



# Does opioid agonist treatment reduce overdose mortality risk in people who are older or have physical comorbidities? Cohort study using linked administrative health data in New South Wales, Australia, 2002–17

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## Abstract

**Aims:** To quantify the association between opioid agonist treatment (OAT) and overdose death by age group; test the hypothesis that across different age groups, opioid overdose mortality is lowest during OAT with buprenorphine compared with time out of treatment or OAT with methadone; and test associations between OAT and opioid overdose mortality in the presence of chronic circulatory, respiratory, liver and kidney diseases.

**Design:** Retrospective observational cohort study using linked administrative data.

**Setting:** New South Wales, Australia.

**Participants:** A total of 37 764 people prescribed OAT, 1 August 2002 and 31 December 2017.

**Measurements:** OAT exposure, opioid overdose mortality and key confounders were measured using linked population data sets on OAT entry and exit, hospitalization, mental health care, incarceration and mortality. ICD-10 codes were used to define opioid overdose mortality and chronic disease groups of interest.

**Findings:** Relative to time out of treatment, time in OAT was associated with a lower risk of opioid overdose death across all age groups and chronic diseases. Among people aged 50 years and older, there was weak evidence that buprenorphine may be associated with greater protection against opioid overdose death than methadone [generalized estimating equation (GEE) adjusted incident rate ratio (aIRR) = 0.47; 95% confidence interval (CI) = 0.21, 1.02; marginal structural models (MSM) aIRR = 0.49; 95% CI = 0.17, 1.41]. Buprenorphine was associated with greater protection against overdose death than methadone for clients with circulatory (MSM aIRR = 0.27; 95% CI = 0.11, 0.67) or respiratory (MSM aIRR = 0.26; 95% CI = 0.07, 0.94) diseases, but not liver (MSM aIRR = 0.59; 95% CI = 0.14, 2.43) or kidney (MSM aIRR = 1.16; 95% CI = 0.31, 4.36) diseases.

**Conclusions:** Opioid agonist treatment (OAT) appears to reduce mortality risk in people with opioid use disorder who are older or who have physical comorbidities. Opioid overdose mortality during OAT with buprenorphine appears to be lower and reduced in clients with circulatory and respiratory diseases compared with OAT with methadone.

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## KEYWORDS

Buprenorphine, comorbidity, methadone, multi-morbidity, older adults, opioid agonist treatment, overdose

## INTRODUCTION

Opioid agonist treatment (OAT) is associated with multiple beneficial outcomes for people with opioid dependence or opioid use disorder, notably reduced mortality across a range of causes [1]. The strongest reductions in mortality are observed in relation to fatal overdose, with risk of death due to unintentional opioid overdose reduced by 69% during OAT relative to periods out of treatment [1]. This protective association between OAT and overdose mortality is apparent for the two most commonly prescribed OAT medicines, methadone and buprenorphine [1, 2], and persists in areas with high overdose mortality linked to illicit fentanyl and fentanyl analogues [3].

In a number of settings the cohort of people seeking treatment for opioid use disorder is ageing, with substantial increases in the proportion of clients aged in their 50s and above [4–7]. The persistence of the protective effects of OAT on opioid overdose mortality in older clients is an important clinical question [8, 9]. Randomized controlled trials of OAT were undertaken with participant samples aged approximately 30 years [10], and are underpowered to examine mortality. Observational studies have provided considerable data on mortality during and after OAT, including important variations during treatment induction [2], but are yet to present data specific to older age groups on the risk of overdose death during OAT relative to that out of treatment. A recent meta-analysis of cohort studies reported that OAT was protective against overdose death in those aged 35 years and older [1], but was not able to give any indication of the relative risk specific to OAT clients approaching or in older adulthood. A study in primary care settings in England suggested that among those aged more than 50 years buprenorphine was more effective in reducing opioid overdose deaths than methadone, but did not compare time in and out of OAT for this age group and was limited by small numbers of overdose deaths in older age groups [8].

Complicating interpretation of these findings and clinical decision-making for older adults in OAT is confounding due to the high prevalence of coexisting chronic diseases [11, 12], which may increase overdose risk independently of age by compromising important physiological functions. Circulatory and respiratory diseases may increase the likelihood of death in an overdose event by increasing susceptibility to opioid-induced hypoxia [13]. Separately, liver and kidney diseases may interfere with metabolism and excretion of opioids and their metabolites as well as other drugs or medicines, potentially increasing overdose risk at previously tolerated opioid levels [14, 15]. Data regarding the risk of opioid overdose death in the presence of these chronic diseases, and implications for OAT provision, are sparse. A study of Scottish methadone clients identified a heightened risk of opioid overdose death in older clients in the presence of chronic diseases (respiratory, circulatory and digestive diseases) [9], but did not account for time in and out treatment and did not include a comparison to people treated with buprenorphine. Hickman *et al.* reported

that for people with chronic disease comorbidities, opioid overdose deaths were less frequent during treatment with buprenorphine than methadone but did not examine specific comorbidities [8]. Given factors such as the lesser respiratory depressant effect of buprenorphine, the long half-life and risk of accumulation and toxicity with methadone in chronic liver disease and the greater number of clinically meaningful drug interactions with methadone, it could be hypothesized that for some people with chronic conditions there may be less clinical risk associated with buprenorphine compared to methadone [16–19].

To more effectively support clinical management of older adults and those with chronic disease comorbidities receiving OAT, we aimed to quantify the association between OAT and overdose death by age group, and tested the hypothesis that among different age groups (and particularly in those aged 50 years and over), opioid overdose mortality rates would be lowest during OAT with buprenorphine compared to time out of treatment or OAT with methadone. We also tested associations between OAT and opioid overdose mortality rates in the presence of specific chronic diseases: circulatory disease, respiratory disease, liver disease and kidney disease.

## METHOD

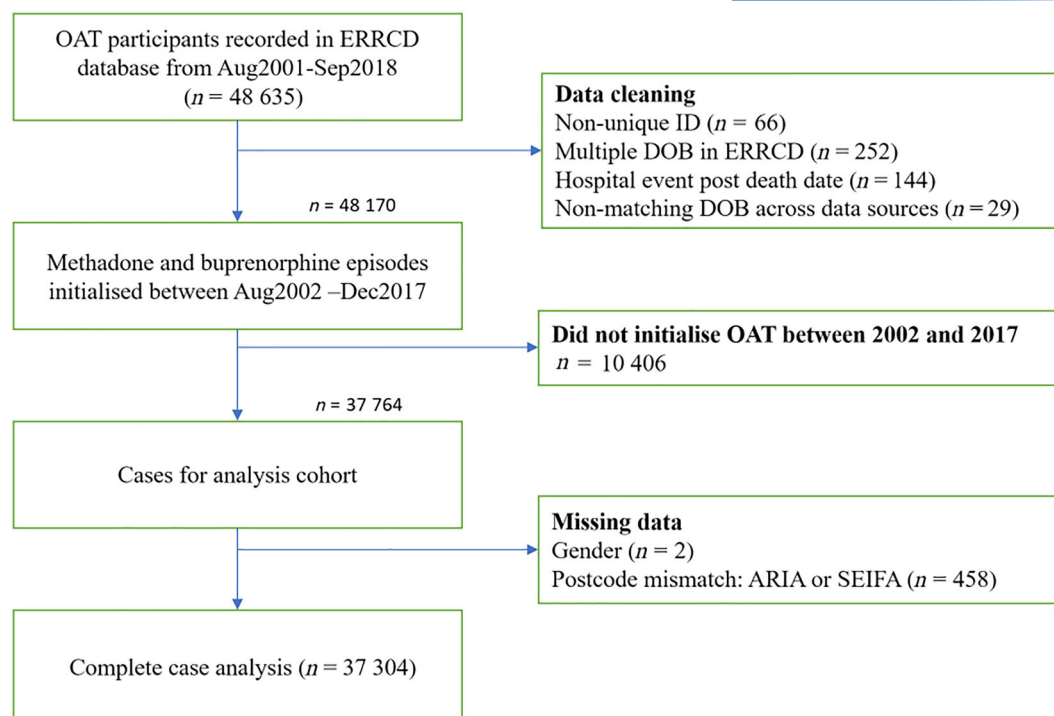
Reporting of this study is in line with the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for reporting of observational studies [20, 21]. The statistical analysis plan was pre-registered with Open Science Framework and can be found at: <https://osf.io/z6cy9/>.

## Overview

The Opioid Agonist Treatment and Safety (OATS) study is a retrospective cohort study using linked administrative data for all people prescribed OAT for the treatment of opioid dependence/opioid use disorder in the Australian state of New South Wales (NSW) between 1 August 2001 and 30 September 2018 [22, 23]. In NSW, OAT is prescribed in a range of settings, including primary care (with dosing usually through community pharmacies), public and private specialist drug treatment clinics and correctional facilities [24].

## Data sources and cohort definition

The data set includes all OAT episodes, hospitalizations, ambulatory mental health contacts and contact with the criminal legal system



**FIGURE 1** Cohort definition. ARIA, accessibility/remoteness index of Australia; DOB, date of birth; ERRCD, Electronic Recording and Reporting of Controlled Drugs; OAT, opioid agonist therapy; SEIFA, socio-economic indexes for areas.

and deaths, with probabilistic linkage to other state and national databases [22, 23]. Details on each data set and variables within them are provided in the Supporting information. For the present analyses, the cohort was restricted to people initiating a treatment episode between 1 August 2002 and 31 December 2017. This start date was selected to permit a 1-year lookback for participant hospitalization and contact with the criminal legal system. The end date was selected as the criminal legal system data ended at 31 December 2017. A flow-chart depicting the cohort definition process is shown in Figure 1.

## Primary outcome

The primary outcome was fatal opioid overdose of unintentional or undetermined intent. We defined opioid overdose as an underlying cause of death of ICD-10 X42, X44, Y12 or Y14 in combination with a contributory cause of death of T40.0–T40.4 or T40.6, or an underlying cause of death of F11 or F19 with contributory causes of death from both of the above groups of codes [25, 26].

## Exposure

Deaths were defined as occurring in or out of OAT based on treatment episode dates, and we defined deaths in treatment as those occurring within 1 day of the end of an authority to prescribe OAT [25]. We modelled opioid overdose mortality rates according to

treatment exposure which had three categories: (i) time prescribed methadone; (ii) time prescribed buprenorphine; and (iii) time out of OAT. The effect of treatment was estimated within age and chronic disease strata groups.

## Time-varying effect modifiers

### Age

Age was categorized as < 30, 30–39, 40–49 and 50+ years, calculated at the beginning of each follow-up year. Ten-year age bands were pre-specified to avoid having small numbers of participants in older age groups.

### Chronic disease groups

Diseases of the circulatory system, respiratory system and chronic liver and kidney diseases were selected for analysis on the basis of plausible mechanisms that could increase the risk of overdose death in the presence of the specific comorbidity [13–15]. Defining ICD-10 codes for each disease grouping are shown in Table 1. Chronic disease status was time-varying, with participants defined as having a chronic disease following a hospital admission with a diagnosis of circulatory disease, respiratory disease, liver disease or kidney disease. Once a participant was identified as having a specific chronic disease, they were assumed to have this for the remainder of follow-up [27–31].

**TABLE 1** International Classification of Diseases—10th revision diagnostic codes used to classify participants as having a chronic disease.

Circulatory disease	I00–I99 (Chapter IX Diseases of the circulatory system, excluding I85 oesophageal varices and I86.4 gastric varices); G45, G46 (selected episodic and paroxysmal disorders)
Respiratory disease	J00–J99 (Chapter X Diseases of the respiratory system); C34 (lung cancer); C45 (mesothelioma); A15, A16 (tuberculosis)
Liver disease	K70–K77 (Diseases of liver); C22 (liver cancer); R18 (ascites); I85 (oesophageal varices); I86.4 (gastric varices)
Kidney disease	N00–N19 (renal diseases and renal failure); C64 (kidney cancer)

## Covariates

Supporting information, Table S1 provides a summary of the confounders used in all models. Covariates identified in the literature and considered a priori to be important were sex, Indigenous status and accessibility/remoteness. Residential remoteness (major cities versus regional/remote) was based on participants' last known postcode of residence using the Accessibility/Remoteness Index of Australia Plus (ARIA+) 2016 [32]. Postcodes were also used to define socio-economic disadvantage, based on the Socio-Economic Indexes for Areas produced by the Australian Bureau of Statistics [33].

When initiating someone into treatment, their previous treatment experience may influence their new treatment plan. Hence, a categorical variable summarizing previous treatment and duration was derived with the following levels: no prior OAT treatment, methadone for less than 29 days, buprenorphine less than 29 days, methadone for greater than 28 days and buprenorphine for greater than 28 days.

## Time-varying confounders

Calendar year was included and grouped into 4-year periods: 2002–05, 2006–09, 2010–13 and 2014–17. Substance use, psychosis and mood disorders have previously been identified as important factors with regard to treatment retention, together with the duration of previous treatment episodes and the tenure of the prescribing clinician [34]. As such, time-varying comorbidities were derived from hospitalizations involving a diagnosis of substance use disorder, psychosis, mood disorder or self-harm and outpatient mental health visits, all within the last 12 months, as well as an indicator as to whether a non-fatal overdose was experienced during a prior treatment episode. Because criminal activity and incarceration were considered important for predicting treatment selection and retention, we derived indicators for recent (past 12 months) criminal charges and incarceration [34, 35].

We used prescriber preference for methadone or buprenorphine as a predictor of treatment selection, defined as a time-varying confounder. The previous five client initiations at each time-point that represented a

change in a confounder status were used to determine whether a prescriber preferred methadone or buprenorphine. If there were five previous initiations, preference was given to the majority. If there were fewer than five and were all for the same treatment, preference was set as that treatment; otherwise, preference was categorized as unknown.

Factors included in each of the models are discussed further below in the specific model sections and in Supporting information, Table S2.

## Statistical models

Analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A complete case approach was used for analysis.

## Descriptive statistics

Socio-demographic characteristics, comorbidities and OAT exposure were summarized with frequencies and percentages.

## Crude mortality rates

Crude mortality rates were estimated using standard person-time methods with 95% confidence intervals.

## Generalized estimating equation model

Assessing treatment effectiveness in observational data can be complex, as participants may change or cease medications over time for a variety of reasons. In addition to the need to control for confounding at baseline due to the lack of randomization, time-dependent confounding may influence treatment changes over time and affect treatment group effectiveness comparisons. To address these issues, we used two approaches to modelling: first, generalized estimating equation (GEE) models, and secondly, marginal structural models (MSM).

A Poisson regression GEE model was fitted adjusting for sex, indigenous status, geographical remoteness, socio-economic disadvantage index and previous treatment duration. Time-varying covariates included calendar year, age and recency measures for release from incarceration and comorbid indicators for mental health, mood disorders, psychosis, substance use, self-harm and the chronic diseases groupings in Table 1. A working correlation structure was applied to provide robust parameter estimates.

## Marginal structural model

Mortality incident rate ratios comparing the different treatment exposure periods were estimated using MSM with inverse probability weighting [36–38]. The purpose of the inverse probability weighting is to adjust for the possibility of treatment bias introduced from the

inability to randomize to treatment. We calculated inverse treatment propensity weights (IPTW) and a weight to adjust for bias introduced through censorship of observations (inverse probability censorship weights; IPCW). We followed the methodology for stabilized weights recommended by Hernán *et al.* [39], with the slight adaptation that weights were estimated for each new record in the data set that represented a change in a time-varying covariate value. In this longitudinal structure there were no structured visits in the design.

The MSM consisted of three models:

- Model 1: estimating a weighting for treatment selection at baseline and each time a confounder changed (time-varying);
- Model 2: estimating a weighting for probability of not ceasing OAT each time a confounder changed (time-varying); and
- Model 3: fitting a weighted repeated-measures model analysis using a GEE.

Full details of each of these models are provided in the Supporting information.

Mortality rates by age and treatment exposure were estimated, as well as mortality rates in the presence of each the chronic diseases of interest. Each disease was modelled in a time-varying manner and an effect modification analysis was used to examine the strength of association between the chronic comorbid diseases of interest and treatment exposure.

Additionally, the impact on mortality in people with none of the co-morbid diseases was estimated. This involved fitting a simplified model: the chronic disease effect modifiers were replaced by an indicator variable, which was derived with a value of 1 if none of the four diseases were present and 0 if any of the four diseases were present.

## Post-hoc analyses

Following the planned analyses, we plotted crude opioid overdose mortality rates, stratified by age group and chronic disease status (yes/no for each chronic disease). Findings from *post-hoc* analyses should be considered exploratory.

## Ethical approval

Approval for this study was obtained from the NSW Population and Health Services Research Ethics Committee (2018/HRE0205) and the NSW Aboriginal Health and Medical Research Council Ethics Committee (1400/18).

## RESULTS

The study population included 37 764 people and 286 948 person-years of observation (Table 2). Just under half of the person-years accumulated during OAT were time spent receiving methadone (121 926 person-years; 42.5%) and 49 095 person-years accumulated

during OAT were time spent receiving buprenorphine (17.1%). More than one in five had a hospitalization for a respiratory disease ( $n = 8681$ ; 23.0%) and/or circulatory disease ( $n = 7871$ ; 20.8%). Fewer people were hospitalized with either kidney disease ( $n = 2715$ ; 7.2%) or liver disease ( $n = 2194$ ; 5.8%). There were 1075 opioid overdose deaths, for a crude mortality rate of 3.75 [95% confidence interval (CI) = 3.53, 3.98] per 1000 person-years (PY).

## Mortality by age group

Opioid overdose mortality rates increased with age, from 2.54 (95% CI = 2.18, 2.94) per 1000 PY for those aged less than 30 years to 5.25 (95% CI = 4.51, 6.09) per 1000 person-years for those aged 50 years or greater (Table 1). Opioid overdose mortality rates during OAT increased with age: during buprenorphine, from 0.8 (95% CI = 0.4, 1.6) per 1000 PY in those < 30 years to 1.8 (95% CI = 1.0, 3.2) per 1000 PY in those 50 years or older, and in methadone, from 1.4 (95% CI = 1.0, 2.0) per 1000 PY to 3.8 (95% CI = 2.9, 4.9) per 1000 PY (Table 3). Unadjusted models of associations between age group, OAT medicine and overdose death are provided in the Supporting information. In adjusted GEE and MSM models, opioid overdose mortality rates were lower during OAT with either methadone or buprenorphine, relative to periods of time out of treatment, for all age groups tested (Table 3). Contrary to our hypothesis, we found only weak evidence of a difference in opioid overdose mortality rates during OAT with buprenorphine compared to methadone. Wide confidence intervals included the null, even among those aged 50 years and over, where we had expected to observe a difference (e.g. for those aged 50 years and over, GEE IRR = 0.47; 95% CI = 0.21, 1.02 and MSM IRR = 0.49; 95% CI = 0.17, 1.41) (Table 3).

## Mortality in the presence of specific chronic diseases

As with age groups, time in OAT was associated with a lower risk of opioid overdose death relative to time out of treatment for each of the analysed chronic disease groups (Table 4). Some disease-specific associations between specific OAT medicines and fatal opioid overdose were observed. Among participants with circulatory diseases, opioid overdose mortality rates were lower during OAT with buprenorphine relative to methadone in both GEE (IRR = 0.37; 95% CI = 0.17, 0.78) and MSM (IRR = 0.27; 95% CI = 0.11, 0.67) models. Among participants with respiratory diseases, mortality rates were lower during OAT with buprenorphine relative to methadone in the GEE and MSM models (0.38; 95% CI = 0.15, 0.91 and 0.26; 95% CI = 0.07, 0.94), respectively. This pattern was not observed in relation to liver or kidney diseases (Table 4).

## Post-hoc analyses of age × disease interactions

In light of the findings of the planned analyses, we undertook exploratory, *post-hoc* analyses of opioid overdose mortality rates

**TABLE 2** Participant and opioid agonist treatment episode characteristics.

Characteristic	n (%)
Sex	37 764
Men	26 018 (68.9%)
Women	11 744 (31.1%)
Unknown	2 (< 0.01%)
Indigenous	8646 (22.9%)
Age at cohort entry	
< 30 years	16 613 (44.0%)
30–39 years	13 013 (34.5%)
40–49 years	6507 (17.2%)
≥ 50 years	1631 (4.3%)
Incarceration history	17 041 (45.1%)
Geographical remoteness	
Major cities of NSW	27 102 (71.8%)
Regional/remote NSW	10 444 (27.7%)
Unknown	218 (0.6%)
SEIFA	
(1) Most disadvantaged	9138 (24.2%)
2nd quintile	7098 (18.8%)
3rd quintile	9864 (26.1%)
4th quintile	6779 (18.0%)
(5) Least disadvantaged	4427 (11.7%)
Unknown	458 (1.2%)
Hospitalization	
Circulatory disease	7871 (20.8%)
Respiratory disease	8681 (23.0%)
Liver disease	2194 (5.8%)
Kidney disease	2715 (7.2%)
> 1 target disease	5468 (14.5%)
Drug-related	6793 (18.0%)
Non-drug mood disorder	10 656 (28.2%)
Self-harm/suicide attempt	7440 (19.7%)
Psychiatric disorder	4291 (11.4%)
Substance use disorder	18 581 (49.2%)
Treatment and exposure	
At least one methadone treatment episode	27 471 (72.7%)
At least one buprenorphine treatment episode	24 087 (63.8%)
At least one hospitalization for a target chronic disease	13 756 (36.4%)
Treatment episodes	
Methadone episodes	60 688 (57.3%)
Methadone PY of observation	121 927 (42.5%)
Buprenorphine episodes	55 535 (52.4%)
Buprenorphine PY of observation	49 095 (17.1%)
PY out of OAT	115 927 (40.4%)
Opioid overdose mortality rates per 1000 PY (95% confidence interval)	
Overall (n deaths = 1075; PY = 286 948)	3.75 (3.53, 3.98)

(Continues)



**TABLE 2** (Continued)

Characteristic	n (%)
< 30 years (n deaths = 172; PY = 67 764)	2.54 (2.18, 2.94)
30–39 years (n deaths = 429; PY = 112 509)	3.81 (3.47, 4.19)
40–49 years (n deaths = 304; PY = 74 318)	4.09 (3.65, 4.57)
≥ 50 years (n deaths = 170; PY = 32 357)	5.25 (4.51, 6.09)

Abbreviations: NSW, New South Wales; SEIFA, socio-economic indexes for areas; PY, person-years.

stratified by both age group and chronic disease status. Given the exploratory nature of these analyses and anticipated low statistical power, significance testing was not undertaken. Very wide confidence intervals were observed around the age-specific mortality rates in those with chronic diseases (Figure 2, Supporting information, Table S5, Figures S1 and S2). Within each age group, comparing mortality rates during methadone and buprenorphine, minimal differences were observed in participants without circulatory or respiratory disease. For participants with circulatory or respiratory disease, the largest apparent disparity in overdose mortality rates was observed in those aged 50 years or over, with rates higher in methadone compared to buprenorphine (Figure 2). Similar analyses were undertaken for kidney and liver disease, with no clear age gradient observed (Supporting information, Table S5, Figures S1 and S2).

## DISCUSSION

OAT with methadone or buprenorphine was associated with reduced risk of opioid overdose death, relative to time out of OAT, throughout the life-span. We confirm that opioid overdose risk increases with age in and out of OAT. We found only weak evidence of a difference in opioid overdose mortality rates during OAT with buprenorphine relative to methadone in people aged 50 years and over, with IRRs well below 1, but wide confidence intervals, particularly in the MSM model, complicating interpretation. Lower opioid overdose risk was observed during OAT with buprenorphine compared to methadone among participants with circulatory and respiratory diseases. This may be linked to buprenorphine's limited effect on respiratory depression, with a 'ceiling effect' at higher doses, in contrast to the linear relationship between methadone dose and respiratory depression [40]. While exploratory, our *post-hoc* analyses suggest that there may be interactions between age and chronic disease; these findings need replication via planned analyses in other data sets with sufficient numbers of participants among different age groups, with and without chronic diseases.

### Other evidence and implications

There is limited published clinical guidance for the prescribing of OAT for older adults or people with comorbid health problems. Some

national clinical guidelines highlight the importance of careful assessment and regular review of older adults in OAT [41, 42], and one set of guidelines recommends buprenorphine as the first-line treatment for older adults in light of fewer adverse drug interactions relative to methadone (although not in reference to evidence on treatment outcomes in older adults) [43]. We are not aware of any clinical guidelines that specifically highlight treatment strategies for OAT clients with chronic diseases. Our findings suggest that particular comorbidities maybe more important than age *per se* in determining opioid overdose risk during OAT; specifically, respiratory and circulatory diseases. This extends and contrasts with findings from the United Kingdom [8, 9]. The reduction in mortality risk associated with buprenorphine relative to methadone in people aged 50 years or older is less and weaker than observed in UK primary care patients [8], and needs further replication and synthesis of results. Our findings also suggest that the type of comorbidity (such as circulatory and respiratory problems) may be of importance, rather than the number of comorbidities as shown previously [8]. Replication studies in other settings are needed to disentangle the effects of age and physical morbidity on overdose risk during OAT, together with analyses that assess the impacts of sex, gender, race, ethnicity and other social determinants of health on the associations identified here. Replication in a range of settings will support generalizability and help to clarify and strengthen clinical recommendations.

Many people with opioid use disorder have poor access to primary health-care, and chronic diseases are likely to be underdiagnosed. Furthermore, adherence to treatment in the event of diagnosis may be difficult for multiple reasons, including ongoing substance use, housing instability and mental health problems. Regular screening and assessment for the presence and severity of cardiovascular and respiratory diseases should be considered, particularly in clients who are at mid-life or older age. Although there is no widespread consensus on what age is considered 'older' with this population, premature ageing as a result of chronic substance use and exposure to multiple social disadvantages [44] suggests that screening should begin at an earlier age than would be considered in the general population. In specific contexts, there may be subpopulations of people in OAT with an elevated risk of chronic disease, such as Indigenous people or racialized populations. Such groups may need enhanced chronic disease screening; for example, beginning at an earlier age or more frequently than otherwise.

These findings, and others relating to potential medication interactions [43], suggest that buprenorphine may be preferred to

**TABLE 3** Adjusted opioid overdose mortality incident rate ratios during time prescribed methadone or buprenorphine, relative to time out of OAT, and during time prescribed buprenorphine relative to time prescribed methadone, by age group.

Age group	Treatment	PY	Opioid overdose deaths, n	Crude mortality rate per 1000 PY (95% CI)	GEE		MSM	
					Adjusted IRR (95% CI)		Adjusted IRR (95% CI)	
					Comparison of each treatment to time out of OAT	Comparison of buprenorphine to methadone	Comparison of each treatment to time out of OAT	Comparison of buprenorphine to methadone
< 30 years	Out of OAT	30 027	123	4.1 (3.4–4.9)	Ref.		Ref.	
	Buprenorphine	11 016	9	0.8 (0.4–1.6)	0.20 (0.09–0.45)	0.58 (0.24–1.38)	0.18 (0.07–0.45)	0.46 (0.17–1.26)
	Methadone	25 533	37	1.4 (1.0–2.0)	0.34 (0.22–0.53)	Ref.	0.39 (0.24–0.63)	Ref.
30–39 years	Out of OAT	45 140	321	7.1 (6.4–7.9)	Ref.		Ref.	
	Buprenorphine	18 229	23	1.3 (0.8–1.9)	0.18 (0.11–0.29)	0.80 (0.46–1.40)	0.17 (0.10–0.31)	0.61 (0.32–1.18)
	Methadone	47 208	77	1.6 (1.3–2.0)	0.22 (0.16–0.30)	Ref.	0.28 (0.20–0.39)	Ref.
40–49 years	Out of OAT	27 428	210	7.7 (6.7–8.8)	Ref.		Ref.	
	Buprenorphine	12 901	17	1.3 (0.8–2.1)	0.17 (0.09–0.31)	0.61 (0.32–1.17)	0.20 (0.09–0.44)	0.70 (0.30–1.64)
	Methadone	32 794	73	2.2 (1.8–2.8)	0.28 (0.20–0.39)	Ref.	0.28 (0.19–0.40)	Ref.
50 + years	Out of OAT	10 800	102	9.4 (7.8–11.5)	Ref.		Ref.	
	Buprenorphine	6195	11	1.8 (1.0–3.2)	0.18 (0.08–0.39)	0.47 (0.21–1.02)	0.22 (0.08–0.61)	0.49 (0.17–1.41)
	Methadone	14 785	56	3.8 (2.9–4.9)	0.39 (0.26–0.58)	Ref.	0.45 (0.29–0.69)	Ref.

Abbreviations: OAT, opioid agonist treatment; PY, person-years; GEE, generalized estimating equation; IRR, incident rate ratio; MSM, marginal structural model; Ref, reference category for IRR; CI, confidence interval.

GEE models are adjusted for year, sex, geographical remoteness, indigeneity, socio-economic disadvantage index, recent: incarceration, mental health ambulatory outpatient activity, previous OAT history, hospital admissions for mood and psychosis disorders, substance use and self-harm. MSM models are weight-adjusted for treatment selection bias using: year<sup>a</sup>, sex, geographical remoteness, Indigenous status, socio-economic disadvantage index, recency of: criminal charges,<sup>a</sup> previous OAT history, most recent OAT,<sup>a</sup> hospital admissions for respiratory,<sup>a</sup> substance use,<sup>a</sup> previous NFOD on OAT, prescriber preference<sup>a</sup> and censorship using: year<sup>a</sup>, sex, geographical remoteness, indigeneity, socio-economic disadvantage index, previous OAT history, treatment<sup>a</sup> and treatment × year interaction<sup>a</sup> and recency of: incarceration,<sup>a</sup> hospital admissions for mood<sup>a</sup> and psychosis disorders,<sup>a</sup> substance use<sup>a</sup> and mental health ambulatory outpatient activity.<sup>a</sup>

<sup>a</sup>Fitted at baseline and time-varying.



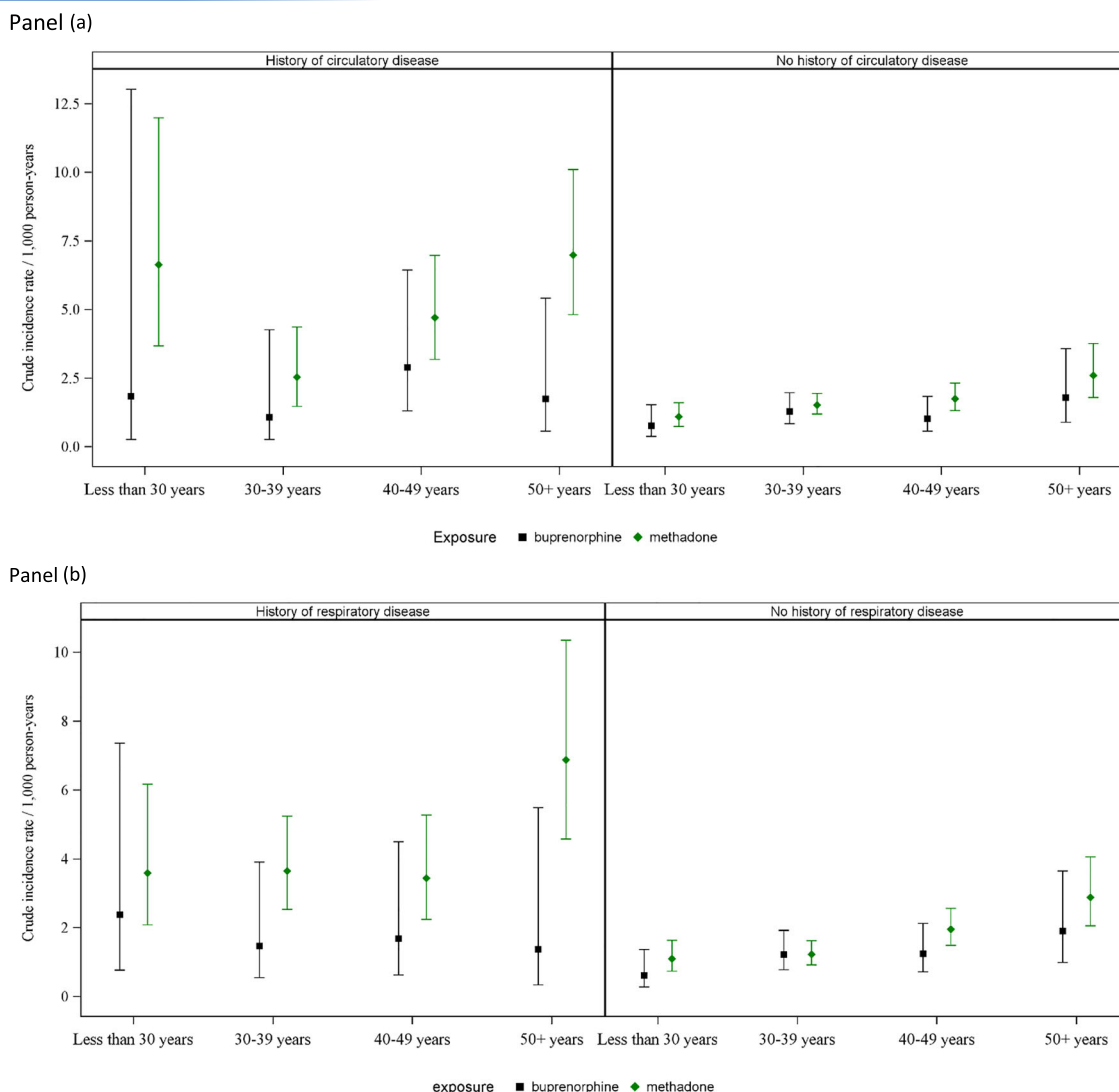
**TABLE 4** Adjusted opioid overdose mortality incident rate ratios during time prescribed methadone or buprenorphine, relative to time out of OAT, and during time prescribed buprenorphine relative to time prescribed methadone, in people with and without evidence of chronic diseases.

Chronic disease	Treatment	PY	Opioid overdose deaths, n	Crude mortality rate per 1000 PY (95% CI)	GEE			MSM	
					Adjusted IRR (95% CI)		Comparison of buprenorphine to methadone	Comparison of each treatment to time out of OAT	Comparison of buprenorphine to methadone
					Comparison of each treatment to time out of OAT	Comparison of buprenorphine to methadone			
No evidence of target chronic diseases	Out of OAT	87 386	424	4.9 (4.4–5.3)	Ref		Ref		
	Buprenorphine	35 762	34	1.0 (0.7–1.3)	0.19 (0.12–0.30)	0.73 (0.46–1.18)	0.21 (0.13–0.35)	0.67 (0.38–1.17)	
	Methadone	87 342	113	1.3 (1.1–1.6)	0.26 (0.20–0.34)	Ref	0.32 (0.24–0.42)	Ref	
Circulatory disease	Out of OAT	12 398	183	14.8 (12.8–17.1)	Ref		Ref		
	Buprenorphine	6213	12	1.9 (1.1–3.4)	0.12 (0.06–0.24)	0.37 (0.17–0.78)	0.10 (0.04–0.24)	0.27 (0.11–0.67)	
	Methadone	16 123	77	4.8 (3.8–6.0)	0.32 (0.22–0.45)	Ref	0.37 (0.25–0.55)	Ref	
Kidney disease	Out of OAT	3656	68	18.6 (14.7–23.6)	Ref		Ref		
	Buprenorphine	1794	8	4.5 (2.2–8.9)	0.25 (0.10–0.59)	0.87 (0.33–2.28)	0.39 (0.12–1.35)	1.16 (0.31–4.36)	
	Methadone	4654	26	5.6 (3.8–8.2)	0.28 (0.16–0.50)	Ref	0.34 (0.18–0.66)	Ref	
Liver disease	Out of OAT	3110	46	14.8 (11.1–19.7)	Ref		Ref		
	Buprenorphine	1445	6	4.2 (1.9–9.2)	0.29 (0.10–0.81)	0.66 (0.22–1.97)	0.32 (0.08–1.23)	0.59 (0.14–2.43)	
	Methadone	3811	25	6.6 (4.4–9.7)	0.44 (0.24–0.81)	Ref	0.54 (0.28–1.07)	Ref	
Respiratory disease	Out of OAT	16 683	228	13.7 (12.0–15.6)	Ref		Ref		
	Buprenorphine	7824	13	1.7 (1.0–2.9)	0.11 (0.05–0.26)	0.38 (0.15–0.91)	0.08 (0.02–0.29)	0.26 (0.07–0.94)	
	Methadone	21 038	86	4.1 (3.3–5.0)	0.29 (0.21–0.40)	Ref	0.32 (0.22–0.46)	Ref	

Abbreviations: OAT, opioid agonist treatment; PY, person-years; GEE, generalized estimating equation; IRR, incident rate ratio; MSM, marginal structural model; Ref, reference category for IRR; CI, confidence interval.

GEE models are adjusted for year, sex, geographical remoteness, Indigenous status, socio-economic disadvantage index, recent: incarceration, mental health ambulatory outpatient activity, previous OAT history, hospital admissions for mood and psychosis disorders, substance use and self-harm. MSM models are weight-adjusted for treatment selection bias using: year,<sup>a</sup> sex, geographical remoteness, Indigenous status, socio-economic disadvantage index, recency of: criminal charges,<sup>a</sup> previous OAT history, most recent OAT,<sup>a</sup> hospital admissions for respiratory,<sup>a</sup> substance use,<sup>a</sup> previous NFOD on OAT, prescriber preference<sup>a</sup> and censorship using: year,<sup>a</sup> sex, geographical remoteness, Indigenous status, socio-economic disadvantage index, previous OAT history, treatment<sup>a</sup> and treatment × year interaction<sup>a</sup> and recency of: incarceration,<sup>a</sup> hospital admissions for mood<sup>a</sup> and psychosis disorders,<sup>a</sup> substance use<sup>a</sup> and mental health ambulatory outpatient activity.<sup>a</sup>

<sup>a</sup>Fitted at baseline and time-varying.



**FIGURE 2** Crude opioid overdose mortality rates, stratified by age group and circulatory disease (a) and respiratory disease (b).

methadone as a first-line treatment when prescribing OAT for patients with significant circulatory and respiratory comorbidities. In some cases, however, clients with these coexisting conditions will have been prescribed methadone for a number of years, and may be reluctant to change to buprenorphine, or will be entering treatment with a preference for methadone. An important opportunity presents for a discussion with the client on the relative risks and benefits of each medicine, as an unwanted change in prescribing may be destabilizing or precipitate treatment exit, thereby increasing overdose risk to a greater extent than if they were to remain on methadone. Recent advances in clinical protocols for transfer from methadone to buprenorphine can assist this process [45]. If, after an informed discussion, there is a client preference to continue with methadone treatment other strategies to reduce risks are warranted, including client and carer education regarding overdose signs and risks and interactions between opioids and alcohol; naloxone provision; and review of concomitantly prescribed medicines that may contribute to respiratory

depression, such as benzodiazepines, gabapentinoids and sedating antidepressants and antipsychotics.

## Limitations

This study used a large linked administrative health data set with analyses that attempted to adjust for non-random treatment assignment and a range of confounders. However, administrative data were lacking in detailed clinical information. For example, chronic disease status was defined using hospitalization data. These probably reflect more serious clinical presentations and underestimate true prevalence [46]. Age may still therefore be somewhat of a proxy for physical comorbidities, which may affect the observed associations. Uncertainty in chronic disease ascertainment may also arise as a result of varying coding practices. The MSM models presented can provide consistent estimates of causal effects when all confounders have been

accounted for and the correct models have been specified [47, 48]. In this analysis, key variables that we were unable to measure or control were adequacy of OAT dose, severity of opioid dependence and use of other central nervous system depressants; if these factors differed by OAT type, it may explain the greater risk observed in those treated with methadone.

Previous studies have used prescriber preference as an instrument to adjust for confounding bias when estimating a treatment effect [49]. However, due to the way in which OAT is regulated in Australia, not all prescribers are permitted to prescribe both methadone and buprenorphine. As such, the assumption that the instrument can detect unmeasured confounders fails. Therefore, rather than undertake an instrumental variable analysis, we incorporated prescriber preference into the marginal structural model. The decision to base prescriber preference on the previous five new prescriptions was based on a consideration of relevant studies [49–51], but is largely subjective given the absence of consensus in the literature.

## Conclusion

OAT reduces opioid overdose mortality risk for older clients relative to time out of treatment. In OAT clients with circulatory or respiratory illnesses, buprenorphine may be preferred as a first-line treatment over methadone for reducing opioid overdose risk. However, other factors, including client preferences and current medications, remain important in determining appropriate treatment plans.

## AUTHOR CONTRIBUTIONS

**Sarah Larney:** Conceptualization; funding acquisition; investigation; methodology; project administration; writing—original draft; writing—review and editing. **Nicola R. Jones:** Conceptualization; data curation; formal analysis; methodology; project administration; writing—original draft; writing—review and editing. **Matthew Hickman:** Conceptualization; formal analysis; funding acquisition; methodology; writing—original draft; writing—review and editing. **Suzanne Nielsen:** Conceptualization; funding acquisition; methodology; writing—original draft; writing—review and editing. **Robert Ali:** Conceptualization; funding acquisition; writing—original draft; writing—review and editing. **Louisa Degenhardt:** Conceptualization; funding acquisition; methodology; writing—original draft; writing—review and editing.

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## DECLARATION OF INTERESTS

In the past 3 years, L.D. has received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior and Seqirus. S.N. has received investigator-initiated untied educational grants from Seqirus and is a named investigator on an implementation trial funded by Indivior. S.L. has previously received an untied educational grant from Indivior.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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