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ORIGINAL RESEARCH

Early Pregnancy Atherogenic Profile in a First Pregnancy and Hypertension Risk 2 to 7 Years After Delivery

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BACKGROUND: Cardiovascular risk in young adulthood is an important determinant of lifetime cardiovascular disease risk. Women with adverse pregnancy outcomes (APOs) have increased cardiovascular risk, but the relationship of other factors is unknown.

METHODS AND RESULTS: Among 4471 primiparous women, we related first-trimester atherogenic markers to risk of APO (hypertensive disorders of pregnancy, preterm birth, small for gestational age), gestational diabetes mellitus (GDM) and hypertension (130/80 mm Hg or antihypertensive use) 2 to 7 years after delivery. Women with an APO/GDM (n=1102) had more atherogenic characteristics (obesity [34.2 versus 19.5%], higher blood pressure [systolic blood pressure 112.2 versus 108.4, diastolic blood pressure 69.2 versus 66.6 mm Hg], glucose [5.0 versus 4.8 mmol/L], insulin [77.6 versus 60.1 pmol/L], triglycerides [1.4 versus 1.3 mmol/L], and high-sensitivity C-reactive protein [5.6 versus 4.0 nmol/L], and lower high-density lipoprotein cholesterol [1.8 versus 1.9 mmol/L]; $P<0.05$) than women without an APO/GDM. They were also more likely to develop hypertension after delivery (32.8% versus 18.1%, $P<0.05$). Accounting for confounders and factors routinely assessed antepartum, higher glucose (relative risk [RR] 1.03 [95% CI, 1.00–1.06] per 0.6 mmol/L), high-sensitivity C-reactive protein (RR, 1.06 [95% CI, 1.02–1.11] per 2-fold higher), and triglycerides (RR, 1.27 [95% CI, 1.14–1.41] per 2-fold higher) were associated with later hypertension. Higher physical activity was protective (RR, 0.93 [95% CI, 0.87-0.99] per 3 h/week). When evaluated as latent profiles, the nonobese group with higher lipids, high-sensitivity C-reactive protein, and insulin values (6.9% of the cohort) had increased risk of an APO/GDM and later hypertension. Among these factors, 7% to 15% of excess RR was related to APO/GDM.

CONCLUSIONS: Individual and combined first-trimester atherogenic characteristics are associated with APO/GDM occurrence and hypertension 2 to 7 years later.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02231398.

Key Words: high blood pressure ■ hypertension ■ lipids ■ preeclampsia/pregnancy ■ pregnancy and postpartum

More than 80% of women experience pregnancy, and there is evidence that adverse pregnancy outcomes (APOs) such as hypertensive disorders of pregnancy (HDP), preterm birth, and gestational diabetes mellitus (GDM) are associated with cardiovascular disease risk as soon as 5 years after delivery.[1–6] APOs are common, affecting 25% of first births, and are associated with a 2.4-fold higher risk of incident

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CLINICAL PERSPECTIVE

What Is New?

- Early pregnancy atherogenic factors portend risk for adverse pregnancy outcomes and later-life risk of chronic hypertension.
- In addition to cardiometabolic factors routinely assessed during pregnancy, higher glucose, high-sensitivity C-reactive protein, and triglycerides are associated with higher risk of hypertension after delivery.
- Among the atherogenic factors associated with hypertension after delivery, only 7% to 15% of excess risk was mediated by occurrence of adverse pregnancy outcomes or gestational diabetes mellitus.

What Are the Clinical Implications?

- Individual and combined first-trimester atherogenic characteristics are associated with adverse pregnancy outcomes and hypertension 2 to 7 years later.
- Assessment of cardiometabolic health early in pregnancy may identify risk for adverse outcomes and recognize opportunities to improve cardiovascular health later in life.

Nonstandard Abbreviations and Acronyms

APO	adverse pregnancy outcome
GDM	gestational diabetes mellitus
HDP	hypertensive disorders of pregnancy

hypertension 2 to 7 years after delivery.[7] Prepregnancy and first trimester cardiometabolic factors have been associated with APOs,[8–11] suggesting that there may be shared antecedents to APOs and subsequent cardiovascular disease (CVD).

Maternal cardiometabolic adaptations to pregnancy are detectable as soon as week 8 of pregnancy, although pregnancy-induced changes are most dramatic in the second half of pregnancy. Cardiovascular risk assessment among young adult women is sparse, whereas pregnancy care is essentially universal. Women with poor healthcare access seek medical care during pregnancy to a degree that may not be paralleled until older adulthood. Thus, pregnancy represents a unique yet still poorly studied opportunity to screen for CVD risk. Furthermore, first pregnancies are of particular importance, because risks for most APOs are higher in the first than in subsequent pregnancies, and APOs in a first pregnancy have strong associations with future pregnancy complications.[12–14] A first pregnancy, therefore, may be a window into cardiometabolic factors that impact a woman's short- and long-term health as well as the well-being of her subsequent pregnancies.

In the nuMoM2b-Heart Health Study,[15] we evaluated whether cardiometabolic risk factors assessed early in a first pregnancy were related to an APO/GDM and subsequent hypertension 2 to 7 years after delivery. Mediation analyses then quantified the portion of hypertension risk that was accounted for by an APO/GDM. We hypothesized that the early pregnancy atherogenic profile would be related both to APOs and hypertension 2 to 7 years after pregnancy.

METHODS

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

Participants and Contact

Details on participant recruitment and data collection for the nuMoM2b study and subsequent Heart Health Study (nuMoM2b Heart Health Study) have been previously described.[15,16] Briefly, 8838 women with singleton gestations were recruited during the first trimester (<14 weeks gestation) of their first pregnancy at 8 US sites between 2012 and 2015, provided a nonfasting blood sample in the first trimester, had good documentation of pregnancy outcome from medical records, and agreed to postpartum follow-up. Interval contacts were performed via telephone interviews or completion of an online survey at 6-month intervals beginning at least 6 months after delivery of the pregnancy to update health status and screen for an in-person study visit at least 2 years postdelivery. A total of 7003 women were successfully contacted, and 4508 women returned for an in-person Heart Health Study visit 2 to 7 years after delivery (mean, 3.2 years; SD, 0.9 years). A total of 427 women were ineligible for the in-person visit because of being pregnant, 978 declined to return for a visit, and 1090 eligible participants agreed but did not return for an in-person visit. We excluded 24 women from this analysis who experienced pregnancy loss or termination before 20 weeks and 13 women who had missing assay data, for a final study population of 4471. Figure 1 provides a flow diagram of participant inclusion in this analysis. Those included compared with those not included in the analysis were more likely to be obese before pregnancy and less likely to be of Black race/ethnicity or to report early-pregnancy nausea/vomiting (Table S1). All participating women gave written informed consent approved by each site's human subjects ethical review board.

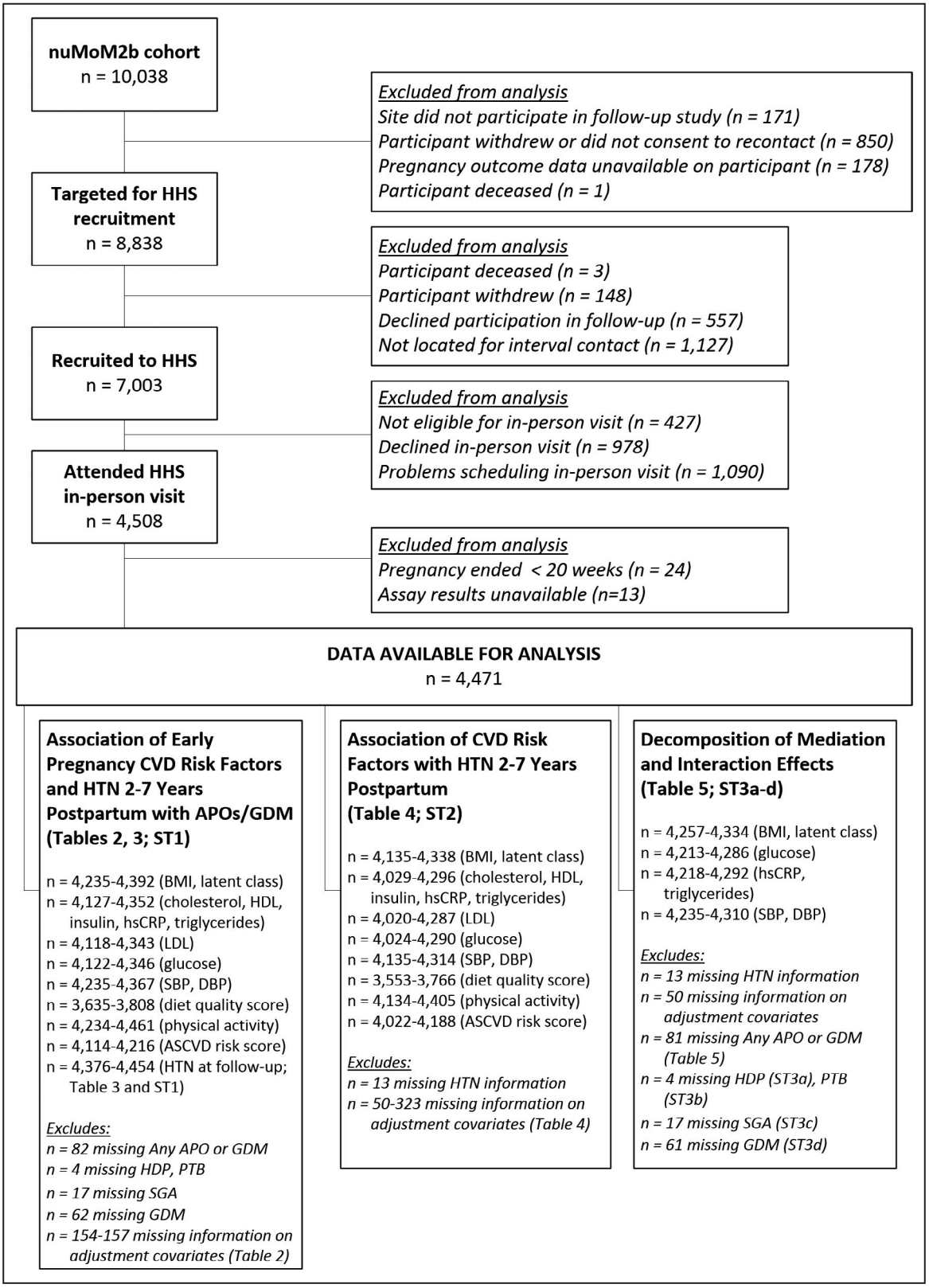

Figure 1. Flow diagram for participation in analysis.
APO indicates adverse pregnancy outcomes; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; HHS, Heart Health Study; HTN, hypertension; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTB, preterm birth; SBP, systolic blood pressure; and SGA, small for gestational age.

Measures, Outcomes, and Definitions

Early pregnancy cardiometabolic risk factors were assessed using nonfasting blood specimens taken via standard venipuncture at the first trimester research visit that took place between 6- and 14-weeks gestation. Serum, plasma, and whole blood specimens were stored at −80°C at a central core biorepository. Assays were completed in batch fashion at the Heart Health Study core lab (Lundquist Institute, Torrance, CA) using standard protocols on a Beckman AU480. These included enzymatic analyses of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose. Hs-CRP (high-sensitivity C-reactive protein) used turbidimetric analyses measured via spectrophotometric assays. Insulin was measured using the Beckman ACCESS 2 ultrasensitive immune-enzymatic assay. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation, with LDL-C set to missing when triglycerides were >10.36 mmol/L. Body mass index (BMI; kg/m^2) was calculated from measures of weight and height obtained using a regularly calibrated balance beam or digital scale for weight and a stadiometer or measuring tape for height measurements. Blood pressure was measured after a 10-minute rest period using aneroid sphygmomanometers.

Waist circumference over the iliac crest was measured to the nearest 0.1 cm using a nonstretch study measuring tape. Prepregnancy diet quality was derived using the diet score component of the Healthy Heart Score[17] using self-reported Block Food Frequency Questionnaire[18] data pertaining to the 3 months before pregnancy. Higher values reflect diets richer in fruits, vegetables, cereal-based fiber, and nuts, and lower in sugar-sweetened beverages and red/processed meats; mean (SD) values for women in the original Healthy Heart Score derivation and validation data sets were 3.6 (1.8).[17] Physical activity during the 4 weeks before the first-trimester study visit was reported as hours of moderate or vigorous exercise (3+ metabolic equivalents/hour) per week. This was calculated from self-report of activities, including duration and frequency, using a questionnaire from the Behavioral Risk Factors Surveillance System.[19] Reported activities were assigned effort values using the Physical Activity Compendium[20] to permit conversion to calculated metabolic equivalents.[21,22] Nausea and vomiting during pregnancy were assessed using the Motherrisk Pregnancy Unique Quantification of Emesis (Motherrisk PUQE) scoring system.[23]

APOs during the first birth were documented at delivery and verified by chart abstraction with adjudication. APOs of interest for this analysis included HDP (antepartum gestational hypertension, preeclampsia, or eclampsia) classified according to a priori study criteria requiring extensive chart review and adjudication by study investigators,[24] preterm birth (delivery <37 weeks), and small-for-gestational-age delivery (calculated using the Alexander growth curves as birth weight for gestational age below the fifth percentile).[25] Occurrence of GDM was also included, defined according to current guidelines.[24]

Hypertension was our primary outcome and was ascertained during the Heart Health Study visit 2 to 7 years after delivery via direct measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) following a standardized research protocol using the same type of device at all sites (Omron HEM-907XL). Manual sphygmomanometer readings were gathered when device results were implausible. Women were categorized as hypertensive according to the 2017 American Heart Association/American College of Cardiology blood pressure guidelines if they had SBP ≥130 mm Hg, DBP ≥80 mm Hg, or self-reported antihypertensive medication use. We also separately evaluated elevated blood pressure (SBP 120–129 and DBP <80 mm Hg) and stage 1 (SBP 130–139 or DBP 80–89 mm Hg) and stage 2 hypertension (SBP ≥140 or DBP ≥90 mm Hg) in secondary analyses.[26]

Statistical Considerations and Analysis

Statistical Analysis

Women's demographic and cardiometabolic characteristics during the first pregnancy and hypertension status 2 to 7 years later were summarized using mean (SD) or median (minimum–maximum) for continuous characteristics and frequency and percent for categorical characteristics. Summary statistics were generated for all participants and for subgroups defined by an APO/GDM occurrence. Comparisons between APO subgroups (not mutually exclusive) and the no-APO/GDM reference category were performed using *t* tests (continuous variables) and χ^2 tests (categorical variables). In the event of small sample sizes, Wilcoxon and exact Pearson χ^2 tests were used as appropriate.

The associations between hypertension 2 to 7 years after a first delivery and first-trimester cardiometabolic risk factors (BMI, total cholesterol, HDL-C, LDL-C, glucose, insulin, hs-CRP, triglycerides, SBP, DBP, prepregnancy diet quality, and physical activity) were estimated using Poisson regression with robust variance estimation.[27–29] This approach was used to estimate adjusted relative risks for each risk factor. Insulin, triglycerides, and hs-CRP were included after log (base 2) transformations because of extreme skewing. Two models were created. In one,

we adjusted for race/ethnicity and baseline values of age, insurance, and smoking (Model A). In a second (Model B), we further adjusted for first-trimester BMI, SBP, and DBP given these are cardiometabolic risk factors routinely assessed during prenatal care (Model B). Time from index pregnancy delivery to the in-person follow-up study visit was not included as a covariate, as mean time to the in-person visit does not vary meaningfully by hypertension status at follow-up (data not shown) or between APO subgroups and thus was not perceived to be a potential confounder. Women with chronic hypertension were included because we were interested in an overall early pregnancy atherogenic profile; however, we also performed a sensitivity analysis among participants without chronic hypertension or pregestational diabetes mellitus (Model C). Models compare each APO/GDM relative to nonoccurrence and a composite of any APO/GDM relative to none. This approach allows evaluation of associations with the distinct pathophysiology of each APO/GDM and the possibility of shared etiologies in the composite.

We also related early pregnancy cardiometabolic risk factors to an APO/GDM occurrence and considered the role of APOs as mediators of the association between cardiometabolic risk factors and hypertension. The associations between an APO/GDM and first-trimester cardiometabolic risk factors were estimated using Poisson regression as described above. with model covariates of age, race, insurance, smoking, BMI, SBP, and DBP. We then used a causal modeling framework with 4-way decomposition of effects as described by VanderWeele.[30] Decomposition of the total excess relative risk (RR) permitted estimation of how much of an effect was mediated by an APO/GDM, how much was because of interaction between an APO/GDM and cardiometabolic factors, how much was because of both mediation and interaction together, and how much was a direct effect of the early pregnancy cardiometabolic risk factor. Mediation models were adjusted for race/ethnicity, age, insurance, and smoking at time of the index pregnancy.

Secondary Analysis: Early Pregnancy Atherogenic Patterns

In addition to considering each cardiometabolic factor individually, we considered two approaches that combined these factors. First, we estimated a first trimester atherosclerotic cardiovascular disease (ASCVD) risk score and related this score to APO/GDM occurrence and hypertension risk 2 to 7 years after delivery. This is an estimator of 10-year risk of a first atherosclerotic CVD event that includes contributions from age, race, cholesterol, HDL-C, blood pressure, smoking, and diabetes mellitus status.[31] We then used latent profile analysis, a type of finite mixture modeling, to identify early-pregnancy clustering of cardiometabolic values and associated subgroups of women. This multivariate approach assumes that when considered collectively, the values of risk factors reflect study participants' membership in a population subgroup (phenotype). The models were grouped by obesity status (BMI ≥30) and included the following participant characteristics measured in early pregnancy: total cholesterol, HDL-C, LDL-C, glucose, insulin, hs-CRP, triglycerides, SBP, DBP, waist circumference, and age. Insulin, triglycerides, and hs-CRP were included after log (base 2) transformations. Models were fit for 2 to 5 latent profiles and were compared qualitatively with respect to likelihood replicability, fit statistics, and practicality of interpretation. MPlus software[32] was used for the latent profile analysis. Details about features of the profiles are summarized in Data S1 and Table S2. Estimated phenotype membership was considered as a categorical CVD risk factor in Poisson regression models (per the above methods). Specifically, Monte Carlo simulations based on the multinomial probabilities of phenotype membership were used to create imputed data sets (100 imputations) that were used together to adjust CIs for the additional variance associated with phenotype membership estimates.

For all analyses, women who were missing data on the primary outcome, APOs, chronic hypertension, or model covariates were excluded from analyses requiring those data. Analyses were completed using SAS V9.4 (SAS Institute, Cary, NC), R Version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and MPlus version 8 (Muthén & Muthén, Los Angeles, CA).

RESULTS

Overall, 24.6% of women experienced an APO/GDM during a first birth (1102/4471; Table 1). Women with at least one of these complications were, on average, more likely to be older than 35 years, to smoke, and to be of non-Hispanic Black race/ethnicity. Also, women with an APO/GDM were more likely to have a first-trimester atherogenic profile; they were more frequently obese (34.2% versus 19.5%); had higher mean blood pressure (SBP 112.2 versus 108.4; DBP 69.2 versus 66.6 mm Hg); had higher mean concentrations of glucose (5.0 versus 4.8 mmol/L); had a higher median level of insulin (77.6 versus 60.1 pmol/L), triglycerides (1.4 versus 1.3 mmol/L), and hs-CRP (5.6 versus 4.0 nmol/L); and had lower mean concentrations of HDL-C (1.8 versus 1.9 mmol/L) (all $P<0.05$) than women with no APO/GDM. All of these markers were

Table 1. Demographic Characteristics and Early Pregnancy CVD Risk Factors by Index Pregnancy APOs[†] and GDM Subgroups Among nuMoM2b-Heart Health Study Participants[‡,§]

Demographic Characteristics and Early Pregnancy CVD Risk Factors	All Participants, N=4471	Index Pregnancy APOs and GDM (Not Mutually Exclusive)							
		No APO or GDM, N=3285	Any APO or GDM, N=1102	HDP, N=608	Preeclampsia, N=297	PTB, N=386	sPTB, N=218	SGA, N=186	GDM, N=191
Maternal age, y, mean (SD)	27.0 (5.6)	26.9 (5.5)	27.2 (5.9)	26.9 (5.7)	26.2 (6.0)*	26.7 (6.0)	26.7 (5.9)	26.5 (6.3)	29.4 (6.2)*
Category, n (%)									
13–21	902 (20.2)	661 (20.1)	219 (19.9)*	122 (20.1)	80 (26.9)*	90 (23.3)*	51 (23.4)	51 (27.4)*	23 (12.0)*
22–35	3262 (73.0)	2425 (73.8)	780 (70.8)*	437 (71.9)	195 (65.7)*	262 (67.9)*	149 (68.3)	119 (64.0)*	136 (71.2)*
>35	307 (6.9)	199 (6.1)	103 (9.3)*	49 (8.1)	22 (7.4)*	34 (8.8)*	18 (8.3)	16 (8.6)*	32 (16.8)*
Gestational age at baseline, wk, median (min-max)	12.3 (6.0–13.9)	12.3 (6.0–13.9)	12.4 (6.1–13.9)	12.4 (6.1–13.9)	12.3 (6.3–13.9)	12.3 (6.1–13.9)	12.3 (6.1–13.9)	12.3 (8.0–13.9)	12.4 (6.3–13.9)
Time from index pregnancy delivery to follow-up, y, mean (SD)	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)	3.3 (0.9)	3.2 (0.9)	3.3 (0.9)
Early pregnancy BMI, kg/m^2, median (min-max)	24.7 (15.8–64.0)	24.2 (15.8–61.3)	26.6 (15.9–64.0)*	28.3 (15.9–61.9)*	28.4 (17.4–61.9)*	26.4 (16.6–58.7)*	24.8 (16.6–49.6)	24.5 (17.1–64.0)	29.2 (16.8–58.7)*
Category, n (%)									
<25	2278 (51.8)	1825 (56.6)	434 (39.0)*	191 (31.6)*	91 (31.0)*	160 (42.4)*	110 (51.6)	97 (53.3)	55 (29.3)*
25 to <30	1078 (24.5)	771 (23.9)	282 (25.9)*	165 (27.3)*	83 (28.2)*	101 (26.8)*	57 (26.8)	45 (24.7)	46 (24.5)*
≥30	1040 (23.7)	628 (19.5)	372 (34.2)*	249 (41.2)*	120 (40.8)*	116 (30.8)*	46 (21.6)	40 (22.0)	87 (46.3)*
Waist circumference over iliac crest, cm, mean (SD)	95.6 (14.8)	94.0 (13.5)	99.5 (16.8)*	102.5 (16.6)*	103.3 (17.6)*	98.6 (16.6)*	94.9 (14.3)	94.6 (15.6)	104.4 (19.3)*
≥88 cm (non-Asian) or ≥80 cm (Asian), n (%)	2958 (67.9)	2088 (65.3)	804 (74.6)*	488 (81.2)*	235 (80.5)*	265 (71.0)*	138 (65.4)	116 (64.1)	155 (83.3)*
Maternal race/ethnicity, n (%)									
White non-Hispanic	2779 (62.2)	2087 (63.5)	657 (59.6)*	383 (63.0)*	153 (51.5)*	218 (56.5)*	128 (58.7)	87 (46.8)*	105 (55.0)*
Black non-Hispanic	614 (13.7)	402 (12.2)	185 (16.8)*	113 (18.6)*	74 (24.9)*	76 (19.7)*	38 (17.4)	45 (24.2)*	22 (11.5)*
Hispanic	734 (16.4)	554 (16.9)	167 (15.2)*	67 (11.0)*	44 (14.8)*	65 (16.8)*	38 (17.4)	38 (20.4)*	39 (20.4)*
Asian	135 (3.0)	102 (3.1)	30 (2.7)*	13 (2.1)*	5 (1.7)*	6 (1.6)*	3 (1.4)	6 (3.2)*	12 (6.3)*
Other[‖]	209 (4.7)	140 (4.3)	63 (5.7)*	32 (5.3)*	21 (7.1)*	21 (5.4)*	11 (5.0)	10 (5.4)*	13 (6.8)*
Type of health insurance, n (%)									
Commercial/military	3096 (69.7)	2333 (71.4)	721 (66.0)*	401 (66.2)*	164 (55.4)*	233 (60.8)*	140 (65.1)	120 (65.9)	118 (61.8)*
Government	1197 (26.9)	826 (25.3)	332 (30.4)*	182 (30.0)*	120 (40.5)*	138 (36.0)*	68 (31.6)	57 (31.3)	63 (33.0)*
Self-pay/other	152 (3.4)	110 (3.4)	40 (3.7)*	23 (3.8)*	12 (4.1)*	12 (3.1)*	7 (3.3)	5 (2.7)	10 (5.2)*
Total cholesterol, mmol/L, mean (SD)	4.8 (0.9)	4.8 (0.9)	4.9 (0.9)	4.9 (0.9)*	4.9 (1.0)	4.7 (0.9)*	4.7 (0.9)*	4.7 (0.9)	5.0 (1.1)*
HDL-C, mmol/L, mean (SD)	1.9 (0.4)	1.9 (0.4)	1.8 (0.4)*	1.8 (0.4)*	1.8 (0.4)*	1.8 (0.4)*	1.8 (0.4)*	1.8 (0.4)	1.8 (0.4)*
LDL-C, mmol/L, mean (SD)	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)	2.4 (0.7)*	2.4 (0.8)	2.2 (0.7)	2.2 (0.7)	2.3 (0.7)	2.4 (0.8)*

(*Continued*)

Table 1. Continued

Demographic Characteristics and Early Pregnancy CVD Risk Factors	All Participants, N=4471	Index Pregnancy APOs and GDM (Not Mutually Exclusive)							
		No APO or GDM, N=3285	Any APO or GDM, N=1102	HDP, N=608	Preeclampsia, N=297	PTB, N=386	sPTB, N=218	SGA, N=186	GDM, N=191
Glucose, mmol/L, mean (SD)	4.9 (0.9)	4.8 (0.8)	5.0 (1.0)*	5.0 (1.0)*	5.0 (1.1)*	5.1 (1.2)*	5.0 (1.0)	4.8 (0.9)	5.4 (1.4)*
Insulin, pmol/L, median (min-max)	65.3 (3.6–7313.4)	60.1 (3.6–3746.0)	77.6 (6.3–2541.5)*	89.9 (7.7–2278.9)*	98.8 (7.7–2278.9)*	75.7 (7.4–2541.5)*	64.8 (7.4–1487.5)	68.4 (6.3–1035.6)	99.1 (7.5–2051.3)*
hs-CRP, nmol/L, median (min-max)	4.3 (0.1–145.1)	4.0 (0.1–145.1)	5.6 (0.1–75.2)*	6.3 (0.2–75.2)*	6.1 (0.3–65.7)*	5.1 (0.1–65.7)*	4.6 (0.1–40.6)	4.2 (0.1–60.9)	8.7 (0.3–42.5)*
Triglycerides, mmol/L, median (min-max)	1.3 (0.1–7.7)	1.3 (0.1–7.7)	1.4 (0.2–5.3)*	1.5 (0.5–5.3)*	1.5 (0.5–5.3)*	1.3 (0.2–5.3)*	1.3 (0.2–4.6)	1.3 (0.5–4.4)	1.7 (0.7–5.0)*
Systolic blood pressure, mm Hg, mean (SD)	109.5 (10.9)	108.4 (10.4)	112.2 (11.5)*	114.7 (11.4)*	115.3 (12.4)*	112.3 (12.2)*	108.9 (10.6)	109.0 (11.1)	113.3 (12.2)*
Diastolic blood pressure, mm Hg, mean (SD)	67.3 (8.4)	66.6 (8.0)	69.2 (8.9)*	70.9 (9.0)*	71.1 (9.6)*	69.3 (9.4)*	67.1 (8.5)	67.5 (8.4)	70.1 (8.9)*
Current smoker, n (%)	249 (5.6)	160 (4.9)	83 (7.6)*	36 (5.9)	17 (5.7)	35 (9.2)*	17 (7.9)	20 (10.8)*	14 (7.4)
Diet quality score, mean (SD)	0.8 (4.1)	1.0 (4.0)	0.4 (4.4)*	0.4 (4.3)*	−0.5 (4.7)*	0.4 (4.0)*	0.8 (4.0)	−0.4 (5.4)*	0.2 (4.0)*
Motherisk PUQE score, n (%)									
No symptoms	1986 (44.4)	1450 (44.1)	495 (45.0)	263 (43.3)	121 (40.9)	169 (43.9)	101 (46.3)	83 (44.9)	91 (47.6)
Mild	1745 (39.0)	1289 (39.2)	419 (38.1)	247 (40.7)	125 (42.2)	151 (39.2)	86 (39.4)	66 (35.7)	67 (35.1)
Moderate	731 (16.4)	541 (16.5)	184 (16.7)	97 (16.0)	50 (16.9)	64 (16.6)	30 (13.8)	35 (18.9)	32 (16.8)
Severe	8 (0.2)	5 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.5)	1 (0.5)	1 (0.5)
Physical activity (h per week of moderate or vigorous activity), mean (SD)	2.0 (2.9)	2.0 (2.9)	1.8 (3.1)	1.8 (3.3)	1.6 (3.6)	1.8 (3.5)	1.9 (3.3)	1.6 (2.2)*	1.5 (2.5)*
ASCVD risk score, mean (SD)	0.3 (1.9)	0.3 (1.1)	0.5 (3.3)*	0.6 (4.3)	0.8 (6.1)	0.5 (1.5)*	0.4 (1.5)	0.4 (0.9)	0.5 (1.2)*
≥5% estimated risk	39 (0.9)	24 (0.8)	15 (1.3)	9 (1.5)	7 (2.5)*	8 (2.2)*	3 (1.5)	4 (2.3)	3 (1.7)
Latent profile estimated class, n (%)									
Class 1: minimal cardiometabolic risk factors	1673 (38.1)	1326 (41.1)	323 (29.7)*	139 (23.0)*	74 (25.2)*	141 (37.4)*	98 (46.0)	73 (40.1)	30 (16.0)*
Class 2: mostly obese with higher insulin, hs-CRP, and BP	900 (20.5)	526 (16.3)	336 (30.9)*	225 (37.2)*	113 (38.4)*	114 (30.2)*	41 (19.2)	36 (19.8)	80 (42.6)*
Class 3: largely nonobese with higher cholesterols	1519 (34.6)	1168 (36.2)	337 (31.0)*	179 (29.6)*	80 (27.2)*	98 (26.0)*	61 (28.6)	66 (36.3)	53 (28.2)*
Class 4: total and LDL-C in the top decile	304 (6.9)	204 (6.3)	92 (8.5)*	62 (10.2)*	27 (9.2)*	24 (6.4)*	13 (6.1)	7 (3.8)	25 (13.3)*

APO indicates adverse pregnancy outcome; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HDP, hypertensive disorders of pregnancy; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; min-max, minimum–maximum; n, number in category; N, sample size; PTB, preterm birth; PUQE, Pregnancy-Unique Quantification of Emesis; SGA, small for gestational age; and sPTB, spontaneous preterm birth.

†APO is defined as any HDP, any PTB, or SGA.

‡Statistically significant comparisons of no APO or GDM vs each of the APO/GDM subgroups ($P<0.05$) are indicated by asterisk. For binary or multilevel demographic characteristics and risk factors, a single global statistical test of association with each APO/GDM subgroup was performed, with no APO or GDM considered the reference group.

§Missing data are as follows: time from index pregnancy delivery to follow-up (n=4), waist circumference over iliac crest (n=114), total cholesterol (n=115), HDL-C (n=115), LDL-C (n=124), glucose (n=121), insulin (n=115), hs-CRP (n=115), triglycerides (n=115), systolic blood pressure (n=100), diastolic blood pressure (n=100), current smoker (n=25), diet quality score (n=659), Motherisk PUQE score (n=1), physical activity (n=6), ASCVD risk score (n=251), and latent profile estimated class (n=75).

‖"Other" category reflects a combination of American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, multiracial, and unknown/not reported.

more likely to be present among those who went on to develop HDP, preterm birth, or GDM (Table 2). For example, a 2-fold higher concentration of triglycerides, roughly equivalent to comparing the 10th percentile to the 75th in our population, was associated with a 1.46-fold higher risk of HDP (95% CI, 1.27–1.68).

A total of 32.8% of women with APOs or GDM were hypertensive (≥130/80 mm Hg or took medication) within 2 to 7 years after delivery compared with 18.1% of women with no APO/GDM (Table 3). Rates of elevated blood pressure (7.6% versus 6.3%) and stage 1 (19.9% versus 13.3%) and stage 2 hypertension (12.9% versus 4.8%) ($P<0.05$) were all higher in women with a first birth complicated by an APO/GDM compared with women with no complications (Table S3). After accounting for confounders (age, race/ethnicity, insurance status, and smoking), early pregnancy BMI, total cholesterol, HDL-C, LDL-C, glucose, insulin, hs-CRP, triglycerides, blood pressure, diet quality, and physical activity were all related to risk of hypertension 2 to 7 years after delivery (Table 4, Model A). Upon further accounting for cardiometabolic factors that are routinely assessed during prenatal care (blood pressure and BMI), higher glucose (RR, 1.03; 95% CI, 1.00–1.06 per 0.6 mmol/L), hs-CRP (RR, 1.06; 95% CI, 1.02–1.11 per doubling), and triglycerides (RR, 1.27; 95% CI, 1.14–1.41 per doubling) remained related to hypertension after delivery (Table 4, Model B; Table S4). Higher BMI was also associated with higher risk of hypertension (adjusted for blood pressure), as were higher SBP (adjusted for BMI and DBP) and higher DBP (adjusted for BMI and SBP). Conversely, higher physical activity was associated with lower risk of hypertension after delivery (RR, 0.93; 95% CI, 0.87–0.99 per 3 hours per week moderate/vigorous activity). Results were similar after restricting analysis to women without chronic hypertension or diabetes mellitus before their first birth (Table 4, Model C). In general, early pregnancy factors were associated with both stage 1 and stage 2 hypertension (Table S5).

When risk factors were aggregated into an early pregnancy ASCVD risk score, women with an APO/GDM in a first birth had a significantly higher mean score than women with uncomplicated pregnancies (ASCVD score 0.5±3.3 versus 0.3±1.1, $P<0.05$; Table 1). This score, however, was not related to risk of later hypertension (Table 4). Latent profile analysis revealed 4 profiles of early pregnancy factors as informative (Table 1): a low-risk profile with minimal cardiometabolic risk factors (class 1, 38.1% of the cohort; generally nonobese with average risk factor values below the cohort means), a mostly obese profile with higher insulin, hs-CRP, and blood pressure (class 2, 20.5%; mean BMI >35 kg/m^2; insulin approximately twice the cohort average; average glucose and triglycerides; and hs-CRP, blood pressure, and waist circumference above the respective cohort means); a largely nonobese profile with higher cholesterol (class 3, 34.6%; cholesterols above the cohort means with waist circumference and BMI below the cohort means), and a profile that had mean total and LDL-C concentrations in the highest decile (class 4, 6.9%). The class 4 profile was 1.28 times as likely to experience an APO or GDM (95% CI, 1.04–1.58) compared with the low-risk profile; no other latent profile with high cardiometabolic risk factors was significantly different from the low-risk class in the development of an APO/GDM (Table 2). In contrast, each of the high-risk latent profiles was associated with higher risk of hypertension 2 to 7 years after delivery, relative to the profile with minimal cardiometabolic risk factors and accounting for race, age, insurance, and smoking. The highest risk of hypertension 2 to 7 years after delivery was among typically obese women (class 2 versus class 1: RR, 2.45; 95% CI, 2.11–2.85; Table 4). After accounting for BMI and blood pressure, however, only the largely nonobese profile with cholesterol in the highest decile had excess hypertension risk 2 to 7 years after delivery (RR, 1.31; 95% CI, 1.04–1.64).

We then considered whether the occurrence of an APO/GDM mediated the association between first trimester cardiometabolic markers and hypertension 2 to 7 years after delivery (Figure 2; Table 5). Among the early pregnancy factors associated with later hypertension, 7% to 15% of the excess RR was because of interaction with or mediation by the occurrence of an APO or GDM. For example, a 2-fold higher concentration of triglycerides was associated with 0.53 excess RR for hypertension after delivery (95% CI, 0.34–0.72), after adjustment for age, race/ethnicity, insurance, smoking, BMI, SBP, and DBP. This decomposed into a direct effect of higher triglycerides (0.47 excess RR [90% of the excess risk]) and the portion attributable to the APO or GDM (0.05 excess RR [10% of the excess risk]). Similarly, at least 85% of the excess hypertension risk associated with the obese/adverse metabolic latent profiles was because of a direct effect, and up to 15% was attributable to the occurrence of the APOs. Results were mixed across specific APOs but were strongest for HDP (Tables S6 through S9).

DISCUSSION

In this contemporary multicenter cohort of women followed from early in their first pregnancy through 2 to 7 years after delivery, adverse cardiometabolic characteristics in the first trimester were associated with more frequent occurrence of an APO/GDM and the occurrence of chronic hypertension 2 to 7 years

Table 2. Relative Risks for Association of Early Pregnancy CVD Risk Factors With APOs* and GDM Among nuMoM2b-Heart Health Study Participants Adjusted for Age, Race, Insurance, Smoking, BMI, and Systolic and Diastolic Blood Pressure (Baseline)†

Early Pregnancy CVD Risk Factors	Any APO or GDM vs No APO or GDM, RR (95% CI)	HDP vs No HDP, RR (95% CI)	PTB vs No PTB, RR (95% CI)	SGA vs No SGA, RR (95% CI)	GDM vs No GDM, RR (95% CI)
BMI, per kg/m†	1.02 (1.02–1.03)	1.04 (1.03–1.05)	1.01 (0.99–1.02)	0.98 (0.95–1.01)	1.07 (1.05–1.09)
Total cholesterol, per 0.3 mmol/L	1.00 (0.99–1.02)	1.02 (1.00–1.04)^	0.96 (0.93–0.98)	0.99 (0.95–1.03)	1.02 (0.98–1.07)
HDL-C, per 0.1 mmol/L	0.97 (0.95–0.99)	1.01 (0.98–1.03)	0.94 (0.90–0.97)	0.98 (0.93–1.02)	0.93 (0.88–0.99)
LDL-C, per 0.3 mmol/L	1.00 (0.99–1.01)	1.00 (0.99–1.02)	0.98 (0.96–0.99)	1.00 (0.97–1.03)	1.01 (0.98–1.03)
Glucose, per 0.6 mmol/L	1.04 (1.01–1.07)	1.02 (0.98–1.07)	1.08 (1.03–1.13)	0.94 (0.85–1.05)	1.21 (1.14–1.28)
Insulin, per doubling in value§	1.08 (1.04–1.12)	1.11 (1.05–1.17)	1.07 (0.99–1.15)	1.00 (0.89–1.11)	1.23 (1.11–1.35)
hs-CRP, per doubling in value§	1.06 (1.02–1.11)	1.06 (1.00–1.13)^	1.01 (0.94–1.09)	1.04 (0.92–1.17)	1.22 (1.08–1.37)
Triglycerides, per doubling in value§	1.34 (1.21–1.48)	1.46 (1.27–1.68)	1.12 (0.92–1.37)	0.99 (0.76–1.30)	2.20 (1.72–2.83)
Systolic blood pressure, per 5 mm Hg‡	1.05 (1.02–1.08)	1.10 (1.05–1.14)	1.07 (1.01–1.13)	0.96 (0.88–1.04)	1.03 (0.96–1.11)
Diastolic blood pressure, per 5 mm Hg‡	1.06 (1.02–1.10)	1.11 (1.06–1.17)	1.08 (1.01–1.15)	1.06 (0.96–1.17)	1.07 (0.96–1.18)
Diet quality score, per 1 unit	0.99 (0.97–1.00)	1.00 (0.97–1.02)	1.01 (0.98–1.04)	0.96 (0.92–1.00)^	0.97 (0.93–1.02)
Physical activity, per 3 h per week of moderate or vigorous activity	0.97 (0.92–1.03)	1.00 (0.92–1.09)	0.97 (0.85–1.10)	0.88 (0.76–1.03)	0.87 (0.73–1.04)
ASCVD risk score, per 1% increase in estimated risk‖	1.02 (1.01–1.03)	1.02 (1.02–1.03)	1.02 (1.00–1.04)	1.01 (0.98–1.04)	1.02 (1.00–1.04)
≥5% estimated risk‖	1.53 (1.02–2.28)	1.68 (0.94–3.00)	2.41 (1.29–4.51)	2.47 (0.97–6.32)	1.79 (0.60–5.37)
Latent profile estimated class (vs class 1)					
Class 2: mostly obese with higher insulin, hs-CRP, and BP	1.21 (0.93–1.58)	1.28 (0.94–1.75)	1.17 (0.69–1.99)	0.98 (0.52–1.83)	2.56 (1.41–4.66)
Class 3: largely nonobese with higher cholesterols	1.04 (0.89–1.21)	1.21 (0.93–1.57)	0.80 (0.61–1.06)	1.09 (0.72–1.67)	1.41 (0.87–2.30)
Class 4: total and LDL-C in the top decile	1.28 (1.04–1.58)	1.61 (1.21–2.14)	0.82 (0.53–1.28)	0.91 (0.43–1.95)	2.87 (1.61–5.11)

APO indicates adverse pregnancy outcome; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HDP, hypertensive disorders of pregnancy; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PTB, preterm birth; RR, relative risk; and SGA, small for gestational age.

*APO is defined as any HDP, any PTB, or SGA.

†When the CI shown includes 1.00 because of rounding, the ^ symbol indicates that the precise CI excludes 1 (ie, is statistically significant at $P<0.05$).

‡The model with this characteristic does not include this characteristic again as an adjustment covariate.

§This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. RRs for log-transformed quantities are interpreted on the multiplicative scale.

‖The models with ASCVD risk score are not adjusted for the covariates of age, race, smoking, insurance, BMI, systolic blood pressure, and diastolic blood pressure, because several of these covariates are included in the calculation of the risk score.

after delivery. No more than 15% of this excess hypertension risk was related to the occurrence of an APO or GDM, which raises several important points. First, there are shared cardiometabolic antecedents to an APO/GDM in a first pregnancy and hypertension after delivery. Second, atherogenic factors including glucose, triglycerides, and hs-CRP measured early in pregnancy are themselves directly related to hypertension after pregnancy. This is important, as cumulative years of hypertension is related to CVD risk later in life.[33,34] Detection and treatment of hypertension is key for prevention of future CVD, and our results indicate that the cardiometabolic profile early in pregnancy, in addition to an APO occurrence, may identify a group of women amenable to intervention to prevent hypertension and thereby improve lifelong cardiovascular health. Strategies to prevent chronic hypertension after delivery to reduce women's CVD risk are sparse, and this is an important area for future work.[35]

Pregnancy, which is now viewed as a cardiometabolic stress test that may unmask CVD risk in the form of APOs, is a unique time to assess such risk in young adult women.[36] Our results, aligned with those from smaller studies in other cohorts,[8] demonstrate that the early pregnancy atherogenic profile is related to both an APO/GDM and hypertension risk 2 to 7 years after delivery. In addition, we have demonstrated that glucose, hs-CRP, and triglycerides may be of particular importance in these associations.

Table 3. Blood Pressure and Hypertension Categories 2 to 7 Years After Delivery by Index Pregnancy APOs[†] and GDM Subgroups Among nuMoM2b-Heart Health Study Participants[‡]

Blood Pressure and Hypertension Categories 2–7 y After Delivery	All Participants, N=4471	Index Pregnancy APOs and GDM (Not Mutually Exclusive)					
		No APO or GDM, N=3285	Any APO or GDM, N=1104	HDP, N=608	PTB, N=386	SGA, N=186	GDM, N=191
Blood pressure, mm Hg, mean (SD)							
Systolic	111.5 (11.1)	110.6 (10.7)	113.9 (11.3)*	115.9 (11.8)*	114.1 (11.8)*	110.9 (11.0)	114.5 (12.0)*
Diastolic	72.1 (9.9)	71.2 (9.4)	74.7 (10.5)*	76.3 (10.8)*	75.0 (11.2)*	72.3 (9.7)	76.5 (11.3)*
N with data	4460	3277	1101	606	386	185	191
Hypertension definitions, n (%)							
Nonhypertensive (normotensive or elevated): SBP <130 and DBP <80	3465 (77.7)	2683 (81.9)	739 (67.2)*	368 (60.8)*	254 (65.8)*	137 (74.1)*	123 (64.4)*
Hypertensive (stage 1 or stage 2): SBP ≥130 or DBP ≥ 80, or antihypertensive medication	993 (22.3)	593 (18.1)	361 (32.8)*	237 (39.2)*	132 (34.2)*	48 (25.9)*	68 (35.6)*
N with data	4458	3276	1100	605	386	185	191

APO indicates adverse pregnancy outcome; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; n, number in category; N, sample size; PTB, preterm birth; SBP, systolic blood pressure; and SGA, small for gestational age.

[†]APO is defined as any HDP, any PTB, or SGA.

[‡]Statistically significant comparisons of no APO or GDM vs each of the APO/GDM subgroups ($P<0.05$) are indicated by asterisk. For categorical hypertension status, each APO/GDM subgroup was compared against no APO or GDM in separate statistical tests.

Our results underscore the possibility that pregnancy may be a valuable time to assess and reduce CVD risk in young adult women. This approach may be simpler and perhaps more informative than other risk assessment paradigms. Hypertension genetic risk scores, for example, identify a 2-fold excess risk when comparing the highest to the lowest decile of score among adults across a broad age range.[37] In contrast, data from our cohort indicate that women with an APO or GDM in a first pregnancy have 1.6-fold higher risk of hypertension within 7 years of pregnancy compared with women with no APO/GDM; risk of stage 2 hypertension is 2.4-fold higher.[7] Thus, cardiometabolic screening at the time of pregnancy may identify women who warrant more intensive follow-up to prevent or treat hypertension. Current American Heart Association/American College of Cardiology IIa recommendations are that adults ages 20 to 39 have assessment of ASCVD risk every 4 to 6 years,[38] and early pregnancy may be a convenient time to assess risk and advocate for healthy lifestyle choices. As pregnancy is a time of essentially universal healthcare access with routine blood draws, the idea that prenatal care can provide a window to future maternal cardiometabolic health is promising, both to improve pregnancy health and longer-term women's health. Of note, our data also point to a protective association between physical activity before pregnancy and lower risk of later hypertension. Lifestyle interventions that are safe during and after pregnancy warrant further study.

Our results are consistent with other studies suggesting that there may be shared antecedents to APOs and later hypertension. In a biracial US cohort, preterm birth was linked to maternal metabolic syndrome after delivery, with metabolic features measured before conception (blood pressure, waist circumference, triglycerides, fasting glucose, and HDL-C) accounting for some but not all the excess risk.[39] Similar results have been reported in a Scandinavian cohort, where 50% of higher blood pressure after delivery among women with HDP (compared with those with a normotensive pregnancy) appeared to be attributed to prepregnancy blood pressure.[40] A recent study of a large Korean population with cardiometabolic features measured before and after a first pregnancy also demonstrated that preexisting risk factors explained some but not all of the excess cardiometabolic risk after delivery associated with preeclampsia.[41] Thus, there are likely novel factors or perhaps de novo vascular impacts of APO occurrence, and these possibilities warrant future study. Our results extend this work by identifying patterns of atherogenic risk factors detected in early pregnancy that may presage progression to chronic hypertension, and we quantify both direct

Table 4. Association of Early Pregnancy CVD Risk Factors With Hypertension* 2 to 7 Years After Delivery Among nuMoM2b-Heart Health Study Participants†

Early Pregnancy CVD Risk Factors	Model A‡, RR (95% CI)	Model B‡, RR (95% CI)	Model C‡,§, RR (95% CI)
BMI, per kg/m^2	1.05 (1.05–1.06)	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Total cholesterol, per 0.3 mmol/L	1.03 (1.01–1.04)	1.01 (1.00–1.03)	1.01 (1.00–1.03)
HDL-C, per 0.1 mmol/L	0.96 (0.94–0.98)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
LDL-C, per 0.3 mmol/L	1.02 (1.01–1.03)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Glucose, per 0.6 mmol/L	1.08 (1.05–1.11)	1.03 (1.00–1.06)^	1.02 (0.98–1.06)
Insulin, per doubling in value‖	1.15 (1.11–1.19)	1.04 (0.99–1.08)	1.02 (0.98–1.07)
hs-CRP, per doubling in value‖	1.20 (1.15–1.25)	1.06 (1.02–1.11)	1.07 (1.02–1.12)
Triglycerides, per doubling in value‖	1.55 (1.39–1.71)	1.27 (1.14–1.41)	1.27 (1.13–1.42)
Systolic blood pressure, per 5 mm Hg	1.20 (1.18–1.23)	1.08 (1.05–1.11)	1.08 (1.04–1.12)
Diastolic blood pressure, per 5 mm Hg	1.29 (1.26–1.33)	1.17 (1.13–1.21)	1.16 (1.11–1.21)
Diet quality score, per 1 unit	0.98 (0.96–0.99)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Physical activity, per 3 h per week of moderate or vigorous activity	0.88 (0.81–0.95)	0.93 (0.87–0.99)	0.93 (0.87–0.99)
ASCVD risk score, per 1% increase in estimated risk¶	1.00 (0.98–1.02)	…	…
≥5% estimated risk¶	0.93 (0.50–1.73)	…	…
Latent profile estimated class (vs class 1)			
Class 2: mostly obese with higher insulin, hs-CRP, and BP	2.45 (2.11–2.85)	1.13 (0.88–1.44)	1.09 (0.83–1.44)
Class 3: largely nonobese with higher cholesterols	1.29 (1.06–1.55)	1.14 (0.94–1.37)	1.10 (0.90–1.35)
Class 4: total and LDL-C in the top decile	1.98 (1.60–2.44)	1.31 (1.04–1.64)	1.28 (1.00–1.63)

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and RR, relative risk.

*Hypertension 2 to 7 years after index pregnancy is defined as ≥ 130 mm Hg systolic blood pressure or ≥80 mm Hg diastolic blood pressure, or self-report of antihypertensive medication use.

†When the CI shown includes 1.00 because of rounding, the ^ symbol indicates that the precise CI excludes 1 (ie, is statistically significant at $P<0.05$).

‡Model A is adjusted for the following covariates: baseline age, race, insurance, and smoking. Models B and C are adjusted for the following covariates: baseline age, race, insurance, smoking, BMI, systolic blood pressure, and diastolic blood pressure. Models B and C do not adjust for BMI, systolic blood pressure, or diastolic blood pressure when they are the risk factor of interest.

§Model C restricts to nuMoM2b-Heart Health Study participants without chronic hypertension or pregestational diabetes mellitus. Chronic hypertension is defined as diagnosis of hypertension before index pregnancy or hypertension present (systolic ≥140 mm Hg or diastolic ≥90 mm Hg on two occasions at least 6 hours apart or on one occasion followed by antihypertensive medication therapy) before 20^{+} weeks gestation per nuMoM2b chart abstraction. Pregestational diabetes mellitus is defined as diagnosis of diabetes mellitus before index pregnancy per nuMoM2b chart abstraction.

‖This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. RRs for log-transformed quantities are interpreted on the multiplicative scale.

¶The models with ASCVD risk score are not adjusted for the covariates of age, race, smoking, and insurance, because the first three of these covariates are included in the calculation of the risk score.

and mediated associations between atherogenic factors and later hypertension. This is consistent with one report that found better early pregnancy cardiovascular health and a composite metric of blood pressure, total cholesterol, glucose, smoking, and BMI were related to reduced risk of subclinical atherosclerosis 10 years later even among women with HDP.[42] We deployed latent class profiles to characterize atherogenic patterns that may identify risk during and after pregnancy. This begins to fill a gap, as current risk algorithms are not designed for young adult women during pregnancy. Of note, the early pregnancy ASCVD risk score in our data was not associated with hypertension after delivery. It is noteworthy, however, that this score was developed using a cohort of nonpregnant adults over the age of 40 years and therefore may not be ideal for evaluating risk in young adult women early in pregnancy. Leveraging pregnancy in new predictive approaches to detect hypertension and CVD risk is a potential avenue of study. This is important, because hypertension in young adulthood is related to CVD events later in life,[34] hypertension contributes to more CVD events in women relative to men,[43] and hypertension is the single largest contributor to racial disparities in mortality in the United States.[44]

Strengths and Limitations

We were limited to first-trimester measurement of cardiometabolic risk factors and did not have prepregnancy measurements. There is evidence, however, that early pregnancy changes in lipids, for example, are modest compared with prepregnancy concentrations (7%–15% different), whereas changes in the second half of pregnancy are more dramatic (30%–123% higher).[45] We also did not evaluate longitudinal pregnancy changes that may be additionally

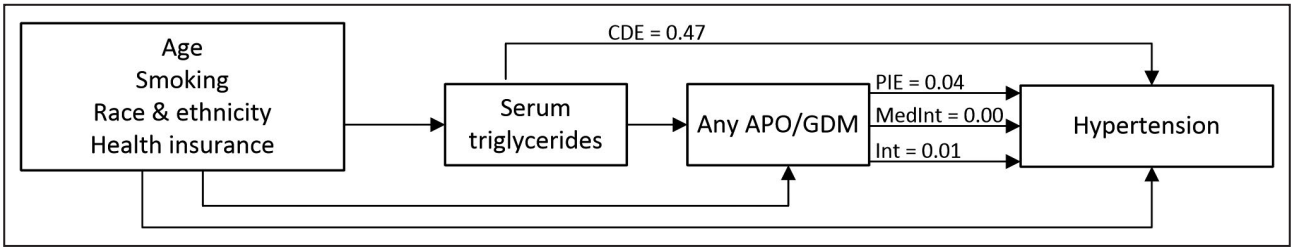

Figure 2. Schematic to assess mediation by APO/GDM of the association between an early pregnancy CVD risk factor (triglycerides) and hypertension 2 to 7 years following delivery after adjustment for covariates.
Estimates are components of excess relative risk. APO indicates adverse pregnancy outcome; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CDE, controlled direct effect; CVD, cardiovascular disease; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; Int, interaction only; LDL, low-density lipoprotein; MedInt, mediation and interaction; PIE, pure indirect effect; PTB, preterm birth; SBP, systolic blood pressure; SGA, small for gestational age; and ST, supplemental table.

informative for an APO/GDM and hypertension risk. In addition, first-trimester samples were nonfasting, as is common in pregnancy studies, and it is uncertain whether fasting values would provide additional information. We evaluated lipid concentrations several years after pregnancy, so we did not have the

Table 5. Mediation Analysis of Early Pregnancy CVD Risk Factors and Index Pregnancy APOs* or GDM on Hypertension† 2 to 7 Years Later Among nuMoM2b-Heart Health Study Participants, Adjusted for Age, Race, Insurance, and Smoking (Baseline)‡

Early Pregnancy CVD Risk Factors	Total Excess Relative Risk (95% CI)	Components of Excess Relative Risk (95% CI) Associating Early Pregnancy Risk Factor With Hypertension 2–7 y After Delivery§				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction With APO/GDM	Interaction and Mediation With APO/GDM	Pure Indirect Effect	
BMI, per kg/m^2	0.06 (0.05–0.07)	0.05 (0.04–0.06)	<0.01‖	<0.01‖	<0.01‖	0.07 (0.01 to 0.13)
Glucose, per 0.6 mmol/L	0.08 (0.03–0.13)	0.08 (0.02–0.13)	0.00 (–0.02 to 0.01)	<0.01‖	0.01 (0.00–0.01)^	0.03 (–0.22 to 0.29)
hs-CRP, per doubling in value¶	0.21 (0.15–0.26)	0.20 (0.14–0.26)	–0.01 (–0.03 to 0.02)	<0.01‖	0.01 (0.01–0.02)	0.03 (–0.11 to 0.16)
Triglycerides, per doubling in value¶	0.53 (0.34–0.72)	0.47 (0.26–0.69)	0.01 (–0.07 to 0.09)	0.00 (–0.02 to 0.03)	0.04 (0.02–0.06)	0.10 (–0.10 to 0.30)
Systolic blood pressure, per 5 mm Hg	0.21 (0.17–0.24)	0.19 (0.15–0.23)	0.00 (–0.01 to 0.02)	<0.01‖	0.01 (0.01–0.01)	0.07 (–0.01 to 0.14)
Diastolic blood pressure, per 5 mm Hg	0.29 (0.24–0.34)	0.27 (0.22–0.33)	0.01 (–0.01 to 0.03)	<0.01‖	0.01 (0.01–0.02)	0.07 (–0.01 to 0.15)
Latent profile estimated class (vs class 1)						
Class 2: mostly obese with higher insulin, hs-CRP, and BP	1.42 (0.96–1.87)	1.21 (0.74–1.67)	0.10 (–0.02 to 0.22)	0.06 (–0.02 to 0.14)	0.05 (0.01–0.10)	0.15 (0.02–0.28)
Class 3: largely nonobese with higher cholesterols	0.32 (0.06–0.58)	0.25 (–0.02 to 0.52)	0.05 (–0.05 to 0.16)	0.01 (–0.01 to 0.02)	0.01 (–0.01 to 0.02)	0.22 (–0.19 to 0.63)
Class 4: total and LDL cholesterols in the top decile	0.96 (0.44–1.49)	0.98 (0.39–1.58)	–0.04 (–0.21 to 0.14)	–0.01 (–0.08 to 0.06)	0.03 (0.00–0.06)	–0.02 (–0.26–0.23)

APO indicates adverse pregnancy outcome; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; and LDL, low-density lipoprotein.

*APO is defined as any hypertensive disorder of pregnancy, any preterm birth, or small for gestational age.

†Hypertension 2 to 7 years after index pregnancy defined as ≥130 mm Hg systolic blood pressure or ≥80 mm Hg diastolic blood pressure, or self-report of antihypertensive medication use.

‡When the CI shown includes 1.00 because of rounding, the ^ symbol indicates that the precise CI excludes 1 (ie, is statistically significant at $P<0.05$).

§Components defined as controlled direct effect (effect because of CVD risk factor only, without mediation or interaction), interaction only (effect because of interaction only), interaction and mediation (mediated interaction, effect because of both mediation and interaction), pure indirect effect (effect because of mediation only), portion eliminated (percent effect because of either mediation or interaction).

‖The designated components are estimated to contribute <0.01 to the excess relative risk and have CI bounds of similar magnitude. For these negligible effects, no CIs are provided.

¶This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Relative risks for log-transformed quantities are interpreted on the multiplicative scale.

ability to recall women if triglycerides were elevated but only 8 women had triglycerides >400 mg/dL. Although our cohort was large, we were restricted to women who returned for a 2- to 7-year follow-up exam. However, demographic features of those who did and did not attend follow-up were similar.[7] There may also have been intervening behaviors and life events between the delivery of the first birth and our follow-up assessment of hypertension, such as subsequent births, that contribute to hypertension risk. Strengths of this analysis include a large, multicenter, diverse, and contemporary cohort with excellent adjudication of APOs. Atherogenic factors were measured following a standardized research protocol, and assays were conducted by a single core laboratory using samples collected during pregnancy. We also uniquely studied first pregnancies, which are at higher risk for many APOs and which may inform both future pregnancy health as well as cardiometabolic health. Focusing on first births limits prior exposures but also introduces other factors, such as younger maternal age, which may impact generalizability. Our cohort is ongoing, and subsequent births as well as longer-term CVD risk will be assessed.

CONCLUSIONS

Atherogenic characteristics present in the first trimester are associated with an APO/GDM and hypertension risk 2 to 7 years after delivery. Up to 15% of the association with hypertension may be mediated by APOs, demonstrating that early pregnancy cardiometabolic risk factors have both direct and indirect associations with hypertension after delivery. Because women typically have access to health care during pregnancy, assessment of cardiometabolic health early in pregnancy may help to identify risk for an APO/GDM and to identify opportunities to improve cardiovascular health later in life.

ARTICLE INFORMATION

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Disclosures

Dr Bairey Merz has served as a speaker or consultant/advisor for iRhythm, Med Intelligence, and Bayer. Dr Saade is a consultant for AMAG Pharmaceuticals and GestVision. Dr Simhan is a cofounder of Naima Health. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S9

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods and Results: Latent profile analysis

Methods. Latent profile analysis (LPA) was used to identify early-pregnancy phenotypes based on risk factors for CVD. Latent profile analysis is a type of finite mixture modeling that relies on maximum likelihood methods to simultaneously fit a system of regression equations and estimate the probability of membership in each phenotype. This multivariate approach assumes that when considered collectively, the values of CVD risk factors reflect study participants' membership in a population subgroup (phenotype). Initial models resulted in the identification of obese and non-obese groups to the exclusion of other characterization. Thus, the models were grouped by obesity status to allow the identification of more nuanced profiling on risk factors within obesity groups, and included the following participant characteristics, measured during the first trimester of the index pregnancy: total cholesterol, HDL, LDL, glucose, insulin, triglycerides, hsCRP, SBP, DBP, age, and waist circumference. Class probabilities were allowed to vary by obesity group membership. Insulin, triglycerides, and hsCRP were log (base 2) transformed due to skewing. Models were fit for 2-5 latent profiles and were compared qualitatively with respect to likelihood replicability, fit statistics (AIC, BIC), and practicality of interpretation. MPlus software was used for the latent profile analysis.

Results. Of 4471 participants, 4396 had sufficiently complete data to permit inclusion in the LPA models. Models with 2-5 latent profiles were fit with stable results. Because several profiles generated by larger models were small in size, we restrict our reported results to the model with 4 profiles (grouped by obesity). The four profiles were associated with distinct characteristics and are labeled with their most dominant within-group features in Table S4. Obese and non-obese participants had similar characteristics for each profile, but the distribution of participants across profiles varied greatly between obese and non-obese participants. In contrast to non-obese participants, the obese participants' most common profile (Class 2) included elevated insulin, hsCRP, blood pressure, waist circumference, and BMI.

Table S1. Demographic Characteristics and CVD Risk Factors during Index Pregnancy of nuMoM2b Participants, nuMoM2b-HHS Participants Included in Analyses, and nuMoM2b and nuMoM2b-HHS Participants Not Included in Analyses*†‡

Early Pregnancy Characteristics	nuMoM2b Participants (N=10038)	nuMoM2b-HHS Participants Included in Analyses (N=4471)	nuMoM2b and nuMoM2b-HHS Participants Excluded from Analyses (N=5567)
Maternal age, mean (SD), years	26.9 (5.7)	27.0 (5.6)	26.9 (5.7)
Category: n (%)			
13-21	2133 (21.3)	902 (20.2)	1231 (22.2)
22-35	7222 (72.0)	3262 (73.0)	3960 (71.3)
> 35	673 (6.7)	307 (6.9)	366 (6.6)
Gestational age at baseline, median (min-max), weeks	12.4 (5.7-18.6)	**12.3 (6.0-13.9)**	12.4 (5.7-18.6)
BMI, median (min-max), kg/m^2	24.6 (13.3-72.3)	**24.7 (15.8-64.0)**	24.4 (13.3-72.3)
Category: n (%)			
< 25	5248 (53.3)	**2278 (51.8)**	2970 (54.6)
25 to < 30	2437 (24.8)	**1078 (24.5)**	1359 (25.0)
≥ 30	2153 (21.9)	**1040 (23.7)**	1113 (20.5)

Waist circumference over iliac crest, mean (SD), cm	94.9 (14.4)	**95.6 (14.8)**	94.3 (14.0)
≥ 88 cm (non-Asian) or ≥ 80 cm (Asian), n (%)	6510/9735 (66.9)	2958/4357 (67.9)	3552/5378 (66.0)
Maternal race: n (%)			
White Non-Hispanic	5989 (59.7)	**2779 (62.2)**	3210 (57.8)
Black Non-Hispanic	1418 (14.1)	**614 (13.7)**	804 (14.5)
Hispanic	1700 (17.0)	**734 (16.4)**	966 (17.4)
Asian	407 (4.1)	**135 (3.0)**	272 (4.9)
Other	514 (5.1)	**209 (4.7)**	305 (5.5)
Type of health insurance: n (%)			
Commercial/military	6834 (68.6)	3096 (69.7)	3738 (67.8)
Government	2744 (27.6)	1197 (26.9)	1547 (28.1)
Self-pay/other	381 (3.8)	152 (3.4)	229 (4.2)
Systolic blood pressure, mean (SD), mmHg	109.1 (10.8)	**109.5 (10.9)**	108.9 (10.7)
Diastolic blood pressure, mean (SD), mmHg	67.0 (8.3)	**67.3 (8.4)**	66.7 (8.1)
Current smoker, n (%)	620/9987 (6.2)	**249/4446 (5.6)**	371/5541 (6.7)
Diet quality score, mean (SD)	0.8 (4.1)	0.8 (4.1)	0.8 (4.1)
Motherisk PUQE score: n (%)			
No symptoms	4604 (45.9)	**1986 (44.4)**	2618 (47.1)

Mild	3815 (38.1)	**1745 (39.0)**	2070 (37.3)
Moderate	1581 (15.8)	**731 (16.4)**	850 (15.3)
Severe	24 (0.2)	**8 (0.2)**	16 (0.3)
Physical activity (hours per week of moderate or vigorous activity), mean (SD)	2.0 (3.0)	2.0 (2.9)	2.1 (3.1)

* Abbreviations: CVD=cardiovascular disease; HHS=heart health study; SD=standard deviation; n=number in category; BMI=body mass index; PUQE=Pregnancy-Unique Quantification of Emesis; N=sample size.

† Missing data as follows: maternal age (n=10), early pregnancy gestational age (n=9), BMI (n=200), waist circumference over iliac crest (n=303), maternal race (n=10), type of health insurance (n=79), systolic blood pressure (n=212), diastolic blood pressure (n=212), current smoker (n=51), diet quality score (n=1779), Motherisk PUQE score (n=14), physical activity (n=27).

‡ Statistically significant comparisons to “nuMoM2b and nuMoM2b-HHS Participants Excluded from Analyses” ($p < 0.05$) are indicated by boldface text. For binary or multi-level early pregnancy characteristic, a single global statistical test of the characteristic’s association with APO/GDM subgroup was performed, with “No APO or GDM” considered the reference group.

Table S2. Characteristics of early pregnancy phenotypes identified by latent profile analysis of CVD risk factors.

	Overall N = 4396	**Non-obese Group N = 3356**		**Obese Group N = 1040**	
	n (%)	n (%)	Characteristics	n (%)	Characteristics
Class 1: Low risk with minimal cardiometabolic risk factors	1673 (38.1%)	1626 (48.5%)	Lowest within-group cholesterol, LDL, glucose, insulin, triglycerides, hsCRP, BP, waist circumference, BMI	47 (4.5%)	Lowest within-group cholesterol, HDL, LDL, glucose, triglycerides, hsCRP, SBP
Class 2: Mostly obese with higher insulin, hsCRP, and BP	900 (20.5%)	40 (1.2%)	**Insulin approximately twice the cohort average;** cholesterols below the mean; glucose, triglycerides, BP, waist circumference, BMI above the mean	860 (82.7%)	**Insulin approximately twice the cohort average;** average glucose, triglycerides, cholesterol; hsCRP, SBP above mean; waist circumference, BMI in top decile
Class 3: Largely non-obese with higher cholesterols	1519 (34.6%)	1491 (44.4%)	**Cholesterols above the means;** average glucose, triglycerides; hsCRP, BP, waist circumference and BMI below the mean	28 (2.7%)	**Cholesterols, triglycerides, BMI above the means**; average glucose, hsCRP, waist circumference; BP, insulin below the mean

Table S3. Hypertension Stages 2-7 Years After Delivery by Index Pregnancy APOs* and GDM Subgroups, Among nuMoM2b-HHS Participants†‡

Hypertension 2-7 Years after Delivery	All participants (N=4471)	Index Pregnancy APOs and GDM (not mutually exclusive)					
		No APO or GDM (N=3285)	Any APO or GDM (N=1104)	HDP (N=608)	PTB (N=386)	SGA (N=186)	GDM (N=191)
Hypertension categories, n (%)							
Normotensive: SBP < 120 AND DBP < 80	3172 (71.2)	2477 (75.6)	**656 (59.6)**	**319 (52.7)**	**233 (60.4)**	**120 (64.9)**	**111 (58.1)**
Elevated: 120 ≤ SBP < 130 AND 80 < DBP	293 (6.6)	206 (6.3)	**83 (7.5)**	**49 (8.1)**	**21 (5.4)**	**17 (9.2)**	**12 (6.3)**
Stage I: 130 ≤ SBP < 140 OR 80 ≤ DBP < 90	669 (15.0)	437 (13.3)	**219 (19.9)**	**138 (22.8)**	**67 (17.4)**	**34 (18.4)**	**31 (16.2)**
Stage II: 140 ≤ SBP OR 90 ≤ DBP, or antihypertensive medication	324 (7.3)	156 (4.8)	**142 (12.9)**	**99 (16.4)**	**65 (16.8)**	**14 (7.6)**	**37 (19.4)**
N with data	4458	3276	1100	605	386	185	191

* APO defined as: any hypertensive disorder of pregnancy, any preterm birth, or small for gestational age.

† Abbreviations: APO=adverse pregnancy outcome; GDM=gestational diabetes; n=number in category; N=sample size; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDP=hypertensive disorders of pregnancy; PTB=preterm birth; SGA=small for gestational age.

‡ Statistically significant comparisons of "No APO or GDM" versus each of the APO/GDM subgroups ($p < 0.05$) are indicated by boldface text. A single global statistical test of the association of hypertension status with each APO/GDM subgroup was performed, with "No APO or GDM" considered the reference group.

Table S4. Association of Early Pregnancy CVD Risk Factors with Hypertension* 2-7 Years After Delivery Among nuMoM2b-HHS Participants, Adjusted for Baseline Age, Race, Insurance, Smoking, BMI, SBP, and DBP: Sensitivity Analysis Comparing Upper to Lower Quartiles of Risk Factors†

Early Pregnancy CVD Risk Factors	Hypertension RR (95% CI)
BMI, upper vs. lower quartile‡	2.14 (1.75, 2.61)
Total cholesterol, upper vs. lower quartile	1.03 (0.99, 1.07)
HDL-C, upper vs. lower quartile	0.98 (0.97, 1.01)
LDL-C, upper vs. lower quartile	1.01 (0.99, 1.03)
Glucose, upper vs. lower quartile	1.04 (0.95, 1.13)
Insulin, upper vs. lower quartile	1.15 (0.96, 1.37)
hsCRP, upper vs. lower quartile	1.24 (1.04, 1.48)
Triglycerides, upper vs. lower quartile	1.35 (1.14, 1.60)
Systolic blood pressure, upper vs. lower quartile‡	7.74 (2.82, 21.27)
Diastolic blood pressure, upper vs. lower quartile‡	42.95 (15.91, 115.97)
Diet quality score, upper vs. lower quartile	0.83 (0.68, 1.02)
Physical activity, upper vs. lower quartile	0.64 (0.41, 1.01)

* Hypertension 2-7 years after index pregnancy defined per ACC guidelines (Whelton et. al., 2017).

† Abbreviations: CVD=cardiovascular disease; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; CI=confidence interval.

‡ The model with this characteristic does not include this characteristic again as an adjustment covariate.

Table S5. Association of Early Pregnancy CVD Risk Factors with Hypertension* Stages 2-7 Years After Delivery Among nuMoM2b-HHS Participants, Adjusted for Baseline Age, Race, Insurance, Smoking, BMI, SBP, and DBP†‡

Early Pregnancy CVD Risk Factors	Elevated BP OR (95% CI)	Stage I HTN OR (95% CI)	Stage II HTN OR (95% CI)
BMI, per kg/m^2§	0.99 (0.97, 1.01)	1.04 (1.03, 1.06)	1.06 (1.05, 1.08)
Total cholesterol, per 0.3 mmol/L	0.99 (0.95, 1.03)	1.03 (1.00, 1.05)^	0.99 (0.96, 1.03)
HDL-C, per 0.1 mmol/L	0.96 (0.92, 1.01)	1.00 (0.97, 1.03)	0.93 (0.89, 0.97)
LDL-C, per 0.3 mmol/L	0.99 (0.95, 1.04)	1.02 (0.99, 1.06)	1.00 (0.95, 1.05)
Glucose, per 0.6 mmol/L	0.92 (0.84, 1.01)	1.02 (0.96, 1.08)	1.09 (1.02, 1.17)
Insulin, per doubling in value‖	1.01 (0.92, 1.11)	1.04 (0.97, 1.11)	1.09 (0.99, 1.20)
hsCRP, per doubling in value‖	0.99 (0.91, 1.09)	1.09 (1.02, 1.17)	1.04 (0.95, 1.15)
Triglycerides, per doubling in value‖	1.16 (0.91, 1.49)	1.35 (1.14, 1.61)	1.63 (1.27, 2.08)
Systolic blood pressure, per 5 mmHg§	1.14 (1.06, 1.23)	1.11 (1.05, 1.17)	1.20 (1.12, 1.29)
Diastolic blood pressure, per 5 mmHg§	1.07 (0.98, 1.17)	1.24 (1.17, 1.33)	1.31 (1.20, 1.43)
Diet quality score, per 1 unit	0.98 (0.94, 1.01)	0.99 (0.96, 1.02)	0.98 (0.95, 1.02)
Physical activity, per 3 hours per week of moderate or vigorous activity	0.97 (0.85, 1.10)	0.88 (0.79, 0.98)	0.95 (0.83, 1.08)

ASCVD risk score, per 1% increase in estimated risk#	1.00 (0.93, 1.07)	1.00 (0.96, 1.05)	1.01 (0.95, 1.06)
≥ 5% estimated risk#	1.62 (0.56, 4.67)	1.05 (0.43, 2.56)	0.76 (0.18, 3.20)
Latent profile estimated class (vs. class 1)			
Class 2: mostly obese with higher insulin, hsCRP, and BP	1.23 (0.66, 2.31)	1.04 (0.71, 1.52)	1.11 (0.63, 1.95)
Class 3: largely non-obese with higher cholesterols	1.01 (0.75, 1.36)	1.14 (0.86, 1.52)	1.13 (0.78, 1.62)
Class 4: total and LDL cholesterols in the top decile	0.70 (0.35, 1.42)	1.28 (0.89, 1.85)	1.35 (0.77, 2.39)

* Hypertension 2-7 years after index pregnancy defined per ACC guidelines (Whelton et. al., 2017).

† Abbreviations: CVD=cardiovascular disease; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; ASCVD=atherosclerotic cardiovascular disease; BP= blood pressure; HTN=hypertension; OR=odds ratio; CI=confidence interval.

‡ When the confidence interval shown includes 1.00 due to rounding, the ^ symbol indicates that the precise CI excludes 1 (i.e., is statistically significant at $p < 0.05$).

§ The model with this characteristic does not include this characteristic again as an adjustment covariate.

‖ This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Odds ratios for log-transformed quantities are interpreted on the multiplicative scale.

The models with ASCVD risk score are not adjusted for the covariates of age, race, smoking, insurance, BMI, SBP, and DBP, as several of these covariates are included in the calculation of the risk score.

Table S6. Mediation Analysis of Early Pregnancy CVD Risk Factors and Index Pregnancy Hypertensive Disorders of Pregnancy (HDP) on Hypertension* 2-7 Years Later Among nuMoM2b-HHS Participants, Adjusted for Age, Race, Insurance, and Smoking (Baseline)†‡

Early Pregnancy CVD Risk Factors	Total Excess Relative Risk (95% CI)	Components of Excess Relative Risk (95% CI) Associating Early Pregnancy Risk Factor with Hypertension 2-7 Years After Delivery‖				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with HDP	Interaction & Mediation with HDP	Pure Indirect Effect	
BMI, per kg/m^2	0.06 (0.05, 0.07)	0.05 (0.04, 0.06)	< 0.01#	< 0.01#	0.01 (0.00, 0.01)^	0.07 (0.02, 0.12)
Glucose, per 0.6 mmol/L	0.08 (0.04, 0.12)	0.08 (0.04, 0.11)	0.00 (-0.02, 0.01)	< 0.01#	0.01 (0.00, 0.01)^	0.04 (-0.15, 0.23)
hsCRP, per doubling in value§	0.20 (0.15, 0.25)	0.19 (0.13, 0.24)	0.00 (-0.02, 0.02)	< 0.01#	0.02 (0.01, 0.03)	0.07 (-0.05, 0.18)
Triglycerides, per doubling in value§	0.53 (0.34, 0.71)	0.44 (0.26, 0.63)	0.02 (-0.04, 0.08)	0.01 (-0.03, 0.05)	0.05 (0.03, 0.08)	0.16 (-0.02, 0.34)
Systolic blood pressure, per 5 mmHg	0.21 (0.17, 0.24)	0.19 (0.16, 0.23)	0.00 (-0.01, 0.01)	< 0.01#	0.02 (0.01, 0.02)	0.06 (0.00, 0.13)^
Diastolic blood pressure, per 5 mmHg	0.30 (0.25, 0.35)	0.29 (0.24, 0.34)	-0.01 (-0.02, 0.01)	< 0.01#	0.02 (0.01, 0.03)	0.04 (-0.02, 0.10)
Latent profile estimated class (vs. class 1)						
Class 2: mostly obese with higher insulin, hsCRP, and BP	1.44 (1.00, 1.89)	1.32 (0.88, 1.76)	0.01 (-0.07, 0.08)	0.01 (-0.10, 0.12)	0.11 (0.03, 0.19)	0.09 (-0.02, 0.19)
Class 3: largely non-obese with higher cholesterols	0.33 (0.07, 0.59)	0.28 (0.03, 0.53)	0.02 (-0.06, 0.09)	0.01 (-0.02, 0.03)	0.03 (0.00, 0.05)	0.14 (-0.15, 0.44)
Class 4: total and LDL cholesterols in the top decile	0.92 (0.42, 1.42)	0.84 (0.32, 1.36)	0.00 (-0.11, 0.11)	0.00 (-0.12, 0.12)	0.08 (0.01, 0.15)	0.09 (-0.14, 0.32)

* Hypertension 2-7 years after index pregnancy defined as 130 ≤ systolic blood pressure OR 80 ≤ diastolic blood pressure, or self-report of antihypertensive medication use.

† Abbreviations: CVD=cardiovascular disease; HDP=hypertensive disorders of pregnancy; BMI=body mass index; hsCRP=high sensitivity C-reactive protein; RR=relative risk; CI=confidence interval.

‡ When the confidence interval shown includes 1.00 due to rounding, the ^ symbol indicates that the precise CI excludes 1 (i.e., is statistically significant at $p < 0.05$).

§ This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Relative risks for log-transformed quantities are interpreted on the multiplicative scale.

‖ Components defined as: controlled direct effect (effect attributable to CVD risk factor only, without mediation or interaction), interaction only (effect attributable to interaction only), interaction & mediation (mediated interaction; effect due attributable to both mediation and interaction), pure indirect effect (effect attributable to mediation only), portion eliminated (% effect attributable to either mediation or interaction).

The designated components are estimated to contribute less than 0.01 to the excess relative risk and have confidence interval bounds of similar magnitude. For these negligible effects, no confidence intervals are provided.

Table S7. Mediation Analysis of Early Pregnancy CVD Risk Factors and Index Pregnancy Preterm Birth (PTB) on Hypertension* 2-7 Years Later Among nuMoM2b-HHS Participants, Adjusted for Age, Race, Insurance, and Smoking (Baseline)†‡

Early Pregnancy CVD Risk Factors	Total Excess Relative Risk (95% CI)	Components of Excess Relative Risk (95% CI) Associating Early Pregnancy Risk Factor with Hypertension 2-7 Years After Delivery‖				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with PTB	Interaction & Mediation with PTB	Pure Indirect Effect	
BMI, per kg/m^2	0.05 (0.05, 0.06)	0.05 (0.04, 0.06)	< 0.01#	< 0.01#	< 0.01#	0.03 (0.00, 0.07)
Glucose, per 0.6 mmol/L	0.08 (0.04, 0.12)	0.08 (0.03, 0.12)	0.00 (-0.01, 0.01)	< 0.01#	0.00 (0.00, 0.01)^	0.03 (-0.06, 0.13)
hsCRP, per doubling in value§	0.20 (0.15, 0.25)	0.20 (0.14, 0.25)	0.00 (-0.01, 0.02)	< 0.01#	< 0.01#	0.02 (-0.05, 0.10)
Triglycerides, per doubling in value§	0.55 (0.36, 0.74)	0.55 (0.36, 0.74)	-0.01 (-0.05, 0.03)	0.00 (-0.01, 0.01)	0.01 (0.00, 0.02)	0.00 (-0.09, 0.09)
Systolic blood pressure, per 5 mmHg	0.20 (0.17, 0.24)	0.20 (0.16, 0.23)	0.00 (0.00, 0.01)	< 0.01#	0.00 (0.00, 0.01)^	0.03 (-0.01, 0.06)
Diastolic blood pressure, per 5 mmHg	0.30 (0.25, 0.34)	0.29 (0.24, 0.34)	0.00 (-0.01, 0.01)	< 0.01#	0.00 (0.00, 0.01)^	0.02 (-0.02, 0.05)
Latent profile estimated class (vs. class 1)						
Class 2: mostly obese with higher insulin, hsCRP, and BP	1.46 (1.02, 1.91)	1.38 (0.93, 1.82)	0.05 (-0.02, 0.13)	0.02 (-0.01, 0.06)	0.01 (-0.01, 0.03)	0.06 (-0.01, 0.13)
Class 3: largely non-obese with higher cholesterols	0.33 (0.07, 0.59)	0.33 (0.07, 0.59)	0.01 (-0.06, 0.07)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.01 (-0.19, 0.20)
Class 4: total and LDL cholesterols in the top decile	0.94 (0.44, 1.44)	0.92 (0.41, 1.44)	0.02 (-0.11, 0.15)	0.00 (-0.02, 0.02)	0.00 (-0.01, 0.01)	0.02 (-0.11, 0.15)

* Hypertension 2-7 years after index pregnancy defined as 130 ≤ systolic blood pressure OR 80 ≤ diastolic blood pressure, or self-report of antihypertensive medication use.

† Abbreviations: CVD=cardiovascular disease; PTB=preterm birth; BMI=body mass index; hsCRP=high sensitivity C-reactive protein; RR=relative risk; CI=confidence interval.

‡ When the confidence interval shown includes 1.00 due to rounding, the ^ symbol indicates that the precise CI excludes 1 (i.e., is statistically significant at $p < 0.05$).

§ This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Relative risks for log-transformed quantities are interpreted on the multiplicative scale.

‖ Components defined as: controlled direct effect (effect attributable to CVD risk factor only, without mediation or interaction), interaction only (effect attributable to interaction only), interaction & mediation (mediated interaction; effect due attributable to both mediation and interaction), pure indirect effect (effect attributable to mediation only), portion eliminated (% effect attributable to either mediation or interaction).

The designated components are estimated to contribute less than 0.01 to the excess relative risk and have confidence interval bounds of similar magnitude. For these negligible effects, no confidence intervals are provided.

Table S8. Mediation Analysis of Early Pregnancy CVD Risk Factors and Index Pregnancy Small for Gestational Age (SGA) on Hypertension* 2-7 Years Later Among nuMoM2b-HHS Participants, Adjusted for Age, Race, Insurance, and Smoking (Baseline)†‡

Early Pregnancy CVD Risk Factors	Total Excess Relative Risk (95% CI)	Components of Excess Relative Risk (95% CI) Associating Early Pregnancy Risk Factor with Hypertension 2-7 Years After Delivery‖				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with SGA	Interaction & Mediation with SGA	Pure Indirect Effect	
BMI, per kg/m^2	0.05 (0.05, 0.06)	0.05 (0.05, 0.06)	< 0.01#	< 0.01#	< 0.01#	-0.01 (-0.04, 0.01)
Glucose, per 0.6 mmol/L	0.08 (0.04, 0.11)	0.08 (0.04, 0.11)	0.00 (-0.01, 0.00)	< 0.01#	< 0.01#	-0.01 (-0.08, 0.05)
hsCRP, per doubling in value§	0.21 (0.15, 0.26)	0.21 (0.16, 0.26)	0.00 (-0.01, 0.00)	< 0.01#	< 0.01#	-0.02 (-0.05, 0.01)
Triglycerides, per doubling in value§	0.55 (0.36, 0.73)	0.54 (0.35, 0.72)	0.01 (-0.02, 0.04)	< 0.01#	< 0.01#	0.02 (-0.04, 0.08)
Systolic blood pressure, per 5 mmHg	0.20 (0.17, 0.24)	0.21 (0.17, 0.24)	0.00 (-0.01, 0.00)	< 0.01#	< 0.01#	0.00 (-0.03, 0.02)
Diastolic blood pressure, per 5 mmHg	0.29 (0.25, 0.34)	0.29 (0.25, 0.34)	0.00 (-0.01, 0.01)	< 0.01#	< 0.01#	0.00 (-0.03, 0.02)
Latent profile estimated class (vs. class 1)						
Class 2: mostly obese with higher insulin, hsCRP, and BP	1.48 (1.03, 1.92)	1.48 (1.02, 1.93)	0.00 (-0.05, 0.05)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.00)	0.00 (-0.03, 0.03)
Class 3: largely non-obese with higher cholesterols	0.33 (0.07, 0.59)	0.31 (0.05, 0.58)	0.01 (-0.03, 0.05)	0.00 (-0.01, 0.01)	< 0.01#	0.04 (-0.09, 0.17)
Class 4: total and LDL cholesterols in the top decile	0.96 (0.45, 1.47)	0.96 (0.45, 1.47)	0.00 (-0.09, 0.08)	0.00 (-0.03, 0.03)	0.00 (-0.01, 0.01)	0.00 (-0.07, 0.06)

* Hypertension 2-7 years after index pregnancy defined as 130 ≤ systolic blood pressure OR 80 ≤ diastolic blood pressure, or self-report of antihypertensive medication use.

† Abbreviations: CVD=cardiovascular disease; SGA=small for gestational age; BMI=body mass index; hsCRP=high sensitivity C-reactive protein; RR=relative risk; CI=confidence interval.

‡ When the confidence interval shown includes 1.00 due to rounding, the ^ symbol indicates that the precise CI excludes 1 (i.e., is statistically significant at $p < 0.05$).

§ This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Relative risks for log-transformed quantities are interpreted on the multiplicative scale.

‖ Components defined as: controlled direct effect (effect attributable to CVD risk factor only, without mediation or interaction), interaction only (effect attributable to interaction only), interaction & mediation (mediated interaction; effect due attributable to both mediation and interaction), pure indirect effect (effect attributable to mediation only), portion eliminated (% effect attributable to either mediation or interaction).

The designated components are estimated to contribute less than 0.01 to the excess relative risk and have confidence interval bounds of similar magnitude. For these negligible effects, no confidence intervals are provided.

Table S9. Mediation Analysis of Early Pregnancy CVD Risk Factors and Index Pregnancy Gestational Diabetes (GDM) on Hypertension* 2-7 Years Later Among nuMoM2b-HHS Participants, Adjusted for Age, Race, Insurance, and Smoking (Baseline)†‡

Early Pregnancy CVD Risk Factors	Total Excess Relative Risk (95% CI)	Components of Excess Relative Risk (95% CI) Associating Early Pregnancy Risk Factor with Hypertension 2-7 Years After Delivery‖				Proportion of Total Eliminated (95% CI)
		Controlled Direct Effect	Interaction with GDM	Interaction & Mediation with GDM	Pure Indirect Effect	
BMI, per kg/m^2	0.05 (0.05, 0.06)	0.05 (0.04, 0.06)	< 0.01#	< 0.01#	< 0.01#	0.01 (-0.01, 0.03)
Glucose, per 0.6 mmol/L	0.08 (0.03, 0.12)	0.07 (0.02, 0.12)	< 0.01#	< 0.01#	0.00 (0.00, 0.01)^	0.05 (-0.03, 0.13)
hsCRP, per doubling in value§	0.20 (0.15, 0.26)	0.20 (0.14, 0.25)	0.00 (-0.01, 0.01)	< 0.01#	0.01 (0.00, 0.01)	0.02 (-0.03, 0.07)
Triglycerides, per doubling in value§	0.54 (0.35, 0.73)	0.53 (0.34, 0.73)	0.00 (-0.02, 0.02)	0.00 (-0.03, 0.03)	0.02 (0.00, 0.04)	0.02 (-0.06, 0.11)
Systolic blood pressure, per 5 mmHg	0.21 (0.17, 0.24)	0.21 (0.17, 0.24)	0.00 (-0.01, 0.00)	< 0.01#	0.00 (0.00, 0.01)^	0.00 (-0.02, 0.03)
Diastolic blood pressure, per 5 mmHg	0.29 (0.25, 0.34)	0.29 (0.24, 0.34)	0.00 (-0.01, 0.01)	< 0.01#	0.00 (0.00, 0.01)	0.01 (-0.01, 0.04)
Latent profile estimated class (vs. class 1)						
Class 2: mostly obese with higher insulin, hsCRP, and BP	1.47 (1.02, 1.93)	1.40 (0.95, 1.86)	0.02 (-0.01, 0.04)	0.05 (-0.04, 0.13)	0.01 (-0.05, 0.07)	0.05 (-0.01, 0.11)
Class 3: largely non-obese with higher cholesterols	0.33 (0.07, 0.59)	0.33 (0.06, 0.59)	0.00 (-0.03, 0.03)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	0.01 (-0.10, 0.11)
Class 4: total and LDL cholesterols in the top decile	0.94 (0.43, 1.45)	0.97 (0.44, 1.50)	-0.01 (-0.04, 0.02)	-0.02 (-0.10, 0.05)	0.01 (-0.04, 0.05)	-0.03 (-0.12, 0.06)

* Hypertension 2-7 years after index pregnancy defined as 130 ≤ systolic blood pressure OR 80 ≤ diastolic blood pressure, or self-report of antihypertensive medication use.

† Abbreviations: CVD=cardiovascular disease; GDM=gestational diabetes; BMI=body mass index; hsCRP=high sensitivity C-reactive protein; RR=relative risk; CI=confidence interval.

‡ When the confidence interval shown includes 1.00 due to rounding, the ^ symbol indicates that the precise CI excludes 1 (i.e., is statistically significant at $p < 0.05$).

§ This characteristic is included in statistical models after a $\log_2$ (logarithm with base 2) transformation. Relative risks for log-transformed quantities are interpreted on the multiplicative scale.

‖ Components defined as: controlled direct effect (effect attributable to CVD risk factor only, without mediation or interaction), interaction only (effect attributable to interaction only), interaction & mediation (mediated interaction; effect due attributable to both mediation and interaction), pure indirect effect (effect attributable to mediation only), portion eliminated (% effect attributable to either mediation or interaction).

The designated components are estimated to contribute less than 0.01 to the excess relative risk and have confidence interval bounds of similar magnitude. For these negligible effects, no confidence intervals are provided.

Class 4: Total and LDL cholesterols in the top decile	304 (6.9%)	199 (5.9%)	**Cholesterol, LDL in the top decile;** HDL, triglycerides in upper quartile	105 (10.1%)	**Cholesterol, LDL in the top decile;** triglycerides, hsCRP, BP, waist circumference, BMI above the mean; average glucose; insulin below the mean