Arteriosclerosis, Thrombosis, and Vascular Biology
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler. Thromb. Vasc. Biol. 2006;26;2373-2379; originally published online Jul 27, 2006;
DOI: 10.1161/01.ATV.0000238354.39875.75
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1079-5642. Online ISSN: 1524-4636

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Objective—To investigate the association between birth weight and lipid levels in a cohort of UK female twins.

Methods and Results—Birth weights and fasting blood lipid levels were available for 2900 women aged 18 to 80 years. Individual level regressions indicated that a 1-kg increase in birth weight was associated with a 0.08-mmol/L decrease in total cholesterol (95% confidence interval [CI], −0.12, −0.04) and a 0.06-mmol/L decrease in low-density lipoprotein (−0.10, −0.03). Using a regression model that includes both mean twin pair birth weight and individual twin's difference from the pair mean, we found that these significant relationships were between twin pairs only and not within pairs. We found no significant relationships for high-density lipoprotein. When monozygotic and dizygotic twins were analyzed separately we found similar effect sizes. Restricting the analysis to postmenopausal women we found stronger relationships between birth weight and lipid levels, which was attenuated after adjustment for body mass index (BMI).

Conclusions—These novel results suggest that significant relationships between birth weight and lipids are mediated through shared influences on the maternal environment and do not support the hypothesis that fetal malnutrition is an important determinant of adult lipid levels. Adjustment for BMI also indicates that postnatal growth may be more important than prenatal growth. **(*Arterioscler Thromb Vasc Biol*. 2006;26:2373-2379.)**

Key Words: birth weight ■ environment ■ epidemiology ■ lipids ■ twins

The inverse associations that have been reported between birth weight or related measures of size at birth and adult cardiovascular disease may result from changes in lipid metabolism that occur during impaired fetal growth.[1–3] However, to date, the results from studies relating markers of fetal growth to adult lipid levels have only shown consistent results for total cholesterol.[4] Recent meta-analyses have estimated that each kilogram increase in birth weight has been associated with a decrease in mean level of ≈0.02 to 0.05 mmol/L.[4–6] For other lipids the results have been inconsistent, partly accounted for by gender and age effects and interactions.[4,6] The association between total cholesterol and birth weight is reported to be stronger for men than women; and the positive relationship between birth weight and high-density lipoprotein (HDL) is most apparent in postmenopausal women.[7,8] Where associations have been shown between birth weight and lipids, it remains unclear whether these might be a direct effect of undernutrition or caused by confounding as a result of parental factors. The association may also be mediated by a shared genetic mechanism.

These influences of birth weight, maternal environment, and genetic factors on lipid levels can be separated by studying twins. Twin pairs are naturally and uniquely matched for age, genetic factors, and a range of covariates in their shared environment. Examining lipid levels in the group overall provides an estimate of effect of birth weight. Studying within-pair differences in the twins provides a measure of the extent to which any association is caused by difference in fetal nutrition as opposed to confounding factors in the maternal environment. Comparing the degree of association in monozygotic (MZ) and dizygotic (DZ) twins gives an indication of the extent to which any putative association might be mediated genetically.

In this study we have examined the relationship between birth weight and adult lipid levels in a sample of adult female twins from the extensively characterized Twins UK Registry.

Methods

Subjects and Study Design

The study subjects comprised a sample of twins enrolled on the Twins UK Registry. This is a national sample of adult twin

Original received March 20, 2006; final version accepted July 18, 2006.

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Arterioscler Thromb Vasc Biol. **is available at http://www.atvbaha.org** **DOI: 10.1161/01.ATV.0000238354.39875.75**

TABLE 1. Characteristics of the Study Population

	All Subjects (n=2900)				MZ Twins Only (n=760)				DZ Twins Only (n=2140)			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Birth weight, kg*	2.40	0.61	0.79	5.40	2.29	0.64	0.79	5.40	2.43	0.59	0.79	2.43
Age, y*	49.17	12.86	18.27	79.53	54.23	12.74	18.83	74.63	47.65	12.50	18.27	79.53
BMI, kg/m^2	24.91	4.45	13.92	52.39	24.96	4.09	16.90	39.26	24.90	4.51	13.92	52.39
Total cholesterol, mmol/L*	5.64	1.23	2.50	9.53	6.08	1.34	2.50	9.40	5.51	1.17	2.55	9.53
HDL, mmol/L	1.53	0.40	0.26	3.70	1.53	0.39	0.61	3.12	1.54	0.40	0.26	3.70
LDL, mmol/L*	3.54	1.12	0.15	7.20	3.94	1.20	1.04	7.20	3.43	1.07	0.15	7.18
Triglyceride, mmol/L*	1.20	0.60	0.20	3.60	1.35	0.66	0.37	3.60	1.16	0.57	0.20	3.60

*$P<0.05$.
§Ln transformed.

volunteers ascertained through successive media campaigns. Twins enrolled onto the register are not selected for disease-specific studies and are representative of the UK population with respect to their frequency of common traits. Zygosity was derived by questionnaire and confirmed by multiplex DNA fingerprinting (PE Applied Biosystems, Foster City, Calif). Ethical approval for this study has been obtained from St. Thomas's Hospital Research Ethics committee and informed consent was obtained from all subjects.

Twins included in this sample were female and between the ages of 18 and 80 years. All attended for clinical assessment at St Thomas Hospital between 1996 and 2000. Height was measured to the nearest 0.5 cm by using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using digital scales. A venous blood sample was also drawn after an overnight fast. For both twins of each pair, blood was taken 5 minutes apart. Body mass index (BMI) was calculated using the Quetelet index. At assessment twins completed

TABLE 2. Regression Analyses of Birth Weight and Total Cholesterol

		βc*		βw†		β_B‡	
	Adjusted for	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)
All twins	Age	−0.080	−0.12, −0.04	0.018	−0.08, 0.12	−0.158	−0.23, −0.08
	Age, height	−0.059	−0.10, −0.02	0.057	−0.06, 0.18	−0.130	−0.21, −0.05
	Age, BMI	−0.087	−0.13, −0.04	−0.004	−0.12, 0.11	−0.166	−0.25, −0.08
	Age, height, BMI	−0.071	−0.11, −0.03	0.028	−0.09, 0.15	−0.145	−0.23, −0.06
All MZ twins	Age	−0.084	−0.16, −0.01	0.157	−0.01, 0.33	−0.145	−0.32, 0.03
	Age, height	−0.073	−0.17, 0.02	0.201	−0.04, 0.44	−0.111	−0.31, 0.09
	Age, BMI	−0.090	−0.18, 0.00	0.136	−0.09, 0.36	−0.122	−0.33, 0.08
	Age, height, BMI	−0.068	−0.16, 0.02	0.177	−0.05, 0.41	−0.106	−0.31, 0.09
All DZ twins	Age	−0.066	−0.11, −0.02	0.003	−0.12, 0.13	−0.141	−0.22, −0.06
	Age, height	−0.049	−0.10, 0.00	0.043	−0.09, 0.18	−0.120	−0.21, −0.03
	Age, BMI	−0.078	−0.12, −0.03	−0.014	−0.14, 0.11	−0.160	−0.25, −0.07
	Age, height, BMI	−0.066	−0.11, −0.02	0.010	−0.12, 0.14	−0.142	−0.23, −0.05
Postmenopausal twins	Age	−0.155	−0.25, −0.06	−0.108	−0.34, 0.12	−0.286	−0.47, −0.11
	Age, height	−0.089	−0.20, 0.02	−0.019	−0.33, 0.29	−0.196	−0.40, 0.01
	Age, BMI	−0.088	−0.20, 0.02	−0.032	−0.33, 0.27	−0.190	−0.40, 0.02
	Age, height, BMI	−0.088	−0.20, 0.02	−0.034	−0.34, 0.27	−0.191	−0.40, 0.01
Postmenopausal MZ twins	Age	−0.161	−0.29, −0.03	0.043	−0.22, 0.31	−0.352	−0.64, −0.07
	Age, height	−0.083	−0.27, 0.11	0.139	−0.28, 0.56	−0.312	−0.72, 0.10
	Age, BMI	−0.093	−0.28, 0.10	0.136	−0.31, 0.59	−0.305	−0.72, 0.11
	Age, height, BMI	−0.090	−0.28, 0.10	0.137	−0.32, 0.59	−0.320	−0.73, 0.09
Postmenopausal DZ twins	Age	−0.119	−0.25, 0.01	−0.151	−0.47, 0.17	−0.215	−0.43, 0.00
	Age, height	−0.076	−0.22, 0.07	−0.086	−0.46, 0.29	−0.152	−0.38, 0.08
	Age, BMI	−0.081	−0.22, 0.06	−0.128	−0.50, 0.25	−0.154	−0.38, 0.07
	Age, height, BMI	−0.080	−0.22, 0.06	−0.126	−0.51, 0.25	−0.154	−0.38, 0.07

*Expected change in lipid (mmol/L) for 1-kg change in birth weight.
†Expected change in lipid (mmol/L) for 1-kg change in the difference between the birth weight and the twin−pair average birth weight value.
‡Expected change in lipid (mmol/L) for a 1-kg change in the twin-pair average birth weight.
§Ln transformed.

TABLE 3. Regression Analyses of Birth Weight and LDL

	Adjusted for	βc*		βw†		β_B‡	
		β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)
All twins	Age	−0.063	−0.10, −0.03	0.050	−0.05, 0.15	−0.130	−0.20, −0.06
	Age, height	−0.038	−0.08, 0.00	0.071	−0.04, 0.19	−0.091	−0.17, −0.01
	Age, BMI	−0.062	−0.10, −0.02	0.022	−0.09, 0.13	−0.122	−0.20, −0.04
	Age, height, BMI	−0.050	−0.09, −0.01	0.047	−0.07, 0.16	−0.107	−0.19, −0.03
All MZ twins	Age	−0.070	−0.14, 0.01	0.208	0.03, 0.38	−0.112	−0.28, 0.05
	Age, height	−0.063	−0.15, 0.03	0.195	−0.05, 0.44	−0.079	−0.28, 0.12
	Age, BMI	−0.063	−0.15, 0.03	0.164	−0.07, 0.40	−0.074	−0.27, 0.12
	Age, height, BMI	−0.053	−0.14, 0.04	0.175	−0.05, 0.40	−0.070	−0.26, 0.12
All DZ twins	Age	−0.051	−0.09, −0.01	0.032	−0.09, 0.16	−0.114	−0.19, −0.03
	Age, height	−0.025	−0.07, 0.02	0.069	−0.06, 0.20	−0.076	−0.16, 0.01
	Age, BMI	−0.054	−0.10, −0.01	0.017	−0.11, 0.14	−0.117	−0.20, −0.03
	Age, height, BMI	−0.042	−0.09, 0.00	0.041	−0.09, 0.17	−0.100	−0.18, 0.01
Postmenopausal twins	Age	−0.150	−0.24, −0.06	−0.079	−0.30, 0.15	−0.261	−0.44, −0.09
	Age, height	−0.053	−0.16, 0.05	−0.015	−0.30, 0.27	−0.104	−0.31, 0.10
	Age, BMI	−0.057	−0.16, 0.05	−0.038	−0.33, 0.25	−0.104	−0.31, 0.10
	Age, height, BMI	−0.052	−0.16, 0.06	−0.029	−0.32, 0.26	−0.100	−0.30, 0.10
Postmenopausal MZ twins	Age	−0.201	−0.33, −0.07	0.061	−0.20, 0.32	−0.395	−0.67, −0.12
	Age, height	−0.123	−0.30, 0.05	0.101	−0.24, 0.44	−0.322	−0.71, 0.07
	Age, BMI	−0.140	−0.32, 0.04	0.087	−0.32, 0.49	−0.335	−0.76, 0.08
	Age, height, BMI	−0.140	−0.32, 0.04	0.087	−0.32, 0.49	−0.349	−0.75, 0.06
Postmenopausal DZ twins	Age	−0.074	−0.19, 0.05	−0.071	−0.40, 0.26	−0.134	−0.34, 0.07
	Age, height	−0.006	−0.14, 0.13	−0.003	−0.39, 0.38	−0.019	−0.24, 0.20
	Age, BMI	−0.017	−0.15, 0.11	−0.068	−0.46, 0.32	−0.029	−0.25.00.19
	Age, height, BMI	−0.013	−0.14, 0.12	−0.048	−0.44, 0.35	−0.026	−0.25, 0.19

*Expected change in lipid (mmol/L) for 1-kg change in birth weight.
†Expected change in lipid (mmol/L) for 1-kg change in the difference between the birth weight and the twin−pair average birth weight value.
‡Expected change in lipid (mmol/L) for a 1-kg change in the twin-pair average birth weight.
§Ln transformed.

a questionnaire detailing their medical history and lifestyle factors. Birth weight was recalled by participants. Medication history, including details of lipid-lowering medication, was coded according to the British National Formula (BNF) Number 40 (2000).

Laboratory Methods

Serum samples were stored at −40°C until analysis. Levels of all lipids were measured by using a Cobas Fara machine (Roche Diagnostics). Total cholesterol, HDL, and triglycerides were determined by a colorimetric enzymatic method. HDL cholesterol was determined after precipitation of larger particles (chylomicron, very-low-density lipoprotein, and low-density lipoprotein [LDL]) by magnesium and dextran sulfate. LDL levels were estimated by using the Friedewald equation. This formula was applied only if the triglyceride concentration of subjects did not exceed 4.52 mmol/L. Subjects with extremely high or low lipid values (3 SD above or below the mean) were excluded from the analyses.

Statistical Methods

Linear regression analysis was first undertaken treating the twins as individuals, allowing a direct comparison with findings in singleton populations:

$$E(Y_{ij}) = \beta_0 + \beta_c X_{ij}$$

where Yij and Xij, respectively, represent the lipid (Y) value and birth weight (X) of twin j from pair i. β_c represents expected change in lipid level per kg increase in birth weight in individuals. The regression analysis took into account the correlated structure of the data. Second, after the approach described in detail by Carlin et al,[9] the effect of birth weight of each individual twin on lipid levels was examined in a model parameterized with birth weight included as: (a) a variable representing the mean birth weight of the pair from which the twin is derived; and (b) a variable representing the individual twin's difference from the pair mean. This approach provides a simultaneous estimation of within-pair and between-pair influences of birth weight on lipid levels:

$$E(Y_{ij}) = \beta_0 + \beta_w(X_{ij}\text{-}X_{i.}) + \beta_B X_{i.}$$

where Xi. is the mean value of X for twin pair i. The within-pair coefficient β_w gives the expected change in Y for 1-unit change in the difference between the individual X and the twin-pair average X value. The between-pair coefficient β_B gives the expected change in Y for a 1-unit change in the twin-pair average X, while holding the individual deviation from the average constant. The within-pair effect β_w represents an association that is free of confounding because of factors that are common to the twin pair. The between-pair effect β_B reflects further variation in Y that can be explained by variation in the twin-pair mean of X. Variation caused by confounding because of the maternal environment would be expected to be detected in β_B but not β_w.[9]

In the analysis, total cholesterol, HDL, and LDL were normally distributed. The triglyceride data were log-transformed to achieve a

TABLE 4. Regression Analyses of Birth Weight and HDL

		βc*		βw†		β_B‡	
	Adjusted for	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)	β (per kg birth weight)	(95% CI)
All twins	Age	0.011	−0.01, 0.03	−0.001	−0.04, 0.04	0.013	−0.02, 0.04
	Age, height	0.016	0.00, 0.03	0.007	−0.04, 0.05	0.020	−0.01, 0.05
	Age, BMI	0.016	0.00, 0.03	0.011	−0.03, 0.06	0.021	−0.01, 0.05
	Age, height, BMI	0.023	0.01, 0.04	0.025	−0.02, 0.07	0.030	−0.01, 0.06
All MZ twins	Age	0.012	−0.01, 0.04	0.0002	−0.08, 0.08	0.007	−0.05, 0.07
	Age, height	0.033	0.00, −0.07	0.047	−0.07, 0.17	0.029	−0.05, 0.11
	Age, BMI	0.018	−0.02, 0.05	0.027	−0.09, 0.15	0.009	−0.06, 0.08
	Age, height, BMI	0.031	0.00, 0.06	0.067	−0.05, 0.19	0.025	−0.05, 0.10
All DZ twins	Age	0.009	−0.01, 0.03	−0.006	−0.05, 0.04	0.012	−0.02, 0.05
	Age, height	0.008	−0.01, 0.03	−0.008	−0.06, 0.04	0.013	−0.02, 0.05
	Age, BMI	0.014	−0.01, 0.03	0.002	−0.04, 0.05	0.020	−0.02, 0.06
	Age, height, BMI	0.019	0.00, 0.04	0.010	−0.04, 0.06	0.026	−0.01, 0.06
Postmenopausal twins	Age	0.028	0.00.0.06	0.054	−0.04, 0.14	0.014	−0.05, 0.08
	Age, height	0.040	0.00, 0.08	0.089	−0.03, 0.21	0.019	−0.06, 0.10
	Age, BMI	0.039	0.00, 0.08	0.096	−0.02, 0.22	0.016	−0.07, 0.10
	Age, height, BMI	0.040	0.00, 0.08	0.098	−0.02, 0.22	0.017	−0.06, 0.10
Postmenopausal MZ twins	Age	0.042	−0.01, 0.09	0.133	0.01, 0.25	0.019	−0.09, 0.13
	Age, height	0.102	0.04, 0.17	0.257	0.09, 0.43	0.093	−0.06, 0.25
	Age, BMI	0.086	0.02, 0.15	0.271	0.08, 0.47	0.046	−0.10, 0.19
	Age, height, BMI	0.096	0.03, 0.16	0.257	0.07, 0.45	0.083	−0.07, 0.23
Postmenopausal DZ twins	Age	0.011	−0.04, 0.06	−0.022	−0.14, 0.09	−0.007	−0.09, 0.08
	Age, height	0.013	−0.04, 0.06	−0.027	−0.15, 0.09	−0.011	−0.10, 0.08
	Age, BMI	0.015	−0.04, 0.07	−0.005	−0.12, 0.11	−0.009	−0.10, 0.08
	Age, height, BMI	0.014	−0.04, 0.07	−0.017	−0.13, 0.10	−0.011	−0.10, 0.08

*Expected change in lipid (mmol/L) for 1-kg change in birth weight.

†Expected change in lipid (mmol/L) for 1-kg change in the difference between the birth weight and the twin−pair average birth weight value.

‡Expected change in lipid (mmol/L) for a 1-kg change in the twin-pair average birth weight.

§Ln transformed.

normal distribution. The regression analyses were performed in MZ and then DZ twins separately, with adjustment for age, and where no significant differences existed between zygosity groups the data were pooled. To investigate the effect of postnatal effects, we examined a sequence of models including: (1) BMI; (2) height; and (3) BMI and height together. The latter model takes into account any residual confounding caused by size that is not accounted for by BMI. Because high lipoprotein levels may be more adverse in postmenopausal than premenopausal women,[10–12] we repeated the analysis only in those subjects aged 60 years and older. Four subjects who were taking cholesterol-lowering drugs were excluded from the study. All statistical analyses were performed using STATA version 9.

Results

Birth weight and lipid data were available for 2900 subjects (1070 DZ pairs and 380 MZ pairs) (Table 1). Mean birth weight was 2.40 kg and was lower in MZ (2.29 kg) twins than in DZ twins (2.43 kg). MZ twins were older (54.2 years) than DZ twins (47.7 years). Mean lipid levels were similar to comparable populations.[13,14] MZ twins had slightly higher levels of total cholesterol, LDL, and triglyceride than DZ twins.

Total Cholesterol

The results from the individual level regression analysis showed a significant inverse relationship between total cholesterol and birth weight (0.08 mmol/L decrease in total cholesterol per 1-kg increase in birth weight). There were no differences in the magnitude of the relationship between MZ (−0.08 mmol/L) and DZ twins (−0.07 mmol/L). Total cholesterol was negatively associated with birth weight between twin pairs but not within pairs, ie, the association was mediated through an effect on the twin pair mean and did not account for individual differences from the pair mean in all analyses (Table 2). When the analyses were confined to all postmenopausal women twin pairs, the relationship between total cholesterol and birth weight was apparent after adjusting for age alone (Table 2). This relationship was also evident in MZ postmenopausal twin pairs. Although the relationship was not significant in postmenopausal DZ twins, the magnitude of the effect was similar to that observed in the MZ pairs.

LDL Cholesterol

The results for LDL cholesterol were similar to those for total cholesterol and indicated a significant inverse relationship

TABLE 5. Regression Analyses of Birth Weight and Triglyceride§

	Adjusted for	βc* β (per kg birth weight)	βc* (95% CI)	βw† β (per kg birth weight)	βw† (95% CI)	$β_B$‡ β (per kg birth weight)	$β_B$‡ (95% CI)
All twins	Age	−0.037	−0.06, −0.02	−0.038	−0.09, 0.01	−0.065	−0.10, −0.03
	Age, height	−0.047	−0.07, −0.03	−0.031	−0.09, 0.03	−0.086	−0.12, −0.05
	Age, BMI	−0.055	−0.07, −0.04	−0.053	−0.11, 0.00	−0.097	−0.13, −0.06
	Age, height, BMI	−0.058	−0.08, −0.04	−0.058	−0.11, 0.00	−0.100	−0.14, −0.06
All MZ twins	Age	−0.039	−0.07, −0.01	0.009	−0.09, 0.11	−0.064	−0.13, 0.01
	Age, height	−0.066	−0.11, −002	−0.035	−0.16, 0.09	−0.108	−0.19, −0.02
	Age, BMI	−0.053	−0.09, −0.01	−0.039	−0.16, 0.08	−0.089	−0.16, −0.12
	Age, height, BMI	−0.057	−0.10, −0.01	−0.057	−0.18, 0.06	−0.096	−0.17, −0.02
All DZ twins	Age	−0.032	−0.05, −0.01	−0.041	−0.10, 0.02	−0.058	−0.10, −0.02
	Age, height	−0.038	−0.06, −0.02	−0.023	−0.09, 0.04	−0.073	−0.12, −0.03
	Age, BMI	−0.052	−0.07, −0.03	−0.049	−0.11, 0.01	−0.092	−0.13, −0.05
	Age, height, BMI	−0.054	−0.08, −0.03	−0.053	−0.11, 0.01	−0.094	−0.14, −0.05
Postmenopausal twins	Age	−0.031	−0.07, 0.01	−0.056	−0.16, 0.05	−0.044	−0.12, 0.03
	Age, height	−0.057	−0.10, −0.01	−0.081	−0.21, 0.04	−0.101	−0.18, −0.02
	Age, BMI	−0.054	−0.10, −0.01	−0.091	−0.21, 0.03	−0.091	−0.17, −0.01
	Age, height, BMI	−0.055	−0.10, −0.01	−0.097	−0.22, 0.02	−0.095	−0.17, −0.02
Postmenopausal MZ twins	Age	−0.021	−0.08, 0.04	0.006	−0.19, 0.20	−0.028	−0.15, 0.09
	Age, height	−0.057	−0.14, 0.03	−0.079	−0.29, 0.13	−0.131	−0.30, 0.04
	Age, BMI	−0.039	−0.12, 0.04	−0.089	−0.29, 0.11	−0.833	−0.24, 0.07
	Age, height, BMI	−0.043	−0.12, 0.04	−0.081	−0.28, 0.12	−0.104	−0.27, 0.06
Postmenopausal DZ twins	Age	−0.034	−0.08, 0.02	−0.083	−0.21, 0.05	−0.052	−0.14, 0.04
	Age, height	−0.049	−0.10, 0.00	−0.072	−0.23, 0.08	−0.084	−0.18, 0.01
	Age, BMI	−0.052	−0.10, 0.00	−0.085	−0.23, 0.06	−0.084	−0.18, 0.01
	Age, height, BMI	−0.053	−0.10, −0.00	−0.096	−0.24, 0.05	−0.086	−0.18, 0.01

*Expected change in lipid (mmol/L) for 1-kg change in birth weight.
†Expected change in lipid (mmol/L) for 1-kg change in the difference between the birth weight and the twin−pair average birth weight value.
‡Expected change in lipid (mmol/L) for a 1-kg change in the twin-pair average birth weight.
§Ln transformed.

between LDL cholesterol and birth weight (0.06 mmol/L decrease in total cholesterol per 1-kg increase in birth weight), which was observed in the individual level regression. There were no significant differences in the magnitude of the relationship between MZ (−0.07 mmol/L) and DZ twins (−0.05 mmol/L). This relationship was also observed between, but not within twin pairs (Table 3). When the analyses were restricted to all postmenopausal women twin pairs, the relationship was similar to that observed for total cholesterol. (Table 3).

HDL Cholesterol

There were no significant relationships between HDL cholesterol and birth weight, and no significant differences in the magnitude of the relationship between MZ and DZ twins (Table 4).

Triglyceride

Results from the individual level regression analysis indicate a significant inverse relationship between triglyceride and birth weight and the magnitude of this effect did not differ between MZ and DZ twins (Table 5). In the models allowing estimation of within-pair and between-pair differences, triglyceride was negatively associated with birth weight between twin pairs only in all twins (Table 5). In postmenopausal women, significant relationships were only observed after adjustment for age alone.

Discussion

These data confirm associations between birth weight and subsequent total cholesterol levels that have already been observed in a number of studies in singletons.[4–6] In the present analysis we have shown that this association is mediated through between pair differences, rather than within pair differences. The similar size of the association in MZ and DZ twins indicates that genetic factors do not influence this relationship. In the group overall, we found a statistically significant inverse relationship between birth weight and total cholesterol levels (0.08 mmol/L per kg increase in birth weight), which remained after adjustment for height and

BMI. We found ≈2-fold larger effect size than has been reported in recent meta-analyses, which estimated a decrease ≈0.02 to 0.05 mmol/L per 1kg increase in birth weight, although the confidence intervals were wide, because of reduced power compared with the meta-analysis[4–6] However relationships of this size have been found, particularly in older female populations,[4] and higher effect sizes are generally found in older women.[4] The difference in effect size from the results found in meta-analyses may also reflect the impact in previous studies of various confounders (perhaps because of more diverse lifestyles of unrelated adults; or different parental influences) that may have obscured the true size of the association. While adjustment for most potential confounders may increase the size of the relationship, adjustment has also been shown to reduce the effect size in some female cohorts.[4] Our results also suggest a stronger relationship between birth weight and total cholesterol after the menopause, although the effect was attenuated after adjustment for BMI. This small difference in effect size in the unadjusted analyses may be due to small cyclic variations in lipid levels in premenopausal and perimenopausal women.[15,16]

This suggests that it is high postmenopausal BMI that is responsible for adverse lipid levels, rather than lack of estrogen after menopause and would indicate that postnatal change in size, rather than fetal growth, is important.[17]

We also found a significant relationship between birth weight and current LDL levels, as would be expected, given the association with total cholesterol. Our analysis has the advantage of being based on fasting lipid levels. While significant relationships have been consistently observed between birth weight and total cholesterol levels in other studies, relationships with other lipid levels have generally only been reported in large-scale studies in which fasting lipid levels have been collected.[7,18–20]

The use of the twin study design has allowed us uniquely to demonstrate that the associations between lipids levels and birth weight are mediated though a relationship with the mean birth weight of each pair and are not apparent in individual differences from the pair mean. This is consistent with the effect being related to factors in the uterine environment that are shared by the twins, for example, differences in the maternal hormone environment and other aspects of maternal health. As birth weight is a crude indicator of intrauterine nutrition, it would suggest that external confounding factors affecting maternal nutrition, such as socioeconomic status, smoking, alcohol, or exercise, rather then the processing of nutrients and in utero delivery of these is responsible. Our data also suggest that the relationship between birth weight and lipid levels is not mediated through genetic influences as a similar effect size in the relationship was found between MZ and DZ twins.

The potential underlying mechanism linking small birth size with adverse lipid levels in adult life remains unclear as shown by the influence on total cholesterol and LDL, but not HDL. Barker et al[21] observed that small abdominal circumference, representing small liver size, was associated with subsequent higher levels of total and LDL cholesterol. As the liver regulates lipid metabolism, impaired in utero growth of the liver may program more adverse levels of total and LDL cholesterol, whereas relationships with HDL and triglycerides may in theory be mediated through genetic factors that influence insulin resistance.[22] However, our results did not indicate such a genetic influence.

This is the only large-scale twin study to our knowledge to investigate the relationships between birth weight and subsequent lipid levels. Some common criticism of the twin design is that twins are not representative of the general population because they may have lower birth weights and lipid levels and intrauterine growth in twins may be different to that in singletons.[23,24] However in this study, while birth weights were lower than for comparable singletons, lipid levels were similar to comparable singleton populations,[13,14] including one female population of a similar age and sex distribution, drawn from the UK population.[25] Our results also indicate that the size of associations in our sample are comparable to those of singleton populations. We used recalled birth weights, rather than more accurate prospective measures, but this would mask any associations, rather than enhance them.[26]

Although we found statistically significant negative relationships between birth weight and total cholesterol and LDL, these relationships are of such a small size that they are unlikely to be of any clinical significance. It is estimated that realistically achievable increases in birth weight would only be associated with a reduction of only 0.005 mmol/L of total cholesterol, which would have a negligible effect on coronary heart disease risk.[27]

In conclusion, this study conducted in a large sample of female twins, drawn from a representative population, has shown significant relationships between birth weight and total and LDL cholesterol. Our results suggest that these associations are mediated through shared influences on the maternal environment such as socioeconomic status, smoking, alcohol, or exercise, and do not support the hypothesis that fetal malnutrition is an important determinant of adult lipid levels.

Sources of Funding

This work was supported in part by The Wellcome Trust and The Chronic Diseases Research Foundation.

Disclosures

None.

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