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Research Paper

Mental health outcomes associated with of the use of amphetamines: A systematic review and meta-analysis

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ABSTRACT

Background: The use of amphetamines is a global public health concern. We summarise global data on use of amphetamines and mental health outcomes.

Methods: A systematic review and meta-analysis (CRD 42017081893). We searched Medline, EMBASE, PsycInfo for methamphetamine or amphetamine combined with psychosis, violence, suicidality, depression or anxiety. Included studies were human empirical cross-sectional surveys, case-control studies, cohort studies and randomised controlled trials that assessed the association between methamphetamine and one of the mental health outcomes. Random effects meta-analysis was used to pool results for any use of amphetamines and amphetamine use disorders.

Findings: 149 studies were eligible and 59 were included in meta-analyses. There was significant heterogeneity in effects. Evidence came mostly from cross-sectional studies. Any use of amphetamines was associated with higher odds of psychosis (odds ratio [OR] = 2.0, 95%CI 1.3–3.3), violence (OR = 2.2, 95%CI 1.2–4.1; adjusted OR [AOR] = 1.4, 95%CI 0.8–2.4), suicidality OR = 4.4, 95%CI 2.4–8.2; AOR = 1.7, 95%CI 1.0–2.9) and depression (OR = 1.6, 95%CI 1.1–2.2; AOR = 1.3, 95%CI 1.2–1.4). Having an amphetamine use disorder was associated with higher odds of psychosis (OR = 3.0, 95%CI 1.9–4.8; AOR = 2.4, 95%CI 1.6–3.5), violence (OR = 6.2, 95%CI 3.1–12.3), and suicidality (OR = 2.3, 95%CI 1.8–2.9; AOR = 1.5, 95%CI 1.3–1.8).

Interpretation: Methamphetamine use is an important risk factor for poor mental health. High quality population-level studies are needed to more accurately quantify this risk. Clinical responses to methamphetamine use need to address mental health harms.

Research in context

Evidence before this study

We searched PubMed up until July 26 2019 for reviews on the use of amphetamines and mental health using the Medical Subject Headings (MeSH) terms ("*amphetamine"[MeSH Terms] OR

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"*amphetamine"[All Fields]) AND ("mental health"[MeSH Terms] OR ("mental"[All Fields] AND "health"[All Fields]) OR "mental health"[All Fields]) AND Review[ptyp]. This gave 107 results, including 14 systematic reviews, one of which examined mental health outcomes. This narrative synthesis of health outcomes amongst young people who used methamphetamine found an association with mental health outcomes, including psychosis, suicide and depression. There were no meta-analyses on this topic.

Added value of this study

Our study represents the only systematic review and meta-analysis of data on mental health outcomes associated with the use of amphetamines. We pooled unadjusted and adjusted odds ratios to show that there are elevated levels of psychosis, violence, suicidality and depression amongst people who use amphetamines. However, we also show that most of the evidence for these associations came from cross-sectional studies. We found that many studies did not adjust for potential confounders. The lack of longitudinal data on the direction of effects meant that it was difficult to assess causality.

Implications of the available evidence

Clinical services and policies need to take into account the poor mental health of people who use amphetamines. There is limited data available to understand the association between the use of amphetamines and mental health outcomes. More evidence is needed, particularly from high-quality population-level studies and longitudinal cohort studies, in order to accurately quantify this risk.

1. Introduction

Methamphetamine use is a growing global public health concern. The UNODC estimated that in 2016, 34 million people worldwide used amphetamines [1]. The Global Burden of Disease 2016 estimated that there were 4.96 million people with dependent use of these drugs [2]. Most illicit use involves methamphetamine, and hereafter both amphetamine and methamphetamine are collectively referred to as amphetamines. Increasing interconnectedness of the global drug market is spreading both manufacture and use [3]. The shift to smoking and injecting high purity crystalline methamphetamine has been associated with a rise in related harms [4].

Mental health harms are a likely consequence of the use of amphetamines. Intoxication with amphetamines can incite transient symptoms of hallucinations and paranoia [5–7] and can also exacerbate psychosis in people with schizophrenia [8,9]. It is less clear whether the use of amphetamines can increase the risk of de novo cases of schizophrenia [10,11]. Chronic exposure to amphetamines has been associated with increased aggression (this is thought to be related to altered serotonin function and mood and impulse regulation) while acute intoxication can increase aggressive responding to threatening situations [12]. Epidemics of use have been associated with increases in violence, although it is difficult to disentangle drug effects from other risk factors (e.g., antisocial personality, polysubstance use, violence of the criminalised drug market) [12]. Amphetamines have been consistently associated with elevated rates of suicide [13], and evidence suggests a likely causal link [14]. Withdrawal from heavy use of amphetamines can lead to monoaminergic down-regulation [15], producing a depressive-like state [16–18]. It is not known whether this can lead to ongoing depression, but depression is pervasive amongst heavy users of the drug [19]. Acute intoxication can induce panic and agitation [5], and it is plausible that the sympathetic arousal produced by intoxication may exacerbate anxiety. However, inconsistencies between individual study outcomes have prevented a clear understanding about the strength or nature of these associations.

We conducted a systematic review and meta-analysis of data on the association between the use of amphetamines and each of these mental health outcomes: psychosis, violence, suicidality, depression and anxiety. We included study designs best suited to estimating risk, namely cross-sectional surveys, case-control studies, cohort studies and randomised controlled trials [20]. We included all patterns of use and undertook meta-analyses where there were sufficient data. Our aim was to (i) estimate the pooled association between the use of amphetamines and each of the five mental health outcomes considered, and (ii) assess whether the available evidence was consistent with a causal association (e.g., whether the associations could be better explained by potential confounding factors, consistency and magnitude of effects, and evidence of directionality).

2. Methods

2.1. Protocol and registration

Our study was conducted in accordance with the PRISMA guideline for transparent scientific reporting in systematic reviews and meta-analyses (see PRISMA checklist in Supplement A). The review protocol was registered on PROSPERO (CRD = 42017081893).

2.2. Searches

We searched three databases (Medline, EMBASE and PsycINFO) combining search terms for 'methamphetamine' or 'amphetamine' with search terms for each of the following mental health outcome categories: psychosis, violence, suicidality, depression and anxiety. Search terms with synonyms and Medical Subject Headings were exploded on titles, abstracts, subject heading, concept, and keywords. The searches were conducted in May 2017. Results were limited to English language peer-review journal articles on humans, with a publication year from 1950. Abstracts, dissertations, books, editorials, review papers and other papers that did not include empirical data were excluded. The full electronic search strategies are available in Supplement B.

2.3. Eligibility criteria

We included all human studies on people exposed to the use of amphetamines (no age or clinical restrictions) that examined the relationship between any measure of the use of amphetamines and mental health outcomes of psychosis, violence, suicidality, depression or anxiety (details in Supplement C). Both methamphetamine and amphetamine use were included due to their similarity and because of the difficulty distinguishing between their self-reported use [21]. Both pharmaceutical and illicit use were included. Ecstasy (3,4-Methyl enedioxymethamphetamine) and other stimulants, or combinations thereof, were not included.

Mental health outcomes needed to be clearly defined, and could include symptoms or events, diagnoses, or proxies thereof (e.g., hospital admissions). Psychosis included positive symptoms of psychosis (delusions and hallucinations) and psychotic disorders. Violence included perpetration only (not victim studies). Suicidality included ideation, attempts, and completed suicides, but not other forms of self-harm.

Included study designs were cross-sectional, case-control, cohort studies, and randomised controlled trials, defined according to the Cochrane study design guide [20]. Cross-over trials were excluded due to potential carry-over effects, although data were in-

cluded from the pre-cross over phase where this met other RCT study design criteria. Reasons for non-eligibility were coded as: (1) non-English language; (2) animal and non-human studies; (3) no empirical data; (4) wrong study design; (5) wrong exposure; (6) wrong outcome; (7) no usable data (including where there was no variation in either the use of amphetamines or the mental health outcome).

2.4. Study selection

Citations were uploaded to an online systematic review tool (© 2019 Covidence, www.covidence.org; Veritas Health Innovation Ltd.). Following the removal of duplicates, titles and abstracts were screened by one researcher for relevance. Full text reports were then reviewed by two independent reviewers against the inclusion criteria. Conflicts were discussed and if consensus was not achieved a third reviewer decided.

2.5. Data extraction

Data were extracted from each paper using a structured template (Supplement D) which covered study details, sample characteristics, the mental health outcome measure, exposure to amphetamines, the reported unadjusted and adjusted effects, variables adjusted for in adjusted analyses (i.e., demographics, other substance use, premorbid risk factors), the nature of the comparison group (where applicable) and raw data for the mental health outcome (e.g., counts, means, variance estimates) for both the amphetamines-exposed and the comparison group. Data extraction was checked by a second reviewer; discrepancies were resolved by discussion initially, and if necessary, by a third reviewer.

2.6. Quality assessment

We assessed study quality using the Joanna Briggs Critical Appraisal Checklists for each study design [22]. A summary score was derived for each study based on the percentage of applicable items positively endorsed on the Checklist (i.e., higher percentages indicate better quality/lower risk of bias). For the quality of the meta-analyses, a weighted average quality score was derived using weights from the meta-analysis. Quality assessments were checked by a second reviewer; discrepancies were resolved by discussion initially, and if necessary, by a third reviewer.

2.7. Data synthesis

We conducted an initial review of data available (Supplement E) against four exposure categories for amphetamines: (1) any use vs. no use; (2) use disorder vs. no use disorder; (3) frequency of use; (4) route of administration (e.g., injecting vs. not injecting use). Based on this initial assessment, the meta-analyses focussed on (1) and (2) due to lack of studies on route of administration, and heterogeneity in the measurement of the frequency of the use of amphetamines.

Studies eligible for the meta-analysis were reviewed for availability of data and authors were contacted to obtain missing data. The principle summary measure used was an odds ratio, as there were few studies with mean differences. In studies that did not report odds ratios, we extracted data in a 2×2 mental health outcome by exposure–contingency table to calculate the unadjusted odds ratios. For longitudinal studies, odds ratios were derived based on the number of cases reported in the exposed (amphetamines) group relative to the non-exposed group for the reported timeframe. If studies reported more than two outcome groups, we aggregated the groups by summing data from the contingency table to form the necessary categories (e.g. combining mild to moderate and severe dependence groups to form an aggregate dependence category). The details of data extracted for each comparison can be found in Supplement E.

We conducted meta-analyses to pool the adjusted and unadjusted odds ratios for (1) any use of amphetamines versus no use of amphetamines, and (2) amphetamine use disorder versus no amphetamine use disorder, respectively, against each mental health outcome. Due to the small number of studies we were unable to conduct meta-regression to test for the effects of demographics or other study characteristics (e.g., study population). Instead, we pooled adjusted effects that were reported in the included studies. The meta-analyses were standard random-effects analyses conducted using the "metan, random" command [23] in Stata Version 14.1 (StataCorp LLC, College Station, Texas, USA). This approach accommodates heterogeneity in effect sizes [24]. Forest plots were generated for visualisation of results. Heterogeneity in effects was assessed using the I^2 statistic. Post-hoc sub-group analyses were conducted where this was of interest (e.g., suicidal ideation vs. suicide attempts).

2.8. Role of the funding source

The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report, or in the decision to submit the paper for publication.

3. Results

3.1. Characteristics of included studies

The number of papers identified by the search strategy, and the number of full-text papers screened for eligibility, are shown in Fig. 1. Studies that met the inclusion criteria ($N = 149$; 48 for psychosis, 29 for violence, 28 for suicidality, 49 for depression and 15 for anxiety) were mostly cross-sectional ($n = 115$), with 27 cohort studies, 4 case-controls studies and 3 randomised controlled trials.

From these eligible studies, 59 were included in the meta-analysis (19 for psychosis, 12 for violence, 15 for suicidality, 16 for depression and 3 for anxiety; see Table 1). Most originated from the USA ($n = 31$; Australia 10, Southeast Asia 8, Europe 6, Canada 2, and 1 each from Saudi Arabia and South Africa) and were cross-sectional ($n = 47$; 11 cohort and 1 case-control study). The average quality of studies included in the meta-analysis (68%) was similar to all included studies (64%). The most common quality shortfalls were failing to identify and control for confounders. Studies on violence suffered from poor measurement of the use of amphetamines (i.e., failure to use reliable or valid measures), and both suicidality and violence studies had weaker outcome measures compared to other mental health outcomes.

There were 31 comparisons for any use of amphetamines and 30 for amphetamine use disorders. There were fewer adjusted comparisons (17 for any use of amphetamines and 9 for amphetamine use disorders). Detailed study characteristics, and effects extracted from each study, can be found in Supplement E. Most comparisons were made within substance-using samples (e.g., within a sample of people who used drugs, those who used amphetamines were compared to those who did not (see Table 1). There were too few included studies to examine publication bias using funnel plots [25].

3.2. Relationship between the use of amphetamines and mental health outcomes

Summary results for the meta-analyses are shown in Table 2 and forest plots for any use of amphetamines and amphetamine

Table 1
Characteristics of the studies included in the meta-analyses.

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Psychosis (any use vs no use of amphetamines)									
Colins (2009) [26]	Belgium	2005–7	Male youth detained from three youth detention centres in Flanders	CS	100	231 (121)	100	16	Any psychotic symptom
Degenhardt (2015) [27]	Australia	NR	Young offenders either serving a community-based order or custodial sentence in Melbourne	CS	75	514 (168)	83	17	Screen for psychosis
Gilfillan (1998) [34]	United States	1993	Individuals entering the psychiatric emergency room of a Dallas hospital	CS	63	56 (2)	50	NR	Diagnosis of psychosis
Glasner-Edwards (2008) [35]	United States	NR	People dependent on methamphetamine entering selected outpatient drug treatment programs	CS	100	526 (156)	40	36	Diagnosis of psychosis
McKetin (2010) [28]	Australia	2008–9	Dance venue attendees in Sydney	CS	88	157 (75)	62	20^	Any psychotic symptom (Psychosis Screen)
McKetin (2013) [29]	Australia	2006–7	Prospective cohort of people recruited on entry to community-based drug treatment programs for methamphetamine use + matched non-treatment controls	CO	82	1064 (612)[a]	72	32	Psychotic symptoms (BPRS)
Riddell (2006) [36]	Australia	2001	NSW prisoners recruited soon after being received into custody	CS	25	921 (302)	NR	NR	Diagnosis of psychosis
Psychosis (amphetamine use disorder vs. no amphetamine use disorder)									
Callaghan (2012) [40]	United States	1990–2000	Patients dependent on amphetamines admitted to Californian hospitals as identified through the California inpatient hospital admissions database	CO	91	10,815,900 (36,162)	35	22	Schizophrenia diagnosis
Dalmau (1999) [39]	Sweden	1985–95	Inpatients admitted to the Department of Psychiatry at Huddinge Hospital	CO	64	773 (89)	NR	NR	Diagnosis of psychotic disorder
Degenhardt (2015) [27]	Australia	NR	Young offenders either serving a community-based order or custodial sentence in Melbourne	CS	75	514 (65)	83	17	Screen for psychosis
Farrell (2002) [41]	United Kingdom	NR	Prisoners within 131 prisons across England and Wales	CS	100	503 (72)	78	NR	Functional psychosis
Kalayasiri (2014) [30]	Thailand	2007–11	People who use methamphetamine and hospitalised for rehabilitation at the Thanyarak Institute	CS	100	727 (581)	47	NR	Methamphetamine-induced paranoia

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Table 1 (*continued*)

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Lechner (2013) [31]	United States	2006–9	Patients sequentially admitted into inpatient substance use treatment facility in Washington D.C.	CS	63	685 (21)	66	43	Psychotic symptoms
Matsumoto (2015) [43]	Japan	2010	Psychiatric in-patients as identified through the 2010 Hospital Survey in Japan	CS	38	480 (350)	71	41	Diagnosis functional psychosis
McKetin (2006) [32]	Australia	NR	A community-based sentinel survey of people who used methamphetamine at least monthly	CS	100	309 (173)	59	28^	Psychotic symptoms (BPRS)
Morasco (2014) [44]	United States	2003–5	Psychiatric in-patients receiving care at a VA facility in the Pacific Northwest	CO	64	1462 (718)	95	50	Psychotic Spectrum Disorder
Polcin (2012) [37]	United States	NR	Individuals residing in Clean and Sober transitional living who were dependent on methamphetamine	CS	63	245 (128)	77	38	Screening for psychotic disorder
Rognli (2015) [42]	Sweden	2001–6	Individuals identified through the Swedish Prison and Probation Service	CO	73	6217 (1676)	88	NR	Hospitalisation due to primary psychosis
Smith (2009) [33]	United States	1990	A community-based sentinel sample of people who injected drugs, used heroin or cocaine	CS	63	424 (109)	72	32	Psychotic symptoms
Toles (2006) [38]	United States	2002	Individuals admitted to the psychiatric emergency department in a Hawaiian hospital	CS	75	904 (166)	59	39	Schizophrenia diagnosis
Violence (any use vs no use of amphetamines)									
Barrett (2013) [54]	Australia	2008–9	Substance dependent individuals admitted to an inpatient detoxification clinic service in Sydney	CS	63	58 (11)	78	35	Violent offending (OTI)
Bunting (2007) [48]	Australia	2006	Individuals with a toxicology-related presentation to the emergency room at St. Vincent's Hospital, Sydney	CS	13	449 (100)	64	NR	Violent, self-destructive behaviour in emergency department
Cartier (2006) [45]	United States	NR	Parolees from two Californian state prisons whereby one prison offered a community substance abuse program and the other did not	CS	75	641 (127)	100	36	Any violent act (self-report)
Greene (1973) [53]	United States	1972	People awaiting pretrial hearing and entering District of Columbia Superior Court Lockup	CS	13	2133 (320)	86	28	Charges for violent offence

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Table 1 (*continued*)

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Iritani (2007) [49]	United States	2001–2	Adolescents drawn from school enrolment rosters and followed into young adulthood	CS	63	7153^ (262)	51	22	Violent behaviour (men)
Iritani (2007) [49]	United States	2001–2	Adolescents drawn from school enrolment rosters and followed into young adulthood	CS	63	6955^ (125)	51	22	Violent behaviour (women)
McKetin (2014) [47]	Australia	2006–7	Prospective cohort of people recruited on entry to community-based drug treatment programs for methamphetamine use + matched non-treatment controls	CO	100	612 (452)[a]	72	32	Severe hostility (BPRS)
Miura (2006) [52]	Japan	2003–4	Adolescents admitted to the Nagoya Juvenile Classification Home	CS	25	1362 (93)	86	17	Confession of violent crime (eg., assault, robbery, rape murder)
Nyamathi (2014) [51]	United States	2010–12	Recently released male parolees identifying as homeless with a history of illicit drug use and recently entered residential drug treatment	CS	50	472 (231)	100	40	Hostility (BSI)
Sigurdsson (2010) [50]	Iceland	2004	Students in secondary education colleges as identified through a population-based survey	CS	38	5150 (499)	49	18	Sexual exploitation or abuse (men)
Sigurdsson (2010) [50]	Iceland	2004	Students in secondary education colleges as identified through a population-based survey	CS	38	5327 (401)	49	18	Sexual exploitation or abuse (women)
Sutherland (2015) [57]	Australia	2013	A community-based sentinel drug-using sample recruited through drug treatment services and peer referrals	CS	88	887 (584)	64	40	Violent offence perpetration (OTI)
[#]Wu (2015) [56]	United States	2004–5	A community-based sentinel MSM drug-using sample recruited through local service agencies, bars, clubs and community events in New York City area	CS	88	74 (57)	100	42	Intimate partner violence (CTS2)
Violence (amphetamine use disorder vs no amphetamine use disorder)									
Watanabe (2005) [46]	Japan	1994	Offenders given a reduction in or exemption from punishment by the court due to mental disorder	CO	43	1108 (52)	88	39	*Re*-offending for violent offences over 7 years

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Table 1 (*continued*)

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Suicide (any use vs no use of amphetamines)									
Capra (2015) [61]	Australia	2011–12	Queensland University of Technology students recruited by student emails and snowballing recruitment methods	CS	75	1610 (162)	24	22	Suicide attempt
Fass (2009) [63]	United States	NR	Youth detainees at Regional Youth Detention Centre in northeast Georgia	CS	38	53 (28)	62	16	Number of suicide attempts
Fernandez (2007) [64]	United States	2003–5	Hispanic MSM recruited via internet and community venues	CS	100	566 (57)	100	31	Suicide attempt
Lowry (2014) [62]	United States	1991–2011	High school students who completed the Youth Risk Behavior Surveys	CS	38	12,654 (442)	49	NR	High suicide risk
Shoval (2006) [65]	Israel	1994–2004	Patients admitted to the adolescent psychiatric inpatient unit at a university affiliated Mental Health Centre	CS	36	178 (8)	66	17	Suicide attempt
Swanson (2007) [59]	United States	2003–5	Patients admitted to Scripps Mercy Hospital as identified through the Scripps Mercy Hospital Trauma Registry	CS	55	4932 (609)	73	37	Suicide attempt
Uchida (1995) [66]	Japan	1993	Psychiatric offenders	CS	38	94 (47)	69	18	Suicide attempt
Suicide (amphetamine use disorder vs no amphetamine use disorder)									
Kalechstein (2000) [58]	United States	NR	Arrestees from the most populous counties in California	CS	50	1580 (170)	NR	NR	Previous suicidal ideation
Matsumoto (2012) [60]	Japan	2009	Outpatients diagnosed with psychoactive substance use disorder who consecutively visited seven hospitals specialising in substance use disorder treatments	CS	50	1420 (190)	78	51	Severe suicidality
McCullumsmith (2013) [70]	United States	2002–7	Enrolees within community-based corrections program in Alabama	CS	75	18,753 (739)	77	32	Suicide attempt
Toles (2006) [38]	United States	2002	Patients admitted to the psychiatric emergency department of a large medical centre in Honolulu	CS	50	904 (166)	59	39	Suicidal
Tunving (1988) [69]	Sweden	1970–78	Individuals consecutively admitted to inpatient drug treatment at St. Lars Hospital for amphetamine, opiate or mixed substance abuse	CO	36	524 (197)	70	23	Completed suicide
Yen (2005) [67]	Taiwan	1999–2002	Adolescents who use methamphetamine recruited from two juvenile abstinence centres in Taiwan	CS	50	200 (65)	63	17	Suicidal ideation

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Table 1 (*continued*)

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Youssef (2016) [68]	Saudi Arabia	2011–12	Male inpatients within Al-Baha Psychiatric Hospital who were abusing two or more substances	CS	63	122 (107)	100	31	Suicidal
Depression (any use vs no use of amphetamines)									
Blazer (2009) [77]	United States	2005–6	Respondents aged 50 or older of National Survey on Drug Use and Health in the United States	CS	75	10,953 (12)	46	>=50	DSM-IV major depression
Briere (2012) [74]	Canada	2003–8	Adolescents within secondary school as identified through the New Approaches New Solutions (NANS) dataset	CO	91	3880 (451)	46	16^	Depression symptoms (CESD >=16)
Daniulaityte (2010) [102]	United States	2003–5	People who used methamphetamine or cocaine in the past 30 days were recruited from Ohio, Arkansas and Kentucky using respondent-driven sampling	CS	75	710 (107)	61	33	Depression symptoms (PHQ-9)
DiMiceli (2016) [71]	Thailand	2011	Adolescents and young adults (14–29 years old) residing in Chiang Mai province	CS	100	2055 (394)	51	20^	Depressive symptoms (CES-$D \geq 22$)
#Embry (2009) [73]	United States	2001–3	Adolescents in Oregon within 8th and 11th grade identified through the Oregon Healthy Teens survey	CS	88	5298 (245)	48	(8th and 11th graders)	Depression symptoms (CES-D)
#Glasner-Edwards (2009) [76]	United States	2004–7	Prospective cohort of adults dependent on methamphetamine entering selected outpatient drug treatment programs in California, Montana and Hawaii	CO	73	526 (NR)	40	33	Major depression (MINI)
#Herbeck (2013) [103]	United States	2009–11	Adults who use methamphetamine recruited based on either receiving treatment for methamphetamine abuse or no enrolment in formal substance abuse treatment	CS	88	373 (26)	59	43	Depression symptoms (BDI)
Liles (2012) [75]	United States	2005–8	Mothers with prenatal amphetamine use recruited shortly after their infant's birth	CO	64	213 (75)	0	23^	Depression symptoms(BDI-II ≥ 14)
Marshall (2011) [104]	Canada	2005–8	People from Vancouver identified through cohorts of At Risk Youth Study (ARYS), Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS)	CO	73	104 (64)	100	33^	Depression symptoms (CES-D >=16) (men)

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Table 1 (*continued*)

Author (year)	Country	Recruitment years	Sample and setting	Design	Quality score (%)	Study N (exposed N)	% Men	Age (mean/ median^)	Outcome
Marshall (2011) [104]	Canada	2005–8	People from Vancouver identified through cohorts of At Risk Youth Study (ARYS), Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS)	CO	73	144 (58)	0	33^	Depression symptoms (CES-*D* >=16) (women)
Plüddemann (2010) [72]	South Africa	NR	Students attending one of the fifteen randomly selected high schools in the South Educational District in Cape Town	CS	88	1561 (74)	47	15	High depression symptoms (BDI)
Depression (amphetamine use disorder vs no amphetamine use disorder)									
Casaletto (2015) [80]	United States	1999–2012	Participants from previous National Institute of Drug Abuse (NIDA) studies who met criteria for methamphetamine abuse of dependence	CS	88	390 (195)	73	38	DSM-IV major depression (SCID)
Lin (1996) [81]	United States	1992	Twin males who both served in the military as identified through the VET Registry	CS	100	1874 (52)	100	45	DSM-III-R major depression (DIS) cf. twins
Moore (2012) [78]	United States	NR	Individuals who are abusing or dependent on methamphetamine and HIV+	CC	63	125 (67)	89	43	DSM-IV major depression (CIDI)
Polcin (2012) [37]	United States	NR	Individuals residing in Clean and Sober transitional living who were dependent on methamphetamine	CS	63	245 (128)	77	38	Screen for major depression (PDSQ)
Toles (2006) [38]	United States	2002	Patients admitted to the psychiatric emergency department of a large medical centre in Honolulu	CS	75	904 (166)	59	39	Major depression
Vik (2007) [79]	United States	NR	Newly incarcerated females in a state prison in Idaho	CS	75	100 (67)	0	31	DSM-IV major depression
Anxiety[b] (amphetamine use disorder vs no amphetamine use disorder)									
Polcin (2012) [37]	United States	NR	Individuals residing in Clean and Sober transitional living who were dependent on methamphetamine	CS	63	245 (128)	77	38	Anxiety symptoms (PDSQ)
Toles (2006) [38]	United States	2002	Patients admitted to the psychiatric emergency department of a large medical centre in Honolulu	CS	75	904 (166)	59	39	DSM-IV anxiety disorder
Vik (2007) [79]	United States	NR	Newly incarcerated females in a state prison in Idaho	CS	75	100 (27)	0	31	DSM-IV panic/generalised anxiety disorder

Abbreviations: Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS), Brief Symptom Inventory (BSI), case-control (CC), Centre for Epidemiologic Studies Depression Scale (CES-D), Composite International Diagnostic Interview (CIDI), cohort (CO), cross sectional (CS), the Revised Conflict Tactic Scale (CTS2), Diagnostic Interview Schedule for Children (DISC), Diagnostic and Statistical Manual for Mental Disorders (DSM), gay, lesbian, bisexual and transgender (GLBT), Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Mini International Neuropsychiatric Interview (MINI), men who have sex with men (MSM), not applicable (NA), National Institute on Drug Abuse (NIDA), not reported (NR), odds ratio (OR), Opiate Treatment Index (OTI), Psychiatry Diagnostic Screening Questionnaire (PDSQ), people who inject drugs (PWID), randomised controlled trial (RCT).

[a] Based on months of observation from 278 participants.

[b] No estimates available for any use.

[#] Adjusted effects only.

[^] Estimated based on reported data.

Table 2
Summary of the pooled unadjusted and adjusted odds ratios for the relationship between the use of amphetamines and mental health outcomes.

	Unadjusted effect OR (95% CI)	Level	*N*	Refs	*n*	I^2	Quality (%)	Adjusted effect OR (95% CI)	Level	*N*	Refs	*n*	I^2	Quality (%)
Any use vs. no use of amphetamines[a]														
Psychosis	2.0 (1.3 – 3.3)**	C	7	[26–28,34–36,105]	3436	80***	77	5.3 (3.4 - 8.3) *** D, O, P	C	1	[105]	1064[b]	NA	82
Violence	2.2 (1.2 – 4.1)*	C	10	[45,48-54,106,107]	30,084	95***	56	1.4 (0.8 – 2.4) D, O, P	C	6	[49-52,56,106]	26,289	25	58
Suicidality	4.4 (2.4 – 8.2)***	D	7	[59,62–66,108]	19,703	84***	56	1.7 (1.0 – 2.9)* D, O, P	E	4	[59,64,108,109]	7066	77**	74
Depression	1.6 (1.1 – 2.2)*	B	7	[71,72,74,75,77,102,104]	19,526	80***	81	1.3 (1.2 – 1.4)*** D, O, P	C	6	[71,73,74,76,103,104]	2684	0	87
Amphetamine use disorder vs. no amphetamine disorder														
Psychosis	3.0 (1.9 – 4.8)***	B	13	[27,30-33,37–44]	81,316	90***	75	2.4 (1.6 - 3.5)*** D, O, P	E	4	[27,30,32,42]	7648	35	88
Violence	6.2 (3.1 – 12.3)**	C	1	[46]	52	NA	43	–	–	0	–	–	–	–
Suicidality	2.3 (1.8 – 2.9)[A] ***	E	7	[38,58,60,67–70]	23,302	57*	57	1.5 (1.3– 1.8)*** D, O, P	E	4	[38,58,60,70]	21,753	0	62
Depression	1.2 (0.5 – 2.7)	D	6	[37,38,78–81]	3584	87***	77	2.8 (0.6 – 11.8)[D]	D	1	[81]	1874[c]	NA	100
Anxiety	0.6 (0.2 – 1.8)	E	3	[37,38,79]	1200	66	69	–	–	0	–	–	–	–

Level of evidence.
A, Experimental or controlled evidence supports this finding.
B, Supported by evidence from cohorts, representative, population-based.
C, Supported by evidence from cohorts of drug users.
D, Supported by evidence from cross-sectional studies, representative population-based, or case-control studies.
E, Evidence supporting this finding based on cross-sectional associations among samples of drug users.
Evidence effect persisted after adjustment for demographics (D), other substance use (O) and premorbid risk (P).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$. Number of studies (N), number of participants (n), not applicable (NA), no data available (-), I^2 Heterogeneity *i*-squared. .
[a] Data not available to conduct the meta-analysis on anxiety for any use of amphetamines vs. no use of amphetamines.
[b] Repeated observations based on 278 participants.
[c] 1874 twin pairs.

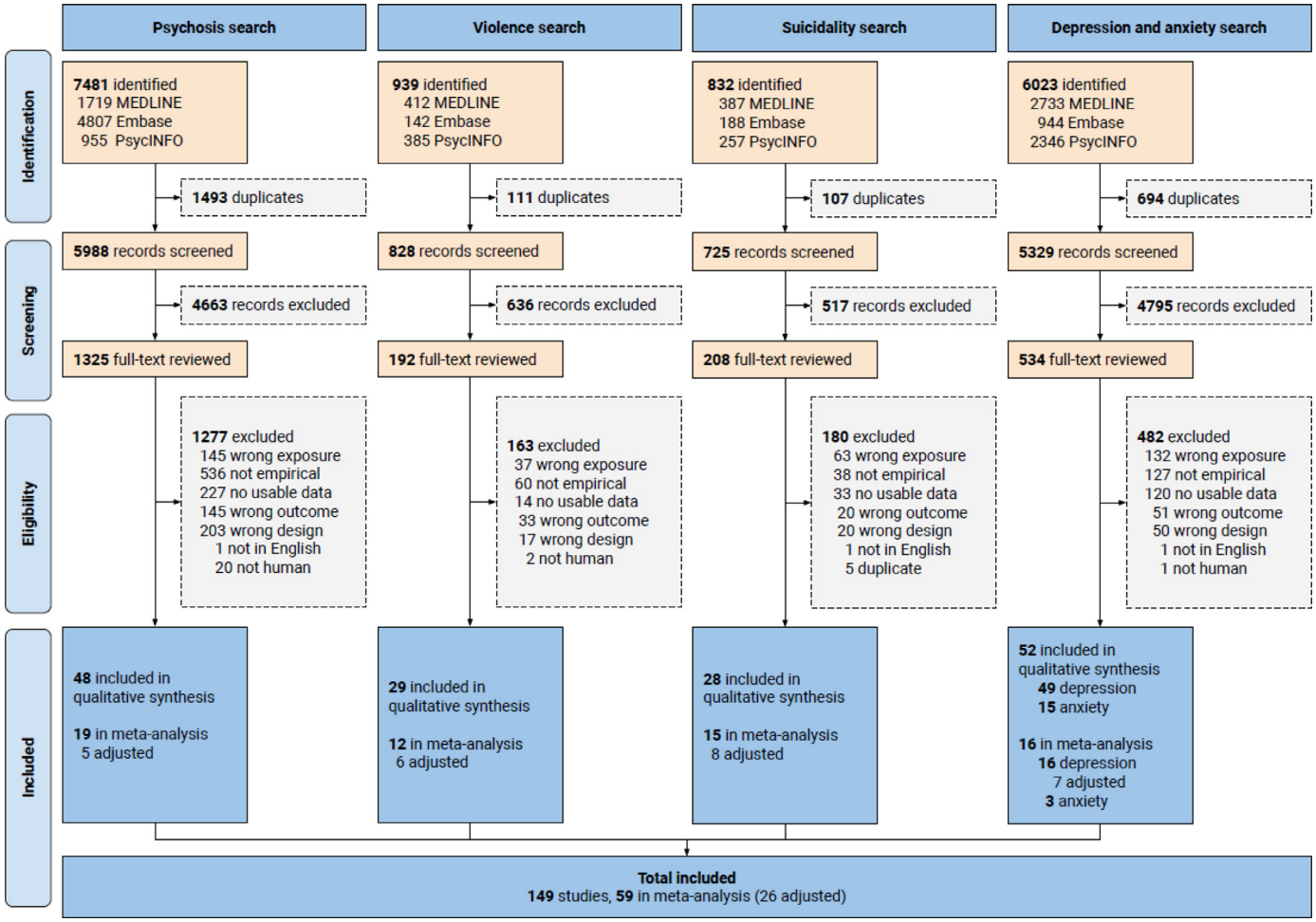

Fig. 1. PRISMA flowchart.

use disorders can be found in Figs. 2 and 3 respectively (the forest plots for anxiety are not presented due to the small number of studies). Meta-analysis results were generally consistent with findings from the narrative reviews of studies not included in the meta-analyses (see Supplement G). There was significant heterogeneity in all effects, which reflects the variation in outcome measures, study methods and settings.

3.3. Psychosis

Any use of amphetamines was associated with double the odds of psychosis, while an amphetamine use disorder was associated with three times the odds (Table 2). Most evidence was derived from high quality cross-sectional studies [26–28,30–38,41,43]. Significant associations were observed in a range of settings (criminal justice [26,27,36,41], drug treatment [29–31], psychiatric [39,43], population-level hospital admissions [40]). Associations were also significant in studies that adjusted for other substance use, demographics and pre-existing psychotic disorders (Table 2).

Pooled ORs tended to be larger for psychotic symptoms than for a diagnosis of a psychotic disorder (psychotic symptoms: any use of amphetamines [26–29] OR 2.7, 95% CI 1.5–4.7 $p = 0.001$, $i^2 = 80\%$ $p = 0.002$, amphetamine use disorder [27,30–33] OR 4.3 95% CI 2.9–6.5 $p < 0.001$, $i^2 = 47\%$ $p = 0.112$; psychotic disorder: any use of amphetamines [34–36] OR 1.3 95% CI 1.0–1.9 $p = 0.087$, $i^2 = 0\%$ $p = 0.604$, amphetamine use disorder [37–44] OR 2.3 95% CI 1.2–4.7 $p = 0.017$, $i^2 = 93\%$ $p < 0.001$).

Longitudinal cohort studies found a dose-related increase in psychotic symptoms during periods when amphetamines were being used [29], and an increased risk of schizophrenia subsequent to the onset of an amphetamine use disorder relative to the general population [40]. However, Rognli et al. [42]. did not find a significant relationship between amphetamine use disorders and subsequent primary psychosis among people released from prison (although subsequent substance-induced psychosis was elevated).

There was some evidence of elevated levels of psychosis relative to other substance use. Callaghan et al. [40]. found a larger risk of schizophrenia for amphetamine use disorders than for most other substance disorders (reported hazard ratios (HR) for amphetamine use disorder relative to those with other SUDs ranged from) except for cannabis (HR 1.2, $p = 0.07$). Two cross-sectional studies found more psychotic disorders associated with amphetamine use disorders when compared to other substance use disorders (opioid use disorders [39] and sedative related disorders [43]).

3.4. Violence

Studies that examined violence as an outcome almost exclusively examined the use of amphetamines (rather than examining amphetamine use disorders) and outcomes were usually behavioural measures of violence (e.g., self-reported interpersonal violence, scales of hostility), rather than convictions for violent offences. Any use of amphetamines was associated with 2.2 times the odds of violence. However, studies that adjusted for other sub-

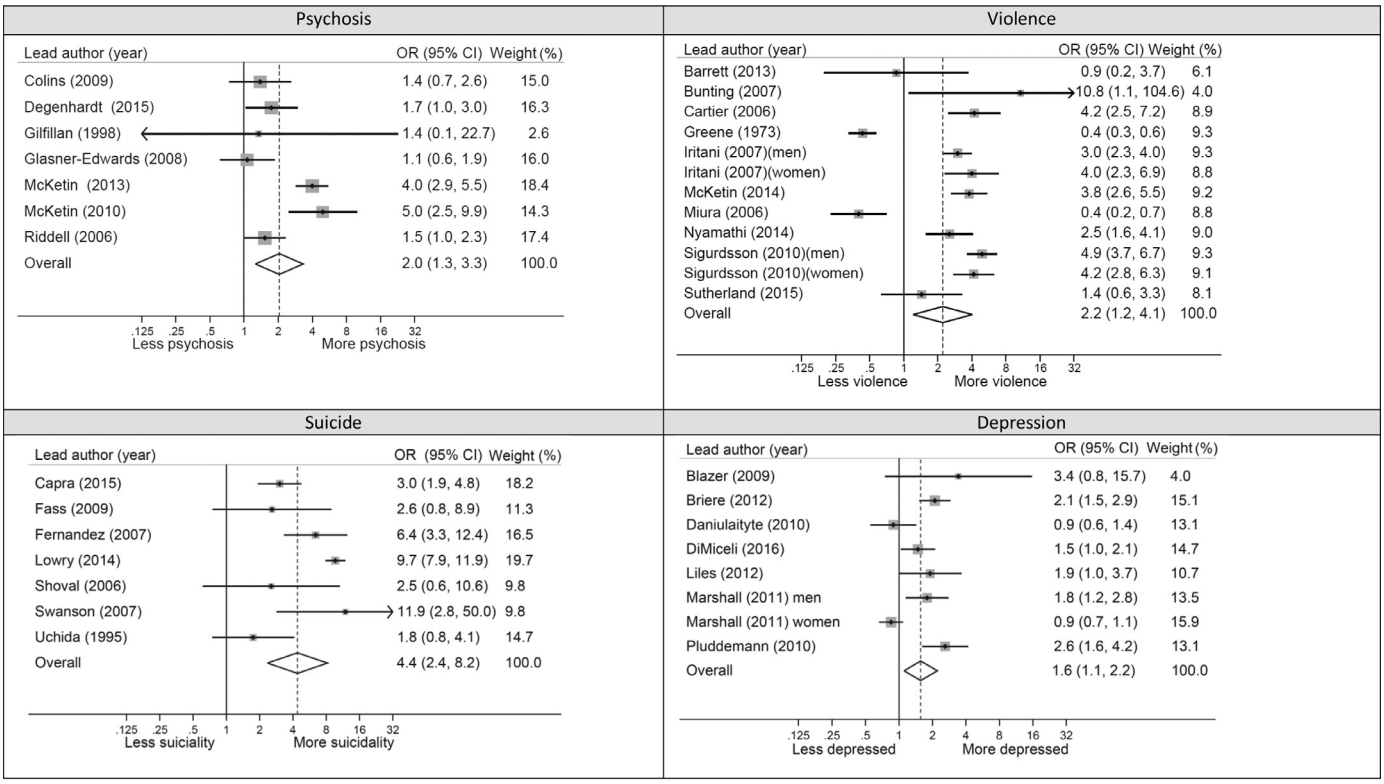

Fig. 2. Forest plots of unadjusted associations between any use of amphetamines and mental health outcomes.

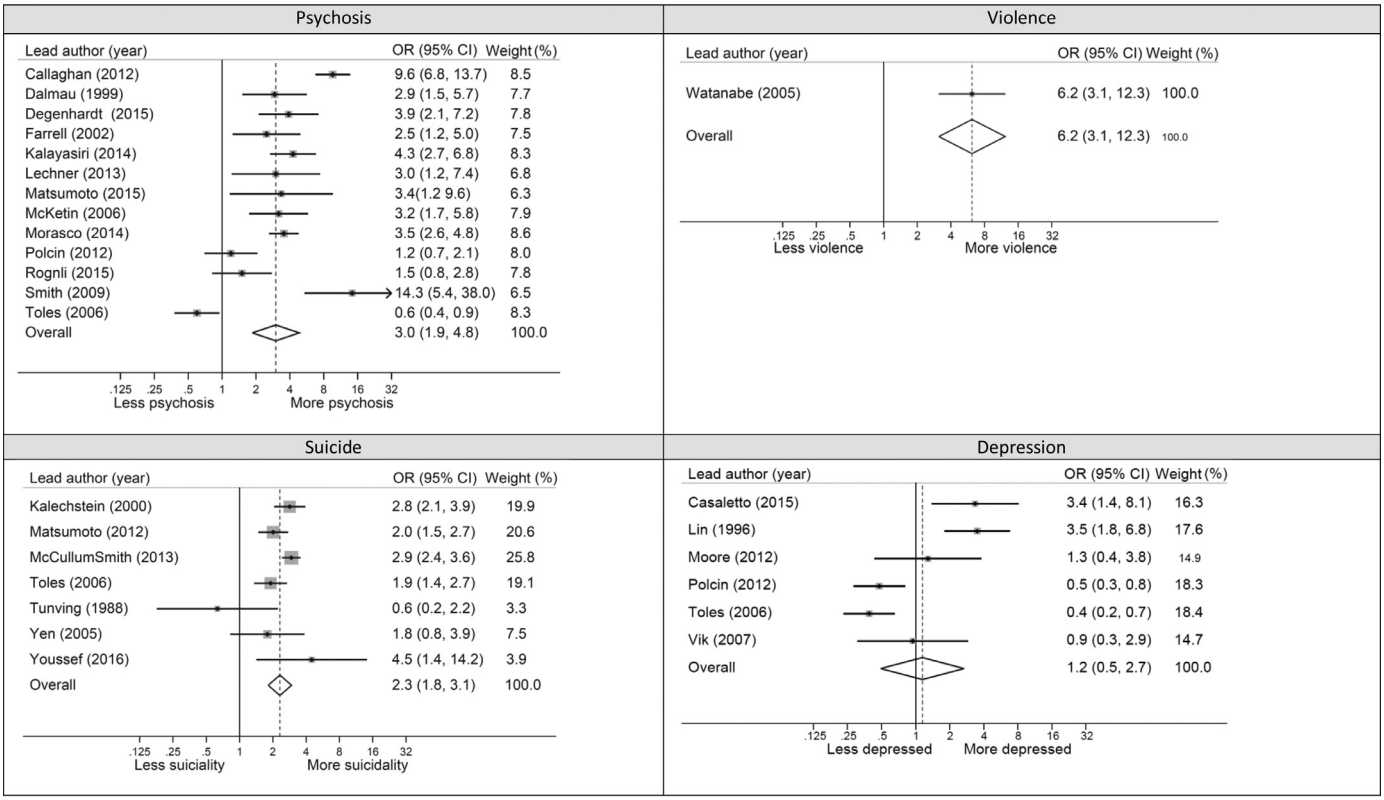

Fig. 3. Forest plots of unadjusted associations between an amphetamine use disorder and mental health outcomes.

stance use, demographics, and premorbid risk factors, yielded a pooled odds of 1.4 which was non-significant (Table 2).

Associations were observed in various settings, including criminal justice settings [45,46], health settings [47,48], and in population level surveys [49,50]. However, the average study quality was low, with poor measurement.

There were differences the strength of the association depending on the measure of violence used. Unadjusted odds ratios were large and consistent for violent behaviour (OR 3.7, 95% CI 3.1–4.5, $p < 0.001$; $i^2 = 34\%$, $p = 0.163$) [47–51]; in contrast there was no significant effect for violent offending (OR 1.0, 95% CI 0.4–2.7, $p = 0.961$; $i^2 = 94\%$, $p < 0.001$) [45,52–55]. One large cross-sectional survey of tertiary students found more perpetration of sexual exploitation/abuse among people using amphetamines [50]; another study of substance users found increased likelihood of intimate partner violence among those using amphetamines [56].

Longitudinal studies provided evidence for increased violent behaviour during periods of when amphetamines were being used (which persisted after adjustment for contemporaneous changes in other substance use) [47], and higher rates of recidivism for violent offences amongst forensic inmates with an amphetamine use disorder post their release [46].

3.5. Suicidality

Any amphetamine use was associated with 4.4 times the odds of suicidality and an amphetamine use disorder was associated with 2.3 times the odds (Table 2). In studies that adjusted for demographics, other substance use, and premorbid factors, these associations were substantially smaller (AORs 1.4 and 1.5 respectively) but still significant (Table 2).

Evidence came mostly from cross-sectional studies. However, consistent effects were observed in a range of populations (arrestees [58], emergency department patients [59], psychiatric patients [38], people in drug treatment [60]) and in representative population-level samples [61,62].

Studies that examined suicide attempts specifically found a 3.6 fold odds of making a suicide attempt amongst people who used amphetamines (95% CI 2.2–5.9, $p < 0.001$; $i^2 = 46\%$ $p = 0.097$) [59,61,63–66]. Most studies that examined suicidal ideation did so for people with amphetamine use disorders, finding 2.2-fold the odds of suicidal ideation (95%CI 1.8–2.8, $p < 0.001$; $i^2 = 22\%$, $p = 0.277$) [38,58,60,67,68]. Only one included study examined completed suicide [69]. This prospective follow-up of drug-treatment entrants found that suicide fatalities were higher than expected for the use of amphetamines, but not significantly elevated relative to opioid use, and that most suicide cases involved premorbid risk [69].

3.6. Depression

Any use of amphetamines was associated with 1.6 times the odds of depression, an association that was smaller (AOR 1.3) but more consistent for studies that adjusted for demographics, other substance use and premorbid risk (Table 2). This association was supported by good quality evidence including large population surveys [71–73] and cohort studies [74,75]. All but one of these studies assessed symptoms of depression (cf. a diagnosis of major depression).

Two longitudinal studies provided evidence to support directionality: Briere et al. [74]. found that the use of amphetamines in adolescent school students significantly increased the odds of subsequent depressive symptoms, even after adjustment for individual and contextual factors. Conversely, Glasner-Edwards et al. [76]. found a reduction in depression amongst drug treatment entrants who had stopped using amphetamines prior to discharge relative to those who did not.

Half of the included studies were conducted in general population samples (or similar), where the association with depression was stronger and more consistent [71,72,74,75,77] (OR 2.0 95% CI 1.6–2.4, $p < 0.001$; $i^2 = 11\%$ $p = 0.346$) than for studies in substance-using samples; in the latter case there was no evidence of an association (OR 1.1 95% CI 0.7–1.7, $p = 0.721$, $i^2 = 76\%$ $p = 0.014$).

There was no significant association between amphetamine use disorders and depression (where major depression was the outcome in all studies). This null effect was driven by studies that were conducted on samples with high levels of substance use and/or other clinical conditions (HIV patients [78], psychiatric inpatients [38], women prisoners [79], people in "sober living houses" [37]).

3.7. [80,81] Anxiety

There were no data available for a meta-analysis on anxiety for any use of amphetamines and only three studies had data on amphetamine use disorders. These showed no significant association between having a use disorder and anxiety (Table 2).

4. Discussion

We have conducted a global review of existing evidence on the association between the use of amphetamines and major mental health outcomes. We found elevated levels of psychosis, depression, suicidality and violence amongst people who use amphetamines. There was significant heterogeneity in the magnitude of associations between studies showing that this is likely to vary depending on the study setting and methods. The evidence in support of a likely causal association varies by outcome (discussed below).

The most compelling evidence for a causal association was between the use of amphetamines and increased risk of psychosis, with consistent moderate to large effects across various populations, including in well-controlled population-level studies and longitudinal studies. Importantly, this effect was seen not only for psychotic symptoms, which are a well-established correlate of acute stimulant use [29], but there was also some evidence of an association with schizophrenia. The evidence for causality in the latter case is more tenuous, and this elevation in risk is likely to reflect the precipitation of the condition in individuals who have a high familial risk [82]. There also appeared to be some level of specificity in this effect, with elevated risk relative to other substance use [39,40,43]. Importantly, effects were not better accounted for by concurrent cannabis use, even though this may confer an additional risk [29]. However, not all premorbid risk factors for psychosis have been controlled for in these studies (e.g., familial risk [83], trauma [84], perinatal factors, immigration and urbanicity [85]) and future studies should control for these factors.

Elevated levels of interpersonal violence were found amongst people who use amphetamines, but the poor quality of studies limits confidence in drawing causal inferences based upon these findings. Moreover, the variety of violence measures used (e.g., aggression vs. violent behaviour that may be economically motivated, such as robbery) made it difficult to interpret pooled effects. The fact that significant large effects were found in two well-controlled population-level studies [49,50] and two longitudinal studies [46,47], suggests that there may be an association between violence and the use of amphetamines, but further research is needed to confirm this relationship and to capture its complexities (e.g., the extent to which it is modified by antisocial personality, polysubstance use or other contextual factors).

Although there was a substantially elevated risk of suicide amongst people who used amphetamines, the quality of evidence was poor, and there was no evidence available from longitudinal studies to understand whether the use of amphetamines either coincided with or preceded suicidality. Moreover, the size of the association was small after adjustment for other substance use, demographics and premorbid risk.

The evidence in favour of a link between the use of amphetamines and depression was much stronger, with evidence from well-controlled population-level studies and longitudinal cohort studies. However, as with suicidality, the size of this association was small after adjustment for other substance use, demographics and premorbid risk. It may be that although both depression and suicide risk are significantly elevated amongst people who use amphetamines, this risk is largely generic to substance use and related demographic and premorbid risk factors.

4.1. Limitations of the evidence

Most evidence was derived from cross-sectional studies; the lack of evidence from cohort studies made it difficult to infer the direction of effects or to demonstrate causality. Samples were often idiosyncratic (e.g., convenience samples) and drawn from substance-using or clinical populations. The scarcity of high-quality population-level studies limits confidence in the generalisability of the findings to the broader population. The quality of measurement was also poor in suicidality and violence studies. Variation in the measurement of mental health outcomes made it difficult to interpret pooled effects (particularly for violence). The small number of included studies also meant that we could not assess publication bias.

There was significant heterogeneity in the size of associations documented by different studies. Such heterogeneity is inevitable and expected when synthesising data across different outcome measures and study methods, and is likely to reflect variation in the true effect size depending on such factors [86]. We used random effects meta-analysis to allow for this heterogeneity; these show overall associations despite variation in individual study outcomes [24]. Unfortunately, the small number of studies that were eligible for inclusion in the meta-analysis meant that we could not robustly examine what factors were driving heterogeneity.

A major weakness in this literature was the failure to identify and adjust for potential confounding variables. Therefore, the unadjusted estimates we have presented are likely to be inflated due to the multitude of risk factors for poor mental health that co-occur with the use of amphetamines. Possible aetiological factors contributing to high rates of mental disorders amongst people who use amphetamines include common risk factors for substance use problems and mental disorders (e.g., familial risk [82], early childhood trauma [84]), the pharmacological effects of amphetamines (e.g., mood enhancement, withdrawal symptoms), the lasting neurophysiological and potential neurocognitive sequelae of chronic heavy use [88], as well as the secondary consequences of substance dependence (e.g., social isolation related to unemployment, stigma) and co-occurring risk factors (e.g., high rates of polysubstance use and low socio-economic background [87]).

In most cases, associations between the use of amphetamines and mental health outcomes were tested in the context of other substance use. These effects are likely to be under-estimates of the odds of mental health outcomes associated with the use of amphetamines in the general population. Effect sizes should also not be directly compared for each mental health outcome because of differences in the study methods (particularly the setting) in each case. Finally, most of the available evidence came from high income countries, whereas use problems from amphetamines are increasingly affecting low to middle income countries [3].

4.2. Limitations of this review

At the outset of conducting this review, we had hoped to explore how different patterns of the use of amphetamines related to mental health outcomes. Despite our best attempts at extracting data on all use patterns, we found that the measures of use were so heterogeneous that they precluded all but the bluntest comparisons. This situation presents a significant challenge for the interpretation of the results, and also for the field, because it remains unclear what level of use of amphetamines conveys a risk. This is important to understand because the majority of people who use amphetamines do so infrequently [89]. Although we also derived effects for amphetamine use disorders, these effects were usually examined in the context of other substance use, so they cannot be compared directly with effects for any use of amphetamines versus no use of amphetamines. We also recognise the potential significant impact of cardiovascular and neuropsychiatric sequelae, such as hypertension, stroke, neurocognitive impairment and Parkinson's disease, on mental health. These were beyond the scope of the current review but have been reviewed elsewhere [88].

4.3. Clinical and policy implications

People who use amphetamines are a high-risk group for poor mental health outcomes. Current treatment responses, and the siloed arrangement of mental health and substance use services in many countries, hinder the provision of care for co-occurring disorders. Examples of where this is problematic include the lack of evidence to guide the prescribing of antidepressants to people who use amphetamines (i.e., where this may be contraindicated or ineffective) [90], and the absence of an evidence base to guide whether or not antipsychotic prophylaxis should be used to manage psychosis related to the use of amphetamines [91]. Limitations are also systemic, with the delivery of drug-related services being skeletal in comparison with the types of support offered to primary mental health care patients [92]. Evidence-based interventions exist for many of the mental health harms associated with the use of amphetamines [93–95] but these need to be applied to, and evaluated for, situations where there is co-occurring use of amphetamines.

The provision of treatment for co-occurring mental health and substance use disorders is hindered by diagnostic issues, particularly whether psychosis or depression is considered to be amphetamine-related or whether it represents a 'primary' or 'independent' disorder [96,97]. Although this is often argued to be because substance-related disorders have a different aetiology that warrants different treatment, there is very little difference between the symptom profile of substance-related mental disorders and their primary counterparts [19,82,98], and often there are no alternative treatments available for the substance-related entity. This can lead to suboptimal management of mental health conditions in cases where symptoms are thought to be amphetamine-related.

Elevated rates of violent behaviour amongst people who use amphetamines indicate that health services need to be equipped to manage this risk. Generic guidelines exist for reducing the risk of violence in health services [95] and managing this risk in psychiatric settings [99], and these need to be adapted and implemented to address violence risk related to the use of amphetamines. Of particular concern is the management of violence risk in acute emergency psychiatry presentations [48], where risks can be compounded by delusional thought processes [100]. Treatment for agitation in acute emergency situations often involves emergency sedation [99], but the safety and feasibility of this approach to people intoxicated with amphetamines needs consideration [48,101]. Support and protection of frontline police and ambulance staff and ap-

proaches to debriefing after acute incidents also need to be given broader consideration.

4.4. Recommendations for future research

Well-controlled population-level surveys and longitudinal cohort studies are needed to understand whether worse mental health outcomes are due to risk factors for mental health problems that co-occur with the use of amphetamines (e.g., low socio-economic status, polysubstance use, exposure to trauma), to demonstrate the direction of effects (i.e., whether the use of amphetamines precedes mental health outcomes), and to eliminate the possibility that poor mental health outcomes and the use of amphetamines are mediated by common antecedents (e.g., familial risk [82]). In doing this, consideration needs to be given to the causal mechanism at play (e.g., effects of intoxication or withdrawal on acute mental health outcomes versus a lasting vulnerability to mental disorders). Comparison of effects between drug classes would help to understand which mental health outcomes are elevated specifically for the use of amphetamines. Such evidence will provide a clearer picture of the likely public health implications of the use of amphetamines globally, and ways in which responses should be implemented (e.g., whether to target premorbid risk factors to reduce harm, whether generic interventions can be applied to all substance use or interventions need to tailored to the use of amphetamines).

5. Conclusion

People who use amphetamines have poorer mental health than people who do not use the drug. There is an urgent need to develop epidemiological research on the use of amphetamines and mental health outcomes in order to better quantify and mitigate this risk. In the meantime, clinical responses to the use of amphetamines need to become better integrated and resourced to enable the management of these co-occurring conditions.

CRediT authorship contribution statement

Rebecca McKetin: Conceptualization, Project administration, Supervision, Methodology, Data curation, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Janni Leung:** Supervision, Methodology, Data curation, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Emily Stockings:** Methodology, Formal analysis, Writing - review & editing. **Yan Huo:** Writing - review & editing. **James Foulds:** Data curation, Validation, Writing - review & editing. **Julia M. Lappin:** Data curation, Validation, Writing - review & editing. **Craig Cumming:** Data curation, Validation, Writing - review & editing. **Shalini Arunogiri:** Data curation, Validation, Writing - review & editing. **Jesse T. Young:** Data curation, Validation, Writing - review & editing. **Grant Sara:** Data curation, Validation, Writing - review & editing. **Michael Farrell:** Writing - review & editing. **Louisa Degenhardt:** Conceptualization, Supervision, Methodology, Data curation, Validation, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2019.09.014.

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