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

Lauren J. Tanz, MSPH[1,2] **[ScD Candidate]**, **Jennifer J. Stuart, MSc**[1,2], **Paige L. Williams, PhD**[1,3], **Eric B. Rimm, ScD**[1,4,5,6], **Stacey A. Missmer, ScD**[1,5,6,7], **Kathryn M. Rexrode, MD, MPH**[8], **Kenneth J. Mukamal, MD, MPH**[4,9], and **Janet W. Rich-Edwards, ScD**[1,2,6]

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[2]Connors Center for Women's Health and Gender Biology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

[4]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[5]Division of Adolescent and Young Adult Medicine, Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA

[6]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[7]Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, Grand Rapids, MI

[8]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[9]Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA

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.

Correspondence to: Lauren Tanz, Connors Center for Women's Health and Gender Biology, 1620 Tremont Street, 3rd Floor, Boston, MA 02120, **Phone:** 203-470-7176, **Fax:** 617-525-7746, ltanz@mail.harvard.edu.

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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 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). Compared to 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 partially accounted for 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. Since 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.

Keywords

epidemiology; cardiovascular disease; pregnancy; women; prevention

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, as 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 25–42 at baseline in 1989. Participants were followed using biennial questionnaires, which collected data on diet, physical activity, smoking, medications, and reproductive history, as well as incident disease since the last questionnaire. In 2001, 91,297 nurses were mailed a supplemental questionnaire containing a pregnancy history assessment that recorded gestation length, infant sex, and birthweight of each pregnancy lasting at least 12 weeks. 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, 8–11, 12–19, 20–27, 28–31, 32–36, 37–39, 40–42, 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–<20, 20–<24, 24–<28, 28–<32, 32–<37, 37–42, and 43+ weeks. For our primary analyses, which utilized 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, as well as 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 to 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, as 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 due 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, while 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 based on *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 prior to the first pregnancy. Since the majority of first pregnancies (82%) occurred prior to 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 additionally 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 less than 18 (n=896) or greater than 45 (n=58) at first birth, or reported MI (n=288) or stroke (n=176) on the 1989 baseline questionnaire, as 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), as 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).[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 based on 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 age 40 when 97% of women had completed their reproductive careers. We excluded women who had births at age 40 or later (n=2,491) and women with CVD events before age 40 (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, while duration of breastfeeding could only increase over time. Before utilizing the publicly available SAS %mediate macro, (https://cdn1.sph.harvard.edu/wp-content/uploads/sites/271/2012/09/mediate_manual_2012_06_06.pdf)[20, 21] we tested the presence of interactions between each intermediate and preterm delivery using likelihood ratio tests of nested models with and without the interactions,[19] and observed no exposure-intermediate interactions (all p-values>0.25). To further ensure that the lack of interactions was not due to insufficient power, we assessed the magnitude of the hazard ratios 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, Cary, NC, USA).

RESULTS

Table 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 greater than or equal to 30 kg/m^2, have pre-pregnancy hypertension and hypercholesterolemia, and a family history of CVD. Women who delivered very preterm in 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. Compared to 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 2, Model 1). This hazard ratio was slightly attenuated, but remained significant, after adjustment for both pre-pregnancy lifestyle and CVD risk factors (1.42, 95% CI: 1.16,

1.72, Table 2, Model 3). When preterm delivery was split into two categories, the hazard ratios 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 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 (Supplementary Table 1). Additionally, we investigated the association between ever having a preterm delivery and CVD and found similar results to those that considered only the first birth (Supplementary Table 2).

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). 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 (Supplementary Table 3).

Since 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 3). Compared to 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, while those with 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 3, Model 3). We did not separate the HDP preterm category into moderate and very preterm due to 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 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 compared to 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 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 >0.10). Only chronic hypertension before first pregnancy appeared to be a modifier (p=0.02). The hazard ratios comparing moderate preterm to term were 0.21 (95% CI: 0.03, 1.52) and 1.30 (95% CI: 1.02, 1.64) in the women with and without pre-pregnancy chronic hypertension, respectively. The hazard ratio comparing very preterm to 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 5, Model 2a). The proportion accounted for increased to 15.9% (95% CI: 8.7, 27.3) when breastfeeding was additionally included as an intermediate (Table 5, Model 4a). 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, while 13.1% (95% CI: 9.0, 18.7) of the very preterm-CVD association was accounted for by these risk factors (Table 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.

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, as 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, compared with the results of the primary analyses in Table 2.

DISCUSSION

Women who deliver a preterm infant are at a 40% increased risk of future CVD events while 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 less than 25% of the association between moderate or very preterm first birth and CVD. Since 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 and CVD are linked. Since 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

Table 1

Baseline characteristics of Nurses' Health Study II study 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	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 study population

Values of categorical variables may not sum to 100% due to rounding

* Value is not standardized to the age distribution

Table 2

Hazard ratios (95% confidence intervals) for preterm delivery in first pregnancy and cardiovascular events (MI 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 BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, physical activity at age 18, 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 MI or stroke before age 60

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

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

‡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

Table 3

Hazard ratios (95% confidence intervals) for preterm delivery in first pregnancy and cardiovascular events (MI 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 BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, physical activity at age 18, 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 MI or stroke before age 60

* Sample size and total case numbers differ from Table 2 due to 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) to 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)

Table 4

Hazard ratios (95% confidence intervals) for history of preterm deliveries and cardiovascular events (MI and stroke) at age 40 or later, among women with no births at age 40 or later

First Pregnancy	2nd+ 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 BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, physical activity at age 18, 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 MI or stroke before age 60

Model 4 is additionally adjusted for parity at age 40

*Sample size and total case numbers differ from those in Table 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 age 40 or after, had an MI or stroke before age 40

Table 5

Hazard ratios (95% confidence intervals) for the association between preterm delivery in first pregnancy and CVD (MI 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, BMI				
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, BMI				
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, BMI, 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 BMI, pre-pregnancy smoking, pre-pregnancy Alternative Healthy Eating Index (AHEI) score (in quintiles), pre-pregnancy alcohol intake, physical activity at age 18, pre-pregnancy oral contraceptive use, and family history of MI or stroke before age 60

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

*Sample size and total case numbers differ from Table 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

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

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

§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