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RESEARCH REPORT

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Prevalence of opioid dependence in Scotland 2015–2020: A multi-parameter estimation of prevalence (MPEP) study

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Abstract

Background and aims: Drug-related deaths in Scotland more than doubled between 2011 and 2020. To inform policymakers and understand drivers of this increase, we estimated the number of people with opioid dependence aged 15–64 from 2014/15 to 2019/20.

Design: We fitted a Bayesian multi-parameter estimation of prevalence (MPEP) model, using adverse event rates to estimate prevalence of opioid dependence jointly from Opioid Agonist Therapy (OAT), opioid-related mortality and hospital admissions data. Estimates are stratified by age group, sex and year.

Setting: Scotland, 2014/15 to 2019/20.

Participants: People with opioid dependence and potential to benefit from OAT, whether ever treated or not. Using data from the Scottish Public Health Drug Linkage Programme, we identified a baseline cohort of individuals who had received OAT within the last 5 years, and all opioid-related deaths and hospital admissions (whether among or outside of this cohort).

Measurements: Rates of each adverse event type and (unobserved) prevalence were jointly modelled.

Findings: The estimated number and prevalence of people with opioid dependence in Scotland in 2019/20 was 47 100 (95% Credible Interval [CrI] 45 700 to 48 600) and 1.32% (95% CrI 1.28% to 1.37%). Of these, 61% received OAT during 2019/20. Prevalence in Greater Glasgow and Clyde was estimated as 1.77% (95% CrI 1.69% to 1.85%). There was weak evidence that overall prevalence fell slightly from 2014/15 (change −0.07%, 95% CrI -0.14% to 0.00%). The population of people with opioid dependence is ageing, with the estimated number of people aged 15–34 reducing by 5100 (95% CrI 3800 to 6400) and number aged 50–64 increasing by 2800 (95% CrI 2100 to 3500) between 2014/15 and 2019/20.

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Conclusions: The prevalence of opioid dependence in Scotland remained high but was relatively stable, with only weak evidence of a small reduction, between 2014/15 and 2019/20. Increased numbers of opioid-related deaths can be attributed to increased risk among people with opioid dependence, rather than increasing prevalence.

KEYWORDS
Bayesian methods, indirect estimation, multi-parameter estimation of prevalence, opioid agonist therapy, people with opioid dependence, prevalence estimation

INTRODUCTION

There is an urgent need to generate more consistent and transparent estimates of the prevalence of problem drug use—especially people who inject drugs (PWID) and people with opioid dependence—to understand better and inform policy makers on the scale of drug-related harm, intervention coverage and priorities for treatment and prevention [1–4]. In Scotland, there is an ongoing public health emergency in drug-related deaths (DRDs), where the number of DRD has more than doubled between 2011 and 2020 and, at 250 to 300 per million population in 2021/22, was 16 times higher than the average in the European Union and on par with rates in North America [5]. In Scotland, nearly 90% of DRDs involve opioids, and the overall DRD mortality rate in a cohort of people who were in or had been in opioid agonist therapy (OAT) increased threefold from 0.6% in 2011 to 2.1% in 2020 [6]. Nonetheless, OAT in Scotland has remained strongly protective, with DRD rates reduced by more than 60% among people retained in OAT compared with those who left OAT—consistent with global evidence [6, 7]. A critical question is whether the substantial increase in DRD in Scotland indicates an increase in prevalence of opioid dependence or is explained entirely by the increased mortality risk within the opioid-dependent population.

It is widely recognised that household surveys and other direct survey methods suffer from too many biases to generate valid estimates of the number of people injecting, or using opioids—often giving estimates below the number of people known to be in drug treatment [8–10]. So-called 'indirect' methods are needed instead, which rely on piecing together information from different administrative data sources, using statistical approaches. The two most commonly used indirect methods, multipliers and capture-recapture, are however subject to a number of assumptions that are not always tenable, and can lead to highly biased estimates if these assumptions are violated (see Box) [11]. This led us to develop and propose an alternative modelling approach for indirect estimation [12, 13], which we call 'multi parameter estimation of prevalence' (MPEP) (see Box).

Globally, the amount of evidence about prevalence of PWID has increased, but there remains considerable uncertainty on whether changes or differences in prevalence estimates are real or a consequence of differences in the methods and data used [3]. In Europe, prevalence estimates of PWID and people with opioid dependence are missing or out of date for many countries, with drug treatment data and other indicators taken as evidence that the population is ageing and frequency of injecting may be in decline [14]. In the United States (US), a recent national estimate suggested that there were 3.7 million PWID (1.5% of adults) in 2018 [15], updating an earlier multiplier study that estimated 1% in US metropolitan areas [16].

In this study, we provide new estimates of prevalence in Scotland for 2014/2015 to 2019/2020. Previous estimates of the number of 'problem drug users' in Scotland were based on capture-recapture, but this is no longer viable because of unavailability of some previously used data sources [17]. This, alongside recognition of the limitations of capture-recapture (see Box), led us to apply an MPEP approach to estimate prevalence of opioid dependence in Scotland. Our estimates are based on joint modelling of OAT prescription and opioid-related deaths and hospital admissions data.

Box: Indirect methods for prevalence estimation

Capture recapture involves linking several administrative datasets (e.g., people arrested for opioid use, opioid non-fatal overdoses leading to hospital admissions, and people in OAT), and fitting a model to describe the overlap of these populations. The model is extrapolated to estimate the number of people with opioid dependence who were not observed in any of these datasets and therefore the total population size. An advantage of the approach is the relative accessibility of modeling, typically with log-linear regression models. In principle, it is straightforward to model dependencies between data sources (e.g., people receiving OAT may have been referred from the criminal justice system) and heterogeneity in 'capture' probability using interaction terms. However, prevalence estimates can be highly sensitive to the assumed dependence structure and biased when the structure is complex or incorrectly specified [11, 12, 18]. **Multiplier methods** estimate population size by generating a 'benchmark', the number of some drug-related event (e.g., opioid overdoses) in a population, and then applying a 'multiplier' which is the reciprocal of the proportion of people with opioid dependence who would be expected to experience this event. This is a very simple approach, but relies heavily on an unbiased estimate of the event probability in the relevant population. A key difficulty in practice is that the multiplier is often 'borrowed' from other regions or time periods, where the event rate might differ. Multiplier methods also assume that the event

modelled is specific to the population of interest [12, 19]. **Multi-parameter estimation of prevalence (MPEP)** is a Bayesian statistical modelling approach, involving fitting simultaneous regression models to rates of adverse events (e.g., opioid-related deaths and hospital admissions) and to (unobserved or 'latent') prevalence [12, 13]. The approach relies on linkage of routinely collected OAT data to adverse event records. The advantages of MPEP over traditional multiplier methods, alongside a more detailed critique of capture-recapture, have been described in an Addiction Methods and Techniques article [12]. In further model development, it was demonstrated how two or more distinct types of adverse event can be included in the model, allowing prevalence to be jointly estimated from these [13]. This offers an additional advantage of allowing consistency of evidence and robustness of estimates to be assessed, by producing results based on each type of event modelled separately as sensitivity analyses.

METHODS

We estimated the prevalence of opioid dependence among the Scottish population aged 15 to 64 years for each financial year 2014/2015 to 2019/2020, using an MPEP approach. Estimates are based on joint modelling of opioid-related deaths and opioid-related hospital admissions data. We produced estimates stratified by age group (15–34, 35–49 and 50–64 years), sex (male, female) and year. We also generated estimates for three regional health authorities ('NHS Boards'), Greater Glasgow and Clyde, Lothian and Tayside. We produced crude estimates of annual OAT coverage or exposure, as the number of people who received at least one OAT prescription during the year as a percentage of the estimated number of people with opioid dependence.

Overview of the MPEP modelling approach

MPEP (see Box) is a Bayesian statistical modelling approach that is conceptually similar to a traditional multiplier method for prevalence estimation, in that population size is inferred based on observed numbers of adverse events and estimates of the rate at which such events occur among people with opioid dependence [12, 13]. MPEP, however, offers multiple advantages over traditional multipliers, including the ability to jointly estimate prevalence from multiple types of adverse events—allowing for consistency checks and increasing robustness of conclusions [12, 13]. The approach involves modelling rich linked administrative data on a large number of individuals from the community of interest, which are identified via treatment records. This ensures that event rates are estimated from the correct geographical region and time period and allows us to accommodate variation in rates by demographic variables and—critically—by treatment status [12, 13]. MPEP also typically produces estimates that are more precise than those based on multipliers, because only the size of the 'unobserved' portion of the population needs to be estimated.

The model relies on administrative data on (at a minimum) all people with opioid dependence who are receiving OAT, linked to adverse event data such as DRDs and/or hospital admissions. We refer to this observed portion of the population as the 'baseline cohort'. Poisson regression models are fitted to aggregated data from the baseline cohort, to estimate how the rate of these adverse events varies with demographic factors, year and OAT status ('on' vs 'off' OAT).

The additional number of people with opioid dependence who were 'unobserved' (i.e. not in the baseline cohort) is inferred from counts of additional adverse events of the same definition that occurred outside of the cohort. This is possible through two key assumptions. First, it is assumed that, among each demographic group, rates of these adverse events among the unobserved population are equal to rates among the baseline cohort during periods not on OAT. Second, it is assumed that these events only occur among the opioid-dependent population. For this reason, it is critical to model only subsets of DRDs and/or hospital admissions that we can be confident are highly specific to people with opioid dependence.

The estimated total number of people with opioid dependence is the number of people in the baseline cohort plus the estimated number 'unobserved'. A regression modelling structure is simultaneously fitted to latent prevalence, defined as the number of people with opioid dependence divided by the total general population size.

The general modelling approach and assumptions have been described, and piloted on case studies of England and Australia, previously [12, 13]. The approach has also been recently applied in Ohio and Massachusetts, United States [20, 21].

The analysis was not pre-registered and, therefore, is considered exploratory.

Data

We used data from the Scottish Public Health Drug Linkage Programme (SPHDLP). This includes administrative data on all individuals receiving OAT prescriptions in the community in Scotland, linked to mortality and hospital admission data. We defined the baseline cohort of people with opioid dependence, for each financial year, as all people living in Scotland, age 15 to 64 years, who received at least one OAT prescription during either the current or preceding 4 years. Because we estimated prevalence from 1 April 2014, this meant that prescription data from 1 April 2010 onward was used. For each individual in the baseline cohort, follow-up time began on 1 April 2014 for those who received an OAT prescription during the preceding 4 years, or at date of first subsequent prescription otherwise. Follow-up was censored at the earliest of date of death, date of known move out of Scotland, the end of financial year lying between 4 and 5 years since last treatment or 31 March 2020. All observation time within

each year was coded as 'on' versus 'off' OAT, using a procedure previously described [12, 13].

Note that this definition of the baseline cohort involves an implicit assumption that individuals remain opioid-dependent for at least 4 years after their last OAT prescription. Some 'off OAT' observation time is required for the model, to estimate event rates. We considered it likely that long-term cessation of opioid use was negligible over a 5-year period, but also performed sensitivity analysis with a shorter time to censoring (see below) [22].

As described above, adverse events included in the MPEP model must be highly specific to people with opioid dependence. We included the following (see the Supporting Information for rationale):

(1) Opioid-related deaths: we included accidental fatal drug-related poisonings (with International Classification of Diseases [ICD]-10 code for main underlying cause of death F11.2, F11.9 or X42), if toxicology reports indicated that heroin/morphine, methadone or buprenorphine was implicated in or potentially contributed to the death. We excluded deaths that occurred among people who had been prescribed strong opioid analgesics on a long-term basis.

(2) Opioid-related hospital admissions: we included non-fatal drug-related poisonings that led to acute hospital admissions, with ICD-10 code indicating poisoning by opium, heroin or methadone (codes T40.0, T40.1, T40.3 in main or secondary position of the first episode).

Deaths and hospital admissions meeting these definitions were included in the model whether they occurred among or outside of the baseline cohort. Baseline cohort data were aggregated by sex, age group, year, treatment status (on and off), and region (Greater Glasgow and Clyde, Lothian, Tayside and the rest of Scotland) for modelling. Numbers of additional opioid-related deaths and hospital admissions that occurred out of the baseline cohort were similarly aggregated by sex, age group, year and region.

A more detailed description of the data and coding is provided in Section 1 of the Supporting Information.

Statistical modelling

The MPEP model is described in detail in Section 2 of the Supporting Information.

In brief, we modelled opioid-related deaths and hospital admissions within the baseline cohort using Poisson regression models, with follow-up time accounted for using offset terms. These regressions included main effects of year, sex, age group, treatment status and region and an interaction between treatment and year, at a minimum. This interaction term was included based on previous evidence for a treatment by year interaction on DRDs [6]. Additional interactions were included if supported by model fit statistics (see below).

Poisson distributions were similarly assumed for the numbers of additional events that occurred outside of the baseline cohort. We assumed that these events occurred at the same rates (within each sex, age, year and region group) among unobserved people with opioid dependence as observed in the cohort during time 'off' OAT. The (unobserved) person-years at risk are specified as a function of prevalence. Prevalence was assumed to follow a linear regression model structure on the log-odds scale. This regression model included main effects of sex, age, year and region at a minimum, with inclusion of interaction terms guided by model fit statistics.

We used the deviance information criterion (DIC) to inform model selection, lower values of which indicate a better fit of the model. All models were fitted using the Bayesian statistical software JAGS [23] run through R. MPEP models are fitted within a Bayesian framework for pragmatic, rather than philosophical reasons. Software such as JAGS facilitates fitting of multiple simultaneous regression models, including regression model structures on unobserved parameters (here, prevalence) and the flexibility to incorporate a wide range of data types.

All Bayesian models require 'prior distributions' to be assigned to parameters such as regression coefficients. A prior distribution represents knowledge or beliefs about the parameter before this is updated from the data. Incorporating external information using prior distributions can be very useful: for example, we previously demonstrated how external information can be incorporated in an MPEP model to account for imperfect linkage [12]. In this study, however, no such external information was incorporated. To increase objectivity of results, or when there is no prior information available, 'vague' or 'non-informative' prior distributions are used with the intention that the results are driven entirely by the data rather than prior beliefs [24]. In our analyses, we used vague prior distributions for all parameters, for example, Normal distributions with mean zero and large variance for regression coefficients. All priors are specified in the Supporting Information (Section 2.8).

Parameter estimates are shown with 95% credible intervals (CrIs). These are similar in essence to confidence intervals, in that they reflect uncertainty about estimates, but have a more direct interpretation as a range in which there is a 95% probability that the parameter lies.

Sensitivity analyses

Because our estimates of prevalence were based on joint modelling of opioid-related deaths and hospital admissions, we performed sensitivity analyses in which we removed each of these two data sources in turn. In an additional sensitivity analysis, we censored baseline cohort follow-up time at 1 to 2 years since last OAT prescription, instead of 4 to 5 years. We also performed a sensitivity analysis in which we changed the mean values of prior distributions for intercept terms in regression models (see Section 2.8 of the Supporting Information). Finally, we performed a sensitivity analysis in which we replaced all assumed Poisson distributions with negative binomial distributions, to assess evidence for and allow for any overdispersion.

RESULTS

Table 1 shows the aggregated data used in the model. The baseline cohort included 43 791 unique individuals over the 6-year period. A

total of 3314 opioid-related deaths and 4160 hospital admissions were modelled.

Figure 1 and Table 2 show the estimated prevalence of opioid dependence in the Scottish population ages 15 to 64 years (overall and by sex) from 2014/2015 to 2019/2020. Results have been jointly published with Public Health Scotland and more detailed stratified estimates are provided online [25].

The overall prevalence and number in 2019/2020 were estimated as 1.32% (95% CrI = 1.28%–1.37%) and 47 100 (95% CrI = 45 700–48 600), respectively (Table 2). Prevalence was estimated at 1.85% in men and 0.82% in women during that year. There was weak evidence of a small reduction in overall prevalence since 2014/2015 when it was estimated as 1.39% or 49 100 (estimated change in prevalence and in number of individuals −0.07%, 95% CrI = −0.14% to 0.00%, and −2000, 95% CrI = −4700 to 400, respectively). Estimated prevalence was, however, slightly lower in 2017/2018, at 1.27%, or 45 000 people. In each of the 6 years, around two-thirds of people with opioid dependence in Scotland were male.

TABLE 1 Aggregate data (by year) used in the model: number of individuals in the baseline cohort, and number with at least one OAT prescription during the year; person-years at risk; number of opioid-related deaths and opioid-related hospital admissions included in the model, stratified by treatment status at time of event.

	2014/2015	2015/2016	2016/2017	2017/2018	2018/2019	2019/2020	Total
No. of people in baseline cohort	35 142	35 329	35 403	35 345	35 036	34 933	43 791[a]
No. of people with at least one OAT prescription	28 302	28 819	29 220	29 356	29 059	28 855	40 059[a]
Person-years at risk							
On OAT	22 464	22 669	22 931	23 580	23 013	22 768	137 425
Off OAT	11 386	11 303	11 011	10 365	10 582	10 739	65 386
Total in baseline cohort	33 850	33 972	33 942	33 945	33 595	33 507	202 811
Deaths							
On OAT	64	80	124	184	199	198	849
Off OAT	135	147	182	218	279	249	1210
Out of baseline cohort	168	156	168	210	269	285	1256
Total	367	383	474	612	747	732	3315
Hospitalisations							
On OAT	223	253	347	398	478	435	2134
Off OAT	142	157	150	181	195	171	996
Out of baseline cohort	147	168	165	156	194	200	1030
Total	512	578	662	735	867	806	4160

Abbreviation: OAT, opioid agonist therapy.
[a]Total number of unique individuals across the 6-year period.

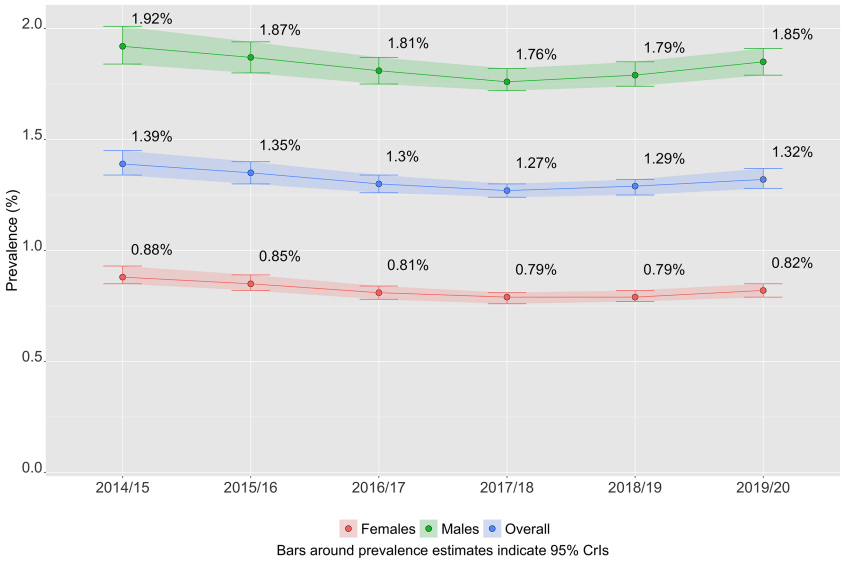

FIGURE 1 Estimated prevalence of opioid dependence among the population aged 15 to 64 years in Scotland; overall and by sex; 2014/2015 to 2019/2020. Abbreviation: CrIs, credible intervals.

TABLE 2 Estimated prevalence of opioid dependence among the population aged 15 to 64 years in Scotland; overall and by sex; 2014/2015 to 2019/2020.

Overall	No. (95% CrI)	Prevalence (95% CrI)	Implied % observed (95% CrI)	Implied % OAT exposure (95% CrI)
2014/2015	49 100 (47 200–51 300)	1.39% (1.34%–1.45%)	72 (69%–74%)	58 (55%–60%)
2015/2016	47 800 (46 100–49 600)	1.35% (1.30%–1.40%)	74 (71%–77%)	60 (58%–63%)
2016/2017	46 100 (44 800–47 600)	1.30% (1.26%–1.34%)	77 (74%–79%)	63 (61%–65%)
2017/2018	45 000 (43 800–46 200)	1.27% (1.24%–1.30%)	79 (77%–81%)	65 (64%–67%)
2018/2019	45 600 (44 400–46 900)	1.29% (1.25%–1.32%)	77 (75%–79%)	64 (62%–65%)
2019/2020	47 100 (45 700–48 600)	1.32% (1.28%–1.37%)	74 (72%–76%)	61 (59%–63%)
Males				
2014/2015	33 300 (32 000–34 800)	1.92% (1.84%–2.01%)	70 (67%–73%)	57 (54%–59%)
2015/2016	32 400 (31 300–33 700)	1.87% (1.80%–1.94%)	73 (70%–75%)	60 (57%–62%)
2016/2017	31 500 (30 600–32 600)	1.81% (1.75%–1.87%)	75 (73%–78%)	62 (60%–64%)
2017/2018	30 800 (30 000–31 700)	1.76% (1.72%–1.82%)	77 (75%–79%)	64 (62%–66%)
2018/2019	31 300 (30 500–32 200)	1.79% (1.74%–1.85%)	75 (73%–77%)	63 (61%–64%)
2019/2020	32 300 (31 400–33 400)	1.85% (1.79%–1.91%)	73 (71%–75%)	60 (58%–62%)
Females				
2014/2015	15 800 (15 200–16 600)	0.88% (0.85%–0.93%)	74 (71%–77%)	59 (57%–62%)
2015/2016	15 300 (14 700–16 000)	0.85% (0.82%–0.89%)	77 (73%–80%)	62 (59%–65%)
2016/2017	14 600 (14 100–15 200)	0.81% (0.78%–0.84%)	80% (77%–83%)	65 (63%–68%)
2017/2018	14 200 (13 800–14 700)	0.79% (0.76%–0.81%)	82 (79%–84%)	67 (65%–69%)
2018/2019	14 300 (13 900–14 800)	0.79% (0.77%–0.82%)	80 (77%–82%)	66 (64%–68%)
2019/2020	14 700 (14 200–15 300)	0.82% (0.79%–0.85%)	77 (74%–80%)	64 (62%–66%)

Note: Numbers in parentheses are 95% CrIs. Implied % observed = the proportion of the estimated number of people with opioid dependence who were in the baseline cohort (i.e. some OAT during the past 5 years). Implied % OAT exposure = the proportion of the estimated number of people with opioid dependence who received at least one OAT prescription during the year.
Abbreviations: CrI, credible intervals; OAT, opioid agonist therapy.

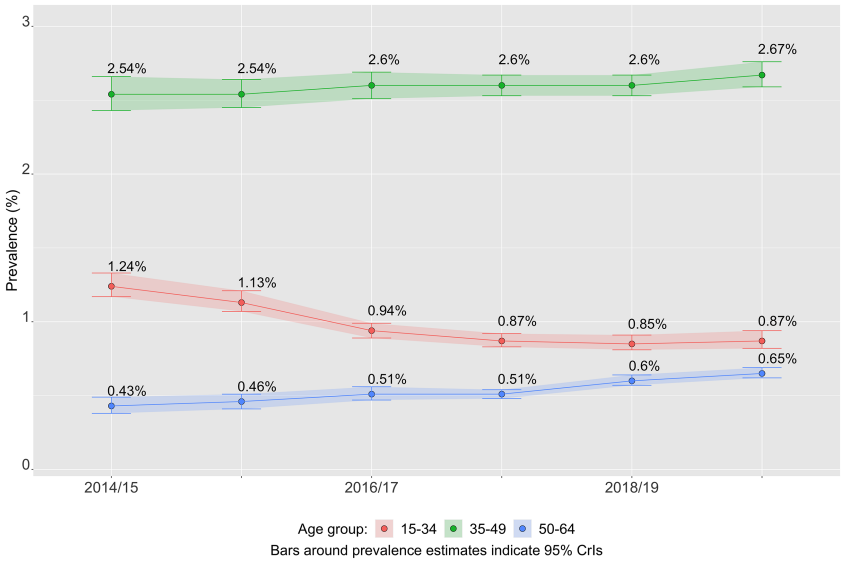

FIGURE 2 Estimated prevalence of opioid dependence among the population aged 15 to 64 years in Scotland; by age-group; 2014/2015 to 2019/2020. Abbreviation: CrIs, credible intervals.

An estimated 61% of people with opioid dependence in 2019/2020 received at least one OAT prescription during that year, whereas a total of 74% were in contact with OAT services at some point over the last 5 years. OAT exposure was estimated to be slightly higher in females than males (Table 2).

Figure 2 shows estimated prevalence by age group for each year. This was highest among those aged 35 to 49 years and lowest among those aged 50 to 64 years in each of the 6 years. However, there was a reduction in the estimated number of people with opioid dependence aged 15 to 34 years (17 200–12 100: change −5100 [95% CrI

= −6400 to −3800]) and an increase in the number aged 50 to 64 years (4600–7400: change 2800 [95% CrI = 2100–3500]) between 2014/2015 and 2019/2020.

Across the time-series, the highest estimated prevalence was among men aged 35 to 49 years. Prevalence in this group was estimated as 3.81% (95% CrI = 3.69%–3.94%) in 2019/2020. Of people with opioid dependence in this group, 66% (95% CrI = 63%–68%) received at least one OAT prescription during 2019/2020, whereas 79% received OAT at some point during the last 5 years. OAT exposure was estimated to be lower among people with opioid dependence aged 15 to 34 years (e.g. 45%, 95% CrI = 42%–49%, in 2019/2020) [25].

Figure 3 shows prevalence estimates for the three NHS Boards modelled. We do not report estimates for 'rest of Scotland' because measures for this large and heterogeneous area are not informative. In Greater Glasgow and Clyde in 2019/2020, there were an estimated 14 100 (95% CrI = 13 500–14 800) people with opioid dependence, or 1.77% (95% CrI = 1.69%–1.85%) prevalence. This was a reduction from the estimated 15 400 (95% CrI = 14 700–16 300) people in 2014/2015 [25].

Sensitivity analyses

Overall prevalence estimates using one of the two adverse event data sources (deaths only or hospitalisations only) differed only slightly (maximum of 0.07% or 2200 people) from the estimates from the primary analysis (based on both data sources simultaneously). Comparing results by age/sex group, we found that estimates were consistent for all groups and years except for males aged 15 to 34 years. In each of the 6 years, estimated prevalence in this group was lower (by between 0.31% and 0.54%) based on hospital admissions data alone than from mortality data alone. For example, in 2019/2020 prevalence of opioid dependence in males aged 15 to 34 was estimated as 1.36% (95% CrI = 1.21%–1.53%) based on deaths data alone or 0.94% (95% CrI = 0.87%–1.01%) based on hospitalisations data alone. This corresponds to a difference of 2800 people (single source estimates 9400 and 6600).

Estimates of prevalence based on censoring baseline cohort follow-up time at 1 to 2 years since last OAT prescription, rather than 4 to 5 years, generated estimates that were slightly lower (by 0.1% or 3000 people on average) than those based on our primary analysis. Results were robust to changing the mean values of prior distributions for intercept terms. Negative binomial, rather than Poisson, for the regression models, had no effect on the width of credible intervals of the estimated prevalence, suggesting no evidence of overdispersion.

More detailed results from these sensitivity analyses are provided in Section 3 of the Supporting Information.

DISCUSSION

Main findings

We estimate that the number of people with opioid dependence in Scotland in 2019/2020 was 47 100 (95% CrI = 45 700–48 600), which corresponds to 1.32% (95% CrI = 1.28%–1.37%) of the population aged 15 to 64. This is high relative to many countries, particularly for Western Europe, and slightly lower than national estimates for the United States [3, 14, 15, 26]. There was some evidence that prevalence fell slightly overall since 2014/2015, although it may have been slightly lower still in 2017/2018. A small reduction in prevalence was most apparent in young people and in Greater Glasgow and Clyde. Over this 6-year period, there were 3315 opioid DRD and an additional 1487 deaths from other causes among our observed cohort. The substantial increase in DRD in Scotland cannot be explained entirely by changes in the underlying population, but appears to have been driven by the increased DRD risk experienced by the population of people who are dependent on opioids (which has been shown in previous analyses) [6]. This increased risk occurred despite

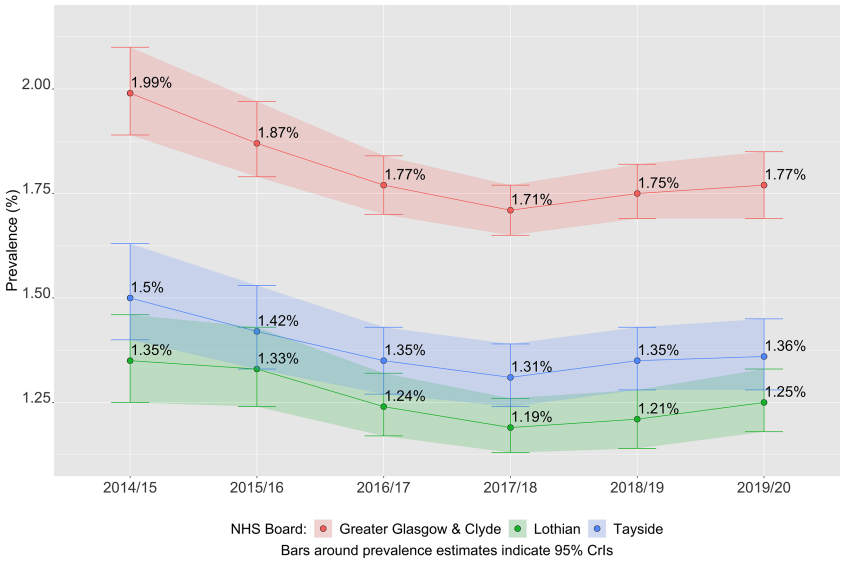

FIGURE 3 Estimated prevalence of opioid dependence among the population aged 15 to 64 years in NHS Boards Greater Glasgow and Clyde, Lothian and Tayside; 2014/2015 to 2019/2020. Abbreviation: CrIs, credible intervals.

comparatively high levels of exposure to OAT compared to many countries globally [2].

Other evidence

This is the first use of MPEP to estimate trends in national estimates that are consistent with multiple indicators of drug-related harm (opioid-related deaths and non-fatal opioid overdoses). Other studies using MPEP were developmental, examined a sub-group of the population on Medicaid or produced estimates for a single year [12, 13, 20, 21]. Our estimates are lower than previous estimates in Scotland from a capture-recapture model of the number of problem opioid and benzodiazepine users in 2015/2016 (estimate 57 300, 95% confidence interval = 55 800–58 900) [17], higher than previous estimates of recent (last 6 months) injecting drug use, but lower than estimates of non-recent injecting drug use (15 400 and 67 200, respectively) in 2009 [27]. Although the population definitions vary, it is more likely that methodological differences are driving the discrepancy with previous 2015/2016 problem drug use estimates. Both studies aimed to estimate the size of the same underlying population, that is, people eligible for OAT and at risk of opioid-related harm (such as DRD, suicide, other causes of premature mortality and blood borne and bacterial infections) [5]. In Scotland, DRD predominantly involve opioids and most people with opioid dependence report an injecting history. There is also considerable polydrug use, especially street and prescribed benzodiazepines, and growing exposure to stimulants [28]. This will not be the case in other settings where separate estimates of people dependent on opioids and stimulants are required to estimate PWID exposure and prevalence [3]. Our estimates of OAT exposure are consistent with public health surveillance data, which report that between 57% and 69% of people attending pharmacies for Needle and Syringe Provision were on OAT in the last 6 months [29].

Scotland has a high prevalence of opioid dependence compared to many other countries. We note some caution when making comparisons, however, as methodology to compute estimates varies across countries and studies. In England, prevalence was estimated as 0.8% or 294 000 people, in 2019/2020, based on capture-recapture analysis [30]. The latest estimates for Western Europe—albeit generated using a variety of methods—were in the majority of cases below 0.5%, with Finland reporting the highest estimate at 0.7% [14]. Our estimates suggest that Scotland also has higher prevalence than most regions globally, slightly higher than Eastern Europe (1.08%) and slightly lower than national estimates for the United States (1.38% or 1.46%) [3, 26].

Recent studies in North America, using similar methods to England, have estimated higher and increasing prevalence in some regions: prevalence was estimated to have increased from 1.6% to 1.9% over 2013 to 2017 in British Columbia and from 2.7% to 4.6% over 2011 to 2015 in Massachusetts [9, 31]. These capture-recapture studies included drug-related deaths as a data source, which could introduce bias as being 'caught' in this data source precludes the possibility of being later 'caught' in one of the others, violating a model assumption. We have shown also that capture-recapture estimates can be biased and over-estimate prevalence if the dependence structure or referral pattern across the data sources or administrative services is complex [11, 18], which is why it is important that the consistency of prevalence estimates generated using indirect methods is tested with other evidence. This was undertaken in Massachusetts, where estimates based on capture-recapture were compared with those from an MPEP model using drug-related deaths [20].

Limitations

We sought to base our estimates on all available evidence and be transparent about the assumptions underpinning the estimates. Our prevalence estimates are informed jointly by both opioid-related deaths and hospital admissions. Overall model fit was good (Supporting Information) and the joint model broadly consistent with results from sensitivity analyses modelling each of the two indicators individually. This increases confidence in the estimates. The only notable difference in estimates across these models was for men aged 15 to 34, where hospitalisations data suggested a lower prevalence than mortality data, with the joint model producing estimates between the two. The joint model still gave lower estimates of OAT exposure in men aged 15 to 34 (ranging from 42%–51% across the 6 years) than women of the same age (ranging from 52%–67%) and other age-groups (ranging from 52% –70%). We have no additional evidence to identify the source of the discrepancy in estimates for this group across models, so view the joint model as the best estimate at present.

As with any indirect estimation method, violation of underlying assumptions of the model could lead to some bias. First, we assume that all OAT patients were included in the baseline cohort. We know that some prescription data has not been matched to patients [32], but further validation has not yet been done to identify and estimate whether whole OAT episodes and patients have been missed. If a non-negligible proportion of the 'unobserved' population were in fact receiving OAT, this would bias our prevalence estimates downward. Second, we assume that all the opioid-related deaths and overdose hospital admission included in our model occurred among people with opioid dependence. If some of these events occurred in people who were not dependent and eligible for OAT, the direction of bias in our estimates would be upward. We took care to avoid this bias by careful identification of subsets of adverse events that we feel confident do not occur outside of the community of interest. The consistency of the OAT exposure measures implied by our estimates with public health surveillance also increases our confidence in their validity.

Third, we assume that adverse event rates observed in people who have been in, but are currently out of OAT (conditional on age, sex and geographical area) are equal to rates of these events in people in the community who have not been in OAT in the last 5 years. If the event rate was higher or lower in the unobserved population our model would over- or under-estimate prevalence, respectively. Evidence in support of this assumption is difficult to obtain, as there are

no contemporary cohorts of people with opioid dependence who have not entered OAT. Small historical cohorts suggest that mortality rates were similar in people yet to enter OAT [33].

In this exercise, we did not generate separate estimates of the number of PWID within the opioid-dependent population. In part, this is because of difficulties in identifying adverse events that are specific to PWID, but also patterns of drug consumption are evolving and it was our aim to estimate the number of people eligible for OAT and at risk of key drug-related harms. We aim to extend the model to estimate also the number of PWID in further updates of the estimates. In further model development, we will also assess the feasibility of enhancing the granularity of age groups modelled and estimating prevalence for additional NHS Boards.

Implications

We are confident that our estimates are as robust as they can be at this time, based on all available evidence and consistent with trends in drug-related harm. Too often, indirect estimates are generated without reference to or comparisons with other evidence or recognition that there may be bias if underlying assumptions are not met. Our MPEP approach builds on the benefits of linking drug treatment with data sets measuring drug-related harms. The method also is extendable and flexible: additional information can be incorporated to account for potential biases and inconsistencies in the evidence. We will be updating the estimates for Scotland and hope to see other sites with linked data adopt MPEP and that further studies comparing different indirect methods can be undertaken.

In Scotland, the key implications are that comparatively high OAT exposure is not sufficient to reduce drug-related deaths in the population. OAT remains highly effective at reducing mortality risk, but model evaluations also suggest that OAT retention and combining interventions are critical to averting DRD in the population [15, 34, 35]. Key additional interventions are in place already in Scotland—such as a national take-home naloxone programme and a heroin assisted treatment service in Glasgow—or being piloted, such as drug consumption rooms and safer prescribing of other drugs for people in OAT [6, 36–40].

AUTHOR CONTRIBUTIONS

Andreas Markoulidakis: Data curation (equal); formal analysis (lead); methodology (supporting); software (lead); visualization (lead); writing—original draft (equal); writing—review and editing (equal). **Matthew Hickman:** Conceptualization (equal); funding acquisition (equal); methodology (equal); supervision (supporting); writing—original draft (equal); writing—review and editing (equal). **Andrew McAuley:** Conceptualization (supporting); funding acquisition (equal); software (equal); supervision (supporting); writing—original draft (supporting); writing—review and editing (supporting). **Lee R. Barnsdale:** Conceptualization (equal); data curation (equal); funding acquisition (equal); project administration (lead); supervision (equal); writing—review and editing (supporting). **Nicky J. Welton:** Methodology (supporting); writing—review and editing (supporting). **Megan Glancy:** Data curation (equal); software (supporting); writing—review and editing (supporting). **Tara Shivaji:** Conceptualization (equal); funding acquisition (equal); project administration (equal); supervision (supporting); writing—review and editing (supporting). **Craig Collins:** Project administration (equal); writing—review and editing (supporting). **Jaroslaw Lang:** Data curation (equal); writing—review and editing (supporting). **Femke de Wit:** Data curation (equal); writing—review and editing (supporting). **Gordon Hunt:** Data curation (equal); writing—review and editing (supporting). **Levin Wilkinson:** Data curation (equal); writing—review and editing (supporting). **Rosalyn Fraser:** Data curation (supporting); writing—review and editing (supporting). **Alan Yeung:** Data curation (supporting); writing—review and editing (supporting). **Kirsten Horsburgh:** Writing—review and editing (supporting). **Saket Priyadarshi:** Writing—review and editing (supporting). **Sharon J. Hutchinson:** Conceptualization (equal); funding acquisition (equal); supervision (supporting); writing—review and editing (supporting). **Hayley E. Jones:** Conceptualization (equal); funding acquisition (equal); methodology (lead); project administration (equal); software (equal); supervision (lead); visualization (supporting); writing—original draft (equal); writing—review and editing (lead).

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DECLARATION OF INTERESTS

N.J.W. declares honoraria from the Association of the British Pharmaceutical Industry for delivery of masterclasses on statistical methodology for submissions to NICE. No other competing interests were declared.

DATA AVAILABILITY STATEMENT

Data (aggregated over regions but stratified by all other relevant variables) are available from https://www.opendata.nhs.scot/dataset/estimated-prevalence-of-opioid-dependence-in-scotland.

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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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