Mortality among individuals prescribed opioid-agonist therapy in Scotland, 2011-2020: a national retrospective cohort study

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SDF Scottish Drugs Forum

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Evaluating the impact of **P**ublic **He**alth interventions in reducing harms related to **S**ubstance **U**se in **S**cotland
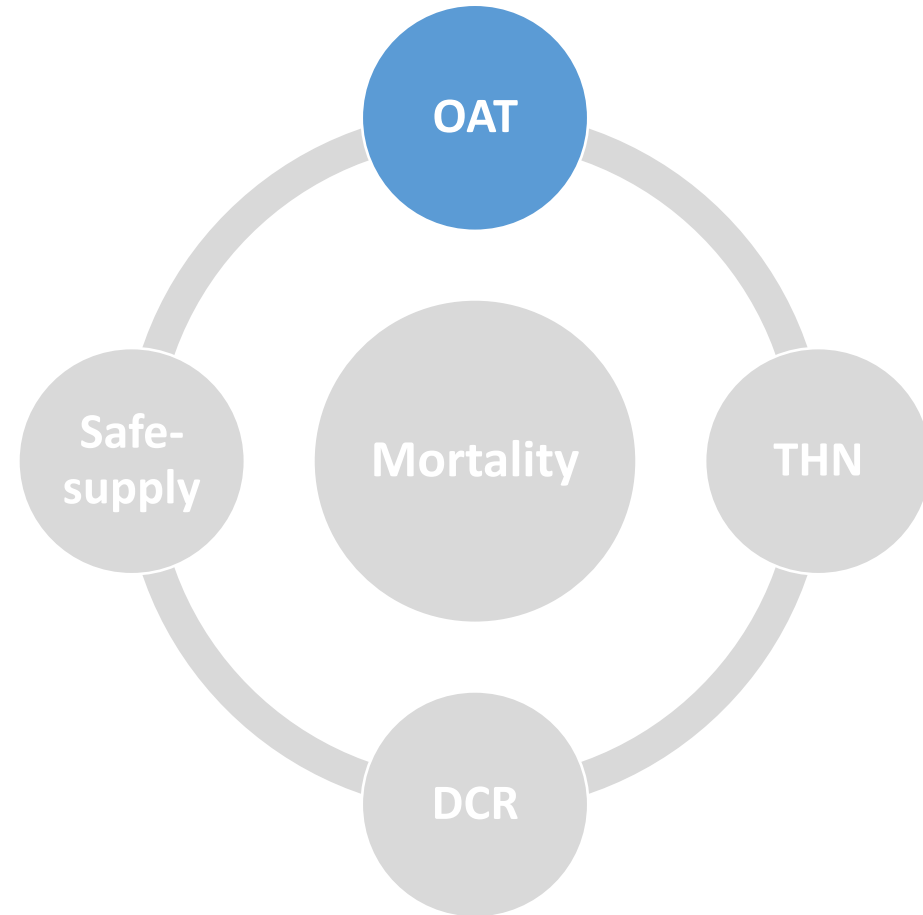
EPHeSUS

EPHeSUS: Aim

- Use linked and unlinked administrative data to measure the risks of mortality related to problem drug use in Scotland, and determine to what extent specific interventions are protective against drug-related deaths.

EPHeSUS

Evaluating the impact of <u>E</u>valuating the impact of <u>P</u>ublic <u>H</u>ealth interventions in reducing harms related to <u>S</u>ubstance <u>U</u>se in <u>S</u>cotland (EPHeSUS)
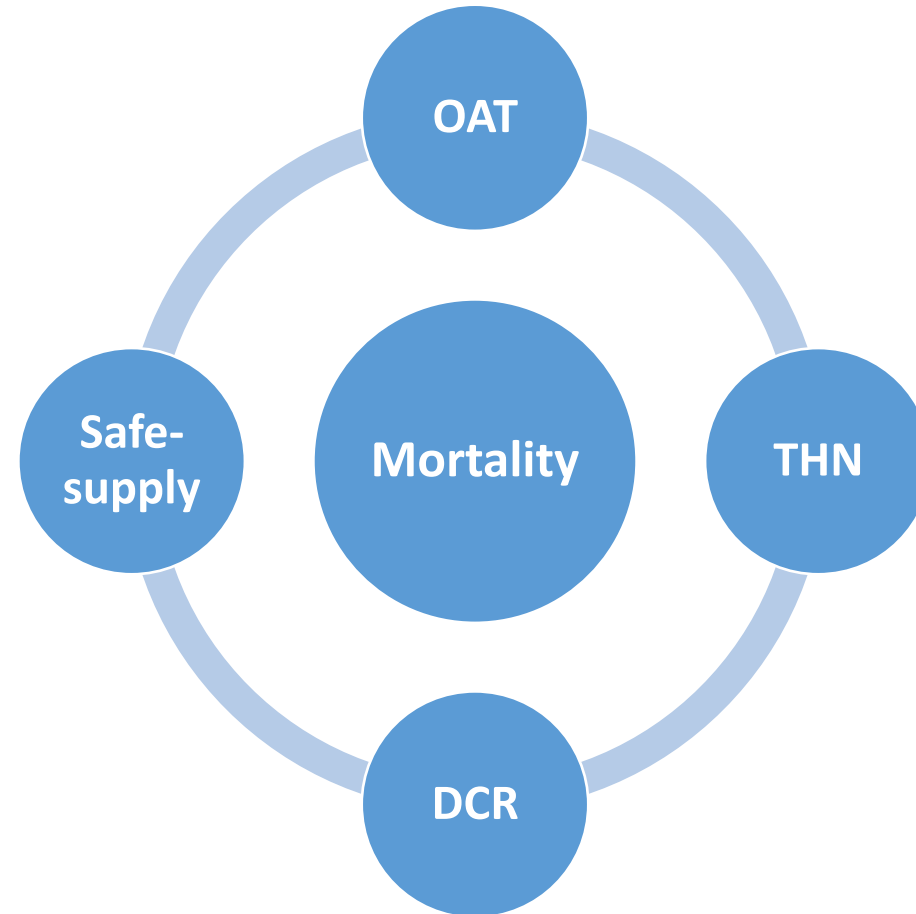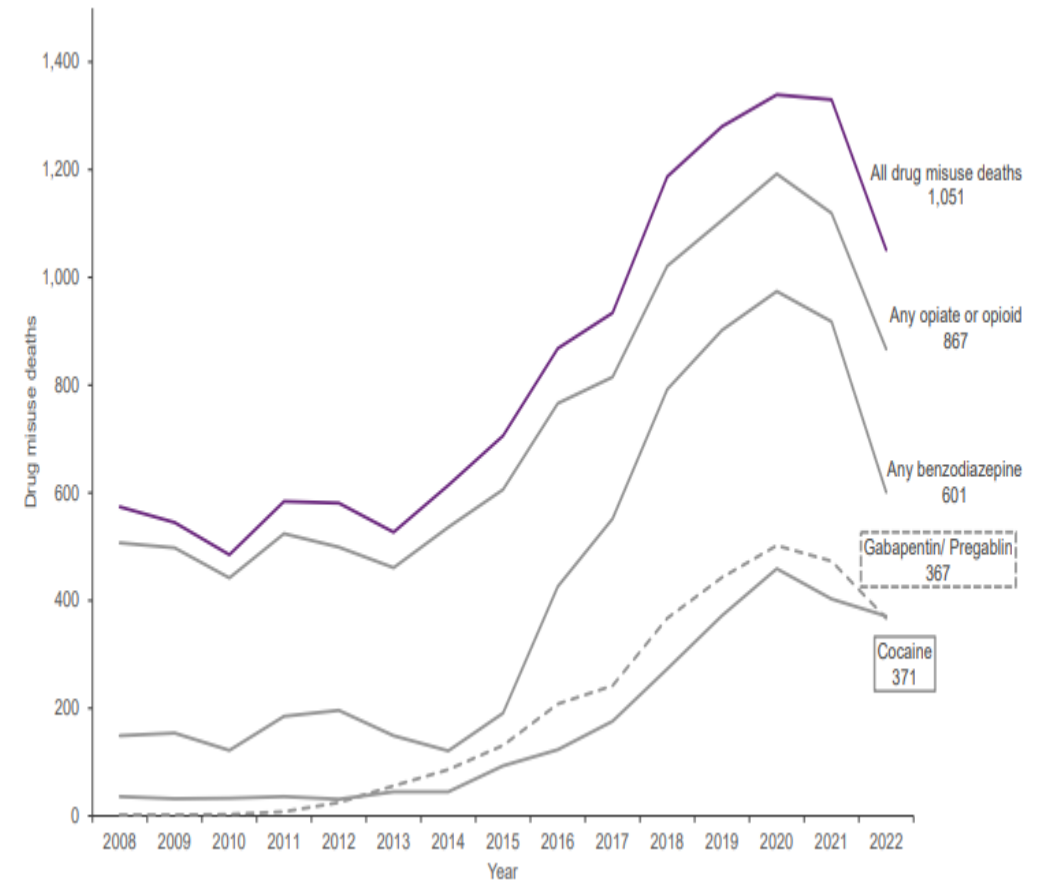
Evaluating the impact of Public Health interventions in reducing harms related to Substance Use in Scotland (EPHeSUS)

Background

- Opioid-agonist therapy (OAT) available free through National Health Service since the 1980s in Scotland

- No recent evaluation of OAT, during a period when Scotland's number of drug-related deaths (DRDs) have more than doubled

- Aim : to examine the extent to which OAT in Scotland is protective against drug-related mortality and how this effect has varied over time

Annual number of drug-related deaths in Scotland, by drugs implicated

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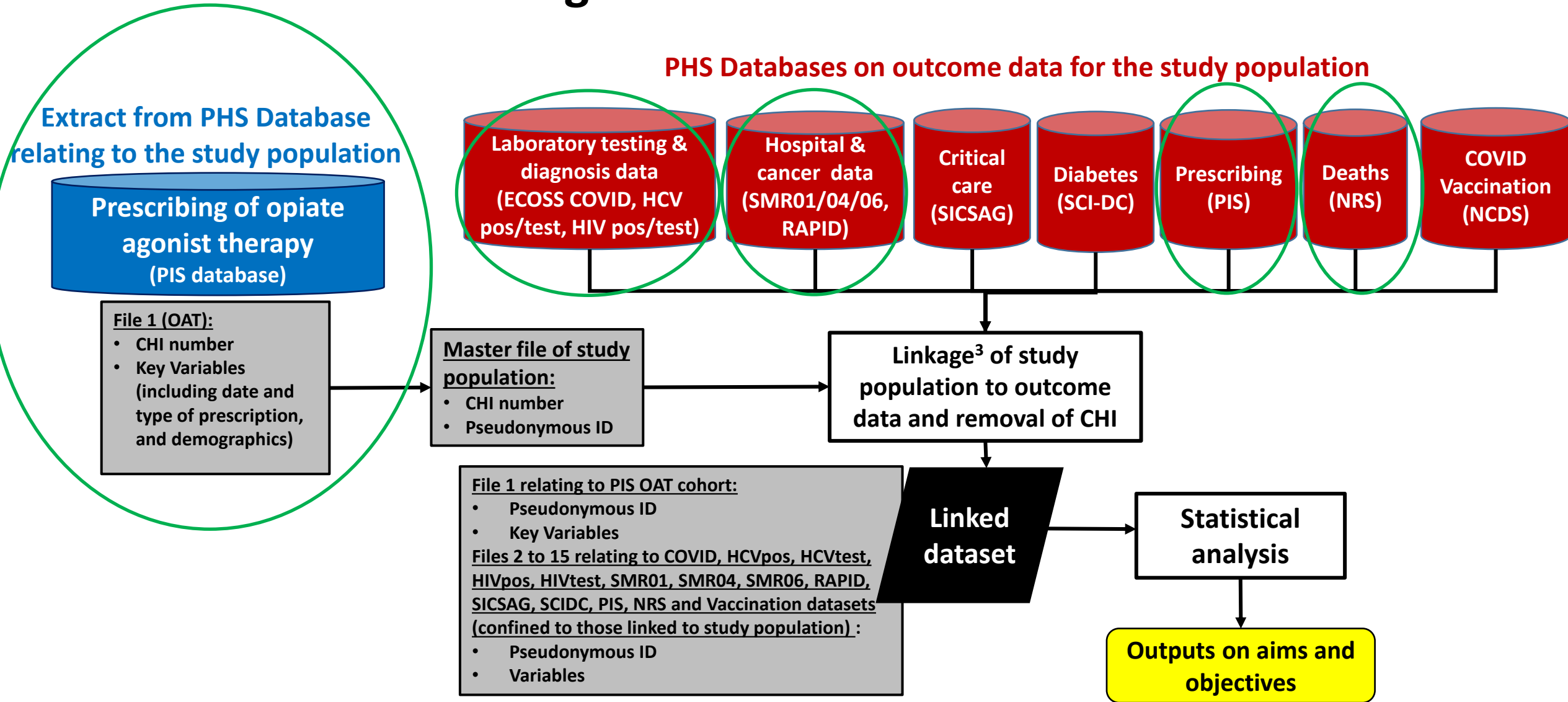**Annual number of drug-related deaths in Scotland, by drugs implicated**

Retrospective cohort study established through linkage of administrative data[1]

PHS Databases on outcome data for the study population

Extract from PHS Database relating to the study population

Prescribing of opiate agonist therapy (PIS database)

Laboratory testing & diagnosis data (ECOSS COVID, HCV pos/test, HIV pos/test)

Hospital & cancer data (SMR01/04/06, RAPID)

Critical care (SICSAG)

Diabetes (SCI-DC)

Prescribing (PIS)

Deaths (NRS)

COVID Vaccination (NCDS)

File 1 (OAT):
- CHI number
- Key Variables (including date and type of prescription, and demographics)

Master file of study population:
- CHI number
- Pseudonymous ID

Linkage[3] of study population to outcome data and removal of CHI

File 1 relating to PIS OAT cohort:
- Pseudonymous ID
- Key Variables

Files 2 to 15 relating to COVID, HCVpos, HCVtest, HIVpos, HIVtest, SMR01, SMR04, SMR06, RAPID, SICSAG, SCIDC, PIS, NRS and Vaccination datasets (confined to those linked to study population):
- Pseudonymous ID
- Variables

Linked dataset

**Statistical analysis**

Outputs on aims and objectives

[1] Approval for linkage provided by NHS Public Benefit and Privacy Panel for Health and Social Care.

OAT cohort, 2011-2020

- 46,453 individuals following exclusions
  - 67% male
  - 78% aged 25-44 years at cohort entry
  - 61% prescribed by GP at cohort entry
    - 68% only prescribed methadone during follow-up
    - 22% methadone or buprenorphine
    - 10% buprenorphine (+/- naloxone)

- 304,042 person years

- 6,947 all-cause deaths (15% of cohort)
  - 4,076 drug-related deaths (47% of all DRDs across Scotland in this period)
  - 3,445 opioid-related deaths (85% of DRDs)
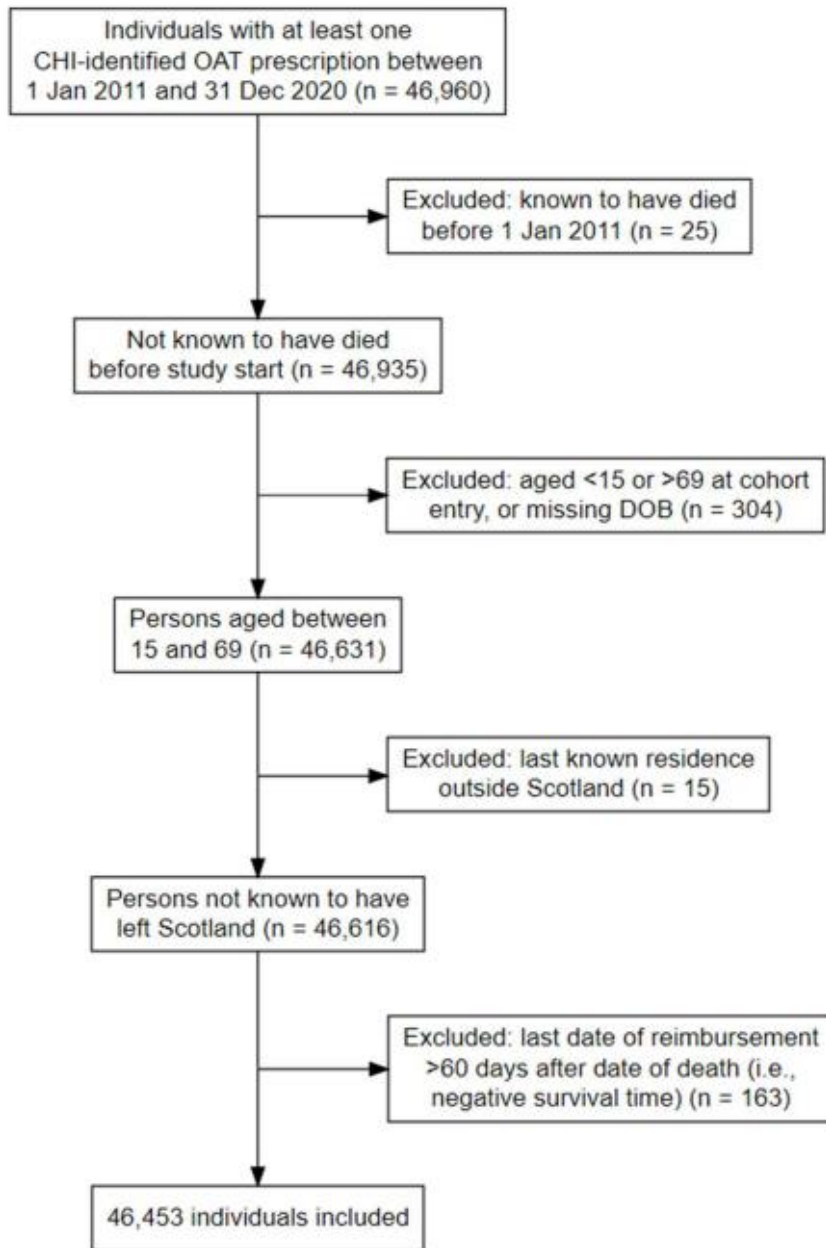
McAuley A, et al. Lancet Public Health, June 2023.

Crude drug-related death rates (log scale) among those prescribed OAT in Scotland, 2011-2020
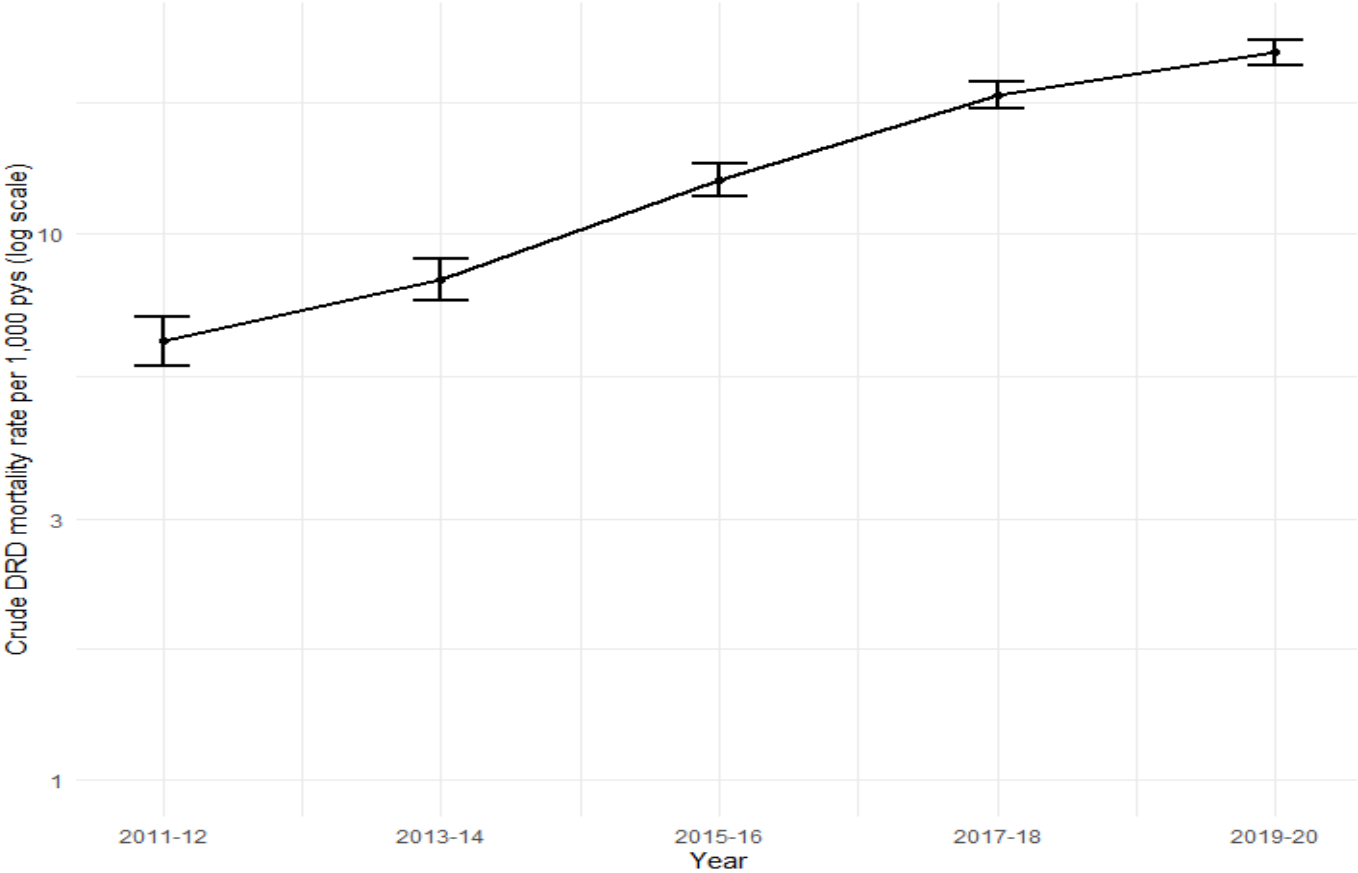
- **DRD rates trebled over the study period** (from 6 per 1000 py in 2011-12 to 21 per 1000 py in 2019-20)

Cohort followed up from 1st Jan 2011 up to earliest of date of death, 31st Dec 2020 or at 24 months following cessation of OAT treatment.

Crude drug-related death rates (log scale) among those prescribed OAT in Scotland by age-group, 2011-2020
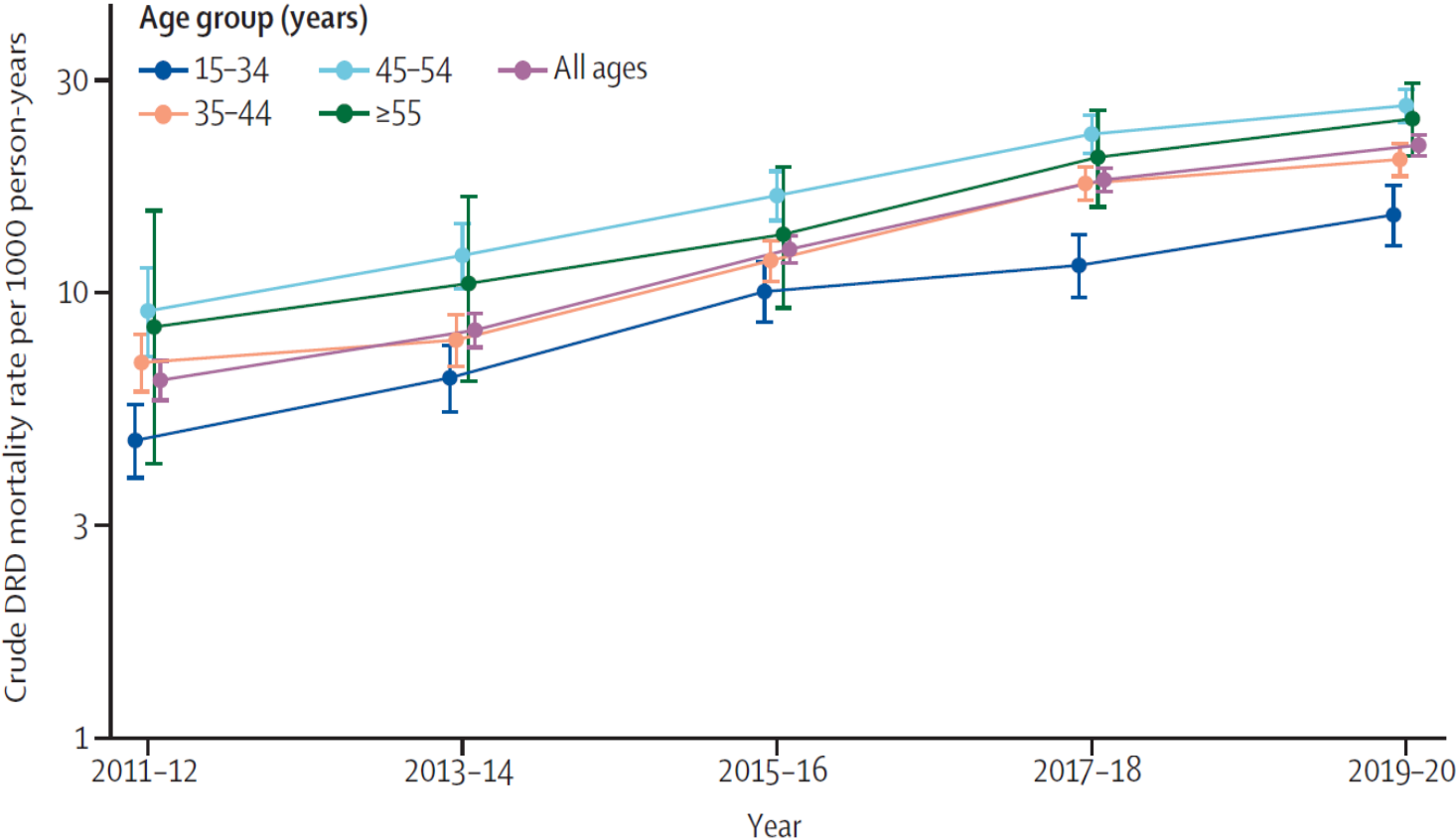
- **DRD rates trebled over the study period** (from 6 per 1000 py in 2011-12 to 21 per 1000 py in 2019-20)
- DRD rates highest among older adults
- **Increases in DRD rates evident across all age-groups**

Cohort followed up from 1st Jan 2011 up to earliest of date of death, 31st Dec 2020 or at 24 months following cessation of OAT treatment.

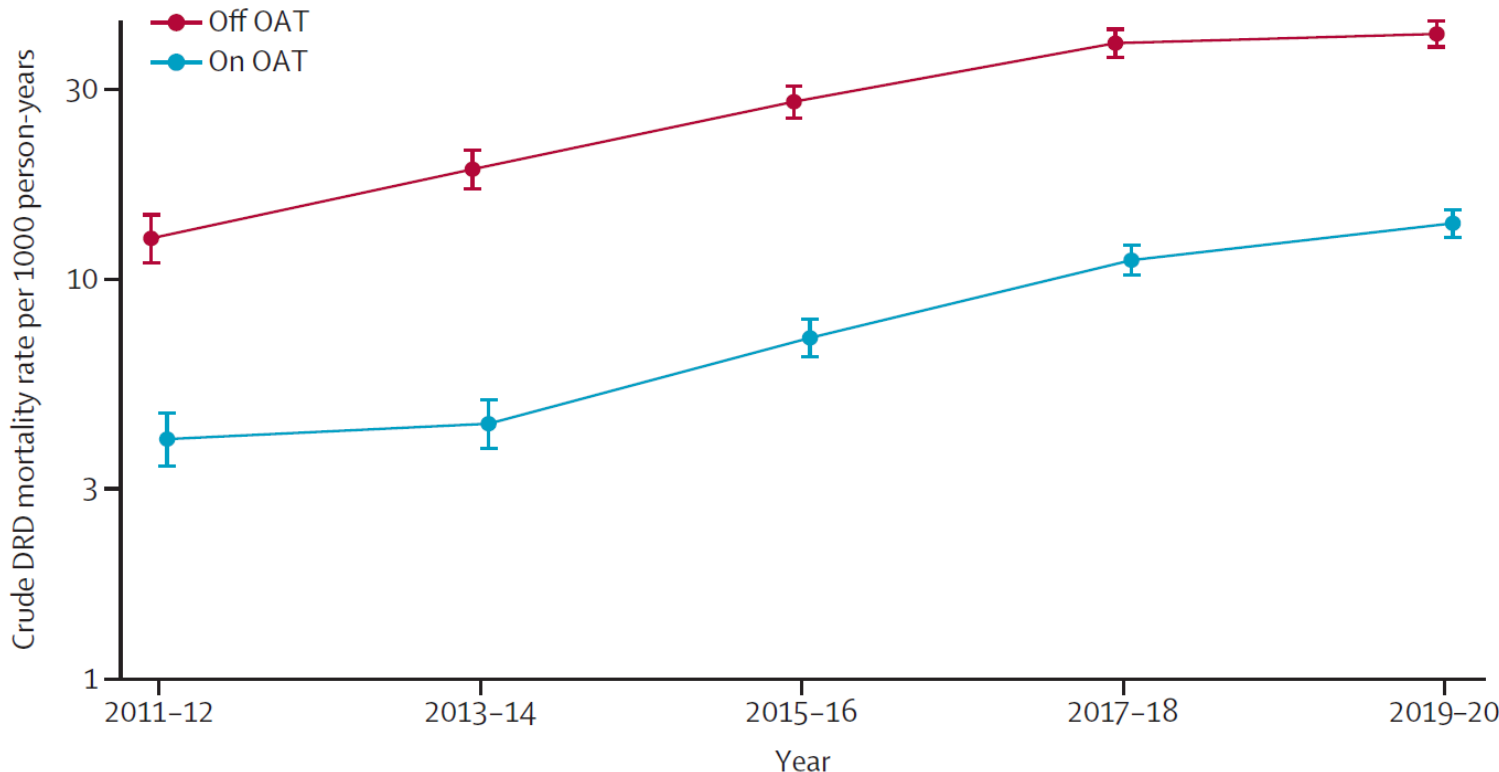McAuley A, et al. Lancet Public Health, June 2023.

Crude drug-related death rates (log scale) among those prescribed OAT in Scotland by OAT status, 2011-2020

- **Overall DRD rates were 3.4 times higher for those off OAT relative to those on OAT**
- However, DRD rates increased over calendar time for both those on OAT as well as off OAT

Prescription dates were not available for all patients; periods on/off OAT were instead based on reimbursements dates which were available for all prescriptions. **On OAT referred to the period from −60 days to −12 days of each reimbursement date**, given a) reimbursements dates were aggregated at the end of the month relating to when prescription is fully dispensed, b) the average number of days between prescription and reimbursement dates was 40 days and b) the duration between consecutive prescription dates was 28 days.

McAuley A, et al. Lancet Public Health, June 2023.

Adjusted hazard ratios (95% CI) for drug-related deaths among those prescribed OAT in Scotland, 2011-2020

	Adjusted hazard ratio (95% CI)
OAT exposure (vs On)	
Off	3.37 (1.74, 6.53)
Sex (vs Male)	
Female	0.94 (0.76, 1.17)
Age (vs 35-44)	
Under 25	0.55 (0.20, 1.53)
25-34	0.71 (0.53, 0.96)
45-54	1.36 (1.08, 1.71)
55+	1.21 (0.77, 1.90)
Year (vs 2011-12)	
2013-2014	1.03 (0.53, 2.01)
2015-2016	1.62 (0.89, 2.95)
2017-2018	2.45 (1.40, 4.30)
2019-2020	2.96 (1.70, 5.15)
Healthboard (vs Other)	
Greater Glasgow & Clyde	1.13 (0.89, 1.42)
Tayside	1.14 (0.79, 1.64)
SIMD quintile (vs 1)	
SIMD 2	0.93 (0.73, 1.18)
SIMD 3, 4, 5	0.82 (0.62, 1.08)
HIV status (vs No diagnosis)	
Diagnosed	1.44 (0.62, 3.34)
HCV status (vs No diagnosis)	
Anti-HCV (not chronic)	1.78 (1.31, 2.44)
Chronic HCV	1.41 (1.14, 1.76)
Prescriber type (vs GP)	
Other	1.02 (0.81, 1.29)
Mental health admission (vs No)	
Yes	1.37 (1.02, 1.82)
Non-fatal overdose (vs No)	
Yes	1.49 (1.18, 1.88)

Drug-related mortality: adjusted hazard ratio (95% CI)

McAuley A, et al. Lancet Public Health, June 2023.

Adjusted hazard ratios (95% CI) for drug-related deaths among those prescribed OAT in Scotland, 2011-2020

	Deaths	Person-years	Mortality per 1000 person-years (95% CI)	HR (95% CI)*†	p value	Adjusted HR (95% CI)†‡	p value	Adjusted HR (95% CI)†§	p value
2011–12									
On OAT	168	42 124	3·99 (3·43–4·64)	1 (ref)	··	1 (ref)	··	1 (ref)	··
Off OAT	200	15 766	12·68 (11·04–14·57)	3·18 (1·79–5·66)	<0·001	3·34 (1·84–6·04)	<0·001	3·37 (1·74–6·53)	<0·001
2013–14									
On	194	44 476	4·36 (3·79–5·02)	1 (ref)	··	1 (ref)	··	1·03 (0·53–2·01)	0·924
Off	306	16 194	18·90 (16·89–21·14)	4·33 (2·41–7·78)	<0·001	4·65 (2·53–8·54)	<0·001	4·85 (2·64–8·89)	<0·001
2015–16									
On	327	45 732	7·15 (6·42–7·97)	1 (ref)	··	1 (ref)	··	1·62 (0·89–2·95)	0·115
Off	446	15 989	27·89 (25·42–30·61)	3·90 (2·39–6·36)	<0·001	4·17 (2·60–6·68)	<0·001	6·72 (3·79–11·91)	<0·001
2017–18									
On	529	47 266	11·19 (10·28–12·19)	1 (ref)	··	1 (ref)	··	2·45 (1·40–4·30)	0·002
Off	588	15 041	39·09 (36·06–42·39)	3·49 (2·32–5·25)	<0·001	3·65 (2·46–5·43)	<0·001	9·01 (5·17–15·70)	<0·001
2019–20									
On	614	44 376	13·84 (12·78–14·98)	1 (ref)	··	1 (ref)	··	2·96 (1·70–5·15)	<0·001
Off	704	17 079	41·22 (38·28–44·38)	2·98 (2·08–4·27)	<0·001	3·11 (2·17–4·46)	<0·001	9·21 (5·34–15·90)	<0·001

HR=hazard ratio. OAT=opioid-agonist therapy. *HR modelled using quasi-poisson regression. †95% CIs were calculated using the quasi-poisson method. ‡Adjusted for age, sex, health board, Scottish Index of Multiple Deprivation, hepatitis C virus status, HIV status, prescriber type, mental health admission, non-fatal overdose admission. §Full model results including an interaction term for OAT exposure by time period.

- Being off OAT consistently associated with higher risk of DRD over time
- **DRD rates increased 3-fold over time for both those on OAT as well as off OAT**, after adjustment for age and other factors

McAuley A, et al. Lancet Public Health, June 2023.

Historical and international context : drug-related mortality

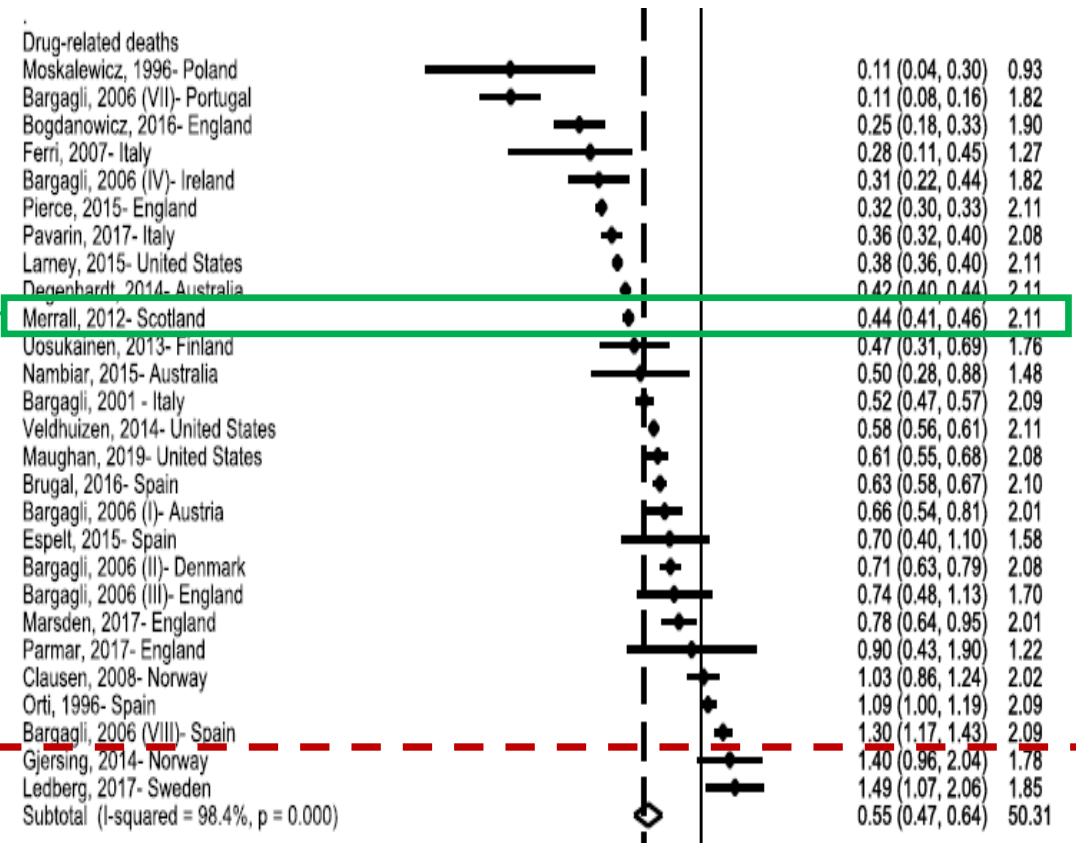- **Merrall et al (2012) – SDMD opiate cohort, 1996-2006 (239,771 py)**

- Drug-related mortality 4.36 per 1000py

- **Gao et al (2019) – methadone cohort, 2009-2015 (193,800 py)**

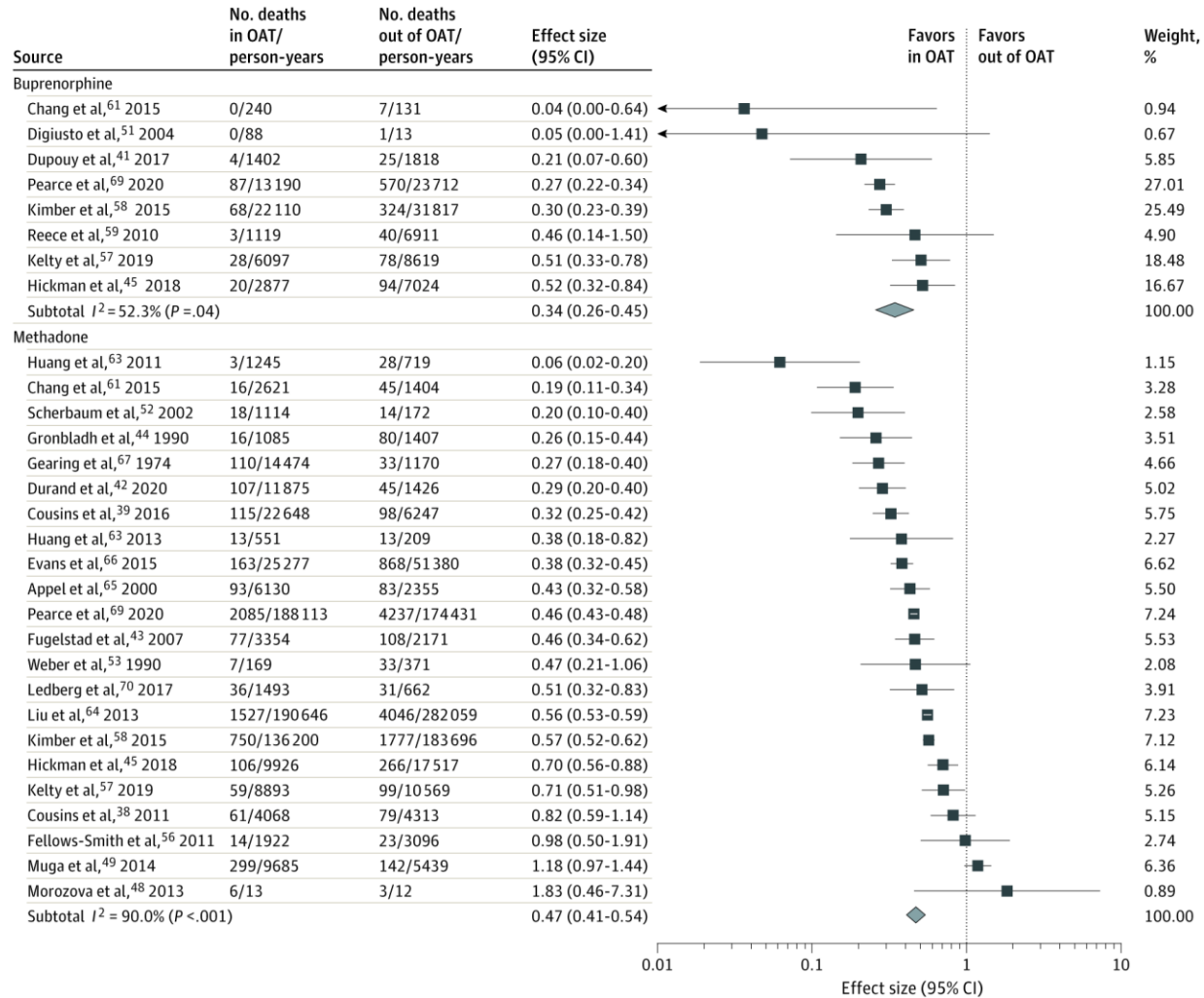- Drug-related mortality 6.83 per 1000py

- **McAuley et al (2023) – OAT cohort, 2011-2020 (304,042 py)**

- Drug-related mortality 13.41 per 1000py

Larney et al, JAMA Psychiatry 2020

International context : strong protective effect of OAT

Source	No. deaths in OAT/person-years	No. deaths out of OAT/person-years	Effect size (95% CI)	Weight, %
Buprenorphine				
Chang et al,[61] 2015	0/240	7/131	0.04 (0.00-0.64)	0.94
Digiusto et al,[51] 2004	0/88	1/13	0.05 (0.00-1.41)	0.67
Dupouy et al,[41] 2017	4/1402	25/1818	0.21 (0.07-0.60)	5.85
Pearce et al,[69] 2020	87/13190	570/23712	0.27 (0.22-0.34)	27.01
Kimber et al,[58] 2015	68/22110	324/31817	0.30 (0.23-0.39)	25.49
Reece et al,[59] 2010	3/1119	40/6911	0.46 (0.14-1.50)	4.90
Kelty et al,[57] 2019	28/6097	78/8619	0.51 (0.33-0.78)	18.48
Hickman et al,[45] 2018	20/2877	94/7024	0.52 (0.32-0.84)	16.67
Subtotal $I^2 = 52.3\%$ (P =.04)			0.34 (0.26-0.45)	100.00
Methadone				
Huang et al,[63] 2011	3/1245	28/719	0.06 (0.02-0.20)	1.15
Chang et al,[61] 2015	16/2621	45/1404	0.19 (0.11-0.34)	3.28
Scherbaum et al,[52] 2002	18/1114	14/172	0.20 (0.10-0.40)	2.58
Gronbladh et al,[44] 1990	16/1085	80/1407	0.26 (0.15-0.44)	3.51
Gearing et al,[67] 1974	110/14474	33/1170	0.27 (0.18-0.40)	4.66
Durand et al,[42] 2020	107/11875	45/1426	0.29 (0.20-0.40)	5.02
Cousins et al,[39] 2016	115/22648	98/6247	0.32 (0.25-0.42)	5.75
Huang et al,[63] 2013	13/551	13/209	0.38 (0.18-0.82)	2.27
Evans et al,[66] 2015	163/25277	868/51380	0.38 (0.32-0.45)	6.62
Appel et al,[65] 2000	93/6130	83/2355	0.43 (0.32-0.58)	5.50
Pearce et al,[69] 2020	2085/188113	4237/174431	0.46 (0.43-0.48)	7.24
Fugelstad et al,[43] 2007	77/3354	108/2171	0.46 (0.34-0.62)	5.53
Weber et al,[53] 1990	7/169	33/371	0.47 (0.21-1.06)	2.08
Ledberg et al,[70] 2017	36/1493	31/662	0.51 (0.32-0.83)	3.91
Liu et al,[64] 2013	1527/190646	4046/282059	0.56 (0.53-0.59)	7.23
Kimber et al,[58] 2015	750/136200	1777/183696	0.57 (0.52-0.62)	7.12
Hickman et al,[45] 2018	106/9926	266/17517	0.70 (0.56-0.88)	6.14
Kelty et al,[57] 2019	59/8893	99/10569	0.71 (0.51-0.98)	5.26
Cousins et al,[38] 2011	61/4068	79/4313	0.82 (0.59-1.14)	5.15
Fellows-Smith et al,[56] 2011	14/1922	23/3096	0.98 (0.50-1.91)	2.74
Muga et al,[49] 2014	299/9685	142/5439	1.18 (0.97-1.44)	6.36
Morozova et al,[48] 2013	6/13	3/12	1.83 (0.46-7.31)	0.89
Subtotal $I^2 = 90.0\%$ (P <.001)			0.47 (0.41-0.54)	100.00

Favors in OAT — Favors out of OAT

Effect size (95% CI)

> **We found a stronger protective effect of OAT in the Scottish cohort (70% reduced risk of DRDs)** compared to that from recent global review and meta-analysis (pooled RR 0.41; 95% CI 0.33-0.52)

Santo et al, JAMA Psychiatry 2021

Key points

- **One of the largest national cohorts** of people prescribed OAT studied in the UK/internationally.

- Amongst the **highest ever recorded mortality rates** in OAT cohort studies; **more than double** international pooled estimates.

- Among people prescribed OAT, **DRD rates have increased over the last decade** _for both those on and off OAT_. **OAT is not a panacea** for Scotland's DRD crisis – other interventions needed.

  - But…mortality rates consistently higher in those off-OAT, therefore **treatment is protective!**

- The **elevated risk** associated with being off OAT was **highest between 2015 and 2018**, a period when Scotland's DRD rate increased markedly to **one of the highest internationally**.

  - Why? Changing polydrug use (e.g. Benzos)? Funding cuts?

- Increases were evident across age-groups, adding weight to the consensus that **Scotland's overdose epidemic is not solely explained by an ageing cohort**.

THE LANCET
Public Health

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Comment

Lost lives and opportunities for the legacy of harm reduction in Scotland, UK

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Thank you for listening

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