SCISPACE
formerly Typeset

Open access • Posted Content • DOI:10.1101/2021.10.07.21264689

Associations of insomnia on pregnancy and perinatal outcomes: Findings from Mendelian randomization and conventional observational studies in up to 356,069 women — Source link

Qian Yang, M. Carolina Borges, Eleanor Sanderson, Maria C. Magnus ...+12 more authors

Institutions: University of Bristol, Norwegian Institute of Public Health, National Health Service, University Hospitals Bristol NHS Foundation Trust

Published on: 10 Oct 2021 - medRxiv (Cold Spring Harbor Laboratory Press)

Topics: Perinatal Depression, Miscarriage, Pregnancy, Gestational diabetes and Mendelian randomization

Related papers:

- Maternal anxiety during pregnancy and adverse birth outcomes: A systematic review and meta-analysis of prospective cohort studies
- Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature
- Hypertensive disorders of pregnancy and the risk of offspring depression in childhood: Findings from the Avon Longitudinal Study of Parents and Children.
- Is there an association between anxiety and depression prior to and during pregnancy and gestational diabetes? An analysis of the Born in Bradford cohort
- Risk of Depression in the Adolescent and Adult Offspring of Mothers With Perinatal Depression: A Systematic Review and Meta-analysis

Share this paper:

View more about this paper here: https://typeset.io/papers/associations-of-insomnia-on-pregnancy-and-perinatal-outcomes-1uwmh87y7n

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint **(which was not certified by peer review)** is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Associations of insomnia on pregnancy and perinatal outcomes: Findings from Mendelian randomization and conventional observational studies in up to 356,069 women

Qian Yang,[1,2]* M. Carolina Borges,[1,2] Eleanor Sanderson,[1,2] Maria C. Magnus,[1,2,3] Fanny Kilpi, [1,2] Paul J. Collings,[4] Ana Luiza Soares,[1,2] Jane West,[4] Per Magnus,[3] John Wright,[4] Siri E. Håberg,[3] Kate Tilling,[1,2,5] Deborah A. Lawlor[1,2,5]

[1]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK

[2]Population Health Sciences, Bristol Medical School, University of Bristol, UK

[3]Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

[4] Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK

[5]National Institute for Health Research Bristol Biomedical Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK

*Corresponding author

Address: Office room OF28, Oakfield House, Oakfield Grove, Clifton, Bristol, BS8 2BN, UK

Email: qian.yang@bristol.ac.uk

Key words: insomnia, pregnancy and perinatal outcomes, Mendelian randomization, ALSPAC, MoBa

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Abstract

Background: Insomnia is common and associated with adverse pregnancy and perinatal outcomes in observational studies. Our aim was to test whether insomnia causes stillbirth, miscarriage, gestational diabetes, hypertensive disorders of pregnancy, perinatal depression, preterm birth, or low/high offspring birthweight (LBW/HBW).

Methods and Findings: We used two-sample Mendelian randomization (MR) with 81 single nucleotide polymorphisms instrumenting for a lifelong predisposition to insomnia. We used data (N=356,069) from the UK Biobank, FinnGen, and three European birth cohorts (Avon Longitudinal Study of Parents and Children (ALSPAC), Born in Bradford, and Norwegian Mother, Father and Child Cohort Study). Main MR analyses used inverse variance weighting (IVW), with weighted median and MR-Egger as sensitivity analyses. We compared MR estimates with multivariable regression of insomnia in pregnancy on outcomes in ALSPAC (N=11,745). IVW showed evidence of an effect of genetic susceptibility to insomnia on miscarriage (odds ratio (OR): 1.60, 95% confidence interval (CI): 1.18, 2.17), perinatal depression (OR 3.56, 95% CI: 1.49, 8.54) and LBW (OR 3.17, 95% CI: 1.69, 5.96). For other outcomes IVW indicated potentially clinically important adverse effects of insomnia (OR range 1.20 to 2.43), but CIs were wide and included the null. Weighted median and MR Egger results were directionally consistent, except for MR-Egger for gestational diabetes, perinatal depression, and preterm birth. Multivariable regression showed associations of insomnia at 18 weeks of gestation with miscarriage (OR 1.30, 95% CI: 1.12, 1.51), stillbirth (OR 2.10, 95% CI: 1.20, 3.69), and perinatal depression (OR 2.96, 95% CI: 2.42, 3.63), but not with LBW (OR 0.92, 95% CI: 0.69, 1.24). Key limitations are potential horizontal pleiotropy and low statistical power in MR, and residual confounding in multivariable regression.

Conclusions: There is evidence of causal effects of insomnia on miscarriage, perinatal depression, and LBW. We highlight the need for larger studies with genomic data and pregnancy outcomes.

(word count: 299)

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint **(which was not certified by peer review)** is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Author summary

Why was this study done?

- Insomnia in pregnancy was associated with higher risks of adverse pregnancy and perinatal outcomes in observational studies.
- It is currently no clear whether insomnia causes adverse pregnancy and perinatal outcomes or whether the unfavourable associations are explained by confounding.
- No Mendelian randomization has been conducted to explore the association of insomnia with adverse pregnancy and perinatal outcomes.

What did the researchers do and find?

- We used data on up to 356,069 women from UK Biobank, FinnGen and three birth cohorts, and assessed whether genetic susceptibility to insomnia was associated with stillbirth, miscarriage, gestational diabetes, hypertensive disorders of pregnancy, perinatal depression, preterm birth, low offspring birthweight, and high offspring birthweight in two-sample Mendelian randomization.
- To triangulate with our Mendelian randomization estimates, we conducted multivariable regression in 11,745 women from the Avon Longitudinal Study of Parents and Children, where insomnia was measured in pregnancy.
- We found consistent evidence from Mendelian randomization and multivariable regression that insomnia was associated with higher risks miscarriage and perinatal depression, and Mendelian randomization also suggested an unfavourable effect on low offspring birthweight.

What do these findings mean?

- Interventions to improve healthy sleep in women of reproductive age might be beneficial to a healthy pregnancy.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Introduction

Insomnia, which affects approximately 10 to 20% of the adult population, is usually defined as a difficulty in getting to sleep or remaining asleep, or having a nonrestorative sleep, and such sleep impairment can be associated with daytime sleepiness [1, 2]. Physical and hormonal changes during pregnancy increase susceptibility to insomnia [3, 4].

Most evidence on the relationship between insomnia during pregnancy and adverse pregnancy and perinatal outcomes has come from observational studies. The most recently updated systematic reviews of observational studies suggest that pregnancy-related insomnia and poor sleep quality are associated with higher risks of gestational diabetes (GD) [5, 6], hypertensive disorders of pregnancy (HDP) [6], perinatal depression [7], and preterm birth (PTB) [6]. Other observational studies have shown that specific conditions that relate to insomnia are also associated with adverse pregnancy and perinatal outcomes. For example, meta-analyses combining four case-control studies showed that going to sleep in a supine position (plausibly exacerbating sleep-disordered breathing that contributes to decreased sleep quality [4, 8]) was associated with higher risk of stillbirth [9] and small-for-gestational age (SGA) [10]. Sleep-disordered breathing, obstructive sleep apnoea and restless legs syndrome have also been shown to associate with higher risks of GD, HDP, large-for-gestational age (LGA) and low offspring birthweight (LBW) [6]. However, it remains unclear whether insomnia causes adverse pregnancy outcomes or whether these associations are explained by confounding, e.g. due to socio-economic status and lifestyle factors. It is also possible that some of these studies reflect reverse causation. For example, all four studies included in the systematic review for perinatal depression were cross-sectional [7]. As disturbed sleep is a symptom of depression it is unclear whether these studies reflect a causal effect of insomnia, or it is part of the diagnostic criteria. Furthermore, most individual studies focus on just one or two outcomes. Examining potential effects on a range of adverse pregnancy and perinatal outcomes is important to understand the overall health impact of insomnia during pregnancy.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Three randomized control trials (RCTs) assessing the effects of interventions to prevent insomnia on adverse pregnancy and perinatal outcomes have been published [11-13]. All three of these used cognitive behavioural interventions targeted at reducing insomnia, with the primary outcome being Edinburgh Postnatal Depression Scale scores. The first RCT reported a difference in mean score of -0.21 (95% confidence interval (CI): -0.30, -0.11) in 208 randomized women, with equivalent results for the other two being -0.24 (95% CI: -0.67, 0.19, N=194) and 0.34 (95% CI: -0.26, 0.93, N=91) [11-13]. The small number of RCTs, their small sample sizes, and directional inconsistency but overlapping CIs make it difficult to draw conclusions, and none of them explored other adverse pregnancy or perinatal outcomes.

Mendelian randomization (MR) provides an alternative way to assess the impact of insomnia on adverse pregnancy and perinatal outcomes by using genetic variants (mostly single nucleotide polymorphisms [SNPs]) as instrumental variables (IVs) for insomnia [14, 15]. MR is less prone to confounding than observational studies, as genetic variants are randomly allocated at meiosis and cannot be influenced by the wide range of socio-demographic or behavioural factors which conventionally confound observational studies, nor can they be influenced by health status [14, 15]. Under key assumptions (discussed in methods), MR can be used to estimate a causal effect from the associations of the SNPs with the exposure and outcome. In two-sample MR, the SNP-exposure and SNP-outcome associations are estimated using different studies [16]. This approach has previously been used to evaluate causal effects of self-reported insomnia on risks of type 2 diabetes [17, 18], hypertension [19] and cardiovascular disease [18, 20, 21] in non-pregnant populations, but not pregnancy and perinatal outcomes.

The aims of this study are to (I) explore the causal effects of maternal genetic susceptibility to insomnia on stillbirth, miscarriage, GD, HDP, perinatal depression, PTB, LBW, and high offspring birthweight (HBW), using two-sample MR, and (II) compare those findings with conventional

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint **(which was not certified by peer review)** is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

multivariable regression analyses of self-reported insomnia during pregnancy with the same outcomes.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Methods

Study populations

This study was undertaken using data from the MR-PREG consortium, which aims to explore causes and consequences of different pregnancy and perinatal outcomes [22]. We used individual-level data from UKB women (N=208,140, recruited between 2006-2010), and mother-offspring pairs from ALSPAC (N=6,826, recruited between 1991-1992), BiB (N=2,940, recruited between 2007-2010) and MoBa (N=14,584, recruited between 1999-2009). To be comparable across all cohorts, only genetically unrelated women of European descent with qualified genotype data (and with singleton offspring in birth cohorts) were eligible for inclusion in our analyses (S1 Fig in S1 File). We also used summary-level genetic association data from FinnGen – the national wide network of Finnish biobanks (N=up to 123,579 women) [23]. All studies had ethical approval from relevant national or local bodies and participants provided written informed consent. Details of the recruitment, information on genetic data and measurements of baseline characteristics of each cohort are described in Supplementary Text (S1 File).

Outcomes measures

We explored potential effects of insomnia on eight binary outcomes: ever experiencing stillbirth, ever experiencing miscarriage, GD, HDP, perinatal depression, PTB (gestational age <37 completed weeks), LBW (<2,500 grams) and HBW (>4,500 grams). Full details about how these outcomes were measured and derived in each participating study, and how we harmonised them across studies can be found in S1 Table (S2 File). We were not able to measure pre-eclampsia and gestational hypertension separately, because of the small number of definite cases of pre-eclampsia, and because of differences between studies in data collection and definitions.

In UKB gestational age was only available for a small subset of women (N=7280) who delivered a child during or after 1989, the earliest date for which linked hospital labour and perinatal data are

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

available [24]. As a result, numbers with data on PTB are smaller than for any other outcome, and we *a priori* decided to examine associations with LBW and HBW rather than SGA and LGA. For most outcomes in UKB, women reported their experience retrospectively in a questionnaire completed at recruitment when they were aged 40-60 years.

In the three birth cohorts most outcomes were prospectively obtained (from self-report or clinical records) during an index pregnancy and the perinatal period. The two exceptions were history of stillbirth and miscarriage, which were retrospectively reported at the time of the index pregnancy when women were asked if they had ever experienced a (previous) stillbirth or miscarriage. We explored the possibility of examining associations with miscarriage and stillbirth in the index pregnancy. However, numbers were too small for reliable results in either MR or multivariable regression, and for miscarriage we were concerned about misclassification or selection bias due to women who had experienced a miscarriage prior to recruitment. If multiple pregnancies were enrolled in the birth cohorts, we randomly selected one pregnancy per woman.

Data from FinnGen were available for four of our outcomes: ever experiencing miscarriage, GD, HDP and PTB, which were defined based on International Classification of Diseases codes.

Insomnia measures

Self-reported information on insomnia was obtained from two of the studies. In UKB information on lifetime insomnia was used to generate SNP-insomnia associations in women for use in MR analyses in UKB and the birth cohorts. ALSPAC collected data on insomnia during pregnancy, and this was used for conventional confounder-adjusted multivariable regression.

In UKB, insomnia was self-reported at recruitment via the question “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” with responses “never/rarely”, “sometimes”, “usually” and “prefer not to answer”. For our analyses we collapsed these categories to generate a binary variable of usually experiencing insomnia (i.e. “usually” [cases] versus

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

"sometimes" + "never/rarely" [controls]) as this was how the responses were categorised in the published genome-wide association study (GWAS) that we have used to select genetic IVs [18].

In ALSPAC, insomnia in pregnancy was self-reported, at 18 and 32 weeks of gestation, using the question "Can you get off to sleep alright?" with options "Very often", "Often", "Not very often" and "Never". At each time point, we compared "Not very often" + "Never" [cases] versus "Very often" + "Often" [controls]. We acknowledge that the two studies are using different questions and that definitions of insomnia vary across published literature [2]. For ease of reading throughout the paper we refer to results reflecting genetic susceptibility to insomnia (MR) and reporting insomnia in pregnancy (multivariable regression).

SNP selection and SNP-insomnia associations

To identify genetic IVs for insomnia, we searched the GWAS published between January 2017 and February 2021 on PubMed and Neale Lab website [25]. We found seven insomnia GWAS reporting genome-wide significant SNPs (details in S2 Table in S2 File). Of these we selected SNPs from the largest GWAS (total N = 709,986 women, 29% from UKB and 71% from 23andMe), which provided female-specific results [18]. This GWAS identified 83 loci containing 87 lead SNPs that were robustly associated with insomnia (P-value $<5\times10^{-8}$) after pooling UKB and 23andMe women together. We removed 6 SNPs that were correlated to other SNPs (*linkage disequilibrium*) at an R^2 threshold of 0.01 or higher, based on all European samples from the 1000 genome project [26]. Associations (reported in log odds ratios [ORs]) of the remaining 81 lead SNPs from the women only GWAS were extracted and listed in S3 Table (S2 File).

We fitted linear regression to individual-level data from 208,140 UKB women to recalculate SNP-insomnia associations for two-sample MR analyses, to avoid non-collapsibility of ORs and difficult interpretation of MR estimates' unit [27]. We adjusted the linear models for genotyping batch, top 40 principal components (PCs) and women's age.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

SNP-outcome associations

We estimated the associations between maternal SNPs and outcomes (log odds ratio (OR) and standard errors) for each of the 81 insomnia-related SNPs. In UKB, we randomly separating women in half (giving two datasets, A and B) for our split cross-over two-sample MR [28], given UKB was also included in the GWAS of insomnia. We then estimated SNP-outcome associations in each split sample using logistic regression, adjusting for genotyping batch, top 40 PCs, and women's age. In the birth cohorts, we estimated the SNP-outcome associations using logistic regression, adjusting for (I) top 20 PCs and women's age in ALSPAC; (II) top 10 PCs and women's age in BiB; and (III) genotyping batch, top 10 PCs and women's age in MoBa. We extracted associations of the 81 SNPs with miscarriage (O15_ABORT_SPONTAN), GD (GEST_DIABETES), HDP (O15_GESTAT_HYPERT), and PTB (O15_PRETERM) from FinnGen, which were generated using SAIGE (mixed-effects logistic regression [29]) adjusting for genotyping batch, top 10 PCs and women's age [23]. Then we meta-analysed those associations from ALSPAC, BiB, MoBa and FinnGen using fixed-effects with inverse variance weights. Three SNPs (i.e. rs10947428, rs9943753, and rs117037340) were excluded from BiB analyses due to their minor allele frequency lower than 1%.

Assessment of confounders in ALSPAC for multivariable regression

We considered maternal age at time of delivery, education, body mass index at 12 weeks of gestation, smoking status in pregnancy, alcohol intake in the first three months of pregnancy and household occupational social class as potential confounders based on their known or plausible associations with maternal insomnia and pregnancy and perinatal outcomes. Details of confounders were based on maternal self-report, and are fully described in Supplementary Text (S1 File).

Statistical analyses

Two-sample MR

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

As shown in Fig 1, we conducted two-sample MR analyses of maternal insomnia on pregnancy and perinatal outcomes. In UKB, we conducted a split cross-over two-sample MR [28]. Specifically, we used SNP-insomnia associations from dataset A and SNP-outcomes associations from dataset B (A on B) and vice-versa (B on A), and then meta-analysed the MR estimates from the two together for each insomnia-outcome pair using fixed-effects (with inverse variance weights). For the two-sample MR using the rest of the cohorts, we used SNP-insomnia associations from UKB women and the pooled SNP-outcome associations combining ALSPAC, BiB, MoBa and FinnGen. For each outcome, we pooled MR estimates from all cohorts using fixed-effects (with inverse variance weights), and used leave-one (study)-out analysis to assess the degree of heterogeneity between cohorts.

In the main analyses, we used the MR IVW method, which is a regression of the estimates for SNP-outcomes associations on SNP-insomnia associations weighted by the inverse of the SNP-outcome associations variances, with the intercept of the regression line forced through zero [30]. The IVW estimates should provide an unbiased estimate of a causal effect in the absence of unbalanced horizontal pleiotropy [30]. To explore potential unbalanced horizontal pleiotropy, our sensitivity analyses included (I) estimating between-SNP heterogeneity (which if present may be due to one or more SNPs having horizontal pleiotropic effects on the outcome) using Cochran's Q-statistic and leave-one (SNP)-out analysis, and (II) undertaking analyses with weighted median [31] and MR-Egger [32], which are more likely to be robust in the presence of invalid IVs. The weighted median method is unbiased so long as less than 50% of the weight is from invalid instruments (i.e. if one SNP contributing more than 50% of the weight across the SNP-insomnia associations or several SNPs that contribute more than 50% introduce horizontal pleiotropy the effect estimate is likely to be biased) [31]. MR-Egger is similar to IVW except it does not constrain the regression line to go through zero; if the MR-Egger intercept is not null it suggests the presence of horizontal pleiotropy, and the MR-Egger slope provides an effect estimate corrected for unbalanced horizontal pleiotropy [32]. However, MR-Egger has considerably less statistical power than IVW. Further details of these MR methods are provided in our previous study [33]. When using MR to assess the effect of maternal

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

exposures in pregnancy on offspring outcomes, results might be biased via a path from maternal genotypes to maternal/offspring outcomes due to fetal genotype [34]. To explore this, we compared SNP-outcome associations with versus without adjustments for fetal genotypes in the pooled birth cohort analyses.

We evaluated the strength of IVs using both proportion of variances of maternal insomnia explained by the 81 SNPs (R^2) and F-statistic [35]. We selected SNPs robustly related to insomnia in the general female population rather than in pregnant women. Therefore, we explored associations of the 81 SNPs with woman's insomnia measured at 18 and 32 weeks of gestation in ALSPAC using logistic regressions to determine whether those SNPs related similarly to insomnia in pregnancy. We adjusted for the top 20 PCs and women's age.

Multivariable regressions in ALSPAC

In ALSPAC, we explored the observational associations of insomnia at 18 and 32 weeks of gestation with binary outcomes using logistic regression, with adjustment for measured confounders. We had to regress stillbirth history on insomnia at 18 and 32 weeks of gestation, and miscarriage history on insomnia at 18 weeks of gestation, assuming that insomnia in the index pregnancy could also represent the situations in previous pregnancies.

All analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sample MR analyses were conducted using the "TwoSampleMR" R package [26].

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Results

Table 1 summarizes the characteristics of included women from UKB, ALSPAC, BiB, MoBa and FinnGen. The SNP-insomnia associations in UKB and ALSPAC are listed in S4 Table (S2 File). The 81 SNPs explained approximately 0.42% variance of insomnia among the 208,140 UKB women included in this study (S4 Table in S2 File), and the mean F-statistic of the 81 SNPs was 11. The pooled 81 SNP-insomnia associations at 18 (OR 1.02 per effect allele, 95% CI: 1.01, 1.03) and 32 (OR 1.02, 95% CI: 1.01, 1.03) weeks of gestation in ALSPAC were in the same direction as (but weaker than) the pooled association in the original GWAS of UKB plus 23andMe women (OR 1.05, 95% CI: 1.05, 1.06). The SNP-outcome associations in UKB, ALSPAC, BiB and MoBa are listed in S5 Table (S2 File).

Two-sample MR

In the analysis combining all cohorts, lifetime tendency to insomnia was associated with higher risks of all outcomes with point estimate OR ranging from 1.20, for GD, to 3.56 for perinatal depression (Fig 2). Despite combining data from the largest genetic studies available estimates were imprecise, with 95% CIs for all but three outcomes including the null. The three that did not include the null were miscarriage (OR 1.60, 95% CI: 1.18, 2.17), perinatal depression (OR 3.56, 95% CI: 1.49, 8.54) and LBW (OR 3.17, 95% CI: 1.69, 5.96). S2 Fig (in S1 File) shows IVW results for leave-one (study)-out analysis. Results were broadly consistent, with the point estimates showing some differences with stillbirth, GD and PTB, though CIs were very wide for some outcomes.

Sensitivity analyses using weighted median and MR-Egger for all outcomes were directionally consistent, with the exception of MR-Egger results for GD, perinatal depression and PTB (Fig 2). Between-SNP heterogeneity for MR analyses was observed with LBW and HDP (S6 Table in S2 File), but leave-one (SNP)-out analyses were consistent with the main IVW estimates including all SNPs for all outcomes (S3-5 Figs in S1 File). The MR-Egger intercept p-value indicated unbalanced horizontal pleiotropy only for perinatal depression in UKB (S6 Table in S2 File). Adjusting for fetal genotype (only possible in the birth cohorts) did not alter the SNP-outcome associations with stillbirth,

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

miscarriage, LBW or HBW; SNP-outcome associations with GD, HDP and perinatal depression were slightly attenuated; SNP-PTB associations moved slightly away from the null (S6 Fig in S1 File).

Multivariable regression in ALSPAC

S7 Table (S2 File) summarizes the characteristics of women from ALSPAC who contributed to these analyses. After adjusting for potential confounders, there were associations of insomnia at 18 and 32 weeks of gestation with stillbirth history, miscarriage history (only assessed for 18 weeks), GD (32 weeks only), HDP and perinatal depression, with similar magnitudes of association to those seen for the MR analyses, and with imprecision meaning some 95% CIs included the null (Fig 3). Associations with stillbirth history (OR for insomnia at 18 weeks 2.10, 95% CI: 1.20, 3.69), miscarriage history (OR for insomnia at 18 weeks 1.30, 95% CI: 1.12, 1.51), and perinatal depression (OR for insomnia at 18 weeks 2.96, 95% CI: 2.42, 3.63), were the most reliable with CIs that did not include the null (Fig 3).

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Discussion

To our knowledge this is the first MR study to explore the relationship of insomnia with pregnancy and perinatal outcomes. We interpreted the MR results as reflecting a lifetime tendency to insomnia on the basis that SNPs are determined at conception, and evidence suggested that with similar analyses of other exposures (e.g. blood pressure and C-reactive protein) this is the case [36, 37]. We interpreted the multivariable regression results as reflecting associations of insomnia during pregnancy, though we could not distinguish this from pre-existing insomnia as we did not have information on sleep traits before conception. The associations of the insomnia genetic IVs with reported insomnia during pregnancy in ALSPAC provided some support that the exposures in our MR and multivariable regression analyses had some consistency with each other. Overall, our MR results provide evidence that a lifetime tendency to insomnia may increase the risk of stillbirth, miscarriage, GD, HDP, perinatal depression, PTB, LBW and HBW, with ORs of potential clinical importance (range 1.20 to 3.56) for all of these. However, we acknowledge that MR analyses are statistically inefficient and despite combining all potentially relevant studies in order to increase the sample size, results were imprecise with all but three outcomes having 95% CI that included the null. Thus, we have strongest MR evidence for insomnia increasing the risk of miscarriage, perinatal depression, and LBW. Results for miscarriage and perinatal depression are replicated in multivariable regression analyses,but with the exception of results for LBW, which were much closer to the null.

Our findings in both MR and multivariable regression of increased risks of perinatal depression are consistent with the systematic review and meta-analysis of observational studies [7], and with RCTs suggesting that pregnancy interventions to reduce insomnia decrease perinatal depression [11, 12]. Whilst previous studies have shown that pregnancy supine sleeping position (which is associated with insomnia) to be associated with stillbirth [6, 9], recent systematic reviews have only identified one cross-sectional study (N=222) of the association of insomnia with stillbirth [6, 8], and we did not identify any previous studies of insomnia associations with miscarriage. Thus, our novel findings of a

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

possible effect of insomnia on miscarriage in both MR and multivariable regression analyses warrants replication. Previous systematic reviews of observational associations of insomnia with GD, HDP and PTB have some consistency with our main MR results, but few observational studies investigated LBW or HBW [6, 8]. For example, ORs from the meta-analyses for GD (1.37 combining 8 studies vs 1.20 in MR), HDP (1.72 combining 2 studies vs 1.71 in MR), PTB (1.49 combining 8 studies vs 1.31 in MR) were very similar to our MR analyses [6], despite the differing definitions of insomnia and outcomes and different assumptions for MR and multivariable regression [38].

Several mechanisms have been suggested for why insomnia might influence pregnancy and perinatal outcomes, including insomnia resulting in increased risks of adiposity, insulin resistance and other cardiometabolic outcomes that could then influence related pregnancy outcomes (GD, HDP, LBW and HBW) and influence placentation and hence miscarriage, stillbirth and PTB. MR analyses support effects of insomnia on coronary heart disease, higher glycated haemoglobin, and higher glycoprotein acetyls (an inflammatory marker) in general populations of women and men [20, 39, 40]. Thus, an increase in cardio-metabolic risk and inflammation may mediate effects of insomnia on miscarriage and LBW, and outcomes for which our MR analyses are currently imprecise. Similarly, MR analyses have found a potential effect of insomnia on depressive symptoms [20], which is coherent with our findings in relation to perinatal depression.

Study strengths and limitations

Key strengths of our study are that (I) it is the first study to use MR to explore potential effects of insomnia on pregnancy and perinatal outcomes; (II) we compared those MR findings with multivariable regression results of insomnia symptoms in pregnancy, adjusting for a *priori* defined key confounders; (III) we explored a range of pregnancy and perinatal outcomes. To our knowledge, this is the first study to explore associations with miscarriage and stillbirth, using either multivariable regression or MR.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Our MR analyses may be biased by horizontal pleiotropy, particularly given our previous research showing that SNPs for insomnia are also associated with several factors that could influence pregnancy and perinatal outcomes, including education, age at first live birth, and smoking [33]. We explored this potential with a range of sensitivity analyses, including exploring between-SNP heterogeneity and using weighted median and MR-Egger methods that are more robust to such bias than IVW [30]. Results from these sensitivity analyses were broadly consistent with our main analyses but were less precise (i.e. had wider CIs). Adjusting for fetal genotype did not alter results suggesting that bias due to fetal genotypic effects is unlikely. We did not further adjust for paternal genotype because of limited data with paternal, maternal and offspring genotype. Furthermore, the most plausible mechanism for paternal genotype to affect pregnancy outcomes is via fetal genotype, which we have adjusted for.

Interpretation of the effect estimates from our MR analyses requires a further assumption of monotonicity in the SNP-insomnia associations. This requires that all of the women with genetic IVs related to higher liability to insomnia symptoms should report more symptoms (compared to those with fewer alleles related to insomnia) – i.e. that they are 'compliers' [41]. Whilst we cannot test this assumption, the similarity of our MR and multivariable regression estimates for miscarriage and perinatal depression, provides some evidence that it may not have been violated for these outcomes.

Both our MR and multivariable regression estimates could be vulnerable to selection bias, which has been extensively discussed in previous papers [42-44]. Specific to UKB, it is a highly selective sample that is healthier and better educated than the general UK adult population [45]. Moreover, information on perinatal depression and PTB was only available in a subsample of UKB women and such missingness might not be at random [46, 47]. By definition our study only includes women who have experienced at least one pregnancy, and if insomnia influences fertility then our results might be biased [48]. However, we are not aware of robust evidence of insomnia (or SNPs related to

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

insomnia) influencing infertility or number of children [49, 50], suggesting any selection bias through only including pregnant women is unlikely to have a meaningful impact on our MR estimates [48, 51].

Insomnia was measured via one self-administrated question in both UKB and ALSPAC, which could mean the binary exposure is misclassified. Non-differential misclassification of insomnia would be expected to bias MR results away from the null (given the attenuated genetic IVs – insomnia associations is the denominator), but multivariable regression results towards the null [52, 53]. Similarly, there may be misclassification in some of our outcomes because of the absence of universal testing (e.g. GD in ALSPAC [54]), assessment via self-report questionnaires (e.g. BW in UKB) or differences between studies in definitions (e.g. in older women in UKB the gestational age thresholds for defining stillbirth and miscarriage would have differed from those used in the more contemporary birth cohorts). Non-differential misclassification of our binary outcomes would be expected to bias both MR and multivariable regression results towards the null [52, 53]. Moreover, the first live-born babies of UKB women are known to be lighter than babies with various birth orders from the more contemporary birth cohorts [55, 56].

Both MR and multivariable regression analyses of miscarriage and stillbirth assessed the associations of ever experiencing either of them mainly up to the point of recruitment. For the multivariable regression analysis in ALSPAC, insomnia was reported after the outcomes had occurred and it is possible that previous miscarriage or stillbirth might have influenced sleep in the index pregnancy (where insomnia was reported), e.g. due to anxiety [3]. The similarity of the multivariable regression and MR results for miscarriage, stillbirth, GD, HDP and perinatal depression suggests residual confounding is unlikely to have biased regression results for these outcomes. The attenuated to the null associations for preterm birth, LBW and HBW compared to MR results suggests possible masked confounding or other biases specifically affecting these but not other outcomes. Despite having a large sample size and our multivariable analyses being larger than most previous studies, several of

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

our MR and multivariable regression estimates are imprecise. Our study is limited to women of European ancestry, and we cannot assume that our results generalize to other populations.

In conclusion, our study raises the possibility of adverse causal effects of insomnia on miscarriage, perinatal depression, and LBW. Interventions to improve healthy sleep in women of reproductive age might be beneficial to a healthy pregnancy. However, we acknowledge the need for further MR studies based on larger GWAS of pregnancy and perinatal outcomes, larger observational studies, and studies in women from ethnic backgrounds other than White European.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

Data Availability Statement

We used both individual participant cohort data and publicly available summary statistics. We present summary statistics that we generated from those individual participant cohort data in S4 & 5 Tables. Full information on how to access UKB data can be found at its website (https://www.ukbiobank.ac.uk/researchers/). All ALSPAC data are available to scientists on request to the ALSPAC Executive via this website (http://www.bristol.ac.uk/alspac/researchers/), which also provides full details and distributions of the ALSPAC study variables. Similarly, data from BiB are available on request to the BiB Executive (https://borninbradford.nhs.uk/research/how-to-access-data/). Data from MoBa are available from the Norwegian Institute of Public Health after application to the MoBa Scientific Management Group (see its website https://www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/data-access/applying-for-access-to-data/ for details). Summary statistics from FinnGen are publicly available on its website (https://finngen.gitbook.io/documentation/data-download).

Funding

This work was supported by the University of Bristol and UK Medical Research Council (MM_UU_00011/1, MM_UU_00011/3 and MM_UU_00011/6), the US National Institute for Health (R01 DK10324), the European Research Council via Advanced Grant 669545, the British Heart Foundation (AA/18/7/34219 and CS/16/4/32482) and the National Institute of Health Research Bristol Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. Q.Y. is funded by a China Scholarship Council PhD Scholarship (CSC201808060273). M.C.B. was funded by a UK Medical Research Council Skills Development Fellowship (MR/P014054/1) and a University of Bristol Vice Chancellor Fellowship during her contribution to this research. M.C.M. has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation programme (grant agreement No 947684). M.C.M and S.E.H are partly funded by the Research Council of Norway through its Centres

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

of Excellence funding scheme (project No 262700). P.J.C. is funded by a British Heart Foundation Immediate Postdoctoral Basic Science Research Fellowship (FS/17/37/32937). D.A.L. is a British Heart Foundation Chair (CH/F/20/90003) and a National Institute of Health Research Senior Investigator (NF-0616-10102).

The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and D.A.L will serve as guarantor for the contents of this paper. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf); This research was specifically funded by Wellcome Trust (WT088806), and child's GWAS data was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. BiB receives core funding from the Wellcome Trust (WT101597MA), a joint grant from the UK Medical and Economic and Social Science Research Councils (MR/N024397/1), British Heart Foundation (CS/16/4/32482), and the National Institute of Health Research under its Applied Research Collaboration for Yorkshire and Humber and Clinical Research Network research delivery support. Further support for genome-wide and multiple 'omics measurements in BiB is from the UK Medical Research Council (G0600705), National Institute of Health Research (NF-SI-0611-10196), US National Institute of Health (R01DK10324), and the European Research Council under the European Union's Seventh Framework Programme (FP7/2007–2013) / ERC grant agreement no 669545. The funders had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and not necessarily those of any funder.

Competing interests

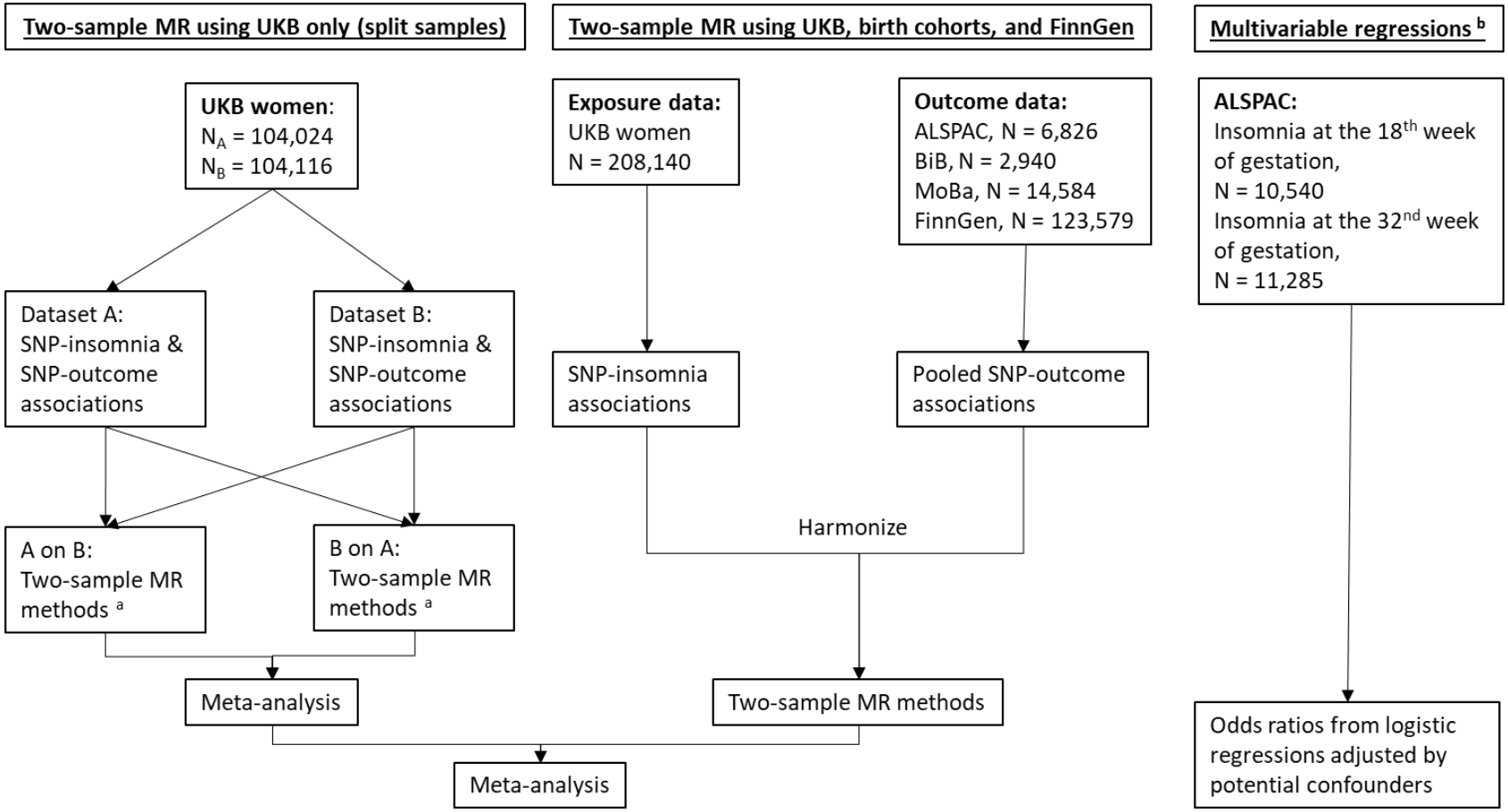
medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

KT has acted as a consultant for CHDI Foundation. DAL has received support from Medtronic LTD and Roche Diagnostics for biomarker research that is not related to the study presented in this paper. The other authors report no conflicts.

Acknowledgments

This research has been conducted using the UKB Resources under application number 23938. The authors would like to thank the participants and researchers from UKB who contributed or collected data. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. BiB is only possible because of the enthusiasm and commitment of the Children and Parents in BiB. We are grateful to all the participants, teachers, school staff, health professionals and researchers who have made BiB happen. This research has been conducted using MoBa data using application number 2552. MoBa is supported by the Norwegian Ministry of Health and Care services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. We thank the Norwegian Institute of Public Health (NIPH) for generating high-quality genomic data. This research is part of the HARVEST collaboration, supported by the Research Council of Norway (#229624). We also thank the NORMENT Centre for providing genotype data, funded by the Research Council of Norway (#223273), South East Norway Health Authority and KG Jebsen Stiftelsen. We further thank the Center for Diabetes Research, the University of Bergen for providing genotype data and performing quality control and imputation of the data funded by the ERC AdG project SELECTionPREDISPOSED, Stiftelsen Kristian Gerhard Jebsen, Trond Mohn Foundation, the Research Council of Norway, the Novo Nordisk Foundation, the University of Bergen, and the Western Norway health Authorities (Helse Vest). The authors thank FinnGen investigators for sharing their summary-level data.

Fig 1. Summary of methods and data contributing to this study.

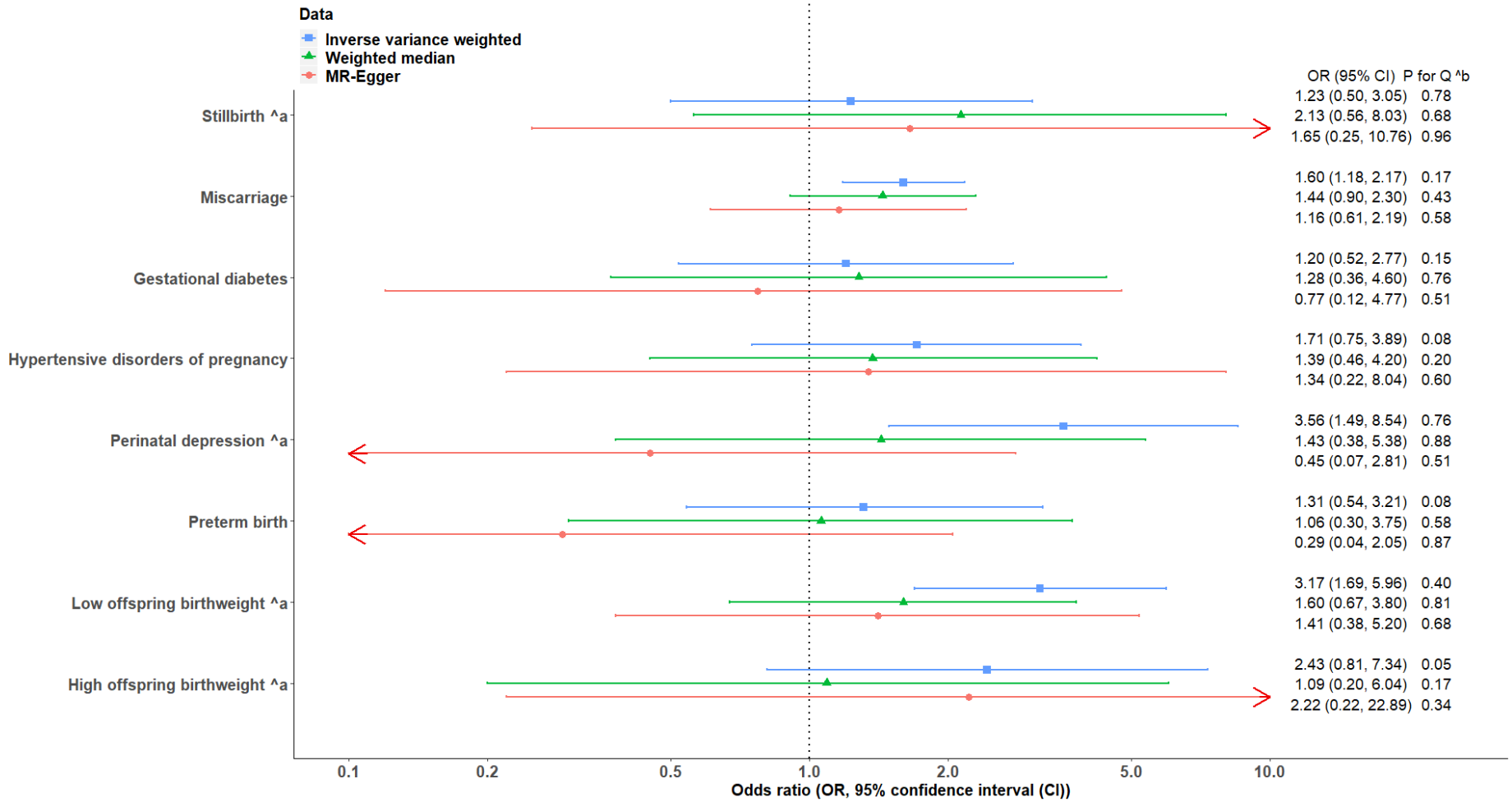


[a] Two-sample MR methods include: IVW, MR-Egger, weighted median, and leave-one-out analysis.

[b] Multivariable regression analysis adjusted for maternal age at time of delivery, social class, education, body mass index at 12 weeks of gestation, smoking status in pregnancy and alcohol intake in the first three months of ALSPAC pregnancy.

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BiB, Born in Bradford; GWAS, genome-wide association study; IVW, inverse variance weighted; MoBa, Norwegian Mother, Father and Child Cohort Study; MR, Mendelian randomization; SNP, single nucleotide polymorphism; UKB, UK Biobank.

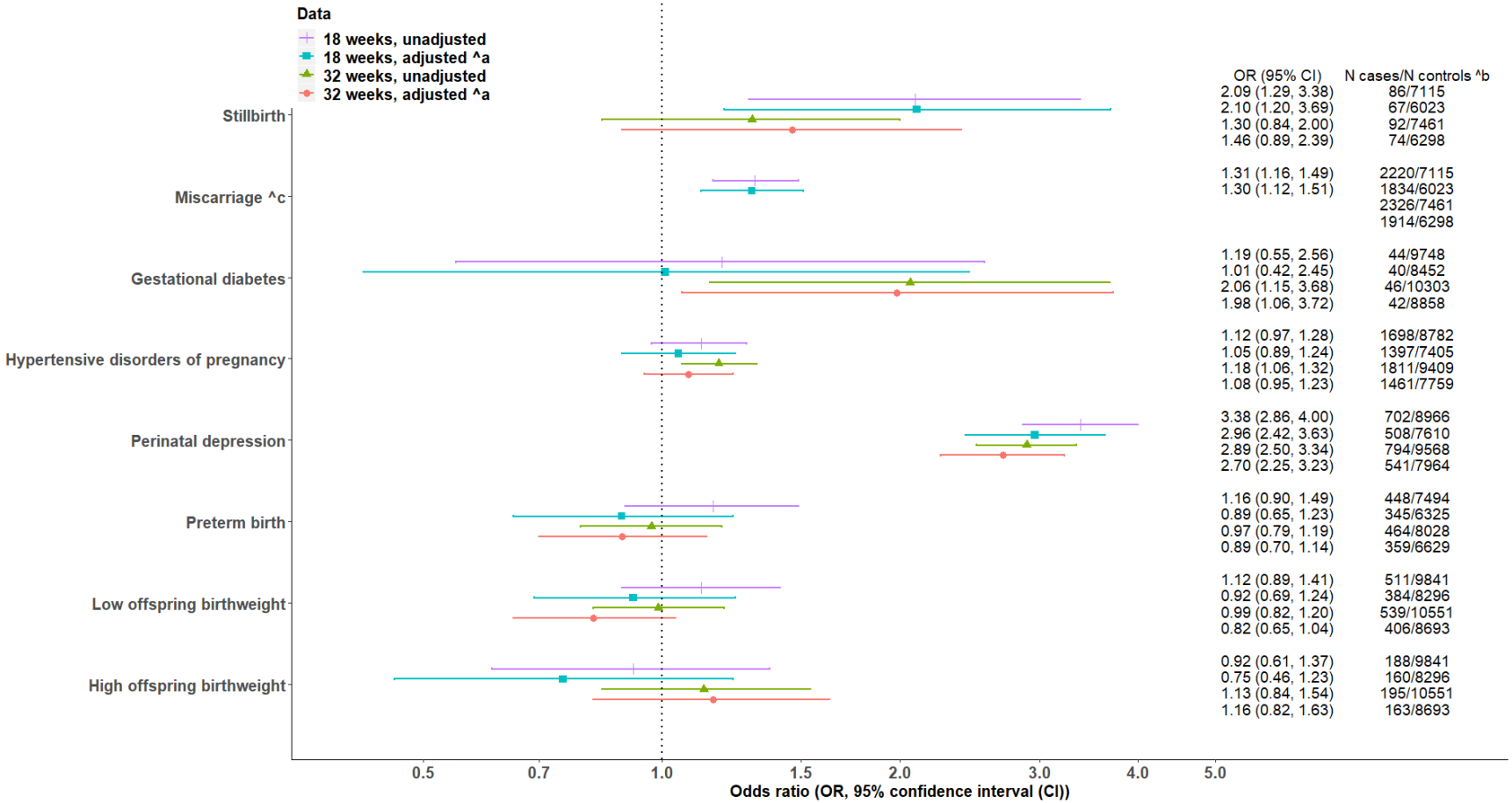
Fig 2. Two-sample Mendelian randomization (MR) estimates for causal effects of insomnia on adverse pregnancy and perinatal outcomes, meta-analysing UK Biobank, the birth cohorts, and FinnGen.



[a] For those outcomes that FinnGen did not contribute to.

[b] P-value for Cochran's Q-statistic <0.05 suggests between-study heterogeneity in the meta-analysis.

Fig 3. Multivariable regression associations of insomnia at 18 and 32 weeks of gestation with adverse pregnancy and perinatal outcomes in Avon Longitudinal Study of Parents and Children (ALSPAC).



[a] We adjusted for maternal age at time of delivery, education, body mass index at 12 weeks of gestation, smoking status in pregnancy and alcohol intake in the first three month of ALSPAC pregnancy, and household occupational social class.

[b] The numbers of women in adjusted models are slightly smaller than those in crude models due to missingness (<8%) in these covariates.

[c] We only report results for insomnia at 18 weeks for miscarriage as by definition that has to occur early in pregnancy (i.e. prior to 20-24 weeks of gestation in the different populations included in the analyses).

Table 1. Characteristics of the women in UK Biobank (UKB), Avon Longitudinal Study of Parents and Children (ALSPAC), Born in Bradford (BiB), Norwegian Mother, Father and Child Cohort Study (MoBa), and FinnGen.

Variable [a]	UKB (N=208,140)	ALSPAC (N=6,826)	BiB (N=2,940)	MoBa (N=14,584)	FinnGen (N=~123,579)
		Mean (standard deviation)			
Maternal age at delivery (years)	25.5 (4.6) [b]	28.7(4.7)	26.8 (6.0)	30.0 (4.4)	Not available
Maternal height (cm)	162.7 (6.2)	164.3 (6.7)	164.4 (6.1)	168.3 (5.5)	Not available
Maternal body mass index (kg/m^2)	27.0 (5.1)	22.9 (3.7)	26.7 (6.0)	24.0 (4.2)	Not available
Gestational age (weeks)	38.9 (3.8) [c]	39.6 (1.7)	39.7 (1.9)	39.6 (1.7)	Not available
Offspring birthweight (grams)	3186.7 (547.6)	3441.5 (523.0)	3357.9 (571.2)	3640.8 (513.4)	Not available
		N (%)			
Maternal education					
O levels/GCSEs or equivalent and below	91,093 (44.2)	4,043 (59.5)	1,400 (47.6)	260 (1.9)	Not available
A levels/AS levels or equivalent	48,059 (23.3)	1,719 (25.3)	485 (16.5)	4356 (31.8)	Not available
College or university degree	66,873 (32.5)	1,035 (15.2)	551 (18.7)	9072 (66.3)	Not available
Maternal ever smoking	85,501 (41.3)	1,450 (21.6) [d]	911 (31.0) [d]	1106 (8.8) [d]	Not available
Maternal ever drinking	191,010 (91.2)	4,580 (70.2) [d]	1,793 (61.0) [d]	3644 (29.7) [d]	Not available
Offspring sex, male	Not available	3,430 (50.2)	1,504 (51.2)	7412 (50.9)	Not available
Number with fetal genotype data	0	4,625 (67.8)	1,855 (63.1)	12,183 (83.5)	Not available
		N cases / N controls (Prevalence, %)			
Stillbirth	4907/139,034 (3.4)	48/4546 (1.0)	31/2588 (1.2)	51/9998 (0.5)	Not available
Miscarriage	42,717/139,034 (23.5)	1378/4546 (23.3)	14/2588 (0.5)	2677/9998 (21.1)	9113/89,340 (9.3)
Gestational diabetes	726/200,536 (0.4)	34/6283 (0.5)	136/2657 (4.9)	113/14,375 (0.8)	5687/117,892 (4.6)
Hypertensive disorders of pregnancy	2138/206,002 (1.0)	1099/5698 (16.2)	347/2159 (13.8)	1892/12,652 (13.0)	4255/114,735 (3.6)
Perinatal depression	5178/25,130 (17.1)	423/5896 (6.2)	312/2245 (12.2)	579/13,865 (4.0)	Not available
Preterm birth	556/4862 (10.3) [c]	285/4931 (5.5)	172/2706 (6.0)	495/12,846 (3.7)	5480/98,626 (5.3)
Low offspring birthweight	13,429/149,084 (8.3)	337/6376 (5.0)	167/2725 (5.8)	245/13,690 (1.8)	Not available
High offspring birthweight	2716/149,084 (1.8)	113/6376 (1.7)	42/2725 (1.5)	621/13,690 (4.3)	Not available

[a] In UKB, these variables were measured at the recruitment that is typically 31.1 years after pregnancy.

[b] We report maternal ages at giving their first live birth. UKB women were recruited with an average age of 56.5 (standard deviation 7.9) years.

[c] Gestational age was available only in a small subset of UKB women (N=7280).

[d] These were maternal ever smoking/drinking in pregnancy.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

References

1. Morin CM, Benca R. Chronic insomnia. Lancet. 2012; 379(9821):1129-41.
2. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007; 3(5 Suppl):S7-10.
3. Pengo MF, Won CH, Bourjeily G. Sleep in Women Across the Life Span. Chest. 2018; 154(1):196-206.
4. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev. 2018; 38:168-76.
5. Zhang X, Zhang R, Cheng L, Wang Y, Ding X, Fu J, et al. The effect of sleep impairment on gestational diabetes mellitus: a systematic review and meta-analysis of cohort studies. Sleep Med. 2020; 74:267-77.
6. Lu Q, Zhang X, Wang Y, Li J, Xu Y, Song X, et al. Sleep disturbances during pregnancy and adverse maternal and fetal outcomes: a systematic review and meta-analysis. Sleep Med Rev. 2020; 58:101436.
7. Yang Z, Zhu Z, Wang C, Zhang F, Zeng H. Association between adverse perinatal outcomes and sleep disturbances during pregnancy: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2020:1-9.
8. Warland J, Dorrian J, Morrison JL, O'Brien LM. Maternal sleep during pregnancy and poor fetal outcomes: A scoping review of the literature with meta-analysis. Sleep Med Rev. 2018; 41:197-219.
9. Cronin RS, Li M, Thompson JMD, Gordon A, Raynes-Greenow CH, Heazell AEP, et al. An Individual Participant Data Meta-analysis of Maternal Going-to-Sleep Position, Interactions with Fetal Vulnerability, and the Risk of Late Stillbirth. EClinicalMedicine. 2019; 10:49-57.
10. Anderson NH, Gordon A, Li M, Cronin RS, Thompson JMD, Raynes-Greenow CH, et al. Association of Supine Going-to-Sleep Position in Late Pregnancy With Reduced Birth Weight: A Secondary Analysis of an Individual Participant Data Meta-analysis. JAMA Netw Open. 2019; 2(10):e1912614.
11. Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. Efficacy of Digital Cognitive Behavioral Therapy for the Treatment of Insomnia Symptoms Among Pregnant Women: A Randomized Clinical Trial. JAMA Psychiatry. 2020; 77(5):484-92.
12. Manber R, Bei B, Simpson N, Asarnow L, Rangel E, Sit A, et al. Cognitive Behavioral Therapy for Prenatal Insomnia: A Randomized Controlled Trial. Obstet Gynecol. 2019; 133(5):911-9.
13. Kalmbach DA, Cheng P, O'Brien LM, Swanson LM, Sangha R, Sen S, et al. A randomized controlled trial of digital cognitive behavioral therapy for insomnia in pregnant women. Sleep Med. 2020; 72:82-92.
14. Davey Smith G, Lawlor DA, Harbord R, Timpson N, Day I, Ebrahim S. Clustered environments and randomized genes: a fundamental distinction between conventional and genetic epidemiology. PLoS Med. 2007; 4(12):e352.
15. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003; 32(1):1-22.
16. Lawlor DA. Commentary: Two-sample Mendelian randomization: opportunities and challenges. Int J Epidemiol. 2016; 45(3):908-15.
17. Yuan S, Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. Diabetologia. 2020; 63(11):2359-71.
18. Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR, et al. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet. 2019; 51(3):394-403.
19. van Oort S, Beulens JWJ, van Ballegooijen AJ, Grobbee DE, Larsson SC. Association of Cardiovascular Risk Factors and Lifestyle Behaviors With Hypertension: A Mendelian Randomization Study. Hypertension. 2020; 76(6):1971-9.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

20. Lane JM, Jones SE, Dashti HS, Wood AR, Aragam KG, van Hees VT, et al. Biological and clinical insights from genetics of insomnia symptoms. Nat Genet. 2019; 51(3):387-93.
21. Larsson SC, Markus HS. Genetic Liability to Insomnia and Cardiovascular Disease Risk. Circulation. 2019; 140(9):796-8.
22. Brand JS, Gaillard R, West J, McEachan RRC, Wright J, Voerman E, et al. Associations of maternal quitting, reducing, and continuing smoking during pregnancy with longitudinal fetal growth: Findings from Mendelian randomization and parental negative control studies. PLoS Med. 2019; 16(11):e1002972.
23. FinnGen. FinnGen Documentation of R5 release. 2021. Available from: https://finngen.gitbook.io/documentation/.
24. UK Biobank Hospital inpatient data Version 3.0. 2020. Available from: https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/HospitalEpisodeStatistics.pdf.
25. NealLab. We're thrilled to announce an updated GWAS analysis of the UK Biobank. 2018.
26. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife. 2018; 7.
27. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. Eur J Epidemiol. 2018; 33(10):947-52.
28. Henry A, Katsoulis M, Masi S, Fatemifar G, Denaxas S, Acosta D, et al. The relationship between sleep duration, cognition and dementia: a Mendelian randomization study. Int J Epidemiol. 2019; 48(3):849-60.
29. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet. 2018; 50(9):1335-41.
30. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum Mol Genet. 2018; 27(R2):R195-208.
31. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol. 2016; 40(4):304-14.
32. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015; 44(2):512-25.
33. Yang Q, Sanderson E, Tilling K, Borges MC, Lawlor DA. Exploring and mitigating potential bias when genetic instrumental variables are associated with multiple non-exposure traits in Mendelian randomization. medRxiv. 2019. Available from: https://www.medrxiv.org/content/10.1101/19009605v1.
34. Lawlor D, Richmond R, Warrington N, McMahon G, Davey Smith G, Bowden J, et al. Using Mendelian randomization to determine causal effects of maternal pregnancy (intrauterine) exposures on offspring outcomes: Sources of bias and methods for assessing them. Wellcome Open Res. 2017; 2:11.
35. Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2012; 21(3):223-42.
36. Ference BA, Bhatt DL, Catapano AL, Packard CJ, Graham I, Kaptoge S, et al. Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease. Jama. 2019; 322(14):1381-91.
37. Kivimäki M, Lawlor DA, Smith GD, Eklund C, Hurme M, Lehtimäki T, et al. Variants in the CRP gene as a measure of lifelong differences in average C-reactive protein levels: the Cardiovascular Risk in Young Finns Study, 1980-2001. Am J Epidemiol. 2007; 166(7):760-4.
38. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol. 2016; 45(6):1866-86.

medRxiv preprint doi: https://doi.org/10.1101/2021.10.07.21264689; this version posted October 10, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY 4.0 International license .

39. Bos MM, Goulding NJ, Lee MA, Hofman A, Bot M, Pool R, et al. Investigating the relationships between unfavourable habitual sleep and metabolomic traits: evidence from multi-cohort multivariable regression and Mendelian randomization analyses. BMC Med. 2021; 19(1):69.
40. Liu J, Richmond RC, Bowden J, Barry C, Dashti HS, Daghlas I, et al. Assessing the causal role of sleep traits on glycated haemoglobin: a Mendelian randomization study. medRxiv. 2021. Available from: https://www.medrxiv.org/content/10.1101/2020.12.18.20224733v2.
41. Labrecque J, Swanson SA. Understanding the Assumptions Underlying Instrumental Variable Analyses: a Brief Review of Falsification Strategies and Related Tools. Curr Epidemiol Rep. 2018; 5(3):214-20.
42. Hughes RA, Davies NM, Davey Smith G, Tilling K. Selection Bias When Estimating Average Treatment Effects Using One-sample Instrumental Variable Analysis. Epidemiology. 2019; 30(3):350-7.
43. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. Int J Epidemiol. 2018; 47(1):226-35.
44. Paternoster L, Tilling K, Davey Smith G. Genetic epidemiology and Mendelian randomization for informing disease therapeutics: Conceptual and methodological challenges. PLoS Genet. 2017; 13(10):e1006944.
45. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017; 186(9):1026-34.
46. Adams MJ, Hill WD, Howard DM, Dashti HS, Davis KAS, Campbell A, et al. Factors associated with sharing e-mail information and mental health survey participation in large population cohorts. Int J Epidemiol. 2020; 49(2):410-21.
47. Davis KAS, Coleman JRI, Adams M, Allen N, Breen G, Cullen B, et al. Mental health in UK Biobank - development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. BJPsych Open. 2020; 6(2):e18.
48. Mahmoud O, Dudbridge F, Davey Smith G, Munafò MR, Tilling K. Slope-Hunter: A robust method for index-event bias correction in genome-wide association studies of subsequent traits. bioRxiv. 2020. Available from: https://www.biorxiv.org/content/10.1101/2020.01.31.928077v1.full.
49. Caetano G, Bozinovic I, Dupont C, Léger D, Lévy R, Sermondade N. Impact of sleep on female and male reproductive functions: a systematic review. Fertil Steril. 2021; 115(3):715-31.
50. Barban N, Jansen R, de Vlaming R, Vaez A, Mandemakers JJ, Tropf FC, et al. Genome-wide analysis identifies 12 loci influencing human reproductive behavior. Nat Genet. 2016; 48(12):1462-72.
51. Gkatzionis A, Burgess S. Contextualizing selection bias in Mendelian randomization: how bad is it likely to be? Int J Epidemiol. 2019; 48(3):691-701.
52. van Smeden M, Lash TL, Groenwold RHH. Reflection on modern methods: five myths about measurement error in epidemiological research. Int J Epidemiol. 2020; 49(1):338-47.
53. Pierce BL, VanderWeele TJ. The effect of non-differential measurement error on bias, precision and power in Mendelian randomization studies. Int J Epidemiol. 2012; 41(5):1383-93.
54. Lawlor DA, Fraser A, Lindsay RS, Ness A, Dabelea D, Catalano P, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia. 2010; 53(1):89-97.
55. Hyppönen E, Power C. An intergenerational study of birthweight: investigating the birth order effect. Bjog. 2004; 111(4):377-9.
56. Ghosh RE, Berild JD, Sterrantino AF, Toledano MB, Hansell AL. Birth weight trends in England and Wales (1986-2012): babies are getting heavier. Arch Dis Child Fetal Neonatal Ed. 2018; 103(3):F264-f70.