Using observational data to determine drug effectiveness and safety in pregnancy

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Up to 1990	199-2002	2016-17	2022-present
Women excluded from a lot of research 1977 FDA: women of child-bearing age to be excluded from early phase trials	CDC & NIH: Clinical research should reflect diverse population who will benefit CIOMS: Pregnant women should be eligible for research	WHO & COIMS: Imperative to undertake RCTs in pregnant & lactating women US Congress: Task force on research specific to pregnant and lactating women	UK MRA 2021 UK Academy of Medical Sciences: Healthy Mum, Healthy, Healthy baby, Healthy future – the UK leadership in the development of safe, effective and accessible medicines for use in pregnancy 2022 US National Academies consensus Advancing clinical research with pregnancy and lactating populations: Over coming real and perceived liability risks. report 2024

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Inclusion of women in research

- The British Regional Heart Study (recruitment: 1978-180) & Women's heart and Health study (recruitment 1999-2001)

- 49 RCTs of statins for primary preventions published between 190-2003; 10 (20%) excluded all women. Median (IQR women recruited: 19% (12-30%)

- 24 GLP-1-receptor agonist RCTs 3 (13%) excluded pregnant, lactating, or planning to get pregnant. 15 (63%) to exclude if participant became pregnant

Fear of litigation / liability

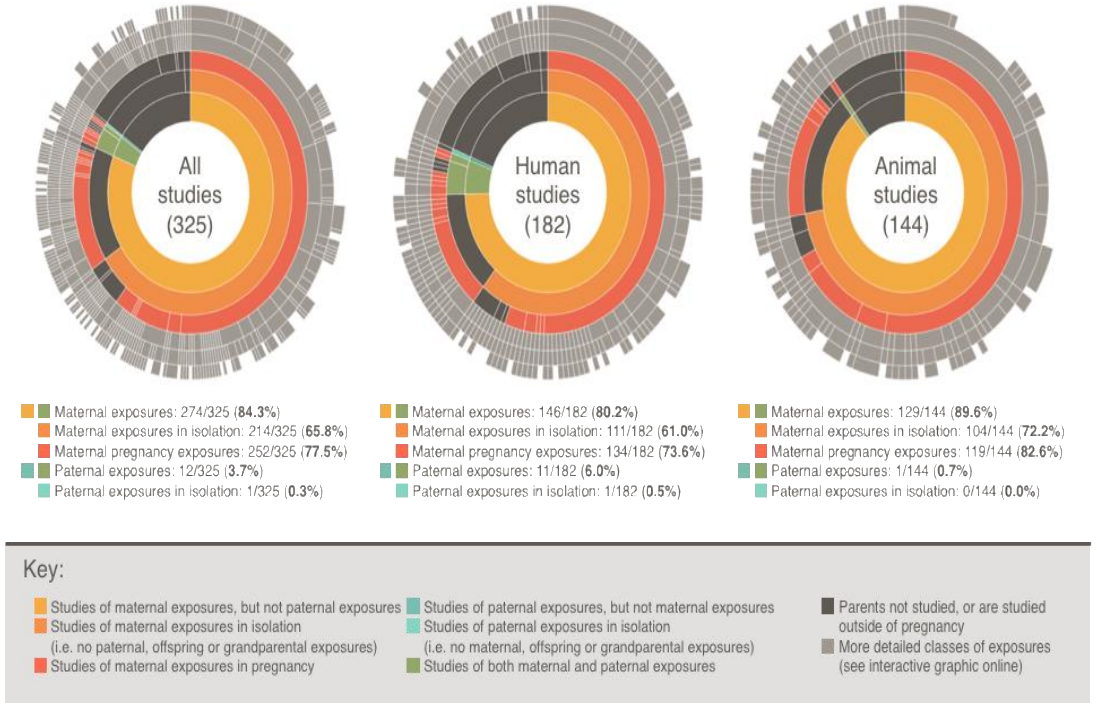
- Thalidomide (late 60s to early 70s)
- Diethylstilbestrol (DES) (1940 to 1970s)
- Sodium valproate

Concern for women and their partners

It's the mother!: How assumptions about the causal primacy of maternal effects influence research on the developmental origins of health and disease.

Sharp, GC, Lawlor DA , Richardson S Soc Sci Med 2018

Time to cut the cord! DoHAD Journal 2019



	Human	Animal
Number	325	143
N (%) female pregnancy exposures only	252 (77%)	119 (83%)

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The problem

Lack of clinical trial data on pregnant women means:

1. We have no idea how to treat women with pre-existing disease
   - Some conditions more common in women of reproductive age, e.g. autoimmune conditions
   - Others common in women (and men) at this age, e.g. asthma, epilepsy, mental health condition
   - Increasing age at pregnancy & obesity epidemic resulting in increase of chronic conditions associated with older age now more common in pregnancy
     - In the US 70% of women start pregnancy on a prescription medication

2. There is no innovation of pregnancy-specific conditions
   - Women who experience hypertensive disorders of pregnancy &gestational diabetes are treated more poorly than those with equivalent conditions outside of pregnancy

The public health cost of this is large and larger than potential teratogenic effects

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Twenty years and still waiting. Maze MA, Daniel PJ, BMC Womens Health 2015

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UK Medical Regulations Authority on medication use in pregnancy 2021

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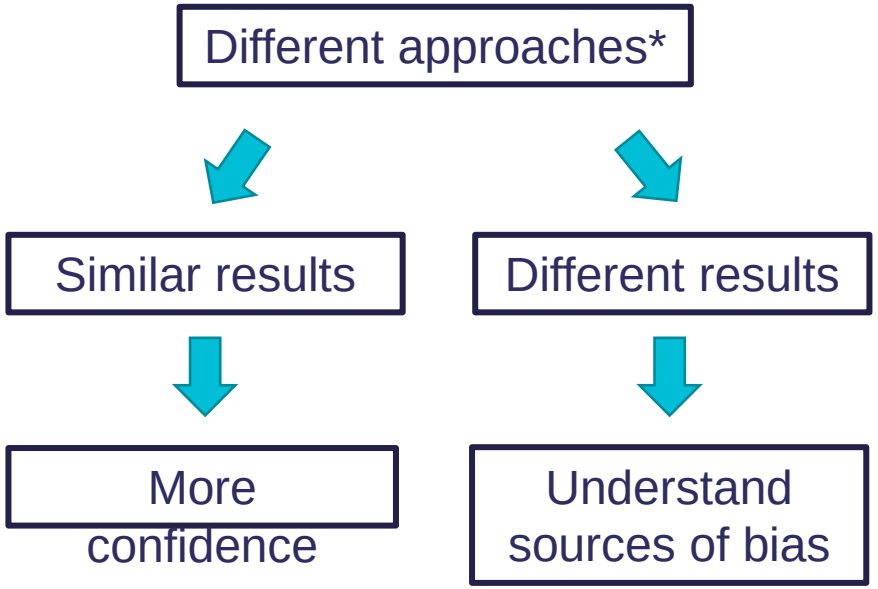
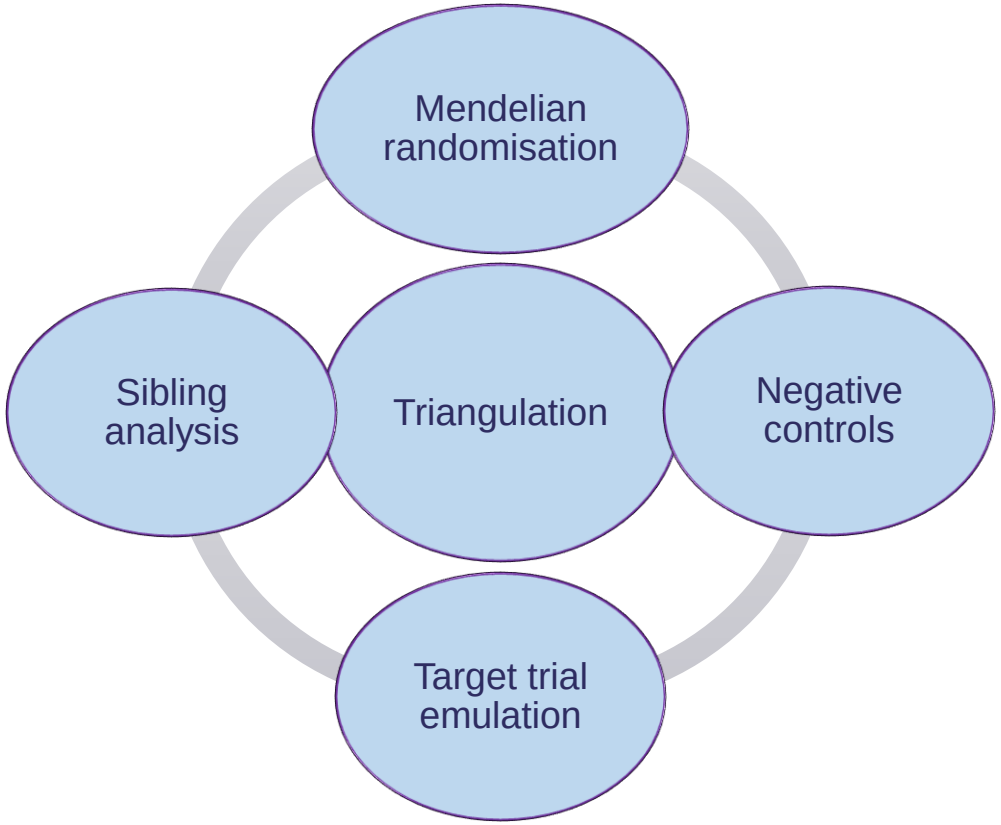
Make better use of observational data

Triangulation of evidence





- With different and unrelated potential biases
  - Preferably that point in opposite directions

DEFINE SPECIFIC CAUSAL RESEARCH QUESTION(S)

IDENTIFY DATA AND APPRPPRIATE/FEASIBLE ANALYTICAL METHODS

WRITE AND PUBLISH PROTOCOL / ANALYSIS PLAN

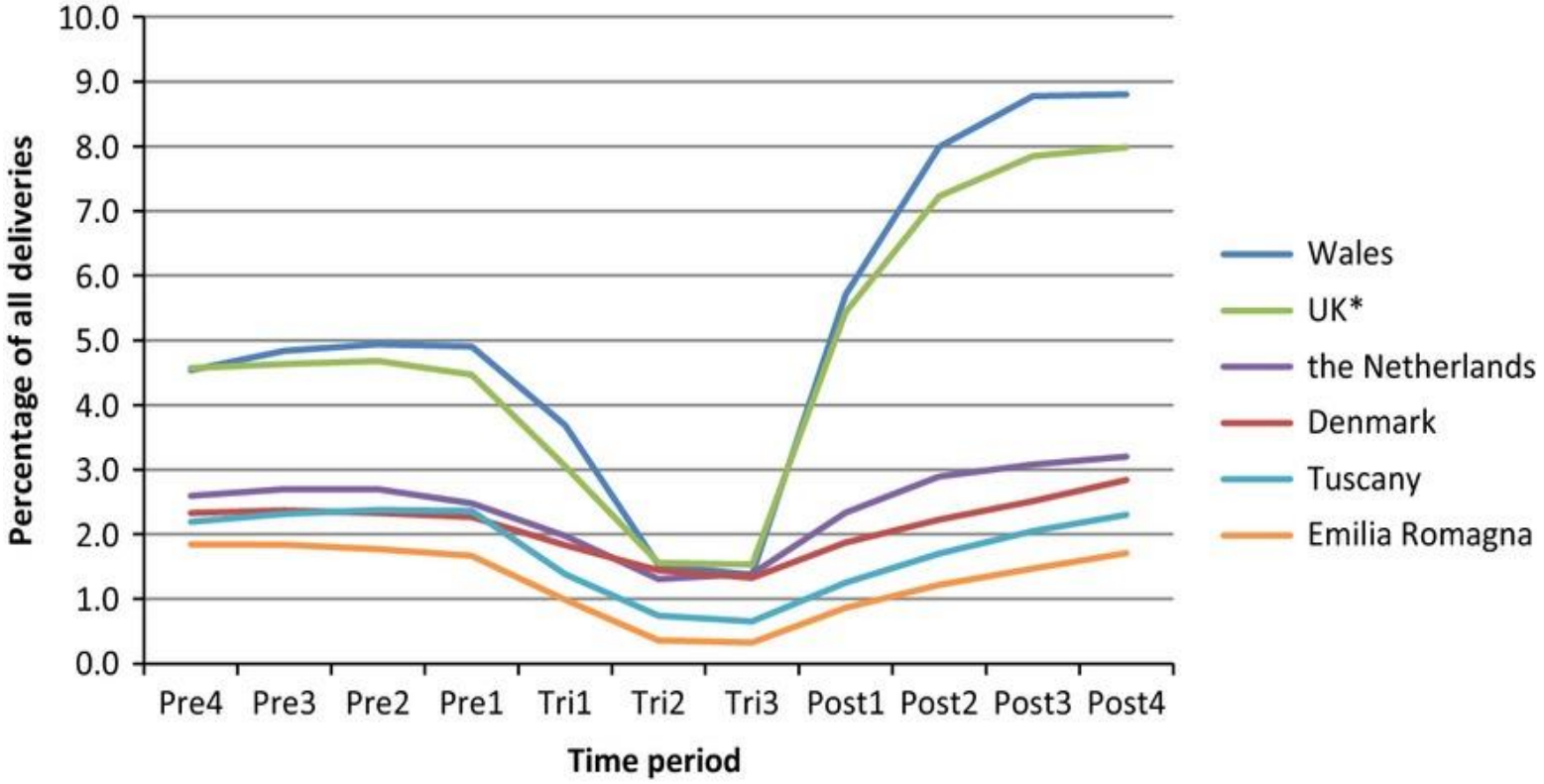
COMPARE / INTEGRATE EVIDENCE FROM DIFFERENT METHODS/DATASETS TAKING ACCOUNT OF DIFFERENT BIASES & OTHER POTENTETIAL DFFERENCES

The importance of descriptive epidemiology

- Identify key questions
- Identify what can be learnt from different populations
- Suggest targets for prevention or treatment
- Inform methods

Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions

Charlton RA et al. BJOG 2015



BJOG, Volume: 122, Issue: 7, Pages: 1010-1020, First published: 28 October 2014, DOI: (10.1111/1471-0528.13143)

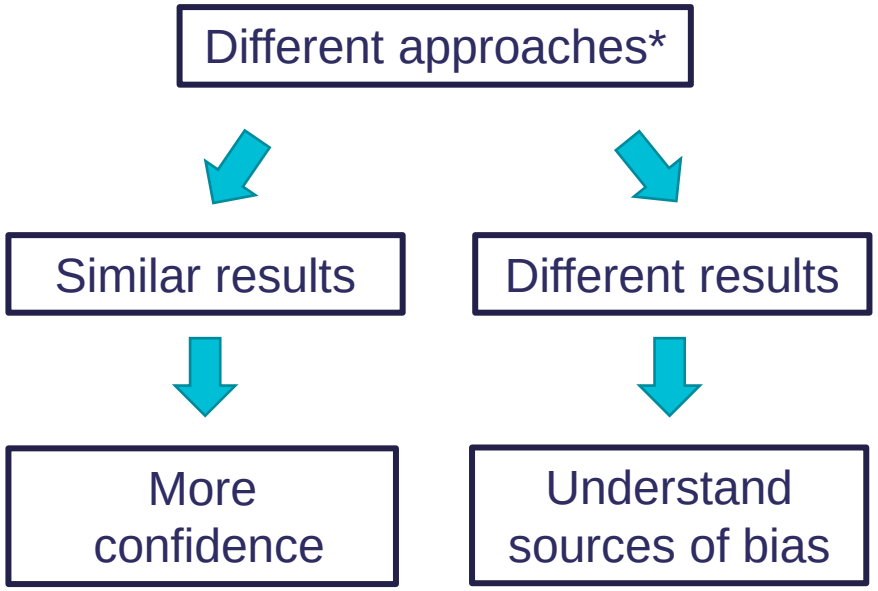
Global trends on use of analgesic opioids in pregnancy. From the Centre for Research Excellence on medical intelligence

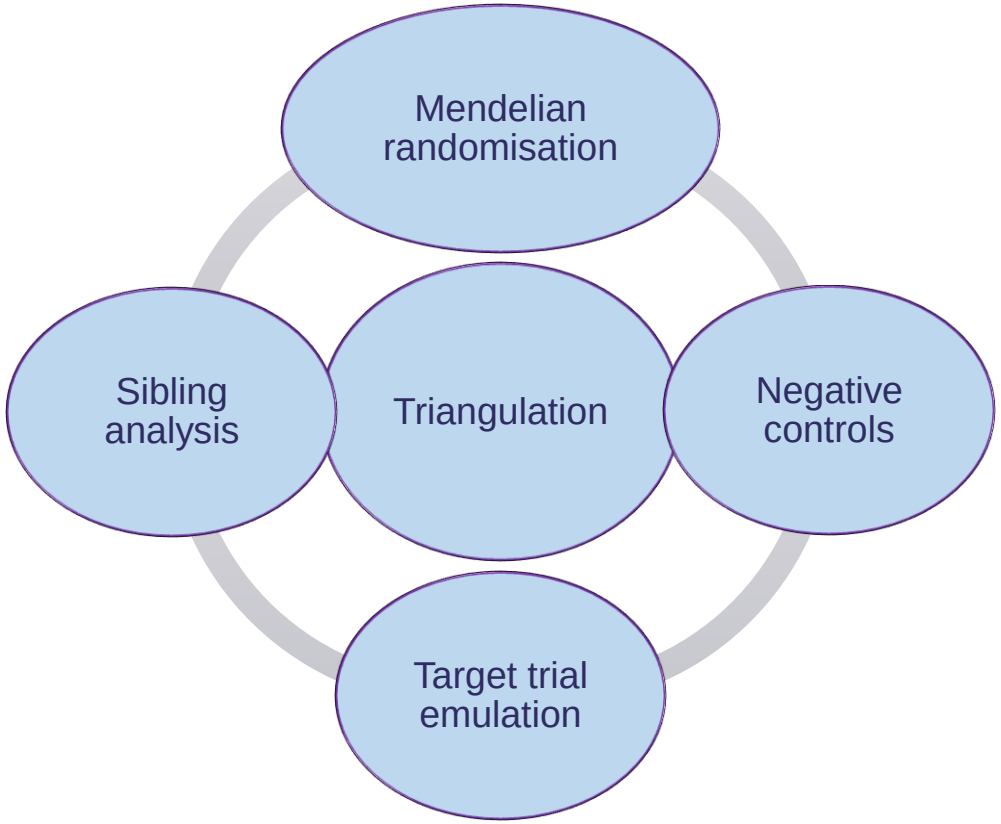
- Increases seen in last 10 years across majority of countries
- In a total of 20,306,228 pregnancies, 1,115,854 (55 per 100 pregnancy) had at least one prescribed opioid analgesic
- Massive variation

  Lowest 4 per 1000 (UK)

  Highest 191 per 2000 (USA)

Triangulation of evidence





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Method / approach	Biases	Other limitations	Strengths
Drug-target MR	relevance, confounding by LD, fetal effects, binding artefacts	Statistically inefficient Limited to on-target effects Mostly protein targets	No need to take/be taking medication, can compare different classes of drugs
Target Trial Emulation	Confounding, immortal time bias, missing eligibility data, problems when comparing to placebo	Statistically inefficient, availability of data, works best if RCT exists	Do not have to restrict to healthy pregnancy
Test negative	Violation of assumption of equivalence between test negative & positive, Misclassification of outcome	Statistically inefficient, Outcome with a good diagnostic test (e.g. GDM), ?generalizability to whole population	Do not have to restrict to healthy pregnancy, works, works OK with no treatment comparison
Within sibs	Selection bias, contamination, individual confounding	Statistically inefficient	Controls for family level confounding
Conventional MVR	Confounding, selection, misclassification		Large cohorts with detailed data in. on mechanisms
Negative / positive controls	Power & misclassification between difference to main	Indicative of bias in other methods	Useful sensitivity analyses across methods

Conclusions

- Possible greater potential now to improve evidence regarding safety and efficacy of medication use in pregnancy
  - Recent reports with potential to affect change
  - Increased access to electronic health data
  - Increase in causal inference methods with acknowledgements of different biases
- Need to work with women and their partners
- Need to work with clinical and laboratory scientists
- Need to work with each other
- We need a register of existing knowledge on drugs crossing the placenta or not
- Important to consider LMIC where the need is greatest, particularly in relation toinfections in pregnancy

THANK YOU


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