The relation and mediation pathways of maternal hyperglycaemia and liability to gestational diabetes mellitus with neonatal outcomes: a two-sample Mendelian Randomization study

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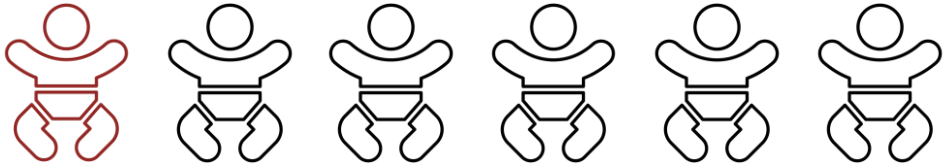
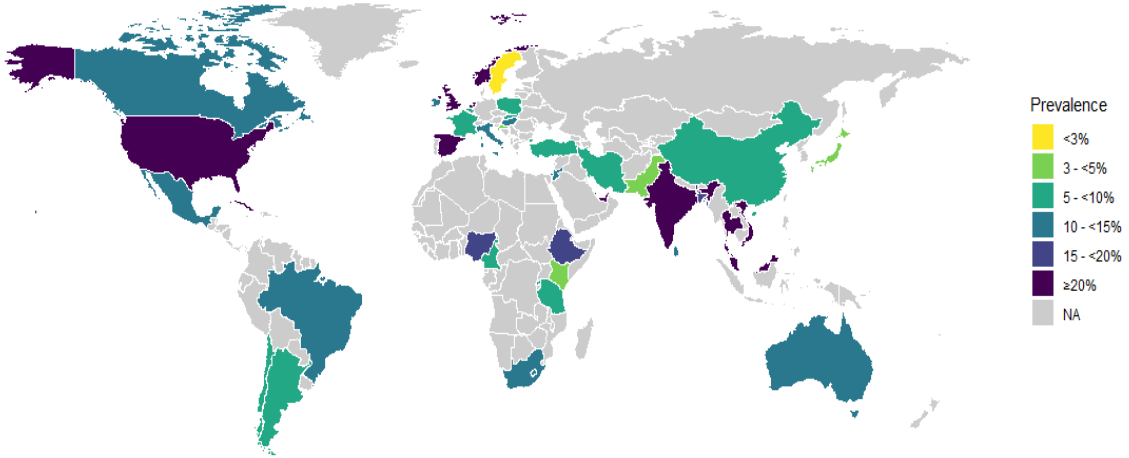
Background

Maternal hyperglycemia and adverse neonatal birth outcomes

Hyperglycaemia in pregnancy: either pre-existing diabetes, diabetes in pregnancy or gestational diabetes mellitus.
Gestational diabetes mellitus (GDM): mother without diabetes develop hyperglycemia during pregnancy.

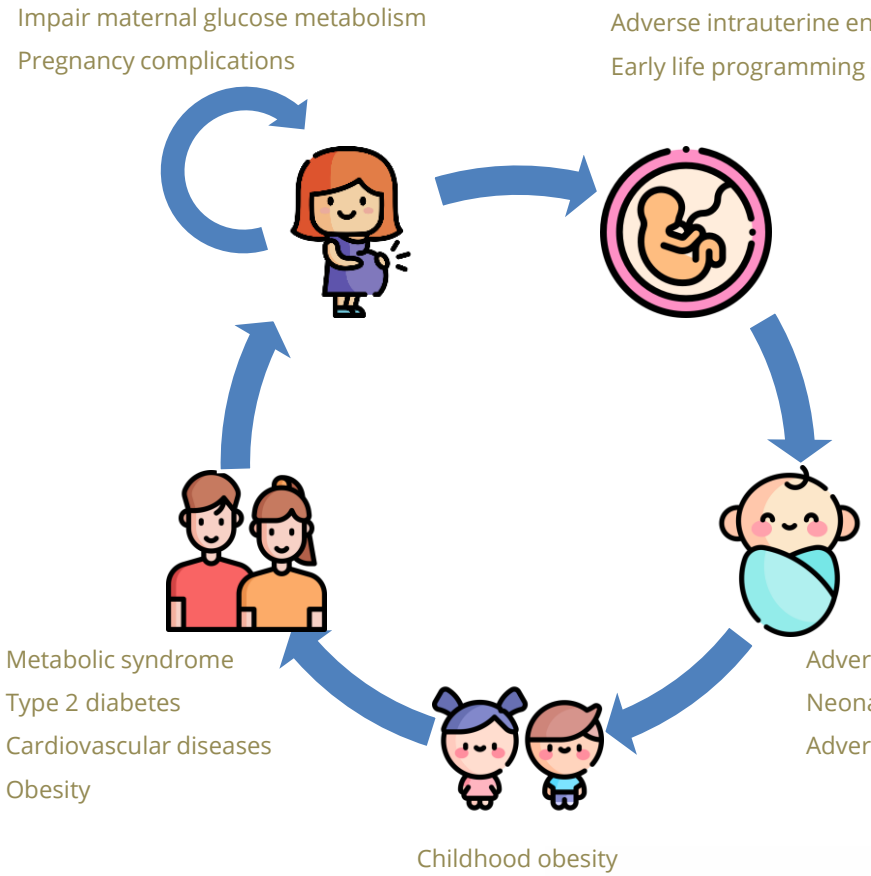
Affecting 1 in every 6 live birth





(Data source: IDF, 2021)

Potential effect on maternal and offspring health



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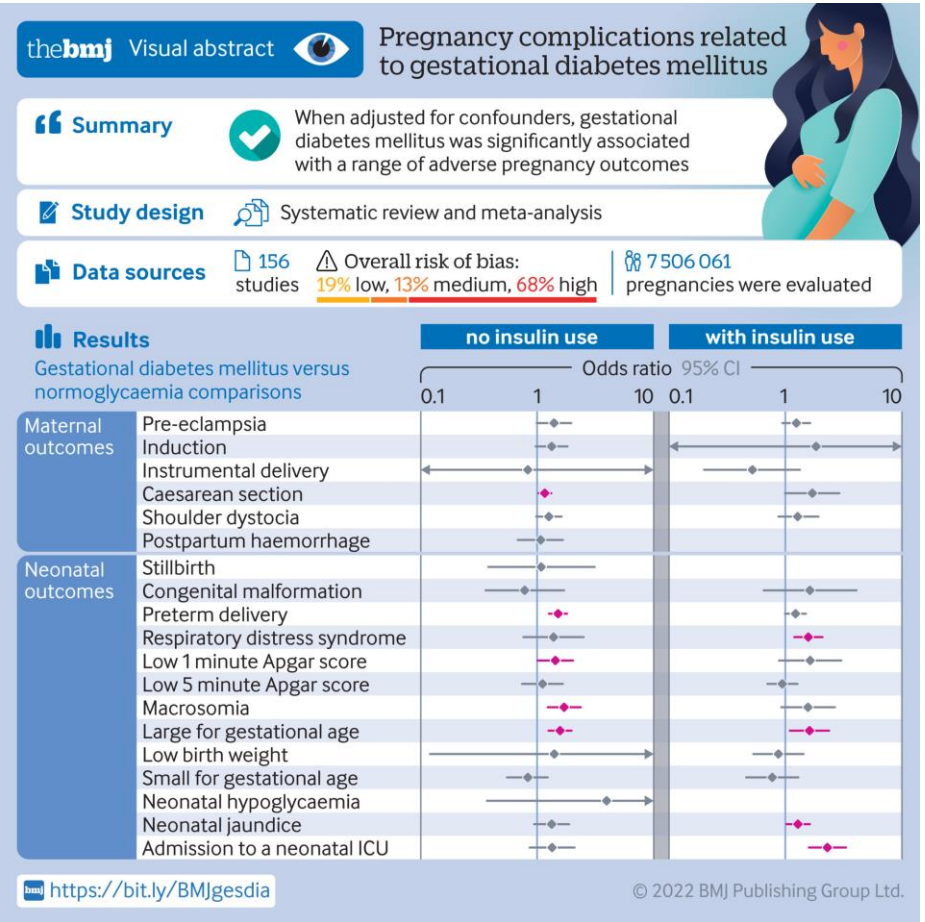
Background

Evidence were limited on maternal hyperglycemia with neonatal birth outcomes.

Evidence from observational studies

(Possibly confounded)



(W. Ye et al. 2020). *BMJ*

Evidence from RCTs

(Small sample size, unclear mechanism)

Table 3 Neonatal outcomes of metformin use during pregnancy

Study	Type	Indication	Control group	GA	PB	CA	BW	MS	LGA	SGA	NH	APGAR	NICU	RDS
Rowan et al. (MiG) [8]	RCT	GDM	Insulin	↓	↑		↔				↓	↔		↔
Niromanesh et al. [75]	RCT	GDM	Insulin	↔	↔	↔	↓	↔	↓	↔	↔	↔	↔	↔
Spaulonci et al. [76]	RCT	GDM	Insulin	↔		↔		↔			↓	↔		↔
Tertti et al. [26]	RCT	GDM	Insulin	↔	↔		↔					↔	↔	
Ainuddinn et al. [10]	RCT	GDM	Insulin				↓		↔	↔	↓	↓		
Rowan et al. (MiG TOFU) [22]	RCT	GDM	Insulin	↓	↔		↔		↑	↔				
Eid et al. [27]	RCT	GDM	Insulin	↔	↔	↔	↓	↓	↓	↔	↓	↔	↔	↔
Gui et al. [29]	SR/MA	GDM	Insulin	↓	↑	↔	↔		↔	↔	↔	↔	↔	↔
Balsells et al. [30]	SR/MA	GDM	Insulin	↓	↑		↔	↔	↔	↔	↔[a]	↔	↔	↔
Feng et al. [28]	SR/MA	GDM	Insulin		↓				↔		↓			↔
Guo et al. [20]	SR/MA	GDM	Insulin	↓	↔	↔	↓	↓	↔	↔	↓	↔	↓	↔
Tarry-Adkins et al. [57]	SR/MA	GDM	Insulin				↓	↓	↓	↔				
Wang X. et al. [38]	SR/MA	GDM	Insulin	↓	↔	↔	↓	↓	↓	↔	↓	↔	↓	↔
Ara Ainuddin et al. [9]	RCT	T2DM	Insulin	↔			↔	↔		↑	↔[b]	↔	↓	
Feig et al. (MiTy) [31]	RCT	T2DM	Placebo + insulin	↔	↔	↔	↓		↔	↑	↔			↔
Lin et al. [55]	Cohort	T2DM	Insulin		↔	↓			↔	↔		↔		
Vanky et al. (PregMet) [43]	RCT	PCOS	Placebo		↔		↔					↔		
Løvvik et al. (PregMet2) [24]	RCT	PCOS	Placebo	↔	↔									
Zeng et al. [44]	SR/MA	PCOS	Placebo		↓									
Syngelaki et al. [17]	RCT	Obesity	Placebo		↔		↔		↔		↔	↔	↔	↔
Dodd et al. (GRoW) [47]	RCT	Overweight, obesity	Placebo	↔	↔		↔		↔	↔			↔	
Gilbert et al. [21]	SR/MA	PCOS, diabetes	No Met exposure			↓								
Given et al. [56]	Case-control	Diabetes, PCOS, infertility or combination	No Met exposure			↔								↓
Diav-Citrin et al. [53]	Cohort	PCOS, T2DM	Insulin and non-teratogenic exposure		↔	↔								
Scherneck et al. [54]	Cohort	PCOS/ Fertility, diabetes, insulin resistance	No Met exposure		↔	↔	↔							
Brand et al. [19]	Cohort	PCOS, GDM, T2DM	Insulin		↔	↔	↓		↔	↑	↔			

BW birth weight, *CA* congenital anomalies, *GA* gestational age at delivery, *GDM* gestational diabetes mellitus, *LGA* large-for-gestational age, *Met* metformin, *MS* macrosomia, *NH* neonatal hypoglycemia, *NICU* admission to neonatal intensive care unit, *PB* preterm birth, *PCOS* polycystic ovary syndrome, *RCT* randomized controlled trial, *RDS* respiratory distress syndrome, *SGA* small-for-gestational age, *SR/MA* systematic review and meta-analysis, *T2DM* type 2 diabetes mellitus

↑ significant increase, ↓ significant reduction, ↔ no significant difference

[a]Significantly lower incidence of severe neonatal hypoglycemia was found in the metformin group compared with the insulin group. Severe neonatal hypoglycemia was defined by authors or by requiring intravenous glucose or NICU admission

[b]Significantly less neonatal hypoglycemia was found in the metformin

(S. A. Paschou et al. 2023). *Endocrine*

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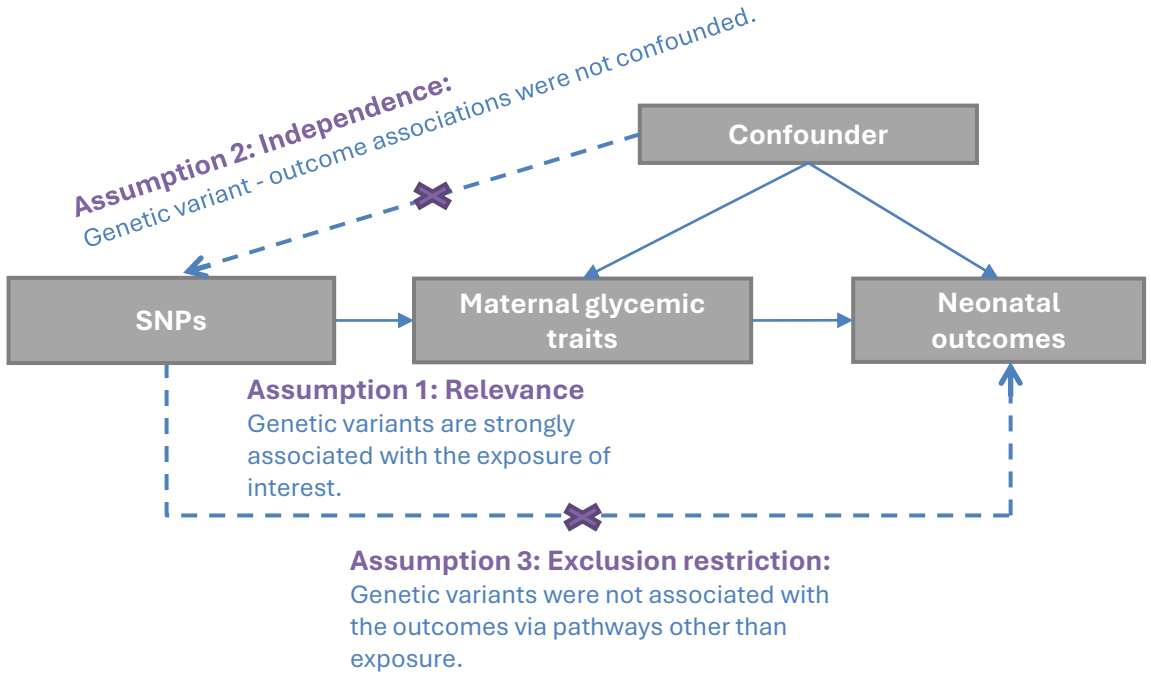
Background

MR study on maternal hyperglycemia and adverse neonatal birth outcomes

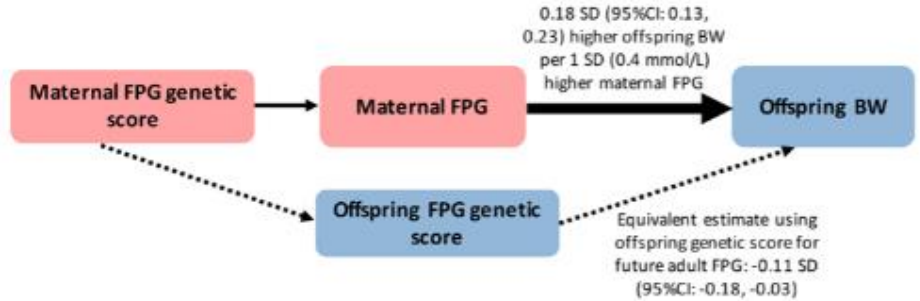
Mendelian randomization (MR) study, a design more robust to confounding due to use of genetics randomly allocated at conception. Is increasingly used to explore



Evidence from Previous MR study

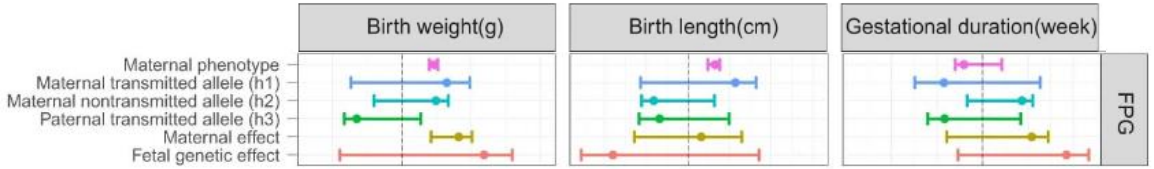
(only a few glycemic traits, without exploring mechanism)

EGG meta-analysis with the UK Biobank



(N.M. Warrington et al. 2019). *Nature Genetics*

The Born in Guangzhou Cohort study



(S. Huang et al. 2024). *Nature*

Research aims:

1. Comprehensively the association of maternal hyperglycemia and neonatal birth outcomes (Analysis I)
2. Assess the potential mediation pathways via placental weight and gestational hypertension (Analysis II)

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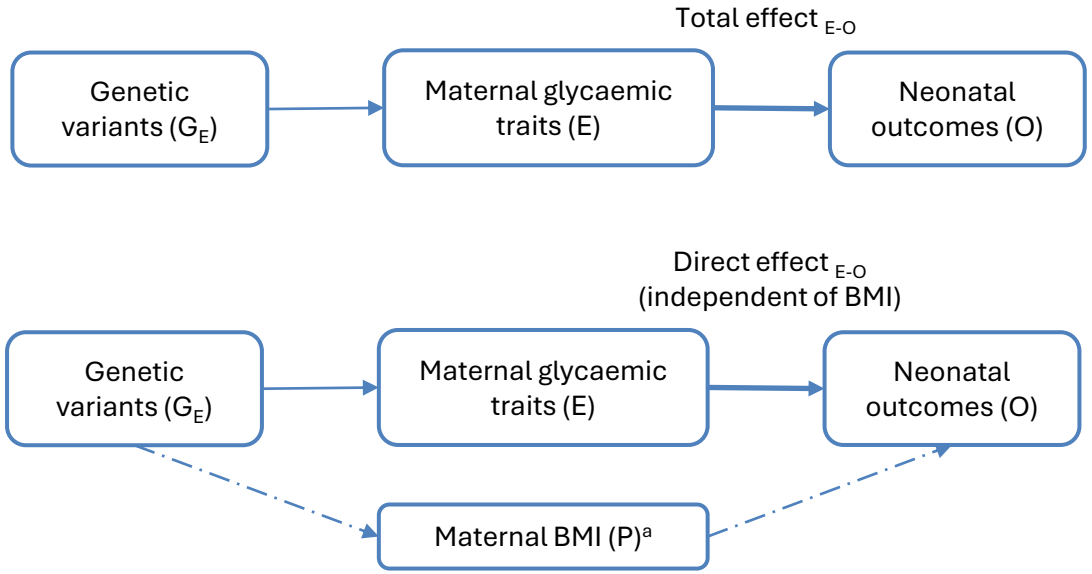
Method

Analysis 1: MR analysis for total effect of maternal glycemic traits on neonatal outcomes

Study design: 2-sample MR



a. SNPs for maternal BMI extracted from a meta analysis of GIANT consortium and UK Biobank (women only, n= 434,794)

Main analysis: Inverse variance weighted (IVW)
Sensitivity analysis: Weighted Median, MR Egger, MR-RAPs, MVMR adjusted for BMI.

Genetic instruments of maternal glycaemic traits ($P<5*10^{-8}$, $r2<0.001$):

Traits, unit	Data source	Women-specific	Sample size	N_{SNP}	R^2	F
Fasting glucose (FG), mmol/L	MAGIC consortium	Yes	73,089	21	3.0%	100.8
Fasting insulin (FI), pmol/L		Yes	50,404	4	0.3%	33.1
Insulin sensitivity index (ISI), SD		No	53,657	8	0.7%	107.0
Insulin fold change (IFC), SD		No	53,287	4	0.3%	248.0
Glycated hemoglobin (HbA1c), SD	UK Biobank	Yes	185,022	199	11.3%	45.3
Liability to gestational diabetes mellitus (GDM), log odds	Finngen (R8)	Yes	Case: 12,332 Control:131,109	10	1.7%	46.0
Liability to type 2 diabetes (T2D), log odds	DIAMANTE	No	Case: 80.154 Control:131,109	87	4.5%	226.3

Maternal genetic association with neonatal outcomes:

Traits, unit	Data source	Sample size
Maternal genetics driven offspring birth weight, SD	EGG consortium combined with other large cohorts	Own birth weight: 297,359 Offspring birth weight: 210,248
Gestational duration, days		151,987
Preterm birth, log odds		233, 290 (Case:15,419)
Post-term birth, log odds		131,279 (Case:15,972)
Sporadic miscarriage, log odds	GWAS from T. Laisk et al.	224,105 (Case: 49,996)

Gestational duration, preterm and post-term birth were limited to spontaneous deliveries.

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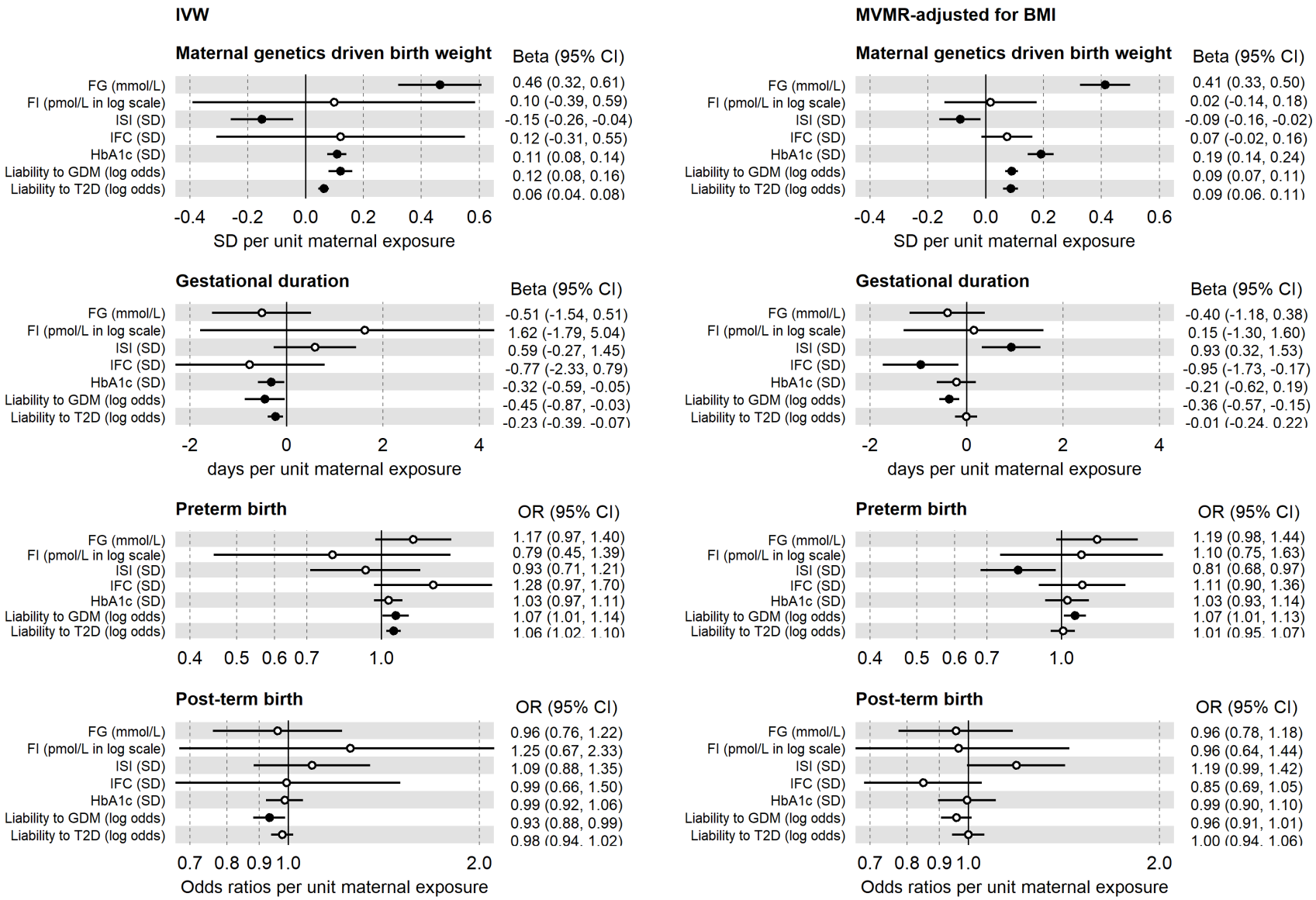
Results

Analysis 1: MR analysis for total effect of maternal glycemic traits on neonatal outcomes



FG - Fasting glucose; FI - Fasting insulin; ISI - insulin sensitivity index; IFC - insulin fold change; HbA1c - Glycated haemoglobin; GDM - Gestational diabetes; T2D - Type 2 diabetes

Total effect $_{E\text{-}O}$

Maternal hyperglycaemia, lower insulin sensitivity, and liability to GDM and T2D were associated with higher birth weight.

Liability to T2D was associated with preterm birth and shorter gestational duration (not exist after adjusted for BMI).

Liability to GDM and lower insulin sensitivity is linked with higher preterm birth and shorter gestational duration (after adjusted for BMI).

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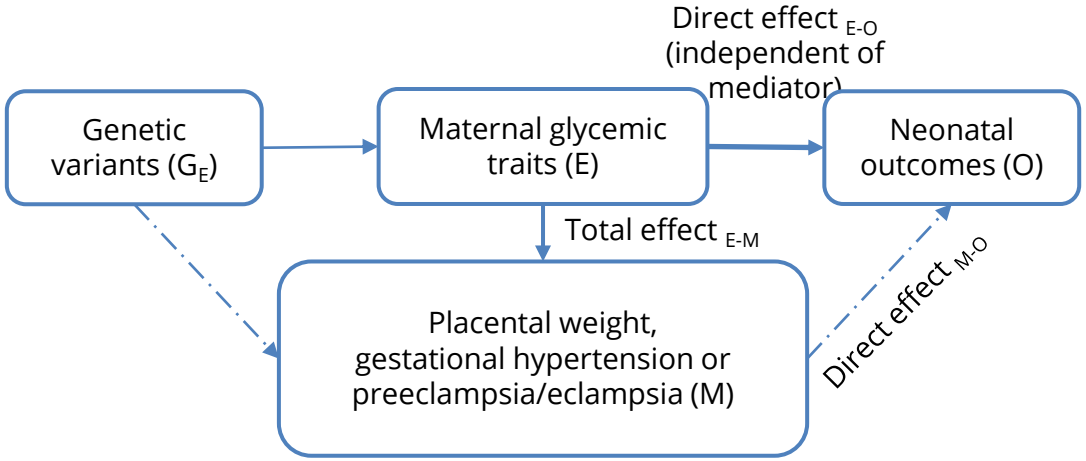
Method

Analysis 2: Mediation pathways via placental growth and gestational hypertension

Study design: 2-step MR and MVMR

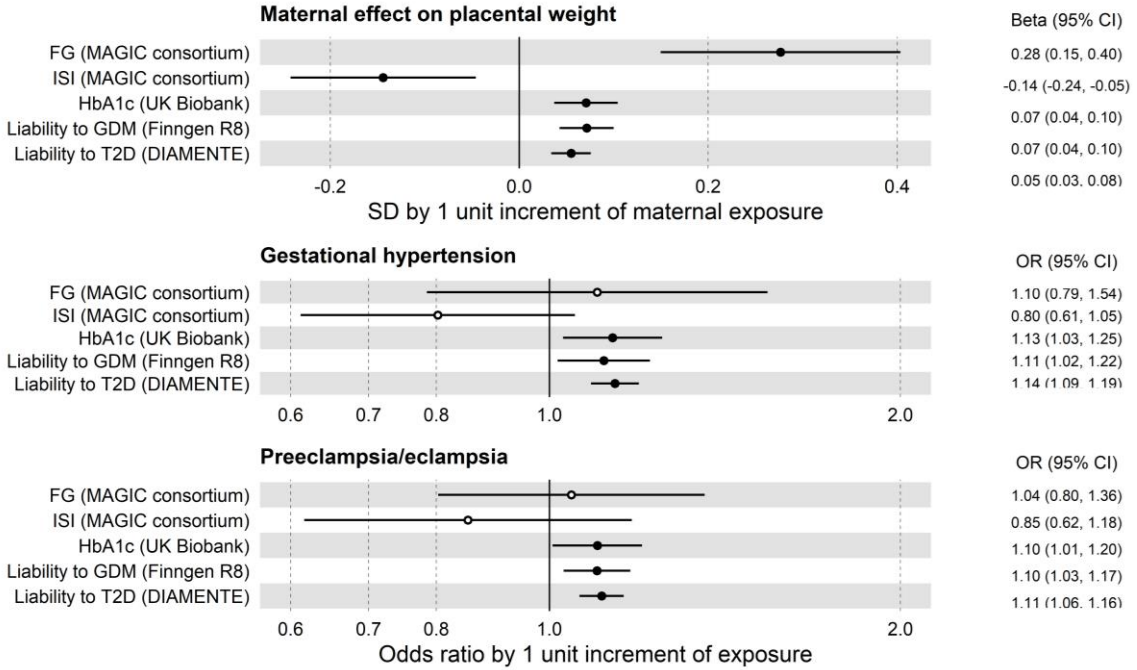


Main analysis: Product of the coefficient methods

Genetic association of putative mediators:

Traits, unit	Data source	Women-specific	Sample size
Placental weight (maternal effect), SD	EGG consortium	Yes	Fetal GWAS: 65,405; Maternal GWAS: 61,228
Gestational hypertension, log odds	GWAS data from M. C. Honigberg et al.	Yes	Case: 11,027 Control: 417,788
Preeclampsia/eclampsia, log odds		No	Case: 17,150 Control: 451,241

Step 1: Total effect $_{E\text{-}M}$



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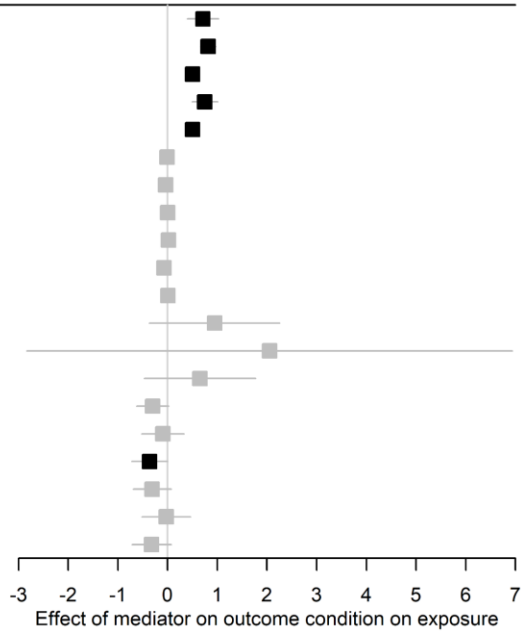
Results

Analysis 2: Mediation analysis using 2-step MR design

Step 2: Direct effect $_{M\text{-}O}$

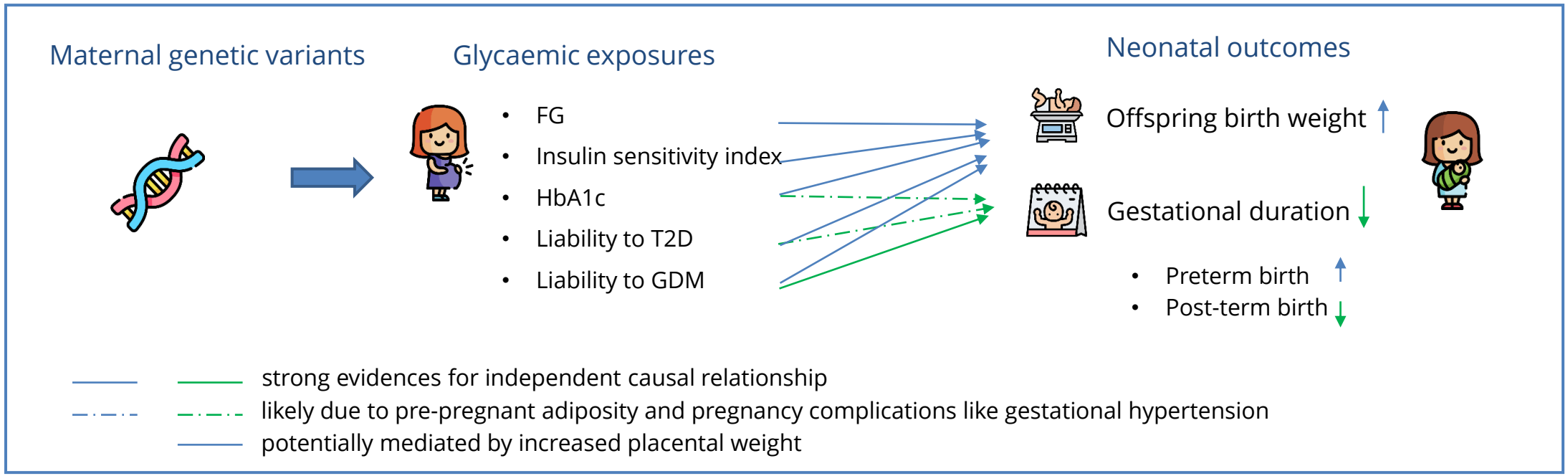
Mediator	Outcome	Adjusted for	Beta	95%CI
Placental weight(SD)	Offspring birthweight (SD)	FG (mmol/L)	0.71	0.40 to 1.02
Placental weight(SD)	Offspring birthweight (SD)	ISI (SD)	0.82	0.67 to 0.97
Placental weight(SD)	Offspring birthweight (SD)	HbA1c (SD)	0.50	0.38 to 0.63
Placental weight(SD)	Offspring birthweight (SD)	Liability to GDM (log odds)	0.75	0.49 to 1.00
Placental weight(SD)	Offspring birthweight (SD)	Liability to T2D (log odds)	0.50	0.40 to 0.60
Liability to gestational hypertension (log odds)	Offspring birthweight (SD)	HbA1c (SD)	-0.01	-0.05 to 0.03
Liability to gestational hypertension (log odds)	Offspring birthweight (SD)	Liability to GDM (log odds)	-0.04	-0.10 to 0.02
Liability to gestational hypertension (log odds)	Offspring birthweight (SD)	Liability to T2D (log odds)	0.00	-0.04 to 0.04
Liability to preeclampsia/eclampsia (log odds)	Offspring birthweight (SD)	HbA1c (SD)	0.02	-0.03 to 0.07
Liability to preeclampsia/eclampsia (log odds)	Offspring birthweight (SD)	Liability to GDM (log odds)	-0.07	-0.16 to 0.02
Liability to preeclampsia/eclampsia (log odds)	Offspring birthweight (SD)	Liability to T2D (log odds)	0.01	-0.04 to 0.06
Placental weight(SD)	Gestational duration (days)	HbA1c (SD)	0.95	-0.37 to 2.26
Placental weight(SD)	Gestational duration (days)	Liability to GDM (log odds)	2.05	-2.83 to 6.94
Placental weight(SD)	Gestational duration (days)	Liability to T2D (log odds)	0.65	-0.47 to 1.77
Liability to gestational hypertension (log odds)	Gestational duration (days)	HbA1c (SD)	-0.30	-0.62 to 0.02
Liability to gestational hypertension (log odds)	Gestational duration (days)	Liability to GDM (log odds)	-0.10	-0.52 to 0.33
Liability to gestational hypertension (log odds)	Gestational duration (days)	Liability to T2D (log odds)	-0.36	-0.72 to 0.00
Liability to preeclampsia/eclampsia (log odds)	Gestational duration (days)	HbA1c (SD)	-0.31	-0.69 to 0.07
Liability to preeclampsia/eclampsia (log odds)	Gestational duration (days)	Liability to GDM (log odds)	-0.03	-0.52 to 0.46
Liability to preeclampsia/eclampsia (log odds)	Gestational duration (days)	Liability to T2D (log odds)	-0.32	-0.71 to 0.07



Identified mediation pathways			Total effect $_{E\text{-}O}$	Direct effect $_{E\text{-}O}$	Indirect effect $_{E\text{-}M\text{-}O}$	Proportion attenuated
Exposure (E)	Mediators (M)	Outcomes (O)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Proportion (95% CI)
FG (mmol/L)	Placental weight (SD)	Offspring birthweight (SD)	0.46 (0.32 to 0.61)	0.26 (0.09 to 0.44)	0.20 (0.07 to 0.32)	42.3% (18.9% to 65.6%)
ISI (SD)			-0.15 (-0.26 to -0.04)	-0.03 (-0.13 to 0.06)	-0.12 (-0.20 to -0.03)	77.7% (22.7% to 132.7%)
HbA1c (SD)			0.11 (0.08 to 0.14)	0.07 (0.04 to 0.10)	0.04 (0.02 to 0.05)	32.8% (17.5% to 48.1%)
Liability to GDM (log odds)			0.12 (0.08 to 0.16)	0.05 (0.00 to 0.10)	0.05 (0.03 to 0.08)	44.5% (23.9% to 65.1%)
Liability to T2D (log odds)			0.06 (0.04 to 0.08)	0.03 (0.02 to 0.05)	0.03 (0.02 to 0.04)	44.3% (27.3% to 61.3%)
Liability to T2D (log odds)	Liability to gestational hypertension (log odds)	Gestational duration (days)	-0.23 (-0.39 to -0.07)	-0.17 (-0.33 to 0.00)	-0.05 (-0.10 to 0.00)	20.4% (1.5% to 39.4%)

Discussion

GDM and adverse neonatal birth outcomes



Possible mechanism:

Excessive placental growth → Increased placental glucose transfer → Excessive birth weight (macrosomia)

Adverse maternal health conditions & Distension demand posed on the uterus to excessive fetal growth velocity → Spontaneous preterm birth

Limitations:

- MR depends on stringent assumptions.
- Cannot assess exposure-mediator interactions.
- Lack of generalizability to other populations
- Limited understanding of long-term offspring health outcomes.

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Acknowledgement

GDM and adverse neonatal birth outcomes

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Teammates

Data sources

Published GWAS:
(T Laisk. et al. 2020) *Nature communication*
(M. C. Honigberg et al. 2023) *Nature Medicine*

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