LifeCycle

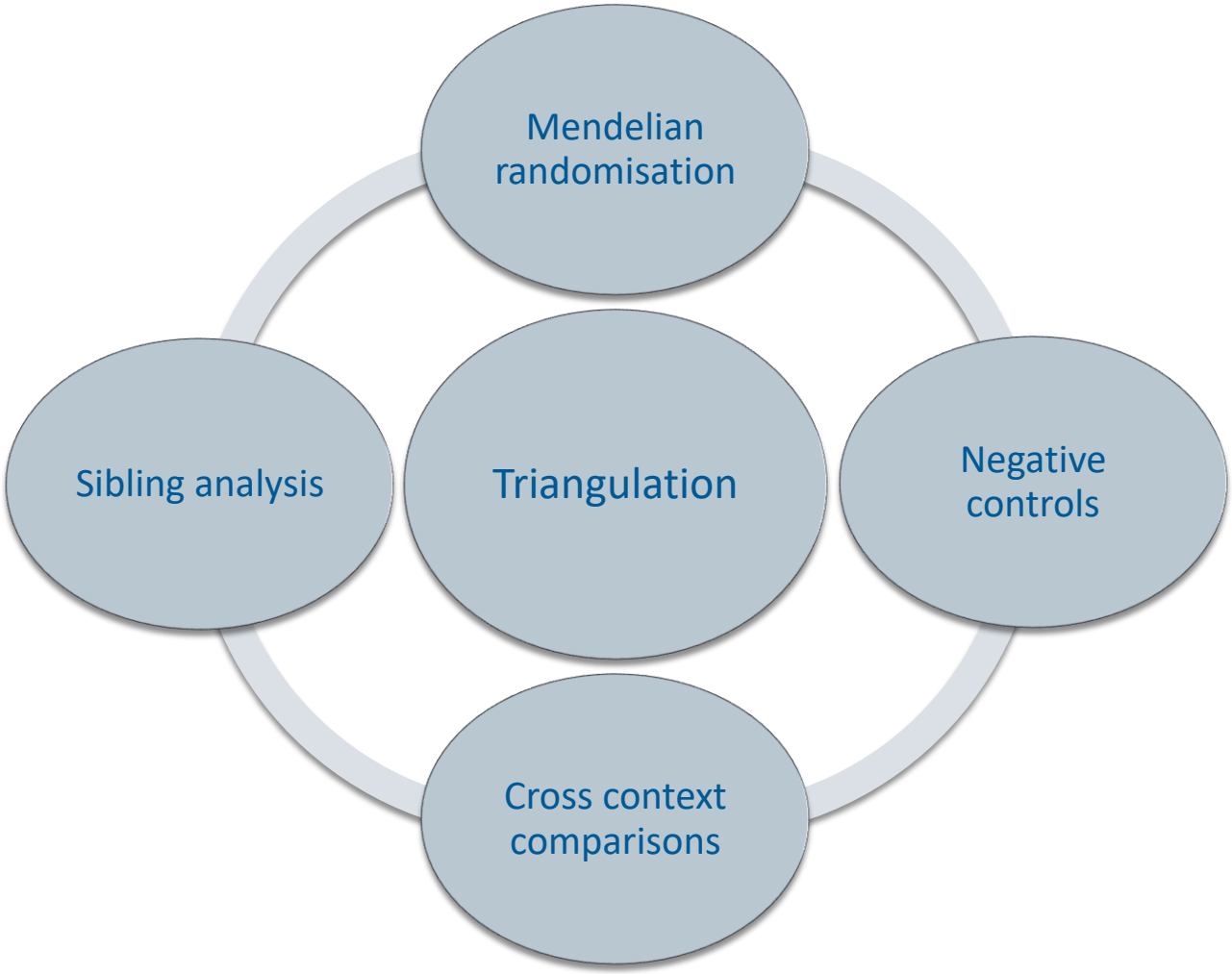
Early life stressors and LifeCycle Health

TRIANGULATION TUTORIAL

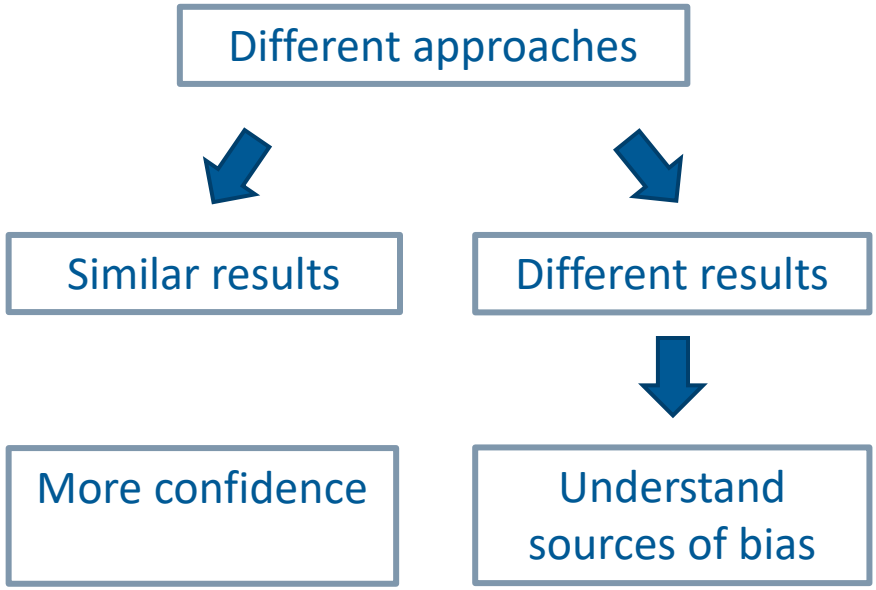
Q3 2022

This project received funding from the European Union's Horizon 2020
Research and Innovation Programme under grant agreement No 733206

Plurality of approaches



This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206



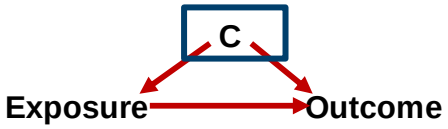
Lawlor, Tilling, Davey Smith IJE 2017

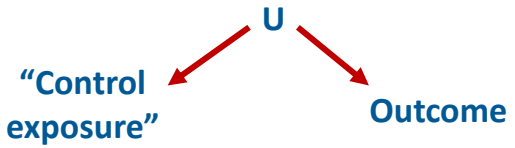
Minimum set of criteria:

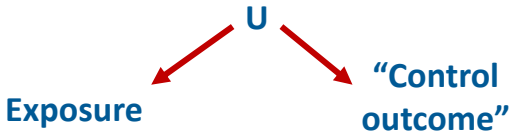
- *Results from at least two, but ideally more, different approaches, with differing and unrelated key sources of potential biases, are compared (better if potential biases are in opposite directions);*
- *The different approaches address the same underlying causal question;*
- *For each approach:*
  - *Account for duration and timing of exposure*
  - *Acknowledge key sources of bias*
  - *Be explicit about the expected direction of all key sources of potential bias (where feasible)*

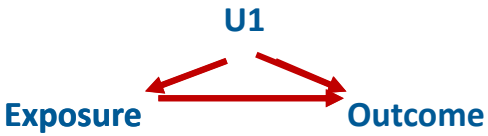
This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

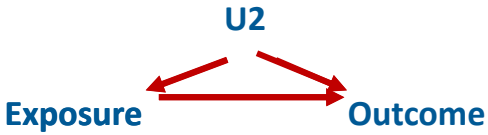
Method	Key assumptions
Multivariable regression, G-estimation, inverse probability etc.	• All confounders measured and fully controlled for • No reverse causality (confounding by prevalent disease)
Negative control study	• No effect of negative control exposure on rea outcome (negative exposure control); No effect of real exposure on negative control outcome • Confounders same for negative control exposure/outcome as for real
Cross context	• Marked differences in confounders between contexts (populations) • No effect modification by context/population





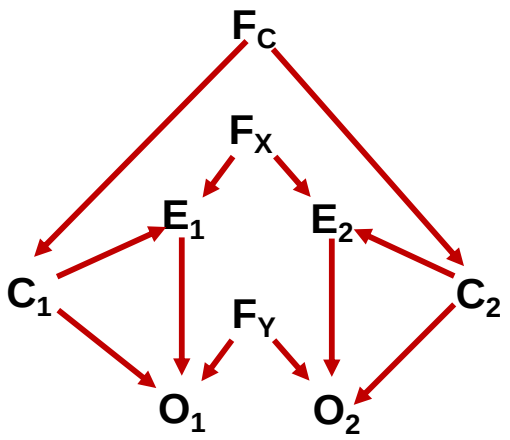


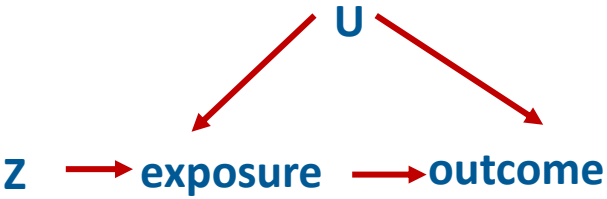




This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Method	Key assumptions
Within sibship (or other matched designs	• Within sibling pairs observed and unobserved confounders matched • No or little residual individual confounding • No contamination between discordant sibs
Instrumental variables	• IV is robustly associated with exposure • No common causes of Z-Y • IV is not associated with outcome by any other path than via the exposure





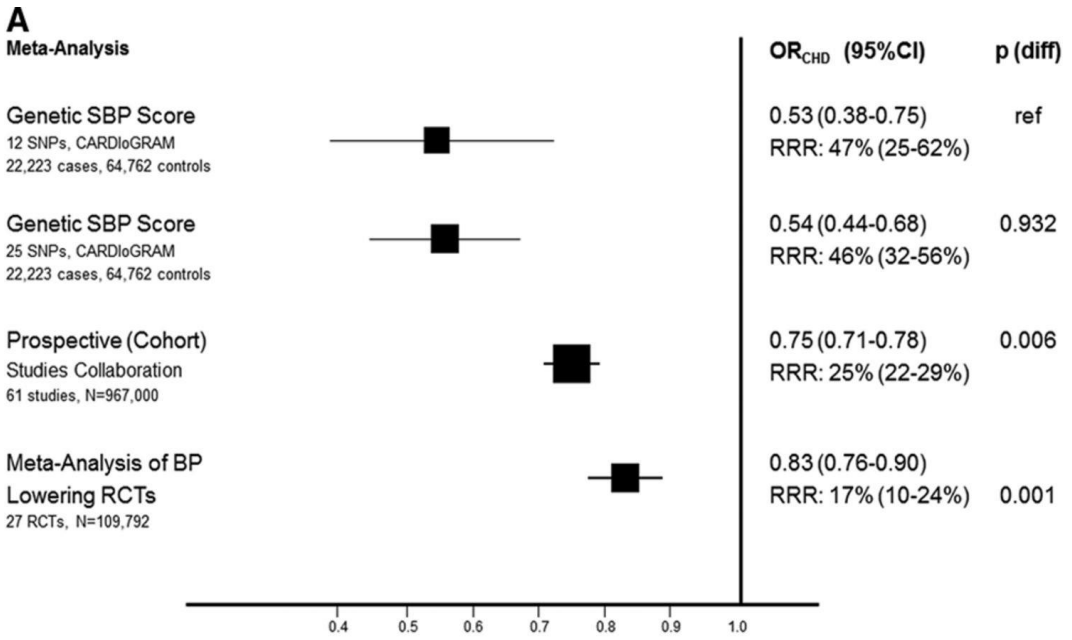
This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Triangulation in practice

- **Specific** research question
- Publish protocol / analysis plan before starting analyses
- (e.g. https://osf.io/e4t8c/ and https://osf.io/s6jv4)
- Identify methods/approaches and data sources based on criteria for triangulation
- **Specific** assessment of sources and risk of bias and likely direction
- Complete main analyses
- Complete sensitivity analyses related to assumptions / sources of bias
- Compare results from different methods

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

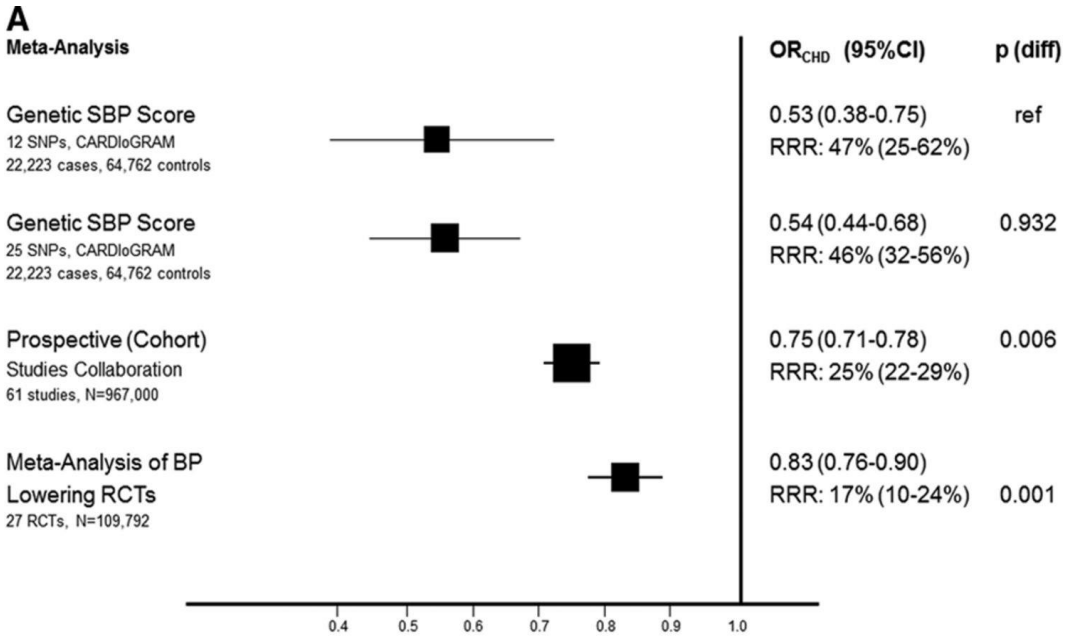
Example 1: SBP and CHD

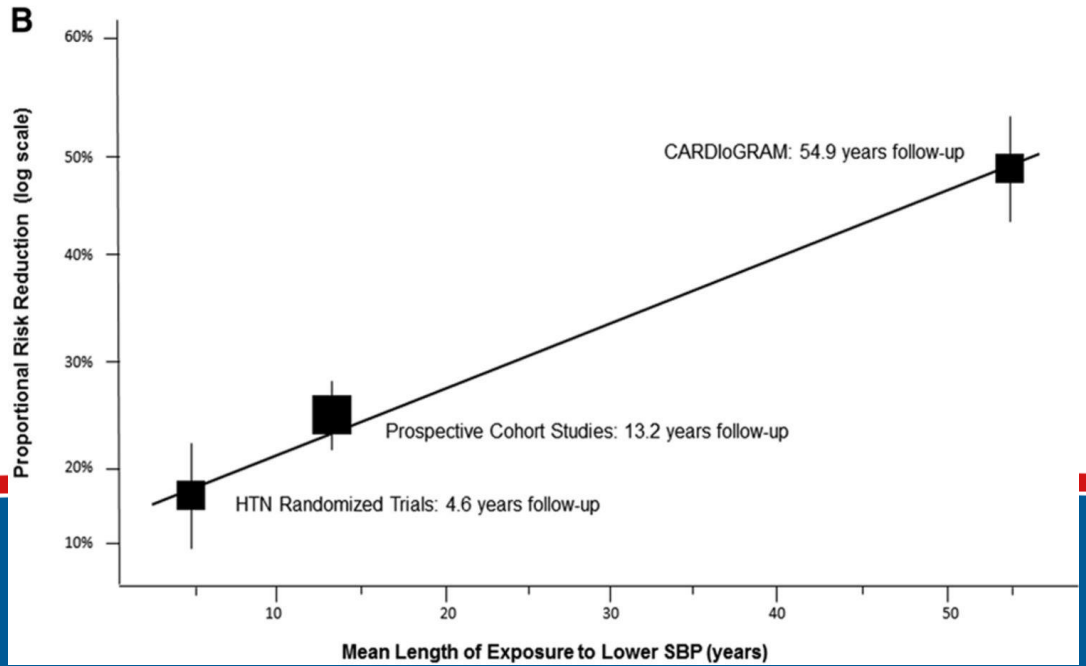


Ference BA, Julius S, Mahajan N, et al. *Hypertension* 2014; **63**(6): 1182-8

- NOTE: Paper does not refer to Triangulation. Focus is largely on MR with prospective cohort and RCT analyses mentioned only briefly at end of methods but highlighted in results and discussion substantially
- Specific policy relevant research question related higher SBP in early life influencing age-related increase in SBP and hence arterial damage and risk of CHD

Example 1: SBP and CHD





Method	Description	Key source of bias & direction
Two-sample MR	Two sample MR. Genetic variants from ICBP that had reached genome-wide levels of statistical significance were used for SBP. CARDIoGRAM used for sample 2 (22 223 fatal or non-fatal CHD cases and 64,762 controls). Ference et al. used MA of wald ratios.	On the basis of sensitivity analyses we did post hoc, we concluded these results were ***unlikely to have major bias if one outlier removed***. But we could not quite replicate his results.
MV regression	Prospective Cohorts Collaboration: an individual participant meta-analysis of 958,074 adults (61 studies) aged 40-69 with no previous history of CVD. Exposure = SBP; Outcome = fatal CHD. Adjustment for age ana sex only. Repeat SBP measurements in a large subgroup were used to adjust the association for regression dilution bias; the estimate of duration of exposure is therefore unlikely to be biased by this	Residual confounding, by adiposity and height, which would ***exaggerate*** any true positive causal effect.
IVs in RCTs	Systematic review and meta-analyses of 25 RCTs including 109,797 participants with no clinical evidence of cardiovascular disease prior to randomization. Authors of the original paper calculated ratios of difference in log odds CHD÷difference in BP by randomised group for each antihypertensive and meta-analysed these. Exposure = SBP & DBP together; outcome = fatal or non-fatal CHD.	Ference et al assumed the results represented a risk reduction in CHD for 10mmHg lower SBP, whereas the estimand = risk reduction in CHD for a 10mmHg lower SBP or 5mmHg lower DBP. Thus the (assumed) SBP effect is ***exaggerated*** in comparison to its true effect.

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Example 2: Effect of maternal gestational smoking on fetal growth

Methods

- Multivariable regression
- Paternal Negative control
- Gene*smoking status interaction in Mendelian randomization framework

Data sources

- Generation R & Born in Bradford
- 8621 European liveborn singletons (Gen R 4682+ Born in Bradford 3939)
  - with repeat fetal USS and birth anthropometry
  - Genome-wide data
  - Smoking data on fathers at time of partners pregnancy.

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Multivariable regression

Residual confounding due to measurement error due to harmonisation of confounders

Expectation **bias away from null**

Explore with sensitivity analyses, including here paterntal negative control

Selection bias due to missing data

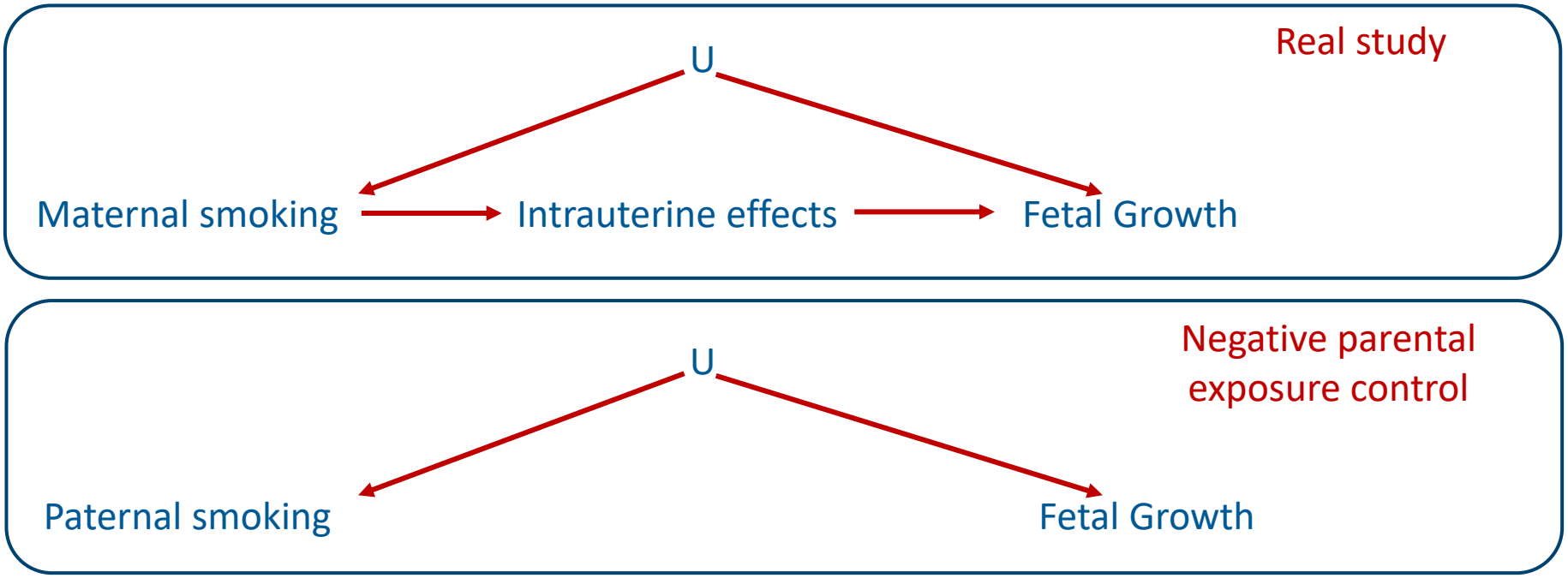
Use MLM and multiple imputation; assumes MAR if incorrect could be **bias in either direction**

Reporting bias – mothers under reporting smoking status & intensity

Expectation **bias towards null**

Explore with sensitivity analyses

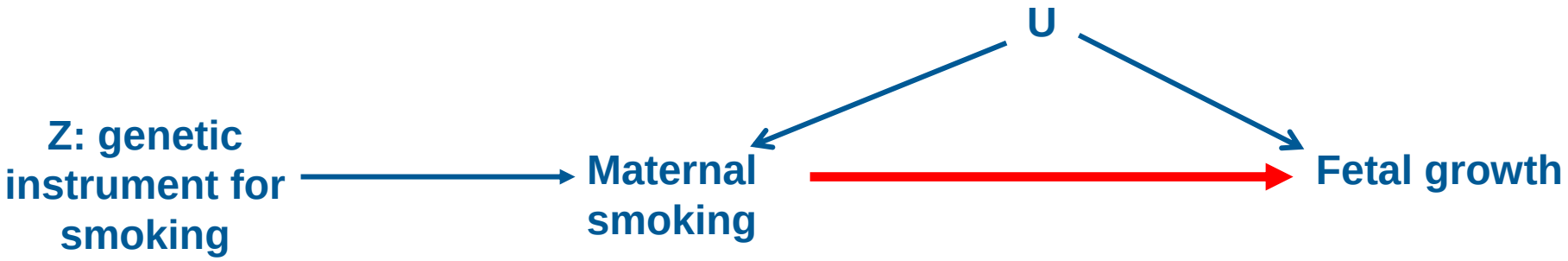
This project received funding from the European Union's Horizon 2020
Research and Innovation Programme under grant agreement No 733206



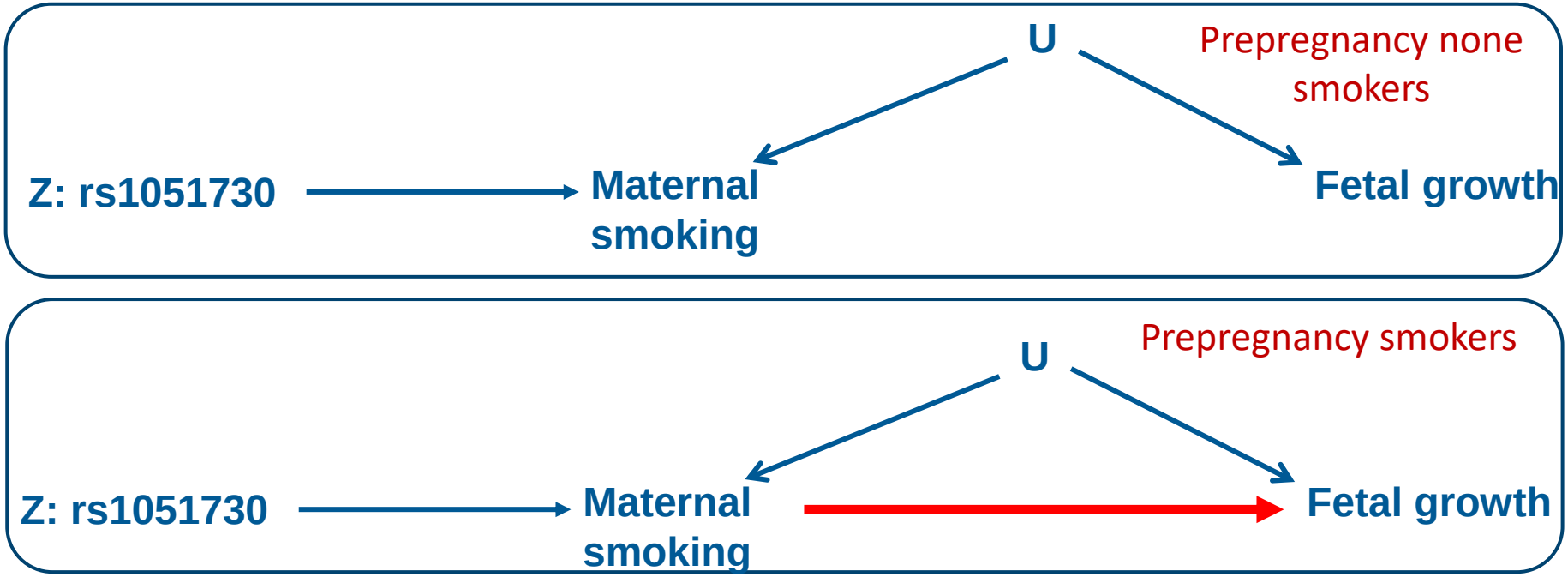
- **Confounders and measurement error similar** for mothers and fathers
- Gen R **mothers reported partners smoking** – could bias negative control towards that of mothers 'real' study. BiB **fathers reported own but sample size ~40%** reduces power to detect association – explore consistency between two studies
- **Fathers could influence fetal growth** via maternal passive smoking or epigenetics. Would expect mothers to be stronger and mutually adjust.

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Mendelian randomization



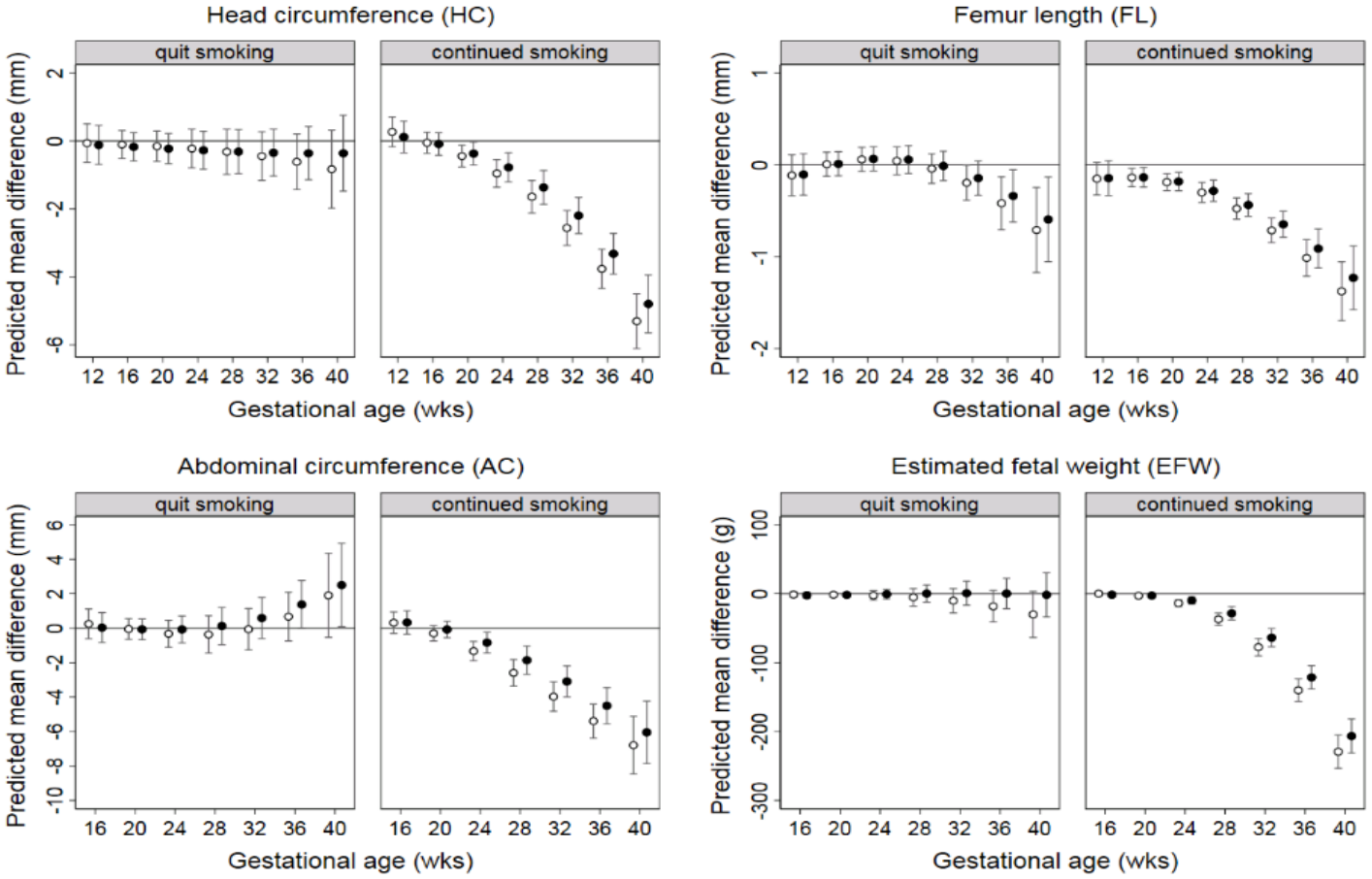
This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206



Horizontal pleiotropy: rs1051730 associates with BMI/adiposity (inc. in never smokers). As maternal BMI increased fetal growth this could bias inverse effects towards null.
Misreporting maternal smoking: could bias results such that never vs current smokers look more similar
Collider bias: In main analyses actually compared results between never smokers, ever smokers who quit before/early pregnancy & ever smokers who continued

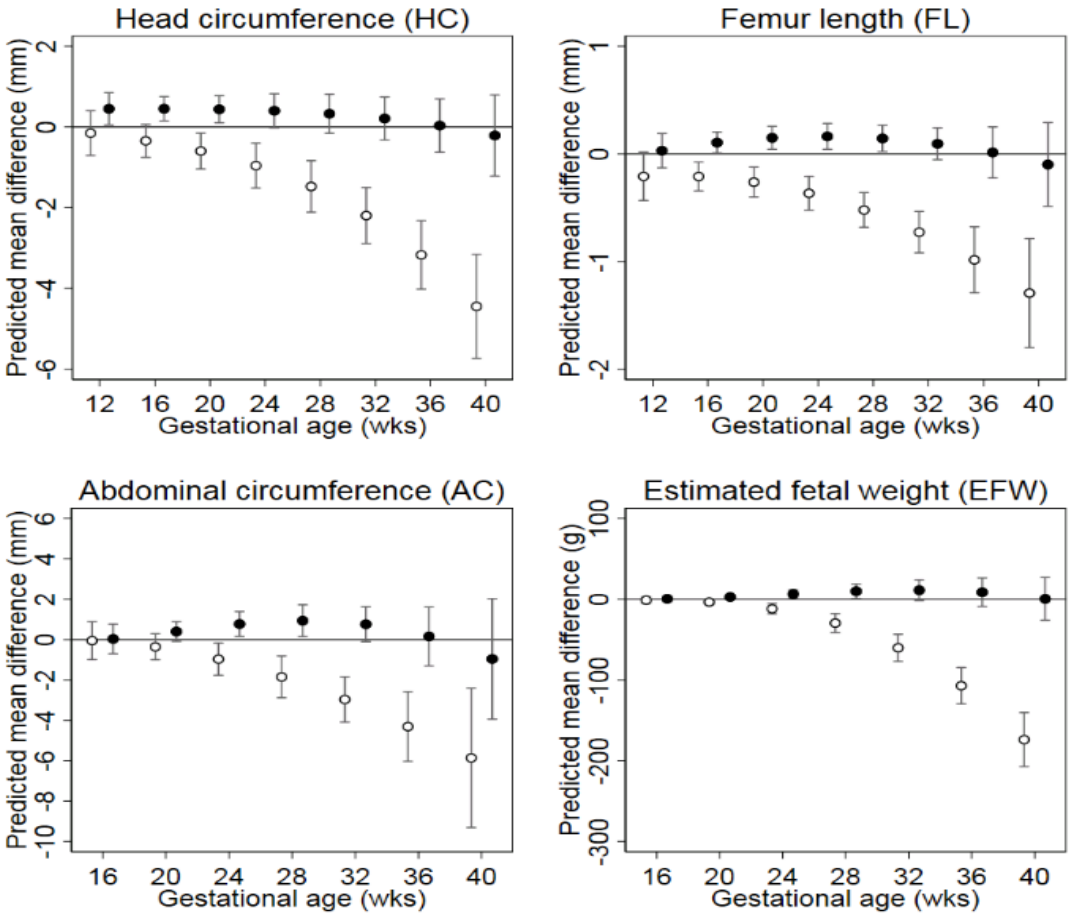
This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Multivariable regression maternal smoking status



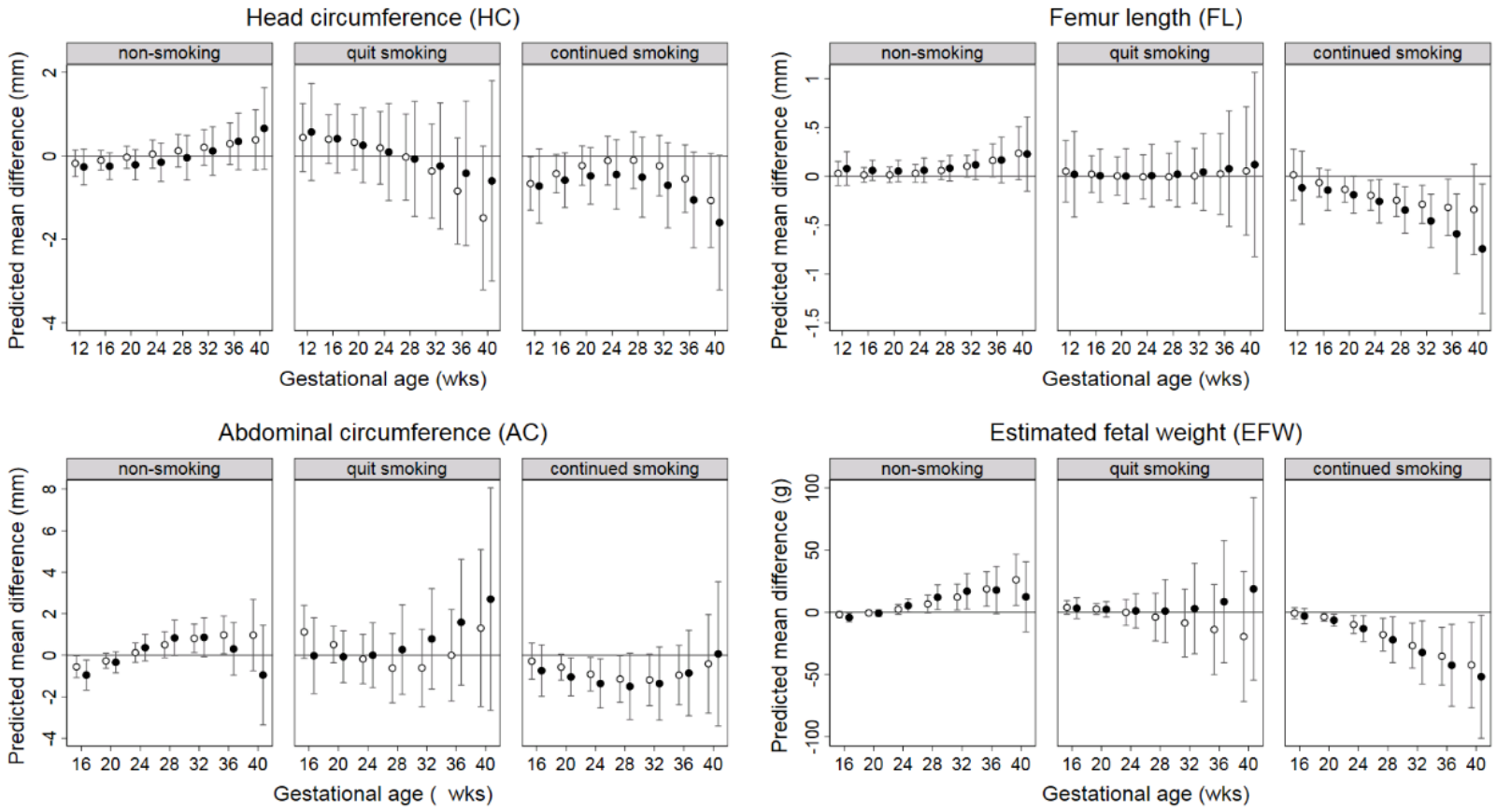
This project received funding from the European Union's Horizon 2020
Research and Innovation Programme under grant agreement No 733206

Negative control paternal smoking during partner's pregnancy



This project received funding from the European Union's Horizon 2020
Research and Innovation Programme under grant agreement No 733206

Mendelian randomization; rs1051730 associations stratified by smoking status



This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

PLOS | MEDICINE

eCycle

RESEARCH ARTICLE

Associations of maternal quitting, reducing, and continuing smoking during pregnancy with longitudinal fetal growth: Findings from Mendelian randomization and parental negative control studies

Judith S. Brand[1,2,3], Romy Gaillard[4,5], Jane West[2,3,6], Rosemary R. C. McEachan[6],

- Pre-pregnancy smokers who continued smoking during pregnancy had a reduced fetal size from early gestation (12-16 wks) onwards.
- In pre-pregnancy smokers who gave up smoking early in pregnancy no overall growth deficit was observed, except for a smaller femur length towards the end of pregnancy.
- There was a dose-response
- These findings were supported by consistency across all 3 methods.
- Women who smoke in early pregnancy and quit once they realise they are pregnant can be reassured their smoking is unlikely to have adversely affected fetal growth.
- For women who find it [illegible] pregnancy support to

educe

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

Going forward

- Triangulation has potential to improve causal inference
- **SHOULD have:**
  - **specific** causal questions
  - Prior publication 0f analysis plan / protocol (iterative & can be changed with date and rationale)
  - **Specific** risk of assessment bias
- Currently, triangulation is mostly selected qualitative comparison
- There is a spectrum from that to fully open quantitative integration
- We are some way from the latter, with challenges including:
  - Time, effort vs current way academics are rewarded
  - Lack of methods / need to develop methods
  - Dealing with multiple sources of bias

This project received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733206

THANK YOU

- All of you

- Chin Yang Shapland
- George Davey Smith
- Julian Higgins
- Kate Tilling
- Marcus Munafo

This project received funding from the European Union's Horizon 2020
Research and Innovation Programme under grant agreement No 733206