Preterm Delivery and Maternal Cardiovascular Disease

PRETERM DELIVERY AND

MATERNAL CARDIOVASCULAR DISEASE

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Abstract

Preterm delivery has been shown to be associated with a two-fold increased risk of maternal cardiovascular disease (CVD). However, it is unknown whether this risk persists after adjusting for pre-pregnancy lifestyle and CVD risk factors, including body mass index (BMI), smoking, and family history of CVD. Similarly, the extent to which this increased risk of CVD is accounted for by development of established CVD risk factors, and when these risk factors emerge, after a preterm delivery has not been assessed. Additionally, there is no evidence on the extent to which incorporating preterm delivery in CVD risk scores improves CVD risk prediction. Thus, we use the Nurses' Health Study II to investigate associations of preterm delivery with CVD events and risk factors and the utility of including preterm delivery in CVD risk prediction.

In Chapter 1, we evaluate the association between preterm delivery and CVD and the proportion accounted for by postpartum development of CVD risk factors. Women who delivered their first infant preterm had a 42% increased rate of CVD while those who delivered before 32 weeks experienced a doubling of risk. Only a modest proportion (13.1%) of the very preterm-CVD association was accounted for by development of traditional CVD risk factors.

In Chapter 2, we investigate associations between preterm delivery and CVD risk factors. Preterm delivery in first birth was associated with an 11% increased rate of chronic hypertension,

17% increased rate of type 2 diabetes mellitus, and 7% increased rate of hypercholesterolemia; this was generally stronger in women who delivered very preterm and within the first 10 years after delivery.

In Chapter 3, we test the utility of including preterm delivery and parity into CVD risk prediction models. Incorporation of preterm delivery and parity improved model fit in 10- and 20-year models, but only resulted in small improvements in discrimination and net reclassification of women with CVD events in 20-year models at age ≥30 years.

Together, these results suggest that preterm delivery may serve as a marker of women at high-risk of CVD that can be used to target prevention and screening efforts, particularly when women are young.

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Chapter 1 Preterm Delivery and Maternal Cardiovascular Disease in Young and Middle-Aged Adult Women

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ABSTRACT

Background: Preterm delivery has been shown to be associated with increased risk of cardiovascular disease (CVD), but it is unknown whether this risk remains after adjustment for pre-pregnancy lifestyle and CVD risk factors.

Methods: We examined the association between history of having delivered an infant preterm (<37 weeks) and CVD in 70,182 parous women in the Nurses' Health Study II. Multivariable Cox proportional hazards models were used to estimate hazards ratios (HRs) and 95% confidence intervals (CIs) for CVD events (myocardial infarction and stroke, n=949); we also adjusted for intermediates to determine the proportion of the association between preterm and CVD accounted for by postpartum development of CVD risk factors.

Results: After adjusting for age, race, parental education, and pre-pregnancy lifestyle and CVD risk factors, preterm delivery in the first pregnancy was associated with an increased risk of CVD (HR, 1.42; 95% CI, 1.16-1.72) compared to women with a term delivery (≥37 weeks) in the first pregnancy. When preterm delivery was split into moderate preterm (≥32 to <37 weeks) and very preterm (<32 weeks), the HRs were 1.22 (95% CI, 0.96-1.54) and 2.01 (95% CI, 1.47-2.75), respectively. The increased rate of CVD in the very preterm group persisted even among women whose first pregnancy was not complicated by hypertensive disorders of pregnancy (HR, 2.01; 95% CI, 1.38-2.93). In comparison with women with at least two pregnancies, all of which were delivered at term, women with a preterm first birth and at least one later preterm birth had a HR of CVD of 1.65 (95% CI, 1.20-2.28). The association between moderate preterm first birth and CVD was accounted for in part by the development of postpartum chronic hypertension,

hypercholesterolemia, type 2 diabetes mellitus, and changes in BMI (proportion accounted for, 14.5%; 95% CI, 4.0-41.1), as was the very preterm-CVD relationship (13.1%; 95% CI, 9.0-18.7).

Conclusion: Preterm delivery is independently predictive of CVD and may be useful for CVD prevention efforts. Because only a modest proportion of the preterm-CVD association was accounted for by development of conventional CVD risk factors, further research may identify additional pathways.

CLINICAL PERSPECTIVE

What Is New?

- Prior studies show an association between preterm delivery and risk of maternal cardiovascular disease (CVD), but these lack control for pre- and post-pregnancy factors that may explain both a higher risk of preterm and CVD.
- We report that women who deliver their first child preterm (<37 weeks) experience a 40% increased risk of CVD, while women with a very preterm first birth (<32 weeks) have double the risk, after adjustment for pre-pregnancy cardio-metabolic risk factors.
- Less than 25% of this increased risk is explained by hypertension, hypercholesterolemia, type 2 diabetes mellitus, and changes in BMI developing after the first birth.

What Are the Clinical Implications?

- Preterm delivery predicts CVD independent of traditional CVD risk factors in young and middle-aged women.
- This remains evident in pregnancies uncomplicated by preeclampsia and gestational hypertension.
- The American Heart Association has included preeclampsia and gestational diabetes as CVD risk factors.
- Our results suggest preterm delivery should be added to this list.

INTRODUCTION

Preterm delivery affects approximately 10% of pregnancies in the United States each year.[1] The 2011 effectiveness-based guidelines released by the American Heart Association for the prevention of cardiovascular disease (CVD) in women included hypertensive disorders of pregnancy (HDP; preeclampsia and gestational hypertension) and gestational diabetes as risk factors for CVD.[2] It has been hypothesized that pregnancy acts as a stress test that exposes subclinical CVD risk under the physiologic stress of pregnancy; specifically, that pregnancy complications, including preterm delivery, as well as HDP and gestational diabetes, provide a warning sign of future CVD risk that could be useful in identifying high-risk women early in adult life prior to the appearance of clinical risk factors.[3-5]

CVD remains the leading cause of morbidity and mortality in women.[6] A growing body of literature indicates that women who deliver preterm are at two-fold increased risk of future CVD events.[7-14] However, it is unknown whether this risk persists after accounting for pre-pregnancy lifestyle and CVD risk factors, because no studies examining this association have collected data on multiple lifestyle risk factors, including pre-pregnancy smoking, physical activity, diet, body mass index (BMI), and family history of CVD, which could explain both a higher risk of preterm delivery and CVD. Furthermore, no study has examined the extent to which the increased risk is accounted for by the development of CVD risk factors after a preterm delivery.

We evaluated the association between preterm delivery and CVD (myocardial infarction (MI) or stroke) and whether this association is accounted for by postpartum development of traditional CVD risk factors (chronic hypertension, hypercholesterolemia, type 2 diabetes mellitus (T2DM), and BMI).

METHODS

Population

The Nurses' Health Study II (NHSII) is a longitudinal cohort of 116,429 U.S. registered nurses aged 25 to 42 at baseline in 1989. Participants were followed by using biennial questionnaires that collected data on diet, physical activity, smoking, medications, and reproductive history, as well as incident disease since the last questionnaire. In 2001, a supplemental questionnaire containing a pregnancy history assessment that recorded gestation length, infant sex, and birthweight of each pregnancy lasting at least 12 weeks was mailed to 91,297 nurses. In 2009, a complete reproductive history questionnaire was mailed to all participants to capture information on pregnancies of all lengths, including gestation length, birthweight, and whether the pregnancy was complicated by 'preeclampsia/toxemia', 'high blood pressure', or 'gestational diabetes'. This study was approved by the Institutional Review Board of Brigham and Women's Hospital. Return of the questionnaire was considered informed consent.

Gestation Length

Gestation length was assessed in categories on both the 2001 and the 2009 questionnaires. In 2009, the primary source of our exposure data, participants were asked the length of each pregnancy in completed weeks within the following nine categories: <8, 8 to 11, 12 to 19, 20 to 27, 28 to 31, 32 to 36, 37 to 39, 40 to 42, and 43+ weeks. For women who did not complete the 2009 reproductive wrap-up (n=10,644), data from the 2001 supplemental questionnaire was used. The 2001 questionnaire queried the length of each pregnancy lasting at least 12 weeks and collected information in the following seven categories: 12 to <20, 20 to <24, 24 to <28, 28 to <32, 32 to <37, 37 to 42, and 43+ weeks. For our primary analyses, which used

only the first pregnancy, gestation length categories were collapsed to create a dichotomous exposure variable (term, ≥37 weeks; preterm, <37 weeks) and a categorical exposure variable (term, ≥37 weeks; moderate preterm, ≥32 to <37 weeks; very preterm, <32 weeks). In secondary analyses, the entire pregnancy history was taken into account by using ever preterm as an exposure, and by classifying women based on their first birth (term or preterm) and all later births (all term, at least one preterm, no future birth), yielding six exposure categories. All analyses include only pregnancies that lasted at least 20 weeks.

We conducted a small validation study on a subset of NHSII participants who reported pregnancy-related high blood pressure or toxemia/preeclampsia on the 1993 or 1995 biennial questionnaires. We compared self-reported gestation length with gestation length from medical records for 403 participants. For dichotomous preterm delivery (<37 weeks, ≥37 weeks), with a prevalence of 31% in this sample, we found a sensitivity of 81% and specificity of 92%. When categorizing preterm delivery into very preterm, moderate preterm, and term, the Spearman correlation coefficient was 0.75, indicating good validity.

Cardiovascular Endpoint Assessment

On the 1989 baseline questionnaire, participants reported whether they ever had physician-diagnosed MI, angina, stroke (cerebrovascular accident), or transient ischemic attack (TIA). Any self-report of these conditions led to exclusion from the analyses, because these pre-baseline events were not confirmed. On each subsequent biennial questionnaire through 2013, participants were asked if they had experienced physician-diagnosed "myocardial infarction (heart attack)" or "stroke (CVA) or TIA" in the past two years. Permission was requested from participants or next of kin to obtain and review medical records following self-reported MI or stroke on any follow-up questionnaire. MI was confirmed by World Health Organization criteria

of acute symptoms and diagnostic electrocardiographic changes or elevated cardiac enzyme levels.[15] Stroke was classified by the National Survey of Stroke criteria, requiring atypical neurological deficit of rapid or sudden onset lasting ≥24 hours or until death attributable to a vascular cause.[16] Cerebrovascular pathology attributable to infection, trauma, or malignancy was excluded, as were "silent" strokes discovered only by radiologic imaging. Cases confirmed by medical record review were considered definite cases, whereas those acknowledged by the participant or relative as correct, but for which permission for medical record release was not provided or records could not be obtained, were considered probable. The endpoint for our primary analyses was definite or probable MI or stroke. TIA was not included in the outcome. Secondary analyses further included coronary revascularization, which was self-reported on biennial questionnaires from 1995 through 2013.

Covariates

Covariates were identified as potential confounders on the basis of a priori assumptions of their relationships with both preterm delivery and CVD. Family history and pre-pregnancy factors included as confounders were age at first birth and in 1989 (continuous), race/ethnicity (white, black, Latina, Asian, other), parental education (<9, 9-11, 12, 13-15, 16+ years), BMI (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2), smoking (never, past, current), diet (quintiles based on the Alternative Healthy Eating Index-2010[17]), alcohol use (none, ≤1 drink per week, 2-6 drinks per week, ≥1 drink per day), physical activity (never, 1-3, 4-6, 7-9, 10-12 months per year of strenuous physical activity), duration of oral contraceptive use (none, <2, 2 to <4 , ≥4 years), chronic hypertension, T2DM, hypercholesterolemia, and family history of MI or stroke. Pre-pregnancy factors were extracted from the biennial questionnaire immediately before the first pregnancy. Because the majority of first pregnancies (82%) occurred before the NHSII baseline

in 1989, questions on the baseline (1989) and supplemental questionnaires that queried about behavior in high school and at varying ages from 13 through 42 were used to assign pre-pregnancy values for women whose first birth occurred before 1989. Pre-pregnancy covariate values were assigned using the information closest to, but preceding, a woman's first delivery. For the small amount of missing data in our covariates we used missing indicators. Pre-pregnancy lifestyle and cardiovascular risk factors were also evaluated as potential effect modifiers of the relationship between preterm delivery and CVD, while cardiovascular risk factors that developed after the first birth, including chronic hypertension, T2DM, hypercholesterolemia, changes in BMI, and breastfeeding were assessed as intermediates. In sensitivity analyses, parity (1, 2, 3, or 4+ pregnancies), self-reported clinician-diagnosed depression (yes/no), and pregnancy-related trauma ("ever experienced complications of a pregnancy or a labor and birth that you found traumatic") were also investigated as possible intermediates.

Exclusions

For the primary analysis, we excluded women who did not complete either the 2001 or 2009 questionnaires documenting reproductive history (n=28,945), were nulliparous in 2009 (n=15,556), were <18 (n=896) or >45 years of age (n=58) at first birth, or reported MI (n=288) or stroke (n=176) on the 1989 baseline questionnaire, because these events were not confirmed. Women who had a confirmed MI or stroke before their first pregnancy were excluded (n=4), as were women with missing information on the gestation length (n=292) or year (n=32) of first pregnancy, yielding 70,182 women in our final analytic sample.

When we evaluated chronic hypertension, hypercholesterolemia, T2DM, and BMI as intermediates, we additionally excluded women who had pre-pregnancy chronic hypertension

(n=754), T2DM (n=185), or hypercholesterolemia (n=2,147), because they were not able to develop these postpartum. Women who reported any of these risk factors on the baseline questionnaire in 1989, but did not provide a date of diagnosis were also excluded (n=1,188), as were women who were missing BMI pre-pregnancy (n=3) or throughout all of follow-up (n=558). This yielded a sample of 65,347 women.

Statistical Analysis

The characteristics of the study population were standardized to the age distribution of our population and summarized by preterm delivery status in the first pregnancy (Table 1.1).[18] We used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between preterm delivery and CVD events (MI and stroke). Women entered the study at first birth and were followed until they experienced one of the censoring events: confirmed MI/stroke, death, their last returned questionnaire, or June 2013 (the end of our follow-up). Categorical preterm delivery in the first birth (term, moderate preterm, very preterm) was modeled using indicator variables, as was preterm delivery over multiple pregnancies.

To evaluate whether a woman's entire pregnancy history with respect to preterm delivery was associated with CVD, we created six categories on the basis of the first birth and all later births (e.g., term-term, term-preterm, term-no later pregnancies, preterm-term, preterm-preterm, preterm-no later pregnancies). For this recurrence analysis and the analysis of ever preterm, follow-up began at 40 years of age when 97% of women had completed their reproductive careers. We excluded women who had births at ≥40 years of age (n=2,491) and women with CVD events before 40 years of age (n=46).

Pre-pregnancy lifestyle risk factors were evaluated as effect modifiers by modeling multiplicative interaction terms between the factor of interest and preterm delivery. Likelihood ratio tests comparing the models with the interactions to models without the interactions provided a global test of effect modification by each pre-pregnancy factor. All potential effect modifiers were modeled as indicator variables except for BMI, which was modeled continuously to increase power.

CVD risk factors that arose after pregnancy, including chronic hypertension, hypercholesterolemia, T2DM, breastfeeding and updated BMI, were evaluated as potential intermediate outcomes by fitting Cox proportional hazards models both with and without the intermediates.[19] Chronic hypertension, hypercholesterolemia, and T2DM were treated individually as time dependent intermediates. Once an intermediate outcome was developed, women were considered to have this risk factor for the remainder of follow-up. BMI and breastfeeding were allowed to change multiple times over follow-up as women reported changes in their weight and cumulative breastfeeding on follow-up questionnaires. BMI was allowed to increase, decrease, or remain the same, whereas duration of breastfeeding could only increase over time. Before utilizing the publicly available SAS %mediate macro,[20, 21] we tested the presence of interactions between each intermediate and preterm delivery by using likelihood ratio tests of nested models with and without the interactions,[19] and observed no exposure-intermediate interactions (all $P>0.25$). To further ensure that the lack of interactions was not attributable to insufficient power, we assessed the magnitude of the HRs for preterm delivery and CVD within levels of each intermediate and confirmed that these exposure-intermediate interactions were not present (e.g. HR of 1.51 and 1.39 in those with and without T2DM, respectively). When we split the preterm category into moderate and very preterm, we found an

interaction with T2DM (*P*=0.01). This observed interaction was based on a small number of cases in women with both moderate preterm and T2DM (5 cases) and very preterm and T2DM (13 cases). We then calculated the proportion of the association between preterm delivery and CVD that was accounted for by chronic hypertension, hypercholesterolemia, T2DM, and BMI together and its 95% confidence interval using the publicly available SAS %mediate macro.[20, 21] All analyses were conducted using SAS 9.4 (SAS Institute).

RESULTS

Table 1.1 summarizes characteristics of the participants by preterm delivery status in the first pregnancy: term (≥37 weeks), moderate preterm (≥32 to <37 weeks), or very preterm (<32 weeks). Nearly 9% of participants delivered preterm in their first pregnancy; 2.1% delivered very preterm, 6.7% delivered moderately preterm, and 91.2% delivered at term. Baseline characteristics were largely similar across first pregnancy preterm delivery status, but women who delivered either moderately or very preterm were slightly more likely to have a BMI ≥30 kg/m^2, pre-pregnancy hypertension and hypercholesterolemia, and a family history of CVD. Women who delivered very preterm in the first pregnancy were more likely to be current smokers, experience a stillbirth in first pregnancy, and have higher final parity.

We followed women for up to 50 years (median, 32; range, 2-50) for incident CVD. During 2,212,774 person-years, we observed 949 CVD events (n=497 MIs, n=455 strokes, total n=952; 3 women experienced an MI and stroke at the same age), of which 584 were considered definite and 365 were probable. In comparison with those reporting a term first birth, women who had a preterm first birth had an increased rate of CVD (HR, 1.54; 95% CI, 1.27-1.87; Table 1.2, Model 1). This HR was slightly attenuated, but remained significant, after adjustment for

Table 1.1: Baseline Characteristics of Nurses' Health Study II Participants, by Preterm Delivery Status in First Pregnancy

	Term: ≥37 weeks (n=64,004)	Moderate Preterm: ≥32 to <37 weeks (n=4,712)	Very Preterm: <32 weeks (n=1,466)
Age at first birth, years, mean (SD)*	27.0 (4.7)	27.8 (5.1)	27.5 (5.6)
Age in 1989, years, mean (SD)*	35.0 (4.7)	34.6 (4.8)	35.4 (4.6)
Education of nurse's mother, more than high school	27.5	25.8	24.7
Education of nurse's father, more than high school	31.8	29.6	30.8
Pre-pregnancy BMI≥30	3.1	3.4	4.0
Pre-pregnancy chronic hypertension	2.1	3.7	3.3
Pre-pregnancy type 2 diabetes mellitus	0.3	1.2	0.6
Pre-pregnancy hypercholesterolemia	3.0	4.3	3.7
Hypertensive disorder or gestational diabetes in first pregnancy	10.5	17.4	10.6
Strenuous physical activity, age 18-22 years			
Never	28.1	27.9	26.0
10-12 months/year	11.3	11.6	13.0
Pre-pregnancy Alternative Healthy Eating Index (AHEI)			
Lowest Quintile (unhealthy)	20.2	20.4	16.9
Highest Quintile (healthy)	19.3	20.1	23.5
White	92.9	90.9	91.0
Family history of MI or stroke before age 60 years	25.5	28.1	28.0
Pre-pregnancy smoking			
Never smoker	67.5	68.4	66.4
Past smoker	10.0	9.2	9.7
Current smoker	21.8	21.7	23.3
Pre-pregnancy alcohol intake			
None	27.8	29.5	28.4
≥1 drink per day	5.8	6.2	5.9
Duration of oral contraceptive use			
None	25.3	24.9	21.6
≥4 years	29.4	33.0	31.4
Final parity			
1 pregnancy	16.4	22.1	20.3
2 pregnancies	49.1	47.7	30.2
3 pregnancies	25.6	22.4	31.8
4+ pregnancies	8.9	7.8	17.7
First pregnancy stillbirth	0.4	1.6	47.8

Percentages are presented unless otherwise indicated.
Values are standardized to the age distribution of the population.
Values of categorical variables may not sum to 100% due to rounding.
*Value is not standardized to the age distribution.

Table 1.2: Hazard Ratios (95% Confidence Intervals) for Preterm Delivery in First Pregnancy and Cardiovascular Events (Myocardial Infarction and Stroke)

	Term: ≥37 weeks (n=64,004)	Preterm: <37 weeks (n=6,178)	Moderate Preterm: ≥32 to <37 weeks (n=4,712)	Very Preterm: <32 weeks (n=1,466)	*P*-trend*
Cases/person-years	831/2,023,726	118/189,048	75/143,199	43/45,849	
Model 1†	1.00 (ref)	1.54 (1.27, 1.87)	---	---	---
Model 2†	1.00 (ref)	1.47 (1.21, 1.79)	---	---	---
Model 3†	1.00 (ref)	1.42 (1.16, 1.72)	---	---	---
Model 1‡	1.00 (ref)	---	1.30 (1.03, 1.65)	2.27 (1.67, 3.08)	<0.0001
Model 2‡	1.00 (ref)	---	1.27 (1.01, 1.61)	2.05 (1.50, 2.81)	<0.0001
Model 3‡	1.00 (ref)	---	1.22 (0.96, 1.54)	2.01 (1.47, 2.75)	<0.0001

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.
Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.
Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.
*For trend test, the measure of prematurity was included model as a continuous variable with most common gestation length as the value to represent each category.
†Compares preterm (<37 weeks) with term (≥37 weeks).
‡Preterm category is split into moderate preterm (≥32 to <37 weeks) and very preterm (<32 weeks).

both pre-pregnancy lifestyle and CVD risk factors (1.42; 95% CI, 1.16-1.72; Table 1.2, Model 3). When preterm delivery was split into two categories, the HRs for moderate preterm and very preterm were 1.22 (95% CI, 0.96-1.54) and 2.01 (95% CI, 1.47-2.75), respectively, with a significant trend (P<0.0001) in the fully adjusted model (Table 1.2, Model 3), indicating that preterm delivery remains predictive of CVD even after adjustment for multiple lifestyle and CVD risk factors present at the time of the delivery. Results did not change substantially when we additionally adjusted for pre-pregnancy miscarriage, when the outcome was expanded to include coronary revascularization, or when multiple gestation pregnancies were excluded. When we evaluated the association between preterm delivery in first pregnancy and MI and stroke separately, the results were slightly stronger for MI than they were for stroke (Appendix Table 1.6). In addition, we investigated the association between ever having a preterm delivery and CVD and found similar results to those that considered only the first birth (Appendix Table 1.7).

We evaluated the association between very preterm in first pregnancy and CVD classified by live birth and stillbirth because 47.8% of very preterm first pregnancies resulted in stillbirth (Table 1.1). The increased rate of CVD persisted in both the very preterm live birth (HR, 1.98; 95% CI, 1.27-3.08) and very preterm stillbirth (HR, 2.07; 95% CI, 1.35-3.18) groups (Appendix Table 1.8).

Because hypertensive disorders of pregnancy (HDP; preeclampsia and gestational hypertension) have been shown to be associated with CVD,[22-27] and because HDP is an indication for preterm delivery,[28] we further investigated whether the association between preterm delivery and CVD was evident for pregnancies not complicated by HDP (Table 1.3). In comparison with a normotensive term first pregnancy, women with a normotensive preterm first pregnancy had a 35% (HR, 1.35; 95% CI, 1.06-1.72) increased rate of CVD, whereas those with

Table 1.3: Hazard Ratios (95% Confidence Intervals) for Preterm Delivery in First Pregnancy and Cardiovascular Events (Myocardial Infarction and Stroke), Among Women Without Hypertensive Disorders of Pregnancy in First Pregnancy

	Non-HDP Term: ≥37 weeks (n=51,343)	Non-HDP Preterm: <37 weeks (n=4,487)	Non-HDP Moderate Preterm: ≥32 to <37 weeks (n=3,372)	Non-HDP Very Preterm: <32 weeks (n=1,115)
Cases/person-years*	613/1,641,456	76/141,478	46/105,585	30/35,893
Model 1†	1.00 (ref)	1.44 (1.13, 1.82)	---	---
Model 2†	1.00 (ref)	1.38 (1.08, 1.75)	---	---
Model 3†	1.00 (ref)	1.35 (1.06, 1.72)	---	---
Model 1‡	1.00 (ref)	---	1.17 (0.87, 1.58)	2.21 (1.53, 3.18)
Model 2‡	1.00 (ref)	---	1.15 (0.85, 1.55)	2.02 (1.39, 2.95)
Model 3‡	1.00 (ref)	---	1.12 (0.83, 1.52)	2.01 (1.38, 2.93)

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.

Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.

Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.

*Sample size and total case numbers differ from Table 1.2 because of additional exclusion criterion: did not complete 2009 reproductive wrap up. The 2001 questionnaire did not include questions regarding HDP.

†Compares non-HDP preterm (<37 weeks) with non-HDP term (≥37 weeks)

‡Non-HDP preterm category is split into non-HDP moderate preterm (≥32 to <37 weeks) and non-HDP very preterm (<32 weeks)

both preterm delivery and HDP in the first pregnancy had a 66% increased rate (HR, 1.66; 95% CI, 1.02-2.70). When the non-HDP preterm category was split into non-HDP moderate preterm and non-HDP very preterm, we observed no significantly higher rate in the normotensive moderate preterm group (HR, 1.12; 95% CI, 0.83-1.52), but a 2-fold (HR, 2.01; 95% CI, 1.38-2.93) increased rate in the normotensive very preterm group (Table 1.3, Model 3). We did not separate the HDP preterm category into moderate and very preterm because of insufficient power. Results were similar when we classified preterm by preeclampsia only, as opposed to HDP.

When comparing the six categories reflecting a woman's entire pregnancy history, all groups experienced a higher rate of CVD relative to women with more than one birth, all of which were at term (Table 1.4). Women with a preterm first birth and at least one later preterm birth had the largest fully adjusted hazard ratio at 1.65 (95% CI, 1.20-2.28). Women who had only one child (either preterm or term) had an increased rate of CVD in comparison with women who had at least two children all of whom were term; mothers with one preterm child (HR, 1.45; 95% CI, 0.97-2.17) were at slightly higher risk than mothers with one term child (HR, 1.21; 95% CI, 0.99-1.46). The results also suggest that, regardless of whether the preterm delivery occurred in the first pregnancy or a later one, the mother was at increased risk of CVD (Table 1.4).

We assessed whether the association between preterm delivery (term, moderate preterm, very preterm) in the first pregnancy and CVD was modified by pre-pregnancy lifestyle and CVD risk factors. We found no effect modification by pre-pregnancy BMI, smoking, physical activity, alcohol, diet, duration of oral contraceptive use, T2DM, hypercholesterolemia, or miscarriage history (all *P*-values of >0.10). Only chronic hypertension before first pregnancy appeared to be a modifier (P=0.02). The HRs comparing moderate preterm with term were 0.21 (95% CI, 0.03-

Table 1.4: Hazard ratios (95% Confidence Intervals) for History of Preterm Deliveries and Cardiovascular Events (Myocardial Infarction and Stroke) at ≥40 Years of Age, Among Women with No Births at ≥40 years of Age

First Pregnancy	Second+ Pregnancies	N (%)	Cases/Person-Years*	Model 1	Model 2	Model 3	Model 4
Term	Term	48,015 (71.2)	558/893,230	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Term	Preterm	3,597 (5.3)	56/66,083	1.34 (1.02, 1.77)	1.31 (1.00, 1.73)	1.30 (0.99, 1.71)	1.34 (1.01, 1.76)
Term	None	9,938 (14.7)	151/190,761	1.35 (1.12, 1.62)	1.26 (1.05, 1.52)	1.23 (1.02, 1.48)	1.21 (0.99, 1.46)
Preterm	Term	2,615 (3.9)	40/46,887	1.43 (1.04, 1.97)	1.41 (1.02, 1.94)	1.37 (0.99, 1.89)	1.38 (1.00, 1.90)
Preterm	Preterm	1,863 (2.8)	40/35,342	1.72 (1.25, 2.38)	1.67 (1.21, 2.30)	1.63 (1.18, 2.25)	1.65 (1.20, 2.28)
Preterm	None	1,399 (2.1)	27/25,897	1.89 (1.28, 2.78)	1.60 (1.07, 2.38)	1.48 (1.00, 2.21)	1.45 (0.97, 2.17)

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.

Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.

Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.

Model 4 is additionally adjusted for parity at 40 years of age.

*Sample size and total case numbers differ from those in Table 1.2 due to additional exclusion criteria: missing gestation length in the 2nd pregnancy on, reported gestation length <20 weeks and live birth, had a birth at ≥40 years of age, had a myocardial infarction or stroke before 40 years of age.

1.52) and 1.30 (95% CI, 1.02-1.64) in the women with and without pre-pregnancy chronic hypertension, respectively. The HR comparing very preterm with term among women with pre-pregnancy chronic hypertension was 0.57 (95% CI, 0.08-4.14), while the HR was 2.12 (95% CI, 1.54-2.92) among women without pre-pregnancy chronic hypertension.

Based on comparisons of models evaluating associations between preterm delivery and CVD with and without postpartum risk factors, 12.8% (95% CI, 7.1-21.9) of the association between preterm delivery and CVD was accounted for by the postpartum development of chronic hypertension, T2DM, hypercholesterolemia, or changes in BMI (Table 1.5, Model 2a). The proportion accounted for increased to 15.9% (95% CI, 8.7-27.3) when breastfeeding was also included as an intermediate (Table 1.5, Model 2b). When we split preterm into moderate and very preterm, 14.5% (95% CI, 4.0-41.1) of the association between moderate preterm delivery and CVD was accounted for by the development of chronic hypertension, T2DM, hypercholesterolemia, or changes in BMI, whereas 13.1% (95% CI, 9.0-18.7) of the very preterm-CVD association was accounted for by these risk factors (Table 1.5, Model 2a). The inclusion of breastfeeding as an intermediate increased the proportion to 20.7% (95% CI, 5.5-53.8) and 14.0% (95% CI, 9.5-20.1) in the moderate and very preterm groups, respectively. Results were similar when parity, depression, and pregnancy-related trauma were included as intermediates.

A number of sensitivity analyses were performed. When we excluded probable cases of MI or stroke and considered only cases definitely confirmed using medical records by study physicians, we found a slightly stronger association between preterm delivery and CVD (HR, 1.50; 95% CI, 1.17-1.91) in our fully adjusted model.

Table 1.5: Hazard Ratios (95% Confidence Intervals) for the Association Between Preterm Delivery in First Pregnancy and Cardiovascular Disease (Myocardial Infarction and Stroke) With and Without Adjustment for Intermediate Outcomes and the Proportion of the Association Through the Intermediates

	Term: ≥37 weeks (n=59,846)	Preterm:* <37 weeks (n=5,501)	Moderate Preterm: † ≥32 to <37 weeks (n=4,173)	Very Preterm: † <32 weeks (n=1,328)
Cases/person-years‡	756/1,912,714	105/171,983	65/129,478	40/42,505
Model 1 intermediate outcomes: chronic hypertension, hypercholesterolemia, type 2 diabetes mellitus, body mass index				
Without intermediates§	1.00 (ref)	1.55 (1.27, 1.91)	1.29 (1.00, 1.66)	2.34 (1.82, 3.02)
With intermediates‖	1.00 (ref)	1.47 (1.19, 1.80)	1.23 (0.96, 1.59)	2.12 (1.64, 2.73)
Proportion through intermediates¶	Ref	13.3% (7.9, 21.4)	17.1% (5.5, 42.5)	12.0% (8.6, 16.5)
Model 2a intermediate outcomes: chronic hypertension, hypercholesterolemia, type 2 diabetes mellitus, body mass index				
Without intermediates§	1.00 (ref)	1.48 (1.21, 1.82)	1.26 (0.97, 1.62)	2.14 (1.66, 2.76)
With intermediates‖	1.00 (ref)	1.41 (1.15, 1.73)	1.21 (0.94, 1.57)	1.94 (1.50, 2.50)
Proportion through intermediates¶	Ref	12.8% (7.1, 21.9)	14.5% (4.0, 41.1)	13.1% (9.0, 18.7)
Model 2b intermediate outcomes: chronic hypertension, hypercholesterolemia, type 2 diabetes mellitus, body mass index, and breastfeeding				
Without intermediates§	1.00 (ref)	1.48 (1.21, 1.82)	1.26 (0.97, 1.62)	2.14 (1.66, 2.76)
With intermediates‖	1.00 (ref)	1.39 (1.14, 1.71)	1.20 (0.93, 1.55)	1.92 (1.49, 2.48)
Proportion through intermediates¶	Ref	15.9% (8.7, 27.3)	20.7% (5.5, 53.8)	14.0% (9.5, 20.1)

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.

Model 2a is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, pre-pregnancy oral contraceptive use, and family history of MI or stroke before 60 years of age.

Model 2b is the same as model 2a, but additionally includes breastfeeding as an intermediate outcome.

*Compares preterm (<37 weeks) with term (≥37 weeks).

†Preterm category is split into moderate preterm (≥32 to <37 weeks) and very preterm (<32 weeks).

‡Sample size and total case numbers differ from Table 1.2 due to additional exclusion criterion: pre-pregnancy chronic hypertension, type 2 diabetes mellitus, or hypercholesterolemia, missing BMI over follow-up, and missing date of diagnosis of risk factors on baseline questionnaire.

§Analogous to the total effect in causal mediation analysis.

‖Analogous to the direct effect in causal mediation analysis.

¶Analogous to the proportion mediated in causal mediation analysis.

As a sensitivity analysis, we also excluded all person time accrued between the first birth and the baseline questionnaire in 1989 as this time is, by definition, immortal.[18] Participants had to survive without having an MI or stroke until 1989 in order to be eligible for inclusion in our study, because the self-reported events prior to 1989 were not validated and these women were excluded from our analytic sample. After excluding 558,846 person-years contributed between first birth and 1989, the association between preterm delivery and CVD remained essentially unchanged, in comparison with the results of the primary analyses in Table 1.2.

DISCUSSION

Women who deliver a preterm infant are at a 40% increased risk of future CVD events, whereas those who deliver before 32 weeks experience a doubling of CVD risk, even after accounting for pre-pregnancy sociodemographic, lifestyle and CVD risk factors. This increased risk is only partially explained by the subsequent development of traditional CVD risk factors such as chronic hypertension, hypercholesterolemia, weight gain and T2DM in the years after the delivery. The increased rate of CVD in women with very preterm deliveries was slightly attenuated, but persisted when we considered pregnancies not complicated by preeclampsia or gestational hypertension. CVD risk factors, including chronic hypertension, T2DM, hypercholesterolemia, and changes in BMI, that developed after the first birth accounted for <25% of the association between moderate or very preterm first birth and CVD. Because part of the association is through the development of traditional CVD risk factors postpartum, this suggests that the reduction of CVD risk factors in women who deliver a preterm infant might mitigate some of their elevated risk. A large portion of the increased rate, however, was not accounted for by the postpartum development of CVD risk factors and indicates the need to explore other pathways through which preterm delivery and CVD are linked. Because

established risk factors will not fully capture this early indicator of CVD risk, preterm delivery may be a valuable additional risk marker in screening.

Other studies, largely without adjustment for pre-pregnancy confounding factors, suggest a 1.2 to 2.5 fold increased risk of CVD in women with a history of preterm delivery, depending on the specific exposure and outcome definition.[7-14] Our estimates of 1.42 in women who delivered preterm, and 1.22 and 2.01 in women in delivered moderately and very preterm, respectively, are consistent with this range. We were able to improve on the current literature in two significant ways: by adjusting for pre-pregnancy confounders and by estimating the proportion of the preterm-CVD association that is accounted for by the emergence of CVD risk factors after the first birth. The current literature hails largely from administrative databases and registries, which preclude adjustment for pre-pregnancy lifestyle factors, such as diet, smoking, alcohol intake, physical activity, oral contraceptive use, and family history of CVD, as these are not available, leaving the possibility of unmeasured confounding. Only one study was able to adjust for pre-pregnancy smoking,[10] while one other adjusted for pre-pregnancy BMI.[12]

Due to the nature of our longitudinal observational study, we collected information on a variety of lifestyle factors over each woman's lifetime, allowing us to simultaneously account for these in our analyses. The inclusion of these variables as confounders in our models led to slight attenuations, the largest of which was in the association between very preterm delivery in the first pregnancy and CVD from a hazard ratio of 2.27 to 2.05. Pre-pregnancy oral contraceptive use was primarily responsible for this attenuation. Since recent oral contraceptive use has been shown to be protective against preeclampsia,[29] an indication for preterm delivery (particularly very preterm),[28, 30] this attenuation is plausible. We were also able to evaluate whether the association between preterm delivery and CVD was modified by pre-pregnancy risk factors,

which has not been explored in prior literature. While we observed effect modification by pre-pregnancy chronic hypertension, among women with pre-pregnancy chronic hypertension, the case numbers were small (n=1 case each in moderate and very preterm) and these findings should be replicated.

We also had the capacity to evaluate whether the preterm-CVD association persisted even in pregnancies not complicated by hypertensive disorders of pregnancy. Two studies have previously investigated the risk of CVD associated with preterm delivery in a pregnancy not complicated by preeclampsia and found hazard ratios ranging from 1.18 to 2.95 depending on the degree of the preterm and the outcome definition.[9, 31] Our results similarly show that preterm delivery remains associated with CVD even in pregnancies not complicated by HDP, suggesting that women with preterm pregnancies alone may benefit from additional prevention and screening along with women who experience both preterm and HDP. This is important as the majority (83%) of preterm pregnancies in our study were not complicated by HDP.

The longitudinal nature of our data allowed us to perform an analysis accounting for intermediate outcomes, which, to our knowledge, has not been previously done for the preterm-CVD association. We found that the association was partially accounted for by the development of chronic hypertension, T2DM, and hypercholesterolemia, and changes in BMI after pregnancy, but there remains a substantial portion that was not accounted for by these factors. These CVD risk factors may act as potential targets for primordial prevention in women with a history of preterm delivery. Additionally, breastfeeding appeared to account for part of this association on top of traditional CVD risk factors; whether breastfeeding itself can mitigate the risk associated with preterm delivery or is a marker for other risk factors cannot be established by these observational data. Prior observational research has shown that longer duration of lactation is

associated with a reduced risk of MI,[32] T2DM,[33] and chronic hypertension.[34] Further research is needed to identify other factors or pathways that may be responsible for the increased risk of CVD in these women.

In addition to the development of CVD risk factors emerging after a preterm delivery, we also hypothesize that preterm delivery and CVD are linked through subclinical shared risk factors that predate both preterm delivery and CVD. The causes of preterm delivery generally depend on whether the premature delivery was spontaneous or medically indicated.[30] Spontaneous preterm deliveries typically result from intrauterine infection or inflammation, uteroplacental ischemia or hemorrhage, uterine overdistension, stress or vascular disease,[30, 35, 36] while medically indicated preterm deliveries are often caused by preeclampsia, intrauterine growth restriction, or other maternal factors including obesity and chronic hypertension.[30] Intrauterine infection, which triggers the release of inflammatory chemokines and cytokines,[30, 35] has been shown to cause approximately 30% of all preterm deliveries.[30] Inflammatory processes also contribute to the development of atherosclerosis, plaque rupture, and, ultimately, CVD.[37] Inflammation, along with pre-pregnancy subclinical vascular disease and obesity, may underlie both preterm delivery and CVD. In support of this hypothesis, high C-reactive protein (CRP) levels in pregnancy, a marker of inflammation, are associated with spontaneous preterm delivery,[38-40] and CRP is also a strong predictor of CVD risk.[41]

The primary limitation of our study is the potential for exposure misclassification as participants self-reported gestation length between 0 and 47 years after their first pregnancy (median=27). Prior studies of maternal recall of preterm delivery, suggest high specificity (86-100%), but lower sensitivity (33-72%).[42-49] Our validation study showed higher sensitivity (81%) and specificity (92%), indicating good validity. Since our validation study included only women

who reported preeclampsia, it is unclear whether we would see similar results in the entire analytic sample. As the exposure is non-differentially misclassified with respect to the outcome, our results may be biased towards the null. There is also the possibility of unmeasured and residual confounding. However, we were able to adjust for multiple pre-pregnancy cardio-metabolic risk factors, which has not previously been done. The adjustment for these additional and well-documented shared risk factors, including diet, physical activity, BMI, smoking, alcohol, oral contraceptive use, and family history did not largely attenuate the results; thus it is unlikely that unmeasured or residual confounding would be large enough to alter the conclusions from our study. We were also unable to perform formal mediation analysis because there is currently no analytic method established to handle multiple, correlated, time-dependent mediators in the context of censored survival outcomes. However, our ability to account for intermediate outcomes that arise after the first birth has not previously been done for CVD-related outcomes and provides some insight as to how preterm delivery and CVD are linked. Additionally, we may have underestimated the proportion of the association explained by the intermediates as blood pressure and lipid levels are continuous and we were only able to include binary indicators for clinical conditions related to these measures. We were unable to explore the associations between spontaneous and induced preterm delivery, preterm labor, or premature rupture of membranes and CVD. Our study also potentially suffers from immortal time bias, as women could not have a CVD event prior to the 1989 baseline questionnaire in order to be included in our analytic sample. However, excluding the immortal person time had no impact on our results, likely due to the limited number of CVD events that would occur prior to baseline in a young, healthy population that was between 25 and 42 years old in 1989. Lastly, our cohort is primarily Caucasian (93%), limiting generalizability. Non-Hispanic black women have a higher

prevalence of preterm compared to both non-Hispanic white and Hispanic women and the proportion of preterm deliveries that are moderate and very preterm differ by race.[1] The mix of causes of preterm may vary between race/ethnicity groups and may be changing over time, particularly as pre-pregnancy BMI rises,[50] suggesting that there may be differences in how predictive preterm is of future CVD in other racial and ethnic groups.

Our study has several strengths. We were able to adjust for multiple pre-pregnancy lifestyle risk factors for CVD, yielding better confounding control than prior studies on preterm delivery and CVD. Similarly, unlike registry-based studies, we had longitudinal data on the development of traditional CVD risk factors, including chronic hypertension, hypercholesterolemia, T2DM, and changes in BMI over time, allowing us to evaluate whether the association between preterm and CVD was accounted for by these factors. On top of the rich data on confounders and mediators, we also had information on the complete reproductive history of our women, enabling us to investigate, not only the association between first pregnancy and CVD, but also recurrent preterm deliveries. Lastly, to our knowledge, this is the longest study on preterm delivery and CVD with follow-up ranging from 2 to 50 years (median=32).

In conclusion, preterm delivery is independently predictive of CVD, even after adjustment for multiple cardio-metabolic risk factors and the association is only partially mediated by the postpartum development of traditional CVD risk factors. We need further research to determine the incidence and timing of the development of these risk factors and establish the most effective screening and prevention protocols for women with a history of preterm delivery. We also need additional research on alternative, novel pathways through which preterm and CVD may be associated and which could also inform prevention methods.

Ultimately, preterm delivery may be a useful prognostic tool to identify high-risk women early in life who would benefit from early screening, prevention, and treatment.

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REFERENCES

1. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. *Natl Vital Stat Rep*. 2015;64:1-64.

2. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation*. 2011;123:1243-1262. doi: 10.1161/CIR.0b013e31820faaf8.

3. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ*. 2002;325:157-160.

4. Rich-Edwards JW. Reproductive health as a sentinel of chronic disease in women. *Womens Health*. 2009;5:101-105. doi: 10.2217/17455057.5.2.101.

5. Rich-Edwards JW, McElrath TF, Karumanchi SA, Seely EW. Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women. *Hypertension*. 2010;56:331-334. doi: 10.1161/HYPERTENSIONAHA.110.156810.

6. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322. doi: 10.1161/CIR.0000000000000152.

7. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *The Lancet*. 2001;357:2002-2006.

8. Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. *Am J Epidemiol*. 2004;159:336-342.

9. Catov JM, Wu CS, Olsen J, Sutton-Tyrrell K, Li J, Nohr EA. Early or recurrent preterm birth and maternal cardiovascular disease risk. *Ann Epidemiol*. 2010;20:604-609. doi: 10.1016/j.annepidem.2010.05.007.

10. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation*. 2011;124:2839-2846. doi: 10.1161/CIRCULATIONAHA.111.034884.

11. Hastie CE, Smith GC, Mackay DF, Pell JP. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750,350 singleton pregnancies. *Int J Epidemiol*. 2011;40:914-919. doi: 10.1093/ije/dyq270.

12. Kessous R, Shoham-Vardi I, Pariente G, Holcberg G, Sheiner E. An association between preterm delivery and long-term maternal cardiovascular morbidity. *Am J Obstet Gynecol*. 2013;209:368.e1-8. doi: 10.1016/j.ajog.2013.05.041.

13. Rich-Edwards JW, Klungsoyr K, Wilcox AJ, Skjaerven R. Duration of pregnancy, even at term, predicts long-term risk of coronary heart disease and stroke mortality in women: a population-based study. *Am J Obstet Gynecol*. 2015;213:518.e1-8. doi: 10.1016/j.ajog.2015.06.001.

14. Lykke JA, Paidas MJ, Damm P, Triche EW, Kuczynski E, Langhoff-Roos J. Preterm delivery and risk of subsequent cardiovascular morbidity and type-II diabetes in the mother. *BJOG*. 2010;117:274-281. doi: 10.1111/j.1471-0528.2009.02448.x.

15. World Health Organization. IHD Registers: Report of the Fifth Working Group: Copenhagen: World Health Organization 1971.

16. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12:I13-44.

17. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr*. 2012;142:1009-1018. doi: 10.3945/jn.111.157222.

18. Rothman KJ, Greenland S and Lash TL. *Modern Epidemiology.* 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008.

19. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology*. 2011;22:582-585. doi: 10.1097/EDE.0b013e31821db37e.

20. The SAS Mediate Macro [computer program]. Boston: Brigham and Women's Hospital; 2009. https://cdn1.sph.harvard.edu/wp-content/uploads/sites/271/2012/09/mediate_manual_2012_06_06.pdf

21. Lin DY, Fleming TR and De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. *Stat Med*. 1997;16:1515-1527.

22. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53:944-951. doi: 10.1161/HYPERTENSIONAHA.109.130765.

23. Kestenbaum B, Seliger SL, Easterling TR, Gillen DL, Critchlow CW, Stehman-Breen CO, Schwartz SM. Cardiovascular and thromboembolic events following hypertensive pregnancy. *Am J Kidney Dis*. 2003;42:982-989.

24. Wikstrom AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG*. 2005;112:1486-1491.

25. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.

26. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845.

27. Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand*. 1995;74:772-776.

28. Sibai BM. Preeclampsia as a cause of preterm and late preterm (near-term) births. *Semin Perinatol*. 2006;30:16-19.

29. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ*. 2007;335:978.

30. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371:75-84. doi: 10.1016/S0140-6736(08)60074-4.

31. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213-1217.

32. Stuebe AM, Michels KB, Willett WC, Manson JE, Rexrode K, Rich-Edwards JW. Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *Am J Obstet Gynecol*. 2009;200:138.e1-8. doi: 10.1016/j.ajog.2008.10.001.

33. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA*. 2005;294:2601-2610.

34. Lee SY, Kim MT, Jee SH, Yang HP. Does long-term lactation protect premenopausal women against hypertension risk? A Korean women's cohort study. *Prev Med*. 2005;41:433-438.

35. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, Chaiworapongsa T, Mazor M. The preterm parturition syndrome. *BJOG*. 2006;113 Suppl 3:17-42.

36. Thomson AJ, Telfer JF, Young A, Campbell S, Stewart CJ, Cameron IT, Greer IA, Norman JE. Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process. *Hum Reprod*. 1999;14:229-236.

37. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473:317-325. doi: 10.1038/nature10146.

38. Catov JM, Bodnar LM, Ness RB, Barron SJ, Roberts JM. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. *Am J Epidemiol*. 2007;166:1312-1319.

39. Lohsoonthorn V, Qiu C, Williams MA. Maternal serum C-reactive protein concentrations in early pregnancy and subsequent risk of preterm delivery. *Clin Biochem*. 2007;40:330-335.

40. Moghaddam Banaem L, Mohamadi B, Asghari Jaafarabadi M, Aliyan Moghadam N. Maternal serum C-reactive protein in early pregnancy and occurrence of preterm premature rupture of membranes and preterm birth. *Journal Obstet Gynaecol Res*. 2012;38:780-786. doi: 10.1111/j.1447-0756.2011.01804.x.

41. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836-843.

42. Casey R, Rieckhoff M, Beebe SA, Pinto-Martin J. Obstetric and perinatal events: the accuracy of maternal report. *Clin Pediatr (Phila)*. 1992;31:200-204.

43. Sanderson M, Williams MA, White E, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Validity and reliability of subject and mother reporting of perinatal factors. *Am J Epidemiol*. 1998;147:136-140.

44. Yawn BP, Suman VJ, Jacobsen SJ. Maternal recall of distant pregnancy events. *J Clin Epidemiol*. 1998;51:399-405.

45. Tomeo CA, Rich-Edwards JW, Michels KB, Berkey CS, Hunter DJ, Frazier AL, Willett WC, Buka SL. Reproducibility and validity of maternal recall of pregnancy-related events. *Epidemiology*. 1999;10:774-777.

46. Buka SL, Goldstein JM, Seidman LJ, Tsuang MT. Maternal recall of pregnancy history: accuracy and bias in schizophrenia research. *Schizophr Bull*. 2000;26:335-350.

47. Buka SL, Goldstein JM, Spartos E and Tsuang MT. The retrospective measurement of prenatal and perinatal events: accuracy of maternal recall. *Schizophr Res*. 2004;71:417-426.

48. Boeke CE, Marin C, Oliveros H, Mora-Plazas M, Agudelo-Canas S, Villamor E. Validity of maternal birthweight recall among Colombian children. *Matern Child Health J*. 2012;16:753-759. doi: 10.1007/s10995-011-0803-z.

49. Walshe M, McDonald C, Boydell J, Zhao JH, Kravariti E, Touloupoulou T, Fearon P, Bramon E, Murray RM, Allin M. Long-term maternal recall of obstetric complications in schizophrenia research. *Psychiatry Res*. 2011;187:335-340. doi: 10.1016/j.psychres.2011.01.013.

50. Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993-2003. *Obesity (Silver Spring)*. 2007;15:986-993.

APPENDIX

Table 1.6: Hazard Ratios (95% Confidence Intervals) for Preterm Delivery in First Pregnancy and Myocardial Infarction and Stroke

	Term: ≥37 weeks (n=64,004)	Preterm: <37 weeks (n=6,178)	Moderate Preterm: ≥32 to <37 weeks (n=4,712)	Very Preterm: <32 weeks (n=1,466)
Myocardial Infarction				
Cases/person-years*	429/2,023,726	68/189,048	44/143,199	24/45,849
Model 1†	1.00 (ref)	1.71 (1.33, 2.22)	1.48 (1.08, 201)	2.43 (1.61, 3.67)
Model 2†	1.00 (ref)	1.63 (1.26, 2.12)	1.45 (1.06, 1.98)	2.17 (1.42, 3.31)
Model 3†	1.00 (ref)	1.55 (1.19, 2.01)	1.36 (0.99, 1.86)	2.10 (1.38, 3.21)
Stroke				
Cases/person-years*	404/2,023,726	51/189,048	32/143,199	19/45,849
Model 1†	1.00 (ref)	1.37 (1.02, 1.84)	1.14 (0.80, 1.64)	2.07 (1.31, 3.28)
Model 2†	1.00 (ref)	1.31 (0.97, 1.75)	1.11 (0.78, 1.60)	1.87 (1.17, 2.99)
Model 3†	1.00 (ref)	1.28 (0.95, 1.71)	1.09 (0.76, 1.56)	1.84 (1.15, 2.95)

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.

Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.

Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.

*Total case numbers differ from those in Table 2 because 3 women experienced a myocardial infarction and stroke at the same age and are included as events in both the myocardial infarction and stroke analysis. Person-years are the same for the stroke and MI analyses because women are censored at their first CVD event (myocardial infarction or stroke), regardless of event type, in both analyses.

†Compares preterm (<37 weeks) to term (≥37 weeks)

‡Preterm category is split into moderate preterm (≥32 to <37 weeks) and very preterm (<32 weeks)

Table 1.7: Hazard Ratios (95% Confidence Intervals) for Ever Preterm Delivery and Cardiovascular Events (Myocardial Infarction and Stroke) at ≥40 Years of Age, Among Women with No Births at ≥40 Years of Age

	Never Preterm: ≥37 weeks (n=57,953)	Ever Preterm: <37 weeks (n=9,474)	Ever Moderate Preterm: ≥32 to <37 weeks (n=6,859)	Ever Very Preterm: <32 weeks (n=2,615)	*P*-trend[*]
Cases/person-years[†]	709/1,083,991	163/174,209	98/124,437	65/49,772	
Model 1[‡]	1.00 (ref)	1.44 (1.21, 1.70)	---	---	---
Model 2[‡]	1.00 (ref)	1.39 (1.17, 1.65)	---	---	---
Model 3[‡]	1.00 (ref)	1.36 (1.15, 1.62)	---	---	---
Model 4[‡]	1.00 (ref)	1.39 (1.17, 1.65)	---	---	---
Model 1[§]	1.00 (ref)	---	1.24 (1.00, 1.53)	1.90 (1.47, 2.45)	<0.0001
Model 2[§]	1.00 (ref)	---	1.22 (0.98, 1.50)	1.79 (1.38, 2.31)	<0.0001
Model 3[§]	1.00 (ref)	---	1.18 (0.96, 1.46)	1.76 (1.36, 2.28)	<0.0001
Model 4[§]	1.00 (ref)	---	1.19 (0.97, 1.48)	1.87 (1.44, 2.43)	<0.0001

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.
Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.
Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.
Model 4 is additionally adjusted for parity at 40 years of age.
[*]For trend test, the measure of prematurity was included model as a continuous variable with most common gestation length as the value to represent each category.
[†]Sample size and total case numbers differ from those in Table 2 due to additional exclusion criteria: missing gestation length in the second pregnancy on, reported gestation length <20 weeks and live birth, had a birth after 40 years of age, or had a myocardial infarction or stroke before 40 years of age.
[‡]Compares ever preterm (<37 weeks) with never preterm (≥37 weeks).
[§]Ever preterm category is split into ever moderate preterm (≥32 to <37 weeks) and ever very preterm (<32 weeks).

Table 1.8: Hazard Ratios (95% Confidence Intervals) for Preterm Delivery in First Pregnancy and Cardiovascular Events (Myocardial Infarction and Stroke), Classified by Live and Still Birth

	Term:* ≥37 weeks (n=63,826)	Moderate Preterm:* ≥32 to <37 weeks (n=4,697)	Very Preterm Live Birth: <32 weeks (n=762)	Very Preterm Stillbirth <32 weeks (n=697)	*P*-trend†
Cases/Person-Years‡	827/2,018,120	75/142,730	20/23,088	23/22,549	
Model 1	1.00 (ref)	1.31 (1.03, 1.66)	2.09 (1.34, 3.26)	2.47 (1.63, 3.73)	<0.0001
Model 2	1.00 (ref)	1.28 (1.01, 1.62)	2.03 (1.30, 3.16)	2.11 (1.37, 3.24)	<0.0001
Model 3	1.00 (ref)	1.22 (0.96, 1.55)	1.98 (1.27, 3.08)	2.07 (1.35, 3.18)	<0.0001

Model 1 is adjusted for age at first birth, age in 1989, race/ethnicity, and parental education.
Model 2 is additionally adjusted for pre-pregnancy body mass index, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index score (in quintiles), pre-pregnancy alcohol intake, physical activity at 18 years of age, and pre-pregnancy oral contraceptive use.
Model 3 is additionally adjusted for pre-pregnancy chronic hypertension, pre-pregnancy hypercholesterolemia, pre-pregnancy type 2 diabetes mellitus, and family history of myocardial infarction or stroke before 60 years of age.
*Contains both live births and stillbirths. There are 245 stillbirths in the term group and 75 stillbirths in the moderate preterm group.
†For trend test, the measure of prematurity was included model as a continuous variable with most common gestation length as the value to represent each category.
‡Case numbers and person years differ from Table 2 due to an additional exclusion criterion: missing outcome for the first pregnancy.

Chapter 2 Preterm Delivery and Maternal Cardiovascular Disease Risk Factors in the Nurses' Health Study II

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ABSTRACT

Background: Preterm delivery has been linked to future maternal cardiovascular disease; however, research investigating clinical cardiovascular disease risk factors is limited.

Objective: We evaluated whether women who have delivered an infant preterm are at higher risk of developing cardiovascular disease risk factors after adjustment for pre-pregnancy confounders.

Study Design: We examined the association between preterm delivery and incident chronic hypertension, type 2 diabetes mellitus, and hypercholesterolemia among 57,904 parous women in the Nurses' Health Study II. The analysis was restricted to those who did not have gestational diabetes or a hypertensive disorder in first pregnancy. Multivariable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between preterm delivery in first pregnancy and each CVD risk factor; adjusted cumulative incidence curves were computed using the Breslow estimator.

Results: Approximately 6% of women delivered their first birth moderately preterm (≥32 to <37 weeks gestation), while 2% delivered very preterm (< 32 weeks). Preterm delivery was associated with HRs of 1.11 (95% CI: 1.06-1.17) for chronic hypertension, 1.17 (95% CI: 1.03-1.33) for type 2 diabetes mellitus, and 1.07 (95% CI: 1.03-1.11) for hypercholesterolemia, adjusting for age, race/ethnicity, parental education, and pre-pregnancy confounders (e.g., body mass index, smoking, family history). HRs were higher in women who delivered very preterm and in the first 10 years after first birth. The cumulative incidence of each risk factor was highest in women who delivered very preterm.

Conclusions: Women with a history of preterm delivery are at higher risk of developing chronic hypertension, type 2 diabetes mellitus, and hypercholesterolemia in the years after pregnancy. This increased risk was particularly pronounced in the first 10 years after a preterm delivery, indicating it may be an important time period to implement lifestyle interventions to prevent or delay the development of cardiovascular disease risk factors.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in the United States, resulting in nearly 400,000 deaths among women in 2014.[1] Pregnancy is a distinctive period of cardio-metabolic stress that may uncover underlying endothelial dysfunction, vascular disease, or susceptibility to subsequent CVD risk as pregnancy complications when women are young and before the development of clinical CVD risk factors.[2-4] The American Heart and Stroke Associations (AHA, ASA) recognize gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP; includes preeclampsia and gestational hypertension) as risk factors for CVD in women.[5, 6] HDP often results in preterm deliveries[7] and, while preterm delivery has not yet been officially recognized as a risk factor for CVD, evidence is growing that preterm delivery, even in the absence of HDP, is associated with an increased risk of CVD.[8-10] These findings have led the AHA to recommend that healthcare professionals screen patients for prior preterm deliveries when obtaining a complete medical history.[6] Additionally, there have been multiple calls to evaluate the trajectories of CVD risk factor development after pregnancy to inform screening protocols in young women with a history of pregnancy complications.[3, 5]

Preterm delivery, which impacts nearly 10% of pregnancies in the United States each year, has been linked to future CVD in mothers,[9-18] but research investigating the development of clinical CVD risk factors (i.e. chronic hypertension, type 2 diabetes mellitus (T2DM), hypercholesterolemia) that often predate CVD events is more limited. The current literature suggests that women with a history of preterm delivery are at 1.2 to 2-fold higher risk of CVD-related risk factors, yet few studies have jointly adjusted for potential pre-pregnancy confounding factors, such as body mass index (BMI), smoking, family history of CVD risk factors, and lifestyle factors (e.g. diet),[17, 19-21] which may explain both a higher risk of preterm

delivery and CVD risk factors. Finally, all but one study have fewer than 20 years of follow-up[17, 19, 20, 22-25] and only one, which evaluated T2DM after a preterm delivery, provides information on when these risk factors begin to appear after pregnancy.[21] We provide new data to inform screening protocols in women who have delivered a preterm infant by providing more complete adjustment for confounding variables and describing the trajectory of risk factor development up to 50 years after preterm delivery.

METHODS

Study Population

The study population for our analysis was drawn from 116,429 female U.S. registered nurses enrolled in the Nurses' Health Study II (NHSII) in 1989 at ages 25-42. This prospective, longitudinal study mailed questionnaires to participants every 2 years to collect sociodemographic information, lifestyle and behavior characteristics, medication use, and incident disease. Data on pregnancy history was reported twice over follow-up: in 2001 and 2009. In 2001, 91,297 women were mailed a supplemental questionnaire about pregnancies lasting at least 12 weeks. As part of the 2009 biennial questionnaire, all women in the NHSII were asked to report their complete pregnancy history, including gestation length, pregnancy complications, and birth outcomes for all pregnancies regardless of gestation length. This 2009 reproductive questionnaire, completed when all women were ≥45 years of age, is the primary source of our exposure data as it obtained a more complete pregnancy history. This study was approved by the Partners Human Research Committee (Institutional Review Board) of Brigham and Women's Hospital. Questionnaire return was considered informed consent.

Gestation Length

As part of the 2009 pregnancy history, women reported the length of each pregnancy in the following categories of completed weeks: <8, 8-11, 12-19, 20-27, 28-31, 32-36, 37-39, 40-42, 43+ weeks. For women who did not complete the 2009 questionnaire or were missing information on gestation length, data from the 2001 questionnaire were used (n=10,644). Gestation length was then dichotomized into preterm delivery (≥20 to <37 weeks) or term delivery (≥37 weeks). We also used a three-category exposure in which preterm delivery was split into moderate (≥32 to <37 weeks) and very preterm (≥20 to <32 weeks). Pregnancies lasting fewer than 20 weeks were not included, as this cutoff separates spontaneous abortions from live and stillbirths.[26] Primary analyses considered only the first birth, while secondary analyses evaluated recurrent preterm deliveries in second or later births.

In the NHSII cohort, a small validation study was conducted among 403 women who reported preeclampsia/toxemia between 1991 and 2001. Self-reported gestation length was compared to the gestation length from medical records. This yielded a sensitivity of 81% and a specificity of 92% for dichotomous preterm delivery (<37 weeks, ≥37 weeks) and a Kappa statistic of 0.74 when we categorized gestation length into term, moderate preterm, and very preterm, suggesting good validity.

Cardiovascular Risk Factors

Chronic Hypertension

Participants provided self-reported physician diagnoses of incident chronic hypertension and the year of diagnosis in categories (e.g. on 1991 questionnaire: 'before September 1989'; 'September 1989 to May 1991'; or 'after June 1, 1991') on each biennial questionnaire. The midpoint of each category was assigned as the date of diagnosis. Validation of self-reported

hypertension in a random sample of NHSII participants resulted in a sensitivity of 94% and specificity of 85%, indicating good agreement with medical records.[27]

Type 2 Diabetes Mellitus

Participants also provided self-reported physician diagnoses of incident diabetes (not during pregnancy) and the year of diagnosis in categories on each biennial questionnaire. Women who noted a diagnosis of diabetes were then mailed a supplementary questionnaire to obtain information on symptoms, diagnostic tests, and hypoglycemic therapy. Definite T2DM required the following based on criteria from the National Diabetes Data Group[28, 29]: 1) presence of one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus, or coma) and fasting plasma glucose ≥ 126 mg/dl or random plasma glucose ≥ 200 mg/dl; or 2) at least two elevated plasma glucose levels on different occasions in the absence of symptoms; or 3) treatment of hypoglycemic medication. Probable T2DM was defined as the following: 1) only 1 elevated plasma glucose, but no symptoms or hypoglycemic therapy; or 2) classic symptoms and 2 or more urine samples positive for glucose. Validation of these confirmation criteria in a similar cohort confirmed 98% of self-reported T2DM diagnoses.[30] The month and year of diagnosis reported on the supplementary questionnaire was used as the date of diagnosis. Primary analyses required a definite T2DM diagnosis, while sensitivity analyses additionally considered probable cases.

Hypercholesterolemia

Participants provided self-reported physician diagnoses of incident elevated cholesterol and the year of diagnosis in categories on each biennial questionnaire. The midpoint of each year of diagnosis category was considered the date of diagnosis. Beginning in 1999, women were asked to report use of cholesterol lowering medication and, from 1999 through the end of follow-

up, hypercholesterolemia was defined as self-report of elevated cholesterol or medication use. Validation of self-reported elevated cholesterol compared to medical records and measured blood samples in a similar cohort yielded a positive predictive value of 86% and negative predictive value of 85%.[31]

Covariates

The following covariates were selected *a priori* as potential confounding variables based on subject matter knowledge of each covariate's relationship with preterm delivery and CVD risk factors: age at first birth and at NHSII enrollment in 1989, race/ethnicity (white, African-American, Latina, Asian, other), education of the nurses' mother and father (<9, 9-11, 12, 13-15, ≥16 years), family history of hypertension (yes/no), family history of diabetes (yes/no), and pre-pregnancy body mass index (BMI in kilograms per meter^2: <18.5, 18.5-<25, 25-<30, ≥30), smoking (never, past, current), Alternative Healthy Eating Index score (in quintiles), alcohol intake (none, <1 drink per week, 2-6 drinks per week, ≥1 drink per day), physical activity (none, 1-3, 4-6, 7-9, 10-12 months per year), and duration of oral contraceptive use (none, <2, 2-<4, ≥4 years). Missing indicators were used for the small amount of missing data in our covariates.

For women with first pregnancies before the start of the NHSII in 1989 (82%), questions on the baseline questionnaire that asked about lifestyle and behavior from age 18 to age at cohort entry were used to assign pre-pregnancy covariate values. Women who delivered their first pregnancy after 1989 were assigned pre-pregnancy covariate values from the biennial questionnaire closest to, but preceding the pregnancy.

Exclusions

We excluded women who were non-responders to both the 2001 and 2009 pregnancy history questionnaires (n=28,945), nulliparous in 2009 (n=15,556), missing gestation length or year of first birth (n=324), or <18 or >45 years of age at first birth (n=954). Women who reported chronic hypertension, hypercholesterolemia, myocardial infarction (MI) or stroke on the 1989 questionnaire, but did not provide a date of diagnosis or reported a diagnosis date before 1980 were also excluded (n=1,366) as we were unable to precisely date these. We additionally excluded women who reported the development of chronic hypertension, hypercholesterolemia, type 1 or type 2 diabetes mellitus, use of anti-hypertensive medication, or those who had a myocardial infarction or stroke before first pregnancy (n=3,127). We excluded women who reported gestational diabetes mellitus (GDM) or hypertensive disorders of pregnancy (HDP) in their first pregnancy (n=6,662) because both are indications for preterm delivery[7, 32] and are also associated with CVD and CVD risk factors.[33-48] Information on GDM and HDP was not collected in 2001, thus women for whom the 2001 questionnaire was the source of their pregnancy history were excluded if they reported GDM or HDP on any biennial questionnaire prior to 2001 (n=1,553). Lastly, because chronic hypertension prior to pregnancy can be incorrectly diagnosed as incident chronic hypertension after pregnancy, women who reported a chronic hypertension diagnosis within one year of first birth were additionally excluded (n=38). These exclusions resulted in an analytic sample of 57,904 women.

Statistical Analysis

Characteristics of NHSII participants in our analytic sample were age-standardized and presented by preterm delivery status in first birth. Women entered the study at first birth and were followed until development of each CVD risk factor (outcomes of interest), MI or stroke,

death, loss to follow-up, or June 2013 (the end of our follow-up). In the chronic hypertension analysis, women were additionally censored at report of anti-hypertensive medication use, as these women were no longer at risk of developing chronic hypertension. Similarly, in the T2DM analysis, women were censored at type 1 diabetes mellitus diagnosis. Multivariable-adjusted Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of preterm delivery with chronic hypertension, T2DM, and hypercholesterolemia. The proportional hazards assumption was assessed using likelihood ratio tests comparing models with interactions between preterm delivery and time since first birth to models without these interactions for each CVD risk factor of interest. The proportional hazards assumption was violated for chronic hypertension and T2DM (both $P<0.04$); therefore, we present hazard ratios within 10-year intervals since first birth. For consistency, we also report hazard ratios in 10-year intervals for hypercholesterolemia.

The Breslow estimator was used to obtain CVD risk profile-specific cumulative incidence curves[49] for each CVD risk factor by preterm delivery for first births. The low risk CVD profile was characterized as having the following characteristics before the first pregnancy: mean age at first birth (age=27) and in 1989 (age=35), white, ≥16 years of maternal and paternal education, healthy BMI (18.5-24.9 kg/m^2), never smoker, healthiest diet (fifth quintile of AHEI), ≥1 alcoholic drink per day, 10-12 months of strenuous physical activity per year, no oral contraceptive use, and no family history of hypertension (for the chronic hypertension curves) or diabetes (for the T2DM curves). In contrast, the following characteristics represent the high risk CVD profile: mean age at first birth (age=27) and in 1989 (age=35), white, <9 years of maternal and paternal education, obese BMI (≥30 kg/m^2), current smoker, unhealthiest diet (first quintile

of AHEI), no alcoholic drinks per day, no physical activity, no oral contraceptive use, and family history of hypertension (for the chronic hypertension curves) or diabetes (for the T2DM curves).

To evaluate the association between recurrent preterm deliveries and each CVD risk factor, we characterized women by preterm delivery status in first birth (term or preterm) and, subsequently, in all later births (all term, any preterm, or no later births), yielding six exposure categories. Follow-up for this analysis began at age 40, when most women (97%) had completed childbearing. Therefore, we additionally excluded women who had any births at age 40 or later (n=2,799); missing or invalid gestation length in a second or later pregnancy (n=188); developed any of the CVD risk factors, type 1 diabetes mellitus, or reported anti-hypertensive medication use before age 40 (n=10,033); or had a CVD event, died, or were lost to follow-up before age 40 (n=122), resulting in 44,762 women in this analytic sample. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Age-standardized characteristics of study participants by preterm delivery in first birth are presented in Table 2.1. Approximately 6% of the 57,904 women delivered their first birth moderately preterm (≥32 to <37 weeks), while 2% delivered very preterm (<32 weeks). Women were generally similar across exposure groups; however, women with a very preterm delivery in first birth were more likely to have a family history of diabetes and have a final parity of ≥4 pregnancies. The higher final parity observed in women who delivered very preterm is likely due to replacement pregnancies since a majority were stillbirths (52.5% in very preterm compared to 1.7% in moderate preterm and 0.4% in term).

Table 2.1: Age-standardized baseline characteristics of study participants by first birth preterm delivery

	Term ≥37 weeks (n=53,341)	Moderate Preterm ≥32 to <37 weeks (n=3,400)	Very Preterm <32 weeks (n=1,163)
Age at first birth, years, mean (SD)[a]	26.7 (4.5)	27.2 (4.8)	26.7 (5.2)
White	93.0	91.3	91.6
Education of the nurse's mother, more than high school	27.6	26.2	25.8
Education of the nurse's father, more than high school	31.9	30.0	31.3
Family history of hypertension	51.3	51.1	52.0
Family history of diabetes	43.2	45.3	49.0
Pre-pregnancy body mass index ≥30 kg/m^2	2.0	2.0	2.9
Strenuous physical activity, age 18-22 years			
Never	28.4	28.3	27.3
10-12 months/year	11.2	11.6	14.4
Pre-pregnancy Alternative Healthy Eating Index			
First quintile	20.0	19.9	16.8
Fifth quintile	19.4	20.1	23.4
Pre-pregnancy smoking			
Never smoker	67.6	67.6	65.4
Past smoker	9.5	8.7	10.3
Current smoker	22.3	22.9	23.5
Pre-pregnancy alcohol intake, drinks			
None	27.6	29.3	27.0
≥1/day	5.7	6.5	5.7
Duration of pre-pregnancy oral contraceptive use			
None	26.1	25.7	21.9
<2 years	23.9	21.8	25.3
2-4 years	21.9	20.0	22.9
≥4 years	28.1	32.5	29.9
First Pregnancy Stillbirth	0.4	1.7	52.5
Final parity			
1 pregnancy	15.0	20.2	19.1
2 pregnancies	49.0	47.9	28.1
3 pregnancies	26.5	23.1	33.5
4+ pregnancies	9.5	8.8	19.3

Values are percentages unless otherwise noted and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

[a]Value is not age adjusted.

Due to censoring criteria that is specific to each risk factor, median length of follow-up differed by CVD risk factor. Median length of follow-up was 28 (interquartile range (IQR): 21, 33) years for chronic hypertension, 32 (IQR: 27, 37) years for T2DM, and 26 (IQR: 19, 32) years for hypercholesterolemia. During follow-up, we observed 18,064 cases of chronic hypertension, 2,821 cases of T2DM, and 31,183 cases of hypercholesterolemia.

Table 2.2 shows multivariable-adjusted hazard ratios for the association between preterm delivery and each CVD risk factor across follow-up (up to 49 years for chronic hypertension and hypercholesterolemia and up to 50 years for T2DM) and within 10-year intervals since first birth. Women who delivered their first infant preterm had an 11% (95% CI: 1.06, 1.17) increased rate of developing chronic hypertension compared to women who delivered at term. The HR for chronic hypertension was highest in the first 10 years following a preterm delivery (1.43; 95% CI: 1.20, 1.70). This increased rate generally diminished over time and was not statistically significant from 11-40 years after first birth. When we split preterm delivery into moderate preterm and very preterm, the HR was stronger in the first 10 years following a very preterm delivery (2.07; 95% CI: 1.56, 2.75) than in the moderate preterm group (1.22; 95% CI: 0.99, 1.51). Women who delivered very preterm had significantly increased rates of chronic hypertension for 30 years following first birth; while in women who delivered moderately preterm, a significantly increased rate did not emerge until 31-40 years after first birth (Table 2.2).

There was a 1.17-fold increased rate (95% CI: 1.03, 1.33) of developing T2DM in women who delivered their first infant preterm compared to those who delivered at term. Similar to chronic hypertension, the fully adjusted HR was strongest in the first 10 years following a preterm delivery (2.83; 95% CI: 1.32, 6.06); the association was generally attenuated over

Table 2.2: Multivariable-adjusted hazard ratios (95% confidence intervals) for preterm delivery in first birth and cardiovascular disease risk factors in 10 year intervals since first birth

	Cases/Person-Years	Term: ≥37 weeks (n=53,341)	Preterm: <37 weeks (n=4,563)	Moderate Preterm: ≥32 to <37 weeks (n=3,400)	Very Preterm: <32 weeks (n=1,163)	p-trend[a]
Chronic Hypertension						
Overall[b]	18,064/1,574,176	1.00 (ref)	1.11 (1.06, 1.17)	1.06 (1.00, 1.13)	1.28 (1.16, 1.41)	<0.0001
1-10 years	1,273/573,557	1.00 (ref)	1.43 (1.20, 1.70)	1.22 (0.99, 1.51)	2.07 (1.56, 2.75)	<0.0001
11-20 years	5,471/520,984	1.00 (ref)	1.07 (0.98, 1.18)	0.96 (0.86, 1.08)	1.45 (1.23, 1.71)	0.002
21-30 years	7,809/351,212	1.00 (ref)	1.08 (1.00, 1.17)	1.05 (0.96, 1.16)	1.17 (1.00, 1.37)	0.03
31-40 years	3,241/117,903	1.00 (ref)	1.10 (0.97, 1.25)	1.17 (1.01, 1.34)	0.92 (0.71, 1.19)	0.54
Type 2 Diabetes Mellitus						
Overall[b]	2,821/1,832,561	1.00 (ref)	1.17 (1.03, 1.33)	1.06 (0.91, 1.24)	1.48 (1.19, 1.83)	0.0007
1-10 years[c]	41/560,826	1.00 (ref)	2.83 (1.32, 6.06)	3.22 (1.39, 7.47)	1.94 (0.44, 8.70)	0.04
11-20 years	528/567,508	1.00 (ref)	1.33 (1.01, 1.76)	1.20 (0.86, 1.67)	1.77 (1.10, 2.84)	0.01
21-30 years	1,300/462,511	1.00 (ref)	1.11 (0.91, 1.34)	1.00 (0.79, 1.26)	1.40 (1.01, 1.94)	0.09
31-40 years	885/201,537	1.00 (ref)	1.13 (0.89, 1.42)	0.99 (0.74, 1.32)	1.46 (1.01, 2.11)	0.09
Hypercholesterolemia						
Overall[b]	31,183/1,454,258	1.00 (ref)	1.07 (1.03, 1.11)	1.06 (1.01, 1.11)	1.09 (1.01, 1.18)	0.002
1-10 years	4,555/563,056	1.00 (ref)	1.13 (1.02, 1.25)	1.10 (0.98, 1.24)	1.23 (1.01, 1.50)	0.01
11-20 years	10,368/483,647	1.00 (ref)	1.07 (1.00, 1.15)	1.05 (0.97, 1.14)	1.11 (0.97, 1.27)	0.05
21-30 years	11,373/305,674	1.00 (ref)	1.02 (0.95, 1.09)	1.01 (0.94, 1.10)	1.02 (0.89, 1.17)	0.66
31-40 years	4,634/94,215	1.00 (ref)	1.07 (0.96, 1.19)	1.09 (0.96, 1.23)	1.03 (0.84, 1.25)	0.39

Models are adjusted for age at first birth, age in 1989, race/ethnicity, parental education, family history of hypertension (for the chronic hypertension model), family history of type 2 diabetes mellitus (for the type 2 diabetes mellitus model), pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, pre-pregnancy (age 18) physical activity, and pre-pregnancy oral contraceptive use.

[a]Exposure (preterm delivery) was included in model as a continuous variable with 40 weeks representing term delivery, 36 weeks representing moderate preterm delivery, and 30 weeks representing very preterm delivery.

[b]Includes all 49 years of follow-up for chronic hypertension and hypercholesterolemia and 50 years for T2DM.

[c]Asian race and other race were combined as there were 0 diabetes cases in Asian women; women who were underweight (n=1,260) or missing BMI (n=501) were excluded because there were 0 cases in these BMI groups.

follow-up, but maintained statistical significance through 20 years after first birth (1.33; 95% CI: 1.01, 1.76). Women who delivered moderately preterm had a 3.2-fold higher rate (95% CI: 1.39, 7.47) of developing T2DM in the first 10 years after first birth compared to women who delivered at term, but no increased rate from 11-40 years after first birth. In contrast, there was no increased rate of T2DM in the first 10 years after a very preterm first birth, but a significantly higher rate from 11-40 years after first birth (Table 2.2).

For hypercholesterolemia, women who delivered preterm had a 1.07-fold increased rate (95% CI: 1.03, 1.11) compared to women who delivered term. We also observed the highest HR for hypercholesterolemia in the first 10 years following preterm delivery (1.13; 95% CI: 1.02, 1.25). This increased rate appeared to be driven by the very preterm group, which had a 23% increased rate (95% CI: 1.01, 1.50) of developing hypercholesterolemia in the first 10 years after first birth compared to women who delivered at term. However, the association between very preterm delivery and hypercholesterolemia became attenuated after the first 10 years (Table 2.2).

To demonstrate the impact of adjustment for various pre-pregnancy lifestyle factors and family history, Appendix Table 2.4 shows HRs over all of follow-up with partial adjustment for confounding. For chronic hypertension and hypercholesterolemia, age- and fully-adjusted models were similar. However, for T2DM, we observed attenuation in the HRs for Model 2 as compared to Model 1, which was driven primarily by adjustment for family history of T2DM.

Figure 2.1 presents CVD risk profile specific cumulative incidence curves by preterm delivery status in first birth. The cumulative incidence of each risk factor was highest in women who delivered very preterm for both the low and high-risk CVD profiles. Differences in absolute risk were more pronounced in the high-risk CVD profile group than the low-risk profile group for chronic hypertension and T2DM, but not for hypercholesterolemia. Divergence in the

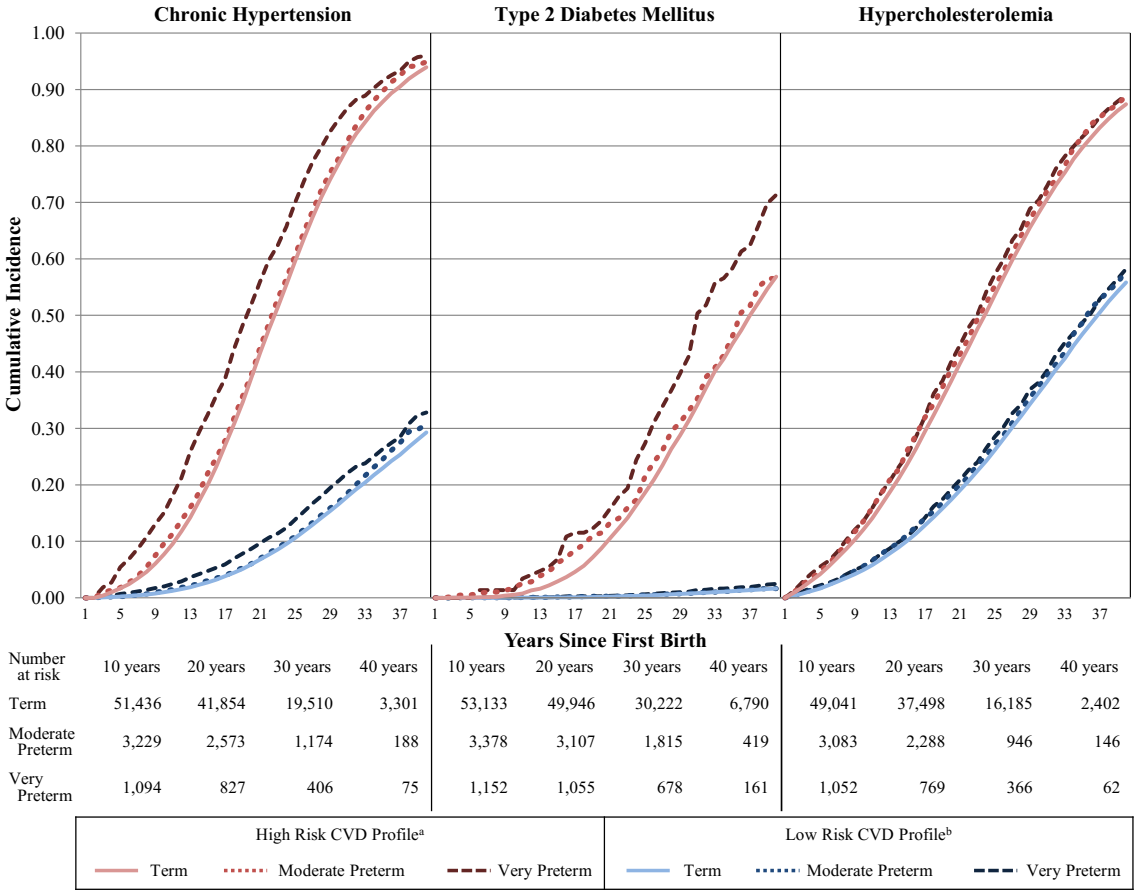

Figure 2.1: CVD risk-profile-specific cumulative incidence curves for CVD risk factor development by preterm delivery in first birth

[a]High Risk CVD Profile denotes the following characteristics before first pregnancy: mean age at first birth (age=27) and in 1989 (age=35), white, <9 years of parental education, obese BMI (≥30 kg/m^2), current smoker, unhealthiest diet (1st quintile of AHEI), no alcohol consumption, no physical activity, no oral contraceptive use, family history of hypertension (hypertension model) or diabetes (diabetes model)

[b]Low Risk CVD Profile denotes the following characteristics before first pregnancy: mean age at first birth (age=27) and in 1989 (age=35), white, ≥16 years of parental education, healthy BMI (18.5-24.9 kg/m^2), never smoker, healthiest diet (5th quintile of AHEI), 1 alcoholic drink per day, 10-12 months of physical activity per year, no oral contraceptive use, no family history of hypertension (hypertension model) or diabetes (diabetes model)

cumulative incidence curves between preterm delivery exposure groups occurred immediately in the high-risk CVD profile for chronic hypertension and at 10 years for T2DM.

Given that over half of the very preterm first births were stillbirths, we further evaluated the very preterm association separately in women whose first pregnancy resulted in a live birth (n=546) and those with a stillbirth (n=611). Risk patterns were generally similar for associations between very preterm live birth and stillbirth and each CVD risk factor; the relative risk primarily decreased over time, although the magnitudes varied between women who delivered live and stillbirths (Appendix Table 2.5). However, in women whose first very preterm delivery resulted in stillbirth, the rate of T2DM increased over time compared to women who delivered at term, with the highest HR occurring 31-40 years after first birth (1.85; 95% CI: 1.18, 2.90).

In examining the association between recurrent preterm deliveries and CVD risk factors in fully adjusted models, there was a 10% higher rate (95% CI: 1.01, 1.19) of chronic hypertension in women who delivered their first pregnancy at term and had at least one additional preterm delivery compared to women who had at least two births all of which were term. There were otherwise no associations between recurrent preterm delivery and chronic hypertension, T2DM, or hypercholesterolemia (Table 2.3).

Sensitivity Analyses

While the first pregnancy in our cohort occurred in 1964, the earliest date a woman could report a diagnosis of chronic hypertension or hypercholesterolemia was 1982 (based on the 1989 questionnaire response categories). Therefore, women whose first births were before 1982 contributed person-time during which, by design, they could not have developed chronic hypertension or hypercholesterolemia (i.e. immortal person-time). To test the impact of including this person-time in our primary analyses, we excluded person-time contributed before 1982

Table 2.3: Multivariable-adjusted hazard ratios (95% confidence intervals) for history of preterm deliveries and cardiovascular risk factors at age 40 or later, among women with no births at age 40 or later

		Chronic Hypertension		**Type 2 Diabetes Mellitus**		**Hypercholesterolemia**	
First Pregnancy	Second or later pregnancies	Cases/Person-Years	HR (95% CI)	Cases/Person-Years	HR (95% CI)	Cases/Person-Years	HR (95% CI)
Term	All Term	9,247/504,927	1.00 (ref)	1,198/614,820	1.00 (ref)	15,341/475,246	1.00 (ref)
Term	Any Preterm	663/33,824	1.10 (1.01, 1.19)	105/41,622	1.23 (1.00, 1.51)	1,066/32,336	1.04 (0.98, 1.11)
Term	No Births	1,785/96,868	1.01 (0.96, 1.07)	244/118,769	1.02 (0.88, 1.18)	2,971/90,498	1.00 (0.95, 1.04)
Preterm	All Term	445/23,042	1.09 (0.99, 1.20)	60/28,114	1.11 (0.86, 1.44)	708/21,798	1.04 (0.96, 1.12)
Preterm	Any Preterm	353/18,036	1.06 (0.95, 1.18)	45/22,244	0.89 (0.66, 1.19)	581/17,026	1.03 (0.95, 1.12)
Preterm	No Births	214/11,089	1.07 (0.93, 1.22)	35/13,851	1.24 (0.88, 1.76)	359/10,588	1.04 (0.94, 1.16)

Models are adjusted for age at first birth, age in 1989, race/ethnicity, parental education, family history of hypertension (for the chronic hypertension model), family history of type 2 diabetes mellitus (for the type 2 diabetes mellitus model), pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, pre-pregnancy (age 18) physical activity, pre-pregnancy oral contraceptive use, and parity at age 40.

(198,461 person-years for chronic hypertension and 199,650 person-years for hypercholesterolemia) and obtained similar results.

Additionally, because preterm delivery was retrospectively reported in 2001 or 2009, we performed a purely prospective analysis with follow-up only from 2009 to 2013, when women were a median of 28 (IQR: 23, 33) years since first birth. We found no significant associations between preterm delivery and the CVD risk factors, which is generally consistent with the attenuation of the relative risk 21-40 years after first birth in the primary analysis.

Finally, analyses using an alternative clinical hypertension outcome (including anti-hypertensive medication use as well as self-reported high blood pressure), including probable cases of T2DM in addition to definite cases, and excluding multiples yielded similar results to primary analyses (data not shown).

DISCUSSION

Women with a history of preterm delivery in first birth were at higher risk of developing chronic hypertension, T2DM, and hypercholesterolemia later in life; this increased risk was strongest in the first 10 years following a preterm delivery. We found a 2.8-fold increased risk of developing T2DM, 43% increased risk of chronic hypertension, and 13% increased risk of hypercholesterolemia in the first 10 years after a preterm delivery. Associations were generally stronger for women who delivered very preterm. For women with high-risk CVD profiles before pregnancy, risk curves diverged immediately following a preterm delivery for chronic hypertension and at 10 years for T2DM, while there was no separation between preterm exposure groups for hypercholesterolemia.

While some studies have reported higher blood pressure in women who have delivered an infant preterm, those that account for HDP are generally null.[22-25] The exception is a large registry-based study from Denmark that followed women 12-15 years after delivery and reported a 1.3 to 1.5 fold increased risk of hypertension for moderate and very preterm delivery, respectively, after adjusting for HDP.[17] Our study, which excluded first pregnancies complicated by HDP, found increased risks of similar magnitude in the first 10 years after preterm delivery, which disappeared in the moderate preterm group, but persisted in the very preterm group for up to 30 years.

Our analysis evaluating the association between preterm delivery and T2DM builds on an earlier NHSII study by incorporating the more comprehensive 2009 reproductive questionnaire data and extending the maximum follow-up time to 50 years.[21] The results from the current analysis are similar to the prior study in that moderate preterm delivery was associated with T2DM only in the first 10 years after first pregnancy and the increased risk in women with very preterm delivery emerged in the second decade after pregnancy. However, with more follow-up, we now observed that the increased risk of T2DM in women who delivered very preterm persists even through 40 years after pregnancy. Although studies examining the associations between preterm delivery and insulin or glucose levels in the years following pregnancy are inconsistent,[19, 24, 25] the studies that evaluate T2DM report elevated risk in women with a history of preterm delivery,[17, 20] consistent with our results.

To our knowledge, no studies have specifically evaluated the association between preterm delivery and the development of hypercholesterolemia, but studies looking at changes in lipid levels after pregnancy are largely consistent with our results.[19, 22-25] We found a significant increased risk of hypercholesterolemia only in the first 10 years after a very preterm delivery; no

associations were found in women who delivered an infant moderately preterm. Three studies report no differences in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides comparing women who delivered preterm to those who delivered at term.[23-25] Since moderate preterm delivery is more common than very preterm delivery,[18] these null results may be driven by moderate preterm delivery, which, in our data, was not associated with hypercholesterolemia. Consistent with our results, two studies with follow-up of less than 12 years since pregnancy show higher lipid levels and odds of hypertriglyceridemia, particularly in women who delivered very preterm.[19, 22]

The primary weaknesses of our study are exposure and outcome misclassification as gestation length, chronic hypertension, and hypercholesterolemia were all self-reported. However, validation studies of preterm delivery and chronic hypertension in the NHSII cohort and hypercholesterolemia in a similar cohort of nurses suggest good accuracy.[27, 31] The lack of information on statin use prior to 1999 may have resulted in additional misclassification of hypercholesterolemia early in follow-up as women may have not reported hypercholesterolemia because it was controlled by statins. We expect non-differential misclassification of the exposure and outcome, yielding bias towards the null. Additionally, the exact timing of the development of chronic hypertension and hypercholesterolemia were not known, but sensitivity analyses using parametric models for interval censored outcomes yielded similar conclusions to our primary analyses.

Since participants had to survive to 2001 or 2009 to report their pregnancy history, there is the potential that women who were lost to follow-up or died before this time were at higher risk of both preterm delivery and CVD risk factors. However, 98.3% of NHSII participants were alive in 2009, and our analysis with follow-up starting in 2009 obtained similar results to the

primary analysis. We were also unable to separate preterm delivery into spontaneous or medically induced, however, as HDP and GDM are both indications for preterm delivery,[7, 32] and women reporting these were excluded, many preterm deliveries in our analysis were likely spontaneous. Our results are subject to residual or unmeasured confounding; however, this study represents the most complete control of confounding for the preterm-CVD risk factors associations in the literature. Furthermore, adjustment for family history and established CVD lifestyle risk factors did not lead to strong attenuation of the associations. Therefore, it is unlikely that an unmeasured confounder would be strong enough to explain away the associations observed. Lastly, 93% of our study population was white, limiting generalizability, particularly because preterm delivery is more common in African-Americans and may result from different underlying causes.[50]

Despite these weaknesses, our study has various strengths. We had a large sample size (n=57,904) with the longest follow-up currently available in the literature. Women were followed for a median of 28 years for chronic hypertension, 32 years for diabetes, and 26 years for hypercholesterolemia, and up to 50 years after first birth. We were able to control for many established pre-pregnancy CVD lifestyle risk factors, including smoking, BMI, family history, and diet. Finally, this is the first study to describe the trajectories of the development of chronic hypertension and hypercholesterolemia after preterm delivery, which may inform prevention and screening protocols.

The causes of preterm delivery are multifactorial and include inflammation, infection, and vascular disease.[50] Dyslipidemia and high C-reactive protein and Interleukin-6 levels during pregnancy have been shown to be associated with preterm delivery.[51-53] Similarly, adverse lipid levels and inflammation are involved in the pathogenesis of atherosclerosis, the development of

clinical CVD risk factors, and ultimately, CVD events.[54-57] Preterm delivery is likely to be a marker of underlying subclinical CVD risk, rather than a cause of vascular and inflammatory changes resulting in a faster trajectory to the development of CVD risk factors and events. Regardless, preterm delivery provides an early look into a woman's future CVD risk, and is generally observed before a woman develops chronic hypertension, T2DM, and hypercholesterolemia, Thus, clinicians may be able to use information regarding a woman's history of preterm delivery to inform targeted prevention strategies and screening protocols that could be implemented soon after a preterm delivery. Linkage of obstetric medical records with primary care records would additionally allow clinicians to easily glean information on a woman's pregnancy history to facilitate the implementation of these protocols.

Further investigation of the association between preterm delivery and the development of clinical CVD risk factors in a more diverse population is warranted as the incidence and causes of preterm delivery vary by race/ethnicity.[50] Additionally, evaluations of spontaneous and medically induced preterm delivery, as well as preterm premature rupture of membranes, may reveal different relationships with CVD risk and provide insight into mechanisms linking preterm delivery and CVD. Prior research has shown that the development of chronic hypertension, T2DM, and hypercholesterolemia after preterm delivery only explains part of the association between preterm delivery and CVD events,[10] thus continued investigation into novel pathways connecting preterm delivery and CVD is necessary. Finally, the utility of including preterm delivery in established CVD risk prediction scores has not yet been assessed and may yield improvements in CVD risk prediction in women.

In conclusion, women who delivered an infant preterm were at higher risk of developing chronic hypertension, T2DM, and hypercholesterolemia after pregnancy. This increased risk was

particularly pronounced in the first 10 years after a preterm delivery, which may be an important time period to implement lifestyle interventions to delay or prevent the development of CVD risk factors.

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REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603.

2. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ. 2002;325(7356):157-60.

3. Rich-Edwards JW, McElrath TF, Karumanchi SA, et al. Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women. Hypertension. 2010;56(3):331-4.

4. Rich-Edwards JW. Reproductive health as a sentinel of chronic disease in women. Women's Health. 2009;5(2):101-5.

5. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(5):1545-88.

6. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. Journal of the American College of Cardiology. 2011;57(12):1404-23.

7. Sibai BM. Preeclampsia as a cause of preterm and late preterm (near-term) births. Seminars in Perinatology. 2006;30(1):16-9.

8. Irgens HU, Reisaeter L, Irgens LM, et al. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ. 2001;323(7323):1213-7.

9. Catov JM, Wu CS, Olsen J, et al. Early or recurrent preterm birth and maternal cardiovascular disease risk. Annals of Epidemiology. 2010;20(8):604-9.

10. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm Delivery and Maternal Cardiovascular Disease in Young and Middle-Aged Adult Women. Circulation. 2017;135(6):578-89.

11. Bonamy AK, Parikh NI, Cnattingius S, et al. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. Circulation. 2011;124(25):2839-46.

12. Hastie CE, Smith GC, Mackay DF, et al. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750 350 singleton pregnancies. International Journal of Epidemiology. 2011;40(4):914-9.

13. Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. American Journal of Obstetrics and Gynecology. 2013;209(4):368.e1-8.

14. Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. American Journal of Epidemiology. 2004;159(4):336-42.

15. Rich-Edwards JW, Klungsoyr K, Wilcox AJ, et al. Duration of pregnancy, even at term, predicts long-term risk of coronary heart disease and stroke mortality in women: a population-based study. American Journal of Obstetrics and Gynecology. 2015;213(4):518.e1-8.

16. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129 290 births. The Lancet. 2001;357(9273):2002-6.

17. Lykke JA, Paidas MJ, Damm P, et al. Preterm delivery and risk of subsequent cardiovascular morbidity and type-II diabetes in the mother. BJOG. 2010;117(3):274-81.

18. Martin JA, Hamilton BE, Osterman MJ, et al. Births: Final Data for 2015. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2017;66(1):1.

19. Catov JM, Dodge R, Yamal JM, et al. Prior preterm or small-for-gestational-age birth related to maternal metabolic syndrome. Obstetrics and Gynecology. 2011;117(2 Pt 1):225-32.

20. James-Todd T, Wise L, Boggs D, et al. Preterm birth and subsequent risk of type 2 diabetes in black women. Epidemiology. 2014;25(6):805-10.

21. James-Todd TM, Karumanchi SA, Hibert EL, et al. Gestational age, infant birth weight, and subsequent risk of type 2 diabetes in mothers: Nurses' Health Study II. Preventing Chronic Disease. 2013;10:E156.

22. Catov JM, Dodge R, Barinas-Mitchell E, et al. Prior preterm birth and maternal subclinical cardiovascular disease 4 to 12 years after pregnancy. Journal of Women's Health. 2013;22(10):835-43.

23. Catov JM, Lewis CE, Lee M, et al. Preterm birth and future maternal blood pressure, inflammation, and intimal-medial thickness: the CARDIA study. Hypertension. 2013;61(3):641-6.

24. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors

in middle age: the Avon Longitudinal Study of Parents and Children. Circulation. 2012;125(11):1367-80.

25. Perng W, Stuart J, Rifas-Shiman SL, et al. Preterm birth and long-term maternal cardiovascular health. Annals of Epidemiology. 2015;25(1):40-5.

26. ACOG Practice Bulletin No. 102: management of stillbirth. Obstetrics and gynecology. 2009;113(3):748-61.

27. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. Hypertension. 2008;52(5):828-32.

28. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes. 1979;28(12):1039-57.

29. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet. 1991;338(8770):774-8.

30. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes care. 1997;20(7):1183-97.

31. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. American Journal of Epidemiology. 1986;123(5):894-900.

32. Spong CY, Mercer BM, D'Alton M, et al. Timing of indicated late-preterm and early-term birth. Obstetrics and Gynecology. 2011;118(2 Pt 1):323-33.

33. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.

34. Brown MC, Best KE, Pearce MS, et al. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. European Journal of Epidemiology. 2013;28(1):1-19.

35. McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. American Heart Journal. 2008;156(5):918-30.

36. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circulation Cardiovascular Quality and Outcomes. 2017;10(2).

37. Heida KY, Franx A, van Rijn BB, et al. Earlier Age of Onset of Chronic Hypertension and Type 2 Diabetes Mellitus After a Hypertensive Disorder of Pregnancy or Gestational Diabetes Mellitus. Hypertension. 2015;66(6):1116-22.

38. Mannisto T, Mendola P, Vaarasmaki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127(6):681-90.

39. Lykke JA, Langhoff-Roos J, Sibai BM, et al. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009;53(6):944-51.

40. Magnussen EB, Vatten LJ, Smith GD, et al. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstetrics and Gynecology. 2009;114(5):961-70.

41. Feig DS, Shah BR, Lipscombe LL, et al. Preeclampsia as a risk factor for diabetes: a population-based cohort study. PLoS Medicine. 2013;10(4):e1001425.

42. Drost JT, Arpaci G, Ottervanger JP, et al. Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM). European Journal of Preventive Cardiology. 2012;19(5):1138-44.

43. Marin R, Gorostidi M, Portal CG, et al. Long-term prognosis of hypertension in pregnancy. Hypertension in Pregnancy. 2000;19(2):199-209.

44. Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ. 2003;326(7394):845.

45. Kaul P, Savu A, Nerenberg KA, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabetic Medicine. 2015;32(2):164-73.

46. Carr DB, Utzschneider KM, Hull RL, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care. 2006;29(9):2078-83.

47. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008;31(8):1668-9.

48. Tobias DK, Hu FB, Forman JP, et al. Increased risk of hypertension after gestational diabetes mellitus: findings from a large prospective cohort study. Diabetes Care. 2011;34(7):1582-4.

49. Julien M, Hanley JA. Profile-specific survival estimates: making reports of clinical trials more patient-relevant. Clinical Trials. 2008;5(2):107-15.

50. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

51. Catov JM, Bodnar LM, Ness RB, et al. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. American Journal of Epidemiology. 2007;166(11):1312-9.

52. Mendola P, Ghassabian A, Mills JL, et al. Retinol-Binding Protein 4 and Lipids Prospectively Measured During Early to Mid-Pregnancy in Relation to Preeclampsia and Preterm Birth Risk. American Journal of Hypertension. 2017.

53. Pitiphat W, Gillman MW, Joshipura KJ, et al. Plasma C-reactive protein in early pregnancy and preterm delivery. American Journal of Epidemiology. 2005;162(11):1108-13.

54. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.

55. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23.

56. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. The New England Journal of Medicine. 2000;342(12):836-43.

57. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

APPENDIX

Table 2.4: Multivariable-adjusted hazard ratios (95% confidence intervals) for preterm delivery in first birth and cardiovascular risk factors

	Term: ≥37 weeks (n=53,341)	Preterm: <37 weeks (n=4,563)	Moderate Preterm: ≥32 to <37 weeks (n=3,400)	Very Preterm: <32 weeks (n=1,163)	p-trend[a]
Chronic Hypertension					
Cases/Person-Years	16,557/1,453,407	1,507/120,769	1,079/90,279	428/30,490	
Model 1	1.00 (ref)	1.12 (1.06, 1.18)	1.06 (1.00, 1.13)	1.29 (1.17, 1.41)	<0.0001
Model 2	1.00 (ref)	1.11 (1.06, 1.17)	1.06 (1.00, 1.13)	1.28 (1.16, 1.41)	<0.0001
Model 3	1.00 (ref)	1.11 (1.06, 1.17)	1.06 (1.00, 1.13)	1.28 (1.16, 1.41)	<0.0001
Type 2 Diabetes Mellitus					
Cases/Person-Years	2,557/1,689,982	264/142,579	173/105,729	91/36,850	
Model 1	1.00 (ref)	1.24 (1.09, 1.40)	1.10 (0.94, 1.28)	1.62 (1.32, 2.00)	<0.0001
Model 2	1.00 (ref)	1.18 (1.04, 1.35)	1.07 (0.92, 1.25)	1.50 (1.22, 1.85)	0.0003
Model 3	1.00 (ref)	1.17 (1.03, 1.33)	1.06 (0.91, 1.24)	1.48 (1.19, 1.83)	0.0007
Hypercholesterolemia					
Cases/Person-Years	28,656/1,342,159	2,527/112,099	1,866/83,267	661/28,832	
Model 1	1.00 (ref)	1.07 (1.03, 1.11)	1.06 (1.01, 1.11)	1.09 (1.01, 1.18)	0.001
Model 2	1.00 (ref)	1.07 (1.02, 1.11)	1.06 (1.01, 1.11)	1.09 (1.01, 1.18)	0.002
Model 3	1.00 (ref)	1.07 (1.03, 1.11)	1.06 (1.01, 1.11)	1.09 (1.01, 1.18)	0.002

Model 1 is adjusted for age at first birth and age in 1989.

Model 2 is additionally adjusted for race/ethnicity, parental education, family history of hypertension (for the chronic hypertension model), and family history of type 2 diabetes mellitus (for the type 2 diabetes mellitus model).

Model 3 is additionally adjusted for pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, pre-pregnancy (age 18) physical activity, and pre-pregnancy oral contraceptive use.

[a]Exposure included in model as a continuous variable with 40 weeks representing term delivery, 36 weeks representing moderate preterm delivery, and 30 weeks representing very preterm delivery.

Table 2.5: Multivariable-adjusted hazard ratios (95% confidence intervals) for preterm delivery in first birth classified by live and stillbirth and cardiovascular risk factors

	Cases/Person-Years	Term: ≥37 weeks (n=53,200)	Moderate Preterm: ≥32 to <37 weeks (n=3,385)	Very Preterm Live Birth: <32 weeks (n=546)	Very Preterm Stillbirth: <32 weeks (n=611)	p-trend[a]
Chronic Hypertension						
Overall[b]	18,004/1,569,964	1.00 (ref)	1.06 (1.00, 1.13)	1.33 (1.16, 1.53)	1.25 (1.09, 1.42)	<0.0001
1-10 years	1,269/571,948	1.00 (ref)	1.22 (0.98, 1.51)	2.21 (1.50, 3.27)	1.97 (1.32, 2.94)	<0.0001
11-20 years	5,455/519,593	1.00 (ref)	0.96 (0.86, 1.08)	1.58 (1.25, 1.99)	1.37 (1.09, 1.73)	0.001
21-30 years	7,779/350,306	1.00 (ref)	1.05 (0.95, 1.15)	1.05 (0.82, 1.33)	1.28 (1.04, 1.57)	0.01
31-40 years	3,233/117,627	1.00 (ref)	1.16 (1.01, 1.34)	1.16 (0.82, 1.62)	0.73 (0.49, 1.07)	0.89
Type 2 Diabetes Mellitus						
Overall[b]	2,814/1,827,461	1.00 (ref)	1.06 (0.91, 1.24)	1.38 (0.99, 1.91)	1.58 (1.20, 2.09)	0.0002
1-10 years[c]	41/559,277	1.00 (ref)	3.37 (1.45, 7.83)	3.88 (0.84, 17.87)	--	0.17
11-20 years	526/565,930	1.00 (ref)	1.20 (0.86, 1.68)	2.21 (1.21, 4.04)	1.37 (0.64, 2.90)	0.03
21-30 years	1,295/461,258	1.00 (ref)	0.99 (0.78, 1.26)	1.18 (0.69, 1.99)	1.61 (1.08, 2.42)	0.04
31-40 years	885/200,962	1.00 (ref)	0.99 (0.74, 1.32)	1.03 (0.55, 1.92)	1.85 (1.18, 2.90)	0.03
Hypercholesterolemia						
Overall[b]	31,090/1,450,172	1.00 (ref)	1.06 (1.01, 1.11)	1.06 (0.94, 1.18)	1.11 (1.00, 1.24)	0.004
1-10 years	4,545/561,485	1.00 (ref)	1.10 (0.98, 1.23)	1.31 (1.01, 1.72)	1.17 (0.88, 1.56)	0.02
11-20 years	10,340/482,278	1.00 (ref)	1.06 (0.98, 1.15)	1.00 (0.82, 1.22)	1.21 (1.01, 1.45)	0.03
21-30 years	11,338/304,799	1.00 (ref)	1.02 (0.94, 1.10)	1.02 (0.84, 1.25)	1.01 (0.84, 1.21)	0.73
31-40 years	4,614/93,958	1.00 (ref)	1.07 (0.95, 1.21)	0.95 (0.70, 1.29)	1.07 (0.83, 1.38)	0.50

Models are adjusted for age at first birth, age in 1989, race/ethnicity, parental education, family history of hypertension (for the chronic hypertension model), family history of type 2 diabetes mellitus (for the type 2 diabetes mellitus model), pre-pregnancy BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, pre-pregnancy (age 18) physical activity, and pre-pregnancy oral contraceptive use.

[a]Exposure included in model as a continuous variable with most common gestation length as the value to represent each category.

[b]Includes all 49 years of follow-up for chronic hypertension and hypercholesterolemia and 50 years for type 2 diabetes mellitus.

[c]Asian race and other race were combined as there were 0 diabetes cases in Asian women; women who were underweight (n=1,256) or missing BMI (n=498) were excluded because there were 0 cases in these BMI groups; there were 0 cases in the very preterm stillbirth group, thus the hazard ratio was inestimable.

Chapter 3 Contributions of Preterm Delivery to Cardiovascular Disease Risk Prediction in Women

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ABSTRACT

Preterm delivery is associated with a 1.4- to 2-fold increased risk of cardiovascular disease (CVD), but the inclusion of preterm delivery in CVD risk prediction algorithms has not been tested. We evaluated whether including preterm delivery and parity in CVD risk scores improved identification of women at high risk compared to scores based on traditional risk factors. We predicted 10-year CVD risk using 120,480 observations contributed by 77,038 women from the Nurses' Health Study II. Cox proportional hazards models were fit with the established CVD risk factors (Model 1) and the established risk factors plus preterm delivery and parity (Model 2). We evaluated model fit, calibration, discrimination, and risk reclassification. Model 2 had improved fit relative to Model 1, but discrimination was not significantly improved in Model 2 based on the C-difference or net reclassification index. Similar models for 20-year CVD risk prediction indicated improved discrimination when including preterm delivery and parity. Incorporating preterm delivery and parity into CVD risk scores appears most useful when women are young, before they develop established CVD risk factors. The observed improvements in risk prediction were small and warrant further investigation to confirm our findings and assess utility in a clinical setting.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in the United States, with nearly 37% of people over the age of 20 living with CVD and resulting in over 800,000 deaths in 2014 (1). Identification of individuals at high risk for CVD is essential to prevent its development, target screening, and ultimately reduce the burden of CVD.

To identify people at high risk, established CVD risk factors, including blood pressure, anti-hypertensive medication use, total and high-density lipoprotein (HDL) cholesterol, smoking, and diabetes have been incorporated into risk prediction scores to predict 10-year and long term CVD risk (2-5). More recently, female-specific CVD markers, such as preeclampsia, gestational diabetes mellitus, preterm delivery, and birth of an infant small for gestational age, have been recognized as predictors of CVD. In 2011, the American Heart Association endorsed some of these pregnancy complications as CVD risk factors and suggested that clinicians obtain a detailed pregnancy history (6). However, the utility of including these female-specific markers into clinical CVD risk prediction scores has not been evaluated.

Ten percent of deliveries in the US are preterm (7) and women who have delivered an infant preterm are at about 1.4- to 2-fold increased risk of CVD depending on the degree of prematurity (8-16). Additionally, less than 20% of the elevated CVD risk appears due to the later development of hypertension, hypercholesterolemia, and type 2 diabetes mellitus (16). Since traditional CVD risk scores utilize information on blood pressure, diabetes, and lipid levels and much of the increased risk associated with preterm delivery is independent of these (16), the addition of preterm delivery into risk algorithms may improve CVD risk prediction in women.

To evaluate whether the inclusion of preterm delivery into 10-year and long term CVD risk scores improves prediction in women, we compared the performance of models using established CVD risk factors from the Pooled Cohort Equation (2) to models that additionally included preterm delivery and parity. We hypothesized that the incorporation of preterm delivery would improve identification of women at high risk. Furthermore, since preterm delivery typically occurs in young adulthood, generally before the development of clinical CVD risk factors, we hypothesized that its inclusion into CVD risk scores would have more impact at younger ages.

METHODS

Study Population

The study population was drawn from the Nurses' Health Study II (NHSII), a longitudinal, prospective cohort of 116,429 nurses with active follow-up beginning 1989, when participants were 25-42 years of age. Every two years, participants were mailed questionnaires which collected information on lifestyle and behavioral factors and incident disease. This study was approved by the Partners Human Research Committee (Institutional Review Board) of Brigham and Women's Hospital. Return of the questionnaires was considered informed consent.

Established Cardiovascular Disease Risk Factors

Participants reported current smoking, anti-hypertensive medication use, and incident diabetes diagnoses (not during pregnancy) on all biennial questionnaires. Self-reported diabetes was subsequently confirmed according to American Diabetes Association criteria (17, 18) using a supplemental questionnaire that collected information about symptoms, diagnostic tests, and hypoglycemic therapy. A validation study in a similar cohort confirmed 98% of self-reported diabetes diagnoses (19). In 1989 and 1999, participants self-reported "current usual blood

pressure (if checked within 2 years)" in categories. The midpoint of each systolic blood pressure (SBP) category was assigned as the continuous SBP for each woman. Validation of self-reported hypertension compared to medical records in a subset of NHSII participants resulted in 94% sensitivity and 85% specificity (20).

Plasma total and HDL cholesterol for all women in the NHSII were predicted from measured blood samples that were available in a subset of NHSII women who were included in previous sub-studies (nested case-control studies of chronic disease or cohort studies of lifestyle exposures). In total, 29,611 women provided a blood sample between 1996 and 2001. Measured total cholesterol was available in 3,994 participants after excluding women who did not complete the questionnaire at the time of blood draw (n=373), did not have total cholesterol measured in their blood sample (n=24,923), had cancer before the blood draw (n=13), were missing lab information (n=2) or data on diet or body mass index (BMI) before blood draw (n=305), or had measured cholesterol >500mg/dl (n=1). Measured HDL cholesterol was available for 1,182 women after excluding those who did not complete the questionnaire at the time of blood draw (n=373), did not have HDL cholesterol measured in their blood sample (n=28,000), had cancer before the blood draw (n=13), or were missing data on diet or body mass index (BMI) before blood draw (n=43).

Multivariable linear regression models were fit separately in women with measured total and HDL cholesterol and included the following covariates as predictors: age, race, smoking, alcohol consumption, body mass index (BMI), physical activity, menopausal status, post-menopausal hormone use, hypertension, type 2 diabetes mellitus, serum cholesterol (self-reported in categories in 1989), elevated cholesterol, family history of CVD before age 60, fiber intake, total caloric intake, and percent calories from polyunsaturated fatty acids,

monounsaturated fatty acids, saturated fat, trans fat, and protein. Covariate information was taken from the blood questionnaire or the biennial questionnaire closest, but prior, to the blood draw. Women who were missing information on the covariates included in the total and HDL cholesterol prediction models were assigned missing total and HDL cholesterol values and were excluded from the CVD risk prediction analysis.

Predicted total and HDL cholesterol were calculated for each woman in NHSII at each questionnaire cycle by multiplying each regression coefficient by that woman's covariate values and summing across covariates. The top and bottom 0.5% of predicted total and HDL cholesterol at each questionnaire cycle were set to missing to avoid extreme values. For the subset of women with measured total and HDL cholesterol, we calculated Spearman correlations between their measured values and predicted values in 1997 and 1999, the questionnaire cycles closest to the blood draw. In 1997 and 1999, we observed correlations of 0.56 and 0.58, respectively, for total cholesterol and 0.52 and 0.50, respectively, for HDL cholesterol.

Preterm Delivery and Parity

In 2009, women provided the gestation length of all pregnancies in the following categories: <8, 8-11, 12-19, 20-27, 28-31, 32-36, 37-39, 40-42, and ≥43 completed weeks. For women who did not complete the 2009 questionnaire (n=10,644), data from the 2001 questionnaire (which queried on the gestation length of pregnancies lasting at least 12 weeks) were used. Categories of gestation length were collapsed into term (≥37 weeks), moderate preterm (32 to <37 weeks), and very preterm (20 to <32 weeks). Women were assigned to the gestation length category that corresponded to their shortest gestation length at the time of entry into the risk prediction model. Women who reported at least one pregnancy lasting 20 weeks or

more were considered to be parous. Gestation length and parity were combined into a 4-category variable for modeling: nulliparous, term, moderate preterm, and very preterm.

Self-reported gestation length was validated against medical records in 403 NHSII participants who reported preeclampsia/toxemia between 1991 and 2001. This resulted in a sensitivity of 81% and specificity of 92% for dichotomous preterm delivery (<37 weeks, ≥37 weeks) and a Kappa statistic of 0.74 for 3 categories of preterm delivery (term, moderate preterm, very preterm), suggesting good validity.

Cardiovascular Disease Endpoints

In 1989, participants reported a previous diagnosis of "myocardial infarction (MI) or angina" or "stroke (CVA) or transient ischemic attack (TIA)". On subsequent biennial questionnaires, participants self-reported physician diagnoses of incident MI or stroke and the year of diagnosis. Permission to obtain medical records was requested from participants who reported a diagnosis or their next of kin if deceased. MIs were confirmed using the World Health Organization criteria of acute symptoms plus elevated cardiac enzymes or diagnostic electrocardiographic findings (21), while fatal coronary heart disease (CHD) was confirmed with hospital or autopsy records if CHD was noted as the cause of death in a woman with a known history of CHD. Strokes were classified according to the National Survey of Stroke criteria, which require a neurological deficit with sudden or rapid onset that persisted for ≥24 hours or until death (22). Events for which medical records were obtained and that met the above criteria were considered confirmed cases, while those which were acknowledged by the participant or their next of kin, but for which records were not acquired were considered probable. Our analysis included definite or probable MI, fatal CHD, and fatal and non-fatal stroke.

Exclusions

To maximize the 25 years of active follow-up from 1989 to 2013 included in our analysis of 10-year risk prediction, we divided the time into three independent intervals of ≤10 years: 1989-1993, 1994-2003, 2004-2013. We created these ≤10 year intervals starting at the end of follow-up in 2013 and going backwards to enable the complete 10-year intervals to capture the years when we expected women to be at the highest risk of CVD. Women were allowed to contribute person-time to one or more of these intervals as long as they met the eligibility criteria at the start of each interval. The following exclusion criteria were applied at the start of each interval and are detailed in Figure 3.1: <40 years of age (since the Pooled Cohort Equations were developed in people ≥40 years old (2)); CVD, death, or lost to follow-up before the start of the interval; did not complete a pregnancy history questionnaire; missing valid year of pregnancy; <14 or >50 years old at first birth; or missing data on model covariates (smoking, systolic blood pressure, total cholesterol, or HDL cholesterol). This resulted in 120,480 observations contributed by 77,038 women.

For longer term CVD risk prediction, we did not divide active follow-up into intervals. Rather, we employed 20-year risk prediction models where women were allowed to contribute person-time to the model from the first questionnaire cycle in which they reached the eligible age for entry (≥40 or ≥30 years of age depending on the model), were under active follow-up, and were not excluded based on the other criteria listed above. For 20-year risk prediction, we tested separate models including women ≥ 30 years (n=73,338) and including women ≥ 40 years (n=73,000).

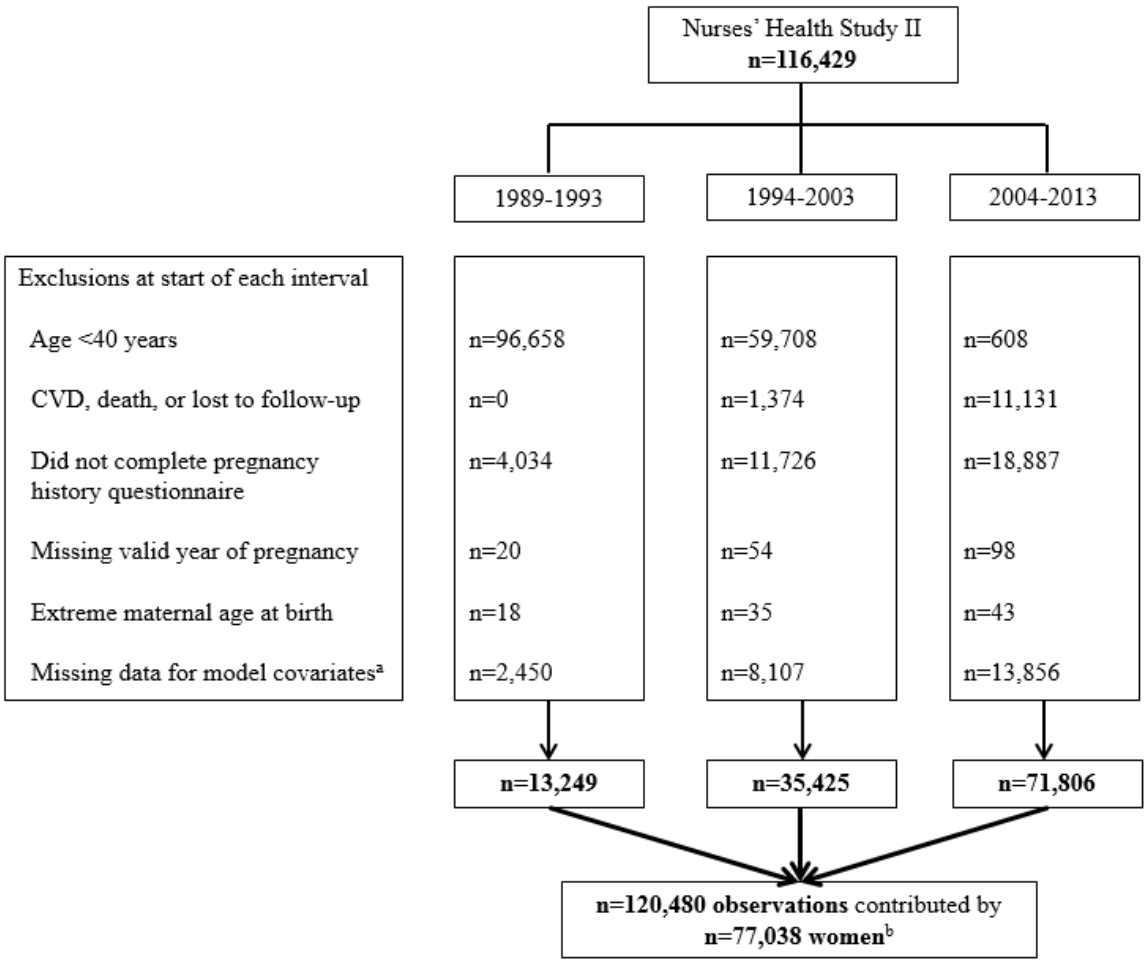

Figure 3.1: Flow diagram of Nurses' Health Study II participants and exclusion criteria by time period of follow-up for 10-year CVD risk prediction

[a] Current smoking, systolic blood pressure, total cholesterol, or HDL-cholesterol
[b] N=44,385 women contributed person-time to the analysis from only 1 interval, n=21,864 women contributed person-time to the analysis from 2 intervals, and n=10,789 women contributed person-time to the analysis from all 3 intervals

Statistical Analysis

Baseline characteristics of the study population were age-standardized and compared by preterm delivery and parity. The parameterization of the established CVD risk factor model was adapted from the Pooled Cohort Equation for white women (2), as 93% of our sample was white. The Pooled Cohort Equation is based on a Cox proportional hazards regression model that includes log transformations of age, age squared, total and HDL cholesterol, treated SBP (takes

the value of SBP if on anti-hypertensive medication and 0 otherwise), and untreated SBP (takes the value of SBP if not using anti-hypertensive medication and 0 otherwise), indicators for current smoking and diabetes, and interactions between age and all variables except diabetes. We evaluated the fit of this model in our data in comparison to simpler models without log transformations and age interactions and found similar or better model fit. Thus, our final model with established CVD risk factors (Model 1) included (untransformed) age, age squared, total and HDL cholesterol, treated SBP, untreated SBP, and indicators for current smoking and diabetes. The new model (Model 2) additionally included indicators for nulliparity, moderate preterm, and very preterm (with term as the reference group).

To evaluate the utility of preterm delivery and parity in CVD risk prediction, we followed the criteria for evaluation of novel risk markers from the American Heart Association (23). Multivariable Cox proportional hazards regression models were fit with the established CVD risk factors (Model 1) and with the established risk factors plus preterm delivery and parity (Model 2). For the 10-year risk prediction model, in which women could contribute multiple observations, we incorporated the robust sandwich covariance matrix estimate to account for correlated data. We compared the fit of these two models using the Akaike information criterion (AIC) and a likelihood ratio test. Calibration of each model was investigated using the Greenwood-Nam-D'Agostino test in which a non-significant *P*-value signifies sufficient calibration (24). Discrimination was determined by calculating the C-index, an extension of the area under the receiver-operating characteristic curve (25) for censored data, for Model 1 and Model 2 and their difference (26). Net reclassification statistics, including the overall net reclassification index (NRI), and the NRIs separately for women with and without a CVD event, were calculated using pre-determined categories of low (<5%), intermediate (5- to <10%), and

high (≥10%) CVD risk given the lower predicted risk of CVD in women compared to men (27, 28). Reclassification was also assessed using the continuous NRI and integrated discrimination improvement, which are not based on risk categories. Confidence intervals for discrimination and reclassification statistics were calculated using 1,000 bootstrap samples.

Sensitivity Analyses

An alternative dichotomous risk cut point of 7.5% was employed for the net reclassification statistics given the American College of Cardiology and American Heart Association's 2013 recommendations for initiation of statin therapy (29). We also incorporated body mass index in the models in place of predicted total and HDL cholesterol based on a previously proposed non-laboratory based CVD risk score (30). Lastly, we corrected for potential overfitting by adjusting for optimism using 1,000 bootstrap samples in discrimination and reclassification statistics. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). Calibration, discrimination, and reclassification statistics were calculated using publicly available SAS macros (31).

RESULTS

Table 3.1 summarizes age-standardized characteristics at each entry into the 10-year risk prediction model. Each woman is represented in this table up to three times based on the number of intervals to which she contributed person-time in the 10-year risk prediction since her covariate values were allowed to change at each time she entered the analysis. Approximately 4% of parous observations delivered at least one infant very preterm and about 10% delivered moderately preterm. Nulliparous women contributed 18% of observations. Established CVD risk factors were generally similar across preterm delivery and parity status, although women who

delivered very preterm were slightly more likely to use anti-hypertensive medication and women who had term births were less likely to be smokers and have diabetes.

Table 3.1: Age-standardized characteristics of Nurses' Health Study II participants by preterm delivery status for 10-year CVD risk prediction

	Nulliparous (n=22,233)	Term (n=84,625)	Moderate Preterm (n=9,572)	Very Preterm (n=4,050)
1989-1993	10.4	11.2	10.4	11.6
1994-2003	31.4	29.3	27.0	32.2
2004-2013	58.2	59.6	62.6	56.1
Age, years[a]	47.2 (5.1)	47.2 (5.1)	47.0 (5.0)	47.3 (5.2)
Total cholesterol[b], mg/dL	200.3 (23.2)	198.4 (22.3)	199.1 (22.4)	198.7 (22.1)
High density lipoprotein-cholesterol[b], mg/dL	62.1 (10.3)	62.1 (9.0)	61.9 (9.2)	61.5 (9.1)
Systolic blood pressure, mmHg	118.0 (12.2)	116.8 (11.8)	117.5 (12.3)	117.0 (12.4)
Anti-hypertensive medication use	9.9	8.6	10.5	11.6
Current smoker	11.2	8.7	10.2	11.3
Diabetes	2.3	1.7	2.3	2.4
Parity				
Nulliparous	100.0	0.0	0.0	0.0
1 birth	0.0	18.3	16.9	12.2
2 births	0.0	49.9	47.5	24.6
≥3 births	0.0	31.8	35.7	63.2

Values are means (SD) or percentages and are standardized to the age distribution of the study population.
Values of polytomous variables may not sum to 100% due to rounding.
Each woman is represented up to three times based on the number of intervals to which she contributed person-time in the 10-year risk prediction, since her covariate values were allowed to change at each time she entered the analysis.
[a]Value is not age adjusted.
[b]Total cholesterol and high density lipoprotein-cholesterol are predicted from measured values in a subset of women.

10-Year Risk Prediction at ≥40 Years of Age

We observed 823 incident cases of CVD over the three ≤10 year intervals. All established CVD risk factors were associated with an increased risk of CVD, except HDL cholesterol, in which higher levels reduced risk of CVD (Table 3.2, Model 1). In a crude model, very preterm delivery was associated with a significantly increased rate of CVD (hazard ratio (HR): 1.76, 95% confidence interval (CI): 1.30, 2.39), which was slightly attenuated, but persisted in the model including the established CVD risk factors (HR: 1.63, 95% CI: 1.20, 2.21; Table 3.2, Model 2). Estimated HRs for moderate preterm delivery suggested an increased risk of CVD, but were not significant in both crude (HR: 1.18, 95% CI: 0.92, 1.51) and adjusted (HR: 1.13, 95% CI: 0.88, 1.45) models (Table 3.2).

When comparing the fit of Models 1 and 2 for 10-year CVD risk prediction, Model 2 offered improved fit with a lower AIC and significant likelihood ratio test (P=0.03, Table 3.3). However, the addition of preterm delivery and parity did not improve discrimination (C-index: Model 1=0.69, Model 2=0.69; C-difference: 0.002, 95% CI: -0.001, 0.005) or calibration, although both models were adequately calibrated with P>0.05 (Table 3.3, Supplemental Figure 1). Similarly, overall net reclassification of observations into risk categories was not improved by Model 2 (NRI: 0.0009, 95% CI: -0.005, 0.006) nor was the NRI for CVD events (NRI for events: 0.001, 95% CI: -0.004, 0.007) (Table 3.4). While Model 2 correctly reclassified four observations (0.5%) who had a CVD event into higher risk categories compared to Model 1, it incorrectly reclassified three observations (0.4%) into lower risk categories (Table 3.4). In contrast, the NRI for non-events was worsened with the inclusion of preterm delivery and parity as 56 observations were incorrectly reclassified into higher risk categories, while only 25 were correctly reclassified into lower risk categories (NRI for non-events: -0.0003, 95% CI: -0.0004, -

0.0001) (Table 3.4). The continuous NRI and IDI – reclassification statistics not based on risk categories – both suggested improved risk reclassification in Model 2 compared to Model 1 (Table 3.4).

Table 3.2: Hazard ratios, 95% confidence intervals, and p-values for preterm delivery and parity in crude models, for the risk factors in the established 10-year CVD risk model (Model 1), and for the risk factors plus preterm delivery and parity in the established 10-year risk model plus preterm delivery and parity (Model 2)

	Hazard Ratio (95% CI)	***P*-value**
Crude Model		
Nulliparous	1.16 (0.98, 1.39)	0.09
Moderate Preterm	1.18 (0.92, 1.51)	0.19
Very Preterm	1.76 (1.30, 2.39)	0.0003
Model 1: Established CVD Risk Factors		
Age, years	1.02 (1.00, 1.04)	0.05
Age squared	1.00 (1.00, 1.00)	0.71
Total cholesterol, per 20 mg/dl	1.23 (1.15, 1.33)	<0.0001
HDL cholesterol, per 10 mg/dl	0.85 (0.79, 0.92)	<0.0001
Treated systolic blood pressure, per 10 mmHg	1.20 (1.13, 1.27)	<0.0001
Untreated systolic blood pressure, per 10 mmHg	1.16 (1.08, 1.23)	<0.0001
Current smoker (yes/no)	2.54 (2.14, 3.01)	<0.0001
Diabetes (yes/no)	1.58 (1.16, 2.16)	0.004
Model 2: Established CVD Risk Factors Plus Preterm Delivery and Parity		
Age, years	1.02 (1.00, 1.04)	0.05
Age squared	1.00 (1.00, 1.00)	0.70
Total cholesterol, per 20 mg/dl	1.23 (1.15, 1.32)	<0.0001
HDL cholesterol, per 10 mg/dl	0.85 (0.79, 0.92)	<0.0001
Treated systolic blood pressure, per 10 mmHg	1.20 (1.13, 1.27)	<0.0001
Untreated systolic blood pressure, per 10 mmHg	1.16 (1.08, 1.23)	<0.0001
Current smoker (yes/no)	2.52 (2.13, 2.99)	<0.0001
Diabetes (yes/no)	1.57 (1.15, 2.15)	0.004
Nulliparous	1.06 (0.89, 1.26)	0.51
Moderate Preterm	1.13 (0.88, 1.45)	0.33
Very Preterm	1.63 (1.20, 2.21)	0.002

Abbreviations: CI: confidence interval, HDL cholesterol: high density lipoprotein cholesterol
Continuous variables centered at the mean
Reference group for preterm and parity is term delivery

Table 3.3: Model fit, discrimination, and calibration statistics in 10- and 20-year CVD risk prediction based on established CVD risk model (Model 1) and on established CVD risk model plus preterm delivery and parity (Model 2)

	Model 1 Established CVD Risk Model	Model 2 Established CVD Risk Model PLUS Preterm Delivery and Parity	95% Confidence Interval	*P*-Value
10-year risk prediction at ≥40 years of age [a]				
Model Fit[d]				
AIC	18,678	18,674		0.03
Discrimination				
C-index	0.69	0.69		
C-difference		0.002	-0.001, 0.005	0.25
Calibration				
GND P-value[e]	0.07	0.06		
Net Reclassification Index[f]		0.0009	-0.005, 0.006	0.74
20-year risk prediction at ≥40 years of age[b]				
Model Fit[d]				
AIC	19,263	19,256		0.003
Discrimination				
C-index	0.66	0.67		
C-difference		0.004	-0.0005, 0.008	0.09
Calibration				
GND P-value[e]	0.80	0.92		
Net Reclassification Index[f]		0.005	-0.006, 0.02	0.39
20-year risk prediction at ≥30 years of age[c]				
Model Fit[d]				
AIC	20,078	20,067		<0.001
Discrimination				
C-index	0.69	0.69		
C-difference		0.004	0.0007, 0.008	0.02
Calibration				
GND P-value[e]	0.63	0.66		
Net Reclassification Index[f]		0.01	0.005, 0.02	0.002

[a]10-year risk prediction model allows women to enter one, two, or three times at the start of each ≤10 year interval (1989-1993, 1994-2003, 2004-2013) if they meet the eligibility criteria at the beginning of each interval.
[b]Women enter the 20-year risk prediction models once: the first questionnaire cycle at which they are ≥40 years of age and meet the eligibility criteria.
[c]Women enter the 20-year risk prediction models once: the first questionnaire cycle at which they are ≥30 years of age and meet the eligibility criteria.
[d]P-value is from a likelihood ratio test comparing nested models.
[e]Greenwood-Nam-D'Agostino Test; non-significant p-value indicates sufficient calibration.
[f]Overall net reclassification index using 3 categories: <5%, 5%-<10%, ≥10%.

Table 3.4: Net reclassification of 10-year CVD risk into low (<5%), intermediate (≥5 - <10%), and high (≥10%) risk groups comparing the established risk factor model (Model 1) to a model with the established risk factors plus preterm delivery and parity (Model 2)

	Model 2: Established Risk Factors Plus Preterm Delivery and Parity Categories of Predicted 10-Year Risk			
Model 1: Established Risk Factors Categories of Predicted 10-Year Risk	**Low Risk: <5%**	**Intermediate Risk: 5% - <10%**	**High Risk: ≥10%**	Total Reclassified
Observations with incident CVD (n=823)				
Low Risk: <5%				
N	795	3	0	3
% Reclassified	---	0.38	0.00	0.38
Intermediate Risk: 5% - <10%				
N	3	19	1	4
% Reclassified	13.04	---	4.35	17.39
High Risk: ≥10%				
N	0	0	2	0
% Reclassified	0.00	0.00	---	0.00
Observations without incident CVD (n=119,657)				
Low Risk: <5%				
N	119,232	49	0	49
% Reclassified	---	0.04	0.00	0.04
Intermediate Risk: 5% - <10%				
N	23	319	7	30
% Reclassified	6.59	---	2.01	8.60
High Risk: ≥10%				
N	0	2	25	2
% Reclassified	0.00	7.41	---	7.41

NRI: 0.0009, 95% CI: -0.005, 0.006, p=0.74
NRI for events: 0.001, 95% CI: -0.004, 0.007, p=0.67
NRI for non-events: -0.0003, 95% CI: -0.0004, -0.0001, p<0.001
Continuous NRI: 0.09, 95% CI: 0.02, 0.15, p<0.01
IDI: 0.0002, 95% CI: 0.0001, 0.0003, p<0.001

20-Year Risk Prediction at ≥40 Years of Age

Very preterm delivery was associated with a 77% (95% CI: 1.34, 2.34; Appendix Table 3.5) increased risk of CVD in the 20-year risk model at ≥40 years of age with the established CVD risk factors. The inclusion of preterm delivery and parity improved model fit and yielded a

lower AIC and significant likelihood ratio test (P=0.003) (Table 3.3). Discrimination and net reclassification statistics were not improved (Table 3.3 and Appendix Table 3.6), but both the model with the established CVD risk factors and the model that additionally included preterm delivery and parity were well calibrated (Model 1: P=0.80, Model 2: P=0.92; Table 3.3, Appendix Figure 3.2).

20-Year Risk Prediction at ≥30 Years of Age

A lower AIC and significant likelihood ratio test (P<0.001) were also observed with the addition of preterm delivery and parity to a 20-year risk prediction model for women ≥30 years of age with the established CVD risk factors (Table 3.3). Additionally, discrimination was improved (C-difference: 0.004, 95% CI: 0.0007, 0.008), and both models were sufficiently calibrated (Model 1: P=0.63, Model 2: P=0.66; Table 3.3, Appendix Figure 3.2). Moreover, overall net reclassification was enhanced with the inclusion of preterm delivery and parity, which was driven by a small improvement in women with CVD events (NRI for events: 0.01, 95% CI: 0.005, 0.02; Table 3.3 and Appendix Table 3.7). Model 2 correctly reclassified 11 women (1.3%) with CVD events into higher risk categories without incorrectly reclassifying anyone. However, the NRI for non-events was significantly diminished (NRI for non-events: -0.0006, 95% CI: -0.0009, -0.0002; Appendix Table 3.7).

Sensitivity Analyses

When we used a dichotomous cut point of 7.5% for risk reclassification, results were similar, with the exception of 20-year risk prediction at ≥30 years of age in which the overall NRI and NRI for events were no longer significantly improved after adding preterm delivery and parity (NRI for events: 0.004, 95% CI: -0.004, 0.01). Adjustment for optimism and restriction to definite cases only also generally yielded similar results (data not shown). Lastly, the use of BMI

in our models instead of predicted total and HDL cholesterol largely did not change our conclusions; however, discrimination in 20-year risk prediction at ≥40 years of age was improved with the inclusion of preterm delivery and parity into the model with established CVD risk factors (C-index: Model 1=0.67, Model 2=0.68; C-difference: 0.005, 95% CI: 0.0006, 0.01).

DISCUSSION

The inclusion of preterm delivery and parity into a model with established CVD risk factors improved model fit in 10- and 20-year risk prediction both for women ≥40 and ≥30 years of age. Calibration, or how close the predicted risk of CVD is to the observed risk of CVD, was improved in both 20-year risk prediction models. However, discrimination, or how well a model separates women who have CVD events from those who do not, and net reclassification of women with CVD events were improved only in the 20-year risk prediction model for women ≥30 years of age. These results are consistent with our hypothesis that preterm delivery and parity would be more useful in risk prediction at younger ages, before women develop established CVD risk factors.

While discrimination was significantly improved in 20-year risk prediction at ≥30 year of age, the C-difference was only 0.004 and, thus, is unlikely to result in meaningful clinical change. However, the small change in the C-index with the inclusion of preterm delivery and parity is not surprising given that the C-statistic is often insensitive to change even with the addition of strong predictors of the outcome (32). While 11 women (1.3%) who went on to have a CVD event were correctly reclassified into higher risk categories based on the model with preterm delivery and parity, this came with a cost, as 97 women (0.1%) who did not have a CVD event were also reclassified into higher risk categories. This may yield appropriate earlier screening, lifestyle modifications, and pharmacologic therapy in women who ultimately will

have a CVD event. However, this may cause unnecessary, although unlikely to be harmful, additional medical care in a small proportion of women who do not need it for CVD risk (but who may benefit for risk reduction for hypertension, hypercholesterolemia, or diabetes). Furthermore, whether this small improvement in risk reclassification for women with CVD risk translates to improved clinical outcomes cannot be determined with this data.

To our knowledge, this is the first evaluation of the utility of preterm delivery in CVD risk scores. Therefore, these results should be confirmed in additional studies. Further research should also assess whether use of preterm delivery in a 20-year risk prediction model improves clinical CVD outcomes relative to women who are managed using the established CVD risk score as well as the cost-effectiveness of incorporating information on preterm delivery into clinical practice (23). Despite the limited improvement in risk prediction with the inclusion of preterm delivery and parity, this information may offer practical advantages over established CVD risk factors in that it is easy to collect, can be provided by the patient without any tests, and is generally available when women are in their 20s or 30s. Additionally, given the availability of information on preterm delivery when women are young - generally before the development of hypertension, hypercholesterolemia, and type 2 diabetes - preterm delivery may be particularly advantageous for clinicians to use in primordial prevention. Electronic health records in which obstetric records are linked with primary care records would also facilitate this transfer of information, further enhancing the practical advantage.

The primary limitation is the reliance on predicted total and HDL cholesterol rather than measured values. However, correlations between measured and predicted values suggested good validity. Additionally, a sensitivity analysis using BMI instead of predicted total and HDL cholesterol yielded similar conclusions to our primary analysis. SBP was self-reported by nurse

participants, which may have resulted in misclassification. A prior validation study utilizing medical records of NHSII participants resulted in a sensitivity of 94% and specificity of 85% for high blood pressure (20). We also relied on self-reported gestation length. However, a validation study in NHSII suggested good validity. Additionally, the use of self-reported preterm delivery mimics the clinical setting in which women would tell their doctors if they had ever delivered an infant preterm. Given that data on gestation length was extracted from the 2001 or 2009 questionnaire, participants had to survive until these years to report the information. However, 98.3% of NHSII participants were still alive in 2009.

We were unable to evaluate the utility of including preterm delivery and parity into 30-year CVD risk prediction models because the longest follow-up in our cohort was 25.6 years. The evaluation of a 20-year risk prediction model is a first step, but further research is needed to investigate longer term CVD risk prediction with preterm delivery. Our study population was predominately white; thus, our results may not be generalizable to other races, particularly African-Americans, in which a history of preterm delivery is more prevalent (33) and may impact CVD risk prediction differently. Additionally, the large majority of women in our population were classified as low risk by both the established risk factor model and the model additionally incorporating preterm delivery and parity. In the 20-year risk prediction at ≥40 years of age, the analysis with the highest predicted probability of CVD, the mean predicted risk was 1.5% and 83% of women had a predicted risk <2%, making it difficult for the new model with preterm delivery and parity to reclassify a substantial proportion of women with CVD into even the intermediate risk category (5%-<10%). Lastly, the prevalence of preterm delivery may limit its utility on a population level; however, given its strong association with CVD, it remains of importance on an individual level.

Despite these limitations, our study has several strengths. We have a large study population with long follow-up, which provided us with the ability to evaluate the inclusion of preterm delivery and parity in 10-year and 20-year risk prediction models as well as at different ages. Additionally, we used CVD events that were confirmed by medical record review. Finally, to our knowledge, this is the first study to investigate the utility of preterm delivery in CVD risk prediction models.

In conclusion, incorporating preterm delivery and parity into CVD risk prediction models appears to be most useful when women are young before they develop the established CVD risk factors that are currently the foundation of clinically used CVD risk scores. However, the observed improvements in risk prediction with the inclusion of preterm delivery and parity were small and warrant further investigation to confirm our findings and assess the utility in a clinical setting.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018.

2. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63(25 Pt B):2935-59.

3. Pencina MJ, D'Agostino RB, Sr., Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119(24):3078-84.

4. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007;297(6):611-9.

5. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.

6. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. Journal of the American College of Cardiology. 2011;57(12):1404-23.

7. Martin JA, Hamilton BE, Osterman MJ, et al. Births: Final Data for 2015. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2017;66(1):1.

8. Bonamy AK, Parikh NI, Cnattingius S, et al. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. Circulation. 2011;124(25):2839-46.

9. Catov JM, Wu CS, Olsen J, et al. Early or recurrent preterm birth and maternal cardiovascular disease risk. Annals of Epidemiology. 2010;20(8):604-9.

10. Hastie CE, Smith GC, Mackay DF, et al. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750 350 singleton pregnancies. International Journal of Epidemiology. 2011;40(4):914-9.

11. Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. American Journal of Obstetrics and Gynecology. 2013;209(4):368.e1-8.

12. Lykke JA, Paidas MJ, Damm P, et al. Preterm delivery and risk of subsequent cardiovascular morbidity and type-II diabetes in the mother. BJOG. 2010;117(3):274-81.

13. Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. American Journal of Epidemiology. 2004;159(4):336-42.

14. Rich-Edwards JW, Klungsoyr K, Wilcox AJ, et al. Duration of pregnancy, even at term, predicts long-term risk of coronary heart disease and stroke mortality in women: a population-based study. American Journal of Obstetrics and Gynecology. 2015;213(4):518.e1-8.

15. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129 290 births. The Lancet. 2001;357(9273):2002-6.

16. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm Delivery and Maternal Cardiovascular Disease in Young and Middle-Aged Adult Women. Circulation. 2017;135(6):578-89.

17. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20(7):1183-97.

18. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes. 1979;28(12):1039-57.

19. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet. 1991;338(8770):774-8.

20. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. Hypertension. 2008;52(5):828-32.

21. Organization WH. IHD Registers: Report of the Fifth Working Group: Copenhagen: World Health Organization 1971.

22. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. Stroke. 1981;12(2 Pt 2 Suppl 1):I13-44.

23. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119(17):2408-16.

24. Demler OV, Paynter NP, Cook NR. Tests of calibration and goodness-of-fit in the survival setting. Statistics in Medicine. 2015;34(10):1659-80.

25. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.

26. Harrell FE, Jr. Regression Modeling Strategies. New York: Springer; 2001.

27. Cavanaugh-Hussey MW, Berry JD, Lloyd-Jones DM. Who exceeds ATP-III risk thresholds? Systematic examination of the effect of varying age and risk factor levels in the ATP-III risk assessment tool. Preventive Medicine. 2008;47(6):619-23.

28. Marma AK, Lloyd-Jones DM. Systematic examination of the updated Framingham heart study general cardiovascular risk profile. Circulation. 2009;120(5):384-90.

29. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014;63(25 Pt B):2889-934.

30. Gaziano TA, Young CR, Fitzmaurice G, et al. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. Lancet. 2008;371(9616):923-31.

31. Cook NR. Risk Prediction Modeling SAS Macros. Boston: Division of Preventive Medicine, Brigham and Women's Hospital.

32. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007;115(7):928-35.

33. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

APPENDIX

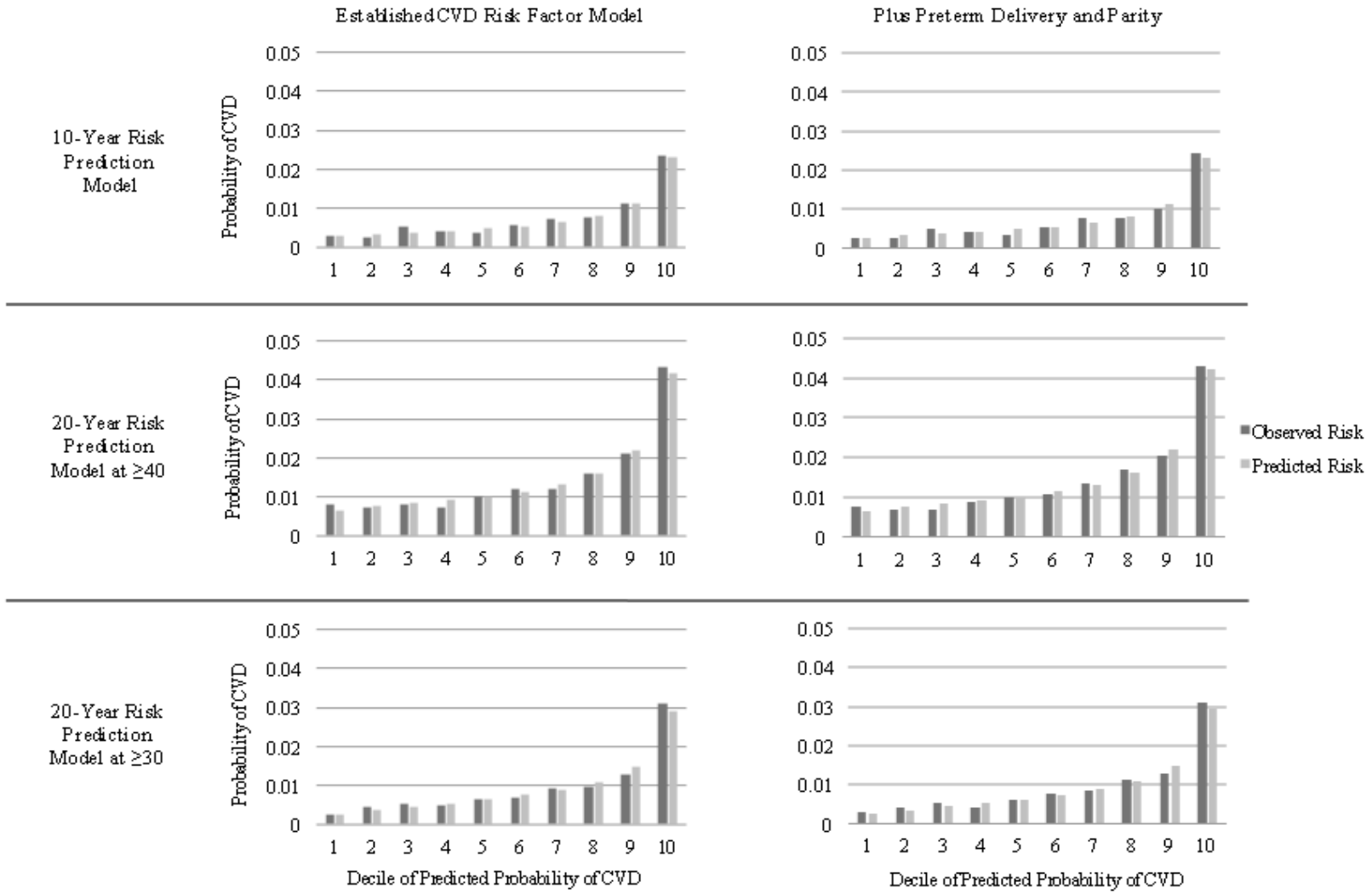

Figure 3.2: Observed and predicted probabilities of CVD by decile of predicted probability using the established CVD risk factor model (Model 1) and the established model plus preterm delivery and parity (Model 2)

Table 3.5: Hazard ratios, 95% confidence intervals, and p-values for preterm delivery and parity in crude models, for the risk factors in the established 20-year CVD risk models (Model 1), and for the risk factors, preterm delivery, and parity in the established 20-year CVD risk models plus preterm delivery and parity (Model 2)

	20-Year CVD Risk Prediction Model			
	At ≥40 years of age		**At ≥30 years of age**	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Crude Model				
Nulliparous	1.19 (1.01, 1.40)	0.04	0.97 (0.83, 1.13)	0.66
Moderate Preterm	1.17 (0.92, 1.49)	0.19	1.24 (0.97, 1.57)	0.09
Very Preterm	1.93 (1.45, 2.55)	<0.0001	2.19 (1.65, 2.91)	<0.0001
Model 1: Established CVD Risk Factors				
Age, years	1.03 (0.93, 1.13)	0.62	1.10 (1.08, 1.13)	<0.0001
Age squared	1.02 (0.93, 1.11)	0.70	0.99 (0.99, 1.00)	0.01
Total cholesterol, per 20 mg/dl	1.24 (1.15, 1.33)	<0.0001	1.23 (1.13, 1.33)	<0.0001
HDL cholesterol, per 10 mg/dl	0.80 (0.74, 0.86)	<0.0001	0.80 (0.73, 0.87)	<0.0001
Treated systolic blood pressure, per 10 mmHg	1.25 (1.19, 1.32)	<0.0001	1.24 (1.18, 1.31)	<0.0001
Untreated systolic blood pressure, per 10 mmHg	1.21 (1.14, 1.28)	<0.0001	1.21 (1.14, 1.28)	<0.0001
Current smoker (yes/no)	2.32 (1.98, 2.72)	<0.0001	2.29 (1.96, 2.68)	<0.0001
Diabetes (yes/no)	1.82 (1.01, 3.26)	0.05	2.32 (0.33, 16.54)	0.40
Model 2: Established CVD Risk Factors Plus Preterm Delivery and Parity				
Age, years	1.03 (0.93, 1.13)	0.62	1.10 (1.08, 1.13)	<0.0001
Age squared	1.02 (0.93, 1.12)	0.70	0.99 (0.99, 1.00)	0.01
Total cholesterol, per 20 mg/dl	1.23 (1.14, 1.33)	<0.0001	1.23 (1.13, 1.33)	<0.0001
HDL cholesterol, per 10 mg/dl	0.80 (0.74, 0.86)	<0.0001	0.80 (0.73, 0.87)	<0.0001
Treated systolic blood pressure, per 10 mmHg	1.25 (1.19, 1.32)	<0.0001	1.24 (1.17, 1.31)	<0.0001
Untreated systolic blood pressure, per 10 mmHg	1.21 (1.14, 1.28)	<0.0001	1.21 (1.14, 1.28)	<0.0001
Current smoker (yes/no)	2.31 (1.97, 2.70)	<0.0001	2.28 (1.96, 2.67)	<0.0001
Diabetes (yes/no)	1.82 (1.02, 3.28)	0.04	2.43 (0.34, 17.30)	0.38
Nulliparous	1.07 (0.91, 1.26)	0.42	1.03 (0.88, 1.20)	0.73
Moderate Preterm	1.11 (0.88, 1.41)	0.38	1.19 (0.93, 1.51)	0.17
Very Preterm	1.77 (1.34, 2.34)	<0.0001	1.89 (1.42, 2.51)	<0.0001

Abbreviations: CI: confidence interval, HDL cholesterol: high density lipoprotein cholesterol.

Continuous variables centered at the mean

Reference group for preterm and parity is term delivery

Table 3.6: Net reclassification of 20-year CVD risk at ≥40 years of age into low (<5%), intermediate (≥5 - <10%), and high (≥10%) risk groups comparing the established risk factor model (Model 1) to a model with the established risk factors plus preterm delivery and parity (Model 2)

	Model 2: Established Risk Factors Plus Preterm Delivery and Parity Categories of Predicted 20-Year Risk			
Model 1: Established Risk Factors Categories of Predicted 20-Year Risk	**Low Risk: <5%**	**Intermediate Risk: 5% - <10%**	**High Risk: ≥10%**	Total Reclassified
Women with incident CVD (n=907)				
Low Risk: <5%				
N	812	11	0	11
% Reclassified	---	1.34	0.00	1.34
Intermediate Risk: 5% - <10%				
N	4	58	5	9
% Reclassified	5.97	---	7.56	13.53
High Risk: ≥10%				
N	0	4	13	4
% Reclassified	0.00	23.53	---	23.53
Women without incident CVD (n=72,093)				
Low Risk: <5%				
N	70,629	166	0	166
% Reclassified	---	0.23	0.00	0.23
Intermediate Risk: 5% - <10%				
N	109	1,030	28	139
% Reclassified	9.34	---	2.40	11.74
High Risk: ≥10%				
N	0	11	120	11
% Reclassified	0.00	8.40	---	8.40

NRI: 0.005, 95% CI: -0.006, 0.02, p=0.39

NRI for events: 0.006, 95% CI: -0.005, 0.02, p=0.29

NRI for non-events: -0.001, 95% CI: -0.002, -0.0006, p<0.0001

Continuous NRI: 0.11, 95% CI: 0.05, 0.19, p=0.002

IDI: 0.0005, 95% CI: 0.0003, 0.0008, p<0.0001

Table 3.7: Net reclassification of 20-year CVD risk at ≥30 years of age into low (<5%), intermediate (≥5 - <10%), and high (≥10%) risk groups comparing the established risk factor model (Model 1) to a model with the established risk factors plus preterm delivery and parity (Model 2)

	Model 2: Established Risk Factors Plus Preterm Delivery and Parity Categories of Predicted 20-Year Risk			
Model 1: Established Risk Factors Categories of Predicted 20-Year Risk	**Low Risk: <5%**	**Intermediate Risk: 5% - <10%**	**High Risk: ≥10%**	Total Reclassified
Women with incident CVD (n=924)				
Low Risk: <5%				
N	874	7	0	7
% Reclassified	---	0.79	0.00	0.79
Intermediate Risk: 5% - <10%				
N	0	32	4	4
% Reclassified	0.00	---	11.11	11.11
High Risk: ≥10%				
N	0	0	7	0
% Reclassified	0.00	0.00	---	0.00
Women without incident CVD (n=72,424)				
Low Risk: <5%				
N	71,937	83	0	83
% Reclassified	---	0.12	0.00	0.12
Intermediate Risk: 5% - <10%				
N	51	304	14	65
% Reclassified	14.05	---	3.78	17.83
High Risk: ≥10%				
N	0	5	19	5
% Reclassified	0.00	20.83	---	20.83

NRI: 0.01, 95% CI: 0.005, 0.02, p=0.002

NRI for events: 0.01, 95% CI: 0.006, 0.02, p=0.001

NRI for non-events: -0.0006, 95% CI: -0.0009, -0.0002, p<0.001

Continuous NRI: 0.08, 95% CI: 0.03, 0.14, p=0.002

IDI: 0.0004, 95% CI: 0.0003, 0.0006, p<0.0001

Conclusion

Women who delivered a preterm infant were at a 40% increased risk of future CVD events, whereas those who delivered before 32 weeks experienced a doubling of CVD risk, even after accounting for pre-pregnancy sociodemographic, lifestyle and CVD risk factors. These women were also at higher risk of developing chronic hypertension, type 2 diabetes mellitus, and hypercholesterolemia later in life; this increased risk was strongest in the first 10 years following a preterm delivery and in women who delivered very preterm. However, the development of chronic hypertension, type 2 diabetes mellitus, hypercholesterolemia, and changes in weight in the years after pregnancy explained only a small proportion of the increased risk of CVD observed in women with a history of preterm delivery. Additionally, inclusion of preterm delivery into CVD risk scores yielded small improvements in CVD risk prediction, but only when women were at younger ages.

These results suggest that preterm delivery may be a useful prognostic tool to identify women at high risk of CVD early in life who would benefit from early screening, prevention, and treatment. However, given that less than 20% of the increased risk of CVD in women with a history of preterm delivery was explained by the established CVD risk factors that early screening, prevention, and treatment would typically target, future research should evaluate novel pathways through which preterm delivery and CVD may be linked to identify more relevant targets in women with a history of preterm delivery. Investigations of spontaneous and medically induced preterm delivery and preterm premature rupture of membranes may reveal different relationships with CVD risk and provide insight into mechanisms linking preterm delivery and CVD.

These results do not suggest that the inclusion of preterm delivery into clinically used CVD risk scores is currently warranted. Future research should evaluate the utility of preterm delivery in CVD risk scores in populations at higher risk of CVD and with more racial and ethnic diversity. Additionally, incorporation of preterm delivery into 30-year or lifetime CVD risk scores may yield more clinically relevant improvements in CVD risk prediction.

In conclusion, targeting CVD risk factors is unlikely to counteract the increased risk of CVD in women with a history of preterm delivery. However, established CVD risk factors remain important targets for prevention, screening, and treatment in all women regardless of their pregnancy history. Future research should focus on identifying specific prevention, screening, and treatment targets that are additionally important in women with a history of preterm delivery. Finally, preterm delivery should be formally added to the list of CVD risk factors in women.