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Hypertensive Disorders of Pregnancy and Maternal Cardiovascular Disease Risk Factor Development

An Observational Cohort Study

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Background: Women with a history of hypertensive disorders of pregnancy (HDP) are nearly twice as likely to develop cardiovascular disease (CVD) as those who are normotensive during pregnancy. However, the emergence of CVD risk factors after HDP is less well-understood.

Objective: To identify associations between HDP and maternal CVD risk factors and chart the trajectory of risk factor development after pregnancy.

Design: Observational cohort study.

Setting: United States.

Participants: 58 671 parous NHS II (Nurses' Health Study II) participants who did not have CVD or risk factors of interest at baseline.

Measurements: Women were followed for self-reported physician diagnosis of chronic hypertension and hypercholesterolemia and confirmed type 2 diabetes mellitus (T2DM) from their first birth through 2013; mean follow-up ranged from 25 to 32 years across these end points. Multivariable Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs, with adjustment for prepregnancy confounders.

Results: Compared with women who were normotensive during pregnancy, those with gestational hypertension (2.9%) or preeclampsia (6.3%) in their first pregnancy had increased rates of chronic hypertension (HRs, 2.8 [95% CI, 2.6 to 3.0] and 2.2 [CI, 2.1 to 2.3], respectively), T2DM (HRs, 1.7 [CI, 1.4 to 1.9] and 1.8 [CI, 1.6 to 1.9], respectively), and hypercholesterolemia (HRs, 1.4 [CI, 1.3 to 1.5] and 1.3 [CI, 1.3 to 1.4], respectively). Although these women were more likely to develop CVD risk factors throughout follow-up, the relative risk for chronic hypertension was strongest within 5 years after their first birth. Recurrence of HDP further elevated risks for all end points.

Limitation: Participants self-reported HDP.

Conclusion: Women with HDP in their first pregnancy had increased rates of chronic hypertension, T2DM, and hypercholesterolemia that persisted for several decades. These women may benefit from lifestyle intervention and early screening to reduce lifetime risk for CVD.

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During reproductive life, approximately 15% of parous women have at least 1 pregnancy complicated by a hypertensive disorder, such as gestational hypertension or preeclampsia (1). Growing evidence suggests that these women are nearly twice as likely as those who are normotensive during pregnancy to develop cardiovascular disease (CVD) (2–4). Hypertensive disorders of pregnancy (HDP) may reveal subclinical CVD risk under the physiologic "stress test" of pregnancy, providing early insight into CVD risk that might be leveraged to identify high-risk women for targeted prevention from an early age (1, 5). Although the 2011 American Heart Association guidelines recommend that clinicians evaluate CVD risk by screening for a history of HDP, few data exist on which risk factors should be screened for as well as the frequency and timing of screening (6).

Hypertensive disorders of pregnancy have been consistently linked to future chronic hypertension despite the fact that blood pressure returns to normal during the postpartum period (2, 7–12). Women with a history of HDP have higher risks for impaired glucose tolerance and insulin resistance and a 3- to 4-fold increased risk for type 2 diabetes mellitus (T2DM) (9, 13–22). Those with a history of preeclampsia also have higher levels of total and low-density lipoprotein cholesterol and triglycerides; however, these differences are not consistently statistically significant (16, 18–21, 23–25). Many previous studies were limited by small sample size; short follow-up; or incomplete adjustment for potential confounders, such as prepregnancy smoking status, body mass index (BMI), and family history. Further, although these associations have been observed over variable lengths of follow-up, little is known about the specific timing of risk factor development, which is critical to inform screening guidelines.

We examined associations of gestational hypertension and preeclampsia with development of chronic hypertension, T2DM, and hypercholesterolemia. These associations were evaluated in a large longitudinal cohort study with up to 50 years of follow-up from first birth.

Methods

Cohort Description and Selection

The NHS II (Nurses' Health Study II) is a prospective cohort study of 116 429 female U.S. registered nurses who were enrolled at age 25 to 42 years in 1989. Par-

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ticipants are followed biennially via questionnaires, which collect information on lifestyle, health-related behaviors, and incident disease.

Study Sample

Analyses were restricted to participants who responded to the 2009 questionnaire (n = 76 840), which allowed pregnancies to be dated and linked to specific complications. We excluded women who were nulliparous (n = 13 253), those who were missing a valid year of first pregnancy (n = 12), those younger than 18 years or older than 45 years at their first birth (n = 846), and those who were missing gestation length or had a value that was incompatible with the pregnancy outcome reported (n = 292). Women also were excluded if they reported chronic hypertension, type 1 or 2 diabetes, hypercholesterolemia, myocardial infarction, or stroke before their first pregnancy (n = 2470) or if they were missing the date of diagnosis or reported diagnosis of these conditions before 1980 (which precluded dating of those events) (n = 1210). Finally, because undetected chronic hypertension before pregnancy may be incorrectly captured as incident chronic hypertension directly after pregnancy, we excluded women who reported chronic hypertension within 1 year after their first birth (n = 86). This yielded an analytic sample of 58 671 women. This analysis was approved by the Institutional Review Board at Brigham and Women's Hospital.

Hypertensive Disorders of Pregnancy

In 2009, women retrospectively reported their complete pregnancy history. Hypertensive disorders of pregnancy were self-reported as "pregnancy-related high blood pressure" (gestational hypertension) or "preeclampsia/toxemia." The primary analysis focused on the first pregnancy because this is when HDP predominantly occurs (24).

To assess the validity of self-reported preeclampsia, we reviewed medical records of 598 women who reported preeclampsia on biennial questionnaires from 1991 to 2001 for provider report of preeclampsia or evidence of gestational hypertension (new-onset high blood pressure [systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg] after 20 weeks' gestation) and proteinuria (protein excretion ≥300 mg per 24 hours, protein–creatinine ratio ≥0.3, or dipstick reading ≥1+) (26). There were 411 cases of preeclampsia confirmed by medical records, for a positive predictive value of 69%. Given the complexity of validating preeclampsia (confirming normotension before 20 weeks and elevated blood pressures and proteinuria after 20 weeks), several components of the medical record are required. We excluded 136 medical records with insufficient information available for validation (for example, those that were missing laboratory data or prenatal and/or labor and delivery records), resulting in a positive predictive value of 89%. Having complete medical record information for all 598 women would likely have resulted in a positive predictive value between 69% and 89%.

Recurrent HDP was analyzed in a secondary analysis with follow-up starting at age 40 years. This analysis was restricted to 45 815 parous women who had not experienced a CVD event or developed CVD risk factors of interest by age 40 years and had no additional pregnancies at this age or later.

CVD Risk Factors

Risk factors for CVD (chronic hypertension, T2DM, and hypercholesterolemia) were self-reported on biennial questionnaires beginning in 1989. The 1989 questionnaire retrospectively captured any physician diagnoses of "high blood pressure (excluding during pregnancy)," "diabetes: not during pregnancy," and "elevated cholesterol" and the year of diagnosis ("before 1980," "1980 to 1984," or "1985 to present"). Women prospectively reported incident diagnoses of CVD risk factors on biennial questionnaires beginning in 1991. The midpoint of each date range was assigned as the year of diagnosis for chronic hypertension and hypercholesterolemia; for T2DM, the year of diagnosis was obtained via a supplemental questionnaire. Previous validation of self-reported high blood pressure in NHS II indicated good agreement, with sensitivity of 94% and specificity of 85% (27). Women who reported a new diagnosis of diabetes received a supplemental questionnaire to report diagnostic test results, symptoms, and treatment. This information was used to classify cases into categories proposed by the National Diabetes Data Group and the American Diabetes Association (28–30). Information on self-reported use of cholesterol-lowering medication has been collected since 1999. We defined hypercholesterolemia as self-report of hypercholesterolemia or cholesterol-lowering medication use. Self-reported hypercholesterolemia was validated in a similar cohort and showed a positive predictive value of 86% and a negative predictive value of 85% (31).

Lifestyle Factors and Medical History

In 1989, participants reported height, current weight, and weight at age 18 years. Participants updated their weight on all biennial questionnaires. Body mass index was calculated from reported height and weight at age 18 years and was updated every 2 years from 1989 to 2013. Body mass index was derived for ages at which weight was not reported, with incorporation of data on weight at age 18 years; weights reported on each questionnaire; and somatograms at ages 20, 30, and 40 years (see the Appendix, available at Annals.org). A previous validation study in NHS II found high correlations between physical examination records and both recalled weight at age 18 years (r = 0.87) and self-reported height (r = 0.94) (32).

Race/ethnicity, family history of chronic hypertension, and strenuous physical activity at ages 18 to 22 years were reported at baseline. History of smoking, alcohol consumption, and oral contraceptive use were also reported in 1989 and updated during follow-up. Biennial questionnaires after 1989 queried participants about family history of diabetes, parental education, and diet. Food-frequency questionnaires were used to derive a dietary quality score from the 2010 Alternative Healthy Eating Index (33). Self-reported physician diagnoses of myocardial infarction and stroke were verified through medical record review.

Prepregnancy information was drawn from the biennial questionnaire immediately before the first pregnancy. Because most first births (85%) occurred before baseline, health-related behavior in high school and within varying age ranges from 13 through 42 years that was retrospectively reported in 1989 was used to assign prepregnancy values for these women.

Statistical Analysis

Characteristics of the analytic sample were age-standardized and stratified by HDP status in the first pregnancy (Table 1). We used Cox proportional hazards models to estimate associations between HDP in the first pregnancy and chronic hypertension, T2DM, and hypercholesterolemia (28). Women contributed person-time from their first birth until development of the CVD risk factor of interest, occurrence of a CVD event (nonfatal myocardial infarction, fatal coronary heart disease, or nonfatal or fatal stroke), death, the last returned questionnaire, or 2013. They also were censored at antihypertensive medication use for the chronic hypertension analysis and at type 1 diabetes diagnosis for the T2DM analysis. For the 85% of women who delivered their first child before 1989, the analysis included an average of 9.8 years (SD, 5.5) of follow-up before enrollment.

Log-rank tests were used to determine whether the distributions of age at and time to CVD risk factor development differed between HDP groups. We calculated multivariable-adjusted hazard ratios (HRs) and 95% CIs, with adjustment for variables identified a priori as potential confounders: age at first birth; age in 1989; race/ethnicity; parental education; strenuous physical activity (at age 18 to 22 y); family history of chronic hypertension (chronic hypertension models only) or diabetes (T2DM models only); and prepregnancy BMI, alcohol consumption, diet, smoking history, and oral contraceptive use. We assessed nonlinearity of the relationships between age at first birth and age in 1989 with each CVD risk factor by using restricted cubic splines with 10 knots at the decile medians (34–36). Because tests for nonlinearity were significant for the associations of age at first birth with chronic hyperten-

Table 1. Age-Standardized Characteristics of NHS II Participants, by Hypertensive Disorders in First Pregnancy*

Characteristic	Hypertensive Disorder Status		
	Normotension (*n* = 53 285 [90.8%])	**Gestational Hypertension (*n* = 1699 [2.9%])**	**Preeclampsia (*n* = 3687 [6.3%])**
Mean age at first birth (SD), *y*†	26.8 (4.5)	27.9 (4.7)	26.8 (4.6)
Mean age in 1989 (SD), *y*†	35.2 (4.6)	34.5 (4.7)	34.6 (4.6)
White, %	93	94	93
Maternal education >12 y, %	32	32	32
Paternal education >12 y, %	38	34	37
Strenuous physical activity at age 18–22 y, %			
Never	29	29	27
10–12 mo/y	11	11	11
Mean physical activity in 1989 (SD), *METs/wk*‡	26.7 (66.7)	24.5 (56.4)	25.9 (59.8)
Mean prepregnancy body mass index (SD), kg/m^2	21.7 (3.5)	23.1 (4.3)	22.8 (4.1)
Quintile of prepregnancy AHEI score, %			
Lowest (unhealthy)	20	22	21
Highest (healthy)	20	20	19
Prepregnancy smoking status, %			
Never	68	69	68
Former	10	9	10
Current	22	21	22
Prepregnancy alcohol intake, %			
None	26	27	28
≤1 drink/wk	37	36	36
2–6 drinks/wk	29	29	28
≥1 drink/d	8	8	8
Prepregnancy oral contraceptive use, %			
Never	26	25	24
<2 y	24	24	25
2–3 y	22	21	21
≥4 y	29	30	30
Family history of chronic hypertension, %	51	62	59
Family history of diabetes, %	42	46	47
Final parity, %			
1	15	21	21
2	49	48	49
3	26	24	23
≥4	10	8	7

AHEI = Alternative Healthy Eating Index; MET = metabolic equivalent for task; NHS II = Nurses' Health Study II.
* Polytomous percentages may not sum to 100 due to rounding.
† Values are not age-adjusted.
‡ Calculated by frequency and duration of participation in several aerobic activities.

Table 2. HRs and 95% CIs for Hypertensive Disorders in First Pregnancy and Cardiovascular Disease Risk Factors*

CVD Risk Factor	Hypertensive Disorder Status		
	Normotension	Gestational Hypertension	Preeclampsia
Chronic hypertension			
Cases/person-years, *n/N*	16 610/1 459 370	979/35 568	1922/84 317
Excess cases per 10 000 person-years, *n*	–	161	122
Median age at development (IQR), *y*†	50 (45–54)	45 (40–50)	46 (40–51)
HR (95% CI)			
Model 1	1.00 (reference)	3.18 (2.98–3.39)	2.45 (2.34–2.57)
Model 2	1.00 (reference)	2.79 (2.61–2.97)	2.21 (2.10–2.32)
Type 2 diabetes mellitus			
Cases/person-years, *n/N*	3137/1 691 624	187/49 948	435/112 344
Excess cases per 10 000 person-years, *n*	–	19	20
Median age at development (IQR), *y*†	53 (48–57)	52 (47–56)	51 (46–56)
HR (95% CI)			
Model 1	1.00 (reference)	2.14 (1.84–2.48)	2.18 (1.98–2.42)
Model 2	1.00 (reference)	1.65 (1.42–1.91)	1.75 (1.58–1.93)
Hypercholesterolemia			
Cases/person-years, *n/N*	29 253/1 350 512	1074/38 045	2279/85 378
Excess cases per 10 000 person-years, *n*	–	66	50
Median age at development (IQR), *y*†	47 (40–53)	46 (40–52)	45 (38–52)
HR (95% CI)			
Model 1	1.00 (reference)	1.43 (1.34–1.52)	1.35 (1.29–1.40)
Model 2	1.00 (reference)	1.36 (1.28–1.45)	1.31 (1.25–1.36)

CVD = cardiovascular disease; HR = hazard ratio; IQR = interquartile range.
* Model 1 was adjusted for age at first birth, age in 1989, race/ethnicity (African American, Latina, Asian, white [reference], or other), and years of parental education (<9, 9 to 11, 12, 13 to 15, or ≥16 [reference]). Model 2 was also adjusted for strenuous physical activity at age 18 to 22 y (never, 1 to 3 mo/y [reference], 4 to 6 mo/y, 7 to 9 mo/y, or 10 to 12 mo/y), prepregnancy smoking status (never [reference], former, or current), prepregnancy body mass index (<18.5, 18.5 to 24.9 [reference], 25 to 29.9, or ≥30 kg/m^2), prepregnancy alcohol consumption (none [reference], ≤1 drink/wk, 2 to 6 drinks/wk, or ≥1 drink/d), quintile of prepregnancy Alternative Healthy Eating Index score (fifth quintile [reference] represented the healthiest diet category), prepregnancy oral contraceptive use (never [reference], <2 y, 2 to 3 y, or ≥4 y), and family history of chronic hypertension (yes or no; chronic hypertension model only) and type 2 diabetes mellitus (yes or no; type 2 diabetes mellitus model only).
† $P < 0.001$ from a global test of the difference in the distribution of age at CVD risk factor development between groups based on HDP status in the first pregnancy.

sion and T2DM and the association of age in 1989 with hypercholesterolemia ($P < 0.001$ for each), corresponding spline terms at 26 years for age at first birth and 28 years for age in 1989 were included. To evaluate departures from the proportional hazards assumption, we used restricted cubic splines to examine the extent to which the effect of HDP on CVD risk factors was modified by the number of years since the first birth. The proportional hazards assumption did not hold for any model in Table 2 ($P < 0.001$ for each test); therefore, HRs were also presented within 5-year intervals (Table 3). We investigated the presence of effect modification by preterm delivery (<37 weeks) by using a likelihood ratio test, comparing a model with multiplicative interaction terms between gestational hypertension and preterm delivery and between preeclampsia and preterm delivery to a model without these terms.

Multivariable-adjusted cumulative incidence curves for each CVD risk factor by HDP status in the first pregnancy were obtained using the Breslow estimator at the mean and mode values of the continuous and categorical covariates, respectively. To address violation of the proportional hazards assumption, time-varying multiplicative interaction terms between HDP status in the first pregnancy and time since the first birth were included. All analyses were conducted using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The National Institutes of Health had no role in the design, conduct, analysis, or reporting of the study.

RESULTS

HDP in First Pregnancy and CVD Risk Factors

First births occurred between 1964 and 2008 at a mean age of 26.8 years (SD, 4.6). A total of 5386 women (9.2%) experienced HDP in their first pregnancy; 2.9% developed gestational hypertension, and 6.3% developed preeclampsia. Women with HDP in their first pregnancy and those who were normotensive during pregnancy generally had similar demographic and lifestyle characteristics (Table 1); however, women with HDP were more likely to have a family history of chronic hypertension and had fewer children. By the end of follow-up in 2013 (Appendix), 33.3% of women had developed chronic hypertension, 6.4% had developed T2DM, and 55.6% had developed hypercholesterolemia.

In models adjusted for age, race/ethnicity, and parental education, women with HDP in their first pregnancy developed chronic hypertension, T2DM, and hypercholesterolemia at higher rates than those who were normotensive during their first pregnancy (Table 2). Hazard ratios were modestly attenuated but remained statistically significant after adjustment for ad-

ditional prepregnancy behaviors and characteristics. Women with gestational hypertension had a 2.8-fold increased rate of chronic hypertension (95% CI, 2.6 to 3.0), whereas those with preeclampsia had a 2.2-fold increased rate (CI, 2.1 to 2.3). Women who were hypertensive during their first pregnancy had an approximately 70% increased rate of T2DM and a 30% increased rate of hypercholesterolemia. Further adjustment for potential mediators, including postpregnancy smoking, diet, alcohol intake, physical activity, and oral contraceptive use, did not change the results (data not shown). Women with HDP in their first pregnancy had elevated rates of CVD risk factor development regardless of whether they had a full-term or preterm delivery (Appendix Table 1, available at Annals.org). However, the elevated rate of hypercholesterolemia associated with HDP was slightly higher for women with preterm deliveries (HR, 1.5 [CI, 1.4 to 1.6]) than for those with full-term deliveries (HR, 1.3 [CI, 1.3 to 1.4]) (P for interaction = 0.031).

The Figure shows the multivariable-adjusted cumulative incidence of chronic hypertension, T2DM, and hypercholesterolemia by HDP status in the first pregnancy through 40 years after the first birth. Women with gestational hypertension or preeclampsia had a higher cumulative incidence of all CVD risk factors than those who were normotensive during pregnancy. Women with HDP also developed the CVD risk factors sooner after their first pregnancy ($P < 0.001$) (Figure) and at earlier ages than those who were normotensive during pregnancy ($P < 0.001$) (Table 2).

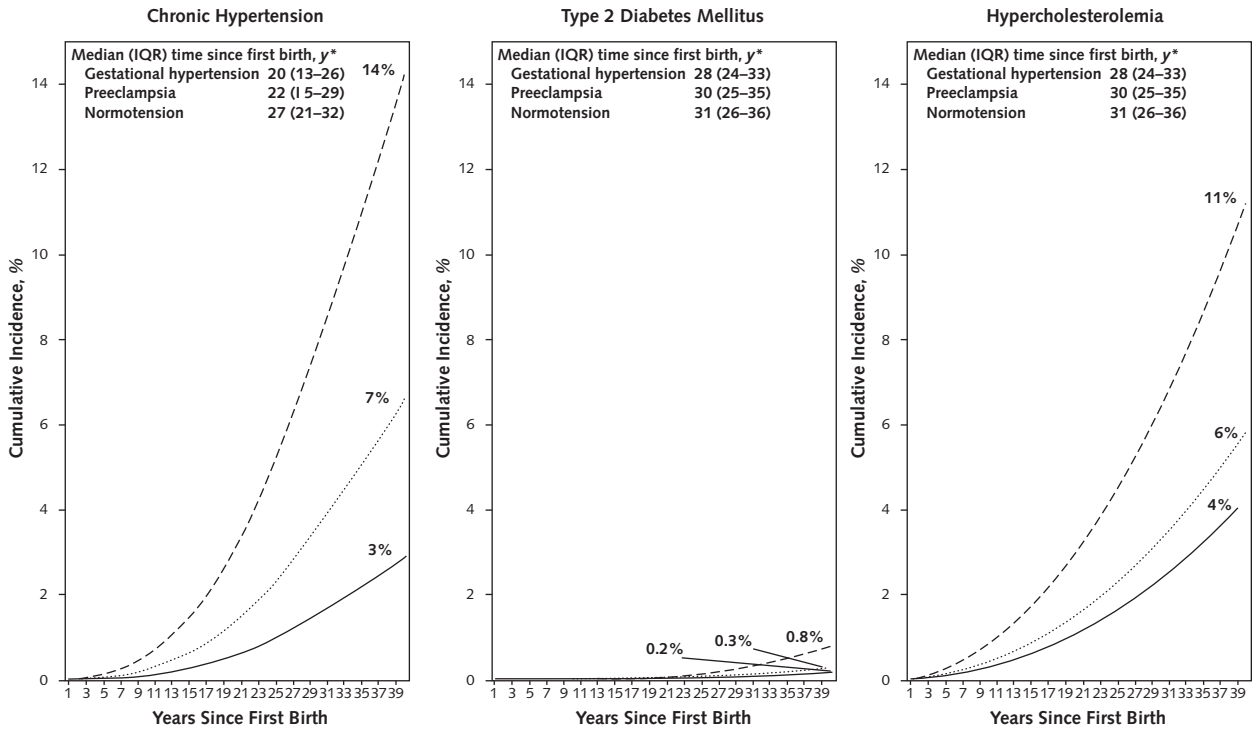
Table 3 shows the relationship between HDP in the first pregnancy and CVD risk factors, stratified by 5-year intervals through 40 years since first birth. Hazard ratios for chronic hypertension were highest in the first 5 years; compared with women who were normotensive during their first pregnancy, those with gestational hypertension had a 4.3-fold increased rate (CI, 3.2 to 5.8) and those with preeclampsia had a 4.0-fold increased

Table 3. HRs and 95% CIs for Hypertensive Disorders in First Pregnancy and Cardiovascular Disease Risk Factors Compared With Normotension During the First Pregnancy, by Years Since First Birth Within 5-Year Intervals*

CVD Risk Factor	Cases/Person-Years, *n/N*	HR (95% CI)	
		Gestational Hypertension	Preeclampsia
Chronic hypertension			
≤5 y	371/292 788	4.29 (3.16–5.84)	3.96 (3.07–5.11)
6–10 y	1228/287 252	3.62 (3.01–4.34)	3.59 (3.11–4.15)
11–15 y	2390/273 710	2.92 (2.51–3.38)	2.62 (2.33–2.95)
16–20 y	3570/248 421	2.87 (2.51–3.28)	2.04 (1.83–2.27)
21–25 y	4290/205 778	2.18 (1.86–2.54)	1.94 (1.75–2.16)
26–30 y	3899/144 421	2.08 (1.72–2.51)	1.78 (1.57–2.00)
31–35 y	2382/81 124	1.81 (1.34–2.43)	1.85 (1.57–2.18)
36–40 y	1029/35 295	2.04 (1.26–3.30)	1.39 (1.03–1.88)
Type 2 diabetes mellitus			
≤5 y	11/284 750	†	†
6–10 y	72/287 619	2.08 (0.97–4.49)	2.64 (1.43–4.87)
11–15 y	220/290 780	1.29 (0.77–2.17)	1.51 (1.01–2.25)
16–20 y	472/283 769	0.86 (0.54–1.37)	2.06 (1.61–2.65)
21–25 y	756/260 885	1.77 (1.30–2.41)	2.03 (1.64–2.50)
26–30 y	863/207 632	1.93 (1.44–2.60)	1.59 (1.27–1.99)
31–35 y	754/134 730	1.67 (1.13–2.46)	1.62 (1.26–2.07)
36–40 y	454/67 523	2.55 (1.62–4.00)	1.85 (1.34–2.56)
Hypercholesterolemia			
≤5 y	1642/291 114	1.37 (1.09–1.72)	1.44 (1.22–1.70)
6–10 y	3050/279 052	1.26 (1.05–1.51)	1.53 (1.35–1.72)
11–15 y	4583/259 806	1.18 (1.01–1.38)	1.30 (1.17–1.45)
16–20 y	5999/229 863	1.38 (1.20–1.57)	1.21 (1.09–1.34)
21–25 y	6356/185 154	1.41 (1.23–1.62)	1.30 (1.18–1.43)
26–30 y	5590/125 494	1.33 (1.13–1.57)	1.16 (1.04–1.30)
31–35 y	3483/67 843	1.28 (1.02–1.62)	1.29 (1.12–1.49)
36–40 y	1566/27 832	1.77 (1.28–2.45)	1.13 (0.88–1.43)

CVD = cardiovascular disease; HR = hazard ratio.
* Models were adjusted for age at first birth, age in 1989, race/ethnicity (African American, Latina, Asian, white [reference], or other), years of parental education (<9, 9 to 11, 12, 13 to 15, or ≥16 [reference]), strenuous physical activity at age 18 to 22 y (never, 1 to 3 mo/y [reference], 4 to 6 mo/y, 7 to 9 mo/y, or 10 to 12 mo/y), prepregnancy smoking status (never [reference], former, or current), prepregnancy body mass index (<18.5, 18.5 to 24.9 [reference], 25 to 29.9, or ≥30 kg/m^2), prepregnancy alcohol consumption (none [reference], ≤1 drink/wk, 2 to 6 drinks/wk, or ≥1 drink/d), quintile of prepregnancy Alternative Healthy Eating Index score (fifth quintile [reference] represented the healthiest diet category), prepregnancy oral contraceptive use (never [reference], <2 y, 2 to 3 y, or ≥4 y), and family history of chronic hypertension (yes or no; chronic hypertension model only) and type 2 diabetes mellitus (yes or no; type 2 diabetes mellitus model only). Because of small cell counts, women with missing prepregnancy smoking status (n = 352), strenuous physical activity from age 18 to 22 y (n = 348), and prepregnancy alcohol consumption (n = 249) were excluded from the analysis for the type 2 diabetes mellitus model from 6 to 10 y.
† Few cases (1 case among women with gestational hypertension and no cases among women with preeclampsia) resulted in unstable estimates for type 2 diabetes mellitus ≤5 y after the first birth.

Figure. Multivariable-adjusted cumulative incidence of chronic hypertension, type 2 diabetes mellitus, and hypercholesterolemia through 40 y since first birth, by hypertensive disorder in first pregnancy.



At risk, *n*	10 y	20 y	30 y	40 y	10 y	20 y	30 y	40 y	10 y	20 y	30 y	40 y
Gestational hypertension	1464	873	254	30	1682	1529	718	143	1484	1027	327	40
Preeclampsia	3261	2245	807	113	3647	3352	1860	354	3215	2313	902	108
Normotension	51 414	42 108	19 843	3396	53 050	49 948	30 395	6883	49 099	37 820	16 543	2502

Gestational hypertension Preeclampsia Normotension

Curves were obtained at the mean and mode values for the following continuous and categorical covariates, respectively: age at first birth (27 y), age in 1989 (35 y), race/ethnicity (white), parental education (12 y), strenuous physical activity at ages 18 to 22 y (1 to 3 mo per year), prepregnancy smoking status (never), prepregnancy body mass index (normal weight [18.5 to 24.9 kg/m^2]), prepregnancy alcohol consumption (≤1 drink per week), prepregnancy Alternative Healthy Eating Index score (third quintile), prepregnancy oral contraceptive use (≥4 y), family history of chronic hypertension (present) (chronic hypertension model only), and family history of type 2 diabetes mellitus (absent) (type 2 diabetes mellitus model only). IQR = interquartile range.

* $P < 0.001$ from a global test of the difference in the distribution of time to CVD risk factor development between groups based on hypertensive disorder status in the first pregnancy.

rate (CI, 3.1 to 5.1). Although women with HDP had elevated rates of chronic hypertension throughout follow-up, the relative rate diminished over time. However, absolute rate differences were lowest in earlier years, when incidence was low, and highest in later years. The statistically significant 1.5- to 2.6-fold increased rate of T2DM among women with preeclampsia appeared as early as 6 to 10 years after their first birth and continued throughout follow-up. Women with gestational hypertension had a statistically significantly increased rate of T2DM beginning 21 to 25 years after their first birth, which ranged from 1.7- to 2.6-fold higher than for women who were normotensive during pregnancy. Women with HDP in their first pregnancy had statistically significant 1.2- to 1.8-fold increased rates of hypercholesterolemia in the interval from immediately after their first birth through 35 years (for women with preeclampsia) or 40 years (for women with gestational hypertension).

Recurrent HDP and CVD Risk Factors

We examined HDP recurrence with follow-up starting at age 40 years (Appendix Table 2, available at Annals.org). Women with HDP in their first and second or later pregnancies had the highest rates of CVD risk factor development, with HRs ranging from 1.3 (CI, 1.2 to 1.5) for hypercholesterolemia to 3.5 (CI, 3.2 to 3.9) for chronic hypertension compared with women with 2 or more pregnancies and no HDP. Women with any HDP, regardless of which pregnancy it occurred in, had increased rates of CVD risk factor development. Further adjustment for parity did not materially alter these results. Starting follow-up at age 45 years rather than 40 years yielded slightly attenuated HRs, but significance

and rank were maintained across HDP groups (data not shown).

Sensitivity Analyses

The majority of women who developed a CVD risk factor during follow-up did so before reporting their pregnancy history in 2009 (73% among T2DM cases, 85% among chronic hypertension cases, and 87% among hypercholesterolemia cases). Given this and the retrospective report of HDP in 2009, we conducted a sensitivity analysis with follow-up from 2009 to 2013. Hazard ratios were attenuated but statistically significant, except for the association between preeclampsia and hypercholesterolemia (HR, 1.1 [CI, 0.9 to 1.2]). Additional analyses that started follow-up in 1982 for chronic hypertension and hypercholesterolemia (the first year of diagnosis we could assign for these risk factors), excluded women with multiple children in their first birth (n = 819), and used an alternative clinical hypertension end point that also included antihypertensive medication use yielded similar results (data not shown). To evaluate the robustness of the results to potential unmeasured confounding, we calculated E-values using the publicly available online E-value calculator (www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials) (37–39). E-values for the observed point estimates ranged from 1.7 for preeclampsia and hypercholesterolemia to 3.4 for gestational hypertension and chronic hypertension (**Appendix Table 3**, available at Annals.org).

DISCUSSION

Women with a history of gestational hypertension or preeclampsia in their first pregnancy developed chronic hypertension at a 2- to 3-fold higher rate and had 70% and 30% higher rates of T2DM and hypercholesterolemia, respectively, than women who were normotensive during their first pregnancy. These associations persisted even after we accounted for prepregnancy confounders, including BMI, smoking, and family history. To our knowledge, this study includes the most complete adjustment for prepregnancy confounders of the relationship between HDP and CVD risk factors, and it is also one of the largest studies with one of the longest follow-ups in the literature. Our ability to describe the trajectory of risk factor development with up to 50 years of follow-up from first birth provides insight into the timing and pathways between HDP and CVD.

This study advances our understanding of the trajectory of CVD risk after HDP. Although higher magnitudes of risk have been observed for chronic hypertension and T2DM, those studies largely did not adjust for prepregnancy confounding, followed women for less time, or had smaller samples (2, 17, 18). Although HDP has been inconsistently related to lipid measures (24) and was not previously associated with hypercholesterolemia (8), we found associations of gestational hypertension and preeclampsia with incident hypercholesterolemia. Only 3 previous studies have analyzed the associations between preterm birth or HDP recurrence and any of these CVD risk factors (10, 11, 17). However, one considered only the first 2 pregnancies when examining recurrence (10), and another used antihypertensive medication use as a proxy for chronic hypertension (11). Our study found that recurrent HDP confers the highest risk for chronic hypertension and T2DM, even after adjustment for prepregnancy confounding, and is the first to reveal a relationship between recurrent HDP and hypercholesterolemia. Our findings also confirm that the increased rate of CVD risk factors is not restricted to preterm preeclampsia but occurs across all combinations of HDP and gestation length. Only a few previous studies examined blood pressure (1), chronic hypertension (9, 10, 17, 40, 41), T2DM (9, 14, 17), and lipid values (1) among women with a history of gestational hypertension. Our finding of a higher magnitude of chronic hypertension risk among women with gestational hypertension compared with those with preeclampsia is consistent with findings of 3 previous studies (9, 10, 40) and may suggest different pathologies in these hypertensive disorders. One previous study calculated 10-year cumulative incidence of chronic hypertension among women with and without HDP (10), but we expanded our understanding by charting the 40-year cumulative incidence of CVD risk factors in these women.

The primary limitation of our study is its reliance on self-reported HDP, which was retrospectively reported in 2009 and may result in recall bias. However, self-reported preeclampsia was validated in a subset of NHS II participants, and most had medical record evidence of preeclampsia. Gestational hypertension has not yet been validated, but the proportions of first pregnancies with gestational hypertension and preeclampsia are consistent with those seen elsewhere (24). Although HDP history was retrospectively reported, length of maternal recall has not been consistently associated with accuracy (42).

Given that 85% of participants contributed person-time to the analysis that occurred before enrollment in NHS II, there may have been selection bias. However, on the basis of the retrospective data collected on the 1989 baseline questionnaire, we were able to assign time of onset for chronic hypertension and hypercholesterolemia cases arising between 1980 and 1989 and for all T2DM cases. Because participants were excluded if they developed chronic hypertension or hypercholesterolemia before 1980, we conducted a sensitivity analysis that excluded person-time between the first birth and 1982 (the year assigned for women who developed end points between 1980 and 1984) and obtained similar results. Although inclusion in our analysis was dependent on survival to 2009, 98.2% of NHS II participants were alive that year. Further, our sensitivity analysis that included follow-up from 2009 to 2013 found results that were consistent with those observed from first birth through 2013.

Information on confounders was also self-reported, which may have resulted in misclassification or residual confounding. However, this study included the most complete adjustment for prepregnancy confounders, and on the basis of our calculated E-values, an unmea-

sured confounder would need to be associated with HDP and the CVD risk factor by a magnitude of 1.7- to 3.4-fold above and beyond the measured confounders to explain away the observed associations. The only measured confounder of similar magnitude was prepregnancy obesity, so it is unlikely that our associations could be explained away by an unmeasured confounder. Because the NHS II cohort includes primarily white nurses, caution should be used when generalizing these findings to other populations. Although our study provided longer follow-up since first birth than many previous studies, NHS II participants were still relatively young at the end of follow-up in 2013. As the cohort ages, the relative risks associated with HDP will likely decrease as the absolute risks for CVD risk factors increase.

It is not yet clear whether HDP unmasks preexisting cardiovascular risk through the "stress test" of pregnancy or whether it induces endothelial or organ damage that alters a woman's trajectory toward development of CVD risk factors. Women who develop preeclampsia tend to have slightly higher blood pressures and a dyslipidemic profile before pregnancy, indicating that preeclampsia may reveal a subclinical trajectory toward development of chronic hypertension and hypercholesterolemia that predates pregnancy (18, 43). Regardless of whether the relationship is correlational or causal, a history of HDP may help identify women who are at increased risk for CVD risk factors and events.

Compared with women who are normotensive during their first pregnancy, those with gestational hypertension or preeclampsia are at increased risk for chronic hypertension, T2DM, and hypercholesterolemia shortly after pregnancy. This increased risk persists for several decades. These women may benefit from lifestyle interventions and screening to reduce cardiovascular risk and delay disease onset. Just as guidelines exist to screen for T2DM among women with a history of gestational diabetes (44), our findings may inform similar guidelines on screening for CVD risk factors among women with a history of HDP.

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Appendix: Expanded Methods

BMI Derivation

In the NHS II, the 1989 baseline questionnaire ascertained height; current weight; weight at age 18 years; and somatograms at ages 5, 10, 20, 30, and 40 years and at the time of completion of the questionnaire (Appendix Figure). Subsequent biennial questionnaires collected current weight. Body mass index was calculated on the basis of height and weight (kg/m^2). To derive prepregnancy BMIs for this analysis, we used the following information provided by participants: self-reported BMI at age 18 years; BMI at the time of completion of each biennial questionnaire; and somatograms at ages 20, 30, and 40 years and at the time of completion of the baseline questionnaire.

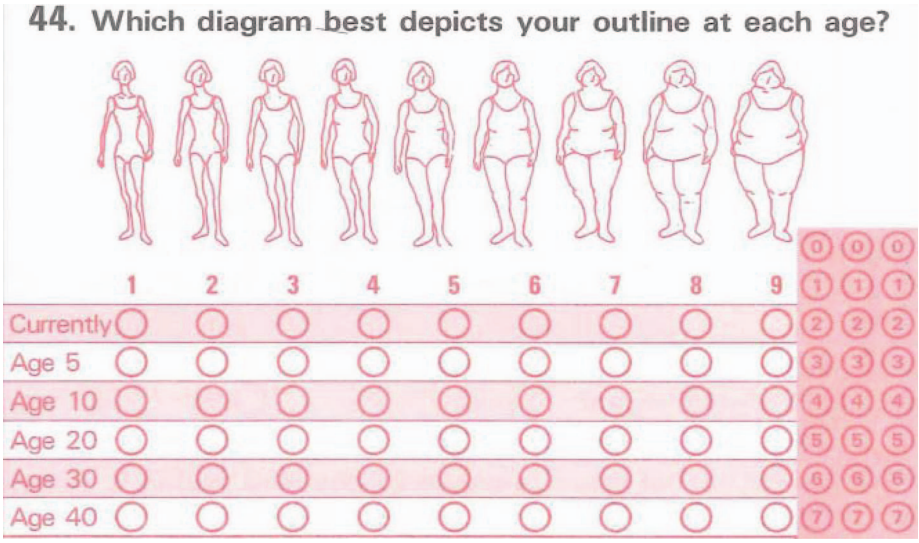
First, we used all available information from the biennial questionnaires to assign BMIs for ages 18 through 69 years (the age of the oldest participant at the time of the 2013 questionnaire submission [end of follow-up for the current analysis]). As such, the BMI calculated at the time of completion of each biennial questionnaire was assigned as the BMI for the age of the participant at the time of completion of that questionnaire (for example, the BMI at age 31 years for a woman who was that age in 1991 was taken from the 1991 questionnaire). If a woman did not complete a biennial questionnaire and provide current weights at ages 20, 30, and 40 years and/or at the time of the baseline questionnaire (which were used to calculate BMIs at those ages), she was assigned the median BMI among participants with known BMIs who reported the same somatogram category for those ages. For example, if a woman's BMI at age 40 years was not known and she had indicated category 5 for her somatogram at that age on the baseline questionnaire, she was assigned the median BMI among women who also indicated category 5 for their somatogram at age 40 years and who provided their current weight on a biennial questionnaire at that age. (If a woman was missing somatogram information, her BMI was interpolated as described in the next paragraph.)

Second, we interpolated BMIs across ages for which BMI was not known using the formula $B_2 = B_1 + ([B_3 - B_1]/[A_3 - A_1]) \times (A_2 - A_1)$. B_2 represents the unknown BMI being estimated (at time 2), B_1 represents the last known BMI (at time 1), and B_3 represents the next known BMI (at time 3). Similarly, A_1 represents the age at the last known BMI (at time 1), A_2 represents the age for the unknown BMI being estimated (at time 2), and A_3 represents the age at the time of the next known BMI (at time 3). Therefore, for each unknown BMI at a given age falling temporally between 2 known BMIs, the unknown BMI was estimated as the last known BMI (B_1), plus the difference between the 2 known BMIs ($B_3 - B_1$), divided by the difference in ages (time) between the 2 known BMIs ($A_3 - A_1$), multiplied by the number of years between the last known BMI and the unknown BMI being estimated ($A_2 - A_1$). This interpolation was repeated until age 69 years or the last age at which the BMI for a given participant was known (based on the BMIs and somatograms from the biennial questionnaires).

Additional Results

Mean length of follow-up and age at censoring varied due to risk factor–specific censoring. Mean follow-up was 26.9 years (SD, 8.8; range, 2 to 49 years) for chronic hypertension, 31.6 years (SD, 7.3; range, 2 to 50 years) for T2DM, and 25.1 years (SD, 9.5; range, 2 to 49 years) for hypercholesterolemia. Mean age at censoring was 52.8 years (SD, 7.9; range, 21 to 67 years) for chronic hypertension, 57.4 years (SD, 5.3; range, 22 to 67 years) for T2DM, and 51.0 years (SD, 8.7; range, 20 to 67 years) for hypercholesterolemia.

Appendix Figure. Somatogram question on the 1989 Nurses' Health Study II baseline questionnaire.



These drawings were used to assess body fatness at different ages among nurse participants. (Reproduced from Stunkard and colleagues [45, 46] with permission of the authors.)

Appendix Table 1. HRs and 95% CIs for Hypertensive Disorders in First Pregnancy and Cardiovascular Disease Risk Factors, by Gestation Length*

CVD Risk Factor	HDP Status and Gestation Length						
	Full-Term (≥37 Weeks)				Preterm (<37 Weeks)		
	Normotension (*n* = 49 099 [83.7%])	Gestational Hypertension (*n* = 1566 [2.7%])	Preeclampsia (*n* = 3112 [5.3%])	HDP (*n* = 4678 [8.0%])	Gestational Hypertension (*n* = 133 [0.2%])	Preeclampsia (*n* = 575 [1.0%])	HDP (*n* = 708 [1.2%])
Chronic hypertension							
Cases/person-years, *n/N*	15 234/1 347 395	903/32 892	1624/72 261	2527/105 153	76/2676	298/12 056	374/14 732
Excess cases per 10 000 person-years, *n*	–	161	112	127	171	134	141
HR (95% CI)							
Model 1	1.00 (reference)	3.19 (2.98–3.41)	2.42 (2.30–2.55)	2.65 (2.54–2.76)	3.36 (2.68–4.21)	2.78 (2.48–3.12)	2.88 (2.60–3.19)
Model 2	1.00 (reference)	2.82 (2.63–3.01)	2.18 (2.07–2.29)	2.37 (2.27–2.47)	2.70 (2.15–3.39)	2.51 (2.24–2.82)	2.54 (2.29–2.82)
Type 2 diabetes mellitus							
Cases/person-years, *n/N*	2836/1 560 189	171/46 261	379/95 969	550/142 230	16/3687	56/16 375	72/20 062
Excess cases per 10 000 person-years, *n*	–	19	21	20	25	16	18
HR (95% CI)							
Model 1	1.00 (reference)	2.15 (1.84–2.51)	2.26 (2.03–2.51)	2.22 (2.03–2.44)	2.49 (1.52–4.07)	2.03 (1.56–2.64)	2.11 (1.67–2.67)
Model 2	1.00 (reference)	1.66 (1.42–1.94)	1.80 (1.62–2.01)	1.76 (1.60–1.93)	1.79 (1.09–2.93)	1.60 (1.23–2.09)	1.64 (1.29–2.07)
Hypercholesterolemia							
Cases/person-years, *n/N*	26 877/1 246 593	992/35 235	1928/73 179	2920/108 414	82/2810	351/12 199	433/15 009
Excess cases per 10 000 person-years, *n*	–	66	48	54	76	72	73
HR (95% CI)							
Model 1	1.00 (reference)	1.43 (1.34–1.52)	1.33 (1.27–1.39)	1.36 (1.31–1.41)	1.52 (1.22–1.89)	1.52 (1.37–1.69)	1.52 (1.38–1.67)
Model 2	1.00 (reference)	1.36 (1.28–1.45)	1.29 (1.23–1.35)	1.31 (1.26–1.36)	1.46 (1.18–1.82)	1.49 (1.34–1.66)	1.49 (1.35–1.63)

CVD = cardiovascular disease; HDP = hypertensive disorders of pregnancy; HR = hazard ratio.
* Tests for effect modification by preterm delivery: $P = 0.076$ for chronic hypertension, $P = 0.68$ for type 2 diabetes mellitus, and $P = 0.031$ for hypercholesterolemia. Model 1 was adjusted for age at first birth, age in 1989, race/ethnicity (African American, Latina, Asian, white [reference], or other), and years of parental education (<9, 9 to 11, 12, 13 to 15, or ≥16 [reference]). Model 2 was also adjusted for strenuous physical activity at age 18 to 22 y (never, 1 to 3 mo/y [reference], 4 to 6 mo/y, 7 to 9 mo/y, or 10 to 12 mo/y), prepregnancy smoking status (never [reference], past, or current), prepregnancy body mass index (<18.5, 18.5 to 24.9 [reference], 25 to 29.9, or ≥30 kg/m^2), prepregnancy alcohol consumption (none [reference], ≤1 drink/wk, 2 to 6 drinks/wk, or ≥1 drink/d), quintile of prepregnancy Alternative Healthy Eating Index score (fifth quintile [reference] represented the healthiest diet category), prepregnancy oral contraceptive use (never [reference], <2 y, 2 to 3 y, or ≥4 y), and family history of chronic hypertension (yes or no; chronic hypertension model only) and type 2 diabetes mellitus (yes or no; type 2 diabetes mellitus model only). These results were drawn from 6 different models: one model with HDP and normotension in first pregnancies split out by full-term and preterm deliveries (i.e., 4 exposure categories), and another model with preeclampsia, gestational hypertension, and normotension in first pregnancies split out by full-term and preterm deliveries (i.e., 6 exposure categories) for each of the 3 CVD risk factor outcomes. The normotensive term was the reference group for all contrasts. Results for women with normotension and preterm deliveries are not shown but were obtained from the same models; fully adjusted HRs were 1.10 (95% CI, 1.04 to 1.16) for chronic hypertension, 1.20 (CI, 1.06 to 1.35) for type 2 diabetes mellitus, and 1.08 (CI, 1.03 to 1.12) for hypercholesterolemia.

Appendix Table 2. HRs and 95% CIs for Hypertensive Disorders of Pregnancy Before Age 40 Years and Cardiovascular Disease Risk Factors After Age 40 Years (n = 45 815)*

Pregnancy History at Age 40 Years	Chronic Hypertension			Type 2 Diabetes Mellitus			Hypercholesterolemia		
	Cases, *n*	Person-Years, *n*	HR (95% CI)	Cases, *n*	Person-Years, *n*	HR (95% CI)	Cases, *n*	Person-Years, *n*	HR (95% CI)
Normotension in first pregnancy									
Second or later pregnancy: normotension in all	9504	554 504	1.00 (reference)	1428	659 537	1.00 (reference)	16 209	526 278	1.00 (reference)
Second or later pregnancy: no further pregnancies	1756	101 586	1.02 (0.97–1.08)	289	122 653	1.01 (0.89–1.15)	3071	95 855	1.05 (1.01–1.09)
Second or later pregnancy: any HDP	434	11 272	2.40 (2.18–2.64)	90	16 224	2.12 (1.71–2.63)	481	12 353	1.30 (1.19–1.43)
HDP in first pregnancy									
Second or later pregnancy: normotension in all	896	29 288	1.85 (1.73–1.98)	147	38 626	1.63 (1.38–1.94)	1071	30 384	1.21 (1.13–1.28)
Second or later pregnancy: no further pregnancies	357	9682	2.24 (2.01–2.49)	72	13 609	1.83 (1.44–2.33)	420	10 121	1.45 (1.32–1.60)
Second or later pregnancy: any HDP	357	6628	3.53 (3.17–3.93)	65	10 545	2.17 (1.69–2.79)	319	8159	1.32 (1.18–1.48)

CVD = cardiovascular disease; HDP = hypertensive disorders of pregnancy; HR = hazard ratio.
* The 6 exposure categories included in this table are normotension in all pregnancies, normotension in first pregnancy and no additional pregnancies, normotension in first pregnancy and HDP (preeclampsia or gestational hypertension) in ≥1 later pregnancy, HDP in first pregnancy and normotension in all subsequent pregnancies, HDP in first pregnancy and no additional pregnancies, and HDP in first pregnancy with recurrence in ≥1 later pregnancy. Women who did not have the end point at age 40 y and with no births after this age contributed person-time to the models starting at age 40 y. Models were adjusted for age at first birth, age in 1989, race/ethnicity (African American, Latina, Asian, white [reference], or other), years of parental education (<9, 9 to 11, 12, 13 to 15, or ≥16 [reference]), strenuous physical activity at age 18 to 22 y (never, 1 to 3 mo/y [reference], 4 to 6 mo/y, 7 to 9 mo/y, or 10 to 12 mo/y), prepregnancy smoking status (never [reference], past, or current), prepregnancy body mass index (<18.5, 18.5 to 24.9 [reference], 25 to 29.9, or ≥30 kg/m^2), prepregnancy alcohol consumption (none [reference], ≤1 drink/wk, 2 to 6 drinks/wk, or ≥1 drink/d), quintile of prepregnancy Alternative Healthy Eating Index score (fifth quintile [reference] represented the healthiest diet category), prepregnancy oral contraceptive use (never [reference], <2 y, 2 to 3 y, or ≥4 y), and family history of chronic hypertension (yes or no; chronic hypertension model only) and type 2 diabetes mellitus (yes or no; type 2 diabetes mellitus model only).

Appendix Table 3. E-Values for the Observed Associations Between Hypertensive Disorders in First Pregnancy and Cardiovascular Disease Risk Factors*

CVD Risk Factor	Gestational Hypertension	Preeclampsia
Chronic hypertension		
Observed association	2.79 (2.61–2.97)	2.21 (2.10–2.32)
E-value (point estimate)	3.45	2.85
E-value (CI)	3.27	2.72
Type 2 diabetes mellitus		
Observed association	1.65 (1.42–1.91)	1.75 (1.58–1.93)
E-value (point estimate)	2.69	2.90
E-value (CI)	2.19	2.54
Hypercholesterolemia		
Observed association	1.36 (1.28–1.45)	1.31 (1.25–1.36)
E-value (point estimate)	1.78	1.70
E-value (CI)	1.66	1.61

CVD = cardiovascular disease.
* The observed associations are the fully adjusted hazard ratios presented in Table 1 and are shown here for reference. E-values were calculated using the publicly available online calculator (www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials) for chronic hypertension and hypercholesterolemia based on a "hazard ratio (outcome prevalence >15%)" and for type 2 diabetes mellitus based on a "hazard ratio (outcome prevalence <15%)." E-values for the point estimate and for the limit of the 95% CI closest to the null (i.e., the lower limit for the above CIs) represent the magnitude of the association that an unmeasured confounder would have to have with both the exposure (hypertensive disorders in first pregnancy) and the outcome (CVD risk factor) above and beyond measured confounding to explain away the observed association and to render the observed association no longer statistically significant, respectively.

Web-Only References

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