

## Supplementary Appendix 2: Confounder Analysis

We conducted a confounder analysis to estimate how large an imbalance of cocaine use (as an unmeasured confounder) would have to be between the cannabis-user and non-user groups to nullify the association with history of myocardial infarction. To do this, we performed a sensitivity analysis based on an array of informed assumptions as outlined by Schneeweiss. (PMID: 16447304) Assumptions for the sensitivity analysis are included in the table below.

Variable	Assumed Value	Justification
Apparent exposure relative risk	2.07	This is the odds ratio from our primary analysis, since the odds ratio provides a reasonable approximation of the relative risk when the outcome is rare.
Prevalence of the confounder in the unexposed	0.05 (5%)	Recent estimates from the National Survey on Drug Use and Health suggest the prevalence of past-year cocaine use among young adults is: (PMID: 32702620) 5.72% (among those aged 18-25 years), 4.47% (among those aged 26-34 years), and 1.65% (among those aged from 35-49 years).
Apparent confounder relative risk #1: among cocaine ever-users	2 (rounded up from 1.77)	The multivariate adjusted odds ratio for history of myocardial infarction between cocaine ever-users vs. never users among young adults (aged 18-45 years) obtained from respondents of the National Health and Nutrition Examination Survey (PMID: 18929694)  This effect estimate was rounded up to the nearest whole number to provide a conservative estimate.
Apparent confounder relative risk #2: among those with >10 instances of cocaine use	4 (rounded up from 3.84)	The multivariate adjusted odds ratio for history of myocardial infarction between those with >10 instances of lifetime cocaine use vs. never users among young adults (aged 18-45 years) obtained from respondents of the National Health and Nutrition Examination Survey (PMID: 18929694)  This effect estimate was rounded up to the nearest whole number to provide a conservative estimate.
Threshold for plausible prevalence of confounder in the exposed	0.126 (12.6%)	In a cohort of young adults (aged 18-25 years), the estimated probability of recent cocaine use among cannabis-users ranged from <5% among monthly cannabis-users to 12.6% among daily cannabis users. The estimated probability of cannabis use increased with greater frequency of cannabis use. (PMID: 25115183)  To provide a conservative estimate, we used the highest estimated probability of recent cocaine use among cannabis-users (0.126) as our threshold for plausible prevalence.

### Confounder Analysis #1: Assuming that Cocaine Users in our Cohort are Ever-Users (Used Cocaine $\geq 1$ Instance During Lifetime)

This confounder analysis assumes a relative risk of 2 for the association between cocaine use and history of myocardial infarction.

Association between exposure and disease outcome	Association between confounder and disease outcome	Prevalence of confounder in the unexposed	Prevalence of confounder in the exposed	"True" or fully adjusted exposure relative risk
2.07	2	0.05	0	2.17
2.07	2	0.05	0.1	1.98
<i>Prevalence of confounder in the exposed values exceeding 0.126 (12.6%) are above our pre-defined threshold of plausibility</i>				
2.07	2	0.05	0.2	1.81
2.07	2	0.05	0.3	1.67
2.07	2	0.05	0.4	1.55
2.07	2	0.05	0.5	1.45
2.07	2	0.05	0.6	1.36
2.07	2	0.05	0.7	1.28
2.07	2	0.05	0.8	1.21
2.07	2	0.05	0.9	1.14
2.07	2	0.05	1	1.09

Therefore, assuming a definition of cocaine use as  $\geq 1$  instance during lifetime, we observe that the “true” or fully adjusted exposure relative risk of history of myocardial infarction in cannabis-users not nullified, even if the prevalence of cocaine use among cannabis-users is 100%, which exceeds our pre-defined threshold for plausible prevalence of confounder in the exposed of 12.6%.

Confounder Analysis #2: Assuming Cocaine Users in our Cohort have >10 Instances of Lifetime Cocaine Use (High Lifetime Frequency of Cocaine Use).

This confounder analysis assumes a relative risk of 4 for the association between cocaine use and history of myocardial infarction.

Association between exposure and disease outcome	Association between confounder and disease outcome	Prevalence of confounder in the unexposed	Prevalence of confounder in the exposed	"True" or fully adjusted exposure relative risk
2.07	4	0.05	0	2.38
2.07	4	0.05	0.1	1.83
<i>Prevalence of confounder in the exposed values exceeding 0.126 (12.6%) are above our pre-defined threshold of plausibility</i>				
2.07	4	0.05	0.2	1.49
2.07	4	0.05	0.3	1.25
2.07	4	0.05	0.4	1.08
2.07	4	0.05	<b>0.5</b>	<b>0.95</b>
2.07	4	0.05	<b>0.6</b>	<b>0.85</b>
2.07	4	0.05	<b>0.7</b>	<b>0.77</b>
2.07	4	0.05	<b>0.8</b>	<b>0.70</b>
2.07	4	0.05	<b>0.9</b>	<b>0.64</b>
2.07	4	0.05	<b>1</b>	<b>0.60</b>

Therefore, assuming a definition of cocaine use as >10 instances during lifetime (high lifetime frequency), we observe that the “true” or fully adjusted exposure relative risk is nullified when the prevalence of cocaine use among cannabis-users is >40% (>0.4; highlighted in table), which exceeds our pre-defined threshold for plausible prevalence of confounder in the exposed of 12.6% by a magnitude of >3 fold.