Genetically determined body mass index and maternal outcomes of pregnancy: a two-sample Mendelian randomization study

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Abstract

Objective: Observational studies have described associations between obesity and adverse outcomes of pregnancy. Mendelian randomization (MR) takes advantage of the 'natural' genetic randomization to risk of an exposure such as body mass index (BMI) to study the effects of the exposure on outcomes. Similar to randomization in a clinical trial, this limits the potential for confounding and bias.

Design: A two-sample MR study.

Setting: Summary statistics from published genome wide association studies (GWAS) in European ancestry populations.

Population or Sample: Instrumental variants for body mass index (BMI) were obtained from a study on 434,794 females. Female-specific genetic association estimates for outcomes were extracted from the sixth round of analysis of the FINNGEN cohort data.

Methods: Inverse-variance weighted MR was used to assess the association between BMI and all outcomes. Sensitivity analyses with weighted median and MR-Egger were also performed.

Results: A 1-SD increase in BMI was associated with higher risk of pre-eclampsia (OR 1.68, 95%CI 1.46-1.94, $p=8.74x10^{-13}$), gestational diabetes (OR 1.67, 95%CI 1.46-1.92, $p=5.35x10^{-14}$), polyhydramnios (OR 1.40, 95%CI 1.00-1.96, p=0.049). There was evidence suggestive of a potential association with higher risk of premature rupture of membranes (OR 1.16, 95%CI 1.00-1.36, p=0.050) and postpartum depression (OR 1.12, 95%CI 0.99-1.27, p=0.062).

Conclusions: Higher maternal BMI is associated with marked increase in risk of pre-eclampsia, gestational diabetes and polyhydramnios. The relationship between BMI and premature rupture of membranes and postpartum depression should be assessed in further

studies. Our study supports efforts to target BMI as a cardinal risk factor for maternal morbidity in pregnancy.

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Keywords: body mass index, pregnancy, outcomes, pre-eclampsia, gestational diabetes

Introduction

Obesity, defined as a body mass index (BMI) >30 kg/m^2, is becoming an increasingly common finding in women if reproductive age in high-income counties[1.] In the United Kingdom the National Maternity and Perinatal Audit 2016/2017 (NMPA) reported that for the first time that more than half of women were overweight or obese at booking[2]. Being overweight or obese in pregnancy is associated with an increased risk of several serious adverse outcomes including miscarriage[3], fetal congenital abnormality[4], gestational diabetes[5], thromboembolism[6], post-partum haemorrhage[7], still-birth[8], increase caesarean section rate[9] and pre-eclampsia[10]. Moreover, obesity is a risk factor for maternal death with the most recent confidential enquiry reporting that 72% of the women who died were overweight or obese[2].

However, evidence from observational studies on the effects of BMI on obstetric outcomes is limited due to issues relating to the high potential for residual confounding and bias in these study designs. Obesity often co-exists not only with other cardiometabolic conditions, but with educational, socio-economic and lifestyle factors such as smoking, diet, exercise and mental health[11]. These confounding factors are complex constructs and can be notoriously difficult to measure accurately[12]. Therefore, estimates of causal effects of obesity and pregnancy outcomes using traditional analytic techniques adjusting for confounders can be subject to residual influence by confounding. Mendelian Randomisation (MR) offers considerable opportunity to overcome these limitations[13–15]. This technique leverages the natural randomisation to a high or low genetic risk for a disease (e.g., obesity) that occurs at the time of conception, and uses this in a similar way to randomisation in a clinical. The genetic factors are utilised in an instrumental variable analysis framework, under a certain set of assumptions, to estimate the effect of an exposure on an outcome.

This study aims to use MR to evaluate the potentially causal effect of BMI on the risk of multiple adverse maternal and foetal outcomes of pregnancy.

Methods

Ethical approval, data availability and reporting

Data used in this study is publicly available and all relevant sources are cited. This study is reported according to recommendations in the STROBE-MR Guidelines[16]. Statistical analysis was carried out using R version 4.0.4 (2021-02-15)[17].

Data sources

Female-specific genetic association estimates for BMI were extracted Pulit et al's genome-wide association study (GWAS) meta-analysis of in UK Biobank and Genetic Investigation of ANthropometric Traits (GIANT) data, on a total of 434,794 females of European ancestry[18].

Genetic association estimates for all outcomes were extracted from the sixth round of analysis of the FINNGEN consortium (https://finngen.gitbook.io/documentation), and include the outcomes of pre-eclampsia and eclampsia (n=4,743 cases), intrahepatic cholestasis of pregnancy (n=1,177 cases), gestational diabetes (n=7,676 cases), polyhydramnios (n=718 cases), placenta praevia (n=725 cases), placental abruption (n=376 cases), fetal distress in labour (n=4,586 cases), premature rupture of membranes (n=3,923 cases), preterm labour and delivery (n=6,736 cases), prolonged pregnancy (n=2,393 cases), postpartum haemorrhage (n=4,714 cases), spontaneous abortion and postpartum depression (n=9,392 cases). Figure 1 displays the study design flowchart and Table 1 outlines further details of the data sources.

Instrumental variable selection

Instrumental SNPs were selected if they had been associated with body mass index at genome-wide significance ($p<5x10^{-8}$). Furthermore, SNPs were selected if they were in pair-wise linkage disequilibrium (LD) with r^2 <0.001; harmonisation and clumping were performed

using TwoSample MR package in R[14]. All analyses were performed using the MendelianRandomisation package in R[19].

Statistical analysis

Inverse-variance weighted (IVW) MR was used as the primary analysis. Effect estimates are presented as odds ratios (OR) and corresponding 95% confidence intervals (CI) and reflect the effect of a 1-SD increase in genetically predicted BMI on risk of the outocome. MR-Egger and weighted median MR were used as sensitivity analyses to check consistency in size and direction of IVW MR effect estimates accounting for potential pleiotropy[20,21]. Pleiotropy describes a situation where a genetic instrument acts through additional pathways to the exposure being studied (e.g., if a SNP influences both BMI and insulin resistance, this represents a pleiotropic pathway for the outcome of gestational diabetes).

In brief, the weighted median approach works by ranking MR estimates for each variant based on their precision, selecting the median of these as the overall MR estimate, and subsequently calculating standard errors for this estimate by bootstrapping[21]. The MR-Egger approach instead is particularly useful in assessing whether a variant has pleiotropic effects on the outcome diverging from zero (directional pleiotropy)[22]. These analyses were chosen as they rely on different assumptions for valid inferences.

Results

Higher genetically predicted maternal BMI (1-SD increase) was associated with higher risk of pre-eclampsia (OR 1.68, 95%CI 1.46-1.94, $p=8.74x10^{-13}$), gestational diabetes (OR 1.67, 95%CI 1.46-1.92, $p=5.35x10^{-14}$), polyhydramnios (OR 1.40, 95%CI 1.00-1.96, p=0.049). There was evidence suggestive of a potential association with higher risk of premature rupture of membranes (OR 1.16, 95%CI 1.00-1.36, p=0.050) and postpartum depression (OR 1.12, 95%CI 0.99-1.27, p=0.062).

There was no evidence of an association between maternal BMI and intrahepatic cholestasis (OR 0.84, 95%CI 0.63-1.11, p=0.224), placenta praevia (OR 0.82, 95%CI 0.59-1.15, p=0.255), placental abruption (OR 1.31, 95%CI 0.83-2.09, p=0.250), fetal distress in labour (OR 0.92, 95%CI 0.79-1.07, p=0.296), preterm labour and delivery (OR 1.01, 95%CI 0.90-1.14, p=0.832), prolonged pregnancy (OR 1.02, 95%CI 0.84-1.23, p=0.871), postpartum haemorrhage (OR 1.00, 95%CI 0.87-1.15, p=0.982), or spontaneous abortion (OR 1.05, 95%CI 0.96-1.15, p=0.271). The results are displayed in Figure 2 and Table 2.

Sensitivity analyses were consistent with the results of the main analysis for pre-eclampsia (Weighted median OR 1.86, 95%ci 1.49 to 2.31, p=2x79x10-8; MR-Egger OR 2.34, 95%CI 1.55 to 3.54, p=6.49x10-5, intercept p=0.09), gestational diabetes (Weighted median OR 1.83, 95%CI 1.51-2.22, p=5.8z10-10; MR-Egger OR 2.05, 95%CI 1.38 to 3.02, p=3.82x10-4, intercept p=0.287) and polyhydramnios (Weighted median or 1.17, OR 0.68 to 2.00, p=0.575; MR-Egger OR 1.16, 95%CI 0.43 to 3.07, p=0.772, intercept p=0.682). The results of all sensitivity analyses are reported in Table S1.

Discussion

In this study we explored the association between BMI and maternal and fetal outcomes using MR in a mostly Caucasian population. Our results demonstrated that genetically predicted BMI is associated with a higher risk of developing pre-eclampsia, gestational diabetes, and polyhydramnios. There was also evidence suggestive of a potential association with higher risk of premature rupture of membranes and post-partum depression. The results of this study provide important information for clinical risk stratification, and support the role of reduction of obesity in prevention maternal morbidity during pregnancy.

Impact of BMI on preeclampsia

Preeclampsia is a disease characterised by hypertension, peripheral oedema and proteinuria occurring after 20-weeks' gestation and is a leading cause of maternal death in developed countries[23]. Previous studies have shown that there is a direct correlation between increasing BMI and risk of developing preeclampsia[10,24–26]. In a prospective cohort study in the United States similarly consisting of a majority Caucasian population, compared with women with a BMI of 21kg/m2, the risk of preeclampsia doubles at a BMI of 26kg/m2, triples at a BMI of 30kg/m2 and increases further with severe obesity[26]. Although the mechanism by which being overweight and development of preeclampsia are associated is not well understood, several theories have been suggested to explain the pathogenesis. One theory is the connection between preeclampsia and insulin resistance[10,27]. Obesity and insulin resistance leading to hyperinsulinemia, a characteristic feature of the metabolic syndrome, and this may in turn cause endothelial dysfunction and overexpression of angiotensin receptors, a key driver of the pathogenesis of preeclampsia[28].

Impact of BMI on gestational diabetes

The impact of obesity on insulin resistance is well described[29], and insulin resistance prior to pregnancy is a key risk factor for development of gestational diabetes. Consistent with this knowledge, our study found that increased maternal BMI was associated with an increased risk of gestational diabetes. Gestational diabetes is a condition characterized by elevated blood glucose during pregnancy which typically resolves after birth. Observational studies have previously described higher risk of gestational diabetes in women with pre-existing obesity: for example, a large population-based mixed-ethnicity cohort of 96,801 singleton births found that both overweight and obese women had a markedly increased risk of gestational diabetes[24]. Furthermore, studies have previously shown that gestational diabetes is often accompanied by other maternal morbidity in pregnancy, including preeclampsia[30]. Despite this clinical association, it remains unclear whether these two conditions are simply associated by confounding due to their strong shared risk factor profile, or whether true causal pathways exist between one disease and the other. The latter option would have important implications for clinical risk stratification, as it implies that gestational diabetes itself is a risk factor for preeclampsia, or that preeclampsia is a risk factor for gestational diabetes. In the phenocode-based survival analysis of the FINNGEN R6 endpoints, a strong association was indeed observed between the two conditions: women with preeclampsia had significantly higher hazard of developing gestational diabetes both before preeclampsia diagnosis (HR 14.82, 95%CI 12.60-17.43, $p<1x10^{-100}$) and after (HR 3.98, 95%CI 3.20-4.94,$p= 1.1x10^{-35}$). However, these analyses are not adjusted for baseline risk factors, and therefore do not provide meaningful information on whether this association is independent of factors such as ethnicity. Due to lack of availability of sufficient instruments from diverse data sources, multivariable MR could not be performed to address this question in our study. This remains a key direction for future research, once sufficient data is available.

Impact of BMI on polyhydramnios

There is an important shared aetiological basis for gestational diabetes and preeclampsia[31,32] . Among the risk factors that the two conditions share, BMI is among the

most prevalent and most associated. Though the two conditions tend to have opposite effects on fetal growth[27,33], with gestational diabetes tending to cause large-for-gestational-age babies and preeclampsia small-for-gestational-age, both are associated with higher risk of polyhydramnios[34]. This is the likely underlying explanation for the association between maternal BMI and polyhydramnios risk uncovered in our study. Indeed, exploration of the phenocode-based survival analyses on polyhydramnios in the FINNGEN R6 (available at: https://r6.risteys.finngen.fi/phenocode) identified a significant association between polyhydramnios and prior diagnosis of gestational diabetes (HR 18.32, 95%CI 14.95-22.46, $p<1x10^{-100}$), and preeclampsia (HR 4.86, 95%CI 3.25-7.27, $p=1.4x10^{-14}$). However, since these analyses were not adjusted for baseline BMI and disease, and since there was insufficient available data to carry out multivariable MR, this remains an unconfirmed hypothesis that should be a key research priority once sufficient data is available to explore it.

Impact of BMI on PPROM

The results of our study support past observational evidence of an association between obesity and preterm prelabour rupture of membranes, but not preterm birth. In a Danish national birth cohort of 62,127 women, the risk of PPROM was high in obese woman than women of a normal weight, especially before 34 weeks' gestation where obesity doubled the risk[35]. Furthermore, this study found that obesity does not increase the risk of preterm birth without PPROM, and similar associations have been described in observational cohorts after being adjusted for preeclampsia, gestational diabetes and hypertension[36,37]. It is widely accepted that both intrauterine and extrauterine infections such as urinary tract infections may activate an inflammatory process which degrades the foetal membranes and studies have shown that obesity is a cardinal risk factor for such infections[38,39]. This may be a direct effect of obesity, or partly relate to higher glucose levels in a diabetic or prediabetic environment that may favour bacterial growth[35].

Impact of BMI on post-partum depression

The existing evidence on the relationship between increased BMI and post-partum depression is currently inconclusive. A systematic review found that the published literature is low quality according to the GRADE guideline and demonstrated conflicting results[40]. It is notoriously difficult to draw conclusions on the role of BMI on risk of depression in observational studies due to the risk of reverse causality. Thus, using MR is particularly useful for establishing causation. In this study, the association between BMI and depression was borderline significant for a potential higher risk of postpartum depression. Since postpartum depression is an important perinatal health issue that carries significant impact on maternal and child health, further research is warranted to investigate this relationship in more detail.

Impact of BMI on postpartum haemorrhage, miscarriage, placenta praevia and abruption

Contrary to the results from other observational evidence[38], our study did not find an association between BMI and postpartum haemorrhage, miscarriage, placenta praevia and abruption. There may be multiple reasons for this. First, it may be that observational association estimates are subject to persistent influence by confounders that could not be accounted for in the analyses, and when utilising MR, which is not impacted by such confounders, the associations no longer exist. However, the absence of an association may also relate to limitations in power for this study. For example, the negative result for placenta praevia and placental abruption should be interpreted with caution as there was only a small number of cases and therefore power for these analyses was limited. Thus, the negative results in this study should not be taken to indicate evidence of absence of an association.

Strengths and Limitations

The strengths of this study include the ability to assess relationships with minimal potential impact of confounding leading to more robust causal inference, which can inform clinical

practice by identifying the direct causal consequences of raised maternal BMI. In practical terms, the results imply that women with obesity are at increased risk of preeclampsia and gestational diabetes, even if they are otherwise healthy.

Limitations include that some outcomes are rare, therefore negative results may be due to underpowered analysis rather than true absence of an underlying association. Furthermore, we could not explore the potential mediating pathways for the relationships we describe due to lack of sufficient instruments for analysis when attempting to derive them from independent populations, which is an essential priority to avoid bias from the 'winner's curse' phenomenon. In addition, population stratification can be a source of residual confounding even in the setting of MR[41]. To limit the potential impact of this, the analysis was limited to populations of European ancestry. This is a necessary step to minimise confounding from population stratification, but it has the downfall of limiting generalisability of the results to non-European populations.

Conclusion

This is the first study to examine the relationship between BMI and multiple maternal outcomes of pregnancy using MR. Our results support a causal effect of BMI on gestational diabetes, preeclampsia, and polyhydramnios. The results of this study have multiple important clinical implications. First, they identify important clinical outcomes of high maternal BMI, and this is information that can be employed in clinical risk stratification and to guide monitoring of pregnancy. Second, by identifying BMI as a causal factor in the development of multiple maternal morbidities, the results highlight the crucial role of targeted prevention by weight reduction, and identify the impact that this can have on maternal health. Finally, this study highlights the need for further research into the role of BMI and maternal morbidity in non-white ethnic groups.

Figures

Figure 1 – Study design flowchart

Figure 2 – Mendelian randomization effect estimates of 1-SD increase in genetically determined body mass index (BMI) levels and maternal outcomes of pregnancy

Disclosure of interests

None declared

Contributing authorship

Conceptualization, MA; methodology, MA; formal analysis, MA; data curation, MA; writing, MA and MGB; writing—review and editing, MGB and AB; visualization, MA; supervision, AB; project administration, MGB. All authors have read and agreed to the published version of the manuscript.

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Ethical approval

All data used in this study are publicly available. The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District has evaluated the project. FinnGen research project is based on samples from Finnish biobanks and data from national health registers. The study applies the permissions to utilise the register data for research purposes from national authorities. The research project complies with existing legislation (in particular the Biobank Law and the Personal Data Act) and will conform to any new laws. The EU Data Protection Regulation that came into force in May 2018 has been taken into account when planning the project.

Consent

All original studies obtained written, informed participant consent for the use of presented data.

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Tables

Table 1 – Information on sources for female-specific summary statistics for the variables and outcomes utilised in the study.

Variable	Study author	N of cases (/ total)	Unit	PMID / link
Exposure Data				
Body mass index	Pulit et al. 2018	434,794	1-SD (kg/m^2)	
Outcomes				
Pre-eclampsia or eclampsia	FINNGEN	4,743 / 136,325	Log(OR) (yes vs no)	https://finngen.gitbook.io/documentation
Diabetes mellitus in pregnancy	FINNGEN	7,676 / 130,424	Log(OR) (yes vs no)	
Polyhydramnios	FINNGEN	718 / 123,117	Log(OR) (yes vs no)	
Placenta praevia	FINNGEN	725 / 123,117	Log(OR) (yes vs no)	
Placental abruption	FINNGEN	376 / 123,117	Log(OR) (yes vs no)	
Fetal distress in labour	FINNGEN	4,586 / 116,219	Log(OR) (yes vs no)	
Premature rupture of membranes	FINNGEN	3,926 / 123,117	Log(OR) (yes vs no)	
Preterm labour and delivery	FINNGEN	6,736 / 116,219	Log(OR) (yes vs no)	
Postpartum haemorrhage	FINNGEN	4,714 / 116,219	Log(OR) (yes vs no)	
Spontaneous abortion	FINNGEN	11,149 / 105,738	Log(OR) (yes vs no)	
Postpartum depression	FINNGEN	9,392 / 69,241	Log(OR) (yes vs no)	

Table 2 – Mendelian randomization effect estimates for 1-SD increase in body mass index (BMI) on the risk maternal outcomes of pregnancy.

Outcome	SNPs	OR	95% CI		p-val
Pre-eclampsia or eclampsia	354	1.68	1.46	1.94	$8.74x10^{-13}$
Intrahepatic cholestasis of pregnancy	354	0.84	0.63	1.11	0.224
Gestational diabetes	354	1.67	1.46	1.92	$5.35\ x10^{-14}$
Polyhydramnios	354	1.40	1.00	1.96	0.049
Placenta praevia	354	0.82	0.59	1.15	0.255
Placental abruption	354	1.31	0.83	2.09	0.250
Fetal distress in labour	354	0.92	0.79	1.07	0.296
Premature rupture of membranes	354	1.16	1.00	1.36	0.050
Preterm labour and delivery	354	1.01	0.90	1.14	0.832
Prolonged pregnancy	354	1.02	0.84	1.23	0.871
Postpartum heaemorrhage	354	1.00	0.87	1.15	0.982
Spontaneous abortion	354	1.05	0.96	1.15	0.271
Postpartum depression	354	1.12	0.99	1.27	0.062

nSNP =number of instrumental single nucleotide polymorphisms OR = Odds ratio LCI= lower confidence interval, UCI = upper confidence interval

Table S1 – Sensitivity analysis MR-Egger and weighted median M

Outcome	Method	OR	95% CI		p-val
Pre-eclampsia or eclampsia	WM	1.86	1.49	2.31	2.79x10^8
Pre-eclampsia or eclampsia	E	2.34	1.55	3.54	6.49 x10^5
Gestational diabetes	WM	1.83	1.51	2.22	5.80x10^10
Gestational diabetes	E	2.05	1.38	3.02	3.82x10^4
Polyhydramnios	WM	1.17	0.68	2.00	0.575
Polyhydramnios	E	1.16	0.43	3.07	0.772

OR = Odds ratio LCI= lower confidence interval, UCI = upper confidence interval WM= weighted medium E=Egger