Hypertension

PREECLAMPSIA

Clustering Longitudinal Blood Pressure Trajectories to Examine Heterogeneity in Outcomes Among Preeclampsia Cases and Controls

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ABSTRACT: Preeclampsia is a heterogeneous disease characterized by new onset of hypertension along with signs of organ damage, affects 2% to 8% of pregnancies, and can result in serious complications to the mother and her child. There is little empirical evidence on the clinical importance of differences in blood pressure trajectories over the course of pregnancy, particularly in pregnancies affected by preeclampsia. We undertook an investigation of longitudinal changes in gestational blood pressure in a nested case-control study of preeclampsia in MoBa (Norwegian Mother, Father and Child Cohort Study). We included 1906 validated preeclampsia cases and 1413 validated controls. We derived blood pressure trajectory clusters using longitudinal k-means clustering and examined demographic and early-pregnancy predictors and birth outcomes, in relation to clusters. Maternal age, prepregnancy body mass index, and parity were substantially different across blood pressure clusters of cases. Pregnancy outcomes, including preterm birth, small for gestational age, and birthweight *Z* score, were meaningfully worse for individuals with a more rapid increase in blood pressure, as well as for individuals with a high starting blood pressure. For example, risk of preterm birth was 11-fold to 35-fold higher for steep and high trajectory clusters, and risk of small for gestational age was 2-fold higher compared with the reference cluster. Future studies may leverage these trajectories to differentiate preeclampsia cases in relation to circulating biomarkers, which may help in the development of preeclampsia prediction tools. **(*Hypertension*. 2021;77:2034–2044. DOI: 10.1161/HYPERTENSIONAHA.120.16239.)** • **Data Supplement**

Key Words: blood pressure ■ cluster analysis ■ hypertension ■ preeclampsia ■ pregnancy complications

Preeclampsia is a heterogeneous condition characterized by new-onset hypertension, in addition to signs of organ damage.[1,2] It has been estimated to affect between 2% and 8% of pregnancies worldwide and is associated with increased risk of complications to both mother and child.[1,3] The only treatment for preeclampsia is delivery of the baby, and as a result, preterm birth (PTB) is common among pregnancies affected by preeclampsia.[3–5] Risk factors for preeclampsia include having a history of preeclampsia, older maternal age, primiparity, nonsmoking, and multifetal pregnancy.[2,4,6,7] Family studies suggest a genetic risk, and recently, the largest and only replicated genome-wide association study found a polymorphism in a locus near the *FLT1* gene to be associated with increased risk of preeclampsia.[8]

The underlying causes of preeclampsia have yet to be identified, and even the clinical definition has changed several times over the past few decades.[8–10] Recent definitions favor a strict blood pressure dichotomy (>140 mm Hg systolic or 90 mm Hg diastolic), whereas prior guidance utilized a relative change over baseline (increase of 30 mm Hg systolic or 15 mm Hg diastolic).[7,11] The implication of favoring a clinical threshold (140/90) over relative criteria (30/15) is that the rate of change (slope) may differ among women depending on their starting blood pressure. However, there is a

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Novelty and Significance

What Is New?

- While several studies have examined blood pressure trajectories in the setting of normal pregnancy, few have examined blood pressure trajectories among preeclampsia cases.
- This study used novel statistical methodology to simultaneously cluster systolic and diastolic blood pressure into trajectories among preeclampsia cases and controls.

What Is Relevant?

- Preeclampsia is a serious complication of pregnancy, characterized by de novo hypertension, often accompanied by proteinuria, which emerges after 20 weeks of gestation. We utilized novel statistical methodology to uncover clusters of blood pressure trajectory that have different associations with patient characteristics and different relationships with pregnancy outcomes. Blood pressure trajectories were analyzed using a longitudinal machine learning algorithm to identify clusters in both preeclampsia cases and controls.

Summary

Blood pressure trajectories among preeclampsia cases and controls were clustered using a nonparametric longitudinal clustering algorithm, to better understand how blood pressure contributes to heterogeneity within preeclampsia cases. A more rapid increase in blood pressure, as well as a higher starting blood pressure, was associated with worse pregnancy outcomes, including small for gestational age and preterm birth. These results may be used in future studies to guide discovery of preeclampsia prediction biomarkers.

Nonstandard Abbreviations and Acronyms

ALSPAC	Avon Longitudinal Study of Parents and Children
MBRN	Medical Birth Registry of Norway
MoBa	Norwegian Mother, Father and Child Cohort Study
PTB	preterm birth
SGA	small for gestational age
vPTB	very preterm birth

lack of empirical evidence to establish the clinical importance of these differences in blood pressure trajectory. Disaggregating intra- from interindividual increases in blood pressure over the course of pregnancy could help in uncovering preeclampsia subtypes and in determining whether continuous changes in blood pressure have clinical implications.

In this study, we utilized a nested preeclampsia case-control subset of MoBa (Norwegian Mother, Father and Child Cohort Study) to examine blood pressure trajectories over the course of pregnancy.[12] Our aims were to derive clusters of blood pressure trajectory among cases and controls, ascertain what pre- or early pregnancy characteristics associate with blood pressure trajectories, and examine whether clusters are differentially associated with adverse outcomes of pregnancy, including very PTB (vPTB) and fetal growth restriction. Understanding differences in cluster membership and trajectories, and their association with pregnancy outcomes, may help to disentangle the widely acknowledged heterogeneity in the preeclampsia phenotype.[13]

METHODS

Norwegian Mother, Father and Child Cohort Study

The MoBa is a population-based, prospective pregnancy cohort that enrolled pregnant women between 1999 and 2008. In total, MoBa enrolled ≈113 000 pregnancies across Norway,[12] representing ≈43.5% of all eligible births in that period.[14] Women provided informed consent at their 17-week ultrasound appointment, donated maternal blood samples at enrollment (88.4%), and returned questionnaires by mail at ≈17 (95.1%), 22 (92.7%), and 34 (91.4%) weeks of gestation.[15]

Medical Birth Registry of Norway

Birth outcome information was obtained through linkage with the Medical Birth Registry of Norway (MBRN).[16] In existence since 1967,[16] the MBRN consists of antenatal, intrapartum, and postpartum clinical information on all births in Norway. A standard antenatal form consisting of blood pressure results from urinalysis, body weight, and other clinical findings; is completed by the clinical provider at antenatal visits; and is brought by the mother to the hospital when she is admitted for delivery. Midwives or clinical care providers transfer data from the antenatal form to the MBRN notification form, along with additional clinical information describing her intrapartum and postpartum experience, obtained by chart review or abstracted from electronic medical records. Midwives designate that a pregnancy was affected by preeclampsia by checking ≥1 boxes on the MBRN form, as described by Klungsoyr et al.[17] Validation of the MBRN registration of preeclampsia is described below.

Preeclampsia Validation Substudy

MBRN registration of preeclampsia was validated using both antenatal records and hospital discharge codes and is described by Klungsoyr et al.[17] All MoBa pregnancies registered as having

preeclampsia in the MBRN were selected (n=4081), along with a random sample of pregnancies without preeclampsia registration (n=2000). Antenatal charts and hospital discharge codes were received from 5340 pregnancies, including 3500 records with preeclampsia registered in the MBRN. Positive validation of preeclampsia status was based on the American College of Gynecology criteria at the time of the MoBa validation study: ≥140 mm Hg systolic or ≥90 mm Hg diastolic after the 20th week of pregnancy, and proteinuria of ≥0.3 g or ≥1+ on urinary dipstick, at the same visit, or the *International Classification of Diseases, Tenth Revision*, codes from hospital discharge diagnoses, irrespective of the MBRN registration (ie, pregnancies originally identified as controls were classified as preeclampsia if they met any of the above criteria despite the lack of MBRN registration).[18]

Study Population in the Present Study

This analysis is nested within the subset of MoBa pregnancies utilized in the preeclampsia validation study (Figure 1). Subsequent to the validation study, 48 women requested their MoBa data not be analyzed and were excluded from the present study. To be included in this study, we additionally had the following eligibility criteria: antenatal visit data were obtained (n=234 excluded), singleton pregnancy (n=196 excluded), birth after 20 weeks of gestation (n=4 excluded), no serious birth defects (n=163 excluded), nonmissing gestational age or birthweight (n=4 excluded), and at least 3 recorded blood pressure measurements between weeks 8 and 38 of gestation (n=423 excluded). Additionally, if a woman had multiple pregnancies at different time points within the cohort, we only used 1 pregnancy from that woman (n=95 excluded), selected at random. We furthermore restricted the primary analysis to cases that contained antenatal evidence of preeclampsia (documented blood pressure meeting diagnostic criteria) as opposed to cases that were identified based only on preeclampsia registration on the MBRN (n=845) or eligible *International Classification of Diseases, Tenth Revision*, codes at discharge (n=9) without supporting antenatal measurements (excluded n=854 preeclampsia cases). Our primary analysis included 1906 validated preeclampsia cases and 1413 validated controls.

Demographic and early-pregnancy covariates were obtained from self-administered MoBa questionnaires and the MBRN. From the MBRN, we obtained maternal age and parity (classified as primparous versus multiparous). From the MoBa questionnaires, we obtained mother's education, marital status, height and prepregnancy weight, which were used to calculate prepregnancy BMI (kg/m^3), and self-reported maternal smoking at enrollment (≈17 weeks of gestation).

Pregnancy outcomes were obtained from the MBRN. Gestational age at delivery in days was modeled as a continuous variable, defined based on second trimester ultrasound when available (≈94%) or last menstrual period. A birthweight *Z* score was calculated using birthweights by gestational age and sex among all Norwegian births from 1967 to 1999 and modeled as a continuous variable.[19] Small for gestational age (SGA) was defined as less than the 10th percentile of the previously defined birthweight *Z* score.[19] We considered a birth preterm if delivery occurred before 37 completed weeks of gestation (PTB). vPTB referred to deliveries that occurred before 34 completed weeks of gestation. To help assess the severity of preeclampsia, we also obtained the mode of delivery (vaginal birth versus cesarean section), and preterm clinical presentation (induced versus spontaneous), from the MBRN.

Statistical Methods

Longitudinal Clustering of Systolic and Diastolic Blood Pressure During Pregnancy

We utilized an unsupervised machine learning approach to cluster longitudinal blood pressure trajectories, simultaneously considering systolic and diastolic blood pressure. Clustering was performed using the kml3d R package—an implementation of a longitudinal approach of the k-means algorithm.[20] The algorithmic approach is based on the expectation maximization class of algorithms. In brief, numerous runs for each number of clusters are performed and cluster partitions are ranked based on various quality criteria. In our analysis, we chose to run the clustering 100× per distinct number of specified clusters. From the 100 clustering runs, we used the runs with the highest criterion score, visual inspection, and literature review for further analyses. Additionally, the number of clusters was assessed visually and mathematically, evaluating within- and between-cluster statistics. Blood pressure measurements were included in the clustering algorithm if they fell between 8 and 38 weeks of gestation.

Clustering was performed separately on 2 subpopulations. In our study, preeclampsia cases are overrepresented relative to their underlying frequency in the population. Therefore, the first subpopulation consisted exclusively of the case samples (n=1906 preeclampsia cases). We clustered cases independently in the first subpopulation to characterize the underlying heterogeneity of the preeclampsia phenotype. The second subpopulation, referred to as the weighted population, aimed at creating a hypothetical cohort where the frequency of preeclampsia roughly matched what one would expect in the general population (3.5%).[21] This was achieved by sampling a random set of cases and adding these to the entire sample of noncases, so that the cases comprised 3.5% of the total population (n=1465: 1413 noncases and 52 preeclampsia cases).

Imputation

Imputation of missing covariate data was conducted using 50 multiple imputations with the Multivariate Imputation by Chained Equations R package.[22] Default imputation methods used are predictive mean matching, logistic regression imputation, and polytomous regression imputation for numeric, binary, and unordered factor variables, respectively. Imputation was performed for the following covariates: marital status (n=228; 4.9%), maternal education (n=277; 5.9%), maternal BMI (n=336; 7.2%), and maternal smoking status (n=581; 12.4%). Imputed values were used as covariates within the statistical models but were reported as missing in the tables. To use the imputed datasets together in the statistical modeling, the POOL function was used, which applies the Rubin rule to combine estimates.

Statistical Modeling

Ordinary linear regression was used to assess relationships involving continuous dependent variables, specifically birthweight *Z* score and gestational age (GLM R package). Logistic regression models were run for binary dependent variables, including SGA, PTB, and mode of delivery analyses (GLM R package). Multinomial logistic regression was performed for dependent variables with multiple categories, for example, cluster membership

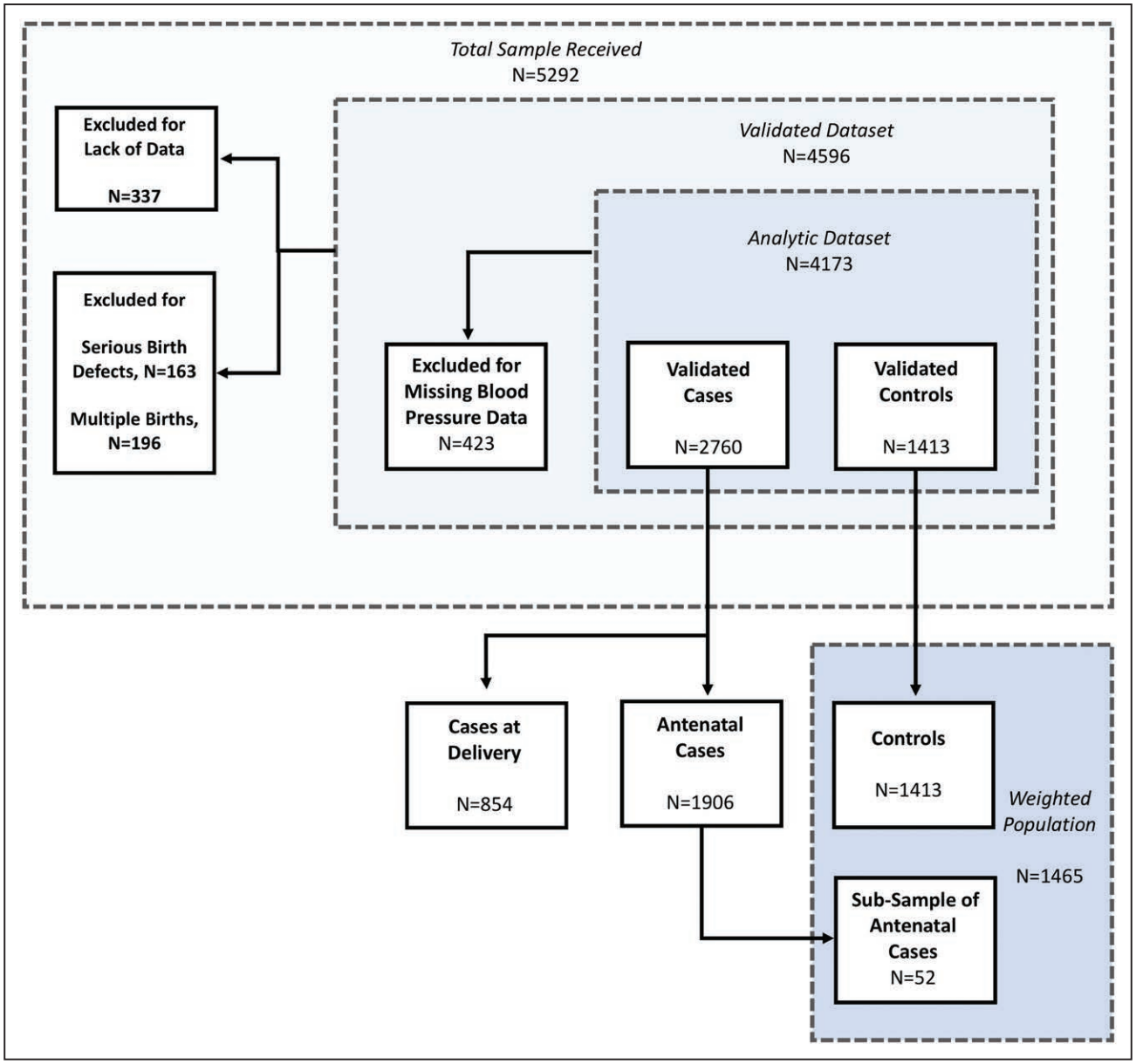

Figure 1. Diagram describing population exclusions, validated cases, validated controls, and the weighted population.

(NNET R package). Confounders were identified a priori using directed acyclic graphs. All statistical models were adjusted for confounders. All analyses were conducted in R, version 3.6.1.

Sensitivity Analyses

We conducted 2 sensitivity analyses. First, to investigate the extent to which preeclampsia cases were driving associations in the weighted population, we conducted analyses excluding preeclampsia cases from the previously derived weighted population clusters (n=1413). Second, a large number of preeclampsia cases in MoBa were identified after the final antenatal visit (no blood pressure evidence of preeclampsia on the antenatal card but evidence of preeclampsia in the MBRN or *International Classification of Diseases, Tenth Revision*, discharge codes; we denote as identified at delivery; n=854).[17] Such cases may represent a rapid-onset phenotype that results in immediate hospitalization, and, therefore, antenatal evidence is not recorded during routine prenatal care. They may also include cases of preeclampsia that emerge intrapartum. For this sensitivity analysis, we rederived the trajectory clusters using the entire case population (antenatal cases and cases identified only at delivery). Because clusters were rederived based on this now much larger population, individual cluster assignment may be different relative to the main analysis. We then conducted inferential analyses of covariates in relation to the new clusters and the new clusters in relation to pregnancy outcomes, as described previously.

RESULTS

Characteristics of preeclampsia cases and noncases are presented in Table S1 in the Data Supplement. On average, preeclampsia cases were slightly younger, less educated, less likely to smoke, and had a higher prepregnancy BMI. They were more likely to be primiparous and

were much more likely to deliver preterm. Preeclampsia cases identified on the antenatal record or at delivery were generally similar; however, cases identified at delivery were less likely to be primiparous and less likely to deliver preterm than cases identified antenatally. Average birthweight was significantly lower among preeclampsia cases, and newborns were more likely to be SGA when compared with controls.

Among preeclampsia cases, we identified 5 blood pressure trajectory clusters (Figure 2). The high group emerged early in gestation. In addition, there were 2 moderate and two low trajectory clusters, which were mainly distinguished by the slope of increase (steep versus steady). In the weighted population, systolic and diastolic blood pressure trajectories clustered into 3 groups, distinguished mainly by starting blood pressure (Figure S1). The high blood pressure trajectory also had a somewhat steeper slope of increase toward the end of gestation.

We present univariate distributions of demographic, early-pregnancy characteristics, and pregnancy outcomes according to blood pressure cluster among antenatal cases in Table 1 and the weighted population in Table S2. Steep clusters (low and moderate) were characterized by a larger fraction of smokers, more preterm deliveries, more growth restriction, and a larger fraction of severe cases. There was a higher prevalence of cesarean section, particularly emergency cesarean, among both of the steep and high clusters. Average gestational age at which preeclampsia clinical criteria were met was the earliest for the high cluster (31.4 weeks), followed by the moderate-steep (33.3 weeks) and low-steep (35.6) clusters. However, in multivariable adjusted models, there were few significant differences among the clusters (Table S3). Women in the high cluster were slightly older. The most evident difference among clusters was related to prepregnancy BMI. As compared with low-steady, members of all the other clusters were considerably more likely to be overweight or obese prepregnancy—the high cluster having the most extreme elevated odds of prepregnancy obesity (odds ratio, 9.7 [95% CI, 6.0–15.8]; Table S3). Prepregnancy obesity was lower in the low-steady cluster as compared with all others. This association was the strongest in both the moderate clusters and the high cluster. Moderate-steady and moderate-steep were also less likely to be primiparous.

Associations of trajectory clusters with pregnancy outcome are found in Table 2 for the antenatally defined case population. There were few differences in pregnancy outcomes comparing the moderate-steady and low-steady clusters, except birthweight *Z* score was slightly higher among women in the moderate-steady cluster. However, both the steep clusters and the high cluster carried significantly increased risk of SGA (approximately a 2-fold increased risk for all groups), and PTB

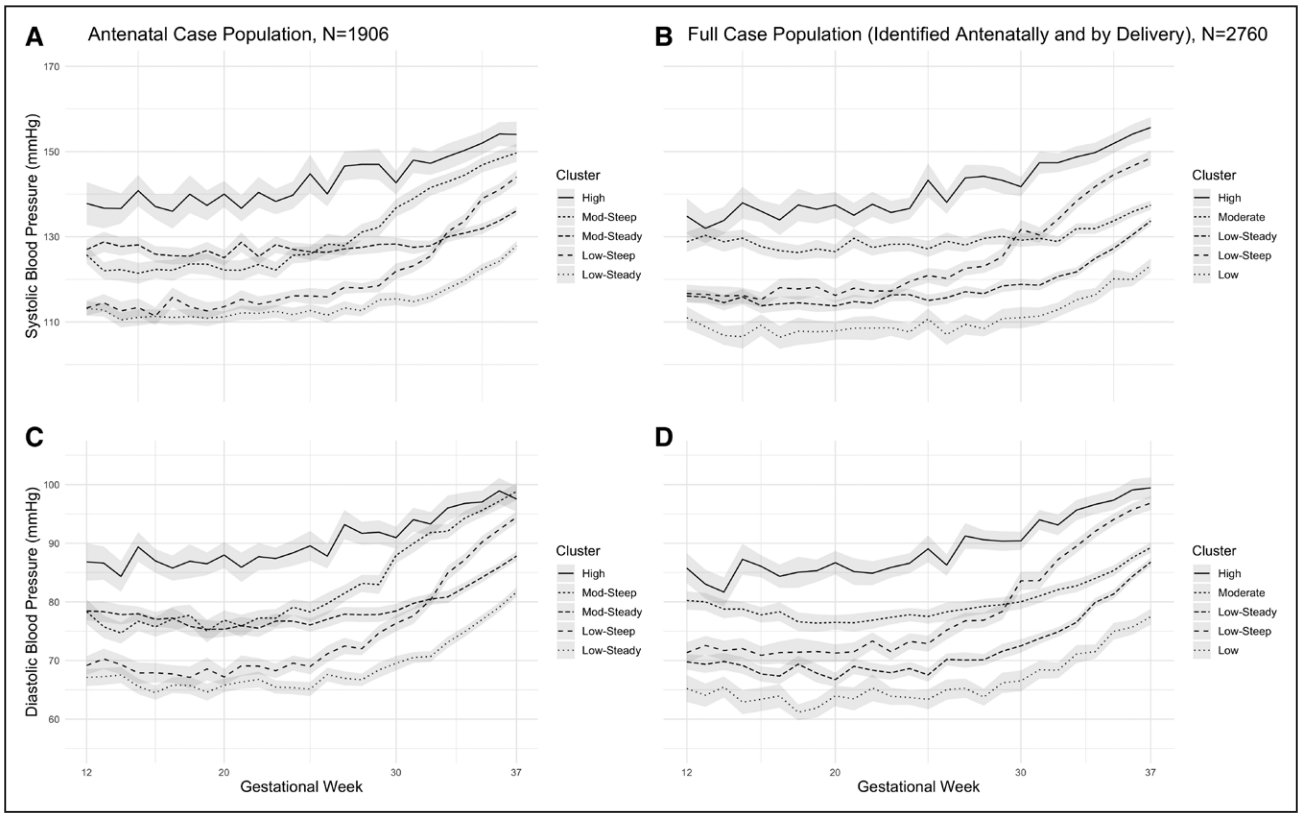

Figure 2. Systolic and diastolic blood pressure trajectory clusters for the antenatal case population (n=1906) and full case population (n=2760).
Shaded area represents the region between the upper 97.5% and lower 2.5% average blood pressure values for each trajectory.

Table 1. Descriptive Frequencies of Demographic and Early Pregnancy Risk Factors, and Pregnancy Outcomes in Relation to BP Trajectory Clusters for the Antenatal Case Population

	BP trajectory clusters				
	Antenatal case population (n=1906)				
	Low-steady	Low-steep	Moderate-steady	Moderate-steep	High
Characteristics	n (%)	n (%)	n (%)	n (%)	n (%)
N	545	427	423	322	189
Mother's age, y; mean (SD)	29.0 (4.84)	29.0 (4.80)	29.7 (4.72)	29.7 (5.12)	31.5 (4.76)
Mother's education					
<College	199 (36.5%)	148 (34.7%)	168 (39.7%)	122 (37.9%)	74 (39.2%)
College	190 (34.9%)	181 (42.4%)	140 (33.1%)	115 (35.7%)	72 (38.1%)
>College	104 (19.1%)	73 (17.1%)	85 (20.1%)	60 (18.6%)	25 (13.2%)
Other	11 (2.0%)	6 (1.41%)	5 (1.2%)	5 (1.6%)	5 (2.7%)
Missing, n	41 (7.5%)	19 (4.5%)	25 (5.9%)	20 (6.2%)	13 (6.9%)
Marital status					
Married/cohabitant	497 (91.2%)	386 (90.4%)	392 (92.7%)	300 (93.2%)	174 (92.1%)
Single/other	20 (3.7%)	24 (5.6%)	10 (2.4%)	7 (2.2%)	5 (2.7%)
Missing, n	28 (5.1%)	17 (4.0%)	21 (5.0%)	15 (4.7%)	10 (5.3%)
Prepregnancy BMI, kg/m^2					
<18.5	15 (2.8%)	9 (2.1%)	1 (0.2%)	5 (1.6%)	0 (0.0%)
18.5–24.9	321 (58.9%)	225 (52.7%)	131 (31.0%)	112 (34.8%)	40 (21.2%)
25–29.9	116 (21.3%)	123 (28.8%)	133 (31.4%)	101 (31.4%)	54 (28.6%)
≥30	52 (9.5%)	47 (11.0%)	121 (28.6%)	82 (25.5%)	81 (42.9%)
Missing, n	41 (7.5%)	23 (5.4%)	37 (8.6%)	22 (6.8%)	14 (7.4%)
Primiparous	386 (70.8%)	306 (71.7%)	254 (60.0%)	197 (61.2%)	108 (57.1%)
Smoking at the time of enrollment (≈17 wk)					
Yes	23 (4.2%)	23 (5.4%)	13 (3.1%)	14 (4.4%)	12 (6.4%)
Missing, n	53 (9.7%)	55 (12.9%)	42 (9.9%)	48 (14.9%)	37 (19.6%)
Average starting systolic BP	113 (9.9)	128 (10.1)	115 (9.7)	124 (9.6)	137 (14.0)
Average starting diastolic BP	68.6 (7.73)	78.2 (7.60)	69.9 (7.25)	77.0 (7.92)	85.6 (8.86)
Average Max systolic BP	146 (11.8)	154 (12.2)	152 (10.5)	160 (13.2)	170 (14.7)
Average Max diastolic BP	95.1 (6.72)	101 (7.17)	98.5 (6.52)	104 (7.78)	107 (8.54)
Average Max protein	1.94 (0.85)	2.07 (0.88)	1.67 (0.78)	2.02 (0.95)	1.97 (0.88)
PE status					
Case	505 (92.7%)	327 (76.6%)	366 (86.5%)	213 (66.1%)	105 (55.6%)
Severe case*	40 (7.3%)	100 (23.4%)	57 (13.5%)	109 (33.9%)	84 (44.4%)
Average gestational week of PE onset	38.4 (1.8)	35.6 (2.1)	36.8 (3.5)	33.3 (3.5)	31.4 (4.8)
BP medication usage during pregnancy	0 (0.0%)	10 (2.4%)	1 (0.2%)	16 (5.0%)	29 (15.3%)
Gestational age, d	279 (11.0)	263 (15.0)	279 (9.69)	254 (21.0)	250 (28.5)
Gestational age category, wk					
<34	2 (0.4%)	24 (5.6%)	1 (0.2%)	71 (22.0%)	55 (29.1%)
34–36	21 (3.9%)	114 (26.7%)	9 (2.1%)	103 (32.0%)	41 (21.7%)
37+	522 (95.8%)	289 (67.7%)	413 (97.6%)	148 (46.0%)	93 (49.2%)
Mode of delivery					
Term					
Spontaneous	186 (34.1%)	73 (17.1%)	149 (35.2%)	41 (12.7%)	17 (9.0%)
Induced	314 (57.6%)	199 (46.6%)	229 (54.1%)	90 (28.0%)	64 (33.9%)
Planned C-section	7 (1.3%)	12 (2.8%)	19 (4.5%)	10 (3.1%)	8 (4.2%)
Emergency C-section	15 (2.8%)	5 (1.2%)	15 (3.5%)	6 (2.0%)	4 (2.1%)

(*Continued*)

Table 1. Continued

Characteristics	BP trajectory clusters Antenatal case population (n=1906) Low-steady n (%)	Low-steep n (%)	Moderate-steady n (%)	Moderate-steep n (%)	High n (%)
Preterm					
Spontaneous	4 (0.7%)	22 (5.2%)	1 (0.2%)	25 (7.8%)	15 (7.9%)
Induced	9 (1.7%)	53 (12.4%)	6 (1.4%)	58 (18.0%)	29 (15.3%)
Planned C-section	1 (0.2%)	16 (3.8%)	1 (0.2%)	27 (8.4%)	14 (7.4%)
Emergency C-section	9 (1.7%)	47 (11.0%)	1 (0.2%)	64 (19.9%)	37 (19.6%)
Missing, n	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.3%)	1 (0.5%)
Birthweight, g	3482 (595)	2915 (680)	3610 (597)	2706 (865)	2606 (1054)
Birthweight *Z* score	−0.13 (1.06)	−0.57 (1.05)	0.14 (1.23)	−0.44 (1.13)	−0.44 (1.12)
SGA	71 (13.0%)	114 (26.7%)	41 (9.7%)	72 (22.4%)	41 (21.7%)

BMI indicates body mass index; BP, blood pressure; PE, preeclampsia; and SGA, small for gestational age.
*At least 1 visit with systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg and proteinuria ≥2+.

(11-fold to 34-fold increased risk), in comparison to the low-steady cluster. Members of the moderate-steep and high clusters delivered on average between ≈25 and 31 days early, and low-steep ≈16 days early, in comparison to the low-steady cluster. Although numbers are small, this translates into considerably elevated odds of vPTB in all of these clusters (16-fold to 159-fold increased risk). Birthweight *Z* scores were also significantly lower for the steep and high clusters.

To assess the impact of including cases identified only at the time of delivery, which may include rapid-onset cases or cases that emerge intrapartum (n=854), we rederived blood pressure trajectory clusters including these cases (Figure 2). While we still saw 5 groups, there seemed to be 3 low groups, defined by their rate of increase, one moderate group, and a high group. The 3 low groups consisted of low (n=489), low-steady (n=841) with a less steep overall trajectory, and low-steep (n=544) with a steep trajectory, while the moderate group (n=562) and high group (n=324) both had less steep trajectories. As before, the high and steep clusters tended to have the worse pregnancy outcomes, experiencing significantly higher risks of SGA, PTB, and vPTB, substantially shorter durations of gestation (≈−21 to 28 days), and lower birthweight *Z* scores (Table S4). In this analysis, the low, low-steady, and moderate clusters were not meaningfully different across most metrics, except a slightly higher risk for SGA in the low-steady group.

For the weighted population (Table S2), we found 3 clusters: low (n=453), moderate (n=729), and high (n=283; Figure S1). Compared with the low cluster, the moderate and high clusters had elevated odds of PTB (Table S5). The moderate and high clusters, compared

Table 2. Associations of Blood Pressure Trajectory Clusters With Adverse Pregnancy Outcomes for the Antenatal Case Population

Outcome	Blood pressure trajectory cluster Antenatal case population (n=1906) Low-steady	Low-steep	Moderate-steady	Moderate-steep	High
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
SGA*	Ref	2.4 (1.7 to 3.4)	0.8 (0.5 to 1.2)	2.1 (1.4 to 3.0)	2.0 (1.3 to 3.1)
PTB (<37 wk)*	Ref	11.6 (7.3 to 18.5)	0.7 (0.3 to 1.4)	32.4 (19.8 to 53.0)	34.4 (19.8 to 59.8)
vPTB (<34 wk)*	Ref	16.6 (3.9 to 70.7)	0.8 (0.1 to 8.6)	92.4 (22.3 to 382.4)	159 (37.4 to 673)
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Gestational age, d†	Ref	−15.9 (−17.9 to −13.8)	−0.6 (−2.7 to 1.5)	−25.3 (−27.6 to −23.1)	−30.8 (−33.6 to −28.0)
Birthweight *Z* score	Ref	−0.4 (−0.6 to −0.3)	0.2 (0.0 to 0.3)	−0.4 (−0.5 to −0.2)	−0.4 (−0.6 to −0.2)

BMI indicates body mass index; OR, odds ratio; PTB, preterm birth; Ref, the reference category in the statistical model used; SGA, small for gestational age; and vPTB, very preterm birth.
*SGA and PTB modeled using logistic regression, adjusted for maternal age (continuous), maternal education (categorical), maternal smoking at enrollment (dichotomous), marital status (categorical), primiparity (dichotomous), and maternal BMI (continuous).
†Gestational age modeled as a continuous outcome in days using linear regression, adjusted for maternal age (continuous), maternal education (categorical), maternal smoking at enrollment (dichotomous), marital status (categorical), primiparity (dichotomous), and maternal BMI (continuous).

with low, also had a short gestational age and slightly higher birthweight *Z* scores. After excluding preeclampsia cases, odds of PTB and vPTB were attenuated relative to the weighted population (Table S5). However, we continued to observe a somewhat shortened gestational duration and higher birthweight Z score in the high cluster (0.2 [95% CI, 0.1–0.4]).

DISCUSSION

Clustering blood pressure trajectories among preeclampsia cases and the weighted population yielded insights into the predictors and clinical correlates of preeclampsia subtypes, as well as blood pressure trajectory more generally among noncases. Among preeclampsia cases, pregnancy outcomes were meaningfully worse for individuals with a more rapid increase in blood pressure over pregnancy regardless of starting blood pressure, as well as for individuals with a high starting blood pressure. Even in the weighted population, where preeclampsia cases only account for 3.5% of the total, we observed increased rates of SGA and earlier gestational ages at delivery for the moderate and high trajectory groups, supporting research suggesting that blood pressure irrespective of preeclampsia plays an important role in pregnancy outcome.[23,24] A number of early pregnancy and demographic factors were significantly associated with blood pressure trajectory clusters; however, after multivariable adjustment, prepregnancy BMI was the most consistent distinguishing factor. Women who were overweight or obese were considerably more likely to be in the more adverse blood pressure trajectories, supporting the potential importance of prepregnancy weight loss as a primary prevention strategy.[25–27]

Change, and the slope of change, in blood pressure over the course of gestation may have important implications on the health of the fetus. For example, the blood pressure of a woman in the low-steep trajectory needs to increase significantly more than the moderate-steep trajectory to reach the current diagnostic threshold. While the durations of the low-steep pregnancies are substantially longer (—15.9 days for low-steep versus —25.3 days for moderate-steep), on average, the infants experience a similar degree of growth impairment (birthweight *Z* score, —0.43 low-steep versus —0.37 moderate-steep; SGA odds ratio, 2.4 low-steep versus 2.1 moderate-steep). These changes, and slope of changes, can be seen both in the antenatal-only and full case populations, though there are slight differences in the clusters themselves. The full case population includes cases identified only through MBRN reporting or *International Classification of Diseases, Tenth Revision*, discharge codes and may represent a more rapid onset of preeclampsia that results in immediate hospital transfer. When these cases are included, the moderate-steep cluster is not found, which may, in part, be due to the inclusion of a large subset of women with normal antenatal blood pressure, resulting in the derivation of more low trajectory clusters. We generally only see worse birth outcomes for the low-steep cluster, providing further evidence for the impact of slope of change.

Previous studies have analyzed the association between blood pressure change during pregnancy and birth outcomes in the ALSPAC (Avon Longitudinal Study of Parents and Children),[28] Generation R,[29] the Calcium Supplementation for the Prevention of Preeclampsia Trial,[30] and the large Chinese Maternal and Newborn's Health Monitoring System.[31] In these studies, the populations, though large, primarily included normotensive women. In general, these studies found that an increase in blood pressure during pregnancy (or increase in the rate of change during specific windows—primarily the second to third trimester) led to worse birth outcomes, including SGA[31,32] and PTB.[30] The subset of analyses in our article that focused on the weighted or control-only populations most closely resembled these studies, and while we found some evidence that blood pressure trajectories were associated with increased risk of SGA and PTB in the moderate and High trajectory clusters, estimates were imprecise and to some extent driven by the small number of preeclampsia cases within these groups. When cases of preeclampsia were excluded, we did not find evidence of clinically meaningful differences in fetal growth or gestational length parameters associated with blood pressure trajectories.

Another set of studies have used blood pressure change in early pregnancy to identify women at risk of hypertensive disorders of pregnancy or to differentiate women according to preeclampsia risk factors. Hauspurg et al,[33] in the nuMoM2b cohort, examined early-pregnancy blood pressure (≈12 weeks) and the difference between the first and second study visits (≈12 to ≈19 weeks) in relation to risk of preeclampsia and found that both the first measurement and the slope of change between the first and second were associated with risk of preeclampsia. Macdonald-Wallis et al,[34] also in the ALSPAC cohort, found that established preeclampsia risk factors such as smoking and BMI were associated with lower and higher blood pressure reference ranges, respectively. Similarly, nulliparity and twin pregnancies had higher starting blood pressures or more rapidly increasing blood pressures through pregnancy.[28] And Wu et al[35] examined stage 1 hypertension during pregnancy in relation to adverse pregnancy outcomes in a retrospective hospital-based population enrolled in Shanghai and found significantly increased risk of adverse pregnancy outcomes. To our knowledge, there have been no previous studies that have examined blood pressure trajectories within preeclampsia cases in relation to birth outcomes, despite the notable heterogeneity within preeclampsia cases.[2,13,36] Blood pressure trajectories may differentiate subphenotypes among preeclampsia cases. Future

studies may use blood pressure trajectory clusters to differentiate women in relation to preeclampsia biomarkers, which may help in the development of preeclampsia prediction approaches.

Our study had several strengths. First, we had access to a large population with longitudinal blood pressure measurements and a validated clinical diagnosis of preeclampsia, which enabled us to perform this unique analysis. MoBa provided prospective covariate data, including important behavioral and clinical factors such as smoking and prepregnancy BMI. Our analytic method enabled us to cluster on systolic and diastolic blood pressure simultaneously, which prior studies have analyzed independently. Moreover, the nonparametric approach we used to cluster blood pressure longitudinally easily accommodated the unstructured nature of blood pressure measurements and makes no distributional assumptions about the blood pressure trajectories. Other approaches have been used, and while they are useful for modeling these longitudinal data and have their own strengths, they often assume a biologically unrealistic piecewise linear growth.[37] Here, we have grouped trajectories without confinement to similar assumptions, allowing for a more natural fit. Additionally, we used the entire collection of data points obtained for each trajectory to form clustering groups, instead of just considering a few points at prespecified weeks, potentially allowing for better alignment of trajectories and more intricate differences between groups.

However, our work also had several limitations. Pregnancies complicated by preeclampsia had more recorded blood pressure measurements than uncomplicated pregnancies. Preeclampsia cases, on average, had 12 measured blood pressure readings, whereas controls had 9.5. Although we required all subjects to have at least 3 recorded measurements, the differences in the frequency of measurements between cases and controls will render estimates of trajectories in the nonpreeclampsia group less precise. Additionally, the clustering algorithm used is somewhat sensitive to the starting point, which can affect the assignments of data to the resultant clusters. To help address this, we ran the algorithm for multiple iterations and used the cluster criterion generated from the kml R package to assess the best fit for the data. However, we cannot exclude the possibility that membership in some clusters may be slightly different with a different starting point. In addition, there is no consensus on the best way to determine the optimal number of clusters for a given dataset.[20] We used the criterion provided by kml, as well as within cluster sum of squares and visual analyses of the resulting clusters and trajectories, to help determine the optimal number of clusters. Nonetheless, other clustering approaches may group women differently.

Furthermore, there are currently no methods available to quantify the imprecision in these longitudinal trajectories, taking into account the reduction in sample size that is likely to occur as gestational length approaches delivery. Prior studies using these methods have simply provided the average trajectories[38,39]—we also provided the 2.5% to 97.5% bounds on the average trajectory. However, these bounds do not fully account for all the relevant components of imprecision. Our blood pressure data were obtained from antenatal charts that are filled out by prenatal care providers[17] and as such are subject to interobserver variability. In addition, while we had access to many important covariates, such as prepregnancy BMI and maternal smoking, Norway did not routinely screen for gestational diabetes during pregnancy during the years under study, nor was pregnancy weight gain routinely recorded through the MBRN or MoBa. Finally, MoBa is a population-based cohort that enrolled almost half of all pregnant women in Norway during the enrollment period. While this analysis only included 1 pregnancy per woman (ie, if a woman had multiple pregnancies in MoBa, we randomly sampled from among them), we cannot account for the potential nonindependence among observations that would arise from unmeasured family relatedness (eg, members of this analytic dataset who are themselves siblings, half-siblings, or cousins).

In conclusion, using longitudinal blood pressure data from a large population of validated preeclampsia cases and controls, we were able to detect blood pressure trajectories among preeclampsia cases that associated with differences in patient characteristics and were differentially associated with pregnancy outcomes. These results may be useful in identifying biomarkers that can distinguish between preeclampsia subtypes prospectively and support close follow-up of women with significant relative changes in blood pressure that do not yet meet the diagnostic criteria.

PERSPECTIVES

Preeclampsia is a heterogeneous disorder for which there are few strongly predictive biomarkers, which may, in part, be due to the heterogeneity of this condition. Using a nonparametric approach to simultaneously cluster longitudinal trajectories of systolic and diastolic blood pressure among preeclampsia cases, we were able to uncover preeclampsia subphenotypes that were associated with different patient characteristics and had different relationships with pregnancy outcomes. Emergence of preeclampsia may occur any time after 20 weeks of gestation, and while in general, the earlier it emerges the more severe and detrimental the effects on both mother and child, our study additionally highlights the importance of the trajectory of blood pressure increase in differentiating effects on pregnancy outcome. The identification of

reliable preeclampsia subtypes may advance discovery of novel predictive biomarkers that are differentially associated with only a subset of the larger phenotype. Future studies can contrast the immune, genetic, or metabolomics profiles across trajectory clusters to discern common and unique determinants, with the ultimate goal of preeclampsia prevention.

ARTICLE INFORMATION

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Disclosures

None.

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