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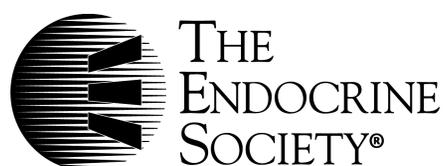
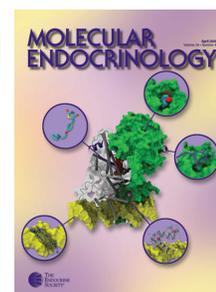
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# Evidence for Genetic Factors Explaining the Association Between Birth Weight and Low-Density Lipoprotein Cholesterol and Possible Intrauterine Factors Influencing the Association Between Birth Weight and High-Density Lipoprotein Cholesterol: Analysis in Twins

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Recent studies have demonstrated an association between low weight at birth and an atherogenic lipid profile in later life. To examine the influences of intrauterine and genetic factors, we investigated 53 dizygotic and 61 monozygotic adolescent twin pairs. Regression analysis demonstrated that low birth weight was associated with high levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and apolipoprotein B ( $-0.17$  mmol/liter per kg,  $P = 0.07$ ;  $-0.18$  mmol/liter per kg,  $P = 0.04$ ; and  $-0.07$  g/liter per kg,  $P = 0.02$ , respectively) and with low levels of high-density lipoprotein (HDL) cholesterol ( $+0.04$  mmol/liter per kg,  $P = 0.1$ ), after adjustment for age, sex, and body mass index. Intrapair differences in birth weight were significantly associated with differences in total cholesterol, LDL cholesterol, and apolipoprotein B in dizygotic twins after adjustment for differences in current body mass index ( $-0.49$  mmol/liter per kg,  $P = 0.02$ ;  $-0.51$  mmol/liter per kg,  $P = 0.01$ ; and  $-0.10$  g/liter per kg,  $P = 0.04$ , respectively), demonstrating that the larger the dif-

ference in birth weight, the higher these risk factors in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. In monozygotic twins, however, the associations between intrapair differences in birth weight and differences in total cholesterol, LDL cholesterol, and apolipoprotein B were in the opposite direction ( $+0.32$  mmol/liter per kg,  $P = 0.03$ ;  $+0.23$  mmol/liter per kg,  $P = 0.08$ ; and  $+0.06$  g/liter per kg,  $P = 0.04$ , respectively). The association between intrapair differences in birth weight and differences in HDL cholesterol was not significant in dizygotic twins ( $+0.04$  mmol/liter per kg,  $P = 0.6$ ) and of borderline significance in monozygotic twins ( $+0.11$  mmol/liter per kg,  $P = 0.05$ ). These data suggest that genetic factors account for the association of low birth weight with high levels of total cholesterol, LDL cholesterol, and apolipoprotein B, whereas intrauterine factors possibly play a role in the association between birth weight and HDL cholesterol. (*J Clin Endocrinol Metab* 86: 5479–5484, 2001)

STUDIES FROM DIFFERENT areas have shown that indices of fetal growth, such as birth weight, are inversely associated with cardiovascular morbidity and mortality in men and women (1–3). Although the mechanisms are not known, it has been suggested that abnormalities in the metabolism of serum lipids may, in part, explain these associations (4). Several recent studies have demonstrated that total cholesterol (4–6), low-density lipoprotein (LDL) cholesterol (4, 5), and apolipoprotein B (4, 7–9), known risk factors for cardiovascular disease, are inversely related to size at birth. In addition, there is some evidence that small size at birth is associated with decreased levels of high-density lipoprotein (HDL) cholesterol (10, 11) and apolipoprotein A1 (12). These associations have been attributed to a programmed response to intrauterine malnutrition that induces permanent changes in the structure and function of organs, which cause an atherogenic lipid profile in adult life (13). This theory is supported by a study (14) demonstrating that exposure to the

Dutch famine *in utero* influenced lipid levels in later life. However, exposure to famine *in utero* during the Leningrad siege was not associated with effects on lipid levels (15). The alternative view is that genetic factors influencing both birth weight and lipid profile could explain the relationships between these two factors (16). Genetic factors play an important role in the determination of serum lipids (17) and, to a lesser extent, birth weight (18). It could be proposed that the genotype responsible for an atherogenic lipid profile might itself cause retarded fetal growth *in utero*.

Twin studies offer a unique opportunity to distinguish between nongenetic intrauterine and genetic influences (19). Specifically, differences within dizygotic twin pairs are a function of both genetic and nongenetic factors, whereas differences within monozygotic (identical) pairs are almost completely caused by nongenetic factors (19). If genetic factors do not play a role in the association between birth weight and cardiovascular risk factors, it could be expected that, both for dizygotic and for monozygotic twins, the twin with the lower birth weight from each pair will also have the highest levels of cardiovascular risk factors, compared with

Abbreviations: BMI, Body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the cotwin with the higher birth weight. In addition, it could be expected that the larger the difference in birth weight, the higher these levels of cardiovascular risk factors in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. If, however, genetic factors do play a role, these associations would hold true only for dizygotic twins, not for monozygotic twins. In a group of adolescent twin pairs still living with their parents, we have previously shown that genetic factors play an important role in the association between low birth weight and high blood pressure (20). We here investigated whether the relationship between birth weight and an atherogenic lipid profile is influenced by nongenetic intrauterine or by genetic factors.

## Materials and 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 (17, 20–22). Addresses of twins living in Amsterdam and neighboring cities were obtained from City Council population registries. Twins still living with their biological parents were contacted by letter. Overall, between 30% and 40% of the families complied (21). Zygosity was determined as described in detail previously (21). 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 the children. This questionnaire was sent to the mothers a few weeks ahead of their visit to our department, allowing them to obtain birth data from birth certificates. Opposite-sex dizygotic twin pairs were excluded because of the effects of sex differences within a pair on both birth weight and serum lipid profile. Subjects using oral contraceptives were also excluded for these analyses. None of the subjects used any other medication that may affect serum lipid profile. Thus, 53 dizygotic and 61 monozygotic twin pairs were eligible for analysis.

### Measurements

Height and weight were measured in a standardized way. After acclimatization EDTA blood was obtained between 0830 h and 1030 h by venipuncture after overnight fasting. Plasma was separated from cells after centrifugation for 10 min at 3000 rpm. Part of the plasma was kept at 4 C for lipid determinations within the next 5 d. The remainder was frozen at –20 C for later use. Total cholesterol and triglyceride levels were determined using enzymatic methods (CHOD-PAP kit number 236691 and GPO-PAP kit number 701904, Roche Molecular Biochemicals, Mannheim, Germany). HDL cholesterol was measured after pre-

cipitation of very low density lipoprotein, intermediate density lipoprotein, and LDL (23). LDL cholesterol was calculated by the formula of Friedewald *et al.* (24), which is valid if triglyceride concentrations do not exceed 4.52 mmol/liter (25). There were no subjects with triglycerides > 4.07 mmol/liter. Apolipoprotein A1 (the structural apolipoprotein linked to HDL) and apolipoprotein B (the structural apolipoprotein linked to LDL) were quantified by radial immunodiffusion (26, 27). Lipoprotein(a) levels were measured with a “bi-site” sandwich ELISA as described previously (22).

### Statistical methods

In the total group, linear regression analysis was used to investigate the influence of birth weight on serum lipids after adjustment for age and sex and after additional adjustment for body mass index (BMI). An interaction analysis was performed to investigate whether zygosity or current BMI influenced the associations between birth weight and serum lipid profile. As in previous twin studies examining the association between birth weight and adult health, intrapair analyses were performed to investigate the influence of intrauterine and genetic factors (20, 28–33). As a first intrapair analysis, we compared twins with the lower birth weight from each pair with their cotwins with the higher birth weight. Because the variability of the within-pair differences rather than between-pair variation is of interest, the paired *t* test was used (34). 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. The differences in dizygotic twin pairs and in monozygotic twin pairs were compared using the independent-samples *t* test. As a first analysis, the comparison of serum lipids between twins with the lower and the higher birth weight is very simple and illustrative. However, twin pairs that differ 1 g in birth weight are not differentiated from twin pairs who differ many hundreds of grams in birth weight.

As a further and better method of analysis, linear regression analysis was used to analyze whether intrapair differences in birth weight influenced intrapair differences in serum lipids before and after adjustment for differences in current BMI in dizygotic and monozygotic twins (including the four twin pairs in which the birth weight of the twins within a pair was equal). To maintain the normal distribution of intrapair differences, intrapair differences in birth weight were calculated by randomly subtracting the cotwin with the lower birth weight from the cotwin with the higher birth weight or vice versa (35). Interaction analysis was performed to investigate whether zygosity influenced the associations between intrapair differences in birth weight and differences in serum lipids and lipoproteins. Serum concentrations of triglycerides had a skewed distribution and were transformed using natural logarithms. For presentation in Table 1, they were transformed back into the original units by taking the antilogs. A two-tailed *P* value < 0.05 was considered significant. All analyses were performed on a personal computer using the statistical software package SPSS, Inc. version 9.0 (SPSS, Inc., Chicago, IL).

**TABLE 1.** Clinical characteristics of the cotwins with the lower and higher birth weight in dizygotic and monozygotic twin pairs

	Dizygotic twin pairs			Monozygotic twin pairs		
	Cotwins with the lower birth weight	Cotwins with the higher birth weight	<i>P</i>	Cotwins with the lower birth weight	Cotwins with the higher birth weight	<i>P</i>
Birth weight (g)	2246 ± 493	2626 ± 558	<0.001	2336 ± 528	2636 ± 485	<0.001
Gestational age (wk)	36 ± 8.4	36 ± 8.4	—	37 ± 2.8	37 ± 2.8	—
n (male/female)	51 (30/21)	51 (30/21)	—	59 (32/27)	59 (32/27)	—
Age (yr)	17.0 ± 1.7	17.0 ± 1.7	—	16.0 ± 1.8	16.0 ± 1.8	—
BMI (kg/m <sup>2</sup> )	20.0 ± 1.9	20.3 ± 2.2	0.5	19.5 ± 2.2	19.7 ± 2.2	0.2
Smoking, n	7	9	—	4	4	—
Total cholesterol (mmol/liter)	4.15 ± 0.71	3.99 ± 0.62	0.1	4.23 ± 0.80	4.32 ± 0.79	0.1
LDL cholesterol (mmol/liter)	2.58 ± 0.68	2.40 ± 0.57	0.07	2.63 ± 0.75	2.69 ± 0.75	0.2
HDL cholesterol (mmol/liter)	1.25 ± 0.24	1.27 ± 0.25	0.5	1.29 ± 0.25	1.33 ± 0.24	0.1
Triglycerides (mmol/liter)	0.63 ± 1.54	0.64 ± 1.45	0.7	0.63 ± 1.38	0.63 ± 1.40	0.9
Apolipoprotein A1 (g/liter)	1.34 ± 0.15	1.38 ± 0.17	0.06	1.35 ± 0.16	1.38 ± 0.17	0.08
Apolipoprotein B (g/liter)	0.78 ± 0.15	0.75 ± 0.18	0.2	0.77 ± 0.16	0.79 ± 0.16	0.2
Lp (a) (g/liter)	0.10 ± 0.10	0.10 ± 0.10	0.9	0.15 ± 0.15	0.15 ± 0.15	0.9

Mean ± SD.

## Results

In the total group of twins, low birth weight was associated with high serum levels of total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B after adjustment for age and sex (Table 2). In addition, low birth weight was associated with low HDL cholesterol and apolipoprotein A1 levels. However, only the association of birth weight with apolipoproteins B and A1 was statistically significant. After additional adjustment for current BMI, the associations with birth weight were similar (Table 2). Interaction analysis indicated that the associations between birth weight and serum lipids were not significantly modified by zygosity (data not shown). The association of birth weight with total cholesterol, LDL cholesterol, and apolipoprotein B was stronger in subjects with a high current BMI ( $P$  for interaction  $< 0.01$ ).

### Comparison between cotwins with the lower and higher birth weight

Birth weight and gestational age were similar in dizygotic and monozygotic twins (Table 1). The differences in birth weight between the cotwins with the lower and those with the higher birth weight from each pair were similar for dizygotic and monozygotic twin pairs (380 g and 300 g, respectively;  $P$  for the difference, 0.2; Table 1). Although none of the differences in serum lipids between the cotwins with the lower and the higher birth weight were statistically significant, several interesting trends could be observed. The dizygotic twins with the lower birth weight had total cholesterol, LDL cholesterol, and apolipoprotein B concentrations that were higher than those of their cotwins with the higher birth weight. However, the monozygotic twins with the lower birth weight had total cholesterol, LDL cholesterol, and apolipoprotein B concentrations that were lower than those of their cotwins with the higher birth weight (Table 1). The differences in total cholesterol, LDL cholesterol, and apolipoprotein B between the cotwins with the lower and higher birth weight were different in dizygotic, compared with monozygotic, twin pairs (for cholesterol,  $P = 0.03$ ; for LDL cholesterol,  $P = 0.03$ ; for apolipoprotein B,  $P = 0.1$ ).

**TABLE 2.** Associations between birth weight and serum lipids and lipoproteins in twins

	Beta (95% CI) <sup>a</sup>	$P$
Adjusted for age and sex		
Total cholesterol (mmol/liter)	-0.16 (-0.35 to 0.02)	0.08
LDL cholesterol (mmol/liter)	-0.17 (-0.35 to 0.01)	0.06
HDL cholesterol (mmol/liter)	+0.04 (-0.02 to 0.10)	0.2
Triglycerides (mmol/liter) <sup>b</sup>	-0.08 (-0.16 to -0.02)	0.08
Apolipoprotein A1 (g/liter)	+0.05 (0.01 to 0.09)	0.03
Apolipoprotein B (g/liter)	-0.07 (-0.11 to -0.03)	0.002
Lp (a) (g/liter)	+2.4 (-0.8 to 6.4)	0.2
Adjusted for age, sex, and BMI		
Total cholesterol (mmol/liter)	-0.17 (-0.35 to 0.01)	0.07
LDL cholesterol (mmol/liter)	-0.18 (-0.36 to -0.01)	0.04
HDL cholesterol (mmol/liter)	+0.04 (-0.02 to 0.10)	0.1
Triglycerides (mmol/liter) <sup>b</sup>	-0.08 (-0.17 to 0.01)	0.08
Apolipoprotein A1 (g/liter)	+0.05 (0.01 to 0.09)	0.02
Apolipoprotein B (g/liter)	-0.07 (-0.11 to -0.03)	0.002
Lp (a) (g/liter)	+0.03 (-0.01 to 0.06)	0.2

CI, Confidence interval.

<sup>a</sup> Beta (95% CI) per kilogram birth weight; <sup>b</sup> log transformed.

Both dizygotic and monozygotic twins with the lower birth weight had HDL cholesterol and apolipoprotein A1 levels that were lower than those of their cotwins with the higher birth weight, whereas levels of triglycerides and Lp (a) lipoprotein were similar.

### Associations between intrapair differences in birth weight and serum lipid profile

To further characterize the relation between birth weight and serum lipid profile, we determined the associations between intrapair differences in birth weight and differences in serum lipids and lipoproteins. Table 3 shows that, in dizygotic twins, intrapair differences in birth weight were associated with differences in total cholesterol, LDL cholesterol, and apolipoprotein B. The larger the difference in birth weight, the higher these risk factors in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. In monozygotic twins, intrapair differences in birth weight were also significantly associated with differences in total cholesterol, LDL cholesterol, and apolipoprotein B. However, the direction of the effect was opposite to that in the dizygotic twins: the larger the difference in birth weight, the lower these risk factors in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. For example, in dizygotic twins, a difference in birth weight of 1 kg within pairs was associated with an LDL cholesterol that was 0.51 mmol/liter higher in the twin with the lower birth weight, compared with the cotwin with the higher birth weight, after adjustment for differences in BMI. In contrast, in monozygotic twins, a difference in birth weight of 1 kg within pairs was associated with an LDL cholesterol that was 0.23 mmol/liter lower in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. Interaction analysis indicated that the associations were significantly different between dizygotic twins and monozygotic twins ( $P < 0.01$  for total cholesterol, LDL cholesterol, and apolipoprotein B). The results were similar before and after adjustment for differences in BMI.

Before and after adjustment for differences in BMI, the association between intrapair differences in birth weight and differences in HDL cholesterol was not significant in dizygotic twins and of borderline significance in monozygotic twins (Table 3). Intrapair differences in birth weight were not associated with differences in triglycerides, apolipoprotein A1, and Lp (a) in either dizygotic or monozygotic twins. Interaction analysis indicated that the associations between intrapair differences in birth weight and differences in HDL cholesterol, triglycerides, apolipoprotein A1, and Lp (a) were not significantly different between dizygotic twins and monozygotic twins ( $P > 0.3$ ).

If subjects with a gestational age shorter than 37 weeks (21 dizygotic and 24 monozygotic twin pairs) were excluded, the results were similar. Adjustment for gestational age or (differences in) smoking did not change the results (data not shown). If the associations were adjusted for (differences in) current weight instead of current BMI, the results were similar.

**TABLE 3.** Associations between intrapair differences in birth weight and serum lipids and lipoproteins in dizygotic and monozygotic twin pairs

	Dizygotic twin pairs		Monozygotic twin pairs	
	Beta (95% CI) <sup>a</sup>	P	Beta (95% CI) <sup>a</sup>	P
<b>Unadjusted</b>				
Total cholesterol (mmol/liter)	-0.47 (-0.86 to -0.09)	0.02	+0.31 (0.02 to 0.61)	0.04
LDL cholesterol (mmol/liter)	-0.50 (-0.87 to -0.13)	0.01	+0.23 (-0.03 to 0.48)	0.08
HDL cholesterol (mmol/liter)	+0.01 (-0.12 to 0.14)	0.9	+0.11 (-0.01 to 0.23)	0.08
Triglycerides (mmol/liter)	+0.03 (-0.13 to 0.18)	0.7	-0.04 (-0.19 to 0.10)	0.5
Apolipoprotein A1 (g/liter)	+0.06 (-0.04 to 0.15)	0.2	+0.04 (-0.04 to 0.13)	0.5
Apolipoprotein B (g/liter)	-0.10 (-0.18 to -0.01)	0.08	+0.06 (0.01 to 0.12)	0.03
Lp (a) (g/liter)	+0.04 (-0.03 to 0.10)	0.3	-0.01 (-0.05 to 0.02)	0.5
<b>Adjusted for differences in BMI</b>				
Total cholesterol (mmol/liter)	-0.49 (-0.89 to -0.08)	0.02	+0.32 (0.03 to 0.62)	0.03
LDL cholesterol (mmol/liter)	-0.51 (-0.90 to -0.13)	0.01	+0.23 (-0.03 to 0.49)	0.08
HDL cholesterol (mmol/liter)	+0.04 (-0.10 to 0.16)	0.6	+0.11 (-0.00 to 0.23)	0.05
Triglycerides (mmol/liter)	-0.02 (-0.17 to 0.14)	0.8	-0.05 (-0.19 to 0.10)	0.6
Apolipoprotein A1 (g/liter)	+0.07 (-0.03 to 0.16)	0.17	+0.04 (-0.04 to 0.13)	0.3
Apolipoprotein B (g/liter)	-0.10 (-0.19 to -0.01)	0.04	+0.06 (0.03 to 0.12)	0.04
Lp (a) (g/liter)	+0.03 (-0.03 to 0.10)	0.3	-0.01 (-0.05 to 0.02)	0.4

CI, Confidence interval.

<sup>a</sup> Beta (95% CI) per kilogram birth weight.

### Discussion

In accordance with previous studies in singletons (4–10), we found that low birth weight was associated with high serum concentrations of total cholesterol, LDL cholesterol, and apolipoprotein B in twins. In dizygotic twin pairs, the twins with the lower birth weight from each pair tended to have higher levels of total cholesterol, LDL cholesterol, and apolipoprotein B, compared with their cotwins with the higher birth weight. In addition, the associations between intrapair differences in birth weight and levels of total cholesterol, LDL cholesterol, and apolipoprotein B demonstrated that the larger the difference in birth weight, the higher these risk factors in the smaller baby, compared with the larger baby. To eliminate the influence of genetic factors on these associations, we also studied monozygotic twin pairs. Despite a similar difference in birth weight as in dizygotic twins, the monozygotic twins with the lower birth weight tended to have lower, not higher, levels of total cholesterol, LDL cholesterol, and apolipoprotein B than their cotwins with the higher birth weight. In addition, the associations between intrapair differences in birth weight and levels of total cholesterol, LDL cholesterol, and apolipoprotein B demonstrated that the larger the difference in birth weight, the lower these risk factors in the twin with the lower birth weight, compared with the cotwin with the higher birth weight. The differences in the intrapair associations between dizygotic and monozygotic twins provide the first evidence that genetic factors importantly influence the association between the variance in birth weight and that in levels of total cholesterol, LDL cholesterol, and apolipoprotein B.

The association between low birth weight and low levels of HDL cholesterol is in accordance with some (10, 11), but not all (4), studies in singletons. In both dizygotic and monozygotic twin pairs, the twins with the lower birth weight from each pair tended to have lower levels of HDL cholesterol, compared with their cotwins with the higher birth weight. In addition, in both dizygotic and monozygotic twins, intrapair differences in birth weight tended to be as-

sociated with intrapair differences in levels of HDL cholesterol. These data suggest that the association between the variance in birth weight and that in levels of HDL cholesterol may be independent of genetic factors.

The association between low birth weight and low levels of apolipoprotein A1 is consistent with one study in singletons (12), but in contrast to other studies (4, 10). Although levels of apolipoprotein A1 tended to be lower in dizygotic and monozygotic twins with the lower birth weight from each pair, compared with their cotwins with the higher birth weight, intrapair differences in birth weight were not associated with intrapair differences in apolipoprotein A1. This makes it difficult to interpret the relative contribution of nongenetic intrauterine *vs.* genetic factors to the association between birth weight and apolipoprotein A1.

Although exposure to famine *in utero* during the Leningrad siege was not associated with lipid levels (15), exposure to the Dutch famine *in utero* influenced lipid levels in later life (14). This may, however, reflect the selection of fetuses genetically susceptible to an increased cardiovascular risk (36). During the famine, the number of conceptions was about 50% lower than the pre-famine level and perinatal mortality as well as mortality in the first year after birth was highest in those who were born during the famine (37). Therefore, selection effects could have influenced the results of studies investigating the influence of maternal malnutrition.

It could be argued that, besides genetic factors, intrauterine factors in monozygotic twins may also be different from those in dizygotic twins. About two-thirds of monozygotic twins are monochorionic (*i.e.*, share a placenta), whereas all dizygotic twins are dichorionic (*i.e.*, have separate placentas). We do not have data on chorionicity in our group of monozygotic twins, but we consider it unlikely that differences in chorionicity between dizygotic and monozygotic twins can fully explain our results. Intrapair differences in birth weight were related to differences in HDL cholesterol and, as reported previously, to differences in height in monozygotic twins (33), suggesting that intrauterine factors in monozy-

gotic twins are capable of permanently influencing adult outcome. Regardless of whether chorionicity plays a role in explaining the differences between dizygotic and monozygotic twins, our finding that the intrauterine growth retardation experienced by the monozygotic twins with the lower birth weight from each pair was significantly associated with beneficial levels of major cardiovascular risk factors (such as total cholesterol, LDL cholesterol, and apolipoprotein B) strongly contradicts the hypothesis that nongenetic intrauterine factors are the cause of the association between low birth weight and these major cardiovascular risk factors. Although this finding was unexpected, it may be consistent with an earlier observation of lower plasma cholesterol concentrations after maternal undernutrition during pregnancy and lactation in rats (38).

It has been demonstrated that serum lipid levels in adolescence track into adulthood. Adolescents with an adverse lipid profile at a given age continue to have an adverse lipid profile as they grow and age (39, 40). In addition, an adverse lipid profile in adolescence is strongly associated with atherosclerosis (41, 42). Therefore, our results in adolescent subjects are relevant for the development of cardiovascular disease in adults.

In our study, there was an important interaction between birth weight and current BMI, such that the associations of birth weight with total cholesterol, LDL cholesterol, and apolipoprotein B were larger in subjects with a high BMI than in subjects with a low BMI. This is consistent with the results from several studies that investigated the association of birth weight with other cardiovascular risk factors, such as blood pressure (43, 44), diabetes (45), and coronary heart disease (1). Previous studies have also shown that adjustment for current size (*i.e.*, weight or BMI) increases the strength of the association between birth weight and cardiovascular risk factors in later life. Therefore, Lucas *et al.* (46) have suggested that it is the change in size from birth to later life rather than size at birth itself that is implicated. However, in our study, the associations were similar after adjustment for differences in current size, suggesting that change in size from birth to later life plays a minor role in the association between birth weight and serum lipid profile in later life.

It has been suggested that improvement of fetal nutrition and thereby intrauterine growth may prevent the development of cardiovascular disease (13). However, if the relationship between low birth weight and elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein B is caused by genetic factors, improvement of fetal nutrition may not prevent the development of cardiovascular disease, at least not through improving these constituents of the lipid profile. On the other hand, the association between inpair differences in birth weight and differences in HDL cholesterol suggests that improvement of fetal growth may also have beneficial effects.

In summary, we found that the association between low birth weight and high levels of total cholesterol, LDL cholesterol, and apolipoprotein B persisted in the inpair analysis in dizygotic twin pairs but was reversed within monozygotic twin pairs. Furthermore, we found that the association between low birth weight and low levels of HDL cholesterol tended to persist in the inpair analysis in both dizygotic

and monozygotic twins. These data suggest that genetic factors account for the association of low birth weight with high levels of total cholesterol, LDL cholesterol, and apolipoprotein B, whereas intrauterine factors possibly play a role in the association of low birth weight with low levels of HDL cholesterol.

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