

Pregestational maternal risk factors for preterm and term preeclampsia: A population-based cohort study

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Abstract

Introduction: Most studies on factors affecting the risk of preeclampsia have not separated preterm from term preeclampsia, and we still know little about whether the predisposing conditions have a differentiated effect on the risk of preterm and term preeclampsia. Our aim was to assess whether diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis and chronic hypertension were differentially associated with preterm and term preeclampsia.

Material and methods: This is a nationwide, population-based cohort study containing all births registered in the Medical Birth Registry of Norway from 1999 to 2016. Multinomial logistic regression analysis was used to estimate relative risk ratios (RRRs) with 95% confidence intervals (95% CIs), adjusting for maternal age, parity, multiple gestation and all other studied maternal risk factors.

Results: We registered 1 044 860 deliveries, of which 9533 (0.9%) women had preterm preeclampsia (<37 weeks) and 26 504 (2.5%) women had term preeclampsia (>37 weeks). Most of the assessed maternal risk factors were associated with increased risk for both preterm and term preeclampsia, with adjusted RRRs ranging from 1.2 to 10.5 (preterm vs no preeclampsia) and 0.9–5.7 (term vs no preeclampsia). Diabetes type 1 and 2 (RRR preterm vs term preeclampsia 2.89, 95% CI 2.46–3.39 and RRR 1.68, 95% CI 1.25–2.25, respectively), chronic kidney disease (RRR 1.55, 95% CI 1.11–2.17) and chronic hypertension (RRR 1.85, 95% CI 1.63–2.10) were more strongly associated with preterm than term preeclampsia in adjusted analyses. For asthma, epilepsy and rheumatoid arthritis, RRRs were closer to one and not significant when comparing risk of preterm and term preeclampsia. Main results were similar when using a diagnosis at <34 weeks to define preterm preeclampsia.

Conclusions: Diabetes type 1 and 2, chronic kidney disease and chronic hypertension were more strongly associated with preterm than term preeclampsia.

KEYWORDS
epidemiology, risk factors, preterm preeclampsia, term preeclampsia

Abbreviations: BMI, body mass index; CI, confidence interval; MBRN, The Medical Birth Registry of Norway; RRR, relative risk ratio.

1 | INTRODUCTION

Preeclampsia is a common cause of morbidity and mortality for both mothers and children worldwide[1] and has been categorized into a preterm and a term entity.[2] However, few population-based studies have assessed risk factors by the two entities separately.[3] Preterm preeclampsia is considered more severe than term preeclampsia, as it is more strongly associated with fetal growth restriction and preterm delivery.[4,5]

No curative treatment is available for either preterm or term preeclampsia. It is shown that preterm preeclampsia can be effectively prevented by prophylactic use of acetylsalicylic acid from around gestational week 12.[6] To offer prophylaxis to women most in need of this treatment, clinicians are dependent on identifying women at high risk of preterm preeclampsia early in pregnancy, preferably during the first trimester.[6]

Risk factors that only increase the risk of preterm preeclampsia and not term preeclampsia will easily be missed in studies not separating the two entities, as term preeclampsia is a much more prevalent pregnancy complication.[6] Chronic hypertension, type 1 diabetes and maternal allergy are more strongly associated with preterm than term preeclampsia.[7,8] However, it is not known whether this is also the case for other well-known predisposing conditions, such as type 2 diabetes, chronic kidney disease, asthma, epilepsy and rheumatoid arthritis. Some studies have found that chronic kidney disease and diabetes (not separating type 1 and 2) are risk factors for term preeclampsia.[8,9] All the predisposing conditions are mainly immunological and have in previous studies been found to be associated with preeclampsia, although not separated by its preterm and term entity.[10–15] Evidence suggests that autoimmune mechanisms are also involved in epilepsy.[16] In addition to increasing the risk for preeclampsia, asthma is associated with allergy, which is found to increase the risk for early-onset preeclampsia.[7] There is also evidence that children born from preeclamptic mothers are at increased risk for developing asthma[17] and allergic sensitization[18] during childhood.

As it has been shown that early prediction and prevention of preeclampsia is possible, it is important to understand how different risk factors are associated with the two entities of preeclampsia. Use of maternal risk factors combined with mean arterial blood pressure, uterine arterial pulsatile index and maternal serum levels of placental growth factor and pregnancy-associated plasma protein-A, is better than screening based on maternal risk factors alone.[3] Ultimately, assessing other well-known maternal risk factors by preterm and term preeclampsia may further improve detection rates when using such algorithms and may enable better prevention of preeclampsia using prophylactic acetylsalicylic acid.

The specific aim of this study was to assess whether diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis and chronic hypertension were more strongly associated with preterm than with term preeclampsia.

Key message

We have little knowledge about whether the well-known risk factors for preeclampsia have a differentiated association on preterm and term preeclampsia. Diabetes type 1 and 2, chronic kidney disease and chronic hypertension were more strongly associated with preterm than term preeclampsia.

2 | MATERIAL AND METHODS

This is a nationwide population-based cohort study with prospectively collected data from The Medical Birth Registry of Norway (MBRN). All women giving birth in Norway from 1999 to 2016 were included. Deliveries of second born twins or higher order, missing gestational age, gestational age <19+6 weeks, and gestational age >44 weeks were excluded.

The MBRN is a compulsory national health register that holds information on pregestational conditions and prenatal-, peri-partum and post-natal care on all births in Norway. Information on pregestational conditions and previous pregnancies is registered at the first antenatal visit by the midwife or the general practitioner and written on the antenatal health card. The general practitioner usually keeps a record of the women's health since childhood. This form is used for follow-up throughout pregnancy and all noted information is sent electronically to the MBRN a few days postnatally by the attending midwife or obstetrician. The MBRN includes information on all pregnancies continuing past gestational week 12.

From the MBRN, we obtained the following pregestational conditions: Diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis and chronic hypertension. In addition, we obtained data on the occurrence of preeclampsia, early-onset preeclampsia, gestational age at delivery in days, date of delivery, maternal age, parity, occurrence of multiple pregnancies and pre-pregnancy body mass index (BMI).

In the MBRN, the infant is the counting unit. This means that all multiple pregnancies are registered as two or more deliveries. To make delivery the counting unit, second twins or higher orders were excluded.

The diagnostic criteria of preeclampsia have been changed in the past few years and it is now defined as new onset of hypertension after 20 weeks of pregnancy accompanied by one or more of the following conditions: proteinuria, renal insufficiency, liver involvement, neurological complications, hematological complications or uteroplacental dysfunction. Our dataset is from 1999 to 2016, and the participants were diagnosed with preeclampsia as it was then defined by the Norwegian Society of Gynecology and Obstetrics. This definition corresponded with the guidelines from the National Institute for Health and Care Excellence (NICE guidelines) at the time: proteinuria ≥ +1 on a dipstick, >0.3 g urine protein loss per 24 hours or a protein/creatinine ratio >0.3 and repeated measurements of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg after 20 weeks' gestational age (ICD-10: O11, O14.0, O14.1, O14.2, O14.9).[19] We defined preterm and term

preeclampsia as preeclampsia resulting in delivery before and after gestational week 37 in our main analyses. This definition is the current definition recommended by the International Society of the Study of Hypertension in Pregnancy.[20] We also did separate analyses where we defined early-onset and late-onset preeclampsia as preeclampsia diagnosed before and after gestational week 34, respectively. Registration of preeclampsia in the MBRN has been validated and found of high quality.[21]

2.1 | Statistical methods

Relative risk ratios (RRRs) with 95% confidence intervals (95% CI) for preterm preeclampsia and term preeclampsia vs no preeclampsia were estimated for each maternal risk factor using multinomial logistic regression. In addition, we compared relative risks of preterm and term preeclampsia. Cluster robust standard errors were used to account for repeated pregnancies in the same woman.

First, RRRs were estimated for each risk factor separately, adjusting for mother's age, parity and multiple gestation. In separate analyses, we additionally adjusted for diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis and chronic hypertension, as well as maternal age, parity and multiple gestation. In both analyses, maternal age was modeled non-linearly using restricted cubic splines with four knots, with number of knots decided by the Bayesian information criterion.

The registration of BMI in the MBRN started in 2006 and the proportion of deliveries where BMI was registered increased successively up until 2014, when the registration exceeded 70%. Thus, BMI was available in a subsample of registered deliveries. Separate analyses were performed for women with registered BMI, using the same strategy as described above, with additional adjustment for BMI modeled with restricted cubic splines with four knots.

Results from the fully adjusted model were illustrated in plots showing predicted proportions of preterm and term preeclampsia with 95% confidence intervals for each maternal risk factor. In addition, we present predicted proportions of preterm and term preeclampsia from unadjusted models given maternal age and BMI, with effects modeled using restricted cubic splines with four knots.

Data preparations were done in IBM SPSS Statistics for Windows (Version 26.0.0.1 Armonk, NY, USA, 2019) and analyses were done in STATA (Release 17. College Station, TX: Stata Corp LLC. Stata Corp, 2019) with functions mlogit, rc_spline, margins, marginsplot and mplotoffset.

We created a focus group of women with preeclampsia that assessed the background of our study and the proposed methods. Useful comments regarding risk factors for preeclampsia were suggested, and valuable insight into the use of patient and public involvement was presented through the discussions in our group. The group members agreed that the data protection seemed satisfactory in the proposed design of our study. The protocol was also assessed by the committee of user representatives at Stavanger University Hospital.

2.2 | Ethics statement

Research using an anonymous health register data are exempt from consent requirements from the research ethics committees in Norway. The exemption was approved by the ethics committee of the Western Norwegian Regional Health Authorities on 7 April 2017 (2017/292/REK vest). The Data Protection Impact Assessment was approved by the data protection officer at Stavanger University Hospital and access to data was approved by the Norwegian Institute of Public Health.

3 | RESULTS

The outline of the study population is presented in Figure 1. The MBRN contained information on 1 075 637 born infants during 1999–2016. After exclusion of second born twins or higher order ($n = 19\,035$), missing gestational age ($n = 7089$), gestational age <19+6 weeks ($n = 4108$) and gestational age >44 weeks ($n = 545$), we were left with 1 044 860 deliveries for the main analyses. Among these, there were 36 037 (3.4%) with preeclampsia – 9533 (0.9%) preterm and 26 504 (2.5%) term preeclampsia.

Population characteristics are outlined in Table 1. Maternal age were similar in the three groups: no preeclampsia, preterm and term preeclampsia. As expected, nulliparous and multiple pregnancies were more common in the preeclampsia groups than in the no preeclampsia group.

Main analyses are presented in Table 2 and illustrated in Figure 2. When adjusting for all other maternal risk factors in addition to age, parity and multiple births, diabetes type 1 (RRR 2.89, 95% CI 2.46–3.39), diabetes type 2 (RRR 1.68, 95% CI 1.25–2.25), chronic kidney disease (RRR 1.55, 95% CI 1.11–2.17) and chronic hypertension (RRR 1.85, 95% CI 1.63–2.10) were more strongly associated with preterm preeclampsia than with term preeclampsia. The adjusted RRRs for asthma, epilepsy and rheumatoid arthritis were 0.93 (95% CI 0.84–1.03), 1.14 (95% CI 0.90–1.45) and 1.33 (95% CI 0.93–1.91), respectively.

Population characteristics in the subgroup of 310 399 women with registered pre-pregnancy BMI are equivalent to the characteristics of the total study population and are presented in Table 3.

In Table 4 we present RRRs adjusted for the same variables as in main analyses (Table 2), plus BMI, for the subgroup for which we had access to BMI. Diabetes type 1 (RRR 2.95, 2.16–4.02) and type 2 (RRR 1.74, 95% CI 1.05–2.88), and chronic hypertension (RRR 1.87, 95% CI 1.46–2.40) were still more strongly associated with preterm than with term preeclampsia, with point estimates similar to estimates from main analyses. For chronic kidney disease, the adjusted RRR was slightly lower than in the main analyses, and not significant (RRR 1.38, 95% CI 0.72–2.66). After adjusting for BMI, the association for diabetes type 2 on term preeclampsia is not as strong as in the main analysis (RRR 1.63, 95% CI 1.19–2.24), indicating the confounding effect of BMI on this association.

The unadjusted effects of maternal age and BMI on risk of preterm and term preeclampsia are presented in prediction plots

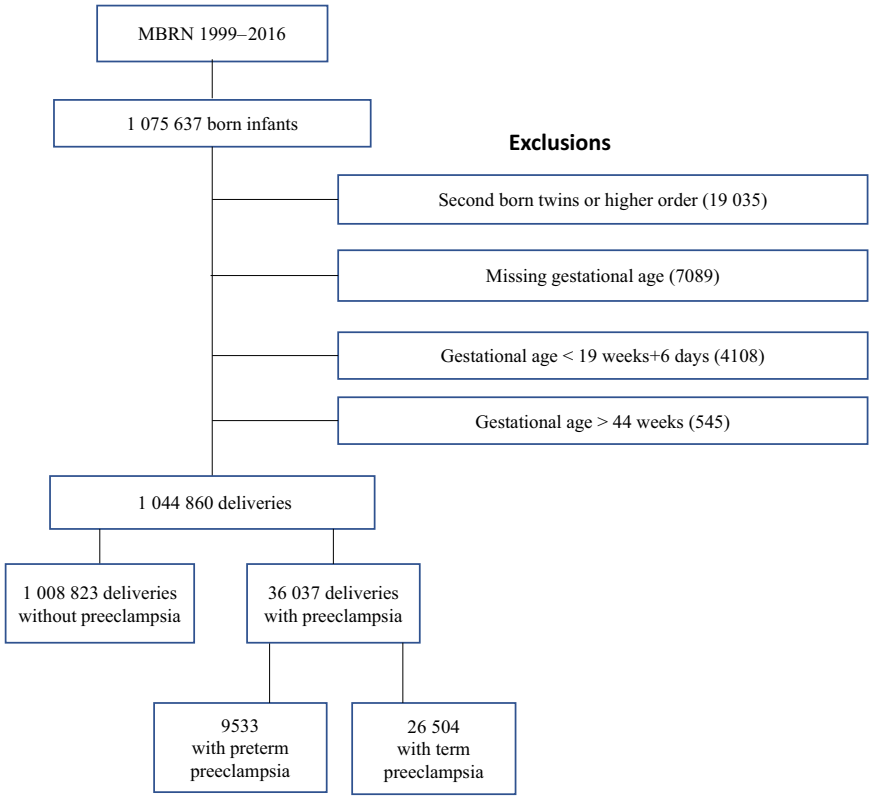

FIGURE 1 Flow chart, Medical Birth Registry of Norway (MBRN), 1999–2016.

TABLE 1 Population characteristics and pregestational maternal risk factors in 1 044 860 pregnancies by preterm, term and no preeclampsia, Medical Birth Registry of Norway, 1999–2016.

	No preeclampsia *n* (%)	Preterm preeclampsia *n* (%)	Term preeclampsia *n* (%)
Total	1 008 823 (96.6)	9533 (0.9)	26 504 (2.5)
Maternal age, mean (SD)	29.7 (5.1)	29.8 (5.6)	29.2 (5.5)
Parity			
Nulliparous (435 501)	413 670 (41.0)	5745 (60.3)	16 086 (60.7)
Multiparous (609 359)	595 153 (59.0)	3788 (39.7)	10 418 (39.3)
Multiple pregnancy			
Singletons (1 026 437)	992 517 (98.4)	8236 (86.4)	25 684 (96.9)
Multiples (18 423)	16 306 (1.6)	1297 (13.6)	820 (3.1)
Predisposing factors			
Type 1 diabetes (4722)	4041 (0.4)	346 (3.6)	335 (1.3)
Type 2 diabetes (2430)	2204 (0.2)	93 (1.0)	133 (0.5)
Kidney disease (3080)	2928 (0.3)	57 (0.6)	95 (0.4)
Asthma (46 555)	44 501 (4.4)	514 (5.4)	1540 (5.8)
Epilepsy (7235)	6887 (0.7)	104 (1.1)	244 (0.9)
Rheumatoid arthritis (3550)	3413 (0.3)	48 (0.5)	89 (0.3)
Hypertension (5885)	4726 (0.5)	480 (5.1)	679 (2.6)

(Figures 3 and 4). Maternal age has a classical U-shaped curve with predicted proportions at the lowest point when the women are in their early thirties. For BMI there is an abrupt increase in predicted proportion around a BMI of 23.

When using the definition for the two entities registered in MBRN, early-onset and late-onset preeclampsia as diagnosed before or after 34 weeks of gestation, respectively, we found that diabetes type 1, diabetes type 2, chronic kidney disease, chronic hypertension and rheumatoid arthritis were more strongly associated with early-onset preeclampsia than with late-onset preeclampsia (Tables S1 and S2).

Crude RRRs for both definitions (preterm/term and early-onset/late-onset) of preeclampsia were similar to the main analysis for diabetes type 1, diabetes type 2, chronic kidney disease, chronic

TABLE 2 Adjusted relative risk ratios (RRRs) with 95% confidence intervals (95% CIs) for preterm preeclampsia vs no preeclampsia (no PE), term preeclampsia vs no PE and preterm vs term preeclampsia by maternal risk factors. Estimates were obtained by multinomial logistic regression in 1 044 860 deliveries, Medical Birth Registry of Norway, 1999–2016.

	Adjusted[a] RRRs (95% CIs)			Adjusted[b] RRRs (95% CIs)		
Maternal risk factors	Preterm vs no PE	Term vs no PE	Preterm vs term	Preterm vs no PE	Term vs no PE	Preterm vs term
Diabetes type 1	9.70 (8.55–11.00)	3.21 (2.86–3.62)	3.02 (2.57–3.54)	8.92 (7.83–10.15)	3.09 (2.74–3.48)	2.89 (2.46–3.39)
Diabetes type 2	4.64 (3.65–5.90)	2.45 (2.05–2.93)	1.89 (1.42–2.53)	3.53 (2.73–4.58)	2.10 (1.75–2.53)	1.68 (1.25–2.25)
Chronic kidney disease	2.01 (1.54–2.64)	1.18 (0.96–1.46)	1.70 (1.22–2.38)	1.74 (1.31–2.29)	1.12 (0.90–1.38)	1.55 (1.11–2.17)
Asthma	1.22 (1.11–1.34)	1.30 (1.23–1.38)	0.94 (0.84–1.04)	1.20 (1.09–1.31)	1.29 (1.22–1.36)	0.93 (0.84–1.03)
Epilepsy	1.60 (1.30–1.96)	1.33 (1.16–1.53)	1.20 (0.94–1.52)	1.44 (1.17–1.77)	1.26 (1.10–1.45)	1.14 (0.90–1.45)
Rheumatoid arthritis	1.39 (1.03–1.86)	0.97 (0.79–1.20)	1.42 (1.00–2.03)	1.23 (0.91–1.66)	0.92 (0.74–1.14)	1.33 (0.93–1.91)
Chronic hypertension	11.65 (10.50–12.93)	5.89 (5.40–6.42)	1.98 (1.75–2.24)	10.46 (9.38–11.66)	5.65 (5.18–6.17)	1.85 (1.63–2.10)

Abbreviation: PE, preeclampsia.

[a]Adjusted for age, parity and multiple births.

[b]Adjusted for maternal age, parity, multiple births and all other risk factors.

hypertension and rheumatoid arthritis, but the associations were a bit stronger (Table S3).

4 | DISCUSSION

Diabetes type 1 and 2, chronic kidney disease and chronic hypertension were more strongly associated with preterm than with term preeclampsia. The first three are all immunological diseases, and we believe that our findings indicate that preeclampsia is a disease with a large immunological component. The risk of preterm preeclampsia has its lowest point when the woman is in her early 30s, possibly when she has her second child and is benefitting from being both multipara and relatively young.

The pathophysiology of preeclampsia is still incompletely understood. Insufficient remodeling of the spiral arteries are thought to be important, in addition to different immunological factors that are believed to play a significant role in development of preeclampsia.[22] Diabetes type 1 and 2, chronic kidney disease and rheumatoid arthritis are all immunological diseases, and a common feature is their increased levels of pro-inflammatory interleukin-6 in affected individuals.[23] Elevated levels of interleukin-6 are also seen in people with high BMI[24] and might explain the increase in predicted proportions when BMI exceeds 23. Levels of interleukin-6 in normal pregnancies decrease from the first and throughout most of the second trimester, when levels slowly increase again through the third trimester. Interleukin-6 levels also continue to rise a few months postpartum.[25] Previous studies show elevated levels of interleukin-6 in women with preeclampsia.[26,27] This indicates that preeclampsia is a condition with a large immunological component. Additional knowledge about pathogenesis, maternal pregestational risk factors and their different association with preterm and term preeclampsia may help in developing more individualized follow-up throughout pregnancy. This may ultimately pave the way for new and better treatments for women at highest risk.

Early screening of preeclampsia is most useful when maternal characteristics and medical history is added in an algorithm based on multivariate regression analyses. If all pregestational risk factors are given the same weight in risk calculations, more than half of the pregnant population is at high risk and would thus need closer follow-up during pregnancy.[28] When constructing such algorithms, one must quantify the association between the different risk factors and preterm and term preeclampsia. This way, development of preterm and term preeclampsia can be more accurately predicted. Previous studies have shown that by using algorithms containing maternal factors, uterine artery pulsatile index, mean arterial blood pressure and biophysical markers such as pregnancy-associated plasma protein-A, placental growth factor, Inhibin-A, Activin-A and s-Endoglin, one can predict 91% of preterm preeclampsia and 61% of term preeclampsia. Both assessments have a false-positive rate of 5%.[29] By estimating risk factors association with both preterm and term preeclampsia, we believe that our study contributes to this field and can help improve the accuracy of existing algorithms.

A noteworthy and interesting finding from our study, particularly related to well-known confounders for preeclampsia, is that preeclampsia increases with increasing maternal age in parallel for both its preterm and term entity, whereas this was not the case for BMI (Figures 3 and 4). Increasing BMI is particularly associated with increasing risk of term preeclampsia. This has earlier been found when using 34 weeks' gestation as a cut-off for early and late onset preeclampsia.[30]

Our study has several strengths. Data were collected from a large national database, with comprehensive clinical data. Information on pregestational conditions was gathered in an interview during the first trimester by the responsible midwife or

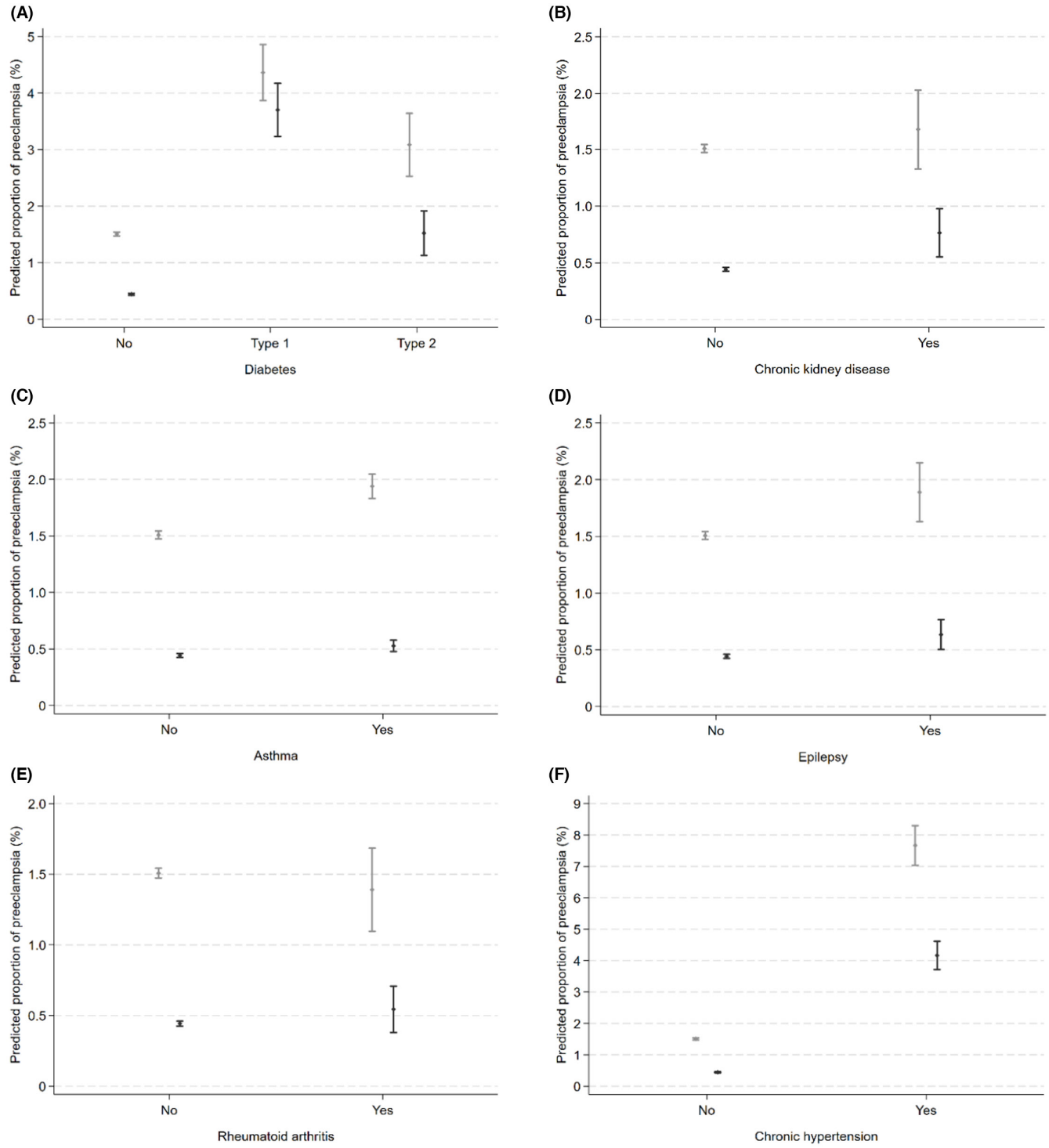

FIGURE 2 Predicted proportions (%) with 95% confidence intervals of preterm (dark gray) and term (light gray) preeclampsia according to presence of maternal risk factors: (A) diabetes, (B) chronic kidney disease, (C) asthma, (D) epilepsy, (E) rheumatoid arthritis and (F) chronic hypertension. Predicted proportions are based on the fully adjusted model presented in Table 2, and given presence of no other risk factors, age 30 years, multiparity and singleton pregnancy.

general practitioner, and additional information was prospectively added throughout pregnancy. All information is noted on the antenatal health card for pregnant women in Norway, and the form is brought to the delivery ward when the woman is in labor. After delivery, all collected information on pregestational and gestational conditions together with information regarding delivery and the postpartum period is sent electronically to the MBRN by the attending midwife.

With a large sample size, we were able to identify associations between preterm preeclampsia, a rare condition in itself, and

TABLE 3 Population characteristics and pregestational maternal risk factors in 310 399 pregnancies with registered maternal BMI by preterm, term and no preeclampsia, Medical Birth Registry of Norway, 2006–2016.

	No preeclampsia	Preterm preeclampsia	Term preeclampsia
	n (%)	<37 (%)	>37 (%)
Total (310 399)	300 867 (96.9)	2433 (0.8)	7099 (2.3)
Maternal age, mean (SD)	29.9 (5.1)	30.3 (5.9)	29.4 (5.6)
BMI, mean (SD)	24.3 (4.7)	26.1 (5.5)	26.5 (5.8)
Parity			
Nulliparous (134 718)	128 820 (42.8)	1487 (61.1)	4411 (62.1)
Multiparous (175 681)	172 047 (57.2)	946 (38.9)	2688 (37.9)
Multiple pregnancy			
Singletons (305 216)	296 267 (98.5)	2064 (84.8)	6885 (97.0)
Multiples (5183)	4600 (1.5)	369 (15.2)	214 (3.0)
Predisposing factors			
Type 1 diabetes (1316)	1141 (0.4)	87 (3.6)	88 (1.2)
Type 2 diabetes (750)	677 (0.2)	28 (1.2)	45 (0.6)
Kidney disease (1261)	1220 (0.4)	14 (0.6)	27 (0.4)
Asthma (16 125)	15 532 (5.2)	152 (6.2)	441 (6.2)
Epilepsy (1946)	1858 (0.6)	28 (1.2)	60 (0.8)
Rheumatoid arthritis (1429)	1387 (0.5)	12 (0.5)	30 (0.4)
Hypertension (1921)	1589 (0.5)	129 (5.3)	203 (2.9)

TABLE 4 Adjusted relative risk ratios (RRRs) with 95% confidence intervals (95% CIs) for preterm preeclampsia vs no preeclampsia (no PE), term preeclampsia vs no PE and preterm vs term preeclampsia by maternal risk factors in 310 399 births with information on body mass index. Estimates were obtained by multinomial logistic regression, Medical Birth Registry of Norway, 2006–2016.

	Adjusted[a] RRRs (95% CIs)		
Maternal risk factors	Preterm vs no PE	Term vs no PE	Preterm vs term
Diabetes type 1	8.32 (6.50–10.64)	2.82 (2.24–3.55)	2.95 (2.16–4.02)
Diabetes type 2	2.84 (1.83–4.41)	1.63 (1.19–2.24)	1.74 (1.05–2.88)
Chronic kidney disease	1.26 (0.73–2.18)	0.91 (0.62–1.35)	1.38 (0.72–2.66)
Asthma	1.08 (0.91–1.28)	1.03 (0.93–1.14)	1.05 (0.87–1.27)
Epilepsy	1.83 (1.21–2.75)	1.29 (0.98–1.68)	1.42 (0.88–2.30)
Rheumatoid arthritis	0.80 (0.44–1.47)	0.83 (0.58–1.20)	0.97 (0.48–1.93)
Chronic hypertension	7.35 (5.94–9.09)	3.93 (3.33–4.63)	1.87 (1.46–2.40)

Abbreviation: PE, preeclampsia.

[a]Adjusted for maternal age, parity, multiple births, all other risk factors and body mass index.

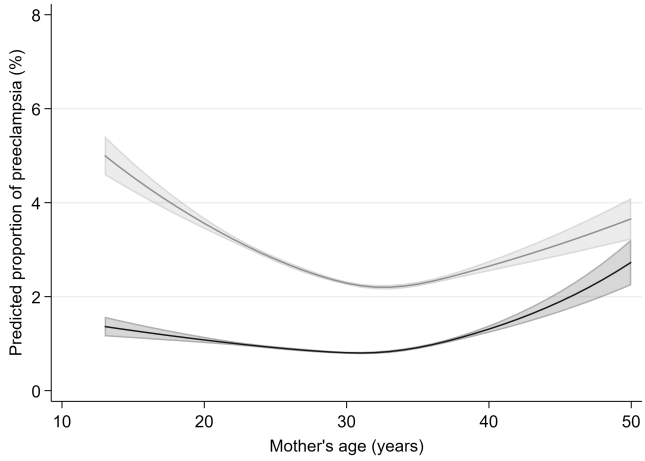

FIGURE 3 Predicted proportions (%) with 95% confidence intervals of preterm (dark gray) and term (light gray) preeclampsia according to maternal age using restricted cubic splines with four knots. Medical Birth Registry of Norway, 1999–2016, based on 1 044 860 pregnancies.

conditions with low prevalence in the obstetric population, such as chronic kidney disease.[11]

The main limitation of our study is that the data are self-reported, so recall bias might be an issue. The information on pregestational conditions is obtained by a midwife or the general practitioner. Although we do not know whether the information on pregestational conditions is the woman's own interpretation of her condition, we do know that most general practitioners in Norway have a thorough knowledge of their patient's medical history gathered from the general practitioner's health record system. Also, self-reported data in pregnancy are considered reasonably valid,[31] and the incidence of pregestational maternal risk factors in our study is in line with previous findings,[10,12,13,32] indicating that our database is most likely valid.[21] The precise gestational age at the time of diagnosis is not specifically recorded in the MBRN. Within the investigated time frame, preeclampsia is defined as either early-onset or late-onset preeclampsia based on whether the diagnosis was set before or after gestational week 34. This is the available variable provided for our

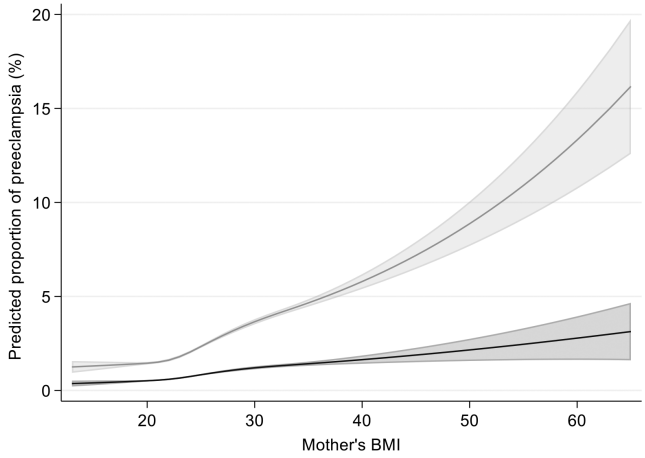

FIGURE 4 Predicted proportions (%) with 95% confidence intervals of preterm (dark gray) and term (light gray) preeclampsia according to maternal body mass index (BMI) using restricted cubic splines with four knots. Medical Birth Registry of Norway, 2006–2016, based on 310 399 pregnancies with available data on BMI.

analysis through the MBRN. However, since we had access to information on ultrasound-based due dates and dates of birth, we could create the variables "Preeclampsia resulting in delivery before or after gestational week 37". In addition, BMI was registered in the MBRN only from 2006, which limited our ability to account for its possibly confounding effect in main analyses.

5 | CONCLUSION

All the assessed risk factors were associated with preeclampsia. Diabetes type 1 and 2, chronic kidney disease and chronic hypertension were more strongly associated with preterm than term preeclampsia. Asthma, epilepsy and rheumatoid arthritis were not associated differently with preterm vs term preeclampsia. We believe our study may be a valuable contribution for creating better accuracy in existing algorithms used for early prediction of preeclampsia.

AUTHOR CONTRIBUTIONS

AKS, EAT, RKS, and NHM have all participated in the conception of the idea, writing of the protocol, application for funding and application for ethical approval. ID conducted the statistical analysis with support from AKS, RKS and NHM. AKS, ID, EAT, RKS and NHM have all participated in writing the paper. All authors have approved the final version.

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CONFLICT OF INTEREST STATEMENT

AKS, ID and EAT have no conflicts of interest to declare. RKS is at the board of the Nordic Federation of Societies of Obstetrics and Gynecology. Other than this, he has no conflicts of interest to declare. NHM is a former associate editor of AOGS. Other than this, he has no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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