that was sufficiently strongly related to age. However, consumption of certain foods is strongly age related (p 404)[3]. For example, in 1986-7, burgers and kebabs were consumed by 45% of 16-24 year olds but by only 13% of 50-64 year olds. By contrast, the consumption of beef or even sausages is not age related.[4]

Let us turn now from young adults to farmers. Will et al confirm that the occurrence of sporadic Creutzfeldt-Jakob disease in farmers is more than happenstance.[5] Molecular marker studies of bovine spongiform encephalopathy reported by Collinge et al effectively proved that the variant form of Creutzfeldt-Jakob disease is caused by the same agent that causes the bovine disease.[6] Hence as well as transmission studies with brain tissue taken at necropsy from farmers dying of Creutzfeldt-Jakob disease, molecular marker studies will be important in determining whether some of the cases in farmers were likely to have been due to occupational exposure to the infectious agent in cattle. It is worth recalling that in July 1996 (that is, before Collinge's work was reported) the degree of belief in the proposition that bovine spongiform encephalopathy causes the variant form of Creutzfeldt-Jakob disease averaged 5.4 (SD 2.8) on a scale of 0 (nil belief) to 10 (absolute certainty).[7]

Will et al report that in addition to the six cases of Creutzfeldt-Jakob disease in lifelong farmers, there had been three other confirmed cases since 1 May 1990 in people who belonged formerly to the occupational group comprising abattoir workers, butchers, meat cutters, and rendering plant workers. This occupational group together with veterinarians accounted for no more than $s = 78\,000$ workers yearly. The "ever employed" person years in this occupational group to be counted in the surveillance period 1990-5 depend on turnover of staff. If all 78 000 remained in the occupational group throughout 1981-95 they would contribute only $6s = 6 \times 78\,000 = 0.468$ million person years to the surveillance period 1990-5. If two thirds of employees stayed for 15 years, one sixth were replaced every year, and one sixth turned over after three years, then the person years contribution would increase considerably. Serious consideration needs to be given to the proper estimation of "ever employed" and "continuously employed" denominators if full use is to be made of occupational histories collected in cases of Creutzfeld-Jakob diseases.


1 Alperovitch A, Brendel JB, Chalclain J, Delasncrio-Laupretre N, Deslys J-P, Dormont D, et al. Situation en France. Incidence de la maladie de Creutzfeldt-Jakob en France. *Bull Epidemiol Hebdom* 1996;48:207-8.
2 Will RG, Knight RSG, Zeidler M, Stewart G, Ironside JW, Cousens SN, et al. Reporting of suspect new variant Creutzfeldt-Jakob disease. *Lancet* 1997;349:847-8.
3 Gore SM, Bingham S, Day N. Age related dietary exposure to meat products from British dietary surveys of teenagers and adults in the 1980s and 1990s. *BMJ* 1997;315:404-5.
4 Gregory JR, Foster K, Tyler H, Wiseman M. *Dietary and nutrition survey of British adults, 1986-7.* London: HMSO, 1990.
5 Gore SM. More than happenstance: Creutzfeld-Jakob disease in farmers and young adults. *BMJ* 1995;311:1416-8.
6 Collinge J, Sidle KCL, Meads J, Ironside J, Hill AF. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature* 1996;383:685-90.
7 Gore SM. Address to the Parliamentary and Scientific Committee. More than happenstance: CJD in farmers and young adults. *Sci Parliament* 1996;53:2-3.


# Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976


Janet W Rich-Edwards, Meir J Stampfer, JoAnn E Manson, Bernard Rosner, Susan E Hankinson, Graham A Colditz, Walter C Willett, Charles H Hennekens

Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA

Division of Preventive Medicine

Janet W Rich-Edwards, *instructor*

JoAnn E Manson, *associate professor*

Charles H Hennekens, *professor*


continued over

*BMJ* 1997;315:396–400


## Abstract

**Objective:** To examine the association between birth weight and non-fatal adult cardiovascular disease while controlling for potential confounders such as socioeconomic group and adult lifestyle.

**Design:** Retrospective self report of birth weight in an ongoing longitudinal cohort of nurses followed up by postal questionnaire every two years.

**Setting:** Nurses' health study, a cohort of 121 700 women followed up since 1976.

**Main outcome measures:** Non-fatal cardiovascular disease, including myocardial infarction, coronary revascularisation, and stroke.

**Results:** Among the 70 297 women free of cardiovascular disease at baseline who reported birth weight in the 1992 questionnaire there were 1309 first cases of non-fatal cardiovascular disease. Increasing birth weight was associated with decreasing risk of non-fatal cardiovascular disease. There were 1216 first cases of non-fatal cardiovascular disease among women who were singletons and had been born full term; their relative risks adjusted for several cardiovascular risk factors were 1.49 (95% confidence interval 1.05 to 2.10) for birth weight $<$2268 g ($<$5 lb 0 oz); 1.25 (0.98 to 1.61) for birth weight 2268-2495 g (5 lb 0 oz to 5 lb 8 oz); 1.12 (0.98 to 1.27) for birth weight $>$2495-3175 g ($>$5 lb 8 oz to 7 lb 0 oz); 1.00 (referent) for birth weight $>$3175-3856 g ($>$7 lb 0 oz to 8 lb 8 oz); 0.96 (0.80 to 1.15) for birth weight $>$3856-4536 g ($>$8 lb 8 oz to 10 lb 0 oz); and 0.68 (0.46 to 1.00) for birth weight $>$4536 g ($>$10 lb 0 oz) (P value for trend = 0.0004). The inverse trend was apparent for both coronary heart disease and stroke.

**Conclusions:** These data provide strong evidence of an association between birth weight and adult coronary heart disease and stroke.


## Introduction

As interest has grown in early determinants of cardiovascular disease, it has been hypothesised that indicators of adult cardiovascular risk are manifest

even at birth. Birth weight and other measures of prenatal growth have been associated with adult blood pressure,[1-7] diabetes,[4 5 8-11] body fat distribution,[4 5 12] and, less consistently, lipid concentrations.[4 13] An inverse association between birth weight and death and illness from coronary heart disease has been reported among men[14 15] and women[16] in England. We examined the association between birth weight and non-fatal cardiovascular disease among women in the United States who had been born between 1921 and 1946.

## Subjects and methods

The nurses' health study was established in 1976, when 121 701 American female registered nurses aged 30 to 55 years responded to postal questionnaires on their medical histories and lifestyles.[17] We excluded the 1709 women who had prevalent cardiovascular disease at baseline. There were 5341 deaths between 1976 and 1992 (including 723 deaths from cardiovascular disease). Of the women who were alive in 1992, 11 863 did not respond to the 1992 questionnaire and a further 32 491 women did not report their birth weight. This analysis includes the 70 297 participants who were free from coronary heart disease and stroke in 1976 and who reported their birth weight.

The 1976 questionnaire requested information about past and current risk factors for cardiovascular disease. Follow up questionnaires were posted every two years to elicit updated information on exposure variables and the incidence of myocardial infarction, angina, coronary revascularisation, and stroke. In 1992 the women indicated their birth weight in categories of pounds. These were not sure, $<5$ lb, 5 lb to 5½ lb, $>5$½ lb to 7 lb, $>7$ lb to 8½ lb, $>8$½ lb to 10 lb, and $>10$ lb, which in this paper are $<2268$ g, 2268-2495 g, $>2495$-3175 g, $>3175$-3856 g, $>3856$-4536 g, and $>4536$ g respectively. The women also said whether they had been born full term or two or more weeks prematurely and whether they were one of a multiple birth (hereafter referred to as twins).

### Validation of self reported birth weight

The validity of self reported birth weights was tested among a younger cohort of female nurses aged 27-44 years.[18] Birth weight was obtained from 220 state birth certificates, and 70% of participants reported the same birth weight category as their birth certificate.[18] The Spearman correlation between categories of self reported and recorded birth weight was 0.74. Participants who were aged 27-34 and 35-44 years recalled their birth weights with similar accuracy.

### Documentation of end points

Because we obtained information in 1992 on birth weight we were able to consider only non-fatal cardiovascular end points that occurred between the 1976 and 1992 questionnaires. Permission to review medical records was sought from participants who reported a non-fatal myocardial infarction or stroke. The records were reviewed by doctors who were blind to the risk factors of the participants. Non-fatal myocardial infarctions and strokes for which we could not obtain hospital records but which required admission and were corroborated by additional information in a letter or from a telephone interview were classed as probable events.

Non-fatal myocardial infarctions were classed as confirmed if they met the criteria of the World Health Organisation: symptoms and either diagnostic electrocardiographic changes or raised cardiac enzyme activities.[19] Thus, silent infarctions and those occurring at an indeterminate time that had been discovered on routine examination were excluded. We combined 507 confirmed and 85 probable cases of non-fatal myocardial infarction because the results did not differ when we considered only confirmed cases. Coronary artery bypass grafting and angioplasty were self reported on the questionnaires.

Stroke was classified according to the criteria established by the national survey of stroke.[20] We required evidence of a typical neurological deficit of sudden or rapid onset that persisted for more than 24 hours. Stroke classifications included ischaemic stroke due to thrombotic or embolic occlusion of a cerebral artery or haemorrhagic stroke due to subarachnoid or intraparenchymal haemorrhage. The results were similar when the 67 probable strokes were analysed with the 322 confirmed strokes, so both were combined in this analysis.

We examined the incidence of total non-fatal coronary heart disease (including non-fatal myocardial infarction and coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and total non-fatal stroke (including ischaemic, haemorrhagic, and unclassified strokes) before separately examining myocardial infarction, coronary revascularisation, and the stroke subtypes. Because the results were similar for coronary heart disease and stroke, these end points were combined as a non-fatal cardiovascular end point.

### Statistical analysis

Age adjusted means and prevalence of baseline characteristics were obtained by direct standardisation to the overall age distribution in years.[21] Incident cases of cardiovascular disease were assigned to the birth weight categories, with follow up dating from the return of the baseline questionnaire in 1976 to the date of occurrence of disease or 1 June 1992, whichever came first. The odds ratio was used to compare the odds of disease for women in a given birth weight category compared with that of women who weighed $>3175$-3856 g at birth. To assess trend across categories, each birth weight category was assigned a representative value in an ordinal variable (2155 g, 2381 g, 2835 g, 3515 g, 4196 g, and 4649 g). Two sided P values and 95% confidence intervals are presented.

All analyses were adjusted for age in years as a continuous variable; multivariate relative risks were derived from proportional hazards models[22] including terms as specified in the tables and text. As information on alcohol consumption, saturated fat intake, and physical activity was first collected in 1980, analyses considering these variables include follow up from 1980 to 1992. Similarly, analyses using the ratios of waist to hip circumference include follow up from 1986 to 1992.

## Results

As reported previously,[7] birth weight was associated with age, adult body mass index (weight (kg)/

Channing Laboratory
Bernard Rosner, *professor*
Susan E Hankinson, *assistant professor*
Graham A Colditz, *professor*
Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA
Meir J Stampfer, *professor*
Walter C Willet, *professor*
Correspondence to: Dr J W Rich-Edwards, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School, 126 Brookline Avenue, Suite 200, Boston, MA 02215, USA (nhjre@gauss.bwh.harvard.edu).

**Table 1** Age adjusted* prevalences of cardiovascular risk factors at baseline (1976) by birth weight. Values are percentages of women unless stated otherwise

| | | Full term births (birth weight (g)) | | | | | |
|---|---|---|---|---|---|---|---|
| | Premature births (n=3608) | <2268 (n=1392) | 2268-2495 (n=3549) | >2495-3175 (n=21 171) | >3175-3856 (n=31 216) | >3856-4536 (n=7723) | >4536 (n=1638) |
| Mean age (years) | 41.1 | 43.0 | 40.9 | 41.4 | 41.5 | 42.5 | 44.5 |
| Twin birth | 7.2 | 19.4 | 6.8 | 1.5 | 0.5 | 0.2 | 0.0 |
| Breast fed† | 48.1 | 49.2 | 56.0 | 61.8 | 66.6 | 70.0 | 73.2 |
| High social class at age 16‡ | 27.4 | 22.8 | 27.8 | 27.7 | 27.1 | 24.7 | 19.8 |
| Mean height (inches) | 64.2 | 63.4 | 63.4 | 64.0 | 64.8 | 65.2 | 65.5 |
| Mean body mass index (kg/m$^2$) | 23.7 | 23.7 | 23.4 | 23.2 | 23.7 | 24.1 | 24.5 |
| Mean waist:hip circumference (×100) | 78.4 | 79.0 | 77.9 | 77.8 | 77.9 | 77.9 | 77.7 |
| Self reported hypertension | 12.4 | 10.7 | 11.5 | 9.9 | 9.6 | 9.8 | 8.7 |
| Current smoker | 29.8 | 30.1 | 31.4 | 30.8 | 30.4 | 32.2 | 32.5 |
| Self reported high cholesterol | 2.9 | 3.1 | 2.8 | 2.8 | 2.7 | 2.9 | 2.4 |
| Diabetes | 1.8 | 2.4 | 1.9 | 1.1 | 1.2 | 1.3 | 1.2 |
| One parent had myocardial infarction before age 60 | 13.7 | 13.4 | 14.3 | 12.9 | 13.2 | 12.6 | 14.2 |
| Non-drinker§ | 33.2 | 38.5 | 32.3 | 30.2 | 30.4 | 32.5 | 33.2 |
| Regular exercise¶ | 47.5 | 46.3 | 47.7 | 47.2 | 48.0 | 46.3 | 46.1 |
| Mother smoked** | 28.7 | 27.0 | 29.0 | 25.6 | 23.8 | 22.7 | 18.3 |
| Postmenopausal | 17.3 | 16.4 | 19.0 | 17.0 | 16.7 | 16.8 | 16.5 |

*By one year intervals.
†From 1992 questionnaire among women who knew whether they had been breast fed.
‡Father's occupation was manager or professional when nurse was aged 16.
§Drank less than one alcoholic beverage per month, among those who responded to the 1980 dietary questionnaire.
¶Long enough to work up a sweat at least once a week, among those responding to the 1980 questionnaire.
**While participant was living with her.

height (m)$^2$), adult hypertension, raised cholesterol concentration, and diabetes (table 1). The heavier the nurse was at birth the less likely it was that her father had been a manager or professional when the nurse was a child and the less likely it was that the nurse's mother smoked during the nurse's childhood. No associations were evident between birth weight and variables reflecting the nurse's adult lifestyle.

From 1976 to 1992, 889 cases of first non-fatal coronary heart disease occurred among women who were singletons and had been born full term, including 461 cases of non-fatal myocardial infarction and 428 cases of coronary revascularisation. An inverse association between birth weight and non-fatal coronary heart disease was evident after adjustment for age (table 2).

Adjustment for baseline hypertension (yes/no) and history of diabetes mellitus (yes/no) somewhat attenuated the association between lower birth weight and non-fatal coronary heart disease, while adjustment for baseline body mass index (in tenths) strengthened the association between higher birth weight and reduced incidence of non-fatal coronary heart disease (table 2). In a multivariate model including these factors, as well as cigarette smoking, parental history of myocardial infarction before the age of 60, raised cholesterol concentration, menopausal state, and the use of postmenopausal hormones, there was a 5% decrease (95%

**Table 2** Relative risks (95% confidence intervals) for coronary heart disease by birth weight in women who were singletons and had been born full term

| | Birth weight (g) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <2268 | >2268-2495 | >2495-3175 | >3175-3856 | >3856-4536 | >4536 | z for trend (P value) |
| **All non-fatal coronary heart disease*** | | | | | | | |
| No of cases | 24 | 50 | 272 | 413 | 109 | 21 | |
| Relative risk: | | | | | | | |
| Age adjusted† | 1.36 | 1.22 | 0.99 | Referent | 0.97 | 0.75 | –1.58 (0.112) |
| Multivariate‡ | 1.32 (0.87 to 1.99) | 1.15 (0.85 to 1.54) | 1.02 (0.88 to 1.19) | Referent | 0.92 (0.75 to 1.14) | 0.68 (0.44 to 1.06) | –2.10 (0.036) |
| **Non-fatal myocardial infarction** | | | | | | | |
| No of cases | 15 | 27 | 163 | 262 | 70 | 13 | |
| Multivariate relative risk‡ | 1.29 (0.77 to 2.18) | 0.95 (0.64 to 1.42) | 0.92 (0.71 to 1.20) | Referent | 0.92 (0.71 to 1.20) | 0.66 (0.38 to 1.15) | –0.84 (0.401) |
| **Coronary revascularisation** | | | | | | | |
| No of cases | 13 | 37 | 164 | 224 | 60 | 14 | |
| Multivariate relative risk‡ | 1.32 (0.75 to 2.31) | 1.61 (1.13 to 2.28) | 1.14 (0.93 to 1.40) | Referent | 0.94 (0.71 to 1.25) | 0.85 (0.50 to 1.47) | –2.71 (0.006) |

*Non-fatal myocardial infarction or coronary revascularisation. Total end point considers only the first event, so the sum of the separate end points is greater than the number of total coronary heart disease events.
†Adjusted for age (continuous) and time period.
‡Further adjusted for body mass index (tenths), cigarette smoking (never; past; current: 1-14, 15-24, ⩾25 cigarettes/day, quantity unknown, missing data), reported hypertension, reported raised cholesterol concentration, parental history of myocardial infarction under 60, diabetes, menopausal status (premenopausal, postmenopausal, dubious, missing data), and use of postmenopausal hormones (premenopausal, never use, past use, current use, missing data).

**Table 3** Relative risks (95% confidence intervals) for non-fatal stroke by birth weight in women who were singletons and had been born full term

| | Birth weight (g) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <2268 | >2268-2495 | >2495-3175 | >3175-3856 | >3856-4536 | >4536 | z for trend (P value) |
| **All non-fatal strokes*** | | | | | | | |
| No of cases | 15 | 22 | 125 | 153 | 42 | 7 | |
| Relative risk | | | | | | | |
| Age adjusted† | 2.39 | 1.42 | 1.23 | Referent | 1.03 | 0.70 | –2.97 (0.003) |
| Multivariate‡ | 2.29 (1.34 to 3.90) | 1.38 (0.89 to 2.15) | 1.25 (0.99 to 1.59) | Referent | 0.99 (0.71 to 1.10) | 0.66 (0.31 to 1.42) | –3.16 (0.002) |
| **Ischaemic stroke** | | | | | | | |
| No of cases | 7 | 19 | 72 | 91 | 28 | 4 | |
| Multivatiate relative risk‡ | 1.80 (0.83 to 3.89) | 2.03 (1.23 to 3.33) | 1.23 (0.90 to 1.67) | Referent | 1.10 (0.72 to 1.67) | 0.61 (0.23 to 1.68) | –2.66 (0.008) |
| **Haemorrhagic stroke** | | | | | | | |
| No of cases | 4 | 3 | 33 | 27 | 8 | 1 | |
| Multivariate relative risk‡ | 3.68 (1.28 to 10.05) | 1.05 (0.23 to 3.46) | 1.83 (1.10 to 3.05) | Referent | 1.11 (0.51 to 2.45) | 0.60 (0.08 to 4.41) | –2.43 (0.015) |

*Includes 301 confirmed cases of non-fatal stroke (221 ischaemic strokes, 76 haemorrhagic strokes, 4 confirmed strokes of unknown type) and 63 probable cases.
†Adjusted for age (continuous) and time period.
‡Further adjusted for body mass index (tenths), cigarette smoking (never; past; current: 1-14, 15-24, or ⩾25 cigarettes/day, quantity unknown, missing data), reported hypertension, reported raised cholesterol concentration, parental history of myocardial infarction under 60, diabetes, menopausal status (premenopausal, postmenopausal, dubious, missing data), and use of postmenopausal hormones (premenopausal, never use, past use, current use, missing data).

confidence interval 0% to 9%) in the risk of non-fatal coronary heart disease for every 454 g increase in birth weight. Inclusion of 3347 women who had been born prematurely, 52 of whom had coronary heart disease, made little difference to the relative risks associated with birth weight.

Non-fatal myocardial infarction and coronary revascularisation were examined separately (table 2). The inverse association in the multivariate model described above seemed to be stronger for coronary revascularisation than for myocardial infarction.

From 1976 to 1992, 364 cases of non-fatal stroke occurred among women who were singletons and had been born full term. A strong inverse association was seen between birth weight and the incidence of non-fatal stroke (table 3). As for coronary heart disease, adjustment for hypertension and diabetes somewhat dampened the association between the lowest category of birth weight and stroke, while control for body mass index had a slight influence on the heaviest category of birth weight. In the multivariate model there was an 11% (5% to 8%) decrease in the risk of non-fatal stroke for every 454 g increase in birth weight. When 3347 women who had been born prematurely were included, 17 of whom had stroke, the trend was somewhat dampened (z for trend = – 2.99, P = 0.002). The inverse trend between birth weight and non-fatal stroke was similar for ischaemic and haemorrhagic stroke (table 3).

Further analyses adjusting for height, aspirin use, alcohol consumption, saturated fat consumption, physical activity, ratio of waist to hip circumference, ethnic group, and whether the nurse's mother smoked cigarettes when the nurse was a child or had diabetes did not materially change the relative risk estimates for myocardial infarction or stroke. Neither did adjustment for socioeconomic group when the nurse was 16 (10 categories each for maternal and paternal occupation when she was 16), her husband's education, whether she was born prematurely, whether she was one of twins or a multiple birth, and whether she had been breast fed.

Figure 1 shows the multivariate association between birth weight and total non-fatal cardiovascular disease among women who were singletons and had been born full term (z for trend = – 3.61, P < 0.001. The trend was somewhat strengthened by eliminating hypertension, diabetes, and raised cholesterol concentration, which are likely intermediates in the causal pathway between in utero growth and cardiovascular disease (z for trend = – 4.12, P < 0.00001; data not shown). The inverse trend was not eliminated by removing body mass index from the full multivariate model (z for trend = – 2.91, P = 0.002).

## Discussion

In this cohort of women aged 46 to 71 in 1992 birth weight was inversely related to the incidence of non-fatal coronary heart disease and stroke. The association was driven by the small proportion of women at the extremes of birth weight; if there is a

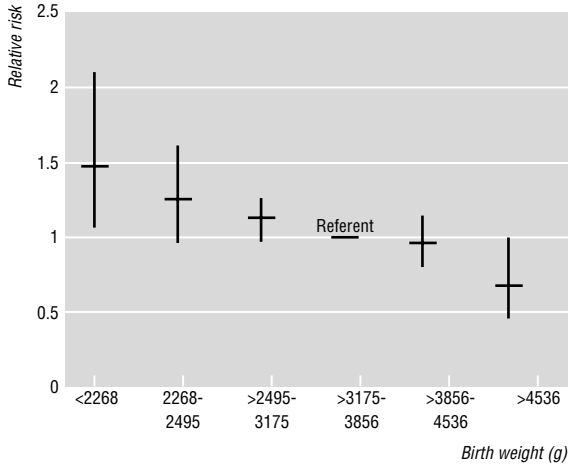


**Fig 1** Relative risks with 95% confidence intervals for non-fatal cardiovascular disease by birth weight. Relative risks were derived from proportional hazards model adjusted for factors given in tables 2 and 3 for multivariate relative risks

difference in cardiovascular risk among the 87% of women of normal birth weight (>2495-4536 g) it seems to be minimal.

The age adjusted associations we observed for non-fatal cardiovascular disease are strikingly similar to those observed for fatal cardiovascular disease among British women.[16] The association was little affected by such potential confounding variables as cigarette smoking, ethnic group, and socioeconomic group. Birth weight is presumably a marker for risk factors directly linked to cardiovascular disease. That the association persisted despite adjustment for hypertension, diabetes, raised cholesterol concentration, height, and body mass index suggests that birth weight is associated with adult cardiovascular risk primarily through other pathways. Childhood socioeconomic group cannot explain our results because the heavier infants tended to be from the poorer socioeconomic groups. In this study we did not have information on several factors known to influence birth weight, including maternal diet, blood pressure, and hormone concentrations during pregnancy.

The results of the validation study indicate that there is some misclassification of self reported birth weight. However, such misclassification is likely to have been random with respect to disease and would have led to underestimation of relative risks.

We were unable to include women who died before 1992. However, the small numbers of deaths cannot explain these findings unless there was a strong tendency for women of normal and high birth weight to develop fatal (as opposed to non-fatal) cardiovascular disease. To invoke missing data to explain the observed association requires a scenario in which we were disproportionately missing women who both had a low birth weight and did not have cardiovascular disease as well as women who had a high birth weight and did have cardiovascular disease. Such a pattern of selectively missing data seems unlikely.

In summary, a moderate but consistent inverse association was observed between birth weight and cardiovascular risk that persisted despite control for a number of risk factors. Women who had a low birth weight (2495 g or less) had a significantly increased risk (by 23%) of non-fatal cardiovascular disease compared with all other women. Only 11% of this cohort born between 1921 and 1946 had a low birth weight. Thus, a low birth weight was associated with no more than 2% of the non-fatal cardiovascular disease in this cohort. This figure would be lower for the generation of children born today because the prevalence of low birth weight in the United States was 7% in 1990.[23]

Although these data suggest that cardiovascular benefits might be reaped from interventions to reduce low birth weight, it is not clear which of the many environmental or genetic factors that determine birth weight might also affect cardiovascular risk. Birth weight is only a crude marker of intrauterine development; further research is needed to identify whether there is a specific mechanism that affects both birth weight and risk of cardiovascular disease in adulthood.

**Key messages**

- Birth weight and mortality from cardiovascular disease are inversely associated in adult women
- This study found that birth weight and the risk of non-fatal cardiovascular disease is also inversely associated in adult women for both coronary heart disease and stroke
- This association is driven by the 13% of women born at the extremes of birth weight
- It seems to be largely independent of established cardiovascular risk factors also associated with birth weight: adult body weight, hypertension, and diabetes
- It is not weakened by controlling for childhood socioeconomic group or adjusting for adult lifestyle

We are grateful for the leading role of Dr Frank Speizer as principal investigator of the nurses' health study and for the dedication of the registered nurses participating in this study.

Funding: The nurses' health study is supported by research grants HL 34594 and CA 40356 from the National Institutes of Health. JWR-E was supported by institutional training grant HL-07575 from the National Heart, Lung and Blood Institute.

Conflict of interest: None.

1 Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298:564-7.
2 Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. *BMJ* 1990;301:259-62.
3 Law CM, de SM, Osmond C, Fayers PM, Barker DJ, Cruddas AM, et al. Initiation of hypertension in utero and its amplification throughout life. *BMJ* 1993;306:24-7.
4 Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995;310:428-32.
5 Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 1994;37:624-31.
6 Holland FJ, Stark O, Ades AE, Peckham CS. Birth weight and body mass index in childhood, adolescence, and adulthood as predictors of blood pressure at age 36. *J Epidemiol Community Health* 1993;47:432-5.
7 Curhan G, Chertow G, Willet W, Spiegleman D, Colditz G, Manson J, et al. Birth weight and adult hypertension and obesity in women. *Circulation* 1996;94:1310-5.
8 Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C. Fetal growth and impaired glucose tolerance at age 64. *BMJ* 1991;303:1019-22.
9 McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowlder WC, Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *BMJ* 1994;308:942-5.
10 Rich-Edwards J, Colditz G, Stampfer M, Willet W, Gillman M, Hennekens C, et al. Birthweight and the risk of non-insulin-dependent diabetes mellitus in adult women. *Am J Epidemiol* 1996;143:S39.
11 Curhan G, Willett W, Rimm E, Spiegelman D, Ascherio A, Stampfer M. Birth weight and adult hypertension, diabetes mellitus and obesity in US men. *Circulation* 1996;94:3246-50.
12 Fall CH, Barker DJ, Osmond C, Winter PD, Clark PM, Hales CN. Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. *BMJ* 1992;304:801-5.
13 Barker DJP MC, Osmond C, Hales CN, Fall CHD. Growth in utero and serum cholesterol concentrations in adult life. *BMJ* 1993;307:1524-7.
14 Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;ii:577-80.
15 Fall CHD VM, Barker DJP, Osmond C, Duggleby S. Weight in infancy and prevalence of coronary heart disease in adult life. *BMJ* 1995;310:17-9.
16 Osmond CBD, Winter PD, Fall CHD, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ* 1993;307:1519-24.
17 Hennekens C, Speizer F, Rosner B, Bain C, Belanger C, Peto R. Use of permanent hair dyes and cancer among registered nurses. *Lancet* 1979;i:1301-3.
18 Troy LM, Michels KB, Hunter DJ, Spiegelman D, Manson JE, Colditz GA, et al. Self-reported birthweight and history of having been breast-fed among younger women: an assessment of validity. *Int J Epidemiol* 1996;25:122-7.
19 Rose GA, Blackburn H. *Cardiovascular survey methods*. 2nd ed. Geneva: World Health Organization, 1982. (WHO monograph series No 58.)
20 Walker AE RM, Weinfeld FD. The National Survey of Stroke: clinical findings. *Stroke* 1981;12(suppl I):I-13-44.
21 Kleinbaum D, Kupper L, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, CA: Lifelong Learning Publications, 1982:336.
22 Cox D. Regression models and life tables (with discussion). *J Roy Stat Soc (B)* 1972;34:187-200.
23 US Bureau of the Census. *Statistical abstract of the United States: 1994*. Washington, DC: US Bureau of the Census, 1994.

*(Accepted 2 July 1997)*