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Incidence and Long-Term Outcomes of Hypertensive Disorders of Pregnancy

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Abstract

Background—Hypertensive disorders of pregnancy (HDP) are associated with increased risks for cardiovascular disease (CVD) later in life. The HDP incidence is commonly assessed using diagnostic codes, which are not reliable; and typically are expressed per-pregnancy, which may underestimate the number of women with a HDP history after their reproductive years.

Objective—We sought to determine the incidence of HDP expressed as both per-pregnancy and per-woman, and to establish their associations with future chronic conditions and multimorbidity, a measure of accelerated aging, in a population-based cohort study.

Methods—Using the Rochester Epidemiology Project medical record-linkage system, we identified residents of Olmsted County, Minnesota, who delivered between 1976 and 1982. We classified pregnancies into normotensive, gestational hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and chronic hypertension using a validated electronic algorithm, and calculated the incidence of HDP both per-pregnancy and per-woman. The risk of chronic conditions between women with versus those without a history of HDP (age

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and parity 1:2 matched) was quantified using the hazard ratio (HR) and corresponding 95% confidence interval (CI) estimated from a Cox model.

Results—Among 9,862 pregnancies, we identified 719 (7.3%) with HDP and 324 (3.3%) with preeclampsia. The incidence of HDP and preeclampsia doubled when assessed on a per-woman basis: 15.3% (281/1839) and 7.5% (138/1839), respectively. Women with a history of HDP were at increased risk for subsequent diagnoses of stroke (HR 2.27; 95% CI 1.37–3.76), coronary artery disease (1.89; 1.26–2.82), cardiac arrhythmias (1.62; 1.28–2.05), chronic kidney disease (2.41; 1.54–3.78), and multimorbidity (1.25; 1.15–1.35).

Conclusions—The HDP population-based incidence expressed per-pregnancy underestimates the number of women affected by this condition during their reproductive years. A history of HDP confers significant increase in risks for future chronic conditions and multimorbidity.

Condensed abstract

Using a population-based study, we reported that the incidence of HDP expressed per pregnancy (7.3%) underestimated the number of affected women after their reproductive years (15.3%). Women with a history of HDP, compared to those with normotensive pregnancies, demonstrated significant increased risks for both kidney and CVD, even at a relatively young median age of 60 years, as well as multimorbidity, a measure of accelerated aging.

Keywords

hypertensive disorders of pregnancy; cardiovascular disease; incidence; multimorbidity

Introduction

Hypertensive disorders of pregnancy (HDP) include four categories - preeclampsia/eclampsia, gestational hypertension, chronic hypertension, and preeclampsia/eclampsia variants superimposed on chronic hypertension (1). HDP remain one of the leading causes of maternal and fetal morbidity and mortality worldwide. In addition, a history of HDP confers an elevated risk for future cardiovascular events, and is now incorporated into guidelines for risk assessment and the prevention of stroke and cardiovascular disease (CVD) for women (2,3). Over the last decade, several concerning trends have become apparent. The prevalence of both MI (4) and self-reported stroke (5) have increased compared to similarly aged men. Further, coronary heart disease death rates have increased in women 35–54 years of age (3) and in patients with severe forms of preeclampsia, who are at risk for CV death as early as the first decade after their affected pregnancies (6). These alarming developments, along with the recent evidence that the rates of HDP have increased over the last 3 decades (7,8), suggest that the role of HDP as a sex-specific CVD risk factor may become even more important in the years to come. Despite the acknowledged importance of HDP in risk assessment and prevention, the incidence of HDP is not well understood. Considerable variations in the incidence of HDP, ranging from 4–25%, and of preeclampsia, ranging from 1–9%, (7–9) make it difficult to estimate the attributable risk of CVD due to HDP. Studies of HDP incidence to date have primarily utilized registry or International Classification of Diseases (ICD) code approaches, which have been shown to be unreliable (10,11). A complete medical record abstraction of blood pressure and other individual-level data

spanning the time before pregnancy through post-partum visits to ascertain severity and type of HDP has not yet been conducted. In addition, when assessing the subsequent risk of chronic disease beyond reproductive age in women with versus without a history of HDP, specifically preeclampsia, the number of affected women (incidence per woman) is more informative than the number of affected pregnancies (incidence per pregnancy). However, the medical literature has focused on the per-pregnancy incidence of HDP and the per-woman incidence is not quantified or appreciated.

The overall aim of this study was to determine the incidence rates of HDP (total and by subtype) per-pregnancy and per-woman in a population-based cohort by using a validated electronic algorithm based on accepted clinical criteria for subtypes of HDP. We postulated that the incidence of HDP, as estimated per number of pregnancies, underestimates the number of women with a history of this condition after their reproductive age. In addition, we aimed to compare the risk of common chronic conditions designated by the US Department of Health and Human Services between women with versus those without a history of HDP. As women with a history of HDP develop these conditions not only at higher rates, but years earlier than women who have had normotensive pregnancies (12), we postulated that women with a history of HDP will demonstrate accelerated aging, as demonstrated by accumulation of multimorbidity, a clinical proxy measure for accelerated aging (13).

Methods

Study Design and Population

The Rochester Epidemiology Project (REP) medical record-linkage system was used to establish a cohort consisting of all women who were residents of Olmsted County and delivered between January 1, 1976 and December 31, 1982 (liveborn or stillborn). The record-linkage system of the REP has been described comprehensively elsewhere (14,15). Briefly, the REP links all of the medical records from all providers in Olmsted County (encompassing Mayo Clinic and Olmsted Medical Center and their affiliated hospitals and medical facilities) using a unit medical record system whereby all outpatient, inpatient, emergency room, and nursing home information is kept in the same unit record. We selected the 1976–1982 time period for HDP assessment so that there was sufficient time for the women i) to complete their reproductive years, which would allow for the study of HDP incidence per woman and ii) to develop age-related chronic conditions in order to examine the relationship between HDP and adverse future outcomes, including cardiovascular and renal disease. This study was approved by the Institutional Review Boards at the Mayo Clinic and Olmsted Medical Center.

Identification of per-pregnancy cohort and per-woman sub-cohort for HDP incidence—Using the REP medical records linkage system, we identified 8,177 women with a delivery (liveborn or stillborn, ≥20 weeks' gestation) between January 1, 1976 and December 31, 1982 while residents of Olmsted County, Minnesota (Figure 1). We excluded women who either did not consent to the use of their medical records for research or with insufficient pregnancy information reported in the medical record. A pregnancy was

classified as having sufficient information to determine HDP status if there was at least one blood pressure measurement from a prenatal visit and at least one blood pressure measurement from admission for delivery. Per-pregnancy HDP incidence was estimated based on all pregnancies (n=9,862) among 7,544 residents of Olmsted County who delivered during 1976–1982. For the incidence of HDP per-woman, a sub-cohort of 1,839 women was identified. These women had their first deliveries between1976 and 1982 while residents of Olmsted County, were residents of Olmsted County by the end of their childbearing years, and had sufficient information reported for all of their pregnancies.

We first identified all women with diagnostic codes indicative of a possible HDP occurring between January 1, 1976 and December 31, 1982, and their charts were fully abstracted (a list of codes is shown in Supplemental Table 1). We then screened every chart of each remaining woman in the cohort without a code suggestive of a possible HDP. A positive screen was defined as two elevated blood pressures, either systolic blood pressures (SBP) >140 mmHg and/or diastolic blood pressures (DBP) >90 mmHg at any prenatal visit, during admission for delivery, or postnatally before leaving the hospital. All screen positive charts were then fully abstracted. Screen-negative charts were categorized as normotensive pregnancies.

Inter- and Intra-rater Reliability—There were six abstractors involved in retrieving data from the medical records over the course of the project. We assessed both inter-rater and intra-rater reliability for the diagnosis of normotensive pregnancy versus HDP and HDP type. For example, there were 21 pregnancies abstracted by the same nurse on different days, several months apart. The diagnosis of normotensive versus HDP and type were the same for all 21 pregnancies, resulting in 100% intra-rater agreement. Additionally, 128 pregnancies were accessed by two different abstractors, of which 126 (98.4%) had the same diagnosis of normotensive versus HDP and HDP type.

Assignment of HDP Exposure Status—From the first prenatal visit through 12 weeks post-partum, all data regarding blood pressures, dipstick protein, and hypertensive medication use at each visit were recorded and dated. The following laboratory values were collected between the first prenatal visit and up to 72 hours post-partum: 24-hour protein, serum creatinine, platelet count, and liver function tests. We used a validated electronic diagnostic algorithm to determine the presence of any HDP and type (16) based on accepted clinical criteria and the diagnosis of hypertension, which required blood pressure elevations in greater than 50% of blood pressure readings (the “50% rule”). The algorithm was validated by comparison of algorithm-based diagnoses to the gold standard, i.e., physician-made diagnoses. The algorithm-based approach demonstrated significant improvements in sensitivity and specificity in the classification of exposure (i.e., HDP) compared to methods that utilized diagnostic codes only (16). The definition of each HDP type used in the algorithm is described in Supplemental Table 2. In addition to the data that were required to classify pregnancies as normotensive vs. HDP, demographic, prenatal and intrapartum data were also collected. All abstracted data were first recorded on paper forms and subsequently entered into a database for future analysis.

Identification of Cohort for Outcome Analysis—For each woman with a pregnancy complicated by HDP, we defined the index date as the date when she first met criteria for HDP. We then randomly identified two referent women with normotensive pregnancies from the women in the birth cohort matched for the date of delivery (±1 year), maternal age (±1 year), and parity at index pregnancy (1 or >1) who had not met criteria for HDP before the index date. Women who first met criteria for HDP based on a delivery prior to 1976 were excluded from this analysis. Women with more than one normotensive pregnancy during 1976–1982 could have been identified as a matched referent for more than one HDP woman.

Ascertainment of Chronic Conditions—We considered 16 of the 20 chronic conditions recommended by the US Department of Health and Human Services (DHHS) (17–19) to study long-term multimorbidity (Supplemental Table 3). The following 4 DHHS conditions were excluded because they were rare in our population: human immunodeficiency virus infections, autism spectrum disorders, schizophrenia, and hepatitis. The six primary outcomes of the study were cardiac arrhythmias, coronary artery disease (CAD), congestive heart failure (CHF), stroke, chronic kidney disease (CKD) and dementia. Secondary outcomes included a number of multimorbidities accumulated over the time of follow up and death from any cause obtained from death certificates. These sixteen conditions were ascertained electronically by retrieving diagnosis codes from inpatient and outpatient visits to REP-affiliated providers from the index date through the women's last visits.

Statistical Analyses—Per-pregnancy HDP incidence (per 100 pregnancies) was calculated considering each pregnancy as a distinct event. Per-pregnancy incidence rates were calculated overall, by HDP subtype, and stratified by calendar year and age (<20, 20–24, 25–29, 30–34, and ≥35 years) within each subtype of HDP. The denominators used to determine the incidence, by age and calendar year, are shown in Supplemental Table 4. For the per-pregnancy incidence rates, 95% confidence intervals (CI) were constructed using a Wilson score interval appropriate for a proportion estimated from clustered binary data given that women could have multiple pregnancies in the cohort (20). The 95% CIs for the per-woman incidence rates were constructed using an exact method for a binomial proportion. Per-woman HDP incidence (per 100 women) was calculated based on classifying each woman using the following hierarchy: eclampsia>preeclampsia superimposed on chronic hypertension>preeclampsia>chronic hypertension>gestational hypertension>normotensive.

Each of the 16 chronic conditions was evaluated separately, and women with the condition prior to the index date (ie for each matched set, the date of the exposed woman's first pregnancy complicated by HDP) were excluded from each analysis in order to evaluate *de novo* conditions. The duration of follow-up was calculated from the index date to the date of the condition diagnosis, last visit to a REP-affiliated provider prior to the end of the study (December 31, 2017), or subsequent HDP diagnosis for the referent women. Cumulative incidence curves were estimated using the Kaplan–Meier method. Cox proportional hazards models (21) were used to estimate hazard ratios (HRs) and corresponding 95% CIs using age as the time scale, with women entering the risk set at their respective index ages. The proportional hazards assumptions for the Cox models were checked using martingale

residuals using a Kolmogorov-type supremum test based on a sample of 1,000 simulated residual patterns. The accumulation of chronic conditions was calculated as the mean number of conditions accumulated over the follow-up after the index date and was represented graphically using Aalen-Johansen curves. Hazard ratios were computed using Anderson-Gill regression models with age as the time scale(22–24). Robust sandwich covariance estimates were used to account for either women included in both cohorts (e.g. referent women with subsequent HDP) or women with multiple pregnancies who were selected as referents more than once. Both unadjusted models and models adjusted for education, smoking, and obesity were fit. Tests of statistical significance were conducted at the two-tailed alpha level of 0.05. Bonferroni correction was used to adjust for type 1 error due to multiple comparisons for six primary outcomes (0.05/6=0.0083). Statistical analyses were performed using the SAS version 9.4 software package (SAS Institute, Inc.; Cary, NC) and R software v3.4.2.

Results

We identified 7, 544 mothers who had 9,862 pregnancies of ≥20 weeks' gestation between January 1, 1976 and December 31, 1982 while residents of Olmsted County, MN for the calculation of incidence per-pregnancy (Figure 1). During the six-year assessment period, we identified 659 women with a total of 719 HDP pregnancies (Supplemental Table 5). Pregnancies with preeclampsia or preeclampsia superimposed on chronic hypertension - compared to pregnancies with gestational hypertension- were less frequently carried to term (302 (86.3%) vs 286 (95.3%), p<0.001), resulted more frequently in small-for-gestational age infants (80 (23.0%) vs 31 (10.5%), p<0.001), and had higher frequencies of stillbirths (10 (2.9%) vs 2 (0.7%), p=0.04).

The per-pregnancy incidence rate was 7.3% (95% CI 6.8–7.9%) for HDP, including, 0.04% for eclampsia and 3.3% for preeclampsia (Table 1). The incidence per-woman calculation was based on a sub-cohort of 1,839 women for whom we had sufficient information on all of their pregnancies ≥20 weeks' gestation (Figure 1), with a median [IQR] number of pregnancies 2 [2, 3] per woman. Of note, demographic and perinatal characteristics between women with and those without sufficient information on all of their pregnancies were similar (Supplemental Table 6). The per-woman incidence was twice that of their incidence rates observed per-pregnancy: 15.3% and 7.5% for HDP and preeclampsia, respectively (Table 1).

The age-specific incidence (per 100 pregnancies) of each HDP subtype is shown in Figure 2 and in Supplemental Table 7. The per-pregnancy incidence of preeclampsia with respect to age was U-shaped, such that the youngest women (i.e., <20 years and 20–24 years) and those ages ≥35 years had the highest incidence. The per-pregnancy incidence of preeclampsia in women less than 20 years of age was higher than in women 20–34 years of age (6.5 [95% CI 4.8–8.6] vs 3.0 [95% CI 2.7–3.4] per 100 pregnancies). Per-pregnancy incidence of gestational hypertension was higher in women ages ≥35 compared to other age groups (6.3 [95% CI 4.4–8.9] vs 2.9 [95% CI 2.5–3.2-] per 100 pregnancies.

The development of chronic conditions after a pregnancy complicated by HDP was studied in 571 women with pregnancies complicated by HDP, and 1142 age- and parity-matched

referents (Table 2). The median length of follow-up was 36.2 years (IQR, 23.5–38.2) and 35.8 years (IQR, 13.7–37.9) for women with a history of HDP and referent women, respectively. Women with a history of HDP compared to referent women demonstrated increased risks of CVD events and risk factors, including cardiac arrhythmias CAD, CHF, stroke, CKD, dementia, hyperlipidemia, hypertension, and diabetes, and in analyses both unadjusted and adjusted for education, smoking, and obesity (Table 2, Figure 3, and Central Illustration). Women with a history of HDP also experienced accelerated rates of accumulation of the 16 chronic conditions considered together (Table 2 and Central Illustration). The difference in the multimorbidity burden remained similar after excluding hypertension (Table 2). However, all-cause death rates were not different between the groups. A sub-analysis of women with a history of preeclampsia/eclampsia/preeclampsia superimposed on chronic hypertension showed that the magnitude of the effect of a history of preeclampsia was similar to that of HDP for most of the outcomes (Table 3). After Bonferroni correction for multiple comparisons for the cohort as a whole (Table 2), all primary endpoints except dementia were still statistically significant in unadjusted analyses; and cardiac arrhythmia, CAD, and CKD were still significant in adjusted analyses. In a sub-group of women with a history of preeclampsia/eclampsia/preeclampsia superimposed on chronic hypertension (Table 3), CAD and CKD were significant in both the unadjusted and adjusted analyses after Bonferroni correction.

Discussion

Our present study reports several novel findings regarding HDP incidence and related long-term outcomes (Central Illustration). First, it assessed the incidence of HDP in a population based cohort by medical record review and chart abstraction, an approach superior to the use of discharge diagnoses or registry data that have been previously used for US populations. Second, it clearly demonstrated that the incidence of HDP expressed per pregnancy (7.3%) underestimated the number of affected women after their reproductive years (15.3%). Third, women with a history of HDP, compared to those with normotensive pregnancies, demonstrated significant increased risks for both kidney and heart disease, including cardiac arrhythmias, CAD, and stroke that can be, at least in part, explained by higher rates of CVD risk factors, such as hyperlipidemia, hypertension, and diabetes. Fourth, a history of HDP identified women at risk for multimorbidity, as these women experienced accelerated rates of accumulation of chronic conditions, primarily those related to CVD risks and events, compared to women with normotensive pregnancies. Taken together, our findings indicate that the risks for kidney and heart disease in women with HDP histories have been underestimated. The proportion of women who may be at risk based on their HDP histories (15.3%) is similar to the proportions of women at risk for CVD based on the presence of traditional risk factors such as, smoking (13.7%) (25), hyperlipidemia (14.8%) (26), and diabetes (12%) (27). Inclusion of HDP history may substantially reduce misclassification using current CVD risk scores, which are particularly inaccurate in women (28).

The wide variations in previously reported rates of HDP and preeclampsia may be attributable to differences in study design, population characteristics and setting, the definition of HDP and type, years of assessment, or to geographical and/or natural variation. Most of the reports of US population-based rates of HDP have used national registries or

databases.(7–8), (29– 34). A comparison of a registry based diagnosis with a “gold standard” chart review in the Medical Birth Registry of Norway for the diagnosis of preeclampsia showed a specificity of 99.2%, but a sensitivity of only 43.0% (35). In particular, mild cases of preeclampsia were most often missed. The use of ICD codes to establish HDP diagnoses have been reported to be no better, with high specificity, but low sensitivity due to significant underreporting of milder disease forms (10,11, 36). Given the unreliability of the ICD codes, we have developed and validated an electronic algorithm for the retrospective diagnoses of HDP (16). The electronic diagnostic algorithm was superior to diagnostic codes and allowed for the consistent application of objective criteria, thus reducing the risk for bias that may be introduced by individual medical experts, while allowing for the analyses of large datasets. However, with respect to long-term outcomes, our results indicate risk estimates that are comparable to previously published studies. For example, we report that women with a history of HDP have twice the risk for CAD compared to women with normotensive pregnancies, similar to the risk that was reported in a prospective, observational UK Biobank study in which HDP was confirmed using diagnostic codes or self-report at enrollment (37).

Most of the prior incidence studies have reported the incidence of HDP and preeclampsia per-pregnancy because this is the most useful information for obstetricians when estimating the risk of HDP and preeclampsia among pregnant women and the related maternal and fetal complications. However, reports of the incidence of HDP per- pregnancy may underestimate the number of affected women, who may have more than one pregnancy and who may be assessed based on their normotensive, rather than their preeclamptic pregnancies. Our previous study that reported CVD outcomes after HDP, reported similar HDP rates per-woman: 643 of 4064 women (13%), with a HDP in at least one of their pregnancies (12). Our current data suggest that 1 in 6 women may have increased risks for CVD and renal disease based on their reproductive histories of HDP. Furthermore, and to the best of our knowledge, none of the published studies that examined the prevalence or incidence of CVD events identified HDP using accepted clinical criteria, but rather, most commonly used diagnostic codes. As these commonly lead to misclassification, our study provides more accurate estimates of the risks for CVD and renal disease that may be attributed to HDP. In addition, we report that women with a history of HDP are at higher risks for multiple chronic conditions which may necessitate sex-specific screening, preventive, and treatment programs. Finally, our results indicate that women with a history of HDP are at risk of multimorbidity, a measure of accelerated aging, which, in turn, may be reflective of multi-system involvement, a key feature of preeclampsia. The underlying mechanism may be cellular senescence - an irreversible cell-cycle arrest mechanism characterized by release of pro-inflammatory markers, commonly referred to as the senescence-associated secretory phenotype (SASP). We (38) and others (39) have demonstrated a role for senescence in the pathophysiology of preeclampsia, which, once established, may persist for years. We hypothesize that senescent cell burden and elevated SASP components may lead to an accelerated aging-like state, and related chronic conditions in women with histories of preeclampsia. Future research should address the role of premature/accelerated aging as a possible mechanism for CVD after pregnancies affected by HDP. This may lead to identification of new biomarkers for early detection of women at risk, and novel therapeutic approaches using drugs that target fundamental aging and senescence processes.

Study Limitations

Our study has following limitations. First, it defined the incidence of HDP in a population which is predominantly v Caucasian. Recent studies have shown that African-American women not only have higher rates of HDP, but also higher risks for CVD compared to white women (40). Taken together, these observations call for studies that address the role of sex-specific risk factors in racially diverse cohorts. A second limitation is that we did use codes to ascertain long-term outcomes. To decrease the risk of false-positive diagnoses, only persons who received two codes for a given condition separated by more than 30 days were considered prevalent for this condition. Finally, our study defines the incidence of HDP in a population of women with pregnancies four decades ago. With the higher rates of HDP risk factors, such as obesity and higher maternal age at gestation, the incidence of HDP is expected to be higher today than between 1976 to 1982. However, the identification of a pregnancy cohort from 4 decades ago facilitated our research seeking to characterize the association between HDP and CVD outcomes later in life.

Conclusions

Our study provides a population based incidence of HDP and preeclampsia, both per pregnancy and per woman, and suggests that the former may underestimate the number of affected women with a history of this condition who may be at risk for future CVD and renal disease. These two measures are not mutually exclusive, but rather are complementary. Studies of HDP and preeclampsia should include incidence estimates, both per pregnancy and per woman, as these may facilitate assessments of risk for pregnancy-related complications and risks for future CVD and renal disease, respectively. Our data underscore the need for future research that will address the mechanisms of the multimorbidity burden in women with a history of HDP, as well as for sex-specific risk scores for prediction of CVD and renal disease that will include reproductive history.

PERSPECTIVES

Competency in Systems-Based Practice

Patient-level health economic analysis suggests that, to optimize value in relation to cost, PCSK9 inhibitor therapy should be directed toward patients at highest risk, such as those with baseline LDL-cholesterol levels ≥100 mg/dL.

Translational Outlook

Additional cost-effective strategies that reduce LDL-cholesterol and lower the risk of ischemic events and death are needed for patients in whom statin therapy is not sufficient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Hypertensive disorders expressed per-pregnancy underestimate the number of affected women and confer increased risks for future multimorbidity

Abbreviations

CAD	coronary artery disease
CHF	congestive heart failure
CVD	cardiovascular disease
DBP	diastolic blood pressure
HDP	hypertensive disorders of pregnancy
REP	Rochester Epidemiology Project
SBP	systolic blood pressure

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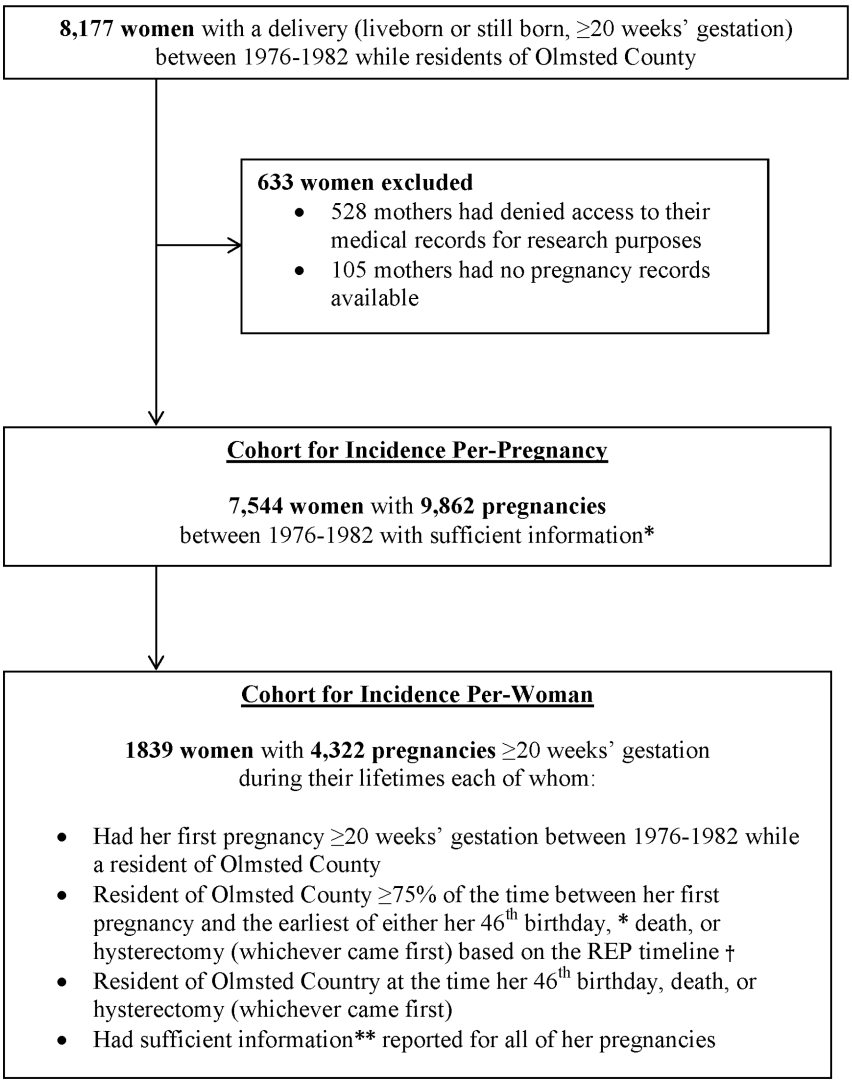


Figure 1. Inclusion criteria and study cohorts.

Using a population-based study, two cohorts of women were identified with the goal to compute and compare the HDP incidence per-pregnancy versus the HDP incidence per woman. * The cut-off of 46 years was chosen as this was the oldest age at which a pregnancy was documented in this cohort. **A pregnancy was classified as having sufficient information to determine HDP status if there was at least one blood pressure measurement from a prenatal visit and at least one blood pressure measurement from admission for delivery. † St. Sauver JL, Grossardt BR, Yawn BP, Melton LJr, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: The Rochester Epidemiology Project. Am J Epidemiol 2011;173:1059–68. REP: Rochester Epidemiology Project

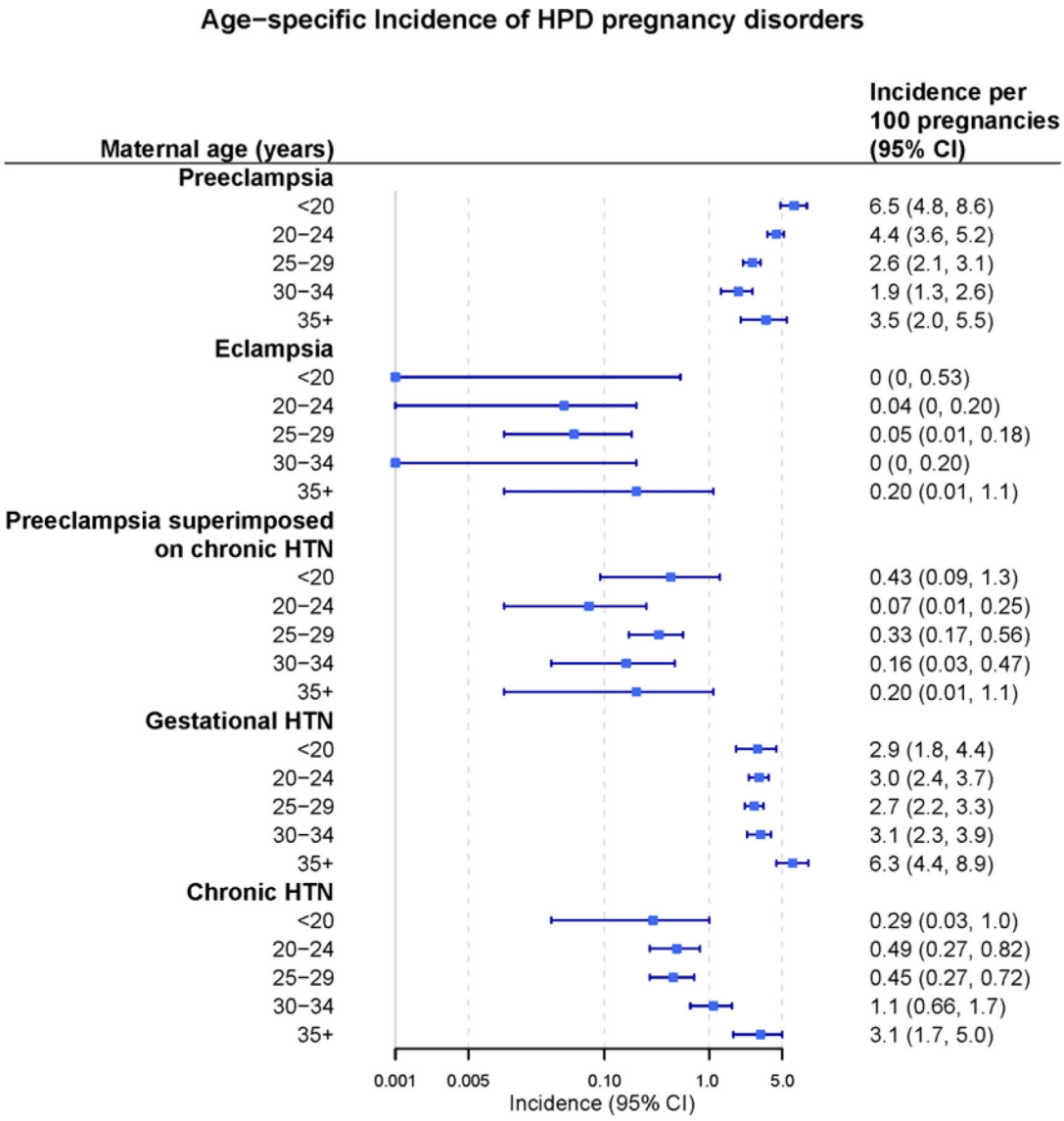


Figure 2. Age-specific per-pregnancy incidence of hypertensive disorders of pregnancy among 9,862 pregnancies during 1976–1982 for residents of Olmsted County, Minnesota.

The per-pregnancy incidence of preeclampsia with respect to age was U-shaped, such that the youngest women (i.e., <20 years and 20–24 years) and those ages ≥35 years had the highest incidence. HTN: hypertension

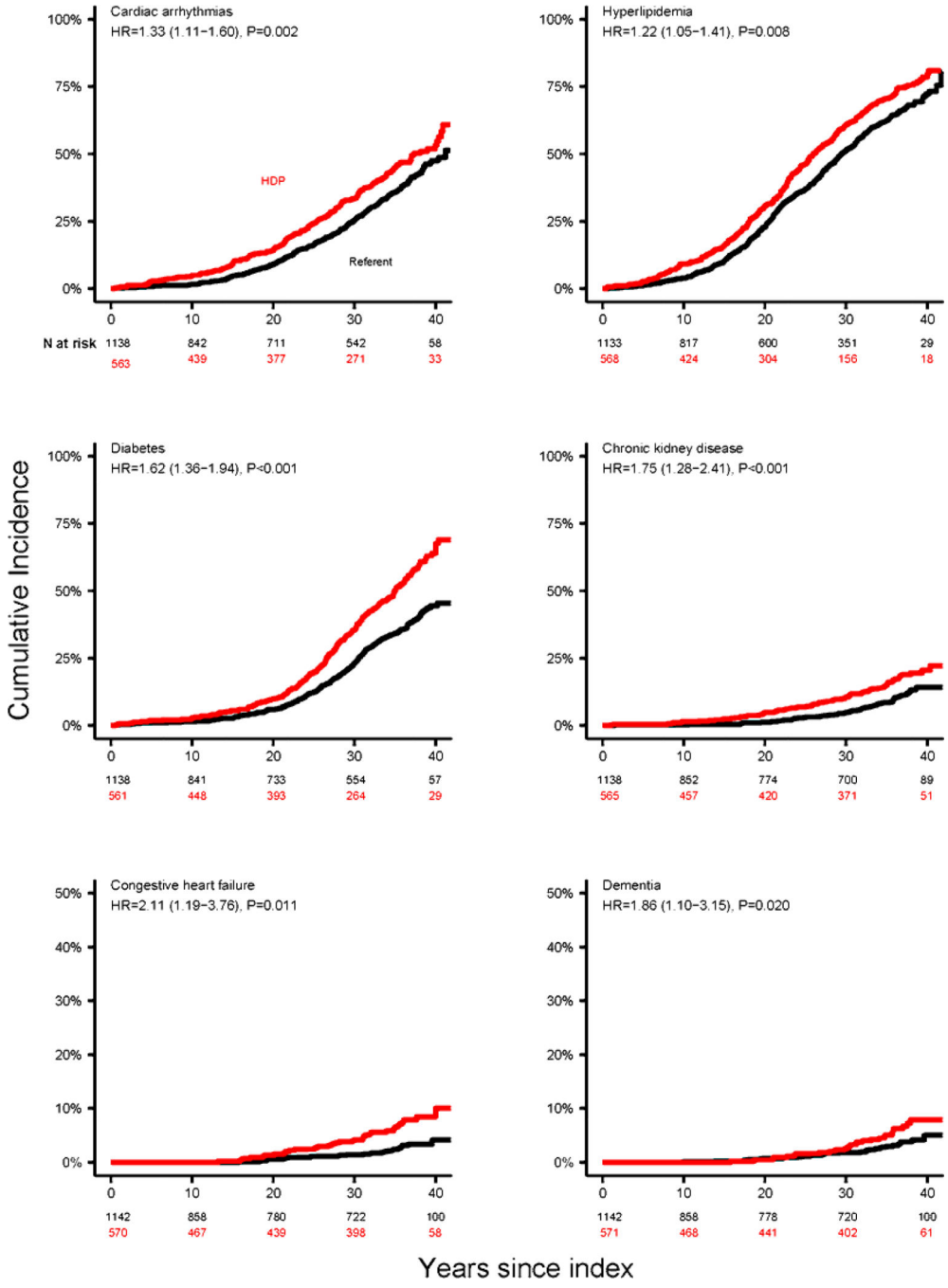
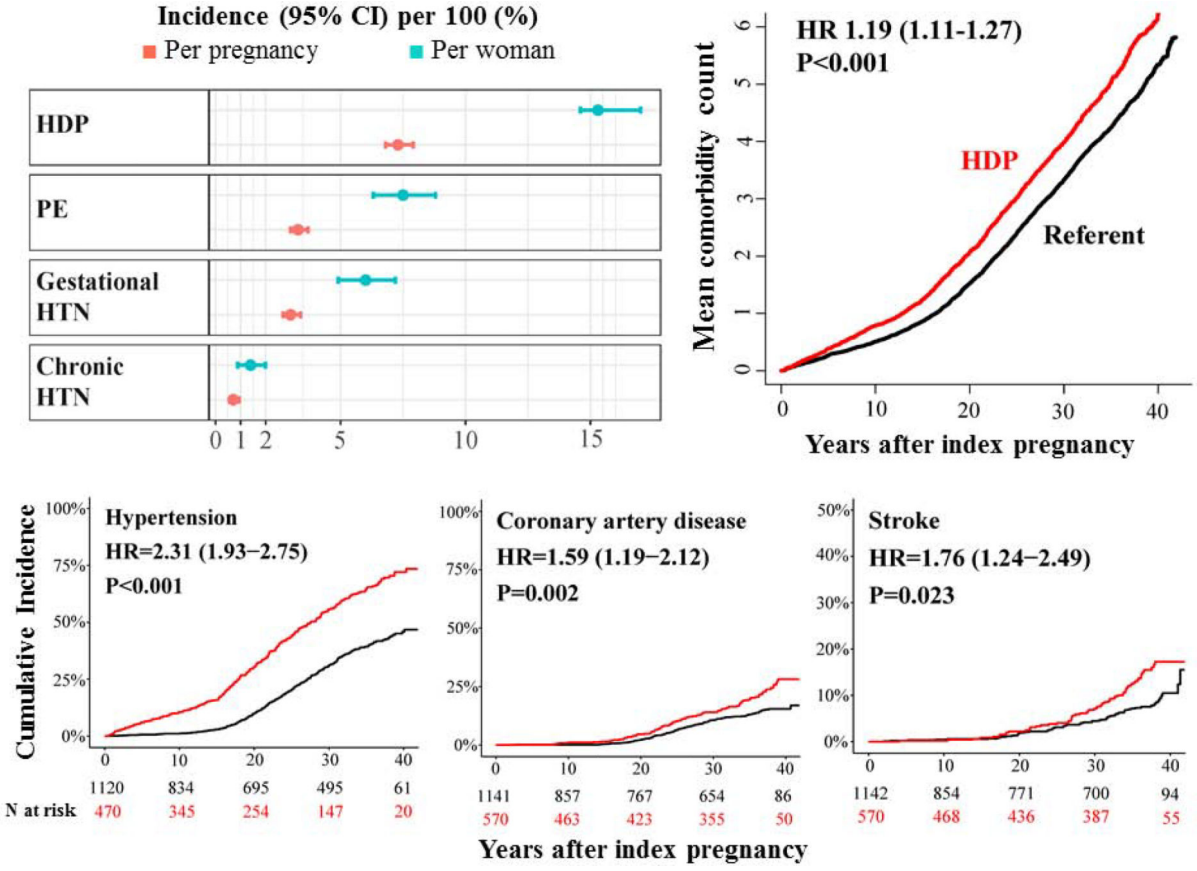


Figure 3. Cumulative incidence curves for cardiovascular and metabolic conditions in women with HDP compared with 1:2 age- and parity-matched referent women.

The reported HRs and corresponding 95% CIs and p-values were estimated from Cox models adjusted for education, smoking, and obesity. Age was used as the time scale. Women with HDP compared to referent women demonstrated increased risks of CVD risk factors and events. HDP: hypertensive disorders of pregnancy. HR: hazard ratio. CI: confidence intervals.



Central Illustration: Hypertension in pregnancy: incidence per-pregnancy and per-woman, outcomes and multimorbidity later in life.

Conventional per pregnancy incidence values underestimate the number of women experiencing HDP by half. Women with a history of HDP compared with referent women, have increased risks for developing multimorbidity, CVD risk factors and events earlier in life.

Table 1.

Per-pregnancy and per-woman incidence (per 100) of hypertensive disorders of pregnancy

Per-pregnancy *	**N**	**Incidence (%)**	**95% CI** †
Any hypertensive disorder of pregnancy	**719**	**7.3**	**6.8–7.9**
Preeclampsia	324	3.3	3.0–3.7
Eclampsia	4	0.04	0.04–0.14
Preeclampsia superimposed on chronic HTN	22	0.22	0.17–0.38
Gestational HTN	300	3.0	2.7–3.4
Chronic HTN	69	0.70	0.56–0.94
Normotensive pregnancies	**9143**	**92.7**	**92.2–93.3**
Per-woman ‡	**N**	**%**	**95% CI** §
Any hypertensive disorder of pregnancy	**281**	**15.3**	**14.6–17.0**
Preeclampsia	138	7.5	6.3–8.8
Eclampsia	0	0	0–0
Preeclampsia superimposed on chronic HTN	8	0.44	0.19–0.86
Gestational HTN	110	6.0	4.9–7.2
Chronic HTN	25	1.4	0.88–2.0
Normotensive	**1558**	**84.7**	**83.0–86.3**

CI, confidence interval; HTN, hypertension

* Per-pregnancy incidence based on 9,862 pregnancies among 7,544 residents of Olmsted County who delivered during 1976–1982.

† 95% CIs for the per-pregnancy incidence rates were constructed using a Wilson score interval appropriate for a proportion estimated from clustered binary data.

‡ Per-woman incidence based on 1,839 residents of Olmsted County considering all of their pregnancies. Each woman was classified using the following hierarchy: Eclampsia>Preeclampsia superimposed on chronic HTN>Preeclampsia>Chronic HTN>Gestational HTN>Normotensive.

§ 95% CIs for the per-woman incidence rates were constructed using an exact method for a binomial proportion.

Table 2.

Comparison of the incidence of chronic conditions first occurring after the index date, between women with hypertensive disorders of pregnancy and 1:2 age- and parity-matched referent women

	HDP (N=571)			Referent (N=1,142)			Unadjusted models		Adjusted models*	
Individual Condition	**N at risk†**	**Person-years**	**N events**	**N at risk‡**	**Person-years**	**N events**	**HR (95% CI)**	**P‡**	**HR (95% CI)**	**P‡**
Cardiac Arrhythmias	563	13803	214	1138	26840	315	1.35 (1.13–1.61)	**<0.001**	1.33 (1.11–1.60)	**0.002**
Coronary Artery Disease	570	15765	101	1141	29246	111	1.73 (1.32–2.28)	**<0.001**	1.59 (1.19–2.12)	**0.002**
Congestive Heart Failure	570	16530	34	1142	30287	24	2.72 (1.60–4.64)	**<0.001**	2.11 (1.19–3.76)	**0.011**
Stroke	570	16333	65	1142	29834	65	1.87 (1.32–2.63)	**<0.001**	1.76 (1.24–2.49)	**0.023**
Chronic Kidney Disease	565	15861	79	1138	29755	86	1.78 (1.31–2.43)	**<0.001**	1.75 (1.28–2.41)	**<0.001**
Dementia	571	16630	28	1142	30237	28	1.85 (1.10–3.12)	**0.021**	1.86 (1.10–3.15)	**0.020**
Depression	555	12463	213	1112	23582	345	1.16 (0.98–1.38)	0.078	1.15 (0.97–1.37)	0.12
Substance abuse	568	15587	84	1134	28877	121	1.30 (0.98–1.71)	0.068	1.37 (1.04–1.82)	**0.028**
Hyperlipidemia	568	11695	324	1133	23045	513	1.31 (1.14–1.51)	**<0.001**	1.22 (1.05–1.41)	**0.008**
Hypertension	470	9763	247	1120	26061	319	2.45 (2.06–2.91)	**<0.001**	2.31 (1.93–2.75)	**<0.001**
Diabetes	561	13982	248	1138	27191	292	1.77 (1.50–2.10)	**<0.001**	1.62 (1.36–1.94)	**<0.001**
Arthritis	569	13184	304	1138	24868	486	1.20 (1.04–1.39)	**0.014**	1.17 (1.00–1.36)	**0.024**
Cancer	566	15392	124	1132	27827	224	0.97 (0.78–1.21)	0.81	0.99 (0.79–1.24)	0.91
Asthma	562	14505	100	1123	27463	155	1.22 (0.94–1.57)	0.13	1.19 (0.92–1.53)	0.20
COPD	526	9695	236	1075	19153	422	1.11 (0.94–1.31)	0.22	1.07 (0.90–1.27)	0.45
Osteoporosis	571	15857	95	1142	28647	204	0.81 (0.63–1.03)	0.085	0.83 (0.64–1.08)	0.17
Accumulation of Multimorbidity										
Considering all of the above	400	11722	-	987	26225	-	1.22 (1.15–1.30)	**<0.001**	1.19 (1.11–1.27)	**<0.001**
All of the above, except HTN	479	14102	-	1001	26509	-	1.18 (1.11–1.26)	**<0.001**	1.15 (1.08–1.22)	**<0.001**

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease, HR, hazard ratio.

P-values in bold denote statistical significance at the 0.05 alpha level.

Age was used as the time scale for all models in the table.

*Adjusted for education (categories include: <high school, high school or GED; some college; ≥college; or unknown), smoking (y/n), and obesity (defined as BMI based on weight taken closest to conception date within 6 months prior and up to 20 gestational weeks, categorized as: <25; 25–29; 30+; or unknown)

† The number of women at risk varied across conditions because we excluded women with that specific condition prior to the index date, based on the diagnosis codes considered for each condition. For hypertension, we also excluded those who had hypertension prior to pregnancy based on chart review or chronic hypertension based on algorithm. For diabetes, we also excluded those who had diabetes prior to pregnancy based on chart review. For multimorbidity, we excluded those with any of the 16 chronic conditions prior to pregnancy.

‡ Using a Bonferroni correction, all primary endpoints except dementia were statistically significant in unadjusted analyses; cardiac arrhythmia, CAD, and CKD were significant in adjusted analyses.

Table 3.

Comparison of the incidence of chronic conditions first occurring after the index date, between women with a history of preeclampsia/eclampsia-superimposed preeclampsia and 1:2 age- and parity-matched referent women

	Preeclampsia (N=298)			Referent (N=596)			Unadjusted models		Adjusted models*	
Individual Condition	**N at risk†**	**Person-years**	**N events**	**N at risk‡**	**Person-years**	**N events**	**HR (95% CI)**	**P‡**	**HR (95% CI)**	**P‡**
Cardiac Arrhythmias	293	7247	110	595	14119	163	1.37 (1.08–1.75)	**0.010**	1.38 (1.07–1.77)	**0.012**
Coronary Artery Disease	297	8377	51	595	15334	51	1.91 (1.30–2.82)	**0.001**	1.85 (1.23–2.78)	**0.003**
Congestive Heart Failure	297	8748	14	596	15833	11	2.48 (1.14–5.39)	**0.022**	2.07 (0.93–4.60)	0.08
Stroke	297	8655	33	596	15535	40	1.48 (0.94–2.33)	0.09	1.40 (0.89–2.22)	0.15
Chronic Kidney Disease	293	8230	43	594	15492	46	1.85 (1.22–2.80)	**0.004**	1.84 (1.19–2.83)	**0.006**
Dementia	298	8759	13	596	15771	17	1.39 (0.68–2.83)	0.37	1.24 (0.62–2.47)	0.54
Depression	292	6614	111	580	12086	191	1.06 (0.84–1.33)	0.65	1.03 (0.81–1.30)	0.83
Substance abuse	296	8239	43	590	15036	68	1.16 (0.79–1.68)	0.45	1.28 (0.88–1.88)	0.20
Hyperlipidemia	296	6272	165	588	12080	259	1.25 (1.03–1.53)	**0.028**	1.19 (0.97–1.47)	0.09
Hypertension	258	5744	118	582	13569	169	1.83 (1.44–2.33)	**<0.001**	1.75 (1.37–2.24)	**<0.001**
Diabetes	293	7428	123	593	14290	149	1.67 (1.31–2.12)	**<0.001**	1.53 (1.20–1.96)	**<0.001**
Arthritis	296	6824	163	595	13183	246	1.38 (1.13–1.69)	**0.002**	1.37 (1.11–1.68)	**0.003**
Cancer	297	8233	58	592	14579	121	0.81 (0.59–1.12)	0.20	0.81 (0.59–1.13)	0.21
Asthma	292	7652	54	588	14237	88	1.13 (0.81–1.59)	0.47	1.11 (0.78–1.58)	0.56
COPD	273	5177	124	564	10015	217	1.11 (0.88–1.39)	0.38	1.09 (0.86–1.37)	0.49
Osteoporosis	298	8269	53	596	15148	85	1.15 (0.81–1.62)	0.44	1.27 (0.89–1.81)	0.19
Accumulation of Multimorbidity										
Considering all of the above	220	6523	-	517	13640	-	1.18 (1.08–1.29)	**<0.001**	1.17 (1.07–1.28)	**<0.001**
All of the above, except HTN	248	7440	-	526	13801	-	1.16 (1.06–1.27)	**<0.001**	1.15 (1.05–1.25)	**0.003**
Death										
All-cause	298	8922	12	596	15949	27	0.80 (0.41–1.57)	0.51	0.77 (0.40–1.50)	0.44

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease, HR, hazard ratio.

Age was used as the time scale for all models in the table.

P-values in bold denote statistical significance at the 0.05 alpha level.

[*] Adjusted for education (categories include: <high school, high school or GED; some college; ≥college; or unknown), smoking (y/n), and obesity (defined as BMI based on weight taken closest to conception date within 6 months prior and up to 20 gestational weeks, categorized as: <25; 25–29; 30+; or unknown)

[†] The number of women at risk varied across conditions because we excluded women with that specific condition prior to the index date, based on the diagnosis codes considered for each condition. For hypertension, we also excluded those who had hypertension prior to pregnancy based on chart review or chronic hypertension based on algorithm. For diabetes, we also excluded those who had diabetes prior to pregnancy based on chart review. For multimorbidity, we excluded those with any of the 16 chronic conditions prior to pregnancy.

[‡] Using a Bonferroni correction, CAD and CKD were significant in both the unadjusted and adjusted analyses.

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