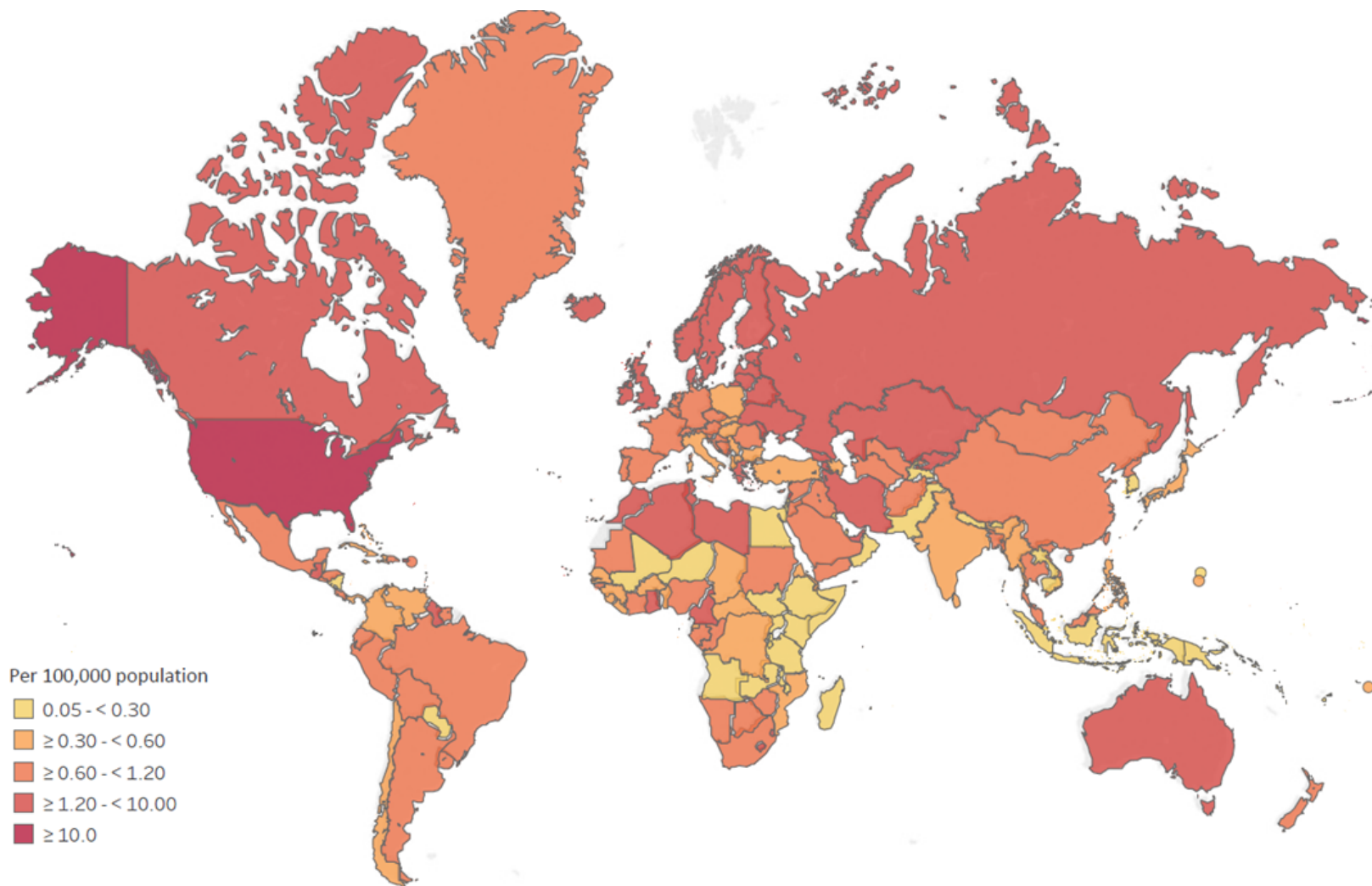


Reducing opioid overdose: a review of the issues and the options

Louisa Degenhardt and Matthew Hickman

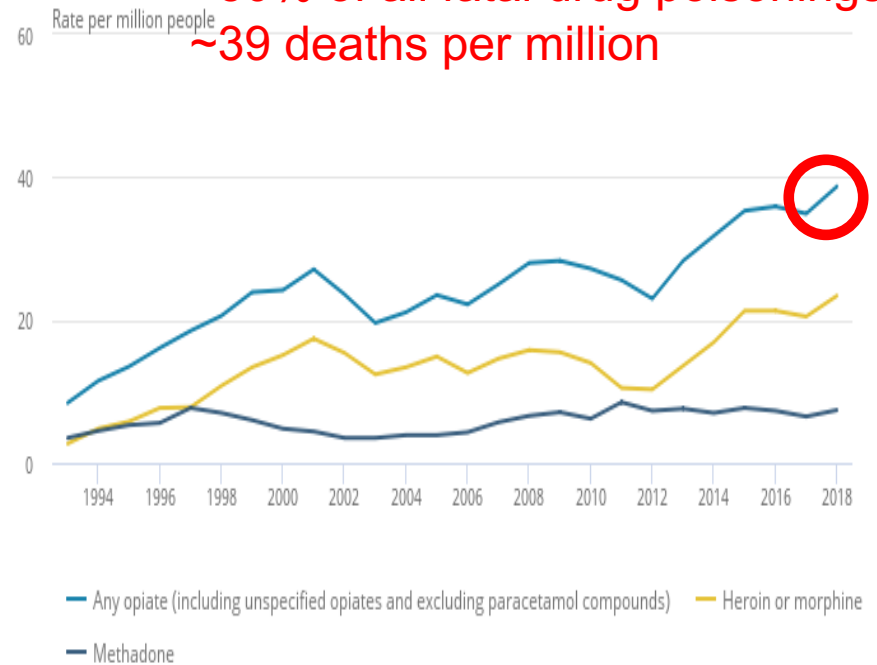
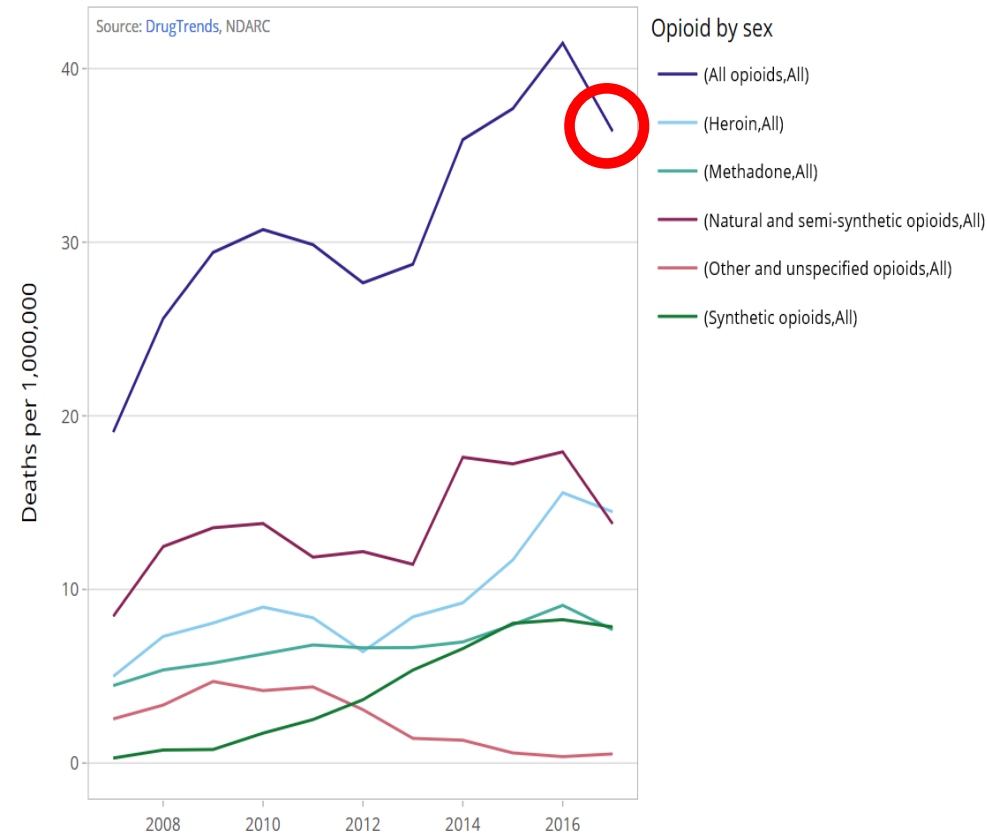
Estimated age-standardised opioid overdose deaths per 100,000 population (GBD 2017)



Opioid overdose deaths increasing...

...in the UK and Australia (rate per million)

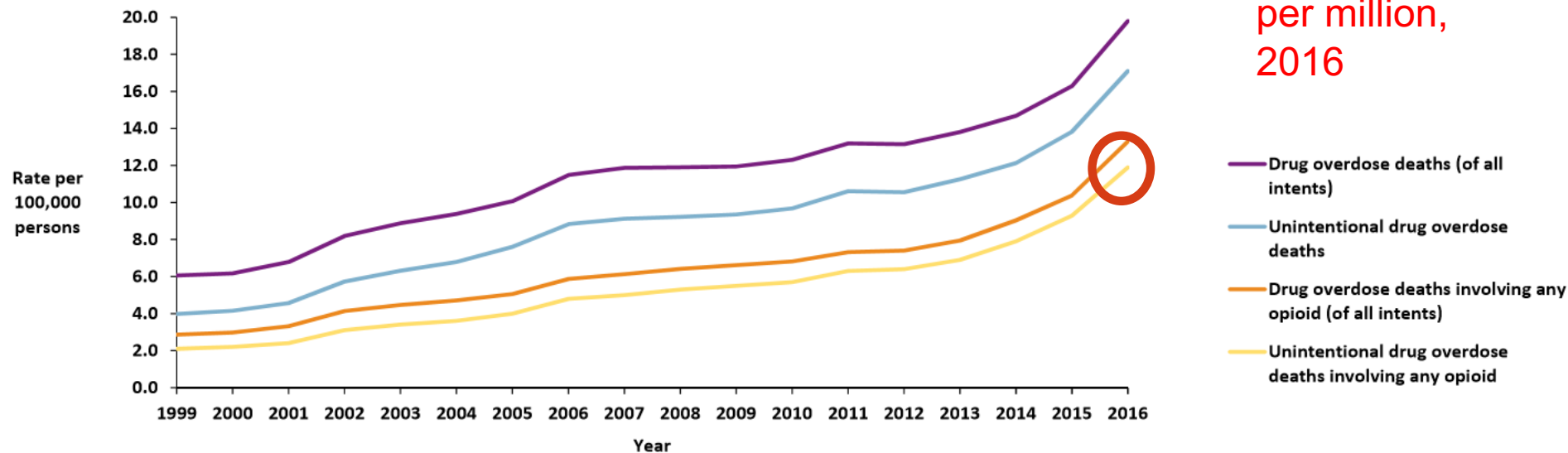
2018: 2208 opioid related deaths
>50% of all fatal drug poisonings
~39 deaths per million



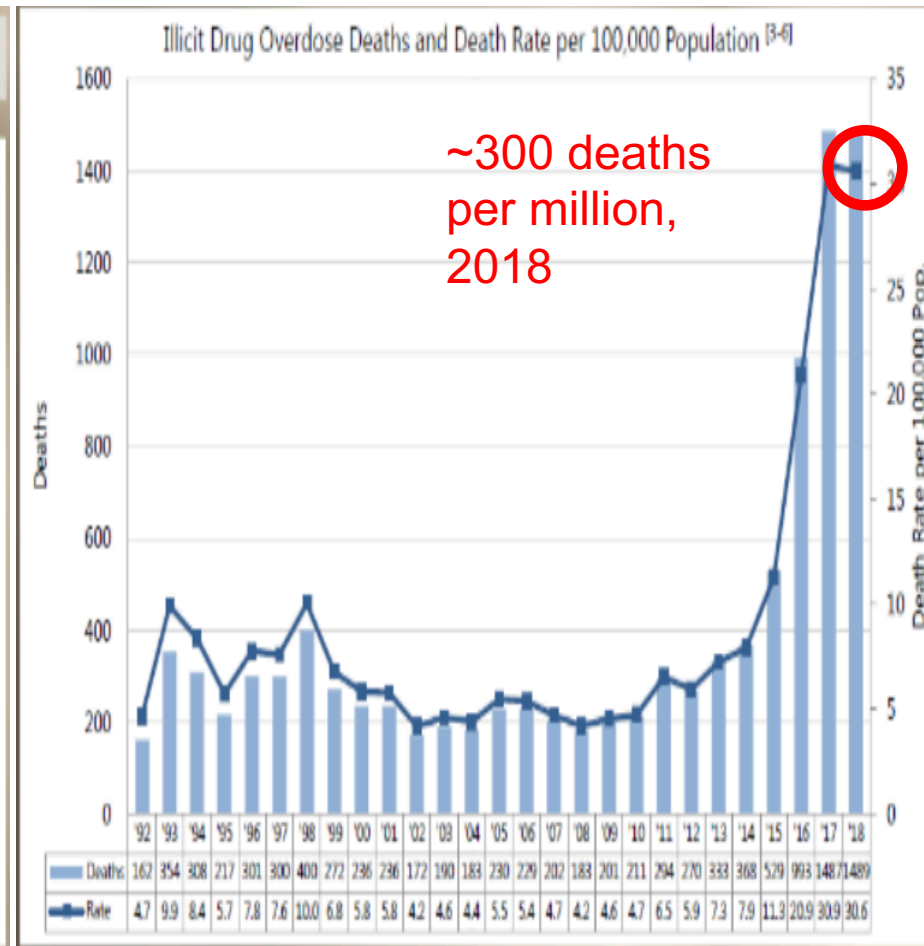
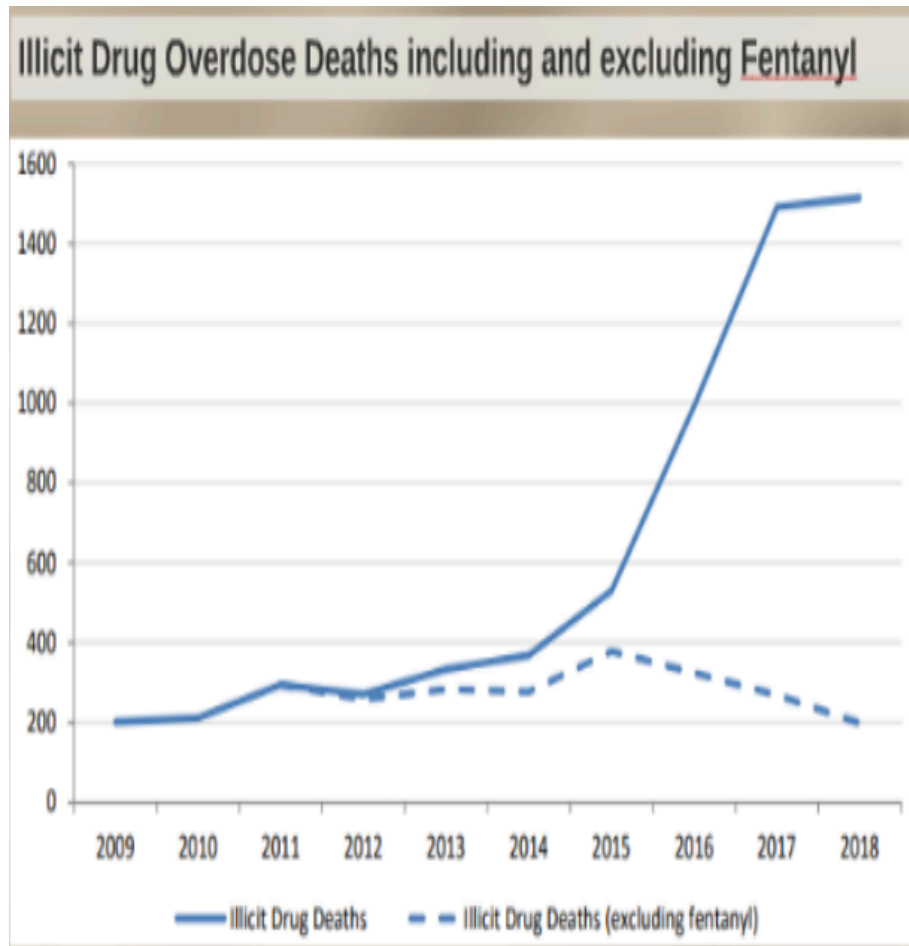
Source: Office for National Statistics

...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



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



Evaluating the impact of OAT on overdose

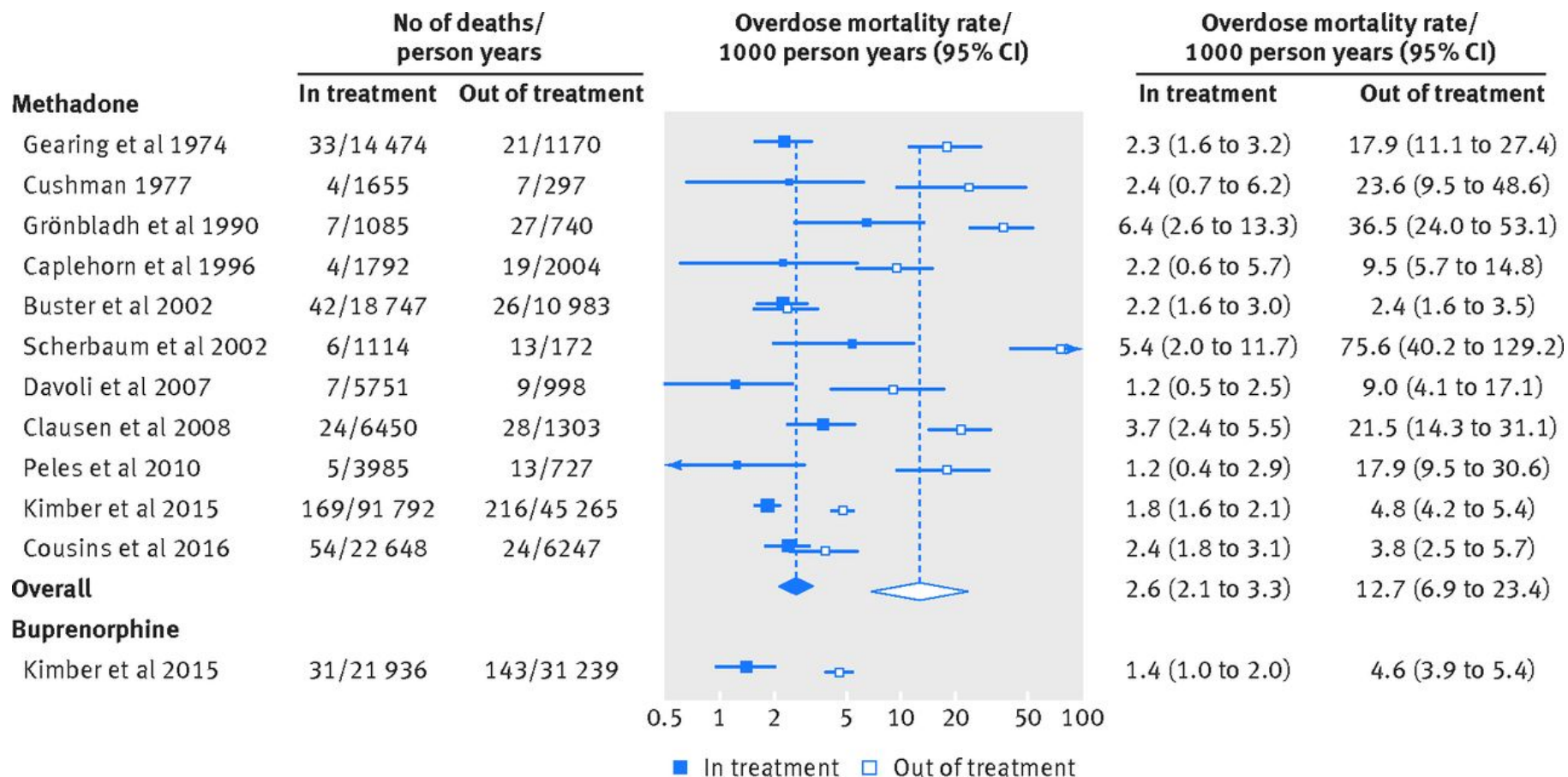
Background

- Randomised controlled trials of OAT with no treatment as control no longer ethical
 - Historically never sufficiently powered to examine impacts on mortality
 - especially during specific risk periods/ or/ among specific sub-populations
- Data linkage represents a unique method with sufficient power to examine rare outcomes, specific time periods, and small populations
 - Typically involves the use of administrative datasets
 - Linkage via details such as date of birth and name
- But subject inevitably to confounding

Do methadone and buprenorphine have differing mortality risk in key periods in/out of treatment?

- Background
 - Clinical guidance recommends methadone over buprenorphine as the first line of treatment as it is more cost-effective, but methadone, a full opioid agonist, can cause potentially hazardous respiratory depression during treatment induction
- We need well-powered, direct comparisons of mortality risks during key risk periods
 - During induction
 - Following cessation
 - Following in-treatment switching from one medication to another
 - ...that consider potential confounders across patient groups

Overdose mortality any time in vs. out of methadone and buprenorphine (Sordo et al, 2017 BMJ)



Differences in mortality risk during specific periods in and after OST

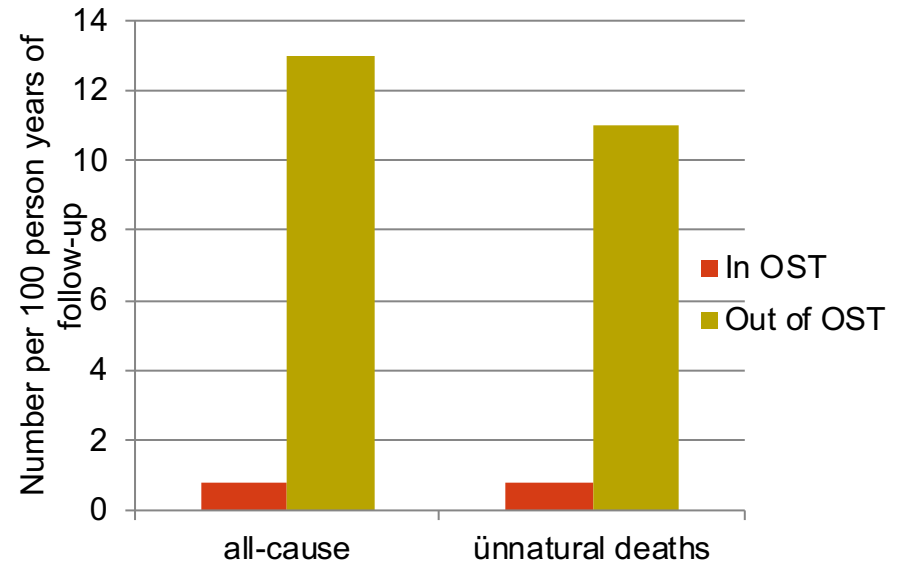
	All cause mortality			Overdose Deaths mortality		
Period	Deaths	Person Years	MR	Deaths	Person Years	MR
On 1-4 wks OAT	48	1541	3.11	8	897	0.89
On rest OAT	179	18240	0.98	27	9165	0.29
Off OST 1-4 wks	165	1730	9.54	18	1044	1.72
Off OST rest	195	8900	2.19	34	5257	0.65

	All cause		Overdose	
Period	IRR	95% CI	IRR	95% CI
On 1-4w	3.17 (2.31 to 4.36)		3.03 (1.37 to 6.66)	
On rest	1 (ref)		1 (ref)	
Off 1-4w	9.72 (7.87 to 12.01)		5.85 (3.22 to 10.63)	
Off rest	2.23 (1.82 to 2.73)		2.20 (1.32 to 3.64)	

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 was independently associated with a **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 was independently associated with an **87% reduction in hazard of unnatural death** (adj.HR 0.13; 95%CI: 0.05, 0.35)



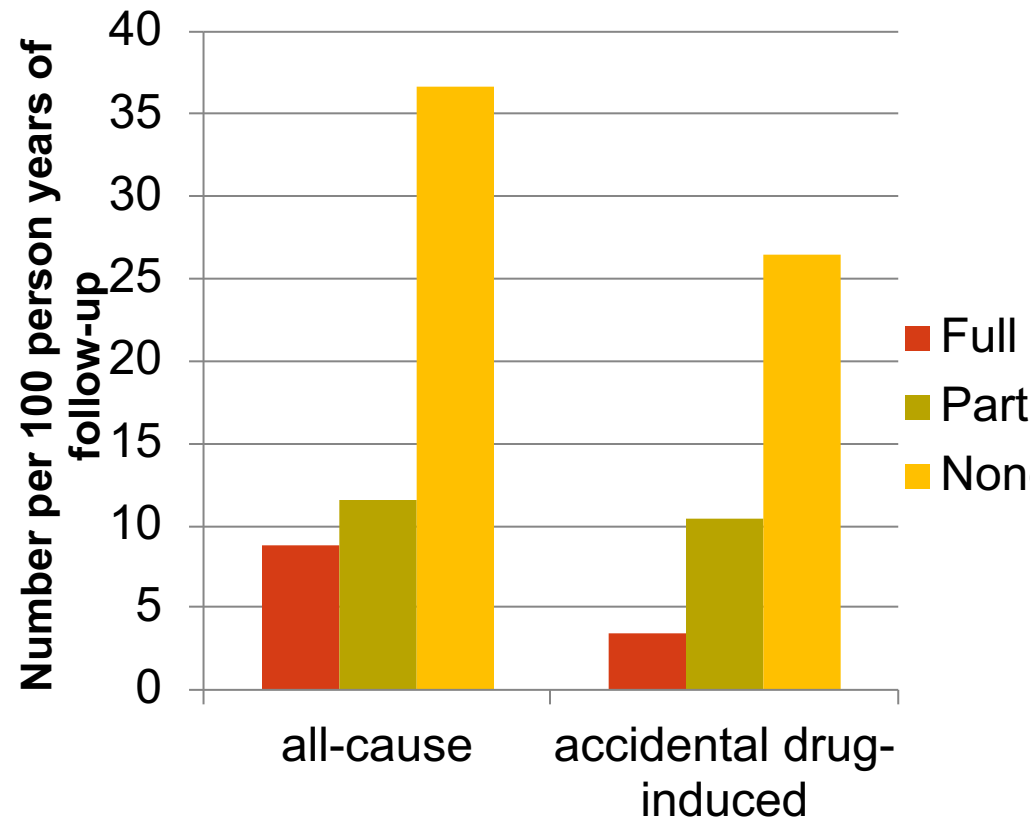
Drug Related Poisoning Mortality risk after leaving prison: OAT vs leaving drug free

	Exposed to OAT at release		Not exposed to OAT at release		Hazard Ratio (95% CI)
	PY at risk (n deaths)	Rate per 100 PY (95% CI)	PY at risk (n deaths)	Rate per 100 PY (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)

Adjusted for age, injecting, problem alcohol, crack, benzodiazepine use & community drug treatment

Mortality according to OAT received in the first 4 weeks post-release

- First 4 weeks post-release
Each day spent in OST was independently associated with a **75% reduction in hazard of death** (adj.HR 0.25; 95%CI:0.1,0.5)
- Total time at liberty post-release from prison
Each day spent in OST was independently associated with **an 83% reduction in hazard of death** (adj.HR 0.17; 95%CI:0.1,0.2)



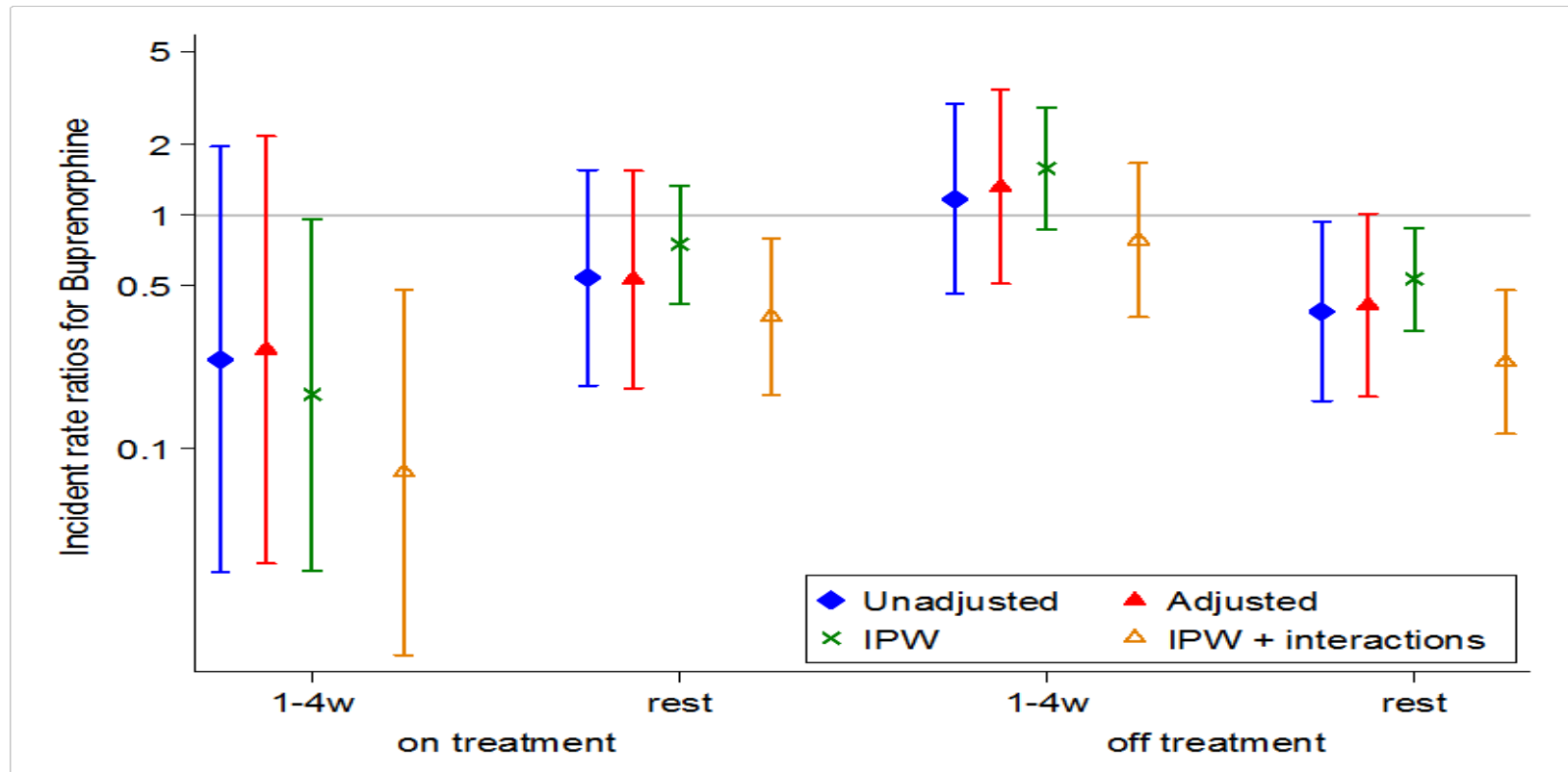
Full exposure: Was in OST for the full month post-release (or else until death or re-incarceration)

Partial exposure: Was in OST for part of the month post-release (or else until death or re-incarceration)

The potential impact of clinical, demographic and treatment variables upon overdose risk (the importance of confounding)

IRR comparing mortality risk for patients on buprenorphine vs. methadone by period on and off treatment¹⁵

(B) Drug related mortality



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.

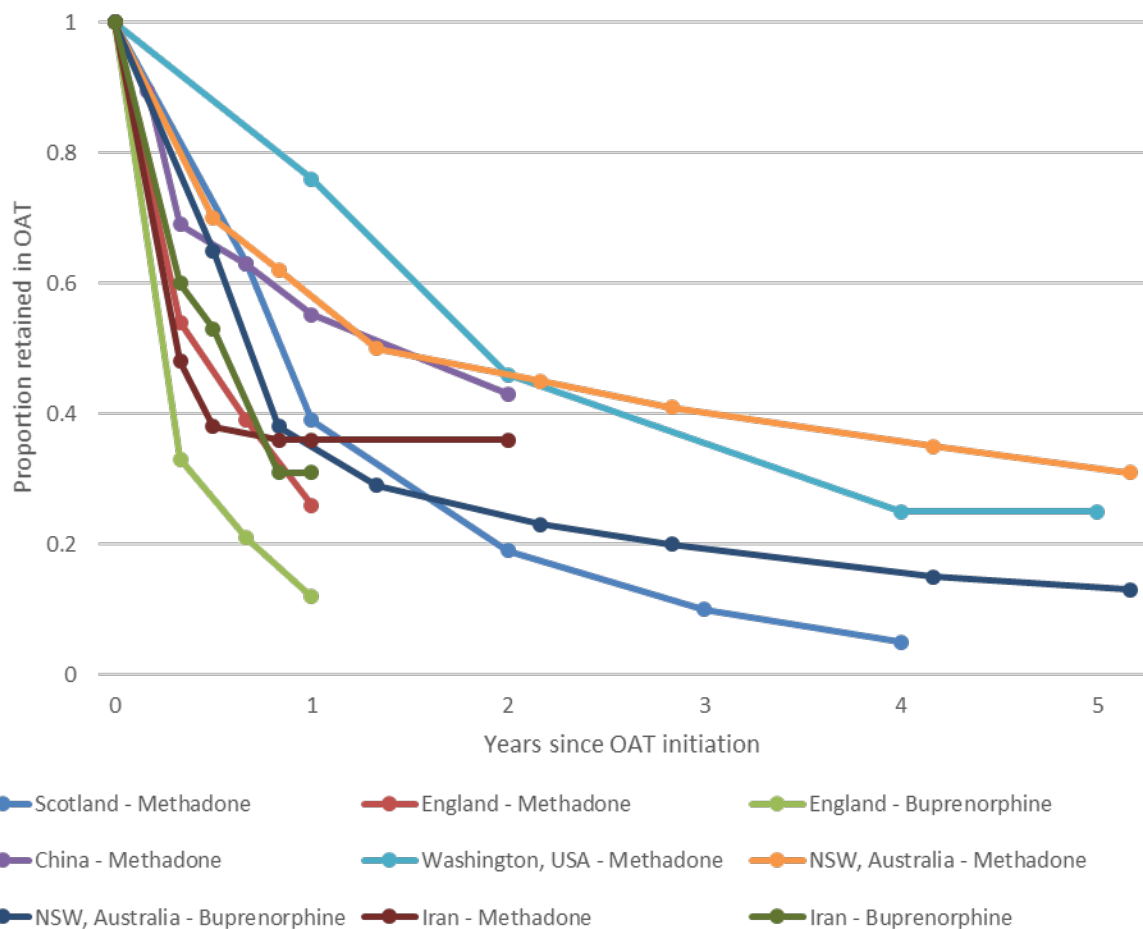
Interaction of OAT modality with comorbidity

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

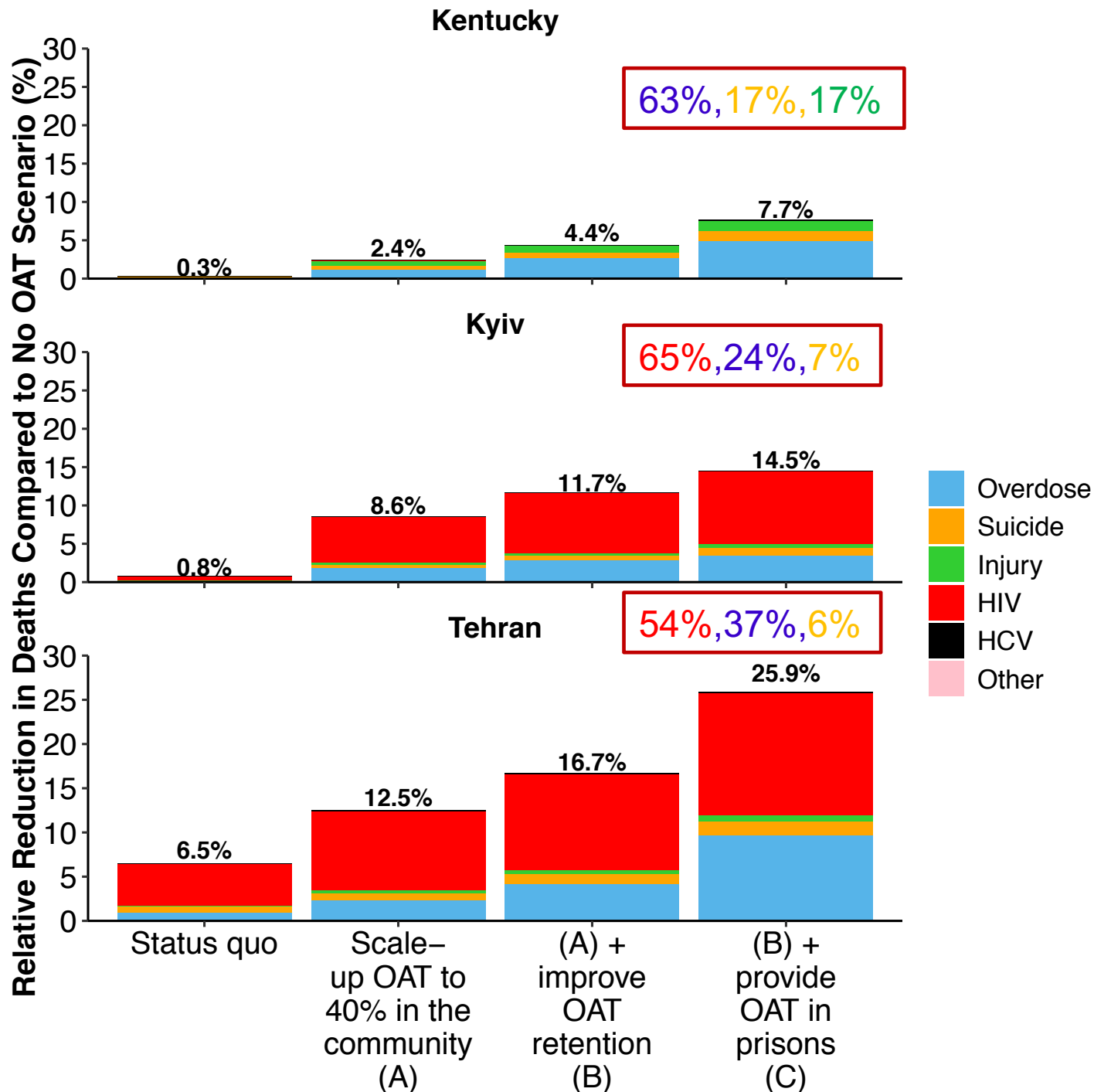
Importance of retention

Retention in OAT

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



Relative Reduction in Deaths among PWID over 2020-2040



Summary

- Clear evidence that:
 - OAT in the community reduces overdose risk
 - Buprenorphine reduces overdose mortality risk compared to methadone – especially 1st 4 weeks. But retention poorer.
 - OAT in prison *almost entirely eliminates* deaths of opioid dependent prisoners in the first 4 weeks of prison
 - OAT on prison releases reduces excess morality in 4 weeks after prison release & increases uptake of community OAT
 - OAT post-release *saves lives and is cheaper*
- OAT retention in UK sub-optimal, reducing public health benefits
- Model projections show potential impact of increasing community OAT coverage, retention, and prison OAT
 - Reduce DRP, HIV, self-harm and injury deaths
 - Cross country comparisons
 - Focus on population effect/benefits
 - Still need other interventions to reduce excess mortality