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Cardiovascular Risk Factors in Parents of Short Children Born Small for Gestational Age

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ABSTRACT: Small for gestational age (SGA) children have a higher prevalence of cardiovascular risk factors at a young age. It is not known whether this increased risk is caused by their size at birth, a familial predisposition for cardiovascular disease or smallness at birth or a combination of these factors. The cardiovascular risk profile of parents of SGA children is unknown. We compared anthropometry, blood pressure, fasting serum lipid, glucose, and insulin levels of 482 parents (mean age 41 y) and 286 short SGA children with age- and sex-matched references. We also investigated whether these parameters correlated between parents and their offspring. Mothers had higher systolic blood pressure, fathers had a higher body mass index and parents had more frequently high fasting glucose levels than age- and sex-matched references. Children had significantly higher systolic and diastolic blood pressure than sex- and height-matched references. Twenty-four percent (mothers) and 10% (fathers) were born SGA but they did not have more cardiovascular risk factors than those born appropriate for gestational age. Cardiovascular risk factors did not correlate between parents and children. In conclusion, parents of short SGA children have a modest increase in some cardiovascular risk factors but risk factors did not correlate between parents and children. **(*Pediatr Res* 64: 91–96, 2008)**

Epidemiologic studies reported an inverse association between birth weight and risk for cardiovascular disease (CVD) in adult life (1–3). In addition, some studies described a relation between birth weight of offspring and subsequent cardiovascular mortality of the parents (4,5). The exact mechanism behind these associations and the relative roles of environmental and genetic factors has not yet been elucidated. A familial component has been proposed (4,5), but others could not find a family history of CVD as explanation for the higher prevalence of cardiovascular risk factors in subjects born with a lower birth weight (6). Clustering of cardiovascular risk factors within families has also been described irrespective of birth weight (7,8), whereas there is a relation between birth weight of parents and offspring (9,10).

Short small for gestational age (SGA) children constitute a special group within the group of low birth weight children because they did not reach a normal height. An increased prevalence of cardiovascular risk factors in short SGA children has been described (11,12). Some parents of short SGA children were born SGA themselves (13,14). It is unknown whether an increased risk for CVD in a short SGA child can be predicted by the presence of risk factors in his/her parents. We hypothesized that parents of short SGA children have an increased risk for CVD. In addition, we hypothesized that a relative high percentage of parents was born SGA themselves and that anthropometric data and cardiovascular risk factors correlate between parents and children. We, therefore evaluated in parents of short SGA children anthropometry, blood pressure, fasting serum lipids, glucose, and insulin levels, which are regarded as predictors of CVD (15). Outcome variables were compared with those of a population-based reference group.

SUBJECTS AND METHODS

Five hundred fifty-one parents (mean age 41 y, 276 (50%) fathers) of 286 white short SGA children (151 (53%) boys) were eligible for inclusion in the period between December 1999 and September 2006. In 482 (87%) of these parents, anthropometric measurements were performed and 472 (86%) parents filled out a questionnaire. A complete dataset (anthropometry and questionnaire) was available in 410 parents (74%). Two children had the same mother but different fathers. Inclusion criteria for the children have previously been described (16). In short, the children were included when prepubertal, with a birth length or birth weight SD score (SDS) and actual height SDS below −2, without signs of catch-up growth in height and without growth failure caused by other disorders. The study was approved by the Medical Ethics Committees of the participating centers and written informed consent was obtained from all parents.[1]

The reference group consisted of 1699 women (aged 45 (8.5) years) and 1630 men (aged 46 (8.5) years), participating in the year 2001 in a Dutch population-based health survey. The aim of this survey was to monitor risk factors or determinants of chronic disease in the general population (17). This reference group was used to calculate age- and sex-matched SD scores in the following manner: SD score = (value of parent − mean for references of the same age and sex)/SD for references of the same age and sex.

Parents. Height, weight, and waist circumference were measured with the subject standing. Body mass index (BMI) was calculated. Systolic and diastolic blood pressure (BP) were measured in the nondominant arm while in a sitting position and the mean of three measurements was used for analysis. Height and weight for height were expressed as SDS using Dutch standards (18,19). Waist circumference, BMI and BP were expressed as SDS adjusted for age and sex using the reference group (17). All parents were asked to fill out a questionnaire about birth characteristics, medical history, present health, and family history on CVD and DM. CVD was defined as the occurrence of myocardial infarction, cerebrovascular accident, pulmonary embolism or deep

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Abbreviations: AGA, appropriate for gestational age; **BP,** blood pressure; **CVD,** cardiovascular disease; **DM,** diabetes mellitus; **HOMA-IR,** homeostatic model assessment for insulin resistance index; **MS,** metabolic syndrome; **SGA,** small for gestational age; **TC,** total cholesterol; **TG,** triglycerides

vein thrombosis. SGA was defined as a birth length and/or birth weight SDS below −2 for gestational age (20). Fasting blood samples were available for parents of 93 children (92 mothers and 78 fathers). The availability of a fasting blood sample in the parents deviated from the year in which their child was included. Parents with an available fasting blood sample were comparable with those without an available blood sample with respect to all outcome variables except for age (38.7 *vs.* 42.1 y, $p < 0.001$) and systolic blood pressure SDS (0.09 *vs.* 0.33 SDS, $p < 0.05$). Of the 92 mothers with an available blood sample, 44 had birth data and 10 were born SGA. Of the 78 fathers with an available blood sample, 33 had birth data and four were born SGA.

Children. Height, weight, head circumference, systolic, and diastolic blood pressure (BP) were measured and BMI was calculated. Height, head circumference, and BMI were expressed as SD scores adjusting for sex and age according to Dutch reference data (19), whereas BP was adjusted for sex and height (21). Fasting blood samples were available for 191 children.

Biochemical measurements. After centrifugation, all samples were frozen (−80°C) until assayed. Fasting serum insulin levels were determined by chemoluminescent assay on an Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA). Fasting glucose was measured on a Hitachi 917 analyzer. HOMA-IR was calculated (22). Serum total cholesterol (TC) and triglycerides (TG) were determined enzymatically and LDL-cholesterol and HDL-cholesterol were determined using a homogeneous assay on a Hitachi 917 (Roche Diagnostics, Mannheim, Germany).

Parental fasting TC and HDL-c levels were expressed as SDS adjusted for age and sex using the reference group (17). For children, we used reference values of our hospital (Erasmus MC-Sophia) to define high TC, LDL-c, and TG levels and low HDL-c levels. Cutoff values for high total cholesterol were ≥5.0 mM for age 0–3 y, ≥5.4 mM for age 4–12 y, and ≥6.5 mM for adults (23). Cutoff values for high LDL-cholesterol levels were ≥3.5 mM for age 0–3 y; ≥3.4 mM for age 4–12 y and ≥4.2 mM for adults (23). As TG and HDL-c levels are components of the ATP III criteria, applied cutoff values for these lipids are described in the section about the definition of metabolic syndrome.

Metabolic syndrome definition. Metabolic syndrome (MS) increases the risk for CVD and DM type 2 (15). According to the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATPIII) criteria, adults have MS when three or more of the following symptoms are present: central obesity [waist circumference ≥102 (males) or 88 cm (females), raised TG levels (TG ≥1.7 mmol/L), reduced HDL-c levels (HDL-c <1.0 (males) or 1.3 (females) mmol/L), high BP (systolic ≥130 and/or diastolic Bp ≥85 mm Hg or current treatment for hypertension)], and increased fasting glucose levels (glucose ≥5.6 mmol/L) (24).

In children, we used the modified ATP III criteria by Weiss *et al.* to diagnose MS (25). High BP was defined as a height- and sex-adjusted systolic or diastolic Bp >95th percentile (21). MS was diagnosed in children if three or more of the following symptoms were present: obesity (BMI ≥2 SDS (19)), TG levels >95th percentile (TG ≥1.2 mmol/L for age 0–3 y, TG ≥1.0 mmol/L for age 4–12 y), HDL-c levels <5th percentile (HDL-c <0.5 mmol/L for age 0–3 y and HDL-c <0.9 mmol/L for age 4–12 y), high BP and increased fasting glucose levels (glucose ≥5.6 mmol/L).

Statistics. Analyses were performed using the statistical package SPSS (version 12.0.1; SPSS Inc., Chicago, IL) for Windows. Results are expressed as means with standard deviations for continuous data and as percentages for dichotomous or categorical variables. Because of a skewed distribution, insulin levels and HOMA-IR are expressed as median (interquartile range). Differences between parents and references were evaluated using the two-tailed one-sample t test and χ^2 test for proportions. χ^2 tests were also used to detect associations between risk factors in children and parents. Independent-sample t tests were used to detect differences between subgroups of parents or children. Correlations within families (child–mother and child–father couples) were analyzed using Spearman's correlation coefficient. All analyses were performed separately for men and women. Because independent samples t tests demonstrated no significant differences between boys and girls, the children were analyzed as one group.

RESULTS

Clinical characteristics. Clinical characteristics of 482 parents and 286 children are shown in Table 1. Parental height SDS and head circumference SDS were significantly lower than zero SDS ($p < 0.001$). Mothers and fathers had a relatively larger head circumference SDS compared with height SDS ($p < 0.01$ and $p < 0.001$, respectively). BMI SDS of the fathers was significantly higher than zero SDS ($p < 0.05$). Systolic BP SDS of the mothers was significantly higher ($p < 0.001$) compared with age-matched female references but diastolic BP SDS was not. BP in fathers was comparable with age- and sex-matched references. In the children, systolic and diastolic BP SDS were significantly higher compared with sex- and height-matched references ($p < 0.001$).

Birth characteristics. Birth characteristics are listed in Table 2. Compared with reference values, mothers had a significantly lower birth weight SDS ($p < 0.001$). Birth length SDS was significantly lower than zero SDS in both mothers ($p < 0.001$) and fathers ($p < 0.05$). Twenty-four mothers (24%) and nine fathers (10%) with known birth characteristics were born SGA themselves. These percentages are significantly higher than the 2.3%, which is by definition the prevalence of SGA birth in live-born neonates. Even when all parents without known birth characteristics were regarded as born AGA, the prevalence of being born SGA in parents [24/275 (9%) mothers and 9/276 (3%) fathers] was still higher than 2.3%.

Biochemical measurements. TC SD scores were significantly higher than zero SDS, *i.e.*, compared with the median for references (Table 3). Nine percent of the mothers had high TC levels compared with 5% of the female references, but this difference was not significant ($p = 0.16$). Fifteen percent of the fathers had high TC levels compared with 7% of the male

Table 1. *Clinical characteristics of parents (n = 482) and children (n = 286)*

	Mothers	*p* value	Fathers	*p* value	Children	*p* value
Age (yr)	39.7 (5.0)	—	42.3 (5.5)	—	6.4 (2.4)	—
Height (cm)	163.4 (6.8)	—	177.0 (7.1)	—	106.1 (13.2)	—
Height SDS	−0.8 (1.1)	<0.001	−0.7 (1.1)	<0.001	−3.0 (0.6)	<0.001
HC (cm)	54.5 (1.6)	—	57.2 (1.6)	—	49.5 (1.9)	—
HC SDS	−0.5 (1.0)	<0.001	−0.3 (0.9)	<0.001	−1.2 (1.0)	<0.001
HC SDS–Ht SDS	0.2 (1.1)	<0.01	0.3 (1.1)	<0.001	1.8 (1.1)	<0.001
BMI	24.9 (4.8)	—	26.4 (3.9)	—	14.1 (1.2)	—
BMI SDS	0.1 (1.2)	0.11	0.2 (1.1)	<0.05	−1.4 (1.0)	<0.001
Waist circ. (cm)	82.8 (11.6)	—	93.1 (12.1)	—	—	—
Waist circ. SDS	0.0 (1.1)	0.74	−0.1 (1.2)	0.14	—	—
Systolic BP (mm Hg)	121.5 (16.2)	—	131.1 (16.2)	—	103.5 (12.8)	—
Systolic BP SDS	0.3 (1.1)	<0.001	0.1 (1.2)	0.15	0.9 (1.1)	<0.001
Diastolic BP (mm Hg)	79.5 (10.7)	—	83.0 (12.1)	—	59.2 (9.2)	—
Diastolic BP SDS	0.0 (1.1)	0.85	0.0 (1.2)	0.82	0.4 (1.1)	<0.001

Values are expressed as mean (SD); *p* values express the difference with age- and sex-matched references.
SDS, standard deviation score; HC, head circumference; Ht, height; BMI, body mass index; BP, blood pressure.

Table 2. *Birth characteristics*

	Mothers		Fathers		Children	
	n		*n*		*n*	
Gestational age	121	39.3 (2.1)	104	39.4 (1.7)	286	36.2 (3.7)
Birth weight (kg)	169	3.0 (0.6)	130	3.3 (0.7)	286	1.9 (0.7)
Birth weight SDS	100	−0.6 (1.2)*	87	−0.2 (1.5)	286	−2.3 (1.0)*
Birth length (cm)	112	48.4 (2.8)	68	49.9 (3.4)	209	42.3 (5.0)
Birth length SDS	67	−1.1 (1.4)*	47	−0.7 (1.8)**	209	−3.1 (1.5)*
Born SGA (%)	101	24%	87	10%	286	100%

Data expressed as mean (SD); n = number of persons with available data.
Compared with gestational age- and sex-matched references: *$p < 0.001$; **$p < 0.01$.

Table 3. *Fasting serum lipid, glucose, and insulin levels*

	Mothers	Fathers	Children
TC (mmol/L)	5.3 (0.9)	5.6 (1.0)	4.1 (0.8)
TC SDS	0.5 (1.1)*	0.4 (1.1)**	—
TG (mmol/L)	1.2 (0.7)	1.7 (1.2)	0.8 (0.4)
HDL-c (mmol/L)	1.5 (0.4)	1.2 (0.3)	1.4 (0.4)
HDL-c SDS	0.5 (1.3)*	0.5 (1.2)*	—
TC/HDL-c ratio	3.7 (1.3)	4.8 (1.4)	3.2 (1.1)
LDL-c (mmol/L)	3.1 (0.9)	3.5 (1.0)	2.3 (0.7)
Glucose (mmol/L)	4.7 (1.1)	4.9 (0.7)	4.4 (0.6)
Insulin (pmol/L)	40.8 (27.8–63.2)	45.7 (25.5–89.4)	14.0 (14.0–22.8)
HOMA-IR	0.8 (0.5–1.1)	0.9 (0.5–1.7)	0.3 (0.2–0.4)

Data expressed as mean (SD) and insulin and HOMA-IR as median (interquartile range).
Compared with age- and sex-matched references: *$p < 0.001$; **$p < 0.01$.
TC, total cholesterol; N, 2.0–5.5 mmol/L (children) or <6.5 mmol/L (adults); TG, triglycerides; N, 0.3–1.6 mmol/L (children) or <1.7 mmol/L (adults); HDL-c, high-density lipoprotein cholesterol; N, 1.1–2.7 mmol/L (children) or >1.0 mmol/L (male adults) or >1.3 mmol/L (female adults); LDL-c, low-density lipoprotein cholesterol; N, 0.0–4.2 mmol/L (children) or <4.2 mmol/L (adults); glucose N, 2.6–6.0 mmol/L; insulin N, < 180 pmol/L.

references ($p < 0.05$). HDL-c SD scores were significantly higher than zero SDS in both mothers and fathers ($p < 0.001$). Prevalence of high LDL-c was 11% in mothers and 25% in fathers. In the reference population, LDL-c, TG, and insulin were not measured. Compared with references, parents had more frequently fasting glucose levels above the ATP III cutoff level of 5.6 mM (Table 4). Nonetheless, mean parental fasting levels of glucose, insulin, TC, TG, HDL-c, and LDL-c were all within the normal range. Median HOMA-IR was 0.8 (0.5–1.1) in mothers, 0.9 (0.5–1.7) in fathers and 0.3 (0.2–0.4) in children. In the SGA children, mean fasting serum levels of TC, TG, HDL-c, and LDL-c were within the normal range (Table 3). Only one child had a TC level above the normal range.

***Parents born SGA* versus *parents born AGA*.** Mothers born SGA had a significantly smaller head circumference (−1.0 SDS *vs.* −0.3 SDS, $p < 0.01$) and shorter stature (−1.5 SDS *vs.* −0.5 SDS, $p < 0.001$) than mothers born appropriate for gestational age (AGA). Fathers born SGA also had a larger head circumference and shorter stature than AGA fathers but these differences were not significant. Glucose and insulin levels and SD scores for waist circumference, BMI, systolic and diastolic blood pressure, TC, and HDL-c of SGA parents were not significantly different from those born AGA.

Metabolic syndrome. Table 4 shows the different components of the MS. According to the ATP III criteria, the prevalence of MS was 15% in mothers and 22% in fathers. The number of MS components in parents born SGA was not significantly different from those born AGA. There was one child (age 5 y) with three components of the MS (elevated blood pressure, high fasting glucose level and a low fasting HDL-c level).

Cardiovascular disease, DM type 2 and family history. One mother and four fathers had suffered from a nonlethal myocardial infarction (mother at age 44 y; fathers at ages 30,

Table 4. *Components of metabolic syndrome according to ATP III criteria*

	Mothers		Reference		Fathers		Reference		Children	
	n	%	%	*P* value	*n*	%	%	*P* value	*n*	%
High sys BP	229	23	20	0.32	204	43	41	0.70	271	13
High dia BP	229	29	27	0.46	204	38	37	0.84	271	6
Central obesity	225	27	34	0.43	199	19	21	0.81	286	None
High glucose	92	7	3	0.05	78	19	8	<0.01	153	5
Low HDL-c	92	30	41	<0.05	78	24	37	<0.05	73	6
High TG	92	17	—	—	78	35	—	—	63	18
≥3 criteria	92	15	—	—	78	22	—	—	64	2

n = number of persons; *p* values express the difference with the reference group.
BP, blood pressure; sys, systolic; dia, diastolic; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides.

36, 45, and 52 y, respectively). One father and two mothers had had deep vein thrombosis and one mother pulmonary embolism. Sixty-three of 254 (25%) mothers and 69 of 249 (28%) fathers had ≥1 first-degree relative with CVD. Of these relatives, CVD occurred before the age of 60 in respectively 12 of 63 (19%) and 19 of 69 (28%). Two mothers and one father had DM type 2, whereas 53 (21%) mothers and 49 (20%) fathers had ≥1 first-degree relative with DM type 2.

Correlations between parents and children. There was no correlation between birth weight SDS, birth length SDS, systolic and diastolic BP SDS, BMI SDS, fasting levels of lipids and insulin, and HOMA-IR within parent–child couples. Glucose levels correlated positively between mothers and children ($r = 0.4$, $p < 0.01$) and fathers and children ($r = 0.3$, $p < 0.05$). χ^2 tests showed no association between parents and children in having a glucose level ≥5.6 mmol/L. Head circumference correlated weakly between mothers and children ($r = 0.2$, $p < 0.01$) and fathers and children ($r = 0.3$, $p < 0.001$).

DISCUSSION

This study shows that parents of short SGA children have a modestly higher prevalence of cardiovascular risk factors than age- and sex-matched references. Mothers had higher mean systolic blood pressure SDS, fathers had higher mean BMI SDS and parents had more frequently high fasting glucose levels. On the other hand, parents had less frequently low HDL-c levels than references. Risk factors did not correlate between parents and offspring. To the best of our knowledge, we provide the first data on cardiovascular risk factors in a large cohort of parents of short SGA children.

Our hypothesis was based on reported associations between low birth weight and cardiovascular risk, within subjects and across generations (26). The exact mechanism behind these associations is not completely understood. The fetal origins hypothesis poses that exposure to an adverse *in utero* environment leads to permanent programming of tissue function and an increased risk of CVD (27). Alternatively, low birth weight and adult cardiovascular disease might be independent features of a genetic predisposition to CVD (28,29). There is also evidence of a nongenetic predisposition to low birth weight and adverse cardiovascular risk across a number of generations (26). Because we found only a modest increase of risk factors in parents and no correlation of risk factors between parents and children, we could not demonstrate a familial cause for an increased risk for CVD in short SGA subjects.

Systolic blood pressure of the mothers was significantly higher than that of age-matched female references. Systolic and diastolic blood pressure of the children was also higher than reference values. However, blood pressure in fathers was normal and there was no significant difference in the percentage of parents with elevated blood pressure according to the ATP III criteria (>130/85 mm Hg) compared with references. A limitation is that blood pressure was measured thrice within 10 min and not during 24 h. Also, parents were significantly shorter than reference subjects. As blood pressure is known to increase with height (30,31), parental blood pressure was relatively high for their shorter height.

The percentage of parents with fasting glucose levels above the ATP III cutoff level of 5.6 mmol/L was higher than in age- and sex-matched references. Higher fasting glucose levels might indicate insulin resistance, which in turn might increase the risk to develop DM and subsequently CVD (32). HOMA-IR, on the other hand, was <1, indicating a low level of insulin resistance (22,33). The percentage of parents with a family history of DM type 2 was comparable with that in a population-based Danish cohort (34).

Parents had higher total cholesterol levels than age- and sex-matched references and fathers had significantly more frequent hypercholesterolemia. LDL-c levels were not measured in references but levels were above the normal range of our laboratory in 11% of the mothers and 25% of the fathers. On the other hand, HDL-c levels were also significantly higher in parents than in references. As HDL-c levels contribute to total cholesterol levels, the higher total cholesterol level in parents might thus be explained. This is supported by the total cholesterol/HDL-c ratio of the parents, which was slightly lower than the ratio of the white participants of the community-based Bogalusa Heart Study (35). Higher HDL-c levels are generally known to lower the risk for cardiovascular disease. Therefore, the higher total cholesterol level in the parents might not reflect an increased risk.

Prevalence of MS was 15% in mothers and 22% in fathers. Comparing the prevalence of MS between parents and the age-matched reference group was not possible because triglyceride (TG) levels were not measured in the reference group. No other study described the prevalence of MS in healthy subjects of the same age as our parents. Most reports on the prevalence of MS in Europe comprise older populations or populations with DM or CVD. For example the Dutch Hoorn study (age 50–75 y) reported a prevalence of MS of 19% in females and 26% in males (36). A German study (PROCAM study, age 36–39 y) reported a prevalence of 18% in females and 25% in males (37). In a Danish cohort of women (age 45 y), the prevalence of MS was 15% (34). Compared with these cohorts, the prevalence of MS in parents of short SGA children was comparable or lower.

Power calculations (alpha 0.05 and power 0.8) showed that correlations within parent–child couples with an $r > 0.3$ were detectable for birth weight, birth length, systolic and diastolic blood pressure, BMI, head circumference, glucose and insulin levels. Thus, for these parameters there was sufficient power to detect clinically relevant correlations. We only found a correlation between parents and children with regard to glucose levels and head circumference. In contrast to previous population-based studies (9,10,38), there were no correlations for birth weight or blood pressure. Lipid levels were measured in a smaller number of children. As a result, our study did not have enough power to detect correlations in lipid levels between parents and children.

A substantial proportion of parents (24% mothers and 10% fathers) with known birth characteristics, was born SGA themselves but they did not have more cardiovascular risk factors than the parents who were born AGA. However, the absolute number of parents born SGA was small and even less of them provided a blood sample. This small number limited

the power to detect differences between parents born SGA and parents born AGA.

Several other factors may have influenced our results. First, the parent group was relatively young. It is possible that increased risk for cardiovascular disease will be detectable when they are 10 y older. On the other hand, in the children, a higher diastolic and systolic blood pressure was already present at a mean age of 6.4 y. Second, parents with an available blood sample were younger and had a lower systolic blood pressure than parents without an available blood sample. Because analyses were performed after the collection of blood samples, we do not think there was a selection bias. Third, the references were 5 y older than the parents. By transforming all outcome variables to SD scores before analysis, we corrected for the difference in mean age of both populations. Therefore, the difference in mean age cannot explain the absence of markedly increased cardiovascular risks.

In conclusion, parents of short SGA children have a modest increase in some cardiovascular risk factors. Mothers had higher mean systolic blood pressure SDS and fathers had a higher mean BMI SDS, whereas parents had more often high fasting glucose levels than age- and sex-matched references. On the other hand, HOMA-IR was low and parents had less frequently low HDL-c levels than references. Also, the prevalence of MS according to ATP III criteria was 15% in mothers and 22% in fathers, which is not higher than the reported prevalence. Risk factors did not correlate between parents and children and a substantial proportion of parents (24% mothers and 10% fathers) with known birth characteristics, was born SGA themselves.

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