Elevated cardiovascular disease risk in low-income women with a history of pregnancy loss

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ABSTRACT

Objective Pregnancy is associated with elevated risk of cardiovascular diseases (CVD), but little is known regarding the association between CVD and specific types of pregnancy losses. The aim of this study is to investigate the effects of pregnancy loss on the risk of subsequent CVD of any type.

Methods This prospective longitudinal study examines medical records between 1999 and 2014 for Medicaid beneficiaries born after 1982 who lived in a state that funds all reproductive health services, including induced abortion. Unique pregnancy outcomes, history of diabetes, hyperlipidaemia or CVD (International Classification of Diseases, Ninth Revision (ICD-9): 401–459) prior to their first pregnancy outcome for each woman. Cumulative incidence rates of a first CVD diagnosis following a first pregnancy were calculated for the observed period, exceeding 12 years.

Results A history of pregnancy loss was associated with 38% (OR=1.38; 95% CI=1.37 to 1.40) higher risk of a CVD diagnosis in the period observed. After controlling for history of diabetes, hyperlipidaemia, age, year of first pregnancy, race, state of residence, months of eligibility, number of pregnancies, births, number of losses before and after the first live birth, exposure to any pregnancy loss was associated with an 18% (adjusted OR=1.18; 95% CI=1.15 to 1.21) increased risk of CVD. Our analyses also reveal an important temporal relationship between the CVD and pregnancy loss. Immediate and short-term increased CVD risk is more characteristic for women whose first pregnancy ended in a birth more than a delayed and more prolonged increased risk of CVD is associated with a first pregnancy loss.

Conclusions Our findings corroborate previous research showing that pregnancy loss is a independent risk factor for CVD, especially for diseases more chronic in nature. Our research contributes to understanding the specific needs for cardiovascular health monitoring for pregnant women and developing a consistent, evidence-based screening tools for both short-term and long-term follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pregnancy is a risk factor for many cardiovascular diseases (CVD), but relatively little research has been done on the effects of pregnancy loss on cardiovascular risk.

WHAT THIS STUDY ADDS

⇒ Our study of a large population of low-income women revealed that compared with women who carry a first pregnancy to term, women whose first pregnancy ends in a pregnancy loss face an elevated cumulative risk of CVD from 2 through 12 years following their first pregnancy outcome. Thus, our analysis provides a better understanding of the association between a first pregnancy outcome and CVD risk over longer periods of time.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Clinicians should consider pregnancy history when advising and evaluating patients. Our analyses of the full range of pregnancy-related CVD diagnoses indicates opportunities for developing more specific cardiovascular health monitoring for pregnant women based on their complete pregnancy histories, including their pregnancy losses.

INTRODUCTION

Profound physiological changes including significant hormonal, metabolic and haemodynamic shifts and their impact on cardiovascular and pulmonary systems during pregnancy are widely recognised. Studies have found that women with any history of pregnancy have increased long-term risk of hypertension,1 ischaemic heart disease (IHD),1 myocardial infarction (MI),2-4 ischaemic stroke and intracerebral haemorrhage,5-9 venous and arterial thromboembolism.10-11 However, research examining the association between history of pregnancy loss and cardiovascular disease (CVD) is limited. Further, the existing research has focused narrowly on several select CVDs such as coronary heart disease (CHD) and MI.

Increased risk of MI and CHD in later life among women with a history of miscarriage and recurring episodes of miscarriage has been suggested in studies linking miscarriage with future risk of CVD.12-17 Positive association has been reported between stillbirth and the risk of subsequent MI and CHD as well.12 17
Relatively little evidence exists regarding any association between induced abortion and risk of future CHD.\textsuperscript{12,14} Research linking death certificates with the Medicaid records of women who had an induced abortion or delivery did find a significantly higher age-adjusted risk of death from all causes, including circulatory diseases and cerebrovascular disease in women who had an induced abortion or a delivery compared with women with completed pregnancy and delivery.\textsuperscript{18}

There is a need for further research to determine the frequency and type of cardiovascular complications associated with pregnancy loss, including both natural losses and induced abortions. Our study examines the hypothesis that pregnancy loss of any type is a risk factor for cardiovascular diseases.

MATERIALS AND METHODS

Study population

Data were obtained from the US Centers for Medicare & Medicaid Services (CMS) using the data submitted to CMS from 16 states (Alaska, Arizona, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, Minnesota, Montana, New Jersey, New Mexico, New York, Oregon, Vermont, Washington and West Virginia) for the years 1999–2014. These states both (1) provided coverage for all reproductive healthcare options, including induced abortion, during the years 1999 through at least 2012, and (2) have reported all reproductive health services to CMS. California was excluded because most state-funded Medicaid abortions are not reported to CMS.

The study was limited to young women born in 1983 or later who had at least one pregnancy outcome before 2013 and had been eligible for Medicaid for at least 12 months between 1999 and of 2015 inclusive. To maximise identification of first pregnancy outcomes, data for each beneficiary was rolled in beginning in the year of her 14th birthday or in 1999, whichever was later, giving us a cohort wherein the oldest beneficiaries were 16 years of age in 1999 and 29 years of age in 2012.

Study variables

The primary outcome variable was any treatment for cardiovascular disease (CVD), defined as any treatment code associated with International Classification of Diseases, Ninth Revision (ICD-9) codes 401–459. The date of a first CVD code, if any, was identified for each woman. In addition, diagnosis codes were identified for diabetes (ICD-9: 250) and hyperlipidaemia (ICD-9: 272.4) were identified along with the first date of diagnosis for each of these known risk factors for CVD.

All pregnancy outcomes were identified for each woman. Pregnancy outcomes were identified using diagnostic ICD-9 codes and clarified with Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes. Pregnancy outcomes were segregated into two categories: live birth or pregnancy loss, the latter including both natural losses (ICD-9: 446–450), and induced abortions (ICD-9: 451).

Our study groups were divided into women whose first pregnancy ended in a loss and women whose first pregnancy ended in a live birth and who had no subsequent known pregnancy losses.

To address coding errors or other conflicts within the data, multiple pregnancy outcome codes within 4 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. In addition, codes indicating an abortion within 36 weeks prior to a live birth was excluded, as well as any data indicating an abortion or natural loss 2 weeks before through 4 weeks after a confirmed code for an induced abortion.

In addition, each woman’s year of birth, age at first pregnancy, state of residence at first pregnancy outcome, months of eligibility, and race were extracted for use as control variables.

Statistical analyses

Logistic regression analyses were conducted to compare subsets of women who experienced CVD to those women who did not. Covariates included the age; race; history of diabetes or hyperlipidaemia; state of residence at time of first pregnancy outcome; year of first pregnancy, total number of months of eligibility; total number of pregnancies, live births and losses prior to and subsequent to a first live birth, and an interaction term for age at first pregnancy and total months of eligibility.

RESULTS

Our population consisted of 1 157 980 Medicaid beneficiaries who had at least one pregnancy outcome. In this population, 5.32% had a history of CVD prior to their first pregnancy and 11.44% had a first diagnosis of CVD after their first pregnancy. Characteristics of this study population are shown in table 1. The first treatment for CVD was over twice as common after a first pregnancy than prior to the first pregnancy. Compared with women without any CVD, women who had their first CVD following their first pregnancy had more pregnancies overall, including more live births, more abortions and more natural losses. Also, women with any history of CVD were eligible for Medicaid for a longer period of time overall and for a longer period of time following their first pregnancy outcome.

After excluding women with CVD prior to their first pregnancy, table 2 shows the differences in the rates of a first CVD diagnosis segregated by first pregnancy outcome, comparing women whose first pregnancy ended in a loss with women whose first pregnancy was a live birth and who had no known subsequent history of pregnancy loss. Overall, women with a history of first pregnancy loss were 38% more likely to develop a CVD than those who had only live births. As would be expected, the percentage of women with a first diagnosis of CVD following their
Table 1  Characteristics of study population. All women and subgroups with and without history of a cardiovascular disease (CVD) treatment

|                          | All          | No CVD       | 1st CVD before 1st Pg | 1st CVD after 1st Pg |
|--------------------------|--------------|--------------|-----------------------|----------------------|
| N (%)                    | 1157 980 (100) | 963 972 (83.25) | 61 574 (5.32)          | 132 434 (11.44)      |
| Avg ages                 |              |              |                       |                      |
| Avg age at 1st pregnancy | 21.4         | 21.4         | 22.4                  | 21.3                 |
| Avg age at 1st cardio diagnosis | 21.8     | N/A          | 22.9                  | 24.2                 |
| Avg months eligibility   |              |              |                       |                      |
| Avg # months of eligibility | 94.2      | 89.1         | 130.4                 | 114.7                |
| Avg # months of eligibility in years after 1st pregnancy outcome | 35.5     | 32.9         | 37.4                  | 53.0                 |
| Avg # of pregnancy outcomes |            |              |                       |                      |
| Avg # live births        | 1.2          | 1.2          | 1.3                   | 1.3                  |
| Avg # abortions          | 1.4          | 1.3          | 1.4                   | 1.5                  |
| Avg # natural losses     | 1.0          | 1.0          | 1.1                   | 1.1                  |
| Prior to 1st pregnancy   |              |              |                       |                      |
| History of diabetes %    | 11 571 (1.00) | 6890 (0.71)  | 2594 (4.21)           | 2087 (1.58)          |
| History of hyperlipidaemia % | 8818 (0.76) | 5621 (0.58)  | 1962 (3.19)           | 1235 (0.93)          |
| After 1st pregnancy      |              |              |                       |                      |
| History of diabetes %    | 13 568 (1.17) | 7401 (0.77)  | 1551 (2.52)           | 4616 (3.49)          |
| History of hyperlipidaemia % | 11 313 (0.98) | 6558 (0.68)  | 1013 (1.65)           | 3472 (2.62)          |

Avg, average; Pg, pregnancy.

first pregnancy was higher for women with a history of diabetes or hyperlipidaemia.

Figure 1 shows that the rate of a first diagnosis of CVD in the months following the first pregnancy outcome and the relative increase in first CVD diagnosis in each subsequent 6-month period. In the first 6 months following a live birth, 3.6% of women who had given a live birth were diagnosed with CVD compared with 2.0% of women whose first pregnancy was lost. But after the first 6-month period, the semiannual risk of a first CVD diagnosis following a first pregnancy loss was higher, and remained higher over a period of at least 12 years.

Table 3 shows the adjusted ORs (Adj OR) of the logistic regression analysis. The strongest effects on a first diagnosis of CVD after a first pregnancy were a history of diabetes (Adj OR=2.01) or a history of hyperlipidaemia (Adj OR=1.55) prior to the first pregnancy. The second strongest predictor was age, with older women more likely than younger women to experience CVD following their first pregnancy.

Compared with women with only live births, women whose first pregnancy ended in a loss were 18% more likely (Adj OR=1.18, 95% CI=1.15 to 1.21) to be subsequently diagnosed with CVD. There was also a small but significant increased risk associated with the number of pregnancy losses that occurred prior to each woman’s first live birth, and the number of losses subsequent to the first live birth, and also to the number of live births.

Racial differences were most notable in regard to Hispanics, who had lower CVD rates following a first pregnancy than all other racial groups. The results relative to the state of residency and the year of first pregnancy outcome reveal significant variances that are not easily explained. These may be due to differences in state regulations not only between states but over the 15 years examined.

Finally, Table 4 shows the frequency of each CVD diagnosis disaggregated according to three-digit ICD codes. Unlike the previous analyses, this table is not restricted to first CVD diagnosis. Each patient with any occurrence of the specific diagnosis following the first pregnancy was counted. Table 4 shows the total number of each CVD diagnosis in the study population, the percentage of women in each group experiencing that diagnosis, and Adj OR for each diagnosis showing the elevated risk of each diagnosis associated with a first pregnancy loss compared with no history of pregnancy loss. The four diseases most strongly associated with a first pregnancy ending in a loss were aortic aneurysm and dissection, atherosclerosis, subarachnoid haemorrhage and old MI.

**DISCUSSION**

We analysed the risk of a first CVD diagnosis in women with a history of pregnancy loss across 59 ICD-9 CVD diagnosis codes. In line with the existing research, our
Table 2  CVD rates and ORs of women with a history of pregnancy loss compared with only live births, segregated by age groups, year of first pregnancy, race, history of risk factors and state

|                                   | Live birth only | First pregnancy lost | Unadjusted OR OR (95% CI) |
|-----------------------------------|-----------------|----------------------|---------------------------|
|                                   | N              | % with CVD           | N              | % with CVD |
| Total                             | 743743         | 10.93                | 352663         | 14.51     | 1.38 (1.37 to 1.40) |
| Age at first pregnancy            |                |                      |                |           |                   |
| 14–19                             | 160554         | 11.75                | 117664         | 16.14     | 1.45 (1.42 to 1.48) |
| 20–24                             | 371807         | 12.72                | 147122         | 17.83     | 1.49 (1.47 to 1.51) |
| 25–29                             | 130128         | 11.62                | 36697          | 16.21     | 1.47 (1.43 to 1.52) |
| Year of first pregnancy outcome   |                |                      |                |           |                   |
| 1999–2000                         | 4442           | 13.57                | 5630           | 19.48     | 1.54 (1.39 to 1.70) |
| 2001–2002                         | 19492          | 13.44                | 18706          | 19.54     | 1.56 (1.49 to 1.65) |
| 2003–2004                         | 51163          | 13.72                | 38278          | 19.13     | 1.49 (1.44 to 1.54) |
| 2005–2006                         | 90923          | 13.28                | 53138          | 18.05     | 1.44 (1.40 to 1.48) |
| 2007–2008                         | 134263         | 12.20                | 63315          | 16.06     | 1.38 (1.34 to 1.41) |
| 2009–2010                         | 192999         | 10.55                | 80066          | 13.25     | 1.30 (1.27 to 1.33) |
| 2011–2012                         | 250461         | 8.86                 | 93530          | 9.33      | 1.06 (1.03 to 1.09) |
| Race                              |                |                      |                |           |                   |
| White                             | 247789         | 11.37                | 82174          | 13.23     | 1.19 (1.16 to 1.22) |
| Black                             | 113592         | 14.87                | 84713          | 17.36     | 1.20 (1.18 to 1.23) |
| Hispanic                          | 172494         | 8.89                 | 65716          | 14.84     | 1.78 (1.74 to 1.83) |
| Other                             | 209868         | 9.93                 | 120060         | 13.20     | 1.38 (1.35 to 1.41) |
| State of residence                |                |                      |                |           |                   |
| Alaska                            | 2583           | 6.16                 | 1130           | 8.41      | 1.40 (1.09 to 1.80) |
| Arizona                           | 110470         | 7.93                 | 13270          | 13.22     | 1.77 (1.68 to 1.86) |
| Connecticut                       | 13462          | 10.42                | 10287          | 11.37     | 1.10 (1.02 to 1.19) |
| Hawaii                            | 6143           | 10.11                | 4329           | 14.28     | 1.48 (1.32 to 1.66) |
| Illinois                          | 176099         | 16.11                | 30434          | 20.76     | 1.36 (1.33 to 1.40) |
| Massachusetts                     | 28596          | 11.26                | 11449          | 14.42     | 1.33 (1.25 to 1.41) |
| Maryland                          | 55678          | 9.38                 | 28128          | 14.87     | 1.69 (1.62 to 1.76) |
| Minnesota                         | 33320          | 9.43                 | 9293           | 14.49     | 1.63 (1.53 to 1.74) |
| Montana                           | 10581          | 4.95                 | 1414           | 8.20      | 1.72 (1.40 to 2.10) |
| New Jersey                        | 12526          | 16.66%               | 31155          | 18.55     | 1.14 (1.08 to 1.20) |
| New Mexico                        | 37583          | 5.08                 | 13825          | 7.56      | 1.53 (1.42 to 1.65) |
| New York                          | 154887         | 11.87                | 125359         | 17.03     | 1.52 (1.49 to 1.56) |
| Oregon                            | 35638          | 6.23                 | 15867          | 8.96      | 1.48 (1.39 to 1.58) |
| Vermont                           | 6067           | 11.59%               | 1273           | 17.83     | 1.66 (1.43 to 1.92) |
| Washington                        | 51203          | 7.24                 | 50818          | 7.28      | 1.01 (0.96 to 1.05) |
| West Virginia                     | 9107           | 9.39                 | 4632           | 8.66      | 0.91 (0.81 to 1.03) |
| Prior diabetes                    |                |                      |                |           |                   |
| No                                | 739528         | 10.84                | 349988         | 14.35     | 1.38 (1.36 to 1.39) |
| Yes                               | 4215           | 26.41                | 2675           | 36.41     | 1.60 (1.46 to 1.74) |
| Prior hyperlipidaemia             |                |                      |                |           |                   |
| No                                | 740281         | 10.88                | 350504         | 14.46     | 1.39 (1.37 to 1.40) |
| Yes                               | 3462           | 21.29                | 2159           | 23.07     | 1.11 (0.99 to 1.24) |

CVD, cardiovascular disease.
findings show that overall, pregnancy loss is associated with elevated CVD risk. In this population of young Medicaid patients, 5.32% had experienced a CVD diagnosis prior to their first pregnancies, as compared with 11.44% who had a first CVD diagnosis after their first pregnancy outcome. This twofold increase in CVD diagnosis after the first pregnancy reflects a cascade of massive haemodynamic, hormonal and metabolic shifts placing a demand on cardiovascular and pulmonary systems in response to increased blood volume, changes in cardiovascular parameters such as heart rate and stroke volume, increase in cardiac output, decrease in systemic and pulmonary vascular resistance, pregnancy-related coagulopathies and vascular changes due to pressure the uterus applies to the vein system. It has also been observed that these changes may unmask previously undiagnosed heart disease and exacerbate a pre-existing disease.19 Our finding that essential hypertension (ICD 401), cardiac dysrhythmias (ICD 427) and haemorrhoids (ICD 455) were the most common first CVD diagnoses can be explained by the above described shifts and add to the existing body of research indicating that hypertensive disorders in pregnancy, including pre-eclampsia/eclampsia (PE/E) are associated with long-term CVD risk.1

However, in our analysis the association between a first pregnancy loss and CVD became clearer over longer periods of time. Specifically, the temporal view of first CVD diagnosis shown in figure 1 shows that a first pregnancy ending in live birth is more likely to be associated with higher first time CVD diagnoses within the first 6 months after a first pregnancy outcome compared with the rate of CVD in the first 6 months following a pregnancy loss. But the same figure shows that in every period following the first 6 months the increased rate of CVD diagnoses following a pregnancy loss is higher and persists longer. Combined with the disaggregated analysis of all CVD diagnoses following a first pregnancy outcome (table 4) these results offer a picture of two different clinical manifestations relative to pregnancy outcome: immediate and delayed. Immediate and short-term increased CVD risk is more characteristic for women whose first pregnancy ended in live birth while a delayed and more prolonged increased risk of CVD is associated with pregnancy loss.

Our findings related to the live birth group shows a clinical picture of pregnancy-related overload of cardiovascular and pulmonary systems and acute complications related to metabolic, haemodynamic and hormonal shifts. For example, cardiomyopathy (ICD 425), phlebitis and thrombophlebitis (ICD 451), other acute and subacute forms of IHD (ICD 411) may be caused by increased blood volume (almost 50% above the non-pregnant level during the second and third trimesters of pregnancy) and pregnancy-related hypercoagulability, which increases the risk of arterial and venous thrombosis7 and IHD.1 Some of these CVDs can be also characterised as the ‘conditions of the third trimester’, for example, other diseases of pericardium (ICD 423), which could be manifested as hydropericardium—the most frequent form of pericardial involvement in pregnancy with clinically silent pericardial effusion present in the third trimester in approximately 40% of healthy pregnant women.20

In addition, many of these CVDs have interconnected aetiological mechanisms. The hormonal and metabolic changes of normal pregnancy are intertwined with insulin resistance, hypercoagulability, and immunological dysfunction each playing important roles in fetal development while potentially contributing as risk factors for CVD diagnosis.21 For example, acute and subacute endocarditis (ICD 421) and septic arterial embolism (ICD 449) may be linked as suggested by the existing evidence of association between septic embolism with infective endocarditis, which among other factors may be caused by pregnancy-related infection events. The risk of arterial thromboembolism is increased threefold to fourfold in pregnant women compared with women who are not pregnant.20

In contrast, CVD diagnoses that are more chronic in nature (eg, other forms of chronic IHD (ICD 414)
hypertensive heart disease (ICD 402), cardiac dysrhythmias (ICD 427), and essential hypertension (ICD 401) are more common among women with any history of pregnancy loss, occur more often after 6 months and continue with prolonged duration (ie, remained higher over a period of 12 years). The underlying mechanisms leading to these CVD complications are unclear. However, existing research has proposed several plausible explanations such as shared metabolic and hormonal changes contributing to both adverse pregnancy outcomes and the development of CVD, vascular pathology contributing to poor placenta implantation and subsequent pregnancy loss and CHD in later life, elimination of a protective effect of high level of oestrogen on cardiovascular health due to shorter duration of pregnancy and specific genetic or epigenetic features predisposing women to both pregnancy loss and CHD. In addition, grief and other mental health issues associated with pregnancy loss may also contribute to increased levels of stress and behavioural changes, including substance use and eating disorders, that may increase cardiovascular risks.

We also note that the total number of pregnancies was slightly negatively associated with CVD risk in this model, but this is most likely due to the effect of the number of pregnancies being distributed across the overlapping continuous variables including the count for the number of live births and number losses prior to and subsequent to a first live birth.

In addition, the results relative to the state of residency and the year of first pregnancy outcome reveal significant variances that are not easily explained. These may be due to differences in Medicaid eligibility not only between states but also over the 15 years examined. For example, for women with their first pregnancy in 2011–2012, the small unadjusted difference between women with and without a history of pregnancy loss shown in table 2 was magnified to an Adj OR of 2.59 in table 3. In part this
## Table 4
The incidence rate (%) of women experiencing each International Classification of Diseases, Ninth Revision (ICD-9) code following a first pregnancy outcome for the entire period examined with adjusted OR comparing first pregnancy loss to no pregnancy loss

| Three digit ICD-9 code | ICD-9 description                                                | N, total with disease | ICD% no Pg loss | ICD% yes Pg loss | Adjusted OR* (95% CI) |
|------------------------|------------------------------------------------------------------|-----------------------|-----------------|-----------------|-----------------------|
| 401                    | Essential hypertension                                           | 37878                 | 3.00            | 4.42            | 1.15 (1.11 to 1.20)   |
| 402                    | Hypertensive heart disease                                      | 1769                  | 0.11            | 0.27            | 1.20 (1.03 to 1.41)   |
| 403                    | Hypertensive chronic kidney disease                             | 1524                  | 0.10            | 0.22            | 1.26 (1.05 to 1.50)   |
| 404                    | Hypertensive heart and chronic kidney disease                   | 145                   | 0.01            | 0.02            | 1.30 (0.71 to 2.39)†  |
| 405                    | Secondary hypertension                                          | 0                     | 0               | 0               | N/A                   |
| 410                    | Acute myocardial infarction                                     | 746                   | 0.06            | 0.09            | 1.09 (0.84 to 1.42)   |
| 412                    | Old myocardial infarction                                       | 488                   | 0.04            | 0.06            | 1.66 (1.19 to 2.31)   |
| 413                    | Angina pectoris                                                 | 1523                  | 0.10            | 0.21            | 1.49 (1.25 to 1.77)†  |
| 414                    | Other forms of chronic ischaemic heart disease                  | 2605                  | 0.16            | 0.40            | 1.24 (1.09 to 1.41)   |
| 415                    | Acute pulmonary heart disease                                   | 2151                  | 0.11%           | 0.38%           | 1.30 (1.14 to 1.47)   |
| 416                    | Chronic pulmonary heart disease                                 | 867                   | 0.07            | 0.10            | 1.14 (0.88 to 1.47)   |
| 417                    | Other diseases of pulmonary circulation                         | 83                    | 0.01            | 0.01            | 1.34 (0.62 to 2.91)†  |
| 420                    | Acute pericarditis                                              | 713                   | 0.06            | 0.07            | 1.17 (0.88 to 1.55)   |
| 421                    | Acute and subacute endocarditis                                 | 2607                  | 0.26            | 0.18            | 0.98 (0.81 to 1.19)   |
| 422                    | Acute myocarditis                                               | 102                   | 0.01            | 0.01            | 1.30 (0.64 to 2.66)   |
| 423                    | Other diseases of pericardium                                   | 1889                  | 0.18            | 0.16            | 0.98 (0.80 to 1.20)†  |
| 424                    | Other diseases of endocardium                                   | 8357                  | 0.68            | 0.94            | 1.08 (0.99 to 1.17)   |
| 425                    | Cardiomyopathy                                                  | 2233                  | 0.20            | 0.22            | 1.14 (0.97 to 1.33)   |
| 426                    | Conduction disorders                                           | 2603                  | 0.19            | 0.34            | 1.28 (1.12 to 1.46)   |
| 427                    | Cardiac dysrhythmias                                           | 30179                 | 2.27            | 3.77            | 1.31 (1.25 to 1.36)   |
| 428                    | Heart failure                                                   | 2829                  | 0.20            | 0.37            | 1.32 (1.16 to 1.51)   |
| 429                    | Ill-defined descriptions and complications of heart disease     | 4320                  | 0.32            | 0.55            | 1.22 (1.09 to 1.36)   |
| 430                    | Subarachnoid haemorrhage                                        | 795                   | 0.06            | 0.09            | 1.75 (1.34 to 2.29)   |
| 431                    | Intracerebral haemorrhage                                       | 844                   | 0.06            | 0.11            | 1.34 (1.06 to 1.74)   |
| 432                    | Other and unspecified intracranial haemorrhage                 | 837                   | 0.06            | 0.10            | 1.25 (0.97 to 1.61)   |
| 433                    | Occlusion and stenosis of precerebral arteries                  | 1399                  | 0.09            | 0.20            | 1.31 (1.10 to 1.56)   |
| 434                    | Occlusion of cerebral arteries                                  | 1806                  | 0.14            | 0.21            | 1.14 (0.96 to 1.35)   |
| 435                    | Transient cerebral ischaemia                                    | 1843                  | 0.14            | 0.23            | 1.18 (1.01 to 1.38)   |
| 436                    | Acute, but ill-defined, cerebrovascular disease                 | 1265                  | 0.09            | 0.16            | 1.41 (1.17 to 1.71)   |
| 437                    | Other and ill-defined cerebrovascular disease                   | 1885                  | 0.15            | 0.22            | 1.17 (0.99 to 1.38)   |
| 438                    | Late effects of cerebrovascular disease                         | 1776                  | 0.14            | 0.20            | 1.14 (0.10 to 1.36)†  |
| 440                    | Atherosclerosis                                                 | 2144                  | 0.14            | 0.31            | 1.72 (1.49 to 2.00)   |
| 441                    | Aortic aneurysm and dissection                                  | 912                   | 0.06            | 0.12            | 2.12 (1.65 to 2.73)   |
| 442                    | Other aneurysm                                                  | 2414                  | 0.25            | 0.15            | 1.45 (1.14 to 1.85)   |
| 443                    | Other peripheral vascular disease                               | 2963                  | 0.20            | 0.42            | 1.36 (1.20 to 1.54)   |
| 444                    | Arterial embolism and thrombosis                                | 466                   | 0.04            | 0.06            | 1.33 (0.97 to 1.83)   |
| 445                    | Atheroembolism                                                  | 18                    | 0.00            | 0.00            | 1.82 (0.11 to 30.34)  |
| 446                    | Polymyalgia nodosa and allied conditions                        | 407                   | 0.04            | 0.04            | 0.96 (0.64 to 1.45)   |
| 447                    | Other disorders of arteries and arterioles                      | 947                   | 0.08            | 0.10            | 1.00 (0.79 to 1.28)   |
| 448                    | Disease of capillaries                                          | 1701                  | 0.15            | 0.16            | 1.02 (0.82 to 1.26)   |

Continued
reflects a magnification of the differences in the age groups. By 2011–2012, the contingent of women having a first pregnancy outcome was older than in those in 1999–2000. Similarly, the proportion of teenagers and women over 25 having each type of first pregnancy outcome (delivery or live birth) was also different.

There were interesting racial differences in our findings, most notably among Hispanic women among whom the greatest difference CVD rates was observed between those whose first pregnancy was delivered (8.89%) and those whose first pregnancy was a loss (14.94%). At the same time, however, Hispanics had the lowest rate of CVD (Adj OR=0.88) of all four racial groups analysed. These findings could be another expression of so-called Latina paradox. This paradox is examined in a systematic review24 of a large number of studies showing that, at the same time, however, Hispanics had the lowest rate of CVD (Adj OR=0.88) of all four racial groups analysed. These findings could be another expression of so-called Latina paradox. This paradox is examined in a systematic review24 of a large number of studies showing that, despite lower economic status, less access to medical care, Latina’s appear to have fewer complications and better pregnancy outcomes compared with other minority groups. This paradox is not well understood. But nation of birth and documentation status may play a significant role.25 Unfortunately, the data set used for our analysis does not allow us to shed any additional light on these questions.

CMS data has many limitations which restricted our ability to analyse the data more carefully. For example, there is no information on height, weight, body mass index (BMI), or patient adherence to prescribed treatments. In addition, ICD coding practices may vary across different states and hospital systems, though it is unlikely that such variations would be so systematically biased as to change the direction of our results. Most importantly, our data also did not allow for further investigation of the underlying mechanisms of CVD. Therefore, we recognise that this exploratory study provides only a first step in a general characterisation of CVD diagnoses associated with a first pregnancy loss. As such, it underscores the importance of additional research to better identify CVD risk profiles based on pregnancy duration, pregnancy outcomes, and the underlying mechanisms that explain the long-term effects of pregnancy loss on CVD risk in order to provide better recommendations for screening and guidance. As an additional limitation of our research, we note our inability to control for major CVD risk factors such as unhealthy diet, BMI, family history of heart disease, physical activity and smoking.

However, we believe that our analysis of a full range of pregnancy-related CVD complications provides a window into understanding the twofold impact of duration of pregnancy. As noted above, such understanding may be critical in (1) revisiting cardiovascular health monitoring for pregnant women and (2) developing a consistent, evidence-based screening tools for both short-term and long-term follow-up, which are currently lacking.26

The underlying pathophysiological mechanisms for the association between pregnancy loss and development of CVD are unclear. Further research is needed to examine whether proposed hypotheses such as shared metabolic and hormonal changes contributing to both adverse pregnancy outcomes and the development of CVD,12 vascular pathology contributing to poor placenta implantation and subsequent pregnancy loss and CHD in later life,22 26 elimination of a protective effect of high level of oestrogen on cardiovascular health due to shorter duration of pregnancy,27 and specific genetic or epigenetic features predisposing women to both pregnancy loss and CHD28 29 will hold.
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