Delayed puberty is a common condition defined as the lack of sexual maturation by an age ≥2 SD above the population mean. In the absence of an identified underlying cause, the condition is usually self-limited. Although self-limited delayed puberty is largely believed to be a benign developmental variant with no long-term consequences, several studies have suggested that delayed puberty may in fact have both harmful and protective effects on various adult health outcomes. In particular, height and bone mineral density have been shown to be compromised in some studies of adults with a history of delayed puberty. Delayed puberty may also negatively affect adult psychosocial functioning and educational achievement, and individuals with a history of delayed puberty carry a higher risk for metabolic and cardiovascular disorders. In contrast, a history of delayed puberty appears to be protective for breast and endometrial cancer in women and for testicular cancer in men. Most studies on adult outcomes of self-limited delayed puberty have been in small series with significant variability in outcome measures and study criteria. In this article, we review potential medical and psychosocial issues for adults with a history of self-limited delayed puberty, discuss potential mechanisms underlying these issues, and identify gaps in knowledge and directions for future research.
therapy should be initiated by a certain age in all individuals with self-limited delayed puberty to prevent or temper any of these effects. These studies were conducted predominantly in Caucasian populations and used traditional cutoffs for delayed puberty and may thus be limited in their generalizability; nonetheless, they provide insight into the potential consequences of self-limited delayed puberty. In this review, we examine consequences of self-limited pubertal delay on height, bone mineral density (BMD), psychosocial functioning, and educational achievement, as well as associations between delayed puberty and the risks for adult cancers and cardiovascular disorders.

METHODS

The PubMed database was searched using the following medical subject heading terms and keywords: delayed puberty, adult height, BMD, fracture, depression, substance use, self-esteem, educational achievement, breast cancer, endometrial cancer, testicular cancer, prostate cancer, cardiovascular disease, myocardial infarction, peripheral arterial disease, stroke, hypertension, and metabolic syndrome. All relevant articles published from 2006 to 2016 were included in the review. Articles published before 2006 were included if they provided key background information, demonstrated a new or significant finding in the field, and/or summarized previous findings in a review and/or meta-analyses. References of selected articles were reviewed for additional articles not identified on the initial search.

HEIGHT

Puberty is marked by a period of rapid skeletal growth, the pubertal growth spurt. Because this growth acceleration is delayed in individuals with self-limited delayed puberty, these individuals are typically shorter during the teenage years than peers with normal pubertal timing. Further compounding the short stature during early adolescence is the fact that, in addition to having a delayed pubertal growth spurt, individuals with self-limited delayed puberty often have a slow growth velocity before puberty. When these individuals do eventually undergo a pubertal growth spurt, the conventional teaching is that this growth spurt, albeit delayed, allows them to “catch up” and attain their full genetic height potential.

Conflicting Observations

Consistent with this teaching, several observational studies report that children with self-limited delayed puberty eventually achieve their genetic height potential, with no significant difference between measured adult height and predicted adult height (ie, midparental target height) (Tables 1 and 2). However, other studies suggest that these individuals fall short of their target height by 0.6 to 1.5 SD, ~4 to 11 cm (Tables 1 and 2). These disparate findings may be due to variation in study populations due to ascertainment criteria, inclusion criteria (which sometimes include growth delay), and/or use of sex-steroid treatment. Thus, these findings have prompted attempts to identify features that may predict which individuals will fail to meet their genetic height potential.

Role of Familial Short Stature

One factor that appears to influence whether target height is ultimately attained in self-limited delayed puberty is the target height itself. Delayed puberty is often (although not always) seen in the context of familial short stature, which can exacerbate concerns regarding short stature. Individuals with self-limited delayed puberty with at least 1 tall parent (defined as height greater than the 90th percentile) or with a target height that is not short (defined as target height less than ~1.5 SDs) were found to reach or exceed their target height (Tables 1 and 2). These studies suggest that individuals with familial short stature in combination with self-limited delayed puberty are particularly likely to fall short of their target height.

Correlations With Prepubertal Growth

Another factor that has been suggested to play a role in determining adult height in individuals with self-limited delayed puberty is the rate of growth during the childhood years before puberty, with a slow rate of prepubertal growth associated with failure to attain target height in both boys and girls with an otherwise unremarkable medical evaluation. In boys, such individuals had adult heights 0.63 SD (~4 cm) less than predicted, whereas those with normal rates of prepubertal growth had no such height deficits (Fig 1). Height gain during the pubertal growth spurt was comparable between the 2 groups, and thus the growth during puberty did not compensate for the prepubertal growth deficit in individuals with slow prepubertal growth (Table 1). In both boys and girls, individuals with slower growth rates in childhood also had shorter parents, which support previous conclusions that familial short stature may limit individuals from reaching their target height and suggests a possible genetic component to the slow growth rate.

Effects of Sex-Steroid Therapy

Sex-steroid therapy (eg, testosterone in boys, estradiol in girls) can be offered to ameliorate psychosocial distress related to delayed puberty. Several observational studies and 2 randomized trials have examined the effects of sex-steroid therapy on height in boys with self-limited
TABLE 1 Final Adult Height and Target Height in Boys with Self-Limited Delayed Puberty

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Subgroup</th>
<th>N</th>
<th>FH (SD or cm)</th>
<th>TH (SD or cm)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramswig et al57</td>
<td>1990</td>
<td>—</td>
<td>37</td>
<td>–0.7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Crowne et al17</td>
<td>1990</td>
<td>—</td>
<td>43</td>
<td>–1.6</td>
<td>–0.6</td>
<td>–1.0 SD</td>
</tr>
<tr>
<td>LaFranchi et al20</td>
<td>1991</td>
<td>—</td>
<td>28</td>
<td>169.5</td>
<td>174.6</td>
<td>–5.1 cm</td>
</tr>
<tr>
<td>von Kalckreuth et al22</td>
<td>1991</td>
<td>—</td>
<td>14</td>
<td>171.3</td>
<td>173.9</td>
<td>–2.6 cm</td>
</tr>
<tr>
<td>Albanese and Stanhope50</td>
<td>1993</td>
<td>—</td>
<td>98</td>
<td>–1.9</td>
<td>–0.5</td>
<td>–1.4 SD</td>
</tr>
<tr>
<td>Albanese and Stanhope51</td>
<td>1995</td>
<td>—</td>
<td>78</td>
<td>–2.0</td>
<td>–0.5</td>
<td>–1.5 SD</td>
</tr>
<tr>
<td>Sperlich et al22</td>
<td>1995</td>
<td>—</td>
<td>1</td>
<td>–1</td>
<td>–0.4</td>
<td>–0.6 SD</td>
</tr>
<tr>
<td>Arrigio et al23</td>
<td>1996</td>
<td>Untreated</td>
<td>27</td>
<td>–0.9</td>
<td>–0.7</td>
<td>–0.2 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone treated</td>
<td>22</td>
<td>–0.6</td>
<td>–0.8</td>
<td>0.2 SD</td>
</tr>
<tr>
<td>Bertelloni et al24</td>
<td>1998</td>
<td>—</td>
<td>7</td>
<td>–0.7</td>
<td>–0.4</td>
<td>–0.3 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone treated</td>
<td>6</td>
<td>–0.6</td>
<td>–0.7</td>
<td>0.1 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxandrolone treated</td>
<td>8</td>
<td>–0.7</td>
<td>–0.7</td>
<td>0 SD</td>
</tr>
<tr>
<td>Rensonnet et al31</td>
<td>1999</td>
<td>Untreated</td>
<td>28</td>
<td>–0.76</td>
<td>–0.56</td>
<td>–0.2 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone treated</td>
<td>11</td>
<td>–0.29</td>
<td>–0.35</td>
<td>0.06 SD</td>
</tr>
<tr>
<td>Kelly et al21</td>
<td>2003</td>
<td>—</td>
<td>64</td>
<td>168.9</td>
<td>170.4</td>
<td>–1.5 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>—</td>
<td>168.2</td>
<td>171.1</td>
<td>–2.9 cm</td>
<td></td>
</tr>
<tr>
<td>Butenandt et al34</td>
<td>2005</td>
<td>—</td>
<td>12</td>
<td>1.9</td>
<td>1.2</td>
<td>0.7 SD</td>
</tr>
<tr>
<td>Poyrazoglu et al35</td>
<td>2005</td>
<td>—</td>
<td>105</td>
<td>–1.8</td>
<td>–0.9</td>
<td>–0.9 SD</td>
</tr>
<tr>
<td>Wehkalampi et al36</td>
<td>2007</td>
<td>Early reduction in height</td>
<td>18</td>
<td>–0.65</td>
<td>–0.02</td>
<td>–0.63 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No early reduction in height</td>
<td>22</td>
<td>0.3</td>
<td>0.25</td>
<td>0.05 SD</td>
</tr>
<tr>
<td>Cools et al37</td>
<td>2008</td>
<td>—</td>
<td>33</td>
<td>–0.2</td>
<td>–0.3</td>
<td>0.1 SD</td>
</tr>
<tr>
<td>Zucchini et al38</td>
<td>2008</td>
<td>Untrained</td>
<td>17</td>
<td>–1.02</td>
<td>–1.12</td>
<td>0.1 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GH treated</td>
<td>25</td>
<td>–0.92</td>
<td>–1.26</td>
<td>0.34 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone treated</td>
<td>12</td>
<td>–1.38</td>
<td>–1.45</td>
<td>0.06 SD</td>
</tr>
</tbody>
</table>

FH, final height; GH, growth hormone; TH, target height; —, not available.

TABLE 2 Final Adult Height and Target Height in Girls With Self-Limited Delayed Puberty

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Subgroup</th>
<th>N</th>
<th>FH (SD or cm)</th>
<th>TH (SD or cm)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramswig et al57</td>
<td>1990</td>
<td>—</td>
<td>32</td>
<td>–0.7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>von Kalckreuth et al22</td>
<td>1991</td>
<td>—</td>
<td>6</td>
<td>155.9</td>
<td>155.7</td>
<td>0.2 cm</td>
</tr>
<tr>
<td>Crowne et al17</td>
<td>1991</td>
<td>—</td>
<td>15</td>
<td>–1.5</td>
<td>–0.8</td>
<td>–0.7 SD</td>
</tr>
<tr>
<td>LaFranchi et al20</td>
<td>1991</td>
<td>—</td>
<td>15</td>
<td>156.4</td>
<td>161.7</td>
<td>–5.3 cm</td>
</tr>
<tr>
<td>Albanese and Stanhope50</td>
<td>1993</td>
<td>—</td>
<td>34</td>
<td>–2.3</td>
<td>–0.8</td>
<td>–1.5 SD</td>
</tr>
<tr>
<td>Butenandt et al34</td>
<td>2005</td>
<td>—</td>
<td>21</td>
<td>2.1</td>
<td>1.5</td>
<td>0.6 SD</td>
</tr>
<tr>
<td>Poyrazoglu et al35</td>
<td>2005</td>
<td>—</td>
<td>46</td>
<td>–1.34</td>
<td>–1</td>
<td>–0.34 SD</td>
</tr>
<tr>
<td>Zucchini et al38</td>
<td>2008</td>
<td>Untreated</td>
<td>16</td>
<td>–0.78</td>
<td>–0.88</td>
<td>0.1 SD</td>
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<tr>
<td></td>
<td></td>
<td>GH treated</td>
<td>7</td>
<td>–0.92</td>
<td>–0.43</td>
<td>–0.49 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estrogen treated</td>
<td>7</td>
<td>0.1</td>
<td>0.3</td>
<td>–0.2 SD</td>
</tr>
</tbody>
</table>

FH, final height; GH, growth hormone; TH, target height; —, not available.

delayed puberty.40,41 These studies have reported no difference in adult height between those treated with sex steroids and those who underwent observation alone (Tables 1 and 2).21–25,33,35,36,38,39 Thus, although there may be other beneficial effects, treatment with sex steroids does not appear to enhance or reduce adult height.

Summary
Some individuals with self-limited delayed puberty, particularly those with familial short stature and slower prepubertal growth, fail to attain their genetic target height. Sex-steroid therapy after the age of 14 years in boys and 12 years in girls does not appear to enhance or reduce adult height. However, if started too early (some suggest bone age <10 years), such therapy may lead to premature closure of the growth plates and loss of adult height.

BMD AND FRACTURE RISK
Most bone mass is acquired during puberty. Peak bone mass is attained at the end of skeletal growth in the mid-20s and is an important predictor of the development of osteoporosis later in life.42 In 2001, the National Institutes of Health Consensus on Osteoporosis Prevention, Diagnosis, and Therapy emphasized the need to better understand how pubertal delay affects bone mass and to develop strategies to maximize peak bone mass.43

BMD in Men
In 1992, Finkelstein et al reported that men with a history of self-limited
delayed puberty had lower areal BMD measured by dual x-ray absorptiometry (DXA) than men with normal timing of puberty (Table 3).

Two additional studies, Kindblom et al and Kuh et al, have similarly reported that men with later puberty have lower volumetric BMD as directly measured by peripheral quantitative computed tomography (Table 3). However, 2 other studies, by Bertelloni et al and Yap et al, found no significant difference in volumetric BMD (derived from areal DXA measurements) between men with a history of self-limited delayed puberty and controls (Table 3).

One potential explanation for the variability in findings is that the studies used different definitions of pubertal delay with varying cutoff ages (14 vs 15 years) and ages at follow-up (mean of 19–64 years; Table 3). In addition, only 2 studies (Kindblom et al and Kuh et al) measured volumetric BMD directly; the other studies reported estimated volumetric BMD as calculated from DXA, and concerns have been raised that such calculations may underestimate BMD in smaller individuals even after corrections for body size. Future studies to resolve these questions may require direct measurements in later adulthood of volumetric BMD.

BMD in Women

Many early studies have associated late menarche, a proxy of delayed puberty, with lower BMD. However, most of these studies did not explicitly exclude women who had underlying causes of late menarche such as hypothyroidism or constitutional delay of growth and puberty. Concerns have been raised that reductions in BMD observed as early as 9 years of age in subjects who went on to have menarche later than the median age (Table 4). These observations suggest that factors other than estrogen exposure may influence BMD, possibly genetic and environmental factors that affect both pubertal timing and bone mass.

Although these studies in women suggest that menarche occurring later but still within the normal age range may be associated with lower BMD during both young and later adulthood, only 1 study specifically reported BMD in women with frankly delayed puberty. In this study of postmenopausal women, late menarche (>15 years) was associated with reduced BMD at the lumbar spine and femoral neck when...
<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Year</th>
<th>Delayed Puberty Criteria</th>
<th>Subgroup</th>
<th>N</th>
<th>Age at Evaluation, Years ± SD</th>
<th>Outcome Variable</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Location</td>
<td></td>
<td></td>
<td>Location</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>aBMD, g/cm²</td>
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<td></td>
<td></td>
<td>vBMD, g/cm³</td>
<td></td>
</tr>
<tr>
<td>Finkelstein et al 1992</td>
<td>1992</td>
<td>Puberty onset &gt; 15 y as defined by pubic hair stage and height</td>
<td>DP</td>
<td>23</td>
<td>26 ± 2</td>
<td>Radius</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>21</td>
<td>24 ± 3</td>
<td>LS</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Radius</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LS</td>
<td>1.15</td>
</tr>
<tr>
<td>Bertonelloni et al 1998</td>
<td>1998</td>
<td>Testicular vol ≥ 4 mL, achieved at ≥ 14 y</td>
<td>DP</td>
<td>21</td>
<td>21.8 ± 1.7</td>
<td>LS</td>
<td>1.101</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Controls</td>
<td>12</td>
<td>19.3 ± 1.3</td>
<td>LS</td>
<td>1.222</td>
</tr>
<tr>
<td>Yap et al 2004</td>
<td>2004</td>
<td>Testicular vol ≥ 4 mL, achieved at ≥ 14 y</td>
<td>DP</td>
<td>32</td>
<td>24.7 ± 3.4</td>
<td>Total body</td>
<td>1.184</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>45</td>
<td>23.5 ± 2.9</td>
<td>Total body</td>
<td>1.237</td>
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<tr>
<td>Kindbloom et al 2006</td>
<td>2006</td>
<td>PHV in the latest tertile</td>
<td>Late-tertile PHV</td>
<td>214</td>
<td>18.9 ± 0.5</td>
<td>Total body</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Middle-tertile PHV</td>
<td>214</td>
<td>18.9 ± 0.5</td>
<td>Total body</td>
<td>1.25</td>
</tr>
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<td></td>
<td></td>
<td>LS</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>FN</td>
<td>1.18</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Tibia</td>
<td>Cort: 4.36; Trab: 0.254</td>
<td></td>
</tr>
<tr>
<td>Kuh et al 2016</td>
<td>2016</td>
<td>Lack of or limited genital development, voice breaking, and pubic hair growth</td>
<td>Preadolescent at 14.5 y</td>
<td>65</td>
<td>60–64</td>
<td>Radii</td>
<td>0.97</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Early puberty at 14.5 y</td>
<td>222</td>
<td>60–64</td>
<td>Total hip</td>
<td>1.01</td>
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<td></td>
<td>LS</td>
<td>1.05</td>
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<td></td>
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<td>Advanced puberty at 14.5 y</td>
<td>200</td>
<td>60–64</td>
<td>Total hip</td>
<td>0.99</td>
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<td></td>
<td>LS</td>
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</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Total hip</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Radius</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fully mature at 14.5 y</td>
<td>Total hip</td>
<td>1.02</td>
</tr>
</tbody>
</table>

aBMD, areal bone marrow density; CI, confidence interval; Cort, cortical; DP, delayed puberty; FN, femoral neck; LS, lumbar spine; NS, not significant; PHV, peak height velocity; Trab, trabecular; vBMD, volumetric bone marrow density; —, not available.
<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>N</th>
<th>Subgroup</th>
<th>Age at Evaluation, Years ± SD</th>
<th>Outcome Variable</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox et al.⁵¹</td>
<td>1993</td>
<td>2230</td>
<td>Late menarche (no criteria provided)</td>
<td>71 ± 4.8</td>
<td>Radius 0.36</td>
<td>Each year increment in age at menarche, postmenopausal BMD decreased by 0.9% (P = .02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early menarche (no criteria provided)</td>
<td></td>
<td>Radius 0.371</td>
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<tr>
<td>Tuppurainen et al.⁵³</td>
<td>1995</td>
<td>223</td>
<td>Late menarche (&gt;15 y)</td>
<td>53.4 ± 2.9</td>
<td>LS 1.077</td>
<td>LS and FN aBMD lower in late menarche vs early menarche group, all Ps &lt;.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1382</td>
<td>Early menarche (&lt;15 y)</td>
<td></td>
<td>FN 0.896</td>
<td></td>
</tr>
<tr>
<td>Chevalley et al.⁵²</td>
<td>2009</td>
<td>62</td>
<td>Later pubertal timing (menarche &gt;12.94 y)</td>
<td>8.9 ± 0.5</td>
<td>Total body 0.599</td>
<td>aBMD lower in later vs earlier pubertal timing group at all sites, all Ps &lt; .02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
<td>Earlier pubertal timing (menarche &lt;12.94 y)</td>
<td>9.0 ± 0.5</td>
<td>Total body 0.620</td>
<td></td>
</tr>
<tr>
<td>Chevalley et al.⁵³</td>
<td>2009</td>
<td>62</td>
<td>Later pubertal timing (menarche &gt;12.94 y)</td>
<td>20.4 ± 0.6</td>
<td>FN 0.838</td>
<td>FN and tibia aBMD and vBMD lower in later vs earlier pubertal timing group in both young adult and premenopausal women, all Ps &lt; .004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>Earlier pubertal timing (menarche &lt;12.94 y)</td>
<td>48.0 ± 3.7</td>
<td>Tibia 0.314</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>62</td>
<td>Earlier pubertal timing (menarche &lt;12.94 y)</td>
<td>20.4 ± 0.6</td>
<td>FN 0.878</td>
<td></td>
</tr>
</tbody>
</table>

aBMD, areal bone marrow density; DP, delayed puberty; FN, femoral neck; LS, lumbar spine; NS, not significant; vBMD, volumetric bone marrow density.
compared with BMD of women who underwent menarche before age 15 years (Table 4). However, it is still unclear from the preceding studies whether the finding of a lower BMD in women with later menarche is due to a protective effect of earlier menarche or a detrimental effect of later menarche. Future studies on BMD specifically in women with frankly delayed puberty in comparison with those with normal pubertal timing are needed to resolve this question.

### Fracture Risk

In young adult men, Kindblom et al found that each 1-year increase in age of puberty was associated with a 39% increase in odds of upper extremity fractures during adolescence (Table 5). A similar association was reported in a longitudinal study of young women; individuals who experienced a fracture in childhood or adolescence had significantly later age of menarche and lower volumetric BMD at the distal radius than those who did not experience a fracture despite similar nutritional intake and physical activity level in the 2 groups (Table 5). However, the risk associated with frankly delayed puberty was not reported.

One study did identify women who had frankly delayed menarche (at 16 years or later) and found that these women had an 80% increased risk of incident vertebral fracture in later adulthood compared with those with menarche before 16 years. Similarly, those with menarche at 15 years or later had a 50% increased risk of Colles fracture compared with those with menarche before 15 years (Table 5). Another study showed a 45% increase in the risk of hip fracture in those with menarche at age 15 years or later compared with those with menarche at 11 years or younger (Table 5). In contrast, at the other end of reproductive life, the age at menopause was not significantly associated with Colles or vertebral fracture and had a smaller effect than age at menarche on the risk of hip fracture, suggesting that lifetime duration of estrogen exposure is not the only factor that influences fracture risk. To date, associations between pubertal timing and fracture risk in men have not been reported, possibly due to a relatively lower fracture incidence in men and difficulty with assessing age at pubertal initiation.

### Sex-Steroid Therapy

One intervention that may temper any reduction in BMD in individuals with self-limited delayed puberty is sex-steroid therapy. However, Yap et al and Bertelloni et al both found that androgen treatment of 6 to 28 months did not significantly affect BMD in young adult men with a history of delayed puberty. The influence of sex-steroid therapy on BMD in women has not been reported.

#### Summary

Studies in men with a history of self-limited delayed puberty variably report low or normal BMD, and previous androgen therapy does not appear to influence BMD in these men. In women, later age at menarche is associated with decreased BMD in early adulthood, late adulthood, and even before pubertal onset. Later age at pubertal initiation has also been associated with an increase in fracture risk during adolescence for both boys and girls and during adulthood for women.

#### Psychosocial Outcomes

In addition to being a period of dramatic physical development, adolescence is also a time of marked psychosocial changes. Studies have examined the effect of pubertal timing on multiple psychosocial aspects, including self-esteem, psychopathology, and behavior, with a predominant focus on the adolescent period and with limited follow-up into adulthood.

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**TABLE 5 Fracture Risk in Individuals With Delayed Puberty**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Name</th>
<th>N</th>
<th>Age at Evaluation, Years ± SD</th>
<th>Outcome Variable</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnell et al64</td>
<td>1995</td>
<td>MEDOS</td>
<td>2086 women</td>
<td>78.1 ± 9.4</td>
<td>Hip fracture</td>
<td>RR: 1.45, 95% CI: 1.12 to 1.87 for age at menarche ≥15 y vs ≤11 y</td>
</tr>
<tr>
<td>Roy et al66</td>
<td>2003</td>
<td>EPOS</td>
<td>3173 men, 3402 women</td>
<td>63.1 ± 7.8 (men), 62.2 ± 7.6 (women)</td>
<td>Vertebral fracture</td>
<td>RR: 1.8, 95% CI: 1.24 to 2.63 for age at menarche ≥16 y vs &lt;16 y</td>
</tr>
<tr>
<td>Silman et al66</td>
<td>2003</td>
<td>EPOS</td>
<td>3173 men, 3402 women</td>
<td>63.1 ± 7.6 (men), 62.2 ± 7.6 (women)</td>
<td>Colles’ fracture</td>
<td>RR: 1.5, 95% CI: 1.1 to 2.0 for age at menarche ≥15 y vs ≤15 y</td>
</tr>
<tr>
<td>Kindblom et al66</td>
<td>2006</td>
<td>GOOD</td>
<td>642 men</td>
<td>18.9 ± 0.6</td>
<td>Upper extremity fracture</td>
<td>OR: 1.39, 95% CI: 1.08 to 1.79, P = .01 for each 1-y increment to PHV</td>
</tr>
<tr>
<td>Chevalley et al65</td>
<td>2012</td>
<td>42 women</td>
<td>20.4 ± 0.6</td>
<td>Fracture</td>
<td>OR: 2.09, 95% CI: 1.13 to 3.3, P = .002 for each 1.2-y delay in menarche; mean age at menarche greater for fracture group vs no fracture group (13.45 vs 12.78, P = .003)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; EPOS, European Prospective Osteoporosis Study; GOOD, Gothenburg Osteoporosis and Obesity Determinants; MEDOS, Mediterranean Osteoporosis Study; OR, odds ratio; RR, relative risk; PHV, peak height velocity.
**Self-Esteem**

Two studies from the 1950s suggested that boys and girls who mature later than their peers have more negative beliefs and attitudes toward self at age 17.67,68 Although a subsequent study suggested that it is short stature rather than delayed puberty itself that affected self-image.69 However, 2 studies in boys and girls with CDGP found no significant difference in self-esteem scores in early adulthood between those with CDGP and those with normal development despite moderately shorter stature (–1.6 and –1.5 SD, respectively). Race and ethnicity may modulate the effect of pubertal timing, as 1 study of adolescents with self-perceived late puberty found a significant decrease in body image with late development in Hispanic and black boys, but not in white or Asian boys. For girls with late development, lower body-image scores were observed in Hispanic girls only.70

**Psychopathology and Behavior**

Many studies have associated early pubertal timing with adverse psychosocial outcomes including depression, delinquency, and early sexual behavior.71–75 Fewer studies have examined psychosocial outcomes for men and women who experienced later pubertal timing (summarized in Table 6). One study of a large UK birth cohort observed that girls with menarche ≥13.5 years had up to a 52% reduction in odds of experiencing depressive symptoms in adolescence compared with girls with normal menarche, but this association disappeared by young adulthood.76 Similarly, a study in New Zealand did not find any association between menarche at ages 14 to 15 and major depression during adolescence.77 In contrast, a study in Finland identified a 70% higher risk of depression in women who had delayed puberty (menarche ≥16 years).78 But in a recent meta-analysis of both the New Zealand and Finland studies, this association was no longer seen.79 Further supporting the overall results of the meta-analysis, 2 recent studies, the Growing Up Today Study, a follow-up of the Nurses’ Health Study II, and the UK Biobank Study found that later menarche (>14.3 and >15 years) was not associated with depressive symptoms in young and later adulthood, respectively.80,81

Although there is no clear evidence for lasting psychosocial consequences of delayed puberty in women, late pubertal timing has been suggested to be associated with psychological issues in men. Perceived late pubertal timing in boys has been associated with higher levels of depression in settings with high levels of peer stress,82 disruptive behavior disorder and substance use in young adulthood,83 and depression and anxiety in later adulthood (Table 6).81 A review of psychological outcomes associated with pubertal timing in boys supported these findings and concluded that the effects of late pubertal timing appear to be limited to higher rates of internalizing symptoms (associated with depression or anxiety) and substance use in both adolescence and young adulthood.84

Studies on educational achievement in individuals with self-limited delayed puberty have reported worse academic performance during childhood85–87 and either no difference88,89 or better performance during young adulthood.83

**Summary**

Delayed puberty may be associated with increased internalizing symptoms and poorer academic performance in adolescence, but it remains to be determined whether it has significant long-term effects on psychological outcomes and academic achievement in later adulthood.

**Malignancy**

**Breast Cancer**

The influence of pubertal timing on the risk for breast cancer is well established, with studies in the 1960s and 1970s demonstrating an association between early age at menarche and increased risk of breast cancer90. Subsequent studies further established an association between delayed age at menarche and reduced breast cancer risk.91,92 One such study found that menarche ≥15 years was associated with a twofold reduction in the risk of breast cancer among premenopausal women compared with normally timed menarche.91 Furthermore, a 2-year delay in menarche has been associated with a 10% decrease in the risk of breast cancer in both pre- and postmenopausal women92 and late initiation of breast development (≥13 years) with a 20% decrease in risk compared with breast development occurring at age 11 to 12 years.93

The protective effect of delayed puberty on breast cancer risk has been proposed to be due to a shorter lifetime duration of estrogen exposure and, in turn, less breast cell proliferation and a lower chance of incurring carcinogenic mutations.93 Another factor that has been suggested to independently affect both pubertal timing and breast cancer risk is genetic variation. A recent study found that 2 single nucleotide polymorphisms associated with earlier age at menarche were also associated with an increased risk for breast cancer even after controlling for age at menarche, suggesting that these genetic loci affect breast cancer risk independently of their effect on menarchal timing.94

**Endometrial Cancer**

Numerous case-control studies have associated early menarche with increased risk of endometrial
cancer, but only 2 studies have specifically evaluated the effect of late menarche. A retrospective case-control study in Italy found that menarche $\geq 14$ years was associated with a 32% decrease in the odds of endometrial cancer compared with menarche at age $<12$ years.95 A prospective study across Europe reported similar findings in women with menarche $\geq 15$ years compared with women with menarche $<12$ years, with a 7% to 8% reduction in risk per year that menarche is delayed.96 Of note, neither study explicitly compared late menarche with normal menarche, so it is unclear if late menarche is protective against endometrial cancer, if early menarche is a risk factor, or both. 

### Testicular Cancer

In men, studies examining the relationship between pubertal timing and testicular cancer have produced inconsistent results. Some studies have suggested that later onset of puberty is associated with an $\sim 40\%$ to 65% decrease in the odds of testicular cancer,97–101 but other studies have reported no association.102–107 A recent meta-analysis of 8 studies found that later age at reported onset of puberty was associated with a 19% reduced odds of testicular cancer.108

### Prostate Cancer

The role of pubertal timing on prostate cancer risk is under active investigation with inconclusive findings. Although some studies have reported up to a 25% decrease in the odds of prostate cancer in individuals with later puberty,109–111 others have reported either no association112,113 or up to a 6% increase in the odds of prostate cancer for each year of pubertal delay.114 Difficulty in assessment of pubertal timing in men may be a contributor to the discrepant results; thus, 1 study used a genetic risk score calculated from 13 single nucleotide polymorphisms as a proxy for pubertal development. Although the researchers did not find a significant association between genetic risk score and the presence of prostate cancer, they did identify an association between a higher genetic risk score (later onset of puberty) and a 24% reduction in the odds of

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Location/Name</th>
<th>N</th>
<th>Age at Evaluation, Years $\pm$ SD or Range</th>
<th>Outcome Variable</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joinson et al176</td>
<td>2013</td>
<td>United Kingdom</td>
<td>3649 women</td>
<td>14–16.5</td>
<td>Depressive symptoms</td>
<td>OR up to 1.52, 95% CI: 1.12 to 2.05 for age at menarche 11.5 to 15.5 y vs $\geq 13.5$ y, $P = .007$</td>
</tr>
<tr>
<td>Boden et al177</td>
<td>2011</td>
<td>New Zealand</td>
<td>497 women</td>
<td>15–18</td>
<td>Major depression</td>
<td>No difference in OR for age at menarche 11.5 to 13.5 y vs $\geq 13.5$ (OR 1.07–1.18, all $P &gt; 0.05$)</td>
</tr>
<tr>
<td>Herva et al178</td>
<td>2004</td>
<td>Northern Finland</td>
<td>3952 women</td>
<td>31</td>
<td>Depression</td>
<td>No difference in % outcome for age at menarche 14–15 y vs 12–13 y (32.5% vs 30.9%, $P &gt; .50$)</td>
</tr>
<tr>
<td>Galvao et al179</td>
<td>2014</td>
<td>Meta-analysis: New Zealand and Northern Finland</td>
<td>4449 women</td>
<td>15–31</td>
<td>Major depression/depression</td>
<td>No significant risk of depression for age at menarche $\geq 14$ y vs $&lt; 14$ y (RR 1.28, 95% CI: 0.87 to 1.88)</td>
</tr>
<tr>
<td>Opoliner et al180</td>
<td>2014</td>
<td>United States/ Growing Up Today Study</td>
<td>9039 women</td>
<td>20–26</td>
<td>Depressive symptoms</td>
<td>No difference in OR for age at menarche $&gt; 14.3$ y vs 12–14.3 y (OR 0.91, 95% CI: 0.70 to 1.18)</td>
</tr>
<tr>
<td>Day et al181</td>
<td>2015</td>
<td>United Kingdom/UK Biobank Study</td>
<td>250 037 women</td>
<td>40–69</td>
<td>Depression</td>
<td>No difference in OR for age at menarche 15–19 y vs 12–14 y (OR 1.07, 95% CI: 1.02 to 1.13, $P &gt; 7.48 \times 10^{-5}$)</td>
</tr>
<tr>
<td>Conley and Rudolph182</td>
<td>2009</td>
<td>United States</td>
<td>82 men</td>
<td>13.4</td>
<td>Depression</td>
<td>Later perceived pubertal timing was associated higher levels of depression ($\beta = -0.31$, $P &lt; .05$)</td>
</tr>
<tr>
<td>Graber et al183</td>
<td>2004</td>
<td>United States</td>
<td>392 men</td>
<td>24.2</td>
<td>Disruptive behavior disorder/ Substance use</td>
<td>OR 2.1, 95% CI: 1.1 to 4.5 for perceived late pubertal timing vs on time</td>
</tr>
<tr>
<td>Day et al184</td>
<td>2015</td>
<td>United Kingdom/UK Biobank Study</td>
<td>197 714 men</td>
<td>40–69</td>
<td>Anxiety/panic attacks</td>
<td>OR 1.43, 95% CI: 1.22 to 1.67 for perceived late voice breaking vs on time, $P &lt; 7.48 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; RR, relative risk.
high-grade prostate cancer per score tertile.\textsuperscript{115}

**Summary**

Late pubertal onset in girls is protective against breast cancer and possibly against endometrial cancer. Recent studies suggest that some genetic loci independently affect both breast cancer risk and age at menarche. Late pubertal onset in boys appears to be protective for testicular cancer, but the role of pubertal timing in prostate cancer remains unclear.

**METABOLIC AND CARDIOVASCULAR OUTCOMES**

Most studies of the effect of pubertal timing on metabolic and cardiovascular disease have focused on early pubertal maturation, which has been linked to increased risk for obesity, metabolic syndrome, and overall cardiovascular mortality.\textsuperscript{116} There is now evidence that delayed puberty has negative effects as well.

Early studies suggested a protective effect of delayed puberty for cardiovascular disease. In a retrospective population-based study in Germany, menarche $\geq 15$ years was associated with a 52\% reduced odds of peripheral arterial disease compared with menarche at age 12 to 15 years.\textsuperscript{117} The same study also found an association between later age at menarche and lower BMI, waist circumference, fasting glucose, and 2-hour glucose, trends that extended into the late menarche group ($\geq 15$ years).\textsuperscript{118}

More recent studies have suggested that later pubertal timing in fact has a negative effect. The association between coronary heart disease and menarchal timing exhibits a U-shaped curve, with an increased risk of coronary heart disease associated with both earlier and later pubertal timing. In a recent study of $>$1 million women in the United Kingdom, both early and late menarche were associated with an increase in risk of coronary heart disease: compared with women with an average age at menarche (13 years), those with menarche at 11 years had a 12\% increase in risk and those with menarche at 15 years had a 6\% increase in risk after adjustment for covariates including BMI, smoking, and socioeconomic status (Fig 2). The highest risks were observed for menarche at $\leq 10$ years and at $\geq 17$ years, with $>20\%$ increase in risk for each group. A similar but less pronounced relationship was found between age at menarche and other conditions, with menarche at $\geq 17$ years associated with a 13\% increase in risk for cerebrovascular disease and a 7\% increase in risk for hypertensive disease compared with age at menarche at 13 years. Whether this increased risk for cardiovascular disease extends to increased risk for mortality remains unclear.\textsuperscript{119–123}

Few studies have examined the effect of pubertal timing on metabolic and cardiovascular disease in men.\textsuperscript{116} One study suggested that an earlier age at perceived age of voice breaking was associated with up to a 39\% increase in the odds of angina, heart attack, hypertension, and type 2 diabetes, with no observed effect in men with later perceived age of voice breaking.\textsuperscript{81}

**Potential Mechanisms Linking Pubertal Timing to Cardiovascular Risk**

One proposed explanation for the association between earlier and...
puberty and cardiovascular risk is the association between early puberty and childhood obesity. A review of studies on childhood BMI showed that in 5 of 8 studies, adjusting for childhood obesity attenuated the association between early menarche and higher adult BMI, but only partially, suggesting the presence of additional, yet-to-be-identified factors. Similarly, later exposure to sex steroids in individuals with delayed puberty may have effects on metabolic function and cardiovascular health either directly or by affecting other factors such as BMI and lipid metabolism.

Notably, recent genome-wide association studies have identified overlap between genetic loci that influence timing of menarche and those associated with adult BMI. In one meta-analysis, the influence of these loci on age at menarche was not attenuated by adjustment for BMI. These findings suggest that these genetic factors affect pubertal timing and BMI independently and serve as a common genetic link that may account, at least in part, for the association between timing of menarche and the risk for cardiovascular disease. Data from large electronic health record databases, phenotyping studies, and genetic studies may reveal how pubertal timing influences cardiovascular disease risk and in turn how this risk is determined more generally.

Summary

Emerging evidence shows a U-shaped association curve, with both earlier and later onset of pubertal timing associated with an increased risk of cardiovascular disease in women. Factors that may contribute to this association include common genetic links and obesity.

CONCLUSIONS AND FUTURE DIRECTIONS

The findings that delayed pubertal timing may have lasting negative consequences raise several questions.

- Does delayed puberty truly have lasting negative consequences? There are discrepancies in the existing literature on nearly all outcomes of delayed puberty that have been examined, and publication bias may be a contributing factor. Nevertheless, the studies reviewed in this article raise the possibility that delayed puberty may not be a completely benign entity, particularly with regard to height, BMD, psychological outcomes, and cardiovascular disease.

- Are there subsets of individuals with self-limited delayed puberty who are at greatest risk for negative outcomes? The studies cited in this review suggest that familial short stature and slow growth rates before puberty are associated with lower adult height, and race and ethnicity may influence psychosocial outcomes (eg, self-esteem). Most reports have studied primarily Caucasian populations, and the implications for other racial and ethnic groups remain unclear. Further identification of subgroups, which could be achieved through large-scale phenotyping studies or “big data” approaches to analyze medical records, may reconcile discrepancies between existing studies. Genetic analyses may identify specific genetic loci associated with these phenotypes and allow for improved prediction of adverse outcomes.

- Does current clinical practice need to change? Reassurance and observation remain the foundations for management of individuals with delayed puberty. We do not feel the existing evidence is sufficiently definitive to alter this approach, but we recommend that reassurance be provided with appropriate caveats. Tempered expectations should be set regarding adult height, and clinicians must be careful to not be dismissive or overly optimistic when counseling these patients.

Treatment with sex steroids is an option for individuals with delayed puberty, but its effects on adult outcomes remain unclear. Because it would be difficult to perform a definitive clinical trial to determine whether treatment can avert potential negative outcomes of delayed puberty, an alternative approach to addressing this question may come from large electronic health record databases. Such data may be limited by clinical confounders, but they can shed light on whether sex-steroid treatment of delayed puberty can modify bone density, cardiovascular disease risk, and other adult outcomes and, if so, the age at which such treatment is maximally effective.

Contrary to what is commonly taught, self-limited delayed puberty may not be an entirely benign entity and may be associated with shorter stature, lower BMD, negative psychological outcomes, and increased risk for cardiovascular disease. Further investigations incorporating pubertal timing into both genotype- and phenotype-association studies can further inform our understanding of the links between pubertal timing and these outcomes and, more broadly, the physiology underlying growth, bone health, psychosocial development, and cardiovascular health.

ABBREVIATIONS

BMD: bone mineral density
CDGP: constitutional delay of growth and puberty
DXA: dual x-ray absorptiometry
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