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The Association between Low Birth Weight and High Levels of Cholesterol Is Not Due to an Increased Cholesterol Synthesis or Absorption: Analysis in Twins

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ABSTRACT

Low birth weight may be associated with high levels of cholesterol in later life through genetic factors that affect both birth weight and cholesterol metabolism. Alterations in cholesterol synthesis and absorption may play an important role in this association. We examined birth weight and plasma ratios of a precursor of cholesterol, lathosterol (an estimate of cholesterol synthesis), and plant sterols, campesterol and β-sitosterol (estimates of cholesterol absorption), to cholesterol in 53 dizygotic and 58 monozygotic adolescent twin pairs. After adjustment for current weight, birth weight was not associated with the ratios of lathosterol, campesterol, and β-sitosterol either in the overall sample [+0.07 μmol/mmol/kg (95% confidence interval: −0.11 to 0.25), $p = 0.5$; +0.02 μmol/mmol/kg (−0.33 to 0.37), $p = 0.9$; and −0.04 μmol/mmol/kg (−0.23 to 0.15), $p = 0.8$, respectively] or in the intrapair analysis in dizygotic twins [+0.27 μmol/mmol/kg (−0.28 to 0.82), $p = 0.3$; −0.03 μmol/mmol/kg (−1.07 to 1.01), $p = 1.0$; and +0.04 μmol/mmol/kg (−0.56 to 0.64), $p = 0.9$, respectively] or in the intrapair analysis in monozygotic twins [+0.54 μmol/mmol/kg (−0.09 to 1.18), $p = 0.09$; −0.60 μmol/mmol/kg (−1.59 to 0.39), $p = 0.2$; and −0.43 μmol/mmol/kg (−0.99 to 0.14), $p = 0.14$, respectively]. Plasma levels of lathosterol, campesterol, and β-sitosterol, which are indicators of cholesterol synthesis and absorption, thus do not explain the association of low birth weight with high levels of total and LDL cholesterol. As an alternative hypothesis, we suggest that a decrease in cholesterol clearance may play an important role. **(*Pediatr Res* 52: 868–872, 2002)**

Low birth weight is associated with an increased risk of cardiovascular morbidity and mortality (1, 2). An atherogenic lipid profile may, in part, explain these associations (3–7). The association between birth weight and an atherogenic lipid profile has been attributed to a programmed response to intrauterine malnutrition that induces permanent changes in the structure and function of organs, which cause increased levels of cholesterol in later life (8). The alternative view is that genetic factors influencing both birth weight and lipid profile could explain the relationships between these two variables (9).

Studies in dizygotic and monozygotic (genetically identical) twin pairs offer a unique opportunity to investigate the influence of intrauterine and genetic factors. Differences within dizygotic twin pairs are a function of both genetic and nongenetic factors, whereas differences within monozygotic pairs are caused by nongenetic factors. In our cohort of adolescent twin pairs, we have previously shown that low birth weight was associated with high total and LDL cholesterol within dizygotic twin pairs, but with low total and LDL cholesterol within monozygotic twin pairs (10). These data suggest that the association of birth weight with total and LDL cholesterol is strongly influenced by the elimination of genetic factors. Therefore, these genetic factors play an important role in the association of low birth weight with elevated levels of total and LDL cholesterol (10).

The metabolic alterations in cholesterol metabolism that underlie these changes in plasma lipids are not known. Direct assessment of cholesterol synthesis is expensive, time consuming, and difficult in large-scale studies, but plasma ratios of lathosterol (a precursor of cholesterol), and campesterol and

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β-sitosterol (plant sterols) to cholesterol are indicators of whole-body cholesterol synthesis and absorption, respectively (11–16). In a study in children born preterm, Mortaz *et al.* (17) demonstrated that low birth weight was associated with an increase in cholesterol synthesis, as indicated by an increase in plasma lathosterol, and a compensatory decrease in cholesterol absorption, as indicated by a decrease in plasma campesterol. They interpreted this association as a consequence of intrauterine programming (17). However, both birth weight (18, 19) and indicators of cholesterol metabolism (20, 21) are influenced by genetic factors. Therefore, the association between them may also be explained by genetic influences.

To examine the association between birth weight and cholesterol metabolism and the possible influence of genetic factors, we investigated birth weight and markers of cholesterol synthesis and absorption in our sample of adolescent dizygotic and monozygotic twin pairs.

METHODS

Subjects. This study is part of a larger project in which cardiovascular risk factors were studied in 160 adolescent twin pairs and their parents (22–25). Addresses of twins living in Amsterdam and neighboring cities were obtained from city council population registries. Twins still living with their biologic parents were contacted by letter. A questionnaire was used to gather information on various factors, including the use of medication and smoking behavior. The maternal questionnaire included questions regarding birth weight and gestational age of their children. Opposite-sex dizygotic twin pairs were excluded because of the effects of sex differences within a pair on both birth weight and indicators of cholesterol metabolism. Subjects using oral contraceptives were also excluded for these analyses. None of the subjects used any other medication that may affect plasma concentrations of lathosterol, campesterol, and β-sitosterol. Thus, 53 dizygotic twin pairs (average age 17.0 y) and 58 monozygotic twin pairs (average age 16.0 y) were eligible for analysis. This study was approved by the institutional review board, and subjects gave their informed consent.

Measurements. Height and weight were measured in a standardized way. After acclimatization, EDTA blood was obtained between 0830 and 1030 h by venipuncture after overnight fasting. Plasma was separated from cells after centrifugation for 10 min at 3000 rpm. Concentrations of lathosterol, campesterol, and β-sitosterol were determined with gas chromatography on a 30-m × 0.25-mm CP Sil 5CB column in a Chrompack model 438S gas chromatograph (Bergen op Zoom, The Netherlands), as described previously (25). Concentrations were expressed as micromole per liter. In addition, values were expressed as micromole per millimole of cholesterol, because the measurements of the sterols are influenced by plasma cholesterol levels (12–15). Cholesterol values of this sample (10, 24, 25) were determined using enzymatic methods (CHOD-PAP kit number 236691, Roche Molecular Biochemicals, Mannheim, Germany). Although some studies investigating indicators of cholesterol metabolism have used gas chromatography to measure cholesterol, the use of enzymatic methods is in accordance with several studies that validated the use of lathosterol, campesterol, and β-sitosterol as indicators of cholesterol metabolism (11–13), and with the study of Mortaz *et al.* (17) in which an association between birth weight and indicators of cholesterol metabolism was found in preterm singletons.

Data analysis. In the overall sample, linear regression analysis was used to investigate the influence of birth weight on indicators of cholesterol metabolism after adjustment for age and sex, and after additional adjustment for current weight. An interaction analysis was performed to investigate whether zygosity or current weight influenced these associations. Intrapair analyses were performed to investigate the influence of intrauterine and genetic factors (10, 23, 26–31). As a first intrapair analysis, the paired *t* test was used to compare twins with the lowest birth weight from each pair with their co-twins with the highest birth weight. For this analysis, two dizygotic and two monozygotic twin pairs had to be excluded, because the birth weight of the twins within a pair was equal. In addition, linear regression analysis was used to analyze whether intrapair differences in birth weight influenced intrapair differences in indicators of cholesterol metabolism before and after adjustment for differences in current weight (including the four twin pairs in which the birth weight of the twins within a pair was equal). Intrapair differences in birth weight were calculated by randomly subtracting the co-twin with the lowest birth weight from the co-twin with the highest birth weight or *vice vera* (32). Interaction analysis was performed to investigate whether zygosity or differences in current weight influenced the associations between intrapair differences in birth weight and indicators of cholesterol metabolism. A two-tailed p value < 0.05 was considered significant. All analyses were performed on a personal computer using the statistical software package SPSS version 9.0 (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

Lathosterol, campesterol, and β-sitosterol (whether expressed as concentration or as ratio to cholesterol) were not

Table 1. *Associations between birth weight and indicators of cholesterol metabolism in the overall sample of twins*

	β (95% CI)†	*p* value
Adjusted for age and sex		
Lathosterol (μmol/L)	0.17 (−0.55 to 0.89)	0.6
Campesterol (μmol/L)	−0.39 (−1.75 to 0.97)	0.6
β-Sitosterol (μmol/L)	−0.40 (−1.15 to 0.35)	0.3
Lathosterol ratio (μmol/mmol)*	0.11 (−0.06 to 0.29)	0.2
Campesterol ratio (μmol/mmol)*	−0.04 (−0.38 to 0.30)	0.8
β-Sitosterol ratio (μmol/mmol)*	−0.06 (−0.24 to 0.13)	0.5
Adjusted for age, sex and current weight		
Lathosterol (μmol/L)	0.02 (−0.72 to 0.76)	1.0
Campesterol (μmol/L)	−0.11 (−1.50 to 1.28)	0.9
β-Sitosterol (μmol/L)	−0.29 (−1.07 to 0.48)	0.6
Lathosterol ratio (μmol/mmol)*	0.07 (−0.11 to 0.25)	0.5
Campesterol ratio (μmol/mmol)*	0.02 (−0.33 to 0.37)	0.9
β-Sitosterol ratio (μmol/mmol)*	−0.04 (−0.23 to 0.15)	0.8

CI, confidence interval.
* Indicates μmol/mmol of total cholesterol.
† β (95% CI) per kilogram birth weight.

related to birth weight in the overall sample (Table 1, *upper panel*). The results were similar after additional adjustment for current weight (Table 1, *lower panel*). Interaction analysis indicated no effect modification by zygosity or current weight (data not shown).

Comparison between co-twins with the lowest and co-twins with the highest birth weight. Birth weight and gestational age were similar in dizygotic and monozygotic twins (Table 2). The differences in birth weight between the co-twins with the lowest birth weight and those with the highest birth weight from each pair were similar for dizygotic and monozygotic twin pairs (380 g and 306 g, respectively, $p = 0.2$; Table 2). Lathosterol, campesterol, and β-sitosterol (whether expressed as concentration or as ratio to cholesterol) were similar in the twins with the lowest and the highest birth weight in both dizygotic and monozygotic twins.

Associations between intrapair differences in birth weight and indicators of cholesterol metabolism. To further explore the relation between birth weight and indicators of cholesterol metabolism, we determined the associations between intrapair differences in birth weight and differences in lathosterol, campesterol, and β-sitosterol. Intrapair differences in the indicators of cholesterol metabolism (whether expressed as concentration or as ratio to cholesterol) were not related to intrapair differences in birth weight in the dizygotic twin pairs either before or after adjustment for differences in current weight (Table 3). In the unadjusted intrapair analysis in monozygotic twins, low birth weight was associated with low concentrations of lathosterol and high concentrations of campesterol and β-sitosterol. However, only the association with lathosterol was statistically significant. After controlling for cholesterol levels by using the ratio of lathosterol to cholesterol, the intrapair association of birth weight with lathosterol was smaller. After additional adjustment for differences in current weight, the association was of borderline significance (Table 3). Interaction analysis indicated that the associations between intrapair differences in birth weight and differences in lathosterol, campesterol, and β-sitosterol (whether expressed as concentration or as ratio to cholesterol) were not significantly influenced by zygosity or differences in current weight ($p > 0.2$).

Additional analyses. After restricting the analyses to subjects born after a gestational age <37 wk, low birth weight was associated with a decreased ratio of lathosterol to cholesterol [+0.30 μmol/mmol/kg (95% confidence interval: 0.04–0.56), $p = 0.03$]. The results of the intrapair analyses in this subgroup, however, were similar compared with the results of the intrapair analyses in the total group. In these subjects, birth weight was not associated with campesterol and β-sitosterol. Adjustment for gestational age or differences in smoking did not change the results (data not shown). The results were also similar if the associations were adjusted for differences in current body mass index instead of current weight.

DISCUSSION

We studied 53 dizygotic and 58 monozygotic adolescent twin pairs. We have previously demonstrated in this sample that low birth weight was associated with high total and LDL cholesterol within dizygotic twin pairs, but with low total and LDL cholesterol within monozygotic twin pairs (10). In addition, indicators of cholesterol metabolism (*i.e.* lathosterol, campesterol, and β-sitosterol) were related to cholesterol and current weight in this sample (25). Therefore, this sample allowed us to investigate whether the association between birth weight and cholesterol is influenced by cholesterol synthesis or absorption, and the possible influence of genetic factors. We could not demonstrate an association of birth weight with indicators of cholesterol synthesis and absorption either in the overall sample or in the intrapair analysis in dizygotic and monozygotic twin pairs.

Several studies have found an association of low birth weight with high total and LDL cholesterol in singletons (3–5) and we have previously reported this association in the overall

Table 2. *Clinical characteristics of the co-twins with the lowest and the highest birth weight in dizygotic and monozygotic twin pairs*

	Dizygotic twin pairs			Monozygotic twin pairs		
	Co-twins with the lowest birth weight	Co-twins with the highest birth weight	*p* Value	Co-twins with the lowest birth weight	Co-twins with the highest birth weight	*p* Value
Birth weight (g)	2246 ± 493	2626 ± 558	< 0.001	2319 ± 529	2625 ± 485	< 0.001
Gestational age (wk)	36 ± 8.4	36 ± 8.4	—	37 ± 2.8	37 ± 2.8	—
No. (male/female)	51 (30/21)	51 (30/21)	—	56 (29/27)	56 (29/27)	—
Age (y)	17.0 ± 1.7	17.0 ± 1.7	—	16.0 ± 1.8	16.0 ± 1.8	—
Current weight (kg)	59.9 ± 7.8	61.8 ± 10.1	0.09	57.5 ± 9.7	58.6 ± 9.5	0.03
Current BMI (kg/m^2)	20.0 ± 1.9	20.3 ± 2.2	0.5	19.5 ± 2.3	19.7 ± 2.3	0.2
Smoking	7	9	—	4	4	—
Total cholesterol (mmol/L)	4.15 ± 0.71	3.99 ± 0.62	0.1	4.23 ± 0.80	4.32 ± 0.79	0.1
Lathosterol (μmol/L)	6.27 ± 2.80	6.43 ± 2.58	0.8	6.37 ± 2.13	7.24 ± 3.21	0.10
Campesterol (μmol/L)	12.76 ± 5.95	12.51 ± 5.75	0.8	12.42 ± 4.48	11.80 ± 4.78	0.4
β-Sitosterol (μmol/L)	7.10 ± 3.56	6.94 ± 2.93	0.8	6.96 ± 2.68	6.36 ± 2.33	0.2
Lathosterol ratio*	1.52 ± 0.58	1.65 ± 0.71	0.3	1.55 ± 0.57	1.71 ± 0.79	0.2
Campesterol ratio*	3.17 ± 1.52	3.17 ± 1.41	1.0	3.02 ± 1.15	2.82 ± 1.21	0.3
β-Sitosterol ratio*	1.77 ± 0.91	1.76 ± 0.72	0.9	1.68 ± 0.64	1.52 ± 0.60	0.12

Mean ± SD. BMI, body mass index. The association between birth weight and total cholesterol has been investigated previously 10.
* Expressed as μmol/mmol of total cholesterol.

Table 3. *Associations between intrapair differences in birth weight and differences in indicators of cholesterol metabolism in dizygotic and monozygotic twin pairs*

	Dizygotic twin pairs		Monozygotic twin pairs	
	β (95% CI)†	*p* Value	β (95% CI)†	*p* Value
Unadjusted				
Lathosterol (μmol/L)	0.56 (−1.60 to 2.73)	0.6	3.55 (0.91 to 6.18)	0.01
Campesterol (μmol/L)	−2.3 (−5.98 to 1.38)	0.2	−0.49 (−4.64 to 3.67)	0.8
β-Sitosterol (μmol/L)	−1.24 (−3.41 to 0.92)	0.3	−1.10 (−3.37 to 1.17)	0.3
Lathosterol ratio (μmol/mmol)*	0.40 (−0.11 to 0.91)	0.12	0.75 (0.10 to 1.40)	0.02
Campesterol ratio (μmol/mmol)*	−0.35 (−1.31 to 0.61)	0.5	−0.24 (−1.26 to 0.79)	0.6
β-Sitosterol ratio (μmol/mmol)*	−0.19 (−0.76 to 0.37)	0.5	−0.33 (−0.88 to 0.23)	0.2
Adjusted for differences in current weight				
Lathosterol (μmol/L)	−0.03 (−2.39 to 2.32)	1.0	2.75 (0.15 to 5.34)	0.04
Campesterol (μmol/L)	−1.04 (−4.99 to 2.92)	0.6	−1.91 (−5.93 to 2.11)	0.3
β-Sitosterol (μmol/L)	−0.27 (−2.56 to 2.02)	0.8	−1.43 (−3.77 to 0.90)	0.2
Lathosterol ratio (μmol/mmol)*	0.27 (−0.28 to 0.82)	0.3	0.54 (−0.09 to 1.18)	0.09
Campesterol ratio (μmol/mmol)*	−0.03 (−1.07 to 1.01)	1.0	−0.60 (−1.59 to 0.39)	0.2
β-Sitosterol ratio (μmol/mmol)*	0.04 (−0.56 to 0.64)	0.9	−0.43 (−0.99 to 0.14)	0.14

CI, confidence interval.

* Indicates μmol/mmol of total cholesterol.

† β (95% CI) per kilogram birth weight.

sample of twins and in the intrapair analysis in dizygotic twin pairs (10). In the present study, we could not demonstrate an association between low birth weight and an increased cholesterol synthesis or absorption, as indicated by elevated plasma levels of lathosterol, campesterol, and β-sitosterol. We cannot exclude the possibility that low birth weight may be associated with other indicators of cholesterol metabolism, such as squalene, methyl sterols, and cholestanol (33), or with direct measurements of cholesterol metabolism using radioactive isotope techniques (33). However, many studies have shown that plasma ratios of lathosterol, campesterol, and β-sitosterol to cholesterol are useful indicators of cholesterol metabolism (12–16). Therefore, we propose that the association between low birth weight and high levels of total and LDL cholesterol may be due to a decreased cholesterol clearance. This could be investigated by studying the *in vivo* kinetics of apolipoprotein B containing lipoproteins using a stable isotope approach (34).

The intrapair association between differences in birth weight and differences in lathosterol in monozygotic twins may suggest an explanation for our previous finding of an association of low birth weight with low total and LDL cholesterol after the elimination of genetic influences (10). However, it should be noted that this association was only of borderline significance. Interestingly, the finding of an association of low birth weight with low cholesterol levels is in line with a study in rats that demonstrated lower plasma cholesterol concentrations after maternal undernutrition (35).

Our results differ from the results from Mortaz *et al.* (17). They demonstrated, in preterm infants, that low birth weight was associated with an increase in cholesterol synthesis, as indicated by an increase in plasma lathosterol, and a compensatory decrease in cholesterol absorption, as indicated by a decrease in plasma campesterol (17). In our study, we could not detect these associations. In the total group of subjects, birth weight was not associated with cholesterol synthesis or absorption. After restricting the analyses to subjects born after a gestational age <37 wk, low birth weight was associated with a decreased, not an increased, ratio of lathosterol to cholesterol. However, the results of Mortaz *et al.* may differ from ours for several reasons. First, the subjects in the study of Mortaz *et al.* were born very prematurely (average gestational age 31.1 wk), whereas our subjects were born after 36.3 wk, which is considered the term period for a twin pregnancy. Second, subjects in the study of Mortaz *et al.* were younger than our twin subjects (11.2 y *versus* 16.5 y).

It has been suggested that intrauterine growth in twins is not comparable to intrauterine growth in singletons. However, birth weight in twins has been associated with many variables that have been related to birth weight in singletons, such as blood pressure (23, 26), diabetes (28, 29), myocardial infarction (30), and height (31). These studies suggest that differences in birth weight in twins can be used as a model for differences in birth weight in singletons.

In summary, we found no evidence that plasma levels of lathosterol, campesterol, and β-sitosterol, which are indicators of cholesterol synthesis and absorption, can explain the association of low birth weight with high levels of total and LDL cholesterol. As an alternative hypothesis, we suggest that the association between low birth weight and high levels of total and LDL cholesterol is due to a decreased cholesterol clearance.

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