

FETAL ORIGINS OF ADULT HEALTH

Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature

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Background It has been suggested that there is a link between fetal growth and chronic diseases later in life. Several studies have shown a negative association between birthweight and cardiovascular diseases, as well as cardiovascular disease risk factors, such as blood pressure and type 2 diabetes. Far fewer studies have focused on the association between size at birth and blood lipid concentrations. We have conducted a qualitative assessment of the direction and consistency of the relationship between size at birth and blood lipid concentrations to see whether the suggested relationship between intrauterine growth and cardiovascular diseases is mediated by lipid metabolism.

Methods A literature search covering the period January 1966 to January 2003 was performed using Medline, Embase, and Web of Science. All papers written in English and reporting the relationship between size at birth and lipid levels in humans were assessed. Bibliographies were searched for further publications.

Results From an initial screen of 1198 references, 39 papers were included involving 28 578 individuals. There was no consistent relationship between size at birth and blood lipid levels; the one exception being triglyceride concentration, which showed statistically significant negative or U-shaped, but not positive, relationships with birthweight.

Conclusion This review does not strongly support a link between birthweight and blood lipid levels in later life. However, the research in this area is limited and in order to make any definitive conclusions, longitudinal studies with sufficient power, data, and prospective follow-up are needed.

Keywords Birthweight, birth length, fetal growth, total cholesterol, HDL, LDL, triglyceride, lipid, hyperlipidaemia, cardiovascular diseases

The influence of early life exposures on risk of cardiovascular diseases (CVD) was first suggested by Forsdahl, who demonstrated a geographical association between past living conditions

and current rates of coronary heart disease mortality¹ and cholesterol values² in Norway. Subsequently, the link between fetal growth and chronic diseases in later life has been investigated in

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numerous studies, and a negative association has been demonstrated between birthweight and risk of CVD,³⁻⁶ blood pressure,⁷⁻¹¹ and type 2 diabetes.^{8,12,13} It has been proposed that adverse conditions *in utero*, such as fetal under-nutrition, can result in metabolic and physiological 'programming' of functions of the body with lifelong effects on disease risk.¹⁴ This has been known as the fetal origins, or 'Barker', hypothesis.

The first study on the association between fetal growth and lipids after Forsdahl's observation was published in 1993,¹⁵ and it has been suggested that the link between fetal growth and CVD may operate via altered lipid metabolism.¹⁶⁻¹⁸ We have conducted a qualitative assessment of the direction and consistency of the relationship between birthweight and blood lipid concentrations in childhood, adolescence, and adulthood, based on a review of existing literature.

Methods

A literature search covering the period January 1966 to January 2003 was performed using Medline, Embase, and Web of Science. The following keywords were used; birth weight, birthweight, birth length, ponderal index, intrauterine growth retardation, fetal growth retardation, and abdominal circumference combined with cholesterol, triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), lipid, lipoprotein, hyperlipidemia, hyperlipidaemia, dyslipidemia, or dyslipidaemia. Traditional measures of size at birth were used, since there were no studies with information on ultrasound measures in pregnancy. The literature search yielded 1198 references. All papers written in English and reporting the relationship between size at birth and lipid levels in humans were assessed by reviewing the abstracts. Bibliographies of the included papers were searched for further publications. Papers were excluded if they reported solely on subjects with a pathological condition such as maternal hypertension during pregnancy or premature birth, or if lipid status was only studied neonatally. All forms of quantitative and qualitative analyses were included. Meta-analysis was not performed due

to the paucity of studies, lack of quantitative information, and inconsistencies in methodology.

Results

The main features of the studies are presented in Tables 1-4. Table 1 includes the number of studies on each lipid in children, adolescents, and adults. Table 2 summarizes the adjustments in the studies, and Table 4 presents the reported regression estimates. The main characteristics of the studies are presented in Table 3, including information on the study type, source of study subjects, source of birthweight, birth year, age at the time of lipid measurements, sample size, birthweight, confounding factors, outcomes considered, the direction of association with birthweight for the significant findings at the 5% level, and correlation coefficients.

A total of 39 papers were published between January 1966 and January 2003 describing, but not necessarily focusing on, the relationship between birthweight and lipid concentrations in later life including total cholesterol (TC), HDL, LDL, and TG. A majority of the studies included both males and females with the subjects' age ranging between 31 months¹⁹ and 84 years,¹⁷ and with year of birth ranging from 1900 to 1992. In total, the studies involved 28 578 individuals. Ten papers reported results in children aged 31 months-12 years, 4 in adolescents aged 13-17 years, and 25 in adults (≥ 18 years) (Table 1). Altogether 33 papers described the relationship between birthweight and TC, 29 papers the relationship between birthweight and HDL, 21 papers the relationship between birthweight and LDL, and 31 papers the relationship between birthweight and TG. The total number of study subjects ranged from 32²⁰ to 7206,²¹ but only six studies included more than 1000 participants.²¹⁻²⁶ A majority of the studies used a longitudinal study design with retrospective information on birth data; only nine^{19,20,23,27-32} of the studies had a prospective follow-up from birth. Adjustments for potential confounding factors varied (Tables 2 and 3), and only a few papers provided regression estimates (Table 4).

Table 1 Number of studies describing the association between birthweight and lipid values

	No. of studies			
	Total cholesterol	High density lipoprotein	Low density lipoprotein	Triglycerides
Age group				
Children (≤ 12 years)	8 ¹	6 ²	5 ³	7 ⁴
Adolescents (13-17 years)	4 ⁵	4 ⁶	3 ⁷	3 ⁸
Adults (≥ 18 years)	21 ⁹	19 ¹⁰	13 ¹¹	21 ¹²
Total No. of studies	33	29	21	31

References:

¹ 19, 20, 23, 25, 27, 29, 37, 45.

² 19, 20, 23, 29, 37, 50.

³ 19, 20, 23, 29, 37.

⁴ 19, 20, 23, 29, 31, 37, 50.

⁵ 38, 39, 42, 43.

⁶ 38, 39, 42, 43.

⁷ 38, 39, 43.

⁸ 38, 39, 43.

⁹ 15, 16, 18, 21, 24, 26, 28, 30, 32, 34-36, 40, 41, 44, 46-49, 55, 63.

¹⁰ 15-18, 21, 22, 24, 28, 30, 32, 34, 35, 41, 47-49, 51, 55, 63.

¹¹ 15, 16, 18, 28, 30, 32, 34, 35, 46, 48, 49, 55, 63.

¹² 15-18, 21, 22, 24, 28, 30, 32, 34, 36, 41, 44, 47-49, 51, 52, 55, 63.

Table 2 Factors adjusted for in the analyses

	Number of studies adjusting for the factors		
	Children	Adolescents	Adults
Potential confounding factor			
Gestational age	–	–	4
Current weight/BMI ^a	5	2	15
Current waist circumference	–	–	4
Current fat mass/Total body fat %/Skinfold thickness	3	–	1
Current height	3	1	–
Socioeconomic parameter ^b	1	–	4
Race/Ethnic origin	2	–	1
Smoking	–	–	2
Alcohol consumption	–	–	2
Breastfeeding	1	–	–
Hereditary for myocardial infarct or stroke	–	–	1
Combination of potential confounding factors			
Gestational age, weight	–	–	1
Age, weight/BMI	1	–	1
Sex, BMI/log sum of skinfolds	1	–	2
Age, sex, current size ^c	4	1	3
Age, sex, weight/BMI social class	1	–	–
Age, BMI, smoking/Alcohol	–	–	2

^a Body mass index.

^b Social class, education or rural/urban residence.

^c Weight/BMI/waist circumference/total body fat %/log sum of skinfolds.

Adjusting for current size has been noted to affect the association between birthweight and blood pressure,³³ and for this reason the following results are presented separating unadjusted analyses and analyses adjusted for current size. Table 5 presents the number and proportion of the reviewed studies supporting the fetal origins hypothesis when unadjusted and adjusted for current size.

Total cholesterol

Unadjusted analyses

Nine papers^{21,25,34–40} described the relationship between birthweight and TC as a quantitative difference in mean TC between birthweight categories. Two of these reported a statistically significant negative association in adults.^{21,35} Other unadjusted analyses^{15,19,20,23,26,27,30,39,41–44} (e.g. those reporting regression or correlation coefficients) showed a statistically significant negative^{41,44} and positive⁴¹ relationship in adults, and a negative relationship in adolescents.⁴²

Analyses adjusted for current size

Altogether 18 papers described the relationship between birthweight and TC adjusting for current size; either weight,^{26,28,37,45} body mass index (BMI),^{16,18,19,21,29,40,41,44,46–49} skinfold thickness,²⁵ or waist circumference.³⁴ Three of these reported a statistically significant negative association in adults,^{26,40,44} while one study reported a positive association.⁴⁶ Both statistically significant positive¹⁹ and negative³⁷ relationships were also reported in children.

The strength of the association

Regression estimates for TC (mmol/l for each 1-kg higher birthweight), both negative^{26,37,40,41,44} and positive,^{19,46} were reported in seven of the reviewed studies (Table 4). The statistically significant negative estimates in males varied between -0.16^{44} and -0.25^{40} and there was 5.3% lower TC for every 1-kg higher birthweight in children (boys and girls analysed together).³⁷ Only one

study²⁶ reported a statistically significant negative estimate (-0.09) in women. Statistically significant positive estimates were also reported, in boys (0.25)¹⁹ and girls (0.30),¹⁹ and in men (0.95).⁴⁶

High density lipoprotein

Unadjusted analyses

Seven papers^{21,34,35,37–39,50} described the relationship between birthweight and HDL as a quantitative difference in mean HDL between birthweight categories, and both statistically significant negative³⁹ and positive⁵⁰ associations were reported in children. Of the other unadjusted analyses^{19,22,23,30,39,41–43} one showed a statistically significant negative relationship between birthweight and HDL in boys.¹⁹

Analyses adjusted for current size

Altogether 14 papers described the relationship between birthweight and HDL adjusting for current size; either weight,^{28,37,43} BMI^{16–19,22,29,47–49,51} or waist circumference.^{17,34} A statistically significant negative association was reported in children.¹⁹ Four studies^{16–18,51} reported a statistically significant positive relationship in adults.

The strength of the association

Regression estimates for HDL (mmol/l for each 1-kg higher birthweight), both negative and positive, were reported by one of the reviewed studies¹⁹ (Table 4). Statistically significant associations were all negative, and were found in 43-month-old boys, so that there was 0.079 mmol/l lower HDL for each 1-kg higher birthweight adjusting for height and BMI, and 0.093 mmol/l lower HDL adjusting for height, BMI, waist circumference:arm circumference, and breastfeeding history. Furthermore, the risk of an unfavourable HDL (≤ 1.4 mmol/l) level in women who were in the lowest birthweight tertile was 1.96 compared with those in the highest tertile adjusting for BMI, and 2.29 adjusting for waist circumference.¹⁷

Table 3 Summary of the literature on the association between birthweight and blood lipid concentrations in the reviewed studies (by first author, country, and publishing year). (See footnote for abbreviations; superscript numbers refer to table footnotes, not to references)

Study type	Source of study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Outcome	Direction of the association between birthweight and outcome	Regression estimates (β) and correlation coefficients (r)
Antal (38) Hungary 1998 CC	High school students from Budapest and throughout the country	NA	NA	14–16	LBW*: M 37, F 42 ABW: M 71, F 51	LBW*: M 1852 F 1884 ABW: NA	None	TC, HDL, LDL, TG	LDL in LBW* boys Lower than on ABW boys	
Barker (15) UK 1993 FR	Born at Jessop Maternity Hospital, Sheffield	Record	1939–1940	50–53	219 MF	M 3282 F 3202	GA	TC, HDL, LDL, TG	n.s.	
Baydekar (37) India 1999 FR	Born at King Edward Memorial Hospital, India	Record	1987–1989	8–9	477 MF	F 2700 M 2800	(BW in 7 categ. in 1.–3.) 1. None 2. Age, sex, weight 3. As above (2.) + social class 4. Age, sex, height, fat mass 5. All above, $n = 190^2$	1. TC, HDL, LDL, TG 2. TC, HDL, LDL, TG 3. TC, LDL 4. TC, TG 5. TC, HDL, LDL, TG	1. –LDL 2. –TC, –LDL 3. –TC, –LDL 4. –TC 5. n.s.	4. β see Table 4
Bergström (43) Sweden 1995 XSR	Students in Umeå, Sweden	Record	NA	14, 17	M 477 F 402	M 3600 F 3400	1. None 2. Weight	1. TC, HDL, LDL, TG 2. HDL	1. M: –HDL 2. n.s.	1. $r = -0.11$, $P = 0.024$ 2. $r = -0.08$, $P = 0.11$
Boulton (29) Australia 1999 FP	Adelaide Nutrition Study	Record	NA	8	128	NA	BMI	TC, HDL, LDL, TG	n.s.	
Byberg (51) Sweden 2000 FR	Uppsala Longitudinal study of Adult Men	Record	1920–1924	70	M 734	3600	(BW in 4 categ. in 1.–4.) 1. Age, lipid-lowering medication (LLM) 2. Age, BMI, LLM 3. As above (2.), men born at Academic Hospital ($n = 326$) 4. As above (3.), term births ($n = 282$)	1. HDL, TG 2. HDL, TG 3. HDL 4. HDL	1. n.s. 2. n.s. 3. +HDL 4. ns	
Clausen (34) Denmark 1997 FR	Part of a cohort of young Danish individuals	Record	1961–1973	18–32	M 162 F 169	NA	1. None (BW in 5 categ.) 2. Age, sex, WC	1. TC, HDL, LDL, TG 2. TC, HDL, LDL, TG	1. M, F n.s. 2. –TG	2. β see Table 4
Cowin (19) UK 2000 FP	ALSPAC study	Record	1991–1992	31 m	385 MF	NA	1. None 2. Height, BMI 3. Height, BMI, WC, AC, breastfeeding history 4. As above (3.) + maternal BMI	TC, HDL, LDL, TG	1. n.s. 2. n.s. 3. n.s. 4. n.s.	1.–3. β see Table 4

Table 3 continued

Study type	Source of study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Outcome	Direction of the association between birthweight and outcome	Regression estimates (β) and correlation and coefficients (r)
									- significant ^a	+ significant ^a
			1991-1992	43 m	470 MF	NA	1. None 2. Height, BMI 3. Height, BMI, WC:AC, breastfeeding history 4. As above (3.) + maternal BMI	1. TC, HDL, LDL, TG 2. TC, HDL, LDL, TG 3. TC, HDL, LDL, TG 4. TC	1. M: -HDL 2. M: -HDL 3. M: -HDL 4. M: +TC, F: +TC	1.-4. β see Table 4
Decsi (20) Hungary 1999	Born at the Neonatal Intensive Care Unit, University Medical School of Pecs	Record	1986-1987	10	SGA 16 Preterm 16	SGA 2112 Preterm 2125	None	TC, HDL, LDL, TG	No difference between SGA and preterm children	
Donker (23) USA 1997	Participants in the Bogalusa Heart Study	Record	1973-1981	7-11	1411 MF WB 464, BB 266, WG 396, BG 285	3291	1. None 2. None (BW in 5 categ.) 3. Age, Quetelet index ³ 4. Age, race, sex, Quetelet index ³	1. TC, HDL, LDL, TG 2. TG 3. TG 4. TG	1. n.s. 2. WB, BB, WG: U-shaped ^b 3. WB: -TG 4. n.s.	1. TC: WB $r = -0.016$, BB $r = 0.2$, WG $r = -0.009$, BG $r = -0.028$, LDL: WB $r = 0.122$, BB $r = 0.157$, WG $r = 0.190$, BG $r = -0.030$. HDL: WB $r = -0.019$, BB $r = 0.103$, WG $r = 0.008$, BG $r = -0.024$. TG: WB $r = -0.091$, BB $r = 0.114$, WG, $r = -0.030$, BG $r = 0.015$. 3. β see Table 4
Eriksson (49) Finland 2002	Born at Helsinki University Hospital	Record	1924-1933	~69	M 176 F 298	M 3452 F 3297	Age, sex, BMI	TC, HDL, LDL, TG	n.s.	
Fall (46) UK 1992	Men born in Hertfordshire	Record	1920-1930	59-70	485 M	NA	1. Not weaned at age 1 ($n = 91$), weight at 1 year 2. Not weaned at age 1, BMI/WC	1. TC, LDL 2. TC	1. +TC, +LDL 2. +TC ^b	1. β see Table 4

Table 3 continued

Study type	Study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Direction of the association between birthweight and outcome		Regression estimates (β) and correlation coefficients (r)
								Outcome	- significant ^a negative + significant ^a positive	
Fall (16) UK 1995	FR	Women born in Hertfordshire	1923-1930	60-71	297 F	3450 (7.6 lb)	1. BMI (BW in 6 categ.) 2. BMI, Alc, social class	1. -2. TC, HDL, LDL, TG	1. +HDL 2. +HDL	
Forrester (45) Jamaica 1996	FR	Born at the University Hospital of the West Indies	NA	6-10	610 MF	M 3178 F 3077	Age, sex, weight	TC	n.s.	
Forsen (27) Finland 1998	FP	Born in a rural county of eastern Finland	1981-1982	7	215 MF	NA	None	TC	n.s.	
Frankel (24) UK 1996	FR	The Caerphilly Study	1920-1938	45-59	1258 M	NA	Age (BW in quartiles)	TC, HDL, TG	-TG	
Garnett (31) Australia 2001	FP	Born at Nepean Hospital, Sydney	1989-1990	7-8	M 118 F 137	3470 MF	1. Age, sex (BW SDS) 2. Age, sex, total body fat % (BW SDS)	1.-2. TG	1.-2. n.s.	1. $r = 0.042$ 2. $r = 0.036$
Hoy (36) Australia 1999	XSR	Participants of a health screen	1956-1976	20-38	317 MF	2712	None	TC, TG	No differences between LWB and NBW group	
Hulman (28) USA 1998	FP	Offspring of women enrolled in the PPCP	1959-1965	28	137 MF	M 3190 F 3020	Height, weight, triceps and subscapular skinfold thickness, circumference of hip, waist, chest and arms	TC, HDL, LDL, TG	n.s.	
Kawabe (42) Japan 1999	XSR	High school students	NA	15-16	M 98 F 80	M 3312 F 3211	None	TC, HDL	M: -TC, F: -TC	TC: M $r = -0.241$ ($P < 0.05$) F $r = -0.351$ ($P < 0.01$)
Kolacek (63) Croatia 1993	FR	Cohort of healthy children	1965-1969	M:19.9 F:19.6	M 89 F 103	NA	NA	TC, HDL, LDL, TG	n.s.	
Leger (47) France 1997	FR	Selected from a population based registry of Haguenau	1971-1978	20.6	SGA*: 236 MF AGA: 281 MF	SGA 2550 AGA 3410	BMI	TC, HDL, TG	No difference between SGA and AGA group	

Table 3 continued

Study type	Source of study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Outcome	Direction of the association between birthweight and outcome	Regression estimates (β) and correlation coefficients (r)
									- significant ^a + significant ^a	negative positive
Levitt (30) South Africa 2000	Born at the Groote Schuur Hospital	Record	1975-1976	20	UFA: M 38, F 53 AGA: M 25, F 39	UFA 2350 AFA 3050	None	TC, HDL, LDL, TG	1. No differences between AFA and UFA group	
Li (50) USA 2001	Part of a longitudinal study	Recall	NA	4-14	White 86 A-A 53 LBW 29 NBW 110	LBW 1950 NBW 3600	1. None 2. None, A-A only	1. HDL, TG 2. HDL	1. No difference between LBW and NBW group 2. HDL lower in LBW than in NBW	
Lithell (22) Sweden 1996	Uppsala Longitudinal study of Adult Men	Record	1920-1924	50	1333 M	NA	1. None 2. BMI 3. None, by thirds of BMI	1.-3. HDL, TG	1. n.s. 2. -TG 3. n.s.	1. HDL: $r = -0.02$ TG: $r = -0.012$ 2. HDL: $r = 0.005$, TG $r = -0.056$ ($P = 0.04$)
Martyn (35) UK 1998	Born at the maternity hospital in Sheffield	Record	1922-1926	66-71	186 MF	NA	None (BW in 3 categ.)	TC, HDL, LDL	-TC	
Mi (18) China 2000	The Peking Union Medical College Hospital	Record	1948-1954	M:45.1 F:45.2	M 309 F 318	M 3196 F 3094	1. Sex, BMI (BW in 4 categ.) 2. As above (1.) + GA	1.-2. TC, HDL, LDL, TG	1. -TG, +HDL 2. -TG, +HDL	
Miura (26) Japan 2001	Ishikawa Prefecture	Record	1965-1974	20	M 2198 F 2428	M 3150 F 3100	1. None 2. Weight, GA 3. Weight, GA, % increase in height ages 3-20	1.-3. TC	1. n.s. 2. M: -TC, F: -TC 3. M: -TC, F: -TC	1. M $r = -0.03$ ($P = 0.22$) F $r = -0.02$ ($P = 0.25$) 2.-3. β see Table 4
Mogren (21) Sweden 2001	Sample of Västerbotten Intervention Program	Record	1955-1966	29-41	NBW: M 1049-3656 ⁶ F 892-3641 ⁷ LBW: M 34-118 ⁸ F 33-151 ⁹	NA	1.-3. None 4. Education 5. Age 6. BMI 7. Pre-eclampsia or hypertension during pregnancy 8. Heredity for myocardial infarct or stroke 9. All in 4.-8.	1. TC, HDL, TG 2. TC ≥ 7.8 (yes/no) 3. TC ≥ 6.5 (yes/no) 4.-9. TC ≥ 7.8 (yes/no) 4.-9. TC ≥ 6.5 (yes/no)	1. M:TC higher in LBW than in NBW. F:TC higher in LBW than in NBW 2.-9. M,F: No difference between LBW and NBW group	

Table 3 continued

Study type	Source of study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Outcome	Direction of the association between birthweight and outcome	Regression estimates (β) and correlation coefficients (r)
									- significant ^a negative	+ significant ^a positive
Monley (39) UK 2000 XSR	Children from comprehensive schools	Record	NA	M:13.6 F:13.7	M 210 F 212	M 3366 F 3213	1. None (BW in 3 categ.) 2. None 3. Weight, age, sex (+ also height, BMI, or log weight) 4. None	1. TC, HDL, LDL, TG 2. TC, HDL, LDL, TG 3. TG 4. TC, HDL, LDL, TG	1. -TG 2. -TG 3. -TG 4. HDL higher in LBW than in NBW group	2, -3. β see Table 4
Phillips (52) UK 1995 FR	Born at Sharoe Green Hospital	Record	1935-1943	47-56	103 MF	NA	None	TG	n.s.	n.s.
Rona (25) UK 1996 XS	The National Study of health and growth	Recall ¹⁰	1983-1984	9	1071 MF	NA	(BW in 5 categ. ¹¹ in 1,-2.) 1. None 2. Log sum of skinfolds, height, sex, ethnic origin, No. of children in the family	1.-2. TC	1. n.s. 2. n.s.	
Roseboom (48) The Netherlands 2000 FR	Born at Wilhelmina Gasthuis in Amsterdam	Record	1944-1946	50	704 MF	3350	1. Sex 2. Sex, BMI	1.-2. TC, HDL, LDL, TG	1. n.s. 2. -TG	
Stein (32) Guatemala 2002 FP	Sample of the supplementation study by INCAP in 4 villages	Record	1969-1976	19.4-29.5	M 187 F 198	M 3140 F 3050	GA, age, supplement type offered, rural/urban residence (BW in tertiles)	TC, HDL, LDL, TG	M,F: n.s.	
Suzuki (44) Japan 2000 XSR	Students of Dokkyo University School of Medicine	Record	1967-1979	M:22.5 F:22.2	M 207 F 92	M 3219 F 3191	1. None 2. Age, BMI, smoking	1.-2. TC, TG	1. M: -TC, -TG 2. M: -TC, -TG	1. TC $r = -0.14$ ($P < 0.05$), TG $r = -0.15$ ($P < 0.05$) 2. β see Table 4
Valdez (55) USA 1994 FR	San Antonio Heart Study	Record	1949-1963	25-64	M:185 F:228 M:66 F:62	M:3400 F:3230 M:3460 F:3330	(BW in tertiles in 1,-2.) 1. Age 2. Age, sex, ethnicity	1.-2. TC, HDL, LDL, TG	1. NHW M: -TG 2. n.s.	
Vestbo (41) Denmark 1996 XSR	Children of study subjects in diabetes study	Record	NA	48 ¹²	620 MF	M 3150-4100 F 3113-3850	1. Sons of diabetic patients 2. Sons of non-diabetic parents	1.-4. TC, HDL, TG 5. TC	1. +TC 2. -TC	1. TC: $r = 0.17$ ($P < 0.05$), 2. -TC

Table 3 continued

Study type	Source of study subjects	Source of birth-weight	Year born	Age ¹	Sample size	Birth-weight (g)	Confounding factors adjusted for in the analysis	Outcome	Direction of the association between birthweight and outcome	Regression estimates (β) and correlation coefficients (r)
Yarbrough (17) USA 1998										
FR	Middle to upper-class	Recall ¹³	1900–1937	50–84	303	1135–5900	(BW in tertiles in 1.–6.)	1. HDL, TG 2. HDL \leq 1.4, TG \geq 2.3	3. n.s.	HDL: $r = -0.01$, TG: $r = 0.11$
	women in Rancho Bernardo	& Record			F		1. Age 2. Age		4. n.s.	2. TC: $r = -0.20$ ($P < 0.05$),
							3. Age, BMI 4. Age, WC 5. Age, BMI 6. Age, WC		5. n.s.	HDL: $r = -0.11$, TG: $r = -0.02$
										3. TC: $r = 0.05$, HDL: $r = -0.05$, TG: $r = -0.02$
										4. TC: $r = -0.03$, HDL: $r = 0.02$, TG: $r = -0.03$
										5. β see Table 4
Ziegler (40) Denmark 2000										
XSR	The Ebeltoft Health Promotion Project	Record	NA	31–51	M 265 F 280	M 3635 F 3436	(BW in quartiles in 1.–2.)	1. HDL, TG 2. HDL \leq 1.4, TG \geq 2.3 (yes/no) 3. HDL, TG 4. HDL, TG 5. HDL \leq 1.4, TG \geq 2.3 (yes/no) 6. HDL \leq 1.4, TG \geq 2.3 (yes/no)	1. n.s. 2. +HDL 3. n.s. ¹⁴ 4. -TG, +HDL ¹⁴ 5. TG: OR 2.04 ¹⁴ (1.04–4.00) HDL: OR 1.96 ¹⁴ (1.26–3.05) 6. TG: OR 2.37 ¹⁴ (1.19–4.73) HDL: OR 2.29 ¹⁴ (1.43–3.65)	1. n.s. 2. β see Table 4

^a Statistically significant (based on 95% CI, or $P < 0.05$).

^b Neither P -value nor 95% CI reported.

Abbreviations: **A-A** = African-American, **ABW** = Appropriate BW (BW >2500 g), **AGA** = Appropriate for gestational age (BW between the 25th and 75th centile), **Alc** = Alcohol consumption, **BB** = Black boys, **BG** = Black girls, **BMI** = Current body mass index, **BW** = Birthweight, **categ** = Category, **CC** = Case-control study, **F** = Females, **FP** = Follow-up from birth, **FR** = Follow-up, birthweight retrospective, **GA** = Gestational age, **HDL** = High density lipoprotein concentration, **INCAP** = Institute of Nutrition of Central America and Panama, **LBW*** = Low BW (BW <2500 g), **LBW*** = Low BW (\leq 2500 g), **LDL** = Low density lipoprotein concentration, **m** = Months, **M** = Males, **MA** = Mexican Americans, **MI** = Myocardial infarction, **NA** = Not available, **NBW** = BW \geq 2500 g, **NHW** = Non-Hispanic white, **n.s.** = Not statistically significant association, **OR** = Odds ratio, **PPCP** = Philadelphia Perinatal Collaborative Project, **SDS** = Standard deviation score, **SGA** = Small for gestational age (BW <10th centile), **SGA*** = Small for gestational age (BW or birth length <3rd centile), **TC** = Total cholesterol concentration, **TG** = Triglyceride concentration, **UFA** = Underweight for gestational age (BW \leq 10th percentile), **WB** = White boys, **WC** = Waist circumference, **WC:AC** = Waist circumference:Arm circumference, **WG** = White girls, **XSR** = Cross-sectional, birthweight retrospective.

Please note that the following key refers to footnotes numbered 1–14 in the table, and not to the references in this paper.

¹Age at the time of lipid measurements. ²Children who took part in an earlier study at age 4. ³Weight (kg)/height (m)². ⁴Maternal and female relative recall. ⁵Maternal recall. ⁶TC 3656, HDL 1049, TG 2380, ⁷TC 3641, HDL 892, TG 3051, ⁸TC 118, HDL 34, TG 74, ⁹TC 151, HDL 33, TG 126, ¹⁰parental recall. ¹¹The highest category as a reference. ¹²Median. ¹³Self recall. ¹⁴Compares the lowest BW tertile with the highest.

Table 4 Reported regression estimates (β , mmol/l if not otherwise stated) for each 1-kg higher birthweight and 95% CI or standard error (SE) in children (≤ 12 years), adolescents (13–17 years), and adults (≥ 18 years). Statistically significant findings in italics; superscript numbers refer to table footnotes, not to references

Age group	Males		Females		Males and females	
	β	SE or 95% CI	β	SE or 95% CI	β	SE or 95% CI
Total cholesterol						
Children	+0.253 ^{*1}	–	+0.302 ^{*1}	–	–5.3% ^{**2}	–8.6%, –1.2%
Adolescents	–	–	–	–	–	–
Adults	+0.95 ^{***3}	–	–0.09 ^{*8}	–0.16, –0.02	–5.2 (10 ^{–5}) ¹⁰	8.1(10 ^{–5})
	–0.18 ^{***4}	–0.25, –0.09	–0.09 ^{*9}	–0.16, 0.00	–	–
	–0.16 ^{***5}	–0.23, –0.07	–0.09 ⁷	–0.30, 0.12	–	–
	–0.16 ^{*6}	–	–	–	–	–
	–0.25 ^{*7}	–0.47, –0.02	–	–	–	–
High density lipoprotein						
Children	–0.051 ¹¹	0.03	+0.044 ¹¹	0.04	–	–
	–0.047 ¹²	0.03	+0.011 ¹²	0.04	–	–
	–0.05 ¹³	0.03	+0.023 ¹³	0.04	–	–
	–0.073 ^{*11}	0.03	+0.036 ¹¹	0.04	–	–
	–0.079 ^{*12}	0.03	+0.028 ¹²	0.04	–	–
	–0.093 ^{**13}	0.03	+0.022 ¹³	0.04	–	–
Adolescents	–	–	–	–	–	–
Adults	–	–	–	–	–	–
Low density lipoprotein						
Children	–0.14 ¹¹	0.08	–0.058 ¹¹	0.15	–	–
	–0.06 ¹²	0.09	–0.11 ¹²	0.16	–	–
	–0.066 ¹³	0.09	–0.092 ¹³	0.16	–	–
	+0.052 ¹¹	0.10	+0.15 ¹¹	0.14	–	–
	+0.096 ¹²	0.10	+0.18 ¹²	0.14	–	–
	+0.13 ¹³	0.11	+0.25 ¹³	0.15	–	–
Adolescents	–	–	–	–	–	–
Adults	+0.86 ^{*3}	–	–	–	–	–
Triglyceride						
Children	+1% ¹¹	–8%, 12%	–6% ¹¹	–18%, 8%	–4.1% ²	–12.2, 4.7
	–2% ¹²	–13%, 11%	–3% ¹²	–15%, 11%	–16.55 ^{†15}	11.00
	–3% ¹³	–14%, 9%	–5% ¹³	–19%, 11%	–	–
	+8% ¹¹	–4%, 21%	+4% ¹¹	–11%, 21%	–	–
	+7% ¹²	–7%, 23%	+8% ¹²	–8%, 26%	–	–
	+8% ¹³	–6%, 24%	+12% ¹³	–6%, 33%	–	–
	–46.77 ^{*†14}	23.77	–28.33 ^{†14}	20.54	–	–
	+11.91 ^{†14}	17.15	+23.09 ^{†14}	23.33	–	–
Adolescents	–0.12 ^{*16}	–0.21, –0.03	–0.10 ^{*16}	–0.20, –0.006	–0.11 ^{**17}	–0.18, –0.047
Adults	–0.15 ^{*6}	–	–	–	–10% ¹⁸	–18%, –2%

* Statistical significance inferred from 95% CI or reported $P < 0.05$, **reported $P < 0.01$, ***reported $P < 0.001$

† mg/dl

Adjustments, reference number in brackets:

¹ Height, body mass index, waist circumference: Arm circumference, breastfeeding history, maternal body mass index, $P = 0.033$ (19)

² Age, sex, height and fat mass (37)

³ Weight at 1 year. Converted from: +0.43 mmol/l for each 1-lb higher birthweight (46)

⁴ Weight, gestational age. Calculated from mmol/l for each 1 SD higher birthweight (26)

⁵ Weight, gestational age, % increase in height ages 3–20. Calculated from mmol/l for each 1 SD higher birth weight (26)

⁶ Age, body mass index, smoking (44)

⁷ Age, smoking, body mass index, alcohol consumption (40)

⁸ Weight, gestational age. Calculated from mmol/l for each 1 SD higher birthweight (26)

⁹ Weight, gestational age, % increase in height from age 3 to 20. Calculated from mmol/l for each 1 SD higher birthweight (26)

¹⁰ Age, sex, body mass index, parental diabetes, parental sex (41)

¹¹ Unadjusted (19)

¹² Height, body mass index (19)

¹³ Height, body mass index, waist circumference: Arm circumference, breastfeeding history (19)

¹⁴ Unadjusted (23)

¹⁵ Race, sex (23)

¹⁶ Age, weight (also height, body mass index, or log weight) (39)

¹⁷ Unadjusted (39)

¹⁸ Age, sex, waist circumference (34)

Low density lipoprotein

Unadjusted analyses

Five papers^{34,35,37–39} described the relationship between birthweight and LDL as a quantitative difference in mean LDL between

birthweight categories. One of these reported a statistically significant negative association in children,³⁷ while one showed a statistically significant positive association in adolescents.³⁸

Table 5 Number and proportion of the reviewed studies supporting the fetal origins hypothesis when unadjusted and adjusted for current size

Lipid	Adjustment for current size ^a	Total No. of studies	% of studies supporting the fetal origins hypothesis
Total cholesterol	No	23	17%
	Yes ^b	18	22%
High density lipoprotein	No	21	10%
	Yes	14	29%
Low density lipoprotein	No	14	7%
	Yes	9	11%
Triglyceride	No	25	20%
	Yes	18	44%

^a BMI, weight, waist circumference, skinfold thickness or total body fat %.

^b One study (41) showed both negative and positive associations with birth weight and was excluded.

Analyses adjusted for current size

Nine papers described the relationship between birthweight and LDL adjusting for current size; either weight,^{28,37} BMI,^{16,18,19,29,48,49} or waist circumference.³⁴ A statistically significant negative association in children was reported by one paper.³⁷

The strength of the association

Regression estimates for LDL (mmol/l for each 1-kg higher birthweight), both negative¹⁹ and positive,⁴⁶ were reported in two of the reviewed studies (Table 4). A statistically significant positive association was shown in men, with 0.86 mmol/l higher LDL for every 1-kg higher birthweight (converted from pounds) adjusting for weight at 1 year of age.

Triglycerides

Unadjusted analyses

Eight papers^{21,23,34,36–39,50} described the relationship between birthweight and TG as a quantitative difference in mean TG between birthweight categories. Two of these reported a statistically significant negative association, in adolescents³⁹ and adults,²¹ and one showed a U-shaped association in children.²³ Of the other unadjusted analyses,^{19–22,30,39,41,43,44,52} one reported a statistically significant negative association in adolescents,³⁹ and one in adults.⁴⁴

Analyses adjusted for current size

Altogether 17 papers described the relationship between birthweight and TG adjusting for current size; either weight,^{28,37,39} BMI,^{16–19,22,23,29,44,47–49,51} waist circumference,^{17,34} or total body fat %.³¹ A statistically significant negative association was reported in children,²³ adolescents,³⁹ and adults.^{18,22,34,44,48}

Strength of the association

Regression estimates for TG, either positive^{19,23} or negative,^{19,23,34,37,39,44} were reported in six of the reviewed studies (Table 4). All the statistically significant associations were negative. One of them³⁴ showed 10% lower TG for every 1-kg higher birthweight. The two other studies reported 0.15 mmol/l⁴⁴ and 0.12 mmol/l³⁹ lower TG in males, and 0.10 mmol/l lower TG in females³⁹ for every 1-kg higher birthweight. Furthermore, the risk of an unfavourable TG level (≥ 2.3 mmol/l) in women who were in the lowest birthweight tertile was 2.04 compared with those in the highest tertile adjusting for BMI, and 2.37 adjusting for waist circumference.¹⁷

Other measures of size at birth

Some studies considered other measures of size at birth than birthweight, such as birth length and ponderal index (birthweight/length³), a measure of thinness. The association between birth length and blood lipids was described in five studies,^{15,29,40,43,45} one of which reported a statistically significant negative association with TC in men, with and without adjusting for age, BMI, smoking, and alcohol.⁴⁰ A negative association was also reported between birth length and HDL in boys, but this disappeared after adjusting for current weight and height.⁴³ In addition, TC and LDL were noted to be higher in adults who were short at birth, but the trend was not significant in a simultaneous analysis with abdominal circumference.¹⁵ The association between ponderal index and lipids was described in eight studies,^{22,27–29,34,40,48,52} one of which reported a positive association with TC and HDL in adults, with and without adjusting for BMI.⁴⁸ Another study reported a negative association with TC and LDL, and a positive association with HDL in children adjusting for BMI.²⁹

Discussion

This overview, based on the limited data so far published does not provide strong evidence of a consistent relationship between birthweight, or any other measure of size at birth, and blood lipid concentrations. One possible exception is TG, which showed statistically significant negative or U-shaped, but not a positive association with birthweight. A majority of the published studies were based on only a small number of study subjects. However, the largest studies in terms of statistical power,^{22,24–26} or studies with representative data,^{18,19,21,37} do not give strong support to the hypothesis either. Overall, the existing literature showed no pattern in the results in terms of age, sex, generation, or any other aspect in the study subjects, possibly due to the sparse and varying information available.

The inconsistencies in the results between the studies may be due to several reasons, such as varying power or differences in the study populations in terms of age, sex, and ethnic or genetic background. The association between birthweight and blood pressure has been noted to amplify with age,⁵³ which may also be the case with lipids, although this was not apparent among the studies reviewed. In addition, lipid levels change with age, remaining relatively stable until the onset of puberty, but increasing after puberty,⁵⁴ which may obscure the results in adolescents. It is also possible that the associations are stronger in older generations, although again this was not apparent in the studies reviewed. The different findings in males and females^{19,40,43} may be due to the difference in the relationship between current body weight and lipids, as has been suggested.⁴² The differences noted in the reviewed studies between races^{23,55} may be due to an interaction between genes/ethnicity and birthweight, as has been suggested⁵⁶ and recently reported in terms of insulin metabolism.^{50,57}

Furthermore, adjustment for possible confounding factors varied to a great extent and was often incomplete (Tables 2 and 3), and this may have affected the results. Socioeconomic status, both in early and adult life, is associated with CVD risk,⁵⁸ but was controlled for in three studies^{16,21,37} only, although it was otherwise taken into account (e.g. in the study design) in 11 studies.^{16–19,32,35,38,39,42,45,46} Although the noted

associations^{16,37} were reported to be independent of social status, it remains unclear whether the associations are confounded in other populations, or in subjects of different age, sex, or generation. In addition, gestational age, which is known to be positively correlated with birthweight,^{59,60} was adjusted for^{15,18,26,32} or otherwise taken into account^{20,47,51} in only a few studies. Reported associations between birthweight and TC²⁶ and TG¹⁸ were independent of gestational age, but the magnitude of the reported association between birthweight and HDL decreased when adjusted for gestational age¹⁸ and there is no information about LDL.

Adjustment for current size was done in most of the studies. However, current size may act as an intermediate rather than a confounding factor, which makes interpretation of the results complex. In studies on the relationship between birthweight and blood pressure, adjustment for current size has been noted to lead to twice as large a negative association as without adjustment.³³ An increase in the magnitude of the association when adjusted for current size was noted in five of the reviewed studies,^{23,26,34,37,40} and in general the studies adjusting for current size tended to give relatively more support for the hypothesis compared with the unadjusted studies (Table 5). In addition, an interaction between the effects of birthweight and current size is possible, but not confirmed in any of the studies which examined this.^{22,37,39} A few studies have reported that those who were small at birth, but who belong to the upper end of the bodyweight distribution in later life, possibly owing to an affluent lifestyle, are more prone to unfavourable lipid levels^{23,37} and cardiovascular risk factor profile^{11,16,17,32,37} than those who were small at birth, but not overweight in later life, thus agreeing with Forsdahl's hypothesis. This also corresponds with the findings of accelerated catch-up growth and its relation to increased risk of high blood pressure,¹¹ diabetes,⁶¹ and death from CVD.⁶² So far, there is little information about the influence of catch-up growth on lipids, but it has been reported that mean heights for age from birth to 10 years in adolescents in the upper quartile of LDL values are lower compared with those in lower LDL quartiles,⁴³ contradicting the findings related to other CVD risk factors.

In addition to the incomplete control for possible confounding variables, the existing study populations are generally fairly small and possibly biased due to the nature of this kind of study where it is not only difficult, but sometimes impossible, to collect fully representative data. Most of the early life information on birth variables in the studies reviewed were retrospective and thus prone to selection and recall bias, although a minority of the birthweights in the studies were recalled.^{17,24,25,63} Maternally recalled birthweights are reasonably accurate compared with recorded birthweights,⁶⁴ but self-recorded birthweights are noted to be inaccurate,⁶⁴ especially in older people.⁶⁵ The problem with prospective studies (follow-up from birth) on the other hand, is the length of the follow-up, which in the studies reviewed was generally short and therefore the associations may not yet be apparent. The two reviewed prospective studies lasting nearly 30 years^{28,32} were based on small study populations with insufficient data to throw light on the hypothesis. Varying statistical power of the studies may also have led to inconsistencies between the results, since at least

among those populations where the associations are weak, a high power would be needed to detect them. In the studies reviewed the reported regression estimates (Table 4) were all small.

As regards biological explanations, the possible underlying mechanisms linking size at birth to subsequent lipid levels in humans are so far unclear, although there is a vast amount of evidence from animal studies.⁶⁶ Barker originally noted that smaller abdominal circumference at birth is associated with higher lipid levels. Based on this observation he suggested that, since abdominal circumference at birth is thought to reflect liver size, and cholesterol metabolism is regulated by the liver, impaired liver growth in uterus re-sets cholesterol concentration towards a more atherogenic profile.¹⁵ This view is supported by one other study that shows a negative association between abdominal circumference and TG in growth-retarded human fetuses.⁶⁷ There is also evidence that uteroplacental insufficiency in rats can lead to lower birthweight and altered hepatic fatty acid metabolism,⁶⁸ and that levels of apolipoprotein B, that can predict atherosclerosis, have been elevated in growth-retarded human fetuses.⁶⁹ However, more research is needed to show whether the association between abdominal circumference and lipids exists in other populations, and how accurately measurement of abdominal circumference reflects the size of the liver in a newborn baby. The concordance between the size of the liver and abdominal circumference in humans is so far weak.⁷⁰ It has also been suggested that in addition to size at birth, infant feeding may affect lipid metabolism,⁴⁶ but the results are contradictory.^{19,43,63,71,72} The relationship between size at birth and lipid levels could also be considered as one feature of a more extensive metabolic disorder involving insulin resistance. This view is in line with the fact that TG, which is positively correlated with insulin,⁷³⁻⁷⁵ was the only lipid showing a somewhat consistent relationship with birthweight. However, this has been contradicted by some earlier studies^{22,34,52} and more research is needed. In addition, the noted associations may also be explained by gene-mediated mechanisms, although there is not much support for this in the published literature so far.⁷⁶⁻⁷⁸

In conclusion, the evidence from the literature reviewed found no consistent relationship between size at birth and subsequent blood lipid concentrations, with the possible exception of a negative association between birthweight and TG. However, the research in this area is limited and most of the studies published so far may have lacked the power to detect apparently weak associations. There is some evidence in humans that the associations are biologically plausible, and this gives good reason for further research. However, longitudinal studies with high quality data, sufficient power, and prospective follow-up are needed.

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KEY MESSAGES

- The literature on the association between birthweight and lipids in later life is limited.
- The existing studies show no consistent relationship between fetal growth and blood lipids in later life, with the possible exception of triglyceride.
- There are plenty of inconsistencies between the studies, which may be due to several reasons, such as varying power and genetic/ethnic background.
- Studies adjusting for current size tended to give relatively more support to the fetal origins hypothesis compared with studies not adjusting for current size.

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Commentary: Developmental origins of raised serum cholesterol

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Human beings are plastic during development, and a single genotype can produce more than one alternative form of structure or physiological state in response to environmental conditions.¹ There is now a considerable body of evidence that coronary heart disease (CHD) originates in developmental plasticity.² That being the case environmental conditions during development should be linked to the major biological risk factors for the disease. In this issue of the *International Journal of Epidemiology*, Liisa Lauren and colleagues³ review the evidence that low birthweight, a marker of an adverse intrauterine environment, is linked to abnormalities in blood lipid concentrations.

Animal experiments have unequivocally demonstrated that undernutrition during gestation permanently changes lipid metabolism.⁴ This is associated with alteration in the microstructure of the liver. The literature, as the authors of the review comment, is 'vast'. They find, however, that the 39 published studies on humans do not strongly support a link between birthweight and blood lipid levels in later life, other than a consistent relationship between small size at birth and elevated serum triglyceride concentrations. The studies include children and adults. Although serum cholesterol concentrations are known to track from early childhood it does not follow that the effects of an adverse prenatal influence would necessarily be apparent in childhood. The effect of low birthweight on childhood blood pressure, for example, is trivial. Presumably for much of life other regulatory mechanisms can compensate for reduced nephron numbers or some other functional limitation

acquired before birth. Ultimately, with ageing, homeostasis can no longer be maintained and disease develops.

Notwithstanding this, it is necessary to consider why an effect on lipid metabolism that is so easily demonstrated in laboratory animals cannot be so readily shown in humans. One explanation could be that there are, as yet, insufficient data; but there are other, more interesting possibilities. An obvious one is that effects of birthweight are being obscured by the subsequent effects of infant feeding. There has been considerable speculation that the high cholesterol and saturated fat content of human milk may be important in establishing how the liver synthesizes and excretes cholesterol in later life. The liver is one of the few organs that continues to be plastic after birth, while other organs such as the kidney have completed their critical periods of development. Although the authors write that the evidence is 'contradictory', a recent systematic review of 37 studies concluded that breastfeeding is associated with lower serum concentrations of total and low-density lipoprotein (LDL) cholesterol in adult life.⁵

Another possibility is that birthweight is not the appropriate marker for these aspects of intrauterine conditions, more specifically nutrition, that affect lipid metabolism. People who were conceived during the Dutch famine had a more atherogenic profile than people not exposed to famine *in utero*.⁶ They had higher ratios of LDL to high-density lipoprotein (HDL) cholesterol. The effect of famine was independent of size at birth. Among middle-aged men in Beijing elevated total and LDL cholesterol concentrations were not related to low birthweight, but were related to low maternal body mass index in early pregnancy—a finding that accords with that in the Dutch famine.⁷ Both these observations in humans resonate with those in animals. In rats a brief 4-day period of maternal