Early-onset preeclampsia in the balance of Immunology and Pregnancy: Risk factors, the Role of Allergy, and potential protection by Antihistamine use

Anne Kvie Sande

Thesis for the degree of Philosophiae Doctor (PhD)
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UNIVERSITY OF BERGEN

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Contents

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UNIVERSITY OF BERGEN
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Stavanger universitetssjukehus

VAKEN I VATN

Ho søv
men
den
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Snart
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og ei stund
vil den ufødde
vaka aleine
medan regnet fell
der ute
bakom ryggtavla hans

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Abbreviations:

ACOG American College of Obstetricians and Gynecologists

ART Assisted Reproductive Techniques

BMI Body Mass Index

CI Confidence Interval

DAO Diamine Oxidase

GLUT1 Glucose transporter 1

hCG Human Chorionic Gonadotropin

HELLP Hemolysis, elevated liver enzymes, and low platelets

HLA Human Leukocyte Antigen

hPL Human Placental Lactogen

IFN-γ Interferon γ

Ig Immunoglobuline

IL Interleukin

ISSHP International Society for the Study of Hypertension in Pregnancy

IUGR Intra Uterine Growth Restriction

KI Konfidensintervall

uNK cells uterine Natural Killer cells

LMP Last Menstrual Period

LMWH Low Molecular Weight Heparin

MBRN Medical Birth registry of Norway

MFR Medisinsk fødselsregister

NGF Norwegian Society of Obstetricians and and Gynecologists

NICE The National Institute for Health and Care Excellence

NIPH Norwegian Institute of Public Health

NorPD Norwegian Prescription Database

NS Non-significant

OR Odds Ratio

PAPP-A Pregnancy Associated Plasma Protein-A

PlGF Placental growth factor

PCOS Polycystic Ovary Syndrome

RCT Randomized Controlled Trial

SGA Small for Gestational Age

SLE Systemic Lupus Erythematosus

TGF-β Transforming Groth Factor β

TNF-α Tumor Necrosis Factor α

VEGF Endothelial vascular growth factor

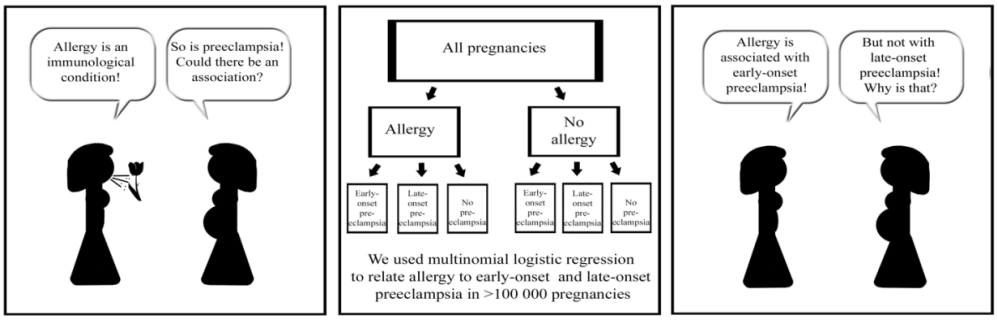
WHO The World´s Health Organization

RR Relative Risk

RRR Relative Risk Ratios

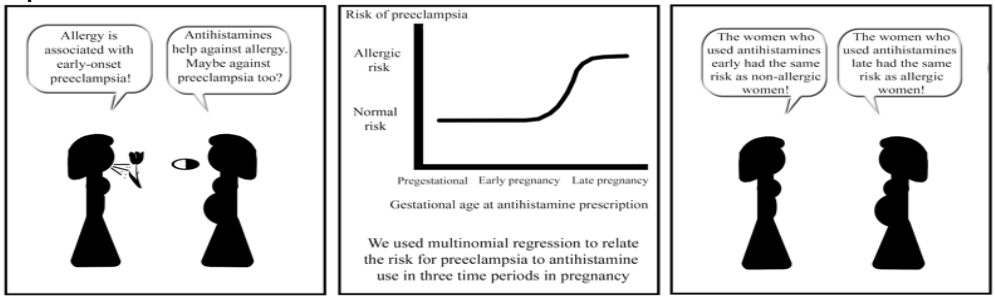
Thesis at a glance

Paper I



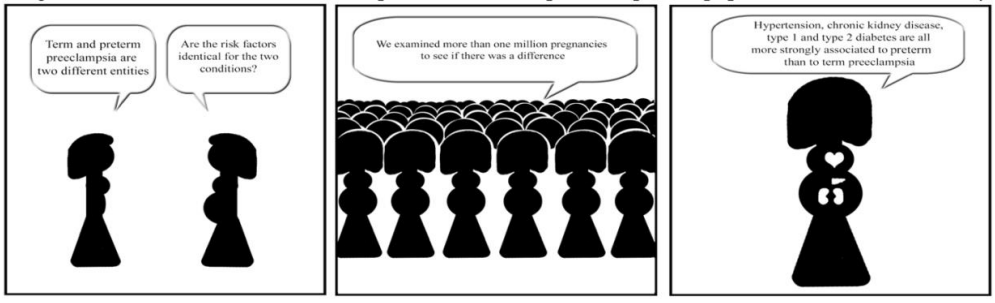
Question: Is pregestational maternal allergy associated with early-onset and late -onset preeclampsia?
Study population and period: Women giving birth in Stavanger and Bergen 1996-2014.
Exposure: Pregestational maternal allergy.
Outcome: Early-onset and late-onset preeclampsia.

Paper II



Question: Can antihistamine use in pregnancy protect against development of early-onset preeclampsia?
Study population and period: All women giving birth in Norway 2004-2016.
Exposure: Use of antihistamines.
Outcome: Early-onset preeclampsia.

Paper III



Question: Is diabetes type I and II, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension differentially associated with preterm and term preeclampsia?
Study population and period: All women giving birth in Norway 1999-2016.
Exposure: Diabetes type I and II, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension.
Outcome: Preterm and term preeclampsia.

Abstract in english

Background: Preeclampsia is divided in an early-onset and a late-onset variant. Current knowledge about well-known risk factors and their association with the two variants of preeclampsia is scarce.

Overall aim:
To investigate associations between maternal pregestational risk factors and early- (<34 and <37) and late-onset (≥34 and ≥37) preeclampsia and to assess whether maternal use of antihistamines in pregnancy affect risk of early-onset preeclampsia.

Methods: Three population-based cohort studies were conducted.
Paper I: Women giving birth in Stavanger (1996-2014) and Bergen (2009-2014) with recorded data in the electronic medical record system were included. Multinomial logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (95% CI) for early and late-onset preeclampsia (< and ≥34 weeks) in women with pre-gestational allergy and compared to women without allergy, adjusting for covariates.
Paper II: Linked data from the Medical Birth Registry of Norway (MBRN) and the Norwegian Prescription Database (NorPD) on all women giving birth in Norway between 2004-2016. We postulated that women who had been prescribed antihistamines containing an ICD-10 code for allergy in the NorPD, suffered from allergy. Use of antihistamines was divided into four groups: Before pregnancy (from 6 months before and to the last menstrual period (LMP)), early pregnancy (From LMP to week 20), and late pregnancy (from week 20 to week 36). Women receiving antihistamines in more than one period were treated as a separate, fourth group. We used binomial logistic regression models, with random effects component to estimate ORs with 95% CIs for development of early-onset preeclampsia (< and ≥34 weeks) by prescribed antihistamines in the four exposure groups compared to women not using antihistamines. Estimates were adjusted for maternal age and stratified for parity and multiple gestation.
Paper III: Data from the MBRN from 1999-2016 were used. We registered type 1 and 2 diabetes, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and hypertension. Multinomial logistic regression was used to estimate relative risk ratios (RRRs) with 95% CIs for preterm and term preeclampsia (delivery< and ≥ 37 weeks), adjusting for maternal age and parity. Separate analyses were done for pregnancies with registered BMI.

Results:
Paper 1: Pregestational maternal allergy enhanced the risk for early-onset preeclampsia with an OR of 1.8 (95% CI: 1.3-2.4). Conversely, pregestational maternal allergy reduces the risk for late-onset preeclampsia with an OR of 0.8 (95% CI: 0.7-0.9). There is a significant difference in the association of allergy on early-onset and late-onset preeclampsia, with an OR of 2.2 (95% CI: 1.6-3.1).
Paper II: Predicted proportions of early-onset preeclampsia <34 weeks were significantly lower in women using antihistamines before (0.41%, 95% CI 0.34-0.49) and in early pregnancy (0.37%, 95% CI 0.31-0.44), compared to women using antihistamines after placentation (0.69%, 95% CI 0.57-0.83). Results were similar for preeclampsia <37 weeks.
Paper III: Four predisposing factors were associated with increased risk for both preterm and term preeclampsia, but with a significantly larger association on preterm preeclampsia: Type 1 and type 2 diabetes (RRR 2.89, 95% CI 2.46-3.39 and 1.68, 95% CI 1.25-2.25, respectively), chronic kidney disease (RRR 1.55, 95% CI 1.11- 2.17), and hypertension

(RRR 1.85, 95% CI 1.63-2.10). Asthma, epilepsy, and rheumatoid arthritis were also associated with an increased risk for both early- and late-onset preeclampsia, but with no significant difference in the association. With cut-off at < and ≥34 weeks, rheumatoid arthritis also had a significantly stronger association with early-onset preeclampsia.

Conclusion and clinical implications:
Maternal allergy is an independent risk factor for early-onset preeclampsia. Interestingly, use of antihistamines before or during early pregnancy among women with allergies reduces risk for developing early-onset preeclampsia. Type 1 and 2 diabetes, chronic kidney disease, and hypertension are more strongly associated with development of preterm preeclampsia than with term preeclampsia. For asthma, epilepsy, and rheumatoid arthritis, there is no significantly different association to preterm and term preeclampsia.
Based on our findings, we recommend pregnant women with allergies to continue antihistamine treatment in pregnancy. Our differentiated risk estimates provide an opportunity to enhance the accuracy of screening algorithms for early detection of early-onset preeclampsia. This, in turn, may enable targeted prophylactic interventions to women at high risk for developing early-onset preeclampsia.

Norsk sammendrag

Bakgrunn:
Preeklampsi er delt inn i en tidlig og en sen variant. Dagens kunnskap om kjente risikofaktorer og deres sammenheng mellom de to variantene av preeklampsi er begrenset.

Mål:
Vårt overordnede mål var å undersøke sammenhengen mellom ulike velkjente og mulige risikofaktorer for utvikling av tidlig (<34 uker og <37 uker) og sen preeklampsi (≥34 og ≥37 uker), og å se om bruk av antihistaminer før eller under svangerskapet beskytter mot utvikling av tidlig preeklampsi.

Metode:
Alle artiklene er populasjonsbaserte kohortstudier.
Artikkel I: Alle kvinner som fødte i Stavanger (1996-2014) og i Bergen (2009-2014) ble inkludert. Data ble hentet fra det elektroniske pasientjournalsystemet Natus. Vi brukte multinomial logistisk regresjonsanalyse for å estimere odds ratioer (OR) med 95 % konfidensintervall (95% KI) for tidlig (<34 uker) og sen (≥34 uker) preeklampsi og justerte for kovariater.
Artikkel II: Vi brukte sammenslåtte data fra Medisinsk fødselsregister (MFR) og Norsk Reseptregister (NorPD) for alle fødende kvinner i Norge mellom 2004-2016. Vi antok at kvinner som hadde fått resept på antihistaminer med ICD-10-kode for allergi i NorPD, led av allergi. Vi delte bruken av antihistaminer i forhold til svangerskapet inn i fire grupper: Før graviditet (fra 6 måneder før og til siste menstruasjon, tidlig graviditet (fra siste menstruasjon – uke 20), sen graviditet (fra uke 20 – uke 36). Kvinner som fikk antihistaminer i mer enn én tidsperiode ble behandlet som en egen gruppe. Binomial logistiske regresjonsmodeller med «random effects component» ble brukt for å estimere odds ratio (OR) med 95 % konfidensintervall (KI) for utvikling av tidlig preeklampsi ved foreskrevet antihistamin i de fire eksponeringsgruppene skissert ovenfor, og sammenlignet med kvinner som ikke brukte antihistaminer. Vi justerte også for mors alder, og stratifiserte for paritet og flerlinger. Separate analyser ble gjort for svangerskap med registrert kroppsmasseindeks.
Artikkel III: Data fra MFR, i perioden 1999-2016. Vi registrerte forekomst av diabetes type 1 og 2, kronisk nyresykdom, astma, epilepsi, revmatoid artritt og hypertensjon. Multinomial logistisk regresjonsanalyse ble brukt til å estimere relativ risk ratio (RRR) med 95 % konfidensintervall (KI) for preterm (<37 uker) og term preeklampsi (≥37 uker), og justerte for mors alder og paritet. Separate analyser ble gjort for svangerskap med registrert BMI.

Resultater:
Artikkel 1: Pregestasjonell allergi hos mor øker risikoen for tidlig preeklampsi (OR 1.8, 95% KI: 1.3-2.4) og reduserer risikoen for sen preeklampsi (OR 0.8, 95% KI: 0.7-0.9). Assosiasjonen mellom allergi og tidlig versus sen preeklampsi er signifikant (OR 2.2, 95% KI: 1.6-3.1).
Artikkel 2: Predikerte andeler for tidlig preeklampsi <34 uker var signifikant lavere hos kvinner som brukte antihistaminer før (0.41%, 95% KI 0.34-0.49) og tidlig i svangerskapet (0.37%, 95% CI 0.31-0.44), sammenlignet med kvinner som brukte antihistaminer etter placentering (0.69%, 95% CI 0.57-0.83). Resultatene var like for preeklampsi <37 uker.
Artikkel 3: Fire predisponerende faktorer var assosiert med økt risiko for både preterm og term preeklampsi, men med signifikant sterkere assosiasjon til preterm preeklampsi: Type 1 og type 2 diabetes (RRR henholdsvis 2.89, 95 % KI 2.46-3.39 og RRR 1.68, 95 % KI 1.11-

2.17), kronisk nyresykdom (RRR 1.55, 95 % KI 1.11-2.17) og hypertensjon (RRR 1.85, 95% CI 1.63-2.10). Astma, epilepsi og revmatoid artritt var også assosiert med økt risiko for både preterm og term preeklampsi, men uten signifikant forskjell i sammenhengen mellom de to. Ved cut-off satt ved ≥og <34 uker var også revmatoid artritt signifikant sterkere assosiert med tidlig variant av preeklampsi.

Konklusjon og kliniske implikasjoner:
Maternell allergi er en isolert risikofaktor for tidlig preeklampsi, og bruk av antihistaminer før eller i tidlig svangerskap blant allergiske kvinner reduserer risikoen for utvikling av tidlig preeklampsi. Type 1-diabetes, type 2-diabetes, kronisk nyresykdom og hypertensjon er sterkere assosiert med utvikling av preterm preeklampsi enn med term preeklampsi. For astma, epilepsi og revmatoid artritt er det ingen signifikant forskjell i assosiasjonen mellom preterm og term preeklampsi.
Basert på våre funn anbefaler vi allergiske kvinner å kontinuere bruk av antihistaminer før og under svangerskapet. Våre differensierte risikoestimater gir en mulighet til å øke nøyaktigheten av eksisterende screening algoritmer for tidlig diagnostisering av senere utvikling av tidlig preeklampsi. Dette vil gjøre det mulig med individualisert profylaktisk intervensjon hos kvinner med høy risiko for utvikling av tidlig preeklampsi.

List of Publications

This thesis is based on the following original research papers, which will be referred to in text by their Roman numerals:

I. Sande AK, Torkildsen EA, Sande RK, Morken NH: Maternal allergy as an isolated risk factor for early-onset preeclampsia: An epidemiological study. J Reprod Immunol. 2018 Jun; 127:43-47. doi: 10.1016/j.jri.2018.04.004. Epub 2018 Apr 20.

II. Sande AK, Torkildsen EA, Sande RK, Dalen I, Danielsson KC, Morken N-H. Use of antihistamines before or during pregnancy and risk of early-onset pre-eclampsia in allergic women: a population-based cohort study. BMJ open. 2022;12(10): e061837.

III. Sande, A K, Dalen I, Torkildsen, EA, Sande, RK, Morken, NH. Pregestational maternal risk factors for preterm and term preeclampsia: a population-based cohort study. (Manuscript in review).

1. Introduction

1.1 Background

Approximately 500 000 women worldwide die each year in relation to pregnancy and childbirth and of these, approximately 75 000 die from hypertensive disorders in pregnancy (1).

Preeclampsia affects about 2-8% of pregnancies worldwide (2) and is divided into an early and a late entity. Early-onset and late-onset preeclampsia differ in terms of both biomarkers and risk factors (3, 4, 5, 6). Understanding a given risk factor´s association to early-onset and late-onset preeclampsia can help identify women at high risk of developing early-onset preeclampsia, and implementing appropriate preventive measures, such as acetylsalisylic acid (7). Identifying risk factors that are more strongly associated with late-onset preeclampsia and predict a woman´s risk for developing this condition, is important for offering individualized antenatal care for better outcome for both mother and child.

Preeclampsia is believed to be caused by a complex interplay of multiple factors, including genetic, environmental, and maternal factors (8). This thesis focuses specifically on chronic pregestational maternal risk factors and their association with early- and late-onset preeclampsia. While not a comprehensive review of all known risk factors for preeclampsia, this thesis provides a summary of conditions related to the mother´s healt prior to pregnancy. However, certain factors, such as body mass index (BMI), age, parity, and family history, are applicable to all pregnant women, and therefore, will be discussed.

1.2 Preeclampsia

1.2.1 Definitions of Preeclampsia

During the work with this thesis, the diagnostic criteria for preeclampsia have undergone revision. The National Institute for Health and Care Excellence (NICE guidelines) now defines preeclampsia as the emergence of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) after 20 weeks of gestation, together with one or more of the following clinical features: Proteinuria, renal insufficiency, liver involvement, neurological complications, hematological complications or uteroplacental dysfunction (9). This corresponds with the Norwegian definition stated by the the Norwegian Society of Obstetrics and Gynecology in 2020 (10).

1.2.2 Clinical implications of preeclampsia

Besides maternal death, there are several maternal complications associated with preeclampsia. The condition is associated with hypertension in affected individuals, which can lead to hypertensive crisis and organ damage, especially to the kidneys (11) and to the brain (12). Preeclampsia can affect several other organ systems as well, including the liver, lungs, and the cardiovascular system, leading to complications such as liver dysfunction, renal failure, stroke, pulmonary edema, and myocardial infarction (13).

HELLP syndrome (Hemolysis, elevated liver enzymes, and low platelets) and eclampsia are particularly severe and life-threatening forms of preeclampsia. HELLP syndrome involves hemolysis, elevated liver enzymes, and low platelet count, whereas eclampsia causes seizures (10).

Evidence shows that women with a history of preeclampsia have a long-term risk of developing cardiovascular disease later in life, such as hypertension, stroke, and heart disease (14).

Preeclampsia, especially early-onset preeclampsia, can lead to intrauterine growth restriction (IUGR) which is associated with metabolic syndrome and diabetes type 2, ADHD, and learning disability later in life. Both preecampsia and IUGR can necessitate preterm delivery, which increase the risk for complications associated with premature birth (15).

Preeclampsia is associated with placental abruption, which can lead to fetal distress/ asphyxia and fetal death (16). In severe cases, preeclampsia can result in fetal demise/ stillbirth (17).

1.2.3 Prevalence and trends of preeclampsia

Hypertensive disorders of pregnancy include preeclampsia, eclampsia, gestational hypertension, and chronic hypertension. The global prevalence of preeclampsia is approximately 10% but exhibits significant regional and ethnic variations (18, 19). In the Caribbean and Latin America, prevalences are comparable to North America and Europe (20). Prevalences are higher for African American women (5.2%) compared to Latin and Asian women (4.0% and 3.5%, respectively). In South Asian and African countries the condition accounts for 9% of maternal deaths (2). High income countries report prevalences of 2-4% (21), whereas low- and middle- income countries observe prevalences of 0.5-9.2% (22). African prevalences is highest in central and western parts of Africa (23).

Chinese women are found to have similar risk for developing preeclampsia as Swedish women in a large cross-sectional study of more than 600.000 Chinese and Swedish women (24). Interestingly, the same study found that in Swedish women, two-thirds of the cases were mild, whereas in Chinese women two-thirds were severe.

Over the past few decades, there have been notable global changes in the prevalences and severity of preeclampsia. High-income countries have reported a decline in incidence rates and deaths, probably due to improved prenatal care, early detection, and management startegies: Regular antenatal care, blood pressure monitoring, early

detection of risk factors, and the use of low-dose aspirin, are some of the strategies that have been promising in reducing the severity and complications of preeclampsia (25).

Unlike most other developed countries, the prevalence of preeclampsia in the United States is increasing. This may be due to increasing overweight, advanced maternal age, diabetes type 2, and chronic hypertension (26). A Canadian study from 2015, reported increasing incidences of preeclampsia in the period from 1989-2012, but with a decline in maternal, infant, and fetal mortality (27).

At the start of the registration in the Medical Birth Registry of Norway (MBRN) in 1967 the Norwegian prevalence of preeclampsia was 2%, increasing to 3.5% in 1985. Up until 1998 the prevalence was constant. Between 1999 and 2002 there was an increase in preeclampsia up to 4.4%, probably due to new reporting routines to the MBRN, followed by a subsequent decrease to 3.6% in 2008 (28). A Norwegian population-based study of more than 1 000 000 women by Sole et al from 2022 found a prevalence of preeclampsia of 4.3% for the timeperiod 1999- 2002, but a reduction from 2015-2018 down to 2.7%, despite increased maternal age, higher BMI, and increased use of assisted reproductive treatment (ART). The reduced prevalence was seen in all age groups, and with a prevalence reduction of 30% for preeclampsia in women aged ≥ 35 (29).

Interestingly, a systematic review by Umesawa et al from 2016 also show seasonal differences, with higher prevalences of preeclampsia in winter in Norway, Sweden and North America (22).

1.2.4 Early-onset and late-onset preeclampsia

While preeclampsia is divided into an early-onset and a late-onset entity, there is no consensus on wether the line between the two should be defined as preeclampsia *occurring* before or after gestational week 34 (30), respectively, or if the definition should be related to *delivery* either before or after 34 (9) or before or after 37 (31) weeks of gestation, respectively. A classification based on time of diagnosis would be

preferred, but time of onset is difficult to decide because of differences in frequencies in the antenatal follow up with measurements of bloodpressure and proteinuria.

While the clinical features of early-onset and late-onset preeclampsia may overlap, their disease spectrum and outcomes differ. Early-onset preeclampsia is associated with more severe placental, maternal, and fetal outcomes than late-onset preeclampsia (32, 33). It is therefore hypothesized that the two subtypes have different origins or pathophysiologies (34), and the identification of subtypes are crucial to understanding the different pathophysiological pathways to maternal and infant morbidity and mortality for developing targeted diagnosis and prevention strategies. Because of the multiple subtypes, and most likely pathways, of preeclampsia, it is unlikely that a one-size-fits-all approach will be effective, and personalized management and care are necessary. Still, targeting one pathway to preeclampsia could have a significant impact on treating the overall disorder (35).

Over the last few decades, there is increasing evidence that there exists more than two subtypes of preeclampsia besides early-onset and late-onset preecampsia, for example subtypes related to placental and maternal features, immunological subtypes, genetic subtypes and subtypes related to affected maternal organ, and finally subtypes connected to the potential long-term effects of preeclampsia (35).

1.2.5 Pregestational maternal risk factors for preeclampsia

There are several well-known risk factors for preeclampsia, as shown by Duckitt et al in 2005 (36). This paper is a systematic review and found that demographic factors like maternal age, obesity, family history, multiple pregnancies, and previous history of preeclampsia were significant risk factors for developing preeclampsia. Regarding pregestational maternal medical conditions, Duckitt et al found that insulin dependent diabetes, chronic hypertension, renal disease, autoimmune disorders, and antiphospholipid syndrome increases the risk for preeclampsia. However, this study does not distinguish between early-onset and late-onset preeclampsia.

According to the literature, there seems to be an international concensus to which risk factors should be considered when assessing risk factors for preeclampsia (3, 37, 38). However, the quality of evidence varies, and the risk factors included in clinical practice guidelines, made to provide health care workers with evidence-based advice when treating patients, also varies to some degree (39). High and moderate risk factors for preeclampsia according to the NICE-guidelines, American College of Obstetricians and Gynecologists (ACOG), International Society for the Study of Hypertension in Pregnancy (ISSHP), and the Norwegian Society of Obstetricians and and Gynecologists (NGF) is outlined in table 1.

Table 1: Risk factors for preeclampsia according to various Clinical Practice Guidelines

	NICE (9)	**ACOG** (40)	**ISSHP** (31)	**NGF*** (41)
High risk	Prior hypertensive disease in pregnancy	Previous preeclampsia	Prior preeclampsia	Prior preeclampsia
	Chronic kidney disease	Chronic kidney disease	Body Mass Index > 30	Chronic kidney disease
	Autoimmune disorders (Lupus. Antiphospholipid syndrome)	Autoimmune disorders (Lupus. Antiphospholipid syndrome)	Systemic Lupus, Antiphospholipid syndrome	Autoimmune disorders (Lupus. Antiphospholipid syndrome)
	Type 1 or type 2 diabetes	Diabetes mellitus	Pregestational diabetes mellitus	Pregestational diabetes mellitus
	Chronic hypertension	Chronic hypertension	Chronic hypertension	Chronic hypertension
		Multiple gestation	Multiple gestation	
		Multiple moderate risk factors	Assisted Reproductive Technology	Assisted Reproductive Technology with oocyte donation
Moderate risk	Nulliparity	Primigravida		Primigravida
	Maternal age ≥ 40 years	Maternal age > 35		Maternal age ≥ 40 years
	Pregnancy interval > 10 years	Pregnancy interval > 10 years		Pregnancy interval > 10 years
	Body Mass Index ≥ 35	Body Mass Index > 30		Body Mass Index > 35
	Family history of preeeclampsia	Family history of preeeclampsia (mother/ sister)		Multiple pregnancy
	Multi-fetal pregnancy	Previous pregnancy complications (SGA)		
		In vitro fertilization (IVF)		
		Black race		
		Lower income		

* The Norwegian list of risk factors also includes factors not classified as high or moderate risk: intrauterine growth restriction (IUGR), gestational diabetes, Uterine artery notch/ elevated Pulsatile Index, low circulating levels of Placental Growth Factor (PlGF), short duration of cohabitatin before pregnancy, women of African inheritance, family history (preclampsia in mothers and sisters, gestational diabetes.
Abbreviations: NICE; National Institute for Health and Care Excellence, ACOG; American College of Obstetricians and Gynecologists, ISSHP; International Society for the Study of Hypertension in Pregnancy, and NGF; the Norwegian Society of Obstetricians and and Gynecologists.

Demographic maternal risk factors

Maternal age

Increasing maternal age have been found to be associated with increased risk for preeclampsia (42), and the risk seems to rise rapidly after 35 years of age (43). A study by Poon et al shows a four percent increase in the relative risk (RR) of late-onset preeclampsia each year after the age of 32 (44). Still, it is found that higher maternal age is more strongly associated with early-onset than late-onset preeclampsia (45). The mechanisms are unclear, but it is plausible that maternal age is positively associated with BMI, hypertension, chronic kidney disease, and immunological conditions.

High Body Mass Index

High BMI is an increasing challenge worldwide. It is a well known risk factor for preeclampsia (46), and more specifically, it increases the risk for both early-onset and late-onset preeclampsia (47). A study from O´Brian et al from 2002 found that the risk for developing preeclampsia doubled for each 5-7 kg/m2 increase in BMI. Studies have found that elevated BMI increases the risk for late-onset, but not early-onset, preeclampsia (48). A study by Robillard from 2019 displays a linear relation between rising BMI and risk of developing late-onset preeclampsia (49). In this study, late-onset preeclampsia was defined as preeclampsia occurring after 37 weeks of gestation (49). In a different study, initially aiming to validate different gestational ages as cut-offs for early-onset versus late-onset preeclampsia, Robillard finds that elevated BMI was more strongly associated with late-onset than early-onset preeclampsia, with a cut-off at 34 gestational weeks. In this study, the association disappeared when using a cut-off at 37 weeks of gestation (30).

Parity, change of partner, and interval between pregnancies

First time pregnancies are shown to triple the risk for preeclampsia (36, 50). Women with previous non-preeclamptic pregnancies and pregnant with the same partner are shown to have a reduced risk for preeclampsia. Being pregnant with a new partner elevates the risk for preeclampsia back to that of primiparity (51), indicating that there is some kind of immune tolerance being passed on to subsequent pregnancies with the same partner (52). A hypothesis for this is that nulliparous women has encountered minimal exposure to paternal antigens, and that the absence of prior desensitization potentially contributes to the development of the syndrome of preeclampsia. This theory is supported not only by the knowledge of elevated risk in multiparas with a change of partner (51), but also of evidence that use of barrier contraception elevates the risk of preeclampsia (53), whereas long duration of sexual activity prior to conception *decreases* the risk for preeclampsia (54).

Reduced risk of developing preeclampsia might also be the case after a miscarriage (55), and it is hypothesized that this is due to the same mechanisms that are involved in the reduction of risk seen in relation to multiparity. However, there are multiple studies showing that women with a history of *recurrent* miscarriages are at an icreased risk of developing preeclampsia in subsequent pregnancies (56, 57).

A long interpregnancy interval increase the risk of preeclampsia and the risk rises proportional to the length of the interval (58). The interpregnancy interval is more important than a change of partner when it comes to the risk of developing preeclampsia. When the interpregnancy interval exceeds ten years, the risk of developing preeclampsia is almost equivlent to the risk of primigravidas with a tripled risk for developing preeclampsia, even after adjusting for maternal age (58).

History of preeclampsia

A previous history of preeclampsia increases the likelihood of developing preeclampsia in later pregnancies with a pooled RR of 8.4 (59). The risk of preeclampsia in subsequent pregnancies are greatest after early-onset preeclampsia, with a recurrence risk of 17%. The same study found that only 32% of women with previous early-onset preeclampsia had a subsequent pregnancy without any complications (60). Odegard et al found an Odds Ratio OR of 42.4 (95% CI: 11.9-151.6) for development of preeclampsia after early-onset preeclampsia in a previous pregnancy (48). Still, the two latter studies are small, which may affect their findings. Individuals who experienced preeclampsia without severe features in their first pregnancy encounter preeclapsia in 7% of later pregnancies (61). In the cohort that formed the basis for paper I, women suffering from preclampsia in their first pregnancy, had a 16.7% risk of preeclampsia in the second pregnancy. Women who did not suffer from preeclampsia in their first pregnancy, had a 1.6% risk of developing preeclampsia in their second pregnancy (unpublished data- analysis performed post publication).

Family history

The presence of a family history of preeclampsia is shown to have an impact on the development of preeclampsia. A population-based register study by Nilsson et al found an OR of 3.3 (95% CI: 3.0-3.6) for development of preeclampsia for a full sister to a preeclamptic woman and an OR of 2.6 (95% CI: 1.6-4.3) for a daughter to a formerly preeclamptic mother to develop preeclampsia herself (62). The same study found that the inheritance is predominantly influenced by maternal factors, but that paternal genes also play a role in a potential subsequent development of preeclampsia, in that women are more likely to develop preeclampsia if the father himself is the result of a preeclamptic pregnancy (63, 64). Being pregnant with a man who previously has fathered a child from a preeclamptic pregnancy, increases the risk for developing preeclampsia with an OR of 1.8 (95% CI: 1.2-2.6) (65).

Recent evidence also shows that women who themselves were small for gestational age, born preterm or with low birth weight are at elevated risk of developing gestational hypertension or preeclampsia during pregnancy (66).

Multiplicity

Multiple pregnancy is a well-known risk factor for preeclampsia. A prospective study of 684 twin pregnancies and 2946 singleton pregnancies conducted by Sibai et al found a Relative Risk of 2.62 (2.03-3.38) for development of preeclampsia and 2.04 (95% CI: 1.60-2.59) for development of gestational hypertension in a twin pregnancy (67). However, a large population-based study from Norway shows a fourfold increased risk for preeclampsia, but no increased risk of gestational hypertension in twin pregnancies (68). Few studies on twin pregnancies have separated early-onset and late-onset preeclampsia, but a study by Robillard from 2021 regarding risk factors for early-onset and late-onset preeaclampsia found an adjusted OR for dizygotic twin pregnancies of 3.7 (p<0.001) and 2.1 (p=0.003) for early-onset and late-onset preeclampsia, respectively, and an adjusted OR for early-onset preeclampsia of 3.98 (p=0.003) and non-significant findings for late-onset preeclampsia in monozygotic twin pregnancies (69).

Ethnic origin

Ethnicity is an important risk factor for the development of preeclampsia. Women of East Asian origin have a significantly lower risk of preeclampsia compared to Caucasian women, possibly due to differences in BMI and lifestyle factors (70). However, women of Afro-Caribbean and South Asian origin are at higher risk of developing preeclampsia compared to Caucasian women (71, 72).

Many of the studies performed on ethnicity have been conducted in the United States and are of limited relevance to the Norwegian population. A Norwegian, population-

based study from 2015 done by Naimy et al shows that migrant women have a lower risk for developing preeclampsia compared to Norwegian born women (73). The risk was lowest for women born in Vietnam, Afghanistan, and Thailand. Interestingly, the risk of developing preeclampsia increased with the length of Norwegian residence (73).

Preeclampsia cases in Reunion Island, an island in the Pacific with a mixed ethnic population, are consideratly higher than other parts of the world, with a prevalence of early-onset preeclampsia of 31% among their preeclampsia cases (74).

These findings emphasize the need for further research to understand the underlying mechanisms and develop effective strategies for prevention and management of preeclampsia in high-risk populations. The elevated risk for preeclampsia in these groups might be related to the increased prevalence of metabolic syndrome and risk for cardiovascular disease found in the same ethnic groups.

Pregestational maternal risk factors

Table 2: Overview of pregestational maternal risk factors

Study	Population	Preeclampsia	Early-onset preeclampsia	Late-onset preeclampsia
Bartsch (59)**, 2016**	25 356 688			
Hypertension		Pooled RR 5.1 (95% CI: 4.0-6.5)		
Diabetes		Pooled RR 3.7 (95% CI: 3.1-4.3		
Lisonkova (3)**, 2013**	456 668			
Hypertension			aHR 11.72 (95% CI: 10.11-13.59)	aHR 5.83 (95% CI: 5.39-6.32)
Diabetes			aHR 1.87 (95% CI:1.6-2.18)	aHR 2.46 (95% CI:2.32-2.61)
Catov∗ (6)**, 2007**	70 924			
Hypertension		aRR 3.4 (95% CI: 2.8-4.1)	aOR 5.4 (95% CI: 3.8-7.6)	
Diabetes		aRR 2.1 (95% CI: 1.4-3.0)	aRR 3.7 (95% CI: 2.3-6.0	
Robillard (69)**, 2021**	81 834			
Hypertension			aOR 7.3 (p<0.0001)	aOR 3.9 (p<0.0001
Diabetes			NS∗∗	aOR 1.2 (p=0.04)
Chronic kidney disorder			NS∗∗	2.9 (p=0.007)
Lin (75)**, 2010**	11 472			
Rheumatoid arthritis		OR 2.22 (95% CI: 1.59-3.11)		
Simard (76)**, 2017**	11 226			
Systemic Lupus Erythematosus			aRR 7.8 (95% CI: 4.8-12.9)	
Borthen (77)**, 2009**	365 107			
Epilepsy			aOR 1.6 (95% CI: 1.2-2.1)	aOR 1.2 (95% CI: 0.9-1.6)
Mendola (78)**, 2013**	223 512			
Asthma		aOR 1.14 (95% CI: 1.06-1.22)		

Dong (79)**, 2020**	9 456 160			
Systemic Lupus Erythematosus		RR 2.99 (95% CI: 2.31-3.88)		
Sande (80)**, 2018**	110 064			
Allergy			aOR 1.8 (95% CI: 1.3-2.4)	aOR 0.8 (95% CI: 0.7-0.9)

∗ Early-onset preeclampsia defined as delivery<37 weeks of gestation.
∗∗Abbreviations: NS; non-significant, aHR; adjusted hazard ratio, aOR; adjusted odds ratio, aRR; adjusted relative risk, pooled RR; pooled relative risk.

Diabetes

Women with diabetes, especially if poorly controlled, have an increased risk of developing preeclampsia (81). Only a few studies assess diabetes and it´s association to early-onset and late-onset preeclampsia, respectively (3, 6). Overweight, insulin resistance, and abnormal lipid profile are discussed as possible cofactors for the increased risk of preeclampsia by pregestational diabetes. A systematic review and meta-analysis by Bartsch et al found a pooled RR of 3.7 (95% CI: 3.1-4.3) for the association between pregestational maternal allergy and preeclampsia (59). In 2013 Lisonkova et al assessed different risk factors and their association to early-onset and late-onset preeclampsia and found that diabetes was more strongly associated with late-onset than early-onset preeclampsia with adjusted hazard ratios of 2.46 (95% CI: 2.32-2.61) and 1.87 (95% CI: 1.6-2.18), respectively. A study from Reunion Island in the Pacific found that gestational diabetes is associated with late-onset preeclampsia with an adjusted OR of 1.2 (p=0.04) but findings are non-significant for early-onset preeclampsia (69). To our knowledge, no previous studies distinguish between diabetes type 1 and diabetes type 2.

Chronic kidney disease

Previous studies show that chronic kidney disease increases the risk for preeclampsia (82, 83, 84), regardless of the cause of the renal failure (84). Some studies report a risk

of 40-60% for developing preeclampsia in women with pregestational kidney disease, and that the degree of the potential preeclampsia is proportional to the severety of the degree of renal failure (85). The same study also indicates that proteinuria at the first antenatal visit is a risk-factor for subsequent development of preeclampsia. A study of 81 834 pregnancies found an adjusted OR of 2.9 for the association between renal disease and late-onset preeclampsia, but a non-significant association between renal disease and early-onset preeclampsia (69). To our knowledge no other study has assessed the association of kidney disease with early-onset and late-onset preeclampsia, respectively.

Urinary tract infections are among the most commonly studied infections, and evidence shows that they are both associated with an increased risk of preeclampsia with an OR of 1.57 (95% CI: 1.45-1.70) (86). However, the definitions used for this condition vary between the studies, which might influence the results. A study conducted by Martinell et al studying the association between urinary tract infections in childhood and risk of development of preeclampsia, found a higher incidence of bacteriuria in women with a previous history of urinary tract infections compared to women without such medical history (37% versus 2%, respectively), but no significant increase in the incidence of preeclampsia (87).

Asthma

Asthma is found to increase the risk for preeclampsia (78, 88), although there are some conflicting studies (89). An American study by Mendola et al found adjusted OR of 1.14 (1.06-1.22) for the association of asthma and preeclampsia. Allergy and asthma share some pathological pathways, so in the light of considering preeclampsia as an immunological condition, we find the possible association interesting. There is also evidence that children born from preeclamptic mothers are at increased risk for developing asthma during childhood (90). To our knowledge no study has assessed the potentially differentiated association of asthma to early-onset and late-onset preeclampsia, respectively.

Allergy

Allergy is a type of immune-mediated hypersensitivity reaction that results from an inappropriate response to an otherwise unharmful substance, known as an allergen. Unlike autoimmune disorders, in which the immune system targets self- antigens, the immune response in an allergic reaction is directed against exogenous antigens (91). Upon initial exposure to an allergen, B-cells recognize the antigen and produces immunoglobuline E (IgE) antibodies. During subsequent exposure to the allergen, IgE molecules bound to the surface of mast cells recognize the allergen, activating the mast cell causing it to release histamine, which is responsible for the symptoms in an allergic reaction (92).

Evidence shows elevated levels of IgE in preeclamptic women (93), and the potential relationship between preeclampsia, allergy and asthma (78, 88) is intriguing, as the two latter are believed to share some common pathogenic pathways (94). It is also shown that children born to preeclamptic mothers are at increased risk for developing allergy, asthma, and eczema during childhood (90, 95).

Epilepsy

Epilepsy has been identified as a potential risk factor for preeclampsia (96, 97), and there is evidence to suggest that autoimmune mechanisms may be involved in some patients with epilepsy (98). The mechanisms are unclear, but elevated levels of interleukin-6 (IL-6), one of the interleukins associated with preeclampsia, has also been observed in individuals with epilepsy (99). Other explanations might be related to antiepileptic drugs, circulating antibodies, or changes in the blood-brain barrier. A Norwegian study by Borthen et al from 2009 found an OR of 1.5 (95% CI: 1.1-2.0) and 1.2 (95% CI: 0.9-1.6) for early-onset and late-onset preeclampsia, respectively. To our knowledge, no other study has investigated the association of epilepsy and early-onset versus late-onset preeclampsia.

Autoimmune disorders

Autoimmune disorders such as Lupus Erythematosus (SLE) (76, 100), and antiphospholipid syndrome (101) are well-known risk factors for preeclampsia. Evidence shows that also rheumatoid arthritis, which is a more prevalent autoimmune disorder among fertile women, is associated with development of preeclampsia with an adjusted OR 2.22 (95% CI: 1.59-3.11) (75). The mechanisms for the increase of developing preeclampsia are unclear, but may be due to inflammation, thrombose tendencies, and microangiopathies. The OR for early-onset preeclampsia in women with SLE is in a study by Simard et al from 2016 found to be as high as 7.8 (95% CI: 4.8-12.9) (76).

Chronic hypertension

It is widely recognized that women who suffer from chronic hypertension prior to pregnancy are at higher risk of developing preeclampsia (102, 103, 104). However, chronic hypertension is relatively rare in women of reproductive age, which means that chronic hypertension is responsible for only about 5% of cases of preeclampsia (105). Evidence indicates that there is a dose-respone relationship between chronic hypertension and preeclampsia; the higher the bloodpressure, the higher the risk of developing preeclampsia (106). Studies separating early-onset and late-onset preeclampsia have shown that chronic hypertension is more strongly associated with early-onset than late-onset preeclampsia, and Lisonkova et al displayed an adjusted HR of 11.72 (95% CI:10.11-13.59) and 5.83 (95% CI: 5.39-6.32) for early- and late-onset preeclampsia, respectively (3). A study by Catov et al from 2007 found an OR of 8.7 for early-onset preeclampsia defined as delivery < 37 weeks of gestation in nulliparas, but without assessing the risk for late-onset preeclampsia (6).

Other potential risk factors

Many conditions have been evaluated and studied for potentially increasing the risk of preeclampsia, but evidence is limited, and most of them are currently not considered risk factors for development of the condition according to Clinical Practice Guidelines (9, 10, 40, 107).

The evidence to whether assisted reproductive technologies (ART) are associated with elevated risk for developing preeclampsia is conflicting. A large systematic review from 2019 by Almani-Hashiani including 156 246 ART pregnancies and 6 558 249 non-ART pregnancies conclude that ART do increase the risk for developing subsequent preeclampsia and that the association for preeclampsia by ART is stronger in Asia and the United States than in Europe (108). Studies suggest that women who conceive through oocyte donation have a higher risk of developing preeclampsia compared to women who conceive naturally or through other form of assisted reproduction (109).

A meta-analysis of ten cohort studies, including 4 844 555 women, conducted by Saccone et al in 2016 reported several adverse outcomes associated with celiac disease during pregnancy, including an increased risk for IUGR but did not find a significant increase in the risk of preeclampsia. (110) Another meta-analysis on women with celiac disease and their risk of reproductive disorders reported an icreased risk of intrauterine growth but did not examine the risk of developing preeclampsia (111). Thus, the evidence suggests that celiac disease may increase the risk of IUGR, but there is currently not found a significant association between celiac disease and preeclampsia.

It is plausible that women with polycystic ovary syndrome (PCOS) may be of increased risk for developing preeclampsia, as this condition is associated with high BMI, insulin resistance, inflammation, and endothelial dysfunction. A systematic review of

pregnancy outcome in women with PCOS demonstrated a 3-4 times increased risk for development of preeclampsia and pregnancy induced hypertension (112).

Normal maternal thyroid function is crucial for a successful pregnancy, and evidence suggest that conditions of the tyroid gland, and especially subclinical hypothyroidism, increase the risk for preeclampsia (113).

Endometriosis is a condition with chronic inflammation, and it is therefore reasonable to assume that this condition is associated with preeclampsia. Interestingly, there are studies indicating the opposite (114). In contrast, a large Australian study from 2023 by Gebremedhin et al found an increased risk of preeclampsia with an OR of 1.18 (95% CI: 1.11-1.26) in women with endometriosis.

Maternal infections can increase the risk of preeclampsia, probably due to a systemic inflammatory response followed by endothelial dysfunction (86). Following the SARS-Co-2 pandemic few studies have investigated the association between SARS-CoV-2 infections and preeclampsia and found an increased risk for the development of preeclampsia in pregnant women with SARS-CoV-2 infection and that the risk is higher with severe infection(115).

1.2.6 Prophylactic treatment for preeclampsia

Several prophylactic treatments have been investigated for their effectiveness in preventing preeclampsia. These include calcium supplementation, statins, antioxidants such as vitamins C and E, and low- dose aspirin.

Calcium supplementation has been shown to reduce the risk for preeclampsia in women with low dietary calcium intake, and a systematic review and meta-analysis done by Hofmeyr et al in 2018 found a 50% reduction of the risk of developing preeclampsia after calcium supplementation, and that the risk reduction was greatest for women at high risk for preeclampsia (116). Extra calcium supplementation during placentation

has not been found to be effective for reducing the risk of developing preeclampsia in high-risk women (117), and is not part of standard treatment In Norway (10).

Several studies have investigated the potential of administration of antioxidants in the attempt to reduce oxidative stress, a potential factor in the pathophysiology of preeclampsia. Vitamin C and E have been the primary antioxidants studied for their role in inhibiting peroxidation reactions and preventing endothelial damage. However, a large systematic review by Rahnemaei et al from 2020 found no effect of neither vitamin C nor E in the prevention of preeclampsia (118).

Low molecular weight heparin (LMWH), both alone and in combination with aspirin, has been investigated as a potential treatment to prevent miscarriage, IUGR, and preeclampsia, and a systematic review and meta-analyses done by Cruz-Lemini et al in 2022 shows a reduced risk of preeclampsia, perinatal death and delivery of a small for gestational age child after use of LMWH (119). The same study finds that the risk reduction is greater if the LMWH is combined with low-dose aspirin, and that the displayed effects were non-significant in women with thrombophilia (119).

Low-dose aspirin has been suggested as prophylactic treatment against preeclampsia for over a decade. The first study investigating the impact of low-dose aspirin on the development of preeclampsia was conducted by Wallenburg et al in 1986 (120). This randomized, placebo-controlled, double-blind trial involved 46 normotensive women, where 23 women received 60 mg aspirin daily and 23 women received placebo daily from gestational week 28 until delivery. The incidence of preeclampsia was significantly reduced in the aspirin group. These findings have led to many later trials investigating the use of low-dose aspirin in pregnancy to reduce the risk of developing preeclampsia.

Aspirin works by inhibiting cyclo-oxygenase 1, an enzyme that converts arachidone acid into prostaglandins. There are several types of prostaglandins, with varied and often opposite effects; Thromboxane A2 is a vasoconstrictor and enhances platelet clotting, while prostacyclin is a vasodilator and inhibits plates to clot. In pregnancy, increased levels of prostacyclin decreas maternal responsiveness to angiotensin II,

leading to decreased systemic vascular resistance. In preeclampsia the altered prostacyclin/ thromboxane A2 ratio leads to increased sensitivity to angiotensin II, resulting in high bloodpressure (121).

The mechanisms underlying the use of low-dose aspirin in pregnancy for women at high risk for preeclampsia is thought to be the irreversible inhibition of cyclooxygenase 1 in platelets, which inhibits the synthesis of thromboxane A2 in the placenta with minimal effect on the systemic levels of prostacyclin (120). In contrast to the irreversible inhibition in platelets, the cyclooxygenase resynthesizes in endothelial cells, and hence the production of prostacyclin in endothelial cells is quickly reestablished. This leads to a more favorable prostacyclin/thromboxane A2 ratio in women of high risk for developing preeclampsia (122).

Studies on the effect of low-dose aspirin on development of preeclampsia have been conflicting, probably due to inconsistent definitions of preeclampsia, inadequate power, differences in dosage and start of intervention, and differences in the study population (high-risk versus low-risk, primipara versus multipara) (122), and has been a challenge to conducting systematic reviews on the prevention of preeclampsia by low-dose aspirin (118). Still, a meta-analysis from 2010 by Bujold et al, stratifying studies by initiation of low-dose aspirin before or after gestational week 16, found a 50% decrease in the incidence of preeclampsia, and a significant decrease in incidence of severe preeclampsi, IUGR, and preterm birth (123).

In 2017 Rolnik et al conducted a multicenter, double-blind, placebo-controlled trial including 1776 high risk women with singleton pregnancies, the ASPRE-trial. They were randomly selected to recieve 150 mg aspirin or placebo from gestational week 11- 14 until gestational week 36 and the outcome was preeclampsia with delivery before week 37 of pregnancy. The incidence of preeclampsia in women of high risk for preeclampsia was decreased with an OR of 0.38 (95% CI: 0.2-0.74) in the aspirin group (7). Unlike women in previous studies on low-dose aspirin and risk of developing preeclampsia, the women in this study were considered high risk after being screened

with an algorithm combining maternal risk factors, biomarkers, uterine pulsatility index and mean arterial pressure.

1.2.7 Early prediction and algorithms

Risk prediction models for preeclampsia aim to identify women who are at high risk for developing preeclampsia. Early identification of high-risk women allows for targeted interventions, such as prophylaxis with low-dose aspirin, to prevent or manage the condition, leading to better outcome for both mother and child. The risk prediction models typically utilize a combination of maternal risk factors, biomarkers, and clinical measurements to calculate an individualized risk score for each woman. Several risk prediction models for preeclampsia have been developed, but before 2020 few had been validated (124).

Examples of maternal characteristics that may be included in these risk prediction models are maternal age, BMI, pregestational medical risk factors, and family history. Biomarkers studied are, among others, placental growth factor (PlGF), soluble fms-like tyrosine kinase (sFlt-1), and pregnancy associated plasma protein-A (PAPP-A). In addition to maternal characteristics and biomarkers, the clinical measurements included are uterine artery doppler ultrasound and/ or maternal blood pressure measurements.

In 2020, two systematic reviews were conducted to evaluate the accuracy of tests for screening for preeclampsia (125, 126). These reviews conclude that the tests are not sufficiently accurate to screen the general population and the methodology in the performed studies were deemed to be poor due to variations in the definitions of preeclampsia, variation in the definition of high- risk versus low- risk women, timing of screening and variation in inclusion criteria. When constructing these algorithms, it is crucial to quantify the associations between various risk factors and the occurrence of early-onset and late-onset preeclampsia, for more accurate prediction of both early-onset and late-onset preeclampsia.

Poon et al found in 2010 when all pregestational risk factors are weighted equally when calculating risk, like in a binary yes/no question form, more than half of the pregnant population is identified as high risk, necessitating closer monitoring during pregnancy. Screening by maternal risk factors alone gave a detection rate of 37% for early-onset preeclampsia and 29% for late-onset preeclampsia, respectively (44).

The Fetal Medicine Foundation Prediction Model is the most validated (127, 128) and the prediction model that is currently most used.

1.3 The placenta and it´s immunological function

1.3.1 The normal placenta

When the blastocyst implants into the endometrium, the outer layer of the blastocyst, the trophoblast, is the first cell line to differentiate, giving rise to two other cell types: cytotrophoblast and syncytiotrophoblast. The cytotrophoblast grows into the myometrium and transform the maternal spiral arteries from narrow, tortuous vessels with low flow and high resistance into straight, wide vessels with high flow and low resistance (129). During the remodelling process the cytotrophoblast form a plug in the terminal parts of the spiral arteries to secure a hypoxic environment for the developing embryo and placenta. Around gestational week 11 the plug resolves and maternal blood enters the intervillous space (130).

Simultaneously, the syncytiotrophoblasts also invade the myometrium, and cause small capillaries in the myometrium to burst and create small lacunae of maternal blood that with time merge until a small sea of maternal blood: The intervillous space (131). The syncytiotrophoblasts form the outermost layer covering the floating villi, thereby creating the barrier, the syncytium, between the pool of maternal blood and the fetus. This layer is expected to be impermeable and is responsible for transport, and prevention of leakage of trophoblast debris, anti-angiogenic factors, and

proinflammatory cytokines to the mother's circulation (132), and also to protect the fetus from pathogens.

The placenta plays various functions, including gas exchange, nutrient transfer, endocrine regulation, and immunological protection. Gas exchange occurs in the terminal parts of the chorionic villi, where oxygen is provided, and carbon dioxide is removed. At this site the maternal and fetal blood are separated by only a few thin cell layers (132).

Nutrients are transferred over the placenta both by active and passive transport, fascilitated by transporter proteins in the syncytium (133).

The syncytium has receptors for several growth factors and hormones such as estrogen and human placental lactogen (hPL) and produces hormones like human chorionic gonadotropin (hCG), which is mainly produced by the syncytiotrophoblasts (134).

PlGF, Vascular Endotelium Growth Factor (VEGF), and Vascular Endothelial growth Factor Receptor (sFlt-1) are also produced by the placenta and are involved in angiogenesis and vascularization (135). PlGF promotes trophoblast invasion and proliferation and reduces apoptosis.

1.3.2 The immunological function of the placenta

The fetal- maternal interface is regulated by complex immunological mechanisms to maintain maternal tolerance towards the semi-allogeneic fetus throughout pregnancy (136). In normal pregnancy, there is a shift towards an anti-inflammatory and tolerogenic immune response, characterized by an increase of regulatory T-cells and production of anti-inflammatory cytokines like IL-4, IL-5, IL-10 and Transforming Groth Factor-β (TGF-β) and the inhibition of pro-inflammatory cytokines such as IL-6, IL-12, Tumor Necrosis Factor-α (TNF)-α and Interferon-γ (IFN-γ) (137, 138). This immune shift is crucial for a successful pregnancy.

There are different immune cells at the fetal- maternal interface, such as macrophages, dendritic cells, mast cells, granulocytes, B-cells, and uterine Natural Killer (uNK) cells. The uNK cells are the most abundant. There are different subtypes of macrophages in the placenta, such as the immune modulating M2 macrophage group, expressing IL-4, IL-10, and TNF-α. There are also active phagocytosis of apoptotic cells during the remodelling of the spiral arteries (138). M1 macrophages inhibit the mobility of the trophoblast (138). The uNK cells produces PlGF, VEGF, and cytokines, and are important for remodelling of the spiral arteries, although the mechanisms for this are unclear (138). Dendritic cells and mast cells are also involved in the immunology of the placenta, though they are not as abundant as macrophages and uNK-cells. The dendritic cells present antigenes to T cells in the endometrium and the placental bed. The concentration of dendritic cells decreases in early pregnancy, with more immature than mature dendritic cells present, enhancing immune tolerace. In normal pregnancy, T-cells shift from the Th1 and Th17 over to the more immune regulatory Th2 and T regulatory cells.

1.3.3 The placenta in preeclampsia

In preeclampsia, the invasion of the trophoblasts into the uterine wall is shallow, and only involves decidua and a small proportion of the myometrium. Consequently, there is inadequate transformation of the spiral arteries, which remain narrow and winded. This leads to reduced flow and high impedance in the placenta. Because the muscular part of the arterial walls is not replaced by fibrotic tissue, the arteries are still elastic and prone to external stimuli. This causes intermittent flow to the intervillous space, leading to a situation of repeated reperfusion. The vasculogenesis and angiogenesis is also affected (139). The syncytiotrophoblasts create an insufficient barrier between mother and fetus, resulting in leakage of trophoblast debris, anti-angiogenic factors, and proinflammatory cytokines to the mother's circulation.

Chronic hypoxia leads to oxidative stress, creating free radicals that damage cells by affecting structures such as lipid membranes, proteins, RNA and DNA. The oxidative

stress causes an increased inflammatory response in the placenta. The shredding of cytokines and the leakage of the damaged syncytium causes cell free DNA, microparticles, proteins like VEGF, PlGF and sFlt-1, and also fetal cells to enter the maternal circulation (140), in turn leading to a maternal systemic inflammatory response. The inflammation, in combination with the substances that are now in the mother´s circulation, affect the endothelium across the maternal vasculature (141).

In preeclampsia there is a decrease in PlGF levels combined with elevated levels of sFlt-1. The low levels of PlGF are due to both reduced expression and reduced availability of free PlGF, as it binds to the excess sFlt-1(142). Because of this, PlGF and sFlt-1levels can be used in combination with maternal risk factors and ultrasound as a screening tool in early pregnancy to predict the subsequent development of early-onset preeclampsia (143).

It has been suggested that there is a failure of the fetal-maternal immune tolerance in preeclampsia, leading to an excessive pro-inflammatory response and endothelial dysfunction (144). The immune cells at the fetal- maternal interface are dysregulated in preclampsia; for example, the macrophages don´t shift from the M1 subgroup to the more immune modulating M2 macrophage group, and the T-cells don´t shift from the Th1 and Th17 over to the more immune regulatory Th2 and T regulatory cells (138, 145). The uNK cells produce PlGF, VEGF, and cytokines, and are important for remodelling of the spiral arteries although the mechanisms for this are unclear (138).

1.3.4 Histamine in the fetal- maternal interface of the placenta

Histaminemia has been demonstrated to have several negative consequences during pregnancy, including miscarriage, premature delivery and also preeclampsia (146). Following conception, levels of histamine in the female body decline, reaching nadir around week 24, which is at the end of placentation, before increasing again and stabilizing at levels slightly below those found in non-pregnant women (147). Additionally, previous research has revealed that pregnant women with reduced levels of Diamineoxidase (DAO), the only extracellular enzyme known to inactivate

histamine in humans, have an elevated risk of developing early-onset preeclampsia (148). DAO levels rise hundredfold during pregnancy, whereas it is nearly non-excistent in non-pregnant females. (148). These findigs suggest that histamine is an essential biological substance that plays a crucial role in the development of a successful pregnancy.

Mast cells, traditionally recognized for their involvement in allergic reactions, also exert a noteworthy influence in the body´s inflammatory responses. These cells are widely distributed in various tissues throughout the body and harbour Ig-E molecules attached to their cell surface. While mast cells primarily are known for being stimulated by allergens binding to Ig-E on their surface, they can also be activated by cytokines and release cytokines and chemokines such as IL-6, IL-8, and TNF-α (figure 1) (149).

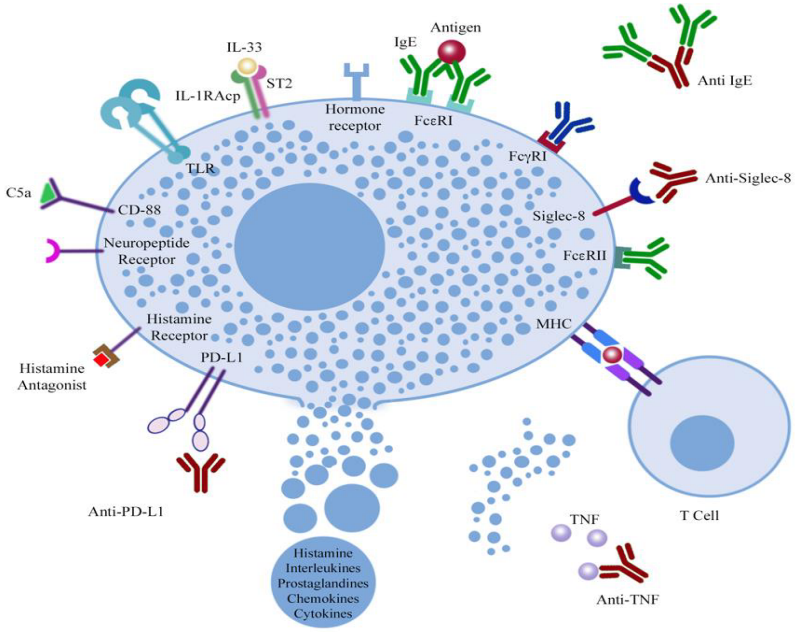


Figure 1: Mast cell release (© Anne Kvie Sande 2023)

2. Aims

The broader purpose of this work has been to improve prediction, treatment, and prophylaxis of preeclampsia, by combining the understanding of early-onset and late-onset preeclampsia as two different conditions with the focus on the immunological basis for the disease.

The overall aim was to investigate associations between well-known and potential risk factors for early- (<34 and <37) and late-onset (≥34 and ≥37) preeclampsia and to investigate wether maternal use of antihistamines in relation to pregnancy affect the risk of early-onset preeclampsia.

The specific aims were:

Paper I: To assess the effect of maternal pre-gestational allergy on the risk of early-onset and late-onset preeclampsia.

Paper II: To see how pregestational maternal use of antihistamines affect the development of early-onset preeclampsia.

Paper III: To assess if diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension were differentially associated with preterm and term preeclampsia.

3. Materials and methods

3.1 Overview of materials and methods in Papers I to III

	Paper I	Paper II	Paper III
Aims	To assess the association of maternal pre-gestational allergy on the risk of early-onset and late-onset preeclampsia.	To investigate whether maternal pregestational antihistamine use affected development of early-onset preeclampsia.	To assess if diabetes type I and II, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension were differentially associated with preterm and term preeclampsia.
Design	Reterospective cohort study	Population-based cohort study with prospectively registered data	Nationwide population-based cohort study
Data source	CSAM Natus	MBRN and NorPD	MBRN
Population	All women giving birth in Stavanger (1996-2014) and in Bergen (2009-2014)	All women giving birth in Norway 2004-2016	All women giving birth in Norway 1999-2016
Exposure	Pregestational maternal allergy, asthma, epilepsy, hypertension, coronary disease, recurrent urinary tract infections, kidney disease, rheumatoid arthritis, and diabetes type I and II	Use of antihistamines in allergic women	Diabetes type I and II, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension
Outcome	Early-onset preeclampsia, late-onset preeclampsia (and early- versus late-onset preeclampsia)	Development of early-onset preeclampsia	Preterm preeclampsia, term preeclampsia (and preterm versus term preeclampsia)
Definition of early- and late-onset preeclampsia	Diagnosis before or after gestational week 34	Two definitions: diagnosis before or after gestational week 34 AND delivery before or after gestational week 37	Two definitions: delivery before or after gestational week 37 AND diagnosis before or after gestational week 34 (numbers in supplementary)
Adjustments	Maternal age and Parity	Maternal age, parity, multiple gestation, and additional BMI in a subgroup where BMI was available	Maternal age, parity, multiple gestation, and additional BMI in a subgroup where BMI was available
Measure of association	Multinomial OR with 95% CI	Binomial OR with 95% CI	Multinomial RRR with 95% CI

Abbreviations: MBRN; Medical Birth Registry of Norway, OR; Odds Ratio, CI; Confidence Interval, RRR; Relative Risk Ratios, NorPD; The Norwegian Prescription Database.

3.2 Data sources

The data sources used for this thesis were:

3.2.1 Natus (Copywright CSAM Health Group) (Paper I)

For our first paper, we used the electronic medical record system Natus™, CSAM Health Group. The Natus system is the successor to a historical database established by Leif Gjessing in 1996, and which is currently located at Stavanger University Hospital. The database encompases pregnancy- and delivery-related information from all deliveries that took place at this hospital from 1996 to 2008. Subsequently, the Natus system was introduced in 2008. Natus contains comprehensive pregnancy, delivery and post-partum information and is still in use. The Natus system is Excel-based, and therefore offers a convenient means of extracting anonymized and analyzable data on more than 200 variables.

Today, all deliveries in Norway are registered in one of two maternity care systems CSAM Natus or CSAM Partus. Births at Haukeland University Hospital are also registered in Natus, which enabled us to easily use data from both departments.

3.2.2 The Medical Birth Registry of Norway, MBRN (Paper II and III)

MBRN is a population-based registry that collects data on all births in Norway. It was established in 1967 and was the world´s first national birth register. It is a national, compulsory health register and captures data on all pregnancies that progress beyond 12 weeks of gestation from 2006 including stillbirths. Up until 2006 the limit was deliveries after week 16. The MBRN collects data on various aspects of pregnancy, delivery, and the post-partum period including live births, stillbirths, and terminations. The data includes maternal demographics, mode of delivery, neonatal outcomes, and congenital abnormalities. It´s aim is systematic surveillance of maternal health and mortality associated with pregnancy, childbirth, and the postpartum period, as well as child health and mortality related to pregnancy and birth (150, 151).

The MBRN is managed by the Norwegian Institute of Public Health which is responsible for data collection and the quality control of the registry. Both collection and processing of data in the MBRN is administered by the MBRN- regulations (152).

The validity of MBRN has been the subject for evaluation of several papers and is found to be of high quality (153, 154, 155).

Data collection by the Medical Birth Registry of Norway.

At the initial antenatal consultation, the midwife or general practitioner records data on pre-existing medical conditions and prior pregnancies. These details are documented on the antenatal health card, which serves as a tracking tool throughout pregnancy. Following delivery, the attending midwife or obstetrician electronically transmits all information noted on the antenatal health card, together with information about the actual delivery, to the MBRN through the birth report.

3.2.3 The Norwegian Prescription Database, NorPD (Paper II)

The Norwegian Prescription Database (NorPD) was established in 2004 and contains information of all prescriptions that has been collected by the patients at the pharmacies. All pharmacies electronically register the prescriptions and transmits the information to the NorPD through Statistics Norway (156). The patient´s personal identification number and the prescriber´s identification number are substituted with a unique pseudonym by Statistics Norway, allowing for the linkage of prescriptions to individuals without revealing their identity.

The legal foundation of the NorPD is the Regulation «Forskrift om innsamling og behandling av helseopplysninger i Reseptbasert legemiddelregister» (156). The aims of the NorPD are: 1) to describe patterns of drug usage and identify trends over time, 2) to aid research and consider the safety of drug usage, 3) monitor, control and plan

the prescription practice to ensure the quality of the service, 4) internal control of the prescribing practice.

3.3 Data linkage

3.3.1 Statistics Norway

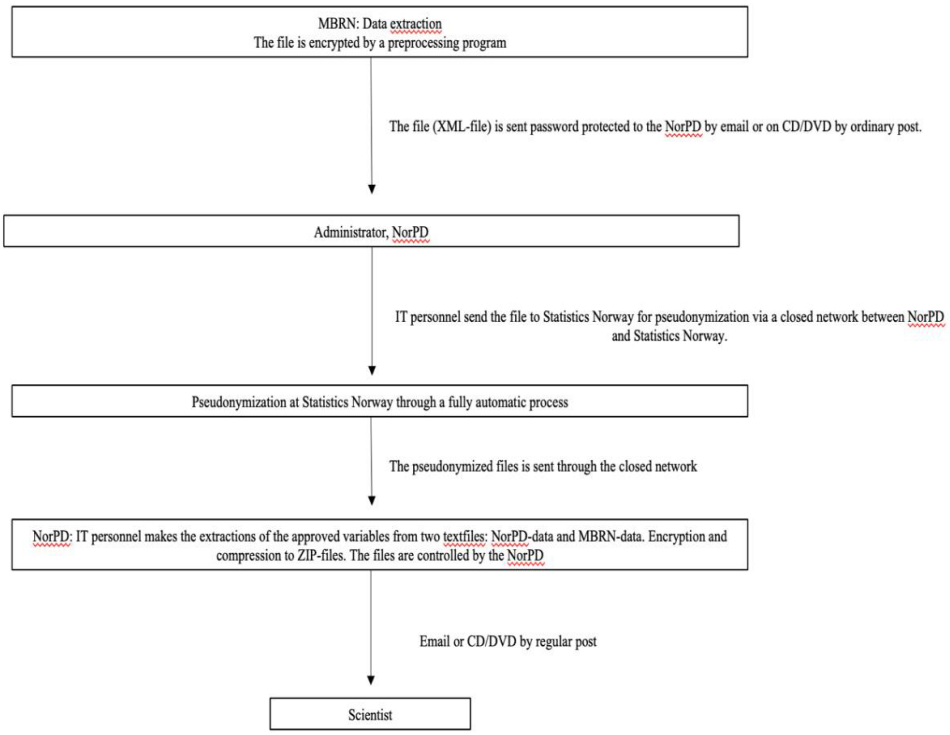
Statistics Norway has not provided any data for this thesis, but they have been involved in the data linkage in paper II. Statistics Norway (in Norwegian: Statistisk sentralbyrå, SSB) is the national statistics institute of Norway. It was established in 1876 and operates under the Ministry of Finance. The organization is responsible for collecting, compiling, and analyzing data and statistics on the Norwegian population, economy, social conditions, environmental factors, and more. In addition to publishing statistics and reports, Statistics Norway also offers varios tools and resources for accessing and analyzing data, including an online database and data visualization tools. In this thesis, the Statistics Norway has been involved in pseudonumization of the data.

3.3.2 Linkage between MBRN and NorPD

The initial collection of data/cohort are done at the MBRN. Because the NorPD is a pseudonym register, it is required that also the MBRN data is pseudonymized. This pseudonymization is performed at Statistics Norway. MBRN sends encrypted data to an administrator at the NorPD by e-mail or on CD/ DVD by ordinary mail. The NorPD sends the file to Statistics Norway via a closed network between the two, and the pseudonymization is completed. The pseudonymized files are returned to the NorPD where authorized personel makes the extraction of the approved variables from two text files; MBRN and NorPD, respectively, and merge the two files before encryption and compression to ZIP-files. The files are controlled by the NorPD before they are sent to the scientist. Through this process, anonymity is ensured by ensuring that the

personal D-number, the pseudonym, and the health data are not kept at the same institution.

Figure 2: Flow chart for data linkage, The Medical Birth Registry of Norway (MBRN) & The Norwegian Prescription Database (NorPD).



3.4 Definitions

The definition of preeclampsia is outlined on page 18 under paragraph 1.2.1.

Because the data sets used in this thesis are from 1996- 2014 (paper I), 2006-2016 (paper II), and 1999- 2016 (paper III), respectively, preeclampsia registered in our datasets (Natus and MBRN) has been diagnosed as it was defined by the Norwegian Society of Obstetrics and Gynecology in the study period: 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 (157), which also corresponded with the NICE guidelines at that time (158).

3.4.1 Early-onset and late-onset preeclampsia

In this thesis we have used two of the definitions mentioned in the Introduction section, see page 20-21: preeclampsia *diagnosed* before or after gestational week 34 (paper I, paper II, and paper III) and preeclampsia resulting in *delivery* before or after 37 weeks of gestation (paper II and paper III). In paper III we have used the terms preterm preeclampsia for preeclampsia resulting in delivery before 37 weeks of gestation, and term preeclampsia for preeclampsia resulting in delivery at or after 37 gestational weeks.

3.5 Study population and design

Paper I

Our first paper is a reterospective cohort study with prospectively collected data and included all women giving birth in Stavanger 1996-2014 and in Bergen 2009-2014.

Deliveries with missing information on maternal age and/or parity were excluded. The flow chart of paper I is shown I Figure 3 below.

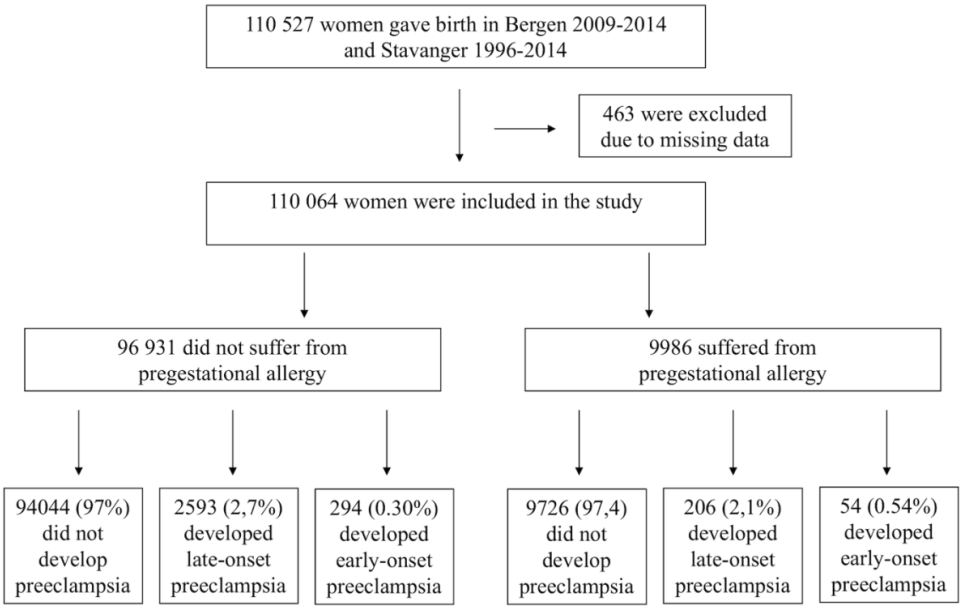


Figure 3: Flow chart, paper I.

Paper II and III are both nationwide population-based cohort studies with prospectively collected data.

Paper II

This is a population-based cohort study with prospectively registered data where we merged data from the MBRN with data from the NorPD on all women giving birth in Norway between 2004-2016. The unique personal identification number provided to all Norwegian citizens enabled linkage of data from the two national registries. All births in Norway during the study period were assessed. Births with gestational age > 44+0 weeks or < 20+0 weeks, births with missing gestational age and birth of the second twin or higher were excluded. The flow chart of paper II is shown in Figure 4.

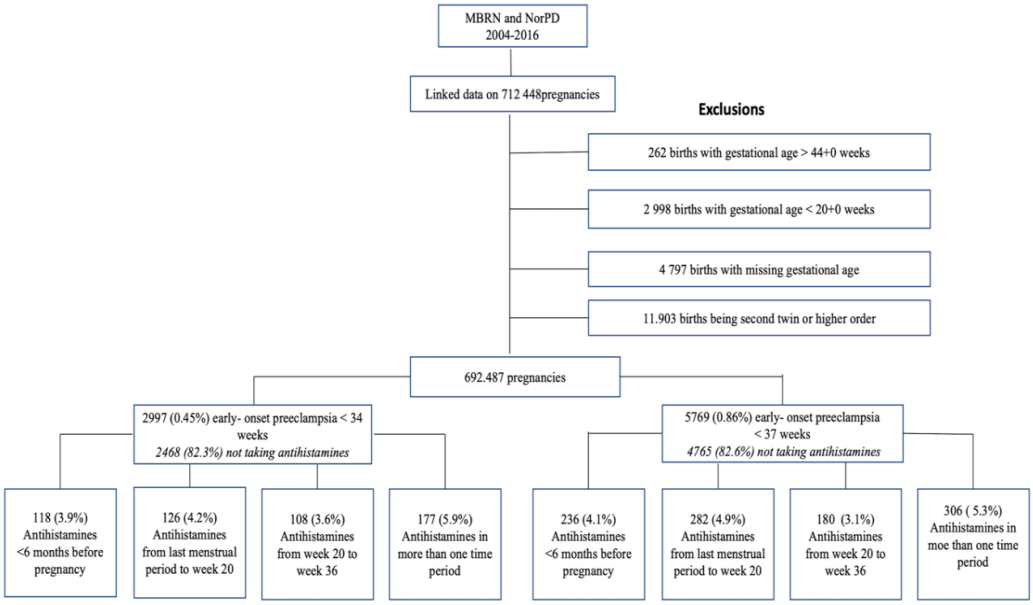


Figure 4: Flow chart, paper II.

Paper III

Paper 3 is a nationwide population-based cohort study of all women who gave birth in Norway from 1999-2016. We excluded deliveries of second-born twins or higher order, those with missing gestational age, and those with gestational age less than 19 weeks + 6 days, or gestational age greater than 44 weeks, to ensure the validity of our analyses, please see flow chart of paper III in Figure 5.

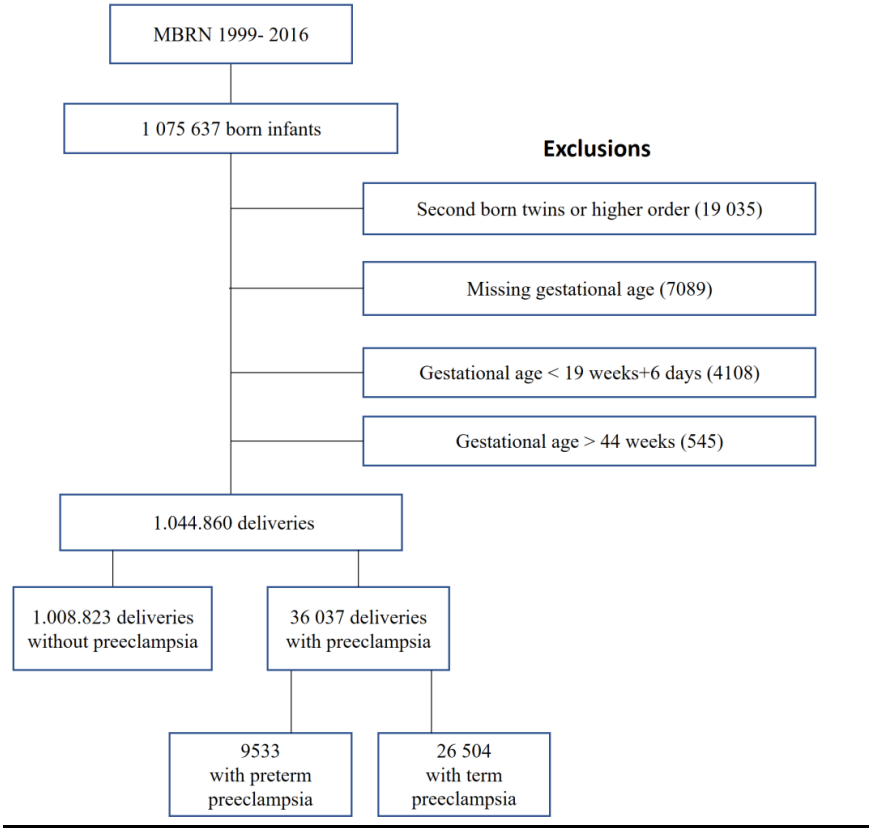


Figure 5: Flow chart, paper III.

It should be noted that in the MBRN, the infant is the counting unit. Therefore, all multiple pregnancies are recorded as two or more deliveries. To make delivery the counting unit, second twins or higher orders were excluded in papers II and III.

3.6 Variables

3.6.1 Exposure variables

Paper I

The exposure variables in this study were self-reported data from the Natus database to investigate several well-known pre-gestational conditions, including allergy, asthma, epilepsy, hypertension, coronary disease, recurrent urinary tract infections, kidney disease, rheumatoid arthritis, and type I and type II diabetes, registered in the Natus database. This information had been collected from the antenatal health card at the first antenatal consultation with the general practitioner or midwife and/or at the third trimester triage consultation.

Paper II

In our second paper the exposure variable was antihistamine use in relation to pregnancy in allergic women. We accessed data from the NorPD on all antihistamines prescribed for systemic use. To ensure that the antihistamines were prescribed specifically for allergy, and not for other conditions, e. g. sleep disorders or hyperemesis gravidarum, we used the Anatomical Therapeutic Chemical Classification System (ATC) code R06, and the corresponding national refund codes from the International Classification of Primary Care (ICPC codes: F71, R97, S98) and the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10 codes: H10.1, J30, L50). As the focus of this study was women with allergies, we used antihistamine prescriptions for allergy to identify women with allergies, as maternal allergy is not registered with an ICD-10 code in

the MBRN. NorPD also provided the type of antihistamine prescribed for each prescription, and the date of dispense. Use of antihistamines was divided into four periods related to pregnancy: 1) Before pregnancy: from 6 months prior and up to LMP, 2) Early pregnancy: from LMP to week 20 of gestation, 3) Late pregnancy: from week 20 to week 36 of gestation, and 4) Women who had used antihistamines in more than one period. The latter group was identified to ensure mutually exclusive groups.

As we had access to data regarding gestational age in days at birth (from the MBRN), we could make the variable "preeclampsia resulting in delivery before or after gestational week 37".

Paper III

In this paper, also using the MBRN, we retrieved data on the pregestational conditions diabetes type I and II, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension.

3.6.2 Outcome variables

For paper I our outcome variables were development of early-onset preeclampsia and late-onset preeclampsia, defined as women who met the diagnostic criteria for preeclampsia before 34 completed weeks of gestation.

Outcome variable in paper II was development of early-onset preeclampsia defined as both preeclampsia diagnosed before gestational week 34 and preeclampsia resulting in delivery before gestational week 37.

For paper III our outcome variable was preterm and term preeclampsia, defined as preeclampsia resulting in delivery before or after 37 completed weeks of gestation. Analyses were also made for women who met the diagnostic criteria for preeclampsia before or after 34 completed weeks of gestation, in supplementary material in the manuscript.

3.6.3 Potential confounding variables

Potential confounders registered from Natus (paper I) were parity and maternal age.

For paper II and III potential confounders were maternal age, parity, occurrence of multiple pregnancies and pre-pregnancy BMI, from the MBRN.

For paper I, Natus did not contain information on BMI in our chosen study period.

The MBRN commenced recording BMI of expectant mothers in 2006. At this time, only 0.1% of the reported pregnancies in MBRN included BMI. However, the registration steadily increased from 2006 until it surpassed 70% in 2014. Notably, even during periods of inadequate registration, the BMI measurements were observed to follow a normal distribution, indicating that the recorded data was representative (159).

3.7 Statistical analyses

Paper I

Univariate analyes were performed to assess potential predictors of early-onset preeclampsia, late-onset preeclampsia, and early-onset versus late-onset preeclampsia, using 2x2 tables and chi-square tests. Multinomial logistic regression was used to investigate the relationship between all parameters influencing the risk of preeclampsia, while sequencially adding each of the remaining parametres, one by one, to determine if they affected the effect size. Multinomial logistic regression analyses were used to assess the association between the predictors and the outcome variables, including no preeclampsia, early-onset preeclampsia, and late-onset preeclampsia. In the final model, factors that significantly altered effect size and/or statistical significance, as well as maternal age, parity, and known confounders, were

included. OR with 95% CI were calculated using this model. When a predictor resulted in no occurrence of the outcome, the "rule of three" was used to calculate the 95% CI (160). Additionally, predicted probabilities were calculated for the most relevant predictors.

Associations were determined with 95% CI´s, but also assessed with 99% CI´s due to multiple hypothesis testing.

SPSS (IBM SPSS Statistics for Windows, Version 23.0.2. Armork, NY) was used for statistical analyses, and STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) was used to calculate predicted probabilities for no preeclampsia, early-onset preeclampsia, and late-onset preeclampsia for women with and without pre-gestational allergy, in a model adjusted for athma, maternal age, and parity.

Paper II

We employed binomial logistic regression models with random effects component to account for the repeat effect of pregnancies to the same woman. OR with 95% CI´s were estimated for early-onset preeclampsia associated with antihistamine use in the four groups outlined above and compared to women not using antihistamines. Maternal age at birth was adjusted for in all analyses. We conducted four secondary analyses, which included stratification by parity and multiple pregnancy, the separation of antihistamines into five main types (cetirizine/levocetirizine, loratadine/desloratadine, dexchlorpheniramine, meclizine and other antihistamines), and adjusted for BMI in women with available data on BMI, specifically 309 617 women in our study sample. We also presented the results from the main analyses as estimated predicted proportions of early-onset preeclampsia in the four groups and for women not prescribed antihistamines. We estimated and plotted the average predicted proportions of early-onset preeclampsia using STATA (Release 17. College Station, TX: StataCorp LLC. StataCorp, 2019) functions margins and margins plot.

All other statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 26.0.0.1 Armork, NY, 2019). Significance testing was two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

Paper III

For our third paper, we used multinomial logistic regression to estimate RRR´s with 95% CI´s for preterm, term, and no preeclampsia, for each pregestational matenal risk factor. To account for repeated pregnancies in the same woman, we used cluster robust standard errors.

First, we estimated RRR´s for each risk factor, adjusting for maternal age, parity, and multiple gestation. We then performed separate analyses by additionally adjusting for all the other pregestational maternal risk factors. Maternel age was modelled non-linealy using restricted cubic splines with four knots in both strategies.

We performed separate analyses for women with registered BMI using the same strategy as mentioned above. The additional adjustments for BMI were modelled with restricted cubic splines with four knots.

Data preparations were conducted using IBM SPSS Statistics for Windows (Version 26.0.0.1 Armork, NY, 2019) and analyses were done in STATA (*Release 17. College Station, TX: Stata Corp LLC. Stata Corp, 2019*).

3.8 Ethical considerations

It is important for scientists to consider the potential violation of individual privacy when accessing health register data. None of the participants and registered individuals in the MBRN are identifyable in the published material, the variables in question are few and so-called green variables (deemed low risk from a

dataprotection viewpoint), and the information has already been collected and thus would not represent any additional involvement from the patients. Still, this is sensitive information regarding women´s health and caution must be exercised. Given the large scale of our dataset, obtaining informed conscent from each participant was not feasible. Therefore, we sought exemption from the written consent requirements by applying to the ethics committee of the Western Norway regional health authorities.

3.9 Ethical approvals

Paper I was approved by the ethics committee of the Western Norway regional health authorities on March 3rd, 2015, ref. 2015/66/REK vest (Appendix 1).

Paper II and III were approved by the Western Norwegian regional health authorities on April 7th, 2017, reference number 2017/292/REK vest (Appendix 2 and 3). The data protection officer at Stavanger University Hospital has approved the Data Protection Impact Assessment (Appendix 4) and access to data was approved by the Norwegian Institute of Public Health (NIPH).

3.10 Patient and Public Involvement

A Focus group with patients suffering from preeclampsia was gathered to discuss the background and methodology of our planned studies. The group found the data protection measures satisfactory. During the discussion, important elements regarding risk factors for preeclampsia came up. The group suggested exploring the differentiation of various forms of allergies and their impact on preeclampsia, as well as investigating the potential use of commonly used allergy medication as prophylaxis or treatment for preeclampsia. The discussions in the group also gave us

valuable insight in the use of patient and public involvement in future studies. The protocol was subsequently reviewed by the user representatives at Stavanger University Hospital in October 2019 who agreed with the Focus group´s comments.

4. Summary of results

4.1 Paper I

The study examined 110 527 pregnancies registered at two University Hospital departments in the Western Norwegian Health Region during the respective study periods. After excluding 463 pregnancies due to missing data, 110 064 pregnancies were included for analyses. Among these 2 799 (2.5%) developed late-onset preeclampsia, and 348 (0.3%) developed early-onset preeclampsia (Table 1).

Pre-gestational allergy increased the risk of early-onset preeclampsia with an OR of 1.8 (95% CI: 1.3- 2.4) and reduce the risk of late-onset preeclampsia with an OR of 0.8 (95% CI: 0.7-0.9). The difference in the effect of allergy on early-onset and late-onset preeclampsia is significant, with an OR of 2.2 (95% CI: 1.6-3.1)

Table 3: Odds ratios (ORs) with 95% confidence intervals (95% CIs) for early-onset (before 34 weeks of pregnancy) and late-onset preeclampsia (PE) in patients with pregestational allergy and asthma.

	Early-onset vs no PE		Late-onset vs no PE		Early- vs late-onset PE	
	OR	95% CI	OR	95% CI	OR	95% CI
Allergy	1.8	1.3 – 2.4*	0.8	0.7 – 0.9*	2.2	1.6 – 3.1*
Astma	1.1	0.6 – 2.0	0.9	0.7 – 1.2	1.2	0.7 – 2.3
Age/10 yrs	1.5	1.2 – 1.9*	1.1	1.0 – 1.2	1.4	1.1 – 1.7*
Primipara	3.0	2.4 – 3.8*	2.6	2.4 – 2.9	1.1	0.9 – 1.5

Confidence intervals marked with * identify associations also significant at a 1% significance level.

4.2 Paper II

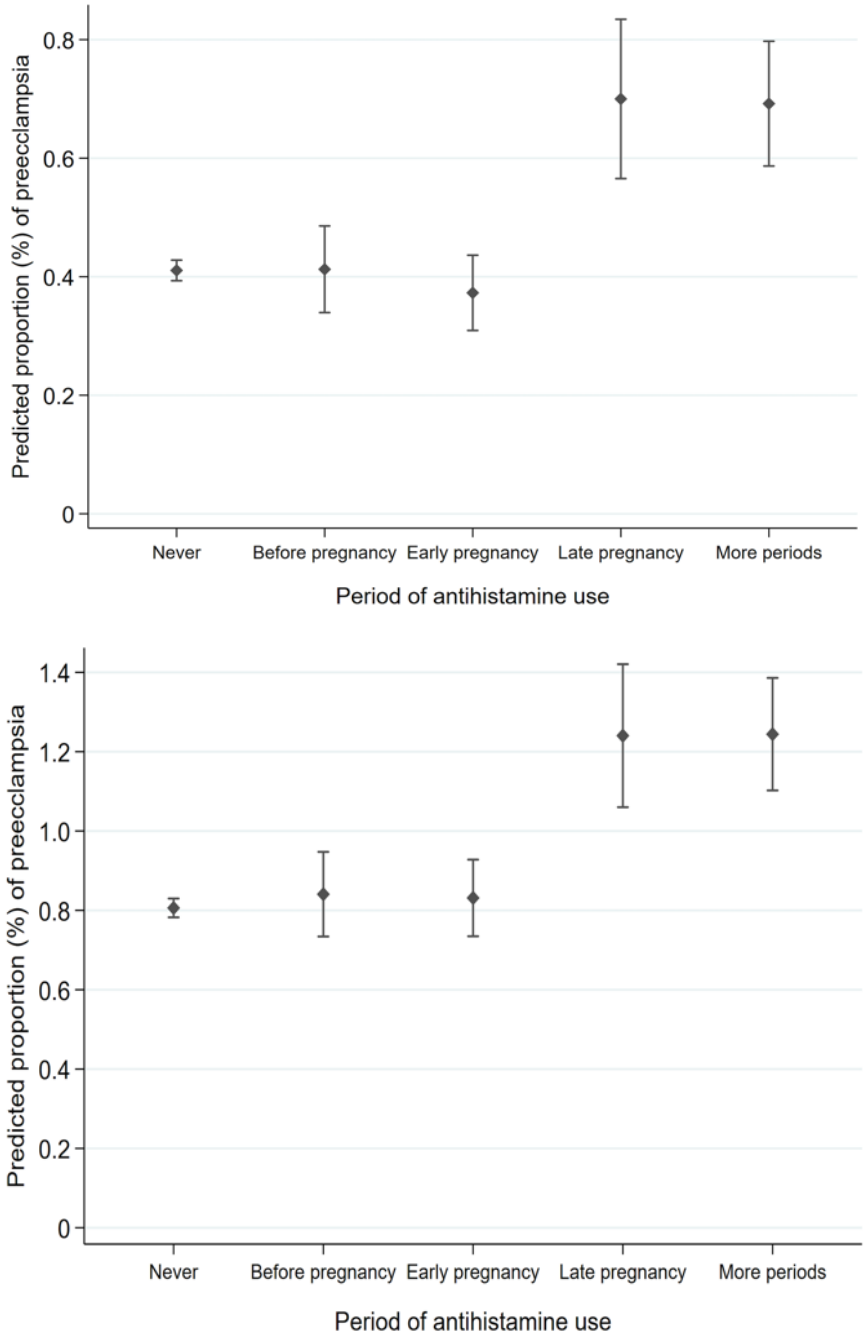
We analyzed a total of 692 487 eligible pregnancies, out of which 101 287 women (14.6%) reported using antihistamines. Preeclampsia was observed in 21 578 pregnancies (3.1%), with 2 997 (0.43%) being diagnosed before 34 gestational weeks and 5 769 (0.83%) delivered with preeclampsia before gestational week 37.

Use of antihistamines before and in early pregnancy was associated with a risk of developing early-onset preeclampsia that was comparable to the background population (OR 1.0, 95% CI 0.8-1.2 and OR 0.9, 95% CI 0.7-1.1, respectively). Antihistamine use only in late pregnancy was not treated as exposure, but as an indicator of allergy, and was associated with an increased risk of early-onset preeclampsia (OR 1.8, 95% CI 1.5-2.2). Predicted proportions of preeclampsia <34 weeks were significantly lower in women using antihistamines before (0.41%, 95% CI 0.34-0.49) and in early pregnancy (0.37%, 95% CI 0.31-0.44), compared to women using antihistamines only after placentation (0.69%, 95% CI 0.57-0.83). Results were similar for preeclampsia <37 weeks.

Table 4: Odds ratios (OR) with 95% confidence intervals (CI) for early-onset preeclampsia (<34 and <37 gestational weeks, respectively) by use of antihistamines in relation to pregnancy compared to no use of antihistamines in 762 399 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database 2004-2016.

	Before pregnancy OR (95% CI)	Early pregnancy OR (95% CI)	Late pregnancy OR (95% CI)	Antihistamines in more than one period
Pre-eclampsia <34 weeks				
Any antihistamine	1.0 (0.8 - 1.2)	0.9 (0.7 - 1.1)	1.8 (1.5 - 2.2)	1.7 (1.5 - 2.0)
Cetirizine / Levocetirizine	1.2 (0.9 - 1.6)	0.9 (0.5 - 1.3)	1.4 (0.8 - 2.2)	2.0 (1.3 - 3.0)
Loratadine / Desloratadine	0.9 (0.6 - 1.3)	1.2 (0.7 - 1.9)	1.9 (1.1 - 3.3)	2.0 (1.2 - 3.3)
Dexchlorpheniramine	0.9 (0.4 - 2.2)	0.5 (0.3 - 0.9)	1.3 (0.9 - 1.8)	1.5 (0.6 - 3.6)
Meclizine	N/A[b]	0.9 (0.6 - 1.3)	3.3 (1.7 - 6.3)	1.9 (0.3 - 14)
Other antihistamines[a]	0.8 (0.5 - 1.4)	0.8 (0.5 - 1.2)	3.1 (2.0 - 4.8)	0.7 (0.2 - 2.9)
More than one type of antihistamine in the period	0.8 (0.5 - 1.3)	1.4 (0.9 - 2.1)	2.3 (1.4 - 3.8)	1.7 (1.4 - 2.1)
Nulliparous	0.9 (0.7 - 1.2)	0.9 (0.7 - 1.2)	1.8 (1.4 - 2.3)	1.7 (1.4 - 2.1)
Parous	1.1 (0.8 - 1.4)	0.8 (0.6 - 1.1)	1.7 (1.3 - 2.3)	1.6 (1.2 - 2.0)
Singleton	1.0 (0.8 - 1.2)	0.9 (0.7 - 1.0)	1.8 (1.4 - 2.2)	1.7 (1.5 - 2.0)
Multiple pregnancy	1.1 (0.6 - 2.0)	1.1 (0.6 - 1.7)	1.2 (0.7 - 2.1)	1.6 (0.99 - 2.6)
Pre-eclampsia <37 weeks				
Any antihistamine	1.0 (0.9 - 1.2)	1.0 (0.9 - 1.2)	1.5 (1.3 - 1.8)	1.6 (1.4 - 1.8)
Cetirizine / Levocetirizine	0.9 (0.8 - 1.2)	1.0 (0.8 - 1.4)	1.2 (0.8 - 1.7)	1.5 (1.0 - 2.1)
Loratadine / Desloratadine	0.9 (0.7 - 1.2)	1.4 (0.98- 1.9)	0.8 (0.5 - 1.5)	1.3 (0.8 - 2.0)
Dexchlorpheniramine	0.9 (0.4 - 1.6)	0.7 (0.5 - 0.9)	1.4 (1.1 - 1.8)	1.7 (0.9 - 3.1)
Meclizine	1.3 (0.3 - 5.2)	1.1 (0.9 - 1.3)	3.2 (2.0- 5.2)	1.2 (0.5 - 7.9)
Other antihistamines[a]	1.4 (1.0 - 1.9)	1.0 (0.7 - 1.3)	2.3 (1.6 - 3.3)	2.1(1.2 - 3.8)
More than one type of antihistamine in the period	1.1 (0.8 - 1.5)	1.3 (0.96 - 1.7)	2.1 (1.4 - 3.0)	1.6 (1.4 - 1.8)
Nulliparous	1.1 (0.9 - 1.3)	1.0 (0.9 - 1.2)	1.5 (1.2 - 1.8)	1.5 (1.3 - 1.8)
Parous	0.9 (0.7 - 1.1)	1.1 (0.9 - 1.3)	1.6 (1.2 - 2.0)	1.4 (1.1 - 1.7)
Singleton	1.0 (0.9 - 1.2)	1.0 (0.9 - 1.2)	1.4 (1.2 - 1.7)	1.6 (1.4 - 1.8)
Multiple pregnancy	0.9 (0.6 - 1.3)	0.8 (0.6 - 1.2)	1.3 (0.9 - 1.8)	1.2 (0.9 - 1.7)

[a] Alimemazine, Ebastine, Phenoxphenidine, Promethazine, Thiethylperazine, Cyclizine, Cinarizine, Clemastine, Doxylamine, Diphenhydramine, Cyproheptadine, Rupatadine, Bilastine.
[b] No women using Meclizine developed early-onset pre-eclampsia <34 weeks



Figures 6 and 7: Predicted proportions with 95% confidence intervals for preeclampsia <34 gestational weeks (left) and preeclampsia <37 weeks (right).

4.3 Paper III

From MBRN we gathered information on 1 075 637 infants born from 1999 to 2016. After exclusions there were 1 044 860 deliveries left for the primary analyses. Among these, 36 037 (3.4%) had preeclampsia, with 9533 (0.9%) women having preterm preeclampsia and 26 504 (2.5%) women having term preeclampsia.

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 versus no preeclampsia) and 0.9 to 5.7 (term versus no preeclampsia). Diabetes type 1 and 2 (RRR preterm versus term preeclampsia 2.89, 95% CI 2.46-3.39 and 1.68, 1.25-2.25, respectively), chronic kidney disease (1.55, 1.11-2.17), and chronic hypertension (1.85, 1.63-2.10) were more strongly association 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. When using diagnosis < 34 weeks as cut-off, also rheumatoid arthritis was significantly stronger associated with early-onset preeclampsia.

Table 5: Adjusted RRR´s with 95% CI´s for preterm versus no preeclampsia, term versus no preeclampsia, and preterm versus term preeclampsia by maternal risk factors.

	Adjusted* RRRs (95% CIs)			Adjusted** 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)

*Adjusted for age, parity, and multiple births.
** Adjusted for maternal age, parity, multiple births, and all other risk factors.
Abbreviations: PE, preeclampsia.

5. Discussion

5.1 Methodological considerations

Epidemiology is the study of distribution and determinants of disease in a population. It involves examining patterns of disease and health in different populations and identifying risk factors for specific diseases. This information is used for developing strategies for prevention and/ or control of a given disease (161).

5.1.1 Sample size and study of rare events

Early-onset preeclampsia is a rare, but serious condition. This makes it particularly suitable for epidemiological studies, requiring large data sets. Initial power calculations during planning of this project indicated that we needed data from more than 1 million pregnant women to have statistical strength to show a difference in the risk for early-onset and late-onset preeclampsia by the different examined risk factors. It has, however, been argued that power calculations are of limited relevance in epidemiological studies, as there are no ways to increase the data sets beyond the existing registers (162).

All three studies (paper I to III) are population-based cohort studies with prospectively collected data. Early-onset preeclampsia is a rare condition (3), and to capture statistically significant associations between the risk factors assessed in this thesis and early-onset preeeclampsia, population-based cohort studies are appropriate. By enrolling a large number of participants, one increases the likelihood of including sufficient cases to draw meaningful conclusions. This is a strength of these studies.

5.1.2 Registration of data

Epidemiological studies are dependent on accurate and complete registration of data. Incomlete registration of data may compromise the validity and generalizability of the results. Examples of poor registration can be missing data or inaccurate registration. It is therefore important that data are properly collected and registered, and that the sources are reliable.

A limitation in paper II, was the lack of registration of over-the-counter sales of antihistamines in the NorPD. However, this limitation only applies to Cetirizin and constitutes a mere 9% of the total sale of antihistamines in the ATC group R06A, according to official data from the NIPH (163). Additionally, maternal allergy is not specifically recorded in the MBRN. To address this, we hypothesized that women who received a prescription containing an ICD-10 code for allergy in the NorPD for reimbursement purposes most likely suffer from allergies. The NIPH asserts that the most reliable data for estimating allergy prevalences among Norwegian adults can be derived from the NorPD (164).

Our findings revealed that 13.9% of women in our study population used antihistamines. While there is a possibility that some women may have received antihistamines incorrectly coded as allergy for other conditions, we do not believe this issue significantliy affects our data quality. Quality-control measures involving refund codes were used to minimize these problems.

The MBRN does not have information on ethnicity, which is known to affect the risk for preeclampsia. Ethnicity is a complex factor that may affect maternal health through several mechanisms, among which genetics probably play a minor part (165). Evidence indicates that the effect in the Norwegian population is mainly mediated through soscioeconomic status (73).

5.1.3 Bias

Biases are systematic errors in the way that the data is collected, analysed, or interpreted and will affect the validity of the results. There are different types of biases, e.g., selection bias, information bias, and confounding. To minimize bias, one can adjust for confounding factors.

The primary limitation of our studies lies in the reliance on self-reported data, which introduces the potential for recall bias. Nonetheless, it is important to note that the general practitioner or midwife perform a detailed medical history assessment during the initial antenatal first-trimester consultation. The gathered information is recorded on the antenatal health card, which accompanies the woman throughout the whole pregnancy and to the delivery department. Many Norwegian general practitioners hold record of the women´s medical history since childhood, but the precise origin of the data regarding prior medical conditions remains uncertain, as it is unknown wether it is derived from the general practitioner´s medical records or if it is the patient´s own subjective preception of her symptoms. Nevertheless, evidence shows that self-reported data during pregnancy have a reasonable level of validity (166). Additionally, the observed incidences of pregestational maternal conditions in our studies align with previous research findings (96, 167, 168, 169).

5.1.4 Confounding

Confounding is a variable that is connected to both the exposure studied and the outcome. It can be considered a third, “confusing” variable that makes it difficult to determine if the association one has found is really between the exposure and the outcome, and not due to the confounding factor.

A challenge in all of our studies is the limited registration of BMI, a well known confounder to preeclampsia (46). The Natus database had no information on BMI during our study period (1996- 2014). Results for conditions where BMI may act as a confounder, such as diabetes type 2, should therefore be interpreted with caution. The

inclusion of BMI in the MBRN commenced in 2006, whith a meager 0.1% of the registered pregnancies reporting BMI that year. Subsequently, there was a progressive increase in registration exceeding 70% in 2014. Notably, even during periods characterized by inadequate registration, the distribution of BMI values adhered to a normal distribution pattern, which implies a representative registration despite variations over time (159).

5.2 Discussion of results

The pathophysiology of preeclampsia is still incompletely understood, but deficient remodelling of the uterine spiral arteries causing intrauterine growth restriction and early-onset preeclampsia, is a well established feature (8). Still, inadequate remodelling of the spiral arteries can not fully explain the complex pathophysiology of preeclampsia, as most women having preeclampsia develop it´s late-onset entity (3). Furthermore, women suffering from late-onset preeclampasia do not deliver growth restricted babies, and conditions related to large for gestational age babies, such as overweight and diabetes, are well known risk factor for preeclampsia (46, 168). In 1996 Ness and Roberts proposed that there were two entities of preeeclampsia, which they designated the placental (early-onset) and the maternal (late-onset), and that their common feature was endothelial damage hypothesized to cause oxidative stress (34). Current theories focus on immunological factors, rather than attributing the developemt of the disease to properties of the mother or the placenta (8). Most risk factors assessed in this study are of interest in this context, as they are all considered to be immunological conditions (75, 99, 170) and conditions of immune dysregulation (78).

5.2.1 Paper I: Allergy as an isolated risk factor early-onset preeclampsia

In our first paper we found that pregestational maternal allergy is an isolated risk factor for early-onset preeclampsia (OR 1.8 (95% CI: 1.3-2.4)). While a novel finding, we believe it to be in line with other studies indicating different levels of immunological factors in early-onset and late-onset preeclampsia (171, 172). Allergy is characterized by elevated levels of IgE in affected individuals. A few studies have investigated the levels of Ig-E in preeclamptic women, and found serum IgE levels to be elevated in women with preeclampsia (93). This supports our finding of allergy as an isolated risk factor for early-onset preeclampsia (80) (paper I). We did not find a similar association between allergy and late-onset preeclampsia (OR 0.8 (95% CI: 0.7-0.9)).

Allergy is caused by the binding of an allergen to the Ig-E molecule on mast cells, causing the mast cells to release histamine. Interestingly, mast cells are an abundant cell in both the uterus and the placenta. In the human uterus the greatest concentration of mast cells is in relation to smooth muscle cells. Histamine contributes to regulation of labour through histamine 1 receptors in the uterus (173), and increased histamine levels can cause premature labor (174). Preterm delivery could be a possible contributor to why women in our study population didn´t develop late-onset preeclampsia. However, when anlayzing data used in our first paper, we observed that allergic women included in our material did not exhibit a higher incidence of preterm birth (analyses performed post publication, results not published elsewhere). Consequently, the known association between histamine and premature birth can not explain the 20% decrease in the risk of developing late-onset preeclampsia in our material.

Current understanding of histamine in pregnancy indicates its significant involvement in trophoblastic cell differentiation and as a regulator of apoptotic cell processes (175, 176). During normal pregnancies, the concentration of histamine in the bloodstream decreases from the beginning of pregnancy, reaching it´s lowest point around gestational week 24, which is at the end of placentation. Subsequently, during the

third trimester, it rises again and stabilizes slightly below the levels found in non-pregnant individuals (147). Elevated levels of histamine in the blood during pregnancy have been linked to various unfavorable outcomes, such as first trimester bleeding, preterm labour, and also preeclampsia (146). A study by Sharma et al from 1984 observed that the severity of preeclampsia was proportional to the increase in histamine levels in blood (177). The same study also found vasoconstrictive effects on umbilical arteries and veins caused by elevated histamine levels (177), which may be the reason why increased histamine levels in either maternal blood or at the fetal-maternal interface is associated with preeclampsia. Research conducted on guinea pig placentas demonstrated that heightened histamine levels resulted in both vasoconstriction and increased permeability to macromolecules (178). Similar effects in humans might account for the elevated risk for preeclampsia observed in not only allergic women, but also women who suffer from increased levels of histamine for other reasons, such as vasculitis, parasitosis, and rare disorders like systemic mastocytosis. Evidence about systemic mastocitosis and it´s effect on pregnancy is limited, but it is plausible that also women suffering from this condition are at increasd risk for developing preeclampsia (179). A polish study from 2016 also found that women with systemic mastocytosis have an increased risk for spontaneous abortions (180). It is plausible that the augmented permeability to large molecules could further facilitate the release of bioactive substances from the compromised placenta, leading to an increased likelihood of preeclampsia as a contributing factor to the complex pathogenesis of the condition.

Histamine becomes biologically active when it is released into the blood stream by mast cells or basophile leukcytes. The active histamine binds to cells in the body´s tissue through different histamine receptors and cause a wide range of symptoms. In humans, DAO (formerly known as histaminase) is the sole extracellular enzyme capable of deactivating histamine (181, 182). Plasma levels of DAO are barely detectable in non-pregnant women but increase several hundred-fold during pregnancy (183). In contrast to high levels of histamine increasing the risk of spontaneous abortions, preterm labor and preeclampsia, there is evidence that low

levels of DAO leads to the same adverse pregnancy outcomes (146), which suggests the need for some sort of balance between the two for a subsequent development of a successful pregnancy (184). A study by Velicky et al from 2018 found that DAO is produced by the trophoblast and that women with early-onset preeclampsia had lower levels of this enzyme compared to controls (148), highlighting the crucial role of histamine in the pathophysiology of early-onset preeclampsia.

Studies on the effect of antihistamines on pregnancy have to a large extent focused on the safety of the drug regarding fetal development and miscarriages. Although evidence is somewhat scarce, antihistamine use in early pregnancy is considered to be safe (185). In the 1950s, there was some interest in exploring the potential of using antihistamines as a *treatment* for eclampsia (186) and preeclampsia (187). However, this did not impact clinical management of either of these conditions. More recently, a case-control study conducted in Finland examined the overall risk of preeclampsia in women using histamines and found no association between antihistamine use and development of preeclampsia (188). This study, however, did not differenciate between early-onset and late-onset preeclampsia.

The findings in paper I prompted us to investigate wether maternal use of antihistamines prior to or during pregnancy could provide a protective effect against development of early-onset preeclampsia in women with allergies, leading to paper II.

5.2.2 Paper II: Use of antihistamines and preeclampsia

There are different kinds of histamine receptors, distributed in different kinds of tissues. Histamine 1 receptors are located in the skin and in the smooth muscles of the airways, while histamine 2 receptors are found in the stomach. Even though the histamine receptors have distinct distribution patterns, there can be some overlap in certain tissues. In the placenta, the feto-maternal interface, and in the smooth muscles of the uterus, the most abundant histamine receptor is the histamine 1 receptor (189).

Antihistamines attach to the histamine 1 receptors and block the receptor site, making it unavailable to histamine. Thus, antihistamines inhibit the action and symptoms caused by histamine release by the mast cells. There are three generations of antihistamines. The first generation is not receptor-selective and therefore blocks other receptors, such as muscarine receptors, as well. They are lipophile and cross the blood brain barrier, resulting in drowsiness. Examples of first-generation antihistamines in our second paper are Alimemazine and Promethazine, both gathered in the group "other antihistamines". Examples of second-generation antihistamines in our material are Cetirizine and Ebastine. Second generation antihistamines have higher specific affinity to histamine 1 receptors in peripheral tissues. They are large, lipophobic molecules and thus do not cross the blood brain barrier. A feature of third-generation antihistamines is that they have an even stronger affinity to histamine 1 receptors than for example Cetirizin. Like the second-generation antihistamines, they do not cross the blood brain barrier. In addition to inhibiting the effect of free histamine through blockage of the histamine 1 receptors, some antihistamines, like Desloratadin, inhibit the release of IL-4, IL-6, IL-8, and IL-13, all of which are involved in the pathophysiology of preeclampsia (190). In paper II we divided antihistamines into five groups and found that the association between antihistamine use and early-onset preeclampsia was not restricted to any specific type of antihistamine.

We found, as hypothesized, that allergic women who use antihistamines before or during early pregnancy had a reduced risk of developing early-onset preeclampsia, compared to women who only use antihistamines in late-pregnancy. The risk of preeclampsia for women suffering from allergy, but using antihistamines early, was reduced to the same level as non-allergic women, defined as women not using antihistamines. It is not likely that use of antihistamines in late pregnancy increase the risk of late-onset preeclampsia, but rather that the early use of antihistamines outweighs the known risk of early-onset preeclampsia. As we have shown in paper I (80), allergic women have an increased baseline risk for early-onset preeclampsia, probably due to their elevated levels of histamine and possibly IL-6, compared to

non-allergic women. Women prescribed antihistamines in late pregnancy, more specifically after the formation of the placenta, do not experience the same risk reduction observed in allergic women who take antihistamines before the formation of the placenta. These findings regarding antihistamines align with studies on aspirin and it´s role in preeclampsia prevention, where initiating the medication before gestational week 16 yield the best results for prevention of early-onset preeclampsia. Women prescribed antihistamines in more than one timeperiod had a risk of early-onset preeclampsia comparable to women prescribed antihistamines only in late pregnancy, even though they had antihistamines prescribed in early pregnancy. We believe this group consists of women with more severe allergy, in whom the ameliorating effect of antihistamines is insufficient to reduce the risk to the level of non-allergic women. This is in line with current theories on differentiated risk of preeclampsia, and the threshold for triggering the disease (8).

5.2.3 Paper III: Pregestational maternal risk factors for preterm and term preeclampsia

While mast cells are well known for their role in allergic reactions, they also play a significant role in the body´s inflammatory responces. They are present in almost all tissues throughout the body and have IgE bound to the cell surface. In addition to being activated by allergens binding to the surface Ig-E, mast cells can also be activated by cytokines (149), which are well-known substances in the pathophysiology of preeclampsia (191, 192). Not only being activated by them-mastcells also release a variety of cytokines, including IL-6, IL-13, TNF-α and IFN-γ, and chemokines such as IL-8 (figure 1, page 42). Knowing that mastcells are both activated by and release IL-6, the association between maternal allergy and early-onset preeclampsia immediately seems more plausible, as a common feature of all the other risk factors assessed in this thesis are related to elevated levels of IL-6 in affected persons (99, 170, 193).

The risk of developing preeclampsia increases with increasing BMI (46), and studies indicate that fatty tissue produces IL-6 and thus causes elevated levels of IL-6 in overweight women (194). In addition, overweight women are prone to metabolic syndrome and chronic inflammation, which in large part also is IL-6 mediated (195). These associations between BMI and IL-6 might explain the increase in predicted proportions between BMI and preeclampsia when BMI exceeds 23 in paper III.

In normal pregnancies, IL-6 levels exhibit a pattern where the serum level of IL-6 decreases during the first and most of the second trimester, followed by a gradual increase during the third trimester. Furthermore, IL-6 levels continue to rise a few months after childbirth (196). The fact that the IL-6 serum levels continue to rise after delivery may be a reason why some women develop preeclampsia after birth. Previous research has demonstrated elevated IL-6 levels in women diagnosed with preeclampsia (197, 198), suggesting that the pathogenesis of preeclampsia indeed has a significant immunological component.

Although there is some conflicting evidence, there are studies reporting elevated levels of IL-6 not only in maternal blood, but also in blood from the umbilical cord, in pregnancies complicated by preeclampsia(172). This prompts the question of what immunological consequences there might be for the offspring after being born from a preeclamptic pregnancy.

Byberg et al. demonstrated in 2014 an association between preeclamptic pregnancies and the development of allergic sensitization and allergic rhinoconjunctivitis in children during late childhood (95). However, this association was not observed for other atopic diseases. Still, other studies have indicated that preeclampsia serve as a common risk factor for eczema, asthma, and allergies in offspring born to mothers with preeclampsia (90).

Enhancing our understanding of the pathogenesis of preeclampsia, as well as identifying specific maternal pregestational risk factors and their distinct association with preterm and term preeclampsia, holds the potential to further facilitate the development of personalized monitoring strategies during pregnancy. This

knowledge may subsequently increase our ability to predict and ultimately prevent the condition from occurring in women with the highest risk for developing preeclampsia.

As stated in the introduction, there seems to be, at least to some extent, a global consensus regarding the risk factors to be considered when assessing a woman´s susceptibility to developing preeclampsia (37). However, there are numerous conditions that have been investigated but have not been incorporated into the various Clinical Practice Guidelines worldwide. Risk factors for consideration for Clinical Practice Guidelines should be either high prevalent in the relevant population, cause a significant impact to the development of the specific condition, or both. In the case of preeclampsia, some of the established risk factors have a low prevalence among the general female population but exert a substantial impact on the risk of development of preeclampsia in affected women. In this thesis, we chose to evaluate risk factors that are more prevalent among women of childbearing age.

SLE is an uncommon, immunological disorder with a global prevalence of 0.079% among the adult female population, although regional differences exist (199). A study conducted by Simard et al. identified a prevalence of 0.05% among Swedish women aged 15-49 (200). Even though it has a low prevalence, this condition has a significant impact on the development of preeclampsia in affected women and thus justifies its inclusion in early screening for preeclampsia (79) Moreover, few studies have distinguished between early-onset and late-onset preeclampsia when examining the association between preeclampsia and SLE (76).

In contrast, there are conditions with much higher prevalence, but they do not confer the same degree of risk, such as epilepsy, diabetes, asthma, and allergy, all of which are studied in this thesis. Allergy has the highest prevalence of all assessed risk factors, with a prevalence of 9.1% in the study population in paper I (80). According to our findings, there is a stronger association between allergy (a prevalent maternal risk factor) and early-onset preeclampsia than late-onset preeclampsia (80).

The differentiation between preterm and term preeclampsia holds particular significance in the development of screening algorithms for early detection of preterm preeclampsia. Early risk assessment and subsequent administration of low dose acetylsalisylic acid can only prevent preterm preeclampsia, but it is still relevant to identify women who are susceptible to develop term preeclampsia. The algorithm proposed by the Fetal Medicine Foundation has demonstrated a predictive capacity of 90% of early-onset preeclampsia occurring before 32 weeks of gestation, 75% of preterm pregnancies<37 weeks, and only 41% of term pregnancies at or beyond 37 weeks, at a false positive rate of 10% (201). An ideal algorithm would be capable of predicting both preterm and term preeclampsia, enabling individualized monitoring of the high-risk mother and child to minimize adverse outcome among those who develop term preeclampsia by determining the appropriate treatment in addition to optimal timing and location for delivery.

Screening for maternal risk factors and subsequent evaluation of individual risk for developing preeclampsia, is traditionally performed at the first prenatal visit by the general practitioner or a midwife. However, early screening for preeclampsia becomes most effective when incorporating maternal characteristics and medical history into an algorithm based on multivaraiate regression analyses. If assigning equal weight to all the pregestational risk factors in risk calculations, more than half of the pregnant population is classified as high risk, necessitating closer monitoring throughout pregnancy (44). When developing these algorithms, it is important to be able to quantify the relationship between the various risk factors and preterm and term preeclampsia, respectively. This approach enables a more precise prediction of both preterm and term preeclampsia. Previous research has demonstrated that algorithms that incorporate maternal factors, uterine pulsatile index, mean arterial blood pressure, and biophysical markers such as PAPP-A, PlGF, Inhibin-A, Activin-A, ans s-Endoglin, can predict 91% of preterm preeclampsia and 61% of term preeclampsia. Both assessments have a 5% false positive rate (5). By examining the association between maternal risk factors and both preterm and term preeclampsia,

paper III aims to enhance the accuracy of existing algorithms and make a valuable contribution to this field.

Science on basic mechanisms and biochemical markers are intriguing and extremely important for the knowledge of the pathophysiological processes leading to the development of preeclampsia, but it is the art of epidemiology that points out the direction in which to look. Epidemiology helps identifying and analyze patterns of occurrence, prevalence, and distribution within polpulations, and through this we gain insight into the burden of disease on both individual and society level. By identifying and quantifying risk factors, clinicians can better understand associations and mechanisms leading to disease. Although epidemiology seldom provides causal effects for disease development, the knowledge gained from epidemiological studies is crucial for developing preventive measures, creating targeted interventions, and by this improving patient outcomes. In addition, epidemiology is important for evaluation of healthcare interventions. An example to all of this is the large number of studies performing external validation of the large number of multivariate models created in the attempt to early predict subsequent development of preeclampsia (126).

6. Conclusion

Paper I:

We have found that maternal allergy is associated with early-onset preeclampsia, but not with late-onset preeclampsia. This is a novel finding, demonstrating the immunological mechanisms underlying the development of early-onset and late-onset preeclampsia.

Paper II:

Maternal use of antihistamines the last six months before and in first half of pregnancy, during the formation of the placenta, is associated with reduced risk of early-onset preeclampsia in allergic women. Allergic women using antihistemines only in the second half of pregnancy, which is after the formation of the placenta, or in more than one timeperiod related to pregnancy, did not share the same risk reduction. Based on our findings in paper II we recommend allergic women to continue using antihistamines during pregnancy.

Paper III:

Finally, we have found that type 1 and type 2 diabetes, kidney disease and hypertension is more strongly associated with preterm than with term preeclampsia. Asthma, epilepsy, and rheumatoid arthritis were not differently associated with preterm and term preeclampsia when cut-off was set at *delivery* before or after 37 gestational weeks. When cut-off was set at preeclampsia *diagnosed* before or after 34 weeks of gestation (early- and late-onset preeclampsia, respectively), rheumatoid arthritis also exhibits a stronger association with early-onset preeclampsia than with late-onset preeclampsia. These findings could be used to create more accurate algorithms used for early prediction of preeclampsia.

7. Clinical implications and future perspectives

Our findings that pregestational maternal allergy is an isolated risk factor for early-onset preeclampsia, and that antihistamines reduce the risk for early-onset preeclampsia in allergic women are both novel findings. Further studies should be conducted in different populations to validate our findings.

Furthermore, since we have found that antihistamines modulate the increased risk for early-onset preeclampsia in allergic women, randomized controlled trials should be performed to investigate antihistamine´s potential as prophylaxis for early-onset preeclampsia. A natural place to start would be to design a double blind randomized controlled trial containing pregnant women with allergies where one half received antihistamines and the other half received placebo to see if this led to reduced incidences of early-onset preeclampsia in the antihistamine group. It would also be interesting to do a trial of the effect of antihistamine use in relation to pregnancy and subsequent development of early-onset preeclampsia in non-allergic, but otherwise high-risk women. Antihistamines are safe in pregnancy, cost-effective, and easily accessable, which is especially important in low- and middle-income settings.

Preeclampsia is a more prevalent condition in low- and middle-income countries, such as African countries (23). It would be interesting to examine if elevated levels of IgE due to parasitic infections might be a contributor to this high prevalence as it is known that preeclamptic women have elevated levels of IgE (93). And if so, will these women benefit from prophylactic antihistamine use?

Regarding the other risk factors in this thesis and their association with preterm and term preeclampsia, our findings can be used to enhance existing algorithms for prediction of early-onset preeclampsia. It might be useful to develop new risk calculators incorporating the risk factors we have examined, with their respective weights in relation to development of both preterm and term preeclampsia, to determine if we can achieve a higher positive predictive value than currently existing algorithms, such as the Fetal Medicine Foundation Prediction Model. A natural next

step in such a scenario would be to externally validate the created algorithm against other excisting algorithms.

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9. Paper I-III

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Maternal allergy as an isolated risk factor for early-onset preeclampsia: An epidemiological study

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ABSTRACT

Immunological mechanisms underlying the development of preeclampsia are well known, but no association to allergy has yet been demonstrated. The aim of this study was to assess the correlation between maternal pre-gestational allergy, and early-onset and late-onset preeclampsia, respectively. It was a retrospective cohort study including all women giving birth in the Norwegian cities of Stavanger (1996–2014) and Bergen (2009–2014). Pre-gestational asthma, allergy, other known risk factors for preeclampsia, maternal age and parity were obtained from the electronic medical record system. The main outcome variables were early-onset and late-onset preeclampsia (before and after 34 completed weeks of gestation, respectively). We used multinomial logistic regression to estimate odds ratios (OR) with 95% confidence intervals (95% CI) for early and late-onset preeclampsia in women with pre-gestational allergy when compared to women without allergy, adjusting for covariates. Predicted probabilities for the outcomes were also calculated. Of the 110 064 included pregnancies, 2 799 developed late-onset preeclampsia (2.5%) and 348 developed early-onset preeclampsia (0.3%). Pre-gestational allergy increased the risk of early-onset preeclampsia (OR 1.7, 95% CI 1.3–2.4), and reduced the risk of late-onset preeclampsia (OR 0.8, 95% CI 0.7–0.9). These findings add valuable information on preeclampsia as an immunological complication of pregnancy and corroborate the understanding of early- and late-onset preeclampsia as two different entities.

1. Introduction

Dysregulation of the immune system is thought to play a key role in the pathogenesis of preeclampsia. Pre-gestational exposure to paternal antigens reduce the risk for preeclampsia (Robillard et al., 1994), and pregnancies resulting from oocyte donation have a three-fold risk for preeclampsia (Blazquez et al., 2016), pointing to an immunological basis for the disease. The interaction between trophoblasts and maternal natural killer cells is thought to play a key role in the physiological regulation of the immune system during pregnancy, and the number and type of natural killer cells in the decidua is indeed altered in pregnancies complicated by preeclampsia (Rieger et al., 2009). There is also an increased number of dendritic cells in the decidua in pregnancies complicated by preeclampsia (Huang et al., 2008). Most autoimmune diseases lead to an increased risk of preeclampsia. This association is strongest for diseases with a vascular component, such as lupus erythematosus (Chakravarty et al., 2006), and less pronounced in diseases with no vascular affection, such as diabetes (Lisonkova and Joseph, 2013). However, for most of these conditions we do not know if they affect the risk for early- and late-onset preeclampsia equally (debuting before and after 34 weeks of gestation, respectively), as few studies have stratified on early- and late-onset preeclampsia (Lisonkova and Joseph, 2013; Catov et al., 2007). To our knowledge, it is not previously shown that preeclampsia is associated with maternal allergy, although one study found increased levels of IgE in preeclamptic women (Alanen, 1984). Risk factors that only increase the risk of early-onset preeclampsia will be missed in studies not separating early-onset and late-onset preeclampsia, as the latter is a much more common condition.

Preeclampsia is a pregnancy specific disease, and occurs in 3–4 % of all Norwegian pregnancies (Vatten and Skjaerven, 2004; Klungsoyr et al., 2012). It is the leading cause of pregnancy-related morbidity and mortality worldwide (Raymond and Peterson, 2011). There are indications that early and late-onset preeclampsia are two separate conditions with different pathogenesis and clinical manifestation (Raymond and Peterson, 2011; Lisonkova and Joseph, 2013; Kucukgoz Gulec et al., 2013; Stubert et al., 2014; Salimi et al., 2014; Sezer et al., 2013, 2012; Tamas et al., 2013; van der Merwe et al., 2010; Watanabe

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et al., 2012; Villa et al., 2013). The diagnostic criteria of preeclampsia were defined by the Norwegian Society of Obstetrics and Gynecology and correspond with the NICE guidelines ((NICE), 2013a, b); proteinuria ≥ +1 on a dipstick, > 0.3 g urine protein loss per 24 h or a protein/creatinine ratio > 0.3 and repeated measurements of systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 after 20 weeks gestational age (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). Early and late-onset preeclampsia was defined as fulfilling the criteria for preeclampsia before and after 34 completed weeks of gestation, respectively. Although late-onset preeclampsia is more common (2.8%), early-onset preeclampsia (0.4%) leads to more morbidity, in particular iatrogenic preterm deliveries (Morken et al., 2008).

We have performed a population- based study to determine if maternal allergy, an immunologically mediated condition, is an isolated risk factor for early-onset preeclampsia.

2. Materials and methods

A historic cohort with prospectively collected data from all women giving birth in the Norwegian cities of Bergen and Stavanger was designed. The annual number of deliveries were between 4000 and 5000 in both cities. We used data from the electronic medical record system (NATUS™, CSAM Health). All women giving birth in Stavanger 1996–2014 and Bergen 2009–2014 were included. Deliveries with missing information on maternal age and/or parity were excluded.

All pregnant women in Norway are offered a free-of-charge antenatal follow-up in pregnancy by a midwife and/or a general practitioner, usually starting in the first trimester. At the first consultation, information on previous pregnancies and miscarriages, chronic diseases, current or previous smoking, use of medications, drug and alcohol use, maternal age and parity are recorded at the personal health record form, a specific form used in the follow-up of all pregnancies in Norway. This information is used to differentiate pregnancies to high-risk or low-risk delivery units, either at a third trimester consultation or when the woman presents in labor. Information from the personal health record form is then registered in the electronic medical record system. In the transferal, data on medication is then limited to that which is directly related to pregnancy follow-up; intake of potentially harmful drugs in the first trimester (necessitating a first trimester scan), antithrombotic treatment, and drugs used to induce labor.

Pregnancy complications, such as preeclampsia and gestational diabetes, are also recorded. Further information is added in the electronic medical record system during delivery. After delivery, the outcome is registered by the attending midwife and all data are sent electronically to the compulsory Medical Birth Registry of Norway.

We used information on pre-gestational allergy, asthma, epilepsy, hypertension, coronary disease, recurrent urinary tract infections, kidney disease, rheumatoid arthritis, type I and type II diabetes, as recorded in the personal health record at the first consultation, and at the third trimester differentiation.

The diagnostic criteria of preeclampsia were defined by the Norwegian Society of Obstetrics and Gynecology and correspond with the NICE guidelines ((NICE), 2013a, b); proteinuria ≥ +1 on a dipstick, > 0.3 g urine protein loss per 24 h or a protein/creatinine ratio > 0.3 and repeated measurements of systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 after 20 weeks gestational age (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). Early and late-onset preeclampsia was defined as fulfilling the criteria for preeclampsia before and after 34 completed weeks of gestation, respectively. In addition, HELLP (Hemolysis, Elevated liver enzymes, Low Platelets) syndrome, eclampsia (convulsions occurring in pregancy,-peri-partum or within one week post-patum, together with preeclampsia) and gestational hypertension, were recorded in the database.

2.1. Statistical methods

Univariate assessments of potential predictors of "early-onset preeclampsia", "late-onset preeclampsia" and "early-onset vs late-onset preeclampsia" were done by 2×2 tables and chi-square tests. Multinomial logistic regression was used to relate all parameters with an effect on preeclampsia to early- and late-onset preeclampsia, respectively, adding each of the remaining parameters, one at a time, to see if any of these altered the *p*-value or effect size. We used multinomial logistic regression analysis to relate the predictors to the outcome variables no preeclampsia, late-onset preeclampsia, and early-onset preeclampsia. In the final model, all factors significantly altering effect size and/or statistical significance, as well as age, parity and any known confounders were added. We used this model to calculate odds ratios (OR) with 95% confidence intervals (CI) and *p*-values. The "rule of three" was used to calculate 95% CI in the cases where a predictor resulted in no occurrences of the outcome (Eypasch et al., 1995). We also calculated predicted probabilities for the most relevant predictors.

Statistical significance was set at the 5% level ($p = 0.05$). We also evaluated all effects at 1% level ($p = 0.01$), due to multiple hypothesis testing. We used SPSS (IBM SPSS Statistics for Windows, Version 23.0.2 Armork, NY), for most of the statistical analysis. We used Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.) to calculate predicted probabilities for no preeclampsia, late-onset preeclampsia and early-onset preeclampsia for women with and without pre-gestational allergy, in a model adjusted for asthma, maternal age and parity.

The ethics review board of the Western Norwegian regional health authorities approved the project (2015/66/REK vest).

3. Results

A total of 110 527 pregnancies were registered at the two departments during the respective study periods (Fig. 1). Of these, 463 were excluded due to missing data. Of the 110 064 pregnancies included in the study (30 607 from Bergen, 79 457 from Stavanger), 2 799 developed late-onset preeclampsia (2.5%), and 348 developed early-onset preeclampsia (0.3%) (Table 1).

In the initial univariate analyses, we found significant effects at 1% significance level for allergy, hypertension and type 1 diabetes when comparing early-onset to no preeclampsia. We also found significant effects at 1% significance level for allergy, hypertension, type 1 diabetes and type 2 diabetes when comparing late-onset to no preeclampsia. We found significant differences in the risk of early-onset compared to late-onset preeclampsia for women with pre-gestational allergy and hypertension. There was no effect of pre-gestational asthma, epilepsy, coronary disease, recurrent urinary tract infection, kidney disease, and rheumatoid arthritis on neither early nor late preeclampsia when compared to no preeclampsia, nor between early and late preeclampsia. When adding the remaining parameters one at a time, none of these were found to alter *p*-values or effect size significantly, with the exception of asthma, which reduced the effect size and increased the *p*-value moderately for the association between allergy and early-onset preeclampsia.

In the final model including parity and maternal age we found that pre-gestational allergy significantly increased the risk of early-onset preeclampsia (OR: 1.8, 95%CI: 1.3–2.4) and significantly reduced the risk of late-onset preeclampsia (OR: 0.8, 95% CI: 0.7–0.9). There was a significantly different effect of pre-gestational allergy on early and late preeclampsia (p-value < 0.001) (Table 2).

Hypertension increased the risk of both early-onset preeclampsia (OR: 17, 95%CI: 9.5–29) and late-onset preeclampsia (OR: 5.0, 95%CI: 3.4–7.4) (see Table 3). Type 1 diabetes also increased the risk of both late-onset preeclampsia and early-onset preeclampsia, more so for early preeclampsia, but the difference was not statistically significant (Table 3). Type 2 diabetes increased the risk of late-onset preeclampsia.

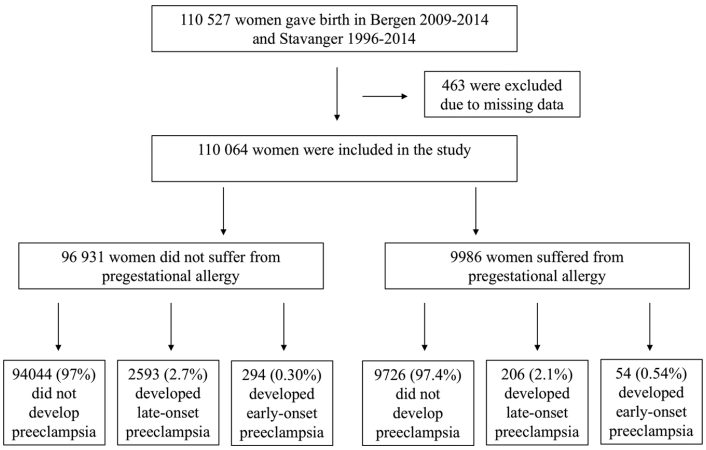

Fig. 1. Flowchart of included and excluded pregnancies. Included pregnancies are shown by predictor variable (pregestational allergy) and outcome variables (early-onset, late-onset, and no preeclampsia).

There were no patients in the group with pre-gestational type 2 diabetes who developed early-onset preeclampsia, the "rule of three" yielding a 95% CI of 0–2.21% for the incidence of early-onset preeclampsia among these patients. This corresponds to an increased risk ranging from 0 to 6.91 times the background risk. This overlaps the CI's for the increased risk of late-onset preeclampsia in patients with pre-gestational type 2 diabetes, and so from our data we cannot conclude that there is a difference in the risk of early-onset and late-onset preeclampsia among patients with pre-gestational type 2 diabetes.

Predicted probability for early-onset preeclampsia in women with pre-gestational allergy was 0.0085, compared to 0.0048 for women without pre-gestational allergy, in the model adjusted for asthma, maternal age and parity. In the same model, predicted probability for late-onset preeclampsia in women with pre-gestational allergy was 0.032, compared to 0.040 for women without pre-gestational allergy.

Table 2
Odds ratios (ORs) with 95% confidence interval (CI) for early-onset (before 34 weeks of pregnancy) and late-onset preeclampsia (PE) by pregestational allergy, asthma, maternal age and parity in 110 064 pregnancies (348 early-onset PE, 2799 late-onset PE, and 106 917 with no PE) obtained by multinomial logistic regression. We looked at the risk for early-onset PE compared to women without PE, the risk for late-onset PE compared to women without PE, and *p*-values for the difference between early- and late-onset effects.

	Early-onset vs no PE		Late-onset vs no PE		Early- vs late-onset PE
	OR	95% CI	OR	95% CI	*p*-value
Allergy	1.8	1.3–2.4[a]	0.8	0.7–0.9[a]	< 0.001
Astma	1.1	0.6–2.0	0.9	0.7–1.2	0.510
Age/10 yrs	1.5	1.2–1.9[a]	1.1	1.0–1.2	0.004
Primipara	3.0	2.4–3.8[a]	2.6	2.4–2.9	0.317

[a] Indicate significance also at the 1% level.

Table 1
Population characteristics and pregestational morbidity by early-onset, late-onset and no preeclampsia in 110 064 pregnancies, Stavanger (1996–2014) and Bergen (2009–2014). Chi-square test *p*-value for the proportional difference between early-onset, late-onset and no preeclampsia for each factor listed.

	No preeclampsia		Late preeclampsia		Early preeclampsia		Chi-square test *p*-value
	n	%	*n*	%	*n*	%	
Total	106917	100	2799	100	348	100	N/A
Maternal age							
< 20 years	2561	2.4	84	3.0	11	3.2	0.916
20–35 years	85430	80	2262	81	270	78	0.916
> 35 years	18926	18	453	16	67	19	0.085
Parity							
Nulliparous	44270	41	1801	64	225	65	> 0.001
Multiparous	62647	59	998	36	123	35	> 0.001
Predisposing factors							
Epilepsy	456	0.43	11	0.39	1	0.29	0.864
Asthma	2712	2.5	58	2.1	13	3.7	0.108
Allergy	9726	9.1	206	7.4	54	16	> 0.001
Recurring UTI	1251	1.2	28	1.0	6	1.7	0.445
Kidney disease	149	0.14	8	0.29	2	0.57	0.014
Hypertension	221	0.21	31	1.1	15	4.3	> 0.001
Rheumatoid arthritis	183	0.17	5	0.18	0	0	0.739
Cardiac disease	440	0.41	9	0.32	3	0.86	0.320
Type 1 diabetes	357	0.33	32	1.1	10	2.9	> 0.001
Type 2 diabetes	120	0.11	16	0.57	0	0	> 0.001

Table 3
Odds ratios (ORs) with 95% confidence interval (CI) for early-onset (before 34 weeks of pregnancy) and late-onset preeclampsia (PE) by pregestational hypertension, type 1, and type 2 diabetes, maternal age and parity in 110 064 pregnancies (348 early-onset PE, 2799 late-onset PE, and 106 917 with no PE) obtained by multinomial logistic regression. We looked at the risk of early-onset PE compared to women without PE, the risk of late-onset PE compared to women without PE, and *p*-values for the difference between early- and late-onset preeclampsia effects. No women with early-onset preeclampsia had pregestational type 2 diabetes.

	Early-onset vs no PE		Late-onset vs no PE		Early- vs late-onset PE
	OR	95% CI	OR	95% CI	*p*-value
Hypertension	17	9.5–29[a]	5.0	3.4–7.4[a]	0.001
Type I diabetes	5.8	2.9–12[a]	3.0	2.1–4.4[a]	0.079
Type II diabetes	n/a	n/a	4.6	2.7–7.9[a]	n/a
Age/10 yrs	1.4	1.1–1.8[a]	1.1	1.0–1.1	0.013
Primipara	0.6	0.5–0.6[a]	0.6	0.6–0.6[a]	0.317

[a] Indicate significance also at the 1% level.

4. Discussion

Pre-gestational maternal allergy was an isolated risk factor for early-onset preeclampsia in this study. This novel finding offers possibilities for further research that in the future may open alleys for prevention and treatment of this common and serious condition.

This study has several strengths. Data were obtained from a population-based comprehensive database, with detailed clinical information recorded for every delivery. We had a large sample of women giving birth at two delivery departments serving two major cities in Norway as first, second and third level clinical departments. Information on pre-gestational conditions was obtained in an interview and supplied with information noted at the personal health record form obtained by the midwife or general practitioner from the first trimester and throughout pregnancy. The population characteristics and pre-gestational morbidity incidences are in line with previous studies (Mendola et al., 2013; Borthen et al., 2009; Yerby et al., 1985; Lin et al., 2010; Katz et al., 1980; Nevis et al., 2011; Minassian et al., 2013; Sorbye et al., 2015), and indicate good external validity of our data, enabling comparison of early-onset and late-onset preeclampsia.

Self-reported data is a limitation, thus recall bias may occur. Self-reported data in pregnancy are considered reasonably valid (O'sullivan et al., 2000; Olson et al., 1997). In addition, occurrence of the examined risk factors in our study correlated well with findings in previous studies (Lisonkova and Joseph, 2013) (Table 1). Midwifes and general practitioners will, during the first consultation in the first trimester, normally perform a detailed medical history and a full clinical status as part of the examination. Information was prospectively recorded at the personal health record form, which accompanied the woman to the delivery department. The general practitioner holds records of the patient´s full medical history, sometimes since early childhood. Body mass index was not available and overweight is a well-known predisposing factor for preeclampsia. Results should be interpreted with caution for conditions where body mass index may be a confounder, such as type 2 diabetes.

Allergy as an isolated risk factor of early-onset preeclampsia is a novel finding, adding to our knowledge of the disease. One possible explanation for our finding might be that maternal allergy leads to changes in the physiological regulation of the maternal immune system in pregnancy. This could then cause poor placentation, followed in turn by early-onset preeclampsia. This supports the idea that early-onset preeclampsia is a fetal condition, while late-onset preeclampsia is considered a maternal condition. (Raymond and Peterson, 2011). While new, the finding is in line with previous studies that have demonstrated different levels of some immunological factors in early-onset and late-onset preeclampsia (Zhang et al., 2013; Sezer et al., 2012). Increased levels of IgE have been detected in women with preeclampsia (Alanen, 1984). In line with our finding, a previous study has shown that pregestational hypertension increases the risk of early onset preeclampsia more than of late-onset preeclampsia (Lisonkova and Joseph, 2013). Previous studies have found a moderately increased risk of preeclampsia in women suffering from asthma (Mendola et al., 2013), non-significant in one study (Tata et al., 2007). We did not confirm this association, probably a matter of sample size (both previous studies had more than twice the number of participants). We found a non-significant trend of asthma being linked to early onset preeclampsia (but not to late onset preeclampsia). This is interesting, as asthma and allergy share some pathogenic pathways (Gould and Sutton, 2008). In our study, we did not find the previously identified increase in risk of preeclampsia amongst women with pre-gestational epilepsy (Borthen et al., 2009; Yerby et al., 1985), rheumatoid arthritis (Lin et al., 2010), chronic kidney disease (Katz et al., 1980; Nevis et al., 2011), and recurrent urinary tract infections (Minassian et al., 2013). This could also be due to sample size.

Several studies have indicated that preeclampsia increase the risk of cardiovascular disease later in life (Skjaerven et al., 2012). Cardiac disease is a heterogeneous group, including both congenital heart disease and cardiovascular disease. Preeclampsia increases the risk of the latter, but few women develop cardiovascular disease while fertile. One study (Roos-Hesselink et al., 2013) show no elevated risk of preeclampsia in women with preexisting cardiovascular disease, but increased risk of preterm birth and low birth weight in the group of patients suffering from ischemic heart disease, most likely because of diffuse vasculopathy that leads to poor perfusion of the placenta and placenta insufficiency. It is shown that preeclamptic pregnancies are associated with allergic sensitization and allergic rhinoconjunctivitis in late childhood in children born after such pregnancies. The same association was not seen for other atopic diseases (Byberg et al., 2014). Other studies have shown that preeclampsia is a shared risk factor for eczema, asthma and allergy (Stokholm et al., 2017).

Maternal allergy was an isolated risk factor for early-onset preeclampsia. This adds to the understanding of the immunological pathogenesis in preeclampsia. Future studies should differentiate between early and late onset preeclampsia when looking at IgE-mediated immunological pathways in preeclamptic women. Studies should also assess the additional predictive value of anamnestic information on maternal allergy in existing predictive models of preeclampsia (Duley et al., 2007; Akolekar et al., 2011; Oliveira et al., 2014).

4.1. Conclusion

Maternal allergy was an isolated risk factor increasing the risk of early-onset preeclampsia (before 34 weeks of gestation), but reduced the risk of late-onset preeclampsia.

Conflicts of interest

None.

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Details of ethics approval

We applied to the regional ethics committee for permission to extract the relevant data from a large number of patient journals without written informed consent from each participant. This is not without ethical implications, but can be permitted if individual data safety is maintained and the proposed research is of sufficient value to science and the society. The Western Norway regional ethics committee

approved the project on 03. March 2015 in line with the revised Helsinki declaration, (2015/66/REK vest).

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Use of antihistamines before or during pregnancy and risk of early-onset pre-eclampsia in allergic women: a population-based cohort study

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ABSTRACT

Objective We have previously found that allergy is a risk factor for early-onset pre-eclampsia. The aim of this study was to assess the association between pregestational maternal use of antihistamines and early-onset pre-eclampsia.

Design A population-based cohort study.

Setting and participants All women giving birth in Norway 2004–2016, including 692 487 pregnancies. Data from the Medical Birth Registry of Norway were linked with data from the Norwegian Prescription Database. Prescriptions of antihistamines were divided into three groups: before pregnancy (<6 months), early pregnancy (<20 weeks) and late pregnancy (20–36 weeks). ORs with 95% CIs for pre-eclampsia <34 and <37 weeks by antihistamine use were estimated by logistic regression and stratified on multiple pregnancy and parity. Predicted proportions (%) with 95% CIs were estimated.

Interventions Use of antihistamines in relation to pregnancy in allergic women.

Main outcome measures Development of early-onset pre-eclampsia.

Results 2997 (0.43%) and 5769 (0.83%) women had pre-eclampsia <34 and <37 weeks, respectively. Use of antihistamines before and in early pregnancy was associated with a risk of developing early-onset pre-eclampsia that was comparable to the background population (OR 1.0, 95% CI 0.8 to 1.2 and OR 0.9, 95% CI 0.7 to 1.1, respectively). Antihistamine use only in late pregnancy was not treated as exposure, but as an indicator of allergy, and was associated with an increased risk of early-onset pre-eclampsia (OR 1.8, 95% CI 1.5 to 2.2). Predicted proportions of pre-eclampsia <34 weeks were significantly lower in women using antihistamines before (0.41%, 95% CI 0.34 to 0.49) and in early pregnancy (0.37%, 95% CI 0.31 to 0.44), compared with women using antihistamines after placentation (0.69%, 95% CI 0.57 to 0.83). Results were similar for pre-eclampsia <37 weeks.

Conclusions Antihistamine use before or during placentation was associated with reduced risk of developing early-onset pre-eclampsia in allergic women compared with women using antihistamines after placentation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a population-based cohort study using linked data from The Medical Birth Registry of Norway and the Norwegian Prescription Database.
⇒ It contains all women giving birth in Norway 2004–2016 and includes 692 487 pregnancies.
⇒ Maternal allergy is not registered with an International Statistical Classification of Diseases and Related Health Problems, 10th edition code in the Medical Birth Registry of Norway, so we used antihistamine prescription for allergy to identify women with allergies.
⇒ We have no information on what kind of allergy the participants suffer from.

INTRODUCTION

Pregestational maternal allergy is associated with early-onset pre-eclampsia.[1] This supports the hypothesis of pre-eclampsia as a disorder of immune regulation, and prompts the question if antihistamines, used to treat allergy, affect the risk of developing pre-eclampsia in allergic women. Levels of histamine in blood are altered in pregnancy, indicating its biological importance for a successful pregnancy.[2] Histamine has been assumed to contribute to embryo–uterine interactions due to its vasoactive, differentiation and growth-promoting properties[3] and elevated levels of blood histamine in pregnancy are known to lead to a variety of adverse outcomes, for example, threatened abortions, preterm labour and pre-eclampsia.[4] It is shown that histamine mediates vasoconstriction in umbilical arteries[5] and veins in human pregnancy,[6] and that severity of pre-eclampsia increases by increasing blood levels of histamine.[7] The pathogenesis of pre-eclampsia is incompletely understood, but inadequate growth of fetal cells along maternal spiral arteries is believed to be important.[8] Increased systemic inflammation leading to endothelial dysfunction

due to increased concentration of pro-inflammatory substances from a dysfunctional placenta is another important pathway.[9 10] It is also shown that sFlt-1 from the placenta is associated with activation of the complement system[11] which can cause mast cells to release histamine.

Pre-eclampsia is diagnosed in second half of pregnancy and consists of an early-onset and a late-onset entity.[12 13] Early-onset pre-eclampsia is defined as fulfilling the diagnostic criteria before 34 weeks of gestation, but also if resulting in delivery before week 37.[14] Merging early-onset and late-onset pre-eclampsia in studies will mask relevant risk factors and effects of treatment that may be specific for early-onset pre-eclampsia.[12] There are few treatment and prevention possibilities for pre-eclampsia. However, low-dose acetylsalicylic acid administered from the first trimester can prevent early-onset pre-eclampsia in women at risk for developing pre-eclampsia.[15]

The aim of this study was to assess the effect of antihistamine use for allergy on risk of early-onset pre-eclampsia, using linked data from two nationwide population-based registries. Allergy is insufficiently registered in the database, so antihistamine prescription in gestational week 20–36 was used as an indicator of allergy. Our hypothesis was that antihistamines reduce the risk of pre-eclampsia in allergic women and that by showing this we would add to the knowledge of pre-eclampsia as an immunological condition.

METHODS

Study population and data sources

A nationwide population-based cohort study with prospectively collected data from the Medical Birth Registry of Norway and the Norwegian Prescription Database from 2004 to 2016 was designed. The Medical Birth Registry of Norway was established in 1967 and is a compulsory health register with information on pregestational conditions, prenatal care, delivery and postnatal care. Pregestational conditions are registered by the general practitioner or the midwife at the first antenatal visit, and information on previous pregnancies is recorded on the personal health record form, a specific form used throughout follow-up of all pregnancies in the country. All information on live births and stillbirths are registered and sent electronically to the Medical Birth Registry of Norway by the attending midwife or obstetrician a few days after delivery. The Norwegian Prescription Database was established in 2004 and holds record of all prescribed drugs in Norway. All births in Norway during the study period were assessed. Births with gestational age >44+0 weeks or <20+0 weeks and births with missing gestational age were excluded (figure 1). In our material, each delivery counts as a separate registration, which means that twin deliveries count as two registered deliveries. Thus, the second twin and above was excluded (figure 1). Women who delivered before April 2005 were excluded because we could not assess their use of antihistamines 6 months prior to their last menstrual period.

The unique personal identification number provided to all Norwegian citizens enabled linkage of data from the two national registries.

Data on occurrence of pre-eclampsia, pre-eclampsia diagnosed before 34 weeks of gestation, gestational age at delivery in days, date of delivery, maternal age, parity, occurrence of multiple pregnancies and pre-pregnancy body mass index (BMI) were obtained from the Medical Birth Registry of Norway. The Norwegian Prescription Database provided data on all antihistamines prescribed for systemic use. The Anatomical Therapeutic Chemical Classification System (ATC) code R06, and the corresponding national refund codes from the International Classification of Primary Care (ICPC codes: F71, R97, S98) and the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10 codes: H10.1, J30, L50) were used to ensure that antihistamines were prescribed due to allergy, and not for other conditions, for example, sleep disorders

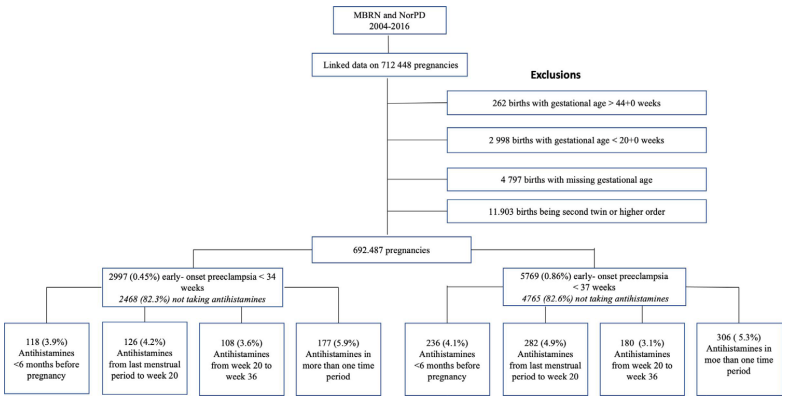

Figure 1 Flow chart for the inclusion of cases. MBRN, Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database.

or hyperemesis gravidarum. For the purposes of this study, we were interested in studying women with allergies. Maternal allergy is not registered with an ICD-10 code in the Medical Birth Registry of Norway, so we used antihistamine prescription for allergy to identify women with allergies. The Norwegian Prescription Database also provided date of dispense and type of antihistamine. We identified use of antihistamines in three periods related to pregnancy: (1) before pregnancy: from 6 months prior to last menstrual period to last menstrual period, (2) early pregnancy: from last menstrual period to week 20 of gestation and (3) late pregnancy: from week 20 to week 36 of gestation. Use of antihistamines in late pregnancy was considered a proxy variable for allergy, not as exposure, as the registration of allergy in the Medical Birth registry of Norway was limited. Women that used antihistamines in more than one period were identified and treated as a separate fourth group to ensure mutually exclusive groups. We divided the antihistamines into five main groups and controlled that there was no overlap between the groups. We only included prescriptions of antihistamines that were dispensed.

Definitions

The diagnostic criteria of pre-eclampsia were 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 and/or diastolic blood pressure ≥90 after 20 weeks of gestation (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). This definition by the Norwegian Society of Gynaecology and Obstetrics is in accordance with the guidelines from the National Institute for Health and Care Excellence[16 17] and the guidelines from The American College of Obstetrics and Gynecology.[18] Registration of pre-eclampsia in the Medical Birth Registry of Norway has previously been validated and found to be of high quality.[19] Early-onset pre-eclampsia was during 2004–2016 defined in the Medical Birth Registry of Norway as fulfilling the diagnostic criteria for pre-eclampsia before 34 completed weeks of gestation. However, the International Society for the Study of Hypertension in Pregnancy defines early-onset pre-eclampsia as leading to delivery before 37 weeks of gestation.[14]

Exposure

Antihistamine use in relation to pregnancy in allergic women. After week 20, antihistamines were considered a marker for allergy, not as exposure.

Outcome

Primary outcomes were early-onset pre-eclampsia, defined both as women fulfilling the criteria for pre-eclampsia before 34 completed weeks of gestation (pre-eclampsia <34 weeks), and pre-eclampsia resulting in delivery before 37 completed weeks of gestation (pre-eclampsia <37 weeks).

Statistical analysis

In our primary analysis, we used binomial logistic regression models with random effects component to account for the repeat effect of pregnancies to the same woman to estimate ORs with 95% CIs for early-onset pre-eclampsia by prescribed antihistamines in the four groups outlined above, compared with women not using antihistamines. In all analyses, we adjusted for maternal age at birth. We did four secondary analyses: stratified by parity, stratified by multiple pregnancy, separated into the five main types of antihistamines (cetirizine/levocetirizine, loratadine/desloratadine, dexchlorpheniramine, meclizine and other antihistamines) and adjusted for BMI in the women where BMI was registered. Registration of BMI in the Medical Birth Registry of Norway started in 2006 and increased successively until 2014, when the registration exceeded 70%, and BMI was therefore registered in only 309 617 women. Results from the main analyses were also presented as estimated predicted proportions of early-onset pre-eclampsia in the four groups, as well as for women not prescribed antihistamines. Average predicted proportions of early-onset pre-eclampsia were estimated and plotted using STATA (Release 17. College Station, Texas, USA: StataCorp LLC. StataCorp, 2019) functions margins and margins plot. IBM SPSS Statistics for Windows (V.26.0.0.1 Armork, New York, USA, 2019) was used for all other statistical analyses. Significance testing was two-sided, and results were considered statistically significant when $p<0.05$.

Power calculations indicated that with an anticipated 44 000 versus 22 000 pregnant women using antihistamines before and after placentation respectively, we would have a power of 82% for detecting an absolute risk reduction from 0.66% to 0.50% for developing early-onset pre-eclampsia at a one-tailed 5% significance level. In our data set, only 4797 cases had missing data. As this is less than 0.7%, we opted to exclude these cases. An exception was BMI, which was registered in about only half the pregnancies. These were handled separately.

Patient and public involvement

We gathered a Focus group with patients suffering from pre-eclampsia where we explained the background of our study and the methods we wanted to use. The group members agreed that the data protection was satisfactory in the proposed design of our study. Important elements regarding risk factors for pre-eclampsia came up, and the group's suggestion to both differentiate different forms of allergy and their effect on pre-eclampsia, and the idea that commonly used allergy medication might be used as prophylaxis or treatment against pre-eclampsia was a valuable contribution to our protocol. The group also gave us valuable insight in the use of patient and public involvement through the discussion in the group. The protocol was also assessed by the user panel at Stavanger University Hospital who agreed with the Focus group in all their comments.

RESULTS

In total 692 487 pregnancies were eligible for analyses, of which 101 287 women used antihistamines (14.6%) and

Table 1 Baseline characteristics

	No pre-eclampsia (n=670 909), No. (%)	Pre-eclampsia <34 weeks (n=2997), No. (%)	Pre-eclampsia <37 weeks (n=5769), No. (%)
Nulliparous	279 612 (41.7)	1722 (57.5)	3492 (60.5)
Mean maternal age (years)	29.9 (N/A)	30.4 (N/A)	30.1 (N/A)
Multiple pregnancy	10 540 (1.6)	299 (10.0)	820 (14.2)
Mean BMI*	24.3 (N/A)	26.5 (N/A)	26.1 (N/A)
Prescribed any antihistamine	97 566 (14.5)	529 (17.7)	1004 (17.4)
Cetirizine/levocetirizine	20 440 (3.0)	110 (3.7)	184 (3.2)
Loratadine/desloratadine	14 116 (2.1)	75 (2.5)	125 (2.1)
Dexchlorpheniramine	13 570 (2.0)	56 (1.7)	120 (2.1)
Meclizine	9954 (1.5)	44 (1.5)	100 (1.7)
Other antihistamines†	11 630 (1.7)	54 (1.8)	128 (2.2)
More than one type of antihistamine	27 856 (4.2)	190 (6.3)	347 (6.0)

Baseline characteristics and prescribed antihistamines for 692 487 pregnancies, linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016. Presented as number of pregnancies and per cent for the total population and for early-onset pre-eclampsia <34 and 37 weeks.
*In a subset of 309 617 pregnancies.
†Alimemazine, ebastine, phenoxphenidine, promethazine, thiethylperazine, cyclizine, cinarizine, clemastine, doxylamine, diphenhydramine, cyproheptadine, rupatadine, bilastine.
BMI, body mass index.

21 578 (3.1%) had pre-eclampsia. Of these, 2997 (0.43%) were diagnosed before 34 gestational weeks and 5769 (0.83%) were delivered with pre-eclampsia before gestational week 37 (figure 1, table 1). Almost 98% of pregnancies were dated by ultrasound estimates.

ORs for pre-eclampsia <34 weeks in pregnancies with prescribed antihistamines before pregnancy and in early pregnancy were 1.0 (95% CI 0.8 to 1.2) and 0.9 (0.7 to 1.1), respectively, compared with women not using antihistamines (table 2). However, in pregnancies with prescribed antihistamines in late pregnancy the OR was 1.8 (1.5 to 2.2). For pre-eclampsia <37 weeks, we saw similar associations: OR for early-onset pre-eclampsia was 1.0 (0.9 to 1.2) in women with prescribed antihistamines before pregnancy, 1.0 (0.9 to 1.2) in women using antihistamines in early pregnancy, while 1.5 (1.3 to 1.8) in women using antihistamines only in late pregnancy (table 2).

In women using antihistamines in more than one period, ORs for developing early-onset pre-eclampsia <34 and <37 weeks were 1.7 (1.5 to 2.0) and 1.6 (1.4 to 1.8), respectively.

Stratified results by nulliparous/parous pregnancies, singleton/multiple pregnancies and grouped by main types of antihistamines are presented in table 2. Effects were comparable across different strata and by types of antihistamine. BMI was recorded in 309 617 pregnancies. This group was analysed separately with maternal BMI included as a covariate, associations between use of antihistamines and early-onset pre-eclampsia were 0.9 (95% CI 0.7 to 1.2), 1.0 (0.8 to 1.3) and 2.2 (1.7 to 2.8) for pre-eclampsia <34 weeks and 1.0 (0.8 to 1.2), 1.1 (0.9 to 1.3) and 1.8 (1.4 to 2.2) for pre-eclampsia <37 weeks by antihistamine use before, early and in late pregnancy, respectively (online supplemental table S1).

Predicted proportions of early-onset pre-eclampsia <34 and <37 weeks are presented in figures 2 and 3, respectively. Women that used antihistamines before or in early pregnancy had significantly lower predicted proportions of early pre-eclampsia, 0.41% (95% CI 0.34% to 0.49%) and 0.37% (0.31% to 0.44%), respectively, compared with women using antihistamines in late pregnancy, 0.69% (0.57% to 0.83%) or in several periods (0.69% (0.59% to 0.80%) (figure 2). Results were the same for early-onset pre-eclampsia <37 weeks (figure 3). Estimated proportions for women using antihistamines before or during placentation were essentially equal to women not using antihistamines.

DISCUSSION

Allergic women using antihistamines before or in early pregnancy had reduced risk of early-onset pre-eclampsia compared with allergic women using antihistamines in late pregnancy only. It is not plausible that it is the use of antihistamines in late pregnancy itself that increases the risk of pre-eclampsia. The effect is most likely due to the known increased risk of early-onset pre-eclampsia associated with pre-existing allergy. Allergic women have an increased baseline risk for early-onset pre-eclampsia compared with non-allergic women. Women prescribed antihistamines in late pregnancy, after the formation of the placenta, do not benefit from the normalisation of risk we see in allergic women prescribed antihistamines before placental formation. Thus, we considered

Table 2 ORs for developing early-onset pre-eclampsia by antihistamine use

	Before pregnancy OR (95% CI)	Early pregnancy OR (95% CI)	Late pregnancy OR (95% CI)	Antihistamines in more than one period
Pre-eclampsia <34 weeks				
Any antihistamine	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.1)	1.8 (1.5 to 2.2)	1.7 (1.5 to 2.0)
Cetirizine/levocetirizine	1.2 (0.9 to 1.6)	0.9 (0.5 to 1.3)	1.4 (0.8 to 2.2)	2.0 (1.3 to 3.0)
Loratadine/desloratadine	0.9 (0.6 to 1.3)	1.2 (0.7 to 1.9)	1.9 (1.1 to 3.3)	2.0 (1.2 to 3.3)
Dexchlorpheniramine	0.9 (0.4 to 2.2)	0.5 (0.3 to 0.9)	1.3 (0.9 to 1.8)	1.5 (0.6 to 3.6)
Meclizine	N/A*	0.9 (0.6 to 1.3)	3.3 (1.7 to 6.3)	1.9 (0.3 to 14)
Other antihistamines†	0.8 (0.5 to 1.4)	0.8 (0.5 to 1.2)	3.1 (2.0 to 4.8)	0.7 (0.2 to 2.9)
More than one type of antihistamine in the period	0.8 (0.5 to 1.3)	1.4 (0.9 to 2.1)	2.3 (1.4 to 3.8)	1.7 (1.4 to 2.1)
Nulliparous	0.9 (0.7 to 1.2)	0.9 (0.7 to 1.2)	1.8 (1.4 to 2.3)	1.7 (1.4 to 2.1)
Parous	1.1 (0.8 to 1.4)	0.8 (0.6 to 1.1)	1.7 (1.3 to 2.3)	1.6 (1.2 to 2.0)
Singleton	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.0)	1.8 (1.4 to 2.2)	1.7 (1.5 to 2.0)
Multiple pregnancy	1.1 (0.6 to 2.0)	1.1 (0.6 to 1.7)	1.2 (0.7 to 2.1)	1.6 (0.99 to 2.6)
Pre-eclampsia <37 weeks				
Any antihistamine	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.5 (1.3 to 1.8)	1.6 (1.4 to 1.8)
Cetirizine/levocetirizine	0.9 (0.8 to 1.2)	1.0 (0.8 to 1.4)	1.2 (0.8 to 1.7)	1.5 (1.0 to 2.1)
Loratadine/desloratadine	0.9 (0.7 to 1.2)	1.4 (0.98 to 1.9)	0.8 (0.5 to 1.5)	1.3 (0.8 to 2.0)
Dexchlorpheniramine	0.9 (0.4 to 1.6)	0.7 (0.5 to 0.9)	1.4 (1.1 to 1.8)	1.7 (0.9 to 3.1)
Meclizine	1.3 (0.3 to 5.2)	1.1 (0.9 to 1.3)	3.2 (2.0 to 5.2)	1.2 (0.5 to 7.9)
Other antihistamines†	1.4 (1.0 to 1.9)	1.0 (0.7 to 1.3)	2.3 (1.6 to 3.3)	2.1 (1.2 to 3.8)
More than one type of antihistamine in the period	1.1 (0.8 to 1.5)	1.3 (0.96 to 1.7)	2.1 (1.4 to 3.0)	1.6 (1.4 to 1.8)
Nulliparous	1.1 (0.9 to 1.3)	1.0 (0.9 to 1.2)	1.5 (1.2 to 1.8)	1.5 (1.3 to 1.8)
Parous	0.9 (0.7 to 1.1)	1.1 (0.9 to 1.3)	1.6 (1.2 to 2.0)	1.4 (1.1 to 1.7)
Singleton	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.4 (1.2 to 1.7)	1.6 (1.4 to 1.8)
Multiple pregnancy	0.9 (0.6 to 1.3)	0.8 (0.6 to 1.2)	1.3 (0.9 to 1.8)	1.2 (0.9 to 1.7)

ORs with 95% CIs for early-onset pre-eclampsia (<34 and <37 gestational weeks, respectively) by use of antihistamines in relation to pregnancy compared with no use of antihistamines in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database 2004–2016. Estimates were obtained using binomial logistic regression with random effects component, adjusting for maternal age. Included in the table are also results for use of main types of antihistamines separately and stratified results by parous/nulliparous and singleton/multiple pregnancies.
*No women using meclizine developed early-onset pre-eclampsia <34 weeks.
†Alimemazine, ebastine, phenoxphenidine, promethazine, thiethylperazine, cyclizine, cinarizine, clemastine, doxylamine, diphenhydramine, cyproheptadine, rupatadine, bilastine.

antihistamine use in late pregnancy as an indirect indicator for allergy. These results based on the timing of antihistamine-use are consistent with studies on aspirin in the prevention of pre-eclampsia, where the drug must be initiated before 16 weeks of gestation for optimal effect.[20]

Current knowledge of histamine in pregnancy suggests an important role in trophoblastic cell differentiation and as an apoptotic cell regulator.[21 22] In normal pregnancies, the level of histamine in blood decreases from the start of pregnancy, reaching nadir around week 24, before rising and stabilising slightly below non-pregnant levels.[2] Elevated levels of blood histamine in pregnancy are known to lead to a variety of adverse outcomes, for example, threatened abortions, preterm labour and pre-eclampsia.[4] Elevated histamine levels cause vasoconstriction,[6] which might explain why high levels of histamine, either in maternal blood or at the maternal–fetal interphase, increase the risk of pre-eclampsia. Nevertheless, there is a study from 2012 that imply that that it is the hypoxia from the impaired placentation that leads to increased excretion of histamine by mast cells in the placenta.[23] One animal study of guinea pig placentas found that elevated histamine levels leads to both vasoconstriction and increased macromolecular permeability.[24] Similar effects in humans could explain the increased risk of pre-eclampsia seen in allergic women with hyperhistaminemia, as it is possible that the increased permeability for large molecules can further increase the leakage of

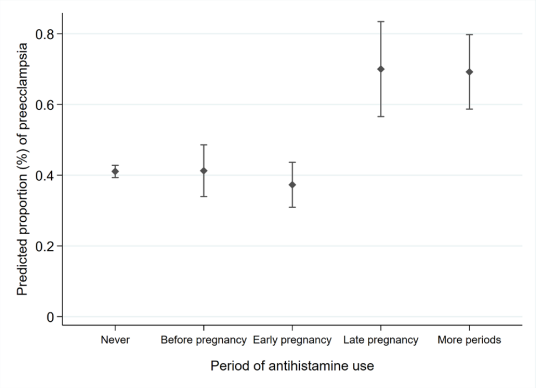

Figure 2 Predicted proportions of early-onset pre-eclampsia before 34 weeks**.** Predicted proportions with 95% CIs for pre-eclampsia (<34 gestational weeks) by no use of antihistamines (Never), use of antihistamines 6 months before pregnancy (Before pregnancy), from last menstrual period to gestational week 20 (Early pregnancy), from week 20 to week 36 (Late pregnancy) and use of antihistamines in more than one time period (More periods) in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016.

bioactive substances from the compromised placenta and thus explain the increased risk of pre-eclampsia. Diamine oxidase is the only extracellular enzyme capable of inactivating histamine in humans.[25 26] Plasma levels of diamine oxidase are almost undetectable in non-pregnant women, but increase several 100-fold during gestation.[3] A recent study has shown that levels of diamine oxidase were significantly lower in samples from women with early-onset pre-eclampsia, compared with controls,[27] indicating a crucial role of histamine in the pathophysiology of early-onset pre-eclampsia.

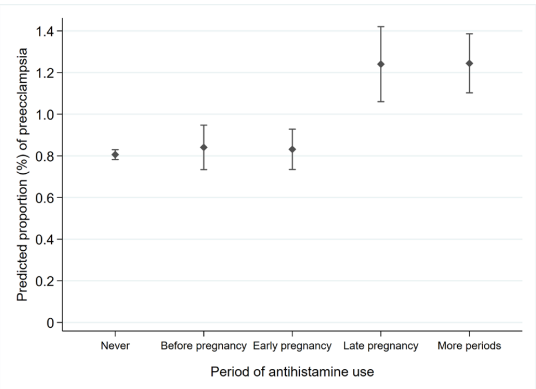

Figure 3 Predicted proportions of early-onset pre-eclampsia before 37 weeks. Predicted proportions with 95% CIs for pre-eclampsia (<37 gestational weeks) by no use of antihistamines (Never), use of antihistamines 6 months before pregnancy (Before pregnancy), from last menstrual period to gestational week 20 (Early pregnancy), from week 20 to week 36 (Late pregnancy) and use of antihistamines in more than one time period (More periods) in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016.

In the 1950s, there was some interest in the use of antihistamines in treatment of eclampsia[28] and pre-eclampsia,[29] but without any impact on clinical management. A recent case–control study from Finland estimated overall risk for pre-eclampsia by histamine use but did not differentiate between early-onset and late-onset pre-eclampsia.[30] To the best of our knowledge, the association between early-onset pre-eclampsia and antihistamine use in allergic women has not been previously studied.

In our study, associations were not restricted to any specific type of antihistamine (see table 2). The effect of antihistamine use does not differ to any significant degree between first-time mothers and in subsequent pregnancies, but findings were less pronounced in multiple gestation. Women with prescribed antihistamines in more than one period related to pregnancy had an increased risk for developing early-onset pre-eclampsia. A possible explanation could be that these women suffer more severely from allergy, and thus have a higher baseline risk, due to a more severe inflammation.[9]

Strengths

The strengths of the study are its large sample of pregnant women with linked data from two nationwide compulsory registers, accurate gestational age determination, high validity of the registered diagnosis of pre-eclampsia in the Medical Birth Registry of Norway[19] and a detailed procedure to ensure that antihistamines were prescribed due to allergy. Early-onset pre-eclampsia is a rare, but serious condition, and a large sample size is necessary to maintain sufficient power to estimate associations. In addition, the large sample of pregnant women also yielded strength to present results by the main types of antihistamines.

Limitations

Over-the-counter sale of antihistamines is not registered in the Norwegian Prescription Database, which is a possible weakness of our study. However, this only applies to cetirizine throughout the study period, which accounts for only 9% of the total sale of antihistamines in the ATC group R06A, according to official data from the Norwegian Institute of Public Health.[31] Maternal allergy is registered as a dicotome variable, and not with an ICD-10 code, in the Medical Birth Registry of Norway. Unfortunately, in our material maternal allergy was only registered in approximately 1% of the registered births, and we have therefore postulated that women suffer from allergy if they have been given a prescription containing an ICD-10 code for allergy in the Norwegian Prescription Database for reimbursement from the state. The Norwegian Institute of Public Health conclude that the

best data to estimate the prevalence of allergy among Norwegian adults are the use of the Norwegian Prescription Database.[32] We found that 14.6% of women in our population used antihistamines. There is a possibility that some women may have received antihistamines coded as allergy for other conditions by mistake. However, we do not believe that this is a large issue in our data, as quality-control measures using refund codes were used to avoid such problems.

Because the diagnosis of allergy was only available to us through the maternal use of antihistamines, the antihistamine use in late pregnancy (weeks 20–36) was considered a proxy variable in our material. As such our group of unexposed pregnancies most likely consist of both allergic and non-allergic women.

Registration of BMI in the Medical Birth Registry of Norway started in 2006, when only 0.1% of the reported pregnancies included BMI. The registration increased successively until 2014, when the registration exceeded 70%. Even in periods with poor registration, the BMI follows a normal distribution, suggesting representative registration.[33] Additional adjustment for BMI did not alter the overall findings from the main analysis. Prophylactic use of acetylsalicylic acid was implemented in Norwegian national guidelines for prevention of pre-eclampsia <34 weeks as late as 2014 and have likely had little impact on our findings.

Clinical implications

Our study sheds light on three important issues: that histamine is indeed an important biological substance necessary for the development of a successful pregnancy, that our findings add to the knowledge of pre-eclampsia as an immunological condition, and that there is no reason to recommend discontinuation of antihistamines in pregnancy for allergic women.

CONCLUSION

Antihistamines used for allergy before and during the timeframe for the formation of the placenta were associated with a reduced risk of developing early-onset pre-eclampsia in allergic women, both <34 and <37 weeks, when compared with pregnancies with use of antihistamines only in late pregnancy. Further clinical research should explore possible beneficial effects of antihistamines before and during first half of pregnancy, timing of use in pregnancy and its possible effects of reducing risk of early-onset pre-eclampsia in allergic women.

Contributors AKS, EAT, RKS, ID, KCD and N-HM have all participated in the conception of the idea, writing of the protocol, application, application for ethical approval and writing of the paper. ID conducted the statistical analysis with support from AKS, RKS and N-HM. AKS, EAT, RKS, ID, KCD and N-HM have all seen and approved the final version. N-HM is the guarantor of the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The ethics committee of the Western Norwegian regional health authorities ID 2017/292/REK vest exempted this study. This is a nationwide population-based cohort study with prospectively collected data from the Medical Birth Registry of Norway and the Norwegian Prescription Database from 2004 to 2016 and contains information on more than 700 000 women. It would not be practically feasible to obtain written consent from all these women. The Medical Birth Registry of Norway is a public register excempt for the obligation to consent and it is therefore possible for the ethics committee to allow access to these data without patient consent. Such exemption has been applied for and granted by the relevant ethics committee.

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Data availability statement Data are available upon reasonable request. Relevant anonymised data will be made available on reasonable request from the corresponding author.

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

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Conflicts of interest:

Anne Kvie Sande has no conflicts of interest to declare.

Ingvild Dalen has no conflicts of interest to declare.

Erik Andreas Torkildsen has no conflicts of interest to declare.

Ragnar Kvie Sande 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.

Nils-Halvdan Morken is a former associate editor of Acta Obstetricia et Gynecologica Scandinavica. Other than this he has no conflicts of interest to declare.

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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 if the predisposing conditions have a differentiated effect on the risk of preterm and term preeclampsia, respectively. Our aim was to assess if diabetes type 1 and 2, chronic kidney disease, asthma, epilepsy, rheumatoid arthritis, and chronic hypertension were differentially associated with preterm and term preeclampsia.

Materials and methods:
This is a nationwide, population-based cohort study containing all births registered in the Medical Birth Registry of Norway from 1999- 2016. Multinomial logistic regression analysis was used to estimate relative risk ratios (RRRs) with 95% confidence intervals (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 26504 (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 versus no preeclampsia) and 0.9 to 5.7 (term versus no preeclampsia). Diabetes type 1 and 2 (RRR preterm versus term preeclampsia 2.89, 95% CI 2.46-3.39 and 1.68, 1.25-2.25, respectively), chronic kidney disease (1.55, 1.11-2.17), and chronic hypertension (1.85, 1.63-2.10) were more strongly association 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 diagnosis < 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:
Preterm preeclampsia, term preeclampsia, risk-factors, epidemiology.

Abbreviations:

BMI: Body Mass Index
CI: Confidence interval
MBRN: The Medical Birth Registry of Norway
RRRs: Relative Risk Ratios

Key message

We have little knowledge if 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.

Main text:

Introduction:

Preeclampsia is a common cause of morbidity and mortality for both mothers and children worldwide (1) and has been categorized into an 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 neither preterm nor 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 in most 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 if 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, 11, 12, 13, 14, 15). Evidence suggests that autoimmune mechanisms are involved also in epilepsy (16). In addition to increase 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 enable better prevention of preeclampsia by use of prophylactic acetylsalicylic acid.

The specific aim of this study was to assess if 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.

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 weeks + 6 days, 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 are 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 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 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 is now defined as newly 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 data set is from 1999-2016, and the participants were diagnosed with preeclampsia as it was defined by the Norwegian Society of Gynecology and Obstetrics at the time. 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).

Statistical methods:

Relative risk ratios (RRRs) with 95% confidence intervals (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 mothers 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

modelled 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 modelled 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, respectively, with effects modelled using restricted cubic splines with four knots.

Data preparations were done in IBM SPSS Statistics for Windows (Version 26.0.0.1 Armork, NY, 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 in the use of patient and public involvement were 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.

Ethics Statement

Research using anonymous health register data are exempted from consent requirements from the ethics research committees in Norway. Exempt was approved by the ethics committee of the Western Norwegian Regional Health Authorities on April 7th, 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.

Results:

The outline of the study population is presented in figure 1. The MBRN contained information on 1 075 637 born infants during 1999 to 2016. After exclusion of second born twins or higher order (n= 19 035), missing gestational age (n= 7089), gestational age < 19 weeks + 6 days (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 (1.68, 1.25-2.25), chronic kidney disease (1.55, 1.11-2.17), and chronic hypertension (1.85, 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 (0.90-1.45) and 1.33 (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, 95% CI: 2.16-4.02) and type 2 (1.74, 1.05-2.88) and chronic hypertension (1.87, 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 (1.38, 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 (1.63, 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 (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 (supporting information 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 hypertension in addition to rheumatoid arthritis, but the associations were a bit stronger (Supporting information Table S3).

Discussion:

Diabetes type 1 and 2, chronic kidney disease and chronic hypertension were more strongly associated with preterm than 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 thirties, 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 are 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 continues to rise a few months post-partum (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 with the 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 late onset preeclampsia, we believe that our study contributes to this field and can help improve 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, while 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 of gestations as cut-off for early and late preeclampsia (30).

Our study has several strengths. Data were collected from a large national database, with comprehensive clinical data. Information on pre-gestational conditions was gathered in an interview during the first trimester by the responsible midwife or 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 post-partum 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 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 pre-gestational conditions is obtained by a midwife or the general practitioner. While we do not know if the information on pre-gestational 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 incidences of pre-gestational maternal risk factors in our study are in line with previous findings (10, 12, 13, 32), indicating that our database, most likely is 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 wether the diagnosis was set before or after gestational week 34. This is the available variable provided for our 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.

Conclusions:

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 differently associated with preterm and term preeclampsia. We believe our study may be a valuable contribution for creating better accuracy in existing algorithms used for early prediction of preeclampsia.

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None.

Author contribution statement

Anne Kvie Sande, Erik Andreas Torkildsen, Ragnar Kvie Sande, and Nils-Halvdan Morken have all participated in the conception of the idea, writing of the protocol, application for funding and application for ethical approval. Ingvild Dalen conducted the statistical analysis with support from Anne Kvie Sande, Ragnar Kvie Sande and Nils-Halvdan Morken. Anne Kvie Sande, Ingvild Dalen, Erik Andreas Torkildsen, Ragnar Kvie Sande, and Nils-Halvdan Morken have all participated in writing the paper. All authors have approved the final version.

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Legends of supporting information:

Supporting information Table S1: Adjusted relative risk ratios (RRRs) with 95% confidence intervals (CIs) for early-onset preeclampsia (EO-PE, diagnosed <34 weeks) versus no preeclampsia (no PE), late-onset preeclampsia (LO-PE, diagnosed >34 weeks) versus no PE and EO-PE versus LO-PE by maternal risk factors. Estimates were obtained by multinomial logistic regression in 1 044 860 births, Medical Birth Registry of Norway, 1999 to 2016.

Supporting information Table S2: Adjusted relative risk ratios (RRRs) with 95% confidence intervals (CIs) for early-onset preeclampsia (EO-PE, diagnosed <34 weeks) versus

no preeclampsia (no PE), late-onset preeclampsia (LO-PE, diagnosed >34 weeks) versus no PE and EO-PE versus LO-PE by maternal risk factors. Estimates were obtained by multinomial logistic regression in 310 399 births with information on body mass index, Medical Birth Registry of Norway, 2006 to 2016.

Supporting information Table S3: Crude relative risk ratios (RRRs) with 95% confidence intervals (CIs) for both definitions: preterm and early-onset preeclampsia (EO-PE) versus no preeclampsia (no PE), term preeclampsia and late-onset preeclampsia (LO-PE) versus no PE and lastly preterm versus term preeclampsia and EO-PE versus LO-PE by maternal risk factors. Estimates were obtained by multinomial logistic regression in 1 044 860 births, Medical Birth Registry of Norway, 1999 to 2016.

Legends of Tables, main text:

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 to 2016.

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

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 to 2016.

Table 4: Adjusted relative risk ratios (RRRs) with 95% confidence intervals (CIs) for preterm preeclampsia versus no preeclampsia (no PE), term preeclampsia versus no PE and preterm versus 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 to 2016.

Legends of Figures, main text:

Figure 1: Flow chart, Medical Birth Registry of Norway (MBRN), 1999 to 2016.

Figure 2: Predicted proportions (%) with 95% confidence intervals of preterm (dark grey) and term (light grey) 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.

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

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

Tables, main text:

Table 1

	No preeclampsia	Preterm preeclampsia	Term preeclampsia
	N (%)	*N (%)*	*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)

Table 2

	Adjusted* RRRs (95% CIs)			Adjusted** 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)

*Adjusted for age, parity, and multiple births.
** Adjusted for maternal age, parity, multiple births, and all other risk factors.
Abbreviations: PE, preeclampsia.

Table 3

	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* 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)

*Adjusted for maternal age, parity, multiple births, all other risk factors, and body mass index.
Abbreviations: PE, preeclampsia.

Figures, main text:

Figure 1

Figure 1. Flow chart, Medical Birth Registry of Norway (MBRN), 1999- 2016.

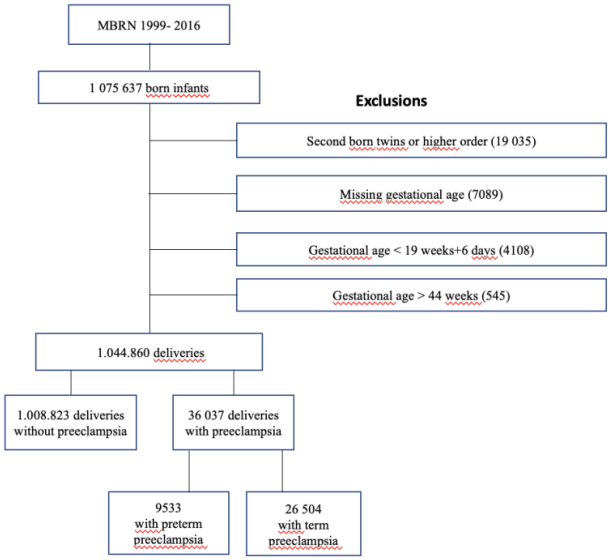
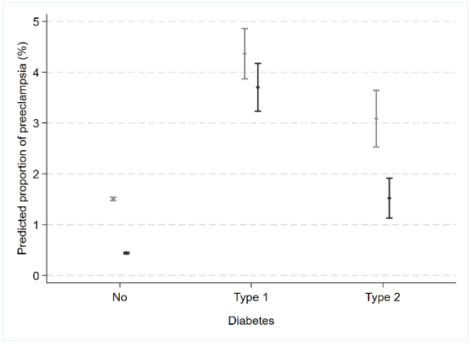
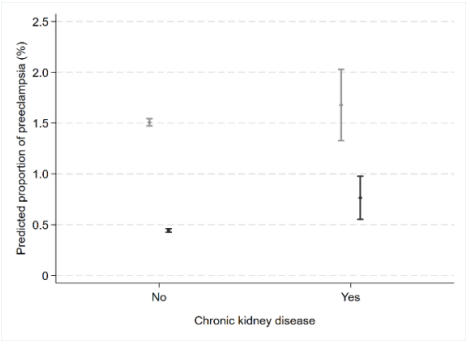


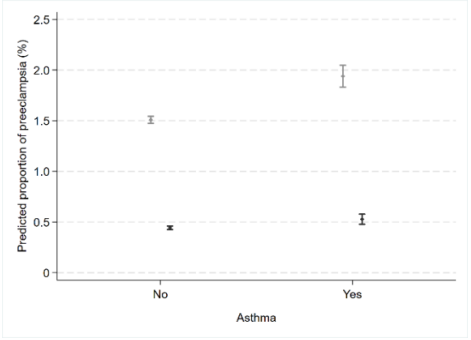
Figure 2



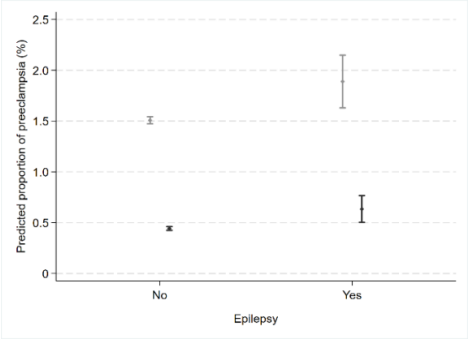
(A)



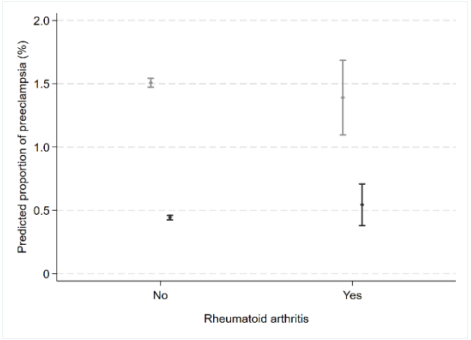
(B)



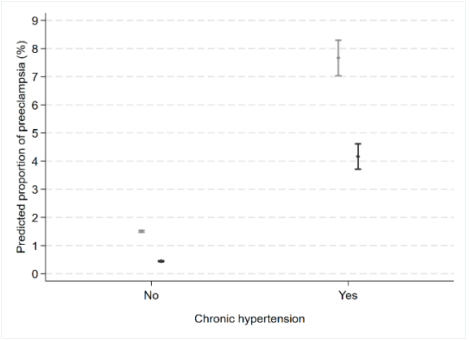
(C)



(D)



(E)



(F)

Figure 3

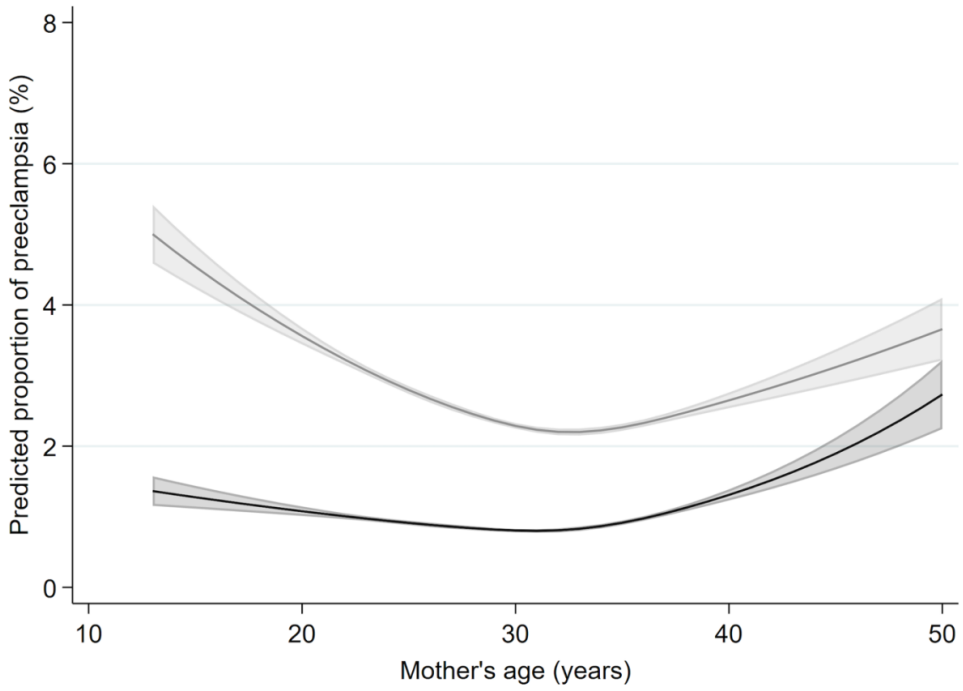
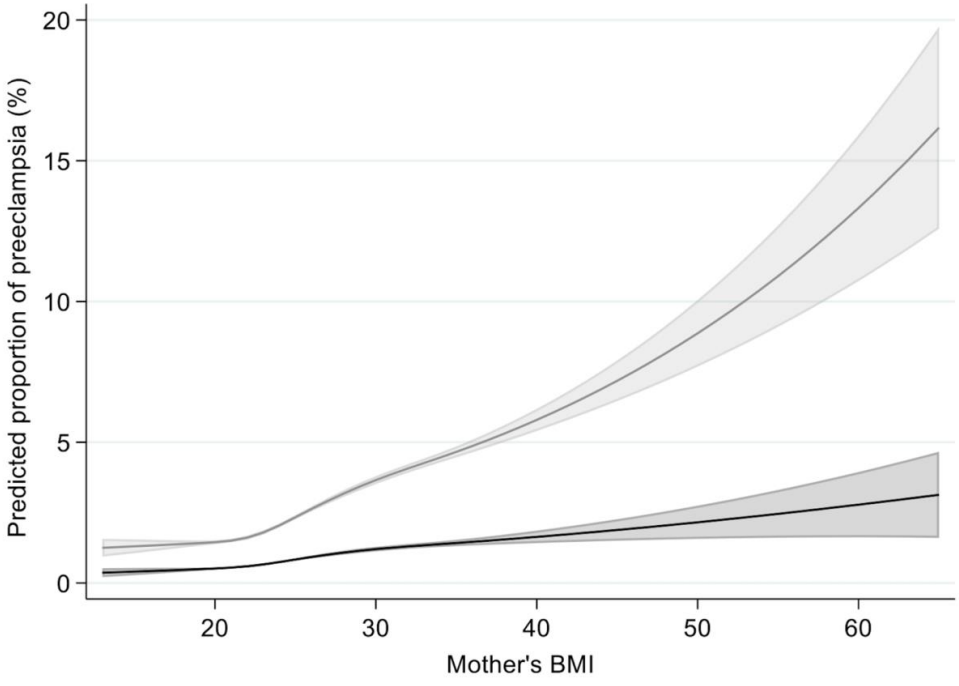

Predicted proportion of preeclampsia (%)
0
2
4
6
8
10
20
30
40
50
Mother's age (years)

Figure 4


Predicted proportion of preeclampsia (%)
0
5
10
15
20
20
30
40
50
60
Mother's BMI

Supplementary material to "Pregestational maternal risk factors for preterm and term preeclampsia: a population-based cohort study".

Supporting information Table S1:

	Adjusted* RRRs (95% CIs)			Adjusted** RRRs (95% CIs)		
Maternal risk factors	**EO-PE vs no PE**	**LO-PE vs no PE**	**EO-PE vs LO-PE**	**EO-PE vs no PE**	**LO-PE vs no PE**	**EO-PE vs LO-PE**
Diabetes type 1	6.83 (5.63, 8.28)	4.55 (4.13, 5.02)	1.50 (1.22, 1.84)	6.08 (4.99, 7.40)	4.34 (3.93, 4.80)	1.40 (1.14, 1.72)
Diabetes type 2	5.00 (3.69, 6.76)	2.73 (2.32, 3.20)	1.83 (1.33, 2.53)	3.56 (2.58, 4.90)	2.32 (1.96, 2.75)	1.53 (1.10, 2.13)
Chronic kidney disease	2.22 (1.55, 3.19)	1.28 (1.06, 1.54)	1.74 (1.17, 2.58)	1.88 (1.30, 2.73)	1.19 (0.99, 1.44)	1.58 (1.06, 2.35)
Asthma	1.40 (1.24, 1.59)	1.26 (1.20, 1.33)	1.11 (0.98, 1.27)	1.37 (1.21, 1.55)	1.25 (1.19, 1.32)	1.10 (0.96, 1.25)
Epilepsy	1.61 (1.21, 2.14)	1.37 (1.21, 1.55)	1.17 (0.87, 1.59)	1.42 (1.07, 1.90)	1.29 (1.14, 1.46)	1.10 (0.81, 1.50)
Rheumatoid arthritis	1.89 (1.32, 2.69)	0.97 (0.79, 1.18)	1.95 (1.31, 2.92)	1.67 (1.17, 2.39)	0.91 (0.74, 1.11)	1.84 (1.23, 2.76)
Chronic hypertension	13.93 (12.24, 15.85)	6.40 (5.92, 6.93)	2.18 (1.89, 2.50)	12.61 (11.04, 14.41)	6.06 (5.59, 6.57)	2.08 (1.80, 2.40)

*Adjusted for maternal age, parity, and multiple births.

** Adjusted for maternal age, parity, multiple births, and all other risk factors.

Abbreviations: PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia.

Supporting information Table S2:

	Adjusted* RRRs (95% CIs)		
Maternal risk factors	**EO-PE vs no PE**	**LO-PE vs no PE**	**EO-PE vs LO-PE**
Diabetes type 1	7.59 (5.50, 10.48)	3.56 (2.92, 4.34)	2.13 (1.50, 3.04)
Diabetes type 2	2.54 (1.45, 4.45)	1.81 (1.35, 2.42)	1.41 (0.78, 2.54)
Chronic kidney disease	0.90 (0.40, 2.01)	1.03 (0.73, 1.45)	0.88 (0.37, 2.07)
Asthma	1.12 (0.90, 1.38)	1.03 (0.94, 1.14)	1.08 (0.86, 1.36)
Epilepsy	2.23 (1.39, 3.56)	1.28 (1.00, 1.65)	1.73 (1.03, 2.92)
Rheumatoid arthritis	0.94 (0.46, 1.93)	0.80 (0.57, 1.14)	1.17 (0.54, 2.56)
Chronic hypertension	8.71 (6.83, 11.11)	4.05 (3.46, 4.73)	2.15 (1.65, 2.81)

*Adjusted for maternal age, parity, multiple births, all other risk factors, and body mass index.
Abbreviations: PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia.

Supporting information Table S3:

	Early- and late-onset preeclampsia defines as delivery before or after gestational week 37			Early- and late-onset preeclampsia defined as diagnosis before or after gestational week 34		
	Preterm vs no PE	**Term vs no PE**	**Preterm vs Term**	**EO-PE vs no PE**	**LO-PE vs no PE**	**EO-PE vs LO-PE**
Maternal risk factors						
Diabetes 1	9.44 (8.36, 10.66)	3.19 (2.84, 3.59)	2.96 (2.53, 3.46)	6.80 (5.61, 8.25)	4.53 (4.11, 4.98)	1.50 (1.22, 1.85)
Diabetes 2	4.65 (3.69, 5.86)	2.32 (1.94, 2.78)	2.00 (1.51, 2.65)	5.20 (3.86, 6.99)	2.60 (2.22, 3.05)	2.00 (1.45, 2.74)
Chronic kidney disease	2.07 (1.58, 2.70)	1.24 (1.00, 1.52)	1.67 (1.20, 2.33)	2.28 (1.59, 3.27)	1.34 (1.11, 1.61)	1.71 (1.15, 2.54)
Asthma	1.23 (1.13, 1.35)	1.34 (1.27, 1.41)	0.92 (0.83, 1.02)	1.42 (1.25, 1.60)	1.29 (1.23, 1.36)	1.09 (0.96, 1.25)
Epilepsy	1.60 (1.31, 1.96)	1.35 (1.18, 1.55)	1.19 (0.93, 1.51)	1.62 (1.22, 2.15)	1.39 (1.23, 1.57)	1.16 (0.86, 1.58)
Rheumatoid arthritis	1.49 (1.11, 1.99)	0.99 (0.80, 1.23)	1.50 (1.06, 2.14)	2.02 (1.42, 2.88)	0.99 (0.82, 1.21)	2.03 (1.36, 3.03)
Hypertension	11.26 (10.21, 12.43)	5.59 (5.14, 6.08)	2.02 (1.79, 2.28)	14.10 (12.44, 15.98)	6.08 (5.64, 6.56)	2.32 (2.02, 2.66)
Multipara	0.46 (0.44, 0.48)	0.45 (0.44, 0.46)	1.02 (0.97, 1.07)	0.51 (0.49, 0.55)	0.44 (0.43, 0.45)	1.16 (1.09, 1.23)
Multiple births	9.59 (9.02, 10.19)	1.94 (1.81, 2.09)	4.93 (4.50, 5.40)	6.60 (5.98, 7.29)	3.41 (3.24, 3.59)	1.93 (1.73, 2.16)

Abbreviations: PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia.

10. Appendices

The following documents are included in the appendices:

1. Ethical approval paper 1
2. Ethical approval paper 2 and 3
3. Application for protocol adjustments paper 2 and 3
4. DIPA paper 2 and 3

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Trine Anikken Larsen	55978497	03.03.2015	2015/66/REK vest
			Deres dato:	Deres referanse:
			20.01.2015	

Vår referanse må oppgis ved alle henvendelser

Anne Kvie Sande
Gerd Ragna Block-Thorsensgate 8

2015/66 Predisponerende faktorer for tidlig og sen preeklampsi

Forskningsansvarlig: Universitetet i Bergen
Prosjektleder: Anne Kvie Sande

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 12.02.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Formålet med studien er å gjøre en retrospektiv kohortstudie med utgangspunkt i den historiske fødedatabasen til Kvinneklinikken i Stavanger og data fra journalsystemet Natus, for å se på hvordan ulike kjente og potensielle predisponerende faktorer øker risikoen for tidlig og sen svangerskapsforgiftning (preeklampsi) i ulik grad. Det skal innhentes data fra Natus i perioden 2009 til 2014, samt data fra fødedatabasen ved Stavanger universitetssjukehus i perioden 1996 til 2008. Dette gjelder til sammen omkring 110 000 fødsler. Det søkes om fritak fra samtykkekravet.

Vurdering
Tidligere prosjekt behandlet prosjekt i REK vest
Komiteen er blitt gjort oppmerksom på at denne søknaden er tilnærmet identisk med prosjekt 2014/1069, "Tidlig og sen preeklampsi - to ulike tilstander", med prosjektleder Nils-Halvdan Morken. På bakgrunn av nærheten til dette prosjektet, diskuterte komiteen om den nye prosjektsøknaden kunne vært formulert som en endringsmelding. En vesentlig forskjell mellom prosjektsøknadene er at datagrunnlaget i dette prosjektet skal utvides kraftig i forhold til tidligere prosjektsøknad. Komiteen konkluderte derfor med at det nye prosjektet skulle behandles som en ny prosjektsøknad.

Søknad/protokoll
Komiteen mener at prosjektet er viktig, og har således ingen innvendinger til søknad og protokoll.

Fritak fra samtykkekravet
Prosjektleder søker om å gjennomføre prosjektet uten å innhente samtykke fra deltakerne. Hovedregelen for medisinsk og helsefaglig forskning er samtykke fra deltakerne. For at helseopplysninger innsamlet i helse- og omsorgstjenesten skal kunne benyttes i forskning uten samtykke, må kravene i helseforskningsloven § 35 være oppfylt. REK vest mener at dette er en samfunnsnyttig studie og at hensynet til deltakernes velferd og integritet er ivaretatt slik studien er lagt opp. Komiteen mener også at det vil være vanskelig å innhente samtykke fra alle deltakerne da dette dreier seg om 110 000 fødsler ved Stavanger universitetssjukehus og Haukeland universitetssjukehus.

Vilkårene for fritak fra samtykkekravet er oppfylte.

Vedtak
REK vest godkjenner prosjektet i samsvar med forelagt søknad.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 23.12.2017, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komitéleder

Trine Anikken Larsen
førstekonsulent

Kopi til:postmottak@uib.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Anna Stephansen	55978496	07.04.2017	2017/292/REK vest
			Deres dato: 14.02.2017	

Vår referanse må oppgis ved alle henvendelser

Anne Kvie Sande
Gerd Ragna Block-Thorsensgate 8

2017/292 Antihistaminer i svangerskapet og utvikling av tidlig preeklampsi

Forskningsansvarlig: Helse Stavanger HF - Stavanger universitetssjukehus
Prosjektleder: Anne Kvie Sande

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 16.03.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Målsetting med studien er å undersøke hvordan BMI, astma, type 2 diabtese, epilepsi, rheumatoid arthritt og kronisk nyresykdom påvirker risiko for henholdsvis tidlig og sen preeklampsi. Dette er en retrospektiv, case-control studie, og der logistisk regresjon skal brukes til å relatere predatorene allergi og bruk av antihistaminer til forekomsten av tidlig, sen og ingen preeklampsi.

Vurdering

F*orsvarlighet*
Dette er en registerstudie der opplysningene som skal brukes i studien allerede er innsamlet og ikke vil innebære mer belastning for deltagerne. Dette er en samfunnsnyttig studie og hensynet til deltakernes velferd og integritet vurderes av REK vest til å være ivaretatt slik studien er lagt opp.

Unntak fra samtykkekravet
Prosjektleder søker om å gjennomføre prosjektet uten a innhente samtykke fra deltakerne. Hovedregelen for medisinsk og helsefaglig forskning er samtykke fra deltakerne. For at helseopplysninger innsamlet i helse- og omsorgstjenesten skal kunne benyttes i forskning uten samtykke, må kravene i helseforskningsloven § 35 være oppfylt.

Dette er en samfunnsnyttig studie og det vil være vanskelig a innhente samtykke fra alle deltakerne. Komiteen for medisinsk og helsefaglig forskningsetikk innvilger fritak fra kravet om å innhente samtykke.

Prosjektslutt og håndtering av data
Data oppbevares i fem år for etterkontroll. REK vest har ingen innvendinger til dette.

Søknad til andre instanser

Vi gjør oppmerksom på at data fra Reseptregisteret kan sammenstilles med data fra lovbestemte helseregistre etter helseregisterloven § 11, jf. reseptregisterforskriften § 5-3 første ledd. Ved sammenstilling

mellom Reseptregisteret og lovbestemte helseregistre etter helseregisterloven § 11 må søker sende melding til Personvernombudet ved institusjonen der søkeren holder til eller til Datatilsynet. Sammenstilling av data fra Reseptregisteret og andre datakilder enn lovbestemte helseregistre krever konsesjon fra Datatilsynet, jf. reseptregisterforskriften § 5-3 andre ledd.

Vedtak
REK vest godkjenner prosjektet i samsvar med forelagt søknad.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2018, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
Prof. dr.med
Komiteleder

Anna Stephansen
Kontorsjef

Kopi til:forskning@sus.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Fredrik Rongved	55978498	15.01.2018	2017/292/REK vest
			Deres dato:	Deres referanse:
			31.12.2017	

Vår referanse må oppgis ved alle henvendelser

Anne Kvie Sande
Gerd Ragna Block-Thorsensgate 8

2017/292 Antihistaminer i svangerskapet og utvikling av tidlig preeklampsi

Forskningsansvarlig: Helse Stavanger HF - Stavanger universitetssjukehus
Prosjektleder: Anne Kvie Sande

Vi viser til søknad om prosjektendring datert 31.12.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet for REK vest på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

Ønsket endring

Prosjektleder ønsker å endre prosjektslutt fra 31.12.2017 til 01.01.2022.

REK vest ved sekretariatet vurderte søknaden.

Vurdering

REK vest har ingen innvendinger mot ønsket endring.

Vedtak
REK vest godkjenner prosjektendringen i samsvar med forelagt søknad.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningsloven § 10 og forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Fredrik Rongved
rådgiver

Kopi til: *forskning@sus.no*

Stavanger Universitetssjukehus
Helse Stavanger HF

Personvernombudet

Til

Anne Kvie Sande

Intern ID	Ephorte saksnr	Saksbehandler:	Dato:
	2018/207	Personvernombud Ina Trane	22.10.18

UTTALELSE FRA PERSONVERNOMBUDET – DPIA VURDERING I ANLEDNING REK PROSJEKTET ; *«Antihistaminer i svangerskapet»*

Det vises til ovennevnte REK prosjekt der personvernombudet har rådet prosjektet til å gjennomføre en DPIA vurdering.

REK prosjektet har i utgangspunktet ikke rådføringsplikt overfor personvernombudet. Det vises her til helseforskningsloven § 33. Det påhviler imidlertid en involveringsplikt etter personvernforordningen artikkel 38 nr. 1.

Videre foreligger det en rådføringsplikt overfor personvernombudet i forbindelse med DPIA vurderingen. Det vises her til forordningen artikkel 35 nr. 2. Det presiseres at personvernforordningen ikke legger noen godkjenningsmyndighet til personvernombudet. Det er likevel antatt at rådet fra personvernombudet bør tillegges vekt ved en evt. godkjennelsen av personvernkonsekvensvurderingen.

Personvernombudet har gjort følgende vurdering;

Personvernombudet har fått seg forelagt DPIA vurderingen, og vurderer denne til å være dekkende og tilfredsstillende hva angår de vurderinger som skal inngå i en personvernkonsekvensvurdering (DPIA). Personvernombudet vurderer at prosjektet har lav personvernulempe og risiko. Videre at prosjektet har tilstrekkelige tiltak som reduserer personvernulempen for de registrerte.

Prosjektets formål: Prosjektet er et REK godkjent prosjekt der formålet med behandlingen er å finne ut om mors bruk av antihistaminer kan føre til mindre forekomst av svangerskapsforgiftning. REK har godkjent at prosjektet gjennomføres uten at det innhentes samtykke i fra pasientene. Prosjektet ønsker å hente data fra Medisinsk fødselsregister og sammenstille disse dataene med data som skal hentes i fra Reseptregisteret. Det er gjort en styrkeberegning, som er godkjent av REK, der en har kommet til at en skal bruke data fra ca 1.7 00 000 fødsler i Norge fra perioden 1999-2016. Prosjektet er ikke samtykkebasert.

Personvernombudet vurderer at databehandlingen i prosjektet skal skje til et spesifikt, uttrykkelig, og klart definert formål.

Behandlingsgrunnlag: Personvernombudet vurdere at prosjektet har nødvendig behandlingsgrunnlag i personvernforordningen artikkel 6 nr. 1 bokstav e) og artikkel 9 nr. 2 bokstav j) jf artikkel 89 nr. 1. Videre foreligger det supplerende rettslig grunnlag i nasjonalrett i helseforskningsloven § 10, jf helseforskningsetikkloven § 4.

Nødvendighet/proporsjonalitet: Personvernombudet vurderer at omfanget på databehandlingen er nødvendig og proporsjonal i forhold til studiens formål. Det vises til redegjørelsen for dette i DPIA vurderingen.

Konfidensialitet/integritet: Personvernombudet vurderer at prosjektets tiltak for å sikre konfidensialitet og integritet, er tilstrekkelig, og ivaretar det som kreves etter forordningen. Det vises til de tiltak prosjektet redegjør for i DPIA vurderingen side 6-8, herunder beskrivelse av dataflyten. Data som utleveres til prosjektet vil være avidentifisert, og kun prosjektleder har tilgang til disse. Alle data som publiseres vil være anonyme.

Lagringsbegrensning: Data skal oppbevares for analyse frem til 1.1.22. De skal deretter oppbevares i inntil 5 år for kontrollhensyn.

Dataminimering: Personvernombudet vurderer at det ikke er mulig å begrense personopplysningene ut over de data prosjektet har bedt om å få utlevert. Videre at prosjektet har et dokumentert behov for de aktuelle data.

Risiko for rettigheter og friheter for de registrerte: Personvernombudet vurderer at prosjektet i utgangspunktet har en lav personvernulempe. Studien får ingen konsekvenser for den enkelte registrerte. Data som skal benyttes er allerede innsamlet, videre er det snakk om et begrenset antall variabler. Datasettet som skal benyttes er pseudonymisert, og det er ikke mulig for forskeren å identifisere enkelt personer. De registrerte har ikke noe valg, og de vil ikke fra prosjektet motta individuell målrettet informasjon om databehandlingen. De registrerte forutsettes i utgangspunktet å være kjent med at data fra de to aktuelle lovbestemte registrene kan brukes til forskning i gitte tilfeller.

Ved eventuell henvendelse fra pasient til prosjektet, er det opplyst at prosjektet på forespørsel vil innfri den/de registrerte sine rettigheter etter forordningen artikkel 12-22.

Personvernombudet vurderer at databehandlingen omfatter nødvendige garantier ihht forordningen, som sikrer de registrertes rettigheter og friheter. Videre at garantiene er innført ved tilfredsstillende tekniske og organisatoriske tiltak, jf artikkel 89 nr. 1.

Personvernombudet mener det i dette prosjektet er hjemmel for unntak fra de registrerte sine rettigheter av ressurshensyn. Det vises her til forordningen artikkel 89 nr. 2, samt personopplysningsloven § 17 første ledd bokstav a), og § 17 andre ledd.

Personvernombudet har ingen innvendinger til at prosjektet gjennomføres som beskrevet av prosjektleder. Det forutsettes at prosjektet gjennomføres i henhold til protokoll, aktuelt regelverk, herunder bestemmelsene i helseregisterloven og relevante forskrifter.

Med vennlig hilsen

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