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ORIGINAL RESEARCH

Life Course Changes in Cardiometabolic Risk Factors Associated With Preterm Delivery: The 30-Year CARDIA Study

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BACKGROUND: Women who deliver preterm infants (<37 weeks) have excess cardiovascular risk; however, it is unclear whether the unfavorable changes in the cardiometabolic profile associated with preterm delivery initiate before, during, or after childbearing.

METHODS AND RESULTS: We identified 1306 women (51% Black) with births between baseline (1985–1986) and year 30 in the CARDIA (Coronary Artery Risk Development in Young Adults) study. We compared life course changes in blood pressure, body mass index, waist circumference, and lipids in women with preterm deliveries (n=318) with those with all term deliveries (n=988), using piecewise linear mixed-effects models. Specifically, we evaluated group differences in rates of change before and after the childbearing period and change in level across the childbearing period. After adjusting for the covariates, women with preterm deliveries had a higher change in diastolic blood pressure across the childbearing period than those with all term deliveries (1.59 versus −0.73 mm Hg, $P<0.01$); the rates of change did not differ by group, both prechildbearing and postchildbearing. Women with preterm deliveries had a larger body mass index increase across the childbearing period (1.66 versus 1.22 kg/m^2, $P=0.03$) compared with those with all term deliveries, followed by a steeper increase after the childbearing period (0.22 versus 0.17 kg/m^2 per year, $P=0.02$).

CONCLUSIONS: Preterm delivery was associated with unfavorable patterns of change in diastolic blood pressure and adiposity that originate during the childbearing years and persist or exacerbate later in life. These adverse changes may contribute to the elevated cardiovascular risk among women with preterm delivery.

Key Words: cardiovascular disease risk factors ■ life course ■ longitudinal cohort study ■ preterm delivery ■ women

Preterm delivery is a common adverse pregnancy outcome, affecting 10% of births in the United States. It is the single largest cause of infant morbidity and mortality.[1] Preterm delivery may also reflect maternal vascular and metabolic maladaptation to pregnancy, potentially unmasking women at high risk for subsequent cardiovascular diseases (CVDs).[2,3]

Accumulating population-based epidemiological studies have indicated that preterm delivery is associated with a 2- to 4-fold increase in future maternal CVD.[4–11] However, the mechanisms responsible for this association are not well understood. Recent studies relating cardiometabolic risk factors to preterm delivery raise the possibility that preterm delivery and maternal CVD are linked through shared risk factors.[12–17] Women with unfavorable blood lipids, blood pressure (BP), and body fat before pregnancy have been found to have an excess risk of subsequent preterm delivery, suggesting that adverse cardiometabolic alterations may precede pregnancy.[12–14] Preterm delivery has also been associated with a worse cardiometabolic profile and higher incidence of metabolic syndrome many years

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CLINICAL PERSPECTIVE

What Is New?

- The present study is the first to investigate the life course patterns of cardiometabolic risk factors among women with preterm deliveries in comparison with women with term deliveries, preserving the temporality of the risk factor changes in relation to each woman's childbearing years.
- Women with preterm deliveries had greater increases in diastolic blood pressure and adiposity across the childbearing period and gained weight more rapidly after the childbearing period compared with women with term deliveries.
- In contrast, the patterns of cardiometabolic risk factors before childbearing did not differ by subsequent preterm delivery status.

What Are the Clinical Implications?

- For women who delivered preterm infants, the adverse vascular and metabolic alterations induced during the childbearing years may contribute to their higher cardiovascular risk later in life and thus warrant closer clinical attention.
- Prevention efforts during the reproductive years may be beneficial for women with prior preterm delivery to improve their lifelong health.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	cardiovascular disease
DBP	diastolic blood pressure
HUNT	Trøndelag Health Study
SBP	systolic blood pressure

after pregnancy.[15–17] However, previous studies either examined risk factor levels at a single point in time or evaluated longitudinal risk factor trajectories without regard to the timing of the pregnancy relative to the measurement of the risk factors. Little is known about the temporal nature of this ongoing dynamic process, including whether the unfavorable patterns of change in risk factors associated with preterm delivery initiate before, during, or after childbearing.

In the present study, we sought to gain a fuller understanding of the critical time periods contributing to the elevated cardiometabolic risk associated with preterm delivery. We evaluated longitudinal changes in cardiometabolic risk factors among parous women in a US cohort followed for up to 30 years and investigated the rates of change before pregnancy, the changes from before to after childbearing, and the rates of change after the childbearing years associated with preterm delivery. We hypothesized that women with preterm delivery would exhibit unfavorable patterns of cardiometabolic risk factors across the life course.

METHODS

Study Population

The CARDIA (Coronary Artery Risk Development in Young Adults) study is a multicenter, prospective, observational study of young Black and White adults designed to examine the development of CVD risk. A total of 5115 participants (2787 women; 52% Black) aged 18 to 30 years were enrolled from 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) in 1985 to 1986. After the baseline examination, participants underwent 8 follow-up examinations at years 2, 5, 7, 10, 15, 20, 25, and 30; the retention rates in the surviving cohort were 90%, 86%, 81%, 79%, 74%, 72%, 72%, and 71%, respectively. Details of the study design and characteristics of the cohort have been previously described.[18–20] The study was approved by institutional review boards at each participating study center and written informed consent was obtained from all participants. The data that support the findings of this study are available from the CARDIA study (https://www.cardia.dopm.uab.edu/) upon reasonable request.

Of the 2787 female participants, 1392 had ≥1 births after enrollment at baseline (Figure 1). We excluded 29 women who did not provide complete information about date of delivery and gestational week at delivery for each birth and 57 women who delivered twins or other multiples, leaving 1306 women in our study population. Compared with the 1481 women who were not included in this analysis (1395 of whom were excluded because of no postbaseline births), women who were included were more likely to be of White race and younger at baseline. Data from specific examinations were additionally excluded if they occurred during the pregnancy or lactation period, within 6 months postpartum, or between consecutive deliveries. In total, 8467 measurements evaluated either before the first postbaseline birth or after the last birth were available for analyses.

Pregnancies and Preterm Status

At each examination, women reported whether they were currently pregnant or breastfeeding and how many pregnancies they experienced since the last CARDIA study visit, along with date of delivery, gestational age

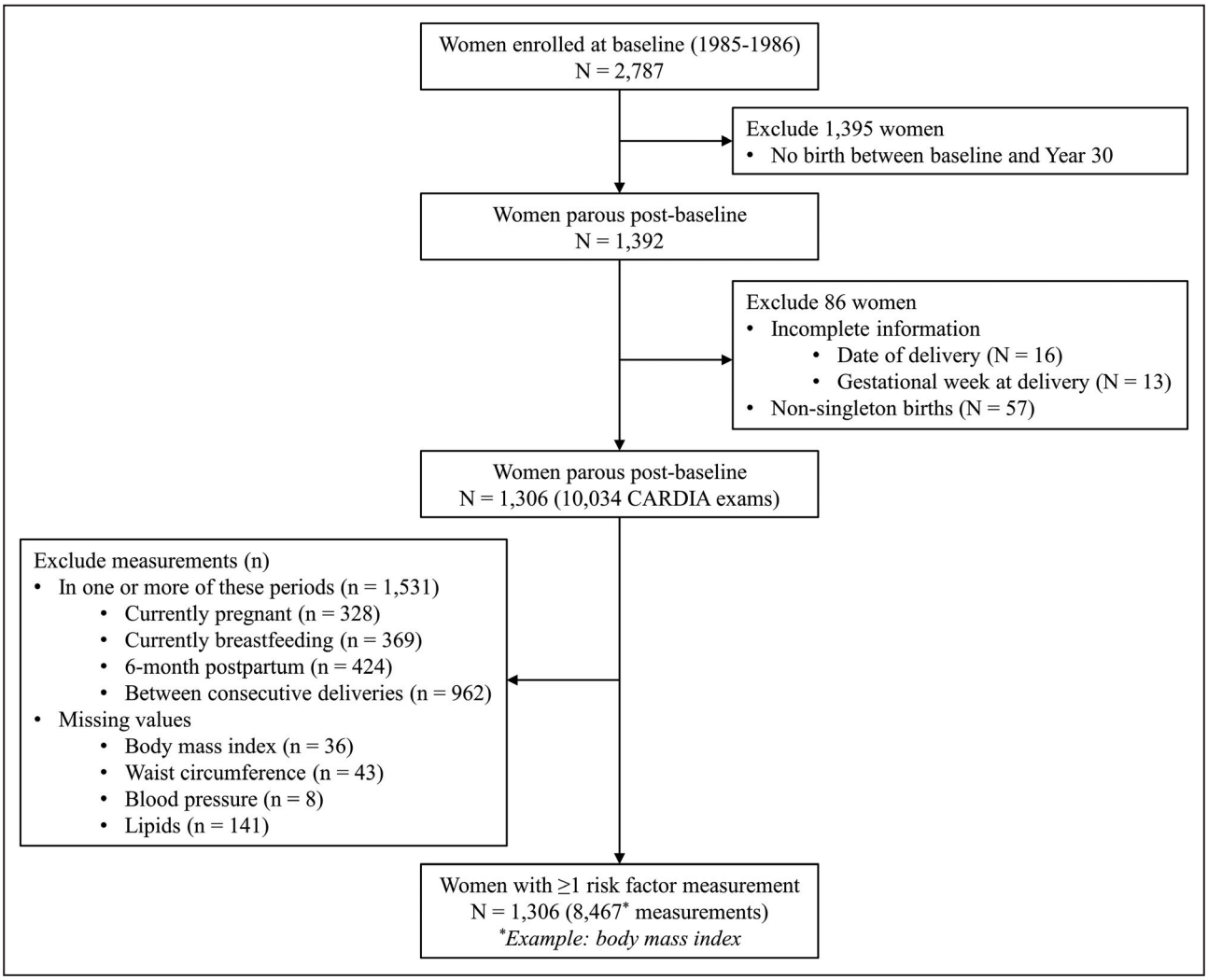

Figure 1. Flow diagram of analytical sample selection, the CARDIA (Coronary Artery Risk Development in Young Adults) study, 1985–2016.

at delivery, multifetal gestation, infant birth weight, and complications developed during pregnancy (ie, hypertensive disorders and gestational diabetes mellitus). Women also completed a pregnancy history form at 30 years postbaseline and reported perinatal outcomes for all pregnancies lasting at least 20 weeks' gestation. Conception date for each birth was computed using the date of delivery and gestational age at delivery. Women were classified as having ≥1 preterm deliveries (20 to <37 weeks) or having all term deliveries (≥37 weeks) based on all births that occurred after the CARDIA study baseline examination. A previous CARDIA validation study compared self-reported gestational age at delivery with medical records among 221 women.[14] The sensitivity for maternal report of ever delivering preterm was 84% (16/19), and the specificity was 89% (170/192). The reporting of early preterm delivery (20 to <34 weeks; 100% sensitivity and 99% specificity) was more precise as compared with late preterm delivery (34 to <37 weeks; 67% sensitivity and 89% specificity).

Women were asked whether they had developed hypertensive disorders of pregnancy (preeclampsia or gestational hypertension). When validated against medical records, hypertensive disorders of pregnancy were overreported (43% positive predictive value).[21] However, high negative predictive value (93%) indicated that pregnancies in our study with no report of hypertensive disorders of pregnancy were largely normotensive. Self-report of gestational diabetes mellitus had excellent sensitivity (100%) and specificity (92%) when compared with medical records.[22]

BP, Anthropometry, and Blood Lipid Measurements

BP, anthropometry, and blood lipids were measured at baseline and each follow-up examination. Before

any blood draw, physical examination, or interview, seated resting BPs were measured 3 times using a Hawksley random zero sphygmomanometer through year 15, or a standard automated BP monitor (Omron model HEM907XL, Omron Healthcare) starting at year 20. Omron-measured BPs were calibrated to sphygmomanometric values to avoid bias using data from a comparability study conducted at year 20.[21] Systolic BP (SBP) and diastolic BP (DBP) values used for analysis were the average of the second and third readings. Height and weight were measured by trained technicians; body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Waist circumference was measured at the level midway between the iliac crest and the bottom of the ribcage.[23]

Participants were asked to fast for ≥12 hours before each examination, and time since last meal was recorded to verify the fasting status before blood draw. Plasma total cholesterol, high-density lipoprotein cholesterol, and triglycerides were assayed in the Northwest Lipid Research Laboratories at University of Washington using enzymatic methods that were consistent across all follow-up examinations and standardized to the Centers for Disease Control and Prevention reference methods.24 Low-density lipoprotein cholesterol was calculated indirectly using the Friedewald equation, except when triglyceride levels were >400 mg/dL (n=20).[25]

Sociodemographic, Lifestyle, and Health Factors

At each CARDIA study visit, women reported their race/ethnicity, highest level of education, smoking habits, use of oral contraceptives, antihypertensive medication, lipid-lowering medication, menopausal status, family medical histories, and physical activity. These data were collected via self- or interviewer-administered study questionnaires. Smoking status was self-reported at each examination and categorized as smoking status (ever versus never). A total physical activity score was derived based on frequency and intensity of physical activities in the past year before each visit. Diet information was queried by interviewer-administered semiquantitative food frequency questionnaire at baseline, year 7, and year 20. A priori diet quality score was calculated by summing category scores 0 to 4 for beneficial foods and scores 4 to 0 in reverse order for adverse foods, which were predefined based on hypothesized health effects.[26] For the current analysis, we averaged the diet quality scores from 3 examinations, to represent each participant's overall dietary habits. Hypertension was defined as SBP/DBP ≥140/90 mm Hg or taking antihypertensive medication. Diabetes mellitus was defined as fasting glucose level ≥126 mg/dL or 2-hour glucose tolerance test ≥200 mg/dL or glycated hemoglobin level ≥6.5% or taking diabetic medications. We also calculated homeostasis model assessment of insulin resistance as [fasting glucose (mg/dL) × fasting insulin (μU/mL)] / 405. Metabolic syndrome was identified based on the Third Report of the Adult Treatment Panel.[27]

Statistical Analysis

We divided the follow-up time into 3 periods for each woman: (1) prechildbearing period during the CARDIA study (abbreviated as "prechildbearing period"), from CARDIA study baseline to the conception of the first postbaseline birth; (2) childbearing period, the intervening time period from conception of the first postbaseline birth to 6 months after the last birth; and (3) postchildbearing period, from 6 months after the last postbaseline birth to the end of follow-up. Baseline characteristics of women with any preterm delivery and with all term deliveries were compared using *t* test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables. Similarly, we compared between-group characteristics during CARDIA study follow-up at: (1) the start of the childbearing period, (2) the end of the childbearing period, and (3) the end of postchildbearing follow-up.

We used piecewise linear mixed-effects models to examine cardiometabolic risk factor changes in the prechildbearing and postchildbearing periods.[28] We included an indicator for adjacent periods (prechildbearing versus postchildbearing), allowing a change in level across the childbearing period (ie, change in level from prechildbearing to postchildbearing) to be evaluated, and included 2 time variables to estimate the mean annual rate of change (ie, slope) in each period, prechildbearing and postchildbearing. There was insufficient data to estimate the rate of change during the childbearing years because of the short time and the limited number of observations (<1 measurement per participant). Random effects were time and intercept, modeling random slope in each period and intercept at the end of the prechildbearing period, respectively. This model assumed that each risk factor increased or decreased linearly with time but allowed the rate of change in each period to be different. Also, the model did not necessarily require that "lines" in the prechildbearing and postchildbearing periods would meet at the same point, which was biologically plausible given that gestation and lactation could induce fluctuations or shifts in cardiometabolic risk factors. This technique was able to accommodate within-individual correlation of repeated measurements and account for unbalanced

data structure with unequal numbers of measurements per individual and unequal spaced follow-up examinations.[28]

Longitudinal, repeated risk factor measurements of SBP, DBP, BMI, waist circumference, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were evaluated in separate models. Triglycerides were transformed to the log scale because of the highly skewed distribution. To assess the differences between women who had any preterm delivery and women who had all term deliveries, we added corresponding multiplicative terms for interactions of preterm status (the group with all term deliveries as the referent) with the indicator for periods (prechildbearing versus postchildbearing) and each time variable. All models were adjusted for race, age at the first postbaseline birth, length of the childbearing period, educational level at baseline, and average diet score as time-invariant covariates. Parity, use of antihypertensive (for analyses of BPs) or lipid-lowering (for analyses of lipids) medications, smoking status (ever/never), physical activity level, and menopause status were included as time-varying covariates. Since BMI likely impacts other cardiometabolic risk factors, we also accounted for time-varying BMI when modeling BPs and lipids. These models were then created to compare the development of risk factors in women who had early preterm delivery or late preterm delivery with those who had all term deliveries. We also stratified our analyses by race to assess the identified associations with preterm delivery in Black and White women.

Several sensitivity analyses were conducted. To examine the robustness of findings in normotensive preterm deliveries, analyses were run adjusting for self-reported hypertensive disorders of pregnancy (ever/never) and were repeated after excluding 282 women reporting hypertensive disorders of pregnancy. To assess the sensitivity of our results to potential misclassification resulted from unavailable prebaseline data for women who had births before baseline, we restricted our analyses to 876 women who were nulliparous at baseline. Additionally, we limited our analyses to 1244 women with at least 2 repeated risk factor measurements to assess the impact of women with only a single measurement. For all analyses, $P<0.05$ (2-tailed) were considered statistically significant. All data were analyzed using SAS 9.4 (SAS Institute Inc.).

RESULTS

Our study included 1306 women (51% Black) with a delivery after the CARDIA study baseline examination. Of these, 318 (24%) had ≥1 preterm deliveries and 988 (76%) had all term deliveries. There was an average of 6.5 measurements per participant: 2.4±1.5 in the prechildbearing period and 4.1±1.9 in the postchildbearing period. The average lengths of the prechildbearing, childbearing, and postchildbearing periods during the CARDIA study were 5.3±4.4, 4.0±3.7, and 18.4±7.2 years, respectively.

At baseline, women who had ≥1 preterm deliveries were younger, more likely to be Black, less likely to achieve more than a high school education, and had lower levels of physical activity and poorer diet quality as compared with women with all term deliveries (Table 1). Baseline cardiometabolic risk factors did not differ according to subsequent preterm delivery status, except for lower triglycerides among women with preterm delivery (57.0 mg/dL versus 59.0 mg/dL, $P=0.03$). As expected, women who had preterm delivery were more likely to experience hypertensive disorders of pregnancy. They also had more births after baseline along with a longer childbearing period (4.9 years versus 3.7 years, $P<0.01$).

Women with preterm deliveries were more likely to develop hypertension after childbearing (13.0% versus 8.7% [$P=0.02$] at the end of the childbearing period and 44.6% versus 33.4% [$P<0.01$] at the end of follow-up) (Table S1) compared with women with term deliveries. Results were similar for metabolic syndrome, and, by the end of follow-up, women with preterm versus term deliveries had higher BP, BMI, and waist circumference.

BP Patterns

We then evaluated the patterns of BP changes across the life course relative to childbearing during the CARDIA study. Estimated trajectories of BP over time are shown in Figure 2. Women with preterm deliveries had a similar pattern of DBP in prechildbearing years after CARDIA baseline compared with those with term deliveries, accounting for covariates (Tables 2 and 3; Tables S2 and S3 for models without BMI as a covariate). DBP increased across the childbearing period in women with preterm deliveries, but decreased in those with term deliveries (change in level from prechildbearing to postchildbearing, +1.59 mm Hg versus −0.73 mm Hg; $P<0.01$). After the childbearing period, DBP increased similarly among women with preterm versus term deliveries. The results were similar for SBP, but the change across the childbearing period was not significantly different in women with preterm versus term deliveries (change in level, −0.51 mm Hg versus −1.81 mm Hg; $P=0.09$). When assessing the severity of preterm deliveries, DBP increased across the childbearing period in women with both early and late preterm deliveries (change in level, early preterm +1.36 mm Hg and late

Table 1. Maternal Characteristics by Women With Any Preterm Delivery and Women With All Term Deliveries

Characteristics	Preterm n=318	Term n=988	*P* Value*
Baseline			
Age (SD), y	23.6 (3.7)	24.1 (3.7)	0.03
Black, No. (%)	215 (67.6)	446 (45.1)	<0.01
Center, No. (%)			
Birmingham, AL	94 (29.6)	214 (21.7)	0.03
Chicago, IL	68 (21.4)	252 (25.5)	
Minneapolis, MN	70 (22.0)	216 (21.9)	
Oakland, CA	86 (27.0)	306 (31.0)	
Education, No. (%)			
High school or less	145 (45.6)	325 (32.9)	<0.01
Some college	161 (50.6)	560 (56.7)	
College education	12 (3.8)	103 (10.4)	
Nulliparous, No. (%)	206 (64.8)	670 (67.8)	0.32
Physical activity level (IQR), median exercise units	253.5 (286.0)	304.0 (330.0)	<0.01*
A priori diet quality score, mean (SD)	61.2 (13.1)	64.6 (13.7)	<0.01
Ever smoking, No. (%)	117 (36.8)	356 (36.0)	0.81
BMI classification, No. (%)			
Normal	217 (68.5)	722 (73.2)	0.20
Overweight	56 (17.7)	158 (16.0)	
Obese	44 (13.9)	106 (10.8)	
BMI (SD), kg/m^2	24.1 (5.1)	23.6 (5.1)	0.18
Waist circumference (SD), cm	72.8 (10.6)	72.4 (10.2)	0.61
SBP (SD), mm Hg	106.6 (9.1)	105.5 (9.3)	0.06
DBP (SD), mm Hg	65.9 (9.0)	65.9 (8.7)	0.96
Plasma lipids (SD), mg/dL			
Total cholesterol	177.8 (34.4)	176.4 (31.9)	0.49
HDL cholesterol	56.9 (13.6)	55.4 (12.4)	0.06
LDL cholesterol	108.6 (32.0)	107.8 (29.6)	0.68
Triglycerides, median (IQR), mg/dL	57.0 (33.0)	59.0 (33.0)	0.03*
Fasting serum glucose (SD), mg/dL	79.9 (8.5)	79.4 (8.1)	0.35
Fasting serum insulin (IQR), median μU/mL	9.9 (7.0)	8.8 (6.5)	0.07*
HOMA-IR, median (IQR)	1.8 (1.7)	1.7 (1.3)	0.10*
Metabolic syndrome, No. (%)	5 (1.6)	12 (1.2)	0.58
Hypertension, No. (%)	4 (1.3)	11 (1.1)	0.77
Diabetes mellitus, No. (%)	5 (1.6)	7 (0.7)	0.18
Reproductive characteristics			
Age at menarche (SD), y	12.7 (1.5)	12.7 (1.6)	0.62
No. of postbaseline births, No. (%)			
1	121 (38.1)	469 (47.5)	<0.01
2	120 (37.7)	375 (38.0)	
>2	77 (24.2)	144 (14.6)	
Length of the childbearing period (SD), y	4.9 (4.6)	3.7 (3.2)	<0.01
Preterm delivery earlier than 34 weeks, No. (%)	107 (33.7)	…	…
Hypertensive disorders of pregnancy, No. (%)	93 (29.3)	189 (19.1)	<0.01
Gestational diabetes mellitus, No. (%)	38 (12.0)	111 (11.2)	0.73

BMI indicated body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

P values were based on *t* test or Wilcoxon rank sum test (*) for continuous variables and chi-square test or Fisher exact test for categorical variables.

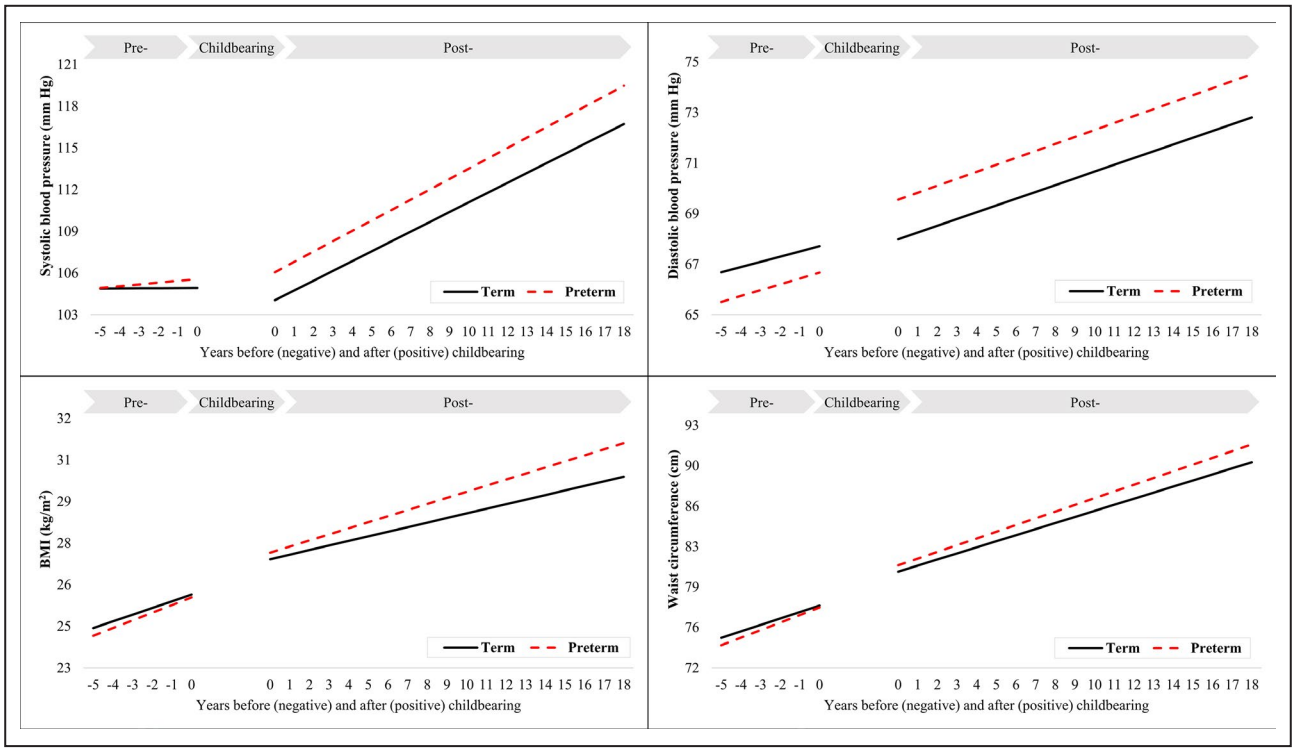

Figure 2. Estimated trajectories of cardiometabolic risk factors across the life course, independent of race, age at the first postbaseline birth, parity, and the childbearing years.
BMI indicated body mass index; and SBP, systolic blood pressure.

preterm +1.64 mm Hg), compared with a decrease of 0.72 mm Hg in women with all term deliveries (P=0.05 and P<0.01, respectively) (Tables S4 and S5). Other BP patterns were not different according to the severity of preterm deliveries.

BMI, Waist Circumference, and Lipid Patterns

Women with preterm and term deliveries had similar BMI and waist circumference patterns in prechildbearing

Table 2. Adjusted Mean Cardiometabolic Risk Factors Before the Childbearing Period and Changes in Level Across the Childbearing Period in Women With Any Preterm Delivery Relative to Women With All Term Deliveries

	Estimated Level Before the Childbearing Period†					Change in Level Across the Childbearing Period‡				
	Preterm	Term	Preterm-Term			Preterm	Term	Preterm-Term		
	Mean	Mean	Mean Difference	SE	*P* Value	Mean	Mean	Mean Difference	SE	*P* Value
SBP, mm Hg	105.32	104.55	0.77	0.79	0.33	−0.51	−1.81	1.30	0.78	0.09
DBP, mm Hg	67.10	67.78	−0.68	0.67	0.31	1.59	−0.73	2.32	0.64	<0.01
BMI, kg/m²	25.31	25.49	−0.18	0.43	0.67	1.66	1.22	0.44	0.20	0.03
WC, cm	77.02	77.42	−0.40	0.90	0.66	3.85	2.98	0.87	0.47	0.06
Total cholesterol, mg/dL	167.06	165.40	1.65	2.25	0.46	−6.91	−8.16	1.24	1.75	0.48
HDL cholesterol, mg/dL	58.44	56.99	1.45	0.89	0.11	−3.43	−3.36	−0.07	0.69	0.92
LDL cholesterol, mg/dL	95.22	94.90	0.32	2.07	0.88	−3.61	−5.77	2.16	1.55	0.16
Triglycerides, ln mg/dL*	4.097	4.125	−0.028	0.032	0.38	0.001	0.029	−0.028	0.028	0.31

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; and SE, standard error.

Models adjusted for time-invariant covariates including race, age at the first postbaseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid-lowering medication use, postmenopausal, and body mass index (BMI; except when modeling BMI and waist circumference [WC] because of collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

†Intercept estimates at the conception of the first postbaseline birth.

‡Change in level from the end of the prechildbearing period to the start of the postchildbearing period.

Table 3. Adjusted Annual Rates of Change (ie, Slopes) in Cardiometabolic Risk Factors Before and After the Childbearing Period in Women With Any Preterm Delivery Relative to Women With All Term Deliveries

	Prechildbearing Period					Postchildbearing Period				
	Preterm	Term	Preterm-Term			Preterm	Term	Preterm-Term		
	Mean	Mean	Mean Difference	SE	*P* Value	Mean	Mean	Mean Difference	SE	*P* Value
SBP, mm Hg	0.06	−0.05	0.11	0.11	0.31	0.71	0.68	0.03	0.06	0.60
DBP, mm Hg	0.15	0.12	0.03	0.10	0.75	0.23	0.23	−0.01	0.04	0.89
BMI, kg/m^2	0.28	0.24	0.04	0.04	0.39	0.22	0.17	0.05	0.02	0.02
WC, cm	0.65	0.56	0.09	0.10	0.36	0.56	0.52	0.04	0.04	0.30
Total cholesterol, mg/dL	−0.26	−0.04	−0.22	0.31	0.47	1.15	1.22	−0.06	0.11	0.57
HDL cholesterol, mg/dL	0.29	0.34	−0.06	0.12	0.63	0.70	0.72	−0.02	0.05	0.72
LDL cholesterol, mg/dL	−0.72	−0.43	−0.29	0.28	0.31	0.32	0.37	−0.05	0.10	0.59
Triglycerides, ln mg/dL*	0.001	−0.002	0.003	0.005	0.57	0.012	0.010	0.002	0.002	0.18

DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; and SE, standard error.

Models adjusted for time-invariant covariates including race, age at the first postbaseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid-lowering medication use, postmenopausal, and body mass index (BMI; except when modeling BMI and waist circumference [WC] because of collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

years after CARDIA baseline. In contrast, women with preterm deliveries had a larger increase in BMI across the childbearing period than women with term deliveries (change in level, +1.66 kg/m^2 versus +1.22 kg/m^2; *P*=0.03) and tended to gain more waist circumference (change in level, +3.85 cm versus +2.98 cm; *P*=0.06), adjusted for covariates. Rates of gain in BMI after the childbearing period were also more rapid in women with preterm compared with term deliveries (slope, 0.22 kg/m^2 per year versus 0.17 kg/m^2 per year; *P*=0.02). Postchildbearing rates of gain (slope) in waist circumference were not different according to preterm delivery status. The increase in BMI and waist circumference across the childbearing period appeared to be larger in women with early preterm deliveries compared with women with term deliveries (change in level, +2.30 kg/m^2 versus +1.23 kg/m^2 for BMI [*P*<0.01]; change in level, +5.16 cm versus +3.01 cm for waist circumference [*P*=0.01]). Gain in BMI after the childbearing period was more rapid in women with late preterm deliveries (slope, 0.23 kg/m^2 per year versus 0.17 kg/m^2 per year; *P*=0.02). The patterns of lipids across time were similar in women with and without preterm deliveries.

Adjusting for self-reported hypertensive disorders of pregnancy did not impact any of the cardiometabolic differences detected in these models (Tables S6 and S7). After excluding 282 women with hypertensive disorders of pregnancy, the adverse changes in BP and adiposity among women with preterm delivery across the childbearing period persisted, as did the more rapid postchildbearing BMI gain among women with preterm deliveries, compared with women with term deliveries.

Across all 3 periods, Black women had higher SBP and DBP, BMI, and waist circumference, but lower lipids compared with White women. When we stratified preterm delivery analyses by race, DBP increased in both Black and White women with preterm deliveries across the childbearing period, as compared with those with all term deliveries (Black women: change in level, +1.90 mm Hg versus +0.05 mm Hg [*P*=0.04]; White women: change in level, +0.55 mm Hg versus −1.62 mm Hg [*P*=0.02] (Figure S1). Higher rate of gain in BMI after childbearing in the preterm versus the term group was detected among Black women (slope, 0.24 kg/m^2 per year versus 0.18 kg/m^2 per year; *P*=0.03), but not White women (slope, 0.17 kg/m^2 per year versus 0.18 kg/m^2 per year; *P*=0.91).

Our findings were similar after restricting our analyses to 876 women who were nulliparous at baseline (Figure S2; Tables S8 and S9). The results also persisted among women with ≥2 repeated measurements.

DISCUSSION

Compared with women with term deliveries, those with preterm deliveries had greater increases in DBP and adiposity across the childbearing period and gained weight more rapidly after the childbearing period. In contrast, the patterns of cardiometabolic risk factor changes in prechildbearing years during the CARDIA study did not differ by subsequent preterm delivery status. Importantly, our study investigated 30-year life course patterns of cardiometabolic risk factors in women with preterm delivery relative to each women's childbearing years. Our data suggest that pregnancy resulting in a preterm birth may exert an adverse impact on metabolism and vascular function. We further

report that an unfavorable cardiometabolic profile appears following childbearing and persists or exacerbates later in life in women who delivered preterm infants.

Our findings are consistent with previous studies showing that women with preterm delivery have elevated BP during the reproductive years.[16,29] Our study further demonstrates that higher BP among women with preterm delivery is detectable after but not before childbearing. This "jump" in BP across the childbearing years in women with preterm delivery persists in the postchildbearing years, but the rate of increase appears to be age-related because the slope was not different by preterm delivery status. DBP is relatively sensitive to the physiologic changes of pregnancy, decreasing in the first half of pregnancy and increasing back to prepregnancy levels in the last trimester.[30,31] Previously, an excessive rise in BP from early to late pregnancy was associated with preterm delivery, possibly related to uteroplacental vascular lesions.[32] The increase in DBP across the childbearing period among women with preterm deliveries (a difference of +2.32 mm Hg relative to women with term deliveries) may reflect an impaired capability of the pregnancy-specific adaptive DBP response that persists after delivery. Interestingly, HUNT (Trøndelag Health Study) in Norway found a difference of +1.72 mm Hg in DBP change from prefirst to postfirst pregnancy when comparing women with preeclampsia with those with a normotensive pregnancy.[33] The difference we detected was independent of self-reported hypertensive disorders of pregnancy, and was of similar magnitude following both early and late preterm deliveries. Taken together, our data suggest that an aberrant BP response to the expected pregnancy-induced drop in systemic vascular resistance may not be specific to hypertensive disorders of pregnancy, but may also occur in other adverse pregnancy outcomes such as normotensive preterm delivery.

This upward shift in DBP following childbearing may have a clinically significant impact on the health of women with preterm delivery. Cook et al,[34] based on published observational studies and randomized trials, reported that a 2-mm Hg reduction in mean DBP could lead to an estimated 17% reduction in prevalent hypertension, as well as a 6% decrease in the risk of coronary heart disease and a 15% decrease in the risk of stroke. Importantly, the DBP increase associated with preterm delivery initiated in our data as early as the first examination after childbearing, which on average occurred 3 years after the last birth and remained higher later in life. Aligned with evidence that above-optimal BP in young adulthood is related to adverse cardiac structure and function,[35] as well as excess CVD risk,[36,37] our findings suggest that women with preterm delivery may have accelerated progression to CVD, and this warrants further study.

Unlike DBP, the unfavorable adiposity pattern detected in women with preterm delivery originated during the childbearing years and was exacerbated over time after childbearing. The modestly steeper BMI gain may signal a lasting metabolic change related to previous preterm delivery independent of sociodemographics and lifestyle factors for which we accounted. As a surrogate for central adiposity, increase in waist circumference also tended to be greater across the childbearing period in women with preterm delivery; however, the rate of increase after the childbearing period was not accelerated. This suggests that the difference in central adiposity may be more related to short-term effects of pregnancy, such as gestational weight gain or retention.

Our data demonstrate parallel patterns of cardiometabolic risk factors before term and preterm deliveries during the CARDIA study. It is possible that, at a relatively young age, the differences in metabolic and vascular function before term and preterm deliveries might be too minimal to detect or have yet to appear. Our finding is consistent with a previous CARDIA study that subsequent preterm delivery risk was not related to prepregnancy low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides measured at baseline; however, our study did not reflect the association of preterm delivery with both low and high prepregnancy total cholesterol reported in that study.[14] Given the heterogenous clinical presentations and pathogeneses (ie, spontaneous or medically indicated, inflammation- or infection-related), such U-shaped associations might imply distinct mechanisms or pathways leading to preterm delivery, but we were not able to make these distinctions in our data.

Strengths of our study include the longitudinal design with serial cardiometabolic risk factor measurements before and after pregnancies and high retention rates during the 30-year follow-up period. Also, the biracial cohort enabled us to examine race-specific patterns, which is important given the race disparities and overall higher rates of preterm delivery in the United States than other high-income countries. Most current evidence about the life course trajectories of CVD risk factors in relation to parity and pregnancy complications is based on European cohorts with predominantly White populations.[33,38,39] Although hampered by sample size, we found that the unfavorable changes in DBP during the childbearing years associated with preterm delivery was detected in both White and Black women. The adverse postchildbearing BMI trend was only present in Black women. Future work is needed to understand how these patterns may contribute to the excess CVD risk in Black women as compared with White women.

Some limitations in this study are worthy of mention. First, pregnancy-related data were based on maternal

recall, which may lead to misclassification of preterm delivery and hypertensive disorders of pregnancy. Although the report of preterm delivery was overall accurate, especially for early preterm delivery, our results may have been biased toward the null by the nondifferential misclassification that occurred in late preterm delivery. As with other epidemiologic studies of women, hypertensive disorders of pregnancy were overreported in the CARDIA study; however, high specificity and negative predictive value meant that women left in the sensitivity analysis after excluding those who reported hypertensive disorders of pregnancy were largely normotensive.[21] Our results should be replicated in cohorts with clinical records of pregnancy characteristics. Second, in the CARDIA study, self-reported pregnancy outcomes were missing or incomplete for some women who had a first birth before baseline; therefore, we were unable to consider births that occurred before baseline and some women identified as having all term deliveries in our study could have previously had a preterm delivery. However, our study findings persisted when restricted to 876 women who were nulliparous at CARDIA study baseline, and thus the possible misclassification introduced by the unavailable prebaseline data likely had only modest effects on our estimates. Similarly, the life-course trajectories we studied began at an average age of 24 years (CARDIA study enrollment) and did not include earlier measures. In addition, multiple measurements between births were unavailable. We assessed the impact of the aggregated childbearing period cautiously, by including the duration of the childbearing years as covariate ($P<0.05$). The time interval of the childbearing period for the preterm versus term delivery groups was similar (difference 1.2 years) such that it would be unlikely to explain the differences in the risk factor changes. More data are needed in future prospective cohort studies to extend the life-course comparisons and incorporate data collected between births, during gestation, and during subsequent lactation. Additionally, although we accounted for the impact of lifestyle (eg, physical activity, diet, and smoking) on maternal cardiometabolic health, data regarding the health of children (eg, admission to the neonatal intensive care unit and disabilities) are unavailable, and therefore the role of caregiver burden warrants future investigation.

CONCLUSIONS

To our knowledge, this is the first study able to investigate the life-course trajectories of cardiometabolic risk factors preserving the temporality of the risk factor changes in relation to the childbearing years across the lifetime experience of preterm delivery. Preterm delivery is associated with increases in DBP and adiposity across the childbearing years, with further accelerated weight gain after childbearing. In contrast, BP and weight gain patterns were not different before childbearing according to subsequent preterm delivery status. For women who delivered preterm infants, the adverse vascular and metabolic alterations induced during the childbearing years may contribute to their higher cardiovascular risk later in life and thus warrant closer clinical attention. Our data support current guidelines for CVD prevention in women that recommend healthcare providers consider women's pregnancy history as a possible risk factor for CVD.[40] Our study also suggests that prevention efforts during the reproductive years may be beneficial for women with prior preterm delivery to improve their lifelong health.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S9
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Maternal characteristics during follow up by women with any preterm delivery and women with all term deliveries.

Characteristics	Start of the childbearing period			End of the childbearing period			End of post-childbearing follow up		
	Preterm N=306	**Term** N=956	P-value*	**Preterm** N=316	**Term** N=970	P-value*	**Preterm** N=316	**Term** N=970	P-value*
Age, year (SD)	26.6 (4.9)	28.1 (4.6)	<0.01	35.9 (6.7)	36.1 (6.4)	0.65	51.3 (6.7)	51.5 (7.5)	0.72
Years since baseline, year (SD)	3.1 (3.9)	4.0 (3.9)	<0.01	12.3 (7.0)	11.9 (6.6)	0.43	27.7 (5.5)	27.4 (6.1)	0.34
Physical activity level, median exercise units (IQR)	231.5 (279.0)	276.0 (308.0)	0.01*	216.0 (285.0)	206.0 (280.0)	0.52*	198.0 (274.0)	222.0 (292.0)	0.05*
Ever smoking, n (%)	127 (41.5)	394 (41.2)	0.93	139 (44.0)	418 (43.1)	0.78	147 (46.5)	427 (44.0)	0.44
BMI, kg/m^2 (SD)	25.0 (5.7)	24.7 (5.8)	0.40	28.2 (7.0)	27.4 (7.2)	0.08	31.4 (7.8)	29.9 (7.8)	<0.01
Waist circumference, cm (SD)	74.9 (11.6)	74.9 (12.1)	0.96	83.9 (14.6)	82.6 (14.5)	0.17	92.7 (15.8)	90.3 (16.7)	0.03
Systolic blood pressure, mm Hg (SD)	105.5 (10.4)	104.0 (9.8)	0.03	109.4 (15.7)	106.1 (12.9)	<0.01	120.7 (19.1)	116.7 (17.2)	<0.01
Diastolic blood pressure, mm Hg (SD)	65.9 (10.2)	66.7 (9.0)	0.23	71.1 (11.4)	68.4 (10.4)	<0.01	75.0 (11.9)	72.7 (11.8)	<0.01
Plasma lipids, mg/dL (SD)									
Total cholesterol	176.3 (33.1)	176.9 (31.1)	0.81	176.2 (35.5)	176.1 (31.3)	0.94	194.6 (38.3)	193.9 (35.5)	0.76
HDL-C	58.0 (13.5)	56.7 (13.3)	0.16	55.0 (14.7)	54.7 (13.8)	0.71	63.3 (18.8)	63.8 (19.2)	0.67
LDL-C	105.6 (30.0)	106.6 (29.5)	0.62	105.7 (32.4)	105.0 (28.9)	0.71	112.6 (34.6)	110.8 (31.3)	0.40
Triglycerides, median mg/dL (IQR)	55.5 (36.0)	60.0 (36.0)	0.04*	65.0 (44.0)	67.0 (47.0)	0.32*	80.5 (49.0)	80.0 (53.0)	0.82*
Metabolic syndrome, n (%)	10 (3.3)	29 (3.0)	0.85	44 (13.9)	95 (9.8)	0.05	127 (40.2)	314 (32.4)	0.01
Diabetes, n (%)	5 (1.6)	8 (0.8)	0.32	14 (4.4)	34 (3.5)	0.49	59 (18.7)	139 (14.3)	0.06
Hypertension, n (%)	8 (2.6)	29 (3.0)	0.85	41 (13.0)	84 (8.7)	0.02	141 (44.6)	324 (33.4)	<0.01
Postmenopausal, n (%)	-	-	-	13 (4.1)	29 (3.0)	0.36	181 (57.3)	545 (56.2)	0.73
Ever oral contraceptive use, n (%)	266 (86.9)	851 (89.0)	0.32	291 (92.1)	911 (93.7)	0.31	298 (94.3)	925 (95.4)	0.45
Ever lipid lowering medication use, n (%)	1 (0.3)	1 (0.1)	0.43	7 (2.2)	8 (0.8)	0.07	51 (16.1)	159 (16.4)	0.92
Ever antihypertensive medication use, n (%)	7 (2.3)	18 (1.9)	0.64	32 (10.1)	55 (5.7)	<0.01	120 (38.0)	263 (27.1)	<0.01

Start of the childbearing period was characterized at the exam immediately preceding the first post-baseline birth; **End of the childbearing period** was characterized at the exam immediately after the last post-baseline birth; **End of post-childbearing follow up** was characterized at the last exam in CARDIA study.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

P-values were based on t-test or Wilcoxon rank sum test (*) for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Table S2. Adjusted mean cardiometabolic risk factors prior to the childbearing period and changes in level across the childbearing period in women with any preterm delivery relative to women with all term deliveries; before adjusting for BMI.

	Estimated level prior to the childbearing period †					Change in level across the childbearing period ‡				
	Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
	Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	104.33	103.84	0.48	0.82	0.55	0.46	-1.12	1.58	0.79	0.05
Diastolic BP (mm Hg)	66.10	67.11	-1.01	0.69	0.14	2.62	0.00	2.63	0.65	<.0001
Total cholesterol (mg/dL)	166.11	164.75	1.35	2.25	0.55	-6.07	-7.60	1.53	1.75	0.38
HDL cholesterol (mg/dL)	60.87	59.09	1.78	0.94	0.06	-5.12	-4.58	-0.54	0.72	0.46
LDL cholesterol (mg/dL)	93.01	93.27	-0.26	2.10	3.85	-1.81	-4.54	2.73	1.57	0.08
Triglycerides (ln mg/dL) *	4.029	4.074	-0.044	0.033	0.021	0.056	0.067	-0.011	0.029	0.703

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal.

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

†Intercept estimates at the conception of the 1st post-baseline birth.

‡Change in level from the end of the pre-childbearing period to the start of the post-childbearing period.

Table S3. Adjusted annual rates of change (i.e., slopes) in cardiometabolic risk factors before and after the childbearing period in women with any preterm delivery relative to women with all term deliveries; before adjusting for BMI.

	Pre-childbearing period					Post-childbearing period				
	Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
	Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	0.13	0.03	0.10	0.11	0.36	0.81	0.76	0.05	0.06	0.43
Diastolic BP (mm Hg)	0.24	0.22	0.02	0.10	0.82	0.32	0.31	0.01	0.04	0.80
Total cholesterol (mg/dL)	-0.15	0.05	-0.21	0.31	0.50	1.24	1.29	-0.04	0.11	0.69
HDL cholesterol (mg/dL)	0.04	0.14	-0.10	0.12	0.42	0.50	0.55	-0.05	0.06	0.35
LDL cholesterol (mg/dL)	-0.50	-0.25	-0.25	0.29	0.38	0.51	0.53	-0.02	0.10	0.85
Triglycerides (ln mg/dL) *	0.005	0.003	0.003	0.005	0.610	0.018	0.015	0.003	0.002	0.061

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal.

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

Table S4. Adjusted mean cardiometabolic risk factors prior to the childbearing period and changes in level across the childbearing period in women who delivered early preterm or late preterm relative to women who delivered all term.

	Model	Estimated level prior to the childbearing period †					Change in level across the childbearing period ‡				
		Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
		Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	Early preterm	104.44	103.84	1.01	1.26	0.42	0.18	-1.78	1.97	1.27	0.12
	Late preterm	104.31	103.84	0.72	0.91	0.43	-0.87	-1.78	0.91	0.90	0.31
Diastolic BP (mm Hg)	Early preterm	66.85	67.77	-0.92	1.07	0.39	1.36	-0.72	2.08	1.05	0.05
	Late preterm	67.27	67.77	-0.51	0.77	0.51	1.64	-0.72	2.36	0.74	<0.01
BMI (kg/m^2)	Early preterm	25.33	25.48	-0.14	0.68	0.84	2.30	1.23	1.07	0.33	<0.01
	Late preterm	25.25	25.48	-0.22	0.50	0.66	1.41	1.23	0.18	0.23	0.43
WC (cm)	Early preterm	76.80	77.39	-0.59	1.42	0.68	5.16	3.01	2.15	0.78	0.01
	Late preterm	77.05	77.39	-0.35	1.04	0.74	3.32	3.01	0.31	0.54	0.57
Total cholesterol (mg/dL)	Early preterm	164.96	165.46	-0.50	3.59	0.89	-7.41	-8.20	0.80	2.89	0.78
	Late preterm	168.06	165.46	2.60	2.60	0.32	-6.69	-8.20	1.52	2.02	0.45
HDL cholesterol (mg/dL)	Early preterm	56.58	56.98	-0.40	1.43	0.78	-2.53	-3.33	0.80	1.14	0.48
	Late preterm	59.42	56.98	2.44	1.03	0.02	-3.91	-3.33	-0.58	0.80	0.47
LDL cholesterol (mg/dL)	Early preterm	95.17	94.97	0.20	3.30	0.95	-4.82	-5.85	1.03	2.57	0.69
	Late preterm	95.17	94.97	0.21	2.39	0.93	-3.01	-5.85	2.83	1.79	0.11
Triglycerides (ln mg/dL) *	Early preterm	4.085	4.124	-0.039	0.051	0.44	0.015	0.030	-0.015	0.046	0.75
	Late preterm	4.101	4.124	-0.023	0.037	0.52	-0.004	0.030	-0.033	0.032	0.30

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

†Intercept estimates at the conception of the 1st post-baseline birth.

‡Change in level from the end of the pre-childbearing period to the start of the post-childbearing period.

Table S5. Adjusted annual rates of change (i.e., slopes) in cardiometabolic risk factors before and after the childbearing period in women who delivered early preterm or late preterm relative to women who delivered all term.

	Model	Pre-childbearing period					Post-childbearing period				
		Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
		Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	Early preterm	0.20	-0.05	0.25	0.19	0.19	0.66	0.68	-0.02	0.09	0.80
	Late preterm	0.02	-0.05	0.07	0.12	0.56	0.74	0.68	0.06	0.07	0.42
Diastolic BP (mm Hg)	Early preterm	0.26	0.12	0.13	0.17	0.44	0.28	0.23	0.05	0.07	0.46
	Late preterm	0.12	0.12	0.00	0.11	1.00	0.20	0.23	-0.03	0.05	0.52
BMI (kg/m^2)	Early preterm	0.21	0.24	-0.03	0.07	0.66	0.20	0.17	0.03	0.03	0.39
	Late preterm	0.30	0.24	0.06	0.05	0.23	0.23	0.17	0.06	0.02	0.02
WC (cm)	Early preterm	0.54	0.56	-0.02	0.17	0.91	0.54	0.52	0.02	0.07	0.72
	Late preterm	0.69	0.56	0.13	0.12	0.27	0.57	0.52	0.05	0.05	0.29
Total cholesterol (mg/dL)	Early preterm	-0.56	-0.04	-0.52	0.54	0.34	1.22	1.22	0.01	0.18	0.98
	Late preterm	-0.15	-0.04	-0.11	0.35	0.76	1.12	1.22	-0.09	0.13	0.47
HDL cholesterol (mg/dL)	Early preterm	0.51	0.34	0.17	0.21	0.42	0.65	0.72	-0.07	0.08	0.42
	Late preterm	0.20	0.34	-0.14	0.14	0.29	0.72	0.72	0.00	0.06	0.94
LDL cholesterol (mg/dL)	Early preterm	-1.17	-0.43	-0.74	0.49	0.13	0.36	0.37	-0.01	0.17	0.95
	Late preterm	-0.54	-0.43	-0.11	0.32	0.74	0.30	0.37	-0.07	0.12	0.54
Triglycerides (ln mg/dL) *	Early preterm	-0.002	-0.002	-0.001	0.008	0.95	0.014	0.010	0.004	0.003	0.13
	Late preterm	0.002	-0.002	0.004	0.005	0.48	0.012	0.010	0.001	0.002	0.46

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

Table S6. Adjusted mean cardiometabolic risk factors prior to the childbearing period and changes in level across the childbearing period in women with any preterm delivery relative to women with all term deliveries, adjusting for HDP (ever/never) or excluding women with HDP (N=282).

		Estimated level prior to the childbearing period †					Change in level across the childbearing period ‡				
	Model	Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
		Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	Adjust for HDP	105.84	105.28	0.56	0.78	0.48	-0.50	-1.78	1.28	0.78	0.10
	Exclude HDP	102.34	103.03	-0.16	0.89	0.86	-0.49	-1.84	1.35	0.87	0.12
Diastolic BP (mm Hg)	Adjust for HDP	67.50	68.37	-0.87	0.66	0.19	1.61	-0.71	2.32	0.64	<0.01
	Exclude HDP	64.74	66.30	-1.56	0.75	0.04	2.29	-0.71	3.00	0.72	<0.01
BMI (kg/m^2)	Adjust for HDP	25.69	26.03	-0.33	0.43	0.44	1.65	1.21	0.44	0.20	0.03
	Exclude HDP	24.42	25.03	-0.62	0.47	0.19	1.92	1.16	0.76	0.23	<0.01
WC (cm)	Adjust for HDP	77.91	78.65	-0.74	0.89	0.41	3.82	2.97	0.85	0.47	0.07
	Exclude HDP	75.06	76.39	-1.33	0.99	0.18	4.34	2.97	1.37	0.53	0.01
Total cholesterol (mg/dL)	Adjust for HDP	167.22	165.63	1.58	2.25	0.48	-6.91	-8.15	1.24	1.75	0.48
	Exclude HDP	166.53	164.53	2.01	2.62	0.44	-7.26	-9.87	2.60	2.04	0.20
HDL cholesterol (mg/dL)	Adjust for HDP	58.41	56.95	1.46	0.90	0.10	-3.43	-3.36	-0.07	0.69	0.92
	Exclude HDP	59.17	57.94	1.24	1.07	0.25	-4.10	-3.48	-0.62	0.82	0.45
LDL cholesterol (mg/dL)	Adjust for HDP	95.46	95.25	0.21	2.07	0.92	-3.61	-5.77	2.16	1.55	0.16
	Exclude HDP	94.63	93.66	0.97	2.41	0.69	-3.34	-7.21	3.87	1.82	0.03
Triglycerides (ln mg/dL) *	Adjust for HDP	4.095	4.121	-0.027	0.032	0.40	0.001	0.029	-0.028	0.028	0.31
	Exclude HDP	4.076	4.120	-0.043	0.037	0.03	-0.005	0.014	-0.019	0.033	0.56

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

†Intercept estimates at the conception of the 1st post-baseline birth.

‡Change in level from the end of the pre-childbearing period to the start of the post-childbearing period.

Table S7. Adjusted annual rates of change (slopes) in cardiometabolic risk factors before and after the childbearing period in women with any preterm delivery relative to women with all term deliveries, adjusting for HDP (ever/never) or excluding women with HDP (N=282).

	Model	Pre-childbearing period					Post-childbearing period				
		Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
		Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	Adjust for HDP	0.08	-0.05	0.12	0.11	0.26	0.72	0.69	0.03	0.06	0.57
	Exclude HDP	-0.05	-0.06	0.02	0.13	0.89	0.76	0.72	0.04	0.07	0.56
Diastolic BP (mm Hg)	Adjust for HDP	0.16	0.13	0.04	0.10	0.72	0.23	0.24	0.00	0.04	0.94
	Exclude HDP	0.06	0.09	-0.04	0.12	0.75	0.21	0.25	-0.04	0.05	0.34
BMI (kg/m^2)	Adjust for HDP	0.28	0.24	0.04	0.04	0.38	0.22	0.17	0.05	0.02	0.02
	Exclude HDP	0.17	0.21	-0.04	0.05	0.39	0.22	0.17	0.05	0.02	0.03
WC (cm)	Adjust for HDP	0.66	0.56	0.10	0.10	0.35	0.56	0.52	0.04	0.04	0.29
	Exclude HDP	0.44	0.53	-0.09	0.12	0.46	0.57	0.52	0.05	0.05	0.28
Total cholesterol (mg/dL)	Adjust for HDP	-0.26	-0.04	-0.22	0.31	0.47	1.15	1.22	-0.06	0.11	0.58
	Exclude HDP	-0.29	0.06	-0.36	0.37	0.33	1.08	1.22	-0.14	0.13	0.27
HDL cholesterol (mg/dL)	Adjust for HDP	0.29	0.34	-0.06	0.12	0.63	0.70	0.72	-0.02	0.05	0.72
	Exclude HDP	0.33	0.38	-0.06	0.15	0.71	0.72	0.71	0.01	0.06	0.80
LDL cholesterol (mg/dL)	Adjust for HDP	-0.72	-0.43	-0.29	0.28	0.31	0.32	0.37	-0.05	0.10	0.60
	Exclude HDP	-0.81	-0.34	-0.47	0.34	0.16	0.27	0.38	-0.11	0.12	0.36
Triglycerides (ln mg/dL) *	Adjust for HDP	0.001	-0.002	0.003	0.005	0.57	0.012	0.010	0.002	0.002	0.18
	Exclude HDP	0.001	-0.002	0.002	0.006	0.67	0.011	0.010	0.001	0.002	0.74

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; HDP, hypertensive disorders of pregnancy; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

Table S8. Adjusted mean cardiometabolic risk factors prior to the childbearing period and changes in level across the childbearing period in women with any preterm delivery relative to women with all term deliveries; restricted to 876 women who were nulliparous at CARDIA baseline.

	Estimated level prior to the childbearing period †					Change in level across the childbearing period ‡				
	Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
	Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	106.15	104.73	1.42	0.92	0.12	-1.43	-2.40	0.98	0.92	0.29
Diastolic BP (mm Hg)	67.94	68.33	-0.38	0.79	0.63	0.04	-1.82	1.86	0.76	0.02
BMI (kg/m^2)	25.42	25.57	-0.15	0.51	0.76	1.35	0.98	0.37	0.23	0.11
WC (cm)	76.84	77.06	-0.21	1.03	0.84	4.32	3.12	1.21	0.54	0.03
Total cholesterol (mg/dL)	162.94	164.49	-1.55	2.72	0.57	-6.81	-7.85	1.04	2.16	0.63
HDL cholesterol (mg/dL)	59.63	59.51	0.13	1.10	0.91	-4.97	-6.07	1.11	0.87	0.20
LDL cholesterol (mg/dL)	90.72	92.84	-2.12	2.54	0.40	-3.48	-4.30	0.83	1.90	0.66
Triglycerides (ln mg/dL) *	4.046	4.051	-0.005	0.038	0.89	0.055	0.094	-0.028	0.028	0.26

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

†Intercept estimates at the conception of the 1st post-baseline birth.

‡Change in level from the end of the pre-childbearing period to the start of the post-childbearing period.

Table S9. Adjusted annual rates of change (slopes) in cardiometabolic risk factors before and after the childbearing period in women who delivered preterm relative to women who delivered term; restricted to 876 women who were nulliparous at CARDIA baseline.

	Pre-childbearing period					Post-childbearing period				
	Preterm	Term	Preterm - Term			Preterm	Term	Preterm - Term		
	Mean	Mean	Mean Diff	SE	P-value	Mean	Mean	Mean Diff	SE	P-value
Systolic BP (mm Hg)	0.12	-0.07	0.20	0.12	0.09	0.62	0.64	-0.02	0.07	0.75
Diastolic BP (mm Hg)	0.22	0.13	0.09	0.11	0.75	0.16	0.19	-0.03	0.05	0.57
BMI (kg/m^2)	0.28	0.23	0.05	0.05	0.29	0.24	0.18	0.06	0.03	0.01
WC (cm)	0.63	0.53	0.10	0.11	0.32	0.58	0.52	0.06	0.05	0.28
Total cholesterol (mg/dL)	-0.34	0.01	-0.36	0.34	0.47	1.22	1.25	-0.03	0.15	0.86
HDL cholesterol (mg/dL)	0.24	0.42	-0.18	0.13	0.17	0.75	0.82	-0.07	0.07	0.33
LDL cholesterol (mg/dL)	-0.76	-0.42	-0.34	0.30	0.27	0.41	0.34	0.06	0.13	0.63
Triglycerides (ln mg/dL) *	0.000	-0.003	0.003	0.005	0.58	0.010	0.009	0.001	0.002	0.64

BMI, body mass index; BP, blood pressure; Diff, difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SE, standard error; WC, waist circumference.

Models adjusted for time-invariant covariates including race, age at the 1st post-baseline birth, length of the childbearing period, baseline education level, average diet score, and time-varying covariates including parity, smoking status (ever/never), physical activity, ever antihypertensive or lipid lowering medication use, postmenopausal, and BMI (except when modelling BMI and WC due to collinearity).

*Estimated G matrix was not positive definite, but results were comparable when removing slopes from random effects.

Figure S1. Estimated trajectories of cardiometabolic risk factors across the life course, independent of age at the first post-baseline, parity, and the childbearing years; by race.

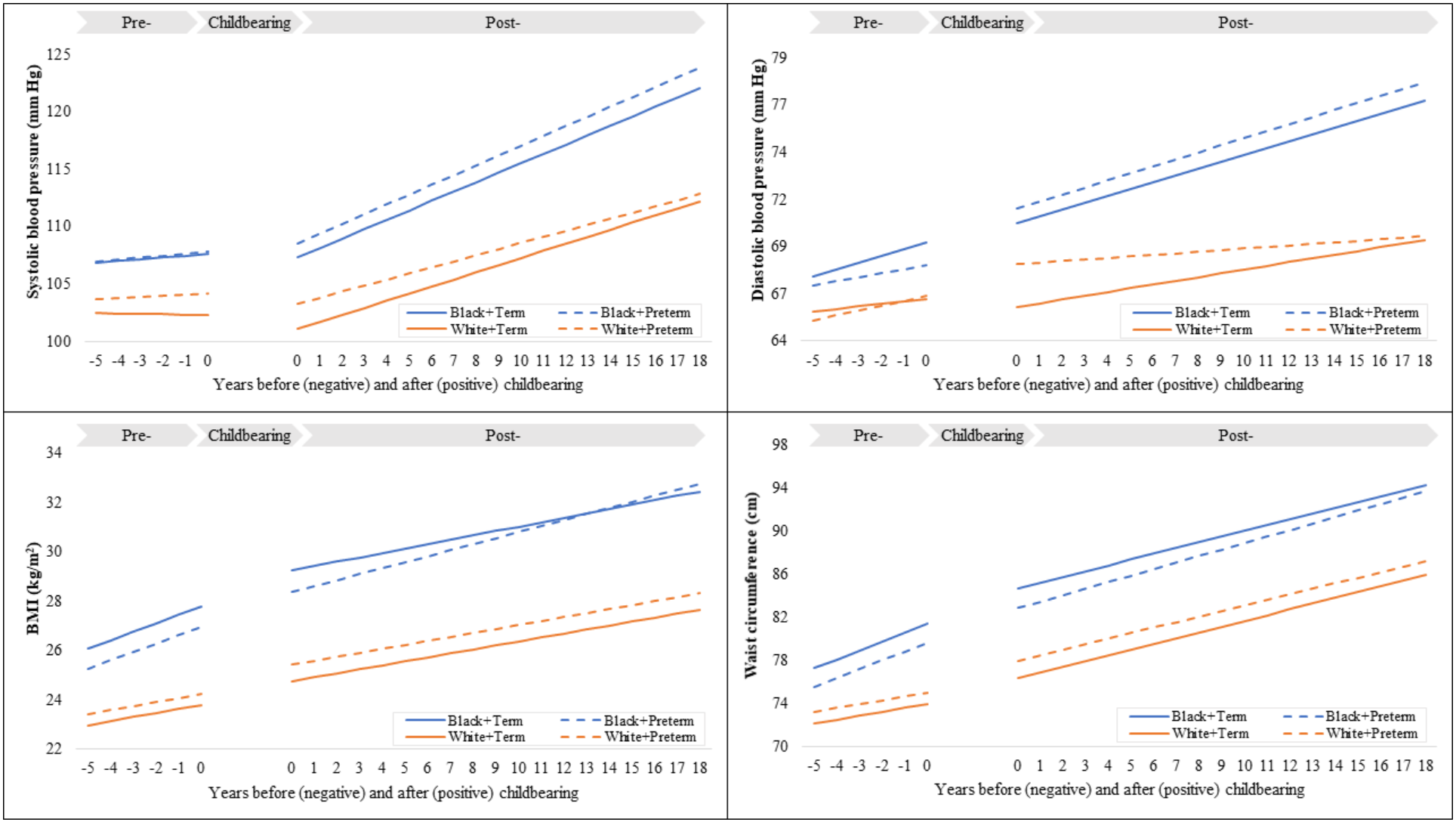

Figure S2. Estimated trajectories of cardiometabolic risk factors across the life course, independent of race, age at the first post-baseline, parity, and the childbearing years, among women who were nulliparous at baseline (N=876).