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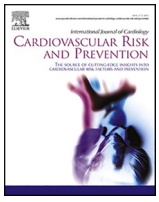

Effects of prior reproductive losses on risk of cardiovascular diseases within six months of a first live birth

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ABSTRACT

Objective: There is emerging evidence suggesting that pregnancy loss (induced or natural) is associated with an increased risk of cardiovascular diseases (CVD). This prospective longitudinal study investigates the effect of prior pregnancy losses on CVD risk during the first six months following a first live birth.
Methods: Medicaid claims of 1,002,556 low-income women were examined to identify history of pregnancy losses, CVD, diabetes, and hyperlipidemia prior to first live birth. The study population was categorized into five groups: A: women with no pregnancy loss or CVD history prior to first live birth; B: women with pregnancy loss and no CVD prior to first live birth. C: women with a first CVD diagnosis after a first pregnancy ending in a loss and before their first live birth. D: women with CVD prior to first live birth and no history of pregnancy loss. E: women with both CVD and pregnancy loss prior to their first live birth.
Results: After controlling for age, race, state of residence, and history of diabetes and hyperlipidemia, the risk of CVD in the six-month period following a first live birth were 15%, 214%, 79% and 129% more common for Groups B, C, D and E, respectively, compared to Group A.
Conclusions: Pregnancy loss is an independent risk factor for CVD risk following a first live birth, both for women with and without a prior history of CVD. The risk is highest when CVD is first diagnosed after a pregnancy loss and prior to a first live birth.

1. Introduction

Pregnancy affects cardiovascular health and is associated with increased long-term risk of hypertension [1], ischemic heart disease [1], myocardial infarction (MI) [2–4], ischemic stroke and intracerebral hemorrhage [5–9], venous and arterial thromboembolism [10,11]. There is also a growing body of research showing that pregnancy losses are especially associated with an increased risk of cardiovascular disease (CVD) [12–20], but relatively little research has explored the differences associated with different types of pregnancy losses (induced or natural) [21]. A history of miscarriage or recurrent miscarriage has been linked to a higher risk of CVD [12–17], and positive associations have been reported between stillbirth and the risk of subsequent MI and coronary heart disease [13,14]. Induced abortion has also been linked to higher CVD risk in a smaller number of studies [19,22,23]. In one such study, a history of abortion was an independent risk factor for significantly lower levels of cardiovascular health and elevated levels of high-sensitivity C reactive protein (hs-CRP), as measured at 24–28 weeks of gestation among nulliparous women [23].

In recent analyses examining the effects of pregnancy on Medicaid recipients, we found that there was an 18% increased risk of a first diagnosis of CVD (Adjusted odds ratio (OR) = 1.18; 95% confidence interval (CI) = 1.15–1.21) among women whose first pregnancy resulted in a pregnancy loss as compared to women whose first pregnancy resulted in a live birth [24]. A graph of the onset of first diagnosis of CVD, however, revealed that during the first six months after a first pregnancy ending in a live birth the cardiovascular risk was higher than that in the same period following the loss of a first pregnancy. Specifically, in the first six months following the end of a first pregnancy outcome, 3.61% of women giving birth had a first CVD diagnosis compared to only 2.04% of women who had a miscarriage or abortion. But while biannual rates of first CVD fell for both groups after the first six months, the cumulative risk of CVD among those with a history of pregnancy loss consistently increased faster than that for women whose

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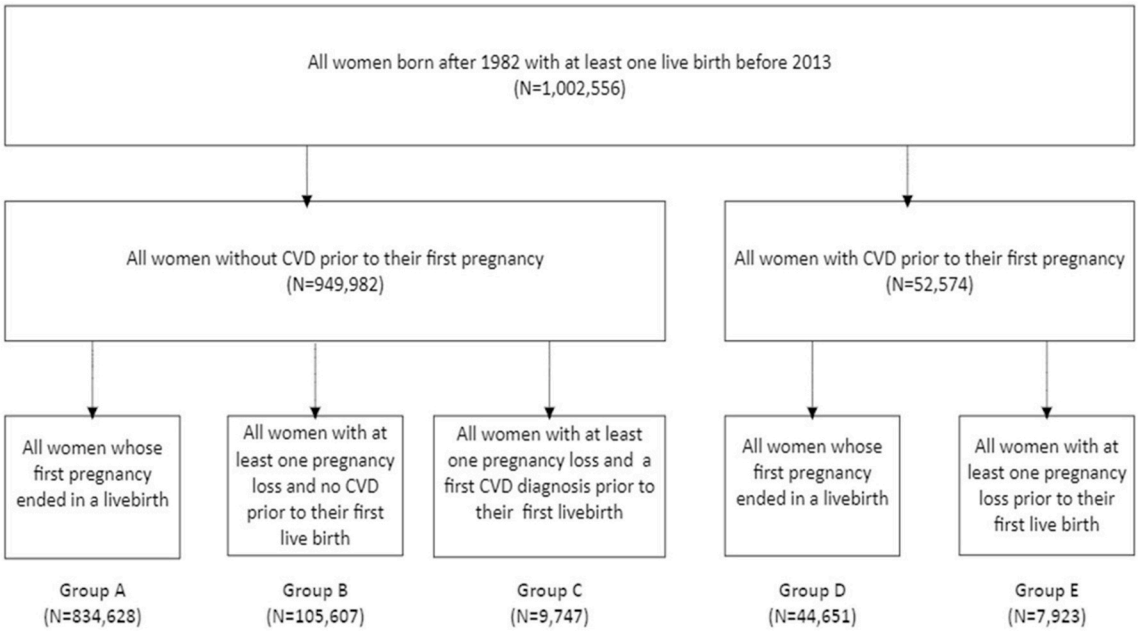

Fig. 1. Division of population into five groups.

Table 1
Characteristics of study population. All women with at least one live birth segregated by history of pregnancy loss and timing of any prior history of a cardiovascular disease treatment (CVD).

First CVD Timing	No CVD prior to 1st Pregnancy		CVD between loss (es) and 1st live birth	Yes CVD prior to 1st Pregnancy		
Pregnancy loss prior to 1st live birth	No	Yes	Yes	No	Yes	
Group	A	B	C	D	E	**All**
N	834,628	105,607	9,747	44,651	7,923	1,002,556
Avg Ages						
Avg Age at 1st pregnancy	21.7	20.55	20.7	22.2	21.9	21.6
Avg Age at 1st cardio diagnosis	22.1	21.95	23.0	19.2	18.7	21.9
Avg Months Eligibility						
Avg # months of eligibility	88.1	118.78	130.0	128.2	143.4	93.9
Avg # months of eligibility from year after 1st pg outcome	33.8	52.33	60.9	36.8	48.2	36.2
Prior to 1st Pregnancy						
History of diabetes %	0.74	0.97	1.97	3.85	3.93	0.93
History of hyperlipidemia %	0.57	0.73	1.17	3.03	3.32	0.72
Any time After 1st Pregnancy						
History of diabetes %	0.99	1.55	4.06	2.29	2.74	1.15
History of hyperlipidemia %	0.92	1.09	3.03	1.63	1.63	0.99

first pregnancy ended in a live birth [24]. This divergence in CVD risk over time suggests that the cumulative risk in the years following a first pregnancy loss may be associated with the combination of exposure to subsequent pregnancies following the first pregnancy loss. That hypothesis was given further credence by the recent finding that a history of pregnancy loss is linked with lower cardiovascular health in women preparing to deliver their first live born child [23]. This observation of lower cardiovascular health during subsequent pregnancies among women with a history of abortion would suggest a corresponding elevated risk of cardiovascular diseases emerging in the postpartum period.

These findings suggested the hypothesis there will be an elevated risk of CVD during the postpartum period (defined herein as six months) among women with a history of prior pregnancy loss for both women with and without a prior history of CVD.

2. Materials and methods

2.1. Data source and study population

Data for the years 1999–2014 was obtained from the United States Centers for Medicaid and Medicaid Services (CMS) for the sixteen states (Alaska, Arizona, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, Minnesota, Montana, New Jersey, New Mexico, New York, Oregon, Vermont, Washington, and West Virginia) that provide for all reproductive health care options and report all Medicaid paid treatments to CMS. To maximize identification of first pregnancy outcomes, data for each beneficiary was rolled in beginning in the year of her 14th birthday or in 1999. Within this data set, we identified all women born in 1983 or later who had at least one live birth before 2013 and who had been eligible for Medicaid for at least 12 months between 1999 and of 2015 inclusive.

Table 2
Percentage of women in each group with least one CVD diagnosis within 6 months after their first live birth, segregated by study groups, age groups, year of first pregnancy, race, history of risk factors, and state.

First CVD Timing	No CVD prior to 1st Pregnancy		CVD between loss (es) and 1st live birth	Yes CVD prior to 1st Pregnancy	
Pregnancy loss (es) prior to 1st live birth	No	Yes	Yes	No	Yes
Group	Group A	Group B	Group C	Group D	Group E
Total	2.90%	2.52%	7.33%	6.21%	6.27%
Age at First Live Birth					
14-19	2.89%	2.64%	8.18%	5.80%	7.26%
20-24	2.68%	2.32%	6.61%	5.56%	5.14%
25-29	3.56%	2.76%	7.79%	7.85%	7.32%
Year of First Live Birth					
1999	1.68%	0.00%			
2000	2.65%	5.95%		9.09%	100.00%
2001	2.58%	1.77%		2.44%	20.00%
2002	2.61%	1.79%	7.69%	7.69%	16.67%
2003	2.31%	2.93%	9.43%	4.34%	8.62%
2004	1.81%	1.44%	4.04%	3.10%	3.51%
2005	1.94%	1.89%	5.59%	4.78%	2.63%
2006	1.97%	1.77%	3.66%	4.12%	4.94%
2007	2.00%	1.77%	5.61%	4.40%	3.83%
2008	2.16%	2.01%	5.88%	4.98%	3.92%
2009	2.39%	2.13%	5.94%	5.33%	4.29%
2010	2.81%	2.25%	5.59%	6.09%	6.38%
2011	3.33%	2.88%	7.30%	6.63%	7.11%
2012	4.91%	4.03%	10.72%	8.77%	8.60%
Race					
White	2.67%	2.25%	7.89%	5.51%	6.08%
Black	4.70%	3.79%	9.06%	8.19%	7.41%
Hispanic	2.68%	2.22%	6.05%	6.13%	5.36%
Other	2.30%	2.12%	6.36%	5.49%	6.05%
State of Pregnancy Outcome					
NY	2.10%	2.17%	5.91%	3.48%	4.99%
AK	1.27%	2.37%	0.00%	4.68%	0.00%
AZ	1.20%	1.30%	6.56%	6.26%	5.68%
CT	1.93%	1.87%	5.45%	3.33%	3.06%
HI	0.77%	1.41%	3.57%	10.16%	8.05%
IL	6.96%	7.25%	13.04%	4.16%	12.02%
MA	2.21%	1.89%	6.25%	4.40%	4.38%
MD	1.96%	2.21%	6.92%	4.06%	5.82%
MN	1.56%	1.74%	8.50%	7.00%	4.23%
MT	1.48%	1.00%	8.00%	2.37%	16.67%
NJ	2.17%	2.57%	4.57%	3.61%	2.94%
NM	1.12%	1.18%	3.35%	4.92%	3.50%
OR	1.22%	1.24%	6.76%	5.01%	3.36%
VT	2.25%	1.52%	9.38%	3.95%	3.64%
WA	1.76%	1.72%	7.03%	4.66%	5.74%
WV	1.87%	2.28%	9.80%	2.64%	12.73%
Diabetes prior to 1st pregnancy					
No	2.89%	2.50%	7.31%	6.14%	6.20%
Yes	4.32%	4.22%	8.23%	7.84%	8.04%
Hyperlipidemia prior to 1st pregnancy					
No	2.89%	2.51%	7.30%	6.18%	6.31%
Yes	3.74%	4.04%	9.89%	6.95%	5.32%

2.2. Data preparation and coding

The primary outcome variable was any treatment for cardiovascular disease (CVD), defined as any treatment code associated with ICD-9 codes 401–459. These codes encompass all diseases of the circulatory system excluding only acute rheumatic fever and chronic rheumatic heart disease. The date of a first CVD code, if any, was identified for each woman. In addition, dates for first diagnosis codes for diabetes (ICD-9: 250) and hyperlipidemia (ICD-9: 272.4), known risk factors for CVD, were also identified.

All pregnancy outcomes were identified for each woman. Pregnancy outcomes were identified using diagnostic ICD-9 codes and clarified with CPT/HCPS codes. Pregnancy outcomes were segregated into four categories: live birth; induced abortion; natural fetal losses (miscarriage, ectopic pregnancy, molar pregnancy, stillbirth) and indeterminate losses (missed abortion, unspecified abortion, and failed attempted abortion) wherein indeterminate losses may include both failed induced abortions and natural losses. Missed abortions were coded as indeterminate due to evidence of coding inconsistencies which precluded the interpretation that all of these were initially spontaneous abortions.

To address coding errors or other conflicts within the data, multiple pregnancy outcome codes within four weeks of the first pregnancy outcome code in that time period were collapsed into a single pregnancy outcome using the first date associated with that cluster of Medicaid claims, codes indicating an induced abortion within 36 weeks prior to a live birth were excluded, and any data indicating an induced abortion or natural loss two weeks before through four weeks after a confirmed code for an induced abortion were excluded.

In addition, each woman's year of birth, age at first pregnancy, state of residence at first pregnancy outcome, and race were extracted for use as covariates.

2.3. Statistical analysis

Logistic regression analyses were conducted to compute the adjusted odds ratios of a CVD diagnosis within six months after a first live birth for women in each of our five groups, using Group A (no CVD diagnosis or pregnancy loss prior to a first live birth) as the reference group. Covariates included the age (treated as a continuous variable), race, type and number of prior pregnancy losses, history of diabetes or hyperlipidemia, and state of residence at time of first pregnancy outcome.

3. Results

Our population consisted of 1,002,556 young Medicaid beneficiaries who had at least one live birth. Overall, 5.24% had a history of CVD prior to their first pregnancy. As shown in Fig. 1, the population was divided into five groups. As seen in the second row of Fig. 1, the first division was based on a presence or absence of any CVD diagnosis prior to each woman's first pregnancy. In the third row, the groups are divided according to (a) they had no history of pregnancy loss prior to their first delivery, (b) they did have a history of pregnancy loss, and (c) they had a history of pregnancy loss and a first CVD diagnosis between their first pregnancy loss and their first live birth. Specifically, women without a history CVD prior to the first pregnancy branch to the left. Group A (n = 834,628) had no history of pregnancy loss and no prior history of CVD. Group B (n = 105,607) had a history of pregnancy loss and no prior history of CVD. Group C (n = 9,747) had a prior history of pregnancy loss no history of CVD prior to a first pregnancy but they have a first diagnosis of CVD between their first pregnancy loss and their first live birth. In the branches to the right, women who did have their first CVD diagnoses prior to their first pregnancy were divided into two groups: Group D (n = 44,651) for women who had no history of pregnancy loss prior to their first live birth and Group E (n = 7,923) for those who had at least one pregnancy loss prior to their first live birth.

The characteristics of the five groups are shown in Table 1. Women with a history of CVD prior to their first pregnancy (Groups D and E) were eligible for Medicare for a longer period of time overall but for a shorter period of time in the years following their first live birth as compared to women who experienced a pregnancy loss prior to their first live birth.

Table 2 shows the percentages of women receiving at least one CVD diagnosis within six months of their first live birth segregated by groups, demographic factors and history of diabetes and hyperlipidemia. The highest rate of CVD in this time period occurred in Group C, those women who had their first CVD diagnosis after a first pregnancy loss and prior to the first live birth. Across all groups, Blacks had the highest rates of postpartum CVD. Overall, CVD rates appeared to be slightly lower for Group B than Group A (2.52% versus 2.90%), but this difference did not

Table 3
Logistic regressions showing adjusted odds ratios and 95% confidence intervals for the effects associated with year of first pregnancy outcome, race, state of residence, prior history of diabetes or hyperlipidemia and group effects using Group A as the reference group, controlling for age as a continuous variable.

CVD Timing	No CVD prior to 1st Pregnancy	CVD between loss (es) and 1st live birth	Yes CVD prior to 1st Pregnancy	Yes CVD prior to 1st Pregnancy
Pregnancy loss prior to 1st live birth	Yes	Yes	No	Yes
Group Effects	Group B	Group C	Group D	Group E
Relative to ref Group A	1.15 (1.10–1.20)	3.14 (2.90–3.40)	1.79 (1.72–1.87)	2.29 (2.08–2.21)
Year of first pregnancy outcome				
1999–2000	ref	ref	ref	ref
2001–2002	1.10 (0.93–1.30)	1.10 (0.92–1.32)	1.10 (0.91–1.33)	1.10 (0.91–1.34)
2003–2004	0.92 (0.78–1.08)	0.91 (0.76–1.08)	0.86 (0.72–1.04)	0.89 (0.74–1.07)
2005–2006	0.94 (0.81–1.11)	0.91 (0.77–1.09)	0.89 (0.74–1.06)	0.90 (0.75–1.08)
2007–2008	0.97 (0.83–1.13)	0.95 (0.80–1.13)	0.93 (0.77–1.11)	0.93 (0.78–1.12)
2009–2010	1.23 (1.05–1.43)	1.20 (1.01–1.42)	1.17 (0.98–1.40)	1.19 (0.99–1.42)
2011–2012	2.02 (1.73–2.37)	2.03 (1.71–2.41)	1.96 (1.64–2.34)	2.01 (1.68–2.41)
Race				
White	ref	ref	ref	ref
Black	1.38 (1.33–1.43)	1.37 (1.33–1.42)	1.35 (1.31–1.40)	1.37 (1.32–1.42)
Hispanic	1.15 (1.11–1.19)	1.15 (1.11–1.20)	1.15 (1.11–1.19)	1.14 (1.12–1.20)
Other	1.09 (1.05–1.13)	1.08 (1.05–1.12)	1.08 (1.04–1.12)	1.09 (1.05–1.13)
State of residence at first pregnancy outcome				
NY	ref	ref	ref	ref
AK	0.72 (0.52–0.99)	0.68 (0.49–0.96)	0.69 (0.50–0.96)	0.68 (0.46–0.95)
AZ	0.63 (0.59–0.67)	0.63 (0.60–0.64)	0.65 (0.62–0.69)	0.64 (0.60–0.68)
CT	0.81 (0.73–0.91)	0.83 (0.74–0.93)	0.83 (0.74–0.93)	0.82 (0.73–0.92)
HI	1.02 (0.87–1.21)	1.06 (0.89–1.27)	1.04 (0.88–1.23)	1.10 (0.93–1.31)
IL	3.66 (3.53–3.79)	3.62 (3.49–3.75)	3.49 (3.37–3.61)	3.65 (3.52–3.79)
MA	0.99 (0.92–1.08)	1.01 (0.93–1.10)	0.99 (0.92–1.07)	1.01 (0.93–1.10)
MD	0.90 (0.85–0.96)	0.90 (0.84–0.96)	0.88 (0.83–0.94)	0.90 (0.84–0.96)
MN	0.79 (0.73–0.86)	0.81 (0.74–0.88)	0.79 (0.72–0.86)	0.79 (0.72–0.87)
MT	0.79 (0.68–0.92)	0.80 (0.69–0.94)	0.86 (0.74–0.99)	0.82 (0.70–0.96)
NJ	1.23 (1.12–1.36)	1.21 (1.09–1.34)	1.17 (1.06–1.29)	1.22 (1.10–1.36)
NM	0.56 (0.51–0.61)	0.55 (0.50–0.61)	0.57 (0.52–0.62)	0.55 (0.50–0.61)
OR	0.63 (0.57–0.68)	0.63 (0.58–0.70)	0.64 (0.58–0.70)	0.62 (0.57–0.68)
VT	1.17 (0.99–1.38)	1.22 (1.04–1.44)	1.16 (0.99–1.36)	1.20 (1.01–1.41)
WA	0.94 (0.88–1.00)	0.96 (0.90–1.03)	0.94 (0.88–1.01)	0.95 (0.89–1.02)
WV	1.24 (1.08–1.43)	1.25 (1.08–1.45)	1.18 (1.02–1.34)	1.28 (1.10–1.48)
Prior diabetes	1.38 (1.23–1.55)	1.35 (1.19–1.52)	1.33 (1.20–1.48)	1.35 (1.20–1.52)
Prior hyperlipidemia	1.34 (1.16–1.54)	1.30 (1.12–1.52)	1.25 (1.10–1.42)	1.25 (1.08–1.45)
Age at first pregnancy	1.01 (1.01–1.02)	1.01 (1.01–1.02)	1.02 (1.01–1.02)	1.01 (1.01–1.02)

hold up across the various states, wherein Group B had higher rates of CVD than Group A in nine of the sixteen states. As would be expected, the risk of CVD was higher for women with a history of diabetes or hyperlipidemia.

Table 3 shows the results of the logistic regression showing adjusted odds ratios between each group relative to race, state of residency at the time of the first pregnancy outcome, and history of diabetes and hyperlipidemia adjusting for age as a continuous variable using Group A (no prior history of pregnancy loss or cardiovascular disease) as the reference group. These result show that there is an independent positive correlation between a first pregnancy loss and subsequent postpartum CVD risk. The elevated odds are especially strong (Adj OR = 3.14) when a first diagnosis occurs between the first pregnancy loss and the first live birth. Postpartum CVD risk is also 129% higher among women who had a history of CVD prior to their first pregnancy if they also had a history of pregnancy loss prior to their first live birth (Adj OR 2.29, 95% CI (2.08–2.21)). Across all groups, Blacks were at higher risk of postpartum CVD. Substantial variation across states of residence remained significant.

Table 4 shows an additional logistic regression to isolate the statistically significant effects of pregnancy loss by the number of exposures to each type of pregnancy loss prior to the first live birth. These finding revealed that both induced abortions and natural losses were each risk factors for elevated risk of postpartum CVD diagnoses within the first six months of a live birth for all three groups with a history of pregnancy loss. There appears to be a mild dose effect, though a relatively low number of cases with three or more losses resulted in wide confidence intervals that negated statistical significance in several cases.

4. Discussion

The analysis of our study population of young Medicaid patients shows that loss of a first pregnancy is an independent risk factor for postpartum CVD within the first six months following a first live birth. Significant differences were observed relative to race and state of residence, which may reflect genetic, dietary, and regional socioeconomic differences. There appears to be little difference between the type of loss, induced or natural (Table 4). However, our findings suggest the possibility of a mild dose effect, with each pregnancy loss exposure increasing the risk of subsequent CVD. This would be consistent with previous research which shows that the risk of CVD is higher with increasing number of pregnancy losses [12,13,16,23].

As compared to women with no history of prior loss, diabetes or hyperlipidemia, the group of women at greatest risk of postpartum CVD were Group C, women who had a first CVD diagnosis after their first pregnancy ended in a loss and prior to their first live birth (Adj OR = 3.14; 95% CI = 2.90–3.40). This may be at least partly due to the associations observed in our previous analyses showing that the cumulative CVD risk associated with pregnancy loss exceeds that of childbirth only after the first six months yet persists for approximately six years [21]. If one or more pregnancy losses contribute to a first CVD diagnosis prior to a first live birth, it is reasonable to expect a heightened risk of a subsequent CVD diagnosis in the postpartum period. Another explanation is that women in Group C may have had more multiple natural and/or induced pregnancy losses. Either or both (a) more time for a CVD diagnosis and/or (b) a dose effect associated with multiple pregnancy losses may contributed to the heightened risk for this group.

Table 4
Logistic regression showing adjusted odds ratios and confidence intervals relative to the number and types of pregnancy losses, year of first pregnancy outcome, race, state of residence, prior history of diabetes or hyperlipidemia and age.

CVD Timing	No CVD prior to 1st Pregnancy	CVD between loss (es) and 1st live birth	Yes CVD prior to 1st Pregnancy
Pregnancy loss prior to 1st live birth	Yes	Yes	Yes
Group	Group B	Group C	Group E
Prior losses by number and type			
# of prior abortions			
0	**ref**	**ref**	**ref**
1-2	1.16 (1.08–1.24)	2.74 (2.39–3.13)	2.04 (1.72–2.42)
3-4	1.25 (1.03–1.52)	2.00 (1.38–2.91)	2.03 (1.25–3.30)
5+	1.27 (0.97–1.66)	3.41 (2.37–4.91)	3.67 (2.10–6.41)
# of prior natural losses			
0	**ref**	**ref**	**ref**
1-2	1.13 (1.07–1.20)	2.40 (2.14–2.70)	2.00 (1.75–2.30)
3-4	1.23 (0.08–1.89)	2.79 (1.66–4.68)	2.49 (1.30–4.78)
5+	2.35 (0.94–5.84)	2.37 (0.56–10.08)	0.00 (0.00–1,000.00)
# of prior indeterminate losses			
0	**ref**	**ref**	**ref**
1-2	0.94 (0.85–1.04)	1.29 (1.05–1.60)	1.30 (1.06–1.61)
3+	1.04 (0.86–1.26)	0.85 (0.55–1.31)	1.18 (0.81–1.72)
Year of first pregnancy outcome			
1999–2000	**ref**	**ref**	**ref**
2001–2002	1.10 (0.93–1.30)	1.11 (0.92–1.33)	1.10 (0.91–1.34)
2003–2004	0.92 (0.78–1.08)	0.91 (0.77–1.09)	0.89 (0.74–1.07)
2005–2006	0.95 (0.81–1.11)	0.92 (0.77–1.09)	0.90 (0.75–1.08)
2007–2008	0.97 (0.83–1.14)	0.96 (0.81–1.14)	0.93 (0.78–1.12)
2009–2010	1.23 (1.05–1.43)	1.21 (1.02–1.43)	1.19 (0.99–1.42)
2011–2012	2.03 (1.73–2.37)	2.05 (1.72–2.43)	2.01 (1.69–2.41)
Race			
White	**ref**	**ref**	**ref**
Black	1.378 (1.332–1.426)	1.371 (1.323–1.42)	1.37 (1.32–1.42)
Hispanic	1.151 (1.11–1.194)	1.152 (1.109–1.196)	1.16 (1.12–1.20)
Other	1.087 (1.049–1.126)	1.081 (1.042–1.122)	1.09 (1.05–1.13)
State of residence at first pregnancy outcome			
NY	**ref**	**ref**	**ref**
AK	0.721 (0.522–0.994)	0.682 (0.485–0.958)	0.68 (0.48–0.96)
AZ	0.632 (0.595–0.674)	0.634 (0.597–0.675)	0.64 (0.60–0.68)
CT	0.812 (0.729–0.905)	0.828 (0.737–0.93)	0.82 (0.73–0.92)
HI	1.026 (0.869–1.212)	1.063 (0.893–1.266)	1.11 (0.93–1.31)
IL	3.671 (3.543–3.808)	3.636 (3.504–3.773)	3.66 (3.53–3.80)
MA	0.996 (0.921–1.078)	1.015 (0.936–1.101)	1.01 (0.93–1.10)
MD	0.903 (0.85–0.96)	0.897 (0.841–0.956)	0.90 (0.84–0.96)
MN	0.794 (0.729–0.864)	0.806 (0.738–0.881)	0.79 (0.73–0.87)
MT	0.791 (0.677–0.924)	0.806 (0.688–0.944)	0.82 (0.70–0.96)
NJ	1.231 (1.117–1.356)	1.213 (1.095–1.345)	1.22 (1.10–1.36)
NM	0.559 (0.51–0.612)	0.551 (0.5–0.607)	0.55 (0.50–0.61)
OR	0.625 (0.572–0.683)	0.635 (0.578–0.697)	0.62 (0.57–0.68)
VT	1.172 (0.996–1.379)	1.228 (1.042–1.448)	1.20 (1.01–1.42)
WA	0.938 (0.881–0.999)	0.959 (0.896–1.026)	0.95 (0.89–1.02)
WV	1.245 (1.078–1.438)	1.254 (1.081–1.455)	1.28 (1.10–1.49)
Prior diabetes	1.378 (1.226–1.549)	1.35 (1.193–1.527)	1.36 (1.21–1.54)
Prior hyperlipidemia	1.337 (1.16–1.54)	1.307 (1.125–1.518)	1.26 (1.09–1.46)
Age at first pregnancy	1.012 (1.007–1.016)	1.012 (1.007–1.016)	1.01 (1.01–1.02)

Since multiple factors contribute to the onset and severity of cardiovascular diseases, it is possible that women with undiagnosed cardiovascular disease may also be at higher risk miscarriage. To the degree this might be true, our findings may reflect instances of reverse causation wherein some experiences of miscarriage may have been due to undiagnosed CVD. However, this risk of reverse causation is unlikely to extend to induced abortions.

Adverse pregnancy outcomes, including miscarriage and stillbirth, have been identified by the American Heart Association as risk factors for CVD [25], and the American College of Obstetricians and Gynecologists has joined them in recommending screening women for their complete history of adverse pregnancy outcomes [26]. While induced abortions are not specifically mentioned in either clinical recommendations, this and previous analyses [19,23,24] underscore that it should be.

Racial differences in our findings, specifically highest rates of postpartum CVD among Black women across all groups, warrant further investigation.

Our study was restricted by the limitations inherent in the CMS data. The data regarding the subjects is not complete, since while Medicaid coverage is more readily available for pregnant women a large portion of the sample population were not covered for the entirety of the time under investigation, especially in the years prior to the first live birth. It is therefore likely that many prior pregnancy losses and first occurrences of cardiovascular diseases were not recorded by Medicaid.

But any resulting misclassification of women into Groups A or D would only tend to dilute the observed statistical effects, leading to results that underestimate, rather than overestimate, the elevated risks associated with pregnancy loss. Therefore, the differences observed between our five groups would most likely be strengthened, rather than weakened, if we had access to more complete medical records.

Another weakness is that we aggregated all forms of natural loss into a single group and also segregated as “indeterminate losses” diagnostic codes for missed abortion, unspecified abortion, and failed attempted abortion into a single aggregate category, indeterminate losses. Future research should be conducted to examine which, if any of these specific outcomes, are more or less associated with subsequent CVD risk.

Additionally, we were unable to adjust for potential confounding factors such as weight, body mass index (BMI), behavioral and socioeconomic factors that may be implicated in developing CVD. However, a recent study controlling for such confounding factors has reported independent associations between pregnancy loss and a heightened risk of cardiovascular disease [23]. Also, in this analysis, we did not investigate specific cardiovascular diseases, While such additional detail was provided in our previous analyses [24], additional research is warranted to identify which CVD treatments during the postpartum period are most associated with prior pregnancy loss. Additional variations among women seen across the various states may be due to differences in state Medicaid coverage and widely varying ICD coding practices across different states and hospital systems.

Finally, while it was not the object of our investigation, the results

shown in Table 1 revealed that there was a 55% higher risk of a subsequent diabetes diagnosis among women whose first pregnancy ended in a loss. In light of a recent study finding that induced abortion is significantly associated with and increased risk of subsequent gestational diabetes, additional research into this association between diabetes and pregnancy loss is warranted [27].

5. Conclusions

In line with the existing research, our findings show that a history of pregnancy loss is an independent risk factor for the onset of cardiovascular disease. Although the strength of the relationships varied between types of pregnancy loss, the relationships generally became stronger with recurrent pregnancy loss [19,23].

Data availability statement

The data used is available from the United States Centers for Medicare and Medicaid Services.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Maka Tsulukidze: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **David C. Reardon:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Christopher Craver:** Data curation, Formal analysis, Investigation, Resources, Software, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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