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Early or Late Pregnancy Loss and Development of Clinical Cardiovascular Disease Risk Factors: a Prospective Cohort Study

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Abstract

Objective: To assess the association between the outcome of a woman's first pregnancy and risk of clinical cardiovascular disease risk factors.

Design: Prospective cohort study.

Setting and population: Nurses' Health Study II

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CONTRIBUTION TO AUTHORSHIP

JH, LT, JS and JRE contributed to the design of this study. JH, LT and JS conducted the analyses and JH, LT, JS, AM, GS, ER, SM and JRE contributed to the interpretation of data. JH drafted the manuscript and all the authors critically revised the manuscript and approved the version to be published.

DISCLOSURE OF INTERESTS

The authors report no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

Methods: Multivariable-adjusted Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between first pregnancy outcome and hypertension, type 2 diabetes, and hypercholesterolemia.

Main outcome measures: Hypertension, type 2 diabetes, and hypercholesterolemia.

Results: Compared to women who reported a singleton live first birth, women with early spontaneous abortion (<12 weeks) had a greater rate of type 2 diabetes (HR 1.20; 95% CI: 1.07–1.34) and hypercholesterolemia (HR 1.06; 95% CI: 1.02–1.10), and a marginally increased rate of hypertension (HR 1.05, 95% CI: 1.00–1.11). Late spontaneous abortion (12–19 weeks) was associated with an increased rate of type 2 diabetes (HR 1.38; 95% CI: 1.14–1.65), hypercholesterolemia (HR 1.11; 95% CI: 1.03–1.19), and hypertension (HR 1.15; 95% CI: 1.05–1.25). The rates of type 2 diabetes (HR 1.45; 95% CI: 1.13–1.87) and hypertension (HR 1.15; 95% CI: 1.01–1.30) were higher in women who delivered stillbirth. In contrast, women whose first pregnancy ended in an induced abortion had lower rates of hypertension (HR 0.87; 95% CI: 0.84–0.91) and type 2 diabetes (HR 0.89; 95% CI: 0.79–0.99) than women with a singleton live birth.

Conclusions: Several types of pregnancy loss were associated with an increased rate of hypertension, type 2 diabetes, and hypercholesterolemia, which may provide novel insight into the pathways through which pregnancy outcomes and CVD are linked.

TWEETABLE ABSTRACT

Pregnancy loss is associated with later maternal risk of hypertension, type 2 diabetes, and hypercholesterolemia

Keywords

Diabetes Mellitus; Hypertension; Hypercholesterolemia; Pregnancy loss; Spontaneous abortion; Stillbirth; Women's Health; Cardiovascular Diseases; Risk factors

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in both men and women worldwide.(1) However, there are considerable sex and gender differences in disease risk, pathophysiology, awareness, and prevention,(2, 3) resulting in a growing interest in gender- and sex-specific risk factors. Pregnancy complications, including preeclampsia, gestational hypertension, preterm birth, and gestational diabetes, have emerged as female-specific risk factors for CVD.(4, 5)

Results from recent studies suggest that pregnancy outcomes, including pregnancy loss, may also help to identify women at increased risk of CVD. Spontaneous abortion and stillbirth have been associated with increased risk of ischemic heart disease and stroke.(6–17) However, little is known about the underlying mechanisms behind the increased risk of CVD in women with a history of spontaneous pregnancy loss. Previous studies indicate that spontaneous pregnancy loss might be associated with higher risk of type 2 diabetes (T2D) (18), higher serum cholesterol (19) and higher blood pressure(20). However, only a few studies have examined the associations of spontaneous pregnancy loss with clinical CVD risk factors and most were unable to distinguish between early and late spontaneous

abortion. Understanding how adverse pregnancy outcomes are associated with clinical CVD risk factors may be useful in improving CVD prevention in women.

To address this question, we prospectively assessed the associations of pregnancy loss with risk of hypertension, T2D and hypercholesterolemia in the Nurses' Health Study II (NHSII).

METHODS

Study population

The NHSII is an ongoing prospective cohort study that began in 1989 when 116,429 female registered nurses aged 25 to 42 years responded to a mailed baseline questionnaire. Participants update information on lifestyle factors and medical history through biennial follow-up questionnaires. Response rates for each questionnaire cycle are over 90%.

Exposure assessment

In 2009, when the youngest participants were 45 years old, the biennial questionnaire collected information on complete reproductive history, including year, pregnancy outcome, and gestation length of every pregnancy. Specifically, women self-reported whether each of their pregnancies resulted in a singleton live birth, multiple birth, miscarriage/stillbirth, tubal/ectopic pregnancy, or induced abortion. Women who reported miscarriage/stillbirth were further categorized based on gestation length: early spontaneous abortion (<12 weeks), late spontaneous abortion (12–19 weeks), and stillbirth (≥ 20 weeks).

Outcome assessment

On each biennial questionnaire, participants were asked if they had incident physician-diagnosed illnesses in the past two years, including high blood pressure and diabetes (not pregnancy related), and elevated cholesterol. Information on cholesterol lowering medication use was collected biennially beginning in 1999. The diagnosis date of hypertension (physician diagnosed) and hypercholesterolemia (physician diagnosed or report of cholesterol lowering medication) was assigned as the midpoint of the range reported on the questionnaire. Diagnoses of T2D and date of diagnosis were confirmed by a validated supplemental questionnaire based on 1997 American Diabetes Association criteria.(21)

In previous validation studies within the Nurses' Health Study or NHSII, 94% of self-reported cases of hypertension,(22) 98% of self-reported cases of diabetes (23) and 86% of self-reported cases of hypercholesterolemia (24) were confirmed by medical records.

Covariates

Variables that predated the first pregnancy and were hypothesized to be associated with both the pregnancy loss and with CVD risk factors of interest were considered potential confounders. The 1989 baseline questionnaire collected information on age, race/ethnicity (white, black, Latina, Asian, other), height, weight (current and at age 18), strenuous physical activity at ages 18–22 years (never, 1–3, 4–6, 7–9, 10–12 months per year), family history of hypertension or diabetes (parents or siblings), smoking status (never, past, current), history of infertility, and menstrual regularity from ages 18–22. Partner's and

parents' education (<9, 9–11, 12, 13–15, 16 years), alcohol intake (none, 1 drink per week, 2–6 drinks per week, 1 drink per day), current weight, smoking status, health care utilization pattern for the purpose of screening and/or curing (yes/no), and diet (in quintiles based on the Alternative Healthy Eating Index-2010(25)) were assessed and/or updated on follow-up questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and categorized into the following: <18.5, 18.5 to <25, 25 to <30, 30 kg/m². Pre-pregnancy values for BMI, smoking, diet, and alcohol intake were taken from the biennial questionnaire before pregnancy for women whose first pregnancy was after NHSII baseline (8.5%). On average, this information was reported 1.8±1.2 years before first pregnancy. However, for women whose first pregnancy occurred prior to the 1989 baseline (91.5%), information about behavior in high school and at age 18 that was retrospectively reported on the 1989 questionnaire was used to assign pre-pregnancy covariate values. Missing data were handled using missing indicators(26); the amount of missing data was small for most covariates except pre-pregnancy diet. In a sensitivity analysis, we excluded participants with missing data on pre-pregnancy diet.

Exclusions

Women were eligible for this analysis if they answered the 2009 reproductive history questionnaire and reported at least one pregnancy (n=67,288). We excluded those with a first pregnancy before age 18 (n=1698) because we lacked pre-pregnancy covariates before age 18. We also excluded women who had a first pregnancy after the age of 39 years (n=777), because of the increasing risk of pregnancy loss due to chromosomal abnormalities in women of advanced age.(27) Additionally, we excluded women with missing data on outcome (n=230), year (n=41), or gestation length (n=292) of first pregnancy as well as women who did not provide a date of diagnosis or reported any of the following before their first pregnancy: chronic hypertension (n=1442), anti-hypertensive medication use (n=114), diabetes (n=10), or hypercholesterolemia (n=1673). Finally, we excluded 360 women who reported myocardial infarction or stroke before their first pregnancy or on the 1989 baseline questionnaire, as the latter were not confirmed by medical record review. The final sample included 60,651 women.

In secondary analyses we examined the relationship between reproductive history before age 40 (including all pregnancies before that age) and the development of CVD risk factors after age 40. For these analyses, we additionally excluded women who reported the endpoint of interest before age 40. Thus, the analyses were limited to 55,544 women for the hypertension analysis, 60,435 for the T2D analysis, and 51,802 for the hypercholesterolemia analysis.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each clinical CVD risk factor using multivariable-adjusted Cox proportional hazards regression models. For our primary analysis of first pregnancy outcome, women with a singleton live birth were the reference group. Women contributed person-time from the year of first pregnancy until the date of diagnosis of the clinical CVD risk factor of interest (hypertension, T2D, or hypercholesterolemia), confirmed myocardial infarction or stroke, death, loss to follow-up,

or end of follow-up (June 2013). Additionally, for analyses of incident hypertension, women were censored at the start of anti-hypertensive medication use. When analyzing incident T2D, women were censored at the date of type 1 diabetes diagnosis.

Models were *a priori* adjusted for age, calendar time, age at first pregnancy (continuous) and race/ethnicity. We then additionally adjusted for parent's and partner's education, physical activity at age 18–22 years, and pre-pregnancy BMI, smoking, alcohol intake, and diet. Analyses of hypertension were additionally adjusted for family history of hypertension while analyses of T2D were adjusted for family history of diabetes.

In secondary analyses evaluating lifetime pregnancy history, instead of starting follow-up at the time of the first pregnancy, we started follow-up at age 40 and investigated the associations between outcomes across all pregnancies before age 40 (both ever history and frequency of each pregnancy outcome of interest) with each clinical CVD risk factor. We constructed separate models for early spontaneous abortion, late spontaneous abortion, stillbirth, and induced abortion. In every model, women who had never reported the pregnancy outcome of interest were the reference group. In addition to the covariates included in the primary models, HRs were additionally adjusted for the number of pregnancies before age 40.

Departures from the proportional hazards assumption were tested by likelihood ratio tests comparing final models with and without interaction terms between each type of pregnancy outcome and time since first pregnancy. While the assumption held for the T2D and hypercholesterolemia analyses (p-value>0.24), the proportional hazards assumption was not met for the hypertension analysis (p-value=0.002). Although the overall hazard ratio for hypertension averages across follow-up,(28) given the violation of the proportional hazards assumption,we additionally provide results stratified by follow-up time in 5-year intervals (Table S1). All analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC). Patients were not involved in the development of this study. This work was supported by grants from the Research Council of Norway (231149/F20), the Ruth L. Kirschstein National Research Service Award (NHLBI F31 HL131222), the Training Grant T32HL098048 from the National Heart, Lung, and Blood Institute, and the American Heart Association (16PRE29690006). The Nurses' Health Study II is supported by UM1CA176726 from National Institutes of Health. The funders had no role in study design, data analysis, or preparation of the manuscript.

RESULTS

Baseline characteristics

Among 60,651 first pregnancies, 44,447 (73%) ended in a singleton live birth and 598 (1%) women gave birth to multiples. A total of 7937 (13%) first pregnancies ended in induced abortion and 458 women (1%) experienced an ectopic first pregnancy. Of pregnancies with spontaneous loss, 5141 (8% of total pregnancies) were early spontaneous abortions, 1466 (2%) were late spontaneous abortions, and 604 (1%) ended in stillbirth.

Compared to women whose first pregnancy ended in singleton live birth, women whose first pregnancies ended in induced abortion were younger at first pregnancy, reported higher levels of parental education, and were more likely to drink alcohol and smoke cigarettes (Table 1). Women with ectopic pregnancies had higher consumption of alcohol and cigarettes than women with singleton live births. Women with spontaneous abortions, especially late abortions, had somewhat higher reports of gestational diabetes in first pregnancy. Compared to women with a singleton live birth, women whose first pregnancy ended in stillbirth were more likely to be overweight or obese, and to report a family history of diabetes, but were no more likely to report gestational diabetes in first pregnancy.

A total of 20,563 incident cases of hypertension, 3546 cases of T2D, and 34,084 cases of hypercholesterolemia occurred during up to 50 years of follow-up (median follow-up, 28 (hypertension); 33 (T2D); 27 (hypercholesterolemia)). Table 2 shows the HRs and 95% CIs for each outcome of first pregnancy with incident hypertension, T2D, and hypercholesterolemia. Table 3 displays associations between lifetime history (as of age 40) of various pregnancy outcomes and each clinical CVD risk factor.

Early spontaneous abortion

History of an early spontaneous abortion in first pregnancy was associated with a marginally increased rate of hypertension (HR 1.05; 95% CI 1.00–1.11), T2D (HR 1.20; 95% CI 1.07–1.34), and hypercholesterolemia (HR 1.06; 95% CI 1.02–1.10) (Table 2). We found similar results for associations between early spontaneous abortion before age 40 with CVD risk factors arising after age 40 (Table 3). Women who experienced an early spontaneous abortion in at least one of their pregnancies had a small increase in the development of hypertension, unless they had experienced three or more early spontaneous abortions, in which case they had a 19% (95% CI 3%–38%) increased rate of hypertension compared to women who never experienced an early spontaneous abortion. Similarly, the increased rate of T2D among women who ever had an early spontaneous abortion (HR 1.11; 95% CI 1.01–1.22) was higher for women with three or more abortions (HR 1.43; 95% CI 1.06–1.92). Ever having an early spontaneous abortion was also associated with incident hypercholesterolemia (HR 1.09; 95% CI 1.05–1.13, *p* for trend <0.0001).

Late spontaneous abortion

Compared to a singleton live birth, late spontaneous abortion in first pregnancy was associated with a higher rate of hypertension (HR 1.15; 95% CI 1.05–1.25), T2D (HR 1.38; 95% CI 1.14–1.65), and hypercholesterolemia (HR 1.11; 95% CI 1.03–1.19) (Table 2).

Compared to women who never had a late spontaneous abortion before age 40, those who ever had a late spontaneous abortion had a higher rate of hypertension (HR 1.12; 95% CI 1.05–1.18), T2D (HR 1.17; 95% CI 1.02–1.33) and hypercholesterolemia (HR 1.06; 95% CI 1.01–1.12) (Table 3). Although there was not a monotonic dose-response relationship, risk of hypertension and hypercholesterolemia generally increased with increasing numbers of late abortions (*p* for trend <0.001 for hypertension; *p* for trend <0.01 for hypercholesterolemia).

Stillbirth

Stillbirth in first pregnancy was associated with an increased rate of hypertension (HR 1.15; 95% CI 1.01–1.30) and T2D (HR 1.45; 95% CI 1.13–1.87), but not hypercholesterolemia (Table 2).

The overall increased rate of hypertension among women with a history of stillbirth was stronger among women with more than one stillbirth (HR 1.34; 95% CI 0.99–1.83, Table 3). However, women with any stillbirth before age 40 had a 36% increased rate of T2D (HR 1.36; 95% CI 1.15–1.61) and a 59% increased rate (HR 1.59; 95% CI 0.94–2.71) with two or more stillbirths (p for trend <0.001).

Induced abortion

Women whose first pregnancy ended in induced abortion appeared to have lower rates of clinical CVD risk factors than women whose first pregnancy ended in a singleton live birth. The multivariable-adjusted HRs for those with induced abortion in first pregnancy were 0.87 (95% CI 0.84–0.91) for hypertension and 0.89 (95% CI 0.79–0.99) for T2D. Induced abortion was not associated with hypercholesterolemia (Table 2).

Women who ever had an induced abortion before age 40 had a lower rate of hypertension (HR 0.88; 95% CI 0.84–0.92, Table 3). Furthermore, a higher number of induced abortions was associated with a lower risk of hypertension (p for trend <0.0001).

Other pregnancy outcomes

Women whose first pregnancy resulted in a multiple birth were not at elevated risk of any CVD risk factor, compared with women who delivered singletons (Table 2). Women who had an ectopic first pregnancy had a higher rate of hypertension (HR 1.21; 95% CI 1.04–1.40, Table 2).

Sensitivity analyses

Adjusting for menstrual cycle length and cycle irregularity at age 18–22 years (as markers for polycystic ovary syndrome (PCOS)) did not substantially change the results. Similarly, estimates for risk of T2D were nearly unchanged when adjusted for gestational diabetes. Since pre-pregnancy diet was primarily collected through a supplemental questionnaire sent to a subset of participants, there was a substantial amount of missingness. However, when we restricted our analysis to the 32,735 women with available information on pre-pregnancy diet we observed similar estimates. Similarly, a sensitivity analysis using multiple imputation for all missing covariates yielded nearly unchanged estimates.

In a post-hoc analysis, we performed a mediation analysis using the difference method to assess whether the unanticipated associations of induced abortion in first pregnancy with reduced risk of hypertension and T2D could be explained by post-pregnancy CVD lifestyle risk factors (see appendix S1 for detailed description). The proportions mediated by post-pregnancy BMI, smoking status, diet, alcohol consumption, and physical activity were 14.8% (95% CI 3.6%–44.7%) for hypertension and 52.8% (95% CI 0.2%–99.9%) for T2D.

Additionally, differences in health care utilization patterns or history of infertility did not explain the associations between induced abortion and CVD risk factors.

DISCUSSION

Main findings

In this large prospective cohort study of US women, the outcome of a woman's first pregnancy was associated with the development of clinical CVD risk factors later in life. Spontaneous fetal loss of any kind, particularly if recurrent, was associated with increased rates of hypertension and T2D. Late spontaneous abortion and stillbirth appeared to have stronger associations than early spontaneous abortion. Both early and late spontaneous abortion were also associated with hypercholesterolemia. In contrast, induced abortion in first pregnancy was associated with reduced rates of hypertension and T2D.

Strengths and limitations

Our prospective cohort study has several limitations. First, it is possible that our analysis suffers from some degree of exposure misclassification, as women tend to underreport induced abortions and spontaneous abortions may occur before the clinical detection of pregnancy, resulting in underreporting, especially of early losses. However, this misclassification would most likely yield an underestimation of the true associations. Information on reproductive history was collected in 2009. Thus, participants had to be alive in 2009 to be included into our study, opening the possibility of survivor bias. Nevertheless, women were 25 to 42 years old at enrollment in 1989 and only 1.7% had died before 2009. As we restricted our analyses to pregnancies occurring before the age of 40 years, our results may not be generalizable to women with pregnancies at older ages. However, only a few women in our study population (0.9%) had their first pregnancy at age 40 or older. Finally, our cohort included mostly white and well-educated women, which may limit the generalizability of our results.

Our study has several strengths, including its prospective design, large sample size with long follow-up, and detailed information on reproductive history. Additionally, we were able to distinguish between early and late spontaneous abortions, which is important as the relationship between pregnancy loss and CVD might differ according to gestational age. We also cannot rule out the possibility of unmeasured or residual confounding. However, unlike most previous studies, we were able to adjust for multiple pre-pregnancy risk factors.

Interpretation

Previous studies investigating the relationship between pregnancy loss and risk of coronary heart disease or stroke also described higher prevalence of hypertension, T2D or hyperlipidemia among women with history of spontaneous abortion or stillbirth.^(6, 7, 10, 14) However, few studies have examined the association between pregnancy loss and clinical CVD risk factors and provided estimates adjusted for confounding factors.

Our findings are consistent with and extend upon previous literature. Among 13,612 women in the European Prospective Investigation into Cancer and Nutrition, Kharazmi et al.

reported a 30% higher risk of T2D among women with history of spontaneous abortion.(18) Their estimates for the association of induced abortion (HR 0.86; 95% CI 0.57–1.29) and stillbirth (HR 1.25; 95% CI 0.61–2.54) with risk of diabetes, although not statistically significant, were of similar magnitude to our results. However, in contrast to our study, the authors did not have information on gestation length and were unable to distinguish between early and late spontaneous abortion. In accordance with the observed increased risk of hypercholesterolemia among women with two or more spontaneous abortions in our cohort, a case-control study by Germain et al. found significantly higher serum cholesterol (193 mg/dl vs 168 mg/dl) among women with recurrent pregnancy loss compared to women with uncomplicated pregnancies.(19) This study did not include women with chronic hypertension, but did report a non-significant elevated blood pressure among women with recurrent pregnancy loss. A recent Swedish cohort study examined the associations between pregnancy complications and risk of elevated blood pressure. In line with our results, the authors described a small, borderline significant elevation of systolic blood pressure (2.41 mmHg) in women with previous stillbirth; however, in the fully adjusted model, stillbirth was no longer associated with increased risk of hypertension.(20) While this study examined blood pressure and hypertension in women at 40 years of age, we were able to follow participants into older age.

Pregnancy loss may be linked with hypertension, T2D, and hypercholesterolemia through shared underlying mechanisms. Endothelial dysfunction has been reported in women with abnormal placentation, including women with history of preeclampsia or spontaneous pregnancy loss,(19) and is also associated with higher risk of hypertension, diabetes and dyslipidemia.(29) Likewise, chronic systemic inflammation has been linked to both recurrent pregnancy loss and the development of clinical CVD risk factors.(30) Evidence suggests that endocrine disorders, like impaired glucose tolerance and PCOS, are associated with higher risk of spontaneous pregnancy loss,(31, 32) T2D, and dyslipidemia. In our analyses, adjustment for menstrual cycle length and irregularity did not alter conclusions, but menstrual cycle pattern may be an insufficient proxy for PCOS. Likewise, adjusting for diagnosis of gestational diabetes only slightly changed our estimates. Prevalence of gestational diabetes, or undiagnosed preexisting diabetes, might be underestimated in women with early pregnancy loss because these women have not reached the second trimester at which screening for gestational diabetes is usually performed. However, we observed the lowest percentage of gestational diabetes among women whose first pregnancy was a stillbirth. This is consistent with a cohort study from Israel that also observed lower rates of gestational diabetes among women with a history of stillbirth (9), and may suggest that gestational diabetes is underdiagnosed among these women or that diagnosis of gestational diabetes serves as a proxy for better prenatal care which lowers the risk of stillbirth.

In a previous review examining the relationship between reproductive history and CVD, the authors hypothesized that pregnancy loss may be causally related to a higher risk of CVD through shorter duration of estrogen exposure compared to full term pregnancies.(33) In our study, women with induced abortion showed a lower risk of hypertension and T2D compared to women with a singleton livebirth. Thus, a lower lifetime exposure to estrogen is

unlikely to explain the increased risk of clinical CVD risk factors among women with spontaneous pregnancy loss.

The reduced risk of hypertension and T2D in women with induced abortion was unexpected and not explained by different patterns in health care utilization or higher fertility among those with a history of induced abortion. Although hampered by low precision, adjustment for post-pregnancy lifestyle factors explained only 15% of the reduced hypertension risk but accounted for 53% of the reduced diabetes risk among women with induced abortions compared to those who had singleton live births.

Conclusion

Spontaneous pregnancy loss, especially late in gestation, was associated with an increased risk of hypertension, T2D, and hypercholesterolemia, while induced abortion was associated with a reduced risk of clinical CVD risk factors. Further studies are needed to verify our results and clarify the mechanisms underlying the reported associations. Information on history of pregnancy loss may help to mark women who could benefit from early screening for CVD risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DETAILS OF ETHICS APPROVAL

This study was approved by the Partners Human Research Committee (Institutional Review Board) of Brigham and Women's Hospital (Boston, MA) on the 23 June 2016 under the following protocol: Improving Women's Health: The Nurses' Health Study II (#1999P003389). Return of the questionnaire was considered informed consent.

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Table 1.
Baseline Characteristics of Nurses' Health Study II Study Participants by First Pregnancy Outcome

	Singleton live birth (n=44,447)	Multiples (n=598)	Ectopic pregnancy (n=458)	Induced abortion (n=7937)	Early spontaneous abortion (n=5141)	Late spontaneous abortion (n=1466)	Stillbirth (n=604)
Age at first pregnancy, years, mean (SD) ^a	26.2 (4.2)	28.0 (4.8)	27.5 (4.7)	22.8 (4.0)	26.3 (4.8)	26.3 (4.5)	25.3 (4.4)
Age at baseline in 1989, years, mean (SD) ^a	35.4 (4.7)	34.4 (4.8)	34.9 (4.2)	34.5 (4.2)	34.7 (4.7)	35.2 (4.7)	36.2 (4.3)
White	93.0	94.3	94.1	91.2	94.4	92.3	92.7
Education of the nurses' mother, more than high school	26.9	26.4	27.6	34.9	27.5	26.9	25.8
Education of the nurses' father, more than high school	30.7	30.6	34.3	41.1	33.7	32.6	32.9
Education of the nurses' partner, more than high school	71.4	70.9	69.3	71.5	73.4	71.5	67.2
Family history of hypertension	50.8	47.9	48.6	50.2	51.3	51.2	51.9
Family history of diabetes	41.6	45.8	42.3	38.8	41.7	43.9	46.1
Pre-pregnancy BMI, kg/m ²							
-Underweight (<18.5)	2.6	1.6	3.7	2.5	3.0	1.8	2.7
Normal weight (18.5–24.9)	85.6	85.0	85.8	85.6	85.6	84.7	82.7
-Overweight (25–29.9)	8.9	8.3	8.8	8.2	8.4	10.2	10.2
Obese (≥ 30)	2.0	3.8	1.1	2.4	2.3	2.3	3.7
Pre-pregnancy smoking							
Never smoker	69.5	70.3	60.9	55.5	67.5	68.6	71.2
Past smoker	7.5	8.1	6.9	7.0	7.2	7.1	5.5
Current smoker	22.3	21.2	32.2	36.6	24.5	23.8	22.9
Pre-pregnancy alcohol intake, drinks							
None	30.3	31.3	18.4	10.2	25.3	26.5	31.0
1/day	5.1	5.4	11.6	15.9	7.7	6.9	5.1
Sirenuous physical activity, age 18–22 years							
Never	29.9	29.3	27.3	24.1	28.7	25.8	29.0
10–12 mo/yr	10.2	12.4	12.1	14.6	12.2	12.3	14.9

	Singleton live birth (n=44,447)	Multiples (n=598)	Ectopic pregnancy (n=458)	Induced abortion (n=7937)	Early spontaneous abortion (n=5141)	Late spontaneous abortion (n=1466)	Stillbirth (n=604)
Pre-Pregnancy Alternative Healthy Eating Index							
First quintile (least healthy diet)	20.8	24.4	19.5	13.4	20.7	17.9	19.0
Fifth quintile (healthiest diet)	18.4	19.7	19.7	27.4	19.0	17.9	21.6
Gestational diabetes in first pregnancy	2.3	2.1	3.7	2.6	3.0	3.6	2.0

Values are percentages unless otherwise noted. Values are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

^aValue is not age adjusted.

Table 2.

Hazard Ratios and 95% Confidence Intervals for Incident Hypertension, Type 2 Diabetes, and Hypercholesterolemia by First Pregnancy Outcome Among Women from the Nurses' Health Study II

	Singleton Live Birth (n=44,447)	Multiples (n=598)	Ectopic Pregnancy (n=458)	Induced Abortion (n=7937)	Early Spontaneous Abortion (n=5141)	Late Spontaneous Abortion (n=1466)	Stillbirth (n=604)
Hypertension							
Cases/person-years	15,195/1,223,840	195/14,975	171/11,885	2503/243,505	1716/137,568	542/39,089	241/16,954
Model 1	1.00 (ref)	1.10 (0.95–1.26)	1.17 (1.00, 1.36)	0.84 (0.80, 0.88)	1.04 (0.99, 1.10)	1.17 (1.07, 1.27)	1.18 (1.04, 1.34)
Model 2	1.00 (ref)	1.07 (0.93, 1.23)	1.21 (1.04, 1.40)	0.87 (0.84, 0.91)	1.05 (1.00, 1.11)	1.15 (1.05, 1.25)	1.15 (1.01, 1.30)
Type 2 Diabetes							
Cases/person-years	2586/1,445,165	29/17,846	28/14,070	392/278,745	332/162,883	118/46,815	61/20,427
Model 1	1.00 (ref)	0.97 (0.67, 1.40)	1.12 (0.77, 1.63)	0.79 (0.71, 0.88)	1.20 (1.07, 1.34)	1.43 (1.19, 1.72)	1.64 (1.27, 2.11)
Model 2	1.00 (ref)	0.87 (0.61, 1.26)	1.18 (0.81, 1.71)	0.89 (0.79, 0.99)	1.20 (1.07, 1.34)	1.38 (1.14, 1.65)	1.45 (1.13, 1.87)
Hypercholesterolemia							
Cases/person-years	25,008/1,139,238	306/14,255	253/11,005	4452/222,156	2859/128,231	856/36,465	350/16,108
Model 1	1.00 (ref)	0.99 (0.88, 1.11)	1.04 (0.92, 1.18)	0.96 (0.93, 0.99)	1.05 (1.01, 1.09)	1.11 (1.03, 1.18)	0.99 (0.89, 1.10)
Model 2	1.00 (ref)	0.99 (0.88, 1.11)	1.04 (0.92, 1.18)	1.01 (0.98, 1.05)	1.06 (1.02, 1.10)	1.11 (1.03, 1.19)	0.98 (0.88, 1.09)

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

^aModel 2 is additionally adjusted for parental education, partner's education, strenuous physical activity at age 18–22, and pre-pregnancy BMI, smoking status, alcohol use, and Alternative Healthy Eating Index (in quintiles). Hypertension analyses are additionally adjusted for family history of hypertension and diabetes analyses are additionally adjusted for family history of diabetes

Table 3.

Hazard Ratios for Incident Hypertension, Type 2 Diabetes and Hypercholesterolemia by Pregnancy History (Nurses’ Health Study II)

Pregnancy Outcome History	Hypertension ^{a, b}				Type 2 Diabetes ^{a, c}				Hypercholesterolemia ^a						
	Women	Cases/Person-years	HR	95% CI	p-trend	Women	Cases/Person-years	HR	95% CI	p-trend	Women	Cases/Person-years	HR	95% CI	p-trend
Early spontaneous abortion															
Never	44,419	13,902/678,418	1	(ref)		48,289	2672/903,752	1	(ref)		41,386	20,253/597,531	1	(ref)	
Ever	11,125	3,353/165,198	1.05	(1.00–1.09)		12,146	704/220,596	1.11	(1.01–1.22)		10,416	5,005/146,248	1.09	(1.05–1.13)	
1	8620	2614/128,597	1.04	(1.00–1.09)		9422	547/171,678	1.11	(1.00–1.22)		8099	3,904/113,906	1.08	(1.04–1.12)	
2	1844	537/27,243	1.04	(0.95–1.14)		1998	106/36,091	1.08	(0.88–1.32)		1703	819/23,767	1.15	(1.06–1.24)	
3 or more	661	202/9,358	1.19	(1.03–1.38)	0.01	726	51/12,827	1.43	(1.06–1.92)	0.01	614	282/8,575	1.15	(1.01–1.30)	<0.0001
Late spontaneous abortion															
Never	51,519	15,980/784,457	1	(ref)		56,009	3101/1,044,174	1	(ref)		48,031	23,458/691,047	1	(ref)	
Ever	4025	1275/59,159	1.12	(1.05–1.18)		4426	275/80,174	1.17	(1.02–1.33)		3771	1800/52,732	1.06	(1.01–1.12)	
1	3593	1139/52,712	1.11	(1.05–1.19)		3941	245/71,219	1.18	(1.03–1.35)		3362	1594/47,033	1.05	(1.00–1.11)	
2 or more	432	136/6447	1.13	(0.95–1.35)	<0.001	485	30/8955	1.04	(0.72–1.51)	0.05	409	206/5699	1.16	(1.01–1.33)	<0.01
Stillbirth															
Never	54,048	16,744/820,691	1	(ref)		58,785	3229/1,092,781	1	(ref)		50,420	24,541/723,418	1	(ref)	
Ever	1496	511/22,925	1.08	(0.99–1.18)		1650	147/31,567	1.36	(1.15–1.61)		1382	717/20,361	1.01	(0.94–1.09)	
1	1401	470/21,492	1.06	(0.97–1.16)		1545	133/29,512	1.34	(1.12–1.60)		1298	668/19,074	1.01	(0.93–1.09)	
2 or more	95	41/1,433	1.34	(0.99–1.83)	0.05	105	14/2055	1.59	(0.94–2.71)	<0.001	84	49/1287	1.09	(0.82–1.45)	0.70
Induced abortion															
Never	46,513	14,604/704,859	1	(ref)		50,561	2857/942,472	1	(ref)		43,581	21,258/626,054	1	(ref)	
Ever	9031	2651/138,757	0.88	(0.84–0.92)		9874	519/181,876	0.92	(0.84–1.02)		8221	4000/117,725	1.00	(0.96–1.03)	
1	6767	2,021/103,281	0.91	(0.87–0.96)		7416	403/136,372	0.97	(0.87–1.08)		6185	3,010/88,292	1.00	(0.96–1.04)	
2	1791	504/28,006	0.79	(0.72–0.86)		1940	88/35,923	0.76	(0.61–0.95)		1611	779/23,500	0.96	(0.89–1.03)	
3 or more	473	126/7470	0.75	(0.63–0.90)	<0.0001	518	28/9581	0.92	(0.63–1.35)	0.05	425	211/5933	1.10	(0.96–1.27)	0.91

HR, hazard ratio; CI, confidence interval.

^aWomen free from the outcome of interest at age 40 contribute person time to the models above from age 40 on. Pregnancy history before age 40 included. Model is adjusted for age in 1989, age at first pregnancy, race/ethnicity, gravidity before age 40, parental education, partner’s education, strenuous physical activity at age 18–22, and pre-pregnancy BMI, smoking status, alcohol use, and Alternative Healthy Eating Index (in quintiles);

^b additionally adjusted for family history of hypertension;

^c additionally adjusted for family history of diabetes