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Drug related mortality prevention – role of opioid substitution/agonist treatment

Matthew Hickman

Acknowledgements

- Louisa Degenhardt, Sarah Larney, Jack Stone, John Marsden, John Macleod
  - Michael Farrell, Garry Stillwell, Hayley Jones, Colin Steer, Kate Tilling, Aaron Lim, John Marsden, Tim Millar, John Strang, Maggie Telfer, Peter Vickerman,
- NIHR HS&DR Project: 12/136/105 - Evaluating the impact of opiate substitution treatment on drug related deaths in the population: a natural experiment using primary care, other drug treatment databases & model projections. ISAC CPRD Protocol 14_073R2.
- NIHR Health Protection Research Unit (HPRU) in Evaluation
- NIHR School of Public Health Research
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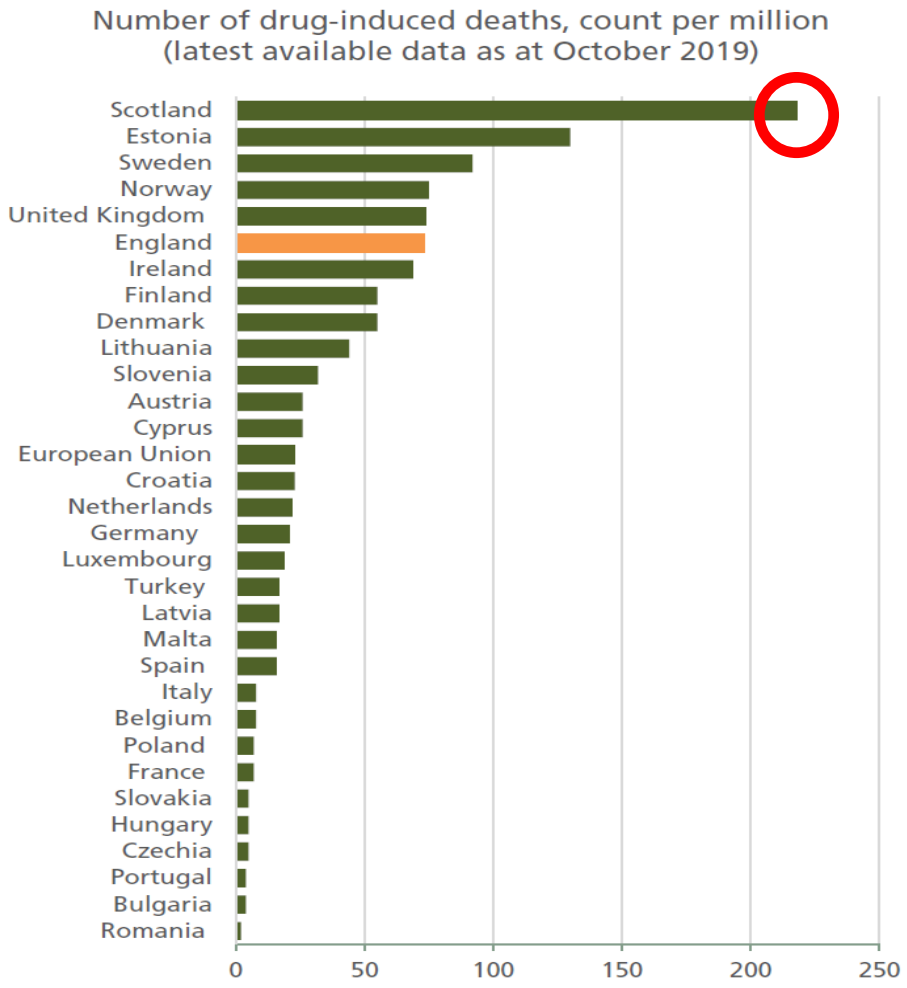
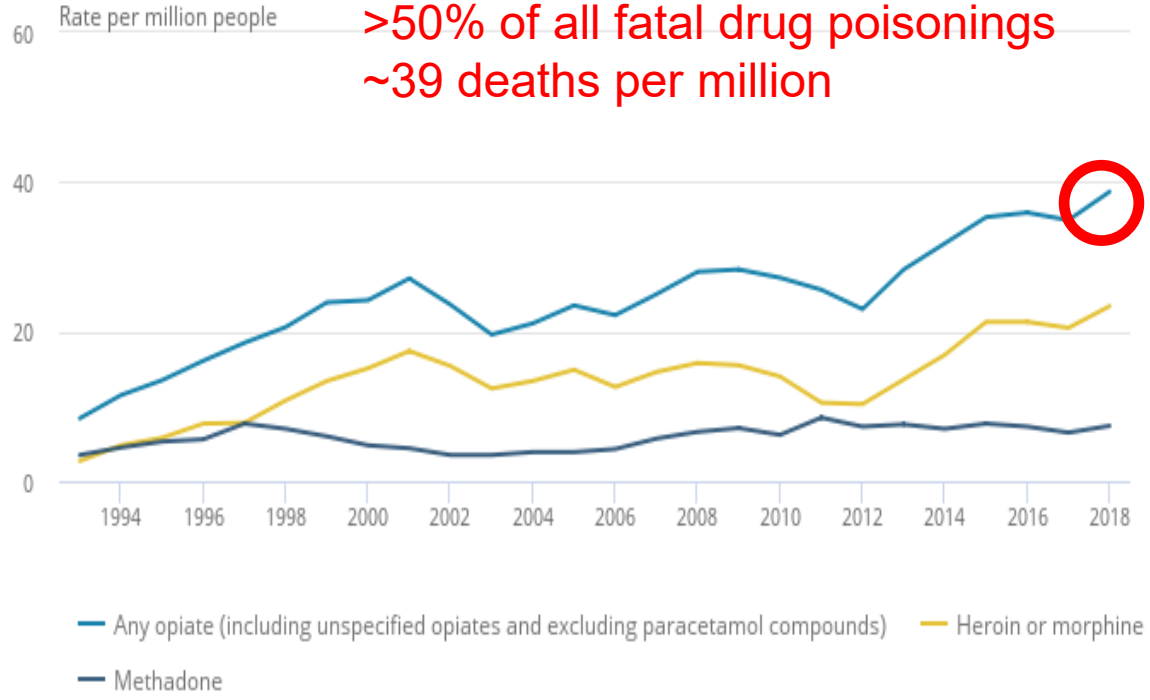
Interaction & Complex Needs

- Trends
- OST duration
- Buprenorphine vs Methadone
- Prison OAT
- Benzos
- Comorbidity

Opioid overdose deaths increasing in the UK (rate per million)

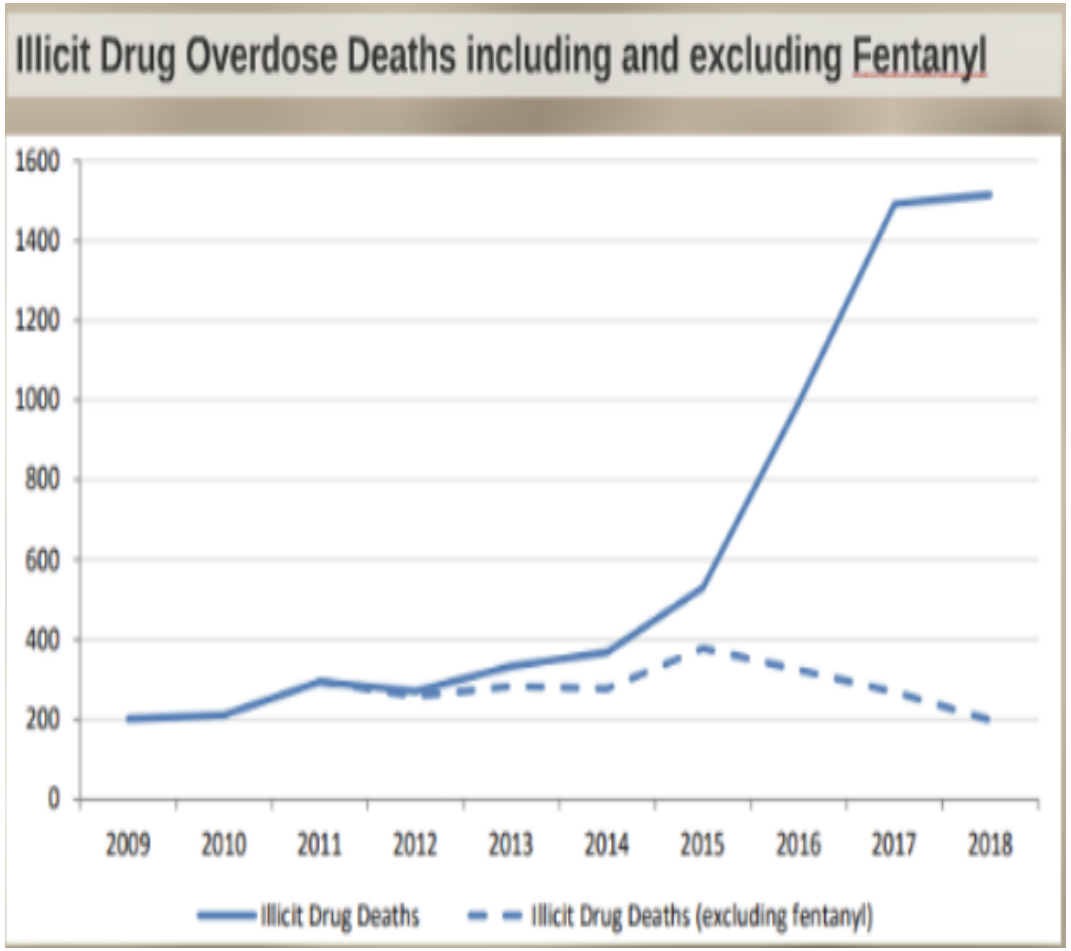


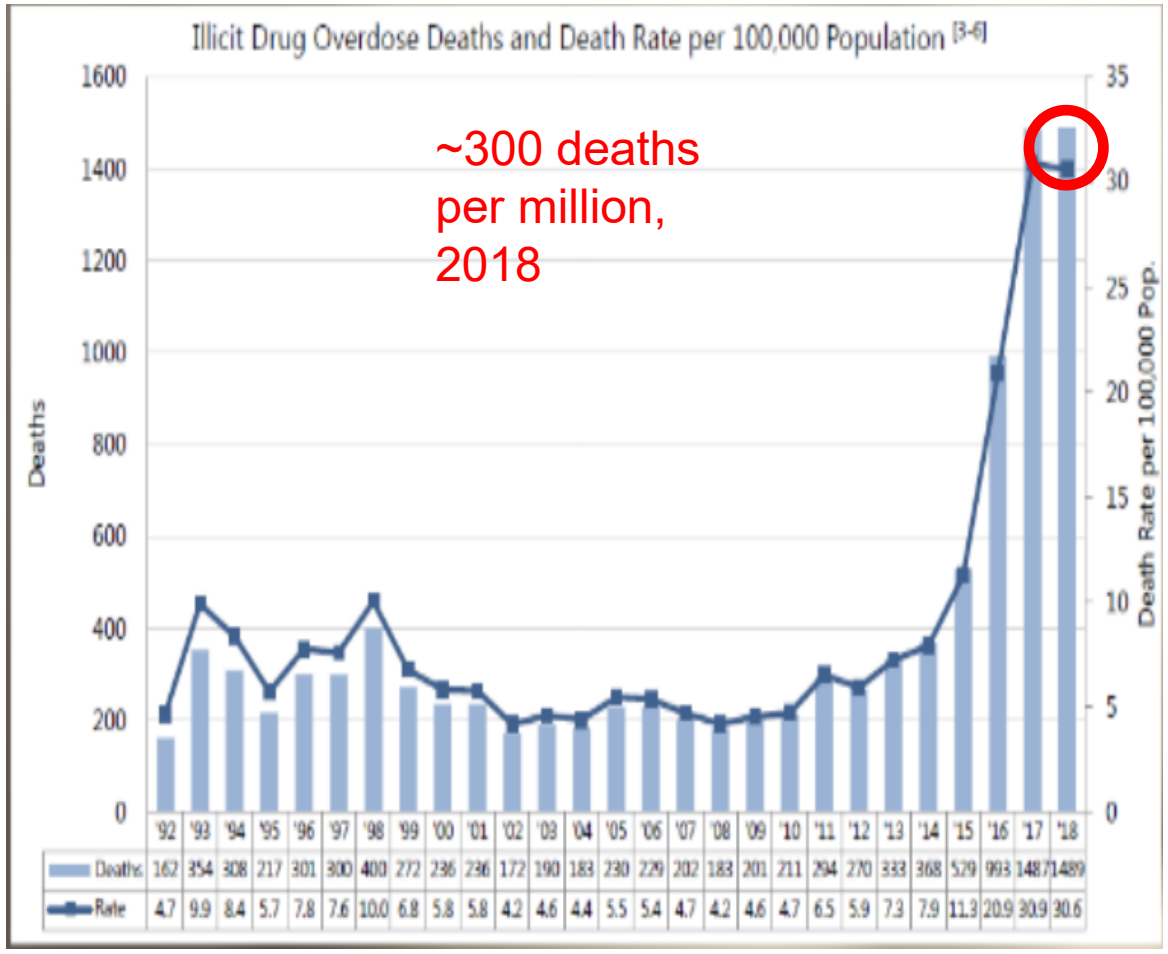
2018: 2208 opioid related deaths
>50% of all fatal drug poisonings
~39 deaths per million



Source: Office for National Statistics

…in British Columbia, Canada (rate per 100,000)





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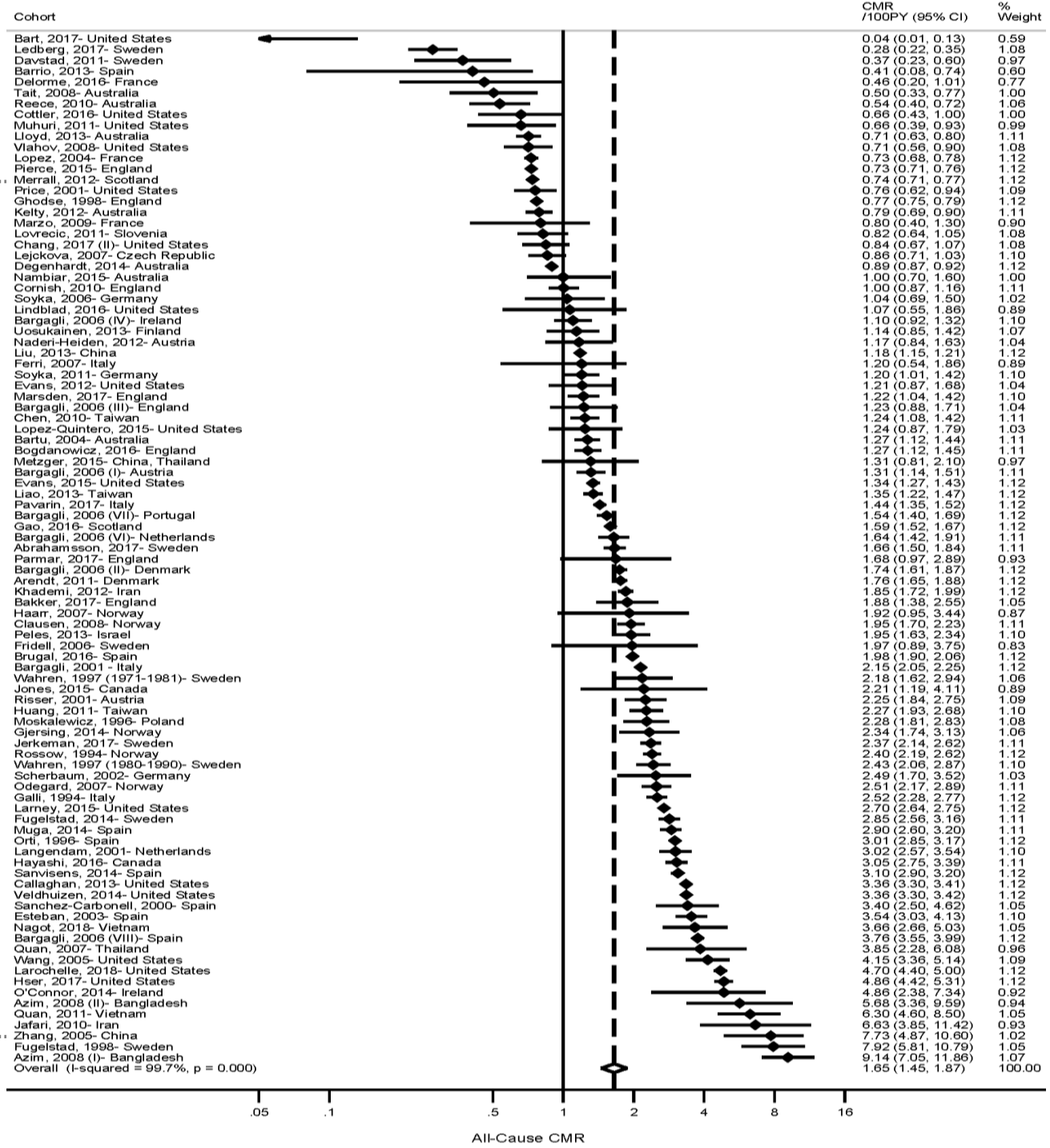
All-cause crude mortality rate:
1.7 (0.3-9.0) per 100py

10* (3-30) higher than gen population



Larney et al, in press JAMA Psych

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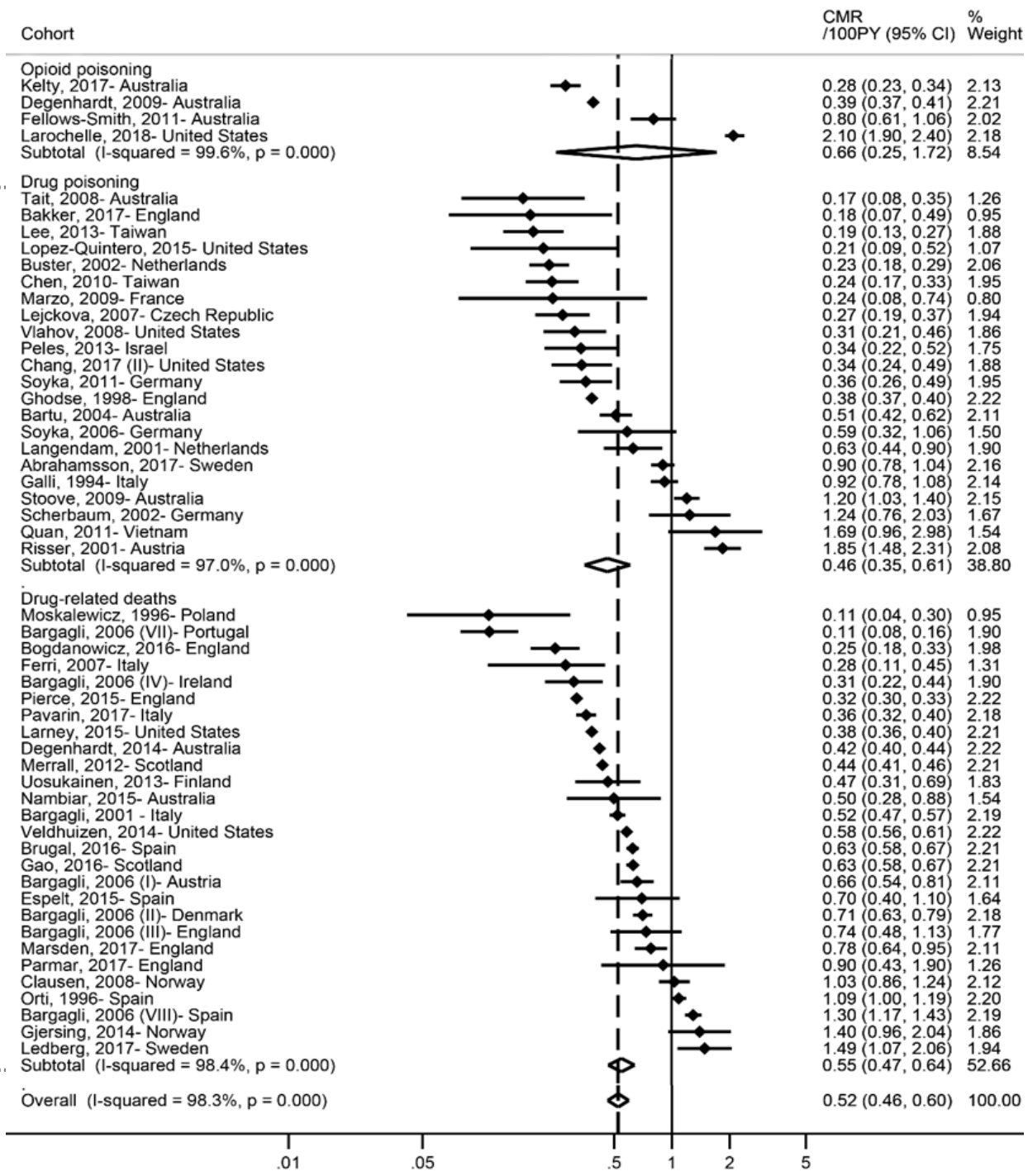
Drug-related deaths: highest cause-specific mortality

0.5 per 100 py

(0.1 to 2.0 100 py)



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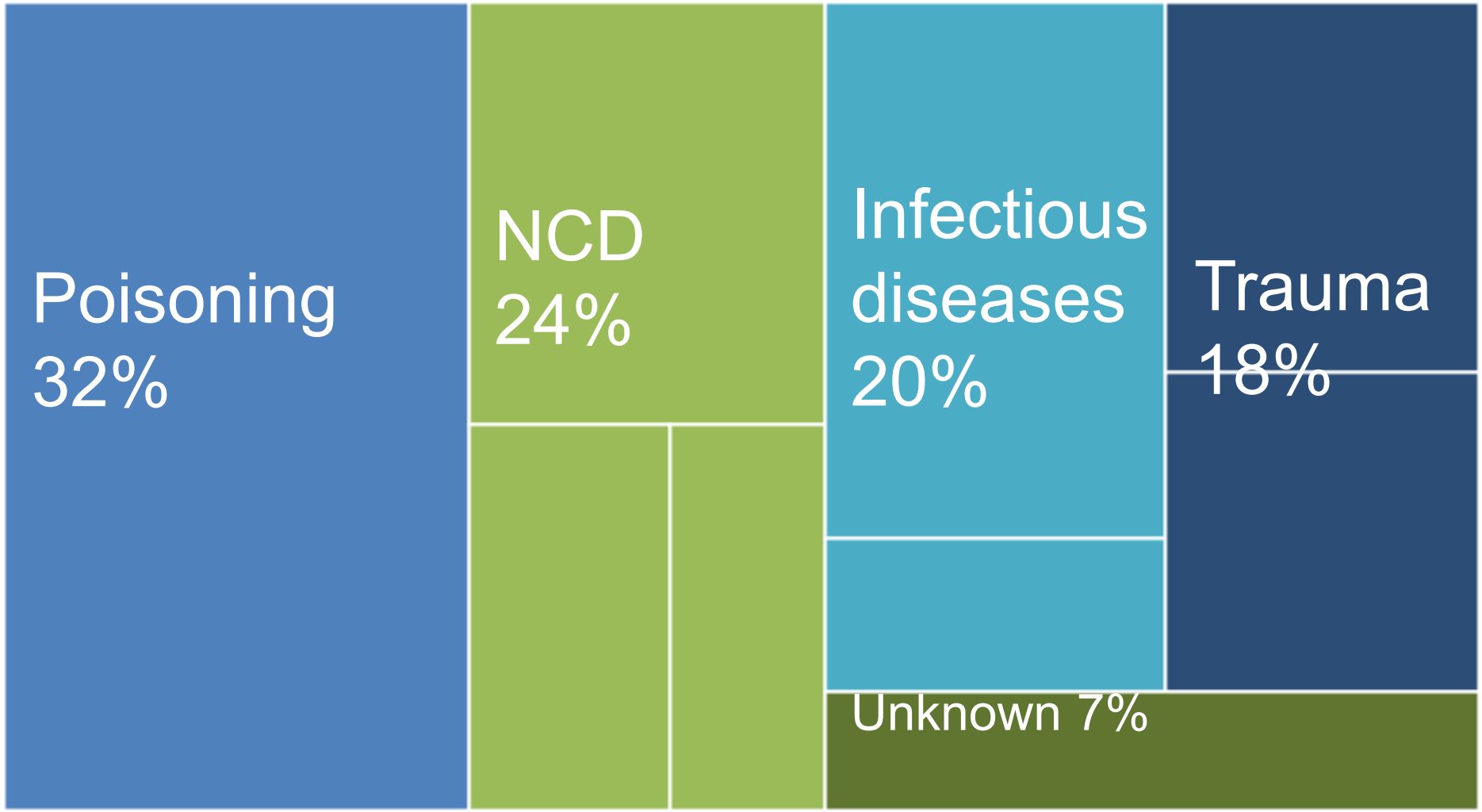
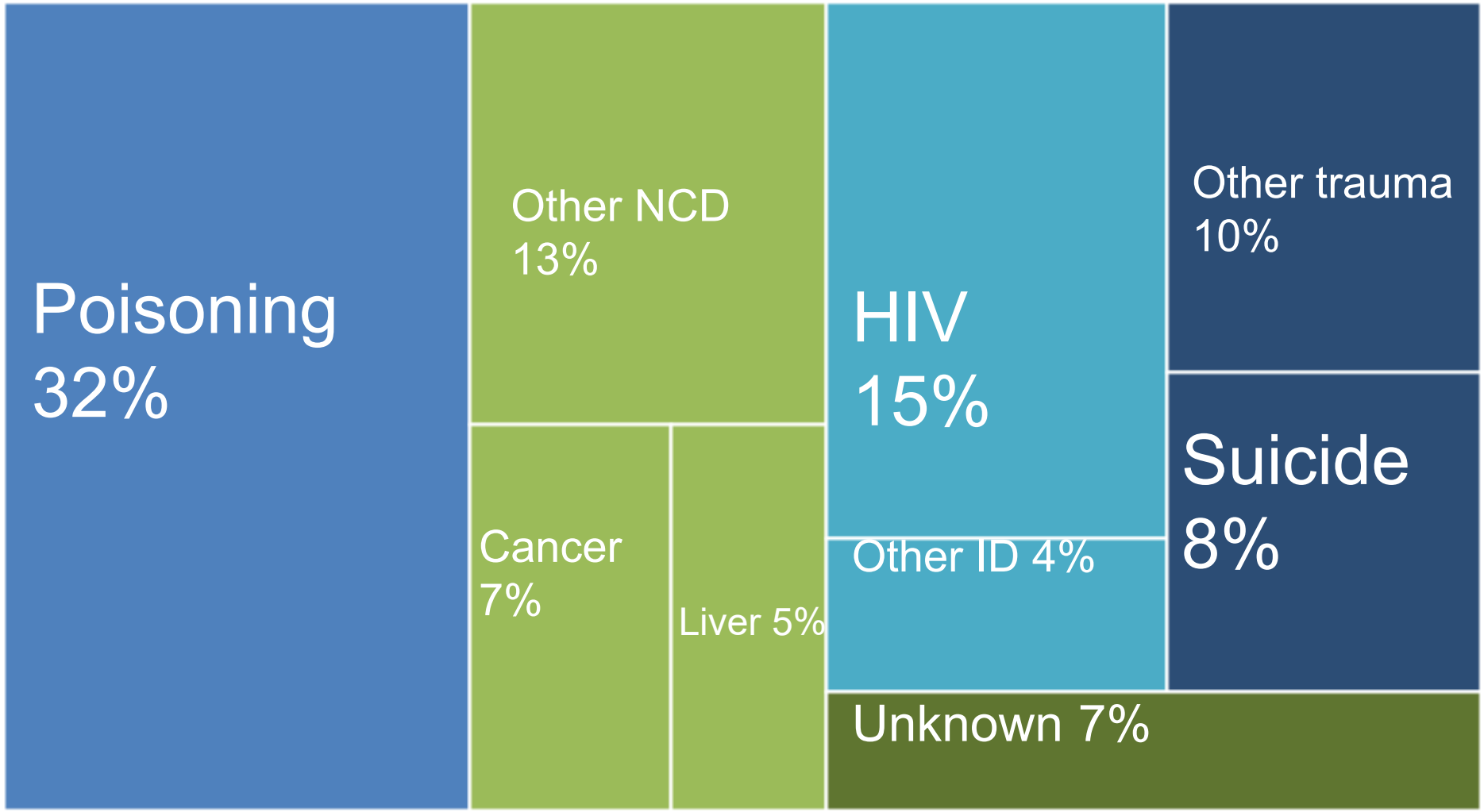
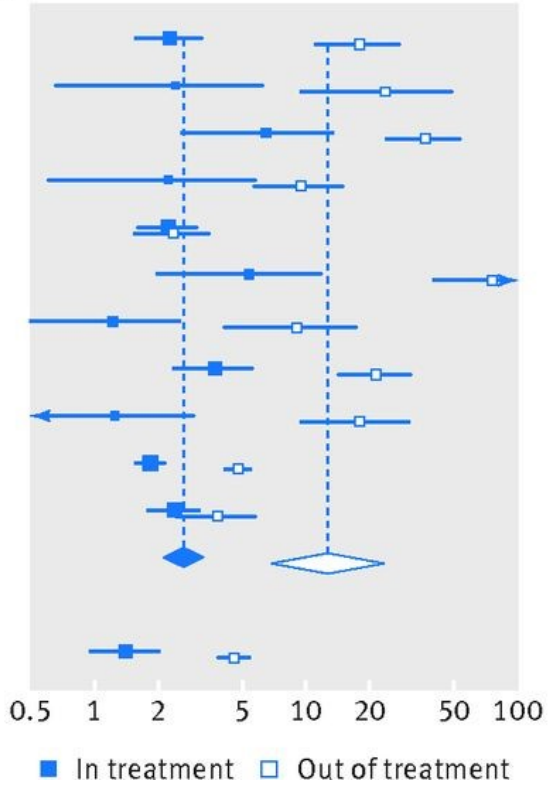


Larney et al, in press JAMA Psych


Poisoning
32%
Other NCD
13%
Cancer
7%
Liver 5%
HIV
15%
Other ID 4%
Other trauma
10%
Suicide
8%
Unknown 7%

Overdose mortality any time in vs. out of methadone and buprenorphine

	No of deaths/ person years		Overdose mortality rate/ 1000 person years (95% CI)	Overdose mortality rate/ 1000 person years (95% CI)	
Methadone	**In treatment**	**Out of treatment**		**In treatment**	**Out of treatment**
Gearing et al 1974	33/14 474	21/1170		2.3 (1.6 to 3.2)	17.9 (11.1 to 27.4)
Cushman 1977	4/1655	7/297		2.4 (0.7 to 6.2)	23.6 (9.5 to 48.6)
Grönbladh et al 1990	7/1085	27/740		6.4 (2.6 to 13.3)	36.5 (24.0 to 53.1)
Caplehorn et al 1996	4/1792	19/2004		2.2 (0.6 to 5.7)	9.5 (5.7 to 14.8)
Buster et al 2002	42/18 747	26/10 983		2.2 (1.6 to 3.0)	2.4 (1.6 to 3.5)
Scherbaum et al 2002	6/1114	13/172		5.4 (2.0 to 11.7)	75.6 (40.2 to 129.2)
Davoli et al 2007	7/5751	9/998		1.2 (0.5 to 2.5)	9.0 (4.1 to 17.1)
Clausen et al 2008	24/6450	28/1303		3.7 (2.4 to 5.5)	21.5 (14.3 to 31.1)
Peles et al 2010	5/3985	13/727		1.2 (0.4 to 2.9)	17.9 (9.5 to 30.6)
Kimber et al 2015	169/91 792	216/45 265		1.8 (1.6 to 2.1)	4.8 (4.2 to 5.4)
Cousins et al 2016	54/22 648	24/6247		2.4 (1.8 to 3.1)	3.8 (2.5 to 5.7)
Overall				2.6 (2.1 to 3.3)	12.7 (6.9 to 23.4)
Buprenorphine					
Kimber et al 2015	31/21 936	143/31 239		1.4 (1.0 to 2.0)	4.6 (3.9 to 5.4)



Sordo et al, 2017 BMJ

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Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study

Jo Kimber, Sarah Larney, Matthew Hickman, Deborah Randall, Louisa Degenhardt

Summary

Background Opioid dependence increases risk of premature mortality. Opioid substitution therapy with methadone or buprenorphine reduces mortality risk, especially for drug-related overdose. Clinical guidelines recommend

Lancet Psychiatry 2015; 2: 901–08

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT

doi:10.1111/add.14188

The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom

Matthew Hickman[1], Colin Steer[1], Kate Tilling[1], Aaron G. Lim[1], John Marsden[2], Tim Millar[3], John Strang[2], Maggie Telfer[4], Peter Vickerman[1] & John Macleod[1]

BMJ

Cite this as: BMJ 2010;341:c5475
doi:10.1136/bmj.c5475

RESEARCH

Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database

Rosie Cornish, statistician,[1] John Macleod, professor in clinical epidemiology and primary care,[1] John Strang, professor in the psychiatry of the addictions,[2] Peter Vickerman, senior lecturer in mathematical modelling,[1,3] Matt Hickman, professor in public health and epidemiology[1]

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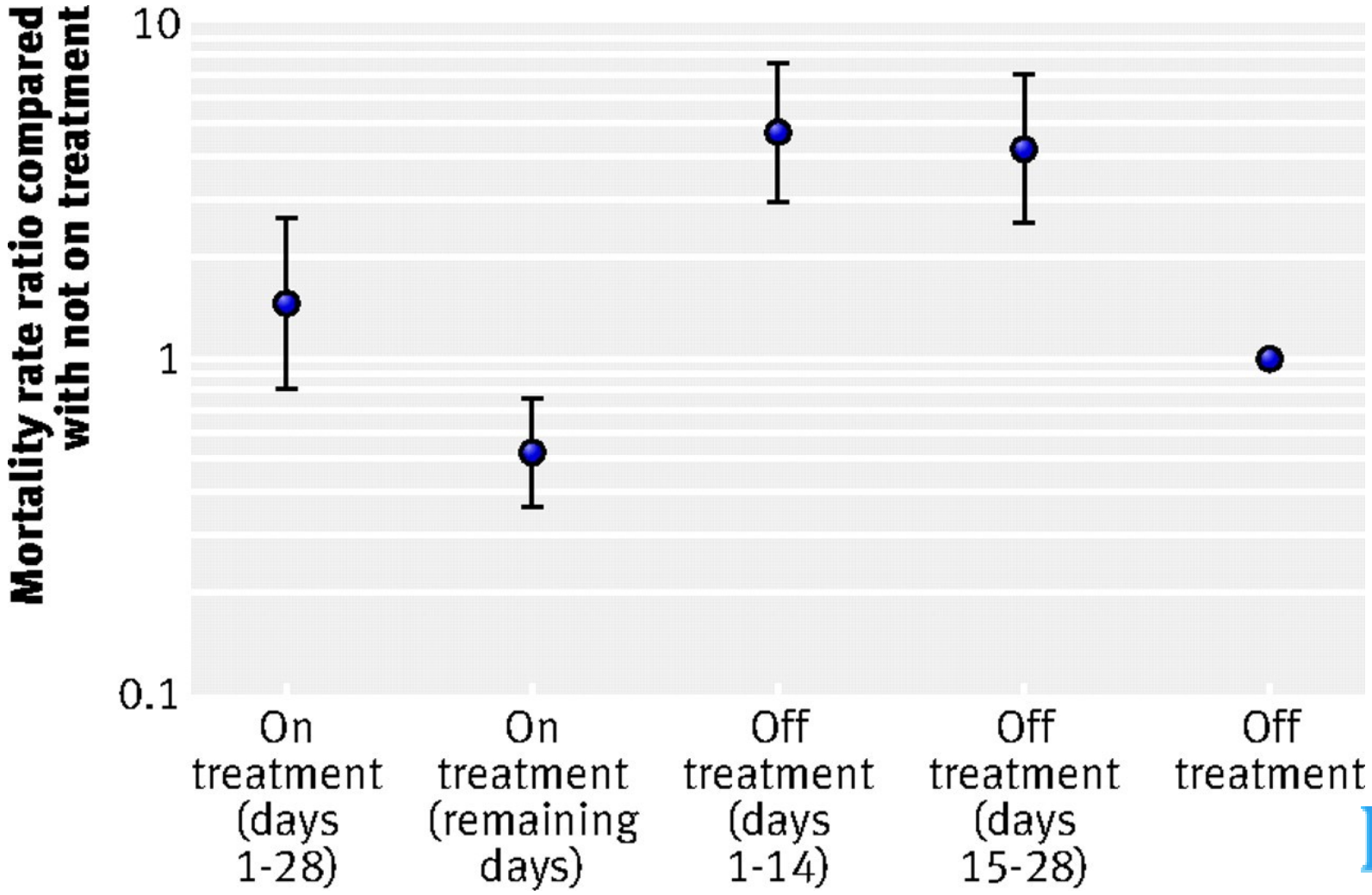
Adjusted risk of death, compared with not being on treatment, during and after opiate substitution treatment.



BMJ

Cornish R et al. BMJ 2010;341:bmj.c5475

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Differences in mortality risk during and after OST

	Overdose Deaths mortality			
Period	Deaths	Person Years	MR	IRR (95% CI)
On 1-4 wks OST	8	897	0.9	3.03 (1.37 to 6.66)
On rest OST	27	9165	0.3	1 (ref)
Off OST 1-4 wks	18	1044	1.7	5.85 (3.22 to 10.63)
Off OST rest	34	5257	0.7	2.20 (1.32 to 3.64)

Hickman et al, Addiction 2017; 112:1408-1418

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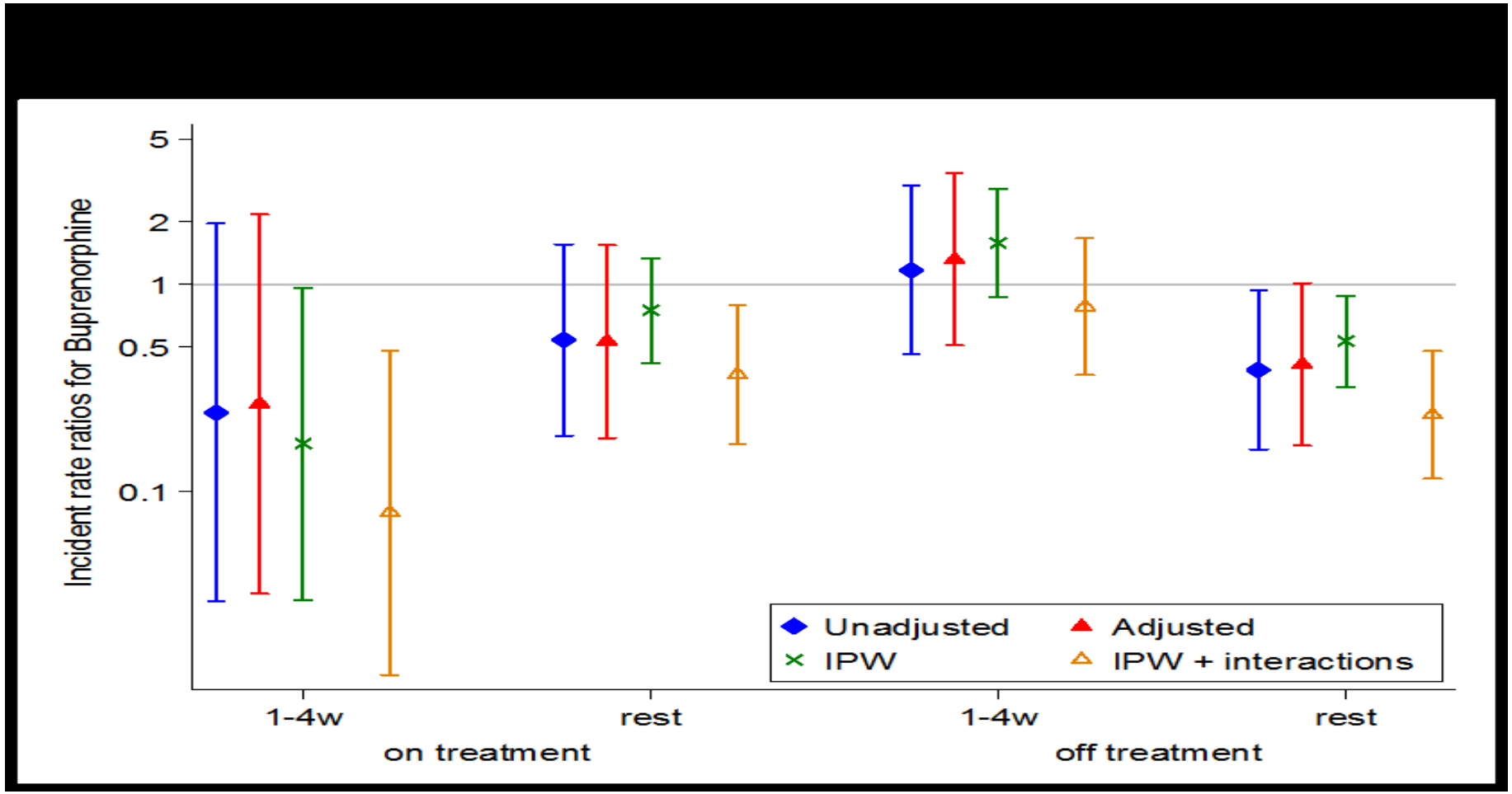
Evidence of Confounding

- Buprenoprhine
  - varies by region, calendar period, practice size
  - ↑ women, older, co-morbid patients
  - ↓ co-prescribed benzodiazepines, reported history of self-harm, overdose, alcohol problems, imprisonment, and homelessness
- Drug Related Poisoning
  - Associated with gender, co-morbidity, co-prescribed benzodiazepines, self-harm, overdose, alcohol problems, imprisonment, and homelessness

IRR comparing mortality risk for patients on buprenorphine or methadone by period on and off treatment



The figure shows the risk of mortality for buprenorphine relative to methadone for the four treatment periods unadjusted and adjusted, propensity score based weighted analyses (IPW), adjustment for interactions of OST with age or comorbidity. Incident rate ratios are shown on a log scale with 95% CIs.

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Interaction OST Modality with Co-morbidity

Comorbidity		DRP
0		1 (ref)
1		1.27 (0.78 to 2.07)
2+		2.69 (1.41 to 5.16)
0	Meth	1 (ref)
	Bup	0.97 (0.52 to 1.78)
1	Meth	1 (ref)
	Bup	0.37 (0.11 to 1.23)
2+	Meth	1 (ref)
	Bup	0.19 (0.04 to 0.90)

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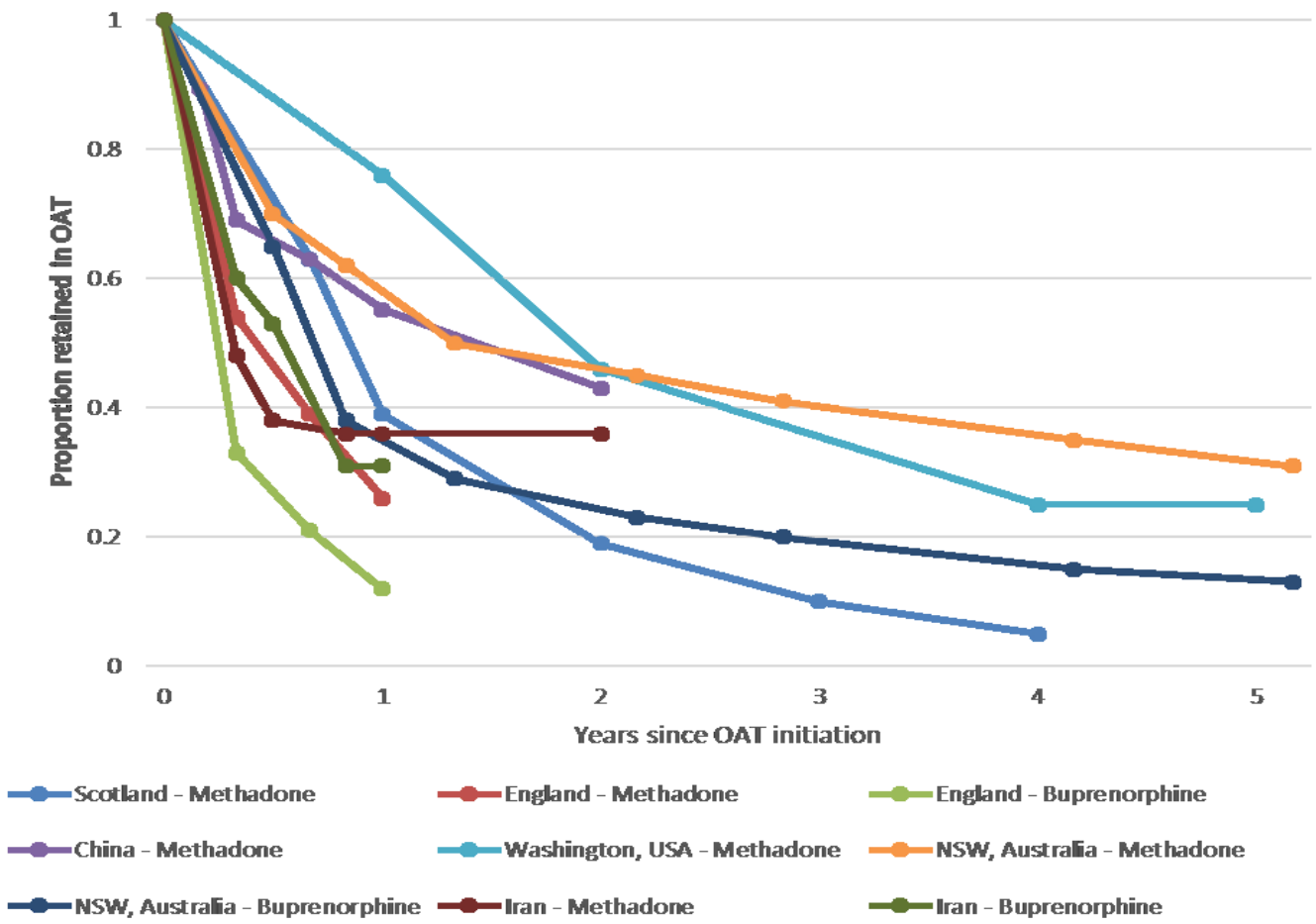
Retention in OAT

- Highly skewed distribution
- Buprenorphine shorter than methadone
- Especially UK
- Mean (median)
  - 319 days (92) for methadone
  - 165 days (42) for buprenorphine



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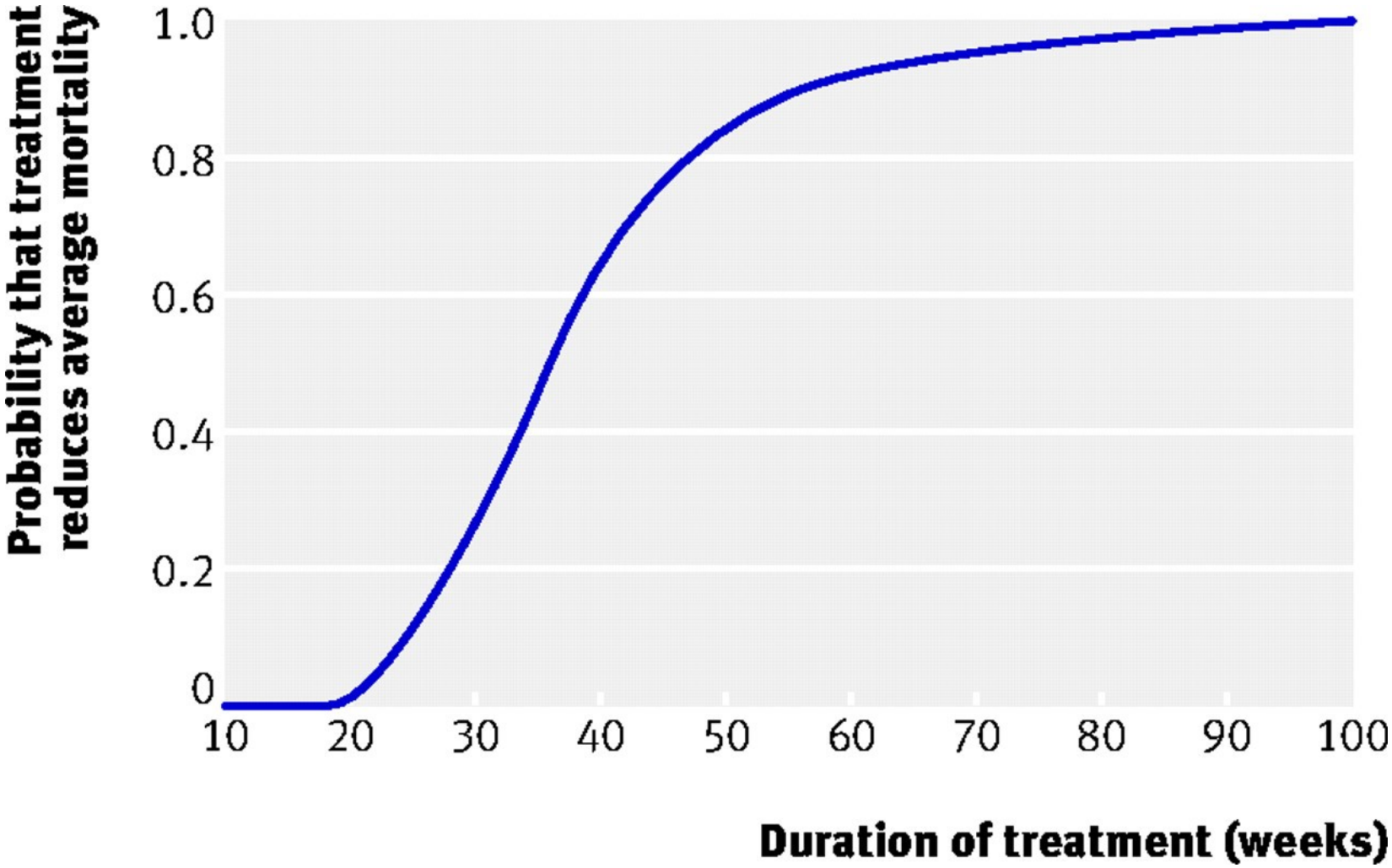
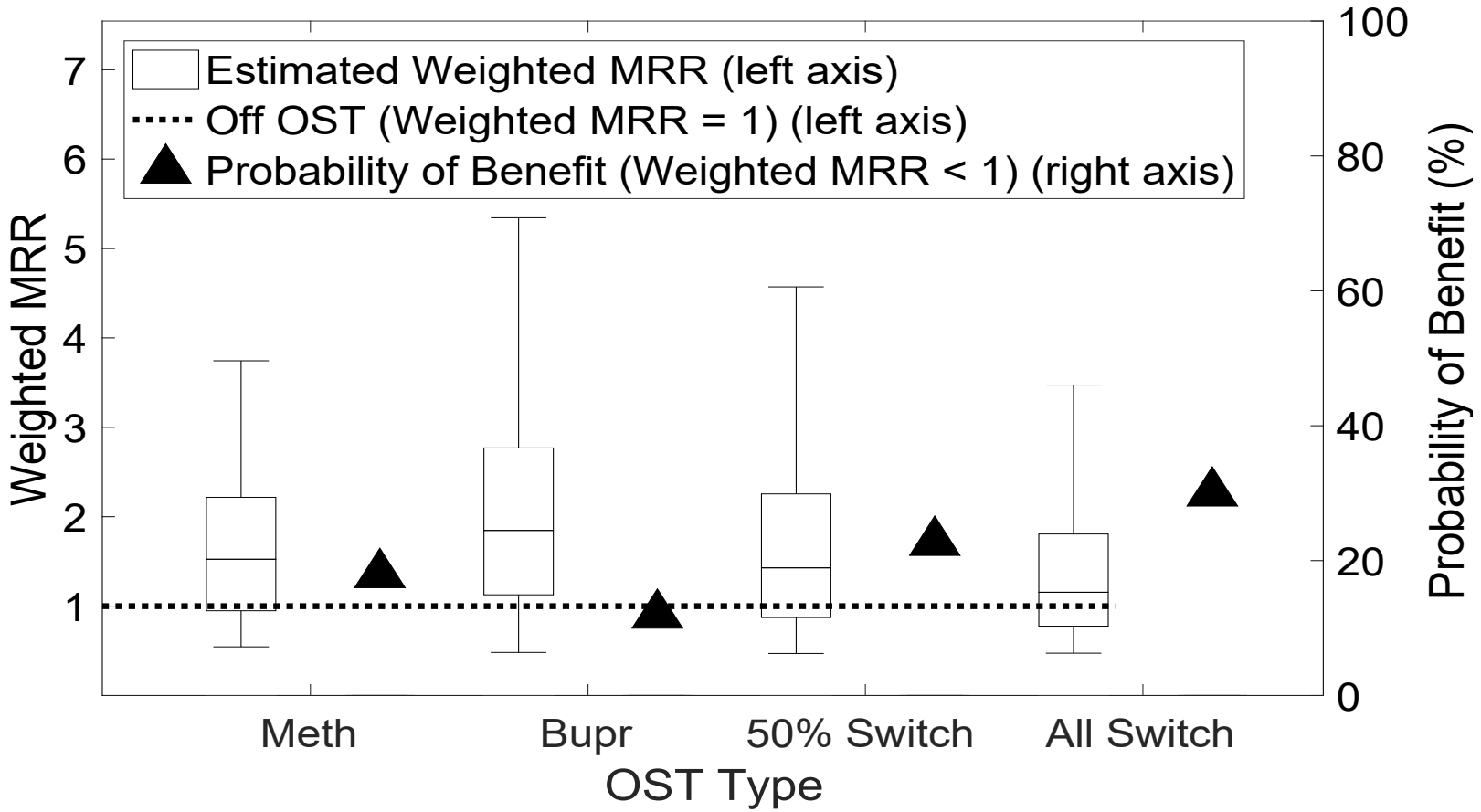
Probability that opiate substitution treatment (OST) reduces overall mortality for different durations of treatment.



Cornish R et al. BMJ 2010;341:bmj.c5475

DRP Weighted Mortality Risk & probability that DRP deaths would reduce in the population for patients on Methadone/Buprenorphine vs no OST



(and assuming 50% or all patients switch from buprenorphine to methadone after 4 weeks) vs no OST

Hickman et al, Addiction 2017; 112:1408-1418

Elevated Risk of Death post prison release

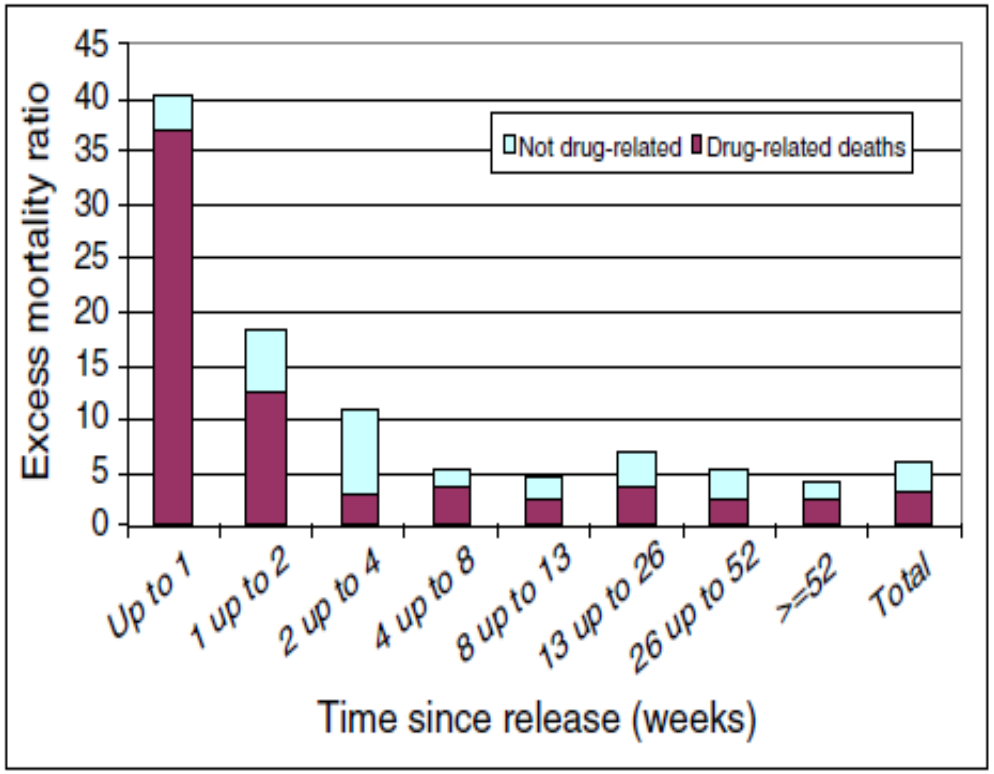
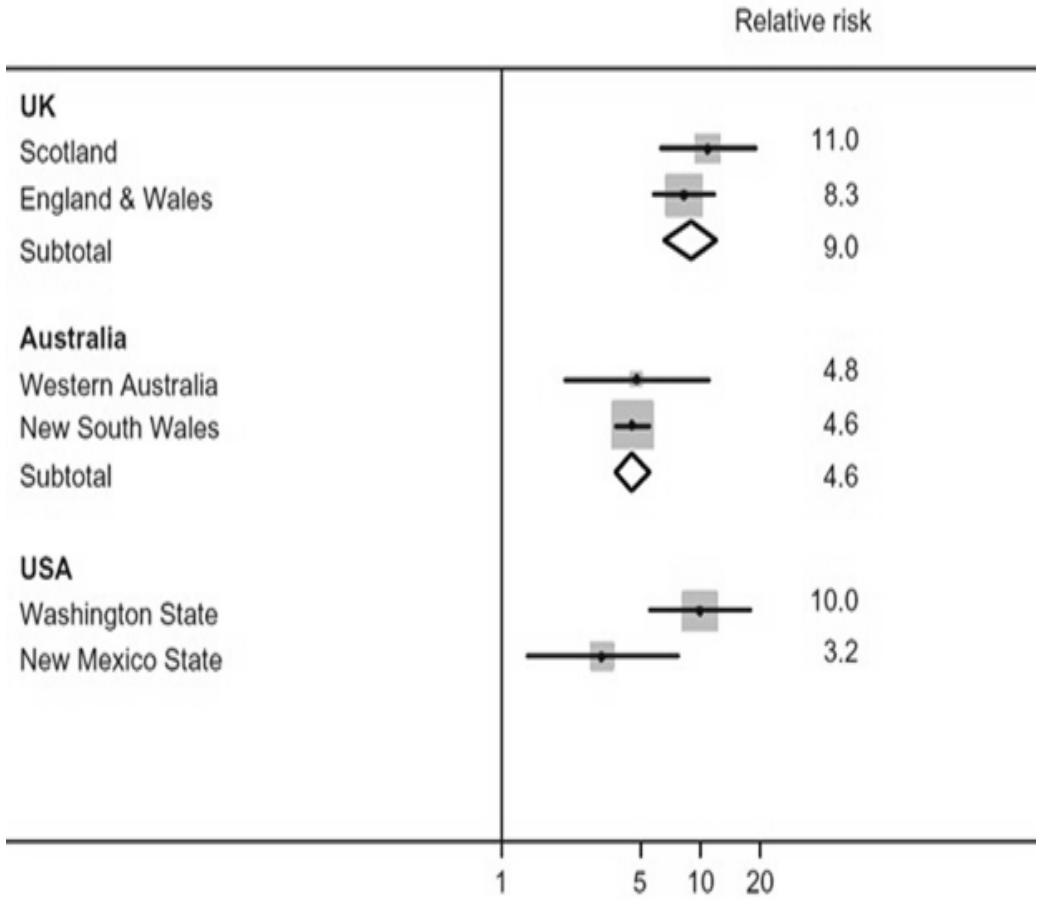


Figure 2 Excess mortality among former heroin users following release from prison (as reported in [10])

Farrell M et al *Addiction* 2008; **103**(2): 251-5



Merrall EL *Addiction* 2010; 105(9): 1545-54

Drug Related Poisoning Post-Prison: OST vs leaving drug free

	Exposed to OST at release		Not exposed to OST at release		
	PY at risk (n deaths)	Rate per 100 PY (95% CI)	PY at risk (n deaths)	Rate per 100 PY (95% CI)	Hazard Ratio (95% CI)
0 – 4 weeks	643 (3)	0.47 (0.15-1.45)	490 (15)	3.06 (1.85-5.08)	**0.15 (0.04-0.53)**
4 weeks – 4 months	1,966 (13)	0.66 (0.38-1.14)	1,555 (11)	0.71 (0.39-1.28)	0.93 (0.42-2.08)
4 months – 1 year	4,654 (31)	0.66 (0.47-0.94)	3,824 (29)	0.76 (0.53-1.09)	0.88 (0.53-1.46)

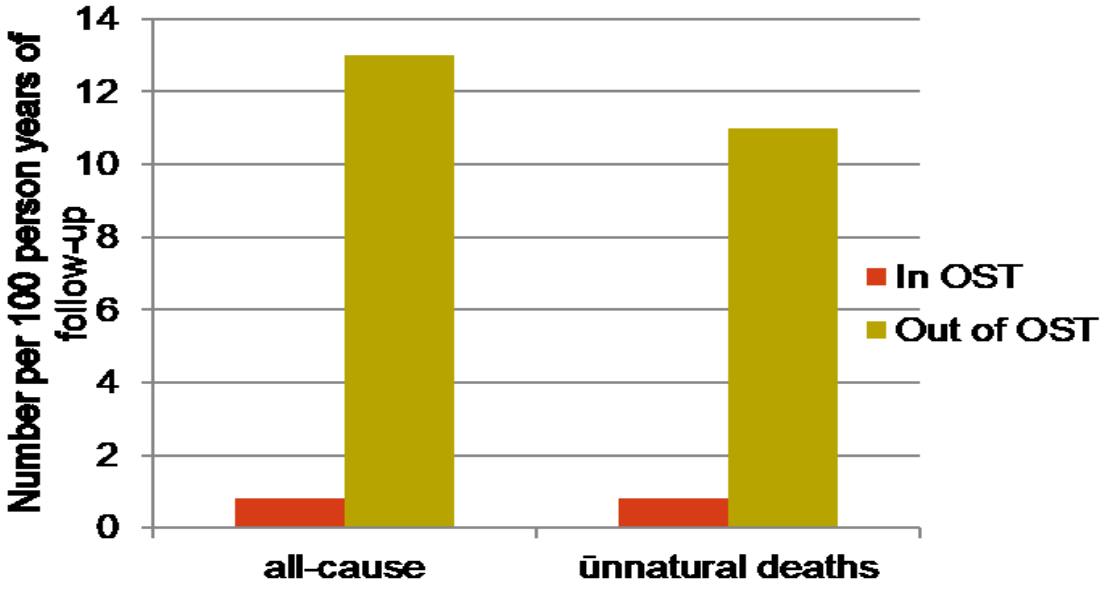
Fully Adjusted (age, injecting, problem alcohol, crack,benzodiazepine use & community drug treatment) **0.15 (0.04-0.54)**

Marsden, et al. Addiction 2017; 112:1408-18

Does OST have an impact on mortality in custody?

- Opioid dependent people may be at particular risk
  - Drug withdrawal as a trigger for suicide; overdose in custody
- ~16,700 people imprisoned for ~31,000 person years

- First 4 weeks of incarceration
  - Each day spent in OST **93% reduction in hazard of unnatural death** (adj.HR 0.07; 95%CI: 0.01, 0.53)
- Total time during incarceration
  - Each day spent in OST **87% reduction in hazard of unnatural death** (adj.HR 0.13; 95%CI: 0.05, 0.35)

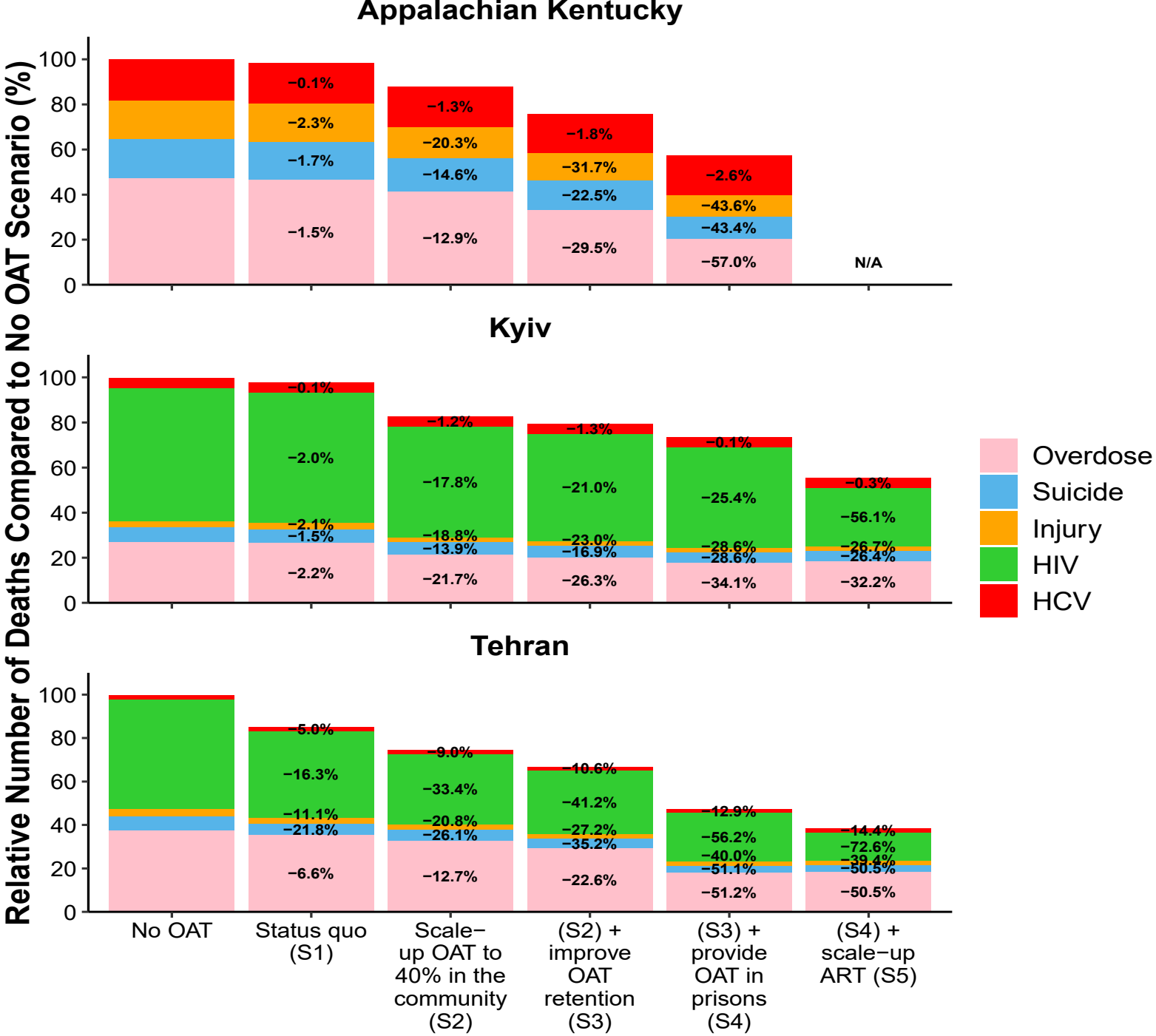


NDARC
National Drug & Alcohol Research Centre

The Difference is Research

Larney et al (2014). Opioid substitution therapy as a strategy to reduce deaths in prison: retrospective cohort study. BMJ Open

Relative Reduction in Deaths among PWID over 2020-2040



Degenhardt et al,, Lancet 2019
Stone et al… under review

Does benzodiazepine co-prescription (prescribed during OAT or 12 months post treatment) increase mortality risk

even if benzos also increase OAT

& is there a stronger interaction (risk of death) if benzos prescribed concurrently (at same time as OAT)

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UK Study Data

- Clinical Practice Research Datalink (CPRD)
  - ~ 674 UK practices, > 11 million patients (7% UK population)
  - 606 GP practices had 1 OST patient
  - 352/395 practices in England linked to ONS data
- OAT >20mg methadone >4mg buprenorphine
  - 12,118 patients & 7,016 with ONS cause of death
  - 29,549 OAT episodes
- Ten benzodiazepine (3 z-drug 2 gabapentinoids)
  - 365,582 benzo prescriptions (75,926 z-drugs 23,451 gabap)
  - 42% benzo co-prescription, 29% benzo concurrent prescription

OAT patients prescribed benzodiazepines associated with prolonged retention

Concurrent Prescription		Episodes	Median	Mean adjusted*
OAT	None	17111	62	244 (236-252)
	Benzos	*7961 (32%)*	*147*	*416 (404-429)*

**Adjusted for sex, age, year, comorbidity, region, OAT type, concurrent prescription of, z-drugs and gabapentinoids*

Macleod et al,, Plos Med in press

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Co-prescription of benzodiazepines increases risk of DRP/OD

Co-prescription	Deaths	PY	MR	HR (95% CI)	*Unadj*	HR (95% CI)	*Adj**
Drug related poisoning (DRP)							
Benzodiazepine Off	74	16270	0.45	1 (ref)	*<0.0001*	1 (ref)	*<0.0001*
On	39	3679	1.06	2.35 (1.6 to 3.5)		2.96 (1.9 to 4.4)	
Benzodiazepine Off	74	16270	0.45	1 (ref)	*<0.0001*	1 (ref)	*<0.0001*
Normal Dose	25	2889	0.87	1.93 (1.2 to 3.0)		2.51 (1.6 to 4.0)	
High Dose	14	790	1.77	3.83 (2.1 to 6.8)		4.57 (2.5 to 8.5)	
linear effect of dose	-	-	-	1.95 (1.5 to 2.5)	*<0.0001*	2.22 (1.7 to 2.9)	*<0.0001*
All Cause Mortality							
Benzodiazepine Off	513	28766	1.78	1 (ref)	*0.717*	(ref)	*0.105*
On	144	7361	1.96	1.03 (0.86 to 1.25)		1.17 (0.97 to 1.4)	

*PY – person years follow-up; MR mortality rate (deaths/100 person-years). HR Hazard ratio; *Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, z-drug and gabapentinoid exposure.*

Macleod et al,, Plos Med in press

Test of whether benzo prescription greater OD risk on or off OAT

OAT	Co-Rx				Unadjusted		Adjusted *	
Period	Benzo	Deaths	PY	MR	HR (95% CI)	p	HR (95% CI)	p
OAT on	Off	24	10091	0.24	1 (ref)	**0.8958**	1 (ref)	**0.997**
	On	20	2914	0.69	2.87 (1.58 to 5.20)	0.0005	2.92 (1.60 to 5.33)	0.0005
OAT off	Off	50	6179	0.81	1 (ref)		1 (ref)	
	On	19	764	2.49	3.02 (1.78 to 5.15)	<0.0001	2.92 (1.70 to 5.02)	0.0001

HR Hazard ratio; PY person years at risk; MR mortality rate (deaths/100 person-years)

**Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, z-drug and gabapentinoid exposure. Interaction p value shown in bold.*

Macleod et al,, Plos Med in press

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Is concurrent exposure to benzodiazepines beneficial – allowing for prolonged OAT

	Concurrent	Unadjusted		Adjusted [a]	
Mortality	Exposure with OAT	HR (95% CI)	p	HR (95% CI)	p
Drug-related	None	1 (ref)	0.0005	1 (ref)	<0.0001
poisoning	Benzodiazepines	1.98 (1.35 to 2.90)		3.34 (2.14 to 5.20)	

[a] *Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, off treatment prescription of benzodiazepine, z-drugs and gabapentinoids and, concurrent prescription of z-drugs and gabapentinoids*

Macleod et al,, Plos Med in press

Implications – Evidence that:

- OAT in the community reduces OD risk
- Bup reduces OD risk compared to methadone
  - But retention poorer
- OAT retention in UK is sub-optimal
  - public health benefit uncertain
- Comorbidity increases risk of death (doh)
  - even with OD & may interact with OAT modality
- Co-prescribing benzos increases mortality risk
  - need alternative interventions

Implications – Evidence that:

- Prison OAT works
  - OAT in prison *almost entirely eliminates* deaths of opioid dependent prisoners in 1st weeks of prison
  - OAT on release *removes excess mortality* risk in 1st 4 weeks after release & increases community OAT
- Model projections on scaling-up community /prison OAT retention & coverage
  - Reduce OD, HIV, self-harm and injury deaths
  - Develop/introduce interventions to address excess in other causes of death

Implications:

- Public health framework to OAT and OD prevention
  - Intervention programme not working / needs overhaul and investment
  - [more applied epidemiology]
  - Cross country comparisons

END

OST modality x Treatment Period

Treatment Period	OST Type	Drug related mortality	
		IRR (95% CI)	MR
1-4w on	M	1 (ref)	1.24
	B	0.08 (0.01 to 0.48)	0.30
Rest on	M	1 (ref)	0.33
	B	0.37 (0.17 to 0.79)	0.18
1-4w off	M	1 (ref)	1.61
	B	0.78 (0.36 to 1.66)	1.89
Rest off	M	1 (ref)	0.83
	B	0.23 (0.12 to 0.48)	0.32
P		0.014	

IPW: inverse proportional weighting based upon propensity scores derived from all previous confounders (age, sex, comorbidity, year, prescription for benzo, gabapentoid prescription,self-harm, evidence of overdose, alcohol problems, prison, homeless, OST patients in practice, Practice size. Additionally adjusted for age x OST type and comorbidity x OST type interactions. MR unadjusted mortality rates weighted using IPW

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Implications for practice

- Evidence support Ho that buprenorphine safer than methadone at treatment initiation
  - But residual confounding by indication possible
- Beneficial effects of buprenorphine on mortality risk after treatment less clear
  - Duration of treatment episodes lower for buprenorphine so may offset benefits
- Experimental evidence needed on:-
  - how to combine bup/meth to reduce mortality risk
  - retain people in OST so that deaths in population fall

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Implications for practice

- Opioid dependent patients prescribed benzos had increased OD risk of death from overdose, despite staying in treatment longer.
  - Evidence of dose response association
  - Specific to OD not ACM
  - Contributor to increase mortality risk in population
  - BUT residual confounding/ confounding by indication?
- Clinicians should be more cautious about prescribing benzos to opioid dep patients

CONCLUSIONS

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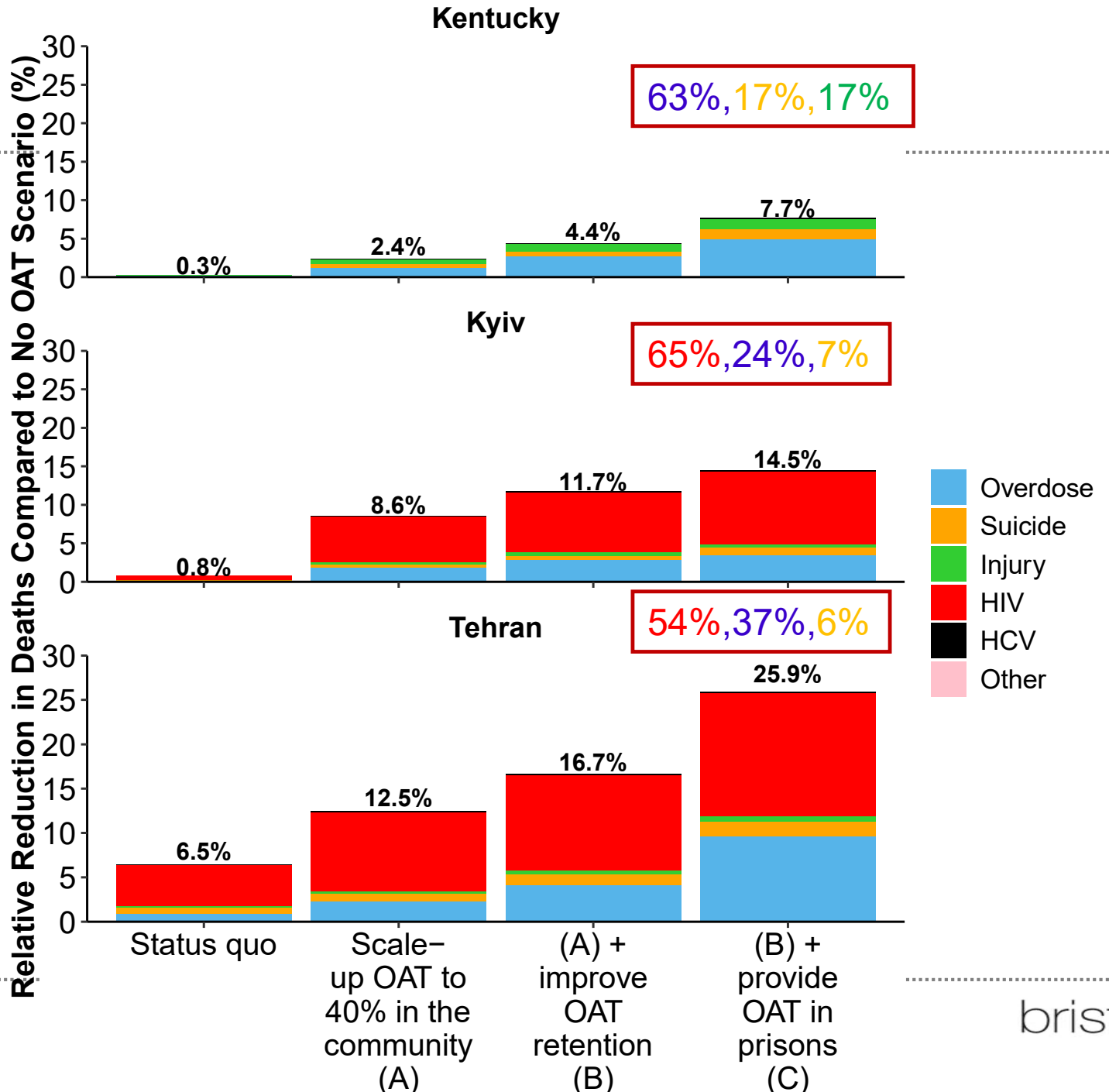
Relative Reduction in Deaths among PWID over 2020-2040



Degenhardt et al,, Lancet 2019
Stone et al… under review

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Conclusions

- Injecting drug use causes significant health loss which can be significantly reduced through scaling-up OAT.
- Our findings highlight the importance of:
  - Scaling-up OAT
  - Improving OAT retention
  - Increasing the availability of OAT in prisons
- The impact of scaling-up OAT on all-cause mortality varies substantially between the three settings
- Primarily because of differences in how the varied harms associated with drug use contribute to

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Conclusions

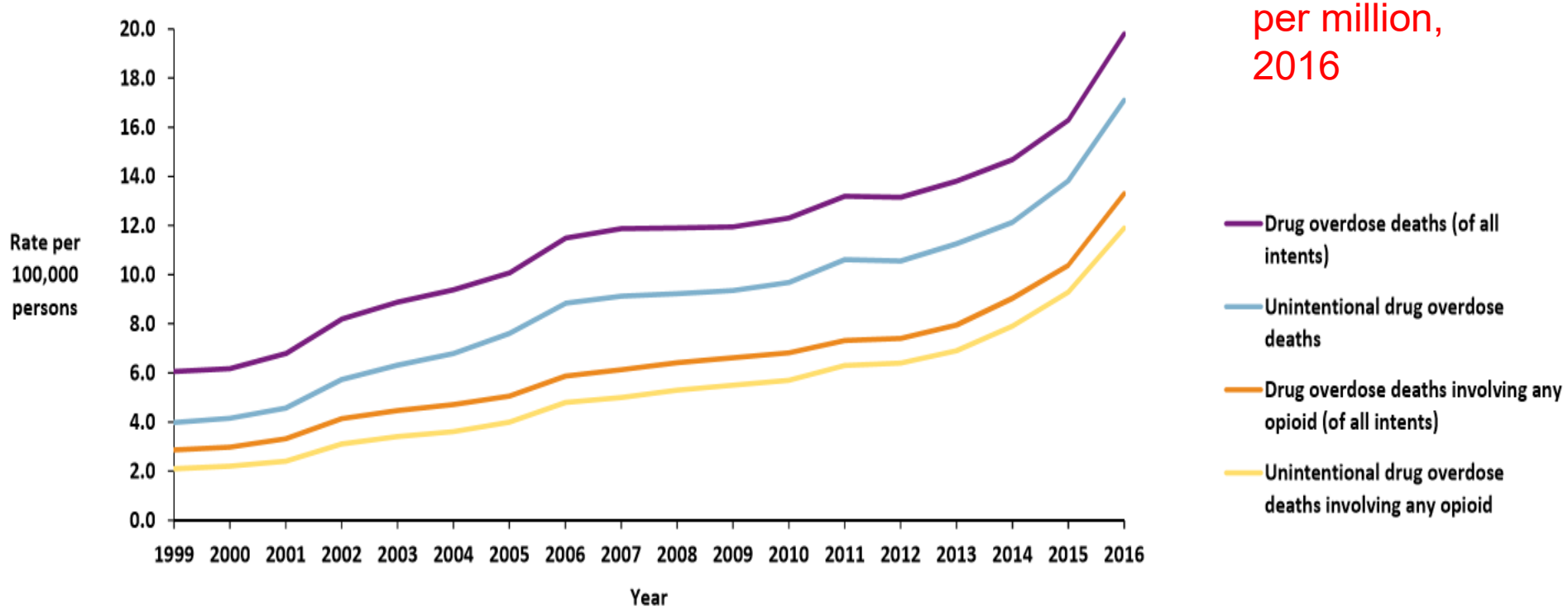
- Even after scaling-up OAT, mortality rates among PWID would still far exceed that among the general population
- There is a need to scale-up and develop other interventions to improve the health of PWID.
- However, unlikely other interventions will have as strong effects on a wide range of different outcomes
- Given extremely low global coverages of OAT[1], a key priority in most countries must be to first scale-up OAT.

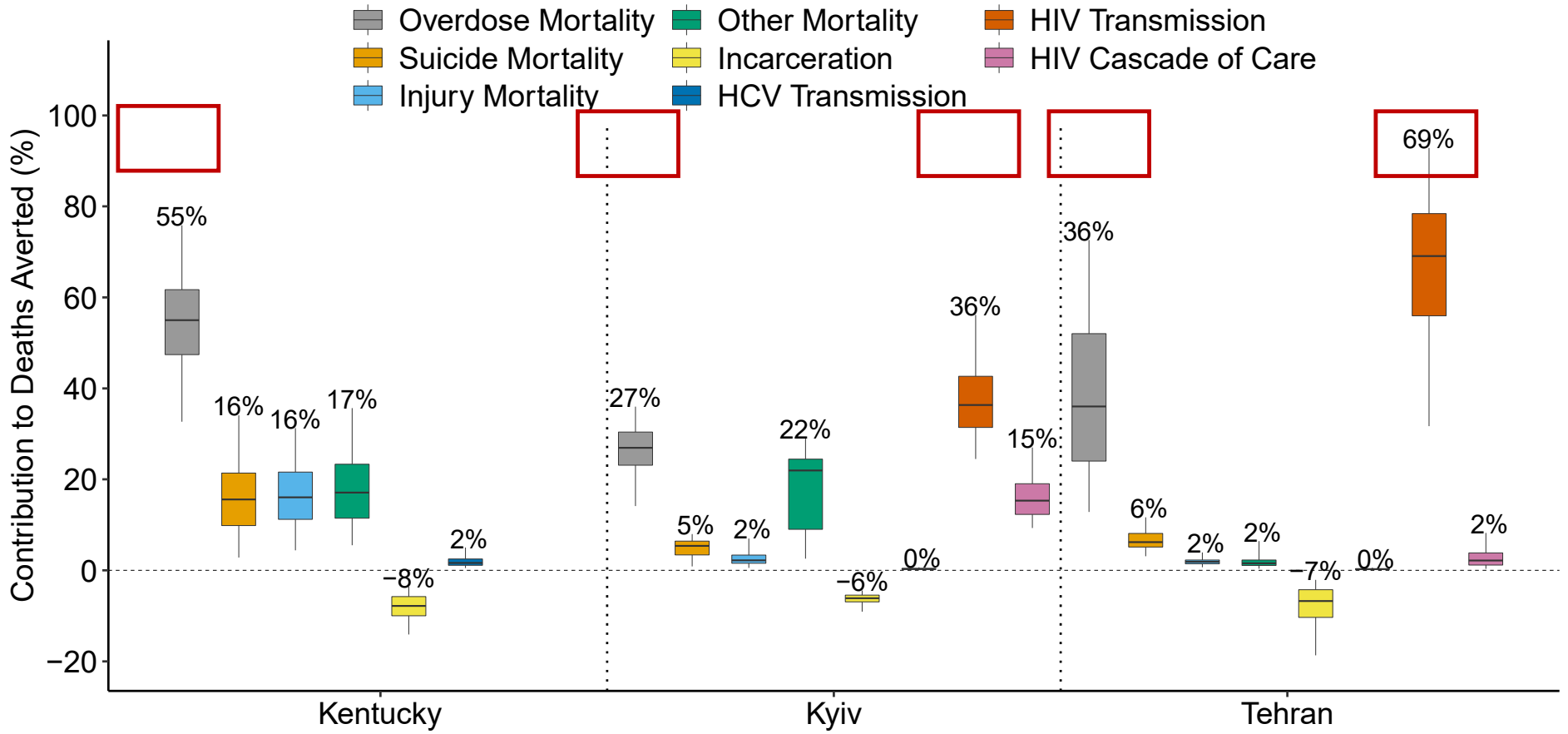
1 Larney Lancet Global Health 2017

…in the United States (rate per 100,000)

Age-adjusted rates of drug overdose deaths[a] and drug overdose deaths involving any opioid[b] for all intents and for unintentional intent by year — United States, 1999–2016

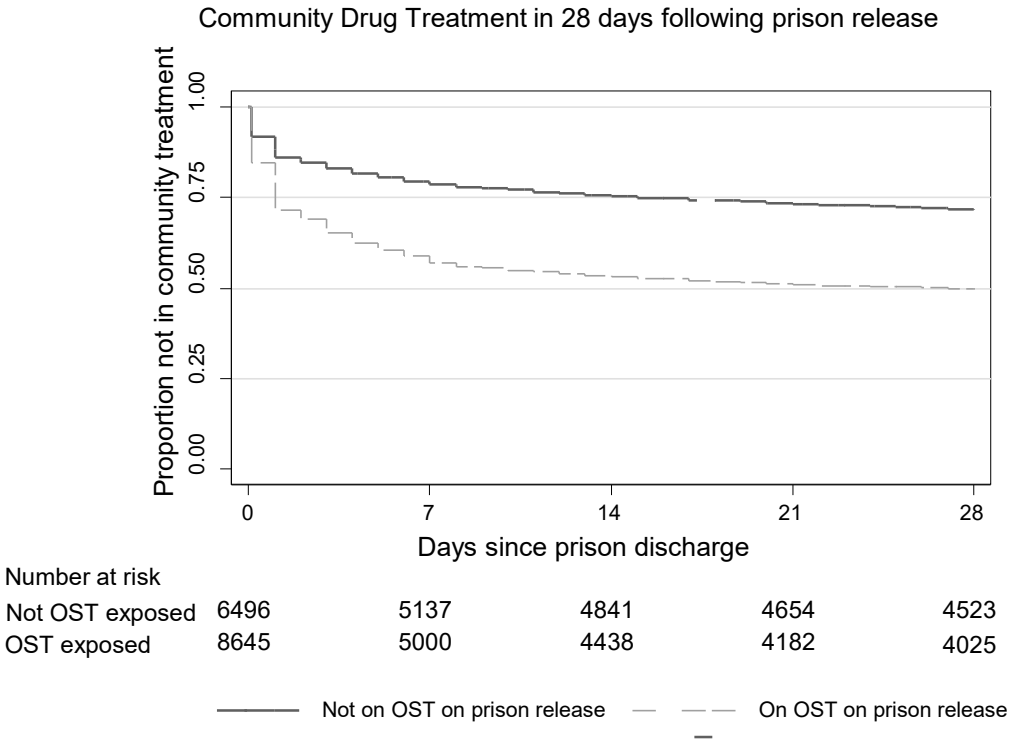
~120 deaths per million, 2016




Overdose Mortality
Suicide Mortality
Injury Mortality
Other Mortality
Incarceration
HCV Transmission
HIV Transmission
HIV Cascade of Care
Contribution to Deaths Averted (%)
100
80
60
40
20
0
−20
55%
16%
16%
17%
−8%
2%
27%
5%
2%
22%
−6%
0%
36%
15%
36%
6%
2%
2%
−7%
0%
69%
2%
Kentucky
Kyiv
Tehran

Leaving prison on OST & entering community treatment: independent benefits

- 6295 (42%) people entered drug treatment in 1st 4 weeks after prison release
- Leaving on OST more likely to enter community Rx:
- HR 2.13, (95%CI 2.01-2.25)
- Community Rx reduces DRP:
- HR 0.39 (95% CI 0.1-1.4)
- Mutually beneficial – no evidence of an interaction/ or mediation



Marsden, et al. Addiction 2017; 112:1408-18

no evidence on an interaction between OST Rx on prison release and community Rx (Ratio of hazard ratios risk (ratio of HR 1.26 (95% CI 0.07-21.29), LRT p-value 0.86)