Sex differences in the associations between birthweight and lipid levels in middle-age: Findings from the 1958 British birth cohort

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Abstract

Objective

To examine sex differences in birthweight-lipid associations.

Methods and Results

Using prospectively collected data on birthweight and non-fasting lipid levels at age 44-45y from the 1958 British birth cohort (3603 men and 3583 women), sex differences in birthweight-lipid associations were examined.

There were inverse associations between birthweight and total and low-density-lipoprotein (LDL)-cholesterol among women (a 1kg increase in birthweight was associated with a 0.13mmol/L reduction in total cholesterol ($p<0.001$) and a 0.07mmol/L reduction in LDL-cholesterol ($p=0.02$)) but no associations among men ($p=0.005$ and $p=0.01$, respectively, for birthweight x sex interactions). There was an inverse association between birthweight and triglycerides of a similar magnitude in both sexes (a 1kg increase in birthweight was associated with a 7% reduction in triglyceride levels in sex-adjusted models ($p<0.001$)). There was no association between birthweight and high-density-lipoprotein-cholesterol. Associations were largely unaltered after adjustment for covariates. Of birthweight, current height and BMI, the latter was the strongest predictor of lipid levels.

Conclusions

The finding of an inverse association between birthweight and triglycerides in both sexes and of inverse associations between birthweight and total and LDL-cholesterol only in women suggests that the mechanisms underlying the associations with birthweight may vary for different lipids.

Key words: birthweight; cholesterol; lipids; sex differences

Introduction

The mechanisms that underlie the associations found between low birthweight and increased risk of adult diseases are still not fully understood.[1] It has been suggested that evidence of sex differences, specifically stronger inverse associations between birthweight and cardiovascular disease risk factors among males than females, would lend support to the fetal 'programming' of cardiovascular disease risk hypothesis.[2-4] 'Programming' has been defined as the permanent alteration of structure and function which can occur as an adaptive response to environmental insults during critical periods of development and which is beneficial for short term survival but often detrimental to subsequent health.[5] Evidence of sex differences in fetal growth patterns and, the nature of these, has led to the proposal that males have greater susceptibility to environmental insults in utero, such as undernutrition, and so may be more likely than females to undergo 'programming' if exposed.[2;6] Some animal studies provide evidence in support of the suggestion that 'programming' effects may be sex-specific.[7-10]

A recent meta-analysis of findings from 30 studies of the association between birthweight and total cholesterol[3] reported a sex difference, with a stronger inverse association among males than females. However, the possibility was recognised[3] that the meta-analysis was driven by results from the only two studies which found this sex difference to be significant,[11;12] especially as one study[11] was much larger than any other (n=25,843). Whilst the sex difference may be a true finding, not detected by some studies because of insufficient power or other study limitations, alternatively the result may be due to chance as for sex differences in the birthweight-blood pressure association.[13] The largest study to be included in the meta-analysis of birthweight and cholesterol[11] was limited by its use of self-reported retrospective measures of birthweight, 'healthy-worker' effects, and only partial information on potential confounding factors. Moreover, if a stronger birthweight-cholesterol association does exist

for males, it is necessary to determine whether this is generalisable across age-groups, populations, and birth cohorts. Given these outstanding issues there has been a call for further examination of sex differences in the association between birthweight and cholesterol.[3;11] Further research is justified given: there is still no clear understanding of the nature of the association between birthweight and lipids in later life due to inconsistencies between and, limitations of existing studies including a failure to take appropriate account of later body size[14;15] and; the restricted focus on sex differences in the association for total cholesterol when other lipid measures also predict cardiovascular disease risk.

Using data from a large British population, the 1958 birth cohort, collected prospectively from birth onwards, the objective of this study was to examine sex differences in the associations between birthweight and lipids in middle-age and, to investigate the effect on associations and, any sex differences in these, of adjusting for a range of covariates, including later body size.

Methods

Study population

The 1958 British birth cohort consists of 17,638 males and females followed up since the time of their births during one week in March 1958 across England, Scotland and Wales.[16] The cohort also includes 920 immigrants with the same birth dates who were recruited into the study up to age 16y. 11,971 cohort members (of whom 467 were immigrants) were invited to participate in a biomedical survey at age 44-45y, 9,377 (78%) responded. Of these, we excluded the 363 immigrant respondents because they lacked perinatal data.

Measures

Non-fasting venous blood samples were taken at age 44-45y by nurses during home visits. Total and high density lipoprotein (HDL)-cholesterol and triglyceride levels were measured by an autoanalyzer (Olympus AU640, Japan) using enzymatic methods. Low density lipoprotein (LDL)-cholesterol levels were calculated using the Friedewald formula.[17] For participants with a triglyceride level >4.5mmol/L, LDL-cholesterol levels were not calculated and for those with a triglyceride level >13mmol/L, HDL-cholesterol levels were not measured.

Birthweight was measured at time of birth in ounces and converted into kilograms. Gestational age, included because recent evidence suggests that this may be associated with cardiovascular disease risk factors,[18-20] was recorded as days since the start of last menstrual period at birth and converted into weeks. Height at age 7y was measured during medical examinations. Height at age 44-45y was measured using Leicester portable stadiometers during physical examinations performed by nurses at study participants' homes. We calculated current body mass index (BMI, kg/m^2) using these height measures and weight measured by nurses using Tanita solar scales during the 44-45y interview. Self-reported weights (n=60) and heights (n=103) were used if measurements were considered to be inaccurate or consent for measurement was not provided.

Father's occupational class at birth (or at age 7y if missing at birth (n=308)) and own occupational class at age 42y (or 33 if missing at age 42 (n=852)) were categorised into four groups using the Registrar General's Social Classification: I or II; IIINM; IIIM; IV or V (or no male head in childhood). Educational level attained was recorded at age 33y and

categorised into five groups: degree or higher; advanced secondary qualifications; ordinary secondary qualifications; below secondary qualifications; no qualifications.

Physical activity was ascertained at age 42y from questions on how often cohort members participated in a range of activities.[21] This information was used to create a variable with four categories: active ≤3 times/month; 1 day/week; 2-3 days/week; 4-7 days/week.

Menopausal status at age 44-45y was ascertained from women's responses to questions on menstrual periods, cessation of these, hysterectomy and hormone replacement therapy (HRT) use. A variable with six categories was created: pre-menopausal (menstruation reported within the last 3 months); peri-menopausal (3-12 months of amenorrhea or reports of periods becoming less regular in the absence of amenorrhea); post-menopausal (at least 12 months of amenorrhea with no reason reported to explain this); periods stopped for other reason (i.e. surgery (including hysterectomy and/or bilateral oophorectomy), chemotherapy or radiation therapy) and not currently using HRT; periods stopped for other reason and currently using HRT; not hysterectomised and currently using HRT.

Smoking status was ascertained at age 42y (or at 33y if missing at age 42 (n=168)). This was categorised into three groups: current; never; ex-smoker. Using participants' responses to two questions about drinking frequency and amount, taken from the Alcohol Use Disorders Identification Test questionnaire[22] asked at age 44-45y, a quantity-frequency index of current alcohol use was created which gave a measure of the average number of standard drinks consumed per week. This was categorised into five groups: non-drinker; 1-7; 7-14; 14-21; >21 drinks/week.

Statistical analyses

Linear regression analyses were performed to test the unadjusted associations between birthweight and each of the four lipids. As the distribution of triglycerides was positively skewed we used a natural log transformation; geometric means are presented and the regression coefficients multiplied by 100 can be interpreted as the percentage difference in triglyceride levels.[23] Tests of deviation from linearity were performed and likelihood ratio tests were used to test birthweight x sex interactions.

Using multivariate regression analyses adjustments were made for covariates. When making adjustments for height at age 7 years and current BMI and height we used the strategy proposed by Lucas and colleagues[24] of examining: the unadjusted association between birthweight and each lipid; the association between birthweight and each lipid adjusted for later size; the unadjusted association between later size and each lipid and; the interactions between birthweight and later size. This strategy has been recommended to overcome potential problems of interpretation when correlated measures of body size are examined simultaneously.[24] In further analyses birthweight, current BMI and height were standardised and the associations between these three measures and lipids were assessed. Because it has been proposed that, in women, there may be variation in the association between birthweight and lipid levels by menopausal status,[12;25] we also tested interactions between birthweight and menopausal status.

All results presented are based on the maximum available sample, with the only exclusion being one woman who was pregnant at the 44-45y survey. We also repeated analyses after excluding: multiple births (n=161); premature births (i.e. gestational age <37 weeks) (n=251); unknown gestational age (n=685); non-Caucasians (n=72); participants taking lipid-regulating

medication (n=120) (British National Formula (BNF) 44 (2002) code 02.12.00 identified from reports of medication use recorded by nurses at age 44-45y); and participants taking other drugs which may affect lipid levels (n=114) i.e. progestins (BNF codes 07.03.02 and 08.03.02), anabolic steroids (BNF code 06.04.03) and corticosteroids (BNF codes 06.03.00, 06.03.01 and 06.03.02). Finally, we adjusted for factors which could affect lipid measures. These factors were: delay in the laboratory receiving the blood sample (measured in days, ranging from blood received by the laboratory within 1 day (n=1401 (19.5%)) to ≥ 4 days (n=616 (8.6%))); time of day of blood collection (in hours ranging from 09:00 to 22:00 (2037 (28.3%) people had blood collected between 09:00 and 12:00, 2513 (35.0%) between 13:00 and 18:00 and, 2636 (36.7%) between 19:00 and 22:00)); month of blood collection (ranging from January (n=558 (7.8%)) to December (n=266 (3.7%))) and; time since last eaten (ranging from <1/2 hour ago (n=721 (10.1%)) to >8 hours (n=106 (1.5%)). Each of these factors was entered into all of the main models run, separately and then simultaneously. Results from these analyses are not presented as neither the exclusions nor adjustments greatly altered the magnitude or significance levels of associations.

Ethical approval was obtained for this study from the South East Multi-centre Research Ethics Committee (ref: 01/1/44) and study participants gave informed consent.

Results

Within the cohort, 3,603 men and 3,583 women had complete data on birthweight and total cholesterol at age 44-45y. Men had higher birthweight, total and LDL-cholesterol and triglyceride levels and lower HDL-cholesterol levels than women (table 1). There were also sex differences in the distribution of lifestyle and socio-demographic factors.

There were sex differences in the associations between birthweight and total and LDL-cholesterol (p=0.005 and p=0.01, respectively, from tests of birthweight x sex interactions). Among women there were inverse associations between birthweight and total and LDL-cholesterol (a 1 kg increase in birthweight was associated with a 0.13 mmol/L reduction in total cholesterol (95% CI, -0.20 to -0.07) and a 0.07 mmol/L reduction in LDL-cholesterol (95% CI, -0.12 to -0.01)) whereas positive, non-significant associations were found among men (table 2). No association was observed between birthweight and HDL-cholesterol in either sex. However, an inverse association between birthweight and triglyceride levels was of a similar magnitude among both sexes; a 1kg increase in birthweight was associated with a 7% reduction in triglyceride levels (95% CI, -10% to -5%) in a sex-adjusted model. There were no significant deviations from linearity in any of the models.

Adjustments for covariates, specifically gestational age, smoking status, alcohol use, physical activity levels, indicators of lifetime socioeconomic position and menopausal status did not alter the study findings. There were no interactions between menopausal status and birthweight.

There were only small changes in the magnitude of most birthweight-lipid associations after adjustment for current height and BMI (table 3). Associations which had been significant in unadjusted analyses tended to remain so after adjustment for measures of later size and, the sex differences for total and LDL-cholesterol remained. While adjustment for current BMI altered the direction of the association between birthweight and total cholesterol among men this association remained non-significant. Adjustment for current BMI strengthened the associations between birthweight and HDL-cholesterol sufficiently for them to become

statistically significant among men and the total sex-adjusted sample. No significant interactions were found between birthweight and current BMI or height.

Current BMI was associated with all four lipid measures: increases in BMI were associated with increased levels of total and LDL-cholesterol and triglycerides and decreased HDL-cholesterol (table 3). Adjustments for birthweight and current height did not alter these associations. The strength of associations between BMI and all lipids except LDL-cholesterol varied by sex; associations were in the same direction in both sexes but increases in BMI were associated with greater increases in total cholesterol and triglyceride levels among men than women (p=0.002 for both BMI x sex interactions) whereas they were associated with greater decreases in HDL-cholesterol among women (p=0.01 for BMI x sex interaction).

Current height was inversely associated with total and LDL-cholesterol and triglyceride levels (table 3) with no evidence of sex differences in these associations. The association between current height and HDL-cholesterol varied by sex (p=0.001 for height x sex interaction); a one standard deviation increase in height was associated with a small reduction in HDL-cholesterol levels among men and a small increase among women. Adjustment for current BMI and birthweight attenuated most associations. Height at age 7y was not associated with HDL-cholesterol or triglyceride levels and associations with total and LDL-cholesterol were similar to those observed for adult height. For example, in unadjusted analyses of men, a one standard deviation increase in height at age 7y was associated with a change in total cholesterol at age 44-45y of -0.07mmol/L (95% CI: -0.11, -0.02). In the same sample (n=3056) a one standard deviation increase in height at age 44-45y was associated with a change of -0.08mmol/L (95% CI: -0.14, -0.03).

When comparing the effects of one standard deviation changes in birthweight, current BMI and height, it is seen that changes in lipid levels are greater in association with current BMI than with either birthweight or current height (table 3).

Discussion

In a large British birth cohort we found inverse associations between birthweight and total and LDL-cholesterol among women in middle-age, but no associations among men. Birthweight was inversely associated with triglyceride levels by a similar magnitude in both sexes. These associations and sex differences were not explained by covariates including later size despite there being sex differences in the associations between current BMI and lipid levels also. There was no independent association between birthweight and HDL-cholesterol. Current BMI was a stronger predictor of lipid levels in middle-age than birthweight or height, with increased adiposity in adulthood associated with a more atherogenic lipid profile.

Methodological considerations

The use of non-fasted blood samples taken at different times of day may be considered a limitation of this study. While total and HDL-cholesterol are not significantly affected by fasting status, fasting triglyceride levels are lower than non-fasting levels,[26] vary by duration of fasting and time of day of blood collection[27] and thus may be inappropriate for screening or clinical purposes. However, misclassification of triglyceride levels by birthweight is unlikely and adjusting for time of blood collection and time since consuming food (as described in the methods section above) did not alter our findings. Further, fasting and non-fasting levels of triglycerides are positively correlated,[28] a meta-analysis found that results from analyses of triglyceride levels did not vary by fasting status[29] and, recent studies have shown that non-fasting triglyceride levels are a significant risk factor for cardiovascular disease.[30;31] This

suggests that for analyses such as ours non-fasting lipid measures, including triglycerides, are acceptable. It has been shown that LDL-cholesterol levels estimated using the Friedewald formula are highly correlated with measures from direct methods such as ultracentrifuge.[32] However, the level of error in estimated levels increases with increasing triglyceride levels, hence it is recommended that the Friedewald formula should not be used when triglyceride levels >4.5mmol/L.[33] Exclusion of people with elevated triglyceride levels from calculations of LDL-cholesterol levels leads to the exclusion of more men than women and could introduce bias. However, sensitivity analyses and the similarity in findings for total and LDL-cholesterol (which are highly correlated) suggest that these exclusions are unlikely to explain our findings on LDL-cholesterol. Bias may also have been introduced due to loss to follow-up between birth and adulthood. Participants not included in analyses were more likely to have lower birthweight and lifetime socioeconomic position than those participants included.

Comparison with other studies

Given that the associations between birthweight and all lipid levels, except HDL-cholesterol, were independent of later size and, there were no interactions between birthweight and later size, our study suggests that birthweight reflects prenatal rather than postnatal conditions. Thus, factors and developmental processes in utero which influence birthweight may affect total and LDL-cholesterol and triglyceride levels in middle-age although some associations were found to be sex-specific. That the association between birthweight and HDL-cholesterol was weak and only significant after adjustment for current BMI, suggests that factors in utero are of lesser importance than postnatal weight gain in determining HDL-cholesterol levels.

Several previous studies have examined the association between birthweight and lipid levels, some of which also examined sex differences in these associations. Reviews[3;14;15;34] have

found that very few studies had prospective follow-up from birth, especially if adult outcomes were examined, most had a sample size <1000 and many had insufficient control for covariates, including a failure to appropriately consider later body size. Such limitations could explain inconsistencies in results between studies. Our study has important strengths in respect of these limitations including its size (only one study[11] in the recent meta-analysis[3] of sex differences was larger), selection to be nationally representative, prospective follow-up since birth, and information collected on a range of covariates from across life.

While the estimated size of the sex-adjusted association between birthweight and total cholesterol from our analyses is similar to the results from other studies[12;34] this combined result masks a significant sex difference. The sex difference in our study is in the opposite direction to that reported in the 1946 cohort,[12] a British occupational cohort[11] and in a meta-analysis of 30 studies.[3] However, ours is not the first study to find a stronger inverse association among females; several studies[35-38] in the recent meta-analysis also reported this finding although these differences were small and usually not significant at conventional levels demonstrating the heterogeneity of results and the lack of power which is a limitation of most previous studies.

The authors of one study which found an inverse association between birthweight and total cholesterol among men but not women proposed that this was due to the pre-menopausal status of the women in their study.[25] However, in our study an inverse association between birthweight and total cholesterol was found among women, the majority of whom (63.7%) were pre-menopausal and, although stronger inverse associations were found among peri- and post-menopausal groups compared to the pre-menopausal group differences were not significant and, associations in all menopausal groups were in the same direction.

In our study population lipid levels were measured in middle-age, similar to two previous studies[11;12] in which stronger associations between birthweight and total cholesterol were found for men. Thus, variation in age of measurement of lipids is unlikely to explain the discrepancies between studies. Methodological differences may partially explain differences between our findings and those from a British occupational cohort,[11] but are an unlikely explanation of the inconsistent results between our study and the similarly designed 1946 British birth cohort.

Of other potential explanations, it seems unlikely that variation in BMI at the time of lipid measurement could explain inconsistencies between studies as adjustments for current BMI were made in analyses. However, such adjustments may be an inadequate representation of lifetime weight trajectories. The 1958 cohort have higher average BMI in adulthood and began gaining weight at younger ages when compared with the 1946 cohort. This and other differences in postnatal characteristics could potentially explain the divergent directions of sex differences found between cohorts. Finally, it is possible that, as for blood pressure,[13] sex differences in the associations between birthweight and lipid levels found in studies including our own are due to chance. In support of this latter explanation, sex differences in the association between birthweight and total cholesterol were abolished when results from the 1958 cohort were added to the meta-analysis[3] (pooled within study sex difference in regression coefficient: -0.02 (95% CI: -0.05, 0.01)) (DA Lawlor, PhD, unpublished data, 2007).

HDL-, LDL-cholesterol and triglycerides are much less well studied than total cholesterol and of these only the latter is consistently inversely associated with birthweight in other studies,

including those with a similar age of outcome measurement to ours.[14;39] Our study results provide further support for the existence of an inverse association between birthweight and triglycerides demonstrating an association in both sexes, independent of later size and growth.

In contrast, associations between birthweight and HDL- and LDL-cholesterol have been less consistent. In the 1946 British birth cohort, neither LDL- or HDL-cholesterol in middle-age were significantly associated with birthweight[12] although a positive association for HDL-cholesterol was found in sex-adjusted models after adjustment for current size, similar to our finding. Other studies[39;40] also with outcome measurement in adulthood found no association between birthweight and LDL-cholesterol levels thus, our finding of an inverse association among women in a larger study population contrasts with these other studies which have lower power to detect any small effects of birthweight.

Explanation of findings

Fetal 'programming' is one potential explanation of an inverse association between birthweight and lipid levels. It has been proposed[41;42] that undernutrition in utero could, as well as restricting birthweight, affect liver development, and as this organ regulates lipid metabolism, cause permanent, detrimental changes to this process. Even though stronger inverse birthweight-lipid associations in males than females might lend support to the 'programming' hypothesis, our finding of a stronger inverse association among females does not rule out this explanation. It is possible that males are not, as has been suggested, more susceptible to 'programming' than females or that 'programming' occurs in both sexes but some postnatal factor overrides a 'programming' effect in males. The latter is possible given that the liver, unlike many other organs, remains plastic after birth[42] and there are sex differences in postnatal factors. However, to test this explanation it would be necessary to

examine associations between birthweight and lipid levels at birth and then again at later ages which no study, as far as we are aware, has done.

The inverse association between birthweight and triglycerides, and the consistency of this association across studies, suggests that there may be different explanations underlying this association and the associations between birthweight and other lipids. It has been proposed that elevated triglyceride levels could be associated with low birthweight via an insulin resistant genotype,[12;14] termed the 'fetal insulin hypothesis'.[43] Finally, other genetic or unidentified postnatal factors could potentially explain associations between birthweight and lipid levels.

Conclusion

This study suggests that prenatal factors which influence birthweight may affect lipid levels in middle-age. However, the finding of an inverse association between birthweight and triglycerides in both sexes and of inverse associations between birthweight and total and LDL-cholesterol only in women suggests that the mechanisms underlying the associations with birthweight may vary for different lipids.

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Conflicts of interest

None

Table 1. Characteristics of the 3,603 men and 3,583 women with data on birthweight and total cholesterol

	Men		Women		p value*
	Total N	Mean (SD) or N(%)	Total N	Mean (SD) or N(%)	
Birthweight (kg)	3603	3.44 (0.52)	3583	3.29 (0.50)	<0.001
Gestational age (weeks)	3264	39.69 (1.72)	3238	39.78 (1.68)	0.04
Lipid levels at age 44-45y (mmol/L)					
Total cholesterol	3603	6.08 (1.15)	3583	5.70 (1.00)	<0.001
HDL cholesterol	3590	1.44 (0.34)	3579	1.69 (0.41)	<0.001
LDL cholesterol	3266	3.58 (0.93)	3514	3.29 (0.87)	<0.001
Triglycerides†	3589	2.09 (1.79)	3576	1.37 (1.71)	<0.001
Height (cm) at age 7y	3060	123.08 (5.69)	3032	122.16 (5.91)	<0.001
Height (cm) at age 44-45y	3598	176.13 (6.66)	3581	162.63 (6.17)	<0.001
BMI (kg/m^2) at age 44-45y	3592	27.72 (4.17)	3577	26.95 (5.55)	<0.001
Smoking status at age 42y	3572		3560		0.18
Never smoker		1673 (46.84)		1707 (47.95)	
Alcohol use at age 44-45y	3582		3568		<0.001
Non-drinker		153 (4.27)		282 (7.90)	
Physical activity level at age 42y	3486		3485		<0.001
4-7 times/week		862 (24.73)		979 (28.09)	
Father's occupational class at birth	3587		3574		0.65
I or II		687 (19.07)		646 (18.07)	
Own occupational class at age 42y	3482		3410		<0.001
I or II		1613 (46.32)		1272 (37.30)	
Educational level attained	3086		3210		<0.001
Degree or higher		961 (31.14)		887 (27.63)	
Menopausal status at age 44-45y	-	-	3478		-
Pre-menopausal, not using HRT				2216 (63.71)	

* from test of difference between sexes (t-test for continuous variables and chi-squared test for categorical variables (testing differences across all categories described in methods rather than just those shown))
† Geometric mean

Table 2. The unadjusted associations between birthweight (kg) and lipid levels (mmol/L) at age 44-45y

	N	β* (95% CI)	p value	p value†
Total cholesterol				
Men	3603	0.005 (-0.07, 0.08)	0.90	
Women	3583	-0.13 (-0.20, -0.07)	<0.001	
Total‡	7186	-0.06 (-0.11, -0.01)	0.01	0.005
LDL-cholesterol				
Men	3266	0.04 (-0.02, 0.11)	0.16	
Women	3514	-0.07 (-0.12, -0.01)	0.02	
Total‡	6780	-0.01 (-0.05, 0.03)	0.58	0.01
HDL-cholesterol				
Men	3590	0.01 (-0.01, 0.03)	0.21	
Women	3580	0.01 (-0.02, 0.03)	0.67	
Total‡	7170	0.01 (-0.01, 0.03)	0.25	0.65
$\log_e$(triglycerides)				
Men	3589	-0.06 (-0.09, -0.02)	0.003	
Women	3576	-0.09 (-0.12, -0.05)	<0.001	
Total‡	7165	-0.07 (-0.10, -0.05)	<0.001	0.19

* change in lipid level (mmol/L) per 1kg increase in birthweight for total, LDL- and HDL-cholesterol and, relative change (which when multiplied by 100 is the % change) in triglyceride levels per 1kg increase in birthweight

† from test of interaction between birthweight and sex

‡ adjusted for sex

Table 3. The associations between standardised measures of birthweight, current BMI and height and lipid levels (mmol/L) at age 44-45 years

		Standardised birthweight β* (95% CI)	Standardised BMI at age 44-45y β* (95% CI)	Standardised height at age 44-45y β* (95% CI)
Total cholesterol				
Men (n=3592)	Unadjusted	0.003 (-0.03, 0.04)	0.18 (0.14, 0.23)†	-0.10 (-0.15, -0.05)†
	Adjusted for birthweight	-	0.19 (0.14, 0.23)†	-0.11 (-0.16, -0.06)†
	Adjusted for BMI	-0.01 (-0.04, 0.03)	-	-0.09 (-0.14, -0.04)†
	Adjusted for height	0.02 (-0.01, 0.06)	0.18 (0.14, 0.23)†	-
	Fully-adjusted‡	0.01 (-0.02, 0.05)	0.18 (0.14, 0.22)†	-0.10 (-0.15, -0.04)†
Women (n=3577)	Unadjusted	-0.07 (-0.10, -0.04)†	0.10 (0.08, 0.13)†	-0.09 (-0.14, -0.04)†
	Adjusted for birthweight	-	0.11 (0.08, 0.14)†	-0.07 (-0.12, -0.02)†
	Adjusted for BMI	-0.08 (-0.11, -0.04)†	-	-0.08 (-0.13, -0.03)†
	Adjusted for height	-0.06 (-0.09, -0.02)†	0.10 (0.07, 0.13)†	-
	Fully-adjusted‡	-0.07 (-0.10, -0.03)†	0.10 (0.08, 0.13)†	-0.05 (-0.10, 0.001)
LDL-cholesterol				
Men (n=3259)	Unadjusted	0.02 (-0.01, 0.05)	0.12 (0.08, 0.16)†	-0.04 (-0.09, 0.002)
	Adjusted for birthweight	-	0.12 (0.08, 0.16)†	-0.06 (-0.10, -0.01)§
	Adjusted for BMI	0.02 (-0.02, 0.05)	-	-0.04 (-0.08, 0.01)
	Adjusted for height	0.03 (0.001, 0.07)§	0.12 (0.08, 0.16)†	-
	Fully-adjusted‡	0.03 (-0.01, 0.06)	0.12 (0.08, 0.15)†	-0.05 (-0.09, -0.003)§
Women (n=3508)	Unadjusted	-0.04 (-0.06, -0.01)§	0.11 (0.09, 0.14)†	-0.08 (-0.12, -0.03)†
	Adjusted for birthweight	-	0.12 (0.09, 0.14)†	-0.07 (-0.11, -0.02)†
	Adjusted for BMI	-0.04 (-0.07, -0.01)†	-	-0.06 (-0.10, -0.02)†
	Adjusted for height	-0.02 (-0.05, 0.01)	0.11 (0.09, 0.14)†	-
	Fully-adjusted‡	-0.03 (-0.06, -0.002)§	0.11 (0.09, 0.14)†	-0.05 (-0.09, -0.001)§
HDL-cholesterol				
Men (n=3579)	Unadjusted	0.01 (-0.004, 0.02)	-0.11 (-0.13, -0.10)†	-0.02 (-0.03, -0.001)§
	Adjusted for birthweight	-	-0.11 (-0.13, -0.10)†	-0.02 (-0.04, -0.005)§
	Adjusted for BMI	0.01 (0.002, 0.02)§	-	-0.02 (-0.04, -0.01)†
	Adjusted for height	0.01 (-0.0005, 0.02)	-0.11 (-0.13, -0.10)†	-
	Fully-adjusted‡	0.02 (0.01, 0.03)†	-0.12 (-0.13, -0.10)†	-0.03 (-0.04, -0.01)†
Women (n=3573)	Unadjusted	0.003 (-0.01, 0.02)	-0.14 (-0.15, -0.12)†	0.03 (0.01, 0.05)†
	Adjusted for birthweight	-	-0.14 (-0.15, -0.12)†	0.03 (0.01, 0.05)†
	Adjusted for BMI	0.01 (-0.003, 0.02)	-	0.01 (-0.01, 0.03)
	Adjusted for height	-0.003 (-0.02, 0.01)	-0.13 (-0.15, -0.12)†	-
	Fully-adjusted‡	0.01 (-0.005, 0.02)	-0.14 (-0.15, -0.12)†	0.004 (-0.02, 0.02)
$\log_e$(triglycerides)				
Men (n=3578)	Unadjusted	-0.03 (-0.05, -0.01)†	0.21 (0.19, 0.24)†	-0.03 (-0.06, -0.01)§
	Adjusted for birthweight	-	0.22 (0.20, 0.24)†	-0.02 (-0.05, 0.01)
	Adjusted for BMI	-0.04 (-0.06, -0.02)†	-	-0.02 (-0.05, 0.003)
	Adjusted for height	-0.02 (-0.04, -0.005)§	0.21 (0.19, 0.23)†	-
	Fully-adjusted‡	-0.04 (-0.06, -0.02)†	0.22 (0.19, 0.24)†	-0.01 (-0.03, 0.02)
Women (n=3570)	Unadjusted	-0.05 (-0.06, -0.03)†	0.17 (0.16, 0.19)†	-0.06 (-0.09, -0.04)†
	Adjusted for birthweight	-	0.17 (0.16, 0.19)†	-0.05 (-0.08, -0.02)†
	Adjusted for BMI	-0.05 (-0.07, -0.04)†	-	-0.04 (-0.06, -0.01)†
	Adjusted for height	-0.04 (-0.06, -0.02)†	0.17 (0.16, 0.19)†	-
	Fully-adjusted‡	-0.05 (-0.07, -0.03)†	0.17 (0.16, 0.19)†	-0.02 (-0.04, 0.01)

* change in lipid level (mmol/L) per 1 standard deviation increase in size for total, LDL- and HDL-cholesterol and, relative change (which when multiplied by 100 is the % change) in triglyceride levels per 1 standard deviation increase in size

† $p \leq 0.01$

‡ adjusted for both other measures of size
§ 0.05≥p>0.01

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