

**DR CAROLINA BORGES, PROF DEBORAH LAWLOR,
DR GEMMA CLAYTON AND DR TOM BOND, MEDICAL
RESEARCH COUNCIL (MRC) INTEGRATIVE
EPIDEMIOLOGY UNIT AT UNIVERSITY OF BRISTOL -
WRITTEN EVIDENCE (FDO0046)**

About the Institution:

The [MRC Integrative Epidemiology Unit](#) at the University of Bristol (MRC IEU) conducts some of the UK's most advanced population health science research. It develops and applies novel causal methods to sociodemographic, clinical, genetics, molecular data in large cohort studies and electronic health record studies. It has also pioneered the use of triangulation of evidence from different types of data and different analytical methods to identify causes of health outcomes, particularly where randomized controlled trial evidence is impossible or very difficult to obtain. One area of work is focussed on women's health before, during and after pregnancy. This [programme](#), co-led by Prof Deborah Lawlor and Dr Carolina Borges, aims to achieve a step change in the evidence on prevention, early detection and treatment of complications related to pregnancy.

Call for evidence addressed in this submission:

This submission addresses the call for evidence on "The impacts of obesity on health, including on children and adolescent health outcomes, and the influence of pre- and post-natal nutrition on the risk of subsequent obesity."

About the submission

Our submission focuses on the impact of higher maternal body mass index (BMI), a common measure of excess weight, on the risk of pregnancy-related complications¹ (*evidence note 1*) and offspring's childhood obesity²⁻⁴ (*evidence note 2*).

Summary

Evidence note 1: Maternal BMI and risk of pregnancy-related complications

Our research provides convincing evidence that women with higher BMI before, or early in, pregnancy have a higher risk of several pregnancy

complications. These findings build on existing studies and are based on data from more than 400,000 women.

Key findings from our study are:

- There is a causal link between higher maternal BMI and increased risk of the following complications: high blood pressure in pregnancy, pre-eclampsia, gestational diabetes, delivery complications (e.g. caesarean section or induction of labour), babies with high birth weight and those who need to be admitted to a neonatal intensive care unit.
- Higher BMI decreases the risk of developing anaemia during pregnancy or having a baby with low birth weight.
- We found no evidence of a causal link between higher BMI and perinatal depression.
- We were not able to confidently conclude if BMI had any (positive or negative) effect on miscarriage, stillbirth and preterm births.

Evidence note 2: Maternal BMI and risk of offspring obesity

Our research²⁻⁴ shows that starting pregnancy with a healthy BMI is unlikely to influence the offspring's risk of obesity in childhood and adolescence.

Key findings from our studies are:

- Although mothers with higher BMI in early pregnancy have children with higher obesity risk, this link is primarily due to genetic inheritance from mothers to children, rather than a causal intrauterine effect of maternal BMI on the child's obesity risk.
- Our results, building on previous work, suggest that higher maternal BMI before or during pregnancy is not a key driver of higher obesity risk in the next generation.

Recommendations

Starting pregnancy with a healthy weight is likely to reduce the risk of several pregnancy complications, but unlikely to influence offspring's risk of obesity in childhood and adolescence. This highlights the need for policymakers and health professionals to support people of all ages, including women of childbearing age, to establish and keep a healthy weight.

Further investigation into the effect of maternal excess weight on miscarriage, stillbirth and preterm births is needed, using future larger

studies that include different methods and different types of data so we can have more confidence in our conclusions.

Further investigation is also warranted into the effect of maternal excess weight on offspring obesity risk and cardiovascular outcomes in adulthood.

More information

Evidence note 1: Maternal BMI and risk of pregnancy-related complications

In the last decades, people across the world have become more obese, including women of childbearing age⁵. In the UK, obesity rates among adult women rose from 11% to 28% between 1975 and 2015⁶.

Many studies using conventional methods have reported that mothers with higher body mass index (BMI), a common measure of excess weight, have a higher risk of several pregnancy complications. The complications reported by those studies include having a miscarriage or stillbirth, high blood pressure in pregnancy, preeclampsia, gestational diabetes, perinatal depression, caesarean deliveries, preterm birth, having a heavier baby, and not being able to breastfeed⁷⁻⁹.

However, these analyses could be confounded - i.e. 'fool' us into thinking that higher maternal BMI causes pregnancy complications when another factor (or factors), such as mothers' education, influence both maternal BMI and pregnancy complications to generate a correlation between the two that is not causal. Therefore, it can be challenging to determine what is cause and what is merely correlation, creating confusion for mother, healthcare workers and policymakers.

As part of the MR-PREG collaboration, we have conducted research including data from more than 400,000 women participating in 14 studies in Europe and North America with recruitment ranging from 1966 to 2018¹. Our research used three different approaches to clarify whether the correlations reported by previous studies reliably reflect a causal role of maternal BMI before or early in pregnancy on 20 pregnancy-related complications. If all approaches point to the same conclusion, this gives us more confidence that BMI has a causal role. If approaches point to different conclusions, this highlights the need for further research.

The three approaches we have used can be summarised as follows.

First, we used similar analyses to previous studies, to explore correlations between maternal BMI and pregnancy complications.

Second, we checked correlations between **paternal/partner** BMI and pregnancy complications (negative control study)¹⁰. If we saw similar correlations between paternal/partner BMI with pregnancy complications and maternal BMI with pregnancy complications, that would suggest both were due to confounding (or some other bias).

Third, we compared the risk of pregnancy complications between mothers genetically-predisposed to having a higher BMI with those genetically predisposed to having a lower BMI (Mendelian randomization^a). This method relies on the fact that our genetic make-up is determined at birth and should not be correlated with confounding factors.

Comparing across methods, our study showed that **higher maternal BMI causally influences 14 out of 20 pregnancy complications** studied, including:

- Increasing the risk of high blood pressure in pregnancy, pre-eclampsia, gestational diabetes, and complications of delivery, such as needing a caesarean section or induction of labour, having babies who are heavier or need to be admitted to a neonatal intensive care unit.
- Decreasing the risk of developing anaemia during pregnancy or having a baby with low birth weight.
- In contrast to previous observational studies, we found no evidence of a higher risk of perinatal depression.
- For miscarriage, stillbirth and preterm births there were inconsistency across methods or too few women with the complication for us to make a confident conclusion.

Evidence note 2: Maternal BMI and risk of offspring obesity

It is well established that **higher maternal BMI before or during pregnancy is correlated with greater risk of obesity and cardiovascular disease in the offspring**¹¹. This could be because maternal obesity alters fetal or pre-conceptual development, thereby causing increased offspring cardiovascular risk in subsequent adult life. However, there is strong evidence that an important part of BMI variation within populations is due to genetic factors¹². Thus, genetic inheritance is an alternative explanation for the correlation between maternal BMI and offspring obesity and cardiovascular risk.

^a A two minute primer on mendelian randomisation:
<https://www.youtube.com/watch?v=LoTgfGotaQ4>

As in the study described in Evidence note 1 above, we triangulated evidence across several complementary study designs to investigate which of these two competing explanations underlies the correlation between maternal BMI and offspring childhood obesity risk.

First, we used Mendelian randomization^a to estimate the causal effect of maternal BMI before or during pregnancy on offspring BMI and fat mass in infancy, childhood and adolescence⁴. We found that **although maternal BMI is likely to influence offspring birth weight, there was no evidence for a causal effect on BMI or fat mass in childhood or adolescence.**

Second, we compared how strongly maternal BMI and paternal BMI were correlated with offspring childhood BMI (a negative control study). We saw no consistent differences in the correlations of maternal and paternal BMI with offspring BMI, suggesting that **factors shared within families (such as genetics) explain the correlation between maternal and offspring BMI.**

Third, we used two complementary genetic techniques to determine the extent to which confounding by genetic inheritance explained the correlations²⁻⁴. This **confirmed that mother-offspring BMI correlations are primarily due to genetic inheritance.**

Taken together with previous studies^{13,14}, our findings provide strong evidence that starting pregnancy with a healthy weight is unlikely to influence the offspring's risk of obesity in childhood and adolescence.

Dr Carolina Borges, Prof Deborah A Lawlor, Dr Gemma Clayton, Dr Tom Bond.

Dr Carolina Borges is an MRC IEU Programme Lead Track at the University of Bristol. Her research is focussed on improving evidence around mechanisms and treatments for chronic diseases and pregnancy complications.

Prof. Deborah A Lawlor is a Professor of Epidemiology with a clinical background. She is Deputy (currently acting) director of the MRC IEU. Her research focuses on applying novel causal methods to understanding the

^a A two minute primer on mendelian randomisation:
<https://www.youtube.com/watch?v=LoTgfGotaQ4>

causes and consequences of ill-health, mainly in relation to fertility, pregnancy, perinatal and cardiovascular health.

Dr Gemma Clayton is a Research Fellow in Health Data Sciences, funded by the British Heart Foundation.

Dr Tom Bond is a Senior Research Associate working on Prof Lawlor's/Dr Borges's programme and previously funded by the British Heart Foundation.

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