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No difference in the association between birth weight and total cholesterol for males and females. A SHARP (Scottish Heart and Arterial Disease Risk Prevention) study

G Libby¹, SR McEwan², AD Morris^{1,3} and JJF Belch^{2,3}

Abstract: We carried out a cohort study in a relatively young healthy working population to assess any difference between males and females in the association between birth weight and adult total cholesterol. Perinatal data came from the Walker database of babies born between 1952 and 1966 in Dundee, Scotland. This was record-linked to information from the SHARP (Scottish Heart and Arterial Risk Prevention) cohort who had undergone a cardiovascular risk screening between 1991 and 1993. There were 1158 individuals (56% male, mean age 32.1 years). For both males and females there was no association between birth weight and cholesterol either unadjusted or after adjustment for BMI and other potential confounders: $B = -0.11$ (95% CI $-0.03, 0.04$) for males, $B = -0.15$ (95% CI $-0.31, 0.01$) for females. All individuals together showed a slight decrease in cholesterol for 1 kg increase in birth weight but only after adjustment for BMI: $B = -0.13$ (95% CI $-0.24, -0.01$). These results suggest no difference in the relationship between birth weight and total cholesterol for males and females.

Key words: birth weight; cholesterol; SHARP; Walker

Introduction

Studies examining the association between birth weight and total cholesterol have generally shown an inverse relationship. It has been noted, however, that in contrast with blood pressure studies, the relationship between birth weight and adult total cholesterol has not been consistent for males and females. A recent meta analysis¹ found some evidence of a stronger effect in males compared with females, but the results were dominated by one very large study.² A further large study published since this review, in contrast, found an association in females but not males and when these results were incorporated into the meta analysis the original sex difference was 'abolished'.³

Despite over 30 publications reporting regression coefficients separately for men and women there have been only five large (>1000 individuals)^{2–6}

such studies in adults. In addition, some studies have used recalled birth weight or had limited data on potential confounding factors that could impact total cholesterol levels in adult life.

We therefore examined the relationship between birth weight and total cholesterol in a large healthy working population with prospectively collected perinatal data and taking into account a range of confounding factors. We set out to examine this relationship in males and females separately, in addition to all individuals together.

Methods

Detailed information on pregnancy and birth came from the Walker cohort,⁷ a database of 48,404 babies out of 64,196 born in Dundee, Scotland between 1952 and 1966, of whom 34,183 have been traced and 21,000 are still resident in the area. Birth weight and gestation (calculated as the time between the date of last menstrual period and the date of birth) were obtained from documented records made at the time of pregnancy and birth. These data were record-linked by a unique patient identifier to extensive information relating to adult environmental, demographic and health factors in the SHARP (Scottish Heart and Arterial disease

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Risk Prevention) cohort,⁸ which consisted of a working population screened for cardiovascular risk factors. In brief, after extensive publicity about the SHARP screening programme, a specially adapted bus staffed by a regular team of experienced nurses visited over 700 workplaces between 1991 and 1993 at the employers' request and employees were invited to volunteer to have a cardiovascular risk assessment. Variables including height, weight and blood pressure were measured and a blood sample was taken. Individuals were questioned on lifestyle and prescribed medication and a detailed family history of cardiovascular disease was taken. Overall, around 75% of employees took up the offer of screening.

Non-fasting total cholesterol was analysed on finger prick blood samples using a Lipotrend C machine (Boehringer Mannheim, Lewes, UK). Strict quality control was maintained by reference samples tested in the regional biochemistry laboratory and the Wolfson Institute in Birmingham, England.

Data analysis

The contribution of birth weight to adult total cholesterol whilst allowing for the influence of other factors in adulthood was assessed using a series of univariable and multivariable regression models as outlined by Lucas, *et al.*⁹

Early life: unadjusted birth weight as a predictor of total cholesterol.

Early life adjusted: birth weight adjusted for gestation and age at time of cholesterol testing.

Later life: adult BMI adjusted for age as a predictor of total cholesterol.

Early and later life: early and later life models combined and adjusted for cigarette consumption, alcohol intake, adult socioeconomic status and family history of cardiovascular disease.

As part of the regression analysis, a formal interaction test of birth weight and sex on the prediction of total cholesterol was carried out.

Socioeconomic status was represented by social class which was defined from information on occupation reported in the SHARP database using standard occupational classifications¹⁰ (i.e. 1: professional; 2: managerial and technical; 3N: skilled (non-manual); 3M: skilled (manual); 4: partly skilled; 5: unskilled).

Results

There were 34,183 traced individuals from the Walker cohort who had a unique patient identifier which could be used to link to the SHARP cohort of 8254 individuals who were born between 1952 and 1966. There were 1158 individuals in the Walker

database who also had information recorded in the SHARP database and these 1158 comprised the study population.

There were few differences in birth characteristics between the study population and the rest of the Walker cohort. Mean birth weight for the study population was slightly higher (3.36 kg (SD 0.49) vs 3.33 kg (SD 0.75)), but is unlikely to be of clinical significance. The study population individuals were less likely to have been breastfed (64.9% vs 70.2%), but there were no differences between the groups for gestation, percentage of males, mother's parity or mothers experiencing pre-eclampsia.

The individuals were aged 24–42 years (median 32 years, SD 4.51) at the time of the cardiovascular risk factor assessment. Their birth weights ranged from 1.52 kg to 5.36 kg, with a median weight of 3.36 g. Fifty-four individuals (4.7%) had a low birth weight of ≤ 2.50 kg compared to 5.2% in the traced Walker cohort. The demographic characteristics of the study population by males and females are shown in Table 1. There were 7% of females and 7.8% of males with a BMI > 30.

Seven individuals reported receiving thyroxine, which may have had an effect on their cholesterol levels. They were all included in the analysis. There were no individuals receiving statin treatment.

There was no interaction between birth weight and sex in the prediction of total cholesterol ($p = 0.57$). This was confirmed by the regression analysis (Table 2), which for both males and females showed no relationship between birth weight and total cholesterol either unadjusted or after adjustment for adult BMI and other potential confounders.

For all individuals together, there was no association between birth weight and adult total cholesterol until adjusted for adult BMI, which showed a slight decrease of 0.13 mmol/l (95% CI -0.24 to -0.01) for each 1 kg increase in birth weight.

Further adjustment for confounders showed that increasing age, BMI and cigarette consumption were all associated with increasing total cholesterol. As shown in previous studies, alcohol intake appeared to be inversely associated with total cholesterol.

Discussion

We were unable to show an inverse association between birth weight and adult total cholesterol for either males or females. This is in contrast with a number of other studies. Rather, for both sexes, adult risk factors had a greater impact on cholesterol levels. For all individuals together there was a small decrease in cholesterol with increasing birth weight, but only after adjusting for adult BMI.

Table 1 Demographic details of study population by males and females

	Males (<i>n</i> = 644)	Females (<i>n</i> = 514)	<i>p</i> -value ^a
Cholesterol, mean mmol/l (SD)	4.89 (0.97)	4.83 (0.85)	NS
Birth weight, mean kg (SD)	3.41 (0.50)	3.31 (0.49)	0.0004
Gestation, mean weeks (SD)	39.9 (1.92)	39.9 (1.99)	NS
Age at screening, mean years (SD)	32.2 (4.49)	31.9 (4.52)	NS
Height, mean cm (SD)	175.1 (6.81)	161.9 (6.42)	<0.0001
Weight, mean kg (SD)	76.2 (11.48)	62.2 (11.6)	<0.0001
BMI, mean kg/m ² (SD)	24.9 (3.49)	23.7 (4.15)	<0.0001
Current smoker, <i>n</i> (%)	188 (29.2)	151 (29.4)	NS
Cigarettes, mean per day (SD) ^b	16.6 (8.28)	15.4 (6.81)	NS
Years of smoking, median (IQR) ^b	15 (10–20)	15 (10–20)	NS
Total alcohol, median total u/w (IQR)	12 (3–22)	1 (0–6)	<0.0001
Social class, <i>n</i> (%)			
1 & 2	136 (21.9)	120 (24.5)	<0.0001
3: non-manual	121 (19.6)	283 (57.9)	
3: manual	198 (31.9)	33 (6.8)	
4 & 5	164 (26.5)	53 (10.8)	
Family history of CVD, <i>n</i> (%)			
None	332 (51.6)	279 (54.3)	
Parental age at diagnosis:			
60–69 years	82 (12.7)	45 (8.8)	NS
50–59 years	109 (16.9)	84 (16.3)	
40–49 years	69 (10.7)	47 (9.1)	
30–39 years	28 (4.4)	32 (6.2)	
20–29 years	24 (3.7)	27 (5.3)	

IQR, interquartile range; u/w, units per week.

^a *t*-test, Wilcoxon or chi-squared test.^b Current smokers only.

Some previous studies have found a difference by sex with a stronger association in either males or females. The smaller numbers in our groups may have obscured any association but the whole study

population of >1000 individuals also failed to show an association until adjustment for BMI.

As our study was not subject to the limitations of some previous studies, it is plausible that we were

Table 2 Regression analyses of the effect of birth weight and adult BMI on total cholesterol

	Males (<i>n</i> = 644) β (95% CI)	<i>p</i>	Females (<i>n</i> = 514) β (95% CI)	<i>p</i>	All (<i>n</i> = 1158) β (95% CI)	<i>p</i>
Early life model						
Birth weight (+1 kg) ^a	-0.06 (-0.21, 0.09)	0.3	-0.12 (-0.27, 0.03)	0.1	-0.08 (-0.19, 0.03)	0.1
Early life adjusted						
Birth weight (+1 kg) ^b	-0.07 (-0.23, 0.09)	0.3	-0.15 (-0.32, 0.02)	0.07	-0.10 (-0.21, 0.02)	0.08
Later life model						
BMI (+1) ^c	0.06 (0.04, 0.09)	<0.0001	0.04 (0.02, 0.05)	<0.0001	0.05 (0.04, 0.06)	<0.0001
Early and later life models combined						
Birth weight (+1 kg) ^d	-0.11 (-0.03, 0.04)	0.1	-0.15 (-0.31, 0.01)	0.07	-0.13 (-0.24, -0.01)	0.03
Gestation (+1 week)	0.02 (-0.02, 0.06)	0.3	0.02 (-0.02, 0.06)	0.3	0.02 (-0.009, 0.05)	0.2
Age (+1 year)	0.05 (0.03, 0.06)	<0.0001	0.02 (0.00, 0.03)	0.04	0.03 (0.02, 0.05)	<0.0001
BMI (+1)	0.07 (0.05, 0.09)	<0.0001	0.04 (0.02, 0.06)	<0.0001	0.05 (0.04, 0.07)	<0.0001
Cigarettes (+10 per day)	0.17 (0.08, 0.25)	<0.0001	0.08 (-0.03, 0.18)	0.2	0.12 (0.05, 0.18)	<0.0001
Total units alcohol (+1 unit per week)	-0.006 (-0.10, -0.002)	0.008	-0.02 (-0.03, -0.003)	0.01	-0.006 (-0.01, -0.002)	0.002
Social class						
3: non-manual vs 1 & 2	0.19 (-0.02, 0.42)	0.08	-0.01 (-0.47, 0.18)	0.8	0.08 (-0.05, 0.22)	0.2
3: manual vs 1 & 2	0.09 (-0.11, 0.28)	0.3	-0.15 (-0.47, 0.18)	0.3	0.01 (-0.15, 0.17)	0.8
4 & 5 vs 1 & 2	0.01 (0.20, 0.23)	0.9	-0.04 (-0.33, 0.25)	0.8	-0.02 (-0.19, 0.15)	0.8
Family history of CVD (yes vs no)	0.04 (-0.11, 0.18)	0.6	0.67 (-0.18, 0.12)	0.7	0.008 (-0.09, 0.11)	0.8
Sex (males vs females)	-	-	-	-	0.15 (-0.03, 0.22)	0.1

^a Unadjusted.^b Adjusted for gestation and age (also adjusted for sex for all individuals).^c Adjusted for age (and sex for all individuals).^d Birth weight adjusted for all covariates.

able to accurately detect no association between birth weight and total cholesterol. Where associations have been found previously they have been generally weak and may have been the result of chance findings.¹¹

Our study had the major advantage of having a relatively large cohort of individuals for whom birth weight was obtained from records collected at birth. We could also adjust for gestation. Though this was provided by calculation (as ultrasound was not available at the time), it is likely that slight under- and over-estimation of gestation would be equally likely, with no bias resulting. We were also able to adjust for a range of consistently collected adult risk factors that could impact cholesterol levels. An additional advantage came from the timing of the risk screening, carried out in the early 1990s before cholesterol-lowering drugs were regularly prescribed.

Cholesterol was measured in the non-fasting state as screening appointments were scheduled throughout the day. It was measured by fingerstick method, which it has been suggested is not as accurate as that recorded from venous samples, with the fingerstick method producing a higher reading.¹² If this was the case, then it would produce an inflated association between birth weight and cholesterol but our results showed no association. In addition, any discrepancy between fingerstick and venous samples would only bias the results if the measures used differed over the birth weight distribution.

Details of LDL and HDL levels would have enhanced the analysis but were not available. Breastfeeding has been associated with lower levels of total cholesterol in adulthood¹³ and infant feeding type could have provided an interesting addition to the analysis. Feeding type was recorded but was highly correlated with age, with older individuals in the cohort being far more likely to have been breastfed than younger ones. Feeding type was therefore not included in the analysis.

Individuals in this study were self-selected and may have participated in a health screening, as they were particularly health conscious but equally may have been prompted by a real concern over their health. The opportunity for a cardiovascular screening was taken by around 75% of those eligible.

The study population comprised only a small sample of the Walker cohort. However, it was broadly similar to the remaining Walker cohort, especially regarding birth weight distribution. It was, however, skewed towards social classes 3, 4 and 5 in adulthood, but importantly these groups are often underrepresented in longitudinal studies where individuals are traced in adulthood and invited to participate in research studies.

The results of this study suggest no difference in the relationship between birth weight and total cholesterol for males and females. They also suggest

only a minor role for birth weight in directly predicting adult cholesterol levels, though it may have a role in its correlation with adult weight and therefore indirectly with cholesterol. Risk factors in adulthood appear to have a greater impact in determining total cholesterol levels.

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