Frequency of healthcare utilisation by adults who use illicit drugs: a systematic review and meta-analysis

Authors

Dan Lewer (1, 3); Joseph Freer (2); Emma King (1); Sarah Larney (4); Louisa Degenhardt (4); Emily J Tweed (5); Vivian D Hope (6); Magdalena Harris (7); Tim Millar (8); Andrew Hayward (1); Dan Ciccarone (9); Katherine I Morley (3, 10)

Author affiliations and addresses

1) UCL Collaborative Centre for Inclusion Health, Institute of Epidemiology and Health Care UCL, 1-19 Torrington Place, London, WC1E 7HB, UK
2) Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Garrod Building, Turner Street, Whitechapel London E1 2AD
3) National Addictions Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 4 Windsor Walk, Camberwell, London SE5 8AF, UK
4) National Drug and Alcohol Research Centre (NDARC), University of New South Wales, 22-32 King St, Randwick NSW 2031, Australia
5) MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, 200 Renfield Street, Glasgow, G2 3AX
6) Public Health Institute, Liverpool John Moores University, Liverpool L2 2QP, UK
7) Department of Public Health, Environments and Society, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place London WC1H 9SH, UK
8) Centre for Mental Health and Safety, The University of Manchester, Oxford Road, M13 9PL, UK
9) Department of Family and Community Medicine, University of California, San Francisco, CA, USA
10) Centre for Epidemiology and Biostatistics, Melbourne School of Global and Population Health, The University of Melbourne, Melbourne, Australia

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ABSTRACT

Aims: To summarise evidence on the frequency and predictors of healthcare utilisation among people who use illicit drugs.

Design: Systematic search of MEDLINE, EMBASE and PsychINFO for observational studies reporting healthcare utilisation published between 1 January 2000 and 3 December 2018. We conducted narrative synthesis and meta-analysis following a registered protocol (identifier: CRD42017076525).

Setting and participants: People who use heroin, powder cocaine, crack cocaine, methamphetamine, amphetamine, ecstasy/MDMA, cannabis, hallucinogens, or novel psychoactive substances; have a diagnosis of 'substance use disorder'; or use drug treatment services.

Measurements: Primary outcomes were the cumulative incidence (risk) and rate of care episodes in three settings: primary care, hospital admissions (inpatient) and emergency department (ED).

Findings: 92 studies were included; 84% from North America and Australia. Most studies focused on people using heroin, methamphetamine or crack cocaine, or who had a diagnosis of drug dependence. We were able to conduct meta-analysis of rates across 25 studies reporting ED episodes and 25 reporting hospital admissions, finding pooled rates of 151 (95% CI 114-201) and 41 (95% CI 30-57) per 100 person-years respectively; on average 4.8 and 7.1 times the general population. Heterogeneity was very high and was not explained by drugs used, country of study, recruitment setting or demographic characteristics. Predictors of healthcare utilisation were consistent across studies and included unstable housing, drug injection and mental health problems. Opioid substitution therapy was consistently associated with reduced ED presentation and hospital admission. There was minimal research on healthcare utilisation by people using ecstasy/MDMA, powder cocaine, hallucinogens or novel psychoactive substances.

Conclusions: People who use illicit drugs are admitted to ED or hospital several times more often than the general population. Further research is needed to understand the quality of healthcare for this group, and healthcare provision in non-acute settings.

INTRODUCTION

Illicit use of drugs is associated with health, social and economic problems. People who are dependent on illicit drugs generally have poor health outcomes, with cohort studies finding mortality rates of up to 15 times the general population, though this varies widely by population and setting [1,2]. As well as overdose, there is excess risk of cancers, cardiovascular, respiratory and liver diseases [3,4]. Excess disease may be due to both the direct effects of illicit drugs and accompanying life circumstances. For instance, people who use illicit drugs are vulnerable to homelessness, imprisonment, and other forms of social exclusion [5], and have high rates of tobacco smoking and harmful alcohol consumption. There are diverse subgroups of people who use drugs, and people who smoke cannabis or use illicit drugs occasionally may have better health outcomes than people who use drugs such as heroin, crack cocaine and methamphetamine [7,8].

Despite the high need for healthcare, qualitative research has identified multiple barriers for people who use illicit drugs. Health professionals may have negative perceptions of patients who use illicit drugs, including poor motivation, seeking prescriptions for non-medical purposes, and violent behaviour; and may feel they lack training and skills to address the needs of this group [9]. Patients report that staff have stigmatising attitudes and that there are barriers to attending appointments, such as inflexible timeslots and transport costs [10]. People who use drugs may delay treatment due to normalisation of pain, fear of stigma in services, and concern about inadequate opioid substitution and pain control when admitted to hospital [11]. These barriers mean that symptoms may not be addressed, leading to presentation late in the course of a disease and use of emergency care. People who use illicit drugs face distinct challenges to healthcare access due to criminalisation and related social exclusion. We have therefore chosen to focus on this group rather than include people who use alcohol, tobacco, or other legal drugs.

Studies of patients visiting emergency departments (ED) have found that 10%-20% report recent use of illicit drugs [12–14]; much higher than the general population, and diagnoses of drug dependence are common among frequent ED users [15,16]. Frequent ED users are particularly likely to use drugs [17]. Such observations have led to a perception that people who use drugs are dependent on ED services, but there is limited population-based research into the frequency and patterns of healthcare utilisation in this group. We aimed to (1) describe the frequencies of healthcare utilisation reported in observational studies of people who use illicit drugs and calculate pooled averages; (2) compare the frequency of healthcare utilisation to the general population; and (3) summarise evidence on the predictors and causes of healthcare utilisation.

METHODS

Review protocol

We conducted a systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [18]. A protocol for this review has been registered with PROSPERO (identifier: CRD42017076525).

Search strategy

We searched Medline, PsychINFO and EMBASE from 1 January 2000 to 27 September 2017 using keywords and MeSH terms related to substance use, healthcare utilisation and observational study designs (full terms included in the Supplementary Information). We also included studies from a manual search of references. On 3 December 2018 we updated our search using the same databases, search terms and inclusion criteria.

Study inclusion and exclusion criteria

We included English-language cohort and cross-sectional studies where 75% or more of participants recently used illicit drugs. Illicit drugs were defined as heroin, powder cocaine, crack cocaine, methamphetamine, amphetamine, ecstasy/MDMA, cannabis, hallucinogens, or novel psychoactive substances. We also included individuals who had a diagnosis of 'substance use disorder' or were recruited from drug treatment services, where we were able to determine that at least 75% used illicit drugs rather than alcohol only. Primary outcomes were the rate or cumulative incidence of ED episodes, hospital admissions and primary care presentation. We excluded studies of participants recruited from acute healthcare services (such as ED), who had acute disease (such as hepatitis A) who were pregnant, or were aged under 18. We also excluded studies with fewer than 30 participants or less than 30 days of observation per participant.

Study quality assessment

Methodological quality was assessed using a modified Newcastle-Ottowa scale [19] that included recruitment bias, non-response, ascertainment of illicit drug use, ascertainment of healthcare utilisation, adequacy of follow-up (for cohort studies), selection of comparison groups (for relative measures), and adjustment (for relative measures). Full details are given in Supplementary Information.

Screening and data extraction

Two authors (DL and JF) independently screened titles and abstracts using Rayyan [20]. There was agreement of 94% (Cohen's Kappa 0.58) and conflicts were resolved through discussion. We accessed full texts and one author (DL, JF or EK) used a piloted data extraction tool to record details including the study design, year, location of the study, recruitment setting (drug treatment services, community or healthcare), participant demographics, predominant drugs used, and denominator and numerator for primary outcomes. Where relative frequencies (such as rate ratios) were reported, we also recorded the ratio and details of the comparison group. Where predictors of healthcare use and cause-specific healthcare use were reported, we marked the study for narrative synthesis. A second author checked that all data was accurate. Queries that could not be resolved were referred to KIM for a final decision.

Analysis

In a narrative review, we described: (i) the range of values of the primary outcomes; (ii) predictors of healthcare utilisation; and (iii) causes of healthcare utilisation by disease.

In quantitative analysis, we displayed frequency rates of ED and inpatient utilisation using forest plots. To provide informal comparisons with the general population, we used published frequencies of healthcare utilisation in the US, Canada, Australia and the UK [21–23], for the general population group with the most similar age- and sex-profile as the study population. Details of the comparison group used for each study are given in the archived dataset.

We conducted random effects meta-analysis to report the average frequency of healthcare utilisation across study populations, limited to results from high-income countries and excluded studies of subgroups likely to have unusual healthcare utilisation (such as people living with HIV and prisoners). We anticipated that the strongest determinants of heterogeneity would be the predominant drug and the country where the study was conducted and therefore stratified results by these variables. As an exploratory analysis of further sources of heterogeneity (not pre-specified), we included each of the following variables in the meta-analysis equation as a moderator [24]: recruitment setting (healthcare, drug treatment services, community or prison), country, study design, study era (1990-1999, 2000-2009, 2010-2018), risk-of-bias score (low or high), age (average age under or over 30) and sex (greater or less than 60% male), using a threshold of $p<0.05$ to identify significant moderators.

All analysis was conducted using R version 3.5.1.

RESULTS

Search results

Our search identified 5,528 studies after deduplication, of which 313 were selected for full-text review and 92 were included. Figure 1 shows a flow-chart of studies. Some studies included groups from distinct regions or with distinct drug use patterns, while others duplicated samples from other studies, and we identified 98 unique populations with 204 relevant data points. The full dataset is available in Supplementary Information.

<< Figure 1 about here >>

Description of study populations

Of the 98 study populations: 53 were in the United States; 16 in Australia; 13 in Canada; 3 in Ireland; 2 each in Taiwan, Italy, New Zealand, UK, Vietnam; and 1 each in Denmark, Finland and Norway.

Although the search strategy included people using any illicit drugs, studies focused on people who used illicit drugs associated with dependence. The largest group was people using opiate substitution (31 populations), mostly recruited from drug treatment services. The next largest was people who inject drugs (29 populations), mostly recruited from community settings. Eight studies focused on cannabis users, seven focused on stimulant users (where injecting was not specified) and five focused on opiate users (where injecting was not specified). Figure 2 shows the number of study populations by predominant drug used and recruitment setting. No studies recruited participants who predominantly used MDMA/ecstasy, powder cocaine, novel psychoactive substances or hallucinogens such as LSD and psilocybin.

<< Figure 2 about here >>

A mean of 68% (sd. 12%) of participants were male and the mean of average ages (reported in some studies as means and in others as medians) was 36.7 (sd. 6.0).

Study quality

58/204 data points had high risk of bias. The main risk was lack of information on non-response. The overall risk of bias was not associated with frequency of healthcare utilisation in meta-analysis (see below). Table 1 summarises results from the quality assessment.

<< Table 1 about here >>

Narrative review

Range of values

Frequencies of all outcomes were high and heterogeneous. ED utilisation ranged from 19 [25] to 1,061 [26] per 100 person-years. The proportion of participants visiting ED in the past 12 months ranged from 10% [27] to 72% [28]. Studies including relative measures showed frequency of ED utilisation of 3-10 times that of comparison groups not using illicit drugs [29–32]. Exceptions were a study in rural Taiwan showing that people who inject heroin had a similar rate of ED presentation as the general population [33], and a study of older people who use cannabis in the United States showing similar odds of ED presentation as those who do not use cannabis [34].

The rate of inpatient episodes ranged from 8 [3] to 852 [29] per 100 person-years. The proportion of participants who were hospitalised in the past 12 months ranged from 8% [35] to 41% [36]. Studies

including relative measures showed frequency of hospital admission of 2-8 times that of comparison groups not using illicit drugs [29–31,37–40]. Again, studies of people who inject drugs in rural Taiwan and older people who use cannabis in the United States were exceptions, showing similar frequencies of hospital admission to the general population [33,41].

There were fewer studies primary care utilisation. Ten studies reported rates, ranging from 231 [42] to 2,087 [37] episodes per 100 person-years. The proportion of participants visiting primary care in the past 12 months ranged from 38% [43] to 90% [44]. Three studies found higher frequency than the general population: a study of insurance data in Canada found people with diagnoses of 'substance abuse' had 4.2 times more primary care visits than those without this diagnosis [37]; a study of patients at a specialist primary care clinic in Ireland that found that those with methadone prescriptions had 4.2 times the odds of a primary care consultation during 6 months, excluding visits for drug-related problems [45]; and a study of people in drug treatment in Australia that found those primarily in treatment for opioids had a median of 12 primary care visits in the past year, compared to 7 for those in treatment for alcohol [44]. Other studies found low absolute frequency of presentation without providing formal comparisons with the general population. For example, only 58% of people who inject drugs in Baltimore saw a primary care doctor over three years [46]; 53% of people who use methamphetamine in Australia saw a primary care doctor over 12 months [47]; and 32% of people who inject drugs in Montreal saw a primary care provider over six months, which was informally compared to 90% in the general population [48].

Studies investigating the frequency of healthcare utilisation in more than one setting showed that primary care episodes are more frequent than ED or inpatient episodes [49–53].

Predictors of healthcare utilisation

ED presentation was consistently associated with regular or recent injecting [54–57], sex work [54,58], diagnosed Hepatitis C [39], diagnosed HIV [31,36,56,59,60] , female sex [36,49,61–64] , homelessness or unstable housing [26,55,56,61,65], crack cocaine or stimulant use [56,61,62], alcohol use [63,66,67], polydrug use [47,68], and mental health problems [36,37,63].

Hospital admission was associated with similar factors: regular or recent injecting [55–57,69,70], diagnosed Hepatitis C [71,72], diagnosed HIV [35,56,69,70,73] , low CD4 count among HIV positive participants [74], female sex [38,39,49,69,70,72,74], homelessness or unstable housing [55,69] alcohol use [72], polydrug use [47], and mental health problems [31,37].

One study (the Melbourne Injecting Drug User Cohort Study) reported similar associations with primary care utilisation: regular injecting, homelessness, cocaine injection and unstable income [48,75].

Opiate substitution treatment was consistently associated with lower frequency of ED presentation and hospital admission [27,36,42,53,57,71,73,76–81] than comparison groups of untreated opiate users. Among substitution patients, consistent medication was associated with a lower rate of ED utilisation [77,78,82]. Some studies looked at different types of treatment. For example, one study found that take-home methadone was associated with lower risk of hospital admission [83]. No studies looked at the effect of treatment for dependence on drugs other than opiates.

Some studies reported non-significant associations with these factors, but none found effects in the opposite direction.

Although some studies show that mental or physical morbidity predicts healthcare utilisation, no studies attempted to show whether increased frequency of healthcare utilisation among people who use illicit drugs was explained by morbidity or other indicators of need for services.

Causes of healthcare utilisation

Studies with cause-specific data showed that a minority of ED and inpatient episodes relate to the direct effects of illicit drugs, such as withdrawal, overdose and intoxication (Figure 3). Infections and particularly skin and soft tissue infections were common causes of ED and inpatient episodes in study populations in Canada [26,31,54,56,59,69], Norway [42] and Taiwan [33]. All infections and particularly pneumonias were important causes of healthcare utilisation in HIV positive opiate users [70,74]. Infections were less important causes of healthcare utilisation in Australia [84,85]. Traumas, injuries and mental health problems were important causes of ED utilisation and hospital admission in all countries [33,54,56,72,84,85].

<< Figure 3 about here >>

Quantitative analysis

We conducted meta-analysis of healthcare utilisation rates (25 studies reporting ED episodes and 25 reporting hospital admission) and 12-month cumulative incidence (11 studies reporting ED episodes and 11 reporting hospital admission). 12 months was the most common period examined in the literature. While we collected data from studies of other periods, we did not analyse this data because the periods varied too widely. We were unable to determine the consistency of the definition of primary care visits across studies and therefore did not attempt quantitative analysis. We restricted the analysis to populations who primarily use heroin, crack cocaine or methamphetamine or have a diagnosis of 'substance abuse disorder' or drug dependence, since there were few studies of people who use cannabis or have other patterns of use.

ED frequencies are shown in figures 4 and 5. An average of 29% (95% CI 24%-35%) of participants visited ED over a 12-month period. The pooled rate was 151 visits per 100 person-years (95% CI 114-201). There was high heterogeneity, with I^2 approaching 100% for both analyses. 32 study populations were matched with published rates for groups of a similar age and sex in the general population. ED presentation ranged from 0.9 to 24.7 times the general population (mean 4.8). Stratified meta-analysis by predominant drug and country did not show significant differences to the overall pooled estimate (see Supplementary Information), and the exploratory meta-regression found no significant moderators.

<< Figures 4 and 5 about here >>

Hospital admission rates and cumulative incidences are shown in figures 4 and 5. An average of 22% (95% CI 15%-31%) of participants were hospitalised over a 12-month period. The pooled rate was 41 episodes per 100 person-years (95% CI 30-57). There was high heterogeneity, with I^2 approaching 100% for both analyses. 27 study populations were matched with published rates for comparable groups in the general population. Hospital admission rates ranged from 1.9 to 35.5 times the general population (mean 7.1). As with the ED results, stratified meta-analysis by predominant drug and country did not show significant differences to the overall pooled estimate, and the exploratory meta-regression found no significant moderators.

DISCUSSION

To our knowledge this is the first systematic review of healthcare utilisation in people who use illicit drugs. The majority of available evidence relates to people who use heroin, methamphetamine and crack cocaine, or have a diagnosis of drug dependence. The results show high but widely varying frequency of ED presentation and hospital admission in this group.

The pooled frequencies of ED and hospital admissions are substantially higher than the general population. In part, this reflects morbidity and greater need for treatment. However, higher utilisation does not necessarily represent good healthcare access. A systematic review in 2009 [86] identified ten studies showing that people with substance use disorders are less likely to receive definitive treatment for specific conditions, despite higher all-cause attendance. For example, a study of veterans with diagnoses of diabetes in the US found that participants with comorbid substance use were less likely to receive foot or retina examinations [87]. Our finding of high utilisation of acute services may not represent good access, but a pattern where primary and preventative healthcare is poor and unplanned healthcare is common.

The results contrast with studies of healthcare among people who use alcohol, which find that drinkers (including heavy drinkers) have lower rates of healthcare utilisation than abstainers [88]. This is likely to be explained by abstention among people who are unwell, rather than a protective effect of alcohol. In contrast, this review found that people who use illicit drugs present to health services much more frequently than the general population. This may be because studies of people who use illicit drugs tend to focus on people who are dependent or use drugs associated with health harms, while studies of alcohol may include large numbers of more moderate drinkers.

Predictors of healthcare utilisation were consistent across studies, including unstable housing, drug injection, and mental health problems. These factors reflect previously identified risk factors for poor health outcomes in people who use drugs [89], and are likely to be associated with greater need for healthcare.

Effectively all of the variation across studies was due to differences between populations rather than within-study error. Despite consistent predictors of healthcare utilisation within studies, we were not able to explain the variation between studies by the predominant drugs used by study participants, the country of the study or any other study-level variables that we collected. Results varied widely even within countries and populations with apparently similar drug use. For example, in the United States, the rate of hospital admission of people in opiate substitution therapy ranged from 51 to 592 per 100 person-years [53,76–78,90–92]. Other research has conceptualised access to health services as a product of individual factors, social contexts and healthcare systems [93,94]. The extent of the heterogeneity in our results is unlikely to be fully explained by individual factors that we did not capture. This suggests that social and healthcare contexts can substantially affect healthcare utilisation. The heterogeneity also highlights the difficulty of generalising results from single studies of healthcare utilisation.

The review identified three main gaps in the evidence. First, 84% of study populations were from the United States, Canada or Australia. We did not identify any studies from low income countries. Second, there were few studies with primary care data, even though existing studies suggest people who use illicit drugs visit primary care more often than acute healthcare settings [49–53], contrary to the stereotype of reliance on ED. Third, almost all studies were of people who use heroin, crack cocaine or methamphetamine, or have a diagnosis of drug dependence. There were only eight studies of people who use cannabis and none of people using MDMA/ecstasy, powder cocaine, hallucinogens, novel psychoactive substances or other drugs.

The results highlight the need for interventions that improve general health outcomes among people who use drugs. Despite a body of research into the effectiveness of opiate substitutes to reduce use of street heroin [95], community-distributed naloxone to prevent overdose deaths [96], strategies to reduce transmission of hepatitis C and improve access to hepatitis C treatment [97], and some strategies to improve treatment of soft tissue infections among people who inject drugs [98], there is limited research into interventions that can improve treatment of health problems that are not specifically associated with drug use. Some studies have shown that Housing First can reduce all-cause ED utilisation, though study outcomes tend to focus on substance use rather than broader health [99]. Case management (where a single case manager is assigned to each patient) can improve drug treatment outcomes, but again evidence of the effect on broader health outcomes is limited [100].

Limitations of the evidence

Most studies in the past have described patients in healthcare services to show the proportion that use drugs, rather than using population-based approaches. This has led in particular to a focus on ED and 'frequent fliers'. To broaden this focus, we synthesised observational studies that often report healthcare utilisation as a secondary outcome. The strength of this approach is that it has shown the wide variation in utilisation of acute hospital services, and in some settings primary care may be attended more frequently. The limitation is that many studies provide limited insight into predictors and patterns of utilisation.

Half the studies in the review (43/92) rely on linked electronic healthcare records, which may have inaccuracies in diagnostic coding. For example, there is evidence that drug-related events such as overdoses are under-recorded in ED data and may be given other diagnostic codes [101,102]. This could contribute to the small proportion of healthcare episodes that are 'drug-related' in our results. In addition, few studies include data from the recent period when synthetic opioids such as fentanyl became more common in North American illicit drug markets. Opioid-related overdoses in the US have increased during this period [103], and the proportion of healthcare episodes that are drug-related may have increased.

The quality assessment identified non-response as the most common problem. This usually resulted from recruitment relying on volunteers or convenience samples rather than a systematic or random approach. These methods are often necessary, since it can be difficult to construct sample frames of people who use drugs. Difficulties in constructing sample frames may also account for the relative lack of studies of people using some illicit drugs, such as powder cocaine, though this may also be due to less severe health outcomes in these groups.

None of the studies included in this review looked at whether higher morbidity explained higher rates of healthcare use, so we were not able to discuss the appropriateness of health service use.

Limitations of the review and meta-analysis

First, we only included English-language studies, which may partially explain the large proportion of studies from English speaking countries – though the English-language restriction only removed 179/5,528 search results. Second, given the heterogeneity of results, meta-analysis is only intended to provide an average across studies rather than a meaningful estimate of healthcare utilisation for any specific population. Third, we defined healthcare utilisation with simple rates or proportions. While this enabled us to perform a traditional systematic review, it meant that the results provide limited insight into the appropriateness or equity of the high rates of healthcare utilisation that we observed. Finally, our review focused on three mainstream healthcare settings (primary care, ED and inpatient hospital care), and did not consider other potential sources of healthcare such as community drug treatment services, which sometimes provide a wider set of interventions. Future research should

consider the full range of healthcare provision for people who use drugs, including opportunities for integration between drug treatment and mainstream health services.

Conclusion

People who use illicit drugs present to acute health services several times more often than comparison groups, across primary care, ED and inpatient settings, reflecting high morbidity. Utilisation rates are highest in those who inject drugs, homeless people and those with mental health problems. Research is needed into the quality of healthcare for people who use illicit drugs, provision of healthcare in non-acute settings, and development of health services that are considered safe and acceptable to this group.

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FIGURES AND TABLES WITH LEGENDS

Table 1: results of quality assessment

	Data points	High risk	Proportion high risk
Recruitment bias	204	28	14%
Non-response	204	121	59%
Ascertainment of illict drug use	204	43	21%
Ascertainment of healthcare utilisation	204	44	22%
Adequacy of follow-up	82	21	26%
Selection of comparison group	47	4	9%
Adjustment for confounders	47	4	9%
Global assessment	**204**	**58**	**28%**

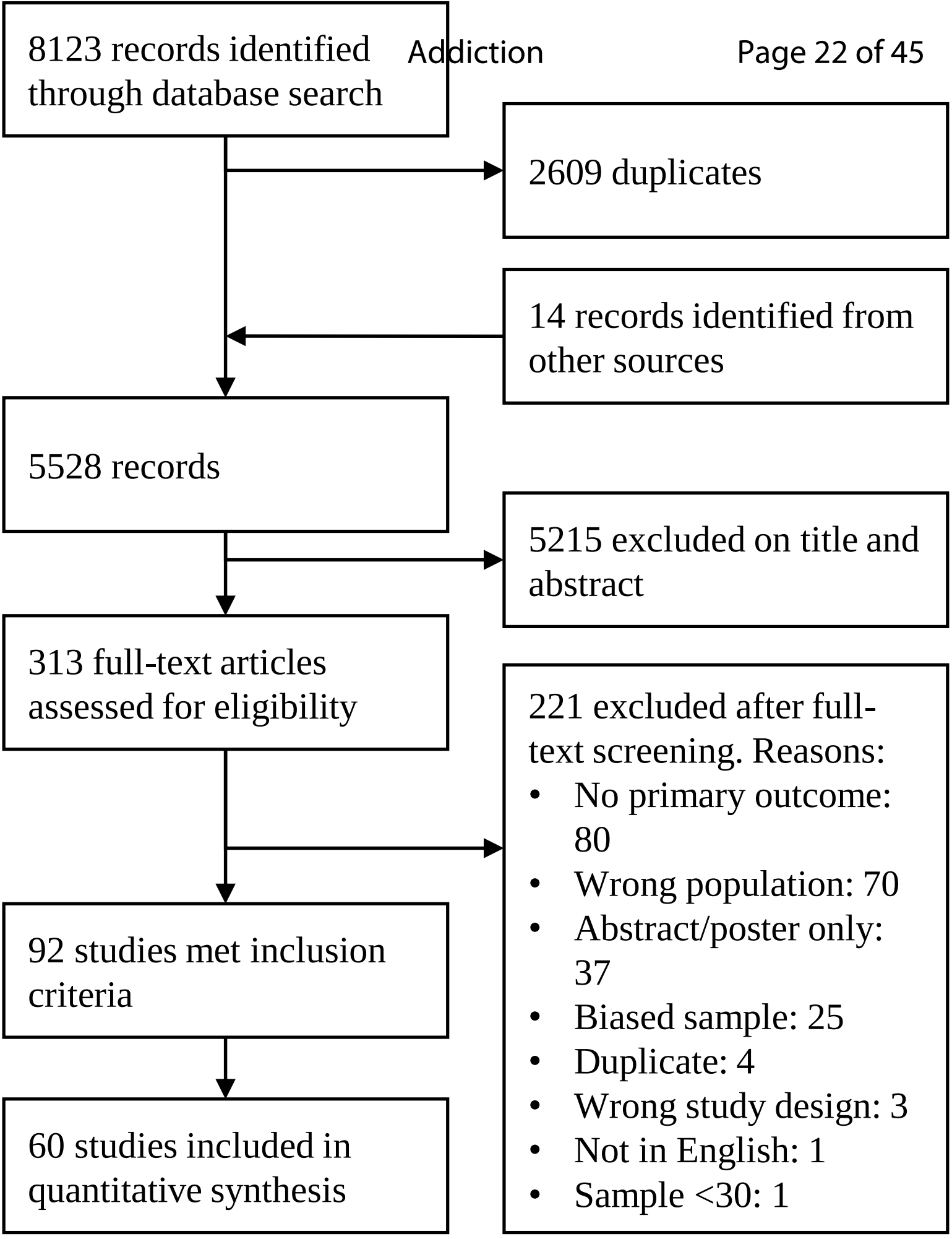
Figure 1: Flow chart of included studies

Figure 2: Unique study populations by predominant drug and recruitment source

Figure 3: Main reason for healthcare utilisation

Figure 4: Forest plot of rates of healthcare utilisation. Studies in grey and italics are not included in the pooled estimate

Figure 5: Forest plot of 12-month cumulative incidence of healthcare utilisation. Studies in grey and italics are not included in the pooled estimate


8123 records identified through database search
2609 duplicates
14 records identified from other sources
5528 records
5215 excluded on title and abstract
313 full-text articles assessed for eligibility
221 excluded after full-text screening. Reasons:
• No primary outcome: 80
• Wrong population: 70
• Abstract/poster only: 37
• Biased sample: 25
• Duplicate: 4
• Wrong study design: 3
• Not in English: 1
• Sample <30: 1
92 studies met inclusion criteria
60 studies included in quantitative synthesis

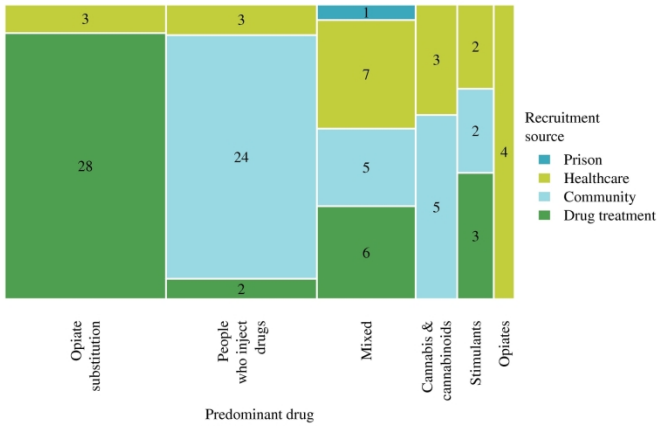


Figure 2: Unique study populations by predominant drug and recruitment source

215x279mm (300 x 300 DPI)

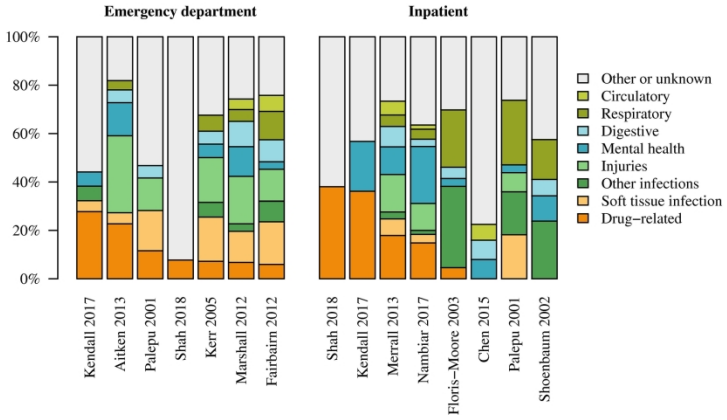


Figure 3: Main reason for healthcare utilisation

215x279mm (300 x 300 DPI)

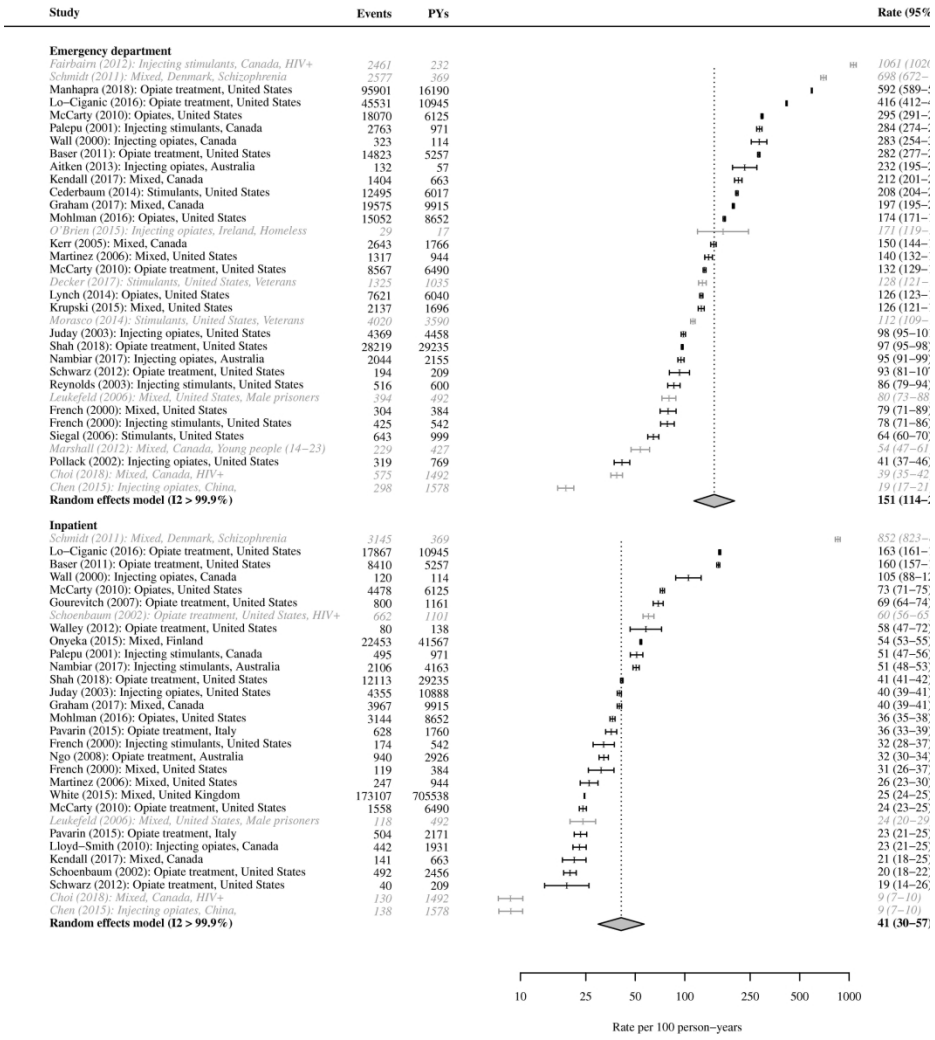


Figure 4: Forest plot of rates of healthcare utilisation. Studies in grey and italics are not included in the pooled estimate

215x279mm (300 x 300 DPI)

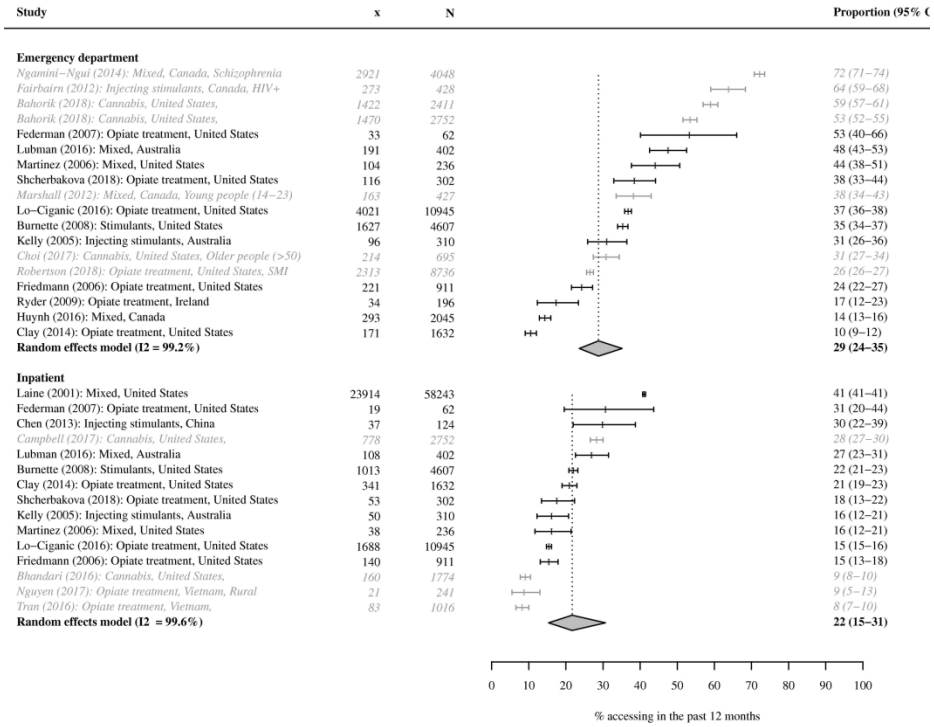


Figure 5: Forest plot of 12-month cumulative incidence of healthcare utilisation. Studies in grey and italics are not included in the pooled estimate

215x279mm (300 x 300 DPI)

Supplementary Information

1. Search terms
2. Modified Newcastle-Ottowa Scale
3. Full list of included studies
4. Stratified forest plots
5. PRISMA checklist

1 Search terms

Medline

1	addict*.mp
2	(chemical adj2 dependenc*).mp
3	(substance adj2 misuse*).mp
4	(substance adj2 abus*).mp
5	substance use.mp
6	drug adj1 user*.mp
7	(drug adj2 abus*).mp
8	(drug adj2 dependen*).mp
9	(inject* adj2 drug*).mp
10	heroin.mp
11	opiate*.mp
12	cocaine.mp
13	crack.mp
14	amphetamine*.mp
15	methamphetamine.mp
16	benzodiazepine.mp
17	mdma.mp
18	ecstasy.mp
19	cannabis.mp
20	Substance-Related Disorders/
21	Amphetamine-Related Disorders/
22	Cocaine-Related Disorders/
23	Heroin Dependence/
24	Substance Abuse, Intravenous/
25	Cannabis/
26	Marijuana abuse/
27	Heroin/
28	Crack Cocaine/
29	Cocaine/
30	Methamphetamine/
31	Amphetamine/
32	Benzodiazepines/
33	or/1-32
34	healthcare use.mp
35	healthcare usage.mp
36	care use.mp
37	care usage.mp
38	service use.mp
39	service usage.mp
40	(hospital* adj3 rate*).mp
41	(hospital* adj3 incidence).mp
42	(hospital* adj3 prevalence).mp
43	("use of" adj2 primary).mp
44	("use of" adj2 secondary).mp
45	("use of" adj2 emergency).mp
46	("use of" adj2 service*).mp
47	("use of" adj2 healthcare).mp
48	("use of" adj2 care).mp
49	(utili* adj2 primary).mp
50	(utili* adj2 secondary).mp
51	(utili* adj2 emergency).mp
52	(utili* adj2 service*).mp
53	(utili* adj2 healthcare).mp

54	(utili* adj2 care).mp
55	(visits adj2 primary).mp
56	(visits adj2 secondary).mp
57	(visits adj2 emergency).mp
58	(visits adj2 service*).mp
59	(visits adj2 healthcare).mp
60	(visits adj2 care).mp
61	Health Resources/
62	Health Expenditures/
63	Primary Health Care/
64	Secondary Care/
65	or/34-64
66	Epidemiologic studies/
67	exp cohort studies/
68	(cohort adj1 stud*).tw.
69	(cohort adj1 analy*).tw.
70	("follow up" adj1 stud*).tw
71	(observational adj1 stud*).tw.
72	Longitudinal.tw
73	Retrospective.tw.
74	cross-sectional.tw.
75	Cross-sectional studies/
76	Surveys and Questionnaires/
77	linkage.tw
78	survey.tw
79	or/66-78
80	33 and 65
81	79 and 80
82	limit 81 to (english language and yr="2000 -Current")

Embase

1	addict*.mp
2	(chemical adj2 dependenc*).mp
3	(substance adj2 misuse*).mp
4	(substance adj2 abus*).mp
5	substance use.mp
6	drug adj1 user*.mp
7	(drug adj2 abus*).mp
8	(drug adj2 dependen*).mp
9	(inject* adj2 drug*).mp
10	heroin.mp
11	opiate*.mp
12	cocaine.mp
13	crack.mp
14	amphetamine*.mp
15	methamphetamine.mp
16	benzodiazepine.mp
17	mdma.mp
18	ecstasy.mp
19	cannabis.mp
20	addiction/
21	drug dependence/
22	amphetamine dependence/
23	cannabis addiction/
24	opiate addiction/
25	cocaine dependence/

26	methamphetamine dependence/
27	heroin dependence/
28	drug misuse/
29	heroin/
30	cannabis/
31	cocaine/
32	amphetamine/
33	methamphetamine/
34	or/1-33
35	healthcare use.mp
36	healthcare usage.mp
37	care use.mp
38	care usage.mp
39	service use.mp
40	service usage.mp
41	(hospital* adj3 rate*).mp
42	(hospital* adj3 incidence).mp
43	(hospital* adj3 prevalence).mp
44	("use of" adj2 primary).mp
45	("use of" adj2 secondary).mp
46	("use of" adj2 emergency).mp
47	("use of" adj2 service*).mp
48	("use of" adj2 healthcare).mp
49	("use of" adj2 care).mp
50	(utili* adj2 primary).mp
51	(utili* adj2 secondary).mp
52	(utili* adj2 emergency).mp
53	(utili* adj2 service*).mp
54	(utili* adj2 healthcare).mp
55	(utili* adj2 care).mp
56	(visits adj2 primary).mp
57	(visits adj2 secondary).mp
58	(visits adj2 emergency).mp
59	(visits adj2 service*).mp
60	(visits adj2 healthcare).mp
61	(visits adj2 care).mp
62	hospital utilization/
63	health care utilization/
64	or/35-63
65	Longitudinal study/
66	Retrospective study/
67	Randomized controlled trials/
68	66 not 67
69	Cohort analysis/
70	(cohort adj1 stud*).mp
71	("follow up" adj1 stud*).tw
72	(observational adj1 stud*).tw.
73	(epidemiologic* adj1 stud*).tw.
74	Longitudinal.tw
75	Retrospective.tw.
76	cross-sectional.tw.
77	linkage.tw
78	survey.tw
79	or/65-78
80	34 and 64
81	79 and 80
82	limit 81 to (english language and yr="2000 -Current")

PsychINFO

1	addict*.mp
2	(chemical adj2 dependenc*).mp
3	(substance adj2 misuse*).mp
4	(substance adj2 abus*).mp
5	substance use.mp
6	drug adj1 user*.mp
7	(drug adj2 abus*).mp
8	(drug adj2 dependen*).mp
9	(inject* adj2 drug*).mp
10	heroin.mp
11	opiate*.mp
12	cocaine.mp
13	crack.mp
14	amphetamine*.mp
15	methamphetamine.mp
16	benzodiazepine.mp
17	mdma.mp
18	ecstasy.mp
19	cannabis.mp
20	Addiction/
21	Drug Abuse/
22	Drug Dependency/
23	Drug Addiction/
24	Substance Use Disorder/
25	Heroin Addiction/
26	Heroin/
27	Opiates/
28	Cocaine/
29	Crack Cocaine/
30	Amphetamine/
31	Methamphetamine/
32	Methylenedioxymethamphetamine/
33	Cannabis/
34	or/1-33
35	healthcare use.mp
36	healthcare usage.mp
37	care use.mp
38	care usage.mp
39	service use.mp
40	service usage.mp
41	(hospital* adj3 rate*).mp
42	(hospital* adj3 incidence).mp
43	(hospital* adj3 prevalence).mp
44	("use of" adj2 primary).mp
45	("use of" adj2 secondary).mp
46	("use of" adj2 emergency).mp
47	("use of" adj2 service*).mp
48	("use of" adj2 healthcare).mp
49	("use of" adj2 care).mp
50	(utili* adj2 primary).mp
51	(utili* adj2 secondary).mp
52	(utili* adj2 emergency).mp
53	(utili* adj2 service*).mp
54	(utili* adj2 healthcare).mp
55	(utili* adj2 care).mp
56	(visits adj2 primary).mp

57	(visits adj2 secondary).mp
58	(visits adj2 emergency).mp
59	(visits adj2 service*).mp
60	(visits adj2 healthcare).mp
61	(visits adj2 care).mp
62	Primary Health Care
63	Health Care utilization
64	or/35-63
65	Longitudinal Studies/
66	Followup Studies/
67	Retrospective Studies/
68	Cohort analysis/
69	(cohort adj1 stud*).tw.
70	("follow up" adj1 stud*).tw.
71	(observational adj1 stud*).tw.
72	(epidemiologic* adj1 stud*).tw.
73	Longitudinal.tw.
74	Retrospective.tw.
75	Cross sectional.tw.
76	cross-sectional.tw.
77	linkage.tw.
78	survey.tw.
79	or/65-78
80	34 and 64
81	79 and 80
82	limit 80 to (english language and yr="2000 -Current")

2 Modified Newcastle-Ottowa scale

Representativeness of people who use illicit drugs

Good representativeness of target population (e.g. random sampling, complete sample)	**1**
Selection process does not ensure representativeness (e.g. snowball sampling, systematic sample), but is clearly described and is unlikely to select low or high healthcare users	**1**
Selection process likely to select low or high healthcare users	**0**
No description of the derivation of sample or unclear	**0**

Non-response

Comparability between respondents and non-respondents was established and/or response rate >=70%	**1**
The comparability between respondents and non-respondents was unsatisfactory and response rate <70% (or not specified)	**0**
No statement or unclear	**0**

Ascertainment of illicit drug use

From structured interview or medical records: clear description of drugs used	**1**
From structured interview or medical records: partial description of drugs used	**1**
Not directly ascertained (e.g. relying drug-related sampling locations)	**0**
No statement or unclear	**0**

Ascertainment of healthcare use

Record linkage	**1**
Self report: questions described and consistently applied	**1**
Self report: questions not described or not consistently applied	**0**
No statement or unclear	**0**

Adequacy of follow-up (cohorts only)

Complete follow up - all subjects accounted for	**1**
Subjects lost to follow up unlikely to introduce bias - small number lost (>=80% follow up) or description provided of those lost showing they are similar	**1**
Follow up rate < 80% and no description of those lost (or description shows they are substantially different)	**0**
No statement or unclear	**0**

Selection of the comparison group (studies with comparative measures (e.g. rate ratios, prevalence ratios)

Drawn from the same population that people who use drugs are drawn from	**1**
Drawn from a different source	**0**
No statement or unclear	**0**

Comparability of groups on the basis of design or analysis (studies with comparative measures (e.g. rate ratios, prevalence ratios)

Study controls for a number of confounders, including the most important (likely to be age)	**1**
Study controls for the most important confounder only	**1**
Study controls for confounders, but not the most important one	**0**
No control for differences between groups	**0**

Determining overall risk of bias

Maximum points available	High risk band
4	0-2
5	0-3
6	0-3
7	0-4

3 Full list of included studies

First author	Title	Year	Journal	Volume	Issue
French	Chronic illicit drug use, health services utilization and the cost of medical care	2000	Soc Sci Med	50	0
Wall	Social costs of untreated opioid dependence	2000	Journal of urban health	77	4
Knowlton	Access to medical care and service utilization among injection drug users with HIV/AIDS	2001	Drug Alcohol Depend	64	0
Laine	Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs	2001	Journal of the American Medical Association	285	18
Palepu	Hospital utilization and costs in a cohort of injection drug users.	2001	CMAJ	165	4
Pollack	The impact of needle exchange-based health services on emergency department use	2002	Journal of General Internal Medicine	17	5
Riley	Health services utilization by injection drug users participating in a needle exchange program	2002	Am J Drug Alco- hol Abuse	28	3
Schoenbaum	Predictors of hospitalization for HIV-positive women and men drug users, 1996-2000.	2002	Public health reports	117	NA
Darke	Health service utilization and benzodiazepine use among heroin users: Findings from the Australian Treatment Outcome Study (ATOS)	2003	Addiction	98	8
Floris-Moore	Gender and hospitalization patterns among HIV-infected drug users before and after the availability of highly active antiretroviral therapy.	2003	Journal of acquired immune deficiency syndromes	34	3
Juday	The role of Medicaid HMO enrollment in the longitudinal utilization of medical care services in a cohort of injecting drug users in Baltimore, Maryland.	2003	Substance Abuse	24	1
Reynolds	Use of emergency room services by out-of-treatment drug users in Long Beach, California	2003	Journal of Addictive Diseases	22	2
Robles	Determinants of health care use among Puerto Rican drug users in Puerto Rico and New York City.	2003	Clinical infectious diseases	37	12
Stein	Injection frequency mediates health service use among persons with a history of drug injection	2003	Drug and Alcohol Dependence	70	2
Turner	Effects of long-term, medically supervised, drug-free treatment and methadone maintenance treatment on drug users<U+0092> mergency department use and hospitalization	2003	Clinical Infectious Diseases	37	S5
Wang	Mortality in HIV-seropositive versus -seronegative persons in the era of highly active antiretroviral therapy: implications for when to initiate therapy.	2004	The Journal of infectious diseases	190	6
Kelly	Health service utilisation among regular methamphetamine users	2005	NDARC Technical Report	NA	0
Kerr	High rates of primary care and emergency department use among injection drug users in Vancouver	2005	Journal of Public Health	27	1
Lundgren	Factors associated with emergency room use among injection drug users of African-American, Hispanic and White-European background	2005	Am J Addict	14	3
Mills	Post-traumatic stress disorder among people with heroin dependence in the Australian treatment outcome study (ATOS): prevalence and correlates.	2005	Drug and Alcohol Dependence	77	3
Friedmann	Do Mechanisms that Link Addiction Treatment Patients to Primary Care Influence Subsequent Utilization of Emergency and Hospital Care?	2006	Medical care	44	1

First author	Title	Year	Journal	Volume	Issue
Leukefeld	A prospective examination of high-cost health services utilization among drug using prisoners reentering the community.	2006	The journal of behavioral health services & research	33	1
Martinez	Impact of Permanent Supportive Housing on the Use of Acute Care Health Services by Homeless Adults.	2006	Psychiatric Services	57	7
Siegal	Emergency department utilization by crack-cocaine smokers in dayton, ohio	2006	Am J Drug Alcohol Abuse	32	1
Darke	Changes in the use of medical services and prescription drugs amongst heroin users over two years	2007	Drug Alcohol Rev	26	0
Federman	Primary care affiliations of adults in a methadone program with onsite care	2007	Journal of Addictive Diseases	26	1
Gourevitch	On-site medical care in methadone maintenance: associations with health care use and expenditures.	2007	Journal of substance abuse treatment	32	2
Baum	Quality of life, symptomatology and healthcare utilization in HIV/HCV co-infected drug users in Miami.	2008	Journal of addictive diseases	27	2
Burnette	Prevalence and health correlates of prostitution among patients entering treatment for substance use disorders.	2008	Archives of General Psychiatry	65	3
Ngo	Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation.	2008	Archives of General Psychiatry	65	4
Skeie	Somatic health among heroin addicts before and during opioid maintenance treatment: A retrospective cohort study	2008	BMC Public Health	8	NA
Benjamin-Johnson	Access to medical care, use of preventive services, and chronic conditions among adults in substance abuse treatment	2009	Psychiatric Services	60	12
Cullen	Chronic illness and multimorbidity among problem drug users: A comparative cross sectional pilot study in primary care	2009	BMC family practice	10	NA
Ryder	Prevalence of problem alcohol use among patients attending primary care for methadone treatment	2009	BMC family practice	10	NA
Hartzler	Dissolution of a harm reduction track for opiate agonist treatment: Longitudinal impact on treatment retention, substance use and service utilization.	2010	International Journal of Drug Policy	21	1
Lloyd-Smith	Determinants of hospitalization for a cutaneous injection-related infection among injection drug users: a cohort study	2010	BMC public health	10	NA
McCarty	Methadone maintenance and the cost and utilization of health care among individ- uals dependent on opioids in a commercial health plan	2010	Drug and Alcohol Dependence	0	0
Robbins	Health and oral health care needs and health care-seeking behavior among homeless injection drug users in San Francisco.	2010	Journal of urban health	87	6
Baser	Cost and utilization outcomes of opioid-dependence treatments	2011	The American journal of managed care	17	NA
Schmidt	The impact of substance use disorders on the course of schizophrenia-A 15-year follow-up study: Dual diagnosis over 15 years.	2011	Schizophrenia Research	130	1
Fairbairn	Emergency department utilization among a cohort of HIV-positive injecting drug users in a Canadian setting	2012	The Journal of emergency medicine	43	2

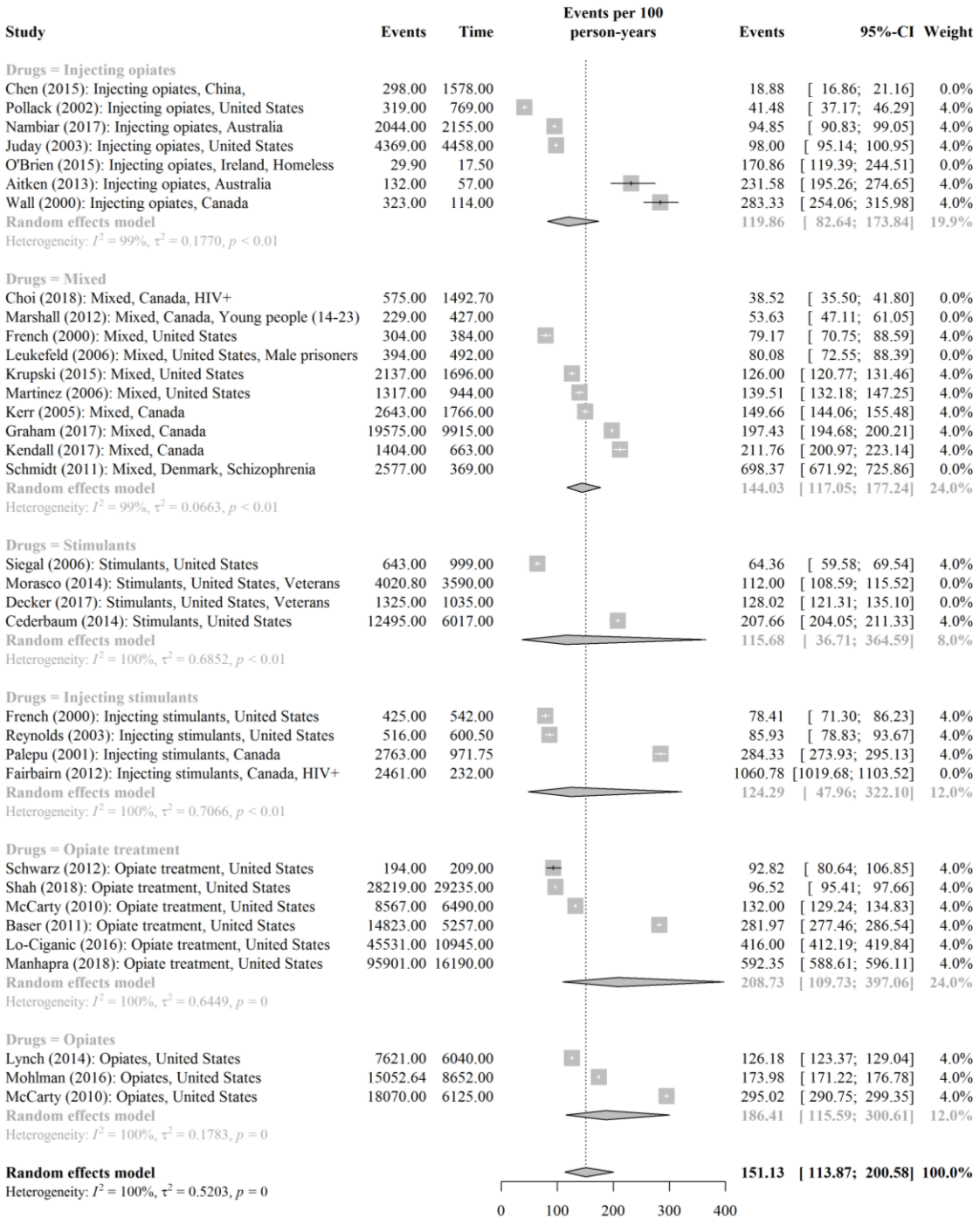
First author	Title	Year	Journal	Volume	Issue
Marshall	Frequent methamphetamine injection predicts emergency department utilization among street-involved youth.	2012	Public Health	126	1
Schwarz	Retention on buprenorphine treatment reduces emergency department utilization, but not hospitalization, among treatment-seeking patients with opioid dependence.	2012	Journal of substance abuse treatment	43	4
Walley	Methadone dose, take home status, and hospital admission among methadone maintenance patients.	2012	Journal of Addiction Medicine	6	3
Aitken	A cross-sectional study of emergency department visits by people who inject drugs	2013	Emergency medicine journal	30	5
Chen	Health care service utilization and associated factors among heroin users in Northern Taiwan.	2013	Addictive Behaviors	38	11
Dietze	The relationship between alcohol use and injecting drug use: Impacts on health, crime and wellbeing	2013	Drug and Alcohol Dependence	128	1
Horyniak	Establishing the Melbourne Injecting Drug User Cohort Study (MIX): Rationale, methods, and baseline and twelve-month follow-up results.	2013	Harm Reduction Journal	10	1
Mark	Psychiatric and medical comorbidities, associated pain, and health care utilization of patients prescribed buprenorphine.	2013	Journal of substance abuse treatment	44	5
Merrall	A record linkage study of hospital episodes for drug treatment clients in Scotland, 1996-2006.	2013	Addiction Research & Theory	21	1
Cederbaum	Utilization of emergency and hospital services among individuals in substance abuse treatment.	2014	Substance Abuse Treatment, Prevention, and Policy	9	NA
Clay	Persistence and healthcare utilization associated with the use of buprenorphine/naloxone film and tablet formulation therapy in adults with opioid dependence	2014	Journal of Medical Economics	17	9
Fuster	No detectable association between frequency of marijuana use and health or healthcare utilization among primary care patients who screen positive for drug use.	2014	Journal of General Internal Medicine	29	1
Lynch	Costs of care for persons with opioid dependence in commercial integrated health systems.	2014	Addiction science & clinical practice	9	NA
Morasco	Comparison of health service use among veterans with methamphetamine versus alcohol use disorders.	2014	Journal of addiction medicine	8	1
Nambiar	A cross-sectional study describing factors associated with utilisation of GP services by a cohort of people who inject drugs	2014	BMC health services research	14	NA
Ngamini-Ngui	High users of emergency departments in quebec among patients with both schizophrenia and a substance use disorder	2014	Psychiatric Services	65	11
Artenie	Visits to primary care physicians among persons who inject drugs at high risk of hepatitis C virus infection: Room for improvement	2015	Journal of Viral Hepatitis	22	10
Chen	Health service utilization of heroin abusers: A retrospective cohort study	2015	Addictive Behaviors	45	NA
Darke	Health Service Utilization among Heroin Users: 11-Year Follow-up of the Australian Treatment Outcome Study Cohort	2015	Addictive Disorders and their Treatment	14	3
Krupski	Clinical needs of patients with problem drug use	2015	Journal of the American Board of Family Medicine	28	5

First author	Title	Year	Journal	Volume	Issue
Nambiar	Mortality in the Melbourne injecting drug user cohort study (MIX)	2015	Harm Reduction Journal	12	1
O'Brien	Health, perceived quality of life and health services use among homeless illicit drug users.	2015	Drug and alcohol dependence	154	NA
Onyeka	Hospitalization in a cohort seeking treatment for illicit drug use in finland	2015	Journal of Substance Abuse Treatment	53	NA
Pavarin	Health status of users of the Bologna local health authority drug addiction treatment services: a study of hospital admissions in the period 2004-2013.	2015	Le infezioni in medicina	23	1
White	Drugs-related death soon after hospital- discharge among drug treatment clients in Scotland: Record linkage, validation, and investigation of risk-factors	2015	PLoS ONE	10	11
Whittaker	Multiply disadvantaged: Health and service utilisation factors faced by homeless injecting drug consumers in Australia	2015	Drug and Alcohol Review	34	4
Bhandari	Marijuana users do not have increased healthcare utilization: A National Health and Nutrition Examination Survey (NHANES) study	2016	European Journal of Internal Medicine	34	NA
Huynh	Factors Influencing the Frequency of Emergency Department Utilization by Individuals with Substance Use Disorders	2016	Psychiatric Quarterly	87	4
Lintzeris	Substance use, health status and service utilisation of older clients attending specialist drug and alcohol services	2016	Drug and Alcohol Review	35	2
Lo-Ciganic	Association between trajectories of buprenorphine treatment and emergency department and in-patient utilization.	2016	Addiction	111	5
Lubman	Characteristics of individuals presenting to treatment for primary alcohol problems versus other drug problems in the Australian patient pathways study	2016	BMC Psychiatry	16	1
Mohlman	Impact of Medication-Assisted Treatment for Opioid Addiction on Medicaid Expenditures and Health Services Utilization Rates in Vermont	2016	Journal of Substance Abuse Treatment	67	NA
Tran	Economic vulnerability of methadone maintenance patients: Implications for policies on co-payment services	2016	International Journal of Drug Policy	31	NA
Wilkins	An exploratory study of the health harms and utilisation of health services of frequent legal high users under the interim regulated legal high market in central Auckland	2016	New Zealand Medical Journal	129	1431
Campbell	The role of marijuana use disorder in predicting emergency department and inpatient encounters: A retrospective cohort study	2017	Drug and Alcohol Dependence	178	NA
Choi	Older adults' marijuana use, injuries, and emergency department visits	2017	American Journal of Drug and Alcohol Abuse	NA	NA
Cucciare	Longitudinal associations between outpatient medical care use and substance use among rural stimulant users	2017	American Journal of Drug and Alcohol Abuse	NA	NA
Decker	Long-term outcomes after residential substance use treatment: Relapse, morbidity, and mortality.	2017	Military Medicine	182	1
Graham	How Much Do Mental Health and Substance Use/Addiction Affect Use of General Medical Services? Extent of Use, Reason for Use, and Associated Costs	2017	Canadian Journal of Psychiatry	62	1

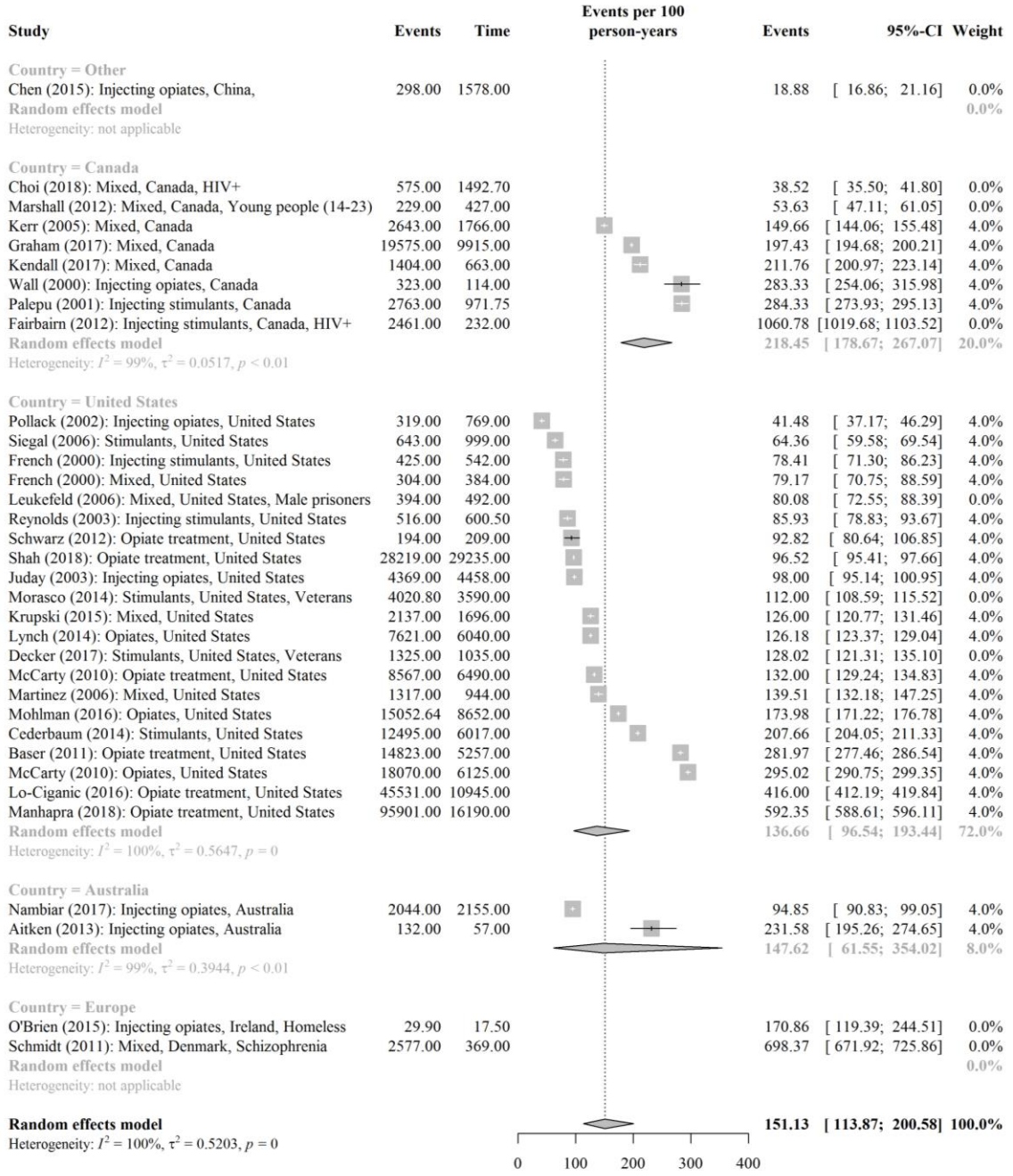
First author	Title	Year	Journal	Volume	Issue
Kendall	A cohort study examining emergency department visits and hospital admissions among people who use drugs in Ottawa, Canada	2017	Harm Reduction Journal	14	1
Nambiar	A prospective cohort study of hospital separations among people who inject drugs in Australia: 2008<U+0096>2013	2017	BMJ Open	7	8
Nambiar	Frequent emergency department presentations among people who inject drugs: A record linkage study	2017	International Journal of Drug Policy	44	NA
Nguyen	Quality of life and healthcare service utilization among methadone maintenance patients in a mountainous area of Northern Vietnam.	2017	Health and Quality of Life Outcomes	15	1
Bahorik	Alcohol, marijuana, and opioid use disorders: 5-Year patterns and characteristics of emergency department encounters.	2018	Substance abuse	0	0
Beaulieu	Major depressive disorder and access to health services among people who use illicit drugs in Vancouver, Canada. [References].	2018	Substance Abuse Treatment, Prevention, and Policy	0	0
Choi	Impact of depression and recreational drug use on emergency department encounters and hospital admissions among people living with HIV in Ontario: A secondary analysis using the OHTN cohort study.	2018	PLoS ONE	0	0
Han	Marijuana use by middle-aged and older adults in the United States, 2015-2016.[Erratum appears in Drug Alcohol Depend. 2018 Sep 25;192:171; PMID: 30266000]	2018	Drug & Alcohol Dependence	0	0
Manhapra	Three-year retention in buprenorphine treatment for opioid use disorder among privately insured adults.	2018	Psychiatric Services	0	0
Robertson	Associations between pharmacotherapy for opioid dependence and clinical and criminal justice outcomes among adults with co-occurring serious mental illness.	2018	Journal of Substance Abuse Treatment	0	0
Shah	Healthcare utilization and costs associated with treatment for opioid dependence.	2018	Journal of Medical Economics	0	0
Shcherbakova	Treatment Persistence Among Insured Patients Newly Starting Buprenorphine/Naloxone for Opioid Use Disorder.	2018	Annals of Pharmacotherapy	0	0

4 Stratified forest plots

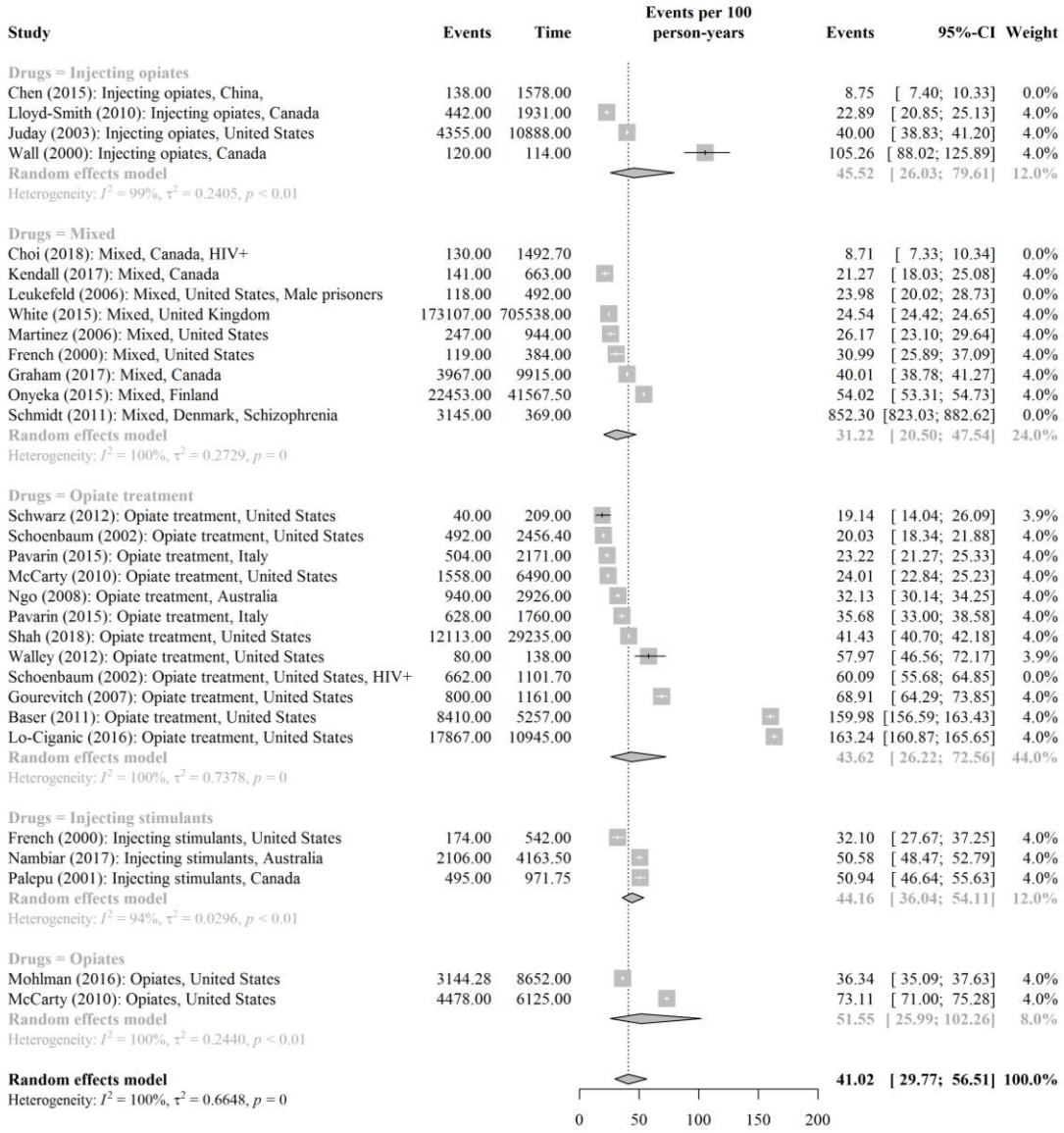
ED rates by predominant drug



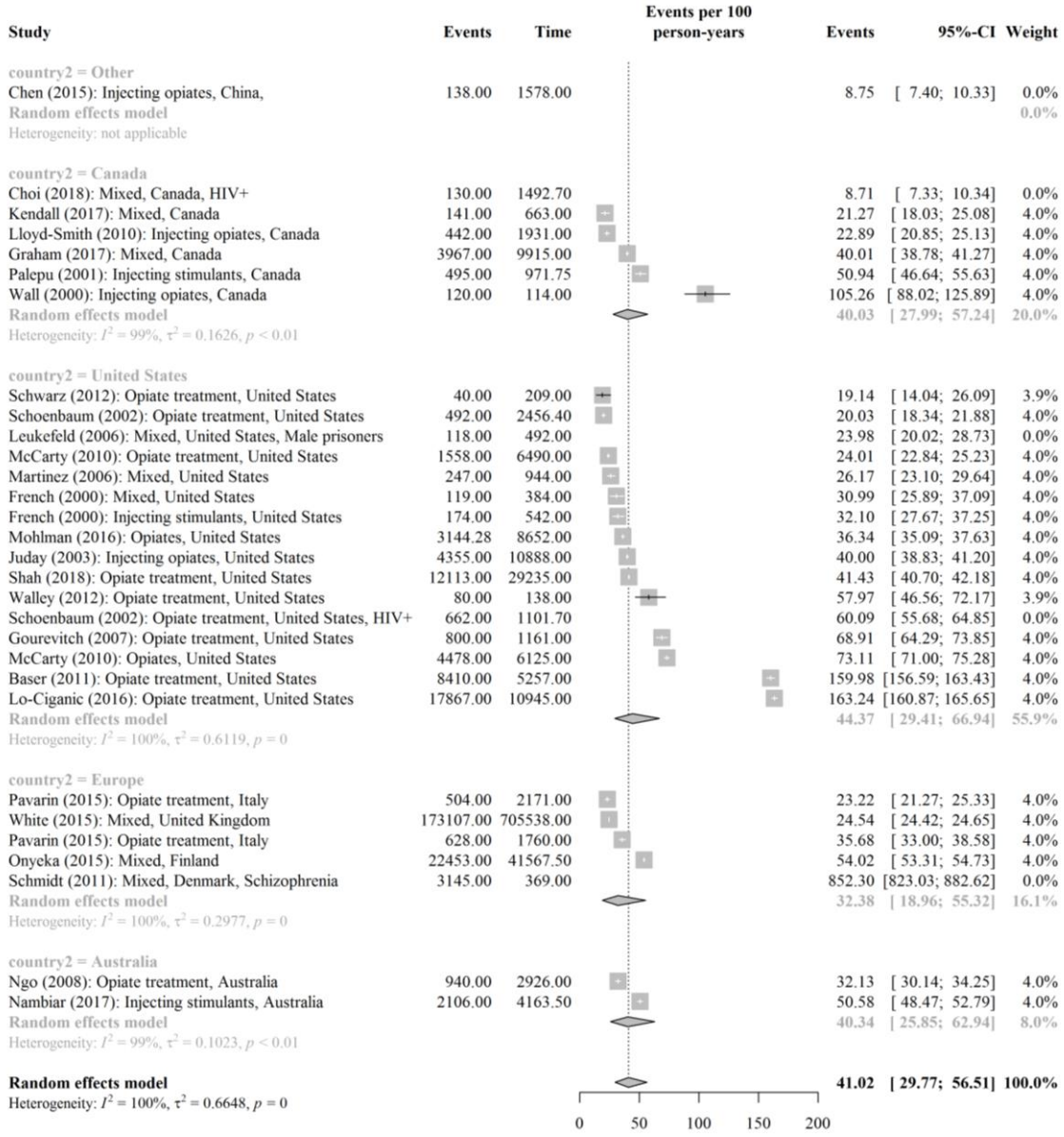
ED rates by country



Inpatient rates by predominant drug



Inpatient rates by country



5 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p4 (no intervention)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. Info.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p4

Section/topic	#	Checklist item	Reported on page #
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p6 Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Info.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1 Suppl. Info.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	pp7-8 Figs. 4-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p6 Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	pp7-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	pp10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p1