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Title

Life expectancy of people who are dependent on opioids: a cohort study in New South Wales, Australia

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Abstract

Background

People who are dependent on opioids have substantially increased risk of premature death, but there are few estimates of life expectancy.

Methods

We calculated age-specific mortality rates in a cohort of people who had at least one prescription of an opioid agonist (methadone or buprenorphine) between 2001 and 2018 in New South Wales, Australia. We estimated life expectancy at age 18 based on life tables. We also estimated the potential years of life lost before age 75, decomposed by cause of death.

Results

The cohort included 47,197 people, with a median of 9.8 years of follow-up. 5,097 participants died, and the standardised mortality ratio (compared to the general population of New South Wales) was 6.06 (95% CI 5.90-6.23). Life expectancy at age 18 was 47.5 years (95% CI 42.9-50.5) for men and 50.7 years (95% CI 45.4-54.8) for women; deficits of 14.7 and 15.8 years respectively when compared to the general population. The largest cause of death was non-communicable physical diseases, which accounted for 47% of deaths in life tables for men and 42% for women. Drug-related deaths accounted for 16% of deaths for men and 19% for women, but due to the young age at which these deaths occur, they contributed approximately one third of potential years of life lost.

Conclusion

In common with people with serious mental illnesses, people who are dependent on opioids have substantially reduced life expectancy. In both populations most excess deaths relate to non-communicable physical diseases.

Keywords

Substance-Related Disorders, Opioid-Related Disorders, Social Marginalization, Life Expectancy, Mortality, Epidemiology

Introduction

People who use opioids such as heroin often use these drugs for many years, which can have a profound impact on health and social wellbeing. A large number of cohort studies have measured the relative mortality risk associated with opioid dependence. Systematic reviews of such studies have found that the risk of death for people who inject drugs (Mathers et al., 2013) and people who regularly use heroin and other opioids (Degenhardt et al., 2011) is typically 15 times the general population, though this varies widely by setting. These relative risks can be difficult to interpret. In particular, the ratio between mortality risk in the general population and the mortality risk for people who use illicit drugs tends to be greater for younger samples than for older samples, even if the absolute difference is smaller for younger samples. Cause-specific mortality risk can also be difficult to interpret. The risk of death due to drug overdoses, suicides, or blood-borne viral infections is many times that of the general population, but long-term conditions such as cardiovascular and respiratory diseases may cause more deaths despite having lower risk ratios (Lewer et al., 2019).

Some studies of other marginalised groups, particularly people with serious mental health problems, have addressed these issues by estimating life expectancy deficits rather than relative risks (Erlangsen et al., 2017; Hjorthøj et al., 2017; Lawrence et al., 2013; Plana-Ripoll et al., 2019). Life expectancy is the average age at which people would die if current mortality rates remain unchanged. A systematic review of studies into the life expectancy of people with schizophrenia found an average deficit of 15 years when compared to the general population (Hjorthøj et al., 2017). As a measure of mortality risk, life expectancy has the benefits of being (i) independent from the study sample's age structure, (ii) intuitive because it relates to a usual lifespan of around 80 years, and (iii) decomposable by cause of death. Despite the large number of studies reporting relative mortality risks for people who use illicit drugs, there are few estimates of the life expectancy of this population.

We aimed to estimate the life expectancy of people who have been prescribed opioid agonist treatment in New South Wales, Australia. Opioid agonists are essential medicines prescribed to people who are dependent on opioids. They aim to prevent withdrawal, reduce the need to use illicit opioids, and reduce health and social harms associated with illicit drugs (Degenhardt et al., 2019). A large proportion of people who use illicit opioids have been prescribed opioid agonists either currently or historically. We also aimed to calculate the contribution of different causes of death to the years of life lost in this population.

Methods

Study population

We included all patients prescribed an opioid agonist (methadone or buprenorphine) in New South Wales between 1 August 2001 and 19 September 2018. The data were drawn from the Opioid Agonist Treatment Safety (OATS) Study, a resource of linked electronic healthcare databases that includes all authorities to prescribe opioid agonists and probabilistic linkage to mortality information from the Cause of Death Unit Record File held by the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence. A detailed description of the OATS Study has been published (Larney et al., 2018).

Individuals entered the cohort at the first treatment after 23 August 2001 (because linked mortality information was available from this date), and exit was at the earliest of death, the final date on which participants were known to be alive, the participant's 75th birthday, or 19 September 2018 (the final date at which mortality information was available). We excluded patients aged younger than 18 or older than 75 at cohort entry. For descriptive purposes, we reported the proportion of patients who identified as Aboriginal or Torres Strait Islanders; were in prison prior to study entry; and had received a previous diagnosis of schizophrenia (ICD-10 codes F20:29) or bipolar disorder (F31) in hospital or specialist mental health services.

Reference data

Our reference data were official population estimates and mortality statistics for the general population of New South Wales, 2001-2018, from the Australian Bureau of Statistics (Australian Bureau of Statistics, 2019).

Mortality rates and ratios

We calculated reference mortality rates in the general population by sex, calendar year, and single-year-of-age from 18 to 74. We then calculated the number of expected deaths by applying these rates to the time-at-risk for the study cohort within these strata. We used the Lexis method to calculate time-at-risk (Clayton and Hills, 2013). This involved disaggregating follow-up time for each participant by day (for example, a participant who joined the cohort on 13 March 2010 and died on 24 April 2018 would have 2,964 days of observation, with calendar year and age-at-last-birthday assigned to each day), and then summarising the number of days of observation by sex, calendar year, and single-year-of age. We calculated the standardised mortality ratio (SMR) as the observed deaths divided by the expected deaths.

Life expectancy at age 18

We estimated life expectancy for men and women using the life table method described by the UK Office for National Statistics (Office for National Statistics, 2018). For ages 25 to 64, we used mortality rates from the OATS cohort. There was limited follow-up time outside of this age range so mortality rates were imprecise, and we therefore used scenarios. Mortality rates increased exponentially between ages 24 and 64 (Fig 1.), and we used Poisson models to predict the mortality rate at ages 18-24 and 65-99, separately for men and women. These models suggested that mortality rates increased by 6.2% per year for men and 6.4% per year for women. The 'base' scenario was the

maximum of this predicted rate and the general population rate (as these rates converged at age 86 for men and 89 for women). The 'low' scenario was the mortality rate in the general population. The 'high' scenario for ages 18-24 was three times the predicted mortality rate; and the 'high' scenario for ages 64-99 was the SMR for ages 18-74 multiplied by the rate in the general population (unrealistically high, because the SMR reduced with age). Mortality of 100% was forced at age 100. We estimated uncertainty using a Monte-Carlo method with 10,000 simulations. Simulations for ages 25-64 were sampled from a Poisson distribution with a mean of the observed number of deaths. Simulations for ages 18-24 and 65-99 were sampled from uniformly spaced trajectories between the 'low' and 'high' scenarios. We calculated life expectancy in each scenario and reported the 2.5% and 97.5% quantiles. For comparison, we also calculated life expectancy in the general population.

We did three sensitivity analyses: (1) with mortality rates based on follow-up truncated at 5, 10 and 15 years; (2) excluding all participants with an episode of opioid agonist treatment before 1 January 2001 (i.e. excluding prevalent cases); and (3) stratifying results by period. Sensitivity analyses 1 and 2 are designed to test whether mortality deficits reduce after longer periods of follow-up (as participants stop using drugs), in which case we expected to see shorter life expectancies under these scenarios. Full results of these analyses are provided in Supplementary Information.

Cause-specific potential years of life lost

We used life tables to estimate the potential years of life lost before age 75, assuming that deaths at age 74 lose 0.5 years; deaths at age 73 lose 1.5 years, etc. For this analysis, we used cause-specific mortality rates in the cohort at each age from 18-74 rather than using scenarios for younger and older age ranges. Causes of death were grouped according to the underlying cause of death into 'drug-related' (ICD-10 codes F11-16, F19, F55, X40-X44, and Y10-Y14), non-communicable physical diseases (ICD-10 chapters II: cancers, III: blood, IV: endocrine/nutritional/metabolic diseases, VI: nervous system, VII: eye, VIII: ear, IX: circulatory, X: respiratory, XI: digestive, XII: skin, XIII: musculoskeletal, and XIV: genitourinary), infections (ICD-10 chapter I: infections), mental health and suicide (ICD-10 codes F00-F10, F20-F99, X60-X84), accidents and homicide (ICD-10 chapters XIX: injuring and poisoning excluding drug-related deaths, and XX: external), and all other causes. Some deaths, particularly those occurring in 2017 and 2018, did not yet have a recorded cause. In these cases we classified the cause as 'to be confirmed'. We divided the total years-of-life lost in each life table by 100,000 to estimate the average years lost per-person.

All analysis was conducted using R version 3.6.0. We have posted code and data that replicate the main results at https://github.com/danlewer/oats.

Ethics and approvals

This study is approved by the NSW Population and Health Services Research Ethics Committee (2018/HRE0205) and Aboriginal Health and Medical Research Council Research Ethics Committee (1400/18).

Role of the funding source

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

Results

The cohort included 47,197 participants, of which 32,048 (68%) were male and the median age at cohort entry was 32.8 (IQR 26.6-40.4). Table 1 provides descriptive information. A large proportion of participants entered the cohort in 2001-2006 as individuals with previous opioid agonist prescriptions joined the study at the start of follow-up (i.e. prevalent cases). Participants had a median of 9.8 years (range 0-17.1, IQR 3.7-15.4) of follow-up and 5,097 (11%) died. The median age of death was 47.1 (IQR 38.1-54.1).

<< Table 1: characteristics of people at first prescription of opioid agonist treatment in New South Wales, Australia, between 2001 and 2018 >>

Mortality rates and ratios

Mortality rates increased exponentially with age (Fig. 1). Men had higher crude mortality rates than women at all ages (table 2). For the whole cohort, the SMR was 6.06 (95% CI 5.90-6.23), and SMRs reduced with age.

<< Fig. 1: mortality rates in a cohort of people prescribed opioid agonists in New South Wales, 2001-2018, by age and sex >>

<< Table 2: Standardised mortality ratios by age and sex >>

Life expectancy at age 18

Life expectancy at age 18 was 47.5 years (95% CI 42.9-50.5) for men with a history of opioid dependence, compared to 62.2 for men in the general population, so the gap in life expectancy was 14.7 years. Life expectancy at age 18 for women with a history of opioid dependence was 50.7 years (95% CI 45.4-54.7), compared to 66.5 for the general population, so the gap in life expectancy was 15.8 years. These values represent years of life expected after age 18 (rather than the average age of death). In sensitivity analyses with truncated follow-up, estimates of life expectancy were between 0.2 years younger and 2.2 years older (with the shortest follow-up having the oldest life expectancy) and in analyses of incident cases only estimates were 2.7 years older for men and 3.5 years older for women (full results of the sensitivity analysis are shown in Supplementary Information 5).

Causes of death and potential years of life lost

Before weighting deaths by age, non-communicable physical diseases caused 42% of deaths for both men and women before age 75 in life-table analysis, while drug overdoses caused 18% and 19% of deaths for men and women respectively. Because drug overdoses occurred at a younger age (mean age of death 40.4 for men, compared to 60.8 for non-communicable diseases), each death contributed more potential years of life lost. After weighting deaths by age, non-communicable physical diseases and drug-related deaths each contributing approximately one-third of years of life lost. Fig. 2 shows the transition from drug-related causes to non-communicable diseases over the life course, and number of deaths by cause are shown in Supplementary Information 6.

<< Fig 2: Cumulative years-of-life lost and deaths, by cause of death >>

Discussion

People who are dependent on opioids have substantially raised risk of death. Our results show that life expectancy in people with opioid use disorders this population is approximately 15 years shorter than the general population; similar to studies of life expectancy among people with serious mental illnesses (Hjorthøj et al., 2017; Lawrence et al., 2013). These large health inequalities are related to multiple causes of death, with drug-related deaths contributing most at younger ages and non-communicable physical diseases at older ages.

Although mortality rates among people who use drugs are extremely high, these results show that a large proportion of people who experience these mortality rates throughout life will survive to an age where non-communicable diseases become the main cause of death and morbidity. The health needs of people in their 50s, 60s and 70s who use opioids (or used to use opioids) are likely to relate primarily to non-communicable diseases, rather than infections or drug-related problems.

Relation to other studies

The life expectancy deficit for people who are dependent on opioids far exceeds that associated with socioeconomic status alone. Life expectancy at birth in the general population of New South Wales was 83.6 in 2017, and was 2.3 years younger for people living in the most deprived quintile of neighbourhoods, and 2.5 years older for people living the least deprived quintile ("HealthStats NSW: Life expectancy," 2019). The high mortality rate among people who use opioids is a result of multiple risk factors, including opioid overdose; chronic toxicity of drugs such as the cardiotoxic effect of methamphetamine (Kaye and McKetin, 2005), which is commonly used in addition to opioids; tobacco smoking, which is nearly universal (Pajusco et al., 2012); hepatitis viral infections and alcohol use, which have a synergistic effect on the risk of cirrhosis and liver cancer (Corrao and Aricò, 1998); poor nutrition; and the high prevalence of mental health problems that increase the risk of suicide (Poorolajal et al., 2016).

We are aware of two prior studies of life expectancy among people who use opioids. One was small, including 106 deaths, finding life expectancy deficits of 9.0 years for men and 17.3 years for women (Hayes et al., 2011). The other included 1,005 deaths and focused on people starting methadone treatment in Spain in the 1990s (Brugal et al., 2005). Half of participants were HIV-positive; much higher than in contemporary samples of people who use opioids in high income countries, including Australia (Degenhardt et al., 2017), and life expectancy in this study was 38 years lower than the general population. Our study has the advantage of size (with 5,097 deaths), long follow-up, and inclusion of the whole population of people prescribed opioid agonists.

There are further studies of life expectancy in other socially excluded groups that often overlap with people who are dependent on opioids. Most studies focus on people with a diagnosis of a serious mental health problem, and a small number of studies focus on people with a history of any substance use disorder (including alcohol), homelessness, or prison. All of these studies found similarly large deficits in life expectancy compared to the general population. For example, a study of 32,711 people with experience of homelessness in Denmark estimated deficits of 22 years for men and 17 years for women (Nielsen et al., 2011). Where these studies decomposed deaths by disease, non-communicable diseases were the main cause of death, in common with our results. A review of studies of life expectancy in populations experiencing social exclusion is given in Supplementary Information.

Limitations

There are four main limitations to the study. First, the period life expectancy method assumed that mortality rates observed in our study are experienced throughout life. Actual mortality rates may differ because: (i) many individuals start using opioids later than age 18. The typical age of initiation varies by setting and period, but is usually between the late teens and mid-20s (Brecht et al., 2007; Hser et al., 2001); (ii) there is often a gap between initiation of drug use and the start of opioid agonist treatment, which is associated with higher mortality risk as people do not have the protective effect of opioid agonists (Sordo et al., 2017). The median age when participants in our study had a first episode of opioid agonist treatment was 30.4 (Supplementary Information 3), which is likely to be older than the age when people first used illicit opioids; and (iii) the episodic nature of drug use and potential cessation. Some members of the cohort may 'recover' after the end of follow-up, meaning that the life expectancy deficits in our study are overstated. Our study had relatively long follow-up (median 10 years) and episodic drug use is therefore partially reflected in our data. Cohort studies with very long follow-up (Oppenheimer et al., 1994; Smyth et al., 2007) show that opioid use and high mortality rates persist for decades, and some consider opioid dependence to be a chronic condition (Kleber, 2008). Also, the large proportion of deaths that relate to non-communicable diseases, rather than the acute effects of drugs, suggests that mortality rates are unlikely to fully recover even at complete cessation of drug use. Our sensitivity analyses did not suggest that life expectancy was shorter with truncated follow-up – in fact there was some evidence that life expectancy was longer in these sensitivity analyses, suggesting that mortality deficits may worsen rather than recover over time. These limitations are common to studies of life expectancy among marginalised groups, which also estimate period life expectancy and do not account for mortality rates prior to diagnosis or 'recovery'.

Second, our study excluded individuals who are dependent on opioids but have never accessed opioid agonist therapy. This is likely to be a minority in Australia. In a community-recruited sample of people who inject drugs in Melbourne, for example, only one in four had never been prescribed an opioid agonist, and this study explicitly aimed to recruit people with limited contact with drug treatment services (Horyniak et al., 2013). This population may have higher mortality risk because they do not have the protective effect of opioid agonists, or lower risk because they have less severe opioid dependence and therefore lower need for opioid agonists.

Third, mortality rates and causes of death in this population are affected by drug markets, which change over time and geographies, limiting the generalisability of our findings. For example, illicitly manufactured fentanyl (which is many times more potent than heroin) has recently become more common in North America. This has been associated with increasing numbers of drug overdoses (Slavova et al., 2017) and may be associated with reductions in life expectancy and an increasing proportion of deaths due to drug overdoses in this population. During the time period covered in this study, fentanyl has not yet been found in illicit opiates in Australia.

Fourth, we did not have data on deaths outside of New South Wales. This is likely to mean that mortality rates are underestimated, and hence life expectancies overestimated. However, we do not think this is a major bias because the sensitivity analyses with truncated follow-up do not show shorter life expectancies. If a substantial number deaths occurred outside of New South Wales, this would likely have a greater impact on analyses with longer follow-up.

Conclusion

In common with people with serious mental illnesses, people who are dependent on opioids have substantially reduced life expectancy. In both populations, most deaths relate to non-communicable physical diseases.

Tables

Table 1: characteristics of people in opioid agonist treatment in New South Wales, Australia, between 2001 and 2018

Variable		**n (%)**
Total		47,197 (100.0)
Age at cohort entry	18-24	8,828 (19.0)
	25-34	18,506 (39.0)
	35-44	13,611 (29.0)
	45-54	5,327 (11.0)
	55-64	839 (2.0)
	65-74	86 (<0.1)
	Median (IQR)	32.8 (26.6-40.4)
Sex	Male	32,048 (68.0)
	Female	15,149 (32.0)
Year of cohort entry	2001-2006	28,473 (60.0)
	2007-2012	9,804 (21.0)
	2013-2018	8,920 (19.0)
Aboriginal and/or Torres Strait Islander		9,859 (21.0)
Previous incarceration		13,297 (28.0)
Previous diagnosis of schizophrenia or bipolar disorder		3,328 (7.0)

Table 2: Standardised mortality ratios by age and sex

Sex	Age group	Person-years	Observed deaths	Crude mortality rate / 10,000 person years (95% CI)	Expected deaths	SMR (95% CI)
Male	18-24	15,160	86	567	10.1	8.50 (6.72-10.38)
	25-34	98,255	554	564	78.5	7.06 (6.49-7.65)
	35-44	124,824	978	784	160.1	6.11 (5.73-6.49)
	45-54	84,097	1,206	1,434	231.7	5.20 (4.91-5.50)
	55-64	27,139	762	2,808	160.5	4.75 (4.41-5.09)
	65-74	2,171	92	4,238	27.2	3.38 (2.72-4.08)
	Total	351,646	3,678	1,046	668.1	5.51 (5.33-5.68)
Female	18-24	10,093	30	297	2.5	12.00 (8.00-16.40)
	25-34	52,121	225	432	17.7	12.72 (11.08-14.42)
	35-44	62,184	392	630	43.1	9.09 (8.21-9.99)
	45-54	40,198	507	1,261	65.8	7.71 (7.04-8.38)
	55-64	11,483	239	2,081	37.9	6.31 (5.52-7.13)
	65-74	779	26	3,338	5.7	4.53 (2.79-6.28)
	Total	176,858	1,419	802	172.7	8.22 (7.79-8.65)
Total	18-24	25,253	116	459	12.6	9.19 (7.53-10.86)
	25-34	150,377	779	518	96.2	8.10 (7.54-8.67)
	35-44	187,008	1,370	733	203.3	6.74 (6.39-7.10)
	45-54	124,295	1,713	1,378	297.5	5.76 (5.49-6.03)
	55-64	38,622	1,001	2,592	198.3	5.05 (4.74-5.36)
	65-74	2,950	118	4,000	32.9	3.58 (2.94-4.25)
	Total	528,505	5,097	964	840.8	6.06 (5.90-6.23)

Additional information

Declarations of interest

MH reports honoraria for speaking at meetings from Gilead, Abbvie, and MSD. SN reports research funding (untied educational grants) from Indivior and Seqirus, and her institution has received honoraria from Indivior for delivery of training on opioid dependence. LD reports untied educational grant funding to conduct studies of new opioid medications in Australia from Indivior, Mundipharma, Seqirus and Reckitt Benckiser.

Contributions

Conceptualisation: DL. Study design: DL, NJ, MH, SN & LD. Data curation: NJ and DL. Formal analysis: DL and NJ. Original draft preparation: DL. Review and editing: DL, NJ, MH, SN & LD.

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Figure 1

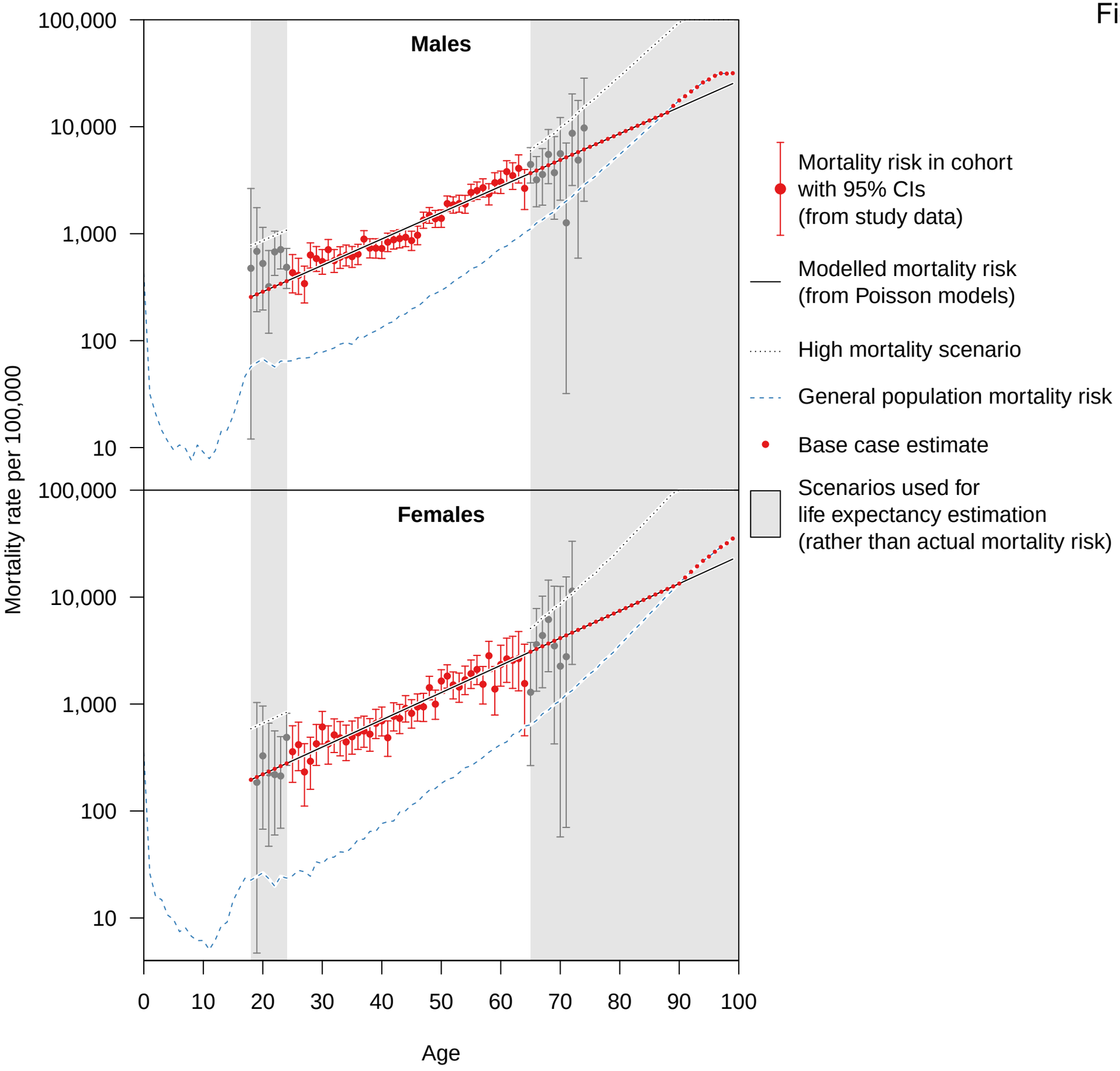
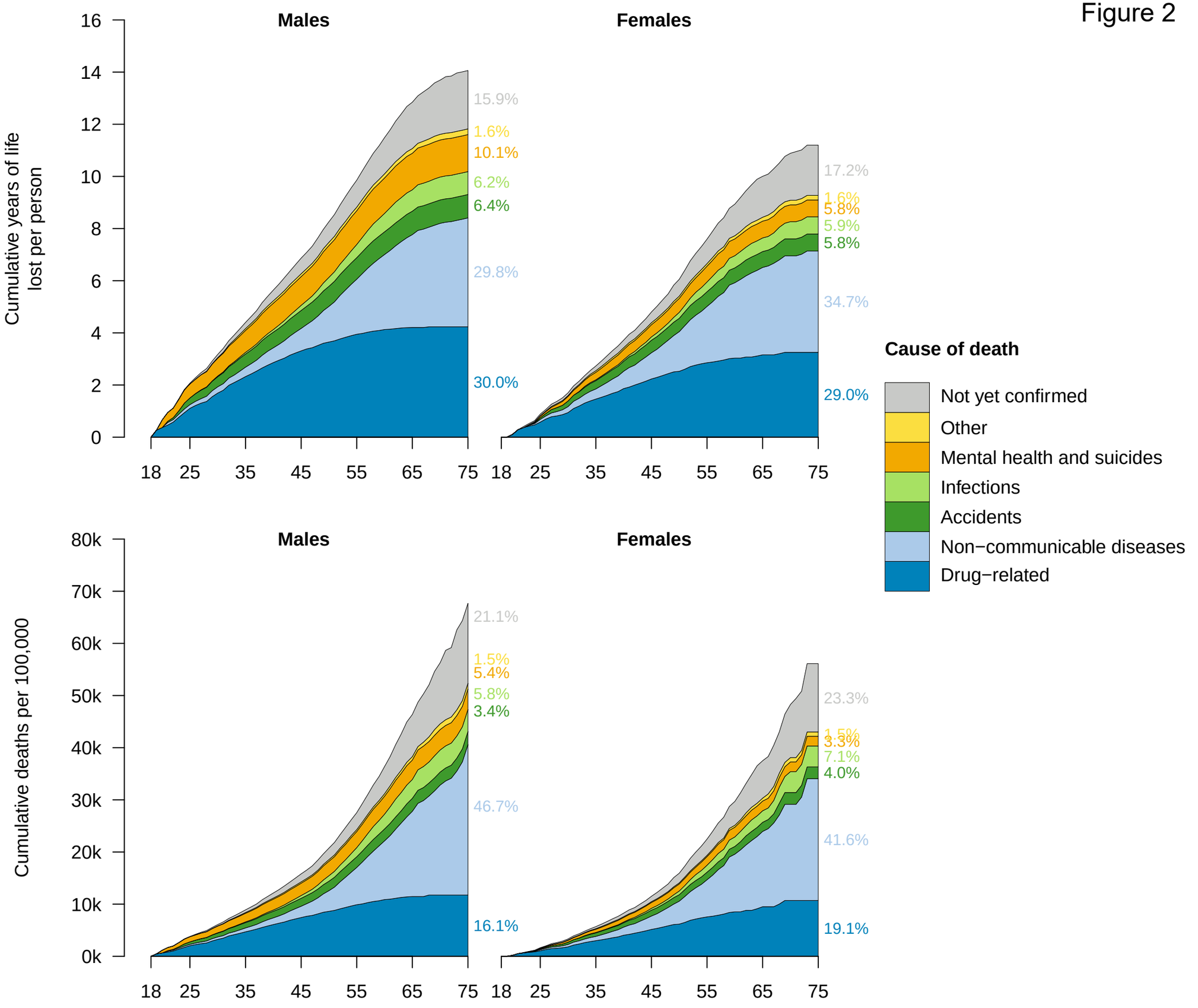

Males
Females
100,000
10,000
1,000
100
10
Mortality rate per 100,000
0
10
20
30
40
50
60
70
80
90
100
Age
Mortality risk in cohort
with 95% CIs
(from study data)
Modelled mortality risk
(from Poisson models)
High mortality scenario
General population mortality risk
Base case estimate
Scenarios used for
life expectancy estimation
(rather than actual mortality risk)

Figure 2


Males
Females
Cumulative years of life lost per person
16
14
12
10
8
6
4
2
0
18
25
35
45
55
65
75
15.9%
1.6%
10.1%
6.2%
6.4%
29.8%
30.0%
17.2%
1.6%
5.8%
5.9%
5.8%
34.7%
29.0%
Cause of death
Not yet confirmed
Other
Mental health and suicides
Infections
Accidents
Non−communicable diseases
Drug−related
Cumulative deaths per 100,000
80k
70k
60k
50k
40k
30k
20k
10k
0k
21.1%
1.5%
5.4%
5.8%
3.4%
46.7%
16.1%
23.3%
1.5%
3.3%
7.1%
4.0%
41.6%
19.1%

Supplementary Information

1 Existing studies of life expectancy in marginalised populations

Studies of relative mortality risk

A large number of studies have measured mortality among marginalised populations and reported the relative mortality risk (typically using standardised mortality ratios). These are summarised in table S1.

These reviews suggest large literatures on the mortality of people who use opiates and alcohol and people with serious mental health problems. There is less research into mortality among people who use other drugs (including cocaine and amphetamines), people who have experience of homelessness, prison, or sex work.

Studies consistently show higher mortality rates among older participants, men, and (for people who use opiates) those who are not in opioid substitution therapy.

Table S1: Systematic reviews of mortality in marginalised populations

Systematic review	Population	Number of studies included	Pooled CMR / 1,000 person-years	Pooled SMR
Mathers 2013[1]	People who inject drugs	76	23.5 (21.2 to 25.8)	14.68 (13.01 to 16.35)
Degenhardt 2011[2]	Regular or dependent users of opioids	58	20.9 (19.3 to 22.6)	14.66 (12.82 to 16.50)
Roerecke 2013[3]	Alcohol use disorder	81	-	Men: 3.38 (2.98 to 3.84); Women: 4.57 (3.38 to 5.42)
Sordo 2017[4]	People with opioid dependence, comparing periods in and out of opioid substitution therapy	19	11.3 in MMT; 36.1 out of MMT; 4.3 in BMT; 9.5 out of BMT	-
Degenhardt 2011[5]	Dependent cocaine users	7	5.3 to 61.1	4-8
Singleton 2009[6]	Amphetamine users	7	0 to 29.5	6.22 (from one study only)
Hayes 2015[7]	Bipolar affective disorder	31	-	2.05 (1.89 to 2.23)
Walker 2015[8]	People with mental health disorders	203	-	2.22 (2.12 to 2.33)
Saha 2007[9]	People with schizophrenia	37	-	2.50 (2.18 to 2.43)
Zlodre 2012[10]	Released prisoners	18	7.2 to 20.5	Men: 1.0 to 9.4; Women: 2.6 to 41.3
Aldridge 2018[11]	Homeless people, prisoners, sex workers, people with substance use disorders	Homeless: 3; Prisoners: 2; Substance use disorders: 23	-	Men: 7.88 (7.03 to 8.74); Women: 11.86 (10.42 to 13.30)

Studies of life expectancy

Methods

We reviewed literature on life expectancy or the life expectancy gap for marginalised groups. We defined the 'life expectancy gap' as the difference between life expectancy for the study group and the general population. Following previous research,[12] marginalised groups were defined as people with experience of serious mental illness, substance use disorders or illicit drug dependence, homelessness, imprisonment, or sex work.

We searched Medline and Google Scholar from inception to 17 February 2020 for 'life expectancy" AND ('substance misuse" OR 'substance abuse" OR 'substance use" OR 'drug dependen*" OR 'illicit drug*" OR heroin OR 'crack cocaine" OR methamphetamine OR (inject* adj2 drug*) OR methadone OR buprenorphine OR \serious mental" OR \severe mental" OR schizophrenia OR bipolar OR psychosis OR homeless* OR \sex work" OR *prison* OR incarcerat*).

Studies

Our search yielded 563 results, of which 45 were relevant after screening titles and abstracts. After full-text review, 33 studies included estimates of life expectancy or a life expectancy gap. Some of these studies included estimates for more than one population. Where studies included data points for multiple mental health disorders, we extracted a data point for schizophrenia. We extracted a total of 38 data points.

Evidence was mostly from Scandinavia and North America. Out of 38 data points, 16 were from Scandinavia, 9 from North America, 6 from the UK (all using the same dataset), 2 from Australia, and 1 from each of Spain, the Netherlands, Hungary and Ethiopia. 23/38 data points related to mental health problems, of which 12/23 have been synthesised in a previous systematic review of life expectancy among people with schizophrenia, which found a pooled life expectancy gap of 14.5 years (95% CI 11.2-17.8).[13] The remaining 11/23 studies focused on people with severe rather than common mental health problems (such as bipolar disorder or major depressive disorder, rather than mild or moderate depression), mainly because samples were drawn from registers of people with mental health diagnoses. 11/38 data points were for people with substance use disorders. 4/11 were of people living with HIV who have a history of injecting drugs;[14–17] 5/11 were for people who use any substances including alcohol;[18–22] and the remaining 2/11 focus on people who use opiates. One is a small sample from London, UK, with only 106 deaths during follow-up.[19] The other included 1,005 deaths, and is of people starting methadone treatment in Spain between 1992 and 1999.[23] 2/38 studies looked at homeless populations; 2/38 at people with experience of prison; and 0/38 on people with experience of sex work.

The average age of participants at study baseline ranged from 29.3[23] to 50.1.[24] Younger study samples (with an average age under 35) were from studies of people with experience of drugs or prison, and one study of people with schizophrenia in Taiwan. Older samples (with an average age over 45) were from studies of people with mental health problems (apart from one study of people living with HIV who have a history of injecting drugs). An average of 29% of samples of people with substance use disorders were female, compared to 50% for sample of people with mental health disorders.

Methodologies

All studies estimated period life expectancy by calculating age-specific mortality rates from a cohort study and using these rates in life tables. No studies estimated a cohort life expectancy (i.e. the expected average of death of a specific cohort of marginalised people, making assumptions about

future mortality rates in that cohort, or following an entire cohort until all have died). Most studies used the abridged life table method that uses mortality rates in age bands rather than by single-year-of-age.[25] Cohorts usually had few participants at older ages and assumptions about mortality rates at older ages were sometimes broad or unclear, such as using mortality rates for participants aged 55+ for all ages until death (when most deaths in the study are at the younger end of this age band). Some studies estimated mortality rate ratios using standardisation or regression models, then applied these ratios to general population life tables.[26–29] The abridged life table method and the approach using ratios are designed to smooth out rates or deal with age strata with zero deaths. Most studies estimated life expectancy at a certain age (for example 15 or 20), while those that estimated life expectancy at birth used mortality rates of the general population until an assumed minimum age of onset or diagnosis.[18,20,23,26,27,30–32] Two studies of people with mental health problems accounted for differing age at onset, arguing that calculating life expectancy from a minimum age of onset can overstate the average life expectancy gap.[22,33] This approach therefore aims to estimate the burden of mental illness across a population, rather than for people at a specific age.

All studies of people with substance use disorders or mental health problems except two[27,31] were based on cohorts of people with certain diagnoses (such as `schizophrenia' or `alcohol dependence') made in healthcare settings, and therefore do not account for survival prior to diagnosis. Studies included a mixture of incident and prevalent cases. The two exceptions recruited people with prevalent mental health problems using community surveys and then followed them up. Studies of people with experience of homelessness and prison were based on samples from relevant services.

Life expectancy results

All studies found large life expectancy gaps. Among the studies of life expectancy of people with substance use disorders, life expectancy gaps were very large among people living with HIV with a history of drug injection, with gaps of around 30 years. The study of people starting methadone treatment in Spain in the 1990s also had a very large life expectancy gap (38 years), which may reect the fact that 51% of the sample were HIV positive and 59% reported injecting. More recent studies of people with substance use disorders found life expectancy gaps ranging from 9.0 to 23.6 years for men and 13.4 to 22.6 years for women. Where studies reported the life expectancy gap separately for people with serious mental health problems and people with substance use disorders, those with substance use disorders had larger gaps.[18,20–22,34]

Causes of death

Almost all studies that decomposed the life expectancy gap by cause of death found that the majority of the gap was attributable to ‘natural’ causes or non-communicable diseases.[18,22,26,32,33,35–40] For example, a large study in Western Australia found that “almost 80% of excess deaths in people with mental illness are due to physical health conditions.”[20] While relative risks are highest for ‘external’ causes of death such as suicide, trauma, homicide and drug overdose, the most deaths in these studies were caused by common non-communicable diseases such as cancers, cardiovascular, and respiratory diseases. The exceptions were a study in rural Ethiopia where over half of deaths among people with serious mental illnesses were due to infectious diseases,[31] and the study of people entering methadone treatment in Spain in the 1990s, where 38% of deaths were due to AIDS.[23]

Mortality rates

Where studies reported mortality rates and rate ratios (comparing the study population to the general population) by age, rates increased with age and rate ratios decreased.[19,30,41–43] Detailed results from four studies suggested that mortality rates may plateau or even decrease in marginalised

populations up to age 30, and then increase,[22,34,39,42] though the robustness of this observation or possible reasons are unclear.

Conclusion

Although marginalised populations differ widely in terms of their demographics and social risk factors, all have substantially reduced life expectancy, with the gap mainly relating to common non-communicable diseases.

Table S2: Studies of life expectancy in marginalised populations

									Study population			General population			Gap		
Study	**Population**	**Study period**	**Setting**	**Sample size**	**Deaths**	**% Female**	**Average age[a]**	**Life expectancy at age**	**Men**	**Women**	**Both**	**Men**	**Women**	**Both**	**Men**	**Women**	**Both**
Newman 1991[26]	Schizophrenia	1976-1985	Canada: Alberta	3,623	301	41%	37.3	0	56.2	66.1		72	79.1		15.8	13	
Hannerz 2000[44]	Functional psychosis	1978-1983	Sweden	41,134	3,049	57%	-	20	41.5	48.7		54.6	60.5		13.1	11.8	
Hannerz 2001[34]	Substance use disorder	1978-1983	Sweden	53,237	1,446	17%	45.3	30	29.4	31.9		45	50.7		15.6	18.8	
	Schizophrenia			13,823	296	45%	48.9	30	37.1	41.2		45	50.7		7.9	9.5	
Brugal 2005[23]	Using heroin and starting methadone treatment	1992-1999	Spain: Barcelona	5,047	1,005	23%	29.3	0			39			77			38
Lloyd-Smith 2006[16]	HIV+ with a history of injection drug use	1996-2003	Canada: Vancouver	430	135	43%	34	20			19.5						
The Antiretroviral Therapy Cohort Collaboration 2008[17]	HIV+ with a history of injection drug use	1996-2005	Canada, Europe & US	6,241	-	-	-	20			32.6						
Tiihonen 2009[45]	Schizophrenia	1996-2006	Finland	66,881	19,735	54%	51	20			37.4			59.9			22.5
Chang 2011[18]	Substance use disorder	2007-2009	UK: South London	10,922	348	30%	43.5	0	63.9	66.9		77.5	81.7		13.6	14.8	
	Schizophrenia		UK: South London	7,018	322	37%		0	62.8	71.9		77.5	81.7		14.6	9.8	
Hayes 2011[19]	Dependent on opioids	2007-2009	UK: South London	4,834	106	30%	37.1	0	68.4	64.3		77.4	81.6		9	17.3	
	Dependent on alcohol			4,961	223			0									
Laursen 2011[35]	Schizophrenia or bipolar disorder	2000-2006	Denmark	48,764	7,497	-	-	15	57.8	64.6		76.5	80.9		18.7	16.3	

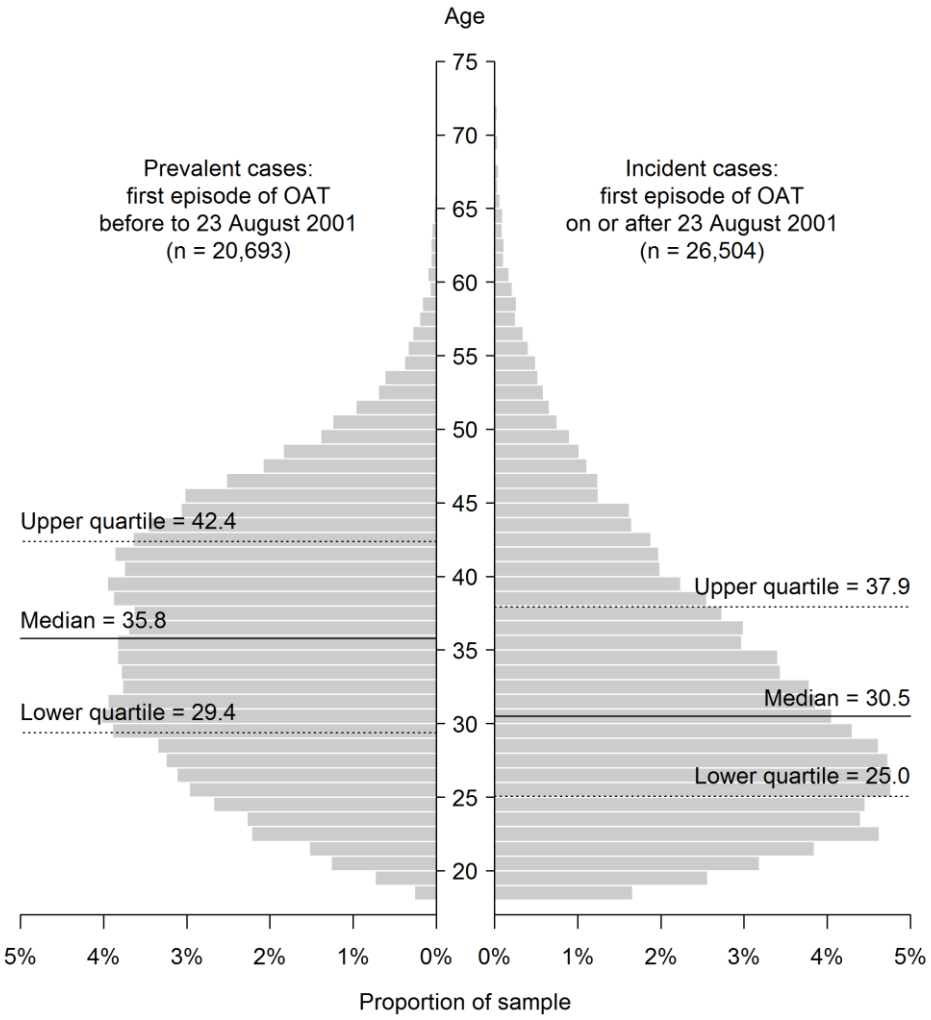
[a] Presented in some studies as a mean and in others as a median. Where the study only presents age categories, we estimated a mean age using the mid-point of categories (i.e. linear interpolation)

Study	Population	Study period	Setting	Sample size	Deaths	% Female	Average age[a]	Life expectancy at age	Study population			General population			Gap		
									Men	Women	Both	Men	Women	Both	Men	Women	Both
Nielsen 2011[42]	Homeless	1999-2009	Denmark	32,711	4,790	30%	38.8	15-24	38.7	47.4		60.3	64.8		21.6	17.4	
Wahlbeck 2011[43]	Any mental disorder excluding intellectual disability	2002-2006	Denmark, Finland & Sweden	280,963	-	-	-	15	39.3-43.3	48.3-53.1		60.8-63.6	65.4-68.0		18.9-21.9	13.6-17.1	
Westman 2011[46]	Schizophrenia; and neurotic, stress-related and somatoform disorders; and substance use disorders	1981-2003	Finland	341,630	91,445	-	-	15							16.3	11.2	
Fok 2012[30]	Personality disorder	2007-2010	UK: South London	1,836	43	60%	36.6	0	59.7	62.9		77.4	81.6		17.7	18.7	
Laursen 2013[36]	Schizophrenia or bipolar disorder	2000-2007	Denmark, Finland & Sweden	105,463	14,971	50%	-	15	40.9-50.3	48.8-55.0					12.7-20.0	11.0-16.9	
Lawrence 2013[20]	Alcohol or drug disorders	2003-2007	Australia: Western Australia	12,163	973	34%	-	0	57.4	63.1		79.1	83.8		21.7	20.7	
	Schizophrenia			13,100	685	38%	-	0	62.7	71.3		79.1	83.8		16.4	12.5	
Nordentoft 2013[21]	Substance use disorder	2000-2005	Denmark, Finland & Sweden	39,393	2,915	-	-	15							21.3-23.6	17.6-22.6	
	Schizophrenia spectrum			21,173	2,248	-	-	15							15.5-20.1	10.9-17.3	
Nusselder 2013[41]	Homeless	2001-2010	Netherlands: Rotterdam	2,096	265	88%	40.6	20	43.1	46.2		57.4	61.9		14.3	15.7	
Patterson 2013[29]	Released from prison to parole	1989-2003	US: New York	111,509	-	93%	30										
Fekadu 2015[31]	Schizophrenia, bipolar disorder or severe depression	1998-2012	Ethiopia: Butajira	919	121	38%	30.7	0	47.2	54		61.5[b]	65.1		14.3	11.1	
Kessing 2015[38]	Bipolar disorder	2000-2012	Denmark	22,635	-	60%	46.2	15	48.6	55.2		60.7	64.1		12.1	8.9	

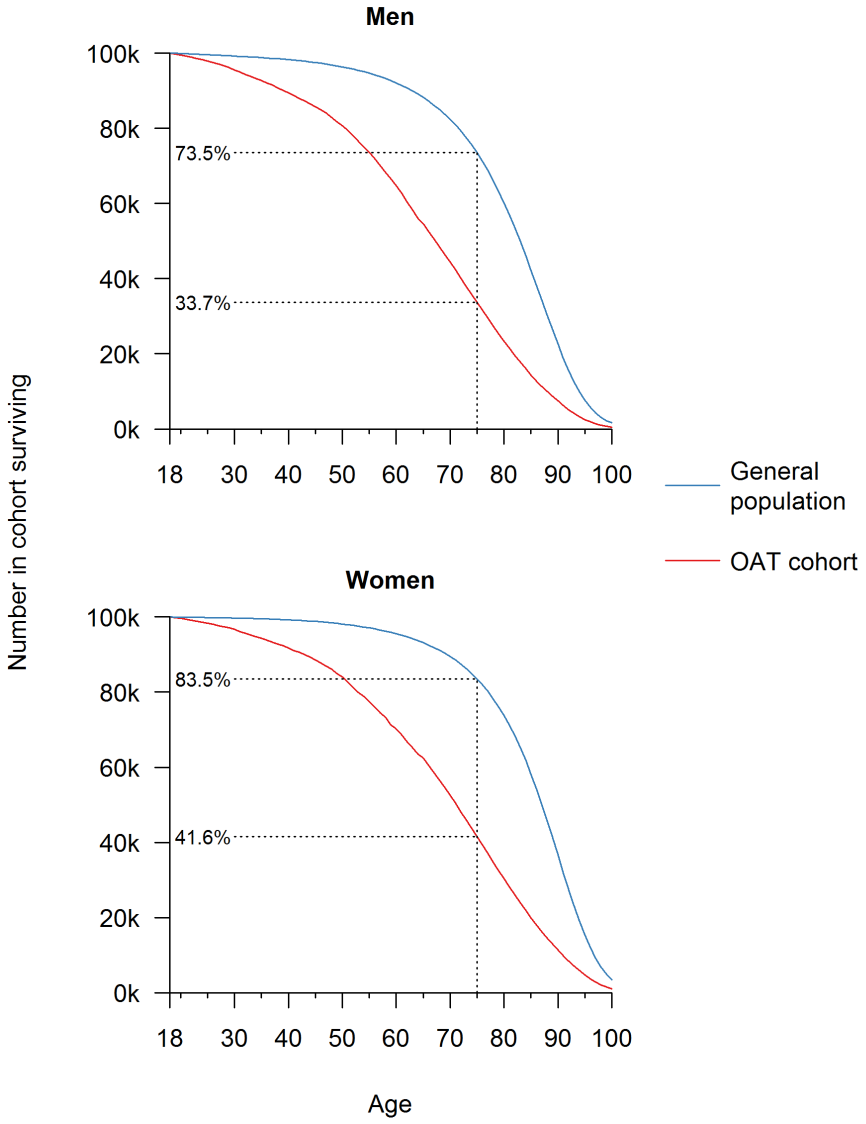
[b] Not provided in published article - we took general population values for 2012 from the World Bank (https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=ET)

Study	Population	Study period	Setting	Sample size	Deaths	% Female	Average age[a]	Life expectancy at age	Study population			General population			Gap		
									Men	Women	Both	Men	Women	Both	Men	Women	Both
Lesage 2015[40]	Schizophrenia	1999-2012	Canada: Quebec	-	-	-	-	1	65.5	72.6		77.7	82.8		12.2	10.2	
Patterson 2015[15]	HIV+ with a history of injection drug use	2000-2012	Canada	2,141	377	-	-	20			28.8			60			31.2
Kouyoumdjian 2016[39]	Admitted to provincial custody	2000-2012	Canada: Ontario	48,116	4,126	90%	32	25	48.4	47.3		52.6	57.9		4.2	10.6	
Laursen 2016[37]	Severe unipolar depression	1995-2013	Denmark	78,516	-	63%	-	15	46.1	54.5		60.1	64.6		14	10.1	
Leng 2016[28]	Schizophrenia	2000-2011	Taiwan	38,429	-	51%	33.3	20-29							15.2	9.2	
Tam 2016[27]	Serious psychological distress' based on a 6-item survey instrument	1997-2011	US	11,563	2,013	63%	49.5	0	63.6	65.6		70.2	73		6.6	7.4	
Bitter 2017[24]	Schizophrenia	2006-2013	Hungary	65,169	14,481	58%	50.1	20	36.5	43.2		48	56.9		11.5	13.7	
Erlangsen 2017[33]	Any psychiatric diagnosis	1995-2014	Denmark	589,327	134,150	66%	-	Diagnosis	29.3	34.6		39.5	41.9		10.2	7.3	
Jayatilleke 2017[32]	Schizophrenia or bipolar disorder	2007-2012	UK: South London	19,106	1,558	-	-	0	67.9	72.2		78.5	82.4		10.6	10.2	
Althoff 2019[14]	HIV+ with a history of injection drug use	2005-2015	US & Canada	17,798	4,672	15%	46.9	20			39.9						
Plana-Ripoll 2019[22]	Substance use disorder	1995-2015	Denmark	154,335	55,844	-	-	Diagnosis							14.8	13.4	
	Schizophrenia			103,848	32,357	-	-	Diagnosis							12.1	9.4	

2 Histograms of age at cohort entry



3 Survival curves



4 Sensitivity analysis with truncated follow-up

Table S3: Results of sensitivity analysis, with truncated follow-up or restricted to incident cases

Sex	Scenario	Life expectancy at age 18	Difference from main analysis
Male	Main analysis (complete follow-up)	47.52 (42.89-50.52)	-
	Follow-up truncated at 15 years	47.32 (42.77-50.37)	-0.20
	Follow-up truncated at 10 years	47.74 (42.39-50.46)	+0.22
	Follow-up truncated at 5 years	48.33 (42.11-50.50)	+0.81
	Incident cases only	50.22 (43.35-51.95)	+2.70
Female	Main analysis (complete follow-up)	50.71 (45.44-54.74)	-
	Follow-up truncated at 15 years	50.57 (45.28-54.70)	-0.14
	Follow-up truncated at 10 years	51.56 (45.44-55.26)	+0.85
	Follow-up truncated at 5 years	52.87 (45.55-56.25)	+2.16
	Incident cases only	54.24 (46.43-56.90)	+3.52

5 Causes of death before age 75

Table S4: Summary of causes of death

Sex	Cause	Number of deaths in cohort (%)	Mean age at death	Number of deaths in a life table of 100,000 (%)	Mean age at death in life table analysis	Years of life lost per person in life table analysis (%)
Male	Drug-related	1,057 (29%)	40.39	11,750 (16%)	40.0	4.2 (30%)
	Non-communicable diseases	1,174 (32%)	51.13	34,012 (47%)	61.5	4.2 (30%)
	Accidents	218 (6%)	40.47	2,497 (3%)	40.1	0.9 (6%)
	Infections	287 (8%)	50.36	4,234 (6%)	55.3	0.9 (6%)
	Mental health and suicide	302 (8%)	40.93	3,917 (5%)	39.8	1.4 (10%)
	Other	58 (2%)	44.34	1,099 (2%)	56.1	0.2 (2%)
	TBC	582 (16%)	49.91	15,337 (21%)	61.4	2.2 (16%)
	Total	**3,678 (100%)**	**46.21**	**72,846 (100%)**	**55.2**	**14.1 (100%)**
Female	Drug-related	414 (29%)	41.12	10,706 (19%)	45.6	3.3 (29%)
	Non-communicable diseases	500 (35%)	48.70	23,350 (42%)	59.4	3.9 (35%)
	Accidents	83 (6%)	39.31	2,259 (4%)	47.1	0.7 (6%)
	Infections	86 (6%)	49.56	4,004 (7%)	59.5	0.7 (6%)
	Mental health and suicide	95 (7%)	40.27	1,867 (3%)	41.4	0.6 (6%)
	Other	19 (1%)	44.92	830 (1%)	54.7	0.2 (2%)
	TBC	222 (16%)	49.51	13,104 (23%)	61.3	1.9 (17%)
	Total	**1,419 (100%)**	**45.50**	**56,121 (100%)**	**56.0**	**11.2 (100%)**

6 Results stratified by time period

We stratified results into three periods: 2001-2006, 2007-2012, and 2013-2018. For each period, we calculated age-specific mortality rates in the study cohort using the 'Lexis' method described in the article. This means that the duration of follow-up and the number of deaths were calculated daily for individuals under observation during each period. We then repeated the procedures described in the article for each period.

The results are shown in table S5. The age of participants increases during the study. This may be primarily a period effect in which people join the cohort at successively older ages, rather than an age effect in which individuals in the cohort age during follow-up (evidenced by the increase in the mean age of incident cases).

The crude mortality rates increase for both men and women, which is expected given the increase in mean age. There is no clear evidence of life expectancy of the study population increasing or decreasing during the study.

Table S5: Results stratified by period

Sex	Value	2001-2006	2007-2012	2013-2018	All years
Male	Person-years	73,954	128,426	149,266	351,646
	Mean age (sd)	36.3 (8.8)	39.6 (9.3)	43.3 (9.8)	40.5 (9.8)
	Mean age: incident (sd)	29.8 (8.3)	32.6 (9.2)	35.0 (10.0)	32.4 (9.4)
	Number of deaths	588	1298	1792	3678
	CMR/100,000 pys	795	1011	1201	1,046
	LE 18: OATS	47.93 (41.40-49.97)	46.40 (42.55-49.97)	47.80 (43.43-51.23)	47.52 (42.89-50.52)
	LE 18: Gen. Pop.	60.87	62.33	63.21	62.21
	Deficit	12.93	15.93	15.41	14.69
Female	Person-years	39,235	63,959	73,664	176,858
	Mean age (follow-up)	35.1 (8.7)	38.7 (9.2)	42.8 (9.7)	39.6 (9.8)
	Mean age: incident	28.5 (8.3)	32.1 (9.1)	35.7 (10.6)	31.9 (9.8)
	Number of deaths	218	485	716	1419
	CMR/100,000 pys	556	758	972	802
	LE 18: OATS	48.80 (45.08-55.32)	50.62 (44.75-54.44)	50.93 (45.38-55.05)	50.71 (45.43-54.73)
	LE 18: Gen. Pop.	65.64	66.56	67.23	66.53
	Deficit	16.85	15.94	16.30	15.81

LE 18 = life expectancy at age 18

OATS = study population (people with a history of opioid agonist therapy)

CMR = crude mortality rate

pys = person-years

Gen. Pop. = general population

'Mean age' is the mean age across all days of follow-up (with age of each participant calculated on each day). 'Mean age: incident' is the mean age of new participants joining the cohort, at cohort entry.

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