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Review

Influence of increased paternal BMI on pregnancy and child health outcomes independent of maternal effects: A systematic review and meta-analysis

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ABSTRACT

Objectives: The influence of maternal body mass index (BMI) on pregnancy and child health outcomes is well characterised, however less is known about paternal BMI. This systematic review investigated the independent effects of increased paternal BMI on conception and pregnancy as well as neonatal and childhood outcomes.
Methods: Our systematic search (Sept. 2018) of PubMed, Embase, Cinahl, Web of Science, ProQuest, and OpenThesis resulted in 11,045 hits from which 17 studies met the inclusion criteria (Participants: men Exposure: BMI or waist circumferences Outcomes: associations with time to pregnancy, incidence of infertility, pregnancy loss, pregnancy complications, birthweight and length, childhood weight and height, or incidence of any childhood disease). Studies had to adjust for maternal age and BMI.
Results: Meta-analysis was only possible for infertility which was significantly more prevalent in obese (OR = 1.49 95%CI 1.30–1.70) and overweight (OR = 1.18 95%CI 1.11–1.26) men. Individual studies showed increased likelihoods of small for gestational age and macrosomia in fathers who had increased BMI – possibly accounting for the general finding of no effect on mean birthweight in other studies. Most studies found increased BMI in fathers correlated with altered growth curves and increased BMI in childhood, while one study found a higher likelihood of autism spectrum disorder.
Conclusion: Our findings support increased paternal BMI negatively affecting pregnancy and child health outcomes. Future studies must include or adjust for paternal contributions, as the longstanding assumption that only maternal factors are relevant is likely to have considerably confounded prior work.

Contents

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Introduction

The developed world is currently affected by an obesity epidemic that includes the USA, UK and parts of Europe [1] as well as Australia where obesity rates have tripled since the late 1970s, with 28.7% of men now classified as obese [2]. In addition, the rates of serve obesity (body mass index (BMI) >35 kg/m^2) has risen 5-fold now affecting over 10% of the Australian adult population [2].

Besides increasing risk of developing chronic diseases including type II diabetes, heart disease and some cancer, obesity is also associated with subfertility [3]. A systematic review found that obese men in the general population had higher odds ratio of experiencing infertility, while those receiving assisted reproductive treatment for their infertility had lower rates of live birth [4]. Although this review did not find that conventional measures of semen quality (sperm count and motility) were significantly impacted by obesity, low sperm mitochondrial membrane potential, increased sperm DNA fragmentation, and abnormal sperm morphology were all increased in men with high BMI [4].

The influence of maternal BMI and obesity on pregnancy and child health has been extensively research, with a review of systematic reviews finding increased rates of pregnancy/gestation complications including; gestational diabetes, pre-eclampsia, hypertension, depression, instrumental and caesarean birth, preterm birth, surgical site infection, and neonatal complications including; perinatal death, macrosomia, fetal defects and congenital anomalies in with women of increasing BMI [5]. The effect of paternal BMI on pregnancy and children's health has received less attention and the inclusion criteria and analyses of many studies reflect a common assumption that there are no meaningful effects. One systematic review published in 2013 looked at parental BMI and child obesity rates, however they focused only on the relative strengths of the maternal and paternal effects and did not report on the paternal effect by itself [6]. Observational studies have found that increased paternal BMI at conception alters methylation patterns in fetal cord blood and decreases neonatal IgM levels [7,8], is associated with delays in personal and social functioning in children at age three [9], increases rates of type II diabetes and insulin resistance [10] and is associated with the severity of childhood obesity[11]. However, the questionable accuracy of health data for fathers at conception, in addition to the potential impact of maternal factors, affects the weight that can be given to individual observational studies. Consequently, the majority of studies assessing the effect of paternal obesity on pregnancy and child health have been completed in animal models where maternal and environmental factors can be strictly controlled.

These studies have found that paternal obesity at conception alters birth weights [12–17], increases offspring susceptibility to metabolic syndrome [12,13,18], sub fertility [19], fatty liver [20], kidney disease [21] and hypertension [22], while decreasing offspring cognitive function [23]. Paternal obesity has been linked to a range of negative effects on sperm health, including increased DNA damage [4] and reactive oxygen species [24], as well as reduced sperm mitochondrial function [25]. Direct signalling has also been found between the sperm and egg at fertilisation, as well as from seminal plasma – which has a greater inflammatory profile in obese men [26,27] – to the uterine environment [28,29]. These factors are well accepted as having the potential to influence early embryo and fetal growth, and it is hypothesised that by influencing this foundational growth – as well as through epigenetic alterations [30] – paternal obesity is able to exert its effects on pregnancy and childhood health outcomes long after conception.

Currently, no systematic reviews have been carried out on the specific influence of paternal BMI on pregnancy and child health outcomes. We have therefore undertaken this systematic review with meta-analysis to determine whether a synthesis of observational studies carried out in humans supports the findings of animal models.

Methods

This review on the association between paternal BMI and conception, pregnancy outcomes, neonatal health and childhood health was carried out in accordance with a pre-published protocol [31].

Inclusion criteria

Participants: Men who have had biological children. Children could have been conceived naturally or though ART (excluding sperm donation).

Exposure of interest: The men's BMI either recorded as a continuous measure or categorized into weight groupings (i.e. normal weight, overweight, obese). Maternal factors (age and BMI as a continuous or categorical measure) had to be controlled for or shown to be unassociated to minimize confounding. Studies where waist circumference was measured instead of BMI were also included. To increase the relationship between measured BMI and BMI at conception, BMI of fathers had to have been assessed prior to the birth of the offspring or during the neonatal period.

Outcomes: Conception and pregnancy; (a) Time to pregnancy, (b) Incidence or prevalence of infertility (generally defined as >2 years of attempting conception), (c) Pregnancy loss (confirmed pregnancy which does not result in a live birth), (d) 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 were accepted, (e) Gestational length. Neonatal and childhood outcomes; (a) Birth weight and length, (b) Childhood weight and height, (c) Incidences of any diseases.

Types of studies: This review considered retrospective and prospective comparative epidemiological study designs, including

cohort, cross-sectional, case-control and longitudinal studies, but not case report or case series studies.

Search strategy

The search strategy (carried out September 2018) aimed to find both published and unpublished studies. A three-step search strategy was utilized. An initial limited search of Medline and Embase was 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 was then undertaken across all included databases. Thirdly, the reference list of all included reports and articles were searched for additional studies. Studies had to be published in English to be included. Studies published before 1974 were not included as this is the year that 'BMI' was defined [32]. Initial search terms included combinations of the following: Male, paternal, father, BMI, body weight, overweight, obesity, pregnancy, pregnant, infertility, conception, miscarriage, stillbirth, birth, delivery, offspring health, child health, growth, development. The full search strategy is included in supplementary material 1. Databases searched included: Medline (Pubmed), Embase, Cinahl and Web of Science for published studies and ProQuest and OpenThesis for unpublished reports.

Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute [33]. Disagreements that arose between the reviewers were resolved through discussion.

Data collection

Data was extracted from papers included in the review using an Excel spreadsheet with fields for 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 were extracted.

Data synthesis

Where possible quantitative data was pooled in statistical meta-analysis using RevMan. Heterogeneity was assessed statistically using the standard Chi-square and I square tests. The small number of studies that could be included in the meta-analyses precluded subgroup or sensitivity analysis as well as the statistical investigation of publication bias through Funnel plots. Due to the nature of observational studies, random effects models were chosen for the analyses. Where statistical pooling was not possible the findings have been presented in narrative form.

Results

The systematic search was first carried out in May 2017 then updated in September 2018, however ultimately no new studies were identified from this search that met the inclusion criteria. In total there were 11,045 hits which was reduced to 7301 by the removal of duplicates. Screening titles and abstracts reduced the number of studies to 103 which was reduced to the final total of 17 on full-text review (Fig. 1). Review of the reference lists from the included studies resulted in two full texts being retrieved, but both were excluded on review. Of the outcomes specified as eligible for inclusion in the methods only pregnancy loss and gestational length did not have any relevant studies. Study sizes ranged from

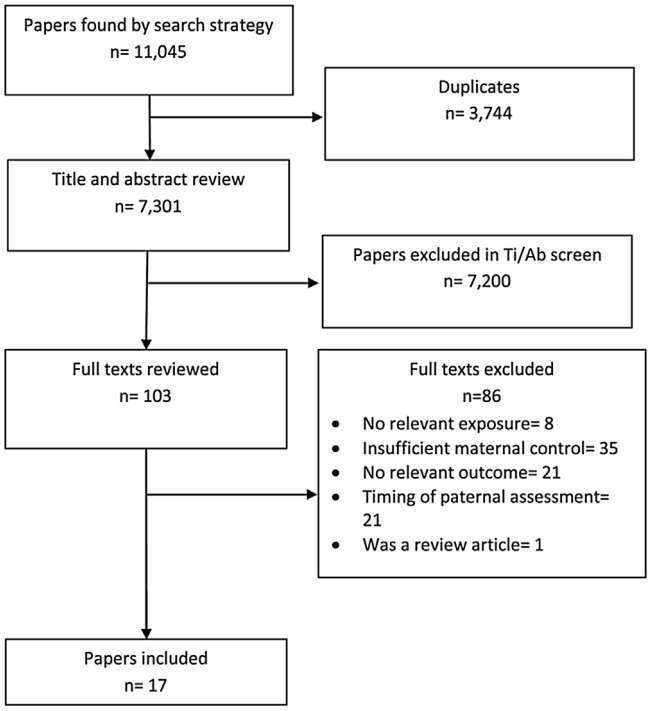

Fig. 1. PRISMA flow chart.

153 [18] to 92 909 [34] and were carried out in numerous countries including China [35,36], the UK [37], the Netherlands [38], Australia and New Zealand [18,39–41], the USA [42–44], Ireland [45], Norway [34,46], Denmark [47], France [48], and Malaysia [49].

The majority of studies followed a cohort design [34,35,37–47] with some including long term follow up [18,48,49], however one study was a case control [36]. Full details of included studies are given in Table 1. For the cohort studies quality was overall high with eight out of eleven domains of quality being met in all studies (Table 2). The most egregious exception was criterion 9, relating to completeness of follow up and description of reasons for loss, which was only adequately addressed in 4 of the 12 studies where it was relevant. However, appropriate strategies to address incomplete follow-up were applied in 8 of 12 relevant studies (criterion 10, Table 2). Finally, 9 of 16 studies measured paternal weight and height in a reliable way (criterion 3, Table 2) which was scored 'Yes' for any measure more reliable than partner recall. This was also the only assessed potential source of bias in the sole case-control study [36].

Conception and pregnancy

Time to pregnancy

Two studies investigated the effect of paternal obesity on time to pregnancy, although their different approaches precluded meta-analysis. Sundaram et al. a long-term study [44] considered 501 females aged 18–40 years with male partners ≥18 years and assessed their fecundability, prospectively measured by their number of observed menstrual cycles before pregnancy over a year. Obesity was considered in terms of both BMI and waist circumference, although significant differences were not observed in either case. In men whose partners had BMI < 25, using men whose BMI was <25 as the reference, men with BMI 25 to <35 had OR = 0.80 95%CI 0.52–1.22, and men with BMI ≥ 35 had OR = 0.67 95%CI 0.29 to 1.51. Where OR < 1 indicates a decreased fecundability as measured by a greater number of menstrual cycles before pregnancy and OR > 1 indicates increased fecundability and fewer menstrual

Table 1
Characteristics of included studies.

Study	Population	Parental age and BMI	Categories/exposure	Outcome	Adjustments
Chen et al. [35]	China: Guangzhou birth cohort. Newborn born without congenital abnormalities, singleton pregnancy, no hepatitis B, C, and D, no HIV and no syphilis.	Paternal: Age 31.36 ± 4.62(SD), BMI 23.28 ± 2.88 Maternal: Age 28.49 ± 3.71, BMI 20.2 ± 2.4	Paternal BMI	Birth weight in boys N = 492 Birth weight in girls N = 407	Maternal BMI, paternal and maternal age, hypertension during pregnancy, maternal glycated serum protein, parity and gestational age (for birth weight)
Davey Smith et al. [37]	England: Avon Longitudinal study of parents and children. Pregnant women living in three health districts with an expected delivery period between April 1991 and December 1992	Paternal: BMI 25.2 ± 3.2 Maternal BMI: 22.9 ± 3.7	Paternal BMI	Child BMI at 7.5 years N = 4654	Paternal age, maternal age and BMI, children's age and sex.
L'Abee et al. [38]	The Netherlands: Drenthe population-based birth-cohort. All children born between April 2006 and 2007, and living at the time of birth in Drenthe were eligible.	Paternal: Age 33.44 +/1 4.95, BMI 25.2 ± 4.95 Maternal: Age 30.71 ± 4.46, BMI 24.71 ± 4.73	Paternal BMI	Birth weight N = 2528	Child gender and gestational age; Paternal and maternal age, birth weight, smoking alcohol, substance abuse, physical activity, diabetes, hypertension, thyroid disease, cholesterolemia, and depression, as well as maternal weight gain, parity and income.
Lawlor et al. [39]	Australia: Mater-University Study of Pregnancy and Its Outcomes. Women who delivered live singleton offspring who neither died nor were adopted prior to leaving the hospital.	Paternal: BMI 23.7 ± 4.7 Maternal: BMI 22.0 ± 4.1	Paternal BMI	Offspring BMI at 14 years N = 7223	Sex, maternal BMI, family income, parental education, maternal age, parity, maternal smoking, birth weight and length (sex standardised)
Linabery et al. [11,42]	USA: Fels longitudinal study. European-American infants born 1928–2008.	NR	Paternal BMI categorised as: normal ≤25, Overweight 25-<30, obese ≥30	Infant BMI growth curve from birth-3.5 years N = 850 Infant weight growth curve N = 872 Infant length growth curve N = 890	Maternal and paternal overweight indicators, sex, gestational age, birth year tertile, firstborn indicator, maternal and paternal age, maternal and paternal age difference, maternal and paternal stature, maternal and paternal smoking status, child's age, child's age, age2, age3, cubic spline terms 1-4, child's sex*age terms (age, age2, age3, cubic spline terms 1-4), maternal and paternal overweight indicator*child's age terms, maternal and paternal obese indicator*child's age terms.
McCarthy et al. [45]	Ireland: BASELINE cohort. Health nulliparous women with singleton pregnancies recruited between November 2007 and February 2011 who did not have pre-eclampsia, delivery of a small for gestational age neonate, or spontaneous preterm birth due to an underlying medical condition, gynaecologic history, three or more miscarriages, three or more terminations of pregnancy or who had received interventions which might modify pregnancy outcome.	NR	Increasing paternal BMI	% body fat at birth N = 1243	Infant sex, maternal BMI, age, smoking and alcohol, socioeconomic index and ethnicity.
McCowan et al. [40]	Australia and New Zealand: SCOPE study. Health nulliparous women with singleton pregnancies recruited between November 2004 and July 2007 who were not considered at high risk of preeclampsia, small for gestational age or spontaneous preterm birth due to underlying medical conditions, previous gynaecological history or who received interventions that may modify these outcomes.	Paternal: Age SGA 31.1 ± 6.3; non SGA 31.0 ± 6.2. BMI ≥ 30: SGA 24.8%, non-SGA 18.3% Maternal: Age SGA 28.8 ± 65.9, non SGA 28.4 ± 65.5. BMI ≥ 30 SGA 20.1%, non-SGA 15.2%	BMI ≥ 30 Waist circumference >102 cm	Small for gestational age (SGA) N = 2002, 209 events	Paternal: age, ethnicity, socioeconomic index, employment, blood pressure, history of hypertension, type 2 diabetes and ischemic heart disease. Maternal: age, ethnicity, BMI, mean arterial pressure, smoking status, gravidity, birthweight.

Nguyen et al. [46]	Norway: Norwegian Mother and Child Cohort Study. Women having their first pregnancy (in study period), who were native Norwegian speakers, living with child's father, planned pregnancy, aged 18–40	NR	BMI: normal weight 20.0–22.4, overweight 25–29.9, obese 30–34.9 BMI: <20, 20.0–22.49, 22.5–24.99, 25.0–27.49, 27.5–29.99, 30.0–3249, 32.5–34.99, ≥35.0	Infertility defined as 12 or more months to conceive (or infertility treatment). N = 2811 with 283 events for normal weight, N = 12,289 with 1862 for overweight, N = 2195 with 329 for obese Median time to pregnancy. N = 26,303	Woman's BMI, smoking habits, ages
Pomeroy et al. [41]	Australia: Mater-University of Queensland Study of Pregnancy dataset	Paternal: BMI 23.6 ± 3.5 Maternal: 25.8 ± 5.0 BMI 22.0 ± 4.0 Paternal: Normal weight: 53%	Paternal BMI	Neck-rump length (no significant association with birthweight after adjusting for all other covariates-data not reported) N = 1041	Male sex, Gestation, mother smoked, Maternal education, previous birth, maternal age, maternal height, maternal BMI, paternal height
Ramlau-Hansen et al. [47]	Denmark: Danish National Birth Cohort. Couples who planned or partially planned their pregnancies from whom BMI data was obtained for both man and woman, excluding those where the woman had a disease which could affect her BMI or fecundity, and couples who used donor sperm.	Maternal: Normal weight: 68% Paternal: BMI < 25 = 709, ≥25 < 30 = 341, ≥30 = 59. Maternal: BMI < 25 1088, ≥25 < 30 = 146, ≥30 = 80	Underweight: BMI < 18.5, normal weight: BMI 18.50–24.99, overweight: BMI 25.00–29.99, obese: BMI ≥ 30.0	Subfecundity (waiting more than 12 months to achieve pregnancy). N = 47,835	Men and women's age, number of previous pregnancies, and socioeconomic group (data was analysed per women's BMI group so did not need adjustment)
Rath et al. [18]	Australia: Western Australian pregnancy cohort. Pregnancies amongst Europeans recruited between 1989 and 1991 excluding participants with congenital abnormalities and those with older siblings included in the cohort	Paternal: BMI 25.1 ± 3.6 Maternal: Age 29.8 ± 4.7 BMI 23.2 ± 4.5,	Pre pregnancy BMI	Offspring BMI. Males N = 517 males, Females N = 510	Age, maternal BMI, birth weight, change in weight over first year of life, maternal smoking, Gestational weight gain at 18 weeks.
Regnault et al. [48]	France: EDEN mother child cohort		Underweight: BMI < 18.5, Normal weight: 18.5–25, Overweight ≥25 to <30, Obese: ≥30	Weight at birth N = 1286 Weight at 3 months and Weight growth velocity at 3 months N = 1285 Length at birth N = 1265 Length at 3 months and Length-growth velocity at 3 months N = 1252	Maternal prepregnancy BMI, 1-h plasma glucose concentration, gestational weight gain, centre, maternal age at delivery, maternal tobacco use, parity, offspring sex, gestational age, heights of mother and father, method of feeding between discharge and 3 months of age.
Sallmen et al. [43]	USA: Agricultural health study	Paternal: Age: 123 < 25, 586 25–29, 802 30–34, 468 35–39, 132 40–54. BMI: 32 < 20, 160 20–22, 503 23–25, 390 26–28, 228 29–31, 105 32 to 34, 50 35+ (644 missing). Maternal: Age: 305 < 25, 787 25–29, 765 30–34, 254 35–39. BMI: 223 < 20, 568 20–22, 461 23–25, 224 26–28, 169 20–31, 85 32–34, 65 35+ (316 missing)	Paternal BMI	Infertility: non-conception after 12 months unprotected intercourse N = 2111, 591 events	Wife's BMI, age, smoking status, use of alcohol, exposure to solvents and pesticides

Table 1 (*Continued*)

Study	Population	Parental age and BMI	Categories/exposure	Outcome	Adjustments
Sundaram et al. [44]	USA: Longitudinal Investigation of Fertility and the Environment Study. Females aged 18-40 years with male partners aged > = 18, married or in a committed relationship, self reported menstrual cycle length between 21 and 42 days, ability to communicate in English or Spanish, no use of injectable hormonal contraception in the prior 12 months. Couples with a physician diagnosis of infertility we ineligible as were couples off contraception for >2 months	Paternal: Age 31.8, ±4.9. BMI 17% <25, 42% 25 to <30, 26% 30 to <35, 15% ≥35 Maternal: Age 30.0 SD 4.1, BMI 46% <25, 27% 25 to <30, 13% 30 to <35, 14% ≥35	BMI < 25, 25 to <35, ≥ 35 Waist circumference (cm): <94, 94–101.6, > = 101.6	Fecundity: number of prospectively observed menstrual cycles required for a couple to become pregnant. N = 501	Female partner's age, difference between male and female age, both partners smoking status, both partners number of days of vigorous physical activity per week, both partner's race, both partner's education, both partners free cholesterol level, average intercourse per cycle and menstrual cycle regularity.
Suren et al. [34]	Norway: Norwegian Mother and Child Cohort Study as well as the Autism Birth Cohort Study. Children born into the MoBa cohort with complete maternal and paternal data	Paternal: Age: <25 4.7%, 25–29 22.6%, 30–34 38.8%, 35–39 23.7%, 40 9.9%. BMI 25–30 45.2%, ≥30 10.0% Maternal: Age: <25 10.7%, 25–29 33.1%, 30–34 38.8%, ≥35 17.2%. BMI 25–30 22.0%, ≥30 9.6%	BMI < 25, 25–29.9, ≥30	Autism disorder N = 92,909 with 419 events Asperger disorder 103 events Pervasive developmental disorder not otherwise specified (PDD-NOS) 154 events Autism spectrum disorder (any of the three) 305 events	Adjusted for parental education levels, child's year of birth, maternal parity and maternal BMI
Yang et al. [36]	China: Population based study. Cases: women with a singleton pregnancy and a gestational age no less than 28 weeks who delivered a live macroscopic baby. Controls: Frequency matched to birth date and district of residency with a singleton pregnancy and gestational age no less than 28 weeks who delivered a normal weight baby (2500-4000 g). Women with multiple pregnancies, pre-existing diseases or who gave birth to a stillborn infant of an infant with a birth defect were excluded.	Paternal: Cases age; 32.09 ± 5.19. Overweight or obese 50.11% Maternal: Cases Age; 29.33 ± 3.91. Overweight or obese 20.12%	BMI: Underweight <18.5, Normal 18.5–23.9, Overweight 24–27.9, Obese ≥28	Macrosomia (birth weight >4000 g) N = 6341 (870 cases, 5471 controls)	Infant's gender, parental age, family income, parental education level, gravidity, parity, paternal smoking, maternal alcohol consumption, maternal pre-pregnancy BMI.
Zalbahar et al. [49]	Malaysia: University Sains Malaysia Pregnancy Cohort. Pregnant women without gestational diabetes, pregnancy induced hypertension or preterm labour.	Paternal: Age: NR. BMI: 24.76 ± 5.80. Maternal: Age 37% >30, BMI 22.58 SD 4.10	Paternal BMI	Weight for age score (measured over 12 months at 2, 6 and 12 m), Length for age z score, Weight for length z score, Body mass index for z age score	Age, education, household income, birth weight, gestational age, maternal physical activities, expenditure of calories, dietary intake at 18 weeks gestation, prenatal less-healthy patern, maternal BMI.

Table 2
Critical appraisal.

Cohort	1	2	3	4	5	6	7	8	9	10	11
Chen et al. [35]	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y
Davey Smith et al. [37]	Y	Y	Y	Y	Y	Y	Y	Y	N	U	Y
L'Abee et al. [38]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Lawlor et al. [39]	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y
Linabery et al. [11,42]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
McCarthy et al. [45]	Y	Y	U	Y	Y	Y	Y	Y	NA	NA	Y
McCowan et al. [40]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Nguyen et al. [46]	Y	Y	N	Y	Y	N	Y	Y	NA	NA	Y
Pomeroy et al. [41]	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Ramlau-Hansen et al. [47]	Y	Y	N	Y	Y	Y	Y	Y	Y	NA	Y
Rath et al. [18]	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y
Regnault et al. [48]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sallmen et al. [43]	Y	Y	N	Y	Y	Y	Y	Y	NA	NA	Y
Sundaram et al. [44]	Y	Y	Y	Y	Y	N	Y	Y	U	Y	Y
Suren et al. [34]	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y
Zalbahar et al. [49]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Totals	16/16	16/16	9/16	16/16	16/16	14/16	16/16	16/16	4/12	8/12	16/16
Case control	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Yang et al. [36]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	

Cohort studies 1. Were the two groups similar and recruited from the same population? 2.Were the exposures measured similarly to assign people to both exposed and unexposed groups? 3. Was the exposure measured in a valid and reliable way? 4. Were confounding factors identified? 5. Were strategies to deal with confounding factors stated? 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? 7. Were the outcomes measured in a valid and reliable way? 8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? 10. Were strategies to address incomplete follow up utilized? 11. Was appropriate statistical analysis used? Case-control: 1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? 2. Were cases and controls matched appropriately? 3. Were the same criteria used for identification of cases and controls? 4. Was exposure measured in a standard, valid and reliable way? 5. Was exposure measured in the same way for cases and controls? 6. Were confounding factors identified? 7. Were strategies to deal with confounding factors stated? 8. Were outcomes assessed in a standard, valid and reliable way for cases and controls? 9. Was the exposure period of interest long enough to be meaningful? 10. Was appropriate statistical analysis used?

cycles. Similarly, when obesity was considered in terms of waist circumference, in men with partners whose waist circumference was <80 cm – using men with waist circumferences <94 cm as the reference – men with waist circumference >94 to 101.6 cm had OR = 0.71 95%CI 0.36–1.36, while men with waist circumferences ≥101.6 cm had OR = 0.76 95%CI 1.07–2.82. Interestingly, when all possible combinations of male and female BMI categories were compared the only significant difference found was between both normal weight partners and both morbidly obese (OR = 0.41 95%CI 0.17 to 0.98). This result was not replicated when waist circumference was used for classification.

A much larger study carried out by Nguyen et al. [46] which retrospectively considered 26,303 women aged 18–40 years who were having their first pregnancy found that median time to pregnancy was two months for each paternal BMI category examined (<20, 20.0–22.49, 22.5–24.99, 25.0–27.49, 27.5–29.99, 30.0–32.49) except for the top two categories (32.5–34.99, ≥35.0) where it was 3 months (although reported this data was not statistically assessed in the original report as it was not the focus of the study).

Infertility

Three studies reported on the effects of paternal BMI on infertility (variously described as infertility, subfertility and subfecundity [43,46,47]. Although there were some differences in how they classified infertility and categorised BMI (Table 1) a meta-analysis was possible comparing normal weight men to obese men (BMI = 30–34.9 in [46], ≥30 in [47] and 32–34 in [43]). This showed that obese men were significantly more likely to be infertile OR = 1.49 95%CI 1.30–1.70 (Fig. 2). Meta-analysis was also possible for the results of Nguyen et al. and Ramlau-Hansen which showed that overweight men also had increased infertility compared to normal weight men (OR = 1.18 95%CI 1.11–1.26) [46,47]. For both meta-analyses statistical heterogeneity was low, as indicated by the I^2 value and not statistically significant as indicated by the Chi^2 value (Fig. 2).

Sallmen et al. [43] also reported that each 3 unit increase in male BMI relative to the 20–22 range resulted in an increase in infertility of OR = 1.12 95%CI 1.01–1.25 in a cohort of 2111 couples. Additionally, they reported that the increase in infertility amongst morbidly obese (BMI ≥ 35) men was not statistically significant, although this finding is likely the result of the relatively few men who fit this category (15% of the study population, Table 1) causing the analysis to be underpowered.

Pregnancy complications

Any studies which reported on pregnancy complications were eligible for inclusion, however only studies on complications relating to birth weight were found. In a prospective cohort study of 2002 couples McCown et al. found that obese men (BMI ≥ 30) were significantly more likely to father babies who were small for gestational age (SGA; OR = 1.50 95%CI 1.05–2.16) compared to non-obese men [40]. This finding was consistent with the results when obesity was defined by waist circumference (<102 cm; OR = 1.53 95%CI 1.06–2.20). Conversely, Yang et al. carried out a case-control study wherein cases (N = 870) of macrosomia (birthweight >4000 g) were matched to normal weight (N = 6341) babies (2500−4000 g) (36). Compared with normal weight mothers and fathers (BMI 18.5–23.9) a non-significant effect was found for underweight men (BMI < 18.5; OR = 1.26 95%CI 0.75–2.13), although overweight (BMI 24–27.9; OR = 1.33 95%CI 1.11–1.59) and obese (BMI ≥ 28; OR = 1.99 95%CI 1.49–2.65) men had significantly increased risks.

Neonatal and childhood outcomes

Birth weight and length

Four studies investigated the effect of paternal weight on birthweight and/or length [35,38,41,48] while a fifth considered percent body fat at birth [45]. Differences in outcomes, classifications and analytical approaches prevented meta-analysis. Chen et al. used multivariate regression analysis to examine the association of paternal BMI as a continuous measure with birthweight in boys (N = 492) and girls (N = 407) separately [35]. A significant association was found for boys (partial regression coefficient (β) = 19.535 95%CI 4.126–34.945, p = 0.013; indicating that a 1 unit increase in

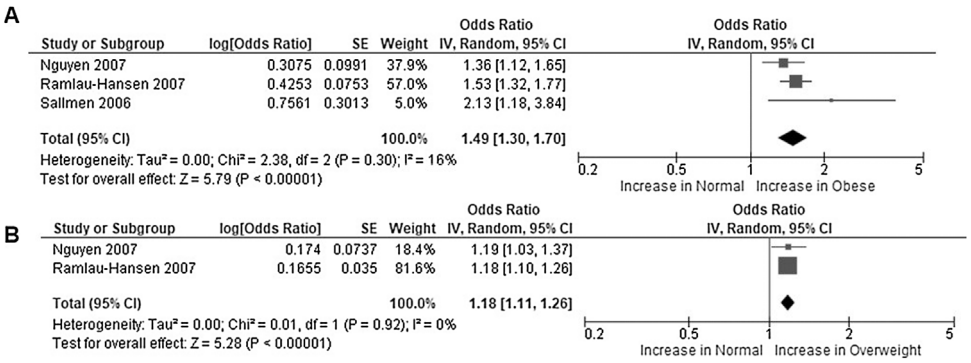

Fig. 2. Meta-analysis of infertility in normal weight men compared with A obese men or B overweight men.

BMI was associated with a 19.535 g increase in birthweight when all other variables in the model were held constant) but the effect was non-significant for girls (β = 6.779 95%CI −7.9829 to 21.387, p = 0.362). L'Abee et al. who did not stratify their analysis by the sex of the offspring, did not find any significant association between paternal BMI and birth weight (β = 7.25 95%CI −2.98 to 17.48, N = 2,528, p = 0.479) [38]. In Pomeroy et al. there was also no significant association between birth weight and paternal BMI after adjusting for covariates (exact values were not reported, N = 1041), however there was an association for neck-rump length (β = 0.12, p = 0.008) [41]. As the start point of a long-term growth study, the full results of which are reported below, Regnault et al. compared the birth weight (N = 1286) and length (N = 1265) of the offspring of normal weight men (BMI 18.5–25) to that of overweight (mean difference (MD) = −6 g, 95%CI -51 to 39, p = 0.79 and 0.01 cm 95%CI −0.19 to 0.21 p = 0.97) and obese men (MD = 22 g 95%CI −54 to 99, p = 0.58 and MD = −0.1 cm 95%CI −0.49 to 0.29, p = 0.59), but did not find any significant differences [48]. Finally, McCarthy et al. reported no effect of increasing paternal BMI on neonatal percent body fat (MD = −0.03 95%CI −0.10 to 0.05, N = 1243) [45].

Child weight and height

Six studies analysed the association between paternal weight and the development of offspring weight, height or BMI either at discreet time points past the neonatal period or as an overall trend [18,37,39,42,48,49]. Davey-Smith et al. reported a significant association between paternal BMI and offspring BMI at 7.5 years (β = 0.202 95%CI 0.175 to 0.229, N = 4654) as did Lawlor et al. at 14 years (β = 0.251 95%CI 0.199 to 0.304, N = 7223) [37]. At three months Regnault et al. reported that the children of obese fathers were significantly heavier than the children of normal weight fathers (MD = 154 g 95%CI −34 to 274, p = 0.01, N = 1285) and had higher weight growth velocities (MD = 1.4 g/d 95%CI 0.62–2.18, p = 0.002) although the effect was not significant for overweight fathers (MD=6 g 95%CI −63 to 75, p = 0.87 and MD=0.2 g/d 95%CI −0.19 to 0.59, p = 0.48) [48]. Length and length-growth velocity at 3 months were not affected for overweight or obese fathers (N = 1252).

Linabery et al. examined infant BMI growth curves from birth to 3.5 years (N = 872) and found that the offspring of obese fathers had curves that differed significantly from the offspring of normal weight fathers (p = 0.02) [42]. The effect was non-significant for overweight fathers (p = 0.39) and when overweight and obese fathers were considered together (p = 0.08). Infant weight growth curves were not affected by paternal overweight or obesity compared to normal weight. However, infant length curves (N = 890) were significantly different between normal weight and overweight fathers (p = 0.03) and between normal weight and overweight or obese fathers (p = 0.05) but was not significantly affected in obese fathers (p = 0.15). These three growth curves were also examined for overweight compared to obese fathers, but no differences were found. Rath et al. reported that there was a significant interaction between paternal BMI and offspring BMI trajectories from 1 to 22 years (male: z-score = 0.008 95%CI 0.0041 to 0.012, p < 0.001, N = 517; female: z-score = 0.005 95%CI 0.0011 to 0.0089, p < 0.001, N = 510) [18]. However, Zalbahar et al. [49] found no association between paternal BMI over 12 months measured at 2, 6 and 12 months (N = 153) for weight for age score (β = 0.00 95%CI −0.02 to 0.03, p = 0.727) length for age score (β = −0.01 95%CI −0.03 to 0.02, p = 0.621), weight for length score (β = 0.01 95%CI −0.01 to 0.04, p = 0.250) or BMI for age score (β = 0.01 95%CI −0.01 to 0.03, p = 0.433).

Incidence of disease

The only study that investigated the effect of paternal weight on the incidence of disease in the offspring was Suren et al. who found that the offspring of obese men (BMI ≥ 30) were significantly more likely to be diagnosed with autism disorder (OR = 1.73 95%CI 1.07–2.82), Asperger disorder (OR = 2.01 95%CI 1.13–3.57) or autism spectrum disorder (OR = 1.53 95%CI 1.07–2.17: a combined index of all three disorders considered) compared to normal weight men (BMI < 25) [34] in a cohort of 92,909 births. This effect was not seen for diagnoses of pervasive developmental disorder not otherwise specified (PDD-NOS: OR = 0.95 95%CI0.53 to 1.65) or for any disorder in overweight men (BMI 24–29.9; Autism disorder: OR = 1.31 95%CI 0.94–1.85; Asperger disorder: OR = 0.85, 95%CI 0.54–1.33; PDD-NOS: OR = 0.93 95%CI 0.66–1.30; Autism spectrum disorder: OR = 1.00 95%CI 0.78–1.28).

Discussion

Meta-analysis showed that both overweight and obese men were more likely to experience infertility compared with normal weight men, however findings for time to pregnancy were mixed, with meta-analysis being prevented by heterogeneity in study designs. Data for pregnancy complications also could not be meta-analysed as the two studies reported on diametrically opposed birthweight outcomes (macrosomia [36] and SGA [40]) although, interestingly, both reported significant effects. Other studies which assessed birthweight as a continuous measure did not find any consistent association, raising the possibility that paternal BMI affects the variability of birthweight, with high BMI in fathers increasing the frequency of unhealthy extremes, while having relatively little effect on the mean. Nonetheless, the included studies on the association between paternal BMI and the development of offspring weight or BMI suggested that fathers with higher BMI had children who themselves developed higher BMIs (again, heterogeneity precluded meta-analysis and this finding is particularly vulnerable to being biased by the offsprings' environment).

The finding of increased diagnoses of infertility in men with increasing BMI mirrors those findings of the previous systematic review assessing male BMI and sperm function [4]. This is likely due to obesity's negative effects on sex hormones (the hypothalamic–pituitary–gonadal (HPG) axis) and sperm function. Men with increasing BMI are more likely to have reduced plasma concentrations of testosterone and increased concentrations of estrogen, both of which are independently associated with subfertility and reduced sperm counts via disrupting spermatogenesis [50–53]. In addition to these hormonal changes, men with increasing BMI are also more likely to have perturbed sperm function including; increased sperm DNA damage [4], increased sperm reactive oxygen species [24], reduced sperm mitochondrial function [25], reduced sperm binding abilities [54] and changes to metabolic and inflammatory profiles of seminal plasma [26,27] – attributes which have been independently associated with male subfertility and the need for assisted reproductive technologies to achieve a pregnancy [55].

The findings that increased male BMI increased rates of both SGA and macrocosmia mirror those for animal models. A rat model of male obesity and metabolic syndrome found that male rats fed a diet high in fat produced smaller offspring at birth [12], while a mouse model of male obesity prior to the onset of metabolic syndrome found that male mice fed a high fat diet produced larger offspring on post-natal day 3 [13]. Both SGA and macrosomia at birth are associated with increased fetal complications including; increased admissions to neonatal intensive care units and foetal mortality [56,57]. They also increase the risk of developing chronic diseases later in life, including but not limited to; hypertension, kidney disease, vascular disease and metabolic dysfunction (i.e. type II diabetes) [58,59]. It should be noted that early signs of a number of these chronic disease states have already been shown in offspring of animal models of paternal obesity [12,13,20–22]. Further, long term cohort studies are needed to confirm if findings are similar in humans, as well as to investigate the effect of paternal BMI on the distribution of birthweights beyond mean differences and low/high categorisation.

Amongst the studies which looked at birthweight as a continuous measure the majority did not adjust or stratify by offspring sex. The one study by Chen et al. [35] which did differentiate between sexes found increases in the birth weight of male babies with increased paternal BMI. Differential effects on birthweights between sexes is commonly seen in other parental pre conception perturbations [60], with male foetuses at an increased risk of altered growth when presented with suboptimal conditions or an environmental challenge [61,62]. In addition, sex specific molecular signatures of X and Y bearing sperm and the way they respond to environmental insults have been shown to differ in paternal programming [63] which could also result in offspring sex differences. Therefore, it is likely that increased paternal BMI is affecting male and female fetuses differently, which is mirrored in animal models of male obesity [13,19].

When assessing the effects of paternal obesity on children's growth post birth, it is hard to differentiate the effects of a common 'obesogenic' nurturing environment and the genetic/epigenetic contributions of paternal obesity at conception. However, there were clear consistencies between studies, with five out of the six showing associations between paternal BMI and the BMI of children between 1 and 22 years, increased fat mass of 3 month old babies and higher weight growth velocities of children until 3.5 years [18,37,39,42,48]. Animal models of paternal obesity have also shown similar weight, growth and adiposity changes of offspring even when the 'obesogenic' raising environment is controlled for [10,13,62,64], indicating that the effect in humans is also likely to be at least partially independent of the shared living environment of the father and child. Studies in animal models have also shown that when offspring of high fat diet fathers are similarly challenged by a high fat diet, increases in offspring adiposity and weight were exacerbated [62,65]. This indicates that a shared 'obesogenic' raising environment could perpetuate the effects in children. In addition, the increased weight growth velocities observed in Regnault et al. [48] could be the result of the 'catch up growth' associated with SGA infants which generally accumulates as increased fat mass [66].

In addition to the genetic/epigenetic contributions delivered at conception, fathers can also influence their children's relationship with food and physical exercise. Parents have the largest influence on their children's food related and physical activity behaviors as children learn about food/exercise through observations and imitation [67]. Compelling evidence shows the strong positive role fathers have in promoting healthy BMI, food intake and physical activity in children. Results from the Longitudinal Study of Australian Children, found that the BMI of children were strongly associated with parenting behaviors and styles of their fathers and not mothers [68], while another Australian study found associations between fathers' dietary intake and their 20 month old child's intake of fruit and sweet snacks independent of mothers dietary habits [69]. Therefore, fathers' lifestyle habits are important indicators for their young children's dietary and physical activity related behaviors.

The results of Suren et al. which showed that paternal obesity was associated with increased risk of children being diagnosed with autism spectrum disorder (ASD), need to be interpreted with caution, given the percentage change in diagnosis of children from obese fathers was only 0.1–0.2% [34]. Further, a recent systematic and meta-analysis assessing parental BMI and risk of ASD diagnosis in children found no association with any paternal BMI categories (normal vs overweight vs obese) [70]. However, this systematic review and meta-analysis only included a low number of studies (N = 3) and only included studies where paternal height and weight were collected pre-pregnancy (accounting for why Suren et al. [34] was not included in their meta-analysis). The fact the association from Suren et al. [34] was independent of any maternal effect (with adjustment for paternal obesity attenuating the maternal association previously attributed to women's BMI in a single sex study [71]), was not present for the ASD subtype PDD-NOS, and was minimally affected by adjustments for sociodemographic and lifestyle characteristics supports that that this correlation is real and not the result of residual cofounding. This study's findings highlight the lack of research around paternal BMI at conception and its associations with ASD diagnosis in children.

The mechanism for transmission of altered health to the next generation from paternal obesity has been attributed to a combination of genetic and epigenetic (non-coding RNAs, histone modifications and methylation) changes delivered by the semen to the female reproductive tract at conception. This includes direct signalling from the sperm to the egg at fertilisation and seminal plasma/sperm to the uterus at copulation [28,29]. A number of genes have been identified to play a part in the heritability of weight [72], however these genetic variants do not fully account for intergenerational transmission, and a number of studies in rodents have directly shown a link between paternal diet at conception, sperm epigenetic changes and altered offspring phenotypes [73–75]. For example, utilising a high fat diet mouse model of obesity, authors found key small non coding RNAs called transfer RNAs (tRNAs) were dysregulated in the sperm of high fat diet fed males and that when these key tRNAs were injected into the male pronucleus of the early embryo they recapitulated metabolic disorders in offspring [73]. In addition, changes to small non coding RNAs and methylation status of sperm have also been shown in men who are obese, with these epigenetic changes in sperm modifiable through weight loss [30].

The main limitation of this systematic review was the heterogeneity in study design and the relatively low number of studies

included for most outcomes which consistently prevented meta-analysis (the investigation of time to pregnancy would particularly benefit from further, well powered studies with rigorous statistical analysis). Additionally, although experimental studies on the effect of parental obesity on pregnancy and child health outcomes can never be ethically carried out, the weakness of observational studies for addressing issues of causality must be acknowledged. Nonetheless, critical appraisal showed that the included studies had relatively rigorous designs, although loss to follow up was infrequently addressed and many studies assessed paternal height and weight by maternal recall which is not reliable. A caveat remains in that a key aspect of quality, appropriate adjustment for maternal factors, was used as an exclusion criteria. With 35 associated exclusions, the overall body of literature on the contribution of paternal BMI to pregnancy and child health is far more confounded than the critical appraisal of the included studies indicates.

Unfortunately, while evidence for the father's role in the transmission of ill health to children is growing, the impacts of paternal obesity on pregnancy and offspring health is still widely unrecognised by the clinical community. In many media and government campaigns women are still heavily targeted for improving the health of their pregnancies and subsequent children [77], with father's contributions ignored. Moving forward, pre pregnancy health messaging should focus on 'healthy couples', which centres on improving the health of both women and men prior to pregnancy. Furthermore, it remains a possibility that the relationship between diet and body mass means that the effects we have attributed to adiposity could also be being affected by diet – postprandial inflammation has been observed following the consumption of fatty meals [76] and raises the possibility that improvements in reproductive health could be achieved independent of weight loss.

While more and more research about the paternal influences on pregnancy and child's health is being published every day, a brief analysis of PubMed results indicates that there is still a ten-fold difference between research focusing on maternal influence compared with paternal influences. Given the huge amount of literature assessing maternal influences on pregnancy and child health outcomes, which does not always control or adjust for paternal influence, it is vital that future human cohort studies collect reliable health information for both partners and appropriately integrate it into the statistical analyses of outcomes in order to determine true parental effects.

Ethical statement

The authors declare that they have read and have abided by the statement of ethical standards for manuscripts submitted to the Obesity Research & Clinical Practice.

Competing interest

The authors declare no competing interests.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.orcp.2019.11.003.

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