Birth weight of offspring and mortality in the Renfrew and Paisley study: prospective observational study

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Abstract

Objective: To investigate the association between birth weight of offspring and mortality among fathers and mothers in the west of Scotland.
Design: Prospective observational study.
Participants: 794 married couples in Renfrew district of the west of Scotland.
Main outcome measures: Mortality from all causes and from cardiovascular disease over 15 year follow up.
Results: Women who had heavier babies were taller, had higher body mass index and better lung function, and were less likely to be smokers than mothers of lighter babies. Fathers of heavier babies were taller and less likely to be smokers than fathers of lighter babies. Mortality was inversely related to offspring's birth weight for both mothers (relative rate for a 1 kg lower birth weight 1.82 (95% confidence interval 1.23 to 2.70)) and fathers (relative rate 1.35 (1.03 to 1.79)). For mortality from cardiovascular disease, inverse associations were seen for mothers (2.00 (1.18 to 3.33)) and fathers (1.52 (1.03 to 2.17)). Adjustment for blood pressure, plasma cholesterol, body mass index, height, social class, area based deprivation category, smoking, lung function, angina, bronchitis, and electrocardiographic evidence of ischaemia had little effect on these risk estimates, although levels of statistical significance were reduced.
Conclusions: Birth weight of offspring was related inversely to mortality, from all causes and cardiovascular disease, in this cohort. The strength of this association was greater than would have been expected by the degree of concordance of birth weights across generations, but an extensive range of potential confounding factors could not account for the association. Mortality is therefore influenced by a factor related to birth weight that is transmissible across generations.

Introduction

The inverse association between birth weight and incidence of cardiovascular disease in adulthood[1 2] indicates that development in early life may influence the risk of disease many years later. Birth weight is influenced by a wide range of environmental and genetic factors,[3] including sex of infant, maternal weight gain during pregnancy, maternal weight before pregnancy, maternal smoking, and socioeconomic conditions. Intergenerational influences have also been shown, with parental birth weight being associated with offspring's birth weight.[4-7] Intergenerational associations are seen with respect to both maternal and paternal birth weight,[4 8-13] although the birth weight of offspring is generally more strongly associated with maternal birth weight than paternal birth weight.

Intergenerational effects may mean that the death rates of current populations depend on the circumstances in early life of previous generations. Parents of heavier babies would be expected to have lower mortality from cardiovascular disease than parents of lighter babies. We have analysed mortality in relation to birth weight of offspring among members of married couples who participated in the Renfrew and Paisley study to explore whether the intergenerational influences on birth weight are mirrored by mortality risk.

Subjects and methods

Renfrew and Paisley study

Participants in the Renfrew and Paisley study were recruited from a door to door census of all households in the two towns.[14 15] All residents aged 45-64 years were invited to attend one of 12 temporary centres for a screening examination for cardiovascular and respiratory disease between 1972 and 1976. Participants completed a questionnaire about symptoms of cardiovascular and respiratory disease, smoking, and social class. Social class was determined by current occupation (or main occupation for unemployed or retired men) according to the registrar general's classification[16] and treated at six levels in the analyses. For retired people, their last full time occupation was used. For housewives, their husband's or, failing this, father's occupation was used.

At the screening clinic blood pressure was recorded as the mean of two measurements; forced expiratory volume in one second (FEV_1) was measured with a Garthur vitalograph, with the best of two expirations being recorded; height and weight were measured; a six lead electrocardiogram was recorded, the results were Minnesota coded, and evidence of ischaemia documented; and plasma cholesterol concentration was ascertained from a non-fasting blood sample.

To estimate impairment of lung function, subjects' FEV_1 was compared with predicted values, which were obtained from linear regressions on age and height:

Predicted FEV_1 for men =
$-1.9302 - (0.0290 \times \text{age (years)}) + (0.0373 \times \text{height (cm)})$

Predicted FEV_1 for women =
$-0.2662 - (0.0289 \times \text{age (years)}) + (0.0238 \times \text{height (cm)})$

Coefficients were derived from a regression for the 878 men and 2796 women from the whole study population who had never smoked and who responded "No" to questions about wheeze, breathlessness, and asthma.

Birth weights of offspring

From the 7058 men and 8353 women taking part in the Renfrew and Paisley study (response rate 78%), we identified 4067 married couples. Between 1993 and 1994, we wrote to these couples (or the surviving

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BMJ 1997;315:1189–93

member if one had died) for information about their offspring, who have been recruited into a study of familial and environmental influences on risk of cardiovascular disease. If both parents were dead we wrote to the informant on the most recent death certificate for this information. The information requested included the name, address, and date of birth of all offspring.

We used the offspring's date of birth and surname (using maiden name for married women) to search the records of two Paisley hospitals (Barrshaw and Thornhill), which are held in the archives of Greater Glasgow Health Board. We obtained a total of 1156 birth weights, but we excluded those for 11 pairs of twins since their birth weights would be lower than expected. Thus we retrieved 1134 birth weights of the offspring for 794 couples (534 couples with one offspring birth weight; 203 couples with two offspring birth weights, and 57 couples with three or more offspring birth weights).

Since birth weight is higher on average in male neonates, we calculated sex specific standard deviation (z) scores and used these to categorise parents according to the birth weight of their offspring. We calculated the average z score for parents for whom birth weight data were available for more than one child.

Parents' mortality

Participants in the Renfrew and Paisley study were flagged at the NHS Central Register in Edinburgh, and notification of deaths have been received for a 15 year follow up. Causes of death were coded to ICD-9 (international classification of diseases, ninth revision).[17] We categorised cause of death as cardiovascular disease (ICD-9 codes 390-459) or all others.

Statistical analyses

Our initial analyses addressed the association of offspring's birth weight with parents' demographic, behavioural, and physiological factors. We calculated age adjusted means for continuous variables using the general linear models procedure of the SAS system,[18] obtaining tests for trend through multiple linear regression, with age and offspring's z scores for birth weight as covariates. Categorical variables were age standardised by the direct method, and we performed tests for trend through multiple logistic regression, with age and offspring's z scores for birth weight as covariates. Parental height was related to offspring's birth weight in a multiple regression model with age as a covariate.

Death rates according to quintile of offspring birth weight were standardised for age by the direct method, with the total study population as the standard. Tests for trend for age adjusted rates were obtained through proportional hazards regression, with age and offspring's z scores for birth weight as covariates.

To explore the influence of confounding factors we calculated proportional hazards coefficients and their standard errors using Cox's model. We adjusted for age and other risk factors by including terms for these in the proportional hazards models. Exponentiated hazards were taken as indicators of relative mortality. We repeated these analyses using offspring's birth weight itself rather than z score as the exposure variable, subtracting 74 g from the male offspring's birth weights—this being the difference between average male and female birth weight in this study. We then calculated relative mortality associated with a 1 kg lower birth weight.

Table 1 Characteristics of 794 mothers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight						
	1	2	3	4	5	Total	Trend
No of subjects	159	166	152	158	159	794	
Mean birth weight of offspring (kg)	2.66	3.13	3.39	3.61	3.99	3.35	
Mean age (years)	51.5	51.0	51.5	51.3	52.0	51.4	P=0.32
Mean blood pressure (mm Hg):							
Systolic	147.0	149.1	148.1	148.1	149.4	148.4	P=0.98
Diastolic	84.1	84.5	83.4	85.6	85.6	84.7	P=0.44
Mean plasma cholesterol (mmol/l)	6.35	6.36	6.30	6.41	6.30	6.34	P=0.28
Mean height (cm)	156.5	157.0	157.5	159.0	158.9	157.8	P=0.0001
Mean body mass index (kg/m^2)	24.7	25.8	25.7	26.5	27.1	26.0	P=0.0001
Mean FEV_1 score (%)	89.7	92.1	91.4	92.9	95.9	92.3	P=0.005
% with angina	6.6	8.7	8.7	8.3	10.7	8.7	P=0.19
% with ischaemia*	10.8	10.6	9.9	8.8	10.3	10.2	P=0.38
% with bronchitis	2.9	2.3	3.4	3.0	3.2	3.1	P=0.32
% who never smoked	27.8	39.5	46.0	45.3	43.0	39.9	P=0.015
% who are current cigarette smokers	62.8	53.6	48.5	47.8	43.3	51.4	P=0.001
Mean No of cigarettes smoked a day†	17.1	14.3	14.4	15.5	13.6	15.1	P=0.0004
% in deprivation category 5-7	62.8	67.1	71.6	65.0	63.6	66.2	P=0.73
% in social class I or II	13.2	15.0	13.4	14.4	19.6	15.1	P=0.17

Means and proportions are adjusted for age.
*Based on electrocardiogram.
†Current smokers only.

Results

We compared the characteristics of the married men and women for whom we had ascertained the birth weights of offspring with those of other couples in the Renfrew and Paisley study for whom no offspring data had been obtained. Differences were small and non-significant for most factors, but the group with no data on offspring were older and were more likely to be in social class I or II and to live in less deprived areas. Women with no offspring data were more likely to have never smoked, while men with no offspring data were more likely to have electrocardiographic evidence of ischaemia at screening. The age adjusted relative mortality for married women with offspring data compared with those with no data was 1.05 (95% confidence interval 0.85 to 1.30); for married men, the equivalent relative risk was 1.23 (1.05 to 1.44).

Mothers

The mean birth weights of female and male offspring were 3.34 kg (SD 0.50 kg) and 3.41 kg (0.52 kg) respectively. Table 1 shows the characteristics of the mothers according to quintile of standardised birth weight of their offspring, together with the mean offspring birth weight within each quintile. Women who had heavier babies were taller, had higher body mass index, better lung function and were less likely to be smokers than women with lighter babies. There was no significant difference in either social class or deprivation category.

Table 2 shows the women's mortality from all causes, cardiovascular disease, and all other causes. Death rates were inversely associated with birth weight of offspring. Table 3 shows relative mortality adjusted for age and other risk factors: for mortality from all causes, the age adjusted relative rate for a 1 kg lower

birth weight was 1.82 (95% confidence interval 1.23 to 2.70); for mortality from cardiovascular disease, the equivalent relative rate was 2.00 (1.18 to 3.33). Adjusting for other risk factors had only modest effects on relative risks, although levels of statistical significance were attenuated.

Fathers

Table 4 shows the characteristics of the fathers according to the birth weight of their offspring. While the association with cigarette smoking was in the same direction as for the mothers, it was considerably weaker. No significant associations were seen between birth weight and fathers' body mass index or lung function. Each 1 cm increase in paternal height translated into a 10 g increase in offspring birth weight, in contrast with the 12 g increase in birth weight per 1 cm increase in maternal height.

Table 5 shows the fathers' mortality by the birth weight of their offspring. Mortality from all causes and from cardiovascular disease was inversely associated with birth weight of offspring (table 6). For mortality from all causes, the age adjusted relative rate for a 1 kg lower birth weight was 1.35 (95% confidence interval 1.03 to 1.79); for mortality from cardiovascular disease, the equivalent relative rate was 1.52 (1.03 to 2.17). Adjusting for other risk factors had a similar effect on the fathers' relative risks as they did on the mothers'.

Discussion

In this study only a quarter of married couples had at least one child whose birth weight could be ascertained. This largely reflects the fact that we obtained data on birth weights from only two hospitals, and that some births (a diminishing proportion with time) would have taken place outside hospital. The average birth weight of the offspring for whom the data were obtained was similar to that of the 1958 birth cohort in Great Britain (3.32 kg)[19] and to births in 1975 in Scotland, the first year for which such data were collected.[20] The sex difference was of the size generally reported.[3]

As expected, married subjects for whom no data on offspring were available were older than those for whom the data were available, reflecting the greater incompleteness of hospital records and the higher percentage of births outside hospital for earlier periods. Socioeconomic position was higher on average for those with no data on offspring—in line with the smaller family sizes, and therefore less chance to obtain birth weight data, of people in more favourable socioeconomic circumstances. In general, however, there were few differences between the study participants for whom data on offspring's birth weight could, and could not, be obtained.

Table 2 Mortality (age adjusted per 10 000 person years) of 794 mothers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight					
Cause of death	**1**	**2**	**3**	**4**	**5**	**Trend**
All causes:						
No of deaths	28	26	21	17	14	
Mortality	115.3	115.0	91.2	75.6	54.6	P=0.003
Cardiovascular disease:						
No of deaths	17	13	10	9	7	
Mortality	72.3	66.0	48.1	41.9	26.3	P=0.011
Other causes:						
No of deaths	11	13	11	8	7	
Mortality	48.8	52.9	45.5	36.5	29.3	P=0.088

Parental characteristics and offspring's birth weight

As expected, mothers of bigger babies were taller, had higher body mass index, and were less likely to smoke than mothers of smaller babies. The fact that these data were obtained many years after the relevant birth indicates the strength of the underlying associations. Differences in social class were in the expected direction but were small and did not reach statistical significance. Fathers' and mothers' heights were both strongly related to their offspring's birth weight; in general, offspring's birth weight is more strongly associated with maternal than paternal height.[3] Part of the association between paternal height and offspring's birth weight could be due to selective marriage, with taller women, who have larger babies on average, marrying taller men. Fathers' body mass index was only weakly and non-significantly related to offspring's birth weight. There was a relatively weak association between fathers' cigarette smoking and offspring's birth weight. This could reflect selective marriage according to smoking status,[21] although passive smoking may affect birth weight.[22]

Mortality for mothers and fathers was related to offspring's birth weight, but the associations were stronger for the mothers. There were twofold differences in mortality from all causes and nearly

Table 3 Relative mortality (95% confidence interval) of 794 mothers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight					Relative mortality for 1 quintile increase in birth weight
Cause of death	**1**	**2**	**3**	**4**	**5**	
All causes:						
Adjusted for age	1	0.96 (0.56 to 1.64)	0.77 (0.44 to 1.35)	0.60 (0.33 to 1.09)	0.46 (0.24 to 0.88)*	0.82 (0.72 to 0.94)**
Adjusted for all risks†	1	1.07 (0.61 to 1.87)	0.89 (0.49 to 1.62)	0.67 (0.36 to 1.27)	0.50 (0.25 to 0.98)*	0.84 (0.73 to 0.97)*
Cardiovascular disease:						
Adjusted for age	1	0.82 (0.40 to 1.70)	0.60 (0.27 to 1.30)	0.52 (0.23 to 1.18)	0.37 (0.15 to 0.89)*	0.79 (0.65 to 0.95)*
Adjusted for all risks†	1	0.94 (0.44 to 2.01)	0.73 (0.32 to 1.67)	0.66 (0.28 to 1.58)	0.46 (0.18 to 1.17)	0.83 (0.68 to 1.02)
Other causes:						
Adjusted for age	1	1.18 (0.53 to 2.63)	1.03 (0.45 to 2.38)	0.71 (0.29 to 1.78)	0.60 (0.23 to 1.56)	0.87 (0.71 to 1.06)
Adjusted for all risks‡	1	1.50 (0.65 to 3.44)	1.38 (0.58 to 3.30)	0.84 (0.33 to 2.15)	0.65 (0.24 to 1.76)	0.88 (0.72 to 1.08)

*P<0.05, **P<0.01.
†Age, diastolic blood pressure, plasma cholesterol, body mass index, height, social class, deprivation category, smoking, FEV_1 score, angina, bronchitis, and electrocardiographic evidence of ischaemia.
‡Age, body mass index, height, social class, deprivation category, smoking, FEV_1 score, and bronchitis.

Table 4 Characteristics of 794 fathers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight						
	1	2	3	4	5	Total	Trend
No of subjects	159	166	152	158	159	794	
Mean age (years)	53.9	53.0	53.3	53.5	54.0	53.5	P=0.77
Mean blood pressure (mm Hg):							
Systolic	148.6	150.4	147.9	146.8	149.4	148.7	P=0.95
Diastolic	86.8	87.4	87.4	84.9	87.2	86.8	P=0.69
Mean plasma cholesterol (mmol/l)	5.91	5.84	5.83	5.82	5.78	5.83	P=0.21
Mean height (cm)	168.3	168.6	169.9	170.0	170.9	169.5	P=0.0008
Mean body mass index (kg/m^2)	26.1	25.7	25.5	26.3	26.5	26.0	P=0.18
Mean FEV_1 score (%)	88.5	89.7	87.8	91.6	89.5	89.4	P=0.94
% with angina	7.2	11.3	10.4	10.7	5.7	8.9	P=0.59
% with ischaemia*	5.9	11.7	8.7	6.5	8.7	8.2	P=0.83
% with bronchitis	2.4	4.3	6.1	5.3	4.1	4.5	P=0.23
% who never smoked	11.8	17.8	17.9	16.6	18.4	16.4	P=0.11
% who are current cigarette smokers	63.3	56.8	57.3	55.1	50.6	56.7	P=0.05
Mean No of cigarettes smoked a day†	21.3	19.5	19.5	19.6	20.2	20.1	P=0.59
% in deprivation category 5-7	64.1	68.3	71.0	65.6	63.6	66.2	P=0.72
% in social class I or II	11.0	16.0	15.0	14.5	16.6	14.5	P=0.24

Means and proportions are adjusted for age.
*Based on electrocardiogram.
†Current smokers only.

Table 5 Mortality (age adjusted per 10 000 person years) of 794 fathers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight					
Cause of death	1	2	3	4	5	Trend
All causes:						
No of deaths	50	43	33	34	32	
Mortality	196.3	182.6	149.7	139.6	128.0	P=0.029
Cardiovascular disease:						
No of deaths	28	24	17	11	19	
Mortality	120.4	115.6	85.7	49.0	82.1	P=0.031
Other causes:						
No of deaths	22	19	16	23	13	
Mortality	99.8	83.1	79.0	99.4	55.1	P=0.36

threefold differences in mortality from cardiovascular disease across quintiles of offspring's birth weight for mothers. Adjusting for an extensive range of measured risk factors had little effect on the associations between offspring's birth weight and mothers' mortality. This reflects the fact that differences in risk factors were not generally large and that the association for body mass index, for example, went in the direction that would attenuate, rather than spuriously generate, differences in mortality from cardiovascular disease in unadjusted analyses.

Possible residual confounding

Several considerations relate to our adjustments for risk factors in this study. Firstly, imprecise measurement of the risk factors considered might lead to underadjustment,[23 24] but such misclassification would need to be extreme if it is to explain the observed associations. Secondly, risk factors that were not measured might have confounded the observed associations. No data on alcohol consumption were available, while other studies show an inverse association between maternal alcohol consumption and birth weight.[3] Alcohol seems to reduce the risk of death from cardiovascular disease, however, and it is not clear how the potential influence of confounding would manifest itself in this instance. Body composition was assessed only by body mass index in this study. The ratio of waist to hip measurements seems to be positively related to birth weight independent of body mass index.[25] Thus the women with larger babies would have had an unfavourable distribution of adipose tissue fat, since a high waist to hip ratio is associated with an increased risk of coronary heart disease,[26 27] hypertension,[28] diabetes,[29] and breast cancer.[30] This should therefore have increased the risk of mortality among the women with larger babies, and this unmeasured confounder would lead to the observed association being an attenuated estimate of the unconfounded association.

Reasons for an association between mortality and offspring's birth weight

The association between offspring's birth weight and parental mortality could reflect three basic processes. Firstly, socioenvironmental factors could influence both the birth weight of offspring and mortality of the parents. This should generate similar associations between offspring's birth weight and mortality for both mothers and fathers. We adjusted for social class and area based socioeconomic deprivation, together with a range of behavioural and physiological risk factors, and these adjustments produced a relatively modest degree of attenuation of the association between offspring's birth weight and mortality.

Secondly, specific characteristics of maternal health, nutrition, and wellbeing that influence birth weight could be related to reduced mortality risk. Such maternal vitality[31] will reflect the experiences of the mothers during their life before pregnancy, not just while pregnant. This effect of maternal vitality would be

Table 6 Relative mortality (95% confidence interval) of 794 fathers in Renfrew and Paisley by birth weight of offspring

	Quintile of average z score of birth weight					Relative mortality for 1 quintile increase in birth weight
Cause of death	1	2	3	4	5	
All causes:						
Adjusted for age	1	0.98 (0.65 to 1.47)	0.74 (0.48 to 1.15)	0.70 (0.45 to 1.08)	0.58 (0.37 to 0.90)*	0.87 (0.79 to 0.96)**
Adjusted for all risks†	1	1.06 (0.70 to 1.61)	0.76 (0.48 to 1.21)	0.75 (0.47 to 1.17)	0.67 (0.42 to 1.05)	0.89 (0.81 to 0.99)*
Cardiovascular disease:						
Adjusted for age	1	0.98 (0.57 to 1.70)	0.69 (0.38 to 1.25)	0.40 (0.20 to 0.81)**	0.61 (0.34 to 1.10)	0.84 (0.73 to 0.96)**
Adjusted for all risks†	1	1.11 (0.63 to 1.94)	0.78 (0.42 to 1.47)	0.48 (0.23 to 0.98)*	0.76 (0.41 to 1.39)	0.88 (0.76 to 1.01)
Other causes:						
Adjusted for age	1	0.97 (0.52 to 1.80)	0.81 (0.43 to 1.55)	1.07 (0.60 to 1.92)	0.53 (0.27 to 1.06)	0.90 (0.79 to 1.04)
Adjusted for all risks‡	1	1.07 (0.57 to 2.00)	0.81 (0.42 to 1.57)	1.09 (0.60 to 1.99)	0.60 (0.30 to 1.20)	0.92 (0.75 to 1.06)

*P<0.05, **P<0.01.
†Age, diastolic blood pressure, plasma cholesterol, body mass index, height, social class, deprivation category, smoking, FEV_1 score, angina, bronchitis, and electrocardiographic evidence of ischaemia.
‡Age, body mass index, height, social class, deprivation category, smoking, FEV_1 score, and bronchitis.

to generate associations between offspring's birth weight and mothers' mortality but not the fathers' mortality.

Thirdly, the intergenerational association of birth weight will lead to parents of low birth weight offspring tending to have been of low birth weight themselves, and thus at increased susceptibility to cardiovascular and respiratory disease. Since the intergenerational association of birth weight has been seen for both mothers and fathers,[4 9-11 13] this should contribute to associations between offspring's birth weight and mortality of both parents.

Given the above three mechanisms, we can view the effect of adjusting for socioenvironmental factors as indicating the contribution of socioeconomic and behavioural characteristics; the difference in magnitude of the adjusted measures of association of offspring's birth weight with maternal and paternal mortality as an indicator of the specific influence of maternal vitality and the stronger intergenerational association of birth weight for mothers than fathers; and the residual association shared by mothers and fathers as a reflection of other intergenerational contributions to risk of mortality.

Conclusion

The magnitude of the association between birth weight and risk of cardiovascular disease in adulthood[1 2 32 33] is not great enough to generate the differences in mortality seen in the present study, given the magnitude of the association between parental birth weight and offspring's birth weight.[4-9 11 13] The actual resemblance in birth weight may be an attenuated reflection of the common factors—genetic, epigenetic,[34] or environmental—that lead to intergenerational similarity in birth weights.

There are many potential weaknesses in our study. The sample size was small, information on offspring's birth weight was available for only a subsample of the original cohort, and information was missing on several determinants of birth weight, particularly length of gestation and weight gain during pregnancy. The strength of the study is the availability of data on both parents and on a considerable range of risk factors for cardiovascular disease. Our core finding is of potentially great importance, and further study of this issue is clearly warranted.

Funding: This study was supported by the Scottish Home and Health Department.

Conflict of interest: None.

Key messages

- Low birth weight is associated with increased mortality from cardiovascular disease in later life, and birth weight is associated across generations so that both maternal and paternal birth weights are associated with the offspring's birth weight
- In this observational study we found that lower birth weight of offspring was associated with higher parental mortality from all causes and from cardiovascular disease
- This elevated mortality could not be explained by a range of social, environmental, behavioural, and physiological risk factors
- The strength of the association was greater than would have been expected by the degree of concordance of birth weights across generations
- We conclude that mortality is influenced by a factor that is related to birth weight and is transmissible across generations

1 Barker DJP. Early nutrition and coronary heart disease. In: Davies DP, ed. *Nutrition in child health*. London: Royal College of Physicians, 1995.
2 Frankel SJ, Elwood P, Sweetnam P, Yarnell J, Davey Smith G. Birthweight, adult risk factors and incident coronary heart disease: the Caerphilly study. *Public Health* 1996;110:139-43.
3 Kramer MS. Determinants of low birthweight: methodological assessment and meta-analysis. *Bull World Health Organ* 1987;65:663-737.
4 Emanuel I. Intergenerational factors in pregnancy outcome: implications for teratology? *Issues Rev Teratol* 1993;6:47-84.
5 Wang X, Zuckerman B, Coffman GA, Corwin MJ. Familial aggregation of low birth weight among whites and blacks in the United States. *N Engl J Med* 1995;333:1744-9.
6 Sanderson M, Emanual I, Holt VL. The intergenerational relationship between mother's birthweight, infant birthweight and infant mortality in black and white mothers. *Paediatr Perinat Epidemiol* 1995;9:391-405.
7 Klebanoff MA, Meirik O, Berendes HW. Second-generation consequences of small-for-dates birth. *Pediatrics* 1989;84:343-7.
8 Alberman E, Emanuel I, Filakti H, Evans SJW. The contrasting effects of parental birthweight and gestational age on the birthweight of offspring. *Paediatr Perinat Epidemiol* 1992;6:134-44.
9 Ounsted MA, Scott A, Ounsted C. Transmission through the female line of a mechanism constraining human fetal growth. *Ann Hum Biol* 1986;13:143-51.
10 Magnus P, Berg K, Bjerkedal T, Nance WE. Parental determinants of birth weight. *Clin Genet* 1984;26:397-405.
11 Little RE. Mother's and father's birthweight as predictors of infant birthweight. *Paediatr Perinat Epidemiol* 1987;1:19-31.
12 Langhoff-Roos J, Lindmark G, Gustavson K-H, Gebre-Medhin M, Meirik O. Relative effect of parental birth weight on infant birth weight at term. *Clin Genet* 1987;32:240-8.
13 Godfrey KM, Barker DJP, Robinson S, Osmond C. Maternal birthweight and diet in pregnancy in relation to the infant's thinness at birth. *Br J Obstet Gynaecol* 1997;104:663-7.
14 Hawthorne VM, Watt GCM, Hart CL, Hole DJ, Davey Smith G, Gillis CR. Cardiorespiratory disease in men and women in urban Scotland: baseline characteristics of the Renfrew/Paisley (midspan) study population. *Scot Med J* 1995;40:102-7.
15 Watt GCM, Hart CL, Hole DJ, Davey Smith G, Gillis CR, Hawthorne VM. Risk factors for cardiorespiratory and all cause mortality in men and women in urban Scotland: 15 year follow up. *Scot Med J* 1995;40:108-12.
16 *General register office classification of occupations*. London: HMSO, 1966.
17 World Health Organisation. *International classification of diseases, ninth revision*. Geneva: WHO, 1977.
18 SAS Institute. *SAS language and procedures: usage 2, version 6*. Cary, NC: SAS Institute, 1991.
19 Peters TJ, Butler NR, Fryer JG, Chamberlain GVP. Plus ça change: predictors of birthweight in two national studies. *Br J Obstet Gynaecol* 1983;90:1040-5.
20 Power C. National trends in birth weight: implications for future adult disease. *BMJ* 1994;308:1270-1.
21 Sutton GC. Assortative marriage for smoking habits. *Ann Hum Biol* 1980;7:449-56.
22 *Fourth report of the Independent Scientific Committee on Smoking and Health*. London: HMSO, 1988.
23 Phillips AN, Davey Smith G. How independent are independent effects? Relative risk estimation when correlated exposures are measured imprecisely. *J Clin Epidemiol* 1991;44:1223-31.
24 Davey Smith G, Phillips AN. Confounding in epidemiological studies: why 'independent' effects may not be all they seem. *BMJ* 1992;305:757-9.
25 Brown JE, Potter JD, Jacobs DR, Kopher RA, Rourke MJ, Barosso GM, et al. Maternal waist-to-hip ratio as a predictor of newborn size: results of the Diana project. *Epidemiology* 1996;7:62-6.
26 Larsson B, Bengtsson C, Bjorntorp P, Lapidus L, Sjostrom L, Svardsudd K, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? *Am J Epidemiol* 1992;135:266-73.
27 Wild RA, Grubb B, Hartz A, Van Nort JJ, Bachman W, Bartholomew M. Clinical signs of androgen excess as risk factors for coronary artery disease. *Fertil Steril* 1990;54:255-9.
28 Emery EM, Schmid TL, Kahn HS, Filozof PP. A review of the association between abdominal fat distribution, health outcome measures, and modifiable risk factors. *Am J Health Promotion* 1993;7:342-53.
29 Schmidt MI, Duncan BB, Canani LH, Karohl C, Chambless L. Association of waist-hip ratio with diabetes mellitus.: strength and possible modifiers. *Diabetes Care* 1992;15:912-4.
30 Sellers TA, Kushi LH, Potter JD, Kaye SA, Nelson CL, McGovern PG, et al. Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med* 1992;326:1323-9.
31 Hart N. Famine, maternal nutrition and infant mortality: a re-examination of the Dutch hunger winter. *Popul Stud* 1993;47:24-46.
32 Rich-Edwards J, Stampfer M, Manson J, Rosner B, Colditz G, Willett W, et al. Birthweight, breastfeeding and the risk of coronary heart disease in the nurses' health study. *Am J Epidemiol* 1995;141:S78.
33 Koupilova I, Leon DA. Birth weight and mortality from ischaemic heart disease and stroke in Swedish men aged 50-74 years. *J Epidemiol Community Health* (in press).
34 Pembrey M. Imprinting and transgenerational modulation of gene expression: human growth as a model. *Acta Genet Med Gemellol (Roma)* 1996;45:111-25.

(Accepted 7 July 1997)