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Birth Size as a Determinant of Cardiometabolic Risk Factors in Children

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Birth weight · Cardiovascular · Childhood · Large for gestational age · Macrosomia · Small for gestational age

Abstract
The association between birth size and cardiometabolic disease risk may be U-shaped. Being born small for gestational age (SGA) has a definitive association with later cardiovascular risk, but the impact of being born large for gestational age (LGA) on cardiometabolic health is more controversial. In addition to birth size, early postnatal growth pattern and later weight gain affect cardiometabolic risk in adulthood. Most SGA-born children have catch-up and LGA-born children have catch-down growth during the first years of life. The extent of this early compensatory growth may contribute to the adverse health outcomes. Both SGA- and LGA-born children are at an increased risk for overweight and obesity. This may have a long-term impact on cardiometabolic health as overweight tends to track to adulthood. Other cardiometabolic risk factors, including alterations in glucose metabolism, dyslipidemia, hypertension, and low-grade inflammation are associated with birth weight. Many of these risk factors are related to overweight or adverse fat distribution. Since later cardiometabolic risk is often mediated by early growth pattern and later overweight in SGA and LGA children, it is important to focus on staying normal weight throughout life. Hence, effective interventions to reduce cardiometabolic risk in LGA and SGA children should be developed.

Introduction

In late 1980s, Barker and Osmond [1] suggested that poor nutrition in early childhood increases the risk of cardiovascular disease (CVD) in adulthood. A couple of years later in 1990, Barker [2] described a hypothesis, known as Barker hypothesis, proposing that poor intrauterine growth caused by fetal undernutrition was also associated with increased prevalence of CVD in adulthood.

The impact of birth size on later cardiometabolic health is acknowledged especially with low [3, 4] but also increasingly with high birth weight [5, 6]. The relationship between birth size and cardiometabolic risk has been suggested to be U-shaped, and some cardiovascular risk factors are present as early as in prepuberty [7, 8]. Many of these alterations are weight-related in large for gestational age (LGA) children. The trend of cardiometabolic

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risk is upwards as the proportional share of high birth weight newborns and the prevalence of childhood overweight and obesity have both been rising in the recent past [9, 10].

Later cardiometabolic health is affected by early growth and childhood overweight [11, 12]. The majority of small for gestational age (SGA) children are compensating the restricted intrauterine growth by early catch-up growth and correspondingly, LGA children are seeking their natural genetic growth patterns by catch-down growth. Catch-up growth (especially in weight) has been demonstrated to increase cardiometabolic risk factors, including overweight, obesity, and insulin resistance, already in childhood [11, 13] independently of birth weight [14]. A recent systematic review suggests that catch-up growth may have a bigger role in later cardiometabolic risk than low birth weight alone [15]. However, this compensatory growth has also positive effects in SGA children, such as increased adult height and better cognitive capacity [11]. Deceleration in growth velocity in early years could be advantageous in LGA children for retaining normal weight [16]. Absence of this catch-down growth seems to increase the risk for adverse cardiometabolic outcomes in young LGA-born adults [12].

The metabolic syndrome is a cluster of cardiovascular risk factors, including obesity, alterations in glucose-insulin metabolism, dyslipidemia, and hypertension. An estimation of its prevalence in obese children and adolescents rises up to 39% depending on the definition used. Obesity in children and adolescents, which is associated with other cardiometabolic risk factors, is becoming more common [17]. Some of the cardiometabolic risk factors present in childhood are prone to track to adulthood [18, 19]. The increasing prevalence of overweight and obesity is a global health risk, and the challenge is to intervene cardiometabolic risk factors properly at the right time most commonly by lifestyle interventions. The efficacy of the interventions seems to be most effective when started early [17].

Birth size, growth trajectories, childhood overweight, and increasing obesity have an impact on cardiometabolic health in childhood and later life. Clinical outcomes of cardiometabolic disease are not visible yet in mid-childhood, but the risk factors are. In this mini review, we focus on the impact of birth size on cardiometabolic risk factors in children. The similarities and differences in cardiometabolic health between LGA and SGA children as well as the future impact of being born LGA or SGA on cardiometabolic risk are also discussed. Recognizing these risk factors is crucial for prevention programs in childhood.

Definitions and Determinants

SGA and LGA are defined by anthropometrics at birth, and the reference for the birth measures used should be relevant to the studied population. SGA and LGA are commonly defined as gestation- and gender-specific birth weight or length < −2.0 and > +2.0 standard deviation scores (SDS), being equivalent to <2.3 and >97.7 percentiles, but also birth weight <10th and >90th percentile, respectively, have been used. The cutoff points based on ±2.0 SDS may identify better those term infants who need continuing growth evaluation [20]. Using the definitions of the 10th percentile for SGA and 90th percentile for LGA is relevant in neonatology to evaluate morbidity and mortality [4, 21]. Intrauterine growth restriction is often incorrectly used as a synonym for SGA, but intrauterine growth restriction refers to a state where the fetus cannot achieve its growth potential due to some underlying pathophysiological process [3]. A consensus definition of growth restriction in the newborn was recently presented [22]; this definition was built on the previously established antenatal definition of fetal growth restriction. Low birth weight, very low birth weight, and extremely low birth weight are defined as birth weight <2,500, <1,500, and <1,000 g, respectively [23]. Macrosomia refers to birth weight independent of gestational age and is most widely defined as birth weight >4,000 g. Still, no consensus agreement on the diagnostic threshold of macrosomia exists [24]. The heterogenous definitions may have an impact on discordant findings between birth size and future cardiometabolic risk.

Growth velocity in weight or height during early life is often accelerated in SGA and decelerated in LGA children. Up to 90% of SGA children have catch-up growth by the age of 2 years [11, 20], whereas 29–81% of LGA children have catch-down growth [12, 16, 25]. The definitions of early catch-up and catch-down growth vary [26]. The cutoff point for considerable change in growth can be determined as percentiles or SDS. The age intervals used vary from few months up to young adulthood [26], although most variation in growth velocity occurs in the first year of life [11]. The most commonly used definition for rapid growth in obesity-related studies was a higher than 0.67 SDS change in weight for age between 2 different ages in childhood [26].

The factors associated with being born SGA are often classified as fetal, uteroplacental, and maternal (Table 1) and those with being born LGA as fetal and maternal (Table 2). In this mini review, genetic disorders and syndromes affecting birth size are not discussed. Fetal growth is strongly affected by maternal body size. A growing fetus

Table 1. Factors associated with an increased incidence of being born SGA or with IUGR (modified from [3, 4, 106])

Fetal
Chromosomal abnormalities
Genetic diseases
Intrauterine infections
Uteroplacental
Structural placental factors
Reduced blood flow
Placenta previa
Placental abruption
Maternal
Demographic factors
Delivery at age <16 or >35 yr
Maternal body size
Low height and pre-pregnancy BMI
Low pregnancy BMI with poor gestational weight gain
Maternal and paternal race
Primi-/nulliparity
Multiple pregnancy
Previous delivery of an SGA infant
Low socioeconomic status
Medical conditions
Malnutrition
Substance use/abuse
Smoking
Alcohol
Illicit drugs
Therapeutic drugs

SGA, small for gestational age; IUGR, intrauterine growth restriction.

Table 2. Factors associated with an increased incidence of being born LGA [24, 107, 108]

Fetal
Genetic, racial, and ethnic factors
Gestational age >40 weeks
Male fetus
Genetic or chromosomal disorders
Congenital hyperinsulinemia
Tumors
Maternal
Maternal body size
Maternal pre-pregnancy obesity
Excess gestational weight gain
Tall maternal height
Diabetes mellitus
Type I and II
Gestational diabetes or MODY
History of macrosomia
Multiparity

MODY, maturity onset diabetes of the young; LGA, large for gestational age.

is dependent on the placenta and disturbances of placental function are related to small birth size. Maternal malnutrition, low pre-pregnancy BMI, and poor gestational weight gain have been shown to lower birth weight. Several maternal diseases as well as substance use or abuse are associated with an increased incidence of infants being born SGA [3, 4]. In LGA-born children, a common reason for excess adipose tissue in fetuses is maternal hyperglycemia that leads to fetal hyperinsulinemia [27], which may be present also in well-balanced gestational diabetes [28]. In addition, maternal pre-pregnancy obesity and excess gestational weight gain without diabetes are associated with high birth weight [29, 30]. In a recent study, late-pregnancy dysglycemia predisposed the offspring of obese, gestational diabetes-negative mothers to increased BMI at age 4 years [31].

Overweight and Obesity

The prevalence of overweight and obesity among children and adolescents has increased along with adults. This alarming trend has been seen in most developed countries and in urban areas of several low-income countries during the last decades as the worldwide obesity has almost tripled since 1975, and is still rising [32]. The number of overweight and obese children aged 0–5 years was 40 million globally in 2018 [32], and it is predicted to increase to 70 million by 2025 [33]. In older children and adolescents (aged 5–17 years), the corresponding number was 224 million in 2013 and predicted to be 268 million by 2025 [34].

The World Health Organization (WHO) defines overweight and obesity in children younger than 5 years as weight-for-height greater than 2 and 3 SD above the WHO Child Growth Standards median, respectively, and in older children and adolescents as BMI for age greater than 1 and 2 SD above the WHO Growth Reference median [32]. Obesity definition based on weight-for-height curves represents the weight distribution in population that will eventually shift to right due to the secular trend. Still, the classifications of childhood overweight and obesity are not unanimous [35]. The International Obesity Task Force references for overweight and obesity equate adult BMI values of 25 and 30 kg/m^2, respectively [36]. Also, sex- and age-specific BMI between 85th and 95th percentile and over 95th percentile are regarded as overweight and obesity, respectively [37].

Overweight and obesity are independent risk factors for adult cardiometabolic disease [38], but they are also

associated with other cardiometabolic risk factors detected already in childhood, such as high blood pressure, liver steatosis, dyslipidemia, adverse glucose metabolism, and increased carotid intima-media thickness (IMT) [39]. The cardiometabolic risk is increased by the severity of obesity [40]. It has been estimated that 6–39% of obese children and adolescents have the metabolic syndrome, which increases morbidity and mortality if tracking to adulthood [17].

The later risk for obesity has been suggested to be elevated in both SGA- and LGA-born children, and the trend is similar in adults [3, 6, 25], although a large meta-analysis suggested that low birth weight might decrease the long-term risk for overweight among persons aged 1–75 years, independently of geographic origin [41]. In SGA children, the decreased risk for overweight could be explained by their tendency to lower lean mass; however, rapid early weight gain predisposes to visceral adiposity. Overweight and obesity may not be visible in young SGA-born children but develop later [25]. This is supported by previous studies reporting the association between small birth size and overweight in adolescents and adults [42]. In addition, several variables, including a genetic component, play a role in later obesity in low birth weight children [43]. However, it is important to recognize that SGA-born children with catch-up growth may develop visceral adiposity without overweight or obesity already prepubertally [44]. In children born LGA, fetal overnutrition and genotype expose children to overweight and obesity, and the risk of overweight is augmented by inadequate catch-down growth [12]. Childhood overweight and obesity create a risk for later cardiometabolic disturbances by tracking from childhood to adolescence and adulthood [18, 45].

Glucose and Insulin

The association between low and high birth weight and the elevated risk of type 2 diabetes has been demonstrated in both children and adults [6, 7, 46]. Compared to appropriate for gestational age (AGA)-born children, reported ORs (95% CI) for type 2 diabetes are 2.91 (1.25–6.76) and 1.78 (1.04–3.06) in SGA- and LGA-born school-aged children, respectively [7]. In adults, low birth weight may have a stronger impact on the risk of type 2 diabetes than high birth weight (OR [95% CI] 0.75 [0.70–0.81]) per kilogram of increase in birth weight [46]. However, there was some heterogeneity between populations in this systematic review, mostly explained by 3 studies (2 of them in native North American populations and 1 in the Saskatchewan general population) where the associations were U-shaped. In addition, the inverse association between birth weight and type 2 diabetes strengthened to OR (95% CI) 0.70 (0.65–0.76) when adjusted for current BMI [46]. However, the risk increases when birth weight is over 4 kg (OR [95% CI] 1.35 [0.67–2.72]) [46] or 3 SDS (hazard ratio [95% CI] 5.44 [2.70–10.96] in males) [6]. Overweight and obesity, especially central, associate with hyperinsulinemia [47, 48], but glucose metabolism is also altered independently of overweight at least in SGA children [49]. In short prepubertal SGA children, age- and BMI-adjusted insulin sensitivity levels were 38% lower than those of short AGA controls assessed by intravenous glucose tolerance test. For maintaining normal glucose tolerance, SGA children compensated reduced insulin sensitivity by almost tripling the acute insulin response [49]. To evaluate glucose-insulin-metabolism, different indexes can be calculated, such as insulinogenic index (index of β-cell function), homeostasis model assessment for insulin resistance, and disposition index (index of β-cell compensation). In obese children, being born SGA or LGA seemed to increase insulin resistance compared to AGA controls, but decreased insulinogenic and disposition indexes were demonstrated only in SGA children [50]. In addition, some studies have indicated increases in insulin levels and insulin resistance, but not in fasting glucose levels in SGA- and LGA-born children compared to AGA-born ones [8, 51].

In addition to birth weight, accelerated early weight gain, seen especially in SGA children, increases the risk of insulin resistance in childhood and young adulthood [11, 52]. There is evidence that insulin sensitivity could be better and insulin levels lower in children with catch-down growth than in children with rapid postnatal growth [53].

Lipids

The impact of birth weight on lipid levels in childhood is somewhat controversial. It seems that low birth weight is associated with adverse lipid levels [54, 55] and poor catch-up growth in height may increase the risk of high total cholesterol (OR [95% CI] 13.8 [2.0–97.5]) [54]. In LGA children, the impact of birth size is not as clear as in SGA children. At some level, high birth weight associates with unfavorable lipid profile (adjusted correlation coefficients 0.27–0.30 between birth weight and total/LDL cholesterol) [56], but overweight and obesity may be more important mediators in dyslipidemia. Dyslipidemia has an important impact on future cardiometabolic health [57, 58]. In adults, both low and high birth weights have been associated with dyslipidemia [6, 59].

Blood Pressure

Elevated blood pressure tracking from childhood to adulthood increases the risk for CVD in adulthood but is fortunately reduceable by early intervention [19, 60, 61]. Current weight is a major determinant of childhood hypertension. A part of the association between birth weight and blood pressure in childhood is derived from the impact of birth weight on childhood overweight. Still, some studies have shown an independent association between birth weight and blood pressure in children and adolescents [62, 63].

Being born SGA and rapid postnatal growth have been reported widely to associate with elevated systolic blood pressure (SBP) in children, adolescents, and adults [64]. A study of a large cohort of Chinese children showed a 4.3-fold increased risk for hypertension in children born small (<2,500 g) with their childhood weights >22.7 kg at the age of 3–6 years compared to those born with normal weight (2,500–4,000 g) and having their childhood weights <22.7 kg at 3–6 years of age [65]. In addition, ORs (95% CI) for adjusted (catch-up growth, height, and father's occupation) association between birth weight Z-score and the risk of hypertension at the age of 5 years or older were 5.67 (3.83–8.39) in boys and 2.58 (1.79–3.73) in girls [65]. However, there were limitations in that study, as only 1% of the studied children were born small and the joint effect of birth weight and current weight was not adjusted for height. It is noticeable that early catch-up growth seems to increase the risk of childhood hypertension also independently [64, 65]. Maternal preeclampsia is associated with increased SBP and diastolic blood pressure in the offspring already in childhood, and being born SGA after a preeclamptic pregnancy increased the risk of higher SBP (OR [95% CI] 8.7 [1.3–57]) [66, 67]. Being born LGA or with high birth weight increased the risk of elevated blood pressure in adolescents [68]. In 7-year-old LGA-born children, the risk of hypertension associated with the lack of catch-down growth (and subsequent obesity) [16]. Overall, the evidence of an independent impact of high birth weight on hypertension is not as strong as that of low birth weight. Gender and different ethnicities could explain some of this variation. A large study of children and adolescents demonstrated recently a U-shaped association between the prevalence of high SBP and birth weight in Hispanic children, whereas in whites, the association was inversely linear, and blacks did not show any significant association. Also, the U-shaped trend in ORs of high SBP was only seen in Hispanic boys, not in girls [69].

Endothelial Function and Vascular Changes

Endothelial dysfunction precedes structural atherosclerotic changes, and it can be assessed noninvasively by flow-mediated dilation, which has been reported to predict cardiovascular events [70]. Low birth weight has been shown to associate with impaired endothelial function in childhood [71–73] and adulthood [74].

Carotid IMT is associated with atherosclerotic vascular changes and predicts the cardiovascular risk [75]. In SGA children, increased carotid IMT has been reported already at the age of 3–6 years, and in the combined SGA and AGA population, excessive weight gain between 3 and 6 years of age was an independent predictor of carotid IMT [76]. In addition, obesity-related increase of carotid IMT can be seen already in children and adolescents [75], and it remains until adulthood, if obesity continues [77].

Adrenal Function

The adrenocortical maturation in mid-childhood, adrenarche, is regarded premature when clinical signs appear in the presence of elevated serum dehydroepiandrosterone sulfate (DHEAS) levels for age before the age of 8 years in girls and 9 years in boys [78]. Premature adrenarche has been associated with overweight/obesity and adverse glucose and lipid metabolism in both AGA- and SGA-born children [79–81]. Still, a recent study did not find an association between high DHEAS levels and adverse cardiometabolic risk factor levels, except higher BMI SDS, in healthy prepubertal primary school children [82]. Low birth weight was associated with higher circulating DHEAS [44, 83] and epinephrine [83] levels in childhood and birth weight had an inverse association with serum DHEAS levels all the way from SGA to LGA children [84, 85]. There may be a weak association of low birth weight with circulating cortisol levels, but it has been difficult to show convincingly the role of the hypothalamo-pituitary-adrenal axis in the reported epidemiological association between birth size and later CVD [86].

Low-Grade Inflammation

Atherosclerosis and CVD risk are strongly affected by low-grade inflammation [87]. As the excess adipose tissue produces inflammatory cytokines, it is not surprising that overweight is associated with low-grade inflammation [88], already in prepubertal children [89]. In addition, Seppä et al. [90] showed recently that elevated interleukin-1 receptor antagonist (IL-1Ra) levels might be associated with higher cardiometabolic risk in 12-year-old children.

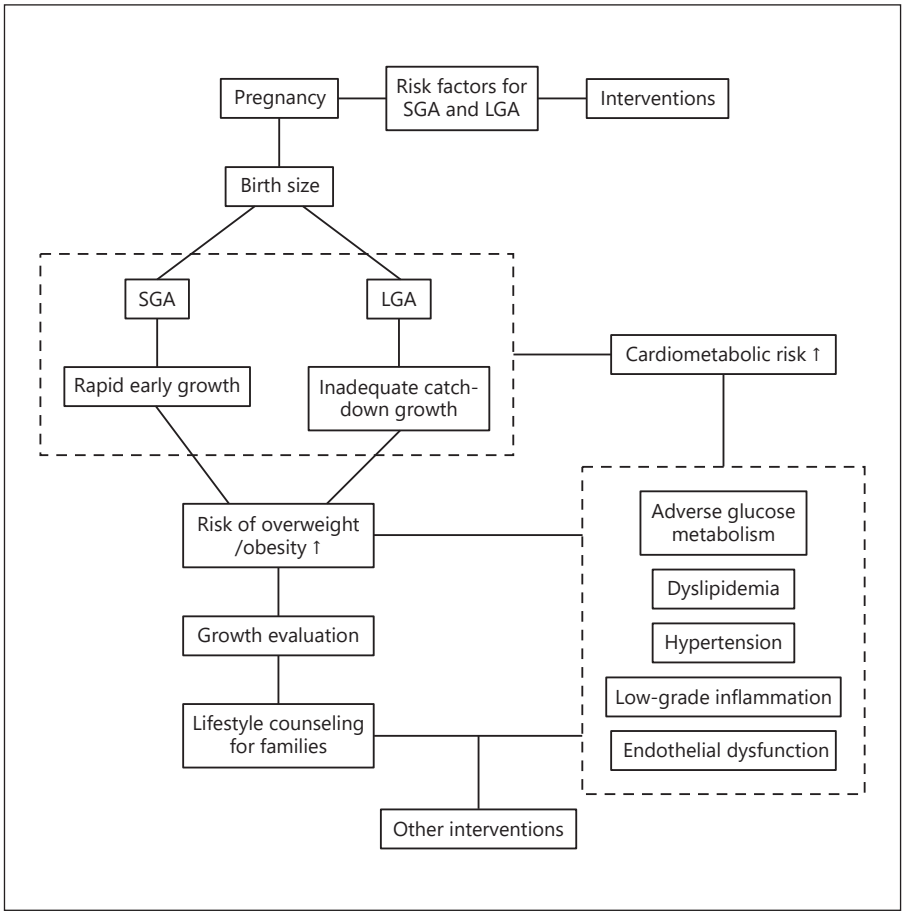

Fig. 1. The impact of birth size and interventions on later cardiometabolic health. To reduce the risk for SGA or LGA during pregnancy, interventions should be addressed to maintain proper balance in maternal weight gain and good management of maternal diabetes, to reduce maternal smoking and alcohol consumption, and to treat other maternal medical conditions, including hypertension and severe chronic diseases. In both SGA and LGA children, the change of weight velocity has an essential impact on later adverse cardiometabolic outcomes. Overweight and obesity are related to most cardiometabolic risk factors. Hence, preventing these by regular growth evaluation and early interventions (including family counseling in nutrition, physical activity, and sleep) improve later cardiometabolic health. In addition, pharmacotherapy and bariatric surgery (from adolescence) are occasionally needed if lifestyle counseling alone is not effective enough. SGA, small for gestational age; LGA, large for gestational age.

C-reactive protein (CRP) is a widely used inflammatory marker, and its elevated concentrations predict CVD in adults [91]. Elevated serum CRP concentrations have been associated with lower birth weight in both children and adults [92, 93]. Inverse association between birth weight and other inflammatory markers, including fibrinogen and IL-1Ra, have been reported in children and adolescents [94, 95]. Still, there is some evidence suggesting that also LGA children have increased low-grade inflammation, and decreased tumor necrosis factor (TNF)-α levels were proposed to associate with insulin resistance [96].

Future Aspects

Traditional cardiometabolic risk factors have been widely reported to associate with birth weight in children and adults [7, 8, 97]. Susceptibility to cardiometabolic disease is a combination of genetics and environment, and the metabolic programming for later diseases, starting before birth and continuing throughout early childhood growth, has been suggested to explain partly the future risk [12, 98]. Epigenetic changes (DNA methylation, histone modification, and noncoding RNAs) have been demonstrated to have an important role in the etiology of cardiometabolic disorders [99]. Studies in this field are increasing also in children. A recent study suggests that alterations in DNA methylation of certain imprinted genes at birth are associated with the risk of obesity at 1 and 3 years of age [100], and previously, changes in DNA methylation were associated with severe obesity also in older children [101]. In addition, birth weight has also been associated with epigenetic changes. In 1 study, birth weight was associated with DNA methylation at several CpG sites at birth, and these changes could be seen partly also in mid-childhood [102]. These results were in concordance with previous studies. When divided in birth weight groups, 1 study did not reveal any differences in genome-wide DNA methylation analysis of umbilical cord tissues between LGA children with catch-down growth and AGA children [103].

Conclusion

Both low and high birth weights have an impact on later cardiometabolic health, and cardiovascular risk factors can be detected already in childhood (Fig. 1). Even though some risk factors originating from the fetal environment cannot be changed after birth, good cardiovascular health can be restored by influencing postnatal risk factors before adulthood [104]. In LGA-born children, overweight and obesity seem to be associated with many of these risk factors, and early catch-down growth would be important for staying normal weight in later life. In SGA children, overweight and obesity may appear later in adolescence or adulthood, and early catch-up growth in weight may contribute to this risk. Contrary to LGA children, cardiometabolic risk is not as much weight-related in SGA children who may have visceral adiposity despite normal weight in childhood.

Many of the cardiometabolic risk factors present in childhood and adolescence track to adulthood. Hence, it is very important to intervene these adverse findings, especially obesity, as soon as they are detected (Fig. 1). Regularly evaluated growth and low-threshold lifestyle counseling (in nutrition, physical activity, and sleep) should be provided in child welfare clinics and school health services from birth to adolescence. Since parental obesity and sedentary lifestyle increase the risk of obesity in the offspring [105], counseling should concern the whole family, not just individuals. Also, effective interventions to reduce and treat cardiometabolic risk in SGA and LGA children should be developed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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