Association of Adverse Pregnancy Outcomes With Hypertension 2 to 7 Years Postpartum

David M. Haas, MD, MS; Corette B. Parker, DrPH; Derek J. Marsh, MS; William A. Grobman, MD, MBA; Deborah B. Ehrenthal, MD, MPH; Philip Greenland, MD; C. Noel Bairey Merz, MD; Victoria L. Pemberton, RNC, MS; Robert M. Silver, MD; Shannon Barnes, MSN; Rebecca B. McNeil, PhD; Kirsten Cleary, MD; Uma M. Reddy, MD, MPH; Judith H. Chung, MD, PhD; Samuel Parry, MD; Lauren H. Theilen, MD, MSCI; Elizabeth A. Blumenthal, MD; Lisa D. Levine, MD, MSCE; Brian M. Mercer, MD; Hyagriv Simhan, MD; LuAnn Polito, RN, JD; Ronald J. Wapner, MD; Janet Catov, PhD, MS; Ida Chen, PhD; George R. Saade, MD; for the NHLBI nuMoM2b Heart Health Study*

Background—Identifying pregnancy-associated risk factors before the development of major cardiovascular disease events could provide opportunities for prevention. The objective of this study was to determine the association between outcomes in first pregnancies and subsequent cardiovascular health.

Methods and Results—The Nulliparous Pregnancy Outcomes Study Monitoring Mothers-to-be Heart Health Study is a prospective observational cohort that followed 4484 women 2 to 7 years (mean 3.2 years) after their first pregnancy. Adverse pregnancy outcomes (defined as hypertensive disorders of pregnancy, small-for-gestational-age birth, preterm birth, and stillbirth) were identified prospectively in 1017 of the women (22.7%) during this pregnancy. The primary outcome was incident hypertension (HTN). Women without adverse pregnancy outcomes served as controls. Risk ratios (RR) and 95% CIs were adjusted for age, smoking, body mass index, insurance type, and race/ethnicity at enrollment during pregnancy. The overall incidence of HTN was 5.4% (95% CI 4.7% to 6.1%). Women with adverse pregnancy outcomes had higher adjusted risk of HTN at follow-up compared with controls (RR 2.4, 95% CI 1.8-3.1). The association held for individual adverse pregnancy outcomes: any hypertensive disorders of pregnancy (RR 2.7, 95% CI 2.0-3.6), preeclampsia (RR 2.8, 95% CI 2.0-4.0), and preterm birth (RR 2.7, 95% CI 1.9-3.8). Women who had an indicated preterm birth and hypertensive disorders of pregnancy had the highest risk of HTN (RR 4.3, 95% CI 2.7-6.7).

Conclusions—Several pregnancy complications in the first pregnancy are associated with development of HTN 2 to 7 years later. Preventive care for women should include a detailed pregnancy history to aid in counseling about HTN risk.

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Key Words: adverse pregnancy outcomes • hypertension • risk • preeclampsia • preterm birth

Cardiovascular disease (CVD) is the leading cause of mortality among women in the United States and developed countries.[1] Young women (<55 years old) in particular are experiencing an increase in CVD risk factor prevalence and severity, and CVD death rates have stagnated in young women compared with other groups.[2] In addition, there is racial disparity in CVD: the US age-adjusted death rate from coronary heart disease and stroke are markedly

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Clinical Perspective

What Is New?

- Hypertensive disorders of pregnancy and preterm birth herald an increased risk of hypertension, particularly high (45.4% by the new criteria) in women who had an iatrogenic preterm birth, many of whom experienced hypertensive disorders of pregnancy.
- When compared with women who developed other adverse pregnancy outcomes, women with hypertensive disorders of pregnancy, those diagnosed with preeclampsia, and women with an iatrogenic preterm birth had a higher risk of subsequent incident hypertension.

What Are the Clinical Implications?

- The short time frame (2-7 years) to the discovery of hypertension after pregnancy among a population of young women highlights the importance of a detailed pregnancy history in preventive health screening, early diagnosis, and intervention.
- First pregnancies might be utilized as an early life stress test to identify women who may benefit from preventive and screening strategies for healthy behaviors and therapies.

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higher for non-Hispanic black than for non-Hispanic white women.[1] Dyslipidemia, inflammation, and central adiposity are strongly related to CVD risk among women.[3-5] Identification of pathophysiology unique to women has considerable potential to augment CVD prevention.[6]

Adverse pregnancy outcomes (APOs), such as hypertensive disorders of pregnancy (HDP) and preterm birth (PTB), were once regarded as obstetrical conditions with implications limited to pregnancy. However, mounting evidence suggests that, after controlling for traditional risk factors for these conditions, women who experience APOs are at higher risk for subsequent development of hypertension (HTN), CVD, and diabetes mellitus at younger ages than those without APOs.[7-10] Most studies have relied on retrospectively collected data and/or self-reported reproductive history[11-16] and thus are prone to misclassification or recall bias. Additionally, these studies have lacked assessment of cardiometabolic status during the index pregnancy, which also limits understanding of CVD risk trajectory.

The nuMoM2b-HHS (Nulliparous Pregnancy Outcomes Study—Monitoring Mothers-to-be Heart Health Study) was designed to overcome these limitations. It had a primary objective of establishing the association between pregnancy outcomes and subsequent cardiovascular health by analyzing data from a large cohort of women, with detailed clinical and biospecimen data available, who were followed prospectively from the beginning of their first pregnancy through 2 to 7 years postpartum.

Methods

The data that support the findings of this study are available from the data-coordinating center on reasonable request.

Participants and Contact

The complete methods of the nuMoM2b-HHS are described elsewhere.[17] The study was approved by all local governing institutional review boards. Briefly, contacts were made and interviews performed by telephone or email at 6-month intervals, beginning at least 6 months after delivery of the index pregnancy. During interviews, women updated contact information and answered questionnaires regarding any subsequent pregnancies, medications, medical conditions, and CVD events or diagnoses. Self-reported APOs or CVD events subsequent to the index pregnancy were verified by obtaining medical records. Details about interval contacts are contained in the methods publication.[17]

Women were eligible to participate in an in-person cardiovascular assessment if they participated in the nuMoM2b study[18] (a prospective cohort of women in their first pregnancy recruited in the first trimester), had obstetrical delivery information from the index pregnancy, agreed to be contacted for future studies, did not subsequently withdraw consent during an interval contact, and were 18 years of age or older, at least 2 years from the delivery of their index pregnancy, and not currently pregnant. All participants gave written informed consent approved by each site's human subjects ethical review board.

An in-person nuMoM2b-HHS visit was conducted 2 to 7 years after the index pregnancy ended. Participants were asked to fast for 8 hours (including a long sleep period) before the visit. Demographic characteristics, health care information, current medication and supplement use, family and personal medical history (including a detailed CVD medical history), alcohol, tobacco, and drug use, and physical activity information were obtained. Participants completed validated self-administered questionnaires detailing food intake and eating habits, sleep characteristics, perceived stress, depression, and gynecologic health. In general, we used questions previously demonstrated to be predictive of a clinical diagnosis and/or standardized in large cohort studies.[19,20] Blood pressure, anthropometric measurements, and biological specimens were collected at the visit using standardized protocols.

Measures, Outcomes, and Definitions

Pregnancy outcomes were recorded by study personnel at the time of delivery and verified by trained, certified clinical chart

abstractors. For participants with HTN, proteinuria, or a related condition possibly consistent with HDP as noted in the medical record, the chart review was more extensive in order to classify HDP according to a priori study criteria or, in cases when uncertainty as to the diagnosis remained, adjudication by study investigators. HDP included all cases of preeclampsia (without severe features, with severe features, superimposed preeclampsia, or eclampsia regardless of the timing of onset) and antepartum gestational hypertension, with full details of the categorization procedure described elsewhere.[21] Other APOs considered as exposures were PTB, small-for-gestational-age birth, and stillbirth, defined per standard obstetrical definitions.[18] PTB was defined as a live birth <37 weeks +0 days gestational age and based on prior study definitions, further subclassified as iatrogenic (medically indicated) PTB or spontaneous PTB. Small-for-gestational-age birth was calculated using the Alexander growth curves from birth weight and gestational age at birth and defined at less than the 5th percentile.[22] Gestational diabetes mellitus was defined as failing standard glucose tolerance testing during pregnancy without preexisting diabetes mellitus.[23] Women with only gestational diabetes mellitus are not included in the current analysis of women with APOs. Analyses excluded women who experienced pregnancy loss before 20 weeks or pregnancy termination.

Blood pressure (BP) and anthropometric measures were obtained during the nuMoM2b-HHS visit.[17] Following a standard protocol, research personnel recorded 3 standardized BP measurements using calibrated automatic devices that were the same at each site. With the participant seated, BP measurements were recorded, and the average of the last 2 systolic and diastolic pressures were used for analysis.[17]

Body composition was assessed as body mass index (kg/m²) from measures of height and weight obtained using a regularly calibrated balance-beam scale for weight and a stadiometer for height measurements. Waist circumference over the iliac crest was measured to the nearest 0.1 cm using a nonstretch study measuring tape. The measurement was taken twice, and if the difference between the 2 was >0.5 cm, a third measurement was recorded. For analyses, the third measurement (if performed) or average of the first 2 measurements was used.

The primary outcome of the study was HTN that developed subsequent to the index pregnancy, as determined by BP measurement or use of an antihypertensive medication for blood pressure control at the 2- to 7-year postpartum study visit. HTN was chosen as the primary outcome due to its strong association with CVD risk and death.[24] The diagnostic threshold for HTN was a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg.[25,26] This diagnostic threshold, determined as a study outcome based on the criteria for HTN extant at the time the study was designed, was used for the primary analyses. Unless specified, incident HTN is diagnosed based on this definition. Recently updated guidelines, however, have redefined the lower threshold for HTN as a systolic BP ≥130 mm Hg or a diastolic BP ≥80 mm Hg.[24] We performed a post hoc analysis using these thresholds as well.

Relevant cardiovascular health biomarkers were analyzed using banked frozen maternal serum (lipid panel) and whole blood (glucose) collected and processed at the nuMoM2b-HHS study visit.[17] Metabolic syndrome was defined as the presence of 3 of the following 5 criteria: elevated waist circumference, elevated triglycerides or taking medication to lower them, elevated fasting glucose or taking associated glucose-lowering medication, elevated blood pressure or taking antihypertensive medication, reduced high-density lipoprotein levels or taking associated medications.[27]

Statistical Considerations and Analysis

The sample size of ≈5000 participants with nuMoM2b-HHS in-person visits was determined a priori by considering detectable HTN risk ratios and detectable mean differences in various continuous measures of CVD risk at 2 to 7 years postpartum for specific APOs versus comparison groups. Details are described elsewhere.[17] Briefly, assuming a 2% incidence of HTN at follow-up for the non-APO controls, unadjusted risk ratios from 2.1 to 2.7 for HTN among women with specific APOs would be detectable with 80% power, assuming prevalence of an individual APO ranging from 4% to 10%.

Index pregnancy characteristics and cardiovascular characteristics at follow-up were summarized using means and standard deviations for continuous variables, and frequency and percentage for categorical variables. After exclusion of women with chronic HTN before the index pregnancy or missing HTN information at the study visit (Figure), univariate associations between APOs and HTN were tested using chi-squared tests for categorical variables and t tests for continuous variables. The incidence of HTN 2 to 7 years after the index pregnancy was estimated using binomial proportions and Wald 95% CIs; exact Clopper-Pearson CIs were used within small APO-specific subgroups (n≤40).

Poisson regression with robust standard errors[28] was used to estimate the risk ratios (RR) and 95% CIs of incident HTN associated with any APOs. Unadjusted and adjusted (with the covariates of age, body mass index, type of health insurance at nuMoM2b enrollment, race/ethnicity, and smoking during the 3 months before pregnancy) associations were estimated. For these analyses, associations between selected APOs and HTN were tested using 3 comparison groups. Women with a specific APO were compared with (1) women who did not have any of the APOs in the index pregnancy, (2) women without the specific APO (ie, any other APO or no APO), and (3) only women with any other APO. These comparisons provide insight into
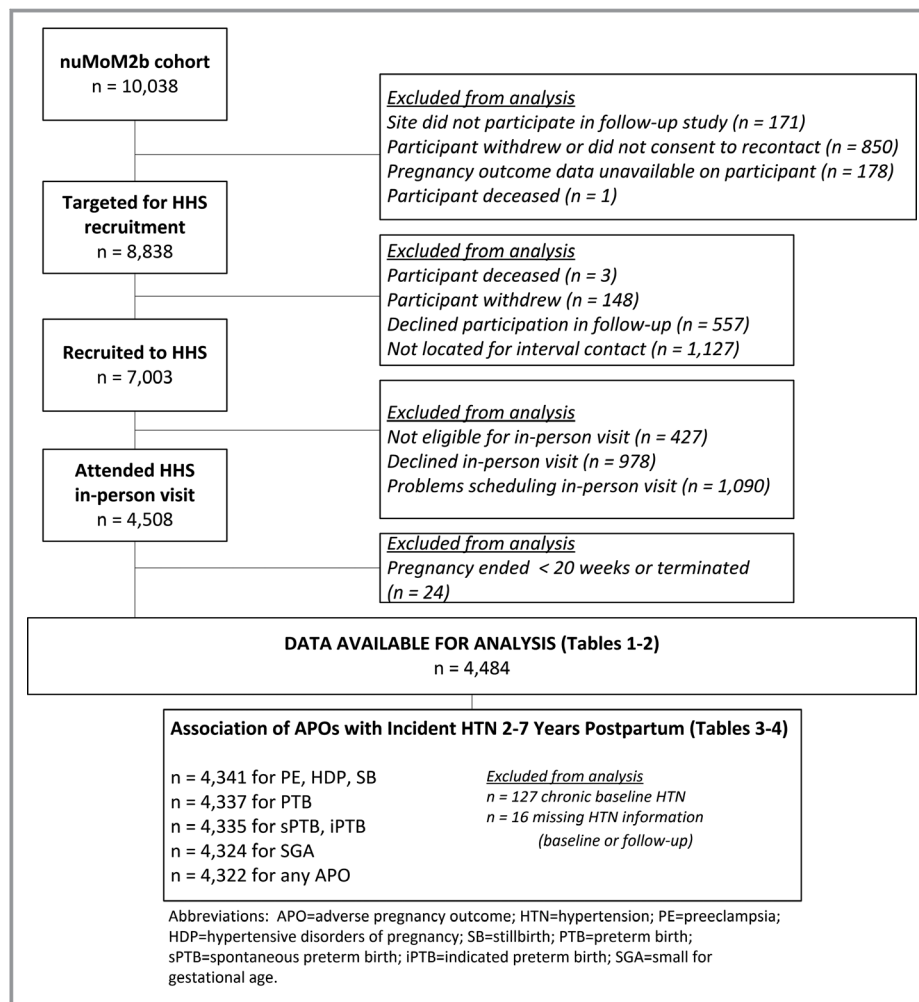
nuMoM2b cohort
n = 10,038

Excluded from analysis
Site did not participate in follow-up study (n = 171)
Participant withdrew or did not consent to recontact (n = 850)
Pregnancy outcome data unavailable on participant (n = 178)
Participant deceased (n = 1)

Targeted for HHS recruitment
n = 8,838

Excluded from analysis
Participant deceased (n = 3)
Participant withdrew (n = 148)
Declined participation in follow-up (n = 557)
Not located for interval contact (n = 1,127)

Recruited to HHS
n = 7,003

Excluded from analysis
Not eligible for in-person visit (n = 427)
Declined in-person visit (n = 978)
Problems scheduling in-person visit (n = 1,090)

Attended HHS in-person visit
n = 4,508

Excluded from analysis
Pregnancy ended < 20 weeks or terminated (n = 24)

DATA AVAILABLE FOR ANALYSIS (Tables 1-2)
n = 4,484

Association of APOs with Incident HTN 2-7 Years Postpartum (Tables 3-4)

n = 4,341 for PE, HDP, SB
n = 4,337 for PTB
n = 4,335 for sPTB, iPTB
n = 4,324 for SGA
n = 4,322 for any APO

Excluded from analysis
n = 127 chronic baseline HTN
n = 16 missing HTN information
        (baseline or follow-up)

Abbreviations: APO=adverse pregnancy outcome; HTN=hypertension; PE=preeclampsia;
HDP=hypertensive disorders of pregnancy; SB=stillbirth; PTB=preterm birth;
sPTB=spontaneous preterm birth; iPTB=indicated preterm birth; SGA=small for
gestational age.

Figure. Flow diagram for participation in analysis. APO indicates adverse pregnancy outcome; HDP, hypertensive disorders of pregnancy; HHS, Heart Health Study; HTN, hypertension; iPTB, indicated preterm birth; nuMoM2b, Nulliparous Pregnancy Outcome Study—Monitoring Mothers-to-Be; PE, preeclampsia; PTB, preterm birth; sPTB, spontaneous preterm birth; SB, stillbirth; SGA, small for gestational age.

relative contributions of each APO to the outcomes. We also performed a sensitivity analysis restricted to women who did not have a reported pregnancy between the end of the index pregnancy and the nuMoM2b-HHS study visit.

We restricted these analyses to women who attended an in-person visit in order to ensure the analyses were based on objective measures of the primary outcome. Women with missing data for the primary outcome, APOs, baseline HTN, or model covariates were excluded from analyses involving those data. Analyses were performed using SAS V9.4 (Cary, NC) and R (Vienna, Austria).[29,30]

Results

After the exclusion criteria had been applied, 8838 of the original 10 038 women enrolled in the nuMoM2b cohort were eligible for nuMoM2b-HHS, and 7003 (79.2%) completed at

least 1 interval contact (Figure). Of these women, 4484 (64.0%) had an index pregnancy delivery at ≥20 weeks of gestation and attended the in-person study visit. Table 1 displays the overall baseline characteristics of women who attended a study visit. The demographic characteristics of the nuMoM2b-HHS cohort were representative of the overall nuMoM2b cohort[18] and similar to women who did not participate in nuMoM2b-HHS (Table S1). Rates of APOs in the nuMoM2b-HHS cohort were also similar to the rates in the overall nuMoM2b cohort (Table S1).

More than 1 in 5 women enrolled in nuMoM2b-HHS had at least 1 APO during their index pregnancy (n=1017, 22.7%, Table 1). HDP was the most common APO (13.6%; 6.6% with preeclampsia and 7.0% with antepartum gestational HTN), while 8.6% of women had a PTB (4.9% spontaneous PTB and 3.7% iatrogenic PTB), 4.2% had a small-for-gestational-age birth, and 0.4% had a stillbirth. Many of the 167 cases of

Table 1. Index Pregnancy Characteristics of nuMoM2b-HHS Participants According to Index Pregnancy APOs

Index Pregnancy Characteristics	All Participants (N=4484)	Index Pregnancy APOs* (Not Mutually Exclusive)									
		No APO (N=3444)	Any APO (N=1017)	HDP (N=612)	Preeclampsia (N=298)	PTB (N=387)	sPTB (N=218)	sPTB <34 wk (N=57)	iPTB (N=167)	SGA (N=187)	SB (N=16)
Maternal age, mean (SD), y	27.0 (5.6)	27.0 (5.5)	26.9 (5.8)	26.9 (5.7)	26.2 (6.0)†	26.7 (6.0)	26.7 (5.9)	26.7 (6.1)	26.7 (6.3)	26.5 (6.3)	27.7 (5.9)
Category, n (%)											
13 to 21	905 (20.2)	678 (19.7)	220 (21.6)†	124 (20.3)	81 (27.2)†	90 (23.3)†	51 (23.4)	15 (26.3)†	38 (22.8)	51 (27.3)†	3 (18.8)
22 to 35	3272 (73.0)	2544 (73.9)	714 (70.2)†	439 (71.7)	195 (65.4)†	263 (68.0)†	149 (68.3)	34 (59.6)†	113 (67.7)	120 (64.2)†	11 (68.8)
>35	307 (6.8)	222 (6.4)	83 (8.2)†	49 (8.0)	22 (7.4)†	34 (8.8)†	18 (8.3)	8 (14.0)†	16 (9.6)	16 (8.6)†	2 (12.5)
Maternal race, n (%)											
White non-Hispanic	2786 (62.1)	2170 (63.0)	606 (59.6)†	385 (62.9)†	153 (51.3)†	218 (56.3)†	128 (58.7)	28 (49.1)	90 (53.9)†	87 (46.5)†	8 (50.0)
Black non-Hispanic	618 (13.8)	425 (12.3)	189 (18.6)†	115 (18.8)†	75 (25.2)†	76 (19.6)†	38 (17.4)	13 (22.8)	38 (22.8)†	45 (24.1)†	3 (18.8)
Hispanic	735 (16.4)	585 (17.0)	143 (14.1)†	67 (10.9)†	44 (14.8)†	66 (17.1)†	38 (17.4)	11 (19.3)	26 (15.6)†	38 (20.3)†	5 (31.3)
Asian	135 (3.0)	112 (3.3)	22 (2.2)†	13 (2.1)†	5 (1.7)†	6 (1.6)†	3 (1.4)	2 (3.5)	3 (1.8)†	6 (3.2)†	...
Other	210 (4.7)	152 (4.4)	57 (5.6)†	32 (5.2)†	21 (7.0)†	21 (5.4)†	11 (5.0)	3 (5.3)	10 (6.0)†	11 (5.9)†	...
Education level, n (%)											
Less than high school graduate	327 (7.3)	219 (6.4)	106 (10.4)†	53 (8.7)†	36 (12.1)†	46 (11.9)†	24 (11.0)†	10 (17.5)†	22 (13.2)†	28 (15.0)†	2 (12.5)
High school graduate or GED completed	508 (11.3)	372 (10.8)	134 (13.2)†	79 (12.9)†	44 (14.8)†	58 (15.0)†	31 (14.2)†	10 (17.5)†	27 (16.2)†	25 (13.4)†	3 (18.8)
Some college credit, no degree	889 (19.8)	668 (19.4)	217 (21.3)†	137 (22.4)†	78 (26.2)†	90 (23.3)†	45 (20.6)†	11 (19.3)†	44 (26.3)†	36 (19.3)†	2 (12.5)
Associate/technical degree	501 (11.2)	370 (10.7)	126 (12.4)†	80 (13.1)†	37 (12.4)†	50 (12.9)†	28 (12.8)†	6 (10.5)†	21 (12.6)†	22 (11.8)†	4 (25.0)
Bachelor's degree	1261 (28.1)	1021 (29.7)	234 (23.0)†	143 (23.4)†	59 (19.8)†	87 (22.5)†	51 (23.4)†	12 (21.1)†	36 (21.6)†	31 (16.6)†	5 (31.3)
Degree beyond bachelor's	996 (22.2)	792 (23.0)	200 (19.7)†	120 (19.6)†	44 (14.8)†	56 (14.5)†	39 (17.9)†	8 (14.0)†	17 (10.2)†	45 (24.1)†	...
Type of health insurance, n (%)											
Commercial	3087 (69.2)	2412 (70.4)	663 (65.8)†	404 (66.2)	164 (55.2)†	232 (60.4)†	139 (64.7)†	31 (55.4)	92 (55.1)†	121 (66.1)	7 (43.8)†
Government/military	1219 (27.3)	898 (26.2)	311 (30.9)†	183 (30.0)	121 (40.7)†	140 (36.5)†	69 (32.1)	22 (39.3)	70 (41.9)†	57 (31.1)	9 (56.3)†
Self-pay/other	152 (3.4)	117 (3.4)	34 (3.4)†	23 (3.8)	12 (4.0)†	12 (3.1)†	7 (3.3)	3 (5.4)	5 (3.0)†	5 (2.7)	...
Smoked during 3 mo before pregnancy, n/N (%)	718/4478 (16.0)	516/3441 (15.0)	196/1014 (19.3)†	110/610 (18.0)	63/297 (21.2)†	83/386 (21.5)†	47/217 (21.7)†	17/57 (29.8)†	36/167 (21.6)†	33/186 (17.7)	6/16 (37.5)†
Early pregnancy BMI, mean (SD), kg/m²	26.6 (6.5)	26.0 (6.1)	28.5 (7.6)†	29.8 (7.8)†	30.2 (8.2)†	28.0 (7.4)†	26.1 (5.9)	28.0 (6.7)†	30.5 (8.4)†	26.4 (7.0)	29.3 (9.2)
Category, n (%)											
<25	2284 (51.8)	1879 (55.6)	395 (39.3)†	193 (31.7)†	91 (31.0)†	161 (42.6)†	110 (51.6)	20 (36.4)†	50 (30.7)†	98 (53.6)	7 (46.7)
25 to <30	1081 (24.5)	809 (23.9)	263 (26.2)†	165 (27.1)†	83 (28.2)†	101 (26.7)†	57 (26.8)	17 (30.9)†	43 (26.4)†	45 (24.6)	4 (26.7)
≥30	1042 (23.6)	692 (20.5)	346 (34.5)†	250 (41.1)†	120 (40.8)†	116 (30.7)†	46 (21.6)	18 (32.7)†	70 (42.9)†	40 (21.9)	4 (26.7)

Table 1. Continued

Index Pregnancy Characteristics	All Participants (N=4484)	Index Pregnancy APOs* (Not Mutually Exclusive)									
		No APO (N=3444)	Any APO (N=1017)	HDP (N=612)	Preeclampsia (N=298)	PTB (N=387)	sPTB (N=218)	sPTB <34 wk (N=57)	iPTB (N=167)	SGA (N=187)	SB (N=16)
Pregestational hypertension: n/N (%)	127/4480 (2.8)	81/3444 (2.4)	46/1017 (4.5)†	28/612 (4.6)†	28/298 (9.4)†	30/387 (7.8)†	4/218 (1.8)	…	26/167 (15.6)†	8/187 (4.3)	1/16 (6.3)
Pregestational diabetes mellitus, n/N (%)	62/4482 (1.4)	25/3443 (0.7)	36/1017 (3.5)	21/612 (3.4)†	12/298 (4.0)†	25/387 (6.5)†	7/218 (3.2)†	2/57 (3.5)	18/167 (10.8)†	1/187 (0.5)	3/16 (18.8)†
Gestational diabetes mellitus, n/N (%)	191/4422 (4.3)	127/3419 (3.7)	63/981 (6.4)†	37/591 (6.3)†	25/286 (8.7)†	23/362 (6.4)†	16/211 (7.6)†	7/55 (12.7)†	7/149 (4.7)	9/186 (4.8)	…

APO indicates adverse pregnancy outcome; BMI, body mass index; GED, general equivalency degree; HDP, hypertensive disorders of pregnancy; iPTB, indicated preterm birth; n, number in category; N, sample size; nuMoM2b-HHS, Nulliparous Pregnancy Outcome Study—Monitoring Mothers-to-Be—Heart Health Study; PTB, preterm birth; SB, stillbirth; SGA, small for gestational age; sPTB, spontaneous preterm birth.
*APO is defined as hypertensive disorders of pregnancy, preeclampsia, preterm birth, spontaneous preterm birth, indicated preterm birth, small for gestational age, or stillbirth.
Statistical significance for "No APO" vs each of the other categories reported as †$P<0.05$.

iatrogenic PTB had concomitant HDP (59.9%), and the proportion was similar when only iatrogenic PTB <34 weeks of gestation was considered (61.5%).

Index pregnancy characteristics of women in the study, stratified by development of individual APOs, are displayed in Table 1. When compared with women who did not have an APO, women who developed an APO in the index pregnancy were more likely to have been younger than 21 or older than 35 years of age, have a body mass index ≥25 kg/m^2 at index pregnancy enrollment, self-identified as non-Hispanic black, had a lower level of education, had government or military health insurance, and smoked during the 3 months before the pregnancy (all $P<0.05$). These associations were present for most individual APOs as well. Women who had APOs were also more likely to have been diagnosed with gestational diabetes mellitus during the pregnancy than women who did not develop APOs (6.4% versus 3.7% respectively, $P<0.05$).

Cardiovascular characteristics of the cohort 2 to 7 years postpartum are shown in Table 2 (characteristics for all subgroups in Table S2). The mean time between the end of the index pregnancy and the study visit was 3.2 years (SD 0.9). A total of 1573 women (35.1%) did not have a pregnancy in the intervening time before the study visit, 1931 (43.1%) had 1 intervening pregnancy, and 980 (21.9%) had 2 or more; 54.5% were overweight or obese, an increase of 6.4% from prepregnancy. Over one-third of all participants either had high-density lipoprotein cholesterol <1.3 mmol/L (<50 mg/dL) or were on a high-density lipoprotein–raising medication (34.5%), whereas 12.0% had elevated triglycerides or were on lipid-lowering medication. Twenty-two women (0.49%) had had a verified cardiovascular event between the index pregnancy and the study visit, 7 of which (31.8%) had occurred among women who had had an APO in the index pregnancy (RR for cardiovascular events for women with APOs compared with women who did not have APOs 1.58, 95% CI 0.65-3.87; Table S3).

The hypertensive status of all nuMoM2b-HHS participants is provided in Table 3. HTN developed in 5.4% of women in the cohort after their index delivery. Of the 235 women meeting criteria for HTN, 196 (83.4%) were diagnosed by BP measurements at the study visit, and 39 (16.6%) by currently taking antihypertensive drugs. Utilizing the new diagnostic thresholds for HTN published in 2018,[24] we determined the incidence of stage II HTN was 20.2%. Women who had been diagnosed with APOs in their first pregnancy had higher mean systolic and diastolic blood pressures ($P<0.05$) and higher prevalence of HTN by all definitions ($P<0.05$). The incidence of HTN in women with any APO was 10.8% but was 14.4% for women who had had preeclampsia during their index pregnancy. Under the newer HTN definitions, these rates were 31.2% and 38.5%, respectively (Table 3). Women with an

Table 2. Cardiovascular Characteristics 2 to 7 Years After Index Pregnancy

Cardiovascular Characteristics 2 to 7 y After Index Pregnancy	All nuMoM2b-HHS Participants (N=4484)
BMI, kg/m^2, mean (SD)	27.8 (7.7)
Category, n (%)	
<25 kg/m^2	2028 (45.5)
25 to <30 kg/m^2	1081 (24.2)
≥30 kg/m^2	1351 (30.3)
Waist circumference over iliac crest, cm, mean (SD)	96.2 (16.5)
≥88 cm (non-Asian) or ≥80 cm (Asian), n/N (%)	2916/4461 (65.4)
Total cholesterol, mmol/L, mean (SD)	4.7 (1.0)
N with data	4403
HDL-C, mmol/L, mean (SD)	1.4 (0.3)
N with data	4403
<1.3 mmol/L or on HDL-raising medication, n/N (%)	1517/4401 (34.5)
LDL-C, mmol/L, mean (SD)	2.8 (0.9)
N with data	4399
Glucose, mmol/L, mean (SD)	5.1 (1.3)
N with data	4395
≥5.6 mmol/L or on glucose-lowering medication, n/N (%)	718/4393 (16.3)
HbA$_{1c}$, %, mean (SD)	5.3 (0.7)
N with data	4384
Insulin, pmol/L, mean (SD)	65.3 (89.0)
N with data	4381
Triglycerides, mmol/L, mean (SD)	1.1 (0.7)
N with data	4404
≥1.7 mmol/L or on lipid-lowering medication, n/N (%)	530/4402 (12.0)
Creatinine, mmol/L, mean (SD)	13.1 (7.7)
N with data	4425
Albumin, mg/dL, mean (SD)	1.8 (6.7)
N with data	4425
Metabolic syndrome*, n/N (%)	732/4365 (16.8)

BMI indicates body mass index; HbA$_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; n, number in category; N, sample size; nuMoM2b-HHS, Nulliparous Pregnancy Outcome Study—Monitoring Mothers-to-Be—Heart Health Study.

*Metabolic syndrome is defined as the presence of 3 of 5 of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, and reduced HDL-C or associated medication.

iatrogenic PTB in their index pregnancy had HTN incidence of 45.4% by the 2018 criteria.

The association of APOs (HDP, PTB, and stillbirth) in the initial pregnancy remained associated with a greater likelihood to develop HTN 2 to 7 years after pregnancy after adjustment for covariates in multivariable regression (Table 4; unadjusted analyses reported in Table S4). Table 4 presents the RRs for APOs with HTN using 3 different reference groups: comparison 1 compares women with APOs to women without any APOs; comparison 2 compares women with APOs to women without that specific APO; and comparison 3 compares women with APOs to women with other APOs.

Compared with women without any APOs in the index pregnancy, women who had any APO had a higher risk of HTN 2 to 7 years later (RR 2.4, 95% CI 1.8–3.1). Specific APOs (HDP, preeclampsia, and PTB; each compared with women without APOs) were also significantly associated with a higher incidence of subsequent HTN (Table 4, comparison 1). Although the risk was high for women with PTB overall, results suggest that women with an iatrogenic PTB had the highest risk of subsequent HTN (RR 4.1, 95% CI 2.8–6.2). When iatrogenic PTB cooccurred with HDP, there was also an increased risk for subsequent HTN (RR 4.3, 95% CI 2.7–6.7).

When compared with women who developed other APOs, women with HDP, those diagnosed with preeclampsia, and women with an iatrogenic PTB had a higher risk of subsequent incident hypertension (HDP: RR 1.6, 95% CI 1.0–2.4; preeclampsia: RR 1.5, 95% CI 1.0–2.1; iatrogenic PTB: RR 2.0, 95% CI 1.4–3.0) (Table 4, comparison 3). These results were mildly attenuated when the newer thresholds for the diagnosis of HTN (>130/80) were used (Table S5).

To explore the degree to which the observed associations were related to pregnancies occurring between the index pregnancy and the nuMoM2b-HHS study visit, we performed a sensitivity analysis limited to women who did not have any pregnancies between these times. The adjusted RRs were similar for women without intervening pregnancies and for those in the overall cohort (data not shown).

Discussion

In this prospective study of women enrolled during their initial pregnancy, women with at least 1 APO in their first pregnancy had a significantly higher risk of HTN at the follow-up assessment than women without APOs. For the cohort in general, increased hypertension was apparent after only 2 to 7 years of follow-up. Our cohort also had high rates of dyslipidemia at their study visits.

Although the prevalence of chronic HTN at the beginning of the first pregnancy was 2.8% for women in this cohort, the incidence of HTN only 2 to 7 years after the first pregnancy was 5.4%. The subgroup of women with a HDP had a 13.1% incidence

Table 3. Incident Hypertension 2 to 7 Years After Index Pregnancy, According to Index Pregnancy APOs Among nuMoM2b-HHS Participants Without Baseline Hypertension

Cardiovascular Characteristics 2 to 7 y After Index Pregnancy	All Participants* (N=4341)	Index Pregnancy APOs (Not Mutually Exclusive)									
		No APO (N=3355)	Any APO (N=967)	HDP (N=581)	Preeclampsia (N=270)	PTB (N=357)	sPTB (N=214)	sPTB <34 wk (N=57)	iPTB (N=141)	SGA (N=178)	SB (N=15)
Blood pressure, mean (SD), mm Hg											
Systolic	111.1 (10.7)	110.4 (10.3)	113.7 (11.3)†	115.4 (11.4)†	115.3 (11.8)†	113.4 (11.1)†	111.3 (10.5)	112.0 (9.6)	116.6 (11.3)†	110.5 (11.0)	117.6 (17.1)
Diastolic	71.8 (9.6)	71.0 (9.2)	74.4 (10.4)†	75.9 (10.5)†	75.4 (10.8)†	74.2 (10.6)†	72.1 (9.9)	73.5 (9.6)†	77.4 (11.0)†	71.9 (9.7)	74.8 (13.4)
N with data	4341	3355	967	581	270	357	214	57	141	178	15
Hypertension definitions, n/N (%)											
HHS: 140≤SBP/90≤DBP, or antihypertensive medication	235/4341 (5.4)	128/3355 (3.8)	104/967 (10.8)†	76/581 (13.1)†	39/270 (14.4)†	43/357 (12.0)†	14/214 (6.5)†	5/57 (8.8)	29/141 (20.6)†	9/178 (5.1)	3/15 (20.0)†
AMA 2018: 130≤SBP/80≤DBP, or antihypertensive medication	878/4341 (20.2)	571/3355 (17.0)	302/967 (31.2)†	212/581 (36.5)†	104/270 (38.5)†	105/357 (29.4)†	41/214 (19.2)	13/57 (22.8)	64/141 (45.4)†	41/178 (23.0)†	6/15 (40.0)†
MetSyn: 130≤SBP/85≤DBP, or antihypertensive medication	501/4341 (11.5)	300/3355 (8.9)	198/967 (20.5)†	142/581 (24.4)†	68/270 (25.2)†	74/357 (20.7)†	28/214 (13.1)†	8/57 (14.0)	46/141 (32.6)†	22/178 (12.4)	4/15 (26.7)†

AMA 2018 indicates hypertension guidelines from American College of Cardiology and American Medical Association 2018; APO, adverse pregnancy outcome; DBP, diastolic blood pressure; HDP, hypertensive disorders of pregnancy; HHS, Heart Health Study; iPTB, iatrogenic preterm birth; MetSyn, metabolic syndrome; n, number in category; N, sample size; nuMoM2b, Nulliparous Pregnancy Outcome Study—Monitoring Mothers-to-Be; PTB, preterm birth; SB, stillbirth; SBP, systolic blood pressure; SGA, small for gestational age; sPTB, spontaneous preterm birth.

*APO is defined as including hypertensive disorders of pregnancy, preterm birth, small for gestational age, or stillbirth.

Statistical significance †P<0.05 for "No APO" vs each of the other categories.

Table 4. Association of Index Pregnancy APOs With Incident Hypertension 2 to 7 Years Later Among nuMoM2b-HHS Participants Without Baseline Hypertension

APOs* During Index Pregnancy	n/N (%)(95% CI)	Hypertension 2 to 7 y After Index Delivery‡			
		n/N (%)(95% CI)§	RR (95% CI)Comparison 1‖	RR (95% CI)Comparison 2¶	RR (95% CI)Comparison 3#
Hypertensive disorders of pregnancy**	581/4341 (13.4%)(12.4%, 14.4%)	76/581 (13.1%) (10.3%, 15.8%)	2.7 (2.0, 3.6)	2.5 (1.9, 3.3)	1.6 (1.0, 2.4)††
Preeclampsia	270/4341 (6.2%)(5.5%, 6.9%)	39/270 (14.4%)(10.3%, 18.6%)	2.8 (2.0, 4.0)	2.3 (1.7, 3.2)	1.5 (1.0, 2.1)††
Preterm birth	357/4337 (8.2%)(7.4%, 9.0%)	43/357 (12.0%)(8.7%, 15.4%)	2.7 (1.9, 3.8)	2.2 (1.6, 3.1)	1.3 (0.9, 1.8)
Spontaneous preterm birth	214/4335 (4.9%)(4.3%, 5.6%)	14/214 (6.5%)(3.2%, 9.9%)	1.6 (0.9, 2.8)	1.2 (0.7, 2.1)	0.6 (0.3, 1.1)
Iatrogenic preterm birth	141/4335 (3.3%)(2.7%, 3.8%)	29/141 (20.6%)(13.9%, 27.2%)	4.1 (2.8, 6.2)	3.3 (2.3, 4.8)	2.1 (1.4, 3.1)
Small for gestational age	178/4324 (4.1%)(3.5%, 4.7%)	9/178 (5.1%)(1.8%, 8.3%)	1.2 (0.6, 2.4)	1.0 (0.5, 1.8)	0.5 (0.3, 1.0)††
Stillbirth	15/4341 (0.3%)(0.2%, 0.5%)	3/15 (20.0%)(4.3%, 48.1%)	3.0 (0.9, 9.7)	2.2 (0.7, 6.8)	1.3 (0.4, 4.1)
Any APO	967/4322 (22.4%) (21.1%, 23.6%)	104/967 (10.8%)(8.8%, 12.7%)	2.4 (1.8, 3.1)	...	...
No APO	3355/4322 (77.6%)(76.4%, 78.9%)	128/3355 (3.8%)(3.2%, 4.5%)	...	...	...

APO indicates adverse pregnancy outcome; BMI, body mass index; n, number in category; N, sample size; nuMoM2b-HHS, Nulliparous Pregnancy Outcome Study—Monitoring Mothers-to-Be—Heart Health Study; RR, risk ratio. Baseline hypertension is defined as prior diagnosis of hypertension per chart abstraction.

* APO is defined as including hypertensive disorders of pregnancy, preterm birth, small for gestational age, or stillbirth.

‡Hypertension 2 to 7 y after index pregnancy is defined as HHS-measured 140≤SBP/90≤DBP or self-report of antihypertensive medication use.

§For denominators ≤40, exact (Clopper-Pearson) CIs are computed. Otherwise, Wald CIs are computed.

‖Risk ratio for the comparison of specific APO vs no APOs, adjusted for age and BMI at index pregnancy enrollment, race/ethnicity, type of health insurance, and smoking status during the 3 mo before index pregnancy.

¶Risk ratio for the comparison of specific APO vs absence of the specific APO, adjusted for age and BMI at index pregnancy enrollment, race/ethnicity, type of health insurance, and smoking status during the 3 mo before index pregnancy.

#Risk ratio for the comparison of specific APO vs other APOs adjusted for age and BMI at index pregnancy enrollment, race/ethnicity, type of health insurance, and smoking status during the 3 mo before index pregnancy.

**Hypertensive disorders of pregnancy include all cases of preeclampsia or eclampsia regardless of the timing of onset) and antepartum gestational hypertension.

††Statistically significant value.

of HTN. These frequencies are even higher (20.2% and 36.5%, respectively) when the new guidelines for the diagnosis of HTN are used.[1] The short time frame to the development of hypertension after pregnancy among a population of young women highlights the potential importance of early diagnosis and intervention. These data support the growing recognition that first pregnancies might be utilized as an early life stress test to identify women who may benefit from preventive and screening strategies for healthy behaviors and therapies.[7-9,31]

Our findings build and expand on the findings of prior research.[32,33] A systematic review of studies that included over 3 million women between 1960 and 2006 demonstrated that women who had preeclampsia had a relative risk of vascular disease of 3.7 after 14 years of mean follow-up, as well as a relative risk of 2.2 and 1.8 for ischemic heart disease and venous thromboembolism, respectively.[10] More recently, a study with a 4- to 12-year follow-up of 487 women demonstrated that those with a PTB developed relatively higher blood pressures and more atherogenic lipid profiles.[34] In the Nurses' Health Study II, women with self-recalled HDP in their first pregnancy had higher rates of HTN, type 2 diabetes mellitus, and hypercholesterolemia within 5 years after their first birth.[16] Higher mean BPs up to 20 years after pregnancy were also seen in 916 women with prior PTB.[12] Using administrative records from deliveries in Florida, 1 report noted that women with HDP had twice the risk of cardiovascular readmissions within 3 years.[35] Our results are consistent in revealing that HDP and PTB herald an increased risk of HTN. In contrast to other studies, our results are from prospectively gathered and validated data for both the pregnancy as well as the clinical outcomes. Because of this approach, we were able not only to provide estimates of association less prone to bias but also to identify additional granular associations, such as the particularly high risk of HTN (45.4% by the new criteria) in women who had an iatrogenic PTB—many of whom experienced HDP. The higher risk for iatrogenic PTB than for spontaneous PTB may be due to selection of a particularly vulnerable subgroup for preterm delivery, whereas the conditions surrounding spontaneous PTB are much more diverse. We are unaware of other groups reporting substantially increased rates of HTN for subgroups of women with particular APOs this soon after a woman's first delivery.

The interval between the index pregnancy and follow-up in our study (mean of 3 years) was less than that in most other cohorts, documenting how soon these risks may present. One small case-control study (n=142) revealed an elevated risk of hypertension at 2 years following delivery for women with preeclampsia.[36] The high rates of HTN in some of our subgroups and the fact that 22 women already had a cardiac event within our follow-up timeframe serve to underscore how critical it is to identify women with increased risk in the early postpartum time.

Bridging the disconnect between obstetric care and adult preventive care is needed.[37] As it is clear that women with APOs are at increased risk of chronic diseases, more detailed pregnancy histories may be important in preventive health screening. The American Heart Association guidelines recommend that providers take a careful and detailed history of pregnancy complications that convey CVD risk and measure BP at annual health screenings.[6] Our findings support these and similar recommendations from the American College of Obstetricians and Gynecologists[38,39] and further highlight the importance of gathering detailed information about pregnancy outcomes, given that APOs other than HDP are clearly, and to different extents, associated with incident HTN.

The prospective nature of our large and socioeconomically diverse cohort is a clear strength. We began following women in the first trimester of their initial pregnancy, thus limiting recall bias of items such as early pregnancy high body mass index and health conditions developed during pregnancy. The rigorous collection of information both from the index pregnancy and afterwards is another strength.[18] Carefully ascertained and verified pregnancy outcomes and cardiovascular outcomes at follow-up lend validity to the associations identified in this study. Additionally, consistent objective measurement of risk factors between the index pregnancy and the numoM2b-HHS study visit, rather than self-report, is another strength.

Our results are subject to limitations typical of observational cohort studies. We attempted to overcome several potential biases by using a priori definitions, data collection beginning in the first trimester of pregnancy, and robust follow-up. It is possible that the women who responded to interval contacts but did not attend an in-person visit would have differed in their outcomes compared with women who did return. Based on similar demographic characteristics among women who did and did not have visits, this is less likely (Table S1). It is also possible that behaviors and life events, including subsequent pregnancies, during the intervening years between the first pregnancy and the in-person visit had a greater impact on the development of cardiovascular risk than outcomes of the first pregnancy. However, such associations do not negate the identified relationships between the first pregnancy and subsequent development of adverse outcomes. In fact, when the analysis was confined to women with no intervening pregnancies, the relationship between APOs and CVD risk persisted.

In conclusion, pregnancy complications during a woman's first pregnancy are associated with increased incidence of HTN within 2 to 7 years, much earlier than previously observed. Identification of high-risk APO combinations and subtypes can guide postpartum counseling, health assessments, and referrals to ensure appropriate monitoring for cardiovascular risk factor development. Furthermore,

engaging women who have had APOs to assess the efficacy of lifestyle and other interventions to prevent CVD offers the possibility of improving future cardiovascular health in a focused and personalized manner.[40]

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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Supplemental Table 1
Index Pregnancy Characteristics of Original nuMoM2b Participants, nuMoM2b-HHS Participants Included in Analyses,
and nuMoM2b and nuMoM2b-HHS Participants Not Included in Analyses

Baseline Characteristics	nuMoM2b (N=10038)	Heart Health Study Included in Analyses (N=4484)	Excluded from Analyses (N=5554)
Maternal age, mean (SD), years	26.9 (5.7)	27.0 (5.6)	26.9 (5.7)
Category: n (%)			
13-21	2133 (21.3%)	905 (20.2%)	1228 (22.2%)
22-35	7222 (72.0%)	3272 (73.0%)	3950 (71.2%)
>35	673 (6.7%)	307 (6.8%)	366 (6.6%)
Maternal race: n (%)			
White Non-Hispanic	5989 (59.7%)	2786 (62.1%)	3203 (57.8%)
Black Non-Hispanic	1418 (14.1%)	618 (13.8%)	800 (14.4%)
Hispanic	1700 (17.0%)	735 (16.4%)	965 (17.4%)
Asian	407 (4.1%)	135 (3.0%)	272 (4.9%)
Other	514 (5.1%)	210 (4.7%)	304 (5.5%)
Education level: n (%)			
Less than high school graduate	816 (8.1%)	327 (7.3%)	489 (8.8%)
High school graduate or GED completed	1171 (11.7%)	508 (11.3%)	663 (12.0%)
Some college credit, no degree	1948 (19.4%)	889 (19.8%)	1059 (19.1%)
Associate/technical degree	1005 (10.0%)	501 (11.2%)	504 (9.1%)
Bachelor's degree	2772 (27.7%)	1261 (28.1%)	1511 (27.3%)
Degree beyond bachelor's	2308 (23.0%)	996 (22.2%)	1312 (23.7%)
Type of health insurance: n (%)			
Commercial	6778 (68.1%)	3087 (69.2%)	3691 (67.1%)
Government/military	2800 (28.1%)	1219 (27.3%)	1581 (28.7%)
Self-pay/other	381 (3.8%)	152 (3.4%)	229 (4.2%)
Smoked during 3 months prior to pregnancy: n / N (%)	1782/10018 (17.8%)	718/4478 (16.0%)	1064/5540 (19.2%)

Supplemental Table 1 (continued)
Index Pregnancy Characteristics of Original nuMoM2b Participants, nuMoM2b-HHS Participants Included in Analyses,
and nuMoM2b and nuMoM2b-HHS Participants Not Included in Analyses

Baseline Characteristics	nuMoM2b (N=10038)	Heart Health Study Included in Analyses (N=4484)	Excluded from Analyses (N=5554)
Early Pregnancy BMI, mean (SD), kg/m^2	26.3 (6.3)	26.6 (6.5)	26.0 (6.2)
Category: n (%)			
<25	5247 (53.3%)	2284 (51.8%)	2963 (54.6%)
25 to <30	2437 (24.8%)	1081 (24.5%)	1356 (25.0%)
≥30	2153 (21.9%)	1042 (23.6%)	1111 (20.5%)
Pre-gestational hypertension: n / N (%)	243/9469 (2.6%)	127/4480 (2.8%)	116/4989 (2.3%)
Pre-gestational diabetes: n / N (%)	151/9476 (1.6%)	62/4482 (1.4%)	89/4994 (1.8%)
Gestational diabetes: n / N (%)	396/9415 (4.2%)	191/4422 (4.3%)	205/4993 (4.1%)
Adverse Pregnancy Outcomes (APOs*): n / N (%)			
Hypertensive disorders of pregnancy	1244/9468 (13.1%)	612/4480 (13.7%)	632/4988 (12.7%)
Preeclampsia	586/9468 (6.2%)	298/4480 (6.7%)	288/4988 (5.8%)
Preterm birth	820/9473 (8.7%)	387/4480 (8.6%)	433/4993 (8.7%)
Spontaneous preterm birth	477/9469 (5.0%)	218/4478 (4.9%)	259/4991 (5.2%)
Indicated preterm birth	339/9469 (3.6%)	167/4478 (3.7%)	172/4991 (3.4%)
Small for gestational age	424/9434 (4.5%)	187/4467 (4.2%)	237/4967 (4.8%)
Stillbirth	51/9484 (0.5%)	16/4484 (0.4%)	35/5000 (0.7%)
No APO: n / N (%)	7318/9414 (77.7%)	3444/4461 (77.2%)	3874/4953 (78.2%)
Any APO: n / N (%)	2096/9414 (22.3%)	1017/4461 (22.8%)	1079/4953 (21.8%)

Abbreviations: BMI=body mass index; APO=adverse pregnancy outcome; n=number in category; N=sample size.
* APO defined as: Hypertensive disorders of pregnancy, preterm birth, small for gestational age, or stillbirth.

Supplemental Table 2
Cardiovascular Characteristics 2-7 Years After nuMoM2b Index Pregnancy, According to Index Pregnancy APOs*†

Cardiovascular Characteristics 2-7 Years After nuMoM2b Index Pregnancy	nuMoM2b Index Pregnancy APOs (not mutually exclusive)									
	No APO (N=3444)	Any APO (N=1017)	HDP (N=612)	Preeclampsia (N=298)	PTB (N=387)	sPTB (N=218)	sPTB<34 weeks (N=57)	iPTB (N=167)	SGA (N=187)	SB (N=16)
BMI, kg/m^2, mean (SD)	27.3 (7.4)	29.9 (8.4)^	31.2 (8.6)^	31.6 (9.0)^	29.4 (8.3)^	27.6 (7.4)	29.9 (8.5)^	31.6 (9.0)^	27.8 (8.3)	30.8 (8.9)
Category: n (%)										
<25 kg/m^2	1681 (49.1%)	339 (33.5%)^	165 (27.0%)^	75 (25.3%)^	133 (34.5%)^	90 (41.5%)	16 (28.1%)^	42 (25.3%)^	88 (47.1%)	3 (20.0%)
25 to <30 kg/m^2	813 (23.7%)	260 (25.7%)^	160 (26.2%)^	81 (27.3%)^	102 (26.5%)^	64 (29.5%)	18 (31.6%)^	37 (22.3%)^	43 (23.0%)	5 (33.3%)
≥30 kg/m^2	930 (27.2%)	414 (40.9%)^	285 (46.7%)^	141 (47.5%)^	150 (39.0%)^	63 (29.0%)	23 (40.4%)^	87 (52.4%)^	56 (29.9%)	7 (46.7%)
Waist circumference over iliac crest, cm mean (SD)	95.0 (15.8)	100.4 (18.0)^	103.0 (18.5)^	103.6 (19.2)^	99.1 (17.9)^	96.0 (16.0)	99.5 (15.8)^	103.4 (19.4)^	95.0 (16.6)	102.5 (17.8)
≥88 (non-Asian); ≥80 (Asian), n/N (%)	2161/3426 (63.1%)	743/1012 (73.4%)^	474/608 (78.0%)^	228/295 (77.3%)^	270/384 (70.3%)^	141/217 (65.0%)	46/57 (80.7%)^	129/165 (78.2%)^	115/187 (61.5%)	12/16 (75.0%)
Total cholesterol, mmol/L, mean (SD)	4.7 (1.0)	4.8 (1.1)^	4.8 (1.1)^	4.8 (1.2)^	4.7 (1.0)	4.7 (0.9)	4.7 (1.0)	4.8 (1.1)	4.6 (0.9)	5.0 (1.2)
N with data	3385	997	603	294	379	216	56	161	182	14
HDL-C, mmol/L, mean (SD)	1.5 (0.3)	1.4 (0.3)^	1.4 (0.3)^	1.3 (0.3)^	1.4 (0.3)^	1.4 (0.4)^	1.3 (0.3)^	1.3 (0.3)^	1.4 (0.3)^	1.4 (0.4)
N with data	3385	997	603	294	379	216	56	161	182	14
<1.3 or on HDL-raising med, n/N (%)	1101/3384 (32.5%)	410/996 (41.2%)^	253/602 (42.0%)^	136/294 (46.3%)^	163/379 (43.0%)^	80/216 (37.0%)	23/56 (41.1%)	81/161 (50.3%)^	73/182 (40.1%)^	7/14 (50.0%)
LDL-C, mmol/L, mean (SD)	2.7 (0.9)	2.8 (0.9)^	2.9 (1.0)^	2.9 (1.0)^	2.8 (0.8)	2.7 (0.8)	2.8 (0.8)	2.8 (1.0)	2.8 (0.8)	3.1 (1.0)
N with data	3381	997	603	294	379	216	56	161	182	14
Glucose, mmol/L, mean (SD)	5.0 (1.1)	5.3 (1.7)^	5.3 (1.6)^	5.4 (1.9)^	5.5 (2.3)^	5.4 (2.2)^	5.6 (2.8)	5.7 (2.5)^	5.0 (0.6)	6.1 (2.2)
N with data	3380	994	602	294	379	216	56	161	180	14
≥5.6 or on glucose-lowering med, n / N (%)	493/3379 (14.6%)	220/993 (22.2%)^	140/601 (23.3%)^	73/294 (24.8%)^	98/379 (25.9%)^	46/216 (21.3%)^	15/56 (26.8%)^	52/161 (32.3%)^	26/180 (14.4%)	4/14 (28.6%)
HbA1c, %, mean (SD)	5.2 (0.6)	5.4 (1.1)^	5.4 (1.0)^	5.5 (1.2)^	5.6 (1.5)^	5.5 (1.4)^	5.6 (1.8)	5.7 (1.6)^	5.2 (0.4)	6.1 (1.9)
N with data	3372	991	596	290	380	217	57	161	180	14
Insulin, pmol/L, mean (SD)	62.0 (88.0)	76.5 (91.8)^	79.8 (96.2)^	90.7 (120.1)^	83.8 (111.8)^	73.6 (95.9)	95.6 (129.8)	97.3 (129.6)^	62.0 (60.2)	76.3 (52.6)
N with data	3367	993	600	293	378	215	56	161	182	14

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Supplemental Table 2 (continued)
Cardiovascular Characteristics 2-7 Years After nuMoM2b Index Pregnancy, According to Index Pregnancy APOs*

Cardiovascular Characteristics 2-7 Years After nuMoM2b Index Pregnancy	nuMoM2b Index Pregnancy APOs (not mutually exclusive)									
	No APO (N=3444)	Any APO (N=1017)	HDP (N=612)	Preeclampsia (N=298)	PTB (N=387)	sPTB (N=218)	sPTB<34 weeks (N=57)	iPTB (N=167)	SGA (N=187)	SB (N=16)
Triglycerides, mmol/L, mean (SD)	1.0 (0.6)	1.2 (0.8)^	1.2 (0.9)^	1.3 (1.0)^	1.3 (1.0)^	1.1 (0.7)^	1.4 (0.8)^	1.4 (1.2)^	1.0 (0.9)	1.2 (0.5)
N with data	3386	997	603	294	379	216	56	161	182	14
≥ 1.7 or on lipid-lowering med, n / N (%)	366/3385 (10.8%)	162/996 (16.3%)^	111/602 (18.4%)^	62/294 (21.1%)^	70/379 (18.5%)^	33/216 (15.3%)^	12/56 (21.4%)^	36/161 (22.4%)^	16/182 (8.8%)	2/14 (14.3%)
Creatinine, mmol/L, mean (SD)	12.9 (7.6)	13.7 (7.9)^	13.7 (8.1)^	14.9 (8.4)^	14.0 (7.9)^	13.7 (7.8)	14.9 (8.1)	14.4 (8.1)^	14.1 (7.9)^	14.1 (5.9)
N with data	3404	999	602	294	382	216	55	164	184	14
Albumin, mg/dL, mean (SD)	1.6 (5.3)	2.7 (9.8)^	2.8 (10.2)^	3.2 (11.3)^	3.9 (14.4)^	2.7 (10.6)	1.7 (3.4)	5.5 (18.2)^	2.0 (4.8)	7.5 (22.8)
N with data	3404	999	602	294	382	216	55	164	184	14
Metabolic syndrome†, n / N (%)	476/3357 (14.2%)	254/987 (25.7%)^	174/596 (29.2%)^	92/291 (31.6%)^	111/376 (29.5%)^	46/215 (21.4%)^	17/56 (30.4%)^	65/159 (40.9%)^	28/180 (15.6%)	4/14 (28.6%)

Abbreviations: SD=standard deviation; n=number in category; N=sample size; BMI=body mass index; HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; APO=adverse pregnancy outcome; GDM=gestational diabetes; HDP=hypertensive disorders of pregnancy; PTB=preterm birth; sPTB=spontaneous preterm birth; iPTB=indicated preterm birth; SGA=small for gestational age; SB=stillbirth. Statistical significance for 'No APO' versus each of the other categories reported as: ^ = P<0.05.

*APO defined as: Hypertensive disorders of pregnancy, preeclampsia, preterm birth, spontaneous preterm birth, indicated preterm birth, small for gestational age, or stillbirth.

† Metabolic syndrome defined as: presence of three of five of the following criteria: elevated waist circumference, elevated triglycerides or associated medication, elevated fasting glucose or associated medication, elevated blood pressure or associated medication, reduced HDL-C or associated medication.

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Supplemental Table 3
Major Cardiovascular Events Experienced
Within 2-7 Years After Index Pregnancy

Cardiovascular Event	N (%)
Congestive Heart Failure	5 (22.7%)
Deep Venous Thrombosis	10 (45.5%)
Peripheral Artery Disease	3 (13.6%)
Pulmonary Embolism	8 (36.4%)
Stroke	1 (4.5%)

N=number with event. 22 women experienced a total
of 27 events.

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Supplemental Table 4
Association of nuMoM2b Index Pregnancy APOs∗ with Incident Hypertension 2-7 Years Later Among nuMoM2b-HHS Participants
without Baseline Hypertension† (Covariate Unadjusted)

APOs During Index Pregnancy	n / N (%) (95% CI)	Hypertension 2-7 years after index delivery‡			
		n / N (%) (95% CI) ∣	RR (95% CI) Comparison 1#	RR (95% CI) Comparison 2∗∗	RR (95% CI) Comparison 3€
Hypertensive disorders of pregnancy§	581/4341 (13.4%) (12.4%, 14.4%)	76/581 (13.1%) (10.3%, 15.8%)	3.4 (2.6, 4.5)	3.1 (2.4, 4.0)	1.8 (1.2, 2.6)
Preeclampsia	270/4341 (6.2%) (5.5%, 6.9%)	39/270 (14.4%) (10.3%, 18.6%)	3.8 (2.7, 5.3)	3.0 (2.2, 4.2)	1.6 (1.1, 2.3)
Preterm birth	357/4337 (8.2%) (7.4%, 9.0%)	43/357 (12.0%) (8.7%, 15.4%)	3.2 (2.3, 4.4)	2.5 (1.8, 3.4)	1.2 (0.8, 1.7)
Spontaneous preterm birth	214/4335 (4.9%) (4.3%, 5.6%)	14/214 (6.5%) (3.2%, 9.9%)	1.7 (1.0, 2.9)^	1.2 (0.7, 2.1)	0.5 (0.3, 0.9)
Indicated preterm birth	141/4335 (3.3%) (2.7%, 3.8%)	29/141 (20.6%) (13.9%, 27.2%)	5.4 (3.7, 7.8)	4.2 (3.0, 6.0)	2.2 (1.5, 3.3)
Small for gestational age	178/4324 (4.1%) (3.5%, 4.7%)	9/178 (5.1%) (1.8%, 8.3%)	1.3 (0.7, 2.6)	0.9 (0.5, 1.8)	0.4 (0.2, 0.8)
Stillbirth	15/4341 (0.3%) (0.2%, 0.5%)	3/15 (20.0%) (4.3%, 48.1%)	5.2 (1.9, 14.6)	3.7 (1.3, 10.3)	1.9 (0.7, 5.2)
Any APO	967/4322 (22.4%) (21.1%, 23.6%)	104/967 (10.8%) (8.8%, 12.7%)	2.8 (2.2, 3.6)	N/A	N/A
No APO	3355/4322 (77.6%) (76.4%, 78.9%)	128/3355 (3.8%) (3.2%, 4.5%)	N/A	N/A	N/A

Abbreviations: APO=adverse pregnancy outcome; RR=risk ratio; CI=confidence interval; n=number in category; N=sample size;
∗ APO defined as: Hypertensive disorders of pregnancy, preterm birth, small for gestational age, or stillbirth.
† Baseline Hypertension defined as: prior diagnosis of hypertension per nuMoM2b chart abstraction.
‡ Hypertension 2-7 years after index pregnancy defined as: HHS measured 140≤SBP/90≤DBP or self-report of antihypertensive medication use.
§ Hypertensive disorders of pregnancy include all cases of preeclampsia (mild, severe, or superimposed preeclampsia or eclampsia regardless of the timing of onset) and antepartum gestational
  hypertension
∣ For denominators ≤40, exact (Clopper-Pearson) confidence intervals are computed. Otherwise, Wald confidence intervals are computed.
Risk ratio for the comparison of specific APO vs. no APOs.
∗∗ Risk ratio for the comparison of specific APO vs. absence of the specific APO.
€Risk ratio for the comparison of specific APO vs. other APOs. The ^ designates instances where the confidence interval includes 1.0 but a boundary value is reported as 1.0 due to rounding.

Supplemental Table 5

Association of nuMoM2b Index Pregnancy APOs* with Incident Hypertension (AMA 2018) 2-7 Years Later Among nuMoM2b-HHS Participants without Baseline Hypertension† (Covariate Adjusted)

APOs During Index Pregnancy	n / N (%) (95% CI)	Hypertension 2-7 years after index delivery‡			
		n / N (%) (95% CI) ∥	RR (95% CI) Comparison 1#	RR (95% CI) Comparison 2**	RR (95% CI) Comparison 3€
Hypertensive disorders of pregnancy§	581/4341 (13.4%) (12.4%, 14.4%)	212/581 (36.5%) (32.6%, 40.4%)	1.7 (1.5, 2.0)	1.7 (1.5, 2.0)	1.5 (1.2, 1.9)
Preeclampsia	270/4341 (6.2%) (5.5%, 6.9%)	104/270 (38.5%) (32.7%, 44.3%)	1.8 (1.5, 2.2)	1.7 (1.4, 2.0)	1.3 (1.1, 1.6)
Preterm birth	357/4337 (8.2%) (7.4%, 9.0%)	105/357 (29.4%) (24.7%, 34.1%)	1.5 (1.3, 1.8)	1.4 (1.2, 1.7)	1.0 (0.8, 1.2)
Spontaneous preterm birth	214/4335 (4.9%) (4.3%, 5.6%)	41/214 (19.2%) (13.9%, 24.4%)	1.0 (0.8, 1.4)	0.9 (0.7, 1.2)	0.6 (0.4, 0.8)
Indicated preterm birth	141/4335 (3.3%) (2.7%, 3.8%)	64/141 (45.4%) (37.2%, 53.6%)	2.2 (1.8, 2.6)	2.0 (1.6, 2.4)	1.6 (1.3, 1.9)
Small for gestational age	178/4324 (4.1%) (3.5%, 4.7%)	41/178 (23.0%) (16.8%, 29.2%)	1.3 (1.0, 1.7)	1.1 (0.9, 1.5)	0.7 (0.5, 1.0)
Stillbirth	15/4341 (0.3%) (0.2%, 0.5%)	6/15 (40.0%) (16.3%, 67.7%)	1.8 (1.0, 3.4)	1.6 (0.9, 3.0)	1.2 (0.7, 2.1)
Any APO	967/4322 (22.4%) (21.1%, 23.6%)	302/967 (31.2%) (28.3%, 34.2%)	1.6 (1.4, 1.8)	N/A	N/A
No APO	3355/4322 (77.6%) (76.4%, 78.9%)	571/3355 (17.0%) (15.7%, 18.3%)	N/A	N/A	N/A

Abbreviations: APO=adverse pregnancy outcome; AMA 2018=hypertension guidelines from American College of Cardiology and American Medical Association 2018; RR=risk ratio; CI=confidence interval; n=number in category; N=sample size.
* APO defined as: Hypertensive disorders of pregnancy, preterm birth, small for gestational age, or stillbirth.
† Baseline Hypertension defined as: prior diagnosis of hypertension per nuMoM2b chart abstraction.
‡ Hypertension 2-7 years after index pregnancy defined as: HHS measured 140≤SBP/90≤DBP or self-report of antihypertensive medication use.
§ Hypertensive disorders of pregnancy include all cases of preeclampsia (mild, severe, or superimposed preeclampsia or eclampsia regardless of the timing of onset) and antepartum gestational hypertension
∥ For denominators ≤40, exact (Clopper-Pearson) confidence intervals are computed. Otherwise, Wald confidence intervals are computed.
Risk ratio for the comparison of specific APO vs. no APOs.
** Risk ratio for the comparison of specific APO vs. absence of the specific APO.
€Risk ratio for the comparison of specific APO vs. other APOs. The ^ designates instances where the confidence interval includes 1.0 but a boundary value is reported as 1.0 due to rounding.