The association between paternal body mass index, pregnancy success and child health outcomes: a systematic review protocol

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Review question: The objective of this review is to investigate the association between paternal body mass index (BMI) (particularly elevated paternal BMI) and complications of conception and pregnancy as well as neonatal and childhood health.

Keywords child health outcomes; obesity; overweight; paternal body mass index; pregnancy


Introduction

Obesity is associated with many conditions including diabetes, cardiovascular disease and certain cancers.1 Additionally, a recent systematic review with meta-analysis showed that obese men have lower success from assisted reproduction therapies (ART) and altered semen parameters which could lead to infertility.2 In Australia, 62% of men aged 18 years and over are overweight or obese,3 with many Western nations, including the United States of America4 and England,5 having similar rates. The prevalence of obesity in young men of reproductive age has tripled since the early 1970s.4

The influence of maternal body mass index (BMI) and obesity on reproductive health and child health outcomes has been extensively researched with numerous systematic reviews having been undertaken. An umbrella review of these systematic reviews found that maternal obesity was associated with the following impacts on maternal health: gestational diabetes, pre-eclampsia, gestational hypertension, depression, instrumental and cesarean birth and surgical site infection, as well as the following impacts on neonatal health: greater risk of preterm birth, large-for-gestational-age babies, fetal defects, congenital anomalies and perinatal death.6

Although it has been the focus of far less research, paternal BMI may also impact on pregnancy outcomes and child health. The systematic review that investigated the effect of paternal obesity on fertility found that although the rate of clinical pregnancy was not significantly affected, the rate of live birth was significantly lower, with analyses supporting that this discrepancy could be attributed to a greater rate of pregnancy loss.2 Observational studies also exist which suggest that the children of obese men have significantly altered growth curves from birth to 3.5 years,7 a greater risk of autism spectrum disorder,8 a greater risk of overweight and obesity,9 and insulin resistance.10 While maternal BMI having an impact on pregnancy and offspring health is easily accepted, the mechanism behind the impact of paternal BMI is less straightforward. Additionally, the phenomena of assortative mating (wherein people with similar characteristics i.e. body weight tend to partner) creates a major confounding factor if not controlled for. However, significant experimental research has been carried out in animal models which firmly establishes biological plausibility.

Most of the work assessing the influences of paternal obesity in programming offspring health has been in rodents. Studies in both mice and rats have shown that feeding a diet high in saturated fat to male mice to induce obesity prior to mating...
changed both neonatal weights and their adult growth trajectory, with accumulation of excess adiposity, glucose and insulin intolerance and sub fertility, with these effects also extending to the second generation.\textsuperscript{11,12} The mechanism of this effect is likely to be epigenetic in nature, with changes to sperm methylation,\textsuperscript{13} small non coding ribonucleic acid content in sperm\textsuperscript{14,15} and global acetylation levels in testes\textsuperscript{16} present in these obese rodents. In addition, changes to methylation and transcription of associated genes have also been shown to be present in offspring pancreatic tissue,\textsuperscript{12} suggesting that these changes to sperm are persisting in the embryo and subsequent offspring. As such, the influence of paternal obesity on the health and characteristics of offspring is an important question for the ongoing health of the community.

No systematic reviews have been carried out on the association between paternal BMI, pregnancy success and child health outcomes. One systematic review published in 2013 looked at parental BMI and offspring obesity, however they focused entirely on the relative strengths of the maternal and paternal effects and did not report on the paternal effect in its own right.\textsuperscript{17} A review of the Cochrane Library, PROSPERO and the JBI Database of Systematic Reviews and Implementation Reports did not show that any further systematic reviews in this area that had been performed or were underway.

As such we are undertaking this systematic review to identify and synthesize all available evidence on the association between paternal BMI and conception, pregnancy outcomes, neonatal health and childhood health.

**Inclusion criteria**

**Participants**
The review will consider studies which have included men who have had biological children. Children can have been conceived naturally or though ART (excluding sperm donation).

**Exposure of interest**
The exposure of interest will be men’s BMI either as a continuous measure or categorized into weight groupings (i.e. normal weight, overweight, obese). Maternal factors must be controlled for in order for data to be included to minimize confounding. At a minimum this must include maternal age and BMI. Studies where waist circumference have been measured instead of BMI will also be included. Body mass index must have been assessed prior to birth of the offspring or during the neonatal period in order to increase the relationship between measured BMI and BMI at conception.

**Outcomes**
Outcomes to be investigated will relate to conception and pregnancy as well as neonatal and childhood outcomes.

**Conception and pregnancy:**
- Time to pregnancy.
- Incidence or prevalence of infertility (generally defined as >2 years of attempting conception).
- Pregnancy loss (confirmed pregnancy which does not result in a live birth). Where possible data will be extracted specific to early and late pregnancy loss as well as stillbirth.
- Pregnancy complications (i.e. pre term birth [<37 weeks], small or large for gestational age, gestational diabetes, pre-eclampsia, hyper tension). Generally, study specific definitions will be accepted.
- Gestational length.

**Neonatal and childhood outcomes:**
- Birth weight and length.
- Weight and height up to and including age 10.
- Incidences of any diseases.

**Types of studies**
This review will consider retrospective and prospective comparative epidemiological study designs. These will include cohort, cross-sectional, case-control and longitudinal studies, but no case report or case series studies.

**Methods**

**Search strategy**
The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and Embase will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all included reports and articles will be searched for additional studies. Studies published...
in English will be considered for inclusion in this review. Studies published before 1974 onwards will not be included as this is the year that BMI was defined.\(^1\)

The databases to be searched will include: MEDLINE (Pubmed), Embase, CINAHL and Web of Science for published studies; and ProQuest Dissertations and Theses Global, and OpenThesis for unpublished reports.

Search terms will include combinations of the following terms: male, paternal, father, BMI, body weight, overweight, obesity, pregnancy, pregnant, infertility, conception, miscarriage, stillbirth, birth, delivery, offspring health, child health, growth, development.

**Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute.\(^2\) Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

**Data extraction**

Data will be extracted from papers included in the review using the standardized JBI data extraction tool.\(^3\) The data extracted will include specific details about the exposure, populations, study methods and outcomes of significance to the review question and specific objectives. The most adjusted outcome estimates presented in the studies will be extracted.

**Data synthesis**

Quantitative data will, where possible, be pooled in statistical meta-analysis using RevMan (Copenhagen: The Nordic Cochrane Centre, Cochrane). All results will be subject to double checking to ensure fidelity. Effect sizes expressed as odds ratio or hazard ratios (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and I square tests and also explored using subgroup analyses based any systematic differences between studies. Sensitivity analysis will be performed where possible. Potential subgroups will be based on study quality, differences in maternal demographics and attrition rates. Due to the nature of observational studies, random effects models are most likely to be appropriate for meta-analysis. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. Publication bias will be investigated using funnel plots and statistical analysis where there are sufficient studies to do so (\(>10\)).

**References**


