

Supplemental Table 1. *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes*

Recreational substances	ICD-9-CM Diagnosis codes
Tobacco use	305.1
Alcohol use	305.00, 305.01, 305.02, 303.90, 303.91, 303.92, 303.93
Cocaine use	304.20; 304.21; 304.22; 304.23; 305.60; 305.61; 305.62; 305.63
Amphetamine use	304.40; 304.41; 304.42; 304.43; 305.70; 305.71; 305.72; 305.73
Cannabis use	304.30; 304.31; 304.32; 304.33; 305.20; 305.21; 305.22; 305.23
Other/unspecified drug use	305.90; 305.91; 305.92; 305.93

Supplemental Table 2. Association between subgroups of recreational substances and premature ischemic heart disease

Recreational substances	Patients with premature IHD (n=104,594) n (%)	Patients with non-premature IHD (n=885,128) n (%)	p-value	*Partially adjusted OR (95% CI)	**Fully adjusted OR (95% CI)
Tobacco use	67,085 (64.1%)	344,835 (39.0%)	<0.01	2.70 (2.66-2.74)	2.15 (2.12-2.19)
Alcohol use	33,186 (31.7%)	117,909 (13.3%)	<0.01	2.79 (2.74-2.83)	1.56 (1.53-1.59)
Illicit Drug use	21,055 (20.1%)	37,034 (4.2%)	<0.01	5.11 (5.01-5.22)	3.11 (3.04-3.18)
Cocaine use	12,484 (11.9%)	18,769 (2.1%)	<0.01	5.24 (5.10-5.38)	2.90 (2.81-2.99)
Amphetamine use	2,999 (2.9%)	4,153 (0.5%)	<0.01	5.58 (5.30-5.87)	2.74 (2.60-2.88)
Cannabis use	13,077 (12.5%)	20,852 (2.4%)	<0.01	5.14 (5.01-5.27)	2.74 (2.60-2.88)
Other drugs/Unspecified	13,503 (12.9%)	21,594 (2.4%)	<0.01	5.12 (5.00-5.25)	2.77 (2.70-2.85)

CI: Confidence Interval, IHD: Ischemic Heart Disease, OR: Odds Ratio

*Partially adjusted model: Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of PAD, presence of ICVD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

**Fully adjusted model: Adjusted for variables in the partially adjusted model and in addition adjusted for other two categories of drug use (For ex. tobacco use regression model was be adjusted for concomitant alcohol abuse and illicit drug use)

Supplemental Table 3. Association between subgroups of recreational substances and premature peripheral arterial disease

Recreational substances	Patients with premature PAD (n=12,263) n (%)	Patients with non-premature PAD (n=183,486) n (%)	p-value	*Partially adjusted OR (95% CI)	**Fully adjusted OR (95% CI)
Tobacco use	8,955 (73.0%)	106,589 (58.1%)	<0.01	1.99 (1.91-2.08)	1.63 (1.56-1.71)
Alcohol use	4,226 (34.5%)	37,683 (20.5%)	<0.01	2.05 (1.96-2.14)	1.30 (1.23-1.36)
Illicit Drug use	2,661 (21.7%)	11,687 (6.4%)	<0.01	3.79 (3.59-3.99)	3.00 (2.82-3.18)
Cocaine use	1,442 (11.8%)	5,693 (3.1%)	<0.01	3.66 (3.42-3.92)	2.76 (2.56-2.98)
Amphetamine use	309 (2.5%)	1,163 (0.6%)	<0.01	3.77 (3.29-4.31)	2.45 (2.14-2.81)
Cannabis use	1,662 (13.6%)	6,919 (3.8%)	<0.01	3.63 (3.41-3.86)	2.65 (2.48-2.84)
Other drugs/Unspecified	1,658 (13.5%)	6,629 (3.6%)	<0.01	3.81 (3.57-4.06)	2.80 (2.61-3.00)

CI: Confidence Interval, OR: Odds Ratio, PAD: Peripheral Arterial Disease

*Partially adjusted model: Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, presence of ICVD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

**Fully adjusted model: Adjusted for variables in the partially adjusted model and in addition adjusted for other two categories of drug use (For ex. tobacco use regression model was be adjusted for concomitant alcohol abuse and illicit drug use)

Supplemental Table 4. Association between subgroups of recreational substances and premature ischemic cerebrovascular disease

Recreational substances	Patients with premature ICVD (n=31,377) n (%)	Patients with non-premature ICVD (n=318,066) n (%)	p-value	*Partially adjusted OR (95% CI)	**Fully adjusted OR (95% CI)
Tobacco use	18,234 (58.1%)	146,299 (46.0%)	<0.01	1.89 (1.84-1.95)	1.50 (1.46-1.55)
Alcohol use	10,030 (32.0%)	59,087 (18.6%)	<0.01	2.17 (2.11-2.23)	1.34 (1.29-1.39)
Illicit Drug use	6,789 (21.6%)	20,638 (6.5%)	<0.01	3.80 (3.66-3.93)	2.96 (2.84-3.09)
Cocaine use	4,088 (13.0%)	11,314 (3.6%)	<0.01	3.51 (3.36-3.67)	2.59 (2.46-2.72)
Amphetamine use	985 (3.1%)	2,258 (0.7%)	<0.01	4.51 (4.14-4.91)	2.79 (2.56-3.03)
Cannabis use	4,100 (13.1%)	11,566 (3.6%)	<0.01	3.73 (3.58-3.90)	2.62 (2.50-2.75)
Other drugs/Unspecified	4,300 (13.7%)	12,275 (3.9%)	<0.01	3.65 (3.50-3.81)	2.56 (2.44-2.68)

CI: Confidence Interval, ICVD: Ischemic Cerebrovascular Disease, OR: Odds Ratio

*Partially adjusted model: Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, presence of PAD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

**Fully adjusted model: Adjusted for variables in the partially adjusted model and in addition adjusted for other two categories of drug use (For ex. tobacco use regression model was be adjusted for concomitant alcohol abuse and illicit drug use)

Supplemental Table 5. Graded-response relationship between illicit drug use and premature atherosclerotic cardiovascular disease

# of illicit drugs used*	Patients with premature ASCVD (n=1,232) n (%)	Patients with non-premature ASCVD (n=3,389) n (%)	p-value	**Adjusted OR (95% CI)
Only 1	860 (69.8%)	2,613 (77.1%)	<0.01	3.83 (3.52-4.17)
Only 2	297 (24.1%)	633 (18.7%)	<0.01	5.21 (4.48-6.06)
Only 3	68 (5.5%)	134 (4.0%)	<0.01	5.24 (3.80-7.23)
Only 4	7 (0.6%)	9 (0.3%)	<0.01	12.28 (4.23-35.68)

*Maximum 4 illicit drugs categories were included: cocaine, amphetamines, cannabis, and others/unspecified drugs

**Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

Supplemental Table 6. Association between different combinations of illicit drugs and likelihood of premature atherosclerotic cardiovascular disease

Combination of illicit drugs	Patients with premature ASCVD (n=135,703) n (%)	Patients with non-premature ASCVD (n=1,112,455) n (%)	p-value	*Adjusted OR (95% CI)
Cocaine, Amphetamine, and Cannabis use	1,670 (1.2%)	1,972 (0.2%)	<0.01	5.57 (5.20-5.98)
Cocaine and Amphetamine use	2,263 (1.7%)	2,840 (0.3%)	<0.01	5.32 (5.01-5.65)
Cocaine and Cannabis use	9,730 (7.2%)	14,287 (1.3%)	<0.01	4.62 (4.49-4.76)
Amphetamine and Cannabis use	2,416 (1.8%)	3,159 (0.3%)	<0.01	5.37 (5.07-5.68)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

Supplemental Table 7. Baseline Characteristics of patients with extremely premature versus non-premature atherosclerotic cardiovascular disease

Characteristics	Patients with extremely premature ASCVD (n=7,716)	Patients with non-premature ASCVD (n=1,112,455)	p-value
<i>Demographics</i>			
Age, mean (SD)	34.22 (4.34)	69.58 (8.92)	<0.01
Males, n (%)	6,576 (85.2%)	1,104,318 (99.3%)	<0.01
Race, n (%)			
Asian, n (%)	111 (1.4%)	4,898 (0.4%)	<0.01
African American, n (%)	1,859 (24.1%)	110,516 (9.9%)	<0.01
White, n (%)	5,171 (67.0%)	891,800 (80.2%)	<0.01
<i>Medical History</i>			
BMI \geq 30kg/m ² , n (%)	4,407 (57.3%)	442,891 (39.9%)	<0.01
Hypertension, n (%)	6,334 (82.1%)	1,064,670 (95.7%)	<0.01
Diabetes Mellitus, n (%)	1,960 (25.4%)	565,444 (50.8%)	<0.01
Hypercholesterolemia, n (%)	3,089 (40.0%)	327,161 (29.4%)	<0.01
Ischemic Heart Disease, n (%)	5,180 (67.1%)	884,063 (79.5%)	<0.01
Myocardial Infarction, n (%)	3,534 (45.8%)	278,025 (25.0%)	<0.01
Ischemic Cerebrovascular Disease, n (%)	2,499 (32.4%)	311,168 (28.0%)	<0.01
Peripheral Arterial Disease, n (%)	587 (7.6%)	178,859 (16.1%)	<0.01
<i>Overall Health Status & Healthcare Utilization</i>			
Diagnostic cost group relative risk score, mean (SD)	1.95 (2.38)	1.54 (2.13)	<0.01

ASCVD: Atherosclerotic Cardiovascular Disease, BMI: Body Mass Index, PCP: Primary Care Provider, SD: Standard Deviation

Supplemental Table 8. Association between subgroups of recreational substances and extremely premature atherosclerotic cardiovascular disease

Recreational substances	Patients with extremely premature ASCVD (n=7,716) n (%)	Patients with non-premature ASCVD (n=1,112,455) n (%)	p-value	*Partially adjusted OR (95% CI)	**Fully adjusted OR (95% CI)
Tobacco use	4,208 (54.5%)	452,122 (40.6%)	<0.01	1.80 (1.71-1.88)	1.44 (1.37-1.51)
Alcohol use	2,325 (30.1%)	164,714 (14.8%)	<0.01	2.39 (2.26-2.52)	1.52 (1.43-1.62)
Illicit Drug use	1,449 (18.8%)	53,045 (4.8%)	<0.01	4.08 (3.82-4.35)	2.81 (2.60-3.02)
Cocaine use	672 (8.7%)	27,415 (2.5%)	<0.01	2.82 (2.58-3.08)	1.62 (1.47-1.78)
Amphetamine use	299 (3.9%)	5,802 (0.5%)	<0.01	6.40 (5.64-7.26)	3.94 (3.46-4.48)
Cannabis use	993 (12.9%)	30,055 (2.7%)	<0.01	4.55 (4.23-4.90)	3.00 (2.76-3.25)
Other drugs/Unspecified	910 (11.8%)	30,941 (2.8%)	<0.01	3.85 (3.56-4.16)	2.39 (2.19-2.60)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Partially adjusted model: Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

**Fully adjusted model: Adjusted for variables in the partially adjusted model and in addition adjusted for other two categories of drug use (For ex. tobacco use regression model was be adjusted for concomitant alcohol abuse and illicit drug use)

Supplemental Table 9. Graded-response relationship between polysubstance use and extremely premature atherosclerotic cardiovascular disease

# of recreational substances used*	Patients with extremely premature ASCVD (n=7,716) n (%)	Patients with non-premature ASCVD (n=1,112,455) n (%)	p-value	**Adjusted OR (95% CI)
Only 1	2,645 (34.3%)	366,389 (32.9%)	<0.01	1.66 (1.57-1.75)
Only 2	1,109 (14.4%)	94,456 (8.5%)	<0.01	2.78 (2.59-3.00)
Only 3	364 (4.7%)	17,228 (1.6%)	<0.01	4.53 (4.03-5.09)
4 or more	742 (9.6%)	23,145 (2.1%)	<0.01	6.32 (5.76-6.92)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Maximum of 6 recreational substances categories were included: tobacco, alcohol, cocaine, amphetamines, cannabis, and others/unspecified drugs

**Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

Supplemental Table 10. Association between different combinations of illicit drugs and likelihood of extremely premature atherosclerotic cardiovascular disease

Combination of illicit drugs	Patients with extremely premature ASCVD (n=7,716) n (%)	Patients with non-premature ASCVD (n=1,112,455) n (%)	p-value	*Adjusted OR (95% CI)
Cocaine, Amphetamine, and Cannabis use	123 (1.6%)	1,972 (0.2%)	<0.01	6.99 (5.76-8.48)
Cocaine and Amphetamine use	165 (2.1%)	2,840 (0.3%)	<0.01	6.40 (5.40-7.58)
Cocaine and Cannabis use	458 (5.9%)	14,287 (1.3%)	<0.01	3.56 (3.21-3.95)
Amphetamine and Cannabis use	187 (2.4%)	3,159 (0.3%)	<0.01	7.20 (6.15-8.43)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Adjusted for patient's gender, race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden)

Supplemental Table 11. Association between females with recreational substance use and extremely premature atherosclerotic cardiovascular disease

Recreational substances	Females with extremely premature ASCVD (n=1,140) n (%)	Females with non-premature ASCVD (n=8,137) n (%)	p-value	*Adjusted OR (95% CI)
Tobacco use	439 (38.5%)	2,510 (30.9%)	<0.01	1.37 (1.17-1.62)
Alcohol use	194 (17.0%)	448 (5.5%)	<0.01	2.04 (1.58-2.63)
Illicit Drug use	133 (11.7%)	96 (1.2%)	<0.01	7.82 (5.49-11.14)
Cocaine use	62 (5.4%)	35 (0.4%)	<0.01	5.55 (3.30-9.33)
Amphetamine use	28 (2.5%)	11 (0.1%)	<0.01	6.21 (2.63-14.66)
Cannabis use	84 (7.4%)	51 (0.6%)	<0.01	8.05 (5.21-12.45)
Other drugs/Unspecified	84 (7.4%)	63 (0.8%)	<0.01	6.07 (3.94-9.35)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Adjusted for patient's race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden). In addition, this model was adjusted for other two categories of drug use (For ex. tobacco use regression model was adjusted for concomitant alcohol abuse and illicit drug use)

Supplemental Table 12. Association between males with recreational substance use and extremely premature atherosclerotic cardiovascular disease

Recreational substances	Males with extremely premature ASCVD (n=6,576) n (%)	Males with non-premature ASCVD (n=449,612) n (%)	p-value	*Adjusted OR (95% CI)
Tobacco use	3,769 (57.3%)	449,612 (40.7%)	<0.01	1.45 (1.38-1.53)
Alcohol use	2,131 (32.4%)	164,266 (14.9%)	<0.01	1.47 (1.38-1.57)
Illicit Drug use	1,316 (20.0%)	52,949 (4.8%)	<0.01	2.73 (2.53-2.95)
Cocaine use	610 (9.3%)	27,380 (2.5%)	<0.01	1.61 (1.46-1.78)
Amphetamine use	271 (4.1%)	5,791 (0.5%)	<0.01	3.87 (3.39-4.42)
Cannabis use	909 (13.8%)	30,004 (2.7%)	<0.01	2.94 (2.71-3.20)
Other drugs/Unspecified	826 (12.6%)	30,878 (2.8%)	<0.01	2.36 (2.16-2.57)

ASCVD: Atherosclerotic Cardiovascular Disease, CI: Confidence Interval, OR: Odds Ratio

*Adjusted for patient's race, obesity, hypertension, diabetes mellitus, hypercholesterolemia, presence of IHD, and diagnostic cost group relative risk score (marker of patient's overall illness burden). In addition, this model was adjusted for other two categories of drug use (For ex. tobacco use regression model was adjusted for concomitant alcohol abuse and illicit drug use)