Pubertal timing in girls and depression: A systematic review


Background: Because the incidence of depression increases after puberty, it is possible that pubertal timing in girls influences the onset of depression. Our objective was to assess the effect of early and late puberty in girls on the incidence of depression.

Methods: We systematically searched relevant databases for controlled studies that assessed the impact of pubertal timing in girls on the incidence of depression or depressive symptoms. The last search was completed in August 2013. Two authors selected the studies, extracted the data, and assessed the quality of the evidence. Meta-analyses of the adjusted and unadjusted results were calculated using random effects.

Results: Four cohort studies were included (n=8055 participants). Early puberty significantly increased the risk of new cases of depression in the unadjusted meta-analysis (RR=1.33; CI 95%: 1.02, 1.73) but not in the adjusted estimate of two of the included studies (RR=1.48; CI 95%: 0.69, 2.28). For late puberty, no significant associations were found (unadjusted RR=1.28; CI 95%: 0.87, 1.88). Two studies assessed the effect of early puberty on depressive symptoms and found positive associations. The quality of the available evidence was rated as very low.

Limitations: The polled results had wide confidence intervals, and the available evidence was of very low quality.

Conclusions: The available evidence supports little confidence regarding the impact of pubertal timing on the onset of depression in girls but suggests that early puberty in girls may increase the risk of depression. Further higher quality studies are needed to clarify the association between pubertal timing and the incidence of depression in girls and women.
1. Introduction

Depression is a globally common disease that has a greater negative effect on overall health than diabetes, angina, arthritis or asthma (Moussavi et al., 2007). Moreover, depression is the leading cause of the global burden of neuropsychiatric diseases (Eaton et al., 2008). Following the onset of adolescence, depression affects more women than men, with a prevalence almost two-folder higher (Hosseinpoor et al., 2012a). Genetic predisposition and negative life events play a major role in the onset of depression and are equally distributed between both genders (Johnson et al., 2013; Rice et al., 2003). Socioeconomic inequalities between genders may account for the increased burden of depression in women, as lower socioeconomic status, which is more frequent in women, is a risk factor for depression (Hosseinpoor et al., 2012b; Lorant et al., 2003). The differences in gender distribution of depression may also be associated with biological characteristics, and gonadal hormones have been highlighted as one such characteristic (Nemeth et al., 2013).

The 1-year prevalence of depression in adolescents is estimated to be 4–5% (Costello et al., 2005; Jane Costello et al., 2006). Depression during adolescence is associated with important current and future morbidity. It can lead to lower educational attainment among those who are depressed during this important developmental period and may play a role in social status (Lewinsohn et al., 1998; Fletcher, 2008; Thapar et al., 2012). In addition, depression during adolescence is a major risk factor for suicide in this age group (Windfuhr et al., 2008).

Puberty is a period of biological and social change that also affects self-esteem and psychological equilibrium. Cohort studies have reported that changes in pubertal timing – deviation from normal development – are associated with cardiovascular diseases (Feng et al., 2008; Kivimaki et al., 2008). Pubertal timing has also been suggested to influence the onset of depression (Patton and Viner, 2007). The basis of this hypothesis is the modulatory effect of gonadal hormones on the neuroendocrine system. Higher levels of estrogen during puberty may change the sensitivity of neurotransmitter systems, particularly the production of serotonin receptors at the transcriptional level (Steiner et al., 2003). The altered distribution or function of serotonin receptor subtypes brought on by changes in the hormonal milieu at menarche may amplify vulnerability to mood disorders, especially when changes in normal timing are present (Steiner et al., 2003).

Despite these predictions, conclusive evidence from epidemiological studies in the field could not be identified. This scenario motivated us to perform a systematic review with meta-analysis of the effect of pubertal timing in girls on the incidence of depression.

2. Methods

2.1. Protocol and registration

The protocol for the current review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42012003074.

2.2. Eligibility criteria

We considered case control and cohort studies that assessed the influence of early or late puberty in girls on the incidence of depressive symptoms or depressive disorders eligible for this review.

2.3. Information sources and search strategy

We searched MEDLINE, EMBASE, Scopus, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Centre for Reviews and Dissemination (CRD), Latin American and Caribbean Center on Health Sciences Information (LILACS), and the Scientific Electronic Library Online (SciELO).


The last search update was performed in August 2013. Additionally, we screened the lists of references of the relevant studies.

2.4. Study selection and data extraction process

Two independent reviewers (IRZ and KMS) selected the studies by assessing titles and abstracts. Disagreements were resolved by consensus or by another reviewer (TFG or MTS). The following data were extracted by one reviewer and checked by another: year, country, study design, sample size, definition of early or late puberty, length of follow-up, definition of depressive disorders or symptoms, and incidence of events in each group. When needed, we contacted the corresponding authors of the studies for additional information.

2.5. Risk of bias and quality of evidence assessment

We based our risk of bias assessment upon the Scottish Intercollegiate Guidelines Network (SIGN) handbook (SIGN, 2013) which has been considered an efficient tool to assess the methodological quality of observational studies (Bai et al., 2012). We guided our assessment of selection, performance, attrition and detection biases according to the following domains: selection of subjects, assessment, confounding and statistical analysis. Checklists items related to blind assessment were not considered relevant and were not included in the study assessment.

We assessed the quality of evidence for the outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt et al., 2011). Five items that could decrease the quality were assessed (limitations, inconsistency, indirectness, imprecision, and publication bias), as well as three items that could upgrade the quality and increase confidence in the estimates (large magnitude of effect, dose-response gradient, and plausible
confounding) (Schünemann et al., 2009; Balsam et al., 2011). The quality of evidence was rated as high, moderate, low or very low.

2.6. Data analyses

Whenever feasible, we recalculated the measures of association using the data available from the included studies and performed a meta-analysis of the crude relative risk (RR) using the Mantel–Haenszel model with random-effects, presented with 95% confidence intervals (95% CI). Adjusted RR across studies was pooled from the confidence intervals using the DerSimonian–Laird random-effects model (Deeks et al., 2001).

We estimated the statistical heterogeneity of the results using the \( \chi^2 \) \((p > 0.10)\) and \( \tau^2 \) tests and estimated the inconsistency magnitude by \( I^2 \). If the heterogeneity was significant, we planned to explore it via sensitivity analysis. STATA software (version 10.1) was used for all calculations.

3. Results

The literature search retrieved 984 records (Figs. 1). After assessing the titles and abstracts, we selected 31 records for full text assessment and included five reports from four distinct cohort studies. The reason for exclusion of the other 26 papers are

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boden 2011</td>
<td>1.25 (0.90, 1.75)</td>
<td>31.21</td>
</tr>
<tr>
<td>Herva 2004</td>
<td>1.15 (0.94, 1.40)</td>
<td>44.90</td>
</tr>
<tr>
<td>Stice 2001</td>
<td>1.90 (1.24, 2.90)</td>
<td>23.89</td>
</tr>
<tr>
<td>Subtotal (I-squared = 55.0%, ( p = 0.108 ))</td>
<td>1.33 (1.02, 1.73)</td>
<td>100.00</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boden 2011</td>
<td>1.05 (0.77, 1.44)</td>
<td>49.68</td>
</tr>
<tr>
<td>Herva 2005</td>
<td>1.56 (1.15, 2.11)</td>
<td>50.32</td>
</tr>
<tr>
<td>Subtotal (I-squared = 67.8%, ( p = 0.078 ))</td>
<td>1.28 (0.87, 1.88)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig. 1. The results of the search, selection and inclusion of studies. Note: No study was retrieved from the search on CRD.

Fig. 2. Risk of depression in early and late puberty.
Depicted in Fig. 1 (Angold et al., 1998; Benoit et al., 2013; Born and Steiner, 2001; Burt and Stein, 2002; Canals et al., 2002; Canals Sans et al., 1991; Carter et al., 2011; Conley and Rudolph, 2009; Conley et al., 2012; Davison et al., 2007; Edwards et al., 2011; Garrison et al., 1990; Ge et al., 2001; Ge et al., 2003; Hayward et al., 1999; Joinson et al., 2012; Koenig and Gladstone, 1998; Kutzcher et al., 2004; Laitinen-Krispijn et al., 1999; Patton et al., 2008; Reinhzer et al., 1993; Rudolph and Flynn, 2007; Rudolph and Troop-Gordon, 2010; Silberg et al., 1999; Skinner et al., 2012; White et al., 2012).

No case-control study that fulfilled the review criteria was found.

The main characteristics of the selected studies are presented in Table 1. There was a wide variation in how depressive symptoms or disorder criteria were measured between studies. All cohorts used age at menarche as an indicator for pubertal timing.

### 3.1. Risk of bias within studies

Based upon the 13 items assessed, the selected studies failed primarily in selection and attrition bias (two items each; Supplementary Fig. 1). Table 2 details the results of risk of bias assessment for each study. All studies had an appropriate definition of exposure (age at menarche) and also controlled for confounding. The lack of representativeness of the source population and the high level of dropouts reduced the validity of the results.

### 3.2. Outcomes and quality of evidence

Three cohort studies provided primary data that could be summarized in a meta-analysis. Early puberty significantly increased the risk of depression in girls and women (RR = 1.33; CI 95%: 1.02, 1.73; $I^2 = 55$%), and a similar association was not observed for late puberty (Fig. 2). However, when the adjusted results available for two studies on early puberty were pooled, no association with depression was observed (RR = 1.48; CI 95%: 0.69, 2.28; $I^2 = 96$%). The meta-analysis suggests high heterogeneity between the included studies. Due to the small number of included studies, it was not possible to perform the planned sensitivity analysis. It is likely that differences in lengths of follow-up, the criteria for diagnosis and the ages for the assessment of depression explain the inconsistencies across the study results.

*Stice et al.* (2001) used an adapted version of the schedule for affective disorders and schizophrenia for school-age children and found that adolescents who experienced early puberty had significantly more depressive symptoms than those with normal

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**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Definition of exposure (age at menarche, years)</th>
<th>Control (age at menarche, years)</th>
<th>Length of follow-up (years)</th>
<th>Sample size</th>
<th>Assessment of depressive symptoms or disorder</th>
<th>Age of measure of depression (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early puberty</td>
<td>Late puberty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stice et al. (2001)</td>
<td>USA</td>
<td>&lt; 11.6</td>
<td>&gt; 11.6</td>
<td>2</td>
<td>496</td>
<td>Major depression and depressive symptom (K-SADS)</td>
<td>13–17</td>
</tr>
<tr>
<td>Herva et al. (2004)</td>
<td>Finland</td>
<td>9–11</td>
<td>&gt; 16</td>
<td>12–15</td>
<td>3952</td>
<td>HSCL-25 depression questionnaire</td>
<td>31</td>
</tr>
<tr>
<td>Joinson et al. (2011)</td>
<td>United Kingdom</td>
<td>&lt; 11.5</td>
<td>11.5–13.5</td>
<td>3.5</td>
<td>3648</td>
<td>Short mood and feelings questionnaire</td>
<td>13–19</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Selection bias</th>
<th>Performance bias</th>
<th>Attribution bias</th>
<th>Detection bias</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Comparability</td>
<td>Absence of outcome</td>
<td>Dropout rate</td>
<td>Definition of outcomes</td>
<td>Assessment of exposure</td>
</tr>
<tr>
<td></td>
<td>Representativeness</td>
<td></td>
<td>Dropout profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stice et al. (2001)</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Herva et al. (2004)</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Boden et al. (2011)</td>
<td>Unclear</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Joinson et al. (2011)</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

* The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

* The study indicates how many of the people who were asked to take part did so, in each of the groups being studied.

* The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.

* The percentage of individuals or clusters recruited into each arm of the study who dropped out before the study was completed.

* Comparison is made between full participants and those lost to follow up, by exposure status.

* A measure of how clearly the outcomes are defined.

* A determination of the reliability of the method of assessment of exposure.

* Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.

* The major potential confounders are identified and taken into account in the design and analysis.

* Confidence intervals have been provided.
puberty (mean difference: 1.61; CI 95%: 0.61–2.62; p < 0.01). No adjusted results were reported.

Using the short mood and feelings questionnaire (SMFQ) to assess depressive symptoms, Joinson et al. (2011) found a similar impact of early puberty on depression among 14 year old girls (difference = 0.24; CI 95%: 0.09, 0.38), while late puberty significantly reduced the levels of depressive symptoms (difference = –0.18; CI 95%: –0.31, –0.05) (Joinson et al., 2011). These results were adjusted for paternal absence, major financial problems and body mass index (BMI). In a subsequent report, the authors performed a case-control analysis with more current data from the cohort, including assessment of depressive symptoms at the ages of 16.5, 18 and 19 years (Joinson et al., 2013). Girls with early puberty had a higher chance of experiencing depressive symptoms (SMFQ > 11) at the ages of 13 (adjusted odds ratio [OR] = 2.07; CI 95%: 1.28, 3.35) and 14 years (adjusted OR = 2.09; CI 95%: 1.41, 3.09) compared to girls at the same age with late puberty. The results were adjusted for age at the time of the assessment of depressive symptoms, indicators of socioeconomic disadvantage, paternal absence and BMI. During later adolescence, no significant results were found; significance was only observed in the unadjusted analysis at the age of 16.5 years.

The quality of the body of evidence was rated as very low. Factors that caused us to down grade the quality of evidence were imprecision and the risk of bias. We were unable to identify reasons to upgrade the quality of evidence. Additional details regarding this assessment are presented in Table 3.

4. Discussion

Evidence from the available unadjusted results of the cohort studies demonstrated that girls who experienced early puberty are at a higher risk of developing depression during adolescence. An adjusted meta-analysis could only be performed for two of the studies, and no significant associations were found. Late puberty was not significantly associated with depression, although fewer individuals were assessed for this exposure. With regard to depressive symptoms, two individual studies identified a significant association between early puberty and higher levels of depressive symptoms in adolescents. One study found that late puberty could be a protective factor for depressive symptoms, although no polling of these data was possible. No clear consensus is available regarding the adjusted or unadjusted results of the meta-analyses; however, unadjusted results may be less affected by selective reporting bias (Peters and Mengersen, 2008). The quality of evidence was rated as very low, implying uncertainty in the estimates (Balshem et al., 2011).

4.1. Limitations

The timing and methods of assessing depression varied largely across studies, which may have introduced an important assessment bias. The accuracy of depression diagnosis varies for each tool, and no gold standard is widely accepted (Williams et al., 2002). The studies used self-reported age at menarche to define early or late puberty, a measure that is prone to recording bias, particularly when assessed in older women (Cooper et al., 2006; Cairns et al., 2011). Such flaws are the primary reason that we judged the quality of evidence to be very low.

The main limitation of our findings is the low number of studies available in the field, and the resulting small size of the sample assessed. The paucity of studies, mainly in the adult phase of life, impedes stronger conclusions by the present review. Our methods were planned to minimize publication bias: we did not apply language or date restrictions, and we performed a sensible search of relevant databases, including some that index gray literature (informally published material). Such procedures reduce the risk of neglecting important studies by presenting the totality of evidence available in the field (Song et al., 2000).

We found several studies that assessed puberty and depression, but the effect of early or late puberty on depression was not evaluated, precluding their inclusion in our review (Angold et al., 1998; Carter et al., 2011; Conley and Rudolph, 2009; Conley et al., 2012; Edwards et al., 2011; Kutcher et al., 2004; Laitinen-Krispijn et al., 1999; Patton et al., 2008; Reinherz et al., 1993; Rudolph and Flynn, 2007; Rudolph and Troop-Gordon, 2010; White et al., 2012). Three cohort studies found a positive correlation between early puberty and depressive symptoms (p < 0.05) (Benoit et al., 2013; Ge et al., 2001, 2003). Because comparisons to control groups with normal puberty and the resulting measures of association were not provided, such studies could not be included in the present

<table>
<thead>
<tr>
<th>Table 3</th>
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</thead>
<tbody>
<tr>
<td>Quality of evidence of the association of pubertal timing and risk of depression and depressive symptoms.</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Risk factor: early puberty</td>
</tr>
<tr>
<td>Depression*</td>
</tr>
<tr>
<td>Depressive symptoms</td>
</tr>
<tr>
<td>Risk factor: late puberty</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Depressive symptoms</td>
</tr>
</tbody>
</table>

Notes: All studies had observational design (initial quality of evidence: low).

* Assessed with DSM-IV symptom criteria for major depression; HSCL-25 depression questionnaire; Major depression by adapted version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) and Short Mood and Feelings Questionnaire (SMFQ). Depressive symptoms were assessed with K-SADS and SMFQ.

a The majority of studies failed against selection and attrition bias, with low representativeness and high dropout rates. By using crude data, the meta-analysis did not consider the potential confounding effects (for the outcome depression).

1 An important heterogeneity was expected as the exposure assessment method varied within studies, although inconsistency cannot be ruled out.

2 One study measured depression in adulthood, but all the others worked primarily with adolescent girls.

3 The overall estimates had wide confidence intervals, crossing or approaching the non-significant threshold.

4 No polled result was able to be calculated.
review. However, their results are consistent with our findings on early puberty and depression.

4.2. Interpretation and generalizability

While a physiological path may explain the linkage between puberty and depression (Steiner et al., 2003), other factors are also associated with both phenomena. Puberty onset is associated with increased BMI (He and Karlberg, 2001; Pierce et al., 2010), potentially due to higher protein intake, which, in its turn, is linked to hormonal maturation (Günther et al., 2010). Longitudinal analyses of overweight, obesity and depression show that obesity (BMI ≥ 30 Kg/m²) and overweight (BMI = 25–29 Kg/m²) increase the risk of depression (Lupino et al., 2010). Conversely, depression may be predictive of developing obesity (Lupino et al., 2010). Two studies included in the present review adjusted their results for BMI, and the association between early puberty and depression or depressive symptoms remained significant (Herva et al., 2004; Joinson et al., 2011).

The age at menarche has been reported to be decreasing significantly in recent decades, a phenomenon that is primarily influenced by improvements in the quality of nutrition (Talma et al., 2013; Cho et al., 2010). This tendency may have increased one of the exposures we assessed (early puberty). It is possible that more girls are labeled as having early puberty based on a criterion (age threshold) that may no longer be accurate. Another trend in recent years is the rise in the burden of depression worldwide. In Denmark, the depression rate in adults increased from 2% in recent years is the rise in the burden of depression worldwide. In Denmark, the depression rate in adults increased from 2% in 2000 to 2006 (Andersen et al., 2011); in Australia, the prevalence of depression in individuals 15 years old and over rose from 6.8–10.3% between 1998 and 2008 (Goldney et al., 2010); and in the United States, from 1991 to 2002, the prevalence among adults rose from 3.33–7.06% (Compton et al., 2006). In this scenario, both the outcome (depression) and one of the risk factors (early puberty) may have increased for different reasons, which may have contributed to the slight significance in the association found between early puberty and depression.

5. Conclusions

Early puberty in girls seems to be a risk factor for the onset of depression, while no increased risk was found for late puberty. Parents and healthcare providers should be aware of mood monitoring in teenagers girls with early puberty. The quality of the evidence could be greatly improved by further well-designed research to better explore how puberty and depression interact. This could be accomplished through ongoing longitudinal studies, particularly birth cohorts for which accurate records of age at menarche are available. Such cohorts could be assessed for the incidence of depression or depressive symptoms during adolescence and adulthood and may help in the prevention and diagnosis of depression in girls and women.

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Conflict of interest
The authors have no conflicts of interest in the context of this work.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.10.034.

References


