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MATERNAL BODY MASS INDEX (BMI) 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 1,689 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 0.83 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 0.92 (0.75 – 1.12). The Cochran's Q P value was 0.05 and the corresponding I^2 was 54%, indicating evidence of statistical heterogeneity. No association was observed when maternal BMI was treated as a continuous variable.

Conclusion—This meta-analysis, which included a small number of studies, showed an inverse association between high maternal BMI and testicular cancer risk of borderline statistical significance. Further primary studies with adjustment for appropriate confounders are required.

INTRODUCTION

In the United Kingdom, 2,109 new cases of testicular cancer were diagnosed in 2005 (Office for National Statistics; ISD Online; Welsh Cancer Intelligence; NICR 2008). 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% (Coleman *et al*, 2004).

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 (Horwich *et al*, 2006). Ninety-five percent of testicular tumours are germ-cell tumours (TGCTs), of which approximately 40–45% are seminomas and a similar percentage are nonseminomas (Bray, 2006). 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 (Storgaard *et al*, 2006; Horwich *et al*, 2006). 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 (Horwich *et al*, 2006; Oosterhuis *et al*, 2003). 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 (Rorth *et al*, 2000) and that subnormal androgen exposure and/or increased oestrogen exposure are potentially important risk factors (Skakkebaek *et al*, 2001). Maternal weight influences the intrauterine hormonal milieu and, as obesity 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 (Godfrey *et al*, 2001). 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.

MATERIALS AND METHODS

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.

Selection Criteria

The titles and abstracts of identified articles were screened by three reviewers (SSA, MMC, LJM) to exclude those that were clearly irrelevant. The full text articles of potentially relevant studies were obtained and independently examined by two reviewers (SSA, MMC) 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) between 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.

Data extraction

From each article two reviewers (SSA, MMC) 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.

Statistical Analysis

The association between testicular cancer risk in sons and maternal BMI was summarised by recalculating 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. The BMI data was stratified into three categories for each study as slightly different thresholds were used.

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 (Higgins *et al*, 2002). Begg's funnel plots were produced and Egger's test (Egger, 1997) was conducted to inspect potential small study bias. Further sensitivity analyses were conducted, whereby each study is omitted in turn. A summary OR per unit BMI (kg/m^2) was calculated assuming a normal distribution across categories for each study (Greenland et al, 1992). Statistical analysis was conducted using Intercooled STATA (version 9.2, College Station, TX, USA).

RESULTS

Search Results

The search strategy results are shown in Figure 1. Seven studies met the pre-defined criteria (Pettersson *et al*, 2008;Sonke *et al*, 2007;Coupland *et al*, 2004;Weir *et al*, 2000;Moller *et al*, 1997;Mori *et al*, 1990;Depue *et al*, 1983). All seven studies were case-control studies, five population-based and two hospital-based. These seven studies included over 2,400 cases and 3,500 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). All studies employed either self-reported or interviewer-administered questionnaires for the men diagnosed with testicular cancer and the controls.

One study (Moller *et al*, 1996) 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 (Depue *et al*, 1983) 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 (Mori *et al*, 1988; Mori *et al*, 1990) involved a very small number of cases (37) and controls (37) and only provided two categories of BMI (high [>25] and moderate [<25]).

Meta-analysis of high maternal BMI versus moderate BMI

The association between high maternal BMI and testicular cancer risk in sons is shown in Figure 2. Six studies contributed data to the meta-analysis (Pettersson *et al*, 2008;Sonke *et al*, 2007;Coupland *et al*, 2004;Weir *et al*, 2000;Moller *et al*, 1997;Mori *et al*, 1990). The

study by Depue *et al.* 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 0.83 and the corresponding I^2 was 0%, both indicating very little variability among studies that cannot be explained by chance (Figure 2). The statistical homogeneity was not changed even when two case-control studies (Mori *et al*, 1988;Moller *et al*, 1997) were excluded in a separate analysis. The results from the study by Mori were excluded as it was a small case-control study (37 cases and 37 controls), receiving a NOS quality score of 5/9 and in comparison with western populations, BMI of the Japanese population is typically lower (Japanese adult mean BMI levels of 22–23 kg/m^2) (WHO 2009). The Moller study was excluded as it only contained three weight categories used as proxy BMI categories. The sensitivity analysis produced a combined unadjusted OR of 0.80 (0.61 – 1.05) and Cochran's Q test had a P value of 0.10 with an I^2 of 0%.

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

Meta-analysis of low maternal BMI versus moderate BMI

The association between low maternal BMI and testicular cancer risk in sons is shown in Figure 4. Six studies were included in the meta-analysis (Pettersson *et al*, 2008;Sonke *et al*, 2007;Coupland *et al*, 2004;Weir *et al*, 2000;Moller *et al*, 1997;Depue *et al*, 1983). One study (Mori *et al*, 1988;Mori *et al*, 1990) 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 0.92 (0.75 – 1.12). 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 statistical heterogeneity was reduced when two case-control studies (Moller *et al*, 1997; Depue *et al*, 1983) were excluded in a separate analysis. The study by Moller was excluded as it only contained three weight categories used as proxy BMI categories. The study by Depue was excluded as it received a NOS quality score of 4/9. The sensitivity analysis produced a combined unadjusted OR of 0.95 (0.68 – 1.34) and Cochran's Q test had a P value of 0.16 with an I^2 of 42%.

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

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 Figure 6. Six studies contributed to the analysis (Pettersson *et al*, 2008;Sonke *et al*, 2007;Coupland *et al*, 2004;Weir *et al*, 2000;Mori *et al*, 1990;Depue *et al*, 1983). The study by Moller et al (Moller *et al*, 1996) 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 0.048 and the corresponding I^2 was 55% indicating evidence of statistical heterogeneity. The statistical heterogeneity was reduced when two case-control studies (Mori *et al*, 1988; Depue *et al*, 1983) were excluded in a separate analysis. The Mori study was excluded based on the small study size and difference in mean BMI as Asian countries tend to be lower than European

and North American countries. The study by Depue was excluded as it received a NOS quality score of 4/9. The sensitivity analysis produced a combined unadjusted OR of 0.99 (0.96 – 1.03) and Cochran's Q test had a P value of 0.30 with an I^2 of 0%.

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 2,400 cases and 3,500 controls obtained from six case-control studies and indicates that high compared with normal maternal BMI is associated with a decrease in testicular cancer risk (OR = 0.82; 95% CI 0.65—1.02), although the results were only borderline statistically significant (p=?). There was no evidence to suggest an association for low compared with normal maternal BMI and TC risk in offspring.

Maternal BMI is positively associated with offspring birth weight (Hindmarsh *et al*, 2008) and high birth weight has recently been shown to be positively, not inversely, associated with testicular cancer risk; Ramlau-Hansen (2009) reported an incidence rate ratio of 1.6 (95% CI 1.0–2.4) for men born with a high birth weight (>4,150 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 (Michos *et al* 2007; Cook *et al* 2007; Akre *et al* 2008). It would be cicumspect 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 example, it is known that multiparous women are more likely to be overweight than nulliparous women (Arroya et al, 1995; Brown et al, 1992) and that increased parity is associated with a decreased risk of TC in offspring compared with nulliparous women (Sabroe and Olsen, 1998; Wanderas et al, 1998; Westergaard et al, 1998; Prener et al, 1992). A number of studies have investigated the link between maternal age and TC risk in offspring (Ramlau-Hansen et al, 2009; Coupland et al, 2004; Dieckmann et al, 2001) and all have reported an inverse association. Several studies have also reported an inverse association between birth order and TC risk (Cook et al, 2009; Richiardi et al, 2004; Coupland et al, 2004; Sabroe and Olsen, 1998; Westergaard et al, 1998). 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 (Bernstein et al, 1986; Panagiotopoulou et al, 1990; Key et al, 1996). According to the circulating oestrogen hypothesis (Sharpe et al 1993; Depue et al, 1983), 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 (Storgaard et al, 2006). Confounding by parity, maternal age or birth order may therefore explain the apparent inverse association between 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 (Stunkard *et al*, 1981; Palta *et al*, 1982). 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 (Greenland et al, 1992).

CONCLUSION

This is the first meta-analytic review of maternal weight in relation to testicular cancer. The meta-analysis provides some evidence that higher pre-pregnancy maternal weight may be associated with a decrease in testicular cancer risk in male offspring.

Further larger epidemiological studies are required that differentiate between seminomas and non-seminomas, 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.

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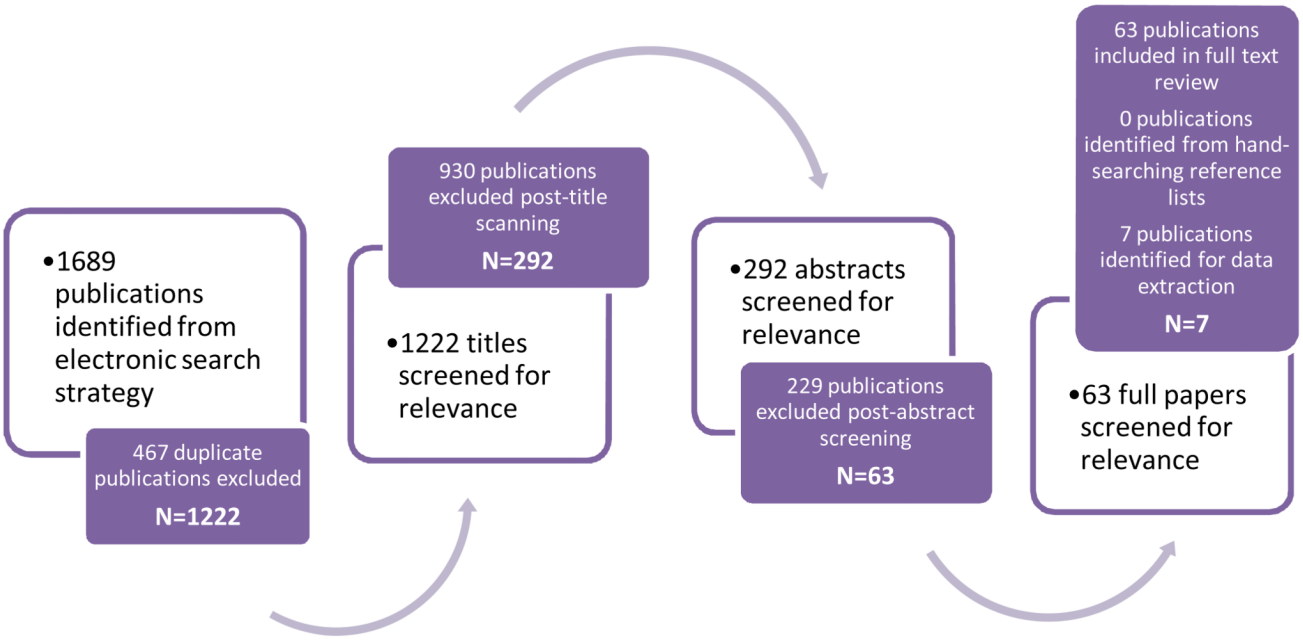
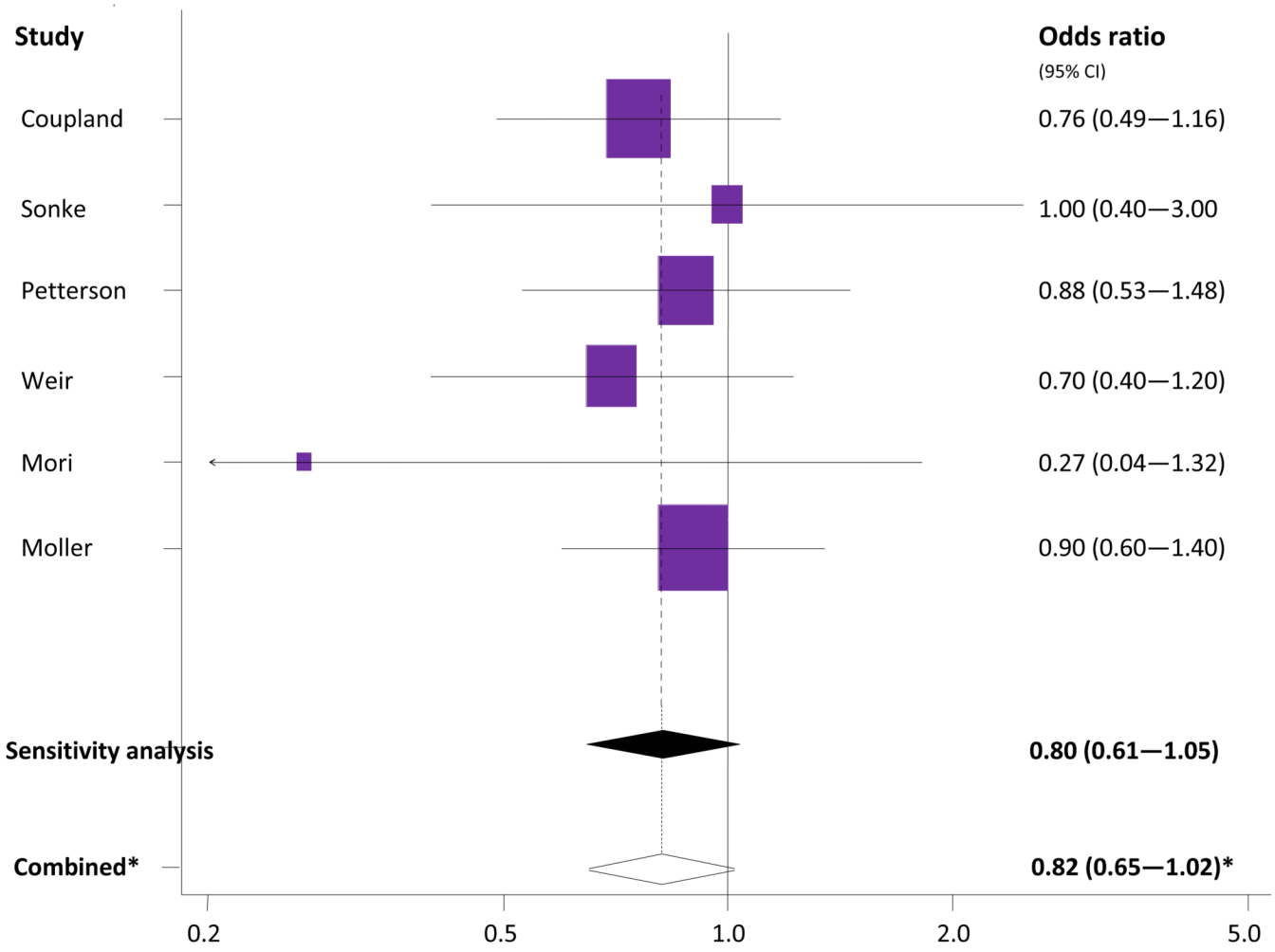


Figure 1.
A flow diagram of study selection for maternal BMI and testicular cancer risk in sons.



*Test for heterogeneity x2=2.18, df=5, P=0.83, I2=0% (95% CI 0-75%)

Figure 2.
Meta-analysis of high maternal BMI versus moderate BMI and testicular cancer risk in sons.

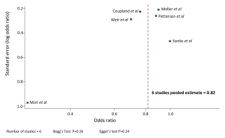


Figure 3.
Funnel plot: test for publication bias in studies comparing high maternal BMI to moderate maternal BMI.

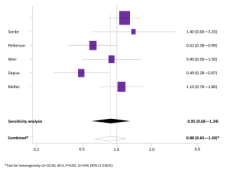


Figure 4.
Meta-analysis of low maternal BMI versus moderate BMI and testicular cancer risk in sons.

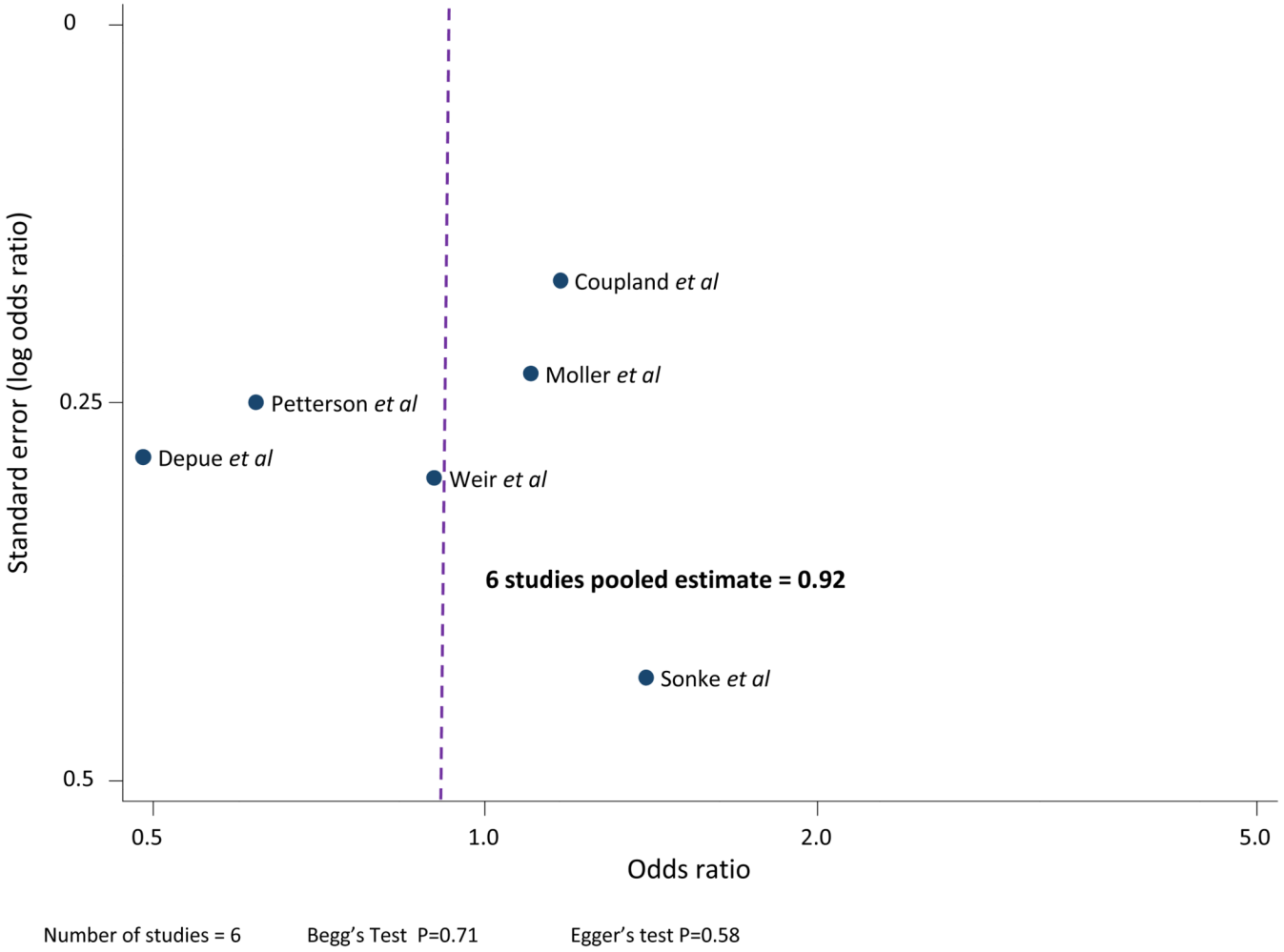
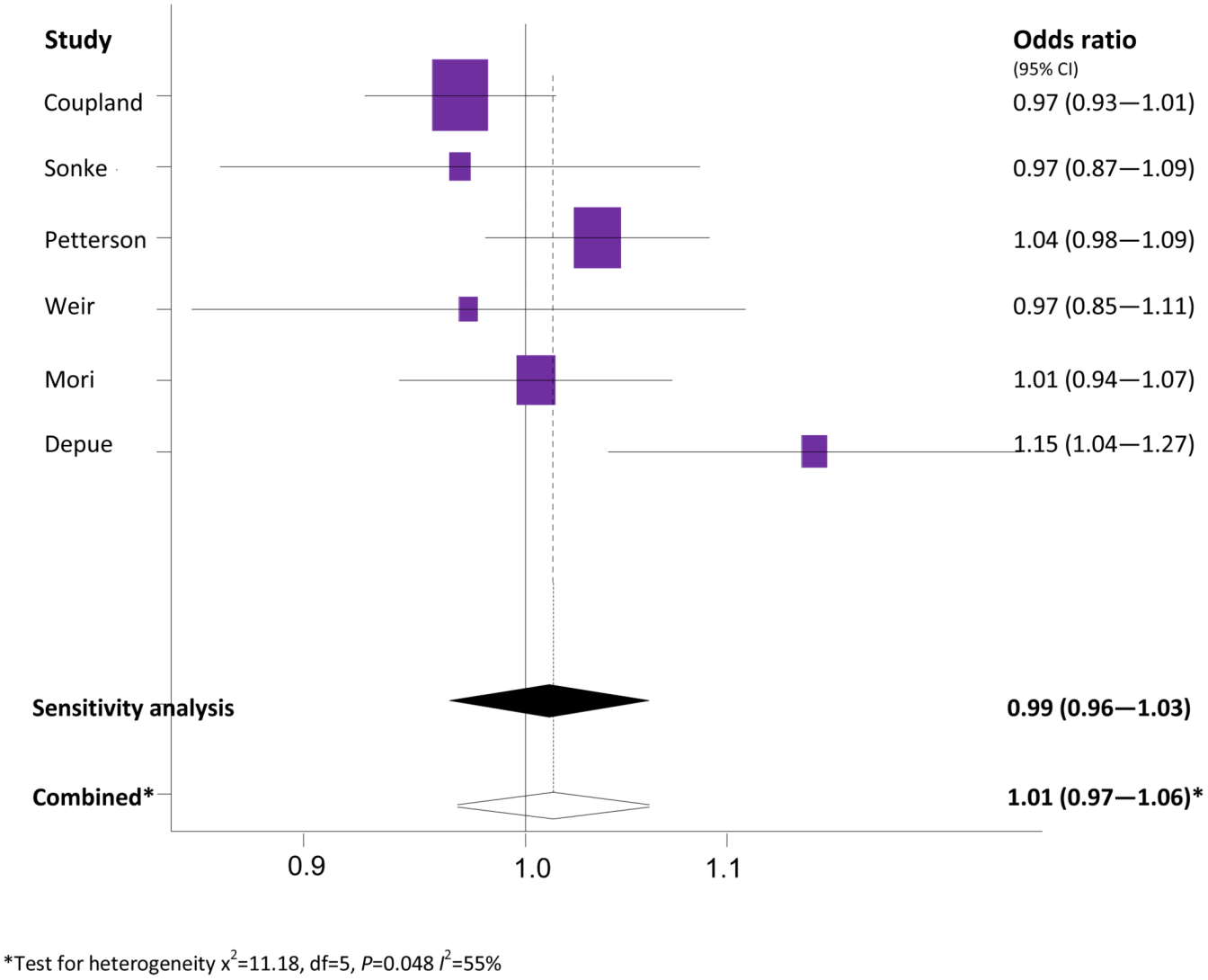


Figure 5.
Funnel plot: test for publication bias in studies comparing low maternal BMI to moderate maternal BMI.



*Test for heterogeneity x^2=11.18, df=5, P=0.048 I^2=55%

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

Table 1

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

Study-year-location	Study design	Cases & source	Controls & source	Matching cases/controls (Frequency or Individually)	Maternal BMI assessment	Newcastle-Ottawa Quality scale score (NOS)	Moderate BMI group (kg/m^2)
Pettersson *et al* (2008) Sweden	Population-based case-control	293 Retrieved from Swedish Cancer Register	861 First three men born at the same hospital after a case	No	Pre-pregnancy BMI Collected during antenatal period in Swedish Medical Birth Register	8/9	20–24
Sonke *et al* (2007) United States	Hospital-based case-control	144 Retrieved from University Cancer Centre and Tumour Registry	86 Cases nominated 4+ cancer- free friends that were of same race	No	Pre-pregnancy BMI Self-reported/ Interviewed on phone	7/9	18.5–24.9
Coupland *et al* (2004) United Kingdom	Population-based case-control	794 Retrieved from major cancer treatment centres and regional cancer registries	794 Selected from GP list where case registered	Individually-matched by age	Pregnancy BMI Self-reported/ collected from postal questionnaire	7/9	20–25
Weir *et al* (2000) Canada	Population-based case-control	502 Retrieved from Ontario Cancer Registry	975 Selected from Ontario census data	No	Pre-pregnancy BMI Self-reported/ interviewed on phone	7/9	18–25
Moller *et al* (1997) Denmark	Population-based case-control	296 Retrieved from Danish Cancer Registry	287 Selected from Danish Central Person Register	Frequency-matched by year of birth	Pre-pregnancy BMI Self-reported/ collected from postal questionnaire	8/9	55–59 kg***
Mori *et al* (1990) Japan	Hospital-based case-control	37 Retrieved from urological ward records of nine hospitals	37 Selected from address registers at five public health centres	Individually-matched by year of birth	Pre-pregnancy BMI Self-reported/ collected from postal questionnaire	5/9	<25
Depue *et al* (1983) United States	Population-based case-control	108 Retrieved from population-based cancer registry	108 Selected from same neighbourhoods as cases	Individually-matched by year of birth and race	Pre-pregnancy BMI Self-reported/ interviewed on phone	4/9	≥19