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CANCERS

A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer—experiences of the son

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Background We undertook a systematic review and meta-analysis of perinatal variables in relation to testicular cancer risk, with a specific focus upon characteristics of the son.

Methods Literature databases Scopus, EMBASE, PubMed and Web of Science were searched using highly sensitive search strategies. Of 5865 references retrieved, 67 articles met the inclusion criteria, each of which was included in at least one perinatal analysis.

Results Random effects meta-analysis produced the following results for association with testicular cancer risk: birth weight [per kilogram, odds ratio (OR) = 0.94, 95% confidence interval (CI) 0.88–1.01, $I^2 = 12\%$], low birth weight (OR = 1.34, 95% CI 1.08–1.67, $I^2 = 51\%$), high birth weight (OR = 1.05, 95% CI 0.96–1.14, $I^2 = 0\%$), gestational age (per week, OR = 0.95, 95% CI 0.92–0.98, $I^2 = 38\%$; low vs not, OR = 1.31, 95% CI 1.07–1.59, $I^2 = 49\%$), cryptorchidism (OR = 4.30, 95% CI 3.62–5.11, $I^2 = 44\%$), inguinal hernia (OR = 1.63, 95% CI 1.37–1.94, $I^2 = 38\%$) and twinning (OR = 1.22, 95% CI 1.03–1.44, $I^2 = 22\%$). Meta-analyses of the variables birth length, breastfeeding and neonatal jaundice did not provide evidence for an association with testicular cancer risk. When low birth weight was stratified by data ascertainment (record/registry vs self-report), only the category of self-report was indicative of an association. Meta-regression of data ascertainment (record/registry vs self-report) inferred that record-/registry-based studies were less supportive of an association with gestational age (per week = 0.97, 95% CI 0.94–1.00, $I^2 = 29\%$; low vs not = 1.08, 95% CI 0.91–1.28, $I^2 = 32\%$).

Conclusion In conclusion, this systematic review and meta-analysis finds evidence that cryptorchidism, inguinal hernia and twinning, and tentative evidence that birth weight and gestational age, are associated with risk of testicular cancer.

Keywords Epidemiology, meta-analysis, pregnancy, review, systematic, testicular neoplasms

Introduction

Testicular cancer is the most common malignancy among adolescent and young adult males of European ancestry,[1,2] the incidence of which has been increasing over the past 40 years.[3–5] The only risk factors consistently associated with testicular cancer are cryptorchidism, prior history of testicular cancer and family history of testicular cancer.[6] However, the natural history of testicular cancer indicates that exposures early in life are likely to be integral in the initial stages of carcinogenic transformation. Carcinoma *in situ* (CIS), the precursor of testicular germ-cell cancer, also referred to as intratubular germ-cell neoplasia, unclassified (IGCNU), is postulated to arise from the primordial germ cells[7] before or during their migration to the embryonic genital ridge.[8] Further evidence for this postulate has been provided by comparative studies, showing the similarity of CIS cells to gonocytes and embryonic stem cells,[9] whereas descriptive analyses of the age-of-onset of CIS and testicular cancer also suggest that the initial stages of carcinogenesis are during early development.[10] This has promoted research of *in utero* and early-life exposures in attempts to further elucidate the aetiopathogenesis of this malignancy.

Developmental abnormalities and exposures during and after the perinatal period are thought to strongly modulate the risk of testicular cancer, the most obvious example of which being cryptorchid testes. While such perinatal variables could arguably be proxies of the maternal *in utero* environment, they may also conceivably modify risk of malignancy directly themselves. A number of studies have assessed the risk of testicular cancer in relation to perinatal characteristics of the son, but many of these have lacked sufficient statistical power for the number of tests they have conducted, a difficult conundrum given the rarity of this cancer and the questions that remain about its aetiology. As such, the testicular cancer literature is far from a state of concurrence[11] and elucidation of risk factors has not been forthcoming. Therefore, we undertook a systematic review and meta-analysis of perinatal variables in relation to testicular cancer risk, with a specific focus upon characteristics of the son.

Method

Highly sensitive search strategies were designed for the literature databases Scopus (Elsevier B.V., Amsterdam, The Netherlands; 1823–2008), EMBASE (Elsevier B.V., Amsterdam, The Netherlands; 1974–2008), PubMed (National Center for Biotechnology Information, US National Institutes of Health, USA; 1950–2008) and Web of Science (Thomson Reuters, New York, USA; 1900–2008) (copies of these search strategies are available on request). These search strategies incorporated a vast array of terms for many perinatal variables in relation to testicular cancer with no restriction on language. The final electronic literature searches were conducted 24 November 2008 and the articles were pooled and managed using Endnote X2.[12] Titles, abstracts and keywords were independently reviewed as needed for selection of potentially relevant references by two individuals (M.B.C., M.P.M.). The full text was retrieved of any reference that gave any indication that it might contain data on at least one perinatal variable and testicular cancer or if it was a review article of testicular cancer exposures. Citations of retrieved articles were checked for references that may have been missed or absent from the databases utilized. Cases had to be identified as testicular cancer cases and the age range could not be restricted to or include infantile testicular cancers. There were no stringent criteria for controls but, if a study had more than one control group, the preference order was population, neighbourhood, hospital and cancer. Inclusion criteria for categorical variable analyses, such as cryptorchidism or inguinal hernia, stipulated that the study had to be a cohort or case–control in design and provide tabulated numbers of cases and controls that were and were not exposed. Similar criteria were applied to continuous variable analyses but the data had to be tabulated into at least three categories of exposure or the study needed to provide the number, mean and standard deviation of the variable for the case and control groups. This data format enables per unit log odds ratios (ORs) and standard errors of the log OR to be estimated for continuous, normally distributed variables, using methods previously described.[13] Authors of references which alluded to, but did not provide, data that met the inclusion criteria necessary for analysis were contacted in a request for Supplementary data available at *IJE* online. If a manuscript and author of a study could not provide data to enable calculation of a log OR and standard error of the log OR but provided an estimate of risk that was minimally adjusted (e.g. adjusted only for age) then this was included in the analysis. If the population base of two or more studies were judged to have overlapped considerably, the preference for retention in the analysis was for: cohort studies over case–control studies, given no discrepancy in the number of categories of the variable available for analysis; larger studies over smaller studies, given studies of the same design; and risk estimates with the lowest error, given studies of

the same design and similar size. The two latter criteria were used to select amongst multiple manuscripts of the same study. Studies that were adjudged to have a small likelihood of geo-temporal overlap in their base populations were retained in analyses. Studies that met the inclusion criteria for an analysis had data extracted into Microsoft Excel, which was subsequently checked twice for consistency. These data were then imported into STATA 10[14] for statistical analysis.

Statistical analysis

For categorical variable analyses, unadjusted log ORs and standard errors of the log OR were calculated for each study using either logistic regression or, for dichotomous variables, the direct approach of the meta-analysis command (*metan*) in STATA. The Woolf method[15] was utilized for estimation of 95% confidence intervals (CIs). For continuous variable analyses, methods previously described were used to estimate per unit log OR and standard errors of the log OR.[13] For dichotomous analyses with zero-count cells, 0.5 was added to each cell for analysis via STATA's *metan* command. Meta-analyses were conducted using a random effects model[16] to allow for variation in true associations across studies. The chosen estimate of heterogeneity was the I^2 statistic, which is the percentage of total variation in risk estimates attributable to genuine variation rather than sampling error.[17] To assess meta-analytic assumptions and explore the relation between precision and magnitude of association, funnel plots were generated with Egger's tests[18] using an arbitrary but conservative *P*-value of <0.1 to assess meta-analytic assumptions and explore the relation between precision and magnitude of association. Sensitivity analyses were also conducted, whereby each study of an analysis was omitted in turn. Meta-analyses using a fixed effects model were also applied as an additional measure of sensitivity. Meta-regression was conducted using the variables: continent of study, data ascertainment (self-report; registry/medical record) and study design (cohort; case–control), which were specified a priori.[19,20] In the interests of space, given the number of meta-analyses undertaken, these additional analyses will only be mentioned if they produced a *P*-value below the arbitrary threshold of 0.05 or if they were deemed necessary for comprehensive interpretation.

Results

After duplicates were deleted from the comprehensive literature search there remained a total of 5865 articles. A total of 358 articles had their full text retrieved, the citations of which were checked for any articles which may have been missed or which were absent in the databases utilized. Subsequently, a further 118 articles were identified and retrieved, giving a total full text article count of 476. Authors of 41 of these studies were contacted in a request for supplementary information. Authors of 33 articles replied and 13 of these were able to provide additional unpublished data. In total there were 67 articles that met the inclusion criteria, each of which was included in at least one perinatal analysis.

This article details the analyses of variables pertaining to characteristics of the son, as opposed to the mother; the results of which have been previously published.[21] Specifically, this manuscript considers the variables birth length, birth weight, gestational age, cryptorchidism, inguinal hernia, neonatal jaundice, twinship and having been breast fed. A meta-analysis of hypospadias could not be included due to so few patients having been exposed from very few studies.[22–24] Articles included in each analysis, and those excluded due to large geo-temporal overlap or being reports of the same study, are detailed in Table 1. The summary estimates of each of these variables using random effects meta-regression are shown in Figure 1. Analysis using fixed effects methods were similar (Supplementary Figure 1; Supplementary data available at *IJE* online), thus only the estimates attained from the random effects models are discussed and presented herein.

The meta-analysis of 15 studies that provided data on birth weight indicated toward an inverse relationship with risk of testicular cancer (OR = 0.94, 95% CI 0.88–1.01, $I^2 = 12\%$). On categorical analysis, low birth weight was associated with an increased risk (OR = 1.34, 95% CI 1.08–1.67, $I^2 = 51\%$; Figure 2), an association that was slightly weakened when restricted to studies comparing <2500 g with a reference group (OR = 1.22, 95% CI 0.98–1.51, $I^2 = 43\%$; Supplementary Figure 2; Supplementary data available at *IJE* online). However, when the unrestricted dataset was stratified by data ascertainment, the category of self-report provided stronger evidence for an association (OR = 1.55, 95% CI 1.19–2.01) than the summary estimate for record or registry-based studies (OR = 1.07, 95% CI 0.77–1.48; Figure 2). In addition, meta-regression of data ascertainment produced a *P*-value of 0.077. The meta-analysis of high birth weight showed no such association (OR = 1.05, 95% CI 0.96–1.14, $I^2 = 0\%$; Supplementary Figure 3; Supplementary data available at *IJE* online) and this did not change when restricted to studies comparing $\geqslant 4000$ g or >4000 g with a reference group (OR = 1.05, 95% CI 0.97–1.14, $I^2 = 0\%$; Supplementary Figure 4; Supplementary data available at *IJE* online) or analysed using a fixed effects model (Supplementary Figure 1; Supplementary data available at *IJE* online).

Gestational age was inversely related to the risk of testicular cancer in both continuous and dichotomous analyses (Figures 1 and 3; Supplementary Figure 5; Supplementary data available at *IJE* online). However, data ascertainment (record/registry vs self-report)

Table 1 Studies included and excluded from each meta-analysis

Analytic variables	Studies		
	Included	Excluded	
		Geo-temporal overlap	Same study
Birth length	(30,34–36,51–54)		(55) due to (52)
Birth weight			
Continuous	(30,31,33–37,42,52–54,56–59)	(60) due to (30)	(55) due to (52); (51) due to (42)
Categorical			
Low vs normal	(30–35,42,52–54,56–59,61–63)	(60) due to (30)	(55) due to (52); (51) due to (42)
High vs normal	(30–35,42,52–54,56–59)	(60) due to (30)	(55) due to (52); (51) due to (42)
Gestational age			
Continuous	(30,33,42,52–54,57,59)	(60) due to (30)	(55) due to (52); (51) due to (42)
Categorical			
Low vs not low	(30,33,36,42,52–54,56,57,59,64,65)	(60) due to (30)	(55) due to (52); (51) due to (42)
Cryptorchidism	(31,34,35,43,58,59,64–91)	(23) due to (74); (24,36,92) due to (84); (51) due to (85); (61) due to (65); (63) due to (79); (60) due to (76)	(22,57) due to (71); (93) due to (88); (56,94) due to (69); (33) due to (87)
Inguinal hernia	(23,24,34,35,63–65,70,71,73, 81–83,85,86,88,90,91,94)	(61) due to (65); (79) due to (63)	(22,57) due to (71)
Neonatal jaundice	(34,42,52)	(60) due to (42)	(55) due to (52)
Twinning	(25,34,56,61,82,95–99)	(54, 100) due to (NV Holm, personal communication); (52) due to (96); (49,50) due to (25)	
Breast fed	(34,57,67,82)		

produced *P*-values of 0.017 and 0.002 for continuous and dichotomous metrics of gestational age, respectively, when interrogated by meta-regression. When the meta-analyses were stratified by data ascertainment (Figure 3 and Supplementary Figure 5; Supplementary data available at *IJE* online), the summary estimates for record- or registry-based studies were less supportive of association (gestational age, per week = 0.97, 95% CI 0.94–1.00, $I^2 = 29\%$; low gestational age vs not low = 1.08, 95% CI 0.91–1.28, $I^2 = 32\%$) than were studies based on self-report (gestational age, per week = 0.90, 95% CI 0.85–0.95, $I^2 = 0\%$; low gestational age vs not low = 1.71, 95% CI 1.32–2.22, $I^2 = 0\%$). In addition, Egger's test for publication bias was below the arbitrary threshold of $P < 0.1$ for both of these analyses (continuous: $P = 0.086$; dichotomous: $P = 0.011$). Interestingly, when the analysis of low gestational age vs not low was stratified by data ascertainment, Egger's test produced a *P*-value of 0.009 for the self-report subgroup ($n = 7$) but only 0.93 for the record/registry subgroup ($n = 5$).

The summary estimate of the meta-analysis of cryptorchidism was 4.30 (95% CI 3.62–5.11, $I^2 = 44\%$; Figure 4). Egger's test gave a *P*-value of 0.028, indicating the presence of small study bias that was also visually apparent from the funnel plot (data not shown) with an excess of small studies reporting stronger associations than the summary estimate; this was true for both groups when stratified by data ascertainment (registry/record $P = 0.002$, self-report $P = 0.081$). In addition, meta-regression of data ascertainment generated a *P*-value of 0.05, although the summary estimate was higher for the record/registry group (OR = 5.51, 95% CI 4.09–7.41, $I^2 = 40\%$) relative to self-report (OR = 3.86, 95% CI 3.11–4.80, $I^2 = 43\%$; Supplementary Figure 6; Supplementary data available at *IJE* online). A large number of studies provided cryptorchidism data by histology, which enabled histology-specific analyses to be conducted for this variable. Fifteen studies providing data on the relationship between cryptorchidism and risk of seminoma gave a summary estimate

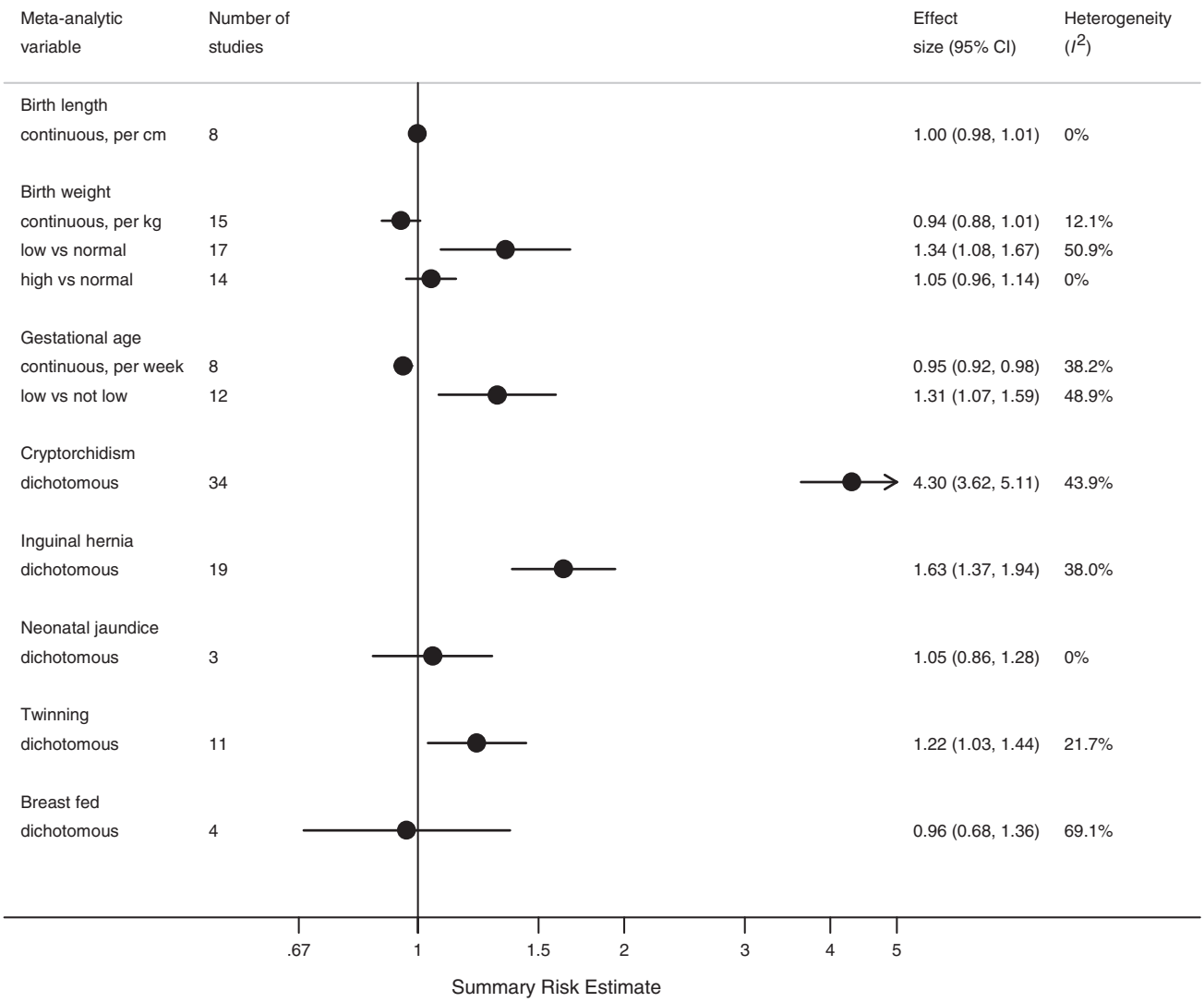

Figure 1 Forest plot of each variable's meta-analytic summary estimate of association with testicular cancer

of 3.80 (95% CI 2.77–5.20, $I^2 = 52\%$), which was similar to the estimate of 3.40 (95% CI 2.47–4.68, $I^2 = 49\%$) for non-seminoma using data from 14 studies (Supplementary Figures 7 and 8; Supplementary data available at *IJE* online).

Meta-analysis of the 18 studies that provided inguinal hernia data indicated a positive association with testicular cancer (OR = 1.63, 95% CI 1.37–1.94, $I^2 = 38\%$; Figure 5). Meta-regression of data ascertainment indicated that this was a potential source of between study heterogeneity ($P = 0.056$), although the point estimate for studies using record or registry data (OR = 2.08, 95% CI 1.56–2.79, $I^2 = 18\%$) was higher than that for self-report (OR = 1.47, 95% CI 1.22–1.78, $I^2 = 32\%$).

The meta-analysis of twinning included 11 studies, which produced a summary risk estimate of 1.22 (95% CI 1.03–1.44, $I^2 = 22\%$; Figure 6). When stratified by study design (cohort vs case–control studies) the estimate for cohort studies was less persuasive of association (1.17, 95% CI 0.96–1.43, $I^2 = 48\%$) and meta-regression of study design produced a *P*-value of 0.054. On sensitivity analysis, after the exclusion of Hemminki *et al.*[25] the summary estimate concurred with the null hypothesis and the measure of heterogeneity became 0% (OR = 1.07, 95% CI 0.93–1.24, $I^2 = 0\%$).

Meta-analyses of the variables birth length, breast feeding and neonatal jaundice, which included eight, four and three studies, respectively, did not indicate that these variables were associated with testicular cancer (Figure 1). Birth length could not be assessed as a categorical variable due to a lack of similarity in the cut-points used across studies.

Discussion

This systematic review and meta-analysis of perinatal variables, with a specific focus upon characteristics of

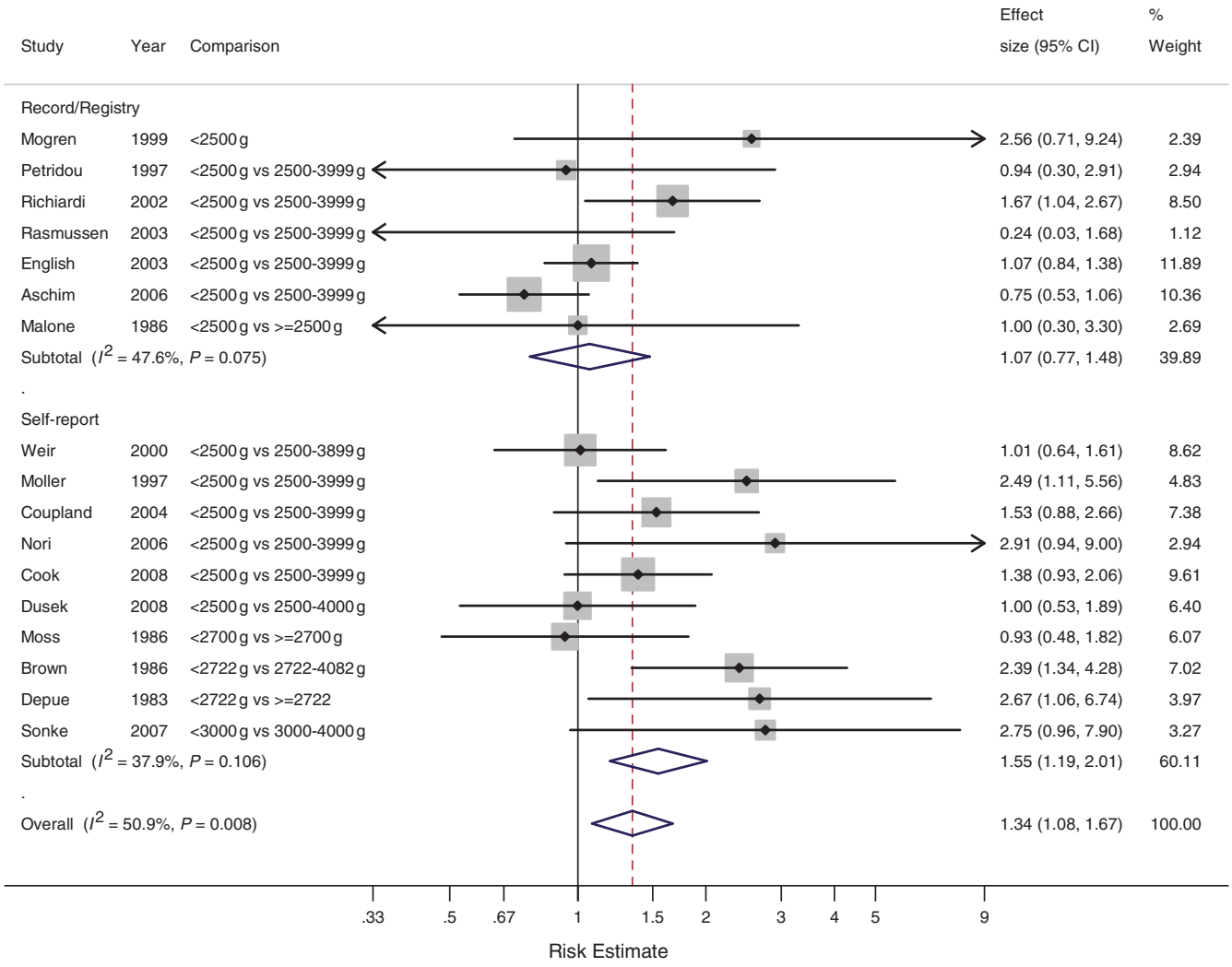

Figure 2 Forest plot of low birth weight and testicular cancer meta-analysis stratified by data ascertainment

the son, provides evidence that low birth weight, gestational age, cryptorchidism, inguinal hernia and twinning are associated with risk of testicular cancer.

Previous meta-analyses of birth weight and testicular cancer[26–29] have provided slightly different summary estimates due to the inclusion of different studies. This study is the most comprehensive yet as it includes an additional six studies[30–35] in comparison with the most recent meta-analysis,[29] specifies the birth-weight categories of each study's analysis to ensure it is explicit which estimates are being combined, and uses a methodology to estimate an OR per unit increase (kg) for each individual study prior to meta-analysis.[13] Two studies[36,37] that were included in the previous meta-analysis[29] were excluded because of failure to provide a CI or standard error[37] and having only provided a maximally adjusted OR.[36]

Our analyses suggest that low birth weight increases risk for testicular cancer, but method of data ascertainment may be biasing this estimate, as has been suggested previously.[26] Studies using self-report for ascertainment of birth weight produce a higher summary risk estimate, compared with record/registry data, and this discrepancy is clearly demonstrated in the stratified forest plot (Figure 2). Although data ascertainment was identified as a variable for meta-regression a priori, caution is still warranted in interpreting such low-powered analyses.

Maternal recall of children's birth weight has been shown to be accurate and reliable in older women,[38] all self-report studies included in this review interviewed the mother of the index case or control for birth-weight information and, while not inconceivable, the idea of recall bias is not easily advocated as it is unlikely many mothers are aware of the potential prenatal origin of testicular cancer. Therefore, it is possible that the difference by data ascertainment may be artifactual; it is worth remembering that

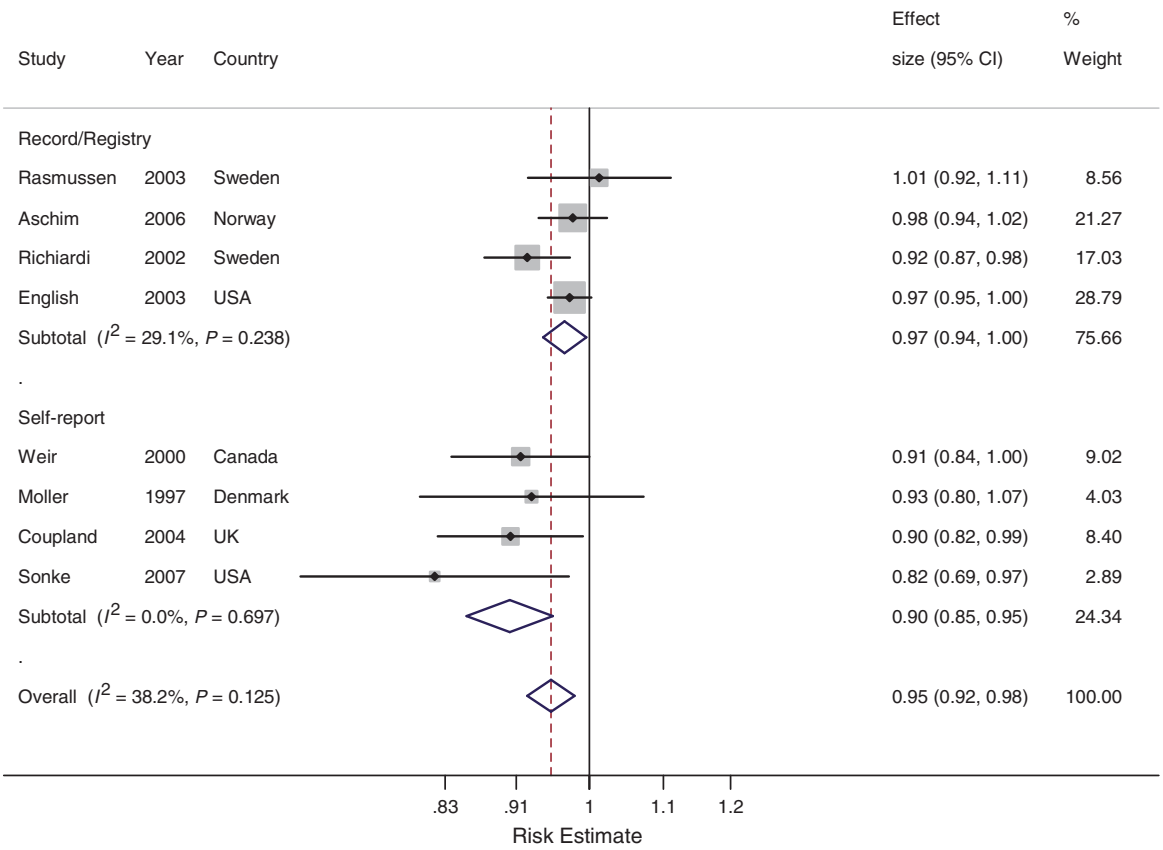

Figure 3 Forest plot of gestational age (per week) and testicular cancer stratified by data ascertainment

meta-regression provided a *P*-value of only 0.077. There is no evidence from this comprehensive analysis that high birth weight affects risk of testicular cancer. The fact that high birth weight is not protective against testicular cancer may be explanatory as to why the estimate for birth weight analysed as a continuous variable was only suggestive of an association; the methodology employed assumes a linear dose–response association. In conclusion, low birth weight remains a tentative risk factor for testicular cancer, whereas high birth weight has no effect on risk.

Gestational age, which obviously shares a correlation with birth weight and is also accurately recalled by mothers,[39,40] was found to be inversely associated with testicular cancer risk both on continuous and categorical meta-analyses. However, similar to the analysis of birth weight, the strength of the summary estimates was driven by studies using self-report for data ascertainment. Although this may be indicative of recall bias, there was also evidence of small study or publication bias, which may be the underlying cause of the positive summary estimates. The correlation between birth weight and gestational age may be interpreted as further reason to believe that the analysis of birth weight is also a false-positive result due to biases in ascertainment and publication, although Egger's test for funnel plot asymmetry for low birth weight was null ($P = 0.15$).

It is contentious whether one should adjust for gestational age in birth weight analyses.[41] This is because it could result in over-adjustment if the variables share a common cause. An alternative analysis is to consider size-(birth weight)-for-gestational-age as this could, theoretically, be the real risk factor.[42] In this study, we have not been able to undertake either of these analyses because we did not have access to the full datasets of each study. Moreover, unless the study has a large sample size (more than about 1000), these analyses often result in unstable estimates or are impossible due to the high correlation of exposures.

The meta-analysis of cryptorchidism generated the largest summary estimate of association with testicular cancer of this review (OR = 4.30; Figure 1). Although this is unsurprising, given that this relationship is well evidenced, the summary estimate derived represents the most comprehensive assessment of this association to date. However, there is no accepted standard definition of cryptorchidism used for research studies, thus data ascertainment via self-report is likely to incorporate different types of maldescensus

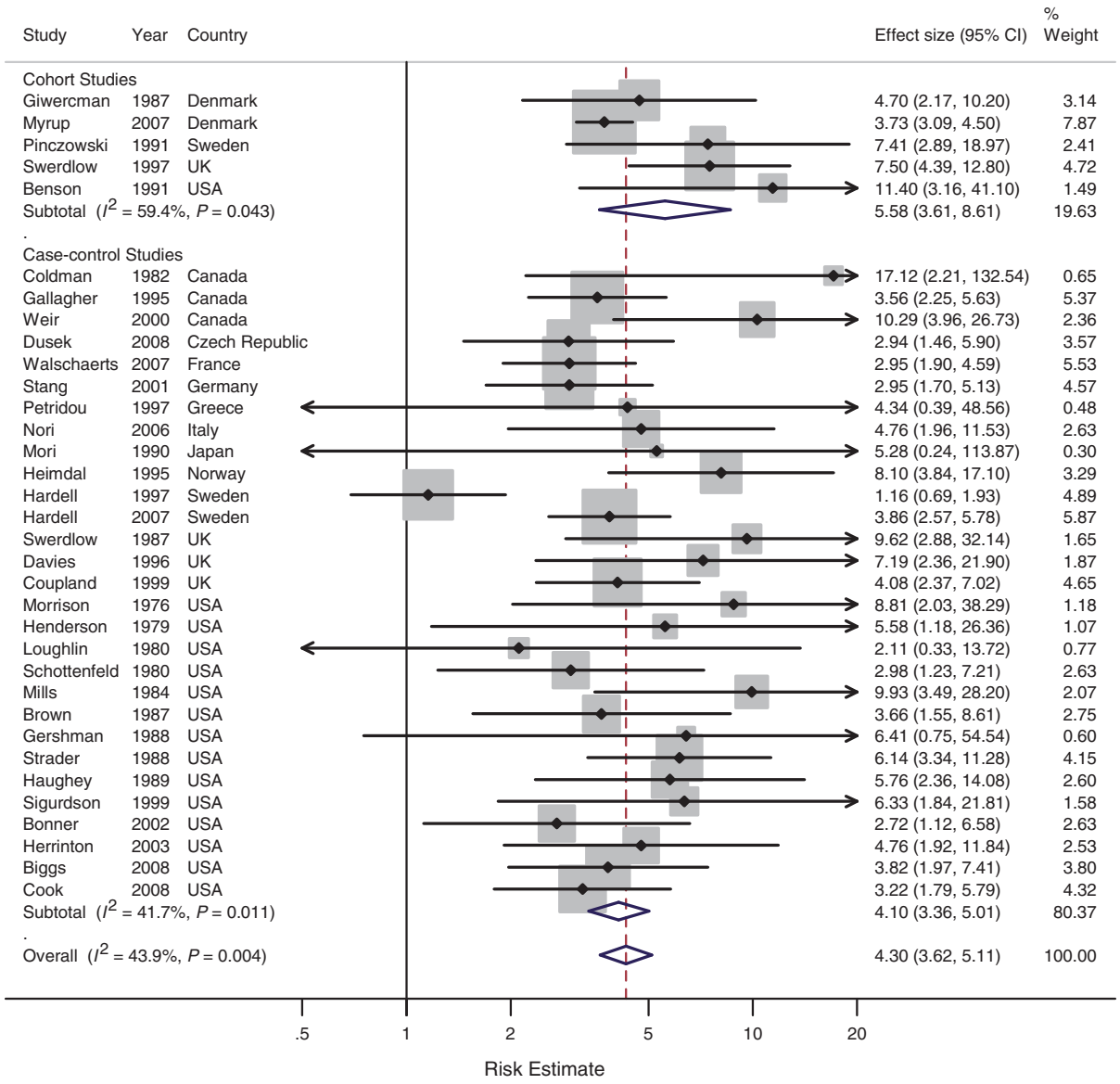

Figure 4 Forest plot of cryptorchidism and testicular cancer meta-analysis stratified by study design

testis, including undescended, gliding and retractile.[43,44] Without having access to questions used to elicit self reported histories, it is impossible to assess how such problems may have contributed to the heterogeneity present in our meta-analysis ($I^2 = 44\%$). Moreover, the majority of questionnaires are unlikely to differentiate between types of maldescensus testis, whereas it remains open to debate whether ascertainment via self-report could provide accurate classification.[43] However, although meta-regression of data ascertainment in the cryptorchidism dataset provided a P-value of 0.05, it is likely that self-report estimates are biased towards the null due to non-differential misclassification. This is because the summary estimate of studies using record/registry data provided the highest summary estimate of all. Conversely, there was also evidence of publication bias, in both the full and data ascertainment stratified datasets, and this may indicate that the summary estimate is artificially high.

Other variables what may have contributed to the heterogeneity detected include age of correction and the specificity of the definition of undescended testis.[43] It remains uncertain if age of orchiopexy affects risk of testicular cancer, but a recent meta-analysis indicates that intervention at earlier ages may be protective.[45] Stratification by histologic tumor type (seminoma, nonseminoma) did not reduce heterogeneity (Supplementary Figures 7 and 8; Supplementary data avaiable at *IJE* online).

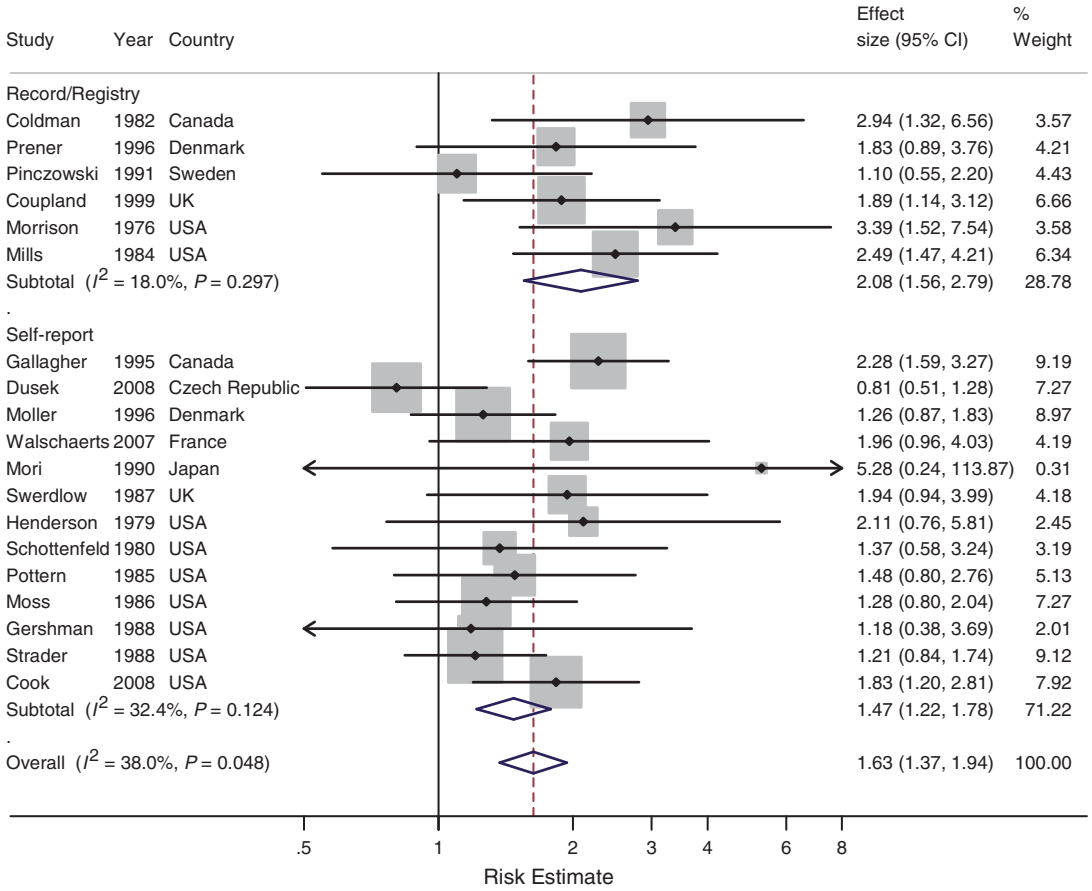

Figure 5 Forest plot of inguinal hernia and testicular cancer stratified by data ascertainment

Inguinal hernia is a protrusion of abdominal contents through the inguinal canal.[46] This is the first meta-analysis of the relationship between inguinal hernia and testicular cancer and the summary estimate suggests that risk is increased by ~63% (Figures 1 and 5). No analysis to date has analysed sub-categories of inguinal hernia in relation to testicular cancer risk, and this is likely to be because, historically, classification has not been common practice and the number of individuals with testicular cancer and inguinal hernia, or vice versa, is often too small to enable further stratification. Further work on the mechanism and association of these two factors is warranted, including potential confounding by cryptorchidism.[47] Lastly, although it has been suggested that positive associations between inguinal hernia and testicular cancer may be attributable to respondent's confusion with cryptorchidism,[24] the fact that the summary estimate in this meta-analysis was higher for studies using record/registry data ascertainment, as compared with self-report, should assuage such concerns.

The sensitive search strategies were able to identify 11 studies for inclusion in the meta-analysis of twinning, with a further 5 studies being excluded due to geo-temporal overlap (Table 1). The summary estimate indicated that risk of testicular cancer is increased in twins by 22% (Figures 1 and 6), which is consistent with a previous review that included seven studies.[48] However, the removal of a single study[25] caused the estimate to weaken. Although this is the only Swedish study included in the analysis, there is no immediate reason to indicate that this study is inherently different compared with those also included. Furthermore, this study's point estimate is not significantly different from the estimates derived from other studies, whereas the change in the summary estimate after its exclusion was small. Lastly, the inclusion of Hemminki *et al*.[25] resulted in the exclusion of two other studies due to geo-temporal overlap and both of these studies also indicated towards a positive association between twinning and risk of testicular cancer (Standardized incidence ratio = 1.42, 95% CI 0.92–2.10;[49] OR = 1.20, 95% CI 0.90–1.59).[50] The inherent limitation of all such studies is the low statistical power available when analysing a rare exposure in a rare malignancy. Such scenarios are ideal candidates for systematic review and meta-analysis, whereas post-hoc sensitivity analyses should be interpreted with caution.

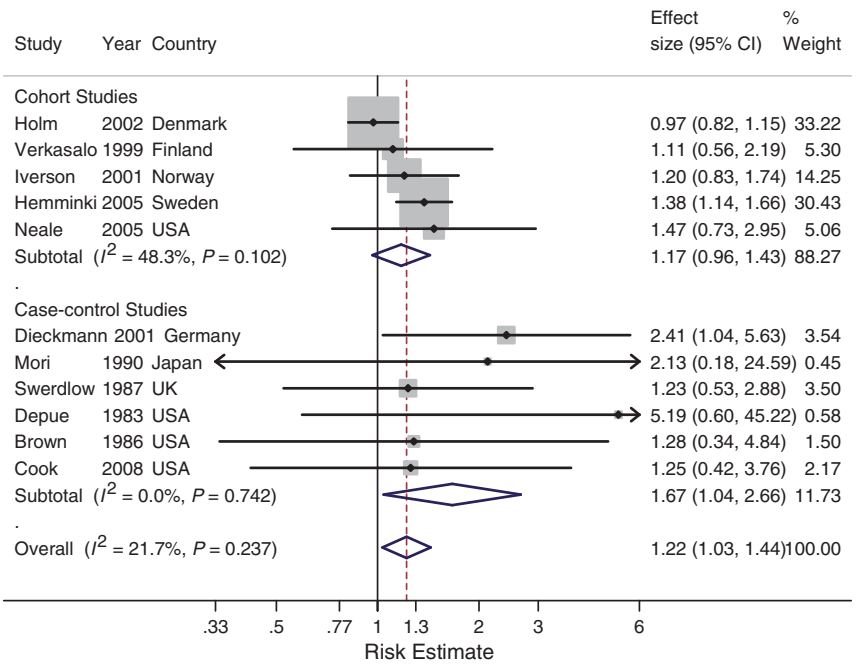

Figure 6 Forest plot of twinning and testicular cancer stratified by study design

The main limitation of this analysis is that the estimates of association from each study are unadjusted or minimally adjusted. Although this is a limitation, insofar as potential confounding variables have not been taken into account, it is also a strength as it ensures that the study specific estimates are derived from the same statistical model, enhancing the validity of the meta-analytic approach. Also, because of the nature of the exposures, being proxies for unidentified or multifactorial underlying exposures, and heterogeneity of the literature, it is not clear, for the majority of analyses, what variables could be confounding. A second limitation is that we have not been able to identify the sources of heterogeneity detected in some of the meta-analyses undertaken. While one may speculate towards variables that may have contributed to the heterogeneity (see discussion of cryptorchidism), it was not excessively high for any particular meta-analysis. The moderate levels of heterogeneity detected in some of the analyses do not necessarily repudiate the summary estimate, rather it should indicate a certain degree of caution in interpretation of the summary estimate with further reference to the underlying study-specific estimates. A third limitation is that we cannot exclude recall bias from our analyses. Meta-regression of data ascertainment (self-report; registry/medical record) indicated that the summary estimates for associations between low birth weight and low gestational age with testicular cancer risk were largely driven by studies using self-report, as opposed to record/registry. However, available evidence suggests that maternal recall of these variables is highly accurate. Coupled with the fact that these secondary analyses have reduced statistical power, a cautious interpretation of these meta-regressions is warranted.

A major strength of this analysis is the systematic approach, which included detailed and sensitive search strategies in a number of literature databases and multiple attempts to contact authors of studies for supplementary information. In addition, this is the first systematic review and meta-analysis of the variables birth length (continuous), birth weight (continuous), gestational age (continuous, categorical), inguinal hernia, neonatal jaundice and having been breast fed in relation to testicular cancer risk.

In conclusion, this systematic review and meta-analysis of perinatal variables pertaining to the son has produced evidence that low birth weight, gestational age, cryptorchidism, inguinal hernia and twinning are associated with risk of testicular cancer. The field must now progress with novel ideas and further analyses to decipher the mechanisms of such associations and further elucidate the aetiopathogenesis of testicular cancer.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- The aetiology of testicular cancer remains largely elusive, although initiation of pathogenesis is thought to occur during the prenatal period.
- Results of testicular cancer studies are often inconsistent; a problem exacerbated by small sample sizes and multiple testing.
- Through systematic review and meta-analysis we find associations of low birth weight, gestational age, cryptorchidism, inguinal hernia and twinning with risk of testicular cancer.

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