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Relation of Pregnancy Loss to Risk of Cardiovascular Disease Among Parous Postmenopausal Women (From the Women's Health Initiative)

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Abstract

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Author Agreement

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Women with history of pregnancy loss (PL) have higher burden of cardiovascular disease (CVD) later in life, yet it is unclear whether this is attributable to an association with established CVD risk factors (RFs). We examined whether PL is associated with CVD RFs and biomarkers among parous postmenopausal women in the Women's Health Initiative, and whether the association between PL and CVD RFs accounted for the association between PL and incident CVD. Linear and logistic regressions were used to estimate associations between baseline history of PL and CVD RFs. Cox proportional hazards regression models were used to estimate the associations between baseline history of PL and incident CVD after adjustment for baseline RFs. Of 79,121 women, 27,272 (35%) had experienced PL. History of PL was associated with higher BMI ($p<0.0001$), hypertension ($p<0.0001$), diabetes ($p=0.003$), depression ($p<0.0001$), and lower income ($p<0.0001$), physical activity ($p=0.01$), poorer diet ($p<0.0001$), smoking ($p<0.0001$) and alcohol use ($p<0.0001$). After adjustment for CVD RFs, PL was significantly associated with incident CVD over mean follow up of 16 years (HR 1.11, 95% CI 1.06-1.16). In conclusion, several CVD RFs are associated with PL, but they do not entirely account for the association between PL and incident CVD.

Keywords

Cardiovascular Disease; Miscarriage; Pregnancy Loss; Women

Introduction

Despite considerable advances in both the prevention and treatment of cardiovascular disease (CVD), it still remains the leading cause of mortality among women.[1,2] Women have a different CVD risk profile compared with men, and key reproductive factors unique to women including pregnancy, complications of pregnancy, and infertility, have been previously associated with incident CVD.[3–6] A history of pregnancy loss (PL), including spontaneous miscarriage and stillbirth, has been associated with up to a 2.7-fold increased odds of maternal CVD later in life.[7–13] Among postmenopausal women in the Women's Health Initiative (WHI) Study, we previously demonstrated a 19% and 27% increased odds of CVD associated with a history of miscarriage and stillbirth, respectively.[12] The exact mechanisms underlying the association between PL and CVD are uncertain. Therefore, we sought to evaluate whether a history of PL is associated with either modifiable CVD risk factors (i.e. hypertension, dyslipidemia, tobacco use, and insulin resistance), or novel pathways including inflammation or hypercoagulability, [14,15] and whether the association between PL and CVD could be fully explained by these risk factors.

Methods

The design of WHI has been described previously.[16,17] Briefly, WHI consists of a set of clinical trials and an observational study in which 161,808 women were enrolled from 1993 to 1998 at 40 clinical centers in the United States. We excluded women with preexisting CVD (n=27,247), including coronary heart disease (CHD), heart failure (HF), or stroke, or with incomplete risk factor and reproductive data (n=43,438) (Figure 1). We additionally excluded women with history of elective abortion (n=l,836) or ectopic pregnancy (n=45). In

our primary analysis we chose to study only parous women (n=79,121), due to known associations between both nulliparity and infertility with CVD, and we studied nulliparous women in secondary analyses (n=10,121).[5,18,19]

PL, the primary exposure, was defined as a self-reported history of either spontaneous miscarriage or stillbirth. Information on pregnancy history was obtained at baseline by questionnaires.[16,17] Women were asked to report the number of live births, stillbirths from pregnancies lasting at least six months, and spontaneous miscarriages that they experienced. Covariates included age at screening, race/ethnicity, and age at first pregnancy lasting at least six months, which was documented as a categorical variable in WHI (<20, 20-24, 25-29, ≥30 years).

CVD RFs were assessed at baseline enrollment.[16,17] For this analysis, RFs included body-mass index (BMI, kg/m^2), systolic blood pressure (mm Hg), hypertension (defined by self-report, systolic blood pressure ≥140 mm Hg or diastolic blood pressure >90 mm Hg at screening, or use of antihypertensive medication), diabetes (defined by self-reported physician diagnosis or use of diabetes medication), hyperlipidemia (defined as self-reported high cholesterol requiring the use of medication, smoking status (current, previous, or never), physical activity (defined as metabolic equivalent hours (MET-hours) per week), alcohol use (current drinks per week, previous alcohol consumption, or never use), annual household income, education level, neighborhood socioeconomic status index (defined in WHI based on census tract data), psychosocial history of depression (defined using the Burnam screening algorithm, a short version of the Center for Epidemiologic Studies – Depression Scale [CES-D]), and diet quality (defined using the Healthy Eating Index [HEI-2005]).[20,21] Serum levels of the biomarkers C-reactive protein (mg/dl), fibrinogen (mg/dl), interleukin-6 (pg/ml), and white blood cell (WBC) count (cells/μL) were available on subsets of the study population, having been measured as part of prior ancillary studies[22].

Incident CVD was a cumulative outcome defined as acute myocardial infarction, stroke, venous thromboembolism, peripheral arterial disease, coronary revascularization, or death attributed to cardiovascular causes. CVD events were systematically adjudicated by physician members of the Cardiovascular Central Adjudication Committee, as described previously.[17]

Baseline characteristics by history of PL are shown as means and standard deviations for continuous variables and frequencies and proportions for categorical variables. For the subset of participants with biomarkers, the median and interquartile range are shown. Linear and logistic regression models were used to estimate the cross-sectional associations between a history of PL and CVD RFs individually, adjusting for age at enrollment, race/ethnicity, history of live birth, and age at first pregnancy lasting at least six months. Cox proportional hazards regression models were used to estimate associations between a history of PL and time to CVD event. We tested the assumption of proportional hazards with Kaplan-Meier survival plots. The baseline model was adjusted for age at enrollment, race/ethnicity, history of live birth, age at first pregnancy lasting at least six months, and WHI study enrollment (clinical trial or observational study component). For secondary analyses, Cox proportional hazards analyses were used to estimate associations between PL and the

individual components of the combined CVD outcome. In the subset of participants with complete biomarker data, we used linear regression to estimate associations between PL and log-transformed biomarkers, and Cox models to estimate the association between PL and incident CVD adjusting for CVD RFs and log-transformed bio markers. We used Fine-Gray models to assess sensitivity of the results to the competing risk of death not due to cardiovascular causes during follow up. All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 79,121 women included in the analysis, 27,272 (35%) reported a history of PL, 25,573 (32%) reporting spontaneous miscarriage and 3,405 (4%) reporting stillbirth. Baseline demographic and reproductive characteristics of this sample are presented in Table 1. The mean age at screening was 63.1 years, and the average number of live births was 3.2.

Baseline levels of CVD RFs are presented in Table 1, along with the corresponding tests for association with a history of PL. PL was associated with higher BMI ($p<0.0001$), systolic blood pressure ($p=0.008$), diastolic blood pressure ($p=0.007$), hypertension ($p<0.0001$), diabetes ($p=0.003$), depression ($p<0.0001$), poorer diet ($p<0.0001$), lower physical activity ($p=0.01$), lower SES index ($p=0.01$), and lower income ($p<0.0001$). PL was associated with lower prevalence of current smoking ($p<0.0001$) and alcohol use ($p<0.0001$). Table 2 presents the biomarkers, along with their tests for association with a history of PL. PL was associated with higher levels of interleukin-6 ($p=0.02$).

The mean and median follow-up duration were 16.6 years and 18.2 years, respectively. There were 8,882 adjudicated incident CVD events during follow up (11%). Table 3 presents the types of incident CVD event experienced during follow-up stratified by history of PL, as well as the hazard ratios and 95% confidence intervals for development of incident CVD based upon a history of PL. In the baseline model PL was associated with 14% higher hazards of incident CVD, (HR 1.14, 95% CI 1.10-1.19). After adjustment for CVD RFs, the association was only minimally attenuated (HR 1.11, 95% CI 1.06-1.16). In the subset of n=3,282 women with complete biomarkers, accounting for inflammation and coagulation biomarkers yielded a similar hazard ratio for the association between PL and CVD (1.19, 95% CI 1.05-1.35). Analyses accounting for competing risks of non-cardiovascular death were not materially different (data not shown).

In secondary analyses among n=10,121 nulliparous women, a history of PL was associated with increased BMI ($p=0.02$), diabetes ($p=0.02$), and lower education level ($p=0.02$), and also with lower prevalence of both smoking ($p=0.0003$) and heavy alcohol use ($p=0.002$) (Table 4). There were no significant associations between a history of PL and levels of C-reactive protein, interleukin-6, white blood cell count, or fibrinogen (Table 5). A history of PL was not associated with a statistically significant increased incidence of CVD during follow up (Table 6).

Discussion

In this large prospective study of postmenopausal women, we extend prior findings that have demonstrated an association between PL and CVD, with four new and important novel findings. [7,8,10,12] First, we found that a history of PL was associated with several important CVD risk factors in mid-life, including hypertension, diabetes, body-mass index, depression, poor diet, and lower income level, lower physical activity as predicted, but also with lower prevalence of smoking or heavy alcohol use (>7 drinks/week). Second, we observed that CVD risk factors in mid-life do not fully explain the association between PL and CVD. Third, we demonstrated that a history of PL is associated with increased serum levels of interleukin-6 in mid-life. Fourth, we observed that among nulliparous women, PL was associated with diabetes, body-mass index, and lower education level, with lower prevalence of smoking or heavy alcohol use.

The previously demonstrated increased hazard of CVD related to PL was reproduced in this analysis, but with a relatively more modest effect size (11-14% excess hazard).[4,7,10–13] Importantly, the estimated excess hazards associated with PL remained essentially unchanged after adjustment for CVD RFs and inflammatory bio markers, suggesting that important underlying mechanisms between PL and CVD may not be reflected in the several risk factors that we considered.

Investigating the association between PL and CVD is challenging, in part due to the heterogeneous causes of PL, and in part due to the significant time-lag between women's reproductive period and the development of CVD. PL is estimated to occur in 20-30% of pregnancies, and multiple PLs are estimated to affect 1-2% of women.[23,24] PL can be caused by maternal, placental, and fetal factors. Fetal factors, such as chromosomal abnormalities or other genetic defects, are estimated to cause about 35% of PL, with placental abnormalities estimated to cause about 27%.[25] The remainder has been attributed to maternal factors such as cervical dysfunction, preterm labor, infection, or other underlying maternal diseases, especially those involving hypercoagulability or autoimmune pathology.[25,26] Maternal factors such as obesity, hypercoagulability, polycystic ovarian syndrome, impaired glucose tolerance, gestational diabetes, and other endocrine abnormalities have each been associated with PL, and likely contribute to CVD risk later in life.[27,28] Importantly, the causes underlying ~ 10% of PL are unknown.[25,26] Our analysis included several of these important maternal factors, but detailed information on gestational diabetes, pregnancy-induced hypertension, preeclampsia, preterm delivery, hypercoagulability, and PCOS was not available in the cohort and may merit further investigation in future studies. Our finding that smoking was inversely associated with PL was somewhat surprising, as smoking has been previously associated with miscarriage, but smoking has also been associated with a reduced risk of preeclampsia.[29,30] What is clear is that cigarette smoking did not underlie the increased risk of CVD with PL in the WHI cohort.

Strengths of our study include the large study population with a long follow up and information on a large number of CVD RFs. Our study also has several limitations. Importantly, all of the pregnancy history, risk factor assessment, and covariate ascertainment occurred at enrollment in WHI, when participants had already reached menopause.

Information on CVD RFs during the reproductive period prior to pregnancy loss were not available, and pregnancy history was determined by self-report. Only 4% of the sample had complete inflammatory biomarker data, and 27% had missing reproductive or CVD RF data. We also did not have available biomarkers of hypercoagulability, which have been associated with pregnancy loss and may have contributed to the increased risk of CVD.[27] Although this was a large population, our results should still be considered to be hypothesis-generating, and the underlying potential mechanisms warrant further investigation. However, this analysis did reproduce a significant association between PL and CVD, albeit with a relatively more modest effect size, which may be related to adjustment for additional RFs.

In conclusion, among postmenopausal women in WHI, a history of PL was significantly associated with incident CVD even after adjustment for CVD RFs, reproductive, sociodemographic, behavioral, and lifestyle factors, as well as inflammatory biomarkers. PL should be recognized as an independent, modest risk marker for CVD, and further investigation into potential underlying mechanisms is warranted.

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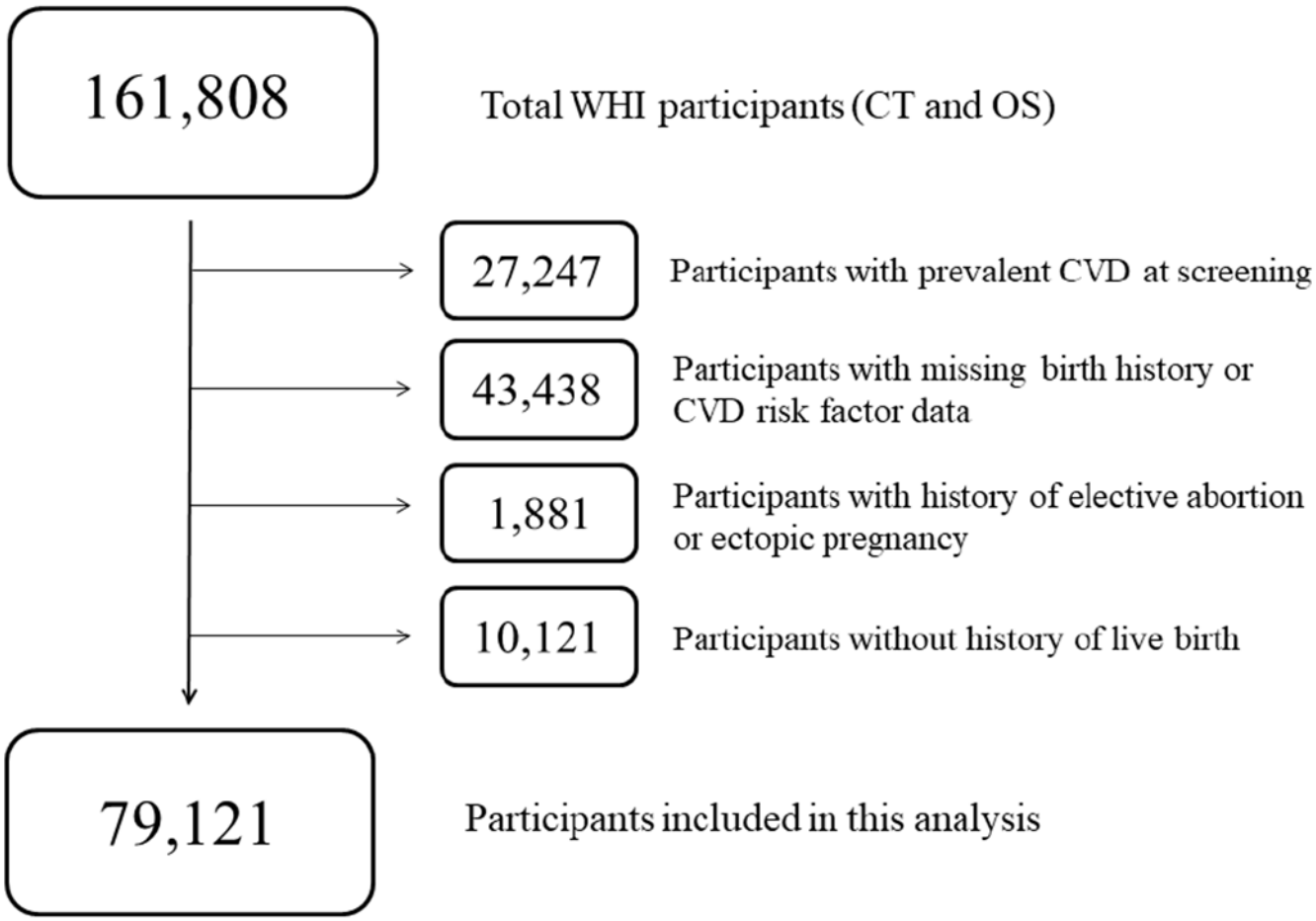

Figure 1: Creation of the Study Sample
CT, clinical trial; OS, observational study

Table 1:

Baseline Demographic and Reproductive Characteristics of the Study Sample (n-79,121), and the Association of Pregnancy Loss with CVD Risk Factors

Patient Characteristics	Pregnancy Loss		
	Yes (n=27,272)	No (n=51,849)	P value*
Age at screening (years)	63.4 (±6.9)	63.0 (±7.1)	
White (non-Hispanic)	22,940 (84.1%)	45,066 (86.9%)	
Black	2,314 (8.5%)	3,161 (6.1%)	
Hispanic/Latino	1,211 (4.4%)	1,826 (3.5%)	
Other	807 (3.0%)	1,796 (3.5%)	
Number of Pregnancies	4.8 (±1.7)	3.0 (±1.4)	
Pregnancy Loss			
Miscarriage	25,573 (93.8%)	0	
Stillbirth	3,405 (12.5%)	0	
Hysterectomy	12,179 (44.7%)	22,149 (42.7%)	
Age at Menopause (years)	47.2 (±6.7)	47.6 (±6.5)	
Oral Contraceptive (ever use)	12,128 (44.5%)	22,432 (43.3%)	
Hormone Therapy (ever use)	6,872 (25.2%)	14,458 (27.9%)	
Body-mass index (kg/m2)	28.2 (±5.9)	27.7 (±5.7)	<0.0001
Hypertension	8,926 (32.7%)	15,741 (30.4%)	<0.0001
Systolic blood pressure (mm Hg)	127.7 (±17.6)	126.9 (±17.4)	0.008
Diastolic blood pressure (mm Hg)	75.4 (±9.2)	75.3 (±9.1)	0.007
Diabetes mellitus	1,246 (4.6%)	2,020 (3.9%)	0.003
Hyperlipidemia	3,376 (12.4%)	6,231 (12.0%)	0.47
Smoking status			<0.0001
Current	13,775 (50.5%)	27,799 (53.6%)	
Former	2,014 (7.4%)	3,159 (6.1%)	
Never	11,483 (42.1%)	20,891 (40.3%)	
Socioeconomic Status Index	75.7 (±8.7)	76.2 (±8.1)	0.01
Psychosocial history of Depression	6,461 (23.7%)	11,478 (22.1%)	<0.0001
Physical Activity, MET - hours/week	12.3 (±13.5)	12.7 (±13.7)	0.01
Healthy Eating Index	64.2 (±10.8)	64.7 (±10.7)	<0.0001
Alcohol use (drinks/week)			<0.0001
>7	3,163 (11.6%)	6,140 (11.8%)	
1-7	7,090 (26.0%)	13,652 (26.3%)	
<1	9,160 (33.6%)	17,204 (33.2%)	
Former	5,022 (18.4%)	8,778 (16.9%)	
Never	2,837 (10.4%)	6,075 (11.7%)	
Household Income ($/year)			<0.0001
<$20,000	4,622 (17.0%)	7,435 (14.3%)	
$20,000-$74,999	17,720 (65.0%)	34,011 (65.6%)	
≥$75,000	4,930 (18.1%)	10,403 (20.1%)	

Patient Characteristics	Pregnancy Loss		
	Yes (n=27,272)	No (n=51,849)	P value*
Education Level			0.50
≤High School	6,427 (23.6%)	12,241 (23.6%)	
≥Some College	17,925 (65.7%)	34,156 (65.9%)	

SD, standard deviation

*Linear or logistic regression adjusted for age at enrollment, race/ethnicity, and age at first pregnancy lasting ≥6 months

Table 2:

Association of Biomarkers with History of Pregnancy Loss

Biomarkers	Pregnancy Loss		
	Yes	No	P-value*
C-reactive protein (mg/dl)	n=8,436 2.80 (1.26-5.90)	n=14,594 2.61 (1.19-5.49)	0.11
Fibrinogen (mg/dl)	n=2,436 284 (222-334)	n=4,207 281 (229-331)	0.64
Interleukin-6 (pg/ml)	n=3,249 2.05 (1.13-4.25)	n=5,923 1.83 (1.00-3.67)	0.02
White blood cell count (cells/μl)	n=27,091 57 (4.8-6.8)	n=51,507 5.6 (4.8-67)	0.93

Values expressed as medians with interquartile range

* Linear or logistic regression adjusted for age at enrollment, race/ethnicity, and age at first pregnancy lasting ≥6 months

Table 3:

Association of Pregnancy Loss with Incident CVD During Follow Up (n=79,121)

	Pregnancy Loss		
	Yes (n=27,272)	**No (n=51,849)**	**Adjusted Hazard Ratio* (95% CI)**
Incident Cardiovascular Disease	**3,369 (12.4%)**	**5,513 (10.6%)**	**1.11 (1.06-1.16)**
Cardiovascular Death	427 (1.6%)	629 (1.2%)	1.20 (1.06-1.36)
Myocardial Infarction	1,051 (3.9%)	1,698 (3.3%)	1.11 (1.03-1.20)
Stroke	1,058 (3.9%)	1,848 (3.6%)	1.03 (0.96-1.11)
Pulmonary Embolism	159 (0.6%)	243 (0.5%)	1.16 (0.95-1.42)
Peripheral Arterial Disease	232 (0.9%)	343 (0.7%)	1.17 (0.99-1.38)
Coronary Revascularization	1,445 (5.3%)	2,338 (4.5%)	1.13 (1.06-1.21)

*Cox Proportional Hazards regression of incident CVD based upon history of pregnancy loss, adjusted for age at enrollment, race/ethnicity, age at first pregnancy lasting at least six months, clinical trial/observational study status, systolic blood pressure, diabetes, hyperlipidemia, smoking status, body-mass index, income, education, socioeconomic status index, alcohol use, depression, physical activity, and Healthy Eating Index 2005.

Table 4:

Baseline Demographic and Reproductive Characteristics of the Nulliparous Women (n=10,121)

Patient Characteristics	Pregnancy Loss		
	Yes (n=l,074)	No (n=9,047)	P value*
Age at screening (years)	62.9 (±7.8)	62.5 (±7.7)	
White (non-Hispanic)	777 (72.4%)	7,731 (85.5%)	
Black	212 (19.7%)	619 (6.8%)	
Hispanic/Latino	45 (4.2%)	331 (3.7%)	
Other	40 (3.7%)	366 (4.1%)	
Number of Pregnancies	1.8 (±1.2)	0	
Pregnancy Loss			
Miscarriage	1,013 (94.3%)	0	
Stillbirth	115 (10.7%)	0	
Hysterectomy	512 (47.7%)	3,542 (39.2%)	
Oral Contraceptive (ever use)	375 (34.9%)	2,650 (29.3%)	
Hormone Therapy (ever use)	262 (24.3%)	2,511 (27.8%)	
Age at menopause (years)	46.3 (±7.0)	47.1 (±6.3)	
Body-mass index (kg/m2)	28.4 (±6.6)	27.4 (±6.1)	0.02
Hypertension	381 (35.5%)	2,628 (29.1%)	0.06
Systolic blood pressure (mm Hg)	128.0 (±18.2)	125.9 (±17.7)	0.10
Diastolic blood pressure (mm Hg)	75.4 (±9.2)	75.3 (±9.1)	0.15
Diabetes mellitus	72 (6.7%)	350 (3.9%)	0.02
Hyperlipidemia	3,376 (12.4%)	6,231 (12.0%)	0.47
Smoking status			0.0003
Current	496 (46.2%)	4,818 (53.3%)	
Former	92 (8.6%)	612 (6.8%)	
Never	486 (45.3%)	3,617 (40.0%)	
Socioeconomic Status Index	73.9 (±9.7)	75.5 (±8.4)	0.54
Psychosocial history of Depression	252 (23.5%)	2,043 (22.6%)	0.28
Physical Activity, MET - hours/week	12.0 (±13.5)	12.7 (±13.7)	0.33
Healthy Eating Index	63.9 (±11.0)	64.5 (±11.0)	0.47
Alcohol use (drinks/week)			0.002
>7	131 (12.2%)	1,325 (14.7%)	
1-7	291 (27.1%)	2,486 (27.5%)	
<1	332 (30.9%)	2,940 (32.5%)	
Former	236 (22.0%)	1,439 (15.9%)	
Never	84 (7.8%)	857 (9.5%)	
Household Income ($/year)			0.17
<$20,000	194 (18.1%)	1,357 (15.0%)	
$20,000-$74,999	683 (63.6%)	6,058 (67.0%)	
≥$75,000	197 (18.3%)	1,632 (18.0%)	
Education Level			0.02

Patient Characteristics	Pregnancy Loss		
	Yes (n=l,074)	No (n=9,047)	P value*
≤High School	166 (15.5%)	1,185 (13.1%)	
≥Some College	799 (74.4%)	7,211 (79.7%)	

Table 5:

Association of Biomarkers with History of Pregnancy Loss Among Nulliparous Women

Biomarkers	Pregnancy Loss		
	Yes	No	P-value*
C-reactive protein (mg/dl)	n=369 2.60 (1.20-6.10)	n=2,354 2.25 (0.97-4.80)	0.85
Fibrinogen (mg/dl)	n=113 292 (238-345)	n=677 286 (222-334)	0.94
Interleukin-6 (pg/ml)	n=133 2.03 (1.23-4.77)	n= 1,049 1.78 (0.97-3.59)	0.55
White blood cell count (cells/μl)	n=l,066 5.6 (4.7-6.7)	n=8,965 5.6 (4.7-6.6)	0.83

Values expressed as medians with interquartile range

* Linear or logistic regression adjusted for age at enrollment, race/ethnicity, and age at first pregnancy lasting ≥6 months

Table 6:

Association of Pregnancy Loss with Incident CVD During Follow Up Among Nulliparous Women (n=10,121)

	Pregnancy Loss		
	Yes (n=1,074)	**No (n=9,047)**	**Adjusted Hazard Ratio* (95% CI)**
Incident Cardiovascular Disease Event	**124 (11.6%)**	**893 (9.9%)**	**1.04 (0.85-1.28)**
Cardiovascular Death	20 (1.9%)	125 (1.4%)	1.37 (0.84-2.24)
Myocardial Infarction	30 (2.8%)	268 (3.0%)	0.90 (0.61-1.35)
Stroke	47 (4.4%)	301 (3.3%)	1.14 (0.81-1.60)
Pulmonary Embolism	5 (0.5%)	36 (0.4%)	0.99 (0.38-2.58)
Peripheral Arterial Disease	7 (0.7%)	68 (0.8%)	0.76 (0.34-1.68)
Coronary Revascularization	58 (5.4%)	329 (3.6%)	1.29 (0.95-1.76)

*Cox Proportional Hazards regression of incident CVD based upon history of pregnancy loss, adjusted for age at enrollment, race/ethnicity, age at first pregnancy lasting at least six months, clinical trial/observational study status, systolic blood pressure, diabetes, hyperlipidemia, smoking status, body-mass index, income, education, socioeconomic status index, alcohol use, depression, physical activity, and Healthy Eating Index 2005.