Adult Consequences of Self-Limited Delayed Puberty

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abstract

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.

Delayed puberty is commonly defined as the absence of physical signs of puberty by an age ≥2 SD beyond the population mean for pubertal entry, a statistical definition necessitated by our incomplete understanding of how the timing of puberty is determined.[1] For girls, delayed puberty is commonly defined as the absence of breast development by age 13 years and for boys as the absence of testicular enlargement by age 14 years. Of note, these clinical conventions do not reflect variation in pubertal timing between racial and ethnic groups or a recent trend toward earlier pubertal timing that has been observed in the United States and other developed countries.[2–13]

In the absence of any identifiable cause, delayed puberty usually resolves by age 18 years, and in this review, this condition is referred to as "self-limited delayed puberty." This condition is also called constitutional delay of puberty, development, or maturation, with the word "growth" also frequently included (eg, constitutional delay of growth and puberty [CDGP]).

Self-limited delayed puberty is considered by many to be a benign developmental variant with no long-term consequences.[14,15] Thus, the mainstay of treatment is an observational, "watchful waiting" approach with reassurance for the patient and family. However, some reports have suggested that the condition can have lasting physical and psychological effects, which raises the question whether sex-steroid

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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.[16] 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.[17,18] 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.[19] 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.[20]

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).[21–25] 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).[26–32] 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.[1] Individuals with self-limited delayed puberty with at least 1 tall parent (defined as height greater than the 90th percentile)[34] or with a target height that is not short (defined as target height less than –1.5 SDs)[37] 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.[36,39] 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).[36] 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.[34,37]

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.[1] 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

Study (Reference)	Year	Subgroup	*N*	FH (SD or cm)	TH (SD or cm)	Difference
Bramswig et al[26]	1990	—	37	−0.7	—	—
Crowne et al[27]	1990	—	43	−1.6	−0.6	−1.0 SD
LaFranchi et al[29]	1991	—	29	169.5	174.6	−5.1 cm
von Kalckreuth et al[22]	1991	—	14	171.3	173.9	−2.6 cm
Albanese and Stanhope[30]	1993	—	98	−1.9	−0.5	−1.4 SD
Albanese and Stanhope[31]	1995	—	78	−2.0	−0.5	−1.5 SD
Sperlich et al[32]	1995	—		−1	−0.4	−0.6 SD
Arrigo et al[23]	1996	Untreated	27	−0.9	−0.7	−0.2 SD
		Testosterone treated	22	−0.6	−0.8	0.2 SD
Bertelloni et al[24]	1998	Untreated	7	−0.7	−0.4	−0.3 SD
		Testosterone treated	6	−0.6	−0.7	0.1 SD
		Oxandrolone treated	8	−0.7	−0.7	0 SD
Rensonnet et al[25]	1999	Untreated	28	−0.76	−0.56	−0.2 SD
		Testosterone treated	11	−0.29	−0.35	0.06 SD
Kelly et al[33]	2003	—	64	168.9	170.4	−1.5 cm
		—		168.2	171.1	−2.9 cm
Butenandt et al[34]	2005	—	12	1.9	1.2	0.7 SD
Poyrazoglu et al[35]	2005	—	105	−1.8	−0.9	−0.9 SD
Wehkalampi et al[36]	2007	Early reduction in height	18	−0.65	−0.02	−0.63 SD
		No early reduction in height	22	0.3	0.25	0.05 SD
Cools et al[37]	2008	—	33	−0.2	−0.3	0.1 SD
Zucchini et al[38]	2008	Untreated	17	−1.02	−1.12	0.1 SD
		GH treated	25	−0.92	−1.26	0.34 SD
		Testosterone treated	12	−1.39	−1.45	0.06 SD

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

Study (Reference)	Year	Subgroup	*N*	FH (SDS or cm)	TH (SDS or cm)	Difference
Bramswig et al[26]	1990	—	32	−0.7	—	—
von Kalckreuth et al[22]	1991	—	6	155.9	155.7	0.2 cm
Crowne et al[28]	1991	—	15	−1.5	−0.8	−0.7 SD
LaFranchi et al[29]	1991	—	13	156.4	161.7	−5.3 cm
Albanese and Stanhope[30]	1993	—	34	−2.3	−0.8	−1.5 SD
Butenandt et al[34]	2005	—	21	2.1	1.5	0.6 SD
Poyrazoglu et al[35]	2005	—	46	−1.34	−1	−0.34 SD
Zucchini et al[38]	2008	Untreated	16	−0.78	−0.88	0.1 SD
		GH treated	7	−0.92	−0.43	−0.49 SD
Wehkalampi et al[39]	2011	Untreated	32	0.1	0.3	−0.2 SD
		Estrogen treated	7	−0.6	−0.1	−0.5 SD

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).[23–25,33,35,36,38,39] 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

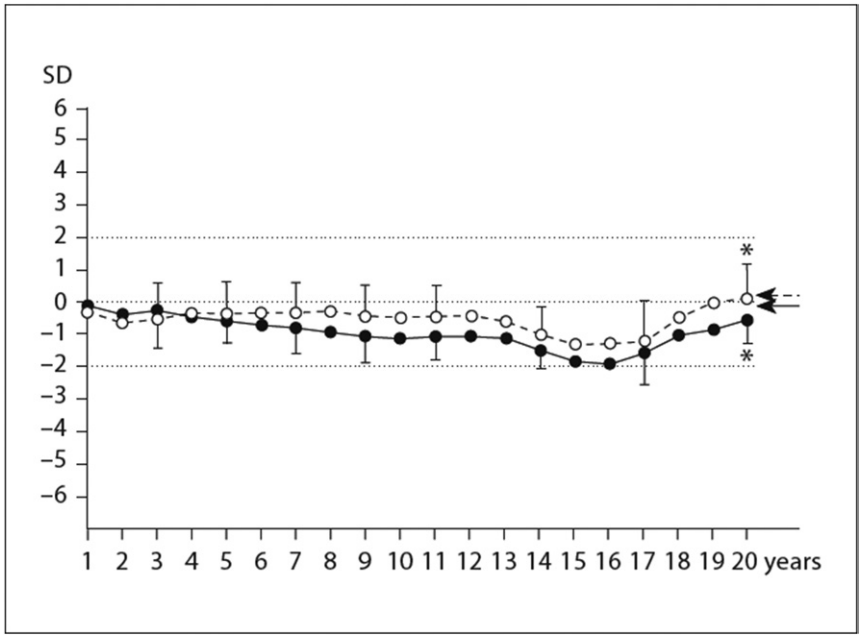


FIGURE 1
Mean SD score for height and mean target height (arrows) of boys with delayed puberty who either had (filled circles and solid line) or did not have (open circles and dashed line) an early reduction in height. *P = .01 between final adult heights. (Reprinted with permission from page 102 of Wehkalampi K, Vangonen K, Laine T, Dunkel L. Progressive reduction of relative height in childhood predicts adult stature below target height in boys with constitutional delay of growth and puberty. *Horm Res.* 2007;68(2):99–104.)

delayed puberty had lower areal BMD measured by dual x-ray absorptiometry (DXA) than men with normal timing of puberty (Table 3).[44,45] 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).[46,47] 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).[24,48]

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[46,47]; 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.[49–51] 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.[52–58] However, most of these studies did not explicitly exclude women who had underlying causes of late menarche such as hypothalamic amenorrhea (a functional form of gonadotropin-releasing hormone deficiency triggered by physical, environmental, and/or psychosocial stressors), which is known to be associated with reduced bone density.[42] One prospective, longitudinal study of 124 healthy women that specifically excluded women with risk factors for hypothalamic amenorrhea reported that subjects with menarche occurring later than the median age for the cohort (12.94 years) had lower BMD at the femoral neck and tibia compared with those with menarche occurring before the median age for the cohort (Table 4), with the negative correlation between menarchal timing and BMD observed across all ages from 8 to 18 years.[59,60] Extending to later adulthood, several observational studies have demonstrated that the age at menarche may influence the risk of osteoporosis during both the premenopausal[52,54,55,61] and postmenopausal years.[53,55,56,58,61]

The effect of pubertal timing on BMD in women has been largely attributed to differences in estrogen exposure. Specifically, both a later age at menarche and earlier age at menopause have been associated with lower BMD, suggesting that a greater lifetime duration of estrogen exposure may have a protective effect on BMD.[42] However, in 1 prospective study, differences in BMD were observed even before the onset of puberty, with a lower areal BMD observed as early as 9 years of age in subjects who went on to have menarche later than the median age (Table 4).[62] 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.[62]

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 3 BMD in Men With a History of Self-Limited Delayed Puberty

Study (Ref)	Year	Delayed Puberty Criteria	Subgroup	N	Age at Evaluation, Years ± SD	Outcome Variable			Conclusion
						Location	aBMD, g/cm^2	vBMD, g/cm^3	
Finkelstein et al[44]	1992	Puberty onset >15 y as defined by pubic hair stage and height	DP	23	26 ± 2	Radius	0.73	0.5	aBMD and vBMD lower in DP vs normal controls at both sites, all *P*s < .009
						LS	1.03	0.13	
			Controls	21	24 ± 3	Radius	0.8	0.54	
						LS	1.13	0.14	
Bertonelloni et al[24]	1998	Testicular vol 4 mL achieved at ≥14 y	DP	21	21.8 ± 1.7	LS	1.101	0.327	aBMD lower in DP vs normal controls, *P* < .009; no difference in vBMD, *P* = NS
			Controls	12	19.3 ± 1.3	LS	1.222	0.337	
Yap et al[48]	2004	Testicular vol 4 mL achieved at ≥14 y	DP	32	24.7 ± 3.4	Total body	1.184	—	Total body aBMD lower in DP vs controls, *P* = .016; LS aBMD lower in DP vs controls, *P* = .044, no difference in LS vBMD, *P* = NS; no difference in FN aBMD or vBMD
						LS	1.2	0.37	
						FN	1.1	0.67	
			Controls	45	23.5 ± 2.9	Total body	1.237	—	
						LS	1.28	0.37	
						FN	1.16	0.67	
Kindbloom et al[46]	2006	PHV in the latest tertile	Late-tertile PHV	214	18.9 ± 0.5	Total body	1.23	—	Total body aBMD lower in late PHV versus average PHV, *P* = .001; no difference in LS or FN aBMD; radius aBMD and vBMD lower in late PHV versus average PHV, *P* all <0.001; tibia vBMD lower in DP versus controls, *P* all < 0.001
						LS	1.21	—	
						FN	1.14	—	
						Radius	0.56	Cort: 1.155; Trab: 0.209	
						Tibia		Cort: 4.36; Trab: 0.254	
			Middle-tertile PHV	214	18.9 ± 0.5	Total body	1.25	—	
						LS	1.24	—	
						FN	1.18	—	
						Radius	0.58	Cort: 1.165; Trab: 0.221	
						Tibia	—	Cort: 4.44; Trab: 0.267	
Kuh et al[47]	2016	Lack of or limited genital development, voice breaking, and pubic hair growth	Preadolescent at 14.5 y	65	60–64	Radius	—	Cort: 1.162; Trab: 0.197	Trab vBMD lower in "preadolescent" by 9% vs "fully mature," 95% CI 14% to −4%; *P* = .001
						LS	1.01	—	
						Total hip	0.97	—	
			Early puberty at 14.5 y	222	60–64	Radius	—	Cort: 1.161; Trab: 0.201	
						LS	1.05	—	
						Total hip	0.99	—	
			Advanced puberty at 14.5 y	200	60–64	Radius	—	Cort: 1.159; Trab: 0.205	
						LS	1.04	—	
						Total hip	1.00	—	
			Fully mature at 14.5 y	168	60–64	Radius	—	Cort: 1.153; Trab: 0.216	
						LS	1.08	—	
						Total hip	1.02	—	

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 4 BMD in Women With a History of Self-Limited Delayed Puberty

Study (Reference)	Year	*N*	Subgroup	Age at Evaluation, Years ± SD	Outcome Variable			Conclusion
					Location	aBMD, g/cm^2	vBMD, g/cm^3	
Fox et al[53]	1993	2230		71 ± 4.8				
			Late menarche (no criteria provided)		Radius	0.36		Each year increment in age at menarche, postmenopausal BMD decreased by 0.9% (P = .02)
			Early menarche (no criteria provided)		Radius	0.371		
Tuppurainen et al[55]	1995			53.4 ± 2.9				
		223	Late menarche (>15 y)		LS	1.077		LS and FN aBMD lower in late menarche vs early menarche group, all Ps <.05
					FN	0.896		
		1382	Early menarche (<15 y)		LS	1.105		
					FN	0.919		
Chevalley et al[62]	2009	62	Later pubertal timing (menarche >12.94 y)	8.9 ± 0.5	Total body	0.599		aBMD lower in later vs earlier pubertal timing group at all sites, all Ps <.02
					Radius	0.445		
					FN	0.636		
					LS	0.630		
				20.4 ± 0.6	Total body	0.900		
					Radius	0.701		
					FN	0.838		
					LS	1.026		
		62	Earlier pubertal timing (menarche <12.94 y)	9.0 ± 0.5	Total body	0.620		
					Radius	0.456		
					FN	0.658		
					LS	0.651		
				20.4 ± 0.6	Total body	0.927		
					Radius	0.719		
					FN	0.878		
					LS	1.060		
Chevalley et al[60]	2009	62	Later pubertal timing (menarche >12.94 y)	20.4 ± 0.6	FN	0.838		FN and tibia aBMD and vBMD lower in later vs earlier pubertal timing group in both young adult and premenopausal women, all Ps <.004
					Tibia		0.314	
		60		46.0 ± 3.7	FN	0.785		
					Tibia		0.295	
		62	Earlier pubertal timing (menarche <12.94 y)	20.4 ± 0.6	FN	0.878		
					Tibia		0.334	
		60		45.6 ± 3.1	FN	0.825		
					Tibia		0.322	

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).[46] 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).[63] 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.[65] 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).[66] 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).[64] In contrast, at the other end of reproductive life, the age at menopause was not significantly associated with Colles or vertebral fracture[65,66] and had a smaller effect than age at menarche on the risk of hip fracture,[64] 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.[65,66]

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.[24,48] 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.

TABLE 5 Fracture Risk in Individuals With Delayed Puberty

Study (Reference)	Year	Name	*N*	Age at Evaluation, Years ± SD	Outcome Variable	Conclusion
Johnell et al[64]	1995	MEDOS	2086 women	78.1 ± 9.4	Hip fracture	RR: 1.45, 95% CI: 1.12 to 1.87 for age at menarche ≥15 y vs ≤11 y
Roy et al[65]	2003	EPOS	3173 men, 3402 women	63.1 ± 7.8 (men), 62.2 ± 7.6 (women)	Vertebral fracture	RR: 1.8, 95% CI: 1.24 to 2.63 for age at menarche ≥16 y vs <16 y
Silman et al[66]	2003	EPOS	3173 men, 3402 women	63.1 ± 7.8 (men), 62.2 ± 7.6 (women)	Colles' fracture	RR: 1.5, 95% CI: 1.1 to 2.0 for age at menarche >15 y vs ≤15 y
Kindblom et al[46]	2006	GOOD	642 men	18.9 ± 0.6	Upper extremity fracture	OR: 1.39, 95% CI: 1.08 to 1.79, *P* = .01 for each 1-y increment to PHV
Chevalley et al[63]	2012		42 women	20.4 ± 0.6	Fracture	OR: 2.09, 95% CI: ∼1.3 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)

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 childhood[85–87] and either no difference[88,89] 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 cancer[90]; 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 women[92] 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

TABLE 6 Psychopathology in Individuals With Delayed Puberty

Study (Reference)	Year	Location/Name	*N*	Age at Evaluation, Years ± SD or Range	Outcome Variable	Conclusion
Joinson et al[76]	2013	United Kingdom	3648 women	14–16.5	Depressive symptoms	OR up to 1.52, 95% CI: 1.12 to 2.05 for age at menarche 11.5 to 13.5 y vs ≥13.5 y, $P = .007$
				18–19		No difference in OR for age at menarche 11.5 to 13.5 y vs ≥13.5 (OR 1.07–1.18, all *P*s >.05)
Boden et al[77]	2011	New Zealand	497 women	15–18	Major depression	No difference in % outcome for age at menarche 14–15 y vs 12–13 y (32.5% vs 30.9%, $P > .50$)
Herva et al[78]	2004	Northern Finland	3952 women	31	Depression	OR 1.7, 95% CI: 1.1 to 1.6 for age at menarche ≥16 y vs 12–15 y
Galvao et al[79]	2014	Meta-analysis: New Zealand and Northern Finland	4449 women	15–31	Major depression/ depression	No significant risk of depression for age at menarche ≥14 y vs <14 y (RR 1.28, 95% CI: 0.87 to 1.88)
Opoliner et al[80]	2014	United States/ Growing Up Today Study	9039 women	20–26	Depressive symptoms	No difference in OR for age at menarche >14.3 y vs 12–14.3 y (OR 0.91, 95% CI: 0.70 to 1.18)
Day et al[81]	2015	United Kingdom/UK Biobank Study	250 037 women	40–69	Depression	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, $P > 7.48 \times 10^{-5}$)
Conley and Rudolph[82]	2009	United States	82 men	13.4	Depression	Later perceived pubertal timing was associated higher levels of depression ($\beta = -0.31$, $P < .05$)
Graber et al[83]	2004	United States	392 men	24.2	Disruptive behavior disorder	OR 2.1, 95% CI: 1.1 to 4.5 for perceived late pubertal timing vs on time
					Substance use	OR 2.5, 95% CI: 1.1 to 5.9 for perceived late pubertal timing vs on time
Day et al[81]	2015	United Kingdom/UK Biobank Study	197 714 men	40–69	Anxiety/panic attacks	OR 1.43, 95% CI: 1.22 to 1.67 for perceived late voice breaking vs on time, $P < 7.48 \times 10^{-5}$
					Depression	OR 1.36, 95% CI: 1.25 to 1.49 for perceived late voice breaking vs on time, $P < 7.48 \times 10^{-5}$

CI, confidence interval; OR, odds ratio; RR, relative risk.

cancer, but only 2 studies have specifically evaluated the effect of late menarche. A retrospective case-control study in Italy found that menarche ≥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 ≥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 ∼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 association[112,113] 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

high-grade prostate cancer per score tertile.[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.[116] There is now evidence that delayed puberty has negative effects as well.

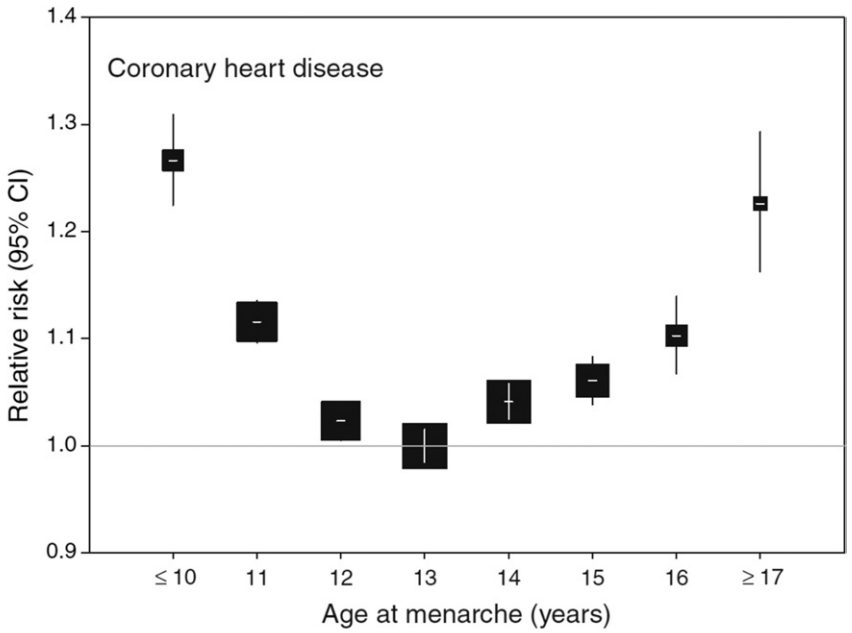
Early studies suggested a protective effect of delayed puberty for cardiovascular disease. In a retrospective population-based study in Germany, menarche ≥15 years was associated with a 52% reduced odds of peripheral arterial disease compared with menarche at age 12 to 15 years.[117] The same study also 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 (≥15 years).[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 ≤10 years and at ≥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 ≥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.[119–123]

Few studies have examined the effect of pubertal timing on metabolic and cardiovascular disease in men.[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.[81]

Potential Mechanisms Linking Pubertal Timing to Cardiovascular Risk

One proposed explanation for the association between earlier



	≤ 10	11	12	13	14	15	16	≥ 17
Mean age at menarche (years)	9.9	11	12	13	14	15	16	17.4
Number with incident CHD	3477	12 759	12 121	16 199	15 064	8784	3614	1360
RR (95% CI)	1.27 (1.22 to 1.31)	1.12 (1.10 to 1.14)	1.02 (1.01 to 1.04)	1.00 (0.98 to 1.02)	1.04 (1.02 to 1.06)	1.06 (1.04 to 1.08)	1.10 (1.07 to 1.14)	1.23 (1.16 to 1.29)

FIGURE 2

Relative risk and 95% confidence intervals (CI) of coronary heart disease by age at menarche. Reference category is menarche at 13 years of age. The area of the square is inversely proportional to the variance of the log risk. CHD, coronary heart disease; CI, confidence interval. (Reprinted with permission from page 240 of Canoy D, Beral V, Balkwill A, et al; Million Women Study Collaborators. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation*. 2015;131(3):237–244.)

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.[116] 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.[124,125] In one meta-analysis, the influence of these loci on age at menarche was not attenuated by adjustment for BMI.[126] 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,[127,128] phenotyping studies,[129] 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,[129] 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.[127,128]

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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