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Title

Prevalence of respiratory conditions among people who use illicit opioids: a systematic review

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Running head

Respiratory health of people who use opioids

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Declarations of competing interest

None

Abstract

Background and Aims

There are growing concerns over the respiratory health of people who use illicit opioids due to high rates of opioid inhalation and tobacco smoking in this group. This study aimed to summarize the evidence relating illicit opioid use with poor respiratory health.

Methods

A systematic review of the literature on the association between illicit opioid use and respiratory health was undertaken in accordance with PRISMA guidance (Prospero ID=CRD42017059953). Electronic searches of MEDLINE, Embase, PsycINFO, CINAHL and the Cochrane Library databases were undertaken (English language, published January 1980 - November 2018). All study designs excluding case studies were considered. Studies were undertaken in community and hospital settings in the US (n= 23), UK (n=7), Australia (n=7), Netherlands (n=2), Canada (n=2), Ireland (n=1), Spain (n=1) and Iran (n=1). Measurements of respiratory disease, including asthma and chronic obstructive pulmonary disease (COPD) and related symptoms were extracted. Data on respiratory related deaths and hospital admissions were also extracted. Meta-analysis of prevalence data was undertaken using a random effects meta-analysis model with parameters estimated using Markov chain Monte Carlo simulation.

Results

Meta-analyses estimated prevalence of asthma in people who inject illicit opioids as 8.5% (95% predictive interval (PrI): 0.2%, 74.0%) and as 20.2% (95% PrI: 4.2%, 59.2%) in people who inhale illicit opioids. Prevalence of COPD in people who inject illicit opioids was estimated as 2.7% (95% (PrI): 0.0%, 50.4%) and as 17.9% (95% PrI: 0.6%, 89.5%) in people who inhale illicit opioids. There was evidence of moderate to extreme heterogeneity across studies.

Conclusions

There is evidence of increased burden of respiratory diseases in people who use illicit opioids. Due to heterogeneity of study design and samples it is difficult to gain accurate estimates of the prevalence of respiratory disease in this population.

Introduction

Increased rates of inhaled opioid use and high prevalence of tobacco smoking in people who use illicit opioids has led to growing concerns over the respiratory health of this population. Recent statistics showed that 68% of the population entering treatment for illicit opioid use in England smoked tobacco and 39% of new presentations in 2017-18 had never injected opioids (1). In addition, the same report found that 45% of people in treatment for illicit opioid use used crack cocaine and 17% used cannabis. Reviews of the literature on substance misuse and asthma suggested that the inhalation of opioids, such as heroin, can trigger severe asthma exacerbations (2, 3). However, there remains a need to fully identify the impact of illicit opioids use on other respiratory conditions such as chronic obstructive pulmonary disease (COPD). COPD is the second most common cause of emergency hospital admissions and accounted for 5.3% of all deaths in the UK in 2012 (4).

The primary aim of the review was to summarise the evidence on the prevalence of chronic respiratory disease in people who use illicit opioids in comparison to the general population. The review summarised prevalence of asthma, COPD and other respiratory disease and symptoms of poor respiratory health (e.g. wheezing, dyspnoea) in people who were using or had used illicit opioids. Individuals who received treatment for opioid dependence (e.g. methadone maintenance patients) were included. Samples of individuals who were prescribed opioid analgesics but who had no history of opioid dependence were not included in the review, as these individuals are unlikely to have been exposed to similar risk factors for poor respiratory health (e.g. high rates of smoking of tobacco and other substances). To further understand the burden of respiratory disease in this population, secondary aims of the review included summarising evidence relating illicit opioid use to respiratory related deaths and hospital admissions.

Methods

Registration

This systematic review was registered in the PROSPERO database (registration number: CRD42017059953) and we adhered to the PRISMA guidance in the conduct of the review (5).

Eligibility criteria

Studies were eligible for inclusion if the study population had illicitly used opioids and measures of respiratory health were recorded. All English language study types excluding case studies, case

reports, conference proceedings and reviews were considered. Inhalation of heroin became internationally prominent during the 1980s (6), therefore studies published prior to 1980 were excluded.

Information sources and search strategy

The following databases were searched: MEDLINE, CINAHL, PsycINFO, EMBASE and the Cochrane Library. Searches were conducted in November 2018. A combination of keyword and Medical Subject Headings (MeSH) relating to illicit opioid use and respiratory health were included in the search strategy. Search terms included: "heroin", "methadone", "opiate" "opioid", "drug", "substance", "addict", "abuse", "use", "misuse", "disorder", "dependence", "chronic obstructive pulmonary disease", "respiratory", "lung", "pulmonary", "airway", "airflow", "disease", "disorder", "obstructive", "asthma" and "COPD". Further details of the search strategy are provided in Table S1. References from all included articles were manually searched to identify further studies suitable for inclusion.

Study selection

Following removal of duplicates, two reviewers (JH, AB) independently screened the studies against the inclusion criteria on the basis of titles and abstracts. Full text copies of articles deemed suitable for inclusion and manuscripts which provided insufficient information in the title and abstract were then independently assessed by the two reviewers. Discrepancies in eligibility of studies were resolved through discussion with a third independent clinician reviewer (CM).

Data Extraction

A data extraction form was developed to extract data on study characteristics and results from the included studies. Data extraction was undertaken independently by JH and AB and discrepancies were resolved through discussion with CM. The following study details were extracted: setting, method of opioid use, age, country, sample size, design. Measures of respiratory health extracted included prevalence of asthma, COPD (Including emphysema and chronic bronchitis) and other respiratory disease in people who use illicit opioids and comparator groups. Respiratory symptoms (wheezing, dyspnoea, coughing), lung function test results and self-report measures (Lung function questionnaire, Asthma Control Test, Asthma quality of life) were also extracted. Estimates of illicit opioid use in

respiratory related deaths and respiratory related admissions were extracted. Statistical test results and adjustment for confounders were reported in all studies.

Data synthesis and analysis

When possible, prevalence data was analysed using a random effects meta-analysis model with parameters estimated using Markov chain Monte Carlo simulation (for further details on analysis see Supplementary data). Results are presented as study-specific population shrunken estimates; the random effects mean and 95% credible interval; and the 95% predictive interval (PrI) for the prevalence in a new study. A narrative synthesis of studies not included in the meta-analyses was undertaken. The methods of data synthesis and analysis relating to each outcome are described below:

Asthma

In order to understand the potential impact of heroin inhalation on the prevalence of asthma in opioid users, studies were pooled in relation to method of opioid use.

Three studies reported prevalence of asthma in IV using samples to controls (7-9), with only one of the studies comparing prevalence with non-using populations (9). Consequently, meta-analysis of prevalence data in the IV using samples was undertaken.

Five studies reported on asthma diagnoses in individuals who primarily identified as heroin smokers (8, 10-13). Two studies compared asthma prevalence with heterogeneous control groups (8, 10). Prevalence data from all five studies were therefore pooled for meta-analysis.

COPD

In order to understand the potential impact of heroin inhalation on the prevalence of COPD in opioid users, studies were pooled in relation to method of opioid use where possible. Two studies reported COPD prevalence in samples consisting predominantly of IV users (7, 8), with neither comparing prevalence with entirely non-using populations. Meta-analyses of the prevalence data from these studies was subsequently undertaken.

Three studies reported prevalence of COPD in heroin smokers (8, 11, 13), with only one study including a control group (8). Meta-analyses of the prevalence data from these studies was undertaken.

Respiratory related deaths

Six studies reported associations between illicit opioid use and cases of asthma related deaths (14-19). Two studies by the same research group were not included in the meta-analyses as it was unclear from reports if all deaths with available toxicology reports included were caused by asthma (15, 17). A further study reporting associations between asthma deaths and illicit opioid use was also excluded from the meta-analysis as prevalence data on illicit opioid use was not reported (19). Data on the prevalence of illicit opioid use in cases of asthma deaths was therefore available from three studies (14, 16, 18) and subsequently pooled for meta-analysis. Five studies also reported associations between illicit opioid use and other respiratory related deaths (19-23). These studies could not be pooled for analysis due to heterogeneity of disease classification.

Hospital admissions

Six studies reported prevalence of illicit opioid use in hospital admissions for asthma exacerbations (8, 24-27). Two of these studies reported prevalence of illicit opioid use in hospital admissions for asthma exacerbations in comparison to controls (24, 25). Heterogeneity of control groups precluded meta-analysis of these data. Furthermore, the case control study reported by Krantz and colleagues (25) did not report data on an individual level. Prevalence data from five of the six studies was therefore available for meta-analysis. The remaining studies which reported associations between illicit opioid use and hospital care for respiratory disease could not be pooled for analysis due to heterogeneity of outcomes (10, 20, 28).

Other respiratory disease and symptoms

A narrative synthesis of the other respiratory health outcomes across the studies was undertaken. The heterogeneity of study design and outcomes precluded meta-analysis.

Quality assessment

Guidelines on the evaluation of prevalence studies were used to perform quality assessment of the included studies (29). Studies were given a score of 0 to 8 based on fulfilment of 8 criteria relating to representativeness of a defined target population, use of reliable and valid measures and the quality of statistical analysis (see table 1).

Results

Study selection

The search identified 25,834 papers which were potentially suitable for inclusion (Figure 1). Following removal of duplicates, title and abstract screening was undertaken for 21,151 studies. Overall, 514 articles were included for full text screening, with 387 excluded. A total of 44 studies were included in the final analysis, with 2 of these studies reported in one article (6). These 44 studies were undertaken in community and hospital settings in the US (n=23), UK (n=7), Australia (n=7), Netherlands (n=2), Canada (n=2), Ireland (n=1), Spain (n=1) and Iran (n=1). Overall, 22 studies excluded individuals aged under 18 years, 11 studies included individuals under the age of 18 years and 11 studies did not report age ranges.

Quality appraisal

Overall, 12 studies reported prevalence of respiratory disease with non-using comparator groups (9, 10, 19, 20, 23, 25, 26, 30-34). None of the included studies met criteria on all quality domains, individual study quality scores are presented in table 1. All the studies fulfilled basic criteria regarding the definition of the target population, through description of average age, gender and treatment setting. Other potentially important sample characteristics such as ethnicity (n=28) and socioeconomic status and/deprivation (n=14) were not consistently reported. Use of randomisation was fully applied in few studies (n=3) and due to the use of retrospective data, criteria regarding response rate was not applicable to the majority of studies.

The majority of studies fulfilled criteria regarding the validity and reliability of measures. Three studies were deemed not to have fulfilled this criteria due to use of self-reports (12) and prevalence data being reported as a percentage of admissions or consultations, as opposed to on an individual level (25, 35). Overall, 16 studies made adjustments in the analysis or matched samples to control for potentially confounding factors. Of these, seven studies controlled for tobacco smoking (8-10, 19, 26, 33, 36). Other common limitations included not taking into account the how dosage, frequency of opioid use and method of opioid use impacted upon respiratory health and not clearly defining which type of respiratory diseases were being studied.

Asthma prevalence

The prevalence of asthma in people who use illicit opioids was recorded in 14 studies undertaken in the UK (11-13, 37, 38) US (7-9, 34, 35, 39), Australia (40, 41) and Spain (10) (Table 2). Three studies reported asthma prevalence primarily in people who used illicit opioids intravenously (IV) (1-17%). Prevalence data from three studies were suitable for meta-analyses (7-9). There was some evidence of extreme heterogeneity, although the true value was uncertain: between-study SD 1.219 (95% CrI: 0.431, 2.795). Prevalence in a new study was estimated as 8.5% (95% PrI: 0.2%, 74.0%).

Five studies reported on asthma diagnoses in individuals who primarily identified as heroin smokers (22-33%) (8, 10-13). Overall, prevalence data from these five studies were suitable for meta-analyses. There was some evidence of moderate heterogeneity, although the true value was uncertain: between-study SD 0.620 (95% CrI: 0.280, 1.587). Prevalence in a new study was estimated as 20.2% (95% PrI: 4.2%, 59.2%). The only study comparing asthma prevalence between inhaled users and non-using populations reported significantly higher prevalence in the inhaled opioid using sample (10).

Five studies did not report method of opioid use and consequently not combined for meta-analysis showed prevalence ranging from 1-15% (see table 2) (34, 38-41). One of these studies compared prevalence with non-using populations and reported a significant association between opioid use disorder and asthma (34).

COPD prevalence

Thirteen studies undertaken in US (7, 8, 30, 34, 39, 42), UK (11, 13, 38), Australia (40, 43, 44) and Canada (32) reported the prevalence of COPD in people who use illicit opioids (3-43%) (Table 3). Two studies reporting COPD prevalence in samples consisting predominantly of IV users were pooled for meta-analyses (7, 8). There was some evidence of extreme heterogeneity, although the true value was uncertain: between-study SD 1.081 (95% CrI: 0.086, 2.944). Prevalence in a new study was estimated as 2.7% (95% PrI: 0.0%, 50.4%).

Three studies reported COPD prevalence in heroin smokers (8, 11, 13). Meta-analyses of prevalence data suggested that there was some evidence of extreme heterogeneity, although the true value was uncertain: between-study SD 1.328 (95% CrI: 0.646, 2.872). Prevalence in a new study was estimated as 17.9% (95% PrI: 0.6%, 89.5%).

Nine studies did not report method of opioid use and consequently not combined for meta-analysis showed prevalence ranging from 0-43% (30, 32, 34, 38-40, 42-44). All three studies comparing

prevalence with non-using populations, reported associations between illicit opioid use and increased prevalence of COPD (30, 32, 34).

Respiratory related deaths

Six studies reported on associations between illicit opioid use and asthma related deaths (14-19) (see table 4). Prevalence on opioid use in cases of asthma related deaths was available from three studies for meta-analysis (14, 16, 18). There was some evidence of extreme heterogeneity, although the true value was uncertain: between-study SD 1.029 (95% CrI: 0.243, 2.626). Prevalence in a new study was estimated as 8.5% (95% PrI: 0.3%, 65.7%). One of the six studies compared asthma related deaths with non-using populations, reporting an increased risk of asthma related deaths in opium users (19).

Associations between illicit opioid use and deaths related to other respiratory disease were also reported across five studies (Table 5) (19-23). Two studies compared mortaility rates with non-using populations (19, 20). Both studies reported increased respiratory related deaths in people who use illicit opioids.

Hospital admissions

Nine studies undertaken in US (8, 20, 24-26, 28) Australia (27) and Spain (10) examined the relationship between illicit opioid use and admissions to hospital services for respiratory disease (see table 6). Data on prevalence of illicit opioid use in hospital admissions for asthma exacerbations from five studies was available for meta-analysis. There was some evidence of extreme heterogeneity, although the true value was uncertain: between-study SD 1.558 (95% CrI: 0891, 2.871). Prevalence in a new study was estimated as 21.8% (95% PrI: 0.6%, 92.5%).

Additional key findings from studies relating illicit opioid use to hospital care for respiratory conditions are reported in table 7.

Other respiratory disease and symptoms

Five studies reported prevalence of other respiratory disease in people who use illicit opioids (31, 33, 45-47). Prevalence across the studies varied greatly from 6.0-50.3% (see table 8). One of these studies compared presence of respiratory disease in people who use illicit opioids with non-users and found

an increased likelihood of respiratory disease in MMT patients in comparison to controls matched for age, gender and socioeconomic status (33).

Varying measures of dyspnoea, coughing and wheezing were reported across seven studies (9-11, 13, 15, 36, 47). Various lung function tests were also reported across eleven studies (9-13, 36, 43, 47-50). Key details of all these outcomes are displayed in Table S2.

Discussion

The findings show a consensus in the research that poor respiratory health is more prevalent among opioid users than the general population and should be considered a serious health risk. However, an accurate estimate of prevalence of conditions such as COPD and asthma could not be provided from meta-analyses of the data. Screening and improved access to respiratory health services may be a necessary addition to substance misuse services.

Prevalence of asthma in people who use illicit opioids ranged from 1-33% (7, 9-13, 34, 35, 37-41). Meta-analysis predicted prevalence of asthma at 8.5% in people who injected opioids and 20.2% in people who inhaled opioids. General population prevalence is estimated at 4-5% (51). COPD prevalence in people who use opioids ranged from 0-49% (7, 11, 13, 30, 32, 34, 38-40, 42-44). Meta-analysis of COPD predicted prevalence at 2.7% in people who injected opioids and 17.9% in people who inhaled opioids. General population prevalence are estimated at 2-3% (51).

Other respiratory disease were also recorded, with one study finding that people who use opioids are significantly more likely to have respiratory disease than matched controls (33). The remaining studies reported prevalence of respiratory disease ranging from 6-50% (31, 45-47)

Prevalence of illicit opioid use in asthma related deaths ranged from 9-18% (14-18), with one study showing an association between opium use and asthma deaths (HR 3.87) (19). Meta-analysis estimated prevalence of opioid use in asthma related deaths in a new study as 8.5%. Evidence of increased risk of 'general respiratory disease' related deaths in this population was also reported (20-23).

Prevalence of illicit opioid use in individuals admitted to hospital for asthma exacerbations ranged from 3-74% (8, 10, 24-28). Meta-analysis estimated prevalence of illicit opioid use in hospital admissions for asthma exacerbations in a new study to be 21.8%.

Due to heterogeneity of study design and included samples it was difficult to gain an accurate estimate of the prevalence of respiratory disease in people who use opioids, with meta-analyses of asthma and

COPD prevalence still demonstrating evidence of heterogeneity when data were pooled in relation to the route of administration. A number of studies also reported respiratory outcomes in individuals receiving MMT or accessing substance misuse services. In order to develop a broader understanding of the prevalence of respiratory disease outcomes in the entire population of people who use illicit opioids, individuals currently not accessing care, who more likely to be at a different stage of recovery, would need to be included.

There was variation between studies with regards to the methods of diagnosing respiratory disease, with some studies relying on self-reports and other studies not reporting how diagnosis was reached. The importance of using recommended diagnostic tools such as spirometry testing was highlighted by Lewis-Burke and colleagues (13) who found that symptom scores were poor discriminators of diagnoses of COPD in heroin smokers. Some studies only reported subsets of COPD (e.g. emphysema, bronchitis), whilst others reported figures on general respiratory illness, which could include reports of diseases caused by bacterial infection such as pneumonia. Not considering the impact of confounding factors was also an issue across the literature, with only seven studies considered the confounding effect of tobacco smoking on respiratory health in their statistical analysis. Measures of socioeconomic status, deprivation and ethnic background were also inconsistently reported.

Recommendations for future research and clinical practice

To fully understand the relationship between illicit opioid use and poor respiratory health it is vital that future research considers the potential confounding impact of factors such as tobacco smoking, poly-drug use, primary method of opioid use and sociodemographic factors. Further studies examining the use of prescribed inhalable heroin treatment could also be used to explore how cutting agents used in illicit heroin relate to the lung function of this population.

Evidence highlighting the feasibility and high uptake of screening in or near settings in which substance users are already engaged (e.g. community substance misuse services and pharmacies), also suggest that there are significant opportunities to intervene in these settings in order to improve symptoms in this population. Delivery of care in these services may help overcome barriers to healthcare experienced by substance users relating to perceived stigma and multiple appointments across services (52).

Conclusions

The quality of the literature examining the association between illicit opioid use and respiratory health is inconsistent. Despite this, there is evidence to suggest increased burden of respiratory diseases in this population. Future research is required to disentangle the relationship between illicit opioid use and respiratory health in relation to tobacco smoking, poly-drug use, living conditions and access to recommended healthcare interventions. Clinical services for people who use drugs may need to take this co-morbidity into account in planning their services.

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*studies included in the systematic review

Figure 1: PRISMA diagram of the study selection process

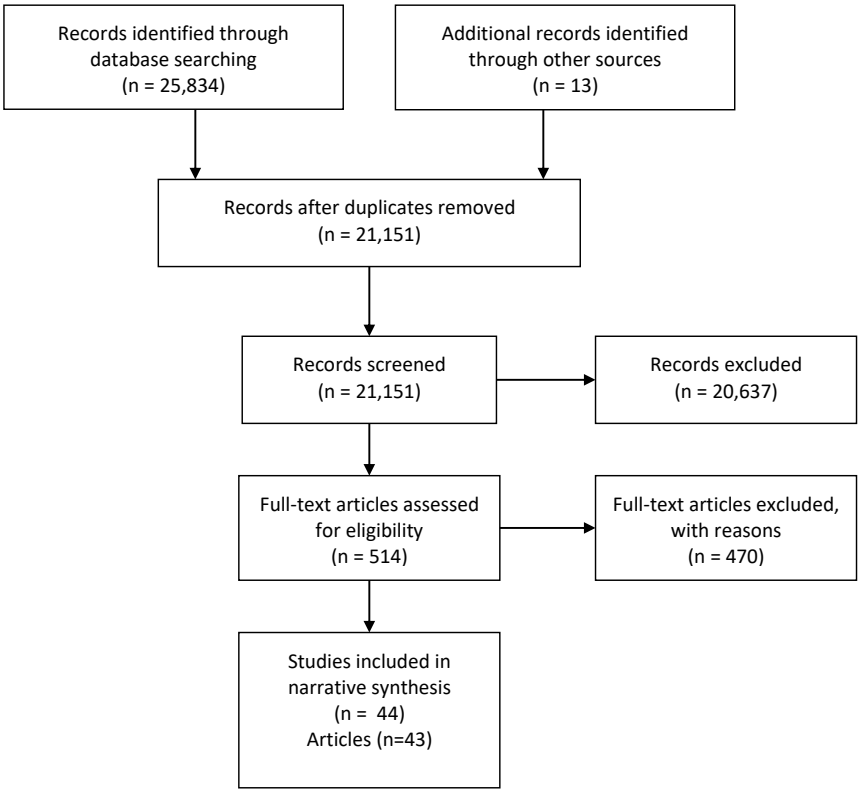

Table 1: Quality assessment

Study (year)	Target population defined?	Was probability sampling used?	Response rate >70%?	Are the data collection methods standardised?	Are the survey instruments reliable?	Are the survey instruments valid?	Were special features of the sampling design accounted for in the analysis?	Do the reports include confidence intervals for statistical estimates?	Quality score
Burhan et al. (2018) [11]	Y	N	Y	Y	Y	Y	N	N	5/8
Kelty et al. (2018) [20]	Y	N	N/A	Y	Y	Y	Y*	Y	6/7
Olfson et al. (2018) [23]	Y	NR	N/A	Y	Y	Y	Y	Y	6/7
Wu et al. (2018) [34]	Y	N	NA	Y	Y	Y	Unclear	Y	5/7
Hser et al. (2017) [45]	Y	N	N/A	Y	Y	Y	Y	N	5/7
Rahmati et al. (2017) [19]	Y	Y	Y	Y	Y	Y	Y	Y	8/8
Gupta et al. (2016) [30]	Y	Y	NA	Y	Y	Y	Unclear	N	5/7
Lewis - Burke et al. (2016) [13]	Y	N	Y	Y	Y	Y	N	N	5/8
Mitchell et al. (2016) [12]	Y	N	NR	Y	N	N	N	N	2/8
Moghaddas et al. (2016) [27]	Y	N	N/A	Y	Y	Y	Y	Y	6/7
Morrison-Griffiths et al. (2016) [38]	Y	N	N	Y	Y	Y	N	N	4/8
Weeks et al. (2016) [28]	Y	N	N/R	Y	Y	Y	N	N	4/8
Choi et al. (2015) [8]	Y	N	NR	Y	Y	Y	Y	Y	6/8

Hlavaty et al. (2015) [16]	Y	N	N/A	Y	Y	Y	N	N	4/7
Leece et al. (2015) [31]	Y	N	N/A	Y	Y	Y	Y	Y	6/7
Pierce et al. (2015) (22)	Y	N	N/A	Y	Y	Y	Unclear	Y	5/7
Walker et al. (2015) [50]	Y	N	NA	Y	Y	Y	N	N	4/7
O'Toole et al. (2014) [33]	Y	N	N/A	Y	Y	Y	Y	Y	6/7
Goeman et al. (2013) [14]	Y	N	N/A	Y	Y	Y	N	N	4/7
Islam et al. (2013) [43]	Y	N	NR	Y	Y	Y	N	N	4/8
Maruyama et al. (2013) [32]	Y	Y	NA	Y	Y	Y	Y*	Y	7/7
Pilgrim et al. (2013) [44]	Y	N	NA	Y	Y	Y	N	N	4/7
Mohiuddin et al. (2012) [18]	Y	N	N/A	Y	Y	Y	N	N	4/7
Buster et al. (2011) [48]	Y	N	NR	Y	Y	Y	N	N	4/8
Batki et al. (2010) [7]	Y	NR	NR	Y	Y	Y	Y*	N	5/8
Darke et al. (2010) [40]	Y	N	NA	Y	Y	Y	Y	Y	6/7
Fareed et al. (2009) [42]	Y	N	NA	Y	Y	Y	N	N	4/7
Rosen et al. (2008) [46]	Y	N	Y	Y	Y	Y	N	N	5/8
Levine et al. (2005) [26]	Y	N	N/A	Y	Y	Y	Y	Y	6/7
Lofwall et al. (2005) (39)	Y	N	Y	Y	Y	Y	N	N	5/8
Maxwell et al. (2005) [21]	Y	N	N/A	Y	Y	Y	Y*	Y	6/7

Hser et al. (2004) [49]	Y	N	NR	Y	Y	Y	N	N	4/8
Krantz et al. (2003a) [25]	Y	N	NA	Y	Y	Y	N	N	4/7
Krantz et al. (2003b) [25]	Y	N	NA	Y	Y	N	N	N	3/7
Buster et al. (2002) [36]	Y	N	NR	Y	Y	Y	Y	Y	6/8
Ernst et al. (2002) [41]	Y	N	NA	Y	Y	Y	N	N	4/7
Los Bueis et al. (2002) [10]	Y	N	NR	Y	Y	Y	Y*	Y	6/8
Gaeta et al. (1996) [24]	Y	N	NR	Y	Y	Y	N	N	4/8
Levenson et al. (1996) [17]	Y	N	NA	Y	Y	Y	N	N	4/7
Greenberger et al. (1993) [15]	Y	N	NA	Y	Y	Y	N	N	4/7
Selwyn et al. (1993) [35]	Y	N	NR	Y	N	N	N	N	2/8
Miller et al. (1991) [9]	Y	N	NR	Y	Y	Y	N	N	4/8
Overland et al. (1980) [47]	N	N	Y	Y	y	Y	Y	N	5/8
Ghodse et al. (1987) [37]	Y	N	NA	Y	Y	Y	N	N	4/7

* Matched with controls on key demographics

Table 2: Asthma outcomes

Author (year)	Population	N	Country	Design	Method of opioid use	Asthma prevalence		Outcomes of statistical analysis
						Opioid users	Control	
Batki et al. (2010) [7] * ‡	Individuals diagnosed with Hepatitis C (MMT v non- MMT; mean age = 44.0)	160	US	Case-control	IV	13.8% (n=80)	18.8% (n=80)	Non-significant difference in asthma prevalence between groups
Miller et al. (1991) [9] *	MMT programme attendees (mean age: males = 35.0, females = 37) v cross sections of general population from previous literature	98	US	Cross sectional	IV	17.0% (n=98)	3.5% (n= NR)	NR
Selwyn et al. (1993) [35] §	HIV-seropositive and seronegative individuals attending MMT program (mean age = 37.9)	386	US	Prospective	IV	4.6%	NA	NA
Choi et al. (2015) [8]*†	Admissions to general medicine service (mean age: inhalational opioids = 46.0, IV opioids = 43.0, cocaine = 46.0, low risk use = 53.0)	9134	US	Prospective	IV and inhaled	10.0% (inhalational opioids; n=341) 1.0% (IV opioids; n=106)	2.5% (cocaine; n=260) 1.0% (low-risk drug use; n=8427)	NR
Los Bueis et al. (2002) [10] †	Individuals from drug rehabilitation centres (mean age = 29.9) and hospital admissions (mean age = 30.9) v tobacco smokers from the general population (mean age = 31.3)	213	Spain	Prospective	Inhaled	22.0% (drug rehabilitation attendees only; n=62)	8.2% (n=122)	Significant difference in asthma prevalence between groups ($p<0.01$)
Burhan et al. (2019) [11] †	Substance misuse service users receiving OST (mean age = 47.0)	753	UK	Pilot study	Inhaled	22.2%	NA	NA
Lewis-Burke et al. (2016) [13]†	Individuals from Crime Reduction Initiatives (mean age = 43.0)	129	UK	Cross sectional	Inhaled	33.0%	NA	NA

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Mitchell et al. [12] (2016) †	Individuals from community substance misuse clinic (mean age = 37.0)	36	UK	Cross sectional	Inhaled	20.6%	NA	NA
Wu et al. (2018) [34]	Individuals with >1 healthcare encounter from 2007-2014 (mean age = 41.3)	211, 880	US	Retrospective	NR	NR	NR	Increased likelihood of OUD in individuals with asthma: OR 1.59; 95% CI 1.42 to 1.78, p <0.05.
Morrison-Griffiths et al. (2016) [38]	Substance misuse service users receiving OST (mean age = 51.0)	205	UK	Pilot study	NR	11.7%	NA	NA
Darke et al. (2010) [40]	Cases of opioid over dose from 1998-2007 relating to heroin (mean age = 33.1) and methadone (mean age = 35.8)	1193	Australia	Case series	NR	1.3% (heroin deaths; n=1000) 3.6% (methadone deaths; n=193)	NA	NA
Lofwall et al (2005) [39]	Older (mean age = 53.9) v younger (mean age = 30.4) Addiction treatment service users receiving OST	67	US	Cross sectional	NR	9.8% (50-66 years; n=41) 23.1% (25-34 years; n=26)	NA	NA
Ernst et al. (2002) [41]	Cases of methadone-related deaths from 1993-1999 (mean age: males = 31.4, females = 31.7)	84	Australia	Case series	NR	15.5%	NA	NA
Ghodse et al. (1987) [37]	Individuals from a drug dependence treatment clinic (mean age = NR)	2276	UK	Case-note review	NR	4.9%	NA	NA

* Included in meta-analysis of IV users

† Included in meta-analysis of inhaled users

‡Comparator group also includes IV opioid users (51%)

§% of primary care consultations in which asthma was mentioned

Table 3: COPD outcomes

Author (year)	Population	N	Country	Design	Method of opioid use	COPD prevalence		Outcomes of statistical analysis
						Opioid users	Control	
Batki et al. (2010)*‡ [7]	Individuals diagnosed with Hepatitis C (MMT v non-MMT; mean age = 44.0)	160	US	Case-control	IV	6.3% (n=80)	11.3%* (n=80)	Non-significant difference in COPD prevalence between groups
Choi et al. (2015) *† [8]	Admissions to general medicine service (mean age: inhalational opioids = 46.0, IV opioids = 43.0, cocaine = 46.0, low risk use = 53.0)	9134	US	Prospective	IV and inhaled	5.0% (inhalational opioids; n=341) 1.0% (IV opioids; n=106)	2.0% (cocaine; n=260) 1.0% low-risk drug use; n=8427)	NR
Burhan et al. (2019) † [11]	Substance misuse service users receiving OST (mean age = 47.0)	753	UK	Cross sectional	Inhaled	34.5%	NA	NA
Lewis-Burke et al. (2016) † [13]	Individuals from Crime Reduction Initiatives (mean age = 43.0)	129	UK	Cross sectional	Inhaled	28.0%	NA	NA
Wu et al. (2018) [34]	Individuals with >1 healthcare encounter from 2007-2014	211, 880	US	Retrospective	NR	NR	NR	Increased likelihood of OUD in individuals with COPD:

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	(mean age = 41.3)							OR 1.66; 95% CI 1.47 to 1.87, p<0.05.
Gupta et al. (2015) [30]	Individuals hospitalised with heart failure who use opioids (mean age = 52.7) v non users (mean age = 72.7)	999,3241	US	Prospective	NR	42.5% (n=29,014)	35.3% (n= 9,964,227)	Significant difference in asthma prevalence between groups: p<0.001
Maruyama et al. (2013) [32]	MMT v non MMT patients (aged > 49 years) matched in terms of age, gender and geographical variables (mean age = 59.4)	398	Canada	Case control	NR	11.6% (n=199)	0.0% (n=199)	Increased likelihood of COPD in MMT group: OR 32.68; 95% CI (7.19–infinity), p < 0.0001
Morrison-Griffiths et al. (2016) [38]	Substance misuse service users receiving OST (mean age = 51.0)	205	UK	Pilot study	NR	12.7%	NA	NA
Islam et al. (2013) [43]	OST patients at a tertiary hospital-based clinic (mean age = 41.0)	58	Australia	Cross sectional	NR	30.2%	NA	NA
Pilgrim et al. (2013) [44]	Cases of methadone associated	206	Australia	Case series	NR	Emphysema: 3.9%	NA	NA

	deaths from 2001-2005 (mean age = 31)							
Darke et al. (2010) [40]	Cases of opioid over dose from 1998-2007 relating to heroin (mean age = 33.1) and methadone (mean age = 35.8)	1193	Australia	Case series	NR	Emphysema: 3.0% (heroin, n=1000) 7.8% (methadone, n=193)	NA	NA
Fareed et al. (2009) [42]	MMT patients at Veterans Affairs medical centre (mean age: retained = 57.0, dropped out = 53.0, deceased = 57.0)	91	US	Chart review	NR	16.0% (retained, n=44) 10.0% (dropped out, n=40) 43.0% (deceased, n=7)	NA	NA
Lofwall et al (2005) [39]	Older (mean age = 53.9) v younger (mean age = 30.4) Addiction treatment service users receiving OST	67	US	Cross sectional	NR	2.4% (50-66 years, n=41) 0.0% (25-34 years, n=26)	NA	NA

* Included in meta-analysis of IV users

† Included in meta-analysis of inhaled users

‡Comparator group also includes IV opioid users (51%)

Table 4: Prevalence of illicit use opioid in asthma related deaths

Author (year)	Population	N	Country	Design	Opioid use prevalence	Outcomes of statistical analysis
Rahmati et al. (2017) [19]	Adults aged 40-75 years recruited from the general population (mean age = 52.1)	50,045	Iran	Prospective	NR	Opium use associated with Increased risk of death from: asthma (HR 3.87; 95% CI 1.85 to 8.11)
Hlavaty et al. (2015)* [16]	Cases of sudden asthma related deaths from 2007-2014 (mean age = 34.6)	68	US	Case series	1.5%	NR
Goeman et al. (2013)* [14]	Cases of asthma related deaths from 2005-2009 (mean age = 44.0)	84	Australia	Case series	17.9%	NR
Mohiuddin et al. (2012)* [18]	Out of hospital asthma related deaths from 2004-2008 (mean age = 32.0)	22	US	Case series	9.1%	NR
Levenson et al. (1996)† [17]	Cases of asthma related deaths from 1992-1994 (mean age = 28.0)	92	US	Case series	14.1%*	NR
Greenberger et al. (1993)† [15]	Cases of asthma related deaths from 1985-1992 (mean age = 30.9)	23	US	Case series	8.7%*	NR

* Included in meta-analysis

† Not all deaths confirmed as asthma-related

Table 5: Associations between illicit opioid use and other respiratory related deaths

Author (year)	Population	N	Country	Design	Outcomes
Kelty et al. (2018) [20]	Patients undergoing OST and age and gender matched non-dependent controls (mean age = 31.5)	11292 Case: 5646 Control: 5646	Australia	Prospective	Significant increase in mortality rates associated with respiratory disease in individuals who use illicit opioids (hazard ratio (HR) = 8.00, 95% CI: 3.15-20.29, p <0.001) compared with age and gender matched non-dependent controls.
Olfson et al. (2018) [23]	Adult Medicaid patients who have experienced nonfatal opioid overdose (mean age = NR)	76, 325	US	Longitudinal	Standardised mortality rate ratio (SMR) for Chronic respiratory disease (41.1; 95% CI, 36.0- 46.8) significantly greater than the standardized reference population.
Rahmati et al. (2017) [19]	Adults aged 40-75 years recruited from the general population (mean age = 52.1)	50,045 Opium users: 8.487 Non-users: 41,558	Iran	Prospective	Opium use associated with Increased risk of death from: • any respiratory disease (adjusted HR 95% CI 3.13 (2.42 to 4.04) • COPD (HR 7.21; 95%CI 4.46 to 11.65)
Pierce et al. (2015) [22]	Deaths of individuals who use illicit opioids from 2005-2009 (median age = 32.1)	3974	UK	Case series	3.3% of deaths 3974 deaths of individuals who used illicit opioids attributable to chronic lower respiratory disease (CMR 2.4; 95% CI 2.0 to 2.8; SMR 12.6; 95%CI 10.6-14.9)
Maxwell et al. (2005) [21]	Patients who died while in methadone treatment from 1994-2002 (mean age = 46.1)	766	US	Retrospective	5.6% of 754 deaths due to respiratory disease (adjusted SMR 1.7; 95% CI 1.6 to 1.8)

Table 6: Illicit opioid use prevalence in hospital admissions for asthma exacerbations in studies

Author (year)	Population	N	Country	Design	Opioid use prevalence in hospital admissions		Outcomes of statistical analysis
					Asthma admissions	Control	
Moghaddas et al. (2016) *[27]	General ward (mean age = 43.0) and ICU (mean age = 37.0) admissions to hospital with primary diagnosis of asthma	482	Australia	Chart review	2.9%	NA	NA
Choi et al. (2015) *[8]	Admissions to general medicine service (mean age = NR)	225	US	Prospective	19.6%	NA	
Levine et al. (2005) *[26]	Admissions to hospital for asthma exacerbations (mean age = 43.2)	152	US	Chart review	30.9%	NA	NA
Gaeta et al. (1996) * [24]	Emergency department admissions (asthma v other complaints; mean age = 35.0)	200	US	Case control	18.0% (n=100)	3.0% (n=100)	NR
Krantz et al. (2003a) * [25]	Patients admitted to ICU with asthma exacerbations (mean age = 35.4)	23	US	Case series	73.9%	NA	NR
Krantz et al. (2003b) † [25]	Admissions to ICU for asthma (mean age = 33.4) v diabetes ketoacidosis (mean age = 32.1)	146		Case control	41.3% (self-reports, n= 92) 65.4% (urine drug screening, n=63)	12.5% self-reports, n=40) 6.7% (urine drug screening, n=15)	Significant difference in prevalence of opioid use between groups based on self-reports and urine screening: p<0.01

* Included in meta-analysis

† data reported as % of admissions, not as % of individuals admitted

Table 7: Other outcomes relating to hospital care for respiratory disease

Author (year)	Population	N	Country	Design	Outcomes
Kelty et al. (2018) [20]	Patients undergoing OST and age and gender matched non-dependent controls (mean age = 31.5)	11292 OST patients: 5646 Non-users: 5646	Australia	Prospective	Individuals who use illicit opioids at an increased risk of hospital admissions for general respiratory disease compared with non-using controls: RR 2.49; 95% CI 2.13-2.83
Weeks et al. 2016 [28]	Individuals who use illicit opioids accessing asthma care in the emergency department (mean age = 47.5)	30	**US**	Pilot study	47% reported that asthma was diagnosed in emergency care 43% used emergency services once a month for respiratory health 73% described emergency care as their main source for asthma medications
Choi et al. (2015)* [8]	Admissions to general medicine service (mean age: inhalational opioids = 46.0, IV opioids = 43.0, cocaine = 46.0, low risk use = 53.0)	9134	US	Prospective	Patients who inhaled heroin were more likely to be admitted for exacerbations compared to patients who had not taken illicit drugs three months prior to admission: OR 7.0; 95% CI 4.7-70.4, p<.01 Individuals who inhaled heroin daily over the past 30 days were more likely to be admitted for asthma exacerbations compared to less frequent users: OR 2.3; 95% CI 1.3-4.1, p<0.01 inhalational heroin users were more likely to be admitted to hospital for general respiratory disease in comparison to low-risk using individuals:

					28.0% vs 8.1%, p<0.01
Levine et al. (2005) [26]	Admissions to hospital for asthma exacerbations (mean age: individuals who use illicit opioids = 38.2, non-drug users = 46.0)	134	US	Chart review	Individuals who use illicit opioids more likely to be intubated than non-drug users when taking into account tobacco smoking: 17.0% v 2.3%, p<0.01
Los Bueis et al. (2002) [10]	Individuals from drug rehabilitation centres (mean age = 29.9) and hospital admissions (mean age = 30.9) v tobacco smokers from the general population (mean age = 31.3)	213	Spain	Prospective	41.9% of 29 of the hospital admissions for patients inhaling heroin mixed cocaine were for bronchospasms (mean admissions = 12) 6.4% of the 62 patients recruited from drug rehab centres had been admitted to hospital for bronchospasms (mean admissions = 1.7)

Table 8: Prevalence of other respiratory disease in illicit opioid users

Author (year)	Population	N	Country	Design	Method of opioid use	Respiratory disease prevalence		Outcomes of statistical analysis
						Cases	Controls	
Hser et al. (2017) [45]	Patients from inpatient and outpatient settings who use illicit opioids (mean age = 48.6)	5307	US	Cross sectional	NR	48.5%	NA	NA
Leece et al. (2015) [31]	Opioid related deaths (median age = 42.0) from 1994-2010 v matched controls (median age = 39.0)	1048	Canada	Case control	NR	50.3% (n= 175)	28.8% (n=873)	Association between chronic lung disease and opioid related deaths: OR = 2.51; 95%CI 1.80 to 3.49 AOR = 1.74 95%CI 1.16 to 2.60
O'Toole et al. (2014) [33]	Individuals receiving MMT v controls matched by gender, age, SES and GP surgery (mean age = 39.2)	414	Ireland	Case control	NR	NR (n=207)	NR (n=207)	Increased likelihood of respiratory disease in MMT patients: OR = 3.3; 95% CI = 1.9-5.9, p <0.001
Rosen et al. (2008) [46]	Individuals receiving MMT over the age of 50 (mean age = 53.9)	140	US	Cross sectional	NR	22.1%	NA	NA

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Overland et al. (1980) [47]*	Hospital admission for individuals who use illicit opioids (mean age = 26.8)	512	US	Cross sectional	IV	6.0%	NA	NA

* lung disease attributed to bronchitis or asthma

† Respiratory symptoms reported in supplementary data

Table 9: Study characteristics of other included studies

Author (year)	Population	N	Country	Design
Walker et al. (2015) [50]	Individuals who smoke opioids recruited from clinical respiratory services with a diagnosis of COPD (mean age = 41.0)	73	UK	Cross sectional
Buster et al. (2011)[48]	Individuals prescribed inhalable heroin for illicit opioid use (mean age = 41.0)	32	Netherlands	Prospective
Hser et al. 2004 [49]	Individuals admitted to the drug treatment programmes (mean age = 29.4)	108	US	Prospective
Buster et al. 2002 [36]	Patients receiving MMT (mean age = 42.4)	100	Netherlands	Cross sectional