

β -Cell Capacity and Insulin Sensitivity in Prepubertal Children Born Small for Gestational Age

Influence of Body Size During Childhood

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Insulin secretion and sensitivity was studied in 28 prepubertal children born small for gestational age (SGA) and in 22 prepubertal children born appropriate for gestational age (AGA). The effect of body size during childhood was also assessed. Insulin sensitivity was measured using the hyperinsulinemic-euglycemic clamp (*M* value), and β -cell function was studied with the hyperglycemic clamp plus arginine. First-phase insulin response (FIR) was used to calculate the disposition index (FIR \times *M* value). Arginine-stimulated second-phase insulin response was used as a measure of β -cell capacity. Δ BMI_{0-1 years}, Δ BMI_{0-2 years}, and Δ BMI_{2-9 years} were classified in tertiles. SGA children were less insulin sensitive than AGA children ($P = 0.009$). β -Cell capacity and disposition indexes were similar in the two groups. In SGA children, *M* values were lower in the tertile with the highest Δ BMI_{2-9 years} than in the tertile with the lowest Δ BMI_{2-9 years} ($P = 0.01$). No association between Δ BMI_{0-2 years} and decreased insulin sensitivity was found. In conclusion, prepubertal SGA children show decreased insulin sensitivity rather than decreased β -cell capacity. Interventions to improve fetal growth and prevent overweight after the second year of life appear to be important factors in the prevention of type 2 diabetes in children born SGA. *Diabetes* 52: 1756-1760, 2003

Epidemiological studies have demonstrated an association between intrauterine growth retardation (IUGR) and an increased risk of developing chronic diseases in adulthood, such as type 2 diabetes (1-5). The mechanism underlying this association is not yet clear. Both insulin resistance and impaired

insulin secretion play a key role in the pathogenesis of glucose intolerance and type 2 diabetes (6,7).

Recently, we showed that children born small for gestational age (SGA) are more insulin resistant compared with children born appropriate for gestational age (AGA) (8), especially SGA children with catch-up growth for height and a high BMI. In individuals with normal islet function, the pancreatic β -cell adapts to lower insulin sensitivity by increasing insulin secretion, thereby preserving euglycemia. However, it has been suggested that fetal malnutrition, resulting in lower birth weight (BW), leads to an altered development of the endocrine pancreas, resulting in impaired insulin secretion in adult life (6,9). Animal studies have demonstrated that a period of protein malnutrition in fetal and early postnatal life permanently impairs β -cell development (10). These data suggest that both β -cell dysfunction as well as insulin resistance are the central defects in the pathophysiology of type 2 diabetes in adult life in individuals that are born SGA.

The aim of the present study was to investigate the relation between insulin sensitivity and β -cell capacity in prepubertal Caucasian children born SGA compared with that in children born AGA. Insulin sensitivity was measured during the hyperinsulinemic-euglycemic clamp, which is the gold standard measurement of insulin action (11). To estimate pancreatic β -cell glucose responsiveness, the hyperglycemic clamp is the gold standard (11,12). Glucose and arginine are known to potentiate each others' effects on insulin release (13-14). Therefore, combined stimulation of insulin release has been used to assess β -cell capacity (15).

Some recent studies suggest that infants who were born SGA and present substantial weight gain in childhood face an increased risk of chronic diseases in adulthood (16,17). Therefore, the role of change in BMI (Δ BMI) from birth until time of the study on insulin sensitivity and β -cell function was also studied.

RESEARCH DESIGN AND METHODS

Study population. This study is part of a larger ongoing project in which endocrine and metabolic variables are being studied in healthy children who live in the same catchment area in Amsterdam and surrounding suburbs. Since 1980, information on all pregnancies, deliveries, and perinatal events of children born in our hospital have been registered. This database was used to trace individuals. SGA was defined as a BW <10th percentile corrected for gestational age (GA), sex, and parity; AGA was defined as a BW \geq 10th percentile, using Dutch references (18). All parents and children received a letter with information about the study and an invitation for an informational

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Received for publication 22 January 2003 and accepted in revised form 31 March 2003.

AGA, appropriate for gestational age; AUC, area under the curve; BW, birth weight; FIR, first-phase insulin response; HtSDS-THSDS, actual height SD scores within 1.3 SD; IUGR, intrauterine growth retardation; SDS, SD scores; SGA, small for gestational age; SIR, second-phase insulin response; THSDS, target height SD score.

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meeting, where they were extensively informed about the aims of the study and where they could address questions.

The study was performed in 28 Caucasian prepubertal SGA children with a mean age of 9.1 ± 1.1 years (range 7.1–11.0). A total of 22 Caucasian children, born AGA, with a mean age of 9.0 ± 1.1 years (7.1–11.8) served as control subjects. All children were born at term. At the time of the study, all subjects were in good health, as assessed by medical history and physical examination. They were at a prepubertal stage according to the criteria of Tanner (19), confirmed by measurements of plasma testosterone in male subjects and estradiol in female subjects. Questionnaires of family history in terms of type 2 diabetes, cardiovascular disease, and hypertension were recorded. None received any medication that could interfere with the tests. After full explanation of the study, all subjects and parents gave written informed consent. The study protocol was approved by the ethics review committee of Vrije Universiteit University Medical Center of Amsterdam.

Methods. Children were studied on 2 separate days after 12 h of overnight fasting.

Day 1. Measurements of the subject's weight, using an electronic scale (SECA), and height, using a stadiometer (Holtain, Crymych, Dyfed, U.K.), were used to calculate the BMI, defined as weight (kg) divided by the height (m) squared. A tape measure was used to measure waist and hip circumferences, and skinfold thickness was measured by a single observer with Harpenden skinfold calipers at the biceps and triceps and at subscapular and suprailliac sites. Total body fat mass was calculated by the sum of the four sites (mm). Data of weight and height of the first 2 years of life were collected; these measurements were performed during regular periodical health examinations by instructed health professionals at well-baby clinics.

Bone ages were determined in all subjects by making an X-ray of the left hand. Catch-up growth for height was defined as an increase of ≥ 0.5 SD scores (SDS) in the first year of life and of an increase of ≥ 0.67 SDS at 2 years of age (25). Catch-up growth for height at time of the study was defined as an actual height SDS within 1.3 SD (HtSDS) of the target height SDS (THSDS) (36). $\Delta\text{BMI}_{0-1\text{years}}$, $\Delta\text{BMI}_{0-2\text{years}}$, and $\Delta\text{BMI}_{2-9\text{years}}$ was classified into tertiles in SGA and AGA children to study the relation with changes in insulin sensitivity and β -cell function.

After the physical examination, a 2-h hyperinsulinemic-euglycemic clamp was performed to determine insulin sensitivity (20). Two venous catheters were inserted after application of a local anesthetic (Emla cream). Insulin (Velosulin; NovoNordisk, Bagsvaerd, Denmark) was infused at a rate of $60 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ after a priming dose of 6 mU/kg . Hepatic glucose production is known to be suppressed in nondiabetic subjects by this insulin infusion rate (21). The blood glucose level was measured every 5 min. Every 15 min, blood was drawn to determine plasma insulin concentrations. Euglycemia (5 mmol/l) was maintained with a 20% D-glucose infusion. Under steady-state conditions of euglycemia, the rate of exogenous glucose infusion is equal to the rate of insulin-stimulated glucose disposal. Insulin sensitivity was calculated from the glucose infusion rate (mg/min) between 60 and 120 min of the euglycemic clamp, divided by body weight (kg) (M value).

Day 2. A hyperglycemic clamp combined with arginine infusion was performed to study β -cell capacity. Again, two venous catheters were inserted after application of a local anesthetic (Emla cream). After a predetermined dose of glucose 20% [$0.03 \text{ g/kg} \times (10 - \text{baseline glucose})$], glucose was infused for 60 min at variable rates to clamp plasma glucose levels at 10 mmol/l . At $t = 30 \text{ min}$, a bolus of arginine HCl 10% (100 mg/kg) was infused, and continuous infusion was started ($15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). At $t = 60 \text{ min}$, glucose and arginine infusions were stopped. Blood samples for glucose and insulin were collected at baseline, every 2.5 min during the first 10 min of the clamp, and at $t = 20 \text{ min}$. During the first 10 min after the start of the arginine infusion ($t = 30 \text{ min}$), glucose and insulin were determined every 2.5 min (until $t = 40$) and further at $t = 50$ and $t = 60 \text{ min}$. First-phase insulin response (FIR) and second-phase insulin response (SIR) were determined. FIR was defined as the area under the curve (AUC) for insulin at 0–10 min ($\text{AUC}_{\text{ins}0-10 \text{ min}}$), SIR as $\text{AUC}_{\text{ins}30-60 \text{ min}}$. FIR was used to calculate the disposition index (M value \times FIR) (22) in all children. SIR, the arginine-stimulated insulin secretion capacity, was used as a measure of β -cell capacity.

Analytical methods. Blood glucose was measured immediately by the glucose oxidase method using a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin concentrations were measured by radioimmunoassay techniques (immunoradiometric assay; Medgenics Diagnostics). Inter- and intra-assay coefficients of variation in the lowest and highest range varied from 6 to 31 and from 2 to 5%, respectively. The detection limit was 10 pmol/l .

Statistical analysis. Statistical analysis was performed using SPSS version 9.0 software. Results are expressed as means \pm SD. Differences between the SGA and AGA groups were tested by χ^2 test for qualitative variables and Student's t test for quantitative variables. Glucose concentrations were

TABLE 1
Family history history in SGA and AGA children

	SGA	AGA	<i>P</i> value
<i>n</i>	28	22	
Family history of			
Type 2 diabetes (<i>n</i> = 15)	10	5	0.27
Hypertension (<i>n</i> = 30)	16	14	0.64
Cardiovascular disease (<i>n</i> = 24)	12	12	0.41

normally distributed. Insulin concentrations were normalized by log transformation. A *P* value ≤ 0.05 was considered to be significant.

RESULTS

Clinical characteristics. Family history in terms of type 2 diabetes, cardiovascular disease, and hypertension was not statistically different between the two groups (Table 1).

Table 2 shows the clinical characteristics of the two groups at birth and at time of the study. As defined, BW was significantly lower in SGA children ($P < 0.001$). Length at birth as well as ponderal index ($\text{g} \times \text{cm}^{-3} \times 100^{-1}$) were significantly lower in SGA children. Gestational age and sex distributions were similar in both groups. At time of the study, mean age, actual length, and BMI did not significantly differ between the two groups (Table 2). Skeletal maturation, expressed as bone age minus chronological age, were not different between SGA and AGA children (-1.8 ± 12.0 months vs. -3.2 ± 10.7 months, respectively; $P = 0.7$) (Table 2).

Catch-up growth in height and weight gain during childhood. We found that 28% of the SGA children did not show catch-up growth in height in the first year of life and at 2 years of age. SGA children showed a significantly higher ΔHtSDS and $\Delta\text{weight SDS}$ between birth and 1 year of age compared with AGA children (ΔHtSDS : 1.2 ± 1.3 vs. -0.5 ± 1.1 , $P = 0.00$; $\Delta\text{weight SDS}$: 1.6 ± 1.2 vs. 0.0 ± 0.6 , $P = 0.00$). Between 1 and 2 years and between 2 and 9 years of age, changes in ΔHtSDS and $\Delta\text{weight SDS}$ were not different between the two groups. ΔBMI between birth and the first year of life tended to be higher in SGA children compared with AGA children (5.3 ± 1.9 vs. $4.1 \pm$

TABLE 2
Clinical characteristics at birth and at time of the study in SGA and AGA children

	AGA	SGA
<i>n</i>	22	28
At birth		
Sex (M/F)	11/11	12/16
Gestational age (days)	277 ± 10	275 ± 10
Birth weight (grams)	$3,439 \pm 482$	$2,425 \pm 270$
Birth length (cm)	51 ± 2.4	47 ± 2.3
Ponderal index ($\text{g/cm}^3 \times 100$)	26.1 ± 3.0	23.9 ± 2.6
Actual		
Age (years)	9.0 ± 1.1	9.1 ± 1.1
Body weight (kg)	31.2 ± 5.6	29.5 ± 7.6
Height (cm)	137.9 ± 6.5	135.2 ± 9.3
HtSDS-THSDS	-0.44 ± 0.78	-0.56 ± 0.85
BMI (kg/m^2)	17.6 ± 3.5	15.8 ± 2.4
Waist circumference (cm)	58.5 ± 4.7	57.2 ± 6.8
Total skinfold thickness (mm)	31.3 ± 14.9	32.6 ± 14.4
Bone age (months)	-3.2 ± 10.7	-1.8 ± 12.0

Data are *n* or means \pm SD.

TABLE 3
Results of the hyperinsulinemic-euglycemic clamp and hyperglycemic clamp

	AGA	SGA
<i>n</i>	22	28
<i>M</i> value* (mg · kg ⁻¹ · min)	15.6 ± 2.3	12.9 ± 4.0
FIR (mmol · l ⁻¹ · min) [†]	2.2 ± 0.8	2.3 ± 1.3
SIR (mmol · l ⁻¹ · min)	32.2 ± 10.9	32.5 ± 16.0
Disposition index (FIR × <i>M</i> value)	33.6 ± 12.8	28.8 ± 15.4

Data are means ± SD. *Investigated data were published previously (8); †adjusted for insulin sensitivity.

1.7, *P* = 0.06). Between 1 and 2 years and between 2 and 9 years of age, changes in BMI were not different between the two groups.

Insulin sensitivity and β-cell function in relation to body size (ΔBMI) in childhood. Results of the hyperinsulinemic-euglycemic clamp were described earlier (8). In short, plasma insulin and blood glucose measured at steady state (60–120 min) did not differ significantly between SGA and AGA children (plasma insulin: 376 ± 89 vs. 402 ± 83 pmol/l; plasma glucose: 5.0 ± 0.2 vs. 5.0 ± 0.2 mmol/l). The *M* value was significantly lower in the SGA group than in the AGA group (12.9 ± 4.0 vs. 15.6 ± 2.3 mg · kg⁻¹ · min, *P* = 0.009, after adjustment for BMI; *P* = 0.001) (Table 3).

The arginine-stimulated insulin secretion as a measure of β-cell capacity did not significantly differ between SGA children and AGA children (32.5 ± 16.0 vs. 32.2 ± 10.9 mmol · l⁻¹ · min) (Table 3). The disposition index (FIR × *M* value) was not significantly different for SGA and AGA children (28.8 ± 15.4 vs. 33.6 ± 12.8 mmol · l⁻¹ · min, *P* = 0.2).

Table 4 shows the absolute BMI values in the tertiles of the SGA and AGA children during childhood. After classifying the ΔBMI_{0–1 year} and ΔBMI_{0–2 years} in tertiles in SGA and AGA children, no significant differences were seen in *M* value, FIR, or SIR between the lowest and the highest tertile (Table 5). However, after classifying the ΔBMI_{2–9 years} in tertiles in SGA and AGA children, the *M* value was significantly lower in SGA children in the tertile with the highest ΔBMI_{2–9 years} compared with the tertile with the lowest ΔBMI_{2–9 years} (12.6 ± 2.3 vs. 15.8 ± 2.8 mg · kg⁻¹ · min⁻¹, *P* = 0.01) (Table 5). In AGA children, no difference in *M* value was seen between the lowest and highest ΔBMI_{2–9 years}. The FIR and SIR were significantly higher in SGA children in the tertile with the highest ΔBMI_{2–9 years} compared with the tertile with the lowest ΔBMI_{2–9 years} (FIR: 2.5 ± 0.6 vs. 1.9 ± 1.2 mmol · l⁻¹ · min, *P* = 0.03; SIR: 41.7 ± 0.7 vs. 34.3 ± 10.4 mmol · l⁻¹ · min, *P* = 0.004) (Table 5). In AGA children, no difference in FIR or SIR was seen between the lowest and highest ΔBMI_{2–9 years}.

TABLE 4
Absolute BMI (kg/m²) values of the tertiles in SGA and AGA children during childhood

	1 year		2 years		9 years	
	AGA	SGA	AGA	SGA	AGA	SGA
Lowest tertile	16.1 ± 1.3	15.1 ± 0.6	16.3 ± 0.4	15.1 ± 1.4	15.5 ± 1.9	15.2 ± 1.4
Middle tertile	18.0 ± 0.5	16.4 ± 0.7	16.8 ± 0.9	15.5 ± 1.5	16.0 ± 1.3	15.7 ± 2.6
Highest tertile	18.7 ± 0.7	17.7 ± 1.5	17.3 ± 2.1	15.9 ± 1.3	18.5 ± 2.8	16.2 ± 2.5

Data are means ± SD.

DISCUSSION

There is no general agreement whether the association between IUGR with type 2 diabetes in adult life is mediated through insulin resistance, through impairment of β-cell function, or a combination of both (6). It has been suggested that during intrauterine malnutrition, the fetus makes metabolic adaptations that not only benefit in the short term by increasing fuel availability but become permanent and last through life. These adaptations may become deleterious when malnutrition is followed by abundant nutrition. In the present study, insulin sensitivity was measured using the hyperinsulinemic-euglycemic clamp technique in young prepubertal children born SGA. Insulin sensitivity was significantly lower in children who were born SGA compared with control subjects.

It has been suggested that malnutrition may also affect the structure and function of the β-cells, causing insulin secretory defects (6,9). In rats, a reduced β-cell mass in offspring at birth is seen after maternal food restriction during late pregnancy. Subsequent renutrition is followed by increased β-cell proliferation, but it is insufficient to fully restore β-cell mass (10). In the present study, however, SIR (arginine-stimulated insulin secretion as a measure of β-cell capacity) was not lower in SGA children than in control subjects. Therefore, we conclude that in SGA children, a decrease in insulin sensitivity and not a decrease in β-cell capacity is the primary defect promoting the development of diabetes type 2 in adult life. However, insulin resistance alone cannot cause type 2 diabetes. Studies in several ethnic groups have established that the progression from normal glucose tolerance to frank type 2 diabetes results from a gradual deterioration in β-cell function in the presence of insulin resistance. It is not clear whether the decline in insulin secretion results from a reduction in the number of β-cells, progressive dysfunction of a number of β-cells, or a combination of both (23). However, in these young prepubertal SGA children, we could not demonstrate a decreased β-cell capacity.

Several studies suggest that SGA children who present a substantial increase in body weight during childhood have an increased risk of chronic diseases in adulthood (16,17, 24). Consistent with these studies, we found that SGA children with the highest current BMI are the most insulin resistant (8), and thus they are especially at risk of developing type 2 diabetes later in life. Interestingly, the *M* value in AGA children with a high BMI was not lower than in AGA children with a BMI ≤ 17 (8). So, being moderately overweight during childhood in AGA children seems not to be a risk factor of similar importance for developing diabetes later in life. However, Ong et al. (25) demonstrated that full-term singletons who showed catch-up growth in height or who had a substantial increase in body

TABLE 5
Tertiles of Δ BMI in SGA and AGA children

	<i>M</i> value (mg · kg ⁻¹ · min)		FIR (mmol · l ⁻¹ · min)		SIR (mmol · l ⁻¹ · min)	
	AGA	SGA	AGA	SGA	AGA	SGA
Tertiles of Δ BMI _{0-1 year} *†						
Lowest tertile	15.5 ± 3.7	13.7 ± 4.8	2.4 ± 0.6	2.5 ± 1.4	30.9 ± 10.0	35.4 ± 16.9
Middle tertile	14.7 ± 1.1	13.1 ± 4.3	2.2 ± 1.1	2.4 ± 1.9	34.9 ± 8.4	30.4 ± 18.0
Highest tertile	14.9 ± 3.5	11.7 ± 4.5	2.2 ± 0.2	2.6 ± 0.6	35.2 ± 7.5	34.8 ± 11.1
Tertiles of Δ BMI _{0-2 years} *†						
Lowest tertile	14.8 ± 2.4	14.7 ± 2.9	1.9 ± 1.1	2.4 ± 0.6	41.6 ± 9.2	27.8 ± 6.1
Middle tertile	14.5 ± 0.8	11.7 ± 3.7	2.4 ± 0.5	2.2 ± 1.0	31.4 ± 5.5	29.2 ± 11.0
Highest tertile	15.6 ± 3.7	13.1 ± 4.5	2.5 ± 1.1	2.5 ± 1.2	35.0 ± 8.7	43.2 ± 20.0
Tertiles of Δ BMI _{2-9 years} *‡						
Lowest tertile	16.2 ± 3.3	16.3 ± 3.3	2.3 ± 1.0	1.8 ± 0.8	30.7 ± 7.3	21.8 ± 6.5
Middle tertile	14.8 ± 0.3	11.6 ± 1.6	2.0 ± 1.1	2.3 ± 0.7	35.8 ± 9.1	32.0 ± 10.5
Highest tertile	14.3 ± 2.9	11.1 ± 3.9	2.5 ± 0.5	2.9 ± 0.9	39.5 ± 8.0	45.0 ± 14.4

Data are means ± SD. *AGA: first vs. third tertile, NS; †SGA: first vs. third tertile, NS; ‡SGA first vs. third tertile, *M* value: *P* = 0.012, FIR: *P* = 0.025, SIR: *P* = 0.004.

weight between 0 and 2 years were heavier and taller and had a greater BMI than other children at 5 years, leading to a higher risk of developing adult diseases.

Catch-up growth in height in SGA children born at term is usually seen during the first 2 years of life (26) and in most of the children in the first 6 months (27,28). In very prematurely SGA-born children, some catch-up growth may take place during the third year (29). In the present study, 72% of the SGA children had shown catch-up growth at 2 years of age. At the time of the study, five SGA children (18%) did not grow within their target height SD score (THSDS) range according to our definition. The *M* value in these children was not different compared with the *M* value of SGA children who did grow within their THSDS range at time of the study (*n* = 23) (data not shown) (8). Therefore, catch-up growth in height during childhood seems not to be a risk factor for the subsequent development of type 2 diabetes later in life in SGA-born children.

In the present study, we classified the gain of BMI between 0–1 year, 0–2 years, and 2–9 years in tertiles in SGA and AGA children. The *M* value was significantly lower in SGA children in the tertile with the greatest increase in BMI between 2 and 9 years of age compared with the tertile with the lowest increase in BMI between 2 and 9 years. In the tertile with the highest Δ BMI between 2 and 9 years, the SIR was significantly higher in SGA children compared with the tertile with the lowest Δ BMI between 2 and 9 years. Because β -cell capacity decreases with aging (30), and possibly faster in obese subjects (31), we hypothesize that in time pancreatic β -cells will not be able to compensate for the decreased insulin sensitivity.

We suggest that SGA children who gain more weight after the second year of life are especially at risk of developing type 2 diabetes later in life. In AGA children, an association between an increase in body size (Δ BMI) after the second year of life and decreased insulin sensitivity was not found. An increase in BMI in the first 2 years of life was not related to decreased insulin sensitivity in both SGA and AGA children. Moreover, recently, it was shown that rapid weight gain in SGA children up to 2 years of life is associated with a lower risk of hospital admissions (32). Because our data demonstrate that an increase in BMI during the first 2 years of life is not associated with a

decrease in insulin sensitivity, and thus does not seem to be risky, we may speculate that high energy intake during infancy might be desirable for low-BW children.

Family history of type 2 diabetes is known to potentiate the risk for insulin resistance associated with fetal growth, thereby suggesting a genetic contribution (33). Recently, it was demonstrated that the reduced insulin sensitivity in people who are born SGA results from the combination of both an unfavorable fetal environment and genetic factors. It was shown that genetic polymorphisms in TNF- α , β 3 adrenoceptor, and peroxisome proliferator-activated receptor, key molecules of the adipose tissue, modulate insulin resistance parameters (insulin-to-glucose ratios after oral glucose loading) in SGA children but not in AGA children (34). These susceptibility genes seem not to have a primary role in the development of type 2 diabetes, but rather they act as response modifiers to triggering factors such as diet and physical exercise by altering lipolysis regulation.

Over the last decade there has been an alarming rise of type 2 diabetes in children, mirroring increasing rates of obesity (35). Based on the findings of the present study, we suggest that SGA children with excessive gain in BMI after the second year of life should be tested for the development of type 2 diabetes and associated risk factors for cardiovascular disease. Early treatment may prevent or postpone long-term complications. But even more important than early treatment is prevention of the development of diabetes by improving insulin sensitivity. Lifestyle changes to prevent obesity by keeping a healthy lifestyle in SGA children should be implemented to improve insulin sensitivity and thus to reduce the incidence of type 2 diabetes. Future research may provide further insight into the interaction between genetic susceptibility and detrimental environmental factors and might result in new therapeutic strategies or even prevention of diabetes type 2 in individuals who were born SGA.

ACKNOWLEDGMENTS

We thank the Netherlands Organization for Scientific Research and Novo Nordisk NL for financial support of the project.

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