University of BRISTOL

The impact of opioid agonist treatment delivered in different settings on all-cause mortality and specific causes of death: A systematic review and meta-analysis

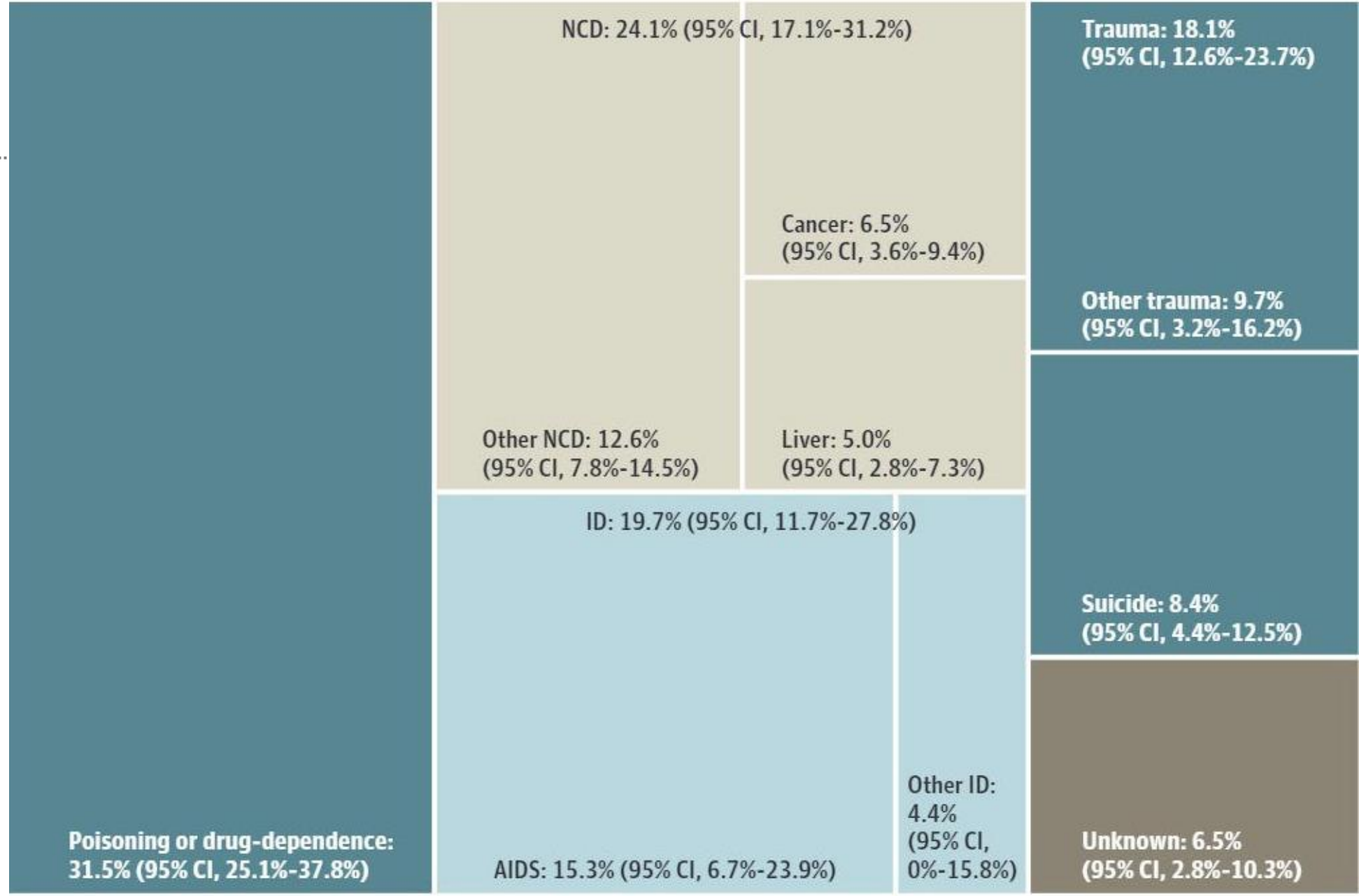
Thomas Santo, Brodie Clark, **Matt Hickman,** Jason Grebely, Gabrielle Campbell, Luis Sordo, Aileen Chen, Lucy Thi Tran, Chrianna Bharat, Prianka Padmanathan, Grainne Cousins, Julie Dupouy, Erin Kelty, Roberto Muga, Bohdan Nosyk, Jeong Min, Raimondo Pavarin, Michael Farrell, Louisa Degenhardt

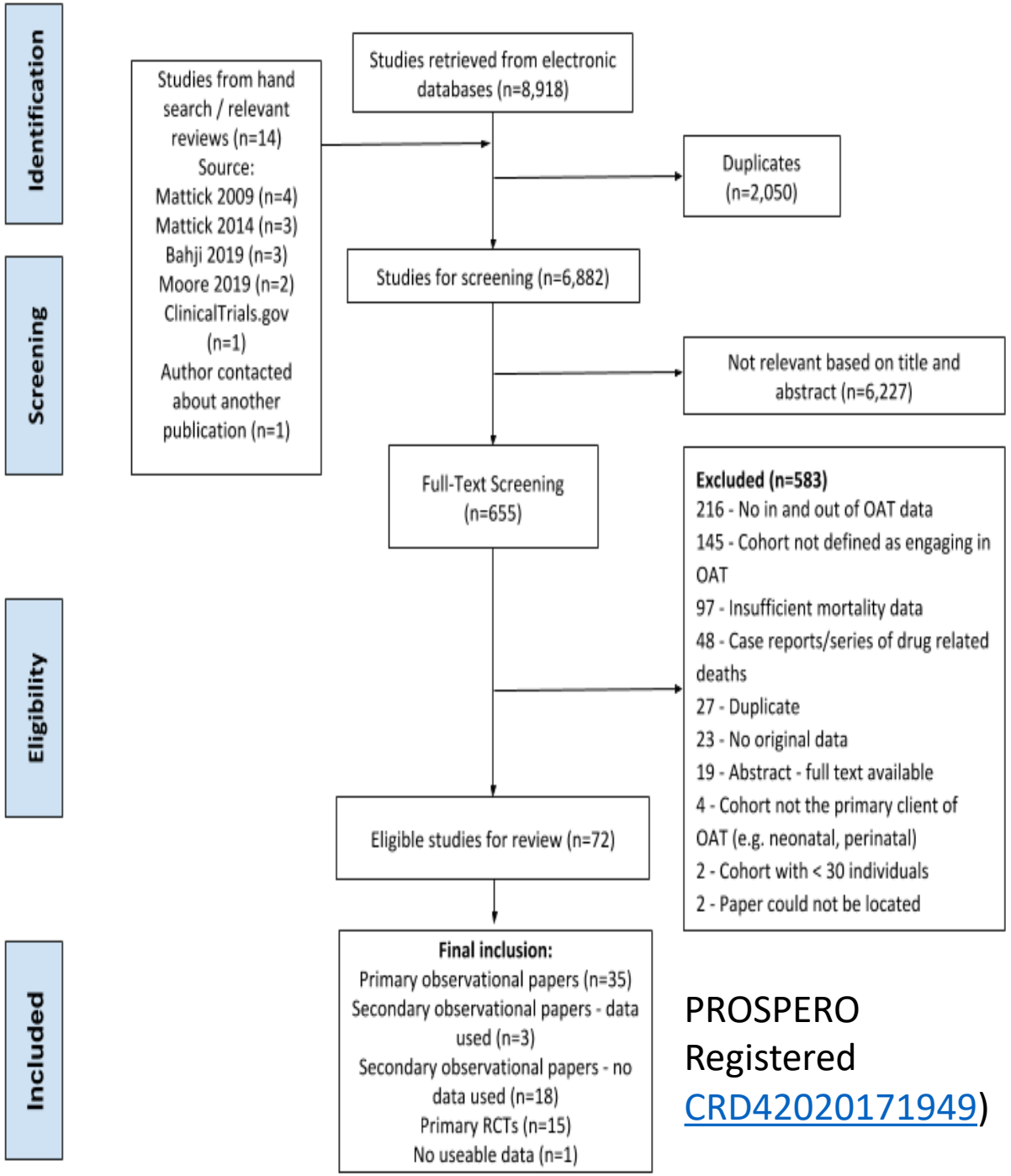
University of BRISTOL

Summary

- Strong consistent evidence that Opioid Agonist Treatment (OAT) halves mortality risk in people with opioid use disorder
  - Risk of overdose and suicide substantially reduced.
  - Weak evidence that other causes also lower (liver, cancer, CVD)
- Little or no evidence from RCT on mortality.
- Mortality risk elevated in first 4 weeks leaving OAT. And elevated in 1st 4 weeks on OAT with methadone but not for buprenorphine.
- OAT reduces mortality risk during and in critical period after prison
- Evaluate OAT delivery and impact on population health in the UK

University of BRISTOL



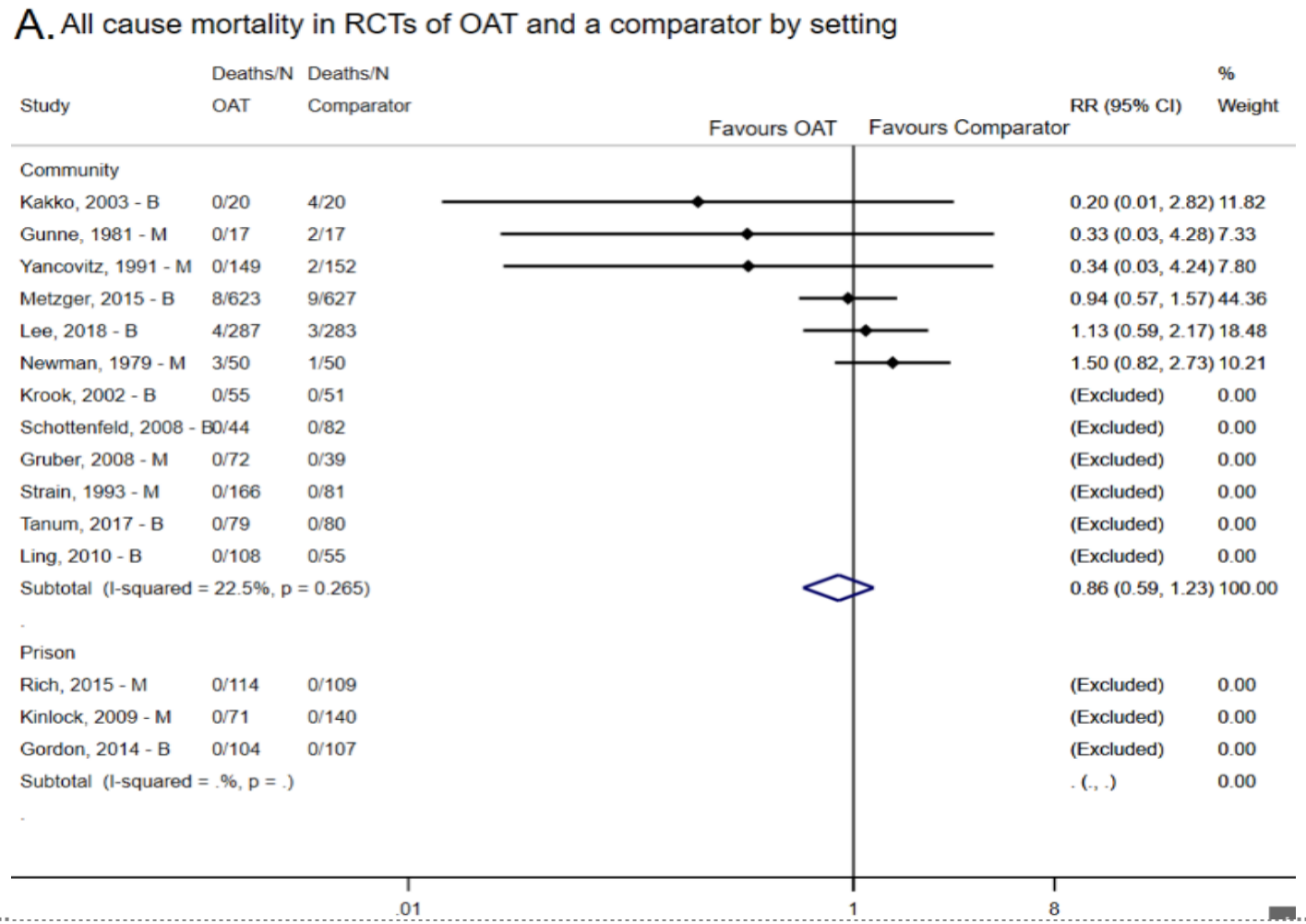


PROSPERO Registered CRD42020171949)

Prisma Flow Diagram

- Multiple Databases and Trial Registries to January 2020
- P – Opioid Use Disorder
- I – Opioid Agonist Treatment (OAT)
- C – not on OAT
- O – mortality risk (All cause, Overdose and other causes)
- 22 eligible RCTs (15 reported on mortality outcomes)
- 36 observational cohort studies
- 2* no. of cohorts, 6* no. patients, 3* PY follow-up than last review (Sordo BMJ 2017)

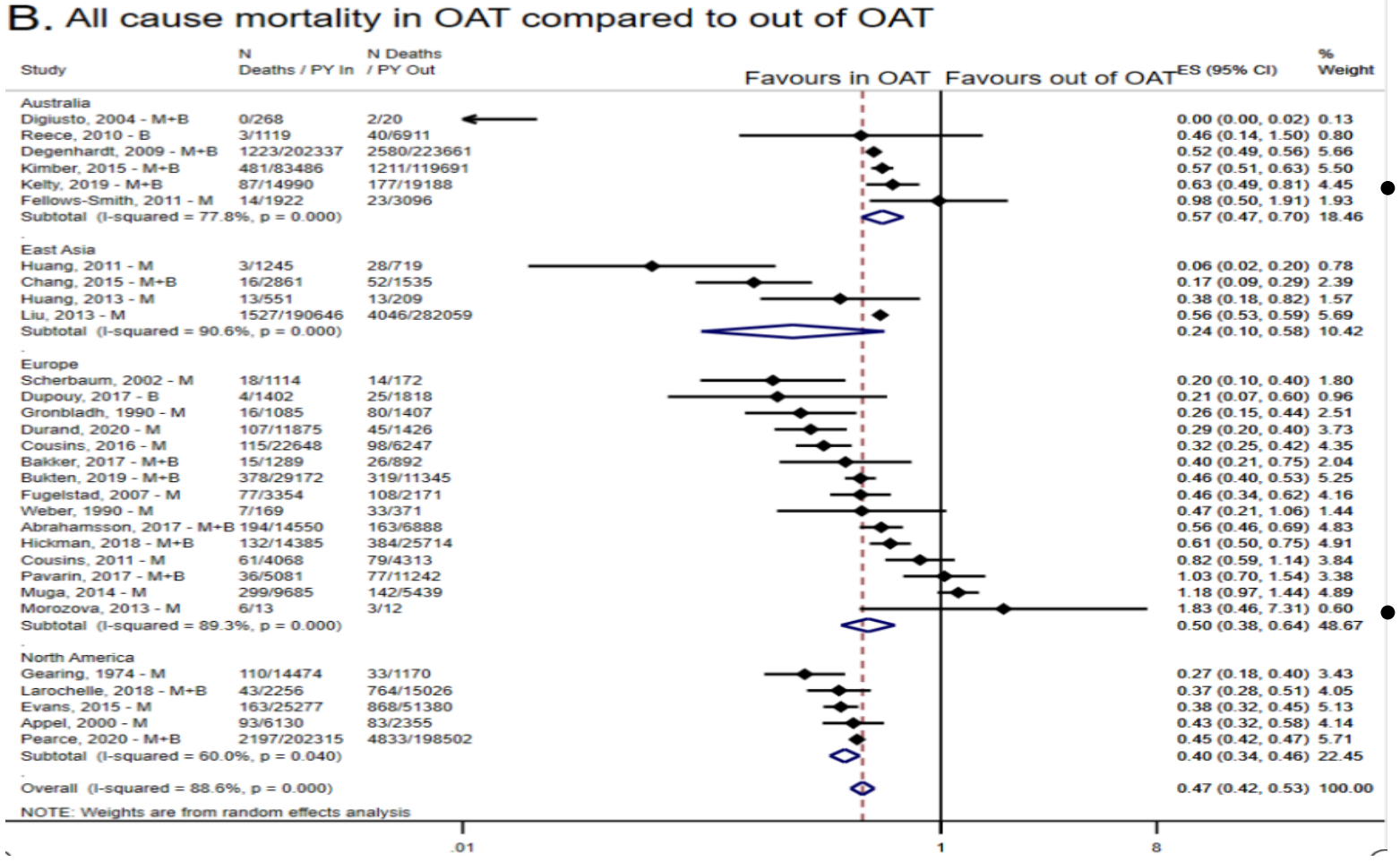
Evidence from Trials



- 15 RCTs (N=3,852 participants).
  - 8 North America; 8 at single clinics; 80% commenced prior to 2010; 60% lasted six months or fewer
- 40 deaths reported
  - 7/15 RCTs with 0 deaths
  - Weak evidence that Mortality lower on those allocated to OAT (RR 0.86; 95%CI 0.59-1.23)
  - No evidence from prison RCT
- Completely underpowered
  - None of the RCTs had survival as the primary outcome; most counted mortality as an adverse event

Santo et al *JAMA Psychiatry. 2021;78(9):979-993. 2021;*

Observational Studies – All Cause Mortality



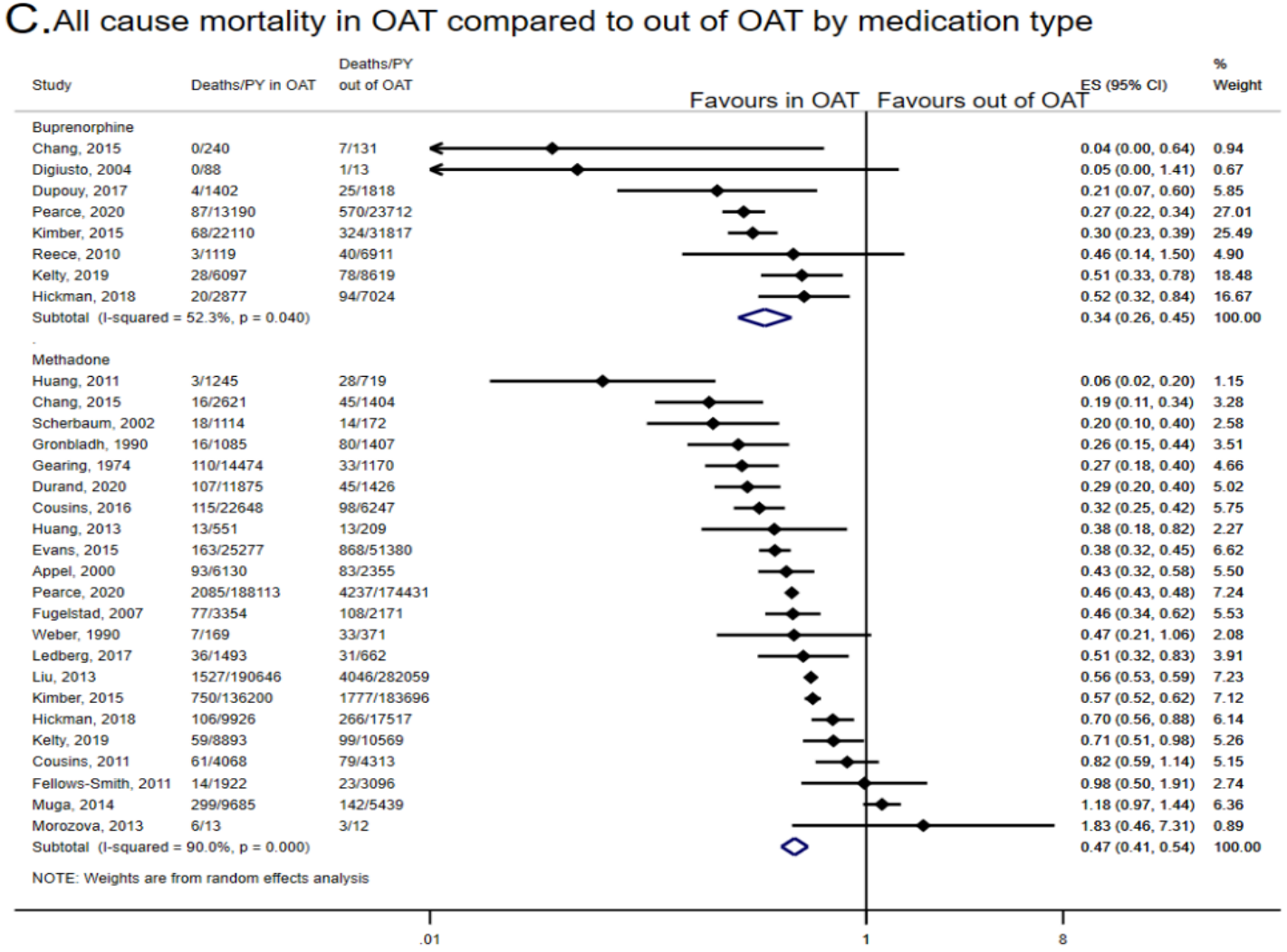
- 36 studies (N~750K (110-300K, 1.9M PY; >20,000 deaths)
- Strong evidence of protective effect of OAT globally
  - pooled all-cause CMR on OAT 1.0 per 100PY vs 2.4 per 100PY
  - pooled RR 0.47; 95%CI 0.42-0.53)
- Meta-regressions no evidence of differential effect
  - by study year, sample size, follow-up, age, gender, comorbidity

All-cause mortality rates

Lower risk of mortality during OAT across **participant, treatment, & study characteristics**

Participant characteristics	Rate Ratios (95% CIs)
Women	↓ **44 %***
Men	↓ **55 %***
Age	
<35 years	↓ **52 %***
>=35 years	↓ **52 %***
People who inject drugs	↓ **48 %***
HIV+	↓ **44 %***
HCV+	↓ **47 %***
Treatment provider	
Specialist	↓ **69 %***
GP/mixed/other	↓ **53 %***

All Cause Mortality – Buprenorphine and Methadone

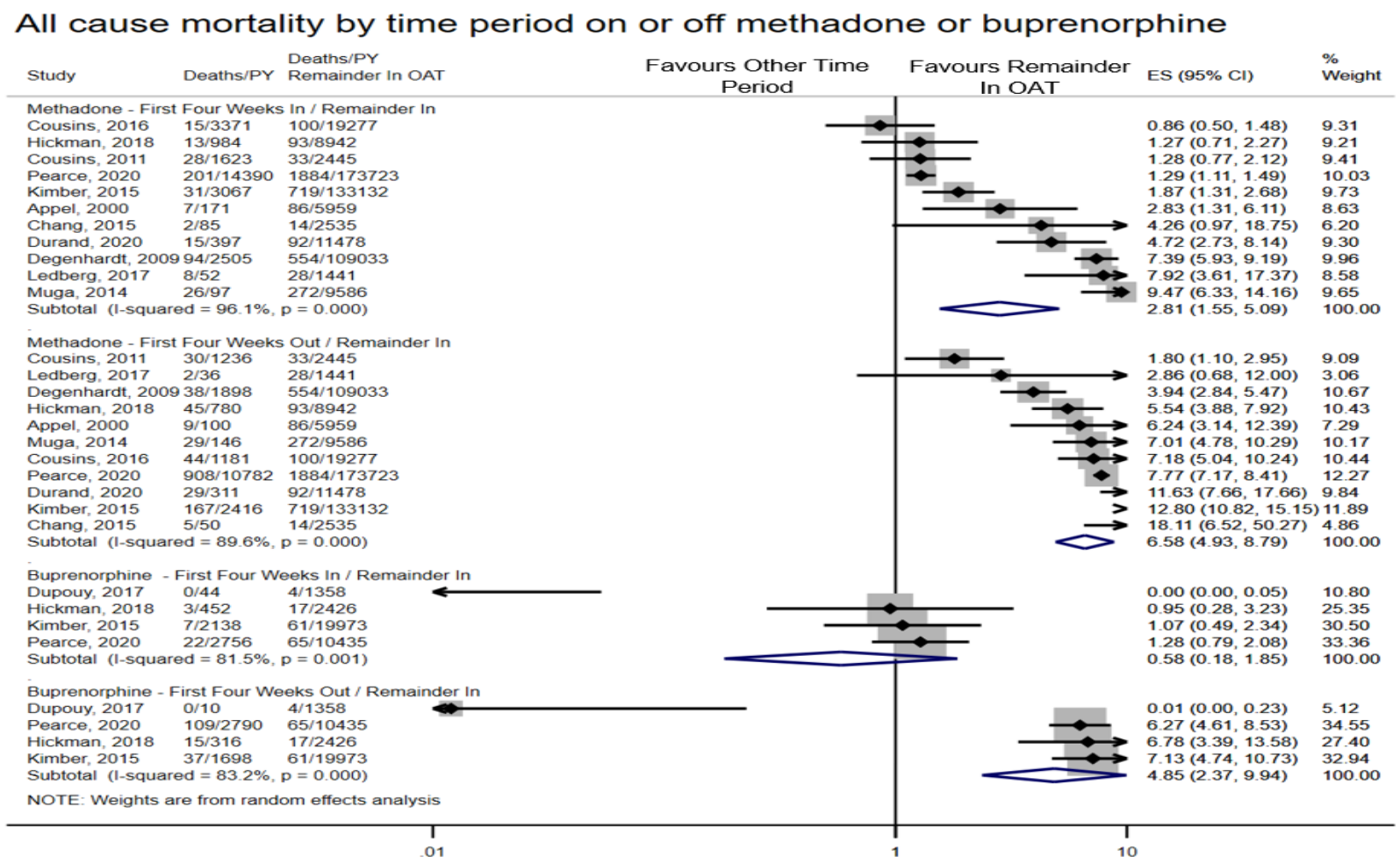


- Stratified by methadone treatment (22 studies) and buprenorphine (8 studies)
- Both OAT treatments showed strong protective effect
- methadone (RR 0.47 95%CI 0.41-0.54)
- buprenorphine (RR 0.34 95%CI 0.26-0.45)

OAT Impact on Other Causes of Death

- All injury: (17S, 563,000PY, 2,014D) - RR 0.34 (95%CI 0.27-0.42)
- Overdose: (22S, 910,000PY 2,351D) – RR 0.41 (95%CI 0.33- 0.52)
- Suicide: (14S, 542,000PY 293D) – RR 0.48 (95%CI 0.37- 0.61)
- Liver Disease: (14S, 520,000PY 597D) – RR 0.89 (95%CI 0.67- 1.19)
- Cancer: (14S 524,000PY, 522D) – RR 0.72 (95%CI 0.54-0.98)
- CVD: (14S 524,000PY, 429D) – RR 0.69 (95%CI 0.60- 0.79)
- HIV-related (15S 493,493PY, 383D) – RR 1.14 (95%CI 0.75- 1.74)
- Bacterial/ SSTI (13S 500,000PY, 144D) – RR 0.90 (95%CI 0.72- 1.12)

Critical Periods in and out of OAT



- Overall – Mortality Risk
  - 6 times higher in 1st month out of OAT (95%CI 4.3-8.4)
  - 1.9 times higher in 1st month in OAT (95%CI 1.10, 3.35)
  - compared to rest of time on OAT
- Mortality risk similar leaving OAT for patients on buprenorphine or methadone
- But big difference in mortality risk in 1st month of OAT for methadone and buprenorphine

OAT in Prison on Mortality in Prison and in 1st 4 weeks after release

Mortality in Prison (1 Study)

- On OAT (11D 16,440PY) 0.67 per 100PY vs
- Not on OAT (40D 14,548PY) 2.75 per 100PY
- **RR OAT impact 0.24 (95%CI 0.12, 0.47)**

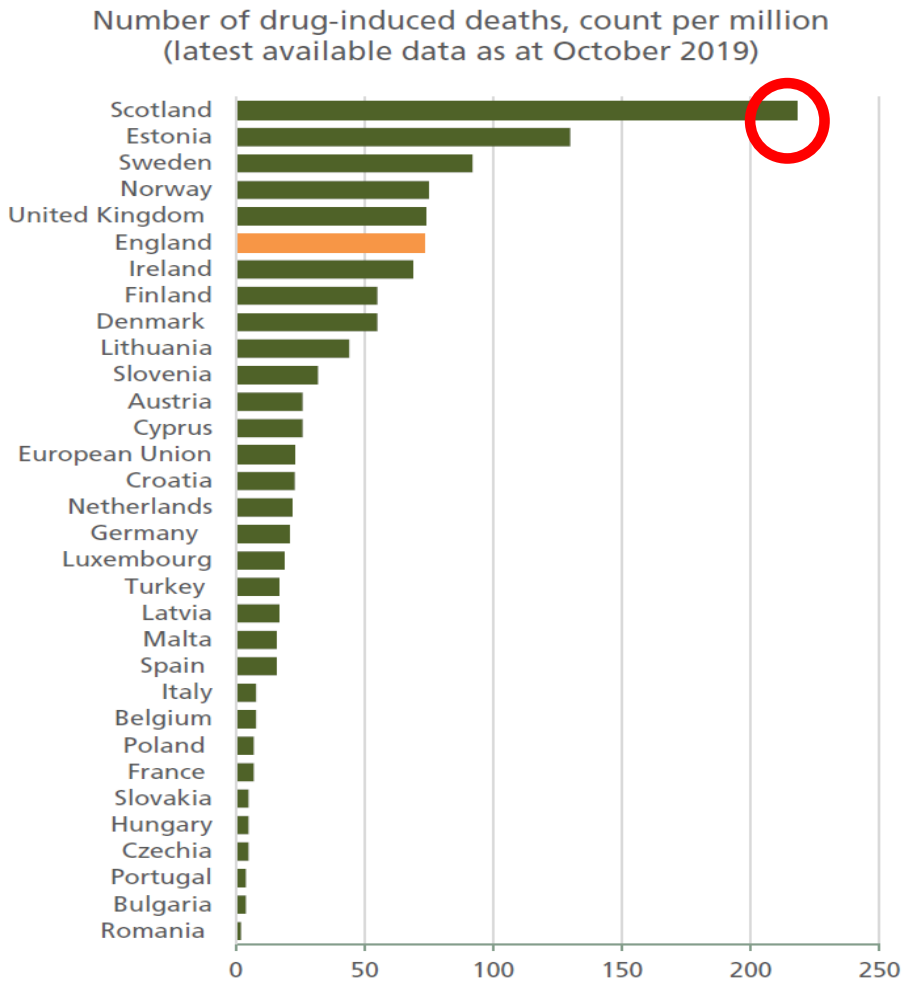
- Drug-related Deaths - First 4 weeks post-release (2 Studies)
  - Release on OAT (10D 2,856PY) 3.5 per 100PY
  - No OAT prior to release (47D 2,578PY) 21.1 per 100Py
  - **RR OAT impact 0.19 (95%CI 0.10, 0.37)**

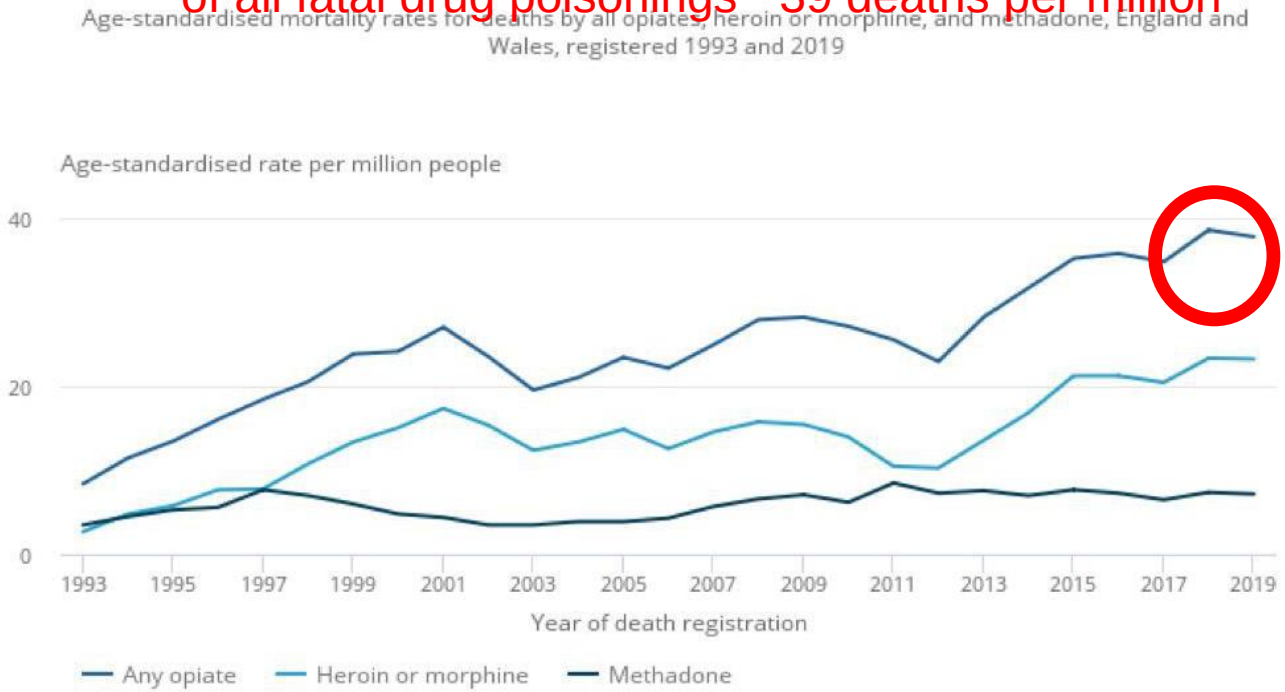
Conclusions

- OAT strongly associated with lower risk of mortality (↓ 51%)
- **Lower** risk of multiple causes of mortality in OAT…
  - Suicide (52%), cancer (28%), alcohol-related (41%), cardiovascular-related (31%), and drug-related mortality (59%)
- Mortality 6 times ↑ leaving OAT in first month vs. in OAT more than 1 month
- ↓ Mortality risk in OAT during and after release from incarceration
- Retention critical to achieve population benefits of OAT
  - Evaluate OAT in UK on averting OD and ACM
- Strengthen evidence on OAT in prison on mortality risk in and out of prison

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

2019: ~2,200 opioid related poisoning deaths (>50% of all fatal drug poisonings ~39 deaths per million

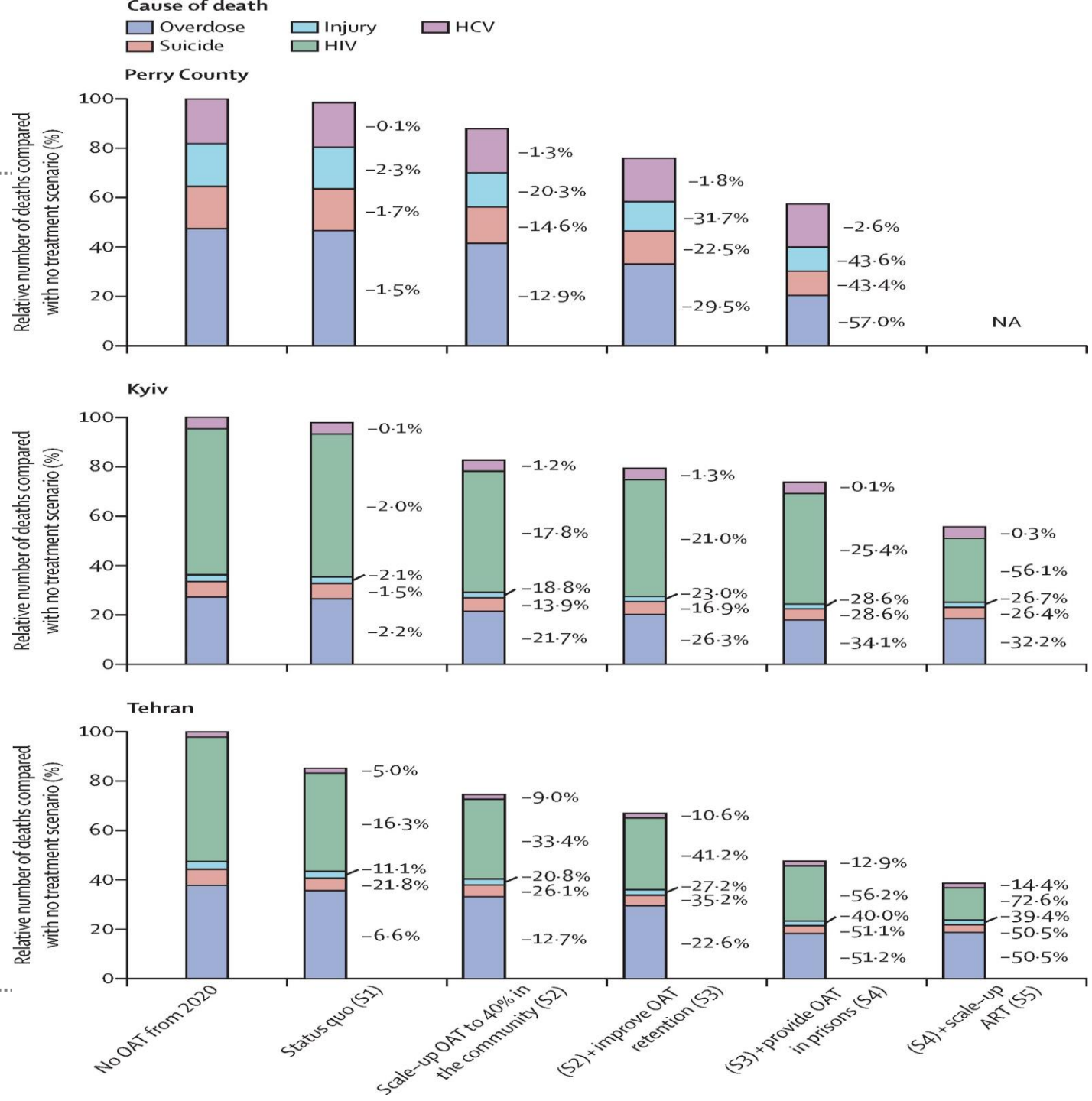




Source: Office for National Statistics - Deaths related to drug poisoning in England and Wales

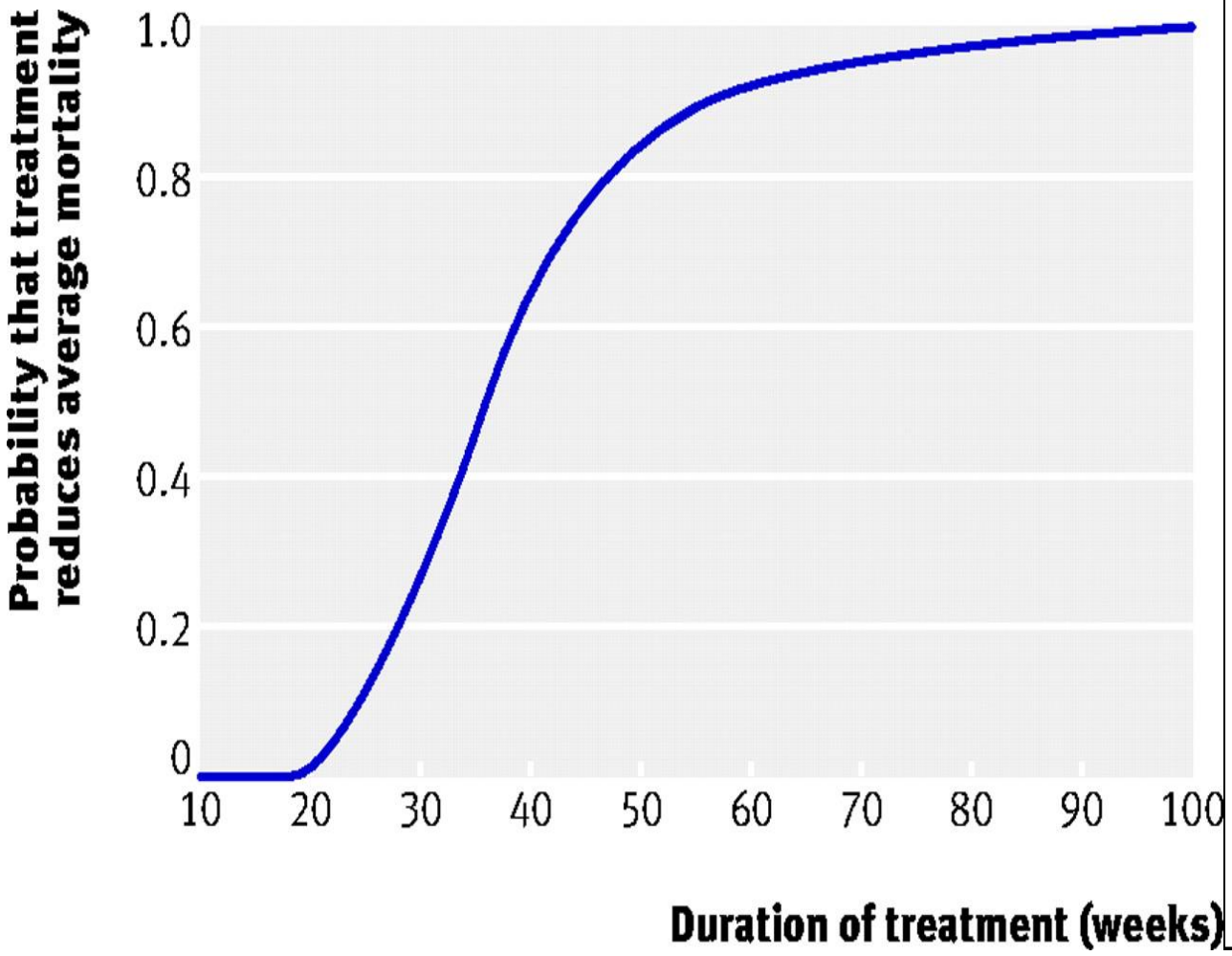
University of BRISTOL

Relative Reduction in Deaths among PWID over 2020-2040



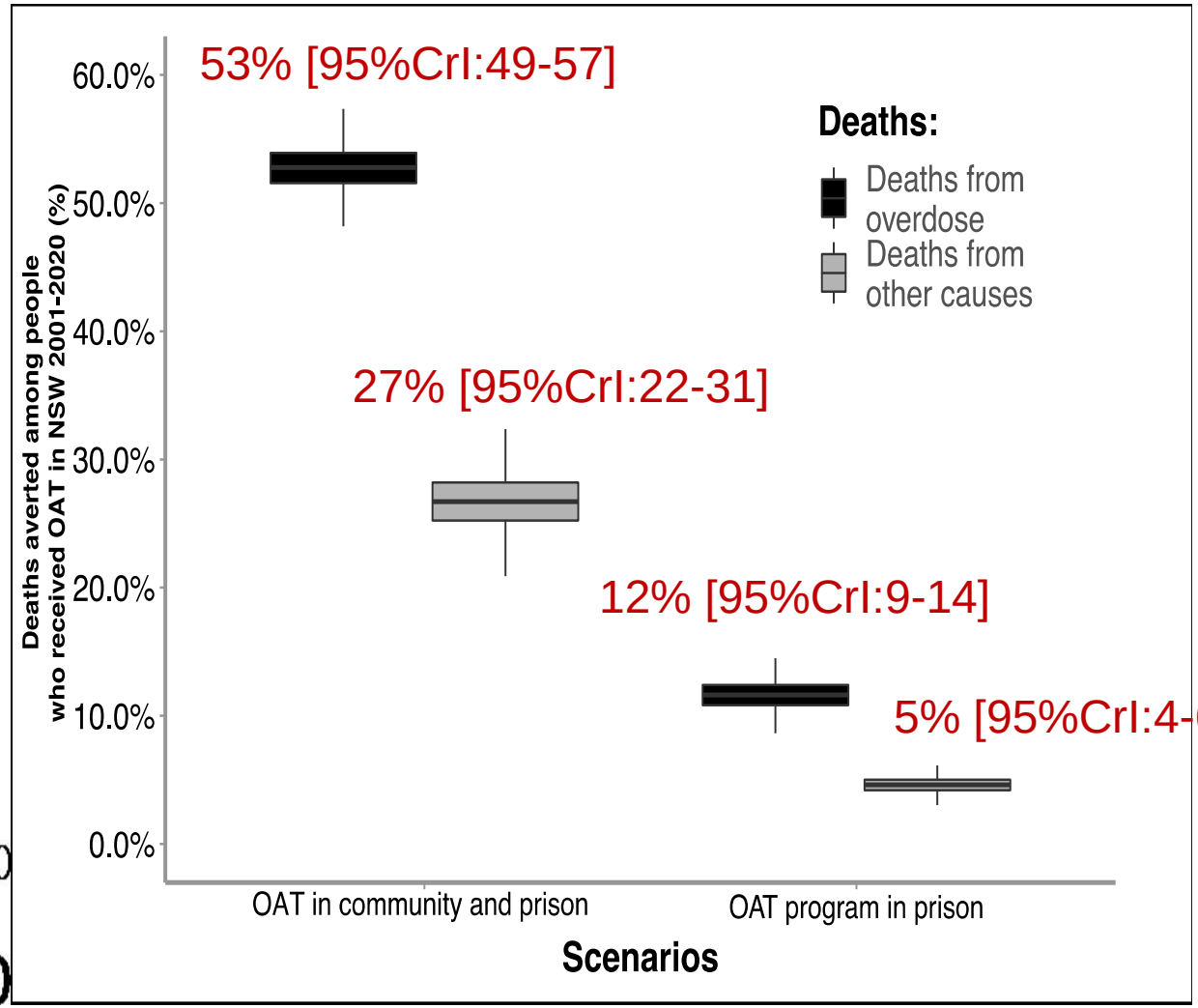
Degenhardt et al,, Lancet 2019
Stone et al…Lancet Psychiatry 2021

Probability that OAT reduces mortality for different durations of treatment



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

Proportion of deaths averted through OAT program from 2001-2020 NSW



Chaillon… Bórquez et al. Addiction 2021 (in press)

University of BRISTOL

Acknowledgements

- Funding from multiple sources: NIHR, NHMRC, NIH, Commonwealth Department of Health, NSW Ministry of Health, UNSW Sydney, Acción Estratégica en Salud, Health Canada Substance Use and Addictions Program, Health Research Board (Ireland), Ministry of Science & Innovation (Spain)
- 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.
- MRC Addiction Research Clinical Training programme (MR/N00616X/1)
- NIHR Health Protection Research Unit (HPRU) in Behavioural Science and Evaluation
- NIHR School of Public Health Research & NIHR BRC at UoB
- The funder had no role in study design, data collection, the analysis and interpretation, or the writing of this report. **The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health**

Evidence for impacts across varied outcomes varies…	**Extra-medical use**	**Injecting risks**	**Opioid overdose**	**HIV incidence**	**HCV incidence**	**Suicide**	**Injuries**
Individual psychosocial interventions	↓?	↓	--	--	--	--	--
Peer-based self-help groups	↓?	--	--	--	--	--	--
Needle syringe programs (NSP)	✕	↓	--	↓	↓?	--	--
Condom provision	--	--	--	↓	--	--	--
Opioid agonist treatment (OAT)	↓	↓	↓	↓	↓	↓	↓
Naltrexone – Oral	✕	✕	--	--	--	--	--
Naltrexone – Implant	↓	↓	↓?	--	--	--	--
Residential rehabilitation	--	✕	--	--	--	--	--
Detoxification alone	✕	--	--	--	--	--	--
HCV antiviral treatment	↓	↓	--	--	↓	--	--
HIV antiretroviral treatment (ART)	--	✕	--	↓	--	--	--
Safe injecting centres (SICs)	✕	↓	↓?	?	?	--	--
Naloxone provision	--	--	↓?	--	--	--	--
Compulsory detention of drug users	--	↑	--	--	--	--	--
Criminalisation of drug use	--	↑	--	↑	--	--	--

Degenhardt et al (2020). *The Lancet*