Risk and protective factors for cannabis, cocaine, and opioid use disorders: an umbrella review of meta-analyses of observational studies

Marco Solmi,[1,2,3,#] Elena Dragioti,[4,#] Giovanni Croatto,[1] Joaquim Radua,[3,5,6] Stefan Borgwardt,[7] Andrè F. Carvalho,[8,9] Jacopo Demurtas,[10] Anna Mosina,[11] Peter Konstantin Kurotschka,[12] Jae Il Shin, [13,§] Paolo Fusar-Poli [3,14-16]

1Neurosciences Department, University of Padua, Padua, Italy

2 Neuroscience Center, University of Padua, Padua, Italy

3 Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology

4 Pain and Rehabilitation center and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

5 Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERSAM, Barcelona, Catalonia, Spain.

6 Department of Clinical Neuroscience, Centre for Psychiatric Research and Education, Karolinska Institutet, Stockholm, Sweden.

7 Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Brain, Behaviour and Metabolism (CBBM), University of Lübeck, Lübeck, Germany

8 Department of Psychiatry, University of Toronto, Toronto, ON, Canada

9 Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada

10 Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

11 Clienia AG, Wetzikon Psychiatric Centre, Switzerland

12 Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy

13 Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea.

14 Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

15 Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

16 Outreach and Support in South London (OASIS) Service, South London and Maudsley NHS Foundation Trust, London, UK

#joint first authors

§joint corresponding author

Corresponding author:

Dr. Marco Solmi

Neurosciences Department, University of Padua, Padua, Italy

Via Giustiniani, 5 – 35100 – Padua, Italy

+39-0498213831 - Marco.solmi83@gmail.com

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Abstract

Several meta-analyses of observational studies have addressed the association between risk and protective factors and cannabis/cocaine/opioid use disorders, but results are conflicting. No umbrella review has ever graded the credibility of this evidence (not significant/weak/suggestive/highly suggestive/convincing). We searched Pubmed-MEDLINE/PsycInfo, last search September 21, 2020. We assessed the quality of meta-analyses with the AMSTAR-2 tool. Out of 3,072 initial references, five were included, providing 19 associations between 12 putative risk/protective factors and cannabis/cocaine/opioid use disorders (cases: 4539; N=1,118,872,721). While 84% of the associations were statistically significant, none was convincing. One risk factor (smoking) had highly suggestive evidence for association with nonmedical use of prescription opioid medicines (OR=3.07, 95%CI:2.27 to 4.14). Convincing evidence emerged in sensitivity analyses on antisocial behavior and cannabis use disoder (OR 3.34, 95%CI 2.53-4.41). Remaining associations had weak evidence. The quality of meta-analyses was rated as moderate in two (40%), low in one (20%), and critically low in two (40%). Future research is needed to better profile risk/protective factors for cannabis/cocaine/opioid use disorders disorders informing preventive approaches.

Introduction

Cannabis, cocaine, and opioid use disorders are defined by a psychopathological set of behaviors related to the use of a substance.(American Psychiatric Association, 2013; Camí and Farré, 2003; Farrell et al., 2019) They share common clinical features namely impaired control, social impairment, risky use, and pharmacological/physiologic signs associated with the use of the substance. Hence, it could be expected that common risk factors increase the risk of cannabis, cocaine, opioid use disorders. Impaired control manifests through craving, inability to cut substance use despite several attempts and to limit time spent by the substance use.(Camí and Farré, 2003; Gobbi et al., 2019; Mendelson and Mello, 1996; Schuckit, 2016) Social impairment manifests through failure to fulfill major role obligations at work, school, and/or home. (Camí and Farré, 2003; Gobbi et al., 2019; Mendelson and Mello, 1996; Schuckit, 2016) Risky use is associated with physical harms related to the substance, including infectious diseases, and also higher odds of motor vehicle crashes. (Camí and Farré, 2003; Gobbi et al., 2019; Li and Chihuri, 2019; Mendelson and Mello, 1996; Nazif-Munoz et al., 2020; Schuckit, 2016; Valen et al., 2019) Pharmacological and physiologic signs are tolerance, and withdrawal. Tolerance is the need to use higher doses of substances to obtains the same effect, and withdrawal, is a syndrome due to declines of the substance's blood or tissue concentrations in subjects with previous maintained prolonged heavy use. (Camí and Farré, 2003; Mendelson and Mello, 1996; Schuckit, 2016)

Cannabis use is highly prevalent on the global scale, with reports from the World Health Organization World Mental Health Survey initiative showing that estimated cumulative incidence can be as high as 42.4% for cannabis, as high as 16.2% for cocaine in the United States of America,(Degenhardt et al., 2008) as well as a past-year prevalence of opioid use of 0.37% globally.(Peacock et al., 2018)

However, only a subset of the world population exposed to those substances ends up developing a substance-use disorder. Notwhithstanding, those developing cannabis, cocaine, or opioid use disorders experience a dramatic drop in functioning and extremely poor health outcomes. Data from the Global Burden of Disease Study 2010 showed that illicit drug related disorders account for 20 million disability-adjusted life years (DALYs) (95% uncertainty interval (UI) 15.3-25.4 million) and for 0.8% (0.6-1.0) of global all-cause DALYs.(Degenhardt et al., 2013b) Cannabis dependence has a prevalence around 0.19%, cocaine dependence around 0.10%, and opioid dependence around 0.22%.(Degenhardt et al., 2013b) There are around 13 milion people with cannabis dependence globally, according to Global Burden of Disease Study 2010, accounting for two million DALYs, which represents a 22% increase since 1990. (Degenhardt et al., 2013a) According to the same study, there are around seven million people addicted to cocaine around the world,(Degenhardt et al., 2014a) However, the major impact comes from opioid dependence,

being responsible alone for 9.2 milion DALYs (95% UI 7.1-11.4),(Degenhardt et al., 2013b) with a rise of 73% of DALYs compared with 1990.(Degenhardt et al., 2014b) While cannabis dependence has not been linked to increased mortality,(Degenhardt et al., 2013a) cocaine and opioid use disorders are ultimately associated with more than 600,000 DALYs and 320,000 DALYs due to suicide, respectively,(Degenhardt et al., 2013b) in addition to an increased risk of infectious diseases, and overall death rates.(Farrell et al., 2019)

Several original studies have investigated putative risk or protective factors for cannabis,(Soler Artigas et al., 2019; Verweij et al., 2018) cocaine,(Keyes et al., 2016) and opioid use disorders.(Cragg et al., 2019; Meisel et al., 2019) However, replicating findings of individual studies across different settings, and pooling them in systematic reviews and meta-analyses provide a higher level of evidence.(Murad et al., 2016) It has been reported that confounding factors are inadequately addressed in original studies, and reporting of bias is frequently ignored in psychiatry evidence, even in high-impact journals.(Munkholm et al., 2020) Furthermore, several sources of bias can affect findings from meta-analyses, whose credibility is frequently questioned, and can be measured by means of umbrella reviews which pool different meta-analyses, re-calculating them with additional tests.(Fusar-Poli and Radua, 2018; Ioannidis, 2009) So far, no umbrella review measured credibility of risk factors for cannabis, cocaine, and opioid related disorder. Hence, in order to fill this gap in the literature, we conducted an umbrella review focused on non-purely genetic risk and protective factors for cannabis, cocaine, and opioid related disorders, in order to identify and measure possible methodological limitations and sources of bias, which might have under-estimated or inflated claimed associations, as previously shown in several previous umbrella.(Bortolato et al., 2017; Kim et al., 2019; Köhler et al., 2018; Solmi et al., 2020, 2018) Hence, this umbrella review aims to grade the evidence from meta-analyses of observational longitudinal (cohort, case-control) studies on protective/risk factors for cannabis, cocaine and opioid related disorders, applying state-of-the-art quantitative criteria.

Methods

This umbrella review applies previously implemented methods of published umbrella reviews,(Belbasis et al., 2015; Bellou et al., 2017; Cortese et al., 2020; Dragioti et al., 2019, 2017; Kim et al., 2019; Radua et al., 2018) adhering to state-of-the-art methodological guidance, namely the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA (eTable 1-2).(Moher et al., 2009; Stroup et al., 2000) and specific empirical recommendations for conducting umbrella reviews.(Fusar-Poli and Radua, 2018) We pre-registered the protocol in the Center for Open Science (Protocol). MS, PFP designed the study, prepared the literature search key, and drafted the protocol. ED ran the statistical analyses. Four investigators (MS,

ED, AM, PK) divided into two couples independently performed literature screening, data extraction, including quality assessment of included meta-analyses.

Literature search strategy

We conducted a systematic search in PubMed and PsycINFO from inception to September 21st, 2020. We included meta-analyses of cohort, case-control, and cross-sectional studies that assessed risk or protective factors for cannabinoid, cocaine, opioid-related disorders, categorized according to ICD or DSM, any version.(American Psychiatric Association, 2013; WHO, 2019, n.d.) The search strategy (fully reported in eTable 3) included key terms on meta-analyses and disorders of interest. We applied no restrictions regarding the year of publication, language, country, ethnicity, or any other characteristic during the search process. We also hand-searched references of included meta-analyses and other relevant articles. When authors did not agree regarding screening or data extraction, a third author (MS) resolved any conflict, reaching a consensus with the two authors.

Eligibility criteria

We only included meta-analyses of observational (cohort, case-control, and cross-sectional) studies reporting on non-genetic factors that may affect the risk of the disorders of interest. Specifically, we included disorders that corresponded to ICD-11 6C41 Disorders due to use of cannabis, 6C43 Disorders due to use of opioids, 6C45 Disorders due to use of cocaine (SUD)*"*.(WHO, n.d.) We deemed eligible both risk or protective factors, regardless of the direction of the association (protective or risk factor).

We excluded meta-analyses of studies on other-than-human populations, genome-wide associations, or single nucleotide polymorphisms. We neither included systematic reviews without a quantitative meta-analytic data synthesis, narrative reviews, and commentaries/letters to the editor.

Finally, if multiple meta-analyses investigated the same risk or protective factor and the same outcome, we only included the meta-analysis with the largest number of studies pooled to measure the association.

Data extraction

We extracted information into a standardised pre-defined template discussed among authors. The list of variables of interest included PMID/DOI of the included study, first author, year of publication, design of included studies, number of included studies in the meta-analysis, specific population cohort (i.e., general population, primary school, secondary school, university students, hospital sample, or a sample with a specific somatic, mental, or

somatic/mental comorbid condition, etc.) as well as the reference/comparison population (i.e. no risk/protective factor in cohort studies, no disorder in case-control studies), tools for the definition of both population and risk/protective factor (DSM, ICD, clinical records, rating scales), specific protective or risk factor, outcome (ICD or DSM code if available, or definition of specific disorders as reported by authors), and its risk estimate. We assessed the methodological quality of included meta-analyses as independent couples of two investigators (JD, PK, AM, MS) using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) version 2. (Shea et al., 2017)

Data analysis

For each association (i.e., between each specific risk or protective factor and the outcome disorder), we calculated the pooled effect size with its 95% confidence intervals (Cis) using random-effects models. (DerSimonian and Laird, 1986) We transformed the effect sizes/modified the direction of the associations reported in the included publications to equivalent Odds Ratios (eOR) to present comparable estimates.(Radua et al., 2018) We measured heterogeneity with the I^2 statistic.(Higgins et al., 2003) Besides, we computed the 95% prediction intervals for the effect sizes to estimate the possible range of future studies' effect size.(Riley et al., 2011) We also examined small-study effect bias, testing whether smaller studies generated larger effect sizes than larger studies.(Belbasis et al., 2015; Bellou et al., 2017; Dragioti et al., 2019, 2018, 2017; Kim et al., 2019; Radua et al., 2018) Specifically, we used both the Egger regression asymmetry test (p-value ≤ 0.10) and whether the random-effects summary effect size was larger than the effect size of the largest study contributing to that association.(Belbasis et al., 2015; Bellou et al., 2017; Dragioti et al., 2019, 2018) We finally measured the presence of excess significance bias by assessing whether the observed number of studies with nominally statistically significant results differed from the expected number of studies with statistically significant results.(Ioannidis, 2013; Ioannidis and Trikalinos, 2007) We calculated the expected number of statistically significant studies per association by summing the statistical power estimates for each component study, assuming the effect size of the largest study (i.e., the smallest SE) per association.(Ioannidis, 2013) For excess significance bias, a p-value ≤ 0.10 was considered statistically significant. (Ioannidis and Trikalinos, 2007) We conducted all analyses in Stata/ MP, version 10.0 (StataCorp LLC).

Finally, to explore whether applying alternative random-effect models changes credibility of evidence, we have run additional analyses using Hartung-Knapp-Sidik-Jonkman (HKSJ) (IntHout et al., 2014) methods insetad of Der Simonian and Laird's one(DerSimonian and Laird, 1986).

Assessment of the credibility of evidence and sensitivity analyses

As done previously in former published umbrella reviews,(Bortolato et al., 2017; Köhler et al., 2018; Papola et al., 2019; Solmi et al., 2018) we classified the strength of the evidence of eligible associations into five levels: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS) (Table 1).

When feasible, we ran the following sensitivity analyses on factors supported by convincing or highly suggestive evidence in main analyses: only cohort studies, only high-quality meta-analyses, age, adjusted / non-adjusted estimates, follow-up duration, disease diagnostic criteria, year of publication, and population of interest. We also run subgroup analyses according to homogeneous definitions of nicotine and alcohol use and removing the criterion on >1,000 cases from the credibility assessment.

Results

Search results

The literature search identified a total of 3,672 abstracts (3,072 after removal of duplicates), of which only 15 were scrutinized for depth eligibility, and finally we included five articles in this umbrella review (Table 2). Figure 1 represents a flowchart depicting the inclusion process and illustrates the reason why studies were excluded. The reasons for exclusion of each study were also described in eTable 4.

Descriptive results of the included associations

The characteristics of included studies are described in Table 2. The five eligible meta-analyses corresponded to 19 associations between 12 potential putative risk/protective factors and cannabis, cocaine, and opioid related disorders, including a total of 180 primary observational studies (Table2; Table 3). Seven associations (36.9%) included cohort design studies, 11(57.9%) included cohort, case-control and cross-sectional design studies, and one (5.2%) used cross-sectional design only (Table 2). The median number of the total sample size per meta-analysis was 22,258 (inter-quartile range [IQR]= 11,055 to 175,063, range 3,128 to 1,118,661,217).

The 19 associations of putative risk/protective factors were based on data of 4,539 total cannabis, cocaine, and opioid related disorders cases with a median of 634 cases per association (IQR= 366 70 to 1,621, range 258 to 2447). The median number of studies per association was 10 (IQR= 7 to 14, range 3 to 22) and the number of cases was greater than 1,000 in one association, while in 13 associations the number of caces was not reported (Table 3).

All the associations (n=19; 110%) used OR as the effect metric. The effect size was larger than 2 in nine associations. Only two factors (age < 25 years and age ≥55 years) were associated with a decreased risk of cannabis, cocaine, and opioid related disorders. (Brady et al., 2017)

Summary of Associations

A summary of all 19 associations is presented in Tables 3 and 4. Sixteen of the 19 examined associations (84.2%) had a nominally statistically significant effect ($p \leq 0.05$) under the random-effects models and 10 of those (52.6%) reached a p-value $\leq 10^{-6}$.

Thirteen associations (68.46%) had large heterogeneity ($I^2 > 50\%$), and for eight associations (42.1%) the 95% prediction intervals excluded the null value. In 15 associations (78.9%), the ESs of the largest study had a nominally statistically significant effect ($p \leq 0.05$). Finally, small-study effects were found for three associations (15.7%) and excess significance bias was found for 12 associations (63.2%).

Quality assessment of included articles

The quality of included meta-analyses according to AMSTAR2 was moderate in two meta-analyses, low in one, and critically low in two meta-analysis. None of the meta-nalyses reached the high quality level (Table 2).

Convincing Evidence and highly suggestive evidence

No association between putative risk factors and cannabis, cocaine, and opioid related disorders was deemed at convincing evidence. Only one association (5.3%) was supported by highly suggestive evidence (Table 3). This was pertained to tobacco smoking and nonmedical use of prescription medicines (Rajabi et al., 2019)

Suggestive, Weak, and No Evidence

None of the associations between putative risk factors and cannabis, cocaine, and opioid related disorders as shown in Table 3 met the criteria for suggestive evidence, while 15 associations (78.9%) were supported by weak evidence. Finally, three associations (15.8%) were ranked as no evidence (i.e., all associations with p-value > 0.05) (Table 4).

Sensitivity analysis

Most sensitivity analyses were not allowed by the scant amount of meta-analyses found. For the only association ranked at highly suggestive evidence in the main analysis, the sensitivity analysis limited to cohort studies showed that this association ie., tobacco smoking as risk factor for nonmedical use of prescription medicines (Rajabi et al., 2019) remained at the highly suggestive evidence.

A further sensitivity analysis limited to significant associations after removing the n>1000 cases criterion showed that one of the associations was upgraded to convincing evidence (Table 3). This included antisocial behaviour life course persistent (Male) as risk factor for cannabis use disorder. Seven additional associations were upgraded to highly suggestive evidence (Table 3). These were age (age < 25 years and age ≥55 years; n=2) as protective factor for prescription drug overdose,

age (35-44 years), white race, psychiatric disorder, and substance use disorders (SUDs) as risk factors for prescription drug overdose (Brady et al., 2017), and antisocial behaviour adolescent limited in males as risk factor for cannabis use disorder (Bevilacqua et al., 2018)
The association between smoking and nonmedical use of prescription medicines (Rajabi et al., 2019) remained at highly suggestive evidence as in main analysis.
Virtually no result changed when using HKSJ method (IntHout et al., 2014) (eTable 5-6)

Discussion

The present work was the first umbrella review assessing the credibility of evidence of putative risk factors for cannabis, cocaine, and opioid use disorders. By pooling data from five published meta-analyses, and applying established quantitative criteria including measure of small study effect and excess of significance bias, this work showed that the highest level of evidence is on smoking as risk factor for non-medical use of prescription medicines in main analyses (highly suggestive), but that in sensitivity analyses antisocial behaviours was a risk factor for cannabis-related disorders (convincing evidence), and white ethnicity, age 33-44, mental disorder, pre-existing substance use disorder were risk factor for non-medical use of opioid prescription medicines (highly suggestive evidence).

Our findings may be clinically relevant in several ways. These observational findings (that can't infer causality), suggest that tobacco smoking preventive strategies could be tested, to understand whether by reducing smoking also therisk of non-medical use of prescription opioid medicine could be reduced. Several smoking prevention and smoking cessation strategies are effective, either in adolescents,(Selph et al., 2020) the general population,(Faber et al., 2017) in disadvantaged socioeconomic strata of the population,(Kock et al., 2019) in subjects with mental disorders,(Siskind et al., 2020) and in subjects who already have SUD.(Secades-Villa et al., 2020) Showing that smoking also increases the risk for subsequent SUD, stresses the importance of resource allocation in support of large-scale smoking prevention campaigns, and in the maintenance/initiation of public health smoke-free policies.

Importantly, this work also identifies several groups at increased risk for SUDs. Two putative risk factors were significantly associated with cannabis use disorders according to the current evidence synthesis, namely antisocial behaviour (Bevilacqua et al., 2018) and attention-deficit/hyperactivity disorder (ADHD) (Lee et al., 2011). Antisocial behaviour is a risk factor for cannabis use disorder supported by the convincing evidence in sensitivity analyses.(Bevilacqua et al., 2018) More in detail, conduct problems are associated with the highest risk of cannabis consumption when such conduct problems onset early, and persist throughout years.(Bevilacqua et al., 2018) The association between antisocial behaviour and cannabis use disorder suggests that school-age kids/adolescents with antisocial behaviour might

be an at-risk group to target with preventive interventions. Apparently, early and persistent conduct problems do not only increase the risk of cannabis use disorders, but also of depression, alcohol use, self-reported aggression, poor general health, poor education, poor employment.(Bevilacqua et al., 2018) Several confounding variables could have influenced this association, which may be not specific for cannabis use disorders. The same may apply to ADHD. A large body of evidence has shown that ADHD is a predictor of poor outcomes across several functioning domains, including academic performance, antisocial behavior, obesity, occupation, services use, and social function outcomes.(Shaw et al., 2012) Solid evidence has also shown that on the other hand medications for ADHD are among the medications with among the most spectacular effect sizes across all the medical fields.(Cortese, 2020; Cortese et al., 2018) When subjects with ADHD do not receive treatment, then outcomes are substantially worse than for those subjects that do receive evidence-based pharmacological treatment.(Shaw et al., 2012) According to this umbrella review, people with ADHD are prone to develop cannabis use disorders, cocaine related disorders, and other substance related disorders. This suggests that unlikely any specific mechanism underlies the increased risk for cannabis related disorder, specifically. Beyond the lack of specific mechanisms, results are of upmmost clinical relevance, since they suggest to strictly monitor subjects with ADHD in order to prevent and early detetct emerging substance abuse. Among all prevention strategies, one is optimal pharmacological treatment of ADHD, since is has been shown that subjects with ADHD had decreased odds of developing substance use disorders when receiving pharmacological treatment compared with those periods when not receiving pharmacological treament. (Cortese, 2020) Specifically, data from large national databases from Sweden and United States of America have shown a 27% to 35% decreased risk of developing SUD within-subject depending on treatment status, favoring pharmacological treatment for ADHD vs no treatment, on the long-term. (Chang et al., 2019) One further factor that increases risk of SUD is being affected by mental disorders. People with mental disorders have a decreased life-expectancy of up to 20 years compared with the general population.(Lawrence et al., 2013; Nordentoft et al., 2013) There is solid and converging evidence showing the poor physical health of subjects with mental disorders,(Correll et al., 2017; Vancampfort et al., 2016, 2015) yet a gap in physical health of people with mental disorders is still there, contributing to poor life-expectancy.(Firth et al., 2019) Since SUD is in turn associated with dramatically poor physical health, it's of upmost importance preventing, screening, and early treating subjects affected by mental disorders against SUD.

Strengths and limitations

The present work has several strengths. First, it is the first umbrella review summarizing data from published meta-analyses on risk factors for cannabinoid, cocaine, opioid related disorders.

Second, it identifies which risk factors are supported by the most credible evidence based on quantiative pre-defined criteria. The present work also has several limitations. First, compared with umbrella reviews summarizing meta-analyses on risk factors for other disorders, we were unable to include as many meta-analyses given the limited availability of research efforts on this topic. Second, no included meta-analyses was of high quality according to the AMSTAR-2 tool. Third, no conving evidence emerged from main analyses. However, one of the most relevant aspects of knowledge synthesis efforts is to identify areas where further studies of higher methodological quality are needed.(Higgins et al., 2020)

Implications and conclusions

In conclusion, this work highlights the possibility of preventing tobacco smoking to avoid increasing the risk of non-medical use of prescription medicines in main analyses, and might suggest the opportunity to test effective preventive interventions in populations at risk, namely people with psychiatric disorders, white, aged 33-44, and those with pre-existing SUDs. However, evidence on risk factor for cannabis, cocaine, opioid related disorders is highly suggestive at best, and on a limited number of putative risk factors compared with other mental disorders. More high quality prospective cohort studies are needed, ideally on large population-based logitudinal cohorts, which can be then pooled in methodologically robust meta-analyses, that can better assess causality, to inform future possible preventive strategies.

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Conflict of interest

ED, GC, JR, SB, AFC, JD, AM, PK, JIS have no conflict of interest to declare. MS has been a consultant and/or advisor to or has received honoraria from Angelini and Lundbeck outside of this work. PFP received research support from Lundbeck and personal fees from Lundbeck, Menarini and Angelini outside this work.

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Figure 1. PRISMA flow-chart

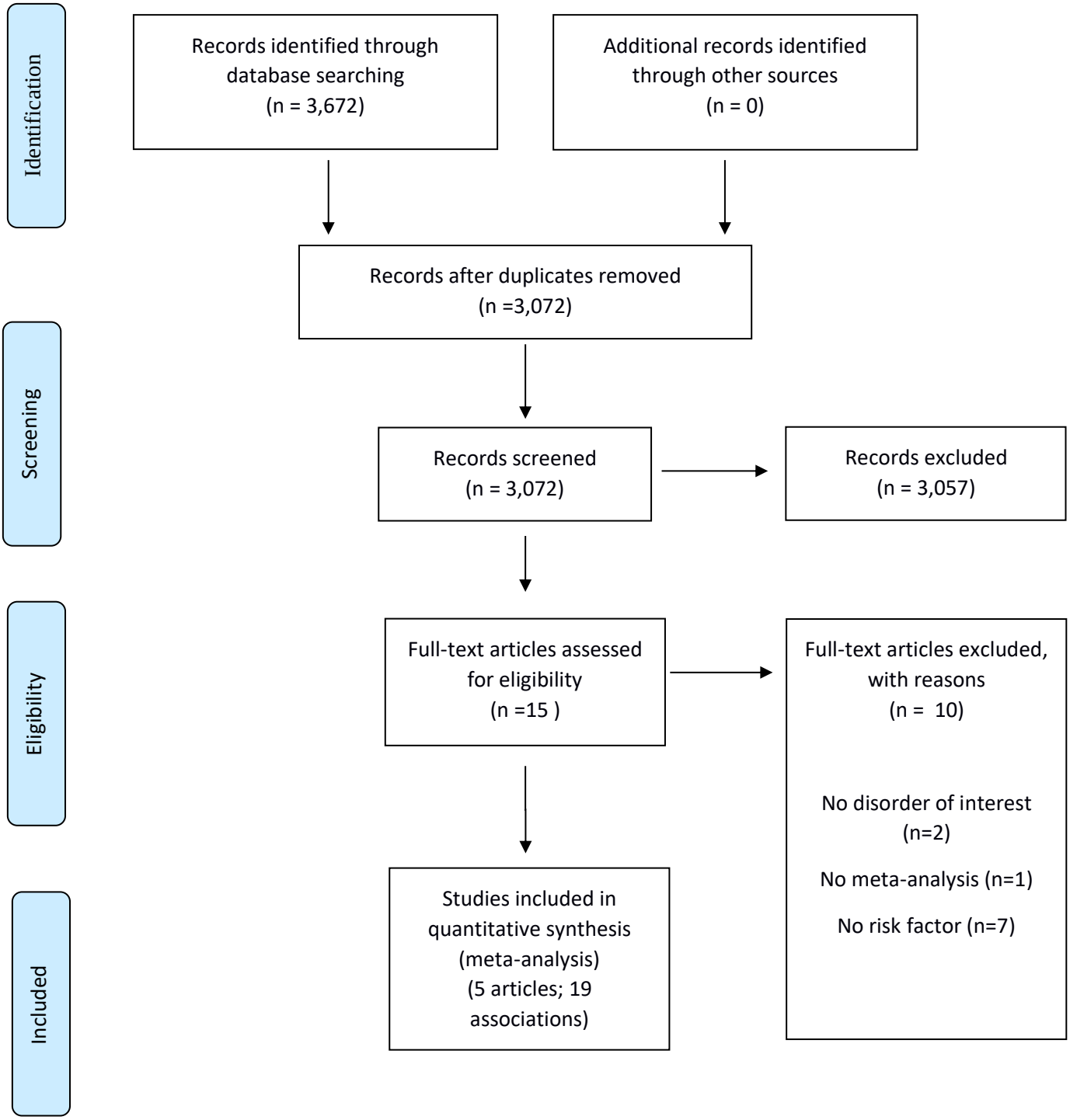

Table 1. Main criteria for evaluation of the credibility of the evidence of observational studies

Classification	**Criteria**
Convincing evidence (Class I)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-6}$) per random-effects calculations 3. No evidence of small-study effects 4. No evidence of excess of significance bias 5. Prediction intervals not including the null value 6. Largest study nominally significant ($p<0.05$) 7. No large heterogeneity (i.e., $I^2< 50\%$)
Highly Suggestive evidence (Class II)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-6}$) per random-effects calculation 3. Largest study nominally significant ($p<0.05$)
Suggestive Evidence (Class III)	1. More than 1000 cases 2. Significant summary associations ($p<1x10^{-3}$) per random-effects calculations
Weak evidence (Class IV)	1. All other associations with $p\leq0.05$
Non-significant associations (NS)	1. All associations with $p >0.05$

Table 2. Characteristics of five eligible meta-analyses

Author, year (ref)	No of associations	Study design	Sample size	Target population	Risk or protective factor	Disorder definition as in included meta-analysis	Disorder definition (DSM, ICD, validated scale with cut-off-specify etc)	AMSTAR 2 appraisal
Rajabi, 2019 (Rajabi et al., 2019)	2	Cross-sectional and cohort	175,063	Students and various young surveys	Smoking; Age at smoking onset (< 14 years vs > 18 years)	Opioid use disorder	DSM-IV; Opioid dependence/abuse; questionnaires; opioid use; interviews	Critically low
Bevilacqua, 2018 (Bevilacqua et al., 2018)	3	Cohort	22, 258	Infants, children, and young adults	Antisocial behaviour life course persistent (Male); Antisocial behaviour adolescent limited (Male); Antisocial behaviour childhood limited (Male)	Cannabis use disorder	DSM-III; DSM-IV; Questionnaires	Critically low
Brady, 2017 (Brady et al., 2017)	9	Cross-sectional, case control, and cohort	1,118,661,217	Males and various age groups, white race, general population overdose decedents, SUD, and urban/rural residence residence	Male sex; Age; Race; Psychiatric Disorder; SUDs; Residence	Prescription drug overdose	ICD-10; Overdose death; ICD-10; Non-fatal overdose; ICD-9; Overdose event	Moderate
Dennis, 2015 (Dennis et al., 2015)	1	Cross-sectional	3,128	Chronic non cancer pain, opioid addiction in substitution treatment	Chronic non cancer pain	Opioid abuse in opioid addiction with substitution treatment	Urine sample	Moderate
Lee, 2011 (Lee et al., 2011)	4	Prospective cohort	11,055	ADHD	ADHD	Marijuana use; Cocaine abuse; Substance abuse/dependence	DSM-III-R, DSM-IV	Low

Notes: SUDs= Substance use disorders; ADHD= Attention-deficit/hyperactivity Disorder ;DSM= Diagnostic and Statistical Manual of Mental Disorders; ICD= International Classification of Diseases

Table 3. Significant (p<0.05) risk/protective factors, by classifying of evidence (no convincing or suggestive evidence)

Author, year	Risk / Protective Factor	Disorder definition as in included MA	K	n/N	Metric	ES (95% CI)	p	PI sign	I^2	SSE	ESB	LS sign	Class 1	Class 2 (-n>1000)	AMSTAR 2
Rajabi, 2019 (Rajabi et al., 2019)	Smoking	Nonmedical use of prescription medicines	10	2447/ 175063	OR	3.07 (2.27, 4.14)	$2.1x10^{-13}$	No	86%	No	No	Yes	II	II	Critically low
Rajabi, 2019 (Rajabi et al., 2019)	Age at smoking onset (< 14 years vs > 18 years)	Opioid use disorder	3	795/ 109534	OR	1.66 (1.28, 2.16)	$1.4x10^{-3}$	Yes	52%	No	No	Yes	IV	III	Critically low
Bevilacqua, 2018 (Bevilacqua et al., 2018)	Antisocial behaviour life course persistent (Male)	Cannabis use disorder	7	258/ 22516	OR	3.34 (2.53, 4.41)	$2.4x10^{-17}$	No	0%	No	No	Yes	IV	I	Critically low
Bevilacqua, 2018 (Bevilacqua et al., 2018)	Antisocial behaviour adoloscent limited (Male)	Cannabis use disorder	7	474/ 22516	OR	3.78 (2.54, 5.63)	$5.9x10^{-11}$	No	65%	No	NP	Yes	IV	II	Critically low
Brady, 2017 (Brady et al., 2017)	Male sex	Prescription drug overdose	22	NR/ 1001130807	OR	1.33 (1.17, 1.51)	$1.0x10^{-4}$	Yes	96%	No	Yes	Yes	IV	III	Moderate
Brady, 2017 (Brady et al., 2017)	Age < 25 years	Prescription drug overdose	14	NR/ 1118661217	OR	0.27 (0.20, 0.37)	$3.5x10^{-16}$	Yes	97%	No	Yes	Yes	IV	II	Moderate
Brady, 2017 (Brady et al., 2017)	Age 35-44 years	Prescription drug overdose	14	NR/ 1118661217	OR	1.52 (1.31, 1.76)	$3.2x10^{-8}$	Yes	92%	No	Yes	Yes	IV	II	Moderate
Brady, 2017 (Brady et al., 2017)	Age 45-54 years	Prescription drug overdose	14	NR/ 1118661217	OR	1.37 (1.17, 1.61)	$7.7x10^{-5}$	Yes	94%	No	Yes	Yes	IV	III	Moderate
Brady, 2017 (Brady et al., 2017)	Age≥ 55 years	Prescription drug overdose	14	NR/ 1118661217	OR	0.37 (0.29, 0.47)	$1.1x10^{-14}$	Yes	97%	Yes	Yes	Yes	IV	II	Moderate
Brady, 2017 (Brady et al., 2017)	White race	Prescription drug overdose	14	NR/ 1106620812	OR	2.28 (1.93, 2.70)	$4.8x10^{-22}$	No	91%	No	Yes	Yes	IV	II	Moderate
Brady, 2017 (Brady et al., 2017)	Psychiatric Disorder	Drug overdose	11	NR/ 3825947	OR	3.93 (3.09, 5.01)	$1.8x10^{-28}$	No	95%	No	Yes	Yes	IV	II	Moderate
Brady, 2017 (Brady et al., 2017)	SUDs	Prescription drug overdose	10	NR/ 3685646	OR	5.24 (3.53, 7.75)	$1.5x10^{-16}$	No	98%	No	Yes	Yes	IV	II	Moderate
Lee, 2011 (Lee et al., 2011)	ADHD	Marijuana use	7	NR/ 3623	OR	2.79 (1.64, 4.74)	$1.5x10^{-4}$	Yes	70%	No	Yes	Yes	IV	III	Low

Lee, 2011 (Lee et al., 2011)	ADHD	Marijuana abuse	8	NR/ 3170	OR	1.58 (1.16, 2.14)	0.003	Yes	32%	Yes	Yes	No	IV	IV	Low
Lee, 2011 (Lee et al., 2011)	ADHD	Cocaine abuse	5	NR/ 1113	OR	2.04 (1.38, 3.04)	$4.0x10^{-4}$	No	0%	No	No	Yes	IV	III	Low
Lee, 2011 (Lee et al., 2011)	ADHD	Substance abuse/dependence	6	NR/ 1168	OR	2.64 (1.76, 3.94)	$2.2x10^{-6}$	No	12%	Yes	Yes	No	IV	III	Low

Abbreviations: Class 1 – class of evidence, Class 2(-n>1000)- class of evidence after removing the n>1000 cases criterion, ADHD– Attention-deficit/hyperactivity disorder, CI – confidence interval, ES – effect size, ESB – excess significance bias, I^2 – heterogeneity, K – number of studies for each factor, LS – largest study with significant effect, MA – meta-analysis, n – number of cases, N – total number of cohort per factor, NR –not reported, OR – odds ratio, PI – prediction interval, SSE – small study effects, sign., – significant, SUD – substance use disorders.

Table 4. Non-Significant (p>0.05) risk/protective factors

Author, year (ref)	Risk / Protective Factor	Disorder definition as in included MA	K	n/N	Metric	ES (95% CI)	p	PI sign	I^2	SSE	ESB	LS sign	Class	AMSTAR 2
Bevilacqua, 2018 (Bevilacqua et al., 2018)	Antisocial behaviour childhood limited (Male)	Cannabis use disorder	7	340/ 22516	OR	1.14 (0.91, 1.43)	0.269	Yes	0%	No	No	No	NS	Critically low
Brady, 2017 (Brady et al., 2017)	Rural residence	Prescription drug overdose	5	NR/ 23745174	OR	0.93 (0.72, 2.19)	0.556	Yes	88%	No	Yes	Yes	NS	Moderate
Dennis, 2015 (Dennis et al., 2015)	Chronic non cancer pain	Opioid abuse in opioid addiction with substitution treatment	2	225/ 405	OR	0.69 (0.41, 1.18)	0.176	NA	0%	No	NP	No	NS	Moderate

Abbreviations: Class – class of evidence, CI – confidence interval, ES – effect size, ESB – excess significance bias, I^2 – heterogeneity, K – number of studies for each factor, LS – largest study with significant effect, MA - meta-analysis, n – number of cases, N – total number of cohort per factor, NA – not assessable, NR –not reported, NP – not pertinent because the number of observed studies is less than the expected, OR – odds ratio, PI – prediction interval, SSE – small study effects. sign., – significant.