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Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based study of first pregnancies

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Abstract

Objectives:

To estimate the risk of hypertensive pregnancy complications in women with epilepsy, with and without antiepileptic drugs, and assess the risk associated with the four most common antiepileptic drugs.

Design:

A population-based cohort study using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database. Women with epilepsy with and without antiepileptic drugs were compared to women without epilepsy.

Setting:

Norway, 2004-2012.

Participants:

All first pregnancies of women with epilepsy and women without epilepsy were included.

Primary and secondary outcome measures:

Main outcome measures were hypertensive pregnancy complications: a compound variable of any hypertensive disorder, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome.

Results:

In total 1778 pregnancies in women with epilepsy and 221 662 in women without epilepsy were analysed. 682 of the women with epilepsy used antiepileptic drugs, the most common in monotherapy being: lamotrigine (N=280), carbamazepine (N=94), levetiracetam (N=71), and valproate (N=51). There was an increased risk of any hypertensive disorder in women with epilepsy (adjusted odds ratio [aOR]: 1.2, 95% CI 1.0-1.5) and in the subcategory using valproat (aOR: 2.9: 95% CI: 1.3-6.4). The most frequent hypertensive complication was mild

preeclampsia and the risk was increased in women with epilepsy (aOR: 1.4, 95% CI: 1.1-1.8) and women with epilepsy with valproat (aOR: 3.3: 95% CI: 1.2-9.4).

Conclusions:

Women with epilepsy have an increased risk of mild preeclampsia, but not for the severe types of hypertensive pregnancy complications. Lamotrigine and levetiracetam do not predispose for mild preeclampsia, whereas valproate was associated with an increased risk of mild preeclampsia.

Strengths and limitations of this study:

+ Large population based national cohort with data from compulsory and reliable national health registries
+ Only first pregnancies were included to avoid bias from recurrent events
+ This is the first study to specify type and degree of Hypertensive complications
– We had no data on type of epilepsy or seizure activity

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Competing interests:

None of the authors have any conflict of interest to disclose.

Hypertensive pregnancy complications in women with epilepsy

Introduction

Epilepsy is the most common neurologic disorder requiring continuous drug treatment during pregnancy, and 30 - 70% of pregnant women with epilepsy (WWE) use antiepileptic drugs (AEDs).[1-4] Consequences of maternal AED use during pregnancy for fetal malformations and early childhood development have been focused.[5-8] In contrast, potential effects of epilepsy and specific AEDs on the pregnancy have been less studied. Optimal therapy in epilepsy is a balance between seizure suppression and side-effects. For women in fertile age, potential AED effects for the fetus as well as on the pregnancy should be of the highest relevance.

Hypertensive pregnancy complications include multiple diagnoses with different risks and implications for fetal and maternal outcomes. Hypertensive pregnancy complications represent a major contributor to global maternal mortality. [9] Most previous studies, including a recent meta-analysis, have found an increased risk of total hypertensive complications in WWE but these studies have not differentiated between the specific hypertensive disorders and therefor the burden of disease in WWE is uncertain.[10-14] [2, 3, 10, 13, 14] Studies on the effect of specific AEDs on pregnant women with epilepsy have been limited by small sample size, selection bias, and lack of detailed information on hypertensive disorders.[2, 3, 10, 12-14] Preferred drugs and drugs to be avoided have not been identified.

The aim of the present study was to estimate the risk of specified hypertensive pregnancy complications in WWE with and without use of AEDs, and to specifically define the risk for the four most common AEDs. This is necessary to guide optimal AED treatment in young women before and during pregnancy.

Materials and Methods

We used data from the compulsory, population-based Medical Birth Registry of Norway (MBRN) collected during 2004-2012. The notification form of the MBRN was unchanged in that period. MBRN includes data on maternal and paternal social factors, maternal health prior to and during pregnancy including chronic diseases such as epilepsy, complications and interventions during pregnancy and birth, perinatal outcome and complications in the children. Data are prospectively registered throughout pregnancy, delivery and postpartum period. All data are forwarded to the MBRN by the attending midwife or obstetrician. All pregnancies from 12 weeks gestation are recorded. The registry is routinely linked to the National Population Database to ensure notification of all births and deaths in the country. All Norwegian citizens are given a unique Social Security Number that enables linkage of data from various national data sources. Only first time pregnancies were included in this study, all singleton and multiple pregnancies at >22 weeks of gestation.

The Norwegian Prescription Database (NorPD), commenced in 2004, provides detailed data on all medications dispensed from pharmacies by prescription. Mandatory registration in NorPD of every dispensed medical prescription is made by the pharmacist. Statistics Norway provided data on maternal level of education.

Main outcome variables were a compound variable of any hypertensive disorder in pregnancy, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets). Exposure variables were a diagnosis of epilepsy and use of AEDs. All hypertensive disorders, except the compound variable, are reported in MBRN in specified checkboxes. Gestational hypertension was defined as persisting elevated blood pressure ≥140 mmHg systolic and/or ≥90mmHg diastolic occurring after 20 weeks of gestation and without pre-existing hypertension.[15] Mild preeclampsia was defined as persisting elevated blood pressure

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≥140 mmHg systolic and/or ≥90mmHg diastolic combined with proteinuria ≥ 0,3g per 24 hours (equivalent to ≥ +1 on urine test strips for protein excretion) occurring after 20 weeks of gestation. Severe preeclampsia was defined as blood pressure ≥160/110mmHg, clinical symptoms of preeclampsia, protein excretion ≥3 g per 24 hours or oliguria, early onset preeclampsia, eclampsia or HELLP syndrome. Eclampsia was defined as generalized seizures occurring simultaneously with preeclampsia or hypertension and without other cause. Early onset preeclampsia was defined as preeclampsia with onset before 34 weeks of gestation. The compound variable of any hypertensive disorder was defined as the presence of any of these hypertensive disorders. Superimposed preeclampsia in women with pre-gestational hypertension was not specified but was included in the respective subcategories of hypertensive complications by severity.

Maternal epilepsy was defined by either ticking the specific checkbox in MBRN or adding this diagnosis in a blank space available for written text. Neither of these provided information about the type of epilepsy or seizure activity. The diagnosis was based on previous medical history and medical charts. The epilepsy diagnosis in MBRN has previously been found to be valid in 92.3 % of cases.[3]

NorPD provided exact data on dispensed AEDs and high-dose folic acid supplementation (4mg/day) including type of medication (according to ATC codes), dose, and time of administration. We defined AED use in pregnancy as dispensed drugs from the pharmacy in the time period coinciding with gestation, dated by ultrasound assessment. In cases with missing ultrasound dates, last menstrual period was used. We assessed drug dispensation also one and three months pre-conception. An a priori decision was made to primarily analyse the four most commonly used AEDs in monotherapy in order to obtain large enough groups and exclude interference of polytherapy. Information about AED use in pregnancy is also

recorded in MBRN on the notification form in an available blank space for written text. This information was used to validate the AED use obtained from MBRN compared to NorPD.

Socio-demographic and background data included maternal age (≤19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years and ≥40 years), maternal educational level (≤10 years, 11-13 years, ≥14 years), other chronic disease (kidney disease, hypertension, diabetes mellitus), multifetal pregnancies, high pre-gestational body mass index (BMI) (BMI ≥30kg/m²), smoking during pregnancy, and use of folic acid supplementation in standard dose (0,4mg/day). The BMI variable was only available from 2006 onwards. Data on ethnicity and marital status were not available for this study.

We further categorized WWE by AED-treatment; all AEDs, no AEDs, AED polytherapy, and the four most common AEDs. Outcome variables for specific AEDs were analysed only in WWE with monotherapy. WWE using other than the four most common AEDs were identified and excluded from the analyses where appropriate. WWE and all treatment subcategories were compared with women without epilepsy. WWE with AED treatment were also compared to WWE without AEDs.

For binary outcomes, proportions and crude odds ratios (OR) were calculated using contingency tables. P-values were calculated using Fisher's exact test. Continuous variables (background variables) were analysed with independent sample t-tests. Statistical significance was defined as non-overlapping 95% confidence intervals (95% CI) and two sided p-values < 0.05. All statistical analyses were performed with IBM SPSS (Statistical Package for Social Sciences) version 22.0 or later.

We used logistic regression to adjust for possible confounding by maternal age, educational level, multifetal pregnancy, use of folic acid supplements, and other relevant chronic diseases (pre-existing hypertension, pre-existing kidney disease, and pre-existing diabetes mellitus). The covariates BMI (only registered since 2006) and smoking were restrained by missing

cases and therefore studied with sensitivity analyses applied on all results and not included in the final logistic regression models. The impact of other relevant chronic diseases was also analysed further with sensitivity analyses.

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Results

223 440 first time pregnancies were eligible after exclusion of multipara pregnancies (309 364), missing personal identification number (1 514, 0.7% [foreigners or immigrants without residence permit]), and pregnancies <23 gestational weeks (340, 0.2%). There were 1778 WWE (0.79 %), of whom 682 (38.4 % of WWE) used AEDs either in monotherapy (554 women) or in polytherapy (128 women). The most common AEDs used as monotherapy were lamotrigine (280 women, 50.5 % of all monotherapies), carbamazepine (94 women, 17.0 %), levetiracetam (71 women, 12.8 %), and valproate (51 women, 9.2 %). Other AEDs in monotherapy were used by 58 WWE. Maternal characteristics are shown in Table 1.

The adjusted odds ratio (aOR) of the compound variable any hypertensive complication, was increased in WWE (aOR 1.2, 95% CI: 1.0-1.5) compared to women without epilepsy. When WWE were subcategorized into WWE with AED and WWE without AED, none of the two subgroups differed significantly from women without epilepsy for any hypertensive disorder. The majority of hypertensive complications were mild preeclampsia (Table 2). The risk of mild preeclampsia was significantly increased in WWE (aOR: 1.4, 95% CI: 1.1-1.8) and in WWE without AED exposure (aOR: 1.4, 95% CI: 1.0-2.0) compared to women without epilepsy. For WWE with AED the risk of mild preeclampsia was not significantly increased although the prevalence was the same as for both WWE and WWE without AEDs. For WWE there was a marginally significant risk of early onset preeclampsia (aOR: 1.7, 95% CI: 1.0-2.8). This risk disappeared after stratification and when including smoking in sensitivity analyses. Mild preeclampsia was therefore the only specified hypertensive disorder increased in WWE. There was no significant difference for any of the outcomes when WWE with AEDs were compared to WWE without AED. There was no significantly increased risk of gestational hypertension, severe preeclampsia, HELLP or eclampsia when WWE, WWE with and WWE without AED were compared to women without epilepsy.

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WWE with valproate monotherapy had an increased risk of any hypertensive complication (aOR: 2.9, 95% CI: 1.4-6.4), gestational hypertension (aOR: 3.3, 95% CI: 1.0-10.8), and mild preeclampsia (aOR: 3.3, 95% CI: 1.2-9.4) compared to women without epilepsy (Table 3). There was no increased risk of hypertensive complications for any other AEDs used in monotherapy.

Sensitivity analyses for smoking included 182 478 women, and modified the results for early onset preeclampsia in WWE compared to women without epilepsy (aOR: 1.6, 95% CI: 0.9-2.9). Sensitivity analyses for BMI >30kg/m^2 included 60 740 women and modified the risk for any hypertensive disorder for WWE (aOR: 1.3, 95% CI: 0.8-1.9), while the risk of mild preeclampsia increased (aOR: 1.8, 95% CI: 1.1-2.9). All increased risks for WWE with VPA disappeared when sensitivity analyses with BMI > 30kg/m^2 was performed. Separate analyses of women with BMI >30kg/m^2 only, showed no significant differences for any of the outcome variables when WWE, WWE with AED, and WWE without AED were compared to women without epilepsy. BMI > 30kg/m^2 and other relevant chronic diseases had no significant interactions with epilepsy in Logistic regression analyses. However these variables had more impact on all hypertensive outcomes than a diagnosis of epilepsy. The impact of standard folic acid and of high-dose folic acid supplementation was examined in all population subcategories. There were no significant differences among WWE for any of the hypertensive outcomes between use and no use of such supplementations.

To validate the AED data in MBRN, positive predictive values were calculated for matching AED dispensation in the NorPD data during pregnancy. Positive predictive value was 0.94 for lamotrigine, 0.82 for carbamazepine, 0.84 for valproate, and 0.95 for levetiracetam. When AED use in NorDP data was assessed one and three months before conception, the total AED population remained unchanged. 95% of WWE with AED in NorPD had more than one

dispensation during pregnancy, illustrating continuous use throughout pregnancy as one dispensation usually corresponds to more than three months use.

Discussion

We found an increased risk of mild preeclampsia in WWE and the hypertensive complications in WWE consisted mostly of cases with mild preeclampsia. The specified newer AEDs used in monotherapy did not predispose for this complication. WWE on valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs. WWE, with and without AEDs, did not have an increased risk of gestational hypertension, severe preeclampsia, early onset preeclampsia, HELLP or eclampsia when compared to women without epilepsy.

The present study shows that most WWE, and in particular when treated with the new AEDs, do not have additional risks of hypertensive complications. WWE without AED seemed to have an increased risk of mild preeclampsia but this risk was no longer significant when sensitivity analyses including other relevant chronic diseases were applied. WWE with AED and WWE without AED had the same prevalence of mild preeclampsia but only WWE without AED had a significantly increased risk. This probably reflects marginal differences influenced by sample size. Collateral risk factors such as smoking, BMI >30kg/m^2, and relevant chronic disease (pre-existing kidney disease, hypertension or diabetes) were relevant for hypertensive complications in WWE. The mechanism for the increased risk of hypertensive complications in WWE in first pregnancies could therefore be partly mediated by modifiable external risk factors and comorbidity.

The specific risk in WWE on valproate was linked to high BMI. Weight gain and metabolic syndrome represent side-effects of valproate.[16] Our study does not support any additional mechanism for valproate associated mild preeclampsia. When pregnancies with BMI > 30 kg/m² were analysed separately, WWE with valproate had a high prevalence of mild preeclampsia, but the increased risk was not significant, possibly due to few cases. A previous study showed increased risk of preeclampsia in women on valproate but this was not

confirmed by later studies.[3, 12, 13] Valproate can induce endocrine changes and polycystic ovary syndrome in WWE and polycystic ovary syndrome is associated with hypertensive pregnancy complications.[16-19] Polycystic ovary syndrome is also associated with overweight so endocrine factors could be important for our findings. Valproate increases the risk of malformations in children exposed during pregnancy.[6, 20] Because of this, as well as delayed neurodevelopment, The European Medicines Agency has strengthened the advice not to prescribe valproate to WWE in fertile age.[21] Valproate is therefore not first line treatment in pregnancy. The observed valproate associated mild preeclampsia could represent bias through confounding by indication, although we would expect valproate to be avoided in women without other risk factors than epilepsy.

The modern AEDs lamotrigine and levetiracetam were not associated with increased risk of mild preeclampsia, and lamotrigine did not increase hypertensive pregnancy complications in general. A small study has previously reported an increased risk of preeclampsia in WWE on lamotrigine.[3] Lamotrigine has been considered a preferred option for WWE in need of AED treatment because children exposed to lamotrigine in pregnancy have a lower rate of malformations and better cognitive function than after exposure to other AEDs.[5, 6, 8] Potential AED effects on the child are highly important for deciding optimal treatment for WWE. The combination of a low rate of adverse fetal effects and no increased risk of hypertensive complications supports the use of lamotrigine in WWE before and during pregnancy. We found an increased risk of early onset preeclampsia in WWE on levetiracetam, but this should be interpreted with caution as the association relayed on only two cases and was not present in sensitivity analyses including BMI. Levetiracetam is a potent, broad-spectrum AED with low rate of adverse fetal outcomes.[5] Levetiracetam use among pregnant WWE is increasing, but levetiracetam is less studied than lamotrigine and maternal safety during pregnancy is not well documented.[5, 6, 22]

Mild, but not more severe preeclampsia was increased among WWE. Proactive management and close surveillance of WWE could explain why the mild disease did not proceed further. Similarly, the close surveillance of WWE could have increased the detection of mild preeclampsia. Alternatively, mild and severe hypertensive complications in pregnancies could have different underlying pathophysiological mechanisms in WWE.

Strengths of our study are that we have analysed first pregnancies only, have specified the types of hypertensive complications, and have analysed WWE on specific AEDs in monotherapy only. Parity is a complex variable in reproductive epidemiology and may lead to bias as the risk of hypertensive complications changes significantly in subsequent pregnancies.[23-25] Our large and unselected nationwide cohort enabled assessment of effects of individual AEDs in monotherapy. Data was linked to the NorPD that showed the exact drug dispensation during pregnancy. The registration and standardized data collection in the national databases that were used provide information of high validity.[3, 26] The prevalence of WWE in our population was 0.79 % and the incidence of preeclampsia was 5.4 %, both in accordance with previous population-based studies.[1, 2, 4, 11, 27, 28]

A limitation of this study was the possible inclusion of previous and non-active epilepsy, and also of women with undefined seizures in the epilepsy group. This could have increased the total epilepsy population and thereby masking some effects in our group with untreated epilepsy. The MBRN did not provide data on type of epilepsy or seizure activity. However, a small study did not find any association between seizure activity and hypertensive complications in pregnancy.[3] Women without epilepsy but using AEDs for other conditions were not excluded in our study. This group constituted 0.1 % in the control population and did not affect the outcomes. Psychiatric and pain conditions are the main reasons for AED use in women without epilepsy. NorPD records dispensed medications which may leave room for variation in actual compliance. As 95% of WWE with AED collected more than one

dispensation during their pregnancy, we presume that the patients used their AED as prescribed.

BMI above or below 30 kg/m² influenced the results for WWE. MBRN has only registered BMI since 2006, thus it was not possible to control for this variable in the complete population. One previous study has indicated an increased risk for preeclampsia in WWE with BMI > 25 kg/m².[29] Regardless of a global rise in BMI, a risk factor for hypertensive disorders, preeclampsia shows a decreasing prevalence over time.[27, 30] A general decrease in preeclampsia is most likely also affecting WWE and thereby possibly narrowing the differences between WWE and women without epilepsy.

HELLP, eclampsia and early onset preeclampsia are rare hypertensive manifestations. Lack of events in some of our subgroups can be insufficient to prove significance, despite our large sample size. Our study lacks information on ethnicity and marital status, not released by MBRN due to ethical considerations.

Conclusion

Mild preeclampsia was the only hypertensive complication to be increased in first pregnancies of WWE. This is of major clinical importance since mild preeclampsia, in contrast to severe forms of preeclampsia, is not associated with increased maternal or fetal morbidity or mortality in pregnancy.[15] WWE have previously been considered as high risk parturients by having a significant increase in several adverse pregnancy outcomes, including hypertensive complications.[2, 3, 10, 14] Our study shows that the increased risk does not include most WWE and especially not WWE on modern AEDs, nor does it include severe hypertensive complications. A healthcare system focusing on risk assessment, prevention of modifiable risk factors and modern treatment options should be the key to a further decrease in hypertensive complications in pregnant WWE.

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Details of Ethics Approval:

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Contribution to Authorship:

KCD conceived and designed the study, analysed the data and drafted the manuscript. IB provided input on design, interpretation and presentation of the study. NHM provided input on design and analyses, interpretation of analyses and critically revised the manuscript. NEG

conceived and designed the study, and critically revised the presentation and discussion of the results in the manuscript. The final manuscript was approved by all authors.

Data sharing statement:

Data from Medical Birth Registry of Norway and Norwegian Prescription Database are available at Norwegian Institute of Public Health.

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Table 1. Maternal characteristics. First pregnancies as recorded in Medical Birth Registry of Norway (2004-2012).

N=223440	Women without Epilepsy	WWE		WWE without AED		WWE with AED		WWE with polytherapy	
	N=221662	N=1778		N=1096		N=682		N=128	
		N (%)	p - value	N (%)	p - value	N (%)	p - value	N (%)	p - value
Maternal age									
<19 years	10519 (4.7)	116 (6.5)	0.001	82 (7.5)	<0.001	34 (5.0)	0.729	8 (6.3)	0.401
20-24 years	52 857 (23.8)	475 (26.7)	0.005	310 (28.3)	0.001	165 (24.2)	0.825	33 (25.8)	0.61
25-29 years	82 004 (37.0)	564 (31.7)	<0.001	332 (30.3)	<0.001	232 (34.0)	0.113	46 (35.9)	0.852
30-34 years	55 199 (24.9)	466 (26.2)	0.205	273 (24.9)	1	193 (28.3)	0.045	32 (25.0)	1
35-39 years	17 992 (8.1)	124 (7.0)	0.083	78 (7.1)	0.245	46 (6.7)	0.208	8 (6.3)	0.52
≥40 years	3091 (1.4)	33 (1.9)	0.099	21 (1.9)	0.153	12 (1.8)	0.41	1 (0.8)	1
Educational level									
0-10 years	31 241 (14.1)	367 (20.6)	<0.001	219 (20.0)	<0.001	148 (21.7)	<0.001	40 (31.3)	<0.001
11-13 years	117 063 (52.8)	950 (53.4)	0.616	576 (52.6)	0.88	374 (54.8)	0.3	59 (46.1)	0.133
≥14 years	23 732 (10.7)	118 (6.6)	<0.001	73 (6.7)	<0.001	45 (6.6)	<0.001	3 (2.3)	0.001
Other	7 659 (3.5)	39 (2.2)	0.004	29 (2.6)	0.162	10 (1.5)	0.004	4 (3.1)	1
Fetal plurality									
Multifetal	4 113 (1.9)	26 (1.5)	0.253	21 (1.9)	0.837	5 (0.7)	0.031	3 (2.3)	0.516
Gestational age									
Mean (days)	278.4	277.3	0.002	277.1	0.006	277.5	0.139	276.1	0.079
Birth weight									
Mean (grams)	3414.4	3381.2	0.019	3363.5	0.004	3410.9	0.876	3355.2	0.254
Body Mass Index									
>30 kg/m2 (form 2006)	60 232 (23.9)	508 (24.6)	0.001	291 (24.5)	0.056	217 (24.7)	0.013	(40) 24.1	0.818
Smoking									
Yes	27 898 (12.6)	322 (18.1)	<0.001	215 (19.6)	<0.001	107 (15.7)	0.016	28 (21.9)	0.002
Preexisting disease									
Hypertension, Kidney Disease, Diabetes	4 117 (1.9)	59 (3.3)	<0.001	31 (2.8)	0.02	28 (4.1)	<0.001	8 (6.3)	0.003
Folic acid supplementation									
Before pregnancy	55 168 (24.9)	563 (33.4)	<0.001	303 (27.6)	0.038	290 (42.5)	<0.001	51 (39.8)	<0.001
During pregnancy	139 157 (62.8)	1 266 (71.2)	<0.001	723 (66.0)	0.031	543 (79.6)	<0.001	98 (76.6)	0.002
High dose	2174 (1.0)	362 (20.4)	<0.001	27 (2.5)	<0.001	312 (45.7)	<0.001	76 (59.4)	<0.001

WWE = Women with Epilepsy
AED = Antiepileptic Drug

Table 2. Hypertensive pregnancy complications in WWE, WWE with and without AED.

N = 223440	Women without Epilepsy	WWE			WWE without AED			WWE with AED			WWE with polytherapy		
	N= 221662	N= 1778			N= 1096			N= 682			N= 128		
	N (%)	N (%)	aOR (95% CI)	p - value	N (%)	aOR (95% CI)	p - value	N (%)	aOR (95% CI)	p - value	N (%)	aOR (95% CI)	p - value
Any Hypertensive Disorder	16542 (7.5)	158 (8.9)	1.23(1.03-1.48)*	0.022	93 (8.5)	1.21(0.96-1.53)	0.102	65 (9.5)	1.27(0.96-1.68)	0.1	10 (7.8)	1.01(0.53-1.93)	0.98
Gestational Hypertension	5381 (2.4)	43 (2.4)	1.04(0.75-1.45)	0.817	22 (2.0)	0.90(0.57-1.43)	0.665	21 (3.1)	1.25(0.77-2.03)	0.367	5 (3.9)	1.78(0.73-4.4)	0.21
Mild Preeclampsia	6445 (2.9)	68 (3.8)	1.42 (1.10-1.84)	0.007	42 (3.8)	1.44(1.04-2.00)***	0.028	26 (3.8)	1.39(0.92-2.10)	0.117	4 (3.1)	0.96(0.36-2.6)	0.943
Severe Preeclampsia	4330 (1.9)	46 (2.6)	1.30(0.97-1.75)	0.081	29 (2.6)	1.32(0.91-1.92)	0.145	17 (2.5)	1.28(0.79-2.07)	0.327	1 (0.8)	0.36(0.05-2.55)	0.303
Early Onset Preeclampsia	1299 (0.6)	19 (1.1)	1.69(1.01-2.82)**	0.047	11 (1.0)	1.67(0.86-3.23)	0.131	8 (1.2)	1.72(0.77-3.87)	0.189	-	-	-
HELLP	518 (0.2)	6 (0.3)	1.18(0.44-3.17)	0.743	2 (0.2)	0.97(0.24-3.91)	0.969	4 (0.6)	1.50(0.37-6.03)	0.571	-	-	-
Eclampsia	191 (0.1)	3 (0.2)	2.18(0.69-6.84)	0.183	2 (0.2)	2.35(0.58-9.49)	0.232	1 (0.1)	1.88(0.26-13.49)	0.529	-	-	-

WWE = Women with Epilepsy
AED = Antiepileptic Drug
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Other relevant chronic disease, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking or BMI >30kg/m^2
*** Not significant in sensitivity analyses when including other relevant diseases

Table 3. Hypertensive pregnancy complications in WWE with specified AEDs.

N=223440	Women without Epilepsy	WWE with LTG			WWE with CBZ			WWE with LEV			WWE with VPA		
	N=221662	N=280			N=94			N=71			N=51		
	N (%)	N (%)	aOR (95% CI)	p-value	N (%)	aOR (95% CI)	p-value	N (%)	aOR (95% CI)	p-value	N (%)	aOR (95% CI)	p-value
Any Hypertensive Disorder	16542 (7.5)	25 (8.9)	1.20(0.76-1.88)	0.434	7 (7.4)	0.97(0.42-2.25)	0.946	7 (9.9)	1.32(0.57-3.05)	0.523	9 (17.6)	2.93(1.35-6.38)*	0.007
Gestational Hypertension	5381 (2.4)	7 (2.5)	1.07(0.48-2.42)	0.865	1 (1.1)	0.48(0.07-3.44)	0.462	2 (2.8)	1.32(0.32-5.41)	0.698	3 (5.9)	3.31(1.02-10.77)**	0.047
Mild Preeclampsia	6445 (2.9)	11 (3.8)	1.41(0.75-2.66)	0.291	2 (2.1)	0.85(0.21-3.49)	0.824	3 (4.2)	1.66(0.52-5.30)	0.39	5 (9.8)	3.32(1.18-9.35)*	0.023
Severe Preeclampsia	4330 (1.9)	6 (2.1)	1.21(0.50-2.53)	0.783	4 (4.3)	2.23(0.81-6.12)	0.120	3 (4.2)	2.36(0.74-7.50)	0.146	1 (2.0)	1.01(0.14-7.37)	0.991
Early Onset Preeclampsia	1299 (0.6)	3 (1.1)	1.45(0.36-5.87)	0.602	2 (2.1)	4.04(0.98-16.76)	0.054	2 (2.8)	6.00(1.47-24.59)*	0.013	-	-	-
HELLP	518 (0.2)	-	-	-	2 (2.1)	5.02(0.69-36-36)	0.11	-	-	-	1 (2.0)	8.54(1.18-61.92)	0.113
Eclampsia	191 (0.1)	-	-	-	1 (1.1)	12.47(1.73-89.91)	0.078	-	-	-	-	-	-

WWE = Women with Epilepsy
AED = Antiepileptic Drug
LTG = Lamotrigine
CBZ = Carbamazepine
VPA = Valproic acid
LEV = Levetiracetam
OR = Odds Ratio
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Pre-existing diseases, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking or BMI >30kg/m^2

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		4
Objectives	3	State specific objectives, including any prespecified hypotheses		4
Methods				
Study design	4	Present key elements of study design early in the paper		5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*5-6*
Bias	9	Describe any efforts to address potential sources of bias		5-7
Study size	10	Explain how the study size was arrived at		4-5

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	9 (Table 1)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9 (Table 2 and 3)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	(Table 2 and 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway

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Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway

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Hypertensive pregnancy complications in women with epilepsy

Abstract

Objectives:

To estimate the risk of hypertensive pregnancy complications in women with epilepsy, with and without antiepileptic drugs, and assess the risk associated with the four most common antiepileptic drugs.

Design:

A population-based cohort study using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database. Women with epilepsy with and without antiepileptic drugs were compared to women without epilepsy.

Setting:

Norway, 2004-2012.

Participants:

All first pregnancies of women with epilepsy and women without epilepsy were included.

Primary and secondary outcome measures:

Main outcome measures were hypertensive pregnancy complications: a compound variable of any hypertensive disorder, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome.

Results:

In total 1778 pregnancies in women with epilepsy and 221 662 in women without epilepsy were analysed. 682 of the women with epilepsy used antiepileptic drugs, the most common in monotherapy being: lamotrigine (N=280), carbamazepine (N=94), levetiracetam (N=71), and valproate (N=51). There was an increased risk of any hypertensive disorder in women with epilepsy (adjusted odds ratio [aOR]: 1.2, 95% CI 1.0-1.5) and in the subcategory using valproat (aOR: 2.9: 95% CI: 1.3-6.4). The most frequent hypertensive complication was mild

preeclampsia and the risk was increased in women with epilepsy (aOR: 1.4, 95% CI: 1.1-1.8) and women with epilepsy with valproat (aOR: 3.3: 95% CI: 1.2-9.4).

Conclusions:

Women with epilepsy have an increased risk of mild preeclampsia, but not for the severe types of hypertensive pregnancy complications. Lamotrigine and levetiracetam do not predispose for mild preeclampsia, whereas valproate was associated with an increased risk of mild preeclampsia.

Strengths and limitations of this study:

+ Large population based national cohort with data from compulsory and reliable national health registries
+ Only first pregnancies were included to avoid bias from recurrent events
+ We have studied type and severity of hypertensive complications in pregnancy and associations with use of specific antiepileptic drugs.
– We had no data on type of epilepsy or seizure activity

Funding

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Competing interests:

None of the authors have any conflict of interest to disclose.

Hypertensive pregnancy complications in women with epilepsy

Introduction

Epilepsy is the most common neurologic disorder requiring continuous drug treatment during pregnancy, and 30 - 70% of pregnant women with epilepsy (WWE) use antiepileptic drugs (AEDs).[1-4] Consequences of maternal AED use during pregnancy for fetal malformations and early childhood development have been focused.[5-8] In contrast, potential effects of epilepsy and specific AEDs on the pregnancy have been less studied. Optimal therapy in epilepsy is a balance between seizure suppression and side-effects. For women in fertile age, potential AED effects for the fetus as well as on the pregnancy should be of the highest relevance.

Hypertensive pregnancy complications include multiple diagnoses with different risks and implications for fetal and maternal outcomes. Hypertensive pregnancy complications represent a major contributor to global maternal mortality. [9] Most previous studies, including a recent meta-analysis, have found an increased risk of total hypertensive complications in WWE but these studies have not differentiated between the specific hypertensive disorders and therefor the burden of disease in WWE is uncertain. [2, 3, 10-14] Studies on the effect of specific AEDs on pregnant women with epilepsy have been limited by small sample size, selection bias, and lack of detailed information on hypertensive disorders.[2, 3, 10-13, 15] Recently, a small cohort study found an increased risk of preeclampsia in WWE with the newer AED lamotrigine.[3] Some studies have also suggested an increased preeclampsia risk with the older AEDs, carbamazepine and valproate.[12, 13] Many AED work by blocking ion channels, enhancing gamma-aminobutyric acid receptors or blocking glutamate receptors, and they stabilize and inactivate neurons. Valproate can induce endocrine changes and metabolic syndrome in WWE and possibly also hypertensive complications in pregnancy.[16] No other AED mode of action is known to pose any increased risk for hypertension or preeclampsia.

Preferred drugs and drugs to be avoided in pregnancy have not been identified, despite an increased use in young women of the newer AEDs lamotrigine and levetiracetam.[17, 18]

The aim of the present study was to estimate the risk of specified hypertensive pregnancy complications in WWE with and without use of AEDs, and to specifically define the risk for the four most common AEDs. This is necessary to guide optimal AED treatment in young women before and during pregnancy.

Hypertensive pregnancy complications in women with epilepsy

Materials and Methods

We used data from the compulsory, population-based Medical Birth Registry of Norway (MBRN) collected during 2004-2012. The notification form of the MBRN was unchanged in that period. MBRN includes data on maternal and paternal social factors, maternal health prior to and during pregnancy including chronic diseases such as epilepsy, complications and interventions during pregnancy and birth, perinatal outcome and complications in the children. Data are prospectively registered throughout pregnancy, delivery and postpartum period. All data are forwarded to the MBRN by the attending midwife or obstetrician. All pregnancies from 12 weeks gestation are recorded. The registry is routinely linked to the National Population Database to ensure notification of all births and deaths in the country. All Norwegian citizens are given a unique Social Security Number that enables linkage of data from various national data sources. Only first time pregnancies were included in this study, all singleton and multiple pregnancies at >22 weeks of gestation.

The Norwegian Prescription Database (NorPD), commenced in 2004, provides detailed data on all medications dispensed from pharmacies by prescription. Mandatory registration in NorPD of every dispensed medical prescription is made by the pharmacist. Statistics Norway provided data on maternal level of education.

Main outcome variables were a compound variable of any hypertensive disorder in pregnancy, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets). Exposure variables were a diagnosis of epilepsy and use of AEDs. All hypertensive disorders, except the compound variable, are reported in MBRN in specified checkboxes. Checkboxes are not mutually exclusive. Therefore, we used the most severe diagnosis to exclude double registration. Gestational hypertension was defined as persisting elevated blood pressure ≥140 mmHg systolic and/or ≥90mmHg diastolic occurring after 20 weeks of

gestation and without pre-existing hypertension.[19] Mild preeclampsia was defined as persisting elevated blood pressure ≥140 mmHg systolic and/or ≥90mmHg diastolic combined with proteinuria ≥ 0,3g per 24 hours (equivalent to ≥ +1 on urine test strips for protein excretion) occurring after 20 weeks of gestation. Severe preeclampsia was defined as blood pressure ≥160/110mmHg, clinical symptoms of preeclampsia, protein excretion ≥3 g per 24 hours or oliguria, and also included all cases of early onset preeclampsia (< 34 weeks), eclampsia or HELLP syndrome. Eclampsia was defined as generalized seizures occurring simultaneously with preeclampsia or hypertension and without other cause. Early onset preeclampsia was defined as preeclampsia with onset before 34 weeks of gestation. The compound variable of any hypertensive disorder was defined as the presence of any of these hypertensive disorders. Superimposed preeclampsia in women with pre-gestational hypertension was not specified but was included in the respective subcategories of hypertensive complications by severity.

Maternal epilepsy was defined by either ticking the specific checkbox in MBRN or adding this diagnosis in a blank space available for written text. Neither of these provided information about the type of epilepsy or seizure activity. The diagnosis was based on previous medical history and medical charts. The epilepsy diagnosis in MBRN has previously been found to be valid in 92.3 % of cases, having been confirmed in hospital medical records.[3]

NorPD provided exact data on dispensed AEDs and high-dose folic acid supplementation (4mg/day) including type of medication (according to ATC codes), dose, and time of administration. We defined AED use in pregnancy as dispensed drugs from the pharmacy in the time period coinciding with gestation, dated by ultrasound assessment. In cases with missing ultrasound dates, last menstrual period was used. We assessed drug dispensation also one and three months pre-conception. An a priori decision was made to primarily analyse the

four most commonly used AEDs in monotherapy in order to obtain large enough groups and exclude interference of polytherapy. Information about AED use in pregnancy is also recorded in MBRN on the notification form in an available blank space for written text. This information was used to validate the AED use obtained from MBRN compared to NorPD. Positive predictive values for AED data in MBRN were calculated by matching with confirmed AED dispensation in NorPD during pregnancy. The positive predictive values were 0.94 for lamotrigine, 0.82 for carbamazepine, 0.95 for levetiracetam and 0.84 for valproate, providing acceptable registration.

Socio-demographic and background data included maternal age (≤19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years and ≥40 years), maternal educational level (≤10 years, 11-13 years, ≥14 years), other chronic disease (kidney disease, hypertension, diabetes mellitus), multifetal pregnancies, high pre-gestational body mass index (BMI) (BMI ≥30kg/m²), smoking during pregnancy, and use of folic acid supplementation in standard dose (0,4mg/day). The BMI variable was only available from 2006 onwards. Data on ethnicity and marital status were not available for this study.

We further categorized WWE by AED-treatment; all AEDs, no AEDs, AED polytherapy, and the four most common AEDs. Outcome variables for specific AEDs were analysed only in WWE with monotherapy. WWE using other than the four most common AEDs were identified and excluded from the analyses where appropriate. WWE and all treatment subcategories were compared with women without epilepsy. WWE with AED treatment were also compared to WWE without AEDs.

For binary outcomes, proportions and crude odds ratios (OR) were calculated using contingency tables. P-values were calculated using Fisher's exact test. Continuous variables (background variables) were analysed with independent sample t-tests. Statistical significance was defined as non-overlapping 95% confidence intervals (95% CI) and two sided p-values <

0.05. All statistical analyses were performed with IBM SPSS (Statistical Package for Social Sciences) version 22.0 or later.

We used logistic regression to adjust for possible confounding by maternal age, educational level, multifetal pregnancy, use of folic acid supplements, and other relevant chronic diseases (pre-existing hypertension, pre-existing kidney disease, and pre-existing diabetes mellitus). The covariates BMI (only registered since 2006) and smoking were restrained by missing cases and therefore studied with stratification-based sensitivity analyses applied on all results and not included in the final logistic regression models. The impact of other relevant chronic diseases was similarly analysed further with stratification-based sensitivity analyses.

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Patient involvement

The Norwegian Epilepsy Association provided input to the research questions in this study.

Results

223 440 first time pregnancies were eligible after exclusion of multipara pregnancies (309 364), missing personal identification number (1 514, 0.7% [foreigners or immigrants without residence permit]), and pregnancies <23 gestational weeks (340, 0.2%). There were 1778 WWE (0.79 %), of whom 682 (38.4 % of WWE) used AEDs either in monotherapy (554 women) or in polytherapy (128 women). The most common AEDs used as monotherapy were lamotrigine (280 women, 50.5 % of all monotherapies), carbamazepine (94 women, 17.0 %), levetiracetam (71 women, 12.8 %), and valproate (51 women, 9.2 %). Other AEDs in monotherapy were used by 58 WWE. Maternal characteristics are shown in Table 1.

Table 1. Maternal characteristics. First pregnancies as recorded in Medical Birth Registry of Norway (2004-2012).

N=223440	Women without Epilepsy	WWE		WWE without AED		W
	N=221662	N=1778		N=1096		
		N (%)	p - value	N (%)	p - value	N (
Maternal age						
<19 years	10519 (4.7)	116 (6.5)	0.001	82 (7.5)	<0.001	34 (
20-24 years	52 857 (23.8)	475 (26.7)	0.005	310 (28.3)	0.001	165 (
25-29 years	82 004 (37.0)	564 (31.7)	<0.001	332 (30.3)	<0.001	232 (
30-34 years	55 199 (24.9)	466 (26.2)	0.205	273 (24.9)	1	193 (
35-39 years	17 992 (8.1)	124 (7.0)	0.083	78 (7.1)	0.245	46 (
≥40 years	3091 (1.4)	33 (1.9)	0.099	21 (1.9)	0.153	12 (
Educational level						
0-10 years	31 241 (14.1)	367 (20.6)	<0.001	219 (20.0)	<0.001	148 (
11-13 years	117 063 (52.8)	950 (53.4)	0.616	576 (52.6)	0.88	374 (
≥14 years	23 732 (10.7)	118 (6.6)	<0.001	73 (6.7)	<0.001	45 (
Other	7 659 (3.5)	39 (2.2)	0.004	29 (2.6)	0.162	10 (
Fetal plurality						
Multifetal	4 113 (1.9)	26 (1.5)	0.253	21 (1.9)	0.837	5 (0
Gestational age						
Mean (days)	278.4	277.3	0.002	277.1	0.006	27

Hypertensive pregnancy complications in women with epilepsy

Birth weight						
Mean (grams)	3414.4	3381.2	0.019	3363.5	0.004	341
Body Mass Index						
>30 kg/m2 (form 2006)	60 232 (23.9)	508 (24.6)	0.001	291 (24.5)	0.056	217 (
Smoking						
Yes	27 898 (12.6)	322 (18.1)	<0.001	215 (19.6)	<0.001	107 (
Preexisting disease						
Hypertension, Kidney Disease, Diabetes	4 117 (1.9)	59 (3.3)	<0.001	31 (2.8)	0.02	28 (
Folic acid supplementation						
Before pregnancy	55 168 (24.9)	563 (33.4)	<0.001	303 (27.6)	0.038	290 (
During pregnancy	139 157 (62.8)	1 266 (71.2)	<0.001	723 (66.0)	0.031	543 (
High dose	2174 (1.0)	362 (20.4)	<0.001	27 (2.5)	<0.001	312 (

WWE = Women with Epilepsy
AED = Antiepileptic Drug

The adjusted odds ratio (aOR) of the compound variable any hypertensive disorder was increased in WWE (aOR 1.2, 95% CI: 1.0-1.5) compared to women without epilepsy. However, the occurrence of any hypertensive disorder in neither the group WWE with AED nor the group WWE without AED differed significantly from women without epilepsy when examined separately.

The majority of hypertensive complications were mild preeclampsia (Table 2).

Table 2. Hypertensive pregnancy complications in WWE, WWE with and without AED.

N = 223440	**Women without Epilepsy**	**WWE**			**WWE without AED**	
	N= 221662	**N= 1778**			**N= 1096**	
	N (%)	N (%)	aOR (95% CI)	p - value	N (%)	aOR (95% CI)
Any Hypertensive Disorder	16542 (7.5)	158 (8.9)	1.23(1.03-1.48)*	0.022	93 (8.5)	1.21(0.96-1.53)
Gestational Hypertension	5381 (2.4)	43 (2.4)	1.04(0.75-1.45)	0.817	22 (2.0)	0.90(0.57-1.43)
Mild Preeclampsia	6445 (2.9)	68 (3.8)	1.42 (1.10-1.84)	0.007	42 (3.8)	1.44(1.04-2.00)***
Severe Preeclampsia	4330 (1.9)	46 (2.6)	1.30(0.97-1.75)	0.081	29 (2.6)	1.32(0.91-1.92)

Hypertensive pregnancy complications in women with epilepsy

Early Onset Preeclampsia	1299 (0.6)	19 (1.1)	1.69(1.01-2.82)**	0.047	11 (1.0)	1.67(0.86-3.23)
HELLP	518 (0.2)	6 (0.3)	1.18(0.44-3.17)	0.743	2 (0.2)	0.97(0.24-3.91)
Eclampsia	191 (0.1)	3 (0.2)	2.18(0.69-6.84)	0.183	2 (0.2)	2.35(0.58-9.49)

WWE = Women with Epilepsy
AED = Antiepileptic Drug
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Other relevant chronic disease, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking or BMI >30kg/m^2
*** Not significant in sensitivity analyses when including other relevant diseases

The risk of mild preeclampsia was significantly increased in WWE (aOR: 1.4, 95% CI: 1.1-1.8) and in WWE without AED exposure (aOR: 1.4, 95% CI: 1.0-2.0) compared to women without epilepsy. For WWE with AED the risk of mild preeclampsia was not significantly increased although the prevalence was the same as for both WWE and WWE without AEDs. For WWE there was a marginally significant risk of early onset preeclampsia (aOR: 1.7, 95% CI: 1.0-2.8). This risk disappeared after stratification and when including smoking or other relevant chronic diseases in sensitivity analyses. Mild preeclampsia was therefore the only specified hypertensive disorder increased in WWE. There was no significant difference for any of the outcomes when WWE with AEDs were compared to WWE without AED. There was no significantly increased risk of gestational hypertension, severe preeclampsia, HELLP or eclampsia when WWE, WWE with and WWE without AED were compared to women without epilepsy.

WWE with valproate monotherapy had an increased risk of any hypertensive complication (aOR: 2.9, 95% CI: 1.4-6.4), gestational hypertension (aOR: 3.3, 95% CI: 1.0-10.8), and mild preeclampsia (aOR: 3.3, 95% CI: 1.2-9.4) compared to women without epilepsy (Table 3).

Table 3. Hypertensive pregnancy complications in WWE with specified AEDs.

N=223440	**Women without Epilepsy**	**WWE with lamotrigine**	**WWE with carbamazepine**	
	N=221662	**N=280**	**N=94**	

Hypertensive pregnancy complications in women with epilepsy

	N (%)	N (%)	aOR (95% CI)	p-value	N (%)	aOR (95% CI)	p-value	N (%)
Any Hypertensive Disorder	16542 (7.5)	25 (8.9)	1.20(0.76-1.88)	0.434	7 (7.4)	0.97(0.42-2.25)	0.946	7 (9.9)
Gestational Hypertension	5381 (2.4)	7 (2.5)	1.07(0.48-2.42)	0.865	1 (1.1)	0.48(0.07-3.44)	0.462	2 (2.8)
Mild Preeclampsia	6445 (2.9)	11 (3.8)	1.41(0.75-2.66)	0.291	2 (2.1)	0.85(0.21-3.49)	0.824	3 (4.2)
Severe Preeclampsia	4330 (1.9)	6 (2.1)	1.21(0.50-2.53)	0.783	4 (4.3)	2.23(0.81-6.12)	0.120	3 (4.2)
Early Onset Preeclampsia	1299 (0.6)	3 (1.1)	1.45(0.36-5.87)	0.602	2 (2.1)	4.04(0.98-16.76)	0.054	2 (2.8)
HELLP	518 (0.2)	-	-	-	2 (2.1)	5.02(0.69-36-36)	0.11	-
Eclampsia	191 (0.1)	-	-	-	1 (1.1)	12.47(1.73-89.91)	0.078	-

WWE = Women with Epilepsy
AED = Antiepileptic Drug
OR = Odds Ratio
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Pre-existing diseases, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking or BMI >30kg/m^2

There was no increased risk of hypertensive complications for any other AEDs used in monotherapy.

The association between early onset preeclampsia and WWE disappeared when applying sensitivity analyses for smoking (182 478 women). Sensitivity analyses for BMI >30kg/m^2 included 60 740 women and the association for any hypertensive disorder disappeared for WWE, while the risk of mild preeclampsia increased (aOR: 1.8, 95% CI: 1.1-2.9). All increased risks for WWE with valproate disappeared when sensitivity analyses with BMI > 30kg/m^2 was performed. Separate analyses of women with BMI >30kg/m^2 only, showed no significant differences for any of the outcome variables when WWE, WWE with AED, and WWE without AED were compared to women without epilepsy. For women with BMI > 30kg/m^2, WWE with valproate had a higher prevalence of mild preeclampsia (16.7 %) than women without epilepsy (6.7 %). This difference was not significant, but the number of cases was low. BMI > 30kg/m^2 and other relevant chronic diseases had no significant interactions with epilepsy in logistic regression analyses. However, these variables had more impact on all hypertensive outcomes than a diagnosis of epilepsy. The impact of standard folic acid and of high-dose folic acid supplementation was examined in all population subcategories. There

were no significant differences among WWE for any of the hypertensive outcomes between use and no use of such supplementations.

When AED use in NorDP data was assessed one and three months before conception, the total AED population remained unchanged. 95% of WWE with AED in NorPD had more than one dispensation during pregnancy, illustrating continuous use throughout pregnancy as one dispensation usually corresponds to more than three months use.

Discussion

We found an increased risk of mild preeclampsia in WWE. The specified newer AEDs, lamotrigine and levetiracetam, used in monotherapy did not predispose for this complication. WWE on valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs. WWE, with and without AEDs, did not have an increased risk of gestational hypertension, severe preeclampsia, early onset preeclampsia, HELLP or eclampsia when compared to women without epilepsy.

The present study shows that most WWE, and in particular when treated with the newer AEDs, do not develop hypertensive complications. WWE with AED and WWE without AED had the same prevalence of mild preeclampsia but only WWE without AED had a significantly increased risk. This probably reflects marginal differences influenced by sample size. Cardiovascular risk factors (smoking, BMI > 30kg/m^2, pre-existing kidney disease, hypertension and diabetes) were relevant for hypertensive complications in WWE. The mechanism for the increased risk of hypertensive complications in WWE in first pregnancies could therefore be partly mediated by modifiable external risk factors and comorbidity.

The specific risk in WWE on valproate was linked to high BMI. Weight gain and metabolic syndrome represent side-effects of valproate.[16] Our study does not support any additional mechanism for valproate associated mild preeclampsia. When pregnancies with BMI > 30 kg/m² were analysed separately, WWE with valproate had a high prevalence of mild preeclampsia, but the increased risk was not significant, possibly due to few cases. A previous study showed increased risk of preeclampsia in women on valproate but this was not confirmed by later studies.[3, 12, 13] Valproate can induce endocrine changes and polycystic ovary syndrome in WWE and polycystic ovary syndrome is associated with hypertensive pregnancy complications.[16, 20-22] Polycystic ovary syndrome is also associated with overweight so endocrine factors could be important for our findings. Valproate increases the

risk of malformations in children exposed during pregnancy.[6, 23] Because of this, as well as delayed neurodevelopment, The European Medicines Agency has strengthened the advice not to prescribe valproate to WWE in fertile age.[24] Valproate is therefore not first line treatment in pregnancy. The observed valproate associated mild preeclampsia could represent bias through confounding by indication, although we would expect valproate to be avoided in women without other risk factors than epilepsy.

The newer AEDs, lamotrigine and levetiracetam, were not associated with increased risk of mild preeclampsia, and lamotrigine did not increase hypertensive pregnancy complications in general. A small study has previously reported an increased risk of preeclampsia in WWE on lamotrigine.[3] Lamotrigine has been considered a preferred option for WWE in need of AED treatment because children exposed to lamotrigine in pregnancy have a lower rate of malformations and better cognitive function than after exposure to other AEDs.[5, 6, 8] The combination of a low rate of adverse fetal effects and no increased risk of hypertensive complications supports the use of lamotrigine in WWE before and during pregnancy. Levetiracetam is a potent, broad-spectrum AED with low rate of adverse fetal outcomes.[5] Levetiracetam use among pregnant WWE is increasing, but levetiracetam is less studied than lamotrigine and maternal safety during pregnancy is not well documented.[5, 6, 25] To our knowledge, there are no previous studies on hypertensive complications in WWE with levetiracetam in pregnancy.

Mild, but not more severe preeclampsia was increased among WWE. Proactive management and close surveillance of WWE could explain why the mild disease did not proceed further. Similarly, the close surveillance of WWE could have increased the detection of mild preeclampsia. Ascertainment bias may have influenced other outcomes as well. Alternatively, mild and severe hypertensive complications in pregnancies could have different underlying pathophysiological mechanisms in WWE.

Strengths of our study are that we have analysed first pregnancies only, have specified the types of hypertensive complications, and have analysed WWE on specific AEDs in monotherapy only. Parity is a complex variable in reproductive epidemiology and may lead to bias as the risk of hypertensive complications changes significantly in subsequent pregnancies.[26-28] Our large and unselected nationwide cohort enabled assessment of effects of individual AEDs in monotherapy. Data was linked to the NorPD that showed the exact drug dispensation during pregnancy. The registration and standardized data collection in the national databases that were used provide information of high validity and include important possible confounders for hypertensive disorders.[3, 29] The prevalence of WWE in our population was 0.79 % and the incidence of preeclampsia was 5.4 %, both in accordance with previous population-based studies.[1, 2, 4, 14, 30, 31]

A limitation of this study was the possible inclusion of previous and non-active epilepsy, and also of women with undefined seizures in the epilepsy group. This could have increased the total epilepsy population and thereby masking some effects in our group with untreated epilepsy. The MBRN did not provide data on type of epilepsy or seizure activity. However, a small study did not find any association between seizure activity and hypertensive complications in pregnancy.[3] Women without epilepsy but using AEDs for other conditions were not excluded in our study. This group constituted 0.1 % in the control population and did not affect the outcomes. Psychiatric and pain conditions are the main reasons for AED use in women without epilepsy. NorPD records dispensed medications which may leave room for variation in actual compliance. As 95% of WWE with AED collected more than one dispensation during their pregnancy, we presume that the patients used their AED as prescribed.

BMI above or below 30 kg/m² influenced the results for WWE. MBRN has only registered BMI since 2006, thus it was not possible to control for this variable in the complete

population. A previous study has indicated an increased risk for preeclampsia in WWE with BMI > 25 kg/m².[32] High BMI represents a risk factor for hypertensive disorders and there is a global rise in BMI in young women.[33] However, a previous study on MBRN data has shown a slight decrease of preeclampsia in the time period for our study.[30] A decrease in preeclampsia is most likely also affecting WWE and thereby possibly narrowing the differences between WWE and women without epilepsy.

HELLP, eclampsia and early onset preeclampsia are rare hypertensive manifestations. Lack of events in some of our subgroups can be insufficient to prove significance, despite our large sample size. Differences in statistical outcome across treatment subcategories for WWE can similarly have been influenced by sample size. Our study lacks information on ethnicity and marital status, not released by MBRN due to ethical considerations.

Conclusion

Mild preeclampsia was the only hypertensive complication to be increased in first pregnancies of WWE. This is of clinical importance for WWE since mild preeclampsia, in contrast to severe forms of preeclampsia, is not associated with increased maternal or fetal morbidity or mortality in pregnancy.[19] WWE have previously been considered as high risk parturients by having a significant increase in several adverse pregnancy outcomes, including hypertensive complications.[2, 3, 10, 11] Our study shows that most WWE do not develop hypertensive complications. WWE on the newer AEDs, lamotrigine and levetiracetam in particular, do not have an additional risk for severe hypertensive complications. A healthcare system focusing on risk assessment, prevention of modifiable risk factors and modern treatment options should be the key to a further decrease in hypertensive complications in pregnant WWE.

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Details of Ethics Approval:

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Contribution to Authorship:

KCD conceived and designed the study, analysed the data and drafted the manuscript. IB provided input on design, interpretation and presentation of the study. NHM provided input on design and analyses, interpretation of analyses and critically revised the manuscript. NEG

conceived and designed the study, and critically revised the presentation and discussion of the results in the manuscript. The final manuscript was approved by all authors.

Data sharing statement:

Data from Medical Birth Registry of Norway and Norwegian Prescription Database are available at Norwegian Institute of Public Health.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		4
Objectives	3	State specific objectives, including any prespecified hypotheses		4
Methods				
Study design	4	Present key elements of study design early in the paper		5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*5-6*
Bias	9	Describe any efforts to address potential sources of bias		5-7
Study size	10	Explain how the study size was arrived at		4-5

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	9 (Table 1)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9 (Table 2 and 3)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	(Table 2 and 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway

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Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway

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Short title:
Hypertensive pregnancy complications in women with epilepsy

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Hypertensive pregnancy complications in women with epilepsy

Abstract

Objectives:

To estimate the risk of hypertensive pregnancy complications in women with epilepsy, with and without antiepileptic drugs, and assess the risk associated with the four most common antiepileptic drugs.

Design:

A population-based cohort study using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database. Women with epilepsy with and without antiepileptic drugs were compared to women without epilepsy.

Setting:

Norway, 2004-2012.

Participants:

All first pregnancies of women with epilepsy and women without epilepsy were included.

Primary and secondary outcome measures:

Main outcome measures were hypertensive pregnancy complications: a compound variable of any hypertensive disorder, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome.

Results:

In total 1778 pregnancies in women with epilepsy and 221 662 in women without epilepsy were analysed. 682 of the women with epilepsy used antiepileptic drugs, the most common in monotherapy being: lamotrigine (N=280), carbamazepine (N=94), levetiracetam (N=71), and valproate (N=51). There was an increased risk of any hypertensive disorder in women with epilepsy (adjusted odds ratio [aOR]: 1.2, 95% CI 1.0-1.5) and in the subcategory using valproat (aOR: 2.9: 95% CI: 1.3-6.4). The most frequent hypertensive complication was mild

preeclampsia and the risk was increased in women with epilepsy (aOR: 1.4, 95% CI: 1.1-1.8) and women with epilepsy with valproat (aOR: 3.3: 95% CI: 1.2-9.4).

Conclusions:

Women with epilepsy have an increased risk of mild preeclampsia, but not for the severe types of hypertensive pregnancy complications. Lamotrigine and levetiracetam do not predispose for mild preeclampsia, whereas valproate was associated with an increased risk of mild preeclampsia.

Strengths and limitations of this study:

+ Large population based national cohort with data from compulsory and reliable national health registries
+ Only first pregnancies were included to avoid bias from recurrent events
+ We have studied type and severity of hypertensive complications in pregnancy and associations with use of specific antiepileptic drugs.
– We had no data on type of epilepsy or seizure activity

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Competing interests:

None of the authors have any conflict of interest to disclose.

Hypertensive pregnancy complications in women with epilepsy

Introduction

Epilepsy is the most common neurologic disorder requiring continuous drug treatment during pregnancy, and 30 - 70% of pregnant women with epilepsy (WWE) use antiepileptic drugs (AEDs).[1-4] Studies have focused on consequences of epilepsy and maternal AED use during pregnancy for fetal malformations and child development.[5-8] In contrast, potential effects of epilepsy and specific AEDs on the pregnancy have been less studied. Optimal therapy in epilepsy is a balance between seizure suppression and side-effects. For women in fertile age, potential AED effects for the fetus as well as on the pregnancy should be of the highest interest.

Hypertensive pregnancy complications include multiple diagnoses with different risks and implications for fetal and maternal outcomes. Hypertensive pregnancy complications represent a major contributor to global maternal mortality. [9] Most previous studies, including a recent meta-analysis, have found an increased risk of total hypertensive complications in WWE but these studies have not differentiated between the specific hypertensive disorders and therefor the burden of disease in WWE is uncertain. [2, 3, 10-14] Studies on the effect of specific AEDs on pregnant women with epilepsy have been limited by small sample size, selection bias, and lack of detailed information on hypertensive disorders.[2, 3, 10-13, 15] Recently, a small cohort study found an increased risk of preeclampsia in WWE with the newer AED lamotrigine.[3] Some studies have also suggested an increased preeclampsia risk with the older AEDs, carbamazepine and valproate.[12, 13] Many AED work by blocking ion channels, enhancing gamma-aminobutyric acid receptors or blocking glutamate receptors, and they stabilize and inactivate neurons. Valproate can induce endocrine changes and metabolic syndrome in WWE and possibly also hypertensive complications in pregnancy.[16] No other AED mode of action is known to pose any increased risk for hypertension or preeclampsia.

Preferred drugs and drugs to be avoided in pregnancy have not been identified, despite an increased use in young women of the newer AEDs lamotrigine and levetiracetam.[17, 18]

The aim of the present study was to estimate the risk of specified hypertensive pregnancy complications in WWE with and without use of AEDs, and to specifically define the risk for the four most common AEDs. This is necessary to guide optimal AED treatment in young women before and during pregnancy.

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Materials and Methods

We used data from the compulsory, population-based Medical Birth Registry of Norway (MBRN) collected during 2004-2012. The notification form of the MBRN was unchanged in that period. MBRN includes data on maternal and paternal social factors, maternal health prior to and during pregnancy including chronic diseases such as epilepsy, complications and interventions during pregnancy and birth, perinatal outcome and complications in the children. Data are prospectively registered throughout pregnancy, delivery and postpartum period. All data are forwarded to the MBRN by the attending midwife or obstetrician. All pregnancies from 12 weeks gestation are recorded. The registry is routinely linked to the National Population Database to ensure notification of all births and deaths in the country. All Norwegian citizens are given a unique Social Security Number that enables linkage of data from various national data sources. Only first time pregnancies were included in this study, all singleton and multiple pregnancies at >22 weeks of gestation.

The Norwegian Prescription Database (NorPD), commenced in 2004, provides detailed data on all medications dispensed from pharmacies by prescription. Mandatory registration in NorPD of every dispensed medical prescription is made by the pharmacist. Statistics Norway provided data on maternal level of education.

Main outcome variables were a compound variable of any hypertensive disorder in pregnancy, gestational hypertension, mild preeclampsia, severe preeclampsia, early onset preeclampsia, eclampsia, and HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets). Exposure variables were a diagnosis of epilepsy and use of AEDs. All hypertensive disorders, except the compound variable, are reported in MBRN in specified checkboxes. Checkboxes are not mutually exclusive. Therefore, we used the most severe diagnosis to exclude double registration. Gestational hypertension was defined as persisting elevated blood pressure ≥140 mmHg systolic and/or ≥90mmHg diastolic occurring after 20 weeks of

gestation and without pre-existing hypertension.[19] Mild preeclampsia was defined as persisting elevated blood pressure ≥140 mmHg systolic and/or ≥90mmHg diastolic combined with proteinuria ≥ 0,3g per 24 hours (equivalent to ≥ +1 on urine test strips for protein excretion) occurring after 20 weeks of gestation. Severe preeclampsia was defined as blood pressure ≥160/110mmHg, clinical symptoms of preeclampsia, protein excretion ≥3 g per 24 hours or oliguria, and also included all cases of early onset preeclampsia (< 34 weeks), eclampsia or HELLP syndrome. Eclampsia was defined as generalized seizures occurring simultaneously with preeclampsia or hypertension and without other cause. Early onset preeclampsia was defined as preeclampsia with onset before 34 weeks of gestation. The compound variable of any hypertensive disorder was defined as the presence of any of these hypertensive disorders. Superimposed preeclampsia in women with pre-gestational hypertension was not specified but was included in the respective subcategories of hypertensive complications by severity.

Maternal epilepsy was defined by either ticking the specific checkbox in MBRN or adding this diagnosis in a blank space available for written text. Neither of these provided information about the type of epilepsy or seizure activity. The diagnosis was based on previous medical history and medical charts. The epilepsy diagnosis in MBRN has previously been found to be valid in 92.3 % of cases, having been confirmed in hospital medical records.[3]

NorPD provided exact data on dispensed AEDs and high-dose folic acid supplementation (4mg/day) including type of medication (according to ATC codes), dose, and time of administration. We defined AED use in pregnancy as dispensed drugs from the pharmacy in the time period coinciding with gestation, dated by ultrasound assessment. In cases with missing ultrasound dates, last menstrual period was used. We assessed drug dispensation also one and three months pre-conception. An a priori decision was made to primarily analyse the

four most commonly used AEDs in monotherapy in order to obtain large enough groups and exclude interference of polytherapy. Information about AED use in pregnancy is also recorded in MBRN on the notification form in an available blank space for written text. This information was used to validate the AED use obtained from MBRN compared to NorPD. Positive predictive values for AED data in MBRN were calculated by matching with confirmed AED dispensation in NorPD during pregnancy. The positive predictive values were 0.94 for lamotrigine, 0.82 for carbamazepine, 0.95 for levetiracetam and 0.84 for valproate, providing acceptable registration. When AED use in NorDP data was assessed one and three months before conception, the total AED population remained unchanged. 95% of WWE with AED in NorPD had more than one dispensation during pregnancy, illustrating continuous use throughout pregnancy as one dispensation usually corresponds to more than three months use. Socio-demographic and background data included maternal age (≤19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years and ≥40 years), maternal educational level (≤10 years, 11-13 years, ≥14 years), other chronic disease (kidney disease, hypertension, diabetes mellitus), multifetal pregnancies, high pre-gestational body mass index (BMI) (BMI ≥30kg/m²), smoking during pregnancy, and use of folic acid supplementation in standard dose (0,4mg/day). The BMI variable was only available from 2006 onwards. Data on ethnicity and marital status were not available for this study.

We further categorized WWE by AED-treatment; all AEDs, no AEDs, AED polytherapy, and the four most common AEDs. Outcome variables for specific AEDs were analysed only in WWE with monotherapy. WWE using other than the four most common AEDs were identified and excluded from the analyses where appropriate. WWE and all treatment subcategories were compared with women without epilepsy. WWE with AED treatment were also compared to WWE without AEDs.

For binary outcomes, proportions and crude odds ratios (OR) were calculated using contingency tables. P-values were calculated using Fisher's exact test. Continuous variables (background variables) were analysed with independent sample t-tests. Statistical significance was defined as non-overlapping 95% confidence intervals (95% CI) and two sided p-values < 0.05. All statistical analyses were performed with IBM SPSS (Statistical Package for Social Sciences) version 22.0 or later.

We used logistic regression to adjust for possible confounding by maternal age, educational level, multifetal pregnancy, use of folic acid supplements, and other relevant chronic diseases (pre-existing hypertension, pre-existing kidney disease, and pre-existing diabetes mellitus). The covariates BMI (only registered since 2006) and smoking were restrained by missing cases and therefore studied with stratification-based sensitivity analyses applied on all results and not included in the final logistic regression models. The impact of other relevant chronic diseases was similarly analysed further with stratification-based sensitivity analyses.

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Patient involvement

The Norwegian Epilepsy Association provided input to the research questions in this study.

Results

223 440 first time pregnancies were eligible after exclusion of multipara pregnancies (309 364), missing personal identification number (1 514, 0.7% [foreigners or immigrants without residence permit]), and pregnancies <23 gestational weeks (340, 0.2%). There were 1778 WWE (0.79 %), of whom 682 (38.4 % of WWE) used AEDs either in monotherapy (554 women) or in polytherapy (128 women). The most common AEDs used as monotherapy were lamotrigine (280 women, 50.5 % of all monotherapies), carbamazepine (94 women, 17.0 %), levetiracetam (71 women, 12.8 %), and valproate (51 women, 9.2 %). Other AEDs in monotherapy were used by 58 WWE. WWE were younger, had lower educational level, were more often obese, smoked more often, and were more likely to have comorbidity compared to women without epilepsy. All maternal characteristics are shown in Table 1.

Table 1. Maternal characteristics. First pregnancies as recorded in Medical Birth Registry of Norway (2004-2012).

N=223440	Women without Epilepsy	WWE		WWE without AED		W
	N=221662	N=1778		N=1096		
		N (%)	p - value	N (%)	p - value	N (
Maternal age						
<19 years	10519 (4.7)	116 (6.5)	0.001	82 (7.5)	<0.001	34 (
20-24 years	52 857 (23.8)	475 (26.7)	0.005	310 (28.3)	0.001	165 (
25-29 years	82 004 (37.0)	564 (31.7)	<0.001	332 (30.3)	<0.001	232 (
30-34 years	55 199 (24.9)	466 (26.2)	0.205	273 (24.9)	1	193 (
35-39 years	17 992 (8.1)	124 (7.0)	0.083	78 (7.1)	0.245	46 (
≥40 years	3091 (1.4)	33 (1.9)	0.099	21 (1.9)	0.153	12 (
Educational level						
0-10 years	31 241 (14.1)	367 (20.6)	<0.001	219 (20.0)	<0.001	148 (
11-13 years	117 063 (52.8)	950 (53.4)	0.616	576 (52.6)	0.88	374 (
≥14 years	23 732 (10.7)	118 (6.6)	<0.001	73 (6.7)	<0.001	45 (
Other	7 659 (3.5)	39 (2.2)	0.004	29 (2.6)	0.162	10 (
Fetal plurality						
Multifetal	4 113 (1.9)	26 (1.5)	0.253	21 (1.9)	0.837	5 (0

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Gestational age						
Mean (days)	278.4	277.3	0.002	277.1	0.006	27
Birth weight						
Mean (grams)	3414.4	3381.2	0.019	3363.5	0.004	341
Body Mass Index						
>30 kg/m2 (form 2006)	60 232 (23.9)	508 (24.6)	0.001	291 (24.5)	0.056	217 (
Smoking						
Yes	27 898 (12.6)	322 (18.1)	<0.001	215 (19.6)	<0.001	107 (
Preexisting disease						
Hypertension, Kidney Disease, Diabetes	4 117 (1.9)	59 (3.3)	<0.001	31 (2.8)	0.02	28 (
Folic acid supplementation						
Before pregnancy	55 168 (24.9)	563 (33.4)	<0.001	303 (27.6)	0.038	290 (
During pregnancy	139 157 (62.8)	1 266 (71.2)	<0.001	723 (66.0)	0.031	543 (
High dose	2174 (1.0)	362 (20.4)	<0.001	27 (2.5)	<0.001	312 (

WWE = Women with Epilepsy
AED = Antiepileptic Drug

The adjusted odds ratio (aOR) of the compound variable any hypertensive disorder was increased in WWE (aOR 1.2, 95% CI: 1.0-1.5) compared to women without epilepsy. However, the occurrence of any hypertensive disorder in neither the group WWE with AED nor the group WWE without AED differed significantly from women without epilepsy when examined separately.

The majority of hypertensive complications were mild preeclampsia (Table 2).

Table 2. Hypertensive pregnancy complications in WWE, WWE with and without AED.

	Women without Epilepsy	**WWE**			**WWE without AED**		
N = 223440	**N= 221662**	**N= 1778**			**N= 1096**		
	N (%)	N (%)	aOR (95% CI)	p - value	N (%)	aOR (95% CI)	p

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Any Hypertensive Disorder	16542 (7.5)	158 (8.9)	1.23(1.03-1.48)*	0.022	93 (8.5)	1.21(0.96-1.53)
Gestational Hypertension	5381 (2.4)	43 (2.4)	1.04(0.75-1.45)	0.817	22 (2.0)	0.90(0.57-1.43)
Mild Preeclampsia	6445 (2.9)	68 (3.8)	1.42 (1.10-1.84)	0.007	42 (3.8)	1.44(1.04-2.00)***
Severe Preeclampsia	4330 (1.9)	46 (2.6)	1.30(0.97-1.75)	0.081	29 (2.6)	1.32(0.91-1.92)
Early Onset Preeclampsia	1299 (0.6)	19 (1.1)	1.69(1.01-2.82)**	0.047	11 (1.0)	1.67(0.86-3.23)
HELLP	518 (0.2)	6 (0.3)	1.18(0.44-3.17)	0.743	2 (0.2)	0.97(0.24-3.91)
Eclampsia	191 (0.1)	3 (0.2)	2.18(0.69-6.84)	0.183	2 (0.2)	2.35(0.58-9.49)

WWE = Women with Epilepsy
AED = Antiepileptic Drug
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Other relevant chronic disease, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking, BMI >30kg/m^2, or other relevant diseases
*** Not significant in sensitivity analyses when including other relevant diseases

The risk of mild preeclampsia was significantly increased in WWE (aOR: 1.4, 95% CI: 1.1-1.8) and in WWE without AED exposure (aOR: 1.4, 95% CI: 1.0-2.0) compared to women without epilepsy. For WWE with AED the risk of mild preeclampsia was not significantly increased although the prevalence was the same as for both WWE and WWE without AEDs. For WWE there was a marginally significant risk of early onset preeclampsia (aOR: 1.7, 95% CI: 1.0-2.8). This risk disappeared after stratification and when including smoking or other relevant chronic diseases in sensitivity analyses. Mild preeclampsia was therefore the only specified hypertensive disorder increased in WWE. There was no significant difference for any of the outcomes when WWE with AEDs were compared to WWE without AED. There was no significantly increased risk of gestational hypertension, severe preeclampsia, HELLP or eclampsia when WWE, WWE with and WWE without AED were compared to women without epilepsy.

WWE with valproate monotherapy had an increased risk of any hypertensive complication (aOR: 2.9, 95% CI: 1.4-6.4), gestational hypertension (aOR: 3.3, 95% CI: 1.0-10.8), and mild preeclampsia (aOR: 3.3, 95% CI: 1.2-9.4) compared to women without epilepsy (Table 3).

Table 3. Hypertensive pregnancy complications in WWE with specified AEDs.

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N=223440	Women without Epilepsy	WWE with lamotrigine			WWE with carbamazepine			
	N=221662	N=280			N=94			
	N (%)	N (%)	aOR (95% CI)	p-value	N (%)	aOR (95% CI)	p-value	N (%)
Any Hypertensive Disorder	16542 (7.5)	25 (8.9)	1.20(0.76-1.88)	0.434	7 (7.4)	0.97(0.42-2.25)	0.946	7 (9.9)
Gestational Hypertension	5381 (2.4)	7 (2.5)	1.07(0.48-2.42)	0.865	1 (1.1)	0.48(0.07-3.44)	0.462	2 (2.8)
Mild Preeclampsia	6445 (2.9)	11 (3.8)	1.41(0.75-2.66)	0.291	2 (2.1)	0.85(0.21-3.49)	0.824	3 (4.2)
Severe Preeclampsia	4330 (1.9)	6 (2.1)	1.21(0.50-2.53)	0.783	4 (4.3)	2.23(0.81-6.12)	0.120	3 (4.2)
Early Onset Preeclampsia	1299 (0.6)	3 (1.1)	1.45(0.36-5.87)	0.602	2 (2.1)	4.04(0.98-16.76)	0.054	2 (2.8)
HELLP	518 (0.2)	-	-	-	2 (2.1)	5.02(0.69-36-36)	0.11	-
Eclampsia	191 (0.1)	-	-	-	1 (1.1)	12.47(1.73-89.91)	0.078	-

WWE = Women with Epilepsy
AED = Antiepileptic Drug
OR = Odds Ratio
aOR = Adjusted Odds Ratio (Adjusted for maternal age, Educational level, Multifetal pregnancy, Pre-existing diseases, Folic acid supplementation)
95% CI = 95% Confidence Interval
*Not significant in sensitivity analyses when including BMI >30kg/m^2
**Not significant in sensitivity analyses when including smoking or BMI >30kg/m^2

There was no increased risk of hypertensive complications for any other AEDs used in monotherapy.

The association between early onset preeclampsia and WWE disappeared when applying sensitivity analyses for smoking (182 478 women). Sensitivity analyses for BMI >30kg/m^2 included 60 740 women and the association for any hypertensive disorder disappeared for WWE, while the risk of mild preeclampsia increased (aOR: 1.8, 95% CI: 1.1-2.9). All increased risks for WWE with valproate disappeared when sensitivity analyses with BMI > 30kg/m^2 was performed. Separate analyses of women with BMI >30kg/m^2 only, showed no significant differences for any of the outcome variables when WWE, WWE with AED, and WWE without AED were compared to women without epilepsy. For women with BMI > 30kg/m^2, WWE with valproate had a higher prevalence of mild preeclampsia (16.7 %) than women without epilepsy (6.7 %). This difference was not significant, but the number of cases was low. BMI > 30kg/m^2 and other relevant chronic diseases had no significant interactions with epilepsy in logistic regression analyses. However, these variables had more impact on all

hypertensive outcomes than a diagnosis of epilepsy. The impact of standard folic acid and of high-dose folic acid supplementation was examined in all population subcategories. There were no significant differences among WWE for any of the hypertensive outcomes between use and no use of such supplementations.

Discussion

We found an increased risk of mild preeclampsia in WWE. The specified newer AEDs, lamotrigine and levetiracetam, used in monotherapy did not predispose for this complication. Use of valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs. WWE, with and without AEDs, did not have an increased risk of gestational hypertension, severe preeclampsia, early onset preeclampsia, HELLP or eclampsia when compared to women without epilepsy.

The present study shows that most WWE, and in particular when treated with the newer AEDs, do not develop hypertensive complications. WWE with AED had comparable prevalence of mild preeclampsia to WWE without AED, but did not reach significance. This probably reflects marginal differences influenced by sample size. Cardiovascular risk factors (smoking, BMI > 30kg/m^2, pre-existing kidney disease, hypertension and diabetes) were relevant for hypertensive complications in WWE. The mechanism for the increased risk of hypertensive complications in WWE in first pregnancies could therefore be partly mediated by modifiable external risk factors and comorbidity.

The specific risk in WWE on valproate was linked to high BMI. Weight gain and metabolic syndrome represent side-effects of valproate.[16] Our study does not support any additional mechanism for valproate associated mild preeclampsia. When pregnancies with BMI > 30 kg/m² were analysed separately, WWE with valproate had a high prevalence of mild preeclampsia, but the increased risk was not significant, possibly due to few cases. A previous study showed increased risk of preeclampsia in women on valproate but this was not confirmed by later studies.[3, 12, 13] Valproate can induce endocrine changes and polycystic ovary syndrome in WWE and polycystic ovary syndrome is associated with hypertensive pregnancy complications.[16, 20-22] Polycystic ovary syndrome is also associated with overweight so endocrine factors could be important for our findings. Valproate increases the

risk of malformations in children exposed during pregnancy.[6, 23] Because of this, as well as delayed neurodevelopment, The European Medicines Agency has strengthened the advice not to prescribe valproate to WWE in fertile age.[24] Valproate is therefore not first line treatment in pregnancy. The observed valproate associated mild preeclampsia could represent bias through confounding by indication, although we would expect valproate to be avoided in women without other risk factors than epilepsy.

The newer AEDs, lamotrigine and levetiracetam, were not associated with increased risk of mild preeclampsia, and lamotrigine did not increase hypertensive pregnancy complications in general. A small study has previously reported an increased risk of preeclampsia in WWE on lamotrigine.[3] Lamotrigine has been considered a preferred option for WWE in need of AED treatment because children exposed to lamotrigine in pregnancy have a lower rate of malformations and better cognitive function than after exposure to other AEDs.[5, 6, 8] The combination of a low rate of adverse fetal effects and no increased risk of hypertensive complications supports the use of lamotrigine in WWE before and during pregnancy. Levetiracetam is a potent, broad-spectrum AED with low rate of adverse fetal outcomes.[5] Levetiracetam use among pregnant WWE is increasing, but levetiracetam is less studied than lamotrigine and maternal safety during pregnancy is not well documented.[5, 6, 25] To our knowledge, there are no previous studies on hypertensive complications in WWE with levetiracetam in pregnancy.

Mild, but not more severe preeclampsia was increased among WWE. Proactive management and close surveillance of WWE could explain why the mild disease did not progress further. Similarly, the close surveillance of WWE could have increased the detection of mild preeclampsia. Ascertainment bias may have influenced other outcomes as well. Alternatively, mild and severe hypertensive complications in pregnancies could have different underlying pathophysiological mechanisms in WWE.

Strengths of our study are that we have analysed first pregnancies only, have specified the types of hypertensive complications, and have analysed WWE on specific AEDs in monotherapy only. Parity is a complex variable in reproductive epidemiology and may lead to bias as the risk of hypertensive complications changes significantly in subsequent pregnancies.[26-28] Our large and unselected nationwide cohort enabled assessment of effects of individual AEDs in monotherapy. Data was linked to the NorPD that showed the exact drug dispensation during pregnancy. The registration and standardized data collection in the national databases that were used provide information of high validity and include important possible confounders for hypertensive disorders.[3, 29] The prevalence of WWE in our population was 0.79 % and the incidence of preeclampsia was 5.4 %, both in accordance with previous population-based studies.[1, 2, 4, 14, 30, 31]

A limitation of this study was the possible inclusion of previous and non-active epilepsy, and also of women with undefined seizures in the epilepsy group. This could have increased the total epilepsy population and thereby masking some effects in our group with untreated epilepsy. The MBRN did not provide data on type of epilepsy or seizure activity. However, a small study did not find any association between seizure activity and hypertensive complications in pregnancy.[3] Women without epilepsy but using AEDs for other conditions were not excluded in our study. This group constituted 0.1 % in the control population and did not affect the outcomes. Psychiatric and pain conditions are the main reasons for AED use in women without epilepsy. NorPD records dispensed medications which may leave room for variation in actual compliance. As 95% of WWE with AED collected more than one dispensation during their pregnancy, we presume that the patients used their AED as prescribed.

BMI above or below 30 kg/m² influenced the results for WWE. MBRN has only registered BMI since 2006, thus it was not possible to control for this variable in the complete

population. A previous study has indicated an increased risk for preeclampsia in WWE with BMI > 25 kg/m².[32] High BMI represents a risk factor for hypertensive disorders and there is a global rise in BMI in young women.[33] However, a previous study on MBRN data has shown a slight decrease of preeclampsia in the time period for our study.[30] A decrease in preeclampsia is most likely also affecting WWE and thereby possibly narrowing the differences between WWE and women without epilepsy.

HELLP, eclampsia and early onset preeclampsia are rare hypertensive manifestations. Lack of events in some of our subgroups can be insufficient to prove significance, despite our large sample size. Differences in statistical outcome across treatment subcategories for WWE can similarly have been influenced by sample size. Our study lacks information on ethnicity and marital status, not released by MBRN due to ethical considerations.

Conclusion

Mild preeclampsia was the only hypertensive complication to be increased in first pregnancies of WWE. This is of clinical importance for WWE since mild preeclampsia, in contrast to severe forms of preeclampsia, is not associated with increased maternal or fetal morbidity or mortality in pregnancy.[19] WWE have previously been considered as high risk parturients by having a significant increase in several adverse pregnancy outcomes, including hypertensive complications.[2, 3, 10, 11] Our study shows that most WWE do not develop hypertensive complications. WWE on the newer AEDs, lamotrigine and levetiracetam in particular, do not have an additional risk for severe hypertensive complications. A healthcare system focusing on risk assessment, prevention of modifiable risk factors and modern treatment options should be the key to a further decrease in hypertensive complications in pregnant WWE.

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Details of Ethics Approval:

This study was approved by the Regional Ethics Committee (REK 2013/186) and the Norwegian Data Protection Authority. The MBRN, NorPD and Statistics Norway approved the use of data. Use of Norwegian national register data does not require consent from the participants.

Contribution to Authorship:

KCD conceived and designed the study, analysed the data and drafted the manuscript. IB provided input on design, interpretation and presentation of the study. NHM provided input on design and analyses, interpretation of analyses and critically revised the manuscript. NEG

conceived and designed the study, and critically revised the presentation and discussion of the results in the manuscript. The final manuscript was approved by all authors.

Data sharing statement:

Data from Medical Birth Registry of Norway and Norwegian Prescription Database are available at Norwegian Institute of Public Health.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found		2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported		4
Objectives	3	State specific objectives, including any prespecified hypotheses		4
Methods				
Study design	4	Present key elements of study design early in the paper		5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable		5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		*5-6*
Bias	9	Describe any efforts to address potential sources of bias		5-7
Study size	10	Explain how the study size was arrived at		4-5

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	9 (Table 1)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9 (Table 2 and 3)*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	(Table 2 and 3)
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.