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## Growth in utero and serum cholesterol concentrations in adult life

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### Abstract

**Objective**—To see whether reduced rates of fetal growth are related to raised serum cholesterol concentrations in adult life.

**Design**—Follow up study of men and women whose size at birth had been recorded.

**Setting**—Jessop and Northern General Hospitals, Sheffield.

**Subjects**—219 men and women born in the Jessop Hospital during 1939-40.

**Main outcome measures**—Serum concentrations of total cholesterol, low density lipoprotein cholesterol, and apolipoprotein B.

**Results**—Men and women who had had a small abdominal circumference at birth had raised serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B. This was independent of the duration of gestation. Serum concentrations of total cholesterol fell by 0.25 mmol/l (95% confidence interval 0.09 to 0.42) with each 1 in (2.54 cm) increase in abdominal circumference. The corresponding figure for serum low density lipoprotein cholesterol was 0.26 mmol/l (0.11 to 0.42) and for serum apolipoprotein B 0.04 g/l (0.02 to 0.07). Small head and chest circumferences at birth and short length were each associated with raised serum low density lipoprotein cholesterol concentrations but the trends disappeared in a simultaneous regression with abdominal circumference at birth. The association between abdominal circumference at birth and low density lipoprotein cholesterol concentration was independent of social class, current body weight, cigarette smoking, and alcohol consumption.

**Conclusion**—Raised serum cholesterol concentrations in adult life are associated with impaired growth during late gestation, when fetal undernutrition has a disproportionate effect on liver growth. Impaired liver growth may permanently alter low density lipoprotein cholesterol metabolism.

### Introduction

The reasons why serum cholesterol concentrations differ widely within and between populations are not understood. They are important because cholesterol may be directly concerned in the pathogenesis of atheroma and is strongly associated with the risk of coronary heart disease.<sup>1,2</sup>

Experiments show that changing the diets of pregnant animals or their newborn offspring may permanently change the rate of cholesterol synthesis and excretion.<sup>3</sup> Permanent changes in cholesterol metabolism may also be induced by cholestyramine given to mothers or neonates.<sup>4,5</sup> Rats that are weaned prematurely have a raised serum cholesterol concentration in later life, which becomes apparent only after seven months,<sup>6</sup> while breast fed baboons have higher ratios of serum low density to high density

lipoprotein cholesterol concentrations in adult life than those fed on infant formulas.<sup>7</sup> These observations suggest that the activity of enzymes controlling cholesterol synthesis and excretion may be programmed by nutrition during early development.

In humans there is limited evidence that nutrition before and immediately after birth influences lipid metabolism throughout life. In a study of men aged 59-70 who were born in Hertfordshire and whose birth weight, infant growth, and feeding were recorded, those who were heavier at birth were found to have lower serum concentrations of apolipoprotein B—the structural apolipoprotein linked to low density lipoprotein.<sup>8</sup> Those who had been breast fed beyond 1 year of age or who had been exclusively bottle fed had higher serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B. These patterns of feeding were also associated with raised death rates from coronary heart disease.

The findings in Hertfordshire are part of a growing body of evidence that the metabolic abnormalities which lead to coronary heart disease are programmed by nutrition in utero and during infancy. Studies show that men and women who had low growth rates in utero or in the first year after birth now have raised blood pressure,<sup>9</sup> impaired glucose tolerance,<sup>10</sup> abnormal blood coagulation,<sup>11</sup> and raised death rates from coronary heart disease.<sup>12,13</sup> These associations are strong, graded, and independent of social class, smoking, and other aspects of adult lifestyle.

We measured serum lipid concentrations in a group of middle aged men and women who were born in a maternity hospital in Sheffield during 1939-40. Our aim was to see whether retarded growth in utero led to the pattern of serum lipid concentrations that is associated with increased risk of coronary heart disease. Retarded intrauterine growth affects body proportions at birth as well as body size, and these particular men and women were studied because their birth records included not only birth weight but also length at birth and circumferences of the head, chest, and abdomen. Abdominal circumference seemed particularly important because it reflects the size of the liver, which has a central role in cholesterol synthesis and excretion.

### Subjects and methods

A standardised record form was kept for each woman admitted to the Jessop Maternity Hospital in Sheffield.<sup>13</sup> Records included the date of the mother's last menstrual period, details of previous pregnancies, and measurement of the external conjugate diameter of the pelvis—the distance between the symphysis pubis and the fifth lumbar vertebra. Birth weight was recorded in pounds and grams (1 lb=454 g). Placental weight was recorded in grams. Head, chest, and abdominal circumferences and crown-heel length were recorded in inches (1 in=2.54 cm).

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We used the NHS central register to trace 1039 (87%) of the singleton infants who were born in the hospital to married mothers during 1939-40 and for whom there were complete records. Of the 419 who were still living in Sheffield, 337 agreed to be interviewed at home and were visited by one of four fieldworkers. The fieldworker, who had not seen the birth data, measured height and weight. Father's occupation was used to define social class at birth, and current social class was derived from the subject's or husband's occupation. Smoking and alcohol consumption were recorded and categorised as described.<sup>9</sup>

After the interview the subjects were asked to come to the Northern General Hospital, Sheffield, after fasting overnight; 235 agreed. Fasting serum samples were analysed for total cholesterol, high density lipoprotein cholesterol, triglyceride, and apolipoprotein A I and B concentrations. Serum total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations were measured by standard enzymatic methods.<sup>14-17</sup> Interassay coefficients of variation for these assays were in the range 1.7% to 2.7%. Low

density lipoprotein cholesterol concentration was derived by the Friedwald-Fredrickson formula.<sup>18</sup> Apolipoprotein A I and B concentrations were measured by immunoturbidimetric assays with interassay coefficients of variation of less than 5%.<sup>19</sup>

**Statistical methods**—We tabulated means to examine the relation between measurements of body size at birth and serum lipid concentrations. Statistical significance of trends was assessed by multiple linear regression. The distributions of serum triglyceride and apolipoprotein A I concentrations were skewed and we transformed them with logarithms. Apolipoprotein B concentrations were raised in people with a high body mass index and we adjusted the values for this by regression.

## Results

Of the 235 men and women who attended hospital for blood sampling after an overnight fast, 219 had complete analyses of serum lipid concentrations. Their ages ranged from 50 to 53 years, with a mean of 52. Table I gives their mean body size measurements at birth, mean body mass index (weight (kg)/height (m) squared), and serum lipid concentrations and the proportions who were in social class IV or V and who were firstborn.

Men and women who had had low birth weights tended to have raised serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B, though the trends were not statistically significant. Duration of gestation, calculated from the date of the last menstrual period, was known for 190 subjects. Serum concentrations of the three lipids tended to be lower in people born before 40 weeks. Table II shows the trends in lipid concentrations in a simultaneous regression with birth weight and duration of gestation. Birth weight is divided into the same groups as used in previous studies.<sup>9</sup> The trends were of borderline significance.

Abdominal circumference at birth had been recorded for all except two subjects. Serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B fell between men and women whose abdominal circumference was 11.5 in (29 cm) or less at birth and those whose abdominal circumference was more than 13 in (33 cm) (table III). These trends were significant. p Values obtained by multiple linear regression were 0.01 for total cholesterol, 0.003 for low density lipoprotein cholesterol, and 0.004 for apolipoprotein B. Table III shows that the significance of each trend was increased by adjustment for length of gestation. Serum cholesterol concentrations fell by 0.25 mmol/l (95% confidence interval 0.09 to 0.42) with each 1 in (2.54 cm) increase in abdominal circumference. Corresponding figures for low density lipoprotein cholesterol were 0.26 mmol/l (0.11 to 0.42) and for apolipoprotein B 0.04 g/l (0.02 to 0.07). The figure shows the values of low density lipoprotein cholesterol for each of the 189 subjects with known gestational age and abdominal circumference. Values

TABLE I—Mean birth measurements, current body mass index, and serum lipid concentrations in men and women aged 50-53, and distribution of subjects with respect to social class and birth order

	Men (n=111)	Women (n=108)	Standard deviation (all)
<b>Birth measurements:</b>			
Birth weight (lb) [g]	7.2 [3282]	7.1 [3202]	1.1 [500]
Length (in) [cm]	19.9 [50.5]	19.9 [50.5]	1.0 [2.5]
Head circumference (in) [cm]	13.6 [34.5]	13.4 [34.0]	0.6 [1.5]
Chest circumference (in) [cm]	13.1 [33.3]	12.9 [32.8]	0.9 [2.3]
Abdominal circumference (in) [cm]	12.3 [31.2]	12.4 [31.5]	1.1 [2.8]
Current body mass index*	26.9	27.0	4.6
<b>Serum lipid concentrations:</b>			
Total cholesterol (mmol/l)	6.4	6.7	1.2
High density lipoprotein cholesterol (mmol/l)	1.3	1.7	0.4
Low density lipoprotein cholesterol (mmol/l)	4.3	4.3	1.1
Triglyceride (mmol/l)	1.7	1.5	0.8
Apolipoprotein A I (g/l)	1.22	1.43	0.24
Apolipoprotein B (g/l)	0.93	0.95	0.18
<b>Social class†:</b>			
No (%) in social class IV or V at birth	45 (46)	39 (41)	—
No (%) social class IV or V currently	26 (24)	18 (17)	—
No (%) firstborn‡	79 (72)	74 (70)	—

\*Body mass index: weight (kg)/(height (m)<sup>2</sup>).  
†Social class at birth unknown for 26 subjects; social class currently unknown for 4 subjects; number firstborn unknown for 3 subjects.

TABLE II—Mean serum lipid concentrations stratified by birth weight in men and women aged 50-53

Birth weight (lb) [g]	No of people	Total cholesterol (mmol/l)	Low density lipoprotein cholesterol (mmol/l)	Apolipoprotein B (g/l)
≤6.5 [≤2951]	56	6.6	4.4	0.95
-7.5 [-3405]	86	6.6	4.4	0.97
>7.5 [>3405]	77	6.3	4.1	0.90
All	219	6.5	4.3	0.94
p Value adjusted for gestational age by regression		0.08	0.08	0.03

TABLE III—Mean serum lipid concentrations stratified by abdominal circumference at birth in men and women aged 50-53

Abdominal circumference (in) [cm]	No of people		Total cholesterol (mmol/l)			Low density lipoprotein cholesterol (mmol/l)			Apolipoprotein B (g/l)		
	Men	Women	Men	Women	All	Men	Women	All	Men	Women	All
≤11.5 [≤29.2]	28	25	6.5	6.8	6.7	4.5	4.6	4.5	0.96	0.99	0.97
-12.0 [-30.5]	22	21	6.8	6.9	6.9	4.8	4.4	4.6	0.95	0.97	0.96
-12.5 [-31.8]	13	18	6.7	6.8	6.8	4.6	4.2	4.4	0.99	0.97	0.98
-13.0 [-33.0]	21	24	6.0	6.5	6.2	3.8	4.2	4.0	0.90	0.93	0.91
>13.0 [>33.0]	26	19	6.0	6.4	6.1	3.9	4.1	4.0	0.87	0.88	0.87
All	110	107	6.4	6.7	6.5	4.3	4.3	4.3	0.93	0.95	0.94
p Value adjusted for gestational age by regression			0.009	0.16	0.003	0.003	0.12	0.0007	0.01	0.07	0.002

TABLE IV—Mean serum low density lipoprotein concentrations stratified by current body mass index in men and women aged 50-53

Current body mass index*	No of people		Low density lipoprotein cholesterol (mmol/l)	
	Men	Women	Men	Women
≤23	14	17	4.0	4.1
-25	19	32	4.5	4.4
-27	30	20	4.5	4.0
-30	30	15	4.1	4.8
>30	17	23	4.1	4.3
All	110	107	4.3	4.3

\*Body mass index: weight (kg)/(height (m)<sup>2</sup>).

TABLE V—Mean serum low density lipoprotein concentrations stratified by current social class and abdominal circumference at birth

Abdominal circumference at birth (in) [cm]	Serum low density lipoprotein (mmol/l)	
	Social class I-III NM*	Social class III M*-V
≤11.5 [≤29.2]	4.3 (n=26)	4.7 (n=27)
-12.0 [-30.5]	4.5 (n=27)	4.7 (n=15)
-12.5 [-31.8]	4.5 (n=12)	4.3 (n=19)
-13.0 [-33.0]	4.3 (n=28)	3.6 (n=15)
>13.0 [≥33.0]	3.8 (n=20)	4.1 (n=24)
All	4.3 (n=113)	4.3 (n=100)

\*NM=Non-manual. M=Manual.

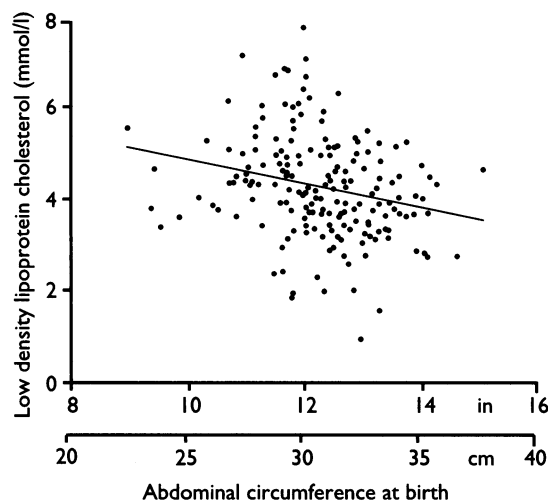
are plotted against abdominal circumference adjusted to 40 weeks of gestation by regression.

Table IV divides the men and women into five groups according to current body mass index. The weak, non-significant trends in serum low density lipoprotein cholesterol concentrations with current body mass contrast with the trends with abdominal circumference (table III).

Concentrations of total and low density lipoprotein cholesterol and apolipoprotein B were higher in people who were short at birth or had a small head or chest circumference, but each of these trends disappeared in a simultaneous regression with abdominal circumference. Abdominal circumference at birth was related to birth weight (correlation coefficient 0.72). Nevertheless, in a simultaneous analysis with abdominal circumference and birth weight lipid concentrations were unrelated to birth weight but remained strongly related to abdominal circumference. Lipid concentrations were not related to placental weight or the mother's external conjugate diameter independently of the baby's abdominal circumference.

Serum concentrations of high density lipoprotein, apolipoprotein A I, and triglycerides showed no significant trends with any measurements at birth or with the mother's external conjugate diameter.

*Confounding variables*—Cigarette smoking and alcohol consumption were associated with higher



Low density lipoprotein cholesterol concentrations plotted against abdominal circumference at birth, adjusted for duration of gestation

serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B. Adjusting for these variables strengthened the associations between serum lipid concentrations and abdominal circumference at birth. p Values for the trends in serum lipid concentrations with abdominal circumference in a simultaneous regression with length of gestation, smoking, and alcohol consumption were 0.001 for total cholesterol, 0.0003 for low density lipoprotein cholesterol, and 0.0009 for apolipoprotein B. Serum lipid concentrations did not differ with social class, either currently or at birth. Table V shows that the trends with abdominal circumference occurred within social class groups. Serum lipid concentrations were unrelated to birth order.

## Discussion

This study shows that middle aged men and women who had had a small abdominal circumference at birth had raised serum concentrations of total and low density lipoprotein cholesterol and apolipoprotein B (table III, figure). This association was independent of gestational age, indicating that it reflected an association with reduced rates of fetal growth rather than with premature birth.

The people in our study were born in hospital at a time when many births occurred at home, and they continued to live in the town where they were born. They were therefore unrepresentative of all people born in the town. As our analyses were based on comparisons within the sample, however, bias would have been introduced only if the relations between serum lipid values and fetal growth were different among people born in and outside hospital and between migrants and non-migrants. This seems unlikely to be the case. The associations between abdominal circumference and adult serum lipid concentrations were independent of possible confounding variables linked to adult lifestyle, including social class (table V), cigarette smoking, alcohol consumption, and obesity. The trends in low density lipoprotein cholesterol concentrations associated with the range of abdominal circumference measurements at birth were stronger than those associated with the range of current body mass indices (table IV). This is remarkable, as our findings are based on routine measurements of newborn babies, which must be liable to error.

Concentrations of total and low density lipoprotein cholesterol and apolipoprotein B tended to be higher in people who had had lower birth weight, though only the trend with apolipoprotein B was statistically significant (table II). These weak associations with birth weight confirm findings among men in Hertfordshire<sup>8</sup> and 50 year old men and women in Preston (unpublished). McCance and Widdowson showed that undernutrition in early intrauterine life tends to produce small but normally proportioned animals, whereas undernutrition later in development leads to selective organ damage and disproportionate growth.<sup>20</sup> During undernutrition those tissues whose maturity is more advanced have a greater priority of growth and may continue to grow at the expense of other tissues. The timing of undernutrition determines which tissues and systems are selectively damaged and hence the pattern of disproportion in size at birth.

## POSSIBLE CAUSES AND EFFECTS

In late gestation the human fetus may respond to nutrient deprivation by maintaining the brain at the expense of growth of the trunk.<sup>21</sup> The liver, which is growing rapidly at this time, may be particularly compromised and its weight at birth is found to be low when compared with the weight of the brain or with total body weight.<sup>22</sup> In ultrasound examination of the

fetus the ratio of head circumference to abdominal circumference is used as a measure of the ratio of brain to liver size in disproportionate growth of this kind.<sup>23</sup> The associations of serum lipid concentrations with small abdominal circumference, but not independently with small head circumference, suggest that lipid concentrations are related to growth failure in late gestation. We found that chest circumference did not predict serum lipid concentrations independently of abdominal circumference, which points to a specific association with growth failure of abdominal viscera, including the liver, rather than failure of growth of the trunk as a whole.

One explanation of our findings is that impaired growth of the liver in late gestation leads to permanent changes in low density lipoprotein cholesterol metabolism. The liver is thought to be the main site for synthesis of low density lipoprotein cholesterol in late gestation, and the human fetus requires large quantities at this time to sustain metabolic activities which include high rates of secretion of steroid hormones by the adrenals.<sup>24</sup> Rates of cholesterol synthesis in the liver just before birth, as judged by the activity of the rate limiting enzyme in cholesterol synthesis, are more than twice those in adults.<sup>25</sup> Babies who are small for dates reportedly have raised serum low density lipoprotein concentrations.<sup>26</sup> Follow up studies show that children maintain their rank order by serum cholesterol concentrations from the age of 6 months.<sup>27,28</sup> In animals manipulation of nutrition and metabolism in the perinatal period permanently changes lipid metabolism.<sup>3,7</sup>

The processes by which impaired liver growth in late gestation could permanently change the metabolism of low density lipoprotein cholesterol are unknown. A study of low density lipoprotein metabolism in samples of middle aged men in five countries, however, led to the suggestion that differences in serum concentrations depend on different activity of low density lipoprotein receptors in the liver.<sup>29</sup> Persisting reduction of low density lipoprotein receptor activity associated with failure of growth of the fetal liver is a possible explanation of our findings.

The causes of fetal growth failure in the last trimester are mostly unknown. We suspect that poor maternal nutrition and consequent fetal undernutrition is a major influence.<sup>30</sup> In our study lipid concentrations were unrelated to the external conjugate diameter of the mother's pelvis, and physiological constraint of fetal growth by maternal size does not therefore seem important.

Lowering serum cholesterol concentrations from 6.5 to 6.0 mmol/l has been estimated to reduce the risk

of coronary heart disease by 30%.<sup>31</sup> The differences in serum cholesterol concentrations associated with the range of abdominal circumference measurements at birth are at least as great (table III). Current public health measures emphasise the importance of reducing weight to lower serum cholesterol concentrations in adult life. Our findings (tables III and IV) suggest that promoting fetal growth is another strategy.

We are grateful to all the men and women who gave their time; to the medical records department at the Jessop Hospital, Sheffield, who preserved the records and allowed us to use them; and to the staff of the NHS Central Register, Southport, and the Sheffield Family Health Services Authority, who helped locate the subjects. Fieldwork was carried out by Dr S Jespersen, Kate Ellis, Catherine Laughton, Rachel Strong, and Catherine Williams. The study was funded by the Medical Research Council and the Wellcome Trust. Dr Jespersen's salary is paid by Children Nationwide.

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### Clinical implications

- It is not known why serum cholesterol concentrations differ between one person and another
- Studies in animals suggest that nutrition in utero permanently programmes lipid metabolism
- 50 year old men and women who had a small abdominal circumference at birth had raised serum low density lipoprotein cholesterol concentrations
- Impaired liver growth in late gestation may permanently alter low density lipoprotein cholesterol metabolism
- Serum cholesterol concentrations in the population may be reduced by improving fetal nutrition