



# BMJ Open Cohort profile: the Olmsted County hypertensive disorders of pregnancy (HDP) cohort using the Rochester Epidemiology Project

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## ABSTRACT

**Purpose** The Olmsted County hypertensive disorders of pregnancy (HDP) cohort is a population-based retrospective study designed to compare the incidence of HDP on a per-pregnancy and per-woman basis and to identify associations between HDP with ageing-related diseases, as well as accumulation of multimorbidity. **Participants** Using the Rochester Epidemiology Project (REP) medical records-linkage system, a cohort was collected consisting of women who gave birth in Olmsted County between 1976 and 1982. After exclusions, a per-pregnancy cohort of 7544 women with 9862 pregnancies between 1976 and 1982 was identified, and their delivery information was manually reviewed. A subset of these women comprised the per-woman cohort of 4322 pregnancies from 1839 women with delivery information available throughout the entirety of their childbearing years, along with decades of follow-up data available for research via the REP.

**Findings to date** By constructing both per-pregnancy and per-woman cohorts, we reported a doubling of HDP incidence rates when assessed on a per-woman basis compared with rates observed on a per-pregnancy basis. Moreover, in addition to finding that women with a history of HDP developed specific diseases at higher rates and at early ages, we also discovered that a history of HDP is associated with accelerated ageing, through accumulation of multimorbidity.

**Future plans** In addition to these outcomes described above, many other potential outcomes of interest for studies of HDP can be ascertained from accessing the electronic health records (EHR) and billing systems available through the REP. These data can include all International Classification of Diseases (ICD)-9 and ICD-10 and Current Procedural Terminology coded diagnoses and procedures, healthcare utilisation, including office visits, hospitalisations and emergency room visits, and full text of the EHR that is available for chart abstraction or for natural language processing of the clinical notes.

## INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are currently major global contributors to

## Strengths and limitations of this study

- The hypertensive disorders of pregnancy (HDP) algorithm has improved sensitivity and specificity to accurately assign exposure status compared with methods that rely on diagnostic codes or registries.
- Use of the HDP algorithm can reduce the risk of bias incurred by chart review by multiple individuals or recall bias from survey-based methods, and allow for HDP ascertainment for large populations of interest.
- Decades of pregnancy-related and follow-up data are available for research via the Rochester Epidemiology Project medical records-linkage system, thus facilitating the calculation of population-based estimates of HDP incidence both on a per-pregnancy and per-woman basis, as well as the ability to study the effects of HDP on a woman's subsequent health decades later in life.
- Our algorithm was developed to diagnose HDP in a historical database; thus, certain subtypes of HDP such as HELLP (ie, haemolysis, elevated liver enzymes and low platelet count) syndrome or pre-eclampsia by severe blood pressure criteria alone are not included in our algorithm as these subtypes were first described well after our study time frame of 1976 to 1982.
- Our population-based cohort is predominantly non-Hispanic white; as previous studies have found evidence that African American women may experience higher rates of HDP, as well as elevated risks for cardiovascular disease compared with white women, these findings necessitate future HDP studies to be conducted in more racially diverse cohorts.

maternal and fetal morbidity and mortality.<sup>1</sup> Prior HDP and subtypes, preeclampsia, eclampsia, gestational hypertension, and chronic hypertension, have also been shown to be a sex-specific risk factor for cardiovascular disease (CVD), and is presently part of the guidelines to assess women's

risk for primary prevention of CVD.<sup>2 3</sup> In addition to increasing risk for CVD, HDP have been associated with the outcomes: hypertension, hyperlipidaemia, diabetes, chronic kidney disease and dementia.<sup>4–11</sup> HDP rates have been rising over the past few decades, particularly for preeclampsia.<sup>12 13</sup> Therefore, the importance of HDP as a risk factor for ageing-related diseases will become even more relevant in the coming years.

One of the primary limitations in HDP research, however, has been the widely varying estimates of HDP incidence rates. Prior studies have estimated that the overall incidence of HDP ranges from 4% to 25%, and preeclampsia from 1% to 9%.<sup>12–14</sup> While per-pregnancy rates can be useful to obstetricians to guide treatment strategies in pregnant women to reduce the risk of maternal and fetal adverse events, per-woman incidence rates of HDP are more clinically pertinent when assessing the long-term risk of ageing-related diseases.

Assessment of HDP is further complicated by the significant time interval (often decades) between exposure and subsequent ageing-related events that may affect the quality of women's recall. In addition, clinical definitions as well as related coding practices of HDP change over decades; likewise, the way data are collected and stored (eg, paper vs electronic records) across decades can affect data consistency and accessibility. An additional obstacle is the lack of standardised procedures and inaccessible pregnancy records when collecting births occurring at different medical institutions. To evaluate both the incidence of HDP and subtypes, as well as their associations with long-term outcomes, accurate determination of the exposure is essential. Currently, the American College of Obstetrics and Gynecology (ACOG) diagnostic criteria paired with medical chart review by a trained expert are considered the gold standard for the diagnosis of HDP.<sup>15–18</sup> However, this approach is laborious and time consuming and thus rarely feasible in studies involving larger cohorts of women. In addition, chart reviews by more than one medical expert, a necessity in larger studies, can introduce bias in exposure ascertainment. Studies involving HDP to date have primarily used either registries, maternal recall or discharge diagnosis codes as alternatives (eg, International Classification of Diseases (ICD) or the Hospital International Classification of Diseases Adapted (HICDA)).<sup>12 13 19–32</sup> When compared with trained expert review, these methods of HDP ascertainment are unable to reliably diagnose HDP and to accurately identify their subtypes.<sup>16–18 29 30 33–41</sup> In particular, codes for gestational hypertension were worse than codes for preeclampsia, illustrating that the sensitivity of the codes is dependent on the severity of the disease.<sup>34</sup> Thus, the reliance on codes can result in biased assessments of the associations between HDP type and the long-term risk of ageing-related diseases.

Therefore, developing a standardised algorithm with high sensitivity and specificity to detect historical HDP diagnoses, coupled by its application and validation in a cohort of women with complete medical record

abstraction of individual-level prenatal and delivery data, could have a significant impact on the ability to conduct accurate and clinically relevant research to assess the long-term sequelae of HDP and subtypes. The Olmsted County HDP cohort thus serves as a resource with longitudinal data to address many scientific questions, including:

- ▶ How do HDP diagnoses via algorithms and diagnostic codes compare to the gold standard of clinician diagnoses in a cohort? We have developed an algorithm that is comparable in sensitivity and specificity to HDP diagnoses based on detailed chart review by trained experts using accepted clinical criteria, which will enable large epidemiological studies of HDP.<sup>42</sup>
- ▶ What is the incidence of HDP and subtypes and how does it compare on a per-pregnancy basis versus a per-woman basis? By determining the incidence rates of HDP and subtypes by per number of pregnancies and per number of women, we have found that HDP incidence on a per-pregnancy basis underestimates the number of women affected by HDP.<sup>43</sup>
- ▶ Is a history of HDP, and specific subtypes, associated with risk of ageing-related diseases? In addition to finding that women with a history of HDP developed specific diseases at higher rates and at early ages, we also discovered that a history of HDP is associated with accelerated ageing, through accumulation of multimorbidity (a proxy for ageing).<sup>43</sup>
- ▶ Is a history of HDP, and specific subtypes, a risk factor for additional ageing-related outcomes?
- ▶ Is a history of HDP in mothers associated with risk of hypertension in offspring?

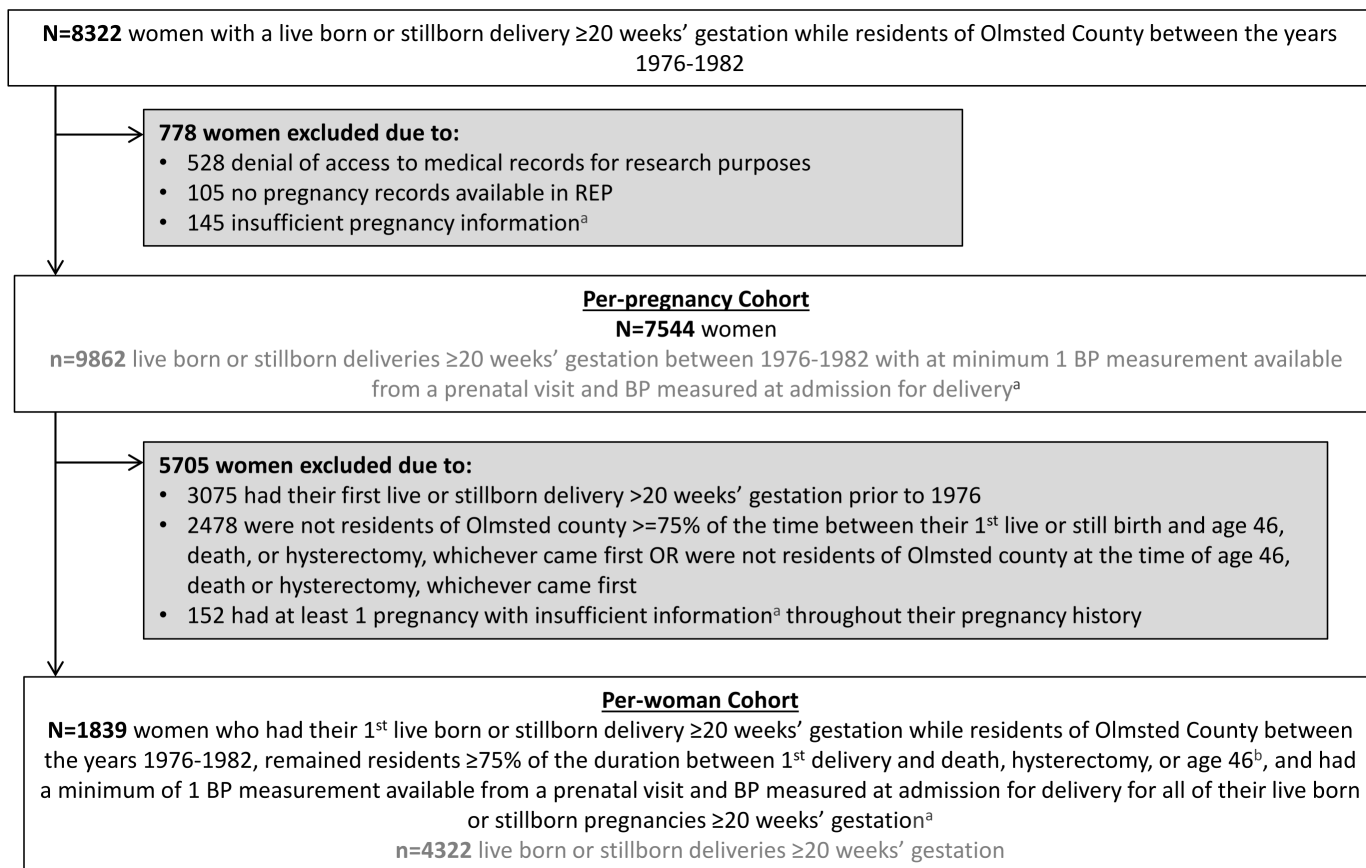
## COHORT DESCRIPTION

### Setting

The Rochester Epidemiology Project (REP) medical records-linkage system is an established institutional resource that has been described in detail elsewhere.<sup>42 44–46</sup> In summary, the REP was created in 1966 and captures healthcare information for the entire population of Olmsted County, Minnesota, USA by linking medical records from multiple healthcare institutions. This database is comprehensive, with only 2% of Olmsted County residents having denied access to their medical records for research purposes. As of 2012, the REP included a cohort of 502 820 unique individuals, with a total contribution of over 6 million person years of follow-up. Moreover, the REP captures virtually the entire population of Olmsted County as compared with the US census (>99.9% of the 1970–2010 census counts).<sup>46</sup>

### Identification of per-pregnancy cohort

As previously described, using the REP, we identified 8322 women who had a live-born or stillborn delivery occurring after 20 weeks' gestation between 1 January 1976 and 31 December 1982 while residents of Olmsted County, Minnesota.<sup>42</sup> This time span was selected for HDP ascertainment in order to allow for adequate follow-up of the women throughout their reproductive years and later



**Figure 1** Inclusion criteria for per-pregnancy and per-woman cohorts. <sup>a</sup>Criteria required for a pregnancy to be deemed to have enough information to determine hypertensive disorders of pregnancy status via the algorithm was at minimum 1 blood pressure (BP) measurement available from a prenatal visit and BP measured at admission for delivery. <sup>b</sup>Age 46 was the oldest age at delivery among the per-woman cohort. REP, Rochester Epidemiology Project.

in life, thus facilitating the study of per-woman HDP incidence and ageing-related outcomes. Women who did not consent to research authorisation or did not have their pregnancy records available in the REP were excluded from the cohort. Pregnancies were excluded if they did not have sufficient information recorded in the medical chart to allow for determination of HDP exposure status, which at minimum required documentation of one or more blood pressure (BP) measurements from a prenatal visit and a BP measurement from the day the woman was admitted for delivery. Our final per-pregnancy cohort consisted of 7544 women with 9862 pregnancies (see figure 1).

#### Identification of per-woman cohort

For calculation of the incidence of HDP on a per-woman basis, a subcohort of 1839 women was identified. These women had their first deliveries between the years 1976 and 1982 while residents of Olmsted County, remained residents of Olmsted County at least 75% of the time up until either age 46, hysterectomy or death, whichever came first, and had sufficient information recorded for all of their deliveries.<sup>43</sup> Among these women, there was a total of 4322 liveborn or stillbirth deliveries of greater than 20 gestational weeks (figure 1).

#### Patient and public involvement statement

Patients and the public were not involved in the development of this research cohort.

#### Cohort characteristics

Table 1 summarises patient characteristics among the per-pregnancy and the per-woman cohorts. While age at first delivery was in the mid-20s for both cohorts, there was a larger percentage of women with unknown race and educational level in the per-pregnancy cohort, compared with the per-woman cohort.

#### Population studies

The Olmsted County HDP cohort enables large-scale population studies by leveraging decades of women's delivery information to calculate HDP incidence rates, as well as HDP subtypes, both on a per-pregnancy and per-woman basis. Moreover, in the per-woman cohort, median (IQR) length of follow-up from last pregnancy to last follow-up in the REP is 36.3 (33.1, 38.7) years, which allows for evaluation of a range of ageing-related outcomes and mortality occurring both early and later in life. Finally, the availability of additional comorbidity, lifestyle and pregnancy data in the per-woman cohort

**Table 1** Patient characteristics of women in the per-pregnancy and per-woman cohorts

Characteristic	In per-pregnancy cohort (N=7544)	In per-woman cohort (N=1839)
Age at 1st delivery in 1976–1982*, mean (SD)	27 (4.8)	25 (4.1)
Race, n (%)		
Black	14 (0.2%)	2 (0.1%)
Asian	58 (0.8%)	15 (0.8%)
Hawaiian/Pacific Islander	2 (0.0%)	0 (0.0%)
American Indian	12 (0.2%)	4 (0.2%)
Other/mixed	82 (1.1%)	21 (1.1%)
White	5261 (70%)	1773 (96%)
Refusal	17 (0.2%)	2 (0.1%)
Unknown	2098 (28%)	22 (1.2%)
Ethnicity, n (%)		
Hispanic	7447 (99%)	1804 (98%)
Not Hispanic or unknown	97 (1.3%)	35 (1.9%)
Education, n (%)		
8th grade or less	10 (0.1%)	2 (0.1%)
Some high school	56 (0.7%)	8 (0.4%)
High school/GED	1001 (13%)	284 (15%)
Some college or 2-year degree	2028 (27%)	782 (43%)
4-year college degree	735 (9.7%)	261 (14%)
Post graduate studies	863 (11%)	348 (19%)
Unknown	2851 (38%)	154 (8.4%)

\*For the per-pregnancy cohort, this measure corresponds to a woman's first delivery captured within the study period from 1976 to 1982, which may not necessarily be the woman's first delivery.  
GED, general equivalency diploma.

can serve to facilitate discovery of confounders and effect modifiers of HDP on such outcomes (see [table 2](#)).

### Demographic and clinical characteristics and comorbidities

**Box 1** specifies the measurements abstracted from medical records for HDP exposed pregnancies in the per-pregnancy cohort and all pregnancies among women in the per-woman cohort, which consist of demographic and clinical characteristics, comorbidities, pregnancy characteristics (including prenatal, during and after delivery) and maternal and fetal outcomes.<sup>47 48</sup> Specific definitions for the variables used in this cohort have already been published.<sup>42</sup>

### Development and validation of algorithm to classify hypertensive disorders of pregnancy and subtypes

Data abstraction of the medical records to confirm a diagnosis of HDP and subtypes has been described in detail.<sup>42</sup> In brief, data from all pregnancies in women who had diagnostic codes indicative of a possible HDP during the years 1976–1982 were abstracted. During this time frame, diagnoses were coded using the Eighth Revision of HICDA coding system, and codes were used for research purposes, not billing purposes. The codes used to identify this cohort included hypertension (malignant, acquired),

preeclampsia, eclampsia, toxemia, hyperreflexia, high BP, labile BP, stillbirth, and low birth weight for gestational age (for full list of codes, see online supplemental table S1). The delivery records of women without one of the aforementioned diagnostic codes were then each screened by trained nurses. A screen positive was defined as at least two elevated BP measurements (defined as systolic BP>140 mm Hg and/or diastolic BP>90 mm Hg) during any prenatal or postnatal visit up to 12 weeks after the date of delivery. If the screen was positive, then the medical record for all of a woman's pregnancies was manually abstracted. If all pregnancies for a woman were screen negative, then her pregnancies were classified as normotensive and her chart was not abstracted.

When developing the algorithm to identify HDP and its subtypes, great care was taken to simulate clinical judgement whenever possible when considering the timeline and trajectory of BP elevations. Thus, when diagnosing gestational hypertension, we developed the '50% rule', which required sustained BP elevations in greater than 50% of readings, starting with the first BP above 140 mm Hg systolic or above 90 mm Hg diastolic. A visual schematic of this rule is available in an earlier publication of our work for clarity.<sup>42</sup> Isolated BP elevations prior to

**Table 2** Maternal and perinatal characteristics across hypertensive disorders of pregnancy subtypes among the n=4322 pregnancies in the per-woman cohort

Characteristic	Preeclampsia/eclampsia (n=158)	Gestational HTN (n=149)	Chronic HTN (n=35)	Normotensive pregnancy (n=3980)
Age at delivery (years), mean (SD)	25 (5.0)	27 (4.5)	29 (4.4)	27 (4.6)
BMI (kg/m <sup>2</sup> )*				
Missing	15	11	3	436
Mean (SD)	24 (4.5)	25 (5.1)	28 (6.2)	24 (4.3)
Number of fetuses, n (%)				
1	155 (98%)	144 (97%)	35 (100%)	3950 (99%)
2+	3 (1.9%)	5 (3.4%)	0 (0.0%)	30 (0.8%)
Parity prior to pregnancy, n (%)†				
0	127 (80%)	81 (54%)	15 (43%)	1616 (41%)
1	18 (11%)	46 (31%)	14 (40%)	1500 (38%)
2+	13 (8.2%)	22 (15%)	6 (17%)	864 (22%)
Gestational weeks, n (%)				
<34 weeks (preterm)	8 (5.1%)	1 (0.7%)	0 (0.0%)	74 (1.9%)
34–36 weeks (preterm)	22 (14%)	8 (5.4%)	2 (5.7%)	129 (3.2%)
≥37 weeks (term)	128 (81%)	140 (94%)	33 (94%)	3777 (95%)
Pregnancy type, n (%)				
Liveborn	154 (98%)	149 (100%)	35 (100%)	3955 (99%)
Stillborn	4 (2.5%)	0 (0.0%)	0 (0.0%)	23 (0.6%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Fetal weight percentile, n (%)‡				
Missing	1	3	0	12
≥10%	123 (78%)	125 (86%)	31 (89%)	3681 (93%)
<10%	34 (22%)	21 (14%)	4 (11%)	287 (7.2%)
APGAR 1 min‡				
Missing	2	2	0	49
Mean (SD)	7.6 (2.1)	7.8 (1.6)	8.2 (1.1)	8.1 (1.6)
APGAR 5 min‡				
Missing	15	12	1	270
Mean (SD)	8.7 (2.0)	9.2 (0.77)	9.3 (0.73)	9.2 (1.1)

Women with preeclampsia superimposed on chronic hypertension were classified as ‘Preeclampsia/Eclampsia’.

\*BMI based on weight taken closest to conception date, within 6 months prior and up to 20 gestational weeks.

†Parity defined as number of pregnancies with a gestational age ≥20 weeks resulting in a live or still birth.

‡Fetal weight considered small for gestational age was defined as <10% by the Brenner 1976 growth curve.<sup>47</sup> If twins, the fetal weight percentile and APGAR scores are based on the baby with the lowest birth weight.

APGAR, appearance, pulse, grimace, activity and respiration; BMI, body mass index; HTN, hypertension.

delivery were also not considered when defining the criteria for HDPs, including elevations occurring due to medications that have been known to raise BP (eg, methylergonovine maleate, non-steroidal anti-inflammatory drugs), elevations due to pain or tobacco use, or elevations during emergency room visits. Isolated BP measurements observed within 24 hours of delivery were not considered indicative of HDP alone without other clinical signs and symptoms.

Notably, we discovered that one of the ACOG criteria for gestational hypertension, defined as the use of BP measurements greater than 140/90 mm Hg on at least two occasions and at least 4 hours apart, was not optimal for making an accurate retrospective diagnosis of gestational hypertension for research studies. For example, a woman may have a single high BP reading at one of her prenatal visits and another high BP while delivering, but all subsequent BPs recorded during delivery and

### Box 1 Summary of measurements manually abstracted from medical records in the hypertensive disorders of pregnancy cohort

#### Measurement type

##### Demographic data

- ▶ Per woman
  - Date of birth
  - Race
  - Ethnicity

##### Clinical data

- ▶ Per pregnancy (at last visit prior to conception)
  - Height
  - Weight
  - Blood pressure

##### Medical conditions and behaviours data

- ▶ Per pregnancy (prior to delivery date)
  - Antihypertensive medication
  - Diabetic medication
  - Immunosuppressive medication
  - Psychotropic medication
  - History of smoking
  - Alcohol use
  - Self-reported history of preeclampsia/eclampsia
  - History of hypertension
  - History of diabetes mellitus
  - History of autoimmune disease
  - History of connective tissue disorders
  - History of congenital/acquired heart disease
  - History of chronic kidney disease

##### Family history data

- ▶ Per pregnancy (prior to delivery date)
  - Preeclampsia
  - Hypertension
  - Hyperlipidaemia
  - Heart disease
  - Diabetes mellitus
  - Stroke
  - Thyroid disease
  - Cancer
  - Lupus
  - Renal disease
  - Dialysis
  - Renal transplant

##### Delivery data

- ▶ Per pregnancy (at time of delivery)
  - Date of delivery
  - Result (live-birth or stillborn)
  - Length of pregnancy (term or preterm\*)
  - Gestational age (weeks) at delivery†
  - Number of fetuses
  - Baby weight (of each fetus)
  - APGAR score 1 min (of each fetus)
  - APGAR score 5 min (of each fetus)
  - Fetal weight percentile‡

##### Prenatal and hospital data

- ▶ Per clinical visit
  - Visit type
    - Prior to admission for delivery (including prenatal, hospital and other, excluding emergency room visits)
    - At admission for delivery

Continued

### Box 1 Continued

- After admission for delivery and within 24 hours post partum
- 24 hours post partum
- 48 hours post partum
- 72 hours post partum
- Visit date
- Systolic and diastolic blood pressure
- Antihypertensive or preeclampsia medication
- Weight
- Dipstick protein (NA, 1+, 2+, 3+, trace)
- Platelet count

##### Laboratory data

- ▶ Per lab draw (throughout pregnancy up to 72 hours post partum)
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Serum creatinine
  - 24-hour urine protein
  - Protein/osmolality ratio§

##### Pregnancy complications data

- ▶ Per pregnancy (after 20 gestational weeks)
  - Seizures (in hospital or as outpatient)
  - Changes in mental health status
  - Coma
  - Hyperreflexia
  - Persistent headaches
  - Epigastric pain

\*Preterm is defined as <37 gestational weeks.

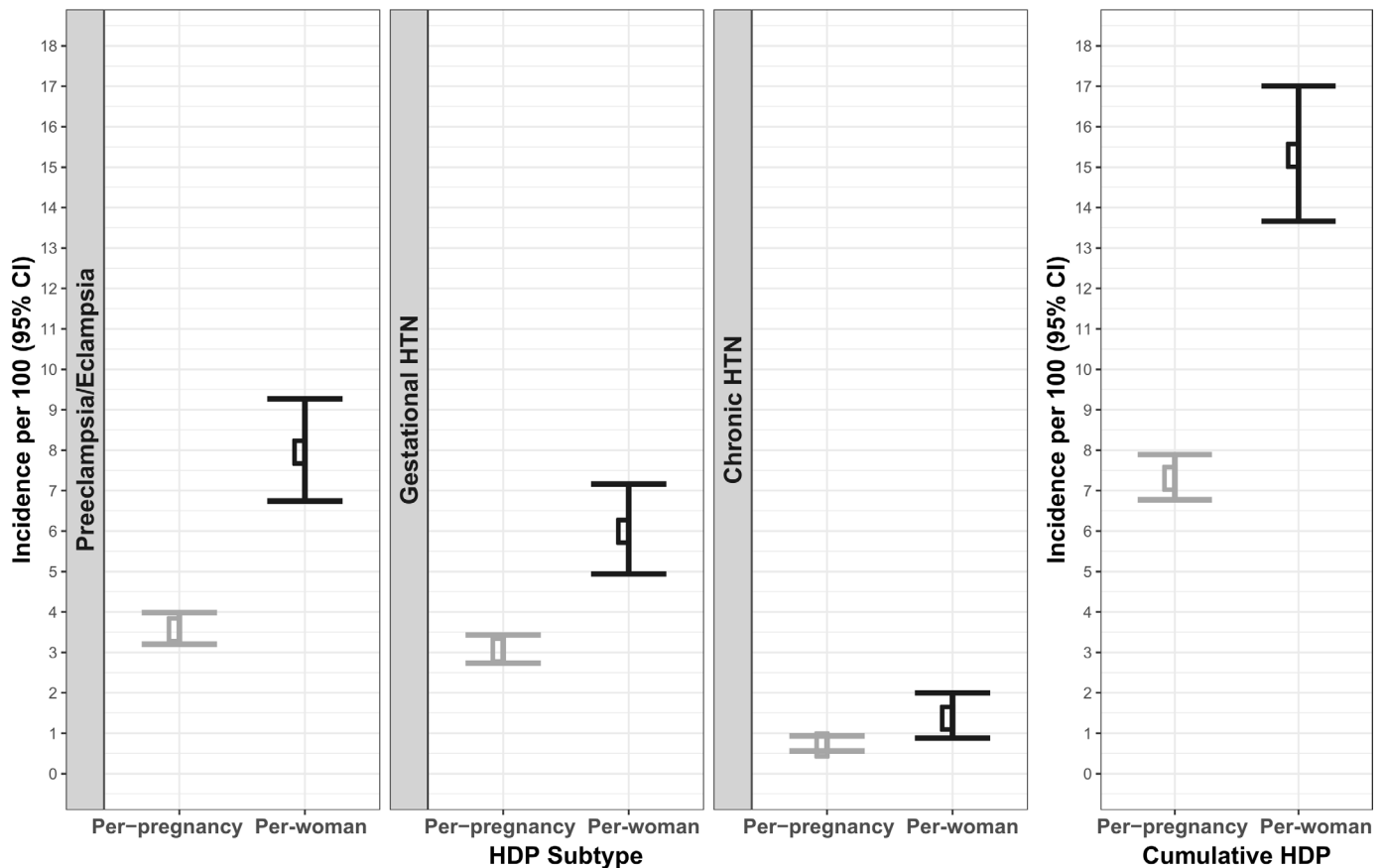
†Gestational age at delivery was estimated based on either the first obstetric ultrasound exam performed prenatally, if available, or else the date of the woman's last menstrual period.

‡Fetal weight percentile was calculated based on gestational age and the Brenner 1976 growth curve.<sup>47</sup>

§Protein/osmolality ratio has been validated as a surrogate measure of 24 hour urine protein in the Mayo Clinic laboratory.<sup>48</sup>

postpartum are normal, and no adverse maternal or fetal events occurred. In this example, she may be categorised by ACOG as having gestational hypertension, while most clinicians would consider her to be normotensive. Thus, diagnosis of gestational hypertension in our algorithm was based on sustained BP elevations.

The final version of the algorithm classified pregnancies into the following HDP subtypes: normotensive, gestational hypertension, chronic hypertension, preeclampsia or preeclampsia superimposed on chronic hypertension (either definitive, probable or possible) or eclampsia (either definitive or probable). See online supplemental table S2 for the full algorithm. The subcategories of definitive, probable and possible preeclampsia and eclampsia reflect the challenges intrinsic to retrospective studies when data are not collected in a systematic manner. When the overall clinical presentation of the pregnancy was indicative of preeclampsia or eclampsia, but limited data were recorded on BP trends and proteinuria assessments, then the pregnancy was categorised as probable or possible, depending on the amount of data available. For deliveries coded as normotensive, but with BP elevations observed at 48 or 72 hours postpartum, one



**Figure 2** Incidence (per 100) of hypertensive disorders of pregnancy (HDP), by subtypes and cumulative, per-pregnancy and per-woman. HTN, hypertension.

of the obstetricians manually reviewed a woman's chart to confirm or rule out a HDP diagnosis. A simplified flow-chart showing which clinical variables lead to each HDP subtype diagnosis can be found in our prior work.<sup>42</sup>

The algorithm using chart abstracted data was validated against clinician-made HDP diagnoses based on both their clinical experiences and ACOG clinical criteria. To accomplish this, the medical records from a random sample of 75 pregnancies from different women with either normotensive, gestational hypertension or preeclamptic pregnancies diagnosed via the algorithm were independently reviewed by two blinded obstetricians, who assigned exposure status based on their clinical expertise. Clinician-made diagnoses were also compared with HDP electronic diagnoses using HICDA codes for additional comparison.

### Incidence of HDP

Per-pregnancy incidence was calculated using the 9862 pregnancies among 7544 women in the per-pregnancy cohort, with 95% CIs estimated using the Wilson score interval as appropriate for binary clustered data (multiple pregnancies per woman). HDP incidence and subtypes of preeclampsia/eclampsia, gestational hypertension and chronic hypertension on a per-pregnancy basis are shown in figure 2. Per-pregnancy incidence among HDP subtypes was also calculated after stratifying by age at delivery (see figure 3).

The per-woman incidence was calculated by classifying each of the 1839 women in the per-woman cohort based on their worst HDP subtype, according to the following hierarchy: eclampsia/preeclampsia>chronic hypertension>gestational hypertension>normotensive; 95% CIs were estimated using the exact method for a binomial proportion, since these data were not clustered. HDP incidence and their subtypes on a per-woman basis are also presented in figure 2. Maternal and perinatal characteristics across HDP subtypes among all pregnancies in the per-woman cohort are reported in table 2. Since HDP is typically a complication of first pregnancies, characteristics among first pregnancies in the per-woman cohort are also presented in online supplemental table S3.<sup>7,49</sup>

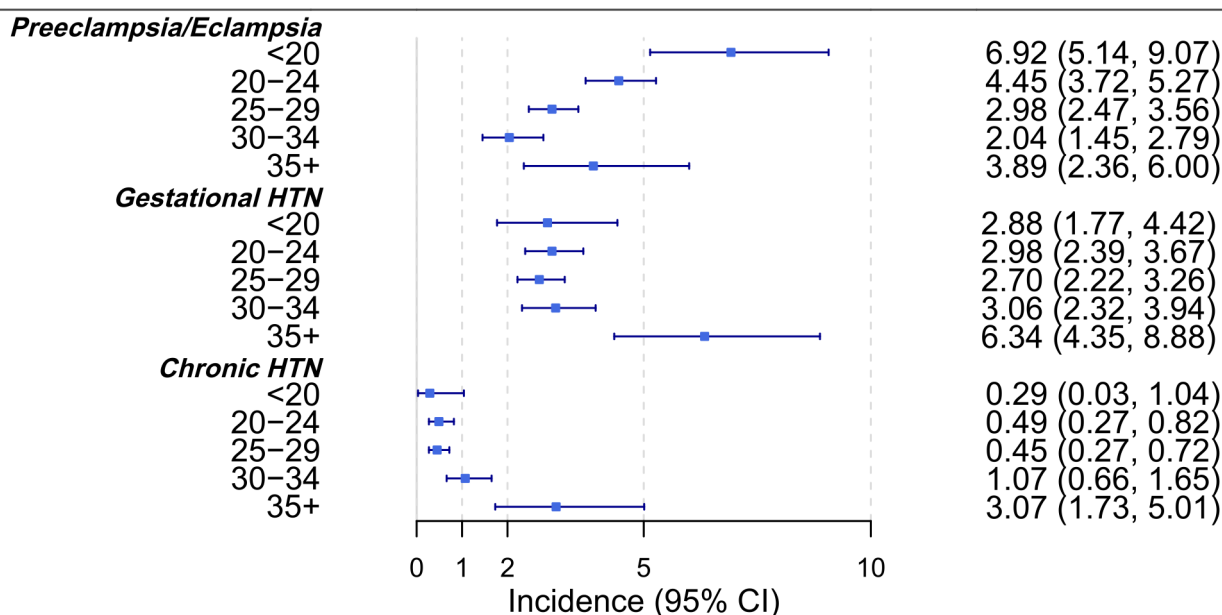
### Outcomes

Short-term adverse outcomes were ascertained via manual review and recorded on a per-pregnancy basis up to 12 weeks postpartum, and included in-hospital death of the mother after giving birth, intensive care unit visits, outpatient visits, seizures observed after birth, postpartum depression, blood transfusions, new diagnosis of diabetes mellitus, stroke, coronary artery disease, congestive heart failure, arrhythmia, thrombotic events, dialysis or oliguria.

Diseases occurring after a woman's childbearing years can be ascertained by electronically retrieving diagnostic codes from both inpatient and outpatient visits to REP-affiliated providers throughout the woman's residency in

## Maternal age (years)

Incidence per 100 pregnancies (95% CI)



**Figure 3** Age-specific per-pregnancy incidence (per 100 pregnancies) of hypertensive disorders of pregnancy subtypes among 9862 pregnancies in the per-pregnancy cohort during 1976–1982 while residents of Olmsted County, Minnesota. HTN, hypertension.

Olmsted County. In this way, our cohort facilitates the use of time to event analyses to evaluate a broad array of long-term outcomes, including mortality. Using our per-woman cohort, we have evaluated the effect of HDP exposure on mortality, as well as chronic conditions recommended by the U.S Department of Health and Human Services to study long-term multimorbidity, which have been detailed elsewhere.<sup>43 50–52</sup> These conditions were determined by retrieving electronic diagnosis codes from inpatient and outpatient visits to REP-affiliated providers. Follow-up duration can be determined from baseline to the last visit to a REP-affiliated provider, and women with prevalent conditions at baseline can be excluded from the analysis to focus on incident outcomes.

In addition to these outcomes described above, many other potential outcomes of interest for studies of HDP can be ascertained from accessing the electronic health records (EHR) and billing systems available through the REP. These data can include all ICD-9 and ICD-10 and Current Procedural Terminology coded diagnoses and procedures, healthcare utilisation, including office visits, hospitalisations and emergency room visits, and full text of the EHR that is available for chart abstraction or for natural language processing of the clinical notes.

### FINDINGS TO DATE

Our studies using the HDP cohort have helped confirm the accuracy and precision of our algorithm compared with the gold standard of clinician review using chart abstracted clinical data for HDP classification. Compared

with clinician-made diagnoses (the gold-standard), the algorithm yielded sensitivities (95% CIs) of 100% (86%–100%), 88% (69%–98%) and 100% (86%–100%), and specificities of 94% (84%–99%), 100% (93%–100%) and 100% (93%–100%) for normotensive, gestational hypertension and preeclamptic pregnancies, respectively.<sup>42</sup> We have also found the algorithm's performance to be superior to using diagnostic codes in historical cohorts, as the HICDA code sensitivities were 96% (80%–100%) for normotensive pregnancies, 32% (15%–54%) for gestational hypertension and 96% (80%–100%) for preeclampsia; specificities were 78% (64%–89%), 96% (86%–100%) and 88% (76%–96%), respectively.<sup>42</sup> This finding is consistent with previously reported accuracies for ICD codes, as well as maternal recall for HDP.<sup>16 20 30 33</sup> Notably, the HDP algorithm was particularly superior in identifying pregnancies with gestational hypertension, achieving an accuracy on par with clinician review while being applicable on a large scale. In contrast, the diagnostic codes exhibited especially poor performance differentiating gestational hypertension and normotensive pregnancies in a historical cohort.

By constructing both per-pregnancy and per-woman cohorts, we reported a doubling of HDP incidence rates when assessed on a per-woman basis (15.3%) compared with rates observed on a per-pregnancy basis (7.5%) (figure 2). Thus, prior studies of HDP incidence, which reported on a per-pregnancy basis, may have significantly underestimated the number of affected women. In addition, when stratified by age at delivery, we found that the



per-pregnancy incidence of both gestational hypertension and preeclampsia exhibited a U-shaped pattern, with younger women <20 years of age and older women >35 years of age with the highest incidence (see [figure 3](#)). As extremes of age have been widely recognised as risk factors for HDP,<sup>1</sup> these findings further validate the results originating from our cohort.

When assessing the development of diseases of ageing among the pregnancies with HDP compared with age-matched and parity-matched normotensive pregnancies from our per-pregnancy cohort, women with a history of HDP exhibited a higher risk of CVD, defined as cardiac arrhythmias, coronary artery disease, congestive heart failure or stroke.<sup>43</sup> Women with HDP also demonstrated increased risks for conditions that have been previously identified as CVD risk factors, including hypertension, diabetes mellitus, chronic kidney disease, hyperlipidaemia, as well as dementia, an outcome in patients with CVD. Results were similar after adjusting for the lifestyle factors of education, smoking and obesity. Accelerated rates of multimorbidity accumulation were also observed in women with HDP compared with referent pregnancies, both before and after excluding hypertension.<sup>43</sup>

## Strengths and limitations

### Strengths

One of the main strengths of our cohorts is the improved sensitivity and specificity of the HDP algorithm to accurately assign exposure status compared with methods that rely on diagnostic codes or registries. Whereas diagnostic codes, registries and ACOG criteria are designed for clinical purposes, our algorithm is explicitly designed for research purposes; thus, its application in research studies will allow investigators to avoid the misclassification of HDP exposure that could obscure future discoveries. Our algorithm also has the additional potential to reduce the risk of bias that could be incurred by chart review by individual medical experts or maternal recall bias from survey-based methods, while at the same time, facilitating HDP ascertainment for large populations of interest. Moreover, while our algorithm was applied to manually abstracted data, this approach could also be applied to data electronically retrieved via EHR for more efficient exposure ascertainment.

Another notable advantage of our cohort is the ability to calculate population-based estimates of HDP incidence, as well as subtypes, both on a per-pregnancy and per-woman basis. As demonstrated in our findings, HDP incidence rates on a per-woman basis are roughly double those found on a per-pregnancy basis, which is consistent with previous findings reported from a prospective UK Biobank study.<sup>53</sup>

### Limitations

Our cohort has some limitations. First, our algorithm was not developed to diagnose HELLP (ie, haemolysis, elevated liver enzymes and low platelet count) syndrome, as this was first described in 1982<sup>54</sup> and our study participants in the

per-pregnancy cohort delivered between the years 1976 and 1982. A recent US Preventive Services Task Force Recommendation Statement, however, has recommended that all pregnant women be screened for preeclampsia with serial BP measurements during pregnancy.<sup>55</sup> A second limitation is that our population-based cohort is predominantly non-Hispanic white. Previous studies have found evidence that African American women may experience higher rates of HDP, as well as elevated risks for CVD compared with white women.<sup>55</sup> These findings necessitate future HDP studies to be conducted in more racially diverse cohorts. Third, we used diagnostic codes to ascertain long-term outcomes. However, further studies could leverage the full breadth and depth of EHR data and employ machine learning algorithms. Finally, our cohort consists of a population of women whose deliveries occurred decades ago. With the medical literature suggesting increased rates of HDP, as well as risk factors for HDP in the last few decades, including obesity and older age at conception, data using this cohort likely underestimate current incidence rates for HDP. However, ascertainment of a pregnancy cohort from four decades ago will facilitate investigations into the long-term effect of HDP on ageing-related outcomes.

## CONCLUSION

The Olmsted County HDP cohort is a large-scale, population-based resource which allows researchers to calculate population-based estimates of HDP incidence and subtypes both on a per-pregnancy and per-woman basis, and follow-up women decades after their childbearing years for study of ageing-related diseases. By constructing both per-pregnancy and per-woman cohorts, we reported evidence of a doubling of HDP incidence rates when assessed on a per-woman basis compared with rates observed on a per-pregnancy basis. Both complementary measures could be beneficial for future research studies by enabling assessment of pregnancy-related outcomes, as well as long-term outcomes. Moreover, in addition to finding that women with a history of HDP developed specific diseases at higher rates and at early ages, we also discovered that a history of HDP is associated with accelerated ageing, through accumulation of multimorbidity.

## COLLABORATION

The algorithm is available on the following website: <http://statistika.mfub.bg.ac.rs/hpd-algorithm/>. (Note: for demonstration purposes, please use 'test' for login and 'dataset' for password. To review test patients, please enter the numbers from 001 to 009 in the 'search patients' tab.) Researchers interested in collaboration and full access to the algorithm for research purposes are invited to submit a request to Dr Vesna Garovic (Garovic.Vesna@mayo.edu). Currently, no data are available to be shared externally.

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**Contributors** VDG is the guarantor of this study. VDG and MM jointly conceived the study. VDG, MM, LV, WMW, YSBT, AK, SP, MDG, JVV and SS performed data abstraction and handled the data management and analysis. LV and NMM jointly programmed the algorithm. All authors critically revised the manuscript for intellectual content and approved the manuscript.

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**Patient consent for publication** Not applicable.

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