Original Article

Lower Birth Weight Associated with Current Overweight Status Is Related with the Metabolic Syndrome in Obese Japanese Children

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The purpose of this study was to clarify the relationship between lower birth weight and current overweight status and to examine the involvement of these factors in the development of the metabolic syndrome (MS) in obese Japanese children. We examined 97 obese boys (mean age 11.3 years; mean percentage overweight [POW] 52.4%) and 29 obese girls (mean age 11.1 years; mean POW 58.3%). The anthropometric measurements, blood pressure, fasting serum insulin and blood glucose, liver enzymes, lipids and lipoproteins were measured. Birth weight and gestational weeks were also recorded. The subjects were divided into either an MS group or a Non-MS group using criteria proposed for Japanese children. We compared the weight parameters (birth weight, current weight and current weight–to–birth weight ratio [WBWR]) between the two groups and analyzed the relationships between the weight parameters and metabolic derangements. There were no significant differences in age or anthropometric measurements between the two groups. However, birth weight in the MS group was lower than that in the Non-MS group, while WBWR of the MS group was higher than that in the Non-MS group. Blood pressure and serum insulin correlated positively with WBWR. These findings suggested that lower birth weight with current overweight status was associated with the MS in obese Japanese children. We were unable to clarify whether subjects with lower birth weight who achieved proper weight gains had the same risk as subjects with appropriate birth weight. However, they should be assisted to grow adequately to prevent future metabolic derangements. (*Hypertens Res* 2007; 30: 627–634)

***Key Words*: birth weight, obesity, child, metabolic syndrome, thrifty phenotype hypothesis**

Introduction

The prevalence of obesity among Japanese children has increased dramatically and recently has become a serious public health problem (*1*). Obesity is the most common cause of insulin resistance and hyperinsulinemia (*2*) and is strongly associated with hypertension, type 2 diabetes mellitus, dyslipidemia and the metabolic syndrome (MS) in childhood. These conditions ultimately lead to life-threatening events such as ischemic heart disease and cerebrovascular disease (*3*, *4*). It therefore goes without saying that preventing the increase in obesity is important for protecting the health of children.

In 1986, Barker *et al*. introduced the thrifty phenotype hypothesis and showed that intrauterine growth retardation (IUGR) was associated closely with cardiovascular disease in later life (*5*) and also increased the risk of developing characteristics of the MS, such as hypertension, hyperlipidemia, and ultimately type 2 diabetes mellitus (*6*). Subsequently, several investigations reported that low birth weight followed by

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Table 1. Clinical Characteristics of the Subjects Grouped According to Gender

	Boys (n=97)				Girls (n=29)			
	Range	Median	Mean	SD	Range	Median	Mean	SD
Birth weight (g)	2,210–4,625	3,370	3,395.6	408.6	2,534–3,976	3,200	3,223.1	349.5
Gestational week (weeks)	34–42	39	39.4	1.2	34–41	40	39.3	1.4
Age (years)	9.6–12.5	11.4	11.3	0.7	9.7–12.4	11.0	11.1	0.8
Height (cm)	135.5–171.3	149.2	150.1	7.5	136.9–159.8	148.2	148.5	5.2
Weight (kg)	46.2–105.0	60.4	63.4	10.9	47.9–82.5	60.6	63.4	9.7
POW (%)	27.5–110.0	50.4	52.4		30.9–114.3	52.3	58.3	
Body fat percentage (%)	26–46	35	34.8		31–43	37	37.6	
Waist circumferences (cm)	76.5–111.0	89.0	89.7		82.0–114.5	88.0	90.8	
Hip circumferences (cm)	83.0–116.0	92.5	93.0		83.5–112.0	93.0	95.2	
WBWR	13.3–30.7	18.4	18.9		14.9–25.9	19.2	19.9	
SBP (mmHg)	93–151	120	120.7	11.1	92–143	121	119.9	11.6
DBP (mmHg)	41–77	58	58.2	7.7	43–78	61	59.9	10.8
P_{max} (mm)	7.5–19.4	12.4	12.4		8.4–20.2	12.9	13.3	
S_{min} (mm)	6.2–28.3	13.2	13.5		8.7–24.8	15.3	14.9	
GOT (IU/L)	16–154	27	36.7		14–88	23	29.7	
GPT (IU/L)	11–272	34	52.3		10–215	28	42.9	
T-Chol (mg/dL)	122–273	184	187.5		133–271	194	194.3	
HDL (mg/dL)	32–73	51	50.6		37–81	48	49.0	
LDL (mg/dL)	67–196	113	118.4		77–194	128	126.5	
TG (mg/dL)	47–443	125	140.0		44–512	127	149.9	
FBG (mg/dL)	70–118	89	90.1	8.5	77–104	89	88.7	6.8
HbA_{1c} (%)	4.1–5.6	4.8	4.8		4.1–5.5	4.7	4.8	
Serum insulin (μU/mL)	4.5–58.1	17.3	20.5		8.2–43.3	23.4	23.7	

POW, percentage overweight; WBWR, current weight–to–birth weight ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; P_{max}, maximum preperitoneal fat thickness; S_{min}, minimum subcutaneous fat thickness; GOT, glutamate-oxaloacetate transaminase level; GPT, glutamic-pyruvic transaminase level; T-Chol, total cholesterol level; HDL, high-density lipoprotein cholesterol level; LDL, low-density lipoprotein cholesterol level; TG, triglyceride level; FBG, fasting blood glucose level; HbA_{1c}, hemoglobin A_{1c}.

excessive weight gain in childhood led to insulin resistance and hypertension in adults (*7*–*9*). The relationship between low birth weight and increased risk of insulin resistance or type 2 diabetes mellitus has also been reported in children (*10*, *11*). We also reported a negative correlation between birth weight and systolic blood pressure in children aged 3 years (*12*).

The purpose of this study was to clarify the relationship between lower birth weight and current overweight status and metabolic derangement in obese Japanese children.

Methods

Subjects

We examined 97 obese boys (mean age 11.3 years; range 9.6–12.5 years) and 29 obese girls (mean age 11.1 years; range 9.7–12.4 years) who lived in Niigata Prefecture, Japan and received regular medical examinations in conjunction with "The Prevention of Cardio- and Cerebrovascular Diseases in Childhood" program. The division of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences and the School Health Division of local governments in Niigata Prefecture undertake this program every year. All subjects were more than 20% overweight based on age- and sex-specified body weight for height (percentage overweight [POW]) and had a body fat percentage >25% for boys or >30% for girls aged <11 years or >35% for girls aged ≥11 years. No subjects had known endocrine disorders or diabetes. The anthropometric measurements and blood examinations were performed after informed consent had been obtained from the parents or guardians of all the subjects. The Ethical Committee of the Niigata University Graduate School of Medical and Dental Sciences approved this study.

Methods

Height was measured by a portable stadiometer to the nearest 1 mm and weight by a digital scale to the nearest 0.1 kg. POW was calculated based on the standard body weight of Japanese children published in 1990 by the Ministry of Education, Science and Culture of Japan (*13*, *14*). Waist and hip circumferences were measured to the nearest 1 mm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were mea-

Table 2. Characteristics of Obese Boys Divided into MS and Non-MS Groups

	Non-MS (n=53)				MS (n=44)				p
	Range	Median	Mean	SD	Range	Median	Mean	SD	
Birth weight (g)	2,626–4,625	3,470	3,508.0	358.8	2,210–4,000	3,215	3,260.3	427.5	<0.005*
Gestational week (weeks)	34–42	39	39.3	1.4	37–42	40	39.5	1.0	n.s.
Age (years)	10.6–12.3	11.5	11.4	0.5	9.6–12.5	11.3	11.2	0.9	n.s.
Height (cm)	137.5–164.7	147.8	149.4	6.5	135.5–171.3	149.9	150.9	8.6	n.s.
Weight (kg)	51.0–105.0	59.6	62.7	11.2	46.2–101.8	63.2	64.2	10.6	n.s.
POW (%)	29.9–110.0	50.1	52.2		27.5–93.8	51.5	52.8		n.s.
Body fat percentage (%)	28–46	35.0	34.9		26–46	34	34.8		n.s.
Hip circumferences (cm)	83.5–116.0	92.0	92.9		83.0–113.0	92.5	93.1		n.s.
WBWR	13.3–30.7	17.0	18.0		13.9–28.2	19.7	19.9		<0.005†
P_{max} (mm)	7.5–18.1	11.7	12.2		7.5–19.4	12.5	12.5		n.s.
S_{min} (mm)	6.5–27.4	13.7	13.7		6.2–28.3	12.4	13.2		n.s.
GOT (IU/L)	16–109	27	30.6		17–154	27	44.0		n.s.
GPT (IU/L)	11–170	30	39.8		16–272	39	67.4		<0.05†
T-Chol (mg/dL)	122–273	182	185.8		133–264	184	189.6		n.s.
LDL (mg/dL)	67–196	111	116.6		74–176	116.5	120.4		n.s.
HbA_{1c} (%)	4.1–5.6	4.8	4.8		4.1–5.4	4.7	4.8		n.s.
Serum insulin (μU/mL)	5.4–41.5	14.4	16.5		4.5–58.1	21.5	25.3		<0.0005†

MS, metabolic syndrome; Non-MS, non metabolic syndrome; n.s., not statistically significant. Other abbreviations are the same as in Table 1. *Analyzed using unpaired *t*-test; †analyzed using the Mann-Whitney *U* test.

sured in triplicate in the right arm, with the subjects seated quietly, using an automated sphygmomanometer (Dinamap Model 8104; Critikon Inc., Tampa, USA). The third measurement was used in the statistical analyses. Body fat percentage was measured by the biological impedance method using a body composition analyzer (RJL Spectrum; RJL Systems, Detroit, USA). Abdominal fat thickness was estimated by ultrasonography (TOSHIBA Model SSA-250A; Toshiba Corp., Tokyo, Japan) (*15*). The subjects were positioned supine and the linear-array probe kept perpendicular to the skin on the upper medial aspect of the abdomen. A longitudinal scan was then performed from the xyphoid process to the navel along the linea alba. Scanning was performed at the optimal position, with the surface of the liver being kept almost parallel to the skin by requesting that subjects hold their breath. The probe was applied lightly to the skin in order to avoid compression of the fat layer. Maximum preperitoneal fat thickness (P_{max}) and minimum subcutaneous fat thickness (S_{min}) were measured directly from the screen using electronic calipers (*16*).

Birth weight and gestational weeks were obtained from maternal and child health handbooks.

Blood samples were collected from the subjects after an overnight fast for the measurement of serum liver enzymes, lipid levels, lipoproteins, fasting blood glucose (FBG), hemoglobin A_{1c} (HbA_{1c}) and fasting serum insulin.

Statistical Analysis

Birth weight, gestational weeks, age, height, weight, SBP, DBP and FBG were normally distributed and were expressed as range, median, mean and SD, while the other parameters were not normally distributed and were expressed as range, median and mean.

The subjects were divided into two groups, those with the MS (MS group) and those without the MS (Non-MS group). Although the criteria for defining the MS in adults have been published by the World Health Organization (*17*) and the National Cholesterol Education Program Adult Treatment III (*18*) and have been proved to be useful for Japanese men (*19*), there are no criteria for children. We therefore used the provisional criteria for Japanese children proposed by the study group of the Ministry of Health, Labor and Welfare of Japan (*20*): 1) waist circumference ≥80 cm; 2) serum triglyceride (TG) levels ≥120 mg/dL or high-density lipoprotein (HDL) cholesterol levels <40 mg/dL; 3) FBG levels ≥100 mg/dL; 4) SBP ≥125 mmHg or DBP ≥70 mmHg. A diagnosis of MS was made in children who complied with 1) and had at least two of the other criteria 2) to 4).

We analyzed all the anthropometric measurements and metabolism-related laboratory data listed in Table 1, grouped according to gender, with the exception of parameters included as criteria for the MS. Birth weight, gestational weeks, age, height, and weight were analyzed using unpaired *t*-tests, while other parameters were analyzed using the Mann-Whitney *U* test.

The relationships between SBP and DBP, laboratory data and body weight parameters (birth weight, current weight and current weight–to–birth weight ratio [WBWR: current weight (kg)/birth weight (kg)]) were analyzed using Spearman's

Table 3. Characteristics of Obese Girls Divided into MS and Non-MS Groups

	Non-MS (n=16)				MS (n=13)				p
	Range	Median	Mean	SD	Range	Median	Mean	SD	
Birth weight (g)	2,998–3,825	3,389.5	3,367.0	240.2	2,534–3,976	2,940	3,045.9	389.0	<0.05*
Gestational week (weeks)	34–41	40	39.3	1.7	37–41	40	39.4	1.2	n.s.
Age (years)	9.8–12.4	11.1	11.1	0.8	9.7–12.4	11.0	11.1	0.8	n.s.
Height (cm)	140.7–153.4	147.6	147.8	3.3	136.9–159.8	150.6	149.4	6.9	n.s.
Weight (kg)	49.4–75.4	58.8	61.0	7.5	47.9–82.5	70.1	66.4	11.4	n.s.
POW (%)	30.9–87.4	51.2	54.2		38.0–114.3	63.2	63.4		n.s.
Body fat percentage (%)	35–42	37	37.7		31–43	37	37.5		n.s.
Hip circumferences (cm)	84.0–104.5	92.3	92.9		83.5–112.0	99.5	97.9		n.s.
WBWR	14.9–24.6	17.2	18.2		16.3–25.9	21.8	21.9		<0.01†
P_{max} (mm)	8.4–20.2	11.9	12.8		9.4–16.8	13.9	13.8		n.s.
S_{min} (mm)	10.0–19.1	15.4	14.7		8.7–24.8	15.0	15.1		n.s.
GOT (IU/L)	14–88	22.5	27.1		19–88	30	32.9		n.s.
GPT (IU/L)	10–215	22	38.8		19–119	37	47.9		<0.05†
T-Chol (mg/dL)	134–271	185	188.1		133–271	204	202.0		n.s.
LDL (mg/dL)	83–194	119	122.1		77–172	136	131.9		n.s.
HbA_{1c} (%)	4.4–5.2	4.7	4.8		4.1–5.5	4.8	4.8		n.s.
Serum insulin (μU/mL)	8.2–40.3	20.2	20.7		9.1–43.3	26.7	27.5		<0.05†

Abbreviations are the same as in Table 2.

Table 4. Spearman's Rank-Correlation Coefficients between Blood Pressure, Metabolism-Related Laboratory Data and Body Weight Parameters (n=126)

	Birth weight		Weight		WBWR	
	r	p	r	p	r	p
SBP		n.s.	0.43	<0.0001	0.47	<0.0001
DBP	−0.34	<0.0005	0.18	<0.05	0.35	<0.0005
GOT		n.s.		n.s.		n.s.
GPT		n.s.	0.18	<0.05	0.27	<0.005
T-Chol		n.s.		n.s.		n.s.
HDL		n.s.		n.s.		n.s.
LDL		n.s.		n.s.		n.s.
TG		n.s.		n.s.	0.24	<0.01
FBG		n.s.		n.s.		n.s.
HbA_{1c}		n.s.	0.19	<0.05	0.21	<0.05
Serum insulin	−0.33	<0.0005	0.48	<0.0001	0.63	<0.0001

Abbreviations are the same as in Table 2.

rank-correlation coefficients without distinction of gender.

Stepwise multiple regression analysis was used to examine the influence of height, weight, birth weight and gender on MS parameters such as waist circumference, SBP, DBP, TG, HDL and FBG levels and also glutamic-pyruvic transaminase (GPT) and serum insulin levels. Waist circumference, HDL, TG, GPT and serum insulin levels were log-transformed before analysis.

All statistical analyses were carried out using StatView for Windows Ver. 5.0 (Abacus Concepts, Berkeley, USA). Probability (p) values <0.05 were considered to be statistically significant in all analyses.

Results

The clinical characteristics of the subjects are summarized in Table 1. Mean POW was 52.4% for boys and 58.3% for girls, while mean birth weight was 3,395.6 g for boys and 3,223.1 g for girls. Two boys and one girl were small for their gestational age (birth weight SD score <−1.5 SD), while one boy and one girl were pre-term gestational infants, being born earlier than 37 weeks.

Table 2 shows the anthropometric measurements and laboratory data of obese boys belonging to the MS (44 boys) or

Table 5. Stepwise Multiple Regression Analysis of MS Parameters and Metabolism-Related Laboratory Data Validating the Involvement of Height, Weight, Birth Weight and Gender (n=126)

	r	F	
Waist circumference			
Height	−0.427	33.0	
Weight	1.177	250.1	R^2=0.755
Birth weight	NO		p<0.0001
Gender	NO		
SBP			
Height	NO		
Weight	0.447	29.7	R^2=0.198
Birth weight	−0.237	8.3	p<0.0001
Gender	NO		
DBP			
Height	NO		
Weight	0.195	5.3	R^2=0.143
Birth weight	−0.388	20.9	p<0.0001
Gender	NO		
HDL			
Height	NO		
Weight	NO		
Birth weight	NO		
Gender	NO		
TG			
Height	NO		
Weight	NO		
Birth weight	NO		
Gender	NO		
FBG			
Height	NO		
Weight	NO		
Birth weight	NO		
Gender	NO		
GPT			
Height	−0.396	7.9	
Weight	0.595	18.0	R^2=0.149
Birth weight	−0.219	6.4	p<0.0001
Gender	−0.202	5.7	
HbA_{1c}			
Height	NO		
Weight	0.264	9.3	R^2=0.062
Birth weight	NO		p<0.005
Gender	NO		
Serum insulin			
Height	NO		
Weight	0.502	43.7	R^2=0.313
Birth weight	−0.396	27.2	p<0.0001
Gender	NO		

NO, not obtained. Other abbreviations are the same as in Table 2. Waist circumference, HDL, TG, GPT and serum insulin levels were log-transformed before analysis.

Non-MS (53 boys) group. There were no significant differences between the two groups in regard to age, height, weight, POW, body fat percentage and hip circumferences. However, birth weight was lower and WBWR was higher in the MS group. GPT and serum insulin levels were also higher in the MS group.

Table 3 summarizes the data for obese girls divided into the MS (13 girls) and Non-MS (16 girls) groups. As with the boys, there were no differences in age, height, current weight, POW, body fat percentage and hip circumferences between the two groups, with birth weight being lower and WBWR higher in the MS group. GPT and serum insulin levels also showed the same tendencies as those observed in the boys.

Table 4 shows the relationships between blood pressure, metabolism-related laboratory data and body weight parameters. SBP was correlated positively with current weight and WBWR, while DBP showed a negative correlation with birth weight and a positive correlation with WBWR. There were also weak positive correlations between GPT, TG levels, HbA_{1c} and WBWR. Serum insulin levels correlated with birth weight, current weight and WBWR, with WBWR showing the strongest correlation.

Table 5 summarizes the results of the stepwise multiple regression analysis and confirms the involvement of height, weight, birth weight and gender in MS parameters and also in the metabolism-related laboratory data that showed correlations with weight parameters in Table 4 (GPT, HbA_{1c} and serum insulin levels). These results demonstrated that waist circumference correlated negatively with current height and positively with current weight. SBP, DBP, GPT, HbA_{1c} and serum insulin levels were correlated positively with current weight, and with the exception of HbA_{1c}, negatively with birth weight. GPT levels were also found to be correlated with current height and gender.

Discussion

A poor intrauterine environment resulting from factors such as maternal malnutrition, smoking habits, excessive alcohol consumption and drug abuse is known to affect fetal growth (*21–23*). In such circumstances, the maternal-placental nutrients fail to supply the fetal nutrient demand and the fetus undergoes changes to the structure and function of its organs. This adaptation, called "programming," is an advantage that helps the fetus to survive. However, it also results in permanent alterations to the metabolic status of the fetus (*24*).

In this study, there were no significant differences between current anthropometric measurements, including height, current weight, POW, hip circumference and body fat percentage between the MS and Non-MS groups in both boys and girls. However, in the MS group, birth weight was significantly lower while WBWR was increased. These findings indicate that in individuals with a similar level of obesity, subjects with a lower birth weight and subsequent greater weight gain tend to be at higher risk of developing the MS. This trend is in

accordance with the thrifty phenotype hypothesis.

In this study we investigated whether there was an increased prevalence of higher blood pressure in individuals with a lower birth weight. The mechanisms of hypertension caused by "programming" have been investigated and include fetal malnutrition resulting in a reduction in the number of nephrons (*25*) and decreased synthesis of elastin in the walls of the aorta and large arteries (*26*). Both these changes have the potential to lead to hypertension. Placental malnutrition also reduces 11β-hydroxysteroid dehydrogenase activity, resulting in disturbed inactivation of maternal glucocorticoids. Fetal exposure to glucocorticoids increases the sensitivity of the arterial walls to angiotensin II and also predisposes the fetus to higher levels of blood pressure (*27*, *28*). The "catch up" growth after birth resets the hypothalamus-pituitary axis, leading to an increase in growth factors such as insulin-like growth factor-1 (IGF-1), that may lead to the development of hypertension and insulin resistance (*29*, *30*). In our study, SBP showed a stronger relationship with WBWR than with weight. Furthermore, DBP was negatively correlated with birth weight and positively with WBWR, indicating that the effects of "programming" followed by inappropriate weight gain result in subjects tending to have higher blood pressure levels and an increased risk of hypertension.

Our results showed that GPT, TG levels and HbA_{1c} were correlated positively with WBWR. Although the association between non-alcoholic fatty liver disease (NAFLD) and birth weight has not been investigated directly (*31*), a relationship between obesity and NAFLD has been reported in both adults and children (*32*, *33*). In addition to the degree of obesity, hyperinsulinemia and insulin resistance are also important factors in NAFLD (*34*). Our results showed that the strongest correlation was between serum insulin levels and WBWR, indicating that hyperinsulinemia has a closer link with the combination of lower birth weight and subsequent weight gain, than with either factor alone. According to these results, the elevation in GPT levels was related to WBWR as a consequence of the effects of hyperinsulinemia. Lower birth weight and subsequent inappropriate weight gain would generate insulin resistance, leading to NAFLD. Hypertriglyceridemia is a common lipid abnormality associated with insulin resistance and diabetic status (*35*). In our results, TG levels and HbA_{1c} showed positive correlations only with WBWR but not with birth weight or current weight alone. This suggested that the rise in TG levels and HbA_{1c} were also associated with WBWR *via* the effects of insulin resistance.

The mechanism by which "programming" causes insulin resistance is considered to be the result of fetal malnutrition disturbing the growth and functional progression of fetal β-cells, leading to decreased secretion of insulin (*36*). One other cause is a change in the structure of muscles and increased number of type II fibers. These fibers have less capillary supply and therefore lower glucose intake from capillaries compared to type I fibers, differences that may predispose to the development of insulin resistance (*37*). Our study showed correlations between serum insulin levels and body weight parameters such as birth weight, current weight and WBWR. Of these parameters, WBWR showed the strongest correlation with insulin levels. We have reported previously that lower birth weight and accumulation of visceral fat are independently related to hyperinsulinemia and insulin resistance (*38*). These facts are consistent with the higher risk of insulin resistance found in individuals with lower birth weight and greater weight gain.

Although WBWR was not influenced by current height, our results showed that SBP, DBP and serum insulin levels correlated with current weight and birth weight, but not with height. We therefore conclude that WBWR may be associated with an increased risk of higher blood pressure and insulin resistance.

Hypertension and insulin resistance are major components of the MS (*17*, *18*). In our study, WBWR correlated with these two conditions, indicating that individuals with lower birth weight and subsequent inappropriate weight gain are at high risk of developing the MS. In other words, the thrifty phenotype hypothesis may play an important role in the etiology of the MS in children. We were unable to clarify whether a subject with a lower birth weight and subsequent normal growth had the same risk of developing the MS as a subject with appropriate birth weight. However, there is evidence that children with low birth weights tend to become obese in later life (*39*, *40*). This fact indicates that subjects with a lower birth weight are at higher risk of developing the MS. Furthermore, the lifestyles of parents relating to fetal malnutrition, especially smoking habits, may also increase the risk of cardiovascular and other lifestyle-related diseases in their children after birth (*41*).

Thus, the strategy for preventing the MS in childhood must be the avoidance, not only of obesity, but also of fetal malnutrition or intrauterine growth retardation. To achieve these goals, we need to make aggressive medical interventions in order to correct the lifestyle habits of obese children, in addition to educating their parents that an excessive diet, alcohol or drug abuse and smoking habits have the potential to harm, not only their health, but also the health of their children as a consequence of "programming."

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