Maternal body mass index and risk of testicular cancer in male offspring a systematic review and meta analysis

Review

Maternal body mass index and risk of testicular cancer in male offspring: A systematic review and meta-analysis

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ABSTRACT

Objectives: To date a number of studies have examined the association between maternal weight and testicular cancer risk although results have been largely inconsistent. This systematic review and meta-analysis investigated the nature of this association. Methods: Search strategies were conducted in Ovid Medline (1950–2009), Embase (1980–2009), Web of Science (1970–2009), and CINAHL (1937–2009) using keywords for maternal weight (BMI) and testicular cancer. Results: The literature search produced 1689 hits from which 63 papers were extracted. Only 7 studies met the pre-defined criteria. Random effects meta-analyses were conducted. The combined unadjusted OR (95% CI) of testicular cancer in the highest reported category of maternal BMI compared with the moderate maternal BMI was 0.82 (0.65–1.02). The Cochran's Q P value was 0.82 and the corresponding I^2 was 0%, both indicating very little variability among studies. The combined unadjusted OR (95% CI) for testicular cancer risk in the lowest reported category of maternal BMI compared to a moderate maternal BMI category was 0.88 (0.65–1.20). The Cochran's Q P value was 0.05 and the corresponding I^2 was 54%, indicating evidence of statistical heterogeneity. The combined unadjusted OR (95% CI) of testicular cancer risk per unit increase in maternal BMI was 1.01 (0.97–1.06). The Cochran's Q test had a P value of 0.05 and the corresponding I^2 was 55% indicating evidence of statistical heterogeneity. Conclusion: This meta-analysis, which included a small number of studies, showed that a higher maternal weight does not increase the risk of testicular cancer in male offspring. Though an inverse association between high maternal BMI and testicular cancer risk was detected, it was not statistically significant. Further primary studies with adjustment for appropriate confounders are required.

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1. Introduction

In the United Kingdom, 2109 new cases of testicular cancer were diagnosed in 2005 [1–4]. With the introduction of combination chemotherapy in the 1970s, survival rates for testicular cancer have increased each year and the most recent population-based five-year survival rate for all patients registered in England and Wales was 98% [5].

Testicular cancer has several distinct epidemiological features compared with other cancers. Firstly, it has an unusual age-distribution, occurring most commonly in young and middle-aged men. Secondly, for reasons as yet unknown, its incidence is rising, particularly in white Caucasian populations throughout the world [6]. Ninety-five percent of testicular tumours are germ-cell

tumours (TGCTs), of which approximately 40–45% are seminomas and a similar percentage are nonseminomas [7]. Nonseminomas tend to occur on average ten years earlier than seminomas and the incidence of nonseminomas peaks in the 20–35 age group while the incidence of seminomas peaks in the 25–45 age group.

The causes of testicular cancer are unclear, but both genetic and environmental factors most likely play a part. Established risk factors for TGCT include cryptorchidism, atrophy, inguinal hernia and infertility [6,8]. It is thought that TGCTs are initiated during foetal development, most likely in the first trimester, and progress to invasive cancer under the influence of adult hormones [6,9]. Therefore, several studies have investigated prenatal and perinatal exposures in relation to TGCT risk, although most of these analyses have included only a small number of cases. Research has also focused on maternal factors which could influence foetal development and it has been suggested that carcinoma in situ of the testis, a precursor of TGCT, has its origins in foetal life [10] and that subnormal androgen exposure and/or increased oestrogen exposure are potentially important risk factors [11]. Maternal weight influences the intrauterine hormonal milieu and, as obesity

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has been increasing in both males and females in western populations in recent decades, it is possible that trends in maternal weight might account for at least part of the increase in testicular cancer incidence seen in these countries [12]. The aim of this study was to synthesise the evidence base for a relationship between maternal weight and testicular cancer risk in male offspring by systematic review and meta-analysis of the existing literature.

2. Materials and methods

2.1. Search strategy

An electronic literature search was conducted using Ovid Medline (US National Library of Medicine, Bethesda, MD, USA) (1950–2009), Embase (Reed Elsevier PLC, Amsterdam, The Netherlands) (1980–2009), Web of Science (Thompson Reuters—New York, NY, USA) (1970–2009), and CINAHL (EBSCO Publishing, Ipswich, MA, USA) (1937–2009) on 13th March 2009. The search included the following keywords or medical subject heading (MeSH) terms; cancer of the testi(s); testi(s) cancer(s); testi(s) neoplasm(s); testicular neoplasm(s); testi(s) tumo(u)r; seminoma(s); testi(s) teratocarcinoma; or testicular germ cell tumo(u)r; and maternal weight; overweight; obesity; pregnancy; body mass index; BMI; adiposity; central adiposity; body composition; body fat; fat distribution; overweight mothers; obese mothers; maternal obesity; body weight; waist circumference; waist–hip ratio; and WHR.

2.2. Selection criteria

The titles and abstracts of identified articles were screened by three reviewers (SA, MC, LM) to exclude those that were clearly irrelevant. The full text articles of potentially relevant studies were obtained and independently examined by two reviewers (SA, MC) to determine whether they met the criteria for inclusion in the review. To be included, observational studies (case–control or cohort) with testicular cancer as an outcome had to include an estimate of the association (odds ratio or relative risk) with maternal body mass index (BMI) or provide data from which this estimate could be calculated. Review publication types were removed but no language restriction was specified. The reference lists of all included articles were also examined to identify any other relevant studies that may have been missed.

2.3. Data extraction

From each article two reviewers (SA, MC) extracted the following information: year of publication, study design and location, sample size, case definitions, population demographics, exclusion criteria, time of BMI measurement in relation to relevant pregnancy, adjustments for confounders, and results from each study. The reviewers applied the Newcastle–Ottawa Quality Assessment Scale (NOS) (http://www.lri.ca) to all studies. The NOS scale was developed to assess the quality of non-randomised studies with its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results.

2.4. Statistical analysis

The association between testicular cancer risk in sons and maternal BMI was summarised by re-calculating an unadjusted odds ratio (OR) and standard error (SE) for testicular cancer in sons in the highest and lowest categories of maternal BMI compared to a moderate category. Unadjusted values for ORs and SE were calculated as no uniformity was observed among adjusted confounders within each study and also because the categories used to classify maternal BMI differed among studies. The reference (moderate) BMI category also varied among studies, consequently we recalculated the unadjusted ORs so that a similar reference category was used for all studies (Table 2). The BMI data was stratified into three categories for each study as slightly different thresholds were used (Table 2).

Random effects models were used to calculate pooled ORs. ORs with 95% confidence intervals were combined and then weighted to produce a pooled estimate. The I^2 statistic estimates between-study heterogeneity that is not due to chance. An I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity [13]. Begg's funnel plots were produced and Egger's test [14] was conducted to inspect potential small study bias. Further sensitivity analyses were conducted, whereby studies were omitted based on NOS quality scores, BMI categorisation and/or study location. A summary OR per unit BMI (kg/m^2) was calculated assuming a normal distribution across categories for each study [15]. Statistical analysis was conducted using Intercooled STATA (version 9.2, College Station, TX, USA).

3. Results

3.1. Search results

The search strategy results are shown in Fig. 1. Seven studies met the pre-defined criteria [16–22]. All seven studies were case–control studies, five population-based and two hospital-based. These seven studies included over 2400 cases and 3500 controls. Three studies were conducted in Europe (Sweden, Denmark, and United Kingdom), three in North America (Canada and United States) and one in Asia (Japan) (Table 1). All studies employed either self-reported or interviewer-administered questionnaires for the men diagnosed with testicular cancer, the controls, and their mothers (Table 1).

One study [20] provided only three pre-pregnancy weight categories, which were used as substitutes for BMI categories (low [<55 kg], moderate [55–59 kg], high [>60 kg]), another study [22] provided three BMI categories (<19, 19–21, 22+), but the data were stratified into two categories for the purpose of this systematic review (low [<19] and moderate [>19]). A third study [21,23] involved a very small number of cases (37) and controls (37) and only provided two categories of BMI (high [>25] and moderate [<25]). References [21,23] are the same study. The BMI categories for all studies included are outlined in Table 2 and are described in the context of the International Classification of BMI [24] according to the World Health Organization (WHO).

3.2. Meta-analysis of high maternal BMI versus moderate BMI

The association between high maternal BMI and testicular cancer risk in sons is shown in Fig. 2. Six studies contributed data to the meta-analysis [16–21]. The Depue study [22] was not included in this meta-analysis as the re-categorised BMI data did not include a 'high' category.

The combined unadjusted OR (95% CI) of testicular cancer in the highest reported category of maternal BMI compared with the moderate maternal BMI was 0.82 (0.65–1.02). Cochran's Q test had a P value of 0.82 and the corresponding I^2 was 0%, both indicating very little variability among studies that cannot be explained by chance (Fig. 2). The combined unadjusted OR (95% CI) was not significantly affected even when two case–control studies [20,21,23] were excluded in separate analyses. The results from the study by Mori [21,23] were excluded as it received a low NOS quality score of 5/9. The sensitivity analysis produced a combined
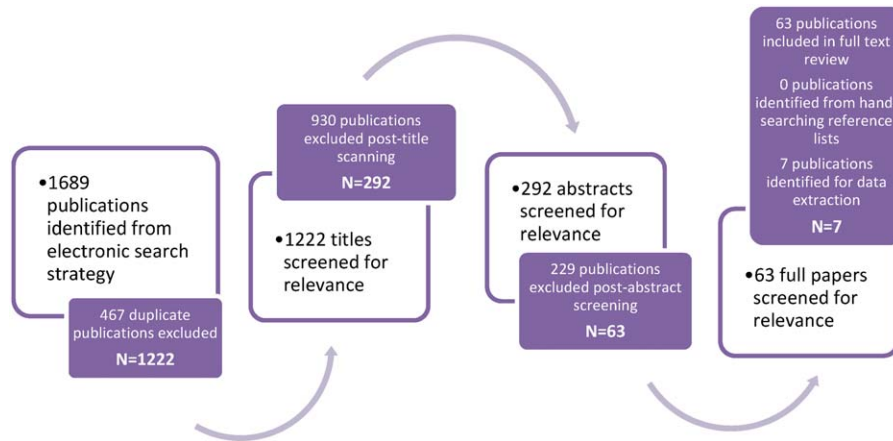
Fig. 1. A flow diagram of study selection for maternal BMI and testicular cancer risk in sons.

unadjusted OR of 0.83 (0.66–1.04) and Cochran's Q test had a P value of 0.93. The Moller study [20] was excluded as it only contained three weight categories used as proxy BMI categories. The sensitivity analysis produced a combined unadjusted OR of 0.78 (0.60–1.02) and Cochran's Q test had a P value of 0.77.

Publication bias is not present as the funnel plot appears symmetrical (Fig. 3) and Begg's and Egger's tests were not statistically significant.

3.3. Meta-analysis of low maternal BMI versus moderate BMI

The association between low maternal BMI and testicular cancer risk in sons is shown in Fig. 4. Six studies were included in the meta-analysis [16–20,22]. One study [21,23] involved a very small number of cases (37) and controls (37) and provided two categories of BMI (high [>25] and moderate [<25]) and therefore was not included in this meta-analysis.

The combined unadjusted OR (95% CI) for testicular cancer in the lowest reported category of maternal BMI compared to a moderate maternal BMI was 0.88 (0.65–1.20). The Cochran's Q test had a P value of 0.05 and the corresponding I^2 was 54%, indicating evidence of statistical heterogeneity. The combined unadjusted OR (95% CI) was not significantly affected when two case–control studies [20,22] were excluded in separate analyses. The Moller study [20] was excluded as it only contained three weight categories used as proxy BMI categories. The sensitivity analysis produced a combined unadjusted OR of 0.84 (0.57–1.22) and Cochran's Q test had a P value of 0.04. The results from the Depue

Table 1
Characteristics of studies included in systematic review of maternal BMI and risk of testicular cancer in sons.

Study–year–location	Study design	Study time period (first TC diagnosis)	Ages of men (diagnosis/recruitment)	Cases	Controls	Matching cases/controls (frequency or Individually)	Maternal BMI assessment	Newcastle–Ottawa Quality scale score
Pettersson [16] (2008) Sweden	Population-based case–control	1988–2002	Age ≥ 15 years	293	861	No	Pre-pregnancy BMI Collected during antenatal period in Swedish Medical Birth Register	8/9
Sonke [17] (2007) United States	Hospital-based case–control	1990–1996	18 years ≤ age ≤ 50 years	144	86	No	Pre-pregnancy BMI self-reported/Interviewed on phone	7/9
Coupland [18] (2004) United Kingdom	Population-based case–control	1984–1987	15 years ≤ age ≤ 49 years	794	794	Individually matched age	Pregnancy BMI self-reported/collected from postal questionnaire	7/9
Weir [19] (2000) Canada	Population-based case–control	1987–1989	16 years ≤ age ≤ 59 years	502	975	No	Pre-pregnancy BMI self-reported/interviewed on phone	7/9
Moller [20] (1997) Denmark	Population-based case–control	1986–1988	16 years ≤ age ≤ 42 years	296	287	Frequency-matched year of birth	Pre-pregnancy BMI self-reported/collected from postal questionnaire	8/9
Mori [21,23] (1990) Japan	Hospital-based case–control	1976–1986	Age ≤ 46 years	37	37	Individually matched year of birth	Pre-pregnancy BMI self-reported/collected from postal questionnaire	5/9
Depue [22] (1983) United States	Population-based case–control	1973–1979	16 years ≤ age ≤ 30 years	108	108	Individually matched year of birth race	Pre-pregnancy BMI self-reported/interviewed on phone	4/9

Table 2
Slightly different BMI thresholds designated for each study and in comparison to the International BMI Classification [24] according to the World Health Organization (WHO).

Study–year	Location	BMI categories					
		Low (kg/m^2)		Moderate reference (kg/m^2)		High (kg/m^2)	
		Study	WHO	Study	WHO	Study	WHO
Pettersson [16] (2008)	Sweden	<19.00	<18.50	20.00–24.00	18.50–24.99	>25.00	≥25.00
Sonke [17] (2007)	United States	<18.50	<18.50	18.50–24.90	18.50–24.99	>25.00	≥25.00
Coupland [18] (2004)	United Kingdom	<20.00	<18.50	20.00–25.00	18.50–24.99	>25.00	≥25.00
Weir [19] (2000)	Canada	<18.00	<18.50	18.00–25.00	18.50–24.99	>25.50	≥25.00
Moller [20] (1997)	Denmark	<55.00 kg[*]	<18.50	55.00–59.00 kg[*]	18.50–24.99	>60.00 kg[*]	≥25.00
Mori [21] (1990)	Japan	N/A	<18.50	<25.00	18.50–24.99	>25.00	≥25.00
Depue [22] (1983)	United States	<19.00	<18.50	>19.00	18.50–24.99	N/A	≥25.00

[*] Moller and Skakkebaek [20] provided only three pre-pregnancy weight categories, which were used as substitutes for BMI categories.

study [22] were excluded as it received a low NOS quality score of 4/9. The sensitivity analysis produced a combined unadjusted OR of 0.99 (0.77–1.28) and Cochran's Q test had a P value of 0.25.

Publication bias is not present as the funnel plot appears symmetrical (Fig. 5) and Begg's test and Egger's tests were not statistically significant.

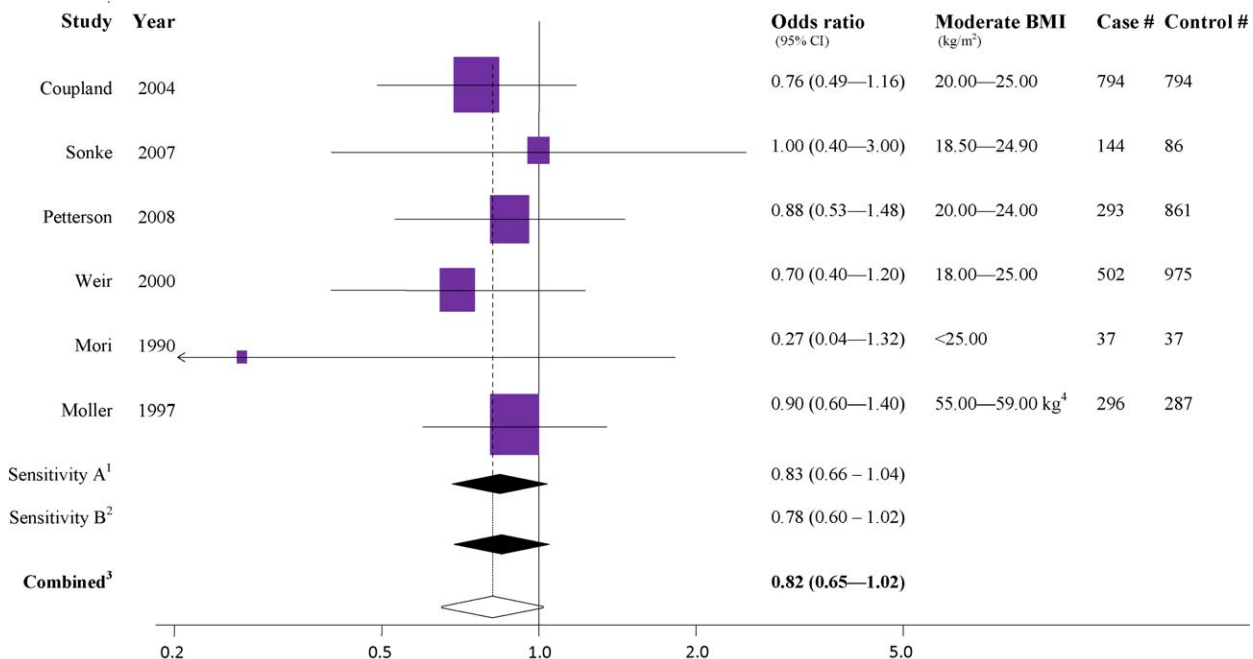### 3.4. Meta-analysis of testicular cancer risk per unit increase in maternal BMI

The odds of testicular cancer per unit increase in maternal BMI are shown in Fig. 6. Six studies contributed to the analysis [16–19,21,22]. The Moller study [20] could not be included in this analysis because it reported weight and not BMI.

The combined unadjusted OR (95% CI) of testicular cancer risk per unit increase in maternal BMI was 1.01 (0.97–1.06). The Cochran's Q test had a P value of 0.05 and the corresponding I^2 was 55% indicating evidence of statistical heterogeneity. The combined

unadjusted OR remained unchanged even when two case–control studies [21,22] were excluded in a separate analyses. The Mori study [21,23] was excluded based on study location as the difference in mean BMI in Asian countries tend to be lower than European and North American countries [25]. The sensitivity analysis produced a combined unadjusted OR of 1.02 (0.96–1.08) and Cochran's Q test had a P value of 0.03. The Depue study [22] was excluded as it received a low NOS quality score of 4/9. The sensitivity analysis produced a combined unadjusted OR of 1.00 (0.97–1.02) and Cochran's Q test had a P value of 0.44.

4. Discussion

This is the first systematic review of the literature on maternal BMI and testicular cancer (TC) risk in male offspring. The pooled estimate was based on data from over 2400 cases and 3500 controls obtained from six case–control studies. The meta-analysis yielded a pooled risk estimate below one for high compared with

Study	Year	Odds ratio (95% CI)	Moderate BMI (kg/m^2)	Case #	Control #
Coupland	2004	0.76 (0.49—1.16)	20.00—25.00	794	794
Sonke	2007	1.00 (0.40—3.00)	18.50—24.90	144	86
Petterson	2008	0.88 (0.53—1.48)	20.00—24.00	293	861
Weir	2000	0.70 (0.40—1.20)	18.00—25.00	502	975
Mori	1990	0.27 (0.04—1.32)	<25.00	37	37
Moller	1997	0.90 (0.60—1.40)	55.00—59.00 kg[4]	296	287
Sensitivity A[1]		0.83 (0.66 – 1.04)			
Sensitivity B[2]		0.78 (0.60 – 1.02)			
Combined[3]		0.82 (0.65—1.02)			

[1] Sensitivity analysis excluding Mori study [21, 23]
[2] Sensitivity analysis excluding Moller study [20]
[3] Test for heterogeneity chi^2=2.18, df=5, P=0.82, I^2=0% (95% CI 0-75%)
[4] The Moller study provided only three pre-pregnancy weight categories, which were used as substitutes for BMI categories

Fig. 2. Meta-analysis of high maternal BMI versus moderate BMI and testicular cancer risk in sons.
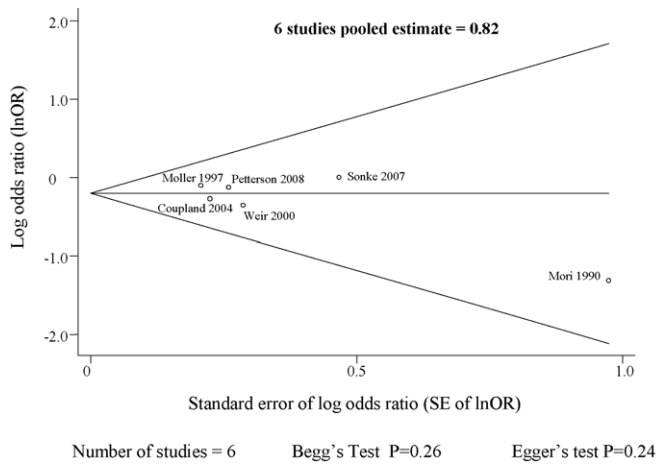
Fig. 3. Funnel plot: test for publication bias in studies comparing high maternal BMI to moderate maternal BMI.
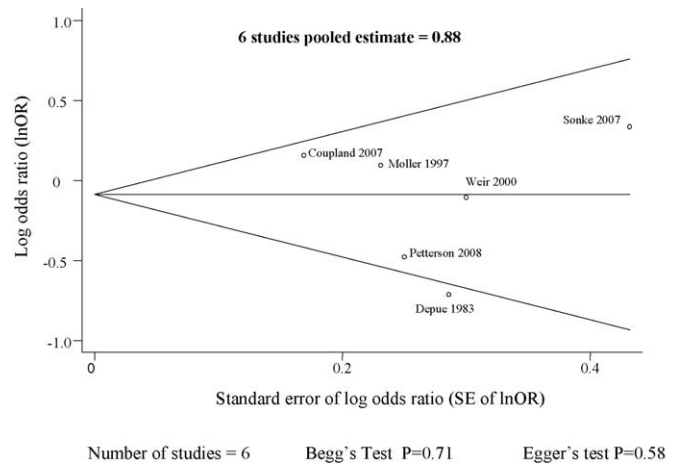

Fig. 5. Funnel plot: test for publication bias in studies comparing low maternal BMI to moderate maternal BMI.

moderate maternal BMI (OR = 0.82; 95% CI 0.65–1.02), but the results were not statistically significant. There was no evidence to suggest an association for low compared with normal maternal BMI and TC risk in offspring. Furthermore, there was no evidence of a trend in risk with increasing maternal BMI.

Maternal BMI is positively associated with offspring birth weight [26] and high birth weight has recently been shown to be positively, not inversely, associated with testicular cancer risk; Ramlau-Hansen et al. [27] reported an incidence rate ratio of 1.6 (95% CI 1.0–2.4) for men born with a high birth weight (>4150 g) compared to those of normal birth weight. However, the issue of

birth weight and testicular cancer is contentious as different studies and differing meta-analyses have shown conflicting findings [28–30]. It would be circumspect to conclude that an association between these two variables remains unsubstantiated, although no studies to date have shown that a high birth weight is associated with a reduced risk of testicular cancer and therefore the inverse association between maternal BMI and TC risk seen in this meta-analysis is unlikely to be mediated by birth weight.

A possible explanation for the inverse association between maternal BMI and TC risk in offspring in this meta-analysis could be confounding by parity, maternal age, or birth order. For
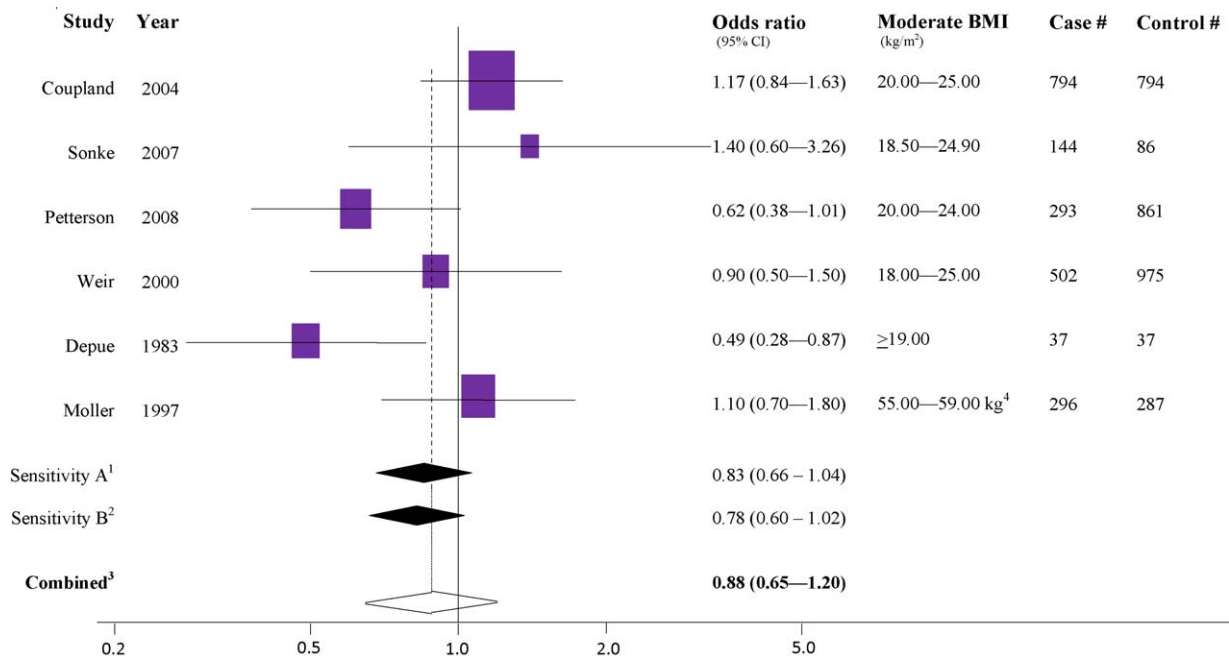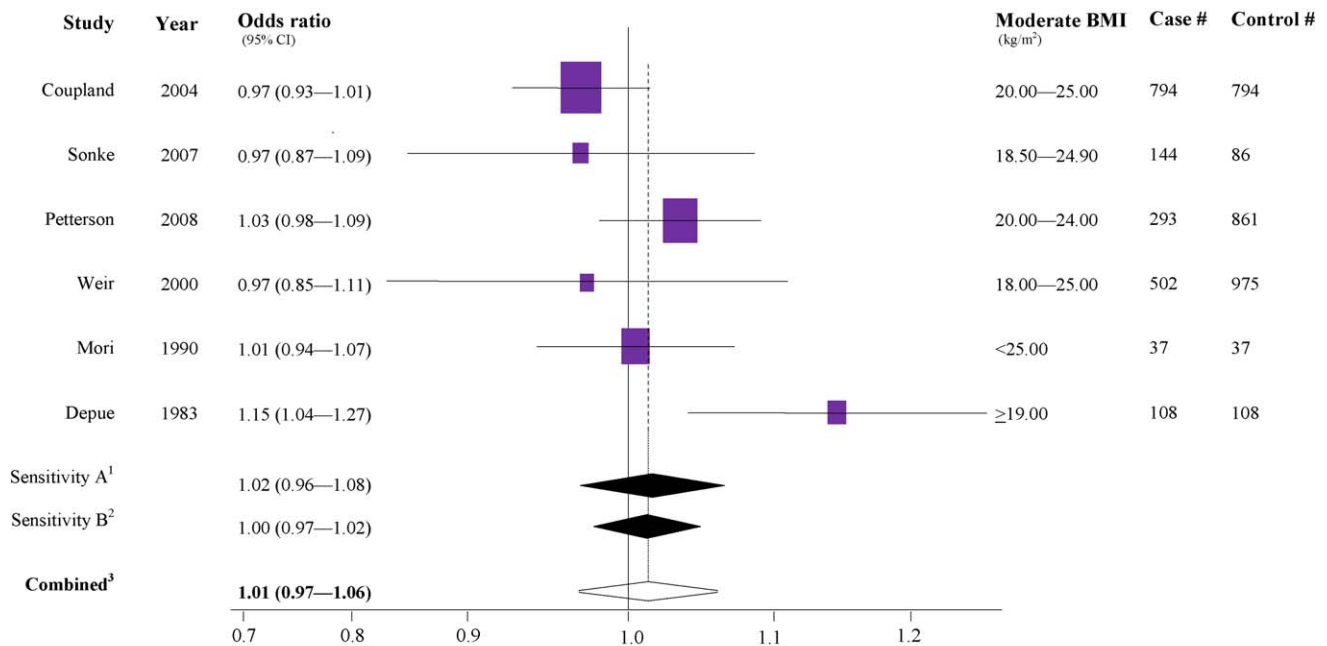

[1] Sensitivity analysis excluding Moller study [20]
[2] Sensitivity analysis excluding Depue study [22]
[3] Test for heterogeneity x^2=10.90, df=5, P=0.05, I^2=54% (95% CI 0-82%)
[4] The Moller study provided only three pre-pregnancy weight categories, which were used as substitutes for BMI categories

Fig. 4. Meta-analysis of low maternal BMI versus moderate BMI and testicular cancer risk in sons.

Fig. 6. Meta-analysis of testicular cancer risk per unit increase in maternal BMI.

example, it is known that multiparous women are more likely to be overweight than nulliparous women [31,32] and that increased parity is associated with a decreased risk of TC in offspring compared with nulliparous women [33–36]. A number of studies have investigated the link between maternal age and TC risk in offspring [18,27,37] and all have reported an inverse association. Several studies have also reported an inverse association between birth order and TC risk [18,33,35,38,39]. In previous studies, maternal age and birth order have been interpreted mainly as proxies for foetal exposure to maternal hormones because higher levels of oestrogens have been measured during first compared with subsequent pregnancies [40–42].

According to the circulating oestrogen hypothesis [22,43], increasing levels of exposure to endogenous oestrogen in foetal life increases the risk of testicular cancer. A review of published epidemiologic studies on male reproductive disorders and indicators of prenatal maternal oestrogens concluded that the studies support the hypothesis that higher prenatal oestrogen exposure is associated with testicular cancer [8]. Confounding by parity, maternal age or birth order may therefore explain the apparent inverse association between high maternal weight and testicular cancer risk seen in this meta-analysis.

The results of this study should be interpreted with caution as there are several limitations. Firstly, a small number of studies met the inclusion criterion; however the majority of studies included were of high quality. Secondly, studies included in the meta-analysis were also of case–control design and it is possible that the results of the individual studies have been affected by recall bias due to the retrospective recording of maternal BMI. Thirdly, measurement error may have also been an issue as mothers self-reported their weight and height [44,45]. Another potential limitation is the pooling of unadjusted estimates in the meta-analyses. However pooling unadjusted estimates is the recommended method, in contrast to combining adjusted estimates or artificially adjusted estimates, where there is variability among adjusted factors within studies [15].

5. Conclusion

This is the first meta-analytic review of maternal weight in relation to testicular cancer. The meta-analysis provides evidence that higher pre-pregnancy maternal weight does not increase the risk of testicular cancer in male offspring.

Further larger epidemiological studies are required that differentiate between seminomas and nonseminomas, include better measures of maternal obesity (such as the waist–hip ratio, weight gain during pregnancy, etc.) and which examine the association between maternal BMI adjusted for important confounders such as birth weight, birth order, maternal age and parity.

Conflict of interest

The authors declared no conflicts of interest.

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