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Cocaine use and the likelihood of cardiovascular and all-cause mortality: data from the Third National Health and Nutrition Examination Survey Mortality Follow-up Study

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Abstract

Background: Numerous case series have implicated cocaine use as a cause of both myocardial infarction (MI) and stroke on the basis of the temporal relationship between drug use and event onset. The relatively high prevalence of cocaine use in the US population, especially in younger individuals, mandates a more extensive investigation of this relationship.

Methods: We determined the relationship between cocaine use and cardiovascular and all-cause mortality in a nationally representative sample of 9013 US adults aged 18 to 45 years who participated in the Third National Health and Nutrition Examination Survey Mortality Follow-up Study using Cox proportional hazards analyses. We categorized the participants as nonusers if they responded to the lifetime cocaine use question as never used, as infrequent users if they responded as using <10 times, and as frequent or regular users if they reported using 10–99 times or >100 times, respectively. Potential confounding factors in the association between cocaine use and death (cardiovascular and all cause) included age, sex, race/ethnicity, cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, educational attainment, body mass index, and insurance status. To estimate the impact of cocaine use on MI or stroke, we calculated the population attributable risk (PAR) percent for cocaine use with cardiovascular and all-cause mortality. We also estimated the years of life lost and total annual financial cost due to premature deaths in persons who reported regular use of cocaine.

Results: A total of 60 cardiovascular deaths and 384 all causes deaths were reported during a mean follow-up period of 14.7 ± 2.6 years. After adjusting for differences in potential confounders, persons who reported regular lifetime cocaine use had a significantly higher likelihood of all-cause mortality (relative risk [RR], 1.9; 95% confidence interval [CI], 1.2–3.0 for ≥100 times in lifetime) but not cardiovascular mortality (RR, 0.6; 95% CI, 0.1–4.7 for ≥100 times in lifetime). The PAR of regular cocaine use for all cause mortality among was 1.79%. The years of life lost due to regular cocaine use was 10.3 years for an adult aged 31 years. The overall yearly cost incurred due to premature deaths related to regular cocaine use was $1.1 billion.

Conclusion: Regular cocaine use was associated with an increased risk of all cause mortality but this effect was not mediated through cardiovascular events. Behavior modification by public awareness and education may reduce the mortality and financial burden associated with cocaine use.

Keywords

cocaine; cardiovascular mortality; all-cause mortality; years of life lost; national survey

Introduction

Cocaine became available for recreational use in the United States almost three decades ago [1]. In 2010, there were 1.5 million current cocaine users, aged 12 or older, comprising 0.6% of the US population [2]. There were another 637,000 persons aged 12 or older who had used cocaine for the first time within the past 12 months in 2010; averaging to approximately 1700 new persons per day. The total number of individuals who reported

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lifetime use increased from 2002 to 2010 among persons aged 26 years or greater. With the growing use of cocaine particular in young- and middle-aged individuals, a better understanding of its effect on cardiovascular diseases is essential. In a previous report, we had found that regular cocaine use was associated with an increased likelihood of nonfatal myocardial infarction (MI) in persons aged 18 to 45 years [3]. Recently, three studies have demonstrated that patients using illicit drugs including crack cocaine have higher mortality [4–6] although it remains unclear whether cocaine use in specific, either sporadic or regular, increases mortality and whether the higher mortality is attributable to higher rate of fatal cardiovascular events. There also appears to be ambiguity whether the higher mortality is related to concurrent cigarette smoking in such individuals. We analyzed the data from the Third National Health and Nutrition Examination survey (NHANES III), a large population-based study, to examine the independent association between cocaine use and cardiovascular and all-cause mortality.

Methods

NHANES III was conducted by the Centers for Disease Control and Prevention between 1988 and 1994 to estimate the prevalence of common chronic conditions and associated risk factors in the US population. The methods have been previously described in detail in several publications [3,7]. Briefly, the NHANES III participants include 40,000 persons aged ≥2 months who were selected from the total civilian non-institutionalized population in the United States. The sampling methods enabled the production of a national, approximately equal, probability sample of households in the United States. The black and Mexican populations were oversampled to obtain statistically reliable estimates of the two largest minority groups in the United States. NHANES III was designed to include equal numbers of males and females in each age and race/ethnic group. The survey included a household interview, a medical examination in a mobile examination center, a brief household medical examination for those unable to travel to the center, and a phlebotomy to measure serum markers including glucose, cholesterol, high-density lipoproteins, triglycerides, and apolipoproteins A-1 and B.

Each participant aged 18 to 45 years was asked about lifetime cocaine use in terms of the following 4 responses: never, <10 times, 10 to 100 times, or >100 times. We categorized the participants as nonusers if they responded to the lifetime cocaine use question as never used, as infrequent users if they responded as using <10 times, as frequent users if they reported using cocaine 10 to 100 times, and regular users if they reported using cocaine >100 times. Persons were considered nonusers, if no response were available for the question. Hypertension was defined as the current use of antihypertensive medication or an average blood pressure >140/90 mm Hg. Hyperlipidemia was defined by a serum cholesterol level >200 mg/dL. Diabetes mellitus was defined as an affirmative response to the question “have you ever been told by a doctor that you have diabetes or sugar diabetes?” Although serum glucose measurements were available, the samples were drawn inconsistently in relation to fasting status and, therefore, were not used to define diabetes mellitus.

Mortality follow-up was conducted for the cohort of 11,989 participants who were aged 18 to 45 years at the time of enrollment in NHANES III as part of the Third National Health and Nutrition Examination Survey Mortality Follow-up Study. The follow-up was based on mortality linkage of the NHANES III to death certificate data found in the National Death Index (NDI). The publically available NHANES III Linked Mortality File provides mortality follow-up data for NHANES III survey participants (1988–1994) through December 31, 2006. Mortality status is ascertained primarily through probabilistic record matching with the NDI using seven methods to match a NHANES III survey participant submission record to a NDI record [8]. The file includes the following variables: survey respondent eligibility status, mortality status, age at death, age last known alive, date of death (month, day, and year), underlying and multiple causes of death, date of birth, and NHANES III interview and examination dates (month, day, and year). The cause-specific death categories are categorized into one of the 113 cause-of-death groups [9]. We included all deaths categorized as 058 1, ischemic heart diseases; 059, acute MI; 060, other acute ischemic heart diseases; 062, atherosclerotic cardiovascular disease; 063, all other forms of chronic ischemic heart disease; and 070 cerebrovascular diseases as cardiovascular deaths. All deaths were classified as all-cause mortality in the analysis.

Statistical analysis

Cox proportional hazards analyses were used to estimate the effect of various categories of cocaine use on cardiovascular and all-cause deaths using relative risks (RR) and 95% confidence intervals (CIs). Potential confounding factors in the relationship between cocaine use and cardiovascular and all-cause deaths included age, sex, race/ethnicity, educational attainment, hypertension, hyperlipidemia, diabetes mellitus, body mass index

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(weight [kg]/height [m^2]), cigarette smoking, and insurance status. Chi-square tests and analysis of variance (ANOVA) were used to compare groups according to frequency of cocaine use. Interactions between cocaine use and potential confounding factors such as cigarette smoking and hypertension were tested. No significant interactions were observed in the model. The survival according to various categories of cocaine use at 5, 10, and 15 years was estimated using Kaplan–Meier survival curves [10]. The stroke-free survival rate is provided with standard error (SE) to indicate the precision of the estimate.

To estimate the impact of cocaine use on cardiovascular and all-cause deaths, we calculated the population-attributable risk (PAR) percent [11]. PAR percent expresses the proportion of disease (cardiovascular and all-cause deaths) in the study population that is attributable to the exposure (cocaine use) and thus could be eliminated if the exposure was eliminated. The PAR percentage was calculated using the following formula: equation where PAR% indicates PAR percent, P_e represents the proportion of the population exposed to the risk factor (frequent cocaine user), and OR indicates odds ratio (multivariate adjusted).

$$PAR\% = \frac{(P_e)(RR - 1) \times 100}{(P_e)(RR - 1) + 100}$$

We used the coefficients from the regression model and US life tables for 2011 to estimate the years of life lost as described previously [12]. The number of years lost was the difference in expected age according to US life table and that of a person with regular lifetime cocaine use for an average adult aged 31 years (mean age of nonusers in the analysis).

To calculate the financial cost of premature deaths, we estimated the number of deaths related to regular use of cocaine every year. We determined the number of deaths every year in the age group 15–44 years in the United States according to the vital statistics of 2009 [13]. The number of deaths related to regular use of cocaine was derived by applying the PAR% value to the total deaths. The cost of each premature death was estimated as $4.5 million based on a previous study that described the cost of premature death related to methamphetamine toxicity [14]. The total cost attributed to regular use of cocaine was calculated as the product of number of deaths (as explained above) and $4.5 million.

Results

A total of 9013 participants aged 18 to 45 years participated in the NHANES III mortality follow-up study. Of these, 1262 persons reported the use of cocaine at the baseline interview; the frequency of lifetime use was characterized as infrequent users (1–10 times) (n = 730), frequent users (>10 times) (n = 354), and regular users (>100 times) (n = 178). The frequency of cocaine use was higher among men and whites (see Table 1). The proportion of patients who were current cigarette smokers increased within groups of patients categorized by frequency of lifetime use of cocaine. There was no difference in the proportion of patients with hypertension, diabetes mellitus, and hyperlipidemia between groups with different frequency of cocaine use.

A total of 60 cardiovascular deaths and 384 all causes deaths were reported during a mean follow-up period of 14.8 ± 2.3 years. The reasons for all cardiovascular cause mortality were either stroke (n = 16) or ischemic heart disease (n = 44). After adjusting for differences in age, sex, race/ethnicity, cigarette smoking, hypertension, diabetes mellitus, hyperlipidemia, educational attainment, body mass index, and insurance status, persons who reported regular lifetime cocaine use had a significantly higher likelihood of all-cause mortality ([RR], 1.9; 95% CI, 1.2–3.0 for ≥100 times in lifetime) (see Table 2). After adjusting for potential confounders, persons who reported regular lifetime cocaine use did not have a significantly higher likelihood of cardiovascular mortality (RR, 0.6; 95% CI, 0.1–4.7 for ≥100 times in lifetime). Persons who reported frequent cocaine use (between 10 and 99 times during lifetime) did not have an increased risk of cardiovascular death (RR, 1.5; 95% CI, 0.5–3.9) or all-cause mortality (RR, 1.4; 95% CI, 0.9–2.1) (see Table 3). The estimated survival according to various categories of cocaine use at 5, 10, and 15 years using Kaplan–Meier survival curves is presented in Figure 1. Survival at 10 years, calculated by using the Kaplan–Meier curve, was 91% ([SE] 2.1%) among persons who reported regular use of cocaine and 98% (SE 0.2%) among nonusers.

The years of life lost due to regular cocaine use was 10.3 years for an adult aged 31 years. The PAR of regular cocaine use for all-cause mortality among was 1.79%. The overall yearly cost incurred due to premature deaths related to regular cocaine use was US$1.1 billion.

Discussion

Regular cocaine use was associated with an increased risk of all-cause mortality but this effect was not mediated through fatal cardiovascular events. There are two potential explanations for the lack of relationship between cocaine use and cardiovascular death. The first

Table 1.

Characteristics of 9013 participants aged 18 to 45 years according to frequency of cocaine use (Third National Health and Nutrition Examination survey mortality follow-up study)

Characteristics	Cocaine nonusers (*n* = 7751)	*Infrequent* cocaine users (1–10 times) (*n* = 730)	*Frequent* cocaine users (>10 times) (*n* = 354)	*Regular* cocaine users (>100 times) (*n* = 178)	*P*-value
Mean age, years ± SD	30.7 ± 8.1	30.6 ± 10.1	32.6 ± 9.1	33.1 ± 6.5	<0.0001
Men	3336(43.0)	429(58.7)	231(65.2)	124(69.6)	<0.0001
Race/ethnicity					
White	4785(61.7)	478(65.5)	262(74.0)	142(79.7)	<0.0001
African American	2639(34.0)	230(31.51)	74(20.90)	33(18.5)	
Other	327(4.2)	22(3.01)	18(5.08)	3(1.6)	
Education					
Less than 12 grade	2479(32.1)	243(33.5)	89(25.2)	58(32.7)	0.04
Completed high school	2702(35.0)	239(32.9)	152(43.0)	61(34.4)	
Higher education	2524(32.7)	243(33.5)	112(31.7)	58(32.7)	
Insurance status					
Medically insured	5419(69.9)	499(68.3)	237(66.9)	120(67.4)	0.004
Cardiovascular risk factors					
Hypertension	661(8.5)	53(7.2)	34(9.60)	19(10.6)	0.38
Diabetes mellitus	233(3.0)	12(1.6)	10(2.8)	6(3.3)	0.21
Mean body mass index, kg/m ± SD	26.7 ± 6.1	25.8 ± 5.8	25.9 ± 5.0	25.8 ± 5.6	<0.001
Mean cholesterol, mg/dL ± SD	190.3 ± 40.1	189.8 ± 37.2	188.5 ± 38.3	184.9 ± 35.9	0.32
Hyperlipidemia	2672(34.5)	249(34.1)	112(31.6)	52(29.4)	0.35
Cigarette smoking status					
Never	2039(60.3)	367(29.7)	217(19.2)	112(14.0)	<0.0001
Former	1038(13.3)	146(20.0)	69(19.4)	41(23.0)	
Current	4674(26.3)	217(50.2)	68(61.3)	25(62.9)	

Table 2.

Relationship between cocaine use and all-cause deaths in persons aged 18 to 45 years (Cox proportional hazards analysis): Third National Health and Nutrition Examination survey mortality follow-up study

Category	Sample size	No. of all-cause deaths	Crude relative risk (95% confidence intervals)	Age-adjusted relative risk (95% confidence intervals)	Multivariate-adjusted relative risk (95% confidence intervals)[a] *a*
Cocaine nonusers	7751	299 (3.8)	Reference	Reference	Reference
Infrequent cocaine users	730	34 (4.6)	1.2 (0.8 – 1.7)	1.30 (0.9 – 1.8)	0.9 (0.6 – 1.4)
Frequent cocaine users	354	30 (8.5)	2.4 (1.6 – 3.4)	2.2 (1.5 – 3.2)	1.4 (0.9 – 2.1)
Regular cocaine users	178	21 (11.8)	3.4 (2.2 – 5.4)	3.2 (2.1 – 4.9)	1.9 (1.2 – 3.0)

[a] Adjusted for age, sex, race/ethnicity, educational attainment, hypertension, hyperlipidemia, diabetes mellitus, body mass index (weight [kg]/height [m^2]), cigarette smoking, and insurance status.

explanation is that cocaine does not result in an increase in the rate of cardiovascular events. The second explanation is that the cardiovascular events associated with cocaine use are mild in severity and unlikely to result in mortality. The current epidemiological and pathophysiological studies would suggest that cocaine plays a role in

Table 3.

Relationship between cocaine use and cardiovascular deaths in persons aged 18 to 45 years (Cox proportional hazards analysis): Third National Health and Nutrition Examination survey mortality follow-up study

Category	Sample size	No. of cardiovascular deaths	Crude relative risk (95% confidence intervals)	Age-adjusted relative risk (95% confidence intervals)	Multivariate-adjusted relative risk (95% confidence intervals)[a]
Cocaine nonusers	7751	50 (0.6)	Reference	Reference	Reference
Infrequent cocaine users	730	4 (0.5)	0.87 (0.3 – 2.4)	0.9 (0.3 – 2.6)	0.7 (0.2 – 1.9)
Frequent cocaine users	354	5 (1.4)	2.4 (0.9 – 6.1)	2.3 (0.9 – 5.8)	1.5 (0.5 – 3.9)
Regular cocaine users	178	1 (0.5)	1.0 (0.1 – 7.4)	0.9 (0.1 – 6.8)	0.6 (0.1 – 4.7)

[a] Adjusted for age, sex, race/ethnicity, educational attainment, hypertension, hyperlipidemia, diabetes mellitus, body mass index (weight [kg]/height [m^2]), cigarette smoking, and insurance status.

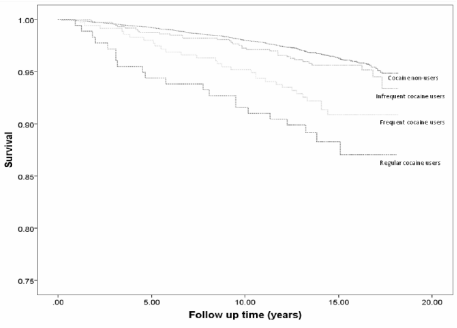

Figure 1. The estimated survival of persons aged 18 to 45 years in groups defined by frequency of cocaine use using Kaplan–Meier survival curves.

predisposing individuals to acute coronary events. In our previous analysis [3], persons who reported frequent lifetime cocaine use had a significantly higher likelihood of non-fatal MI than nonusers (odds ratio, 6.9) after adjusting for differences in cardiovascular risk factors. In the Determinants of Myocardial Infarction Onset Study, cocaine use was associated with a large abrupt and transient increase in the risk of acute MI in relatively low-risk patients [15]. There are pathophysiological reasons to support a relationship between cocaine use and acute myocardial ischemia [16]. Cocaine increases both heart rate and blood pressure through α-adrenergic stimulation. Concurrently, cocaine leads to coronary vasoconstriction creating an environment of increased oxygen demand and decreased oxygen supply. Other reports have suggested a relationship with stroke occurrence based on the temporal proximity of cocaine use and stroke [17].

There is evidence that patients with cocaine related acute coronary syndromes have low rates of complications and mortality which may explain the lack of relationship between cardiovascular mortality and cocaine use. A retrospective cohort study at 29 hospital centers of 136 MI events related to cocaine use [18], found no events that led to in-hospital death. Complications including congestive heart failure (n = 9), and ventricular tachycardia (n = 23), were transient and infrequent after the first 12 h. The Cocaine Associated Chest Pain (COCHPA) Study Group reported two deaths in 246 patients presenting with cocaine related chest pain [19]. Elevation in cardiac enzyme, arrhythmias, and congestive heart failure were seen in <10% of the patients. Another study of 101 consecutive patients with cocaine related chest pain found that 43% of patients had ST-segment elevation but none of them experienced any complications [20]. The lower rate of complications and mortality associated with cocaine related acute coronary syndrome may be attributable to the low rate of myocardial ischemia and coronary artery disease in these patients. A substudy of a multicenter prospective clinical trial (the Acute Cardiac Ischemia-Time Insensitive Predictive Instrument [ACI-TIPI] Clinical Trial) found that the rate of confirmed unstable angina or MI was significantly lower among patients with chest pain or other symptoms consistent with acute coronary syndrome among subjects with identified cocaine use [21]. Another cross-sectional study on 175 patients with chest pain and concomitant cocaine use who underwent coronary computerized tomographic angiography (CTA) reported stenosis ≥ 50% in 18 patients [22].

We estimated the societal impact of cocaine use and found that 1.8% of the deaths in persons aged 18–45 years are attributable to cocaine use. The years of life lost due to regular cocaine use was estimated at 10.3 years for an adult aged 31 years. The overall yearly cost incurred due to premature deaths related to regular cocaine use was estimated at US$1.1 billion. Therefore, our results highlight the large societal impact of regular cocaine use that could potentially be prevented or reduced. The intent of our analysis was not to identify the non-cardiovascular reasons for mortality among

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cocaine users. A study of a cohort of 131 Brazilian crack/cocaine-dependent patients found that exposure to violence was the main cause of death over 12 years[6].

Another study involving ascertainment of mortality among 20,983 adults who responded to the 1991 National Health Interview Survey Drug and Alcohol Use found that those persons whose lifetime cocaine use had a significantly higher rate of death associated with human immunodeficiency virus diseases [5]. The unadjusted rates of deaths from diseases of the heart were 37 and 31 per 100,000 person years among nonusers and lifetime cocaine users, respectively. Further studies would be required to identify reasons, particularly preventable reasons, for death among cocaine users.

We used data derived from death certificates to identify incident cases of fatal MI and stroke. Therefore, the accuracy of diagnosis documented in the death certificate is likely to influence the results of the analysis. A study evaluated the certified cause of death in people aged 35–74 years after admission for MI or stroke using linked hospital and mortality statistics [23]. Of deaths occurring within 30 days of MI and stroke, 85.2% and 80.0%, respectively, were certified with MI or stroke as the underlying cause of death. Another study compared admissions for principal diagnosis for MI or stroke with death certificate register within the same cohort and reported that 70% and 75% of deaths occurring within 30 days of MI and stroke, respectively, were certified with MI or stroke as the underlying cause of death [24]. Another study that compared abstracts of hospital records and death certificates for people who died within 4 weeks of MI or stroke found that MI (78%) and stroke (83%), respectively were listed on the death certificate as the underlying cause of death [25]. Other studies that have focused on only mortality within hospitalization have reported a higher positive predictive value. In the Minnesota Heart Survey, relative to a standardized physician diagnosis, positive predictive values for the death certificate diagnosis were 100% for all types of stroke, 82% for intracranial hemorrhage, and 97% for non-hemorrhagic stroke [26]. However, all studies concur that death certificate diagnosis of MI or stroke as the primary cause of death is highly specific and unlikely to include patients who did not die from MI or stroke.

Conclusion

In our study, we found that regular cocaine use was associated with an increased risk of all-cause mortality but this effect was not mediated through cardiovascular events. Nonetheless, the societal financial impact of this potentially preventable risk factor for premature death is estimated at US$1.1 billion every year in the United States. Further studies are required to identify the underlying reasons for the increased mortality among regular cocaine users so that targeted behavior modification, public awareness, and education can be implemented to reduce the mortality and cost associated with cocaine use.

References

1. Warner EA. Cocaine abuse. *Ann Intern Med* 1993;119(3):226–35.
2. Administration SAaMHS. Results from the 2010 national survey on drug use and health: summary of national findings. *NSDUH Series H-41, HHS Publication No. (SMA) 11-4658* 2010
3. Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the third national health and nutrition examination survey. *Circulation* 2001;103(4):502–6.
4. Hser YI, Kagihara J, Huang D, Evans E, Messina N. Mortality among substance-using mothers in california: a 10-year prospective study. *Addiction* 2012;107(1):215–22.
5. Muhuri PK, Gfroerer JC. Mortality associated with illegal drug use among adults in the United States. *Am J Drug Alcohol Abuse* 2011;37(3):155–64.
6. Dias AC, Araujo MR, Dunn J, Sesso RC, de Castro V, Laranjeira R. Mortality rate among crack/cocaine-dependent patients: a 12-year prospective cohort study conducted in brazil. *J Subst Abuse Treat* 2011;41(3):273–8.
7. Xu F, Lu B. Prospective association of periodontal disease with cardiovascular and all-cause mortality: Nhanes iii follow-up study. *Atherosclerosis* 2011;218(2):536–42.
8. Statistics NCfH. The third national health and nutrition examination survey (nhanes iii) linked mortality file, mortality follow-up through 2006: Matching methodology. 2006
9. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between icd-9 and icd-10: preliminary estimates. *Natl Vital Stat Rep* 2001;49(2):1–32.
10. Qureshi AI, Ziai WC, Yahia AM, Mohammad Y, Sen S, Agarwal P, et al. Stroke-free survival and its determinants in patients with symptomatic vertebrobasilar stenosis: a multicenter study. *Neurosurgery* 2003;52(5):1033–9. 1039–40.discussion
11. Hennekens CH, Buring JE, Mayrent SL. *Epidemiology in medicine* 1987Bostonlittle, Brown
12. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology* 1993;82(2):191–222.
13. Reports NVS. Deaths: preliminary data for 2009. 2011;59:1–51.
14. Viscusi WK, Aldy JE. The value of a statistical life: a critical review of market estimates throughout the world. *J Risk Uncertainty* 2003;27(1):5–76.
15. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. *Circulation* 1999;99(21):2737–41.
16. Schwartz BG, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. *Circulation* 122(24):2558–69.
17. Levine SR, Brust JC, Futrell N, Ho KL, Blake D, Millikan CH, et

al. Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med* 1990;323(11):699–704.

18. Hollander JE, Hoffman RS, Burstein JL, Shih RD, Thode HC Jr. Cocaine-associated myocardial infarction. mortality and complications. cocaine-associated myocardial infarction study group. *Arch Intern Med* 1995;155(10):1081–6.
19. Hollander JE, Hoffman RS, Gennis P, Fairweather P, DiSano MJ, Schumb DA, et al. Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine associated chest pain (cochpa) study group. *Acad Emerg Med* 1994;1(4):330–9.
20. Gitter MJ, Goldsmith SR, Dunbar DN, Sharkey SW. Cocaine and chest pain: clinical features and outcome of patients hospitalized to rule out myocardial infarction. *Ann Intern Med* 1991;115(4):277–82.
21. Feldman JA, Fish SS, Beshansky JR, Griffith JL, Woolard RH, Selker HP. Acute cardiac ischemia in patients with cocaine-associated complaints: results of a multicenter trial. *Ann Emerg Med* 36(5):469–76.
22. Chang AM, Walsh KM, Shofer FS, McCusker CM, Litt HI, Hollander JE. Relationship between cocaine use and coronary artery disease in patients with symptoms consistent with an acute coronary syndrome. *Acad Emerg Med* 2011;18(1):1–9.
23. Goldacre MJ, Roberts SE, Griffith M. Place, time and certified cause of death in people who die after hospital admission for myocardial infarction or stroke. *Eur J Public Health* 2004;14(4):338–42.
24. Slobbe LC, Arah OA, de Bruin A, Westert GP. Mortality in dutch hospitals: trends in time, place and cause of death after admission for myocardial infarction and stroke. an observational study. *BMC Health Serv Res* 2008;8:52.
25. Goldacre MJ. Cause-specific mortality: understanding uncertain tips of the disease iceberg. *J Epidemiol Community Health* 1993;47(6):491–6.
26. Iso H, Jacobs DR Jr, Goldman L. Accuracy of death certificate diagnosis of intracranial hemorrhage and nonhemorrhagic stroke. the minnesota heart survey. *Am J Epidemiol* 1990;132(5):993–8.