CLINICAL RESEARCH STUDY

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Cocaine and the Long-Term Risk of Cardiovascular Disease in Women

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ABSTRACT

BACKGROUND: Cocaine is associated with acute cardiovascular complications, but the long-term cardiovascular risks of cocaine use are poorly understood. We examined the association between cocaine use disorders and long-term cardiovascular morbidity in women.

METHODS: We analyzed a longitudinal cohort of 1,296,463 women in Quebec, Canada between 1989 and 2020. The exposure included cocaine use disorders prior to or during pregnancy. The outcome was cardiovascular hospitalization up to 31 years later. We used adjusted Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of cocaine use disorders with cardiovascular hospitalization.

RESULTS: The cohort included 2954 women with cocaine use disorders. Compared with women without an identified cocaine disorder, women with cocaine use disorders had 1.55 times greater risk of future cardiovascular hospitalization during 3 decades of follow-up (95% CI, 1.37-1.75). Cocaine use disorders were strongly associated with inflammatory heart disease (HR 4.82; 95% CI, 2.97-7.83), cardiac arrest (HR 2.93; 95% CI, 1.46-5.88), valve disease (HR 3.09; 95% CI, 2.11-4.51), and arterial embolism (HR 2.22; 95% CI, 1.19-4.14). The association between cocaine use disorder and cardiovascular hospitalization was most marked after 5 to 10 years of follow-up (HR 2.15; 95% CI, 1.70-2.72).

CONCLUSIONS: Women with cocaine use disorders have a high risk of cardiovascular hospitalization up to 3 decades later. Substance use reduction and cardiovascular risk surveillance may help reduce the burden of cardiovascular disease in women with cocaine use disorders.

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KEYWORDS: Cardiovascular diseases; Cocaine; Heart disease risk factors; Substance-related disorders; Women

INTRODUCTION

Cardiovascular disease is a leading cause of death in women,[1] yet little attention is paid to illicit substances that can adversely affect the cardiovascular system.[2-4] Mortality due to substance use is increasing in women, including deaths from stimulants such as cocaine.[5] Cocaine is derived from *Erythroxylum coca* (coca bush) and is one of the most frequently used illicit substances in North America. Reports

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suggest that about 1% of adolescent girls and young women use cocaine.[6-8] Cocaine is extremely addictive and may lead to cocaine use disorders that have a significant impact on women.[6,9] Cocaine contributes considerably to substance-related mortality in young women,[5] but the influence of cocaine use disorders on risk of cardiovascular disease in women of reproductive age has not been studied.

The acute effects of cocaine on the cardiovascular system are well known. Short-term use of cocaine is associated with greater atherosclerotic plaque volume, increased incidence of myocardial infarction, and sudden cardiovascular death.[4,9] However, the medium and long-term cardiovascular risks of cocaine use are less understood, particularly among women. In an analysis of approximately 2000 patients, women who used cocaine on a regular basis were twice as likely as non-users to suffer from hypertension up to 5 years later, while there was no association in men.[10] Women who use cocaine during pregnancy have greater odds of myocardial infarction and cardiac arrest during pregnancy and delivery.[11] A study of 321 women suggested that cocaine use during pregnancy was associated with a greater risk of heart failure 10 years later.[12] Cocaine use during pregnancy is associated with a two- to threefold greater risk of adverse birth outcomes, including preterm birth, low birth weight, and placental disorders.[13,14] These pregnancy complications are also associated with an increased risk of cardiovascular disease.[15] Characterizing the link between cocaine use disorders and future cardiovascular events is needed to tailor prevention and surveillance efforts in women. We therefore examined the relationship between cocaine use disorders and risk of cardiovascular hospitalization over the course of 3 decades in a large population of parous women.

CLINICAL SIGNIFICANCE

- Cocaine use was associated with risk of cardiovascular disease up to 30 years later.
- Women who used cocaine were at risk of a wide range of cardiovascular problems.
- Risks were more pronounced 5 to 10 years after the start of follow-up.

MATERIALS AND METHODS

Study Design and Population

We designed a longitudinal cohort study of 1,296,463 parous women in Quebec, Canada between 1989 and 2019. We extracted the women from the Maintenance and Use of Data for the Study of Hospital Clientele registry.[16] The dataset contains discharge abstracts for all hospitalizations in Quebec since April 1989, including 99% of deliveries. The cohort is representative of parous women in the province and is extensively validated to ensure accuracy of data.[16]

Using health insurance numbers, we followed women from their last pregnancy to the end of the study on March 31, 2020, to identify cardiovascular hospitalizations. Follow-up extended from the last pregnancy up to 31 years later. We excluded women with a history of cardiovascular disease prior to their last pregnancy to focus on the long-term implications of cocaine use among women with no known short-term cardiovascular complications. We also excluded women who could not be followed over time due to missing health insurance numbers.

Cocaine Use Disorders

The main exposure was a cocaine use disorder prior to or during pregnancy, including cocaine abuse, dependence, overdose, or poisoning. We identified women with cocaine use disorders using data from the delivery hospitalization. Hospital charts at delivery contain information on a woman's entire obstetric history, including cocaine use in any pregnancy that was self-reported or detected through toxicology tests during prenatal care. We additionally identified women who were hospitalized with cocaine use disorders prior to pregnancy.

We further determined whether cocaine was used alone or combined with other substances (cocaine with other substance use disorder, cocaine use disorder alone, other substance use disorder alone, no substance use disorder). As data suggest that cannabis may increase the risk of cardiovascular disease,[2] we also examined the use of cocaine combined with cannabis. We identified the timing of cocaine use (during pregnancy, prior to pregnancy, no cocaine use). We used diagnostic codes from the 9th and 10th revisions of the International Classification of Diseases to identify cocaine and other substance use disorders.[2] Duration of substance use was not known.

Cardiovascular Outcomes

The main outcome consisted of hospitalization for cardiovascular disease between the start and end of follow-up. We used International Classification of Diseases codes to identify admissions for cardiovascular disease, including heart failure, myocardial infarction, other ischemic heart disease, angina, cardiac arrest, inflammatory heart disease (pericarditis, endocarditis, myocarditis), conduction disorder, valve disease, cardiomyopathy, pulmonary heart disease (pulmonary embolism, other pulmonary vascular disease), cerebrovascular disease (ischemic stroke, hemorrhagic stroke, other cerebrovascular disease), hypertension, atherosclerosis, aortic aneurysm or dissection, other vessel aneurysm, and arterial embolism.[2]

We additionally used procedure codes from the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the Canadian Classification of Health Interventions to capture cardiovascular interventions, including heart procedures (coronary angioplasty, coronary artery bypass graft, valve surgery, pacemaker insertion, cardiac transplant, cardiopulmonary resuscitation, open heart

resuscitation), vessel procedures (aorta surgery, intracranial surgery), and admission to a coronary care unit.[2]

Covariates

We considered potential confounders, including age (<25, 25-34, ≥35 years); parity (1, 2, ≥3 deliveries); history of mental illness, defined as schizophrenia, depression, bipolar, anxiety, stress, personality disorders, and suicide attempt; other substance use disorders (alcohol, opioids, cannabis, stimulants, hallucinogens, sedatives, hypnotics, and volatile solvents), tobacco use disorders; and comorbidity defined as preexisting or gestational diabetes, obesity, and dyslipidemia.[2] We accounted for socioeconomic deprivation defined as the most deprived fifth of the population, based on a neighborhood-level composite measure of income, education, and employment.[2] Finally, we included rural residence and time period (1989-1998, 1999-2008, 2009-2019) as covariates. We measured all covariates at the last pregnancy when follow-up started.

Data Analysis

We followed the cohort of women over time until their first cardiovascular hospitalization, death, or the study end. We calculated the incidence of cardiovascular hospitalization per 10,000 person-years in women with and without a history of cocaine use disorder. We used Cox proportional hazards regression models adjusted for age, parity, mental illness, other substance use disorders, tobacco use, comorbidity, socioeconomic deprivation, place of residence, and time period to measure the association of cocaine use disorders with the subsequent risk of cardiovascular hospitalization. Upon verification of the proportional hazards assumption through survival curves, we used the Cox models to estimate hazard ratios (HR) and 95% confidence intervals (CI), comparing cocaine use disorder relative to no cocaine use disorder. The time scale consisted of the number of days since the start of follow-up. We accounted for death as a competing event,[17] and censored women who did not have a cardiovascular event prior to the end of the study.

In secondary analyses, we assessed how comorbid substance use and the timing of cocaine exposure influenced the association of cocaine use disorders with cardiovascular hospitalization. We also determined how cocaine use disorders were associated with different cardiovascular diseases and interventions. Finally, we assessed whether the risk of cardiovascular disease varied over time by examining associations at different follow-up intervals (<5, 5-9, 10-14, and ≥15 years).

In sensitivity analyses, we analyzed cocaine use disorders as a time-varying exposure, starting follow-up at the first delivery rather than the last. We also tested models that were not adjusted for other substance use disorders and models that were restricted to primiparous women aged 35 years or more. All analyses were carried out in SAS version 9.4 (SAS Institute Inc., Cary, NC). We use deidentified data and therefore obtained an ethics waiver from the institutional review board of our research institution.

RESULTS

In this longitudinal cohort of 1,296,463 parous women, 2954 women (0.2%) had a cocaine use disorder prior to or during pregnancy. A large proportion of the women in the cohort were between the ages of 25 and 34 years (67.0%) and nulliparous (42.8%). Approximately 18% lived in rural areas and 3.6% had a history of mental illness. Only 2.8% had a tobacco use disorder and 0.8% other substance use disorders.

Among women with cocaine use disorders, 42.6% used cocaine during pregnancy (Table 1). Women with cocaine use disorders during pregnancy were more likely to be under 25 years of age, have greater parity, and be socioeconomically deprived, compared with no cocaine use disorder or disorders prior to pregnancy. Women with cocaine use disorders prior to pregnancy were, however, more likely to have a history of mental illness and other substance use disorders and live in rural areas, compared with no cocaine use disorder or cocaine use during pregnancy.

Mean and median length of follow-up of patients in the cohort were 15.0 and 14.2 years, respectively. A total of 64,653 women were hospitalized for a cardiovascular condition during 18,958,171 person-years of follow-up, including 345 women (0.5%) with cocaine use disorders (Supplementary Table, available online). Cardiovascular hospitalization rates were higher in women with cocaine use disorders (97.6 per 10,000 person-years; 95% CI, 87.8-108.4) than no cocaine use disorder (34.0 per 10,000 person-years; 95% CI, 33.7-34.2).

After adjusting for covariates such as age and other substance use, cocaine use disorders were associated with an increased risk of cardiovascular hospitalization during follow-up (Table 2). Compared with no cocaine disorder, having a cocaine use disorder was associated with 1.55 times the risk of cardiovascular hospitalization (95% CI, 1.37-1.75). Relative to no substance use disorder of any type, women who used cocaine alone or with other substances both had more than 2 times the risk of cardiovascular hospitalization, whereas the association was slightly less pronounced for women who used other substances without cocaine. Compared with no cocaine or cannabis use disorder, women who used cocaine alone or with cannabis also had elevated risks of cardiovascular hospitalization. Compared with no cocaine disorder, cocaine use disorders during and prior to pregnancy were both associated with the risk of cardiovascular hospitalization.

Cocaine use disorders were associated with several cardiovascular outcomes (Table 3). Compared with no cocaine use disorder, women with cocaine use disorders had more than 3 times the risk of valve disease and inflammatory heart disease. Cocaine use disorders were associated with more than twice the risk of cardiac arrest, other pulmonary vascular disease, other cerebrovascular disease, and arterial

Table 1 Baseline Characteristics of Women with and Without Cocaine Use Disorders

	No. Women (%)		
	Cocaine Use Disorder During Pregnancy*	Cocaine Use Disorder Prior to Pregnancy†	No Cocaine Use Disorder
Age, years			
<25	235 (18.7)	271 (16.0)	152,774 (11.8)
25-34	752 (59.8)	1052 (62.0)	867,129 (67.0)
≥35	270 (21.5)	374 (22.0)	273,606 (21.2)
Parity			
1	380 (30.2)	665 (39.2)	554,398 (42.9)
2	333 (26.5)	553 (32.6)	532,426 (41.2)
≥3	544 (43.3)	479 (28.2)	206,685 (16.0)
Mental illness‡	354 (28.2)	1255 (74.0)	45,324 (3.5)
Other substance use disorder§	786 (62.5)	1336 (78.7)	13,477 (1.0)
Tobacco use	372 (29.6)	473 (27.9)	35,086 (2.7)
Comorbidity‖	204 (16.2)	312 (18.4)	145,316 (11.2)
Socioeconomic deprivation	488 (38.8)	553 (32.6)	246,980 (19.1)
Rural residence	252 (20.0)	434 (25.6)	235,600 (18.2)
Time period			
1989-1998	335 (26.7)	327 (19.3)	429,496 (33.2)
1999-2008	388 (30.9)	525 (30.9)	339,012 (26.2)
2009-2019	534 (42.5)	845 (49.8)	525,001 (40.6)
Total	1257 (100.0)	1697 (100.0)	1,293,509 (100.0)

*Women with cocaine use disorders documented during pregnancy, whether or not they used cocaine prior to pregnancy.
†Women with cocaine use disorders documented only prior to pregnancy.
‡Schizophrenia, depression, bipolar, anxiety, stress, personality disorders, and suicide attempt.
§Alcohol, opioids, cannabis, stimulants, hallucinogens, sedatives, hypnotics, and volatile solvents.
‖Preexisting or gestational diabetes, obesity, and dyslipidemia.

embolism. Cocaine use disorders were associated with more than 1.5 times the risk of heart failure, myocardial infarction, conduction disorder, pulmonary embolism, and admission to a coronary care unit.

Cocaine use disorders were associated with cardiovascular hospitalization at all points over time (Table 4). Women with cocaine use disorders were, however, at greatest risk of cardiovascular hospitalization at 5 to 9 years of follow-up (HR 2.15; 95% CI, 1.70-2.72). At 5 to 9 years, cocaine use disorders were associated with 3 to 9 times the risk of pulmonary embolism, other pulmonary vascular disease, and cardiac complications such as heart failure, myocardial

Table 2 Association Between Cocaine Use Disorder and Cardiovascular Hospitalization

	No. Women	No. Cardiovascular Hospitalizations	Incidence per 10,000 Person-Years (95% Confidence Interval)	Hazard Ratio (95% Confidence Interval)	
				Unadjusted	Adjusted*
Cocaine use disorder					
Yes	2954	345	97.6 (87.8-108.4)	3.34 (3.00-3.73)	1.55 (1.37-1.75)†
No	1,293,509	64,308	34.0 (33.7-34.2)	Referent	Referent
Comorbid substance use					
Cocaine with other substance use disorder	2122	235	102.3 (90.1-116.3)	3.73 (3.27-4.25)	2.11 (1.84-2.42)
Cocaine use alone	832	110	88.7 (73.6-106.9)	2.80 (2.31-3.40)	2.15 (1.77-2.61)
Other substance use alone	13,477	859	66.2 (61.9-70.8)	2.55 (2.38-2.73)	1.59 (1.48-1.72)
No substance use	1,280,032	63,449	33.8 (33.5-34.0)	Referent	Referent
Comorbid cannabis use					
Cocaine with cannabis use disorder	776	62	89.2 (69.6-114.4)	3.67 (2.85-4.73)	1.44 (1.11-1.86)†
Cocaine use alone	2178	283	99.6 (88.7-111.9)	3.29 (2.91-3.71)	1.62 (1.42-1.85)†
Cannabis use alone	3472	113	49.7 (41.3-59.7)	2.51 (2.09-3.02)	1.19 (0.98-1.43)†
No substance use	1,290,037	64,195	34.0 (33.7-34.2)	Referent	Referent
Timing of cocaine use					
During pregnancy	1257	147	90.9 (77.3-106.8)	2.92 (2.47-3.46)	1.73 (1.46-2.06)†
Prior to pregnancy	1697	198	103.4 (89.9-118.8)	3.72 (3.22-4.29)	1.43 (1.23-1.68)†
No cocaine use	1,293,509	64,308	34.0 (33.7-34.2)	Referent	Referent

*Adjusted for age, parity, mental illness, tobacco use, comorbidity, socioeconomic deprivation, place of residence, and time period.
†Additionally adjusted for other substance use disorders.

Table 3 Association of Cocaine Use Disorder with Specific Cardiovascular Outcomes

	Cocaine Use Disorder		No Cocaine Use Disorder		Hazard Ratio (95% Confidence Interval)*
	No. Events	Incidence per 10,000 Person-Years	No. Events	Incidence per 10,000 Person-Years	
Heart					
Heart failure	34	9.0	3081	1.6	1.88 (1.25-2.81)
Myocardial infarction	38	10.1	5667	2.9	1.67 (1.16-2.40)
Other ischemic heart disease	13	3.4	1565	0.8	1.87 (1.01-3.46)
Angina	12	3.2	2843	1.5	1.33 (0.70-2.53)
Cardiac arrest	15	4.0	891	0.5	2.93 (1.46-5.88)
Inflammatory heart disease	34	9.0	960	0.5	4.82 (2.97-7.83)
Conduction disorder	62	16.6	11,754	6.1	1.57 (1.18-2.09)
Valve disease	37	9.8	2700	1.4	3.09 (2.11-4.51)
Cardiomyopathy	15	4.0	1910	1.0	1.37 (0.77-2.44)
Lungs					
Pulmonary embolism	37	9.8	4648	2.4	1.83 (1.26-2.67)
Other pulmonary vascular disease	18	4.8	1262	0.7	2.37 (1.40-4.02)
Cerebrovascular					
Ischemic stroke	18	4.8	2802	1.4	1.50 (0.87-2.60)
Hemorrhagic stroke	11	2.9	2227	1.1	1.42 (0.72-2.79)
Other cerebrovascular disease	22	5.8	2169	1.1	2.43 (1.48-4.00)
Hypertension	162	44.0	40,663	21.3	1.16 (0.98-1.39)
Atherosclerosis	42	11.2	7592	3.9	1.42 (1.00-2.01)
Aortic aneurysm or dissection	<5	0.3	366	0.2	0.79 (0.08-8.03)
Aneurysm of other vessels	8	2.1	1626	0.8	1.58 (0.70-3.58)
Arterial embolism	14	3.7	1018	0.5	2.22 (1.19-4.14)
Cardiovascular intervention	66	17.7	10,986	5.7	1.62 (1.24-2.13)
Heart procedure	30	8.0	6462	3.3	1.30 (0.88-1.93)
Vessel procedure	9	2.4	2055	1.1	1.32 (0.65-2.69)
Coronary care unit admission	36	9.6	4706	2.4	1.77 (1.22-2.57)

*Hazard ratio for cocaine use disorder vs. no disorder, adjusted for age, parity, mental illness, other substance use disorders, tobacco use, comorbidity, socioeconomic deprivation, place of residence, and time period.

infarction, cardiac arrest, inflammatory heart disease, and valve disease. At 10 to 14 years of follow-up, women with cocaine use disorders remained at risk of pulmonary embolism, other pulmonary vascular disease, heart failure, and inflammatory heart disease. Cocaine use disorders were associated with cerebrovascular disease at 15 years of follow-up or more.

In sensitivity analyses, the association with cardiovascular hospitalization strengthened when cocaine use disorders were measured as a time-varying exposure (HR 2.17; 95% CI, 1.94-2.42). The association between cocaine use disorders and cardiovascular hospitalization strengthened in models not adjusted for other substance use disorders (HR 2.01; 95% CI, 1.79-2.24) and in models restricted to primiparous women aged 35 years or more (HR 1.70; 95% CI, 1.12-2.59).

DISCUSSION

Cocaine use is an understudied public health problem that is prevalent in North America, but has considerable potential to contribute to cardiovascular morbidity. In this cohort of 1.3 million women of reproductive age followed for up to 31 years, women with cocaine use disorders had an elevated risk of a range of adverse cardiovascular outcomes, including inflammatory heart disease, cardiac arrest, valve disease, and arterial embolism. Women with cocaine use disorders were at greatest risk of cardiovascular events 5 to 10 years after the start of follow-up. The data suggest that cocaine use may increase the risk of cardiovascular disease in the medium term.

Cocaine use increases heart rate and blood pressure,[10] and is known for its acute cardiovascular complications after short-term use, including heart failure, myocardial infarction, stroke, and sudden death.[18,19] However, data on the medium- or long-term risk of cardiovascular disease remain limited or inconclusive.[10,20-23] A retrospective cohort study of 2097 young adults with a history of myocardial infarction reported that cocaine use was associated with 2.3 times the risk of cardiovascular death and 1.9 times the risk of all-cause mortality during a median of 11 years of follow-up.[22] In contrast, regular cocaine use was associated with all-cause but not cardiovascular mortality in a study of 9013 adults aged <45 years with a mean of 15 years of follow-up.[23] Another study of 16,820 individuals found that cocaine use disorders were not associated with

Table 4 Association of Cocaine Use Disorder with Specific Cardiovascular Outcomes According to Follow-Up Period

	Hazard Ratio (95% Confidence Interval)*			
	<5 Years	5-9 Years	10-14 Years	≥15 Years
Any cardiovascular event	1.59 (1.24-2.03)	2.15 (1.70-2.72)	1.26 (0.95-1.68)	1.38 (1.10-1.72)
Heart				
Heart failure	1.01 (0.39-2.58)	4.08 (1.78-9.33)	4.18 (1.98-8.80)	1.15 (0.53-2.49)
Myocardial infarction	1.15 (0.32-4.11)	3.46 (1.62-7.38)	1.43 (0.68-3.03)	1.44 (0.84-2.48)
Other ischemic heart disease	7.38 (2.48-21.9)	0.66 (0.08-5.23)	1.99 (0.50-7.96)	0.71 (0.17-2.92)
Angina	2.73 (0.66-11.3)	1.58 (0.42-5.95)	0.36 (0.05-2.69)	1.47 (0.54-3.99)
Cardiac arrest	1.01 (0.22-4.55)	7.96 (2.37-26.8)	3.36 (0.79-14.3)	3.47 (0.90-13.4)
Inflammatory heart disease	4.19 (1.65-10.6)	6.93 (3.25-14.8)	8.03 (2.59-24.9)	2.79 (0.86-9.10)
Conduction disorder	1.45 (0.80-2.63)	2.30 (1.38-3.84)	1.21 (0.58-2.52)	1.46 (0.86-2.50)
Valve disease	3.73 (1.75-7.93)	7.27 (3.69-14.3)	2.28 (0.75-6.92)	1.56 (0.74-3.33)
Cardiomyopathy	1.73 (0.66-4.52)	0.48 (0.06-3.67)	3.26 (0.99-10.7)	1.13 (0.40-3.17)
Lungs				
Pulmonary embolism	0.97 (0.44-2.15)	3.71 (1.84-7.48)	2.61 (1.13-5.98)	1.28 (0.58-2.85)
Other pulmonary vascular disease	4.81 (1.54-15.1)	3.81 (1.38-10.5)	4.20 (1.25-14.2)	1.14 (0.44-2.90)
Cerebrovascular				
Ischemic stroke	2.65 (0.73-9.58)	0.71 (0.15-3.34)	1.19 (0.37-3.83)	1.86 (0.84-4.11)
Hemorrhagic stroke	0.95 (0.20-4.54)	1.12 (0.26-4.88)	1.05 (0.25-4.41)	2.56 (0.85-7.74)
Other cerebrovascular disease	2.47 (0.86-7.05)	3.38 (1.26-9.06)	1.41 (0.42-4.71)	2.84 (1.29-6.27)
Hypertension	0.95 (0.62-1.48)	1.43 (1.00-2.05)	1.01 (0.68-1.48)	1.25 (0.96-1.63)
Atherosclerosis	2.37 (0.93-6.05)	2.48 (1.08-5.68)	1.48 (0.73-2.98)	0.97 (0.56-1.68)
Aortic aneurysm or dissection	-	-	-	3.82 (0.28-52.5)
Aneurysm of other vessels	-	1.64 (0.24-11.3)	2.29 (0.57-9.21)	2.03 (0.60-6.89)
Arterial embolism	2.78 (0.87-8.84)	2.83 (0.89-9.04)	1.09 (0.14-8.29)	2.16 (0.71-6.53)
Cardiovascular intervention	1.89 (1.09-3.29)	3.31 (1.98-5.52)	0.83 (0.38-1.77)	1.36 (0.86-2.17)
Heart procedure	1.50 (0.62-3.62)	3.34 (1.65-6.79)	0.88 (0.33-2.32)	0.85 (0.41-1.76)
Vessel procedure	1.18 (0.27-5.11)	0.70 (0.10-5.35)	0.78 (0.08-7.83)	2.09 (0.82-5.33)
Coronary care unit admission	2.10 (1.01-4.38)	5.20 (2.61-10.4)	0.62 (0.19-1.99)	1.26 (0.64-2.48)

*Hazard ratio for cocaine use disorder vs. no disorder, adjusted for age, parity, mental illness, other substance use disorders, tobacco use, comorbidity, socioeconomic deprivation, place of residence, and time period.

cardiovascular disease over a mean of 7.5 years; however, the comparison group included patients with other substance use disorders.[21] In our study with larger sample and longer follow-up, cocaine use disorders were associated with approximately 50% greater risk of cardiovascular disease compared with no cocaine use disorder.

Sex-specific associations are less understood, particularly for women. A growing number of women use cocaine over time.[5] A sex-stratified analysis of 2121 young women found that lifetime cocaine use was associated with a nonsignificant twofold greater odds of hypertension up to 5 years later.[10] Women who use cocaine during pregnancy are more likely to report poor physical and mental health 10 years after delivery.[12] Prenatal cocaine use is associated with 1.8 times greater odds of acute myocardial infarction and cardiac arrest during pregnancy and delivery.[11] These scattered analyses are the extent of what is known about the adverse effects of cocaine in women. Our study provides novel evidence that women with cocaine use disorders prior to or during pregnancy are at greater risk of cardiovascular events several years later.

Cocaine blocks presynaptic reuptake of dopamine and norepinephrine, decreasing blood flow and increasing demand for oxygen.[4,20] These changes may be followed by acute increases in blood pressure and heart rate contributing to early coronary events, including myocardial infarction.[4,20] Regular cocaine use is associated with 1.3 times greater odds of acute arrhythmias and 3 times greater odds of myocardial infarction,[24] with the greatest risk of myocardial infarction in the first hour after use.[25] However, we demonstrated that the threefold greater risk of myocardial infarction may extend up to 5 to 9 years later.

Short-term use of cocaine is associated with acute cerebrovascular complications, including hemorrhagic and ischemic stroke,[24] with the greatest risk occurring within 24 hours of use.[26] However, our findings suggest that cocaine use may also be associated with the risk of cerebrovascular disease and cerebrovascular vessel interventions more than 15 years later.

Cocaine may, moreover, be associated with arterial embolism and pulmonary disease up to 15 years after use. While little is known of the association between cocaine and these cardiovascular outcomes, chronic use of cocaine is a suspected cause of endothelial cell dysfunction, bradycardia, and aortic stiffness, even in the absence of an acute cardiovascular event.[9,20] Lack of recovery of normal

cardiovascular physiology after cocaine use could explain the associations we observed, although more research is needed to identify the pathways involved.

In our population, women who used cocaine alone or with other substances had similar risks of cardiovascular hospitalization later in life. In contrast, other studies report greater risks of cardiovascular disease when cocaine is combined with other substances.[2,11,27] Alcohol increases plasma concentration of cocaine compared with cocaine taken alone, and concurrent use of these 2 substances is associated with a higher risk of sudden cardiac death.[28] Although in our study both isolated and combined cocaine use disorders were associated with cardiovascular hospitalization, we cannot rule out the possibility that polysubstance use exacerbates the risk of adverse cardiovascular events.

We analyzed a large population-based cohort of parous women with 3 decades of follow-up, but the study is not without limitations. We could not account for cocaine use disorders that did not lead to hospitalization prior to pregnancy and cannot confirm that women were screened for drug use. The number of women with cocaine use disorders may therefore be underestimated. The rate of cocaine use disorders in our study (0.2%) is comparable with the United States (0.3%),[11] but findings may not generalize to the larger number of women who use cocaine only occasionally. We could not determine whether cocaine use was self-reported or detected through toxicology screen. We were unable to determine the frequency, quantity, and duration of cocaine use; studies with access to such information are needed to develop and improve interventions for long-term health. We suspect that the risk of cardiovascular disease may be greater among chronic cocaine users. Results for rare cardiovascular events should be interpreted with caution. In addition, results may be affected by residual confounding due to incomplete data on potential confounders, such as smoking, body mass index, nutritional factors, and ethnicity. We lacked data on number of postnatal visits, although all women have free universal health care in Quebec. More studies are needed to determine the generalizability of the findings to nulliparous women.

CONCLUSIONS

Cocaine use is common among young women, yet its long-term cardiovascular effects are poorly understood. This large cohort study suggests that women with cocaine use disorders early in life are at risk of cardiovascular disease several decades later. The findings highlight the need to better document the implications of cocaine for health over the life course. Interventions and strategies targeting young women at high risk of cocaine use, including women who misuse other substances or are in precarious situations, may be merited. Women may stop using cocaine to protect their fetus, thus, drug cessation interventions may be more effective during pregnancy and may also help prevent postpartum relapse. Pregnancy may be an optimal time to screen for cocaine use and educate or counsel women. Clinicians and public health practitioners should be aware of the long-term risk of cardiovascular disease in women with cocaine use disorders to ensure appropriate surveillance and clinical management.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.04.002.

Supplementary Table Incidence of Cardiovascular Hospitalization According to Women's Characteristics at Start of Follow-Up

	No. Women	No. Cardiovascular Hospitalizations	Person-Years	Incidence per 10,000 Person-Years (95% Confidence Interval)
Cocaine use disorder				
Yes	2954	345	35,360	97.6 (87.8-108.4)
No	1,293,509	64,308	18,922,811	34.0 (33.7-34.2)
Age, years				
<25	153,280	6510	2,354,359	27.7 (27.0-28.3)
25-34	868,933	42,293	13,060,575	32.4 (32.1-32.7)
≥35	274,250	15,850	3,543,237	44.7 (44.0-45.4)
Parity				
1	555,443	33,626	8,988,440	37.4 (37.0-37.8)
2	533,312	22,609	7,512,775	30.1 (29.7-30.5)
≥3	207,708	8418	2,456,956	34.3 (33.5-35.0)
Mental illness*	46,933	2539	419,350	60.5 (58.2-62.9)
Other substance use disorder†	15,599	1094	152,752	71.6 (67.5-76.0)
Tobacco use	35,931	2208	403,911	54.7 (52.4-57.0)
Comorbidity‡	145,832	10,040	1,587,601	63.2 (62.0-64.5)
Socioeconomic deprivation	248,021	14,093	3,473,574	40.6 (39.9-41.2)
Rural residence	236,286	13,750	3,527,000	39.0 (38.3-39.6)
Time period				
1989-1998	430,158	45,492	10,834,872	42.0 (41.6-42.4)
1999-2008	339,925	14,341	5,301,037	27.1 (26.6-27.5)
2009-2019	526,380	4820	2,822,262	17.1 (16.6-17.6)
Total	1,296,463	64,653	18,958,171	34.1 (33.8-34.4)

*Schizophrenia, depression, bipolar, anxiety, stress, personality disorders, and suicide attempt.
†Alcohol, opioids, cannabis, stimulants, hallucinogens, sedatives, hypnotics, and volatile solvents.
‡Preexisting or gestational diabetes, obesity, and dyslipidemia.