

## RESEARCH REPORT

# Birth weight is inversely associated with coronary heart disease in post-menopausal women: findings from the British women's heart and health study

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**Objectives:** (1) To assess the association between birth weight and coronary heart disease (CHD) risk in a cohort of post-menopausal women, (2) to determine the combined effects of birth weight and adult body mass index on CHD, (3) to assess the role of insulin resistance as a mediating factor in the associations.

**Design:** Cross sectional survey.

**Setting:** 23 British towns.

**Participants:** 1394 women aged 60–79 years.

**Main outcome measures:** coronary heart disease (n = 199 cases).

**Results:** Birth weight was inversely associated with CHD: age and survivor status of participant's mother adjusted odds ratio (95% confidence intervals) per 1 standard deviation (0.80 kg) increase in birth weight was 0.84 (0.72 to 0.97). This association strengthened to 0.80 (0.68 to 0.93) with further adjustment for adult body mass index, but there was no evidence of an interaction between birth weight and adult body mass index ( $p=0.61$ ). The association was not confounded by childhood or adulthood socioeconomic position or by adult smoking status of the participant. Adjustment for components of the insulin resistance syndrome attenuated the association to 0.87 (0.72 to 1.03).

**Conclusions:** Intrauterine exposures that affect fetal growth also affect future adult CHD risk. The inverse association between birth weight and CHD may in part be mediated via insulin resistance.

Birth weight seems to be inversely associated with coronary heart disease (CHD) risk factors, such as hypertension, dyslipidaemia, and glucose intolerance.<sup>1,2</sup> However, only a small number of studies have looked at the association between birth weight and CHD. Most,<sup>3–9</sup> though not all<sup>10,11</sup> of these studies, have shown an inverse association between birth size and CHD in women and men, though results in women have often been imprecise because of the small number of CHD cases among women in several studies.<sup>12</sup>

The existence of a causal association between birth size and adult cardiovascular disease has been questioned, and in particular it has been suggested that socioeconomic position in childhood as well as adulthood may confound this association.<sup>13</sup> In addition, with respect to the association of birth weight with blood pressure, which has been extensively investigated, the inverse association in many studies has been dependent upon adjustment for contemporary body mass index.<sup>13,14</sup> This finding has led to the suggestion that post-natal factors that affect growth may be more important than intrauterine factors.<sup>14</sup> To this end Lucas *et al* have proposed a series of four regression models to assess the individual and combined effects of birth weight and body mass index, in order to assess the fetal origins compared with post-natal hypotheses.<sup>14</sup> In one study an interaction between birth weight and adult body mass index was found, such that the inverse association between birth weight and CHD was only present among men in the highest third of adult body mass index.<sup>6</sup> In a second study men with CHD, compared with those without, had low birth weight and low weight at 1 year, followed by accelerated post-natal increase in weight and body mass index and, to a lesser extent, height.<sup>9</sup> However, in most studies the inverse association between birth weight and CHD is not dependent upon adjustment for body mass index.<sup>4,7,8</sup> To date, studies assessing the

association of birth weight with CHD have not systematically applied the regression models suggested by Lucas *et al*.<sup>14</sup>

Insulin resistance may be an important mediator in the association between birth weight and CHD, either because of programming of changes in insulin metabolism and action<sup>15</sup> or via genetic factors with pleiotropic effects on both insulin mediated fetal growth and insulin resistance in later life.<sup>16</sup> However, no studies have specifically assessed the role of insulin resistance as a mediating factor in the birth weight-CHD association. As ovarian function may be programmed during the intrauterine period, life time exposure to endogenous oestrogen may also mediate any association between birth weight and CHD in women. This could be assessed to some extent by examining the effect on any association of adjustment for menopausal age, though again to date this has not been investigated.

The aims of this study are to assess the association between birth weight and CHD risk in a cohort of post-menopausal women, to determine whether this is confounded by socioeconomic position in childhood and adulthood, to examine the combined effects of birth weight and adult body mass index on CHD, and to assess the role of insulin resistance and menopausal age as mediating factors in the association.

## METHODS

### Participants

This is a cross sectional examination of baseline data collected for the British women's heart and health study. Full details of the selection of participants and measurements have been previously reported.<sup>17,18</sup> Women aged 60–79 years

**Abbreviations:** CHD, coronary heart disease; HOMA, homeostasis model assessment

**Table 1** Prevalence of CHD and means and prevalences of other characteristics across thirds of birth weight

	Birth weight third (range kg)			p linear trend across thirds
	Lowest (1.50 to 3.06) n=477	Middle (3.07 to 3.64) n=532	Highest (3.65 to 4.57) n=385	
Age (y)	67.3 (66.8 to 67.8)	68.0 (67.5 to 68.5)	68.3 (67.7 to 68.8)	0.006
CHD (%)	17.4 (14.2 to 21.1)	13.9 (11.3 to 16.8)	12.1 (9.2 to 15.9)	0.01
<b>Adult anthropometric measures</b>				
Weight (kg)	68.9 (67.7 to 70.1)	70.3 (69.2 to 71.5)	72.4 (70.9 to 73.8)	<0.001
Height (m)	1.58 (1.57 to 1.59)	1.60 (1.59 to 1.61)	1.62 (1.61 to 1.63)	<0.001
Body mass index (kg/m <sup>2</sup> )	27.5 (27.1 to 28.0)	27.7 (27.2 to 28.1)	27.9 (27.2 to 28.3)	0.55
Waist to hip ratio	0.823 (0.817 to 0.830)	0.817 (0.810 to 0.823)	0.817 (0.809 to 0.824)	0.15
<b>Potential mediating factors (components of the insulin resistance syndrome and menopausal age)</b>				
Diabetes (%) <sup>a</sup>	7.5 (5.4 to 10.3)	5.5 (3.8 to 10.3)	6.8 (4.6 to 9.8)	0.62
HOMA score†	1.76 (1.64 to 1.88)	1.68 (1.59 to 1.79)	1.44 (1.34 to 1.55)	0.001
Systolic BP (mm Hg)	144.8 (142.6 to 147.1)	146.5 (144.3 to 148.7)	144.0 (141.5 to 146.7)	0.74
Diastolic BP (mm Hg)	78.8 (77.7 to 79.9)	79.1 (78.1 to 80.1)	78.2 (77.0 to 79.4)	0.55
HDLc (mmol/l)	1.66 (1.62 to 1.70)	1.67 (1.62 to 1.72)	1.67 (1.62 to 1.72)	0.76
Triglyceride values (mmol/l)†	1.72 (1.64 to 1.79)	1.68 (1.61 to 1.76)	1.64 (1.55 to 1.72)	0.19
Age menopause (y)	49.7 (48.2 to 50.2)	49.3 (48.8 to 49.9)	49.4 (48.9 to 49.9)	0.40
<b>Potential confounding factors (indicators of childhood and adult socioeconomic position and smoking)</b>				
Childhood manual social class (%)	77.9 (73.8 to 81.5)	75.5 (71.8 to 79.0)	73.6 (69.1 to 77.8)	0.07
No bathroom in house as a child (%)	38.4 (34.1 to 42.8)	33.0 (28.5 to 37.8)	25.4 (21.9 to 29.2)	0.06
No hot water in house as a child (%)	33.3 (29.2 to 37.7)	32.2 (27.7 to 37.0)	25.4 (21.9 to 29.2)	0.03
No family access to car as a child (%)	77.8 (73.8 to 81.3)	75.6 (71.7 to 79.0)	77.7 (73.5 to 81.8)	0.97
Left full time education younger than 15 years (%)	25.6 (21.9 to 30.0)	25.2 (21.7 to 29.0)	13.1 (11.4 to 14.8)	0.07
Adult manual social class (%)	48.2 (43.6 to 52.8)	45.0 (40.7 to 49.4)	42.7 (37.6 to 47.7)	0.05
No car access as adult (%)	23.6 (20.0 to 27.6)	22.6 (19.2 to 26.3)	22.7 (18.9 to 27.0)	0.74
Living in local authority housing (%)	9.6 (7.3 to 12.6)	8.8 (6.7 to 11.6)	10.9 (8.2 to 14.4)	0.57
No private or work pension (%)	22.2 (18.7 to 26.2)	24.4 (21.0 to 28.3)	22.6 (18.7 to 27.0)	0.85
Ever smoker (%)	50.0 (45.5 to 54.5)	43.8 (39.6 to 48.0)	50.6 (45.7 to 55.6)	0.97

<sup>a</sup>Doctor diagnosis of diabetes and/or fasting glucose concentration  $\geq 7.8$  mmol/l; †geometric means. CHD, coronary heart disease; HOMA, homeostasis model assessment (assessed in non-diabetics only); HDLc, high density lipoprotein cholesterol.

### Key points

- Birth weight is inversely associated with coronary heart disease
- This association is not dependent upon adjustment for contemporary body size and is not confounded by socioeconomic position
- If maternal smoking during pregnancy is associated with offspring coronary heart disease then this may confound the association
- The association is in part mediated via insulin resistance

were randomly selected from general practitioner lists in 23 British towns. A total of 4286 women (60% of the invited 7173) participated and baseline data (self completed questionnaire, research nurse interview, physical examination, and primary care medical record review) were collected between April 1999 and March 2001. Participants were slightly younger than non-responders but the prevalence of medical records of CHD were the same in participants and non-responders.<sup>17</sup> Local ethics committee approvals were obtained.

### Birth weight

The women were asked to report their birth weight in pounds (lb) and ounces (oz) in the self completed questionnaire. For comparisons with other studies the self reported birth weights were converted from lb to kg by multiplying by a factor of 0.4545. Of the 4286 participants, 1394 (33%) provided details of their birth weight. The analyses presented in this paper are restricted to those women with birthweight data.

### Coronary heart disease

Prevalent CHD was defined as any participant with a primary care medical record (obtained from a review of the written notes, computer notes, and hospital discharge letters) of myocardial infarction or angina (including those with a medical record of having had an angioplasty or coronary artery bypass), or any participant who reported ever being diagnosed by a doctor with one of these conditions or having one of these operative procedures.<sup>17</sup> Eighty per cent of those defined as having CHD were identified in both their medical records and from self report, 13% were identified in their medical records only, and 7% by self report only. When sensitivity analyses were conducted including only those women with a medical record of CHD as a case the results did not differ from those presented here.

### Other variables

Blood samples were taken after a minimum six hour fast (except for insulin dependent diabetics) using evacuated tubes. Serum insulin was measured using an enzyme linked immunosorbent assay (ELISA) assay that does not cross react with proinsulin.<sup>19</sup> Insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/l) and insulin ( $\mu$ U/ml) divided by the constant 22.5.<sup>20</sup> HOMA scores were not calculated for women with a fasting glucose of  $\geq 7.8$  mmol/l or those with a diagnosis of diabetes as the results are inaccurate in these groups.<sup>20</sup> In total 98 (7%) women of the 1394 included in the analysis had a diagnosis of diabetes and/or a fasting glucose level  $\geq 7.8$  mmol/l; for the

purpose of this analysis these women were all defined as having diabetes.

A Dinamap 1846SX vital signs monitor was used to measure blood pressure. Arm circumference was measured and the appropriate cuff size was used. The mean of two seated and resting measures was used in all analyses. Standing height was assessed using a Harpenden stadiometer that measured to the nearest millimetre. Weight was measured in light clothing without shoes to the nearest 0.1 kg using Soehnle portable scales. Waist measurements were taken using the midpoint between the lowest rib and iliac crest and hip measurements using the largest circumference below the waist. A flexible metal tape was used and the mean of two measurements taken to the nearest millimetre was used in the analyses.

Adult social class was defined on the basis of the longest held occupation of her husband for married women and her own longest held occupation for single women, childhood social class was defined on the basis of the longest held occupation of the participants' father, and both were classified according to the registrar general's classification.<sup>21</sup> Additional assessment of socioeconomic position in childhood and adulthood included self reports of whether the house the woman had lived in for the longest period as a child had an internal bathroom and whether it had a hot water supply, whether the family had access to a car when she was a child, the number of years of full time education completed by the participant, the participants current (adult) car access, housing tenure, and pension arrangements. Age at menopause was obtained from the self completed questionnaire in which women were asked to report in years the date of their last menstrual period. Women who had a hysterectomy before natural cessation of periods ( $n = 28$  with data on birth weight) were assigned the median (50 years) age of menopause for the remainder of the cohort.

### Statistical analysis

#### Validation of self reported birth weight

A  $\chi^2$  test for independence and Student's  $t$  test were used to compare differences between women who reported their birth weight and those who did not. The validity of recalled birth weight was assessed by examining its association with adult anthropometric measures as in a previous study.<sup>6</sup> As a further validation the distribution of birth weights among women in this study were compared with obstetric record recorded birth weights of British women of a similar age from two other studies: the Hertfordshire birth cohort (women born between 1923 and 1930) and the British 1946 birth cohort.

#### Combined effects of birth weight and contemporary size

The four models proposed by Lucas *et al*<sup>14</sup> were fitted. These are: (a) the association between birth weight and CHD; (b) that between adult body mass index and CHD; (c) a model including both birth weight and adult body mass index, and (d) a model additionally including the interaction between birth weight and adult body mass index.

#### Role of confounding and mediating factors in the association between birth weight and CHD

Birth weights were divided into thirds (the slightly unequal sizes of these thirds are because participants tended to round their birth weights to the nearest pound). The nature and magnitude of the association between CHD and other characteristics with birth weight was assessed by presenting means and prevalences across these thirds of birth weight. Multiple linear regression was used to examine the

**Table 2** Association of birth weight with CHD with adjustment for potential confounding and mediating factors

Model	Number with complete data	Age and maternal survival adjusted OR for CHD per 1 SD (0.80 kg) increase in birth weight (95% CI)	Fully adjusted OR for CHD per 1 SD (0.80 kg) increase in birth weight (95% CI)
<b>Potential confounding factors</b>			
Indicators of childhood social circumstances*	1387	0.84 (0.72 to 0.97)	0.83 (0.71 to 0.96)
All confounding factors†	1383	0.84 (0.72 to 0.97)	0.84 (0.72 to 0.97)
<b>Potential mediating factors</b>			
Insulin resistance (HOMA score)‡	1083	0.82 (0.69 to 0.98)	0.85 (0.72 to 1.01)
Insulin resistance/diabetes categories and other components insulin resistance syndromes§	1246	0.82 (0.70 to 0.97)	0.87 (0.72 to 1.03)
Menopausal age¶	1342	0.83 (0.72 to 0.97)	0.83 (0.71 to 0.97)

\*Indicators of childhood social circumstances: childhood occupational social class (entered as indicator variables: I, II, III non-manual, III manual, IV, V), childhood house with bathroom, childhood house with hot water, family access to car as a child (all binary variables); †all confounders: childhood and adulthood occupational social class (both entered as indicator variables: I, II, III non-manual, III manual, IV, V, VI), childhood house with bathroom, childhood house with hot water, family access to car as a child, car access as adult, living in local authority housing, no private or work pension (all binary variables), age at leaving full time education (split into thirds and entered as indicator variable) and smoking (never, past, and current—includes those who stopped in past six months, entered as indicator variable); ‡analysis among non-diabetics only; §components of insulin resistance syndrome: insulin resistance/diabetes (quarters of HOMA score with fifth category=diabetes, entered as an indicator variable), triglyceride concentrations (logged), waist to hip ratio (both entered as continuous variable), high density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure (all categorised into quarters and entered as indicator variables); ¶menopausal age categorised into quarters and entered as indicator variable.

associations of birth weight with insulin resistance and components of the insulin resistance syndrome. Multiple logistic regression was used to examine the associations of birth weight with prevalent CHD, with adjustment for potential confounding factors and mediating factors. As HOMA scores are not calculated for subjects with diabetes, this measurement could not be entered into a regression model without exclusion of all individuals with diabetes. To enter full data on insulin resistance diabetes status in logistic regression models, a categorical variable combining both HOMA scores and diabetic status was created, with the first four categories defined by the quarters of the HOMA score and a fifth category containing individuals with diabetes.

HOMA scores and triglyceride values had positively skewed distributions but logged values were normally distributed; geometric means are presented and logged values were used in the regression models. With these transformations residuals were normally distributed in all models. Where HOMA scores and triglyceride values were considered as outcomes the regression coefficients were exponentiated and proportionate changes per change in birth weight presented. In all analyses robust confidence intervals were estimated which take into account the clustering between participants from the same towns.

## RESULTS

### Validation of recalled birth weight

Women who recalled their birth weight were younger (67.9 versus 69.4 years,  $p < 0.001$ ) and more likely to have a mother who was still alive (10.9% versus 4.5%,  $p < 0.001$ ) than those who did not recall their birth weights. However, the prevalence of CHD and the distributions of other characteristics of the women considered in the analyses presented here did not differ between those with and without birth weight data (all  $p$  values  $> 0.22$ ). The mean (standard deviation) of recalled birth weights was 3.28 (0.80) kg, which is consistent with hospital records of women born between 1923 and 1930 in Hertfordshire (3.42 kg, SD not provided)<sup>4</sup>

and also with women participants in the 1946 British birth cohort (3.32 (0.49) kg (Dr D Kuh, University College London, personal communication). Table 1 shows the characteristics of women across thirds of birth weight. There was a graded positive association between recalled birth weight and both adult weight and adult height, as would be predicted from studies that have assessed the associations between observed birth weight and these adult anthropometric measures.<sup>22</sup> There was a weak inverse linear association between birth weight and waist to hip ratio, which has also been demonstrated with recorded birth weight.<sup>23</sup> Recalled birth weight was not strongly linearly associated with adult body mass index.

### Associations of birth weight and body mass index with CHD

Of the 1394 women with birthweight data 199 had CHD, giving a prevalence (95% CI) of 14.4% (12.6 to 16.4). Because of the associations between age and having a mother who was still alive with ability to report birth weight all multivariable analyses have been adjusted for participant age and maternal survival status. There was an inverse association between birth weight and CHD prevalence without adjustment for body mass index: age and maternal survival status adjusted odds ratio of CHD for a one standard deviation increase in birth weight (0.80 kg) was 0.84 (0.72 to 0.97),  $p = 0.02$ . There was a positive association between body mass index and CHD prevalence: age and maternal survival status adjusted odds ratio of CHD for a one standard deviation (5.01 kg/m<sup>2</sup>) increase in body mass index was 1.25 (1.08 to 1.45)  $p = 0.003$ . When birth weight and body mass index were simultaneously included in the regression model the inverse association between birth weight and prevalence CHD strengthened to 0.80 (0.68 to 0.93)  $p = 0.004$  and the positive association between body mass index and CHD remained unchanged. There was no evidence of a statistical interaction between birth weight and body mass index in their association with prevalent CHD ( $p = 0.61$ ).

### Effects of confounding and mediating factors on the associations between birth weight and CHD

Table 1 shows the distributions of potential confounding and mediating factors across thirds of birth weight. Birth weight was inversely associated with insulin resistance (HOMA score) and triglyceride concentrations. For a one standard deviation increase in birth weight (0.80 kg) the HOMA score decreased by 8% (95% CI: 4% to 13%),  $p < 0.001$ , with adjustment for age and maternal survival status and triglyceride levels decreased by 3% (0% to 5%),  $p = 0.08$ . Diabetes prevalence was lowest among those in the middle third of the birth weight distribution and there was no evidence of linear associations between birth weight and any of systolic or diastolic blood pressure or high density lipoprotein cholesterol. Birth weight was not strongly linearly associated with age at menopause. There were inverse associations between birth weight and belonging to a manual social class as a child, living in a house without a bathroom as a child, living in a house without hot water as a child, and belonging to a manual social class adulthood, but birth weight was not linearly associated with other indicators of socioeconomic position. Adult smoking status was not linearly associated with birth weight.

Table 2 shows the association between birth weight and CHD, with adjustment for potential confounding and mediating factors. There were small amounts of missing data on some potential confounding and mediating variables and HOMA scores were calculated only for women without diabetes. In this table age and maternal survival status adjusted odds ratios among only those with complete data on all variables included in the fully adjusted model are compared with the fully adjusted effect so that any change is not related to the fully adjusted analyses being performed on a subgroup. The age and maternal survival status adjusted odds ratios (third column) are all consistent with each other and with that for all 1394 women with birthweight data (0.84 (0.72 to 0.97)), suggesting that missing data have not lead to selection bias. In the fully adjusted models variables that were not linearly associated with birth weight (table 1) have been categorised and entered into models as indicator variables so that assumptions of linearity are not made. The inverse association between birth weight and CHD was not affected by adjustment for indicators of childhood socioeconomic position alone or by adjustment for all potential confounding factors (childhood and adult socioeconomic position and adult smoking status). To further assess the role of socioeconomic position as a confounding factor (or possible effect modifier) stratified analyses were performed with indicators of socioeconomic position that were strongly associated with birth weight. A variable "poor childhood housing" was derived, which indicated anyone who had lived in a house without a bathroom and/or hot water as a child. The age and maternal survivor status adjusted inverse association between birth weight and CHD was the same among both those who lived in poor childhood housing (0.84 (0.69 to 1.09)) and those who were not living in such circumstances (0.82 (0.67 to 0.98)),  $p$  for heterogeneity = 0.40. Similarly, the inverse association was the same among women from manual social classes in childhood (0.82 (0.70 to 0.97)) compared with non-manual social classes (0.87 (0.61 to 1.28)),  $p$  for heterogeneity = 0.83, and among those from manual social classes in adulthood (0.82 (0.68 to 0.99)) and those from non-manual social classes (0.84 (0.65 to 1.08)),  $p$  for heterogeneity = 0.39.

Adjustment for both insulin resistance alone (among non-diabetics) and for all components of the insulin resistance syndrome attenuated the association, though did not fully explain it. Adjustment for menopausal age did not affect the association between birth weight and CHD.

### DISCUSSION

Birth weight was inversely associated with CHD, independently of childhood and adult social class and smoking status, in this cohort of post-menopausal women. The association between birth weight and CHD prevalence was not dependent upon adjustment for contemporary body mass index. These findings suggest that intrauterine exposures that affect fetal growth also affect CHD risk. Adjustment for components of the insulin resistance syndrome moderately attenuated the association, suggesting that insulin resistance may play a part as a mediator in this association. Age at menopause did not seem to be an important mediator in this association.

#### Is the association attributable to confounding?

Adverse childhood socioeconomic circumstances, independently of adult socioeconomic position, predict CHD<sup>24</sup> and are associated with low birth weight.<sup>25</sup> We have previously shown a strong and graded linear association between childhood socioeconomic position and CHD risk in this cohort of women.<sup>26</sup> Here we have demonstrated that a number of childhood indicators of socioeconomic position (poor housing conditions and manual social class) are associated with low birth weight. Of the adult indicators of socioeconomic position only adult manual social class was linearly associated with birth weight. Clearly adult socioeconomic position cannot directly influence an individual's birth weight, but may act as a proxy for early life socioeconomic position. For this reason associations of early life socioeconomic position with birth weight are likely to be more robust than those with adult socioeconomic position, and complete control for the potential confounding effect of socioeconomic position in the association between birth weight and CHD will be best achieved by controlling for a number of indicators of socioeconomic circumstances from across the life course. Only one previous study has adjusted for socioeconomic position in both childhood and adulthood, and as with our study found that the association was not confounded by these factors.<sup>8</sup> Our results together with this study suggest that the association is not attributable to confounding by socioeconomic position.

A second potential important confounder to consider is maternal smoking during pregnancy. Maternal smoking is strongly predictive of low birth weight and may affect offspring CHD risk as maternal smoking is associated with offspring lung function in adulthood, a risk factor for CHD,<sup>27</sup> and because offspring of mothers who smoke may be more likely to smoke themselves.<sup>28</sup> We adjusted for adult smoking status among participants and found that this did not confound the association. However, adjustment for maternal smoking status during pregnancy is likely to be more important. In particular, in this study we did not find that women who had ever smoked had lower birth weights than those who had never smoked. No other study has been able to adjust for maternal pregnancy smoking in the association between birth weight and CHD risk and if maternal smoking is associated with increased offspring CHD risk then this is a potentially important source of confounding in the association.

#### Study limitations

An important limitation was the use of self reported birth weight, and the fact that only one third of the original cohort had data on birth weight. Recalled birth weight was associated with adult anthropometric measures in the ways one would expect and the distribution of recalled birth weights in this cohort was similar to those of recorded weights for women in the Hertfordshire cohort and the 1946 British birth cohort. In a number of studies self reported birth weight has been found to correlate well with hospital records

(correlation coefficients in the range of 0.64 to 0.86), though absolute levels of accuracy may be poor.<sup>29</sup> High correlation coefficients between hospital recorded and self reported birth weights will mean that in analyses using self reported data, subjects will be ranked in a similar way to that which they would have been with hospital records, and linear associations should be only minimally diluted. Recall of birth weight in other studies, as in ours, is associated with age and whether the participants mother is still alive; in addition women are more likely to recall birth weight than are men.<sup>29</sup> Participant age and the survival status of the participant's mothers are also likely to be associated with the participant's CHD risk. We therefore adjusted results for these characteristics.

We do not have data on gestational age of these women. Birth weight adjusted for gestational age in other cohorts has tended to be more strongly inversely associated with CHD than birth weight alone,<sup>8,9</sup> and so our results may underestimate the association between intrauterine growth and CHD risk. As this analysis is cross sectional, survivor bias may be a problem. However, mortality from CHD before the age of 67 years (the mean age of women in this analysis) is rare and therefore survivor bias is unlikely to have importantly biased our results. Importantly, the magnitude of the association between birth weight and CHD found in our study is consistent with that found in two large prospective cohort studies with nearly 100% follow up and use of hospital recorded birth weights.<sup>8,9</sup> A further limitation is the use of a single measure of fasting insulin and glucose for the assessment of insulin resistance. As the secretion of insulin is pulsatile this may have resulted in some inaccuracy of our assessment of insulin resistance and resulted in incomplete adjustment for its effect in the association. Thus the role of insulin resistance may be greater than suggested by these results.

## Conclusion

We conclude that birth weight is inversely associated with CHD, that this association is not attributable to confounding by socioeconomic position in childhood or adulthood, and that insulin resistance may, at least in part, mediate the association. Several mechanisms have been proposed to explain this association, and all may be relevant. Adverse intrauterine environmental factors may "programme" permanent changes in organ development and metabolism (particularly those involved with insulin/glucose and lipid metabolism), leading to future adult disease.<sup>15</sup> It has also been suggested that genetic polymorphisms with pleiotropic effects are associated both with insulin mediated fetal growth and insulin resistance, and thence CHD in later life.<sup>16</sup> Although we found no interaction between birth weight and adult body mass index this finding does not preclude an important effect of accelerated post-natal growth in addition to intrauterine effects, as shown with data from the Helsinki cohort in which detail infant and childhood anthropometric measures are available.<sup>9</sup> Future research should try to elucidate the pathophysiology underlying in this association.

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## Contributors

All authors developed the study aim and design. DAL undertook the initial analysis and coordinated writing of the paper. All authors contributed to the final version. DAL acts as guarantor for the paper.

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