

Puberty in Children Born Small for Gestational Age

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Key Words

Children born light for gestational age · Children born short for gestational age · Growth · Puberty · Adrenarche · Precocious pubarche

Abstract

Small for gestational age (SGA) children are more prone to have precocious pubarche and exaggerated precocious adrenarche, an earlier onset of pubertal development and menarche, and faster progression of puberty than children born of appropriate for gestational age (AGA) size. The majority of studies investigating the onset of puberty in children born SGA and AGA established that, although puberty begins at an appropriate time (based on chronological age and actual height) in SGA children, onset is earlier relative to AGA children. Evaluating pubertal growth in SGA children, a more modest bone age delay from chronological age at the onset of puberty and more rapid bone maturation during puberty compared to AGA children were reported. Peak height velocity in adolescence is reached at an earlier pubertal stage and lasts for a shorter period in children born SGA than in those born AGA. These differences lead to an earlier fusion of the growth plates and a shorter adult height. The pathophysiological mechanism underlying the unique pu-

bertal growth pattern of children born SGA remains unclear. However, it seems that this is not only related to birth weight, gestational age, adiposity or obesity, but that there may also be an influence of rapid weight gain in early childhood on pubertal onset: excess weight gain in childhood may be related to central adiposity, decreased insulin sensitivity, and increased IGF-I levels and might thus predispose to precocious pubarche.

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Small for Gestational Age: Definition and Implications

Being born small for gestational age (SGA) according to either weight or length is a risk factor for some growth and development disorders, as well as chronic diseases later in life. Children born SGA are at higher risk of attaining an adult height below their target height, as well as of developing metabolic disorders, obesity, diabetes and cardiovascular diseases [1].

Postnatal growth of SGA children has been analyzed in many studies. It has been estimated that the mean adult height of individuals born SGA is approximately 1 SD lower than those born appropriate for gestational age

(AGA) [2–6]. Furthermore, adult height is lower in subjects born short for gestational age than in those born light for gestational age [2]. In general, adult height is influenced by many factors such as target height, presence of chronic diseases, some medications and pubertal development [7].

Puberty is one of the most important milestones in life and involves important body and physiological changes: pubertal growth spurt, changes in body shape and physiological functions. Pubertal development disorders influence not only sexual maturity, but also adult height, bone mass density, psychology and reproductive health later in life. Being born SGA predisposes to a number of developmental disorders, including precocious pubarche.

Pubertal Physiology and Hormonal Changes

Puberty is the period of transition from childhood to adolescence and is marked by the development of secondary sexual characteristics, accelerated growth and behavioral changes [8]. Pubertal onset and progression is commonly assessed based on pubic hair development (pubarche), axillary hair development, odor changes due to adrenal activation (adrenarche) and development of genitalia (gonadarche). Breast development (telarche) and cyclic bleeding (menarche) are also important markers for assessing puberty in girls. The normal onset of puberty is defined as the development of secondary sexual characteristics between 8 and 13 years in girls and between 9 and 14 years in boys [7, 9]. Menarche usually begins 2 years after telarche, typically occurring between 12 and 13 years of age [9]. Variations in pubertal timing and progression are likely to be related to many factors, including ethnicity, genetic background, nutrition, coexisting disorders, medications, physical activity, socioeconomic status and other unknown factors [7, 9].

Pubertal changes are regulated by the hypothalamic-pituitary-gonadal axis. Puberty is manifested by an increase in frequency and amplitude of gonadotropin-releasing hormone (GnRH) pulses in the hypothalamus, leading to a rise in pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), especially at night. Gonadotropins stimulate the gonads to produce androgens and estrogens, which lead to the development of secondary sexual characteristics. Maturation of the zona reticularis of the adrenal gland leads to increased secretion of sex steroids, especially dehydroepiandrosterone sulfate (DHEAS), and manifests in the development of axillary and pubic hair, and axillary odor [7, 9].

The regulation mechanism of adrenarche is not yet clear. Girls and boys with premature pubarche have higher free IGF-I and insulin levels than controls [10–13]. It is thought that these hormones may stimulate phosphorylation of P450c17, increase activity of 17,20-lyase and stimulate androgen synthesis in the adrenals [10].

Patterns of Puberty in Children Born SGA

Studies on pubertal development in children born SGA are scarce, and most explore the relationship between precocious/early puberty and SGA or pubertal growth in children born SGA.

The Relationship between Precocious Pubarche, Adrenarche and SGA

Precocious puberty is related to advanced bone maturation, faster epiphyseal closing and compromised adult height. Precocious pubarche and pronounced and precocious adrenarche have been shown to be associated with low birth weight [14, 15].

At 8 years of age, adrenal androgen and DHEAS levels were found to be inversely related to birth weight, length and ponderal index, and positively related to current body size in one of the largest growth cohorts in the UK, ‘The Avon Longitudinal Study of Parents and Children’ (ALSPAC). In addition, children who showed rapid postnatal weight gain had the highest adrenal androgen levels. According to these data, both lower birth weight and larger body weight at 8 years independently predicted higher adrenal androgen levels. The association of lower birth weight with higher adrenal androgen levels was significant in both boys and girls [16]. Furthermore, in children from the ALSPAC cohort, the combination of low birth weight and rapid postnatal weight gain predicted increased total and central adiposity and higher IGF-I levels at 5 years of age, and lower insulin sensitivity at 8 years of age [17–19].

Similar results were obtained by François and de Zegher [20] in 13 pairs of discordant siblings who were born from twin, triplet or quadruplet pregnancies (one of each pair was SGA and the other AGA). At the age of 8 years, higher DHEAS levels were observed only in the SGA children who matched their AGA sibling for current weight. By contrast, in SGA children whose weight remained lower than -2 SD at the age of 8 years, serum DHEAS levels were lower than in AGA siblings.

A significant relationship between low birth weight and precocious pubarche and pronounced adrenarche

(elevated androstenedione and/or DHEAS levels) was found in a group of Spanish Catalan girls compared to short normal girls with a normal onset of pubarche. Furthermore, prenatal growth restriction was associated with idiopathic functional ovarian hyperandrogenism and hyperinsulinism at 18 years in these girls [14].

In a retrospective Australian study of 89 children with precocious pubarche, 35% of the children ($n = 28$, 3 boys) were born SGA (birth weight and/or ponderal index <10th percentile). Weight SDS increased from birth until the occurrence of precocious pubarche in 91% of children, and the mean change in weight was greater in those who were born SGA. 65% of those with precocious pubarche were overweight or obese. However, although SGA children experienced a greater change in weight SDS, there was no difference in the incidence of overweight/obesity in SGA and AGA children. The authors concluded that being born SGA according to weight and/or length is an independent risk factor for precocious pubarche, as is prematurity and being overweight/obese. A total of 88% of children had at least one of these three risk factors for precocious pubarche. It was suggested that rapid weight gain in childhood might predispose to precocious pubarche in susceptible individuals [21].

Veening et al. [22] compared pubertal development and hormonal levels in SGA and AGA children. None of the studied children (29 SGA and 24 AGA) had signs of precocious pubarche but DHEAS concentration was higher in prepubertal SGA children than in those born AGA. Dahlgren et al. [23] found an inverse correlation between weight at birth and DHEAS levels in young children before adrenarche (<9 years of age), when adjusted for age at investigation. Accordingly, preliminary data from our study following a cohort of SGA and AGA children from birth showed higher DHEAS levels in pubertal boys born SGA, but not SGA girls, compared to those born AGA (33 SGA and 58 AGA children at the age of 11–14 years, data not yet published).

By contrast, in a Chilean cohort of children with precocious pubarche (158 girls and 15 boys, 9.8% born SGA), hormone levels (DHEAS, testosterone and 17-OHP) and body mass index (BMI) were similar in SGA and AGA children, although changes in weight SDS were greater in SGA (2.4 ± 0.2) than AGA children (1.1 ± 0.1) [24]. Exaggerated adrenarche was not more common in SGA than in AGA children, and none of the SGA children had non-classical adrenal hyperplasia [24].

Despite some controversial findings, most authors agree upon the existence of a relationship between being born SGA and premature pubarche and exaggerated pre-

cocious adrenarche. Among the possible causes underlying this association are increased central adiposity, decreased insulin sensitivity and increased IGF-I levels between the ages of 2 and 4 years; these metabolic and hormonal patterns are common in SGA children with excess weight gain in early childhood. Insulin resistance and high levels of free IGF-I stimulate adrenal androgen secretion and the development of precocious pubarche [7, 16, 25, 26]. However, there is some evidence that enhanced peripubertal adrenal androgen secretion disappears by early adulthood in SGA subjects born full term [27].

The Onset of Puberty in SGA Children

A number of studies have been published on the timing and progression of puberty in children born SGA, yet the results are difficult to compare due to variations in SGA definitions, inclusion criteria, methodologies and follow-up periods.

In a large population-based study on postnatal growth of 3,650 healthy Swedish children, 111 were light, 141 were short and 54 were both light and short at birth; 87% of SGA children showed full catch-up growth and attained puberty at a normal age. In this study, the onset of puberty was calculated according to pubertal peak height velocity [5, 28]. SGA children who remained short, i.e. without catch-up growth throughout childhood (13%), reached puberty somewhat earlier than those with catch-up growth [5, 29].

In another Swedish study, Persson et al. [30] assessed changes in height until 16 years of age. Children were divided into groups depending on perinatal risk factors: born after preeclampsia ($n = 62$), prematurely ($n = 129$), SGA ($n = 90$), large for gestational age ($n = 175$), short for gestational age ($n = 49$), tall for gestational age ($n = 38$) and children without perinatal risk factors ($n = 688$). The onset of puberty was determined according to pubertal growth spurt. The mean age at onset of puberty did not differ between normal boys and those with perinatal risk factors. By contrast, girls born light or short for gestational age started puberty at a younger age compared to normal girls, although the difference was statistically significant only in girls born light for gestational age [30] (table 1).

In a similar study by Lazar et al. [31] following a group of 76 SGA (birth weight <-2 SD) and 52 AGA children from early infancy to the completion of puberty, all children entered puberty at a normal age, but SGA children started puberty significantly earlier than AGA children, and the difference was significant in both sexes (table 1).

Table 1. The onset of puberty in children born SGA and AGA

		SGA, years	AGA, years	p value
<i>Data from Persson et al. [30]</i>				
Girls	light for GA	10.7±1.0	11.1±1.0	0.02
	short for GA	10.6±1.2		0.06
Boys	light for GA	12.1±1.2	12.1±1.1	0.97
	short for GA	12.4±1.0		0.29
<i>Data from Lazar et al. [31]</i>				
Girls	light for GA	10.4±0.9	11.4±1.3	<0.01
Boys	light for GA	12.0±0.9	13.0±1.1	<0.01

SGA and AGA values are presented as mean ± SD. GA = Gestational age.

The onset of puberty in this study was determined according to gonadarche with or without pubarche.

Interestingly, Lazar et al. found that 20% of SGA girls and 13% of SGA boys started puberty early (onset of puberty between 8.0 and 9.5 years in girls and between 9.0 and 10.5 years in boys). By contrast, early puberty was observed in only 3% of girls and 5% of boys born AGA [31].

It has been shown that starting puberty before reaching a height of 140 cm may compromise adult height. In the study by Persson et al. [30], boys and girls born SGA were on average 4 cm shorter at the onset of puberty than children without perinatal risk factors.

An Israeli study revealed that the only prepubertal predictor of age at onset of puberty is birth weight SD score [31]. Other prepubertal factors (gestational age, BMI, bone age delay from chronological in early childhood) had no correlation with age at onset of puberty [31].

In summary, most authors agree that puberty starts within the normal range of age (based on chronological age and actual height) in SGA children, but that onset is generally earlier relative to AGA children.

Progression of Puberty and Menarche in SGA Girls

There is no general agreement on the existence of differences in age at menarche between SGA and AGA girls. Several longitudinal follow-up studies (comparing different groups of SGA and AGA children: SGA with short or normal height, SGA categorized as full-term/preterm, SGA categorized as light/short for gestational age, SGA with or without catch-up growth with AGA children) did not find any significant difference in the progression of puberty or age at menarche between girls born SGA and AGA [3, 32] (table 2).

However, other studies showed an earlier age of menarche in girls with fetal growth restriction relative to girls born of appropriate birth weight. Girls from one of the largest prospective cohorts were followed from fetal life to adolescence (12–14 years, n = 349) in West Australia. Girls with a birth weight below the median had a significantly earlier menarche compared to girls with a birth weight above the median. In this study, a higher BMI at 8 years of age was also independently predictive of earlier age at menarche [33].

Similar results were obtained in the earlier-quoted study from Israel investigating persistently short SGA and AGA children followed from early childhood to completion of puberty. Although menarche occurred within the normal age range in all girls, it was significantly earlier in the SGA compared to the AGA group [31] (table 2). A slightly earlier age at menarche in girls born light for gestational age was also reported in the Swedish study [30, 34] (table 2).

In another Indian study evaluating the development of premature AGA (n = 79) and full-term SGA (n = 45) children, menarche occurred 6 months earlier in the preterm group and 12 months earlier in the SGA group than in full-term AGA controls; however, the interval between onset of puberty and menarche was similar in all groups [35]. In the study by Ibanez et al. [36] following pubertal development in 187 girls with precocious pubarche, menarche before the age of 12 was 3-fold more prevalent among girls born SGA (n = 50); their age at menarche was advanced by 8–10 months compared with girls of normal birth weight (>0 SD, n = 43) [36].

In a study from Poland on 1,060 girls, earlier age at menarche was found in girls who had lower birth weight and higher BMI at the age of 14 years than in AGA girls or girls born SGA with a lower current BMI [37]. An influence of BMI on the timing of menarche in SGA girls was also observed in a Western Australian study: menarche occurred earlier in girls with lower birth weight and higher BMI at 8 years of age [33].

Pubertal Growth Spurt and Bone Age Development

In addition to other factors such as target height, the onset of puberty, chronic diseases and medications, adult height is influenced by the total pubertal growth spurt and bone age advancement.

Studies analyzing bone age development in SGA subjects are scarce. Lazar et al. [31] reported a similar bone age delay from chronological age in early childhood in both SGA and AGA children. However, bone age maturation started earlier in SGA children: it corresponded to

Table 2. Age at menarche in SGA and AGA girls

Study	Reference	SGA		AGA		p value
		Subjects, n	Age at menarche, years	Subjects, n	Age at menarche, years	
French Haguenu cohort	Leger et al. [3]	133	12.6±1.6	152	12.9±1.7	NS
Indian cohort	Chaudhari et al. [32]					
Full-term		15	12.7 (8.8–14.3)	35	12.8 (10.8–14.5)	NS
Preterm		34	12.5 (10.4–13.8)	29	12.5 (10.4–14.0)	NS
Israeli cohort	Lazar et al. [31]	45	12.6±1.6	30	13.0±1.4	<0.01
Swedish cohort	Persson et al. [30]					
Light for GA		47	12.7±1.1	320	13.1±1.0	0.032
Short for GA		23	12.8±1.0			NS

Age at menarche is presented as mean ± SD or mean with range. GA = Gestational age.

chronological age already at the onset of puberty in SGA girls and at Tanner stages 2–3 in SGA boys compared with only towards Tanner stages 4–5 in AGA girls and Tanner stage 4 in AGA boys. Furthermore, in the same study the peak height velocity was reached earlier in children born SGA (Tanner stages 3 for boys and 2 for girls) compared to children born AGA (Tanner stages 4–5 for boys and 3–4 for girls) [31].

Although similar total pubertal growth in SGA and AGA children indicates a sufficient growth spurt in children born SGA [38], there is some evidence that pubertal height gain may be smaller than expected in children born SGA. Lazar et al. [31] reported similar adult heights in SGA and AGA children; however, after adjusting for target height a significant adult height deficit was evident in the SGA group. A possible explanation might be an earlier onset of puberty and earlier bone maturation and fusion of the growth plates in SGA children [31].

Hormonal Differences between SGA and AGA Children

Prenatal growth restraint has been shown to be associated with FSH hypersecretion in infancy [7, 9, 39]. Ibanez et al. [39] reported 2-fold higher FSH levels in 3- to 6-month-old girls and 4-fold higher FSH levels in boys of the same age born SGA compared to infants born AGA. Secretion of other hormones (inhibin B, LH, estradiol, free androgen index) was similar in both groups. The mechanism of FSH hypersecretion in SGA infants remains unclear. Nevertheless, it is suggested that sex hormone disorders may cause subsequent fertility and metabolic impairments.

In line with these observations, postmenarcheal adolescent SGA girls (born full term, current BMI <25) have been found to have higher serum levels of FSH and lower estradiol concentrations compared to AGA girls. It was suggested that this may be associated with gonadal resistance to gonadotropins [40]. Discordant findings were reported by a Chilean group: at the beginning of puberty (Tanner stage 2 of breast development), SGA girls with BMI between 10th and 95th percentiles had higher basal and GnRH-stimulated estradiol levels compared with AGA girls, whereas basal FSH and LH concentrations were similar in SGA and AGA children; 2 years later, FSH concentration was lower, but GnRH-stimulated LH and basal estradiol levels were higher in SGA children compared with AGA. Authors suggest that these differences may allow faster transition through puberty in SGA girls [7, 41].

During puberty there is not only an increase in levels of gonadotropins but also a dramatic qualitative shift early in puberty towards more acidic isoforms with longer circulatory half-lives (for both FSH and LH in boys and for FSH in girls) [42]. The same magnitude in shift towards more basic forms of gonadotropins was found in children on GnRH treatment for precocious puberty born either SGA or AGA [43].

In the prospective study by Jensen et al. [44] on hormonal profiles of 16- to 18-year-old SGA (n = 20) and AGA (n = 32) boys, no significant differences between AGA and SGA groups were found in testosterone and inhibin B levels, overnight secretory patterns of gonadotropins or LH/testosterone ratio. In this study, and the study by Ibanez et al. [45], subjects born SGA were shorter than subjects born AGA; however, data from SGA subjects

with and without catch-up growth were analyzed together.

Our own preliminary data on pubertal development of a cohort of SGA and AGA children showed no difference in basal age-adjusted and pubertal stage-adjusted LH, FSH and estradiol levels between 10- to 14-year-old SGA and AGA boys and girls. However, SGA girls had significantly lower sex hormone-binding globulin and higher testosterone levels, resulting in an increased free androgen index compared with AGA girls [Petraitiene et al., in preparation].

In summary, studies did not find clear differences in steroid hormone patterns between SGA and AGA groups at puberty that might cause gonadal resistance to gonadotropins or faster transition through puberty; however, these data are controversial and further studies are needed.

Gonadal Morphology and Fertility

There are only a few studies on gonadal morphology and fertility in SGA individuals and the results are controversial.

According to data from Ibanez et al. [45], reduced prenatal growth might be associated with reduced size of internal genitalia (ovarian and uterine), a reduced ovarian fraction of primordial follicles, ovarian hyperandrogenism and anovulation in late adolescence.

Hernandez et al. [41] reported divergent results. At the beginning of puberty, SGA girls had slightly larger uterine size, ovarian volume and number of follicles compared to AGA girls. After 2 years of follow-up, no significant differences were found in ultrasound measurements of internal genitalia between both groups. Positive correlations were observed between LH and estradiol concentrations and average ovarian volume in the AGA group but not the SGA group.

Some authors suggested a higher risk for polycystic ovary syndrome and subsequent fertility problems in girls who experienced intrauterine growth retardation [46, 47]. However, further studies are needed to support the relationship between being born SGA and ovarian dysfunction, reduced fertility and early menopause.

Data on fetal growth and male gonadal function is scarce. In the prospective cohort study conducted by Jensen et al. [44], no significant differences were observed in testicular size and morphology or the secretion of sex steroids between SGA and AGA adolescents. It was concluded that testicular function is not impaired in adolescent males born SGA.

The majority of studies have focused on the relationship between low birth weight and testicular dysgenesis syndrome, cryptorchidism, hypospadias and testicular cancer in adult life [9]. François et al. [48] established the association between low birth weight and smaller testicular volume and subfertility. However, these results cannot be applied to the general population because the sample of this study consisted of men recruited as having a reduced fertility. Epidemiological studies on adult men treated for testicular cancer showed that low birth weight (<2,500g) increased the risk for developing testicular cancer by 2- to 3-fold [9, 49]. Furthermore, low birth weight was a specific risk factor for seminomas [50]. On the other hand, multiple factors have been identified that affect the risk of testicular cancer: cryptorchidism, parity, twinning, family history, ethnicity, chromosomal anomalies, drugs and maternal uterine bleeding [9].

Growth Hormone Treatment and Pubertal Development

Short children born SGA have been shown to have either low growth hormone (GH) secretion or low GH responsiveness [6, 51–53]. Therefore, a number of studies have assessed the effectiveness and safety of GH treatment in short SGA children [51, 54–56]. Boonstra et al. [57] analyzed pubertal development in short children born SGA treated with GH. GH had no effect on pubertal onset, progression of puberty, age at menarche and the interval between the onset of breast development and menarche. In addition, there was no GH dose (1 mg/m²/day or 2 mg/m²/day) effect on the onset or duration of puberty or pubertal height gain. The pubertal height gain was greater in children who were younger, shorter and had a greater bone age delay at the onset of puberty.

In contrast, Hokken-Koelega and colleagues [58] have shown that treatment with a higher dose of GH (2 mg/m²/day) during puberty resulted in a significantly better adult height than low-dose (1 mg/m²/day) GH treatment. Although GnRH analog treatment might reduce growth velocity, evidence suggests that combined GH and GnRH analog treatment may improve adult height in SGA children who are short at the start of puberty (<140 cm) and have a poor adult height expectation. These children might also need a higher GH dose [58].

Proposed Mechanisms of Earlier Pubertal Development in SGA Children

The sequence from a low birth weight to precocious pubarche has been proposed to be a classic referral point in the progression to an early menarche followed by a polycystic ovary syndrome phenotype and, ultimately, a shorter adult height [36, 59].

One of the possible mechanisms responsible for this sequence may be early accumulation of visceral fat following postnatal catch-up growth in SGA children, leading to insulin resistance and hyperinsulinism, which in turn is thought to play a pivotal role in the development of a hyperandrogenic state in SGA girls [13]. Therefore, insulin sensitizer therapy has been proposed as potentially beneficial for SGA girls with early-onset puberty. Ibanez et al. [60] studied the effect of 36 months of metformin therapy for SGA girls with early-onset breast development [Tanner stage 2 (B2) at age 8–9 years ($n = 10$) compared with untreated SGA girls ($n = 12$)]. In this study, metformin therapy was associated with slower pubertal development (prolonged time span between B2 and menarche), prolonged pubertal height gain and increased near-adult height. Metformin treatment was also associated with relatively lower insulin, leptin and IGF-I levels and higher sex hormone-binding globulin and IGFBP-1 levels, as well as a less atherogenic lipid profile and leaner body composition. There were no effects on bone mineral density and growth of internal genitalia. This study emphasizes the role of insulin as an important codeterminant of pubertal tempo and pubertal height gain in SGA girls [60]. These improvements in body composition (lower total and abdominal fat mass), fasting insulin, high-density lipoprotein cholesterol and triglyceride levels also persisted 12 months after treatment discontinuation. In a previously metformin-treated group, lower BMI and waist circumference was evident even 18 months after treatment discontinuation [61]. Furthermore, metformin-treated girls were less hyperandrogenic and less likely to be postmenarcheal than untreated girls [62]; 7 years after metformin therapy, girls who were

treated early had a lower prevalence of polycystic ovary syndrome, were taller, had less central fat distribution, and had lower BMI, fasting insulin, HOMA-IR, DHEAS and triglycerides than girls treated later [63].

Conclusion

The timing and progression of puberty is linked to being born SGA (according to weight and/or length): SGA children are more prone to present with precocious pubarche and show an earlier onset of pubertal development and menarche or faster progression of puberty.

The main differences between the pubertal growth patterns of SGA and AGA children are that accelerated bone maturation and peak height velocity occur at an earlier pubertal stage in SGA children, resulting in a shorter duration of pubertal growth and a smaller than expected pubertal growth spurt. However, one should acknowledge the limitations of published data on the pubertal development of SGA children since most of the studies were of retrospective design and pubertal development was evaluated based on pubertal peak height velocity or time of menarche.

The pathophysiological mechanism underlying the unique pubertal growth pattern of children born SGA remains unclear. However, it seems that, in addition to known factors, rapid weight gain and visceral adiposity leading to insulin resistance in early childhood may influence pubertal onset in children born SGA.

Acknowledgments

The authors' study was funded by the Lithuanian Research Council (grant No. MIP-103/2011) and the Swedish Research Council (No. 7509).

Disclosure Statement

The authors have no conflict of interest.

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