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Abbreviations:
OR: Odds Ratio
CI: Confidence Interval
ES: Effect Size

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Abstract

Background. Testicular cancer is one of the most rapidly increasing tumour types but its aetiology is still largely unexplained. Cryptorchidism and familial testicular cancer, established risk factors, explain less than 10% of all cases. Among investigated postnatal factors, early puberty was suggested as a potential risk factor but the topic has been poorly investigated. We undertook a meta-analysis of the effect of age at puberty on testicular cancer risk, attempting at enhancing the homogeneity in the definition of the exposure among studies to obtain valid pooled estimates.

Methods. Search strategies were conducted in PubMed on December 2011. All markers of puberty onset (age at voice change, age when started shaving, and reported age at onset) were considered. We re-categorized age at puberty from all studies into a common three-level variable: younger than peers, same age as peers, older than peers.

Results. A total of 391 references were retrieved, of which 12 met the inclusion criteria. Later puberty appeared to be protective. In particular late vs. same age at start shaving gave an OR of 0.84 (95%CI: 0.75-0.95, 5 studies); late vs. same age at voice change gave an OR of 0.87 (95% CI: 0.75-1.01, 5 studies); and later age than peers at reported onset of puberty gave an OR of 0.81 (95%CI: 0.73-0.89, 8 studies). Early puberty showed no effect on testicular cancer risk.

Conclusions. This meta-analysis has found consistent evidence of a decreased risk of testicular cancer in association with later puberty, suggesting that postnatal factors may contribute to testicular cancer risk.

Introduction

Testicular cancer is one of the most rapidly increasing types of cancer worldwide (Bray et al. 2006; Chia et al. 2010) and its etiology is largely unexplained (Richiardi et al. 2007). In the last thirty years, most research on the etiology of testicular cancer has focused on potential prenatal exposures, but this has yielded somewhat inconclusive results (Cook et al. 2009, 2010). Besides cryptorchidism and family history, which are well-established risk factors, evidence suggests a higher risk of testicular cancer associated with low birth order (or small sibship size), being a twin, low birth weight and short duration of gestation.

Postnatal factors have been investigated to a lesser extent. Consistent evidence indicates that the risk of testicular cancer increases with height (Lerro et al. 2010). A number of studies have also investigated the possible effect of age at puberty although there is no consensus on whether an association exists and on its possible direction. Results are often inconsistent and some of the studies have a small sample size; in addition, male age at puberty is poorly measured retrospectively, and different studies use different indicators.

We have therefore carried out a systematic review and meta-analysis on age at puberty and testicular cancer risk, attempting at enhancing the homogeneity in the definition of the exposure among studies to obtain valid pooled estimates.

Material and methods

We searched the literature for studies on the association between age at puberty onset and testicular cancer risk using the database PubMed (National Center for Biotechnology Information, US National Institutes of Health, USA; 1950–2010). The electronic search was conducted on 7 December 2011 using the terms ("Testicular Neoplasms" [Mesh] OR "testicular cancer" OR "testicular tumor") AND "puberty". Titles, abstracts and keywords of 391 references were reviewed to select the relevant articles, and 11 case-control studies were identified (Depue et al. 1983; Moss et al. 1986; Swerdlow et al. 1989; UK TC study group 1994; Gallagher et al. 1995; Moller and Skakkebaek 1996; Weir et al. 1998; Coupland et al. 1999; Walcott et al. 2002; McGlynn et al. 2007; Trabert et al. 2010) (Table 1). Citations of selected articles were scrutinized for references that may have been missed or absent from the initial search on Pubmed, and a further study (Haughey et al. 1989) was identified. Four case-control studies were excluded: the study by Coupland et al. (1999) because of overlapping with the UK testicular cancer (UK TC) study group's study (UK TC study group 1994) that includes a larger number of cases; the study by Walcott et al. (2002) because of overlapping with the study by Trabert et al. (2010) that reports a more detailed analysis on puberty onset; the studies by Depue et al. (1983) and

Haughey et al. (1989) because they did not include sufficient information to obtain a quantitative estimate of the association.

As summarized in Table 1, the eight selected studies used different indicators of age at puberty onset, among which the most frequent were age when individuals started shaving, age at voice change, and self-reported age at puberty onset (or age at growth spurt). In five studies (Moss et al. 1986; UK TC study group 1994; Gallagher et al. 1995; Moller and Skakkebaek 1996; McGlynn et al. 2007; Trabert et al. 2010), the actual recalled age at the occurrence of the considered indicator (e.g. age at voice change) was reported. In three studies, age at puberty onset was reported by comparison with that of subjects' peers (e.g. age at voice change compared to classmates), and classified into earlier, later, or same age as peers (Swerdlow et al. 1989; Moller and Skakkebaek 1996; Weir et al. 1998). In one of these three studies (Weir et al. 1998), information about the subjects' age at puberty was obtained both from the subjects themselves and from their mothers. For homogeneity with the other studies, we chose to use the information reported by the study subjects.

In our analysis, we considered the three indicators of puberty onset most frequently assessed by the studies, namely age when started shaving, age at voice change, and age at puberty onset.
As shown in Figure 1, the age cumulative distributions of the different indicators in control subjects varied among the studies included in the meta-analyses. By the age of 14 years, the proportion of controls reporting having started shaving was 8% in the studies by the UK TC study (1994), between 2% (<14 years) and 20% (≤15 years) in the study by Gallagher et al. (1995), 27% in McGlynn et al. (2007), and 20% in Trabert et al. (2010). Similarly, at 14 years of age, 72% of controls in the UK TC study (1994), 60% in Gallagher et al. (1995), 74% in McGlynn et al. (2007), and 76% in Trabert et al. (2010) reported having changed voice. This pattern was expected as age at puberty is known to vary largely among populations and over time. The distribution of age at puberty onset in control subjects was more uniform in studies where it was assessed by comparison with that of subjects' peers: 12% of controls in Møller and Skakkebæk (1996), 11% in Swerdlow et al. (1989), and 18% in Weir et al. (1998) reported to have had the puberty onset earlier than their classmates and friends (Figure 1).

It follows that it was not possible to use the same age cut-offs in all studies to define early, normal and late puberty. Hence, for studies in which age at puberty was assessed in comparison with peers, we kept the variable as reported in the original paper ("younger than peers", "same age as peers", "older than peers"); for studies in which age at puberty was reported in age intervals, we defined a study-specific category "same age as peers" by identifying, in each study, the closed age category with the largest number of subjects. For example, for age at start shaving, "same age as peers" corresponded to age 16-17 years in the study by Gallagher et al. (1995) and to age 15-16 years in the study by McGlynn et al. (2007). Younger and older than peers were defined accordingly (Figure

1). If two central categories had a similar number of subjects (less than 10% difference) we used both categories to define the same age as peers (e.g. "same age at peers" for start shaving corresponded to ages 15 and 16 years for the study by Trabert et al. (2010)).

Using these newly created categories, we computed crude odds ratios (OR) and exact 95% confidence intervals for early and late puberty *vs.* same age as peers using the original number of cases and controls reported in the papers.

Statistical analysis

The different puberty indicators were analyzed separately. Specifically, three studies (Swerdlow et al. 1989; Moller and Skakkebaek 1996; Weir et al. 1998) were included in the meta-analysis of self-reported age at puberty onset, and five studies (UK TC study group 1994; Gallagher et al. 1995; Weir et al. 1998; McGlynn et al. 2007; Trabert et al. 2010) were included in each of the meta-analyses of age at start shaving and age at voice change. We also conducted a further meta-analysis to estimate the effect of late age *vs*. same or early age at puberty onset compared with peers, based on all identified studies, including the study by Moss et al. (1986) which could not be included in any of the indicator-specific meta-analyses but provided the number of cases and controls who had puberty before 14 years of age (classified as "same age as or younger than peers") or above (classified as "older than peers"). In this meta-analysis, each study contributed with only one indicator of puberty out of reported age at puberty, age when started shaving or age at voice change, in this order of priority. The choice of giving priority to age when started shaving rather than to age at voice change when both indicators were available was due to a much smaller heterogeneity among studies of the former indicator. We also carried out a sensitivity analysis giving priority to age at voice change.

Meta-analyses were conducted using a fixed effects model available in the command metan in STATA (StataCorp LP, College Station, USA). Heterogeneity was assessed through the I^2 statistics (Higgins and Thompson 2002). Sensitivity analyses were conducted omitting in turn each study from the analysis. Random effects models were also used in the meta-analyses as an additional measure of sensitivity analysis. The possibility of publication bias was assessed through the Egger test (Egger et al. 1997) and visual inspection of funnel plots.

Results

Table 1 summarizes basic characteristics of the 12 identified studies, including the eight studies eventually retained for the meta-analyses. Studies were published between 1983 and 2010 and conducted in North America, UK and Denmark.

Results of the meta-analyses on the specific indicators of puberty onset are reported in Figure 2. Compared with subjects who started shaving at the same age as peers, late shaving was associated with an OR of testicular cancer of 0.84, (95% CI: 0.75-0.95, I^2: 0%, Figure 2b), while early shaving was associated with an OR of 0.98 (95% CI: 0.85-1.12, I^2: 12%, Figure 2a). The same figures for age at voice change were an OR of 0.87 (95% CI: 0.75-1.01, I^2: 76%, Figure 2d) for a late change and an OR of 1.04 (95% CI: 0.90-1.21, I^2: 0%, Figure 2c) for an early change. Finally, the overall ORs using self-reported age at puberty onset were 0.67 (95% CI: 0.54-0.83, I^2: 0%, Figure 2f) for late onset and 0.89 (95% CI: 0.71-1.11, I^2: 0%, Figure 2e) for early onset. These results were robust to all sensitivity analyses, did not change using a random effect model (with the exception of the OR of late *vs.* same age at voice change: OR: 0.91, 95% CI: 0.66-1.26) and did not show evidence of publication bias (all Egger's test p-values > 0.20).

Including all eight studies in a meta-analysis of the effect of late age *vs.* early age or same age as peers at puberty onset, using as puberty indicators self-reported age at puberty onset and age when started shaving, yielded on OR of 0.81 (95% CI: 0.73-0.89, I^2: 48%, Figure 3). When we used age at voice change instead of age at start shaving, the OR did not change more than marginally (OR: 0.81, 95% CI: 0.72-0.90), but the heterogeneity was higher (I^2: 77%). In either cases, there was no evidence of publication bias (Egger's tests: p=0.07 and p=0.71, respectively). In the sensitivity analysis carried out omitting in turn each study, the heterogeneity dropped to 4% when the study by McGlynn et al. (2007) was omitted, and the corresponding overall OR was 0.74 (95% CI: 0.66-0.84). The OR estimated with a random effect model was 0.77 (95% CI: 0.66-0.90).

Discussion and conclusions

We found evidence that late age at puberty is inversely associated with testicular cancer risk whereas we did not find an effect of early puberty. Results were fairly consistent among studies even if they used different puberty indicators. There were only eight studies eventually included in the meta-analyses but the total number of cases and controls involved was sufficient to obtain a relatively precise estimate of the effect.

Some biases might have affected the studies included in our meta-analysis homogeneously. First, since the age at puberty was assessed retrospectively, there is the possibility of recall bias, which would have affected to a similar extent all puberty indicators. However, among testicular cancer patients and the scientific community, there is no common awareness of a specific effect of puberty on testicular cancer risk, and more recent studies did not find a larger effect than earlier publications. In addition, we did not find an association between early puberty and testicular cancer risk which, in the presence of recall bias, would have been expected to parallel the decreased risk found in association

with late puberty. Assuming that cases and controls had a similar recall of their age at puberty, it should be noted that all the different puberty indicators are poorly recalled. This is an important source of non-differential misclassification which is expected to have biased our results towards the lack of an effect. This source of bias is therefore of concern mainly for our finding of no effect of early puberty, in that we cannot rule out that early puberty is positively or negatively associated with risk of testicular cancer.

A second possible relevant source of bias is that we used crude estimates calculated by us from the original information reported in the papers. This approach was necessary to create a comparable categorization of the exposure among the studies but it might have introduced problems of confounding. In most of the studies, however, crude and adjusted estimates for age at puberty were very similar. Although this most likely reflects our lack of knowledge of potential confounders rather than a true lack of confounding, the inclusion of adjusted estimates would not have changed our results. Indeed, adult height is a possible exception, as it has been reported to be positively associated with late age at puberty, at least within the normal range of age at puberty (Lorentzon et al. 2011), and is a risk factor for testicular cancer (Lerro et al. 2010). It is unclear, however, if height should be treated as a proxy of the same underlying mechanism, as a mediator or as a true negative confounder in the analysis of the association between puberty and testicular cancer risk. Even if height were a true confounder, lack of adjustment for height would have biased our finding of a decreased risk associated with late age at puberty towards the null, making our estimates conservative.

Results of our meta-analysis were fairly homogeneous among studies, with the exception of the last two published articles (McGlynn et al. 2007; Trabert et al. 2010), and especially the last one (Trabert et al. 2010) in the meta-analysis on age at voice change that, accordingly, had an I^2 estimate above 70%. In addition to age at voice change, the study by Trabert et al. (2010) however, includes other two indicators of puberty: age when started shaving, which was used in our meta-analysis, and age at first appearance of pubic hair, which was not used. Both indicators were associated with a 20% decreased risk of testicular cancer in the comparison of late *vs.* same age at puberty, which is consistent with the overall finding of the meta-analysis.

It has been suggested that age at puberty has been progressively declining in several populations, although this is better documented in girls than in boys, and the occurrence of the decline in the last decades are debated (Cole 2000; Aksglaede et al. 2008; Euling et al. 2008). A secular trend in declining age at puberty onset would fit well with the secular increasing trend in incidence of testicular cancer (Richiardi et al. 2004), by decreasing the impact of a potentially protective effect of late puberty.

Our finding of a decreased risk of testicular cancer in association with late puberty has plausible biological explanations.

The first simpler explanation refers to the time-scale of the period at risk for testicular cancer. The age distribution in incidence of testicular cancer, with almost no cases occurring between 2-3 years of age and age 15 years, suggests that the period at risk starts with puberty. The shape of the age-distribution in incidence of testicular cancer parallels closely changes in gonadotropin levels (Golub et al. 2008). As it has been noticed before (Weir et al. 1998; Moller 1993), late puberty could then be associated with a late entry into the risk period, decreasing the incidence of testicular cancer. According to this hypothesis, incidence of testicular cancer would depend on time since puberty rather than on age at puberty, although these two variables are strongly correlated. However, it should be noted that the age peak in testicular cancer incidence appears to be fairly constant over time and among populations (Moller 1993), despite the strong temporal trends and the large geographical variations characterizing testicular cancer descriptive epidemiology.

A second possible explanation is that testicular cancer and age at puberty share genetic factors or postnatal risk factors, such as childhood nutrition, childhood obesity and exposure to specific chemicals (Buck Louis et al. 2008), among other potential mechanisms.

Thirdly, if puberty represents a window of susceptibility, a change in age at puberty might imply a change in the type and level of exposures occurring during that time window. For example, a large Swedish registry-based study found in 2007 that the risk of testicular cancer associated with cryptorchidism increases further by two-folds if the orchiopexy is carried out after age 13, taken as an arbitrary threshold for puberty (Pettersson et al. 2007). This result, which is supported by some (Walsh et al. 2007) but not all (Myrup et al. 2007) other studies on the same determinant, could suggest that puberty acts as a window of susceptibility and that exposures acting during puberty may affect testicular cancer risk (Richiardi et al. 2007).

In conclusion, in this meta-analysis of eight case-control studies we found consistent evidence of a decreased risk of testicular cancer among men who had a late puberty compared to peers. Our findings suggest that testicular cancer risk is modified by postnatal risk factors.

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Figure 1. Cumulative frequency distribution of age at puberty onset (age when started shaving, age at voice change, and reported age at onset) among controls in selected studies.

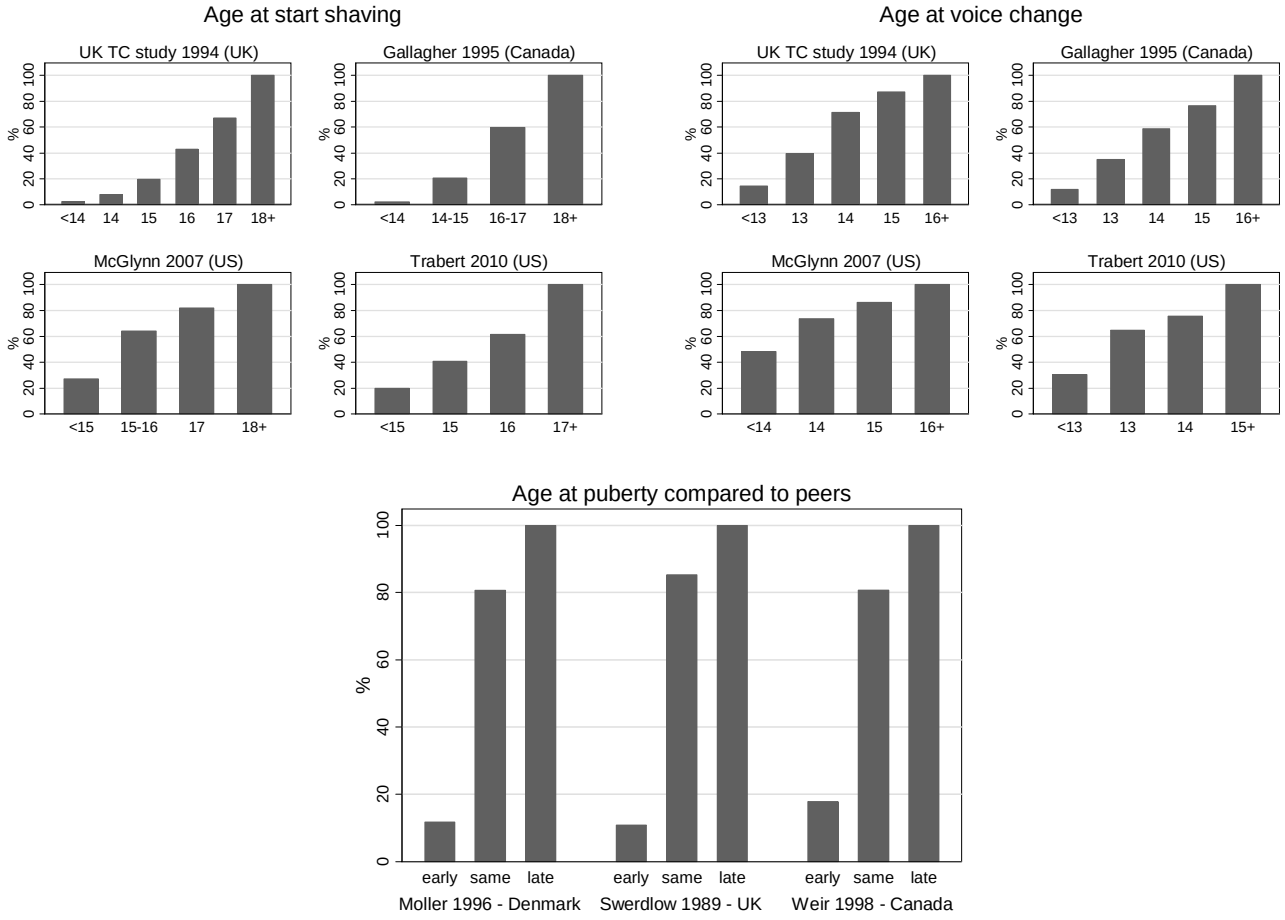

Figure 2. Forest plots of odds ratios for early (a, c, e) or late (b, d, f) age at puberty onset and testicular cancer, by puberty indicator (age when start shaving (a, b), age at voice change (c, d) and self-reported age at puberty (e, f)). ES: effect size.

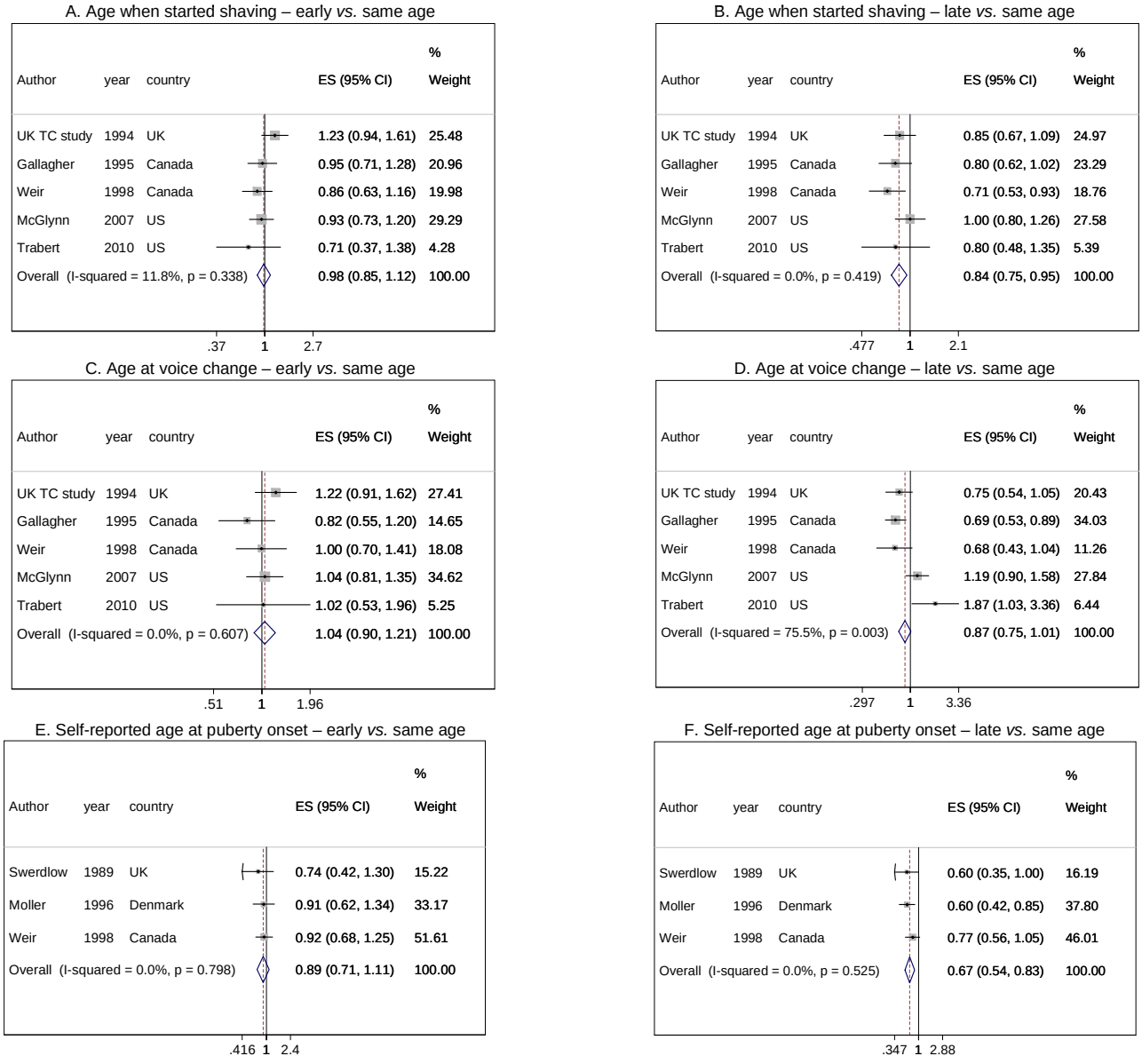

Figure 3. Forest plots of odds ratios for late age at puberty onset and testicular cancer, using any indicator of puberty. ES: effect size.

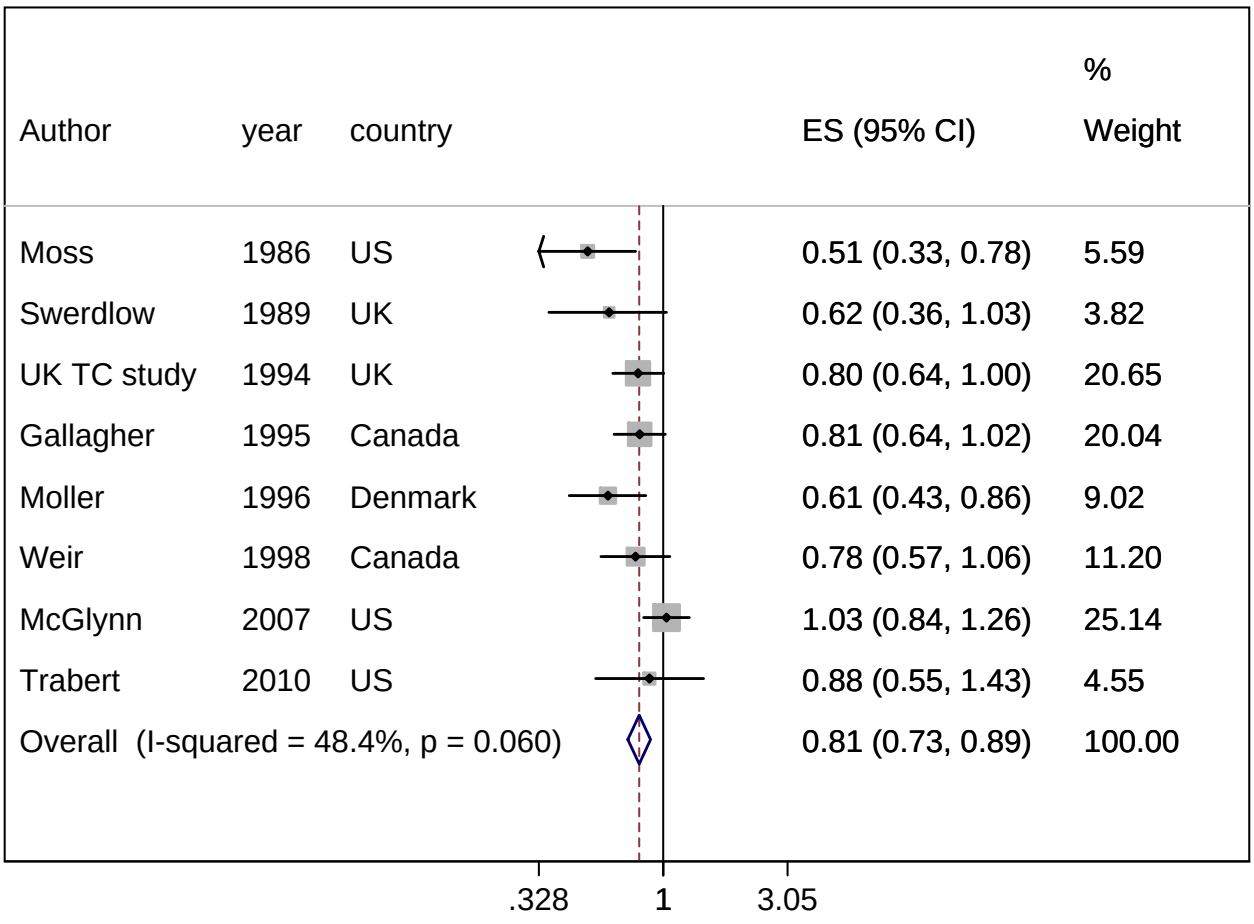

Table 1. Presentation of the case-control studies included in the meta-analysis.

Study	Year	Country	Exposure (indicator of age at puberty[b])	Cases	Controls
Depue *et al*.[a]	1983	USA	Age when started shaving, age at voice change	124	108
Moss *et al*.	1986	USA	Age at puberty < 14 years	254	248
Swerdlow *et al*.	1989	UK	Age at puberty compared to classmates	247	458
Haughey *et al.*[a]	1989	US	Age at first orgasm, age when started shaving, age at voice change	250	250
UK TC study group	1994	UK	Age voice broke (years) Age started shaving (years) Age at first nocturnal emission (years) Age when first masturbated to orgasm (years)	552 749 652 665	550 757 628 696
Gallagher *et al*.	1995	Canada	Age began shaving (years) Age voice broke (years)	501 440	986 878
Møller and Skakkebæk	1996	Denmark	Age at puberty (years) Age at puberty compared with classmates	401 484	583 670
Weir *et al*.	1998	Canada	Appearance of hair (compared to peers)[c] Starting to shave (compared to peers)[c] Growth spurt (compared to peers)[c] Voice change (compared to peers)[c]	470 478 476 472	910 931 928 916
Coupland *et al*.[a]	1999	UK	Age at first nocturnal emission (years) Age voice broke (years)	652 552	628 550
Walcott *et al*.[a]	2002	USA	Age reported noticing pubic hair < 13 years	138	116
McGlynn *et al*.	2007	USA	Age at first nocturnal emissions (years) Age when voice first changed (years) Age when started to shave (years)	662 714 760	830 866 922
Trabert *et al*.	2010	USA	Age voice deepened (years) Age at first appearance of pubic hair (years) Age began shaving (years)	164 162 182	131 127 140

[a] Studies excluded from the meta-analysis (see text for details)
[b] as reported in the original articles
[c] based on subjects' reports