Evans, D. M., Moen, G. H., Hwang, L. D., Lawlor, D. A., & Warrington, N. M. (2019). Elucidating the role of maternal environmental exposures on offspring health and disease using two-sample Mendelian randomization. *International Journal of Epidemiology, 48*(3), 861-875. [dyz019]. https://doi.org/10.1093/ije/dyz019

Publisher's PDF, also known as Version of record

Link to published version (if available): 10.1093/ije/dyz019

Link to publication record in Explore Bristol Research

PDF-document

This is the final published version of the article (version of record). It first appeared online via Oxford University Press at https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyz019/5366230. Please refer to any applicable terms of use of the publisher.

**University of Bristol - Explore Bristol Research**

**General rights**

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
Table 1 Potential limitations of MR studies of maternal exposures and offspring outcomes and suggestions of how to deal with them. We do not list limitations that are endemic to all types of MR studies, but rather focus on issues that are specific to MR studies of maternal exposures and offspring outcomes.

| Potential Limitation | Description | Solution |
|----------------------|-------------|----------|
| Suitability of genetic variants to proxy maternal environmental exposure of interest | A key question is whether genetic variants identified in GWAS of men and (non-pregnant) women are appropriate instruments for the research question e.g. if the interest is on the effect of maternal environmental exposures during pregnancy on offspring outcomes, is it appropriate to use SNP effects from a GWAS of the environmental exposure in another population? | Where possible utilize estimates of the association of SNPs with maternal exposures in population of interest during time period of interest. |
| Timing of Maternal exposure | Since an individual’s genetic variants are present from conception, causal estimates derived from MR studies are often thought to represent life-long effects of the environmental exposure. Interpretation of these estimates may be difficult if the investigator is interested in the effect of the maternal exposure during a particular time period (e.g. prenatal exposures). | See above. Examining the causal effect of paternal exposures on offspring outcomes may be informative. Evidence for similar maternal and paternal effects on offspring outcomes is consistent with post-natal effects of the environmental exposure, whereas evidence for maternal specific effects on offspring outcomes in the absence of (or considerably weaker) paternal effects is more consistent with pre-natal effects of the environmental exposure, although maternal specific effects for some exposures may reflect a stronger postnatal maternal effect. |
| Paternal Genetic Effects | Paternal genotypes at the same (or correlated) SNPs may have effects on the study exposure/outcome. Failure to take these effects into account may result in biased | Include paternal genotypes in the statistical model where possible. |
estimates of the causal effect of the maternal exposure on the offspring outcome.

| Low Power | MR studies may have low power because individual SNPs explain small portions of variance in the exposure and the outcome. This potential limitation may be exacerbated in MR studies of maternal exposures because the causal effect of the maternal exposure on the offspring outcome may be smaller than the effect of the maternal exposure on maternal outcomes (as is examined in typical MR studies). | Utilize multiple instruments that explain more variance in the maternal exposure. Utilize two sample MR methods described in this manuscript to increase sample size and statistical power. |
|----------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Violation of exclusion restriction criteria via offspring genetic effects on offspring outcome | Maternal SNPs may be associated with offspring outcome via their association with offspring genotype violating the exclusion restriction assumption of MR and biasing causal estimates. | Perform MR analyses conditioning on offspring genotype. Utilize two sample MR methods described in this manuscript. |
| Paucity of genotyped mother-offspring pairs | There is a dearth of cohorts worldwide that contain large numbers of genotyped mother-offspring pairs for MR analyses of maternal exposures meaning that these sorts of analyses may lack power. | Utilize two sample MR methods described in this manuscript to combine summary results information across many different cohorts. |
Table 2. Causal estimates of maternal (and offspring) susceptibility to type 2 diabetes on offspring birthweight using two sample Mendelian randomization. Results are presented using unadjusted estimates (i.e. estimates of the SNP-birthweight association used in the MR analysis were not corrected for the correlation between maternal and offspring genotypes) and adjusted estimates where the maternal and offspring genetic effects on birthweight were first obtained through the SEM (i.e. estimates of the SNP-birthweight association used in the MR analysis were first corrected for the correlation between maternal and offspring genotypes using the SEM). Causal estimates are presented ($\beta$), their standard errors (in parentheses) and P values from the analysis. Causal estimates represent the estimated difference in mean birthweight in standard deviation units comparing infants whose mothers are susceptible to type 2 diabetes to those mothers who are not (Maternal effect), and the estimated difference in mean birthweight in standard deviation units comparing infants who are themselves susceptible to type 2 diabetes versus those who are not (Offspring effect).

| Method          | Maternal effect | Offspring effect | Maternal effect | Offspring effect |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| IVW MR          | $\beta = 0.036$ (0.007), $P = 1.8x10^{-7}$ | $\beta = -0.043$ (0.007), $P = 7.0x10^{-9}$ | $\beta = 0.015$ (0.007), $P = 0.022$ | $\beta = -0.024$ (0.007), $P = 3.7x10^{-3}$ |
| Egger regression| $\beta = 0.030$ (0.013), $P = 0.021$ | $\beta = -0.028$ (0.014), $P = 0.042$ | $\beta = 0.016$ (0.012), $P = 0.198$ | $\beta = -0.013$ (0.013), $P = 0.313$ |

IVW MR = Inverse variance weighted Mendelian randomization
| Cohort                                                                 | Approximate number of genotyped mother-phenotyped child pairs* |
|-----------------------------------------------------------------------|---------------------------------------------------------------|
| 1958 British Birth Cohort (B85C-T1DGC) 43                             | 858 5                                                        |
| 1958 British Birth Cohort (B85C-WTCCC) 43                             | 836 5                                                        |
| Add Health - National Longitudinal Study of Adolescent to Adult Health 44 | ~1000                                                        |
| Autism Genome Project (AGP) 45                                         | 2594 46                                                     |
| Avon Longitudinal Study of Parents and Children (ALSPAC) 47            | 7304 5                                                       |
| Berlin Birth Cohort (BBC) 48                                           | 1357 2                                                       |
| Born in Bradford Study (BiB) 49                                        | ~10000                                                      |
| Chicago Food Allergy Study 50                                          | 541 51                                                      |
| Children's Hospital of Philadelphia (CHOP)                             | 312 2                                                       |
| Copenhagen Prospective Study on Asthma in Childhood (COPSAC-2000) 52   | 282 2                                                       |
| Danish National Birth Cohort - Genomics of Young Adolescent (DNBC-GOYA) 53 | 1805 5                                                      |
| Danish National Birth Cohort - Preterm Birth Study (DNBC-PTB) 54       | 1656 5                                                      |
| deCODE (Genealogy Database) 55                                         | 54546 13                                                    |
| Environmental Risk (E-Risk) Longitudinal Twin Study 56                | 804 57                                                      |
| Exeter Family Study of Childhood Health (EFSOCH) 58                    | 746 2                                                       |
| Family Atherosclerosis Monitoring In earLY life (FAMILY) study 59       | 406 60                                                      |
| Finnish Twin Cohort 61                                                 | ~4000 62                                                    |
| Hispanic B-cell Acute Lymphoblastic Leukemia Study 63                  | 323 63                                                      |
| HUNT Study 42                                                          | ~18000                                                      |
| Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO) 64            | 4437 64                                                     |
| Millennium Cohort 65                                                  | 12000                                                      |
| Minnesota Center for Twin and Family Research (MCTFR) 66               | 1404 66                                                     |
| Netherlands Twin Register (NTR) 67                                     | 707 5                                                       |
| Northern Finland 1966 Birth Cohort Study (NFB1966) 68                 | 2035 5                                                      |
| Norwegian Mother and Child Cohort Study (MoBa) 40                      | ~46000                                                     |
| Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction Study (PREDO) 69 | ~1000                                                      |
| Pune Maternal Nutrition Study (PMNS) 70                                | 533 70                                                      |
| QIMR Berghofer Cohort 71                                               | 892 5                                                       |
| Simons Simplex Collection 72                                           | 2576 72                                                     |
| Sister Study 73                                                        | 715 73                                                      |
| Study                      | Number |
|----------------------------|--------|
| STORK Study 74             | 529    |
| STORK Groruddalen 75       | 634    |
| TwinsUK 76                 | 1603   |
| UK Biobank** 77            | 221528 |

*The number of genotyped mother-phenotyped child duos is based on information provided in peer-reviewed papers including on birthweight and gestational weight gain, on the cohort’s official website, or from discussions with the study principal investigators. These numbers are liable to change as more individuals are recruited/genotyped, and should only be considered approximations.

**Birthweight only