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WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

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Summary Environmental influences that impair growth and development in early life may be risk factors for ischaemic heart disease. To test this hypothesis, 5654 men born during 1911–30 were traced. They were born in six districts of Hertfordshire, England, and their weights in infancy were recorded. 92·4% were breast fed. Men with the lowest weights at birth and at one year had the highest death rates from ischaemic heart disease. The standardised mortality ratios fell from 111 in men who weighed 18 pounds (8·2 kg) or less at one year to 42 in those who weighed 27 pounds (12·3 kg) or more. Measures that promote prenatal and postnatal growth may reduce deaths from ischaemic heart disease. Promotion of postnatal growth may be especially important in boys who weigh below 7·5 pounds (3·4 kg) at birth.

Introduction

THE known causes of ischaemic heart disease explain only part of the differences in risk between populations and between individuals, and do not explain why in Britain the highest rates of the disease are in the poorest areas and lowest income groups.[1,2] The geographical differences in death rates from ischaemic heart disease in England and Wales are related to differences in infant mortality seventy years ago.[3] This relation is with both neonatal mortality (deaths before one month of age) and post neonatal mortality (one month to one year).[4] Impaired growth and development in prenatal and early postnatal life may be an important risk factor for ischaemic heart disease. To investigate this hypothesis, we have studied death rates in men born in Hertfordshire during 1911–30, whose weights at birth and one year were recorded.

Subjects and Methods

The registration districts of Royston, Bishops Stortford, Ware, Hertford, Hatfield, and Barnet are grouped in east Hertfordshire. At the 1921 census most of the men were employed in agriculture or in trade and services.[5] There were no major industries. The combined population of the districts was 103 211. Infant mortality in the county was below the national average. In 1921–25 the rate was 49 deaths per 1000 births, 27 neonatal and 22 postneonatal.[6] The corresponding figures for England and Wales were 76, 33, and 43.

From 1911 the attending midwife was required to notify every birth to the county medical officer of health within thirty-six hours. Almost all births occurred at home. The name and address of the mother, the date of birth, and the birthweight were registered. The local health visitor recorded her observations on a form when she visited the home periodically throughout the first year. After a year the form was returned to the county health visitor and data were abstracted onto the register, including weight at one year and whether breast fed from birth, bottle fed, or both.

More deaths were expected in men than in women and men are more readily traced because they did not change their surnames. 17 464 boys were born alive in the six districts from 1911 to 1930. 1477 of them died during childhood. We excluded twins and triplets, leaving 15 664 singletons of whom 7991 had both birthweight and weight at one year recorded. Boys whose weights were recorded at ages other than one year but not at one year, were excluded. Weights were measured in pounds (2·2 pounds = 1 kg)

TABLE I—SMRS ACCORDING TO WEIGHT AT ONE YEAR OF AGE AND BIRTHWEIGHT

Weight (pounds)	Cause of death			
	Ischaemic heart disease	Chronic obstructive lung disease	Lung cancer	All causes
One year old				
≤18 (n=324)	111 (37)*	129 (6)	98 (11)	89 (85)
19–20 (n=971)	81 (76)	86 (11)	99 (31)	89 (238)
21–22 (n=1850)	98 (163)	41 (9)	87 (48)	85 (405)
23–24 (n=1464)	71 (98)	61 (11)	57 (26)	68 (265)
25–26 (n=769)	68 (49)	52 (5)	97 (23)	73 (150)
≥27 (n=276)	42 (11)	29 (1)	70 (6)	58 (43)
Birthweight				
≤5·5 (n=251)	104 (25)	93 (3)	113 (9)	101 (69)
6–6·5 (n=752)	77 (51)	59 (5)	101 (22)	69 (131)
7–7·5 (n=1598)	90 (129)	75 (14)	68 (32)	83 (340)
8–8·5 (n=1757)	85 (141)	50 (11)	85 (47)	80 (380)
9–9·5 (n=868)	62 (53)	69 (8)	67 (19)	70 (170)
≥10 (n=428)	81 (35)	33 (2)	109 (16)	77 (96)
Total (n=5654)	82 (434)	61 (43)	83 (145)	79 (1186)

*Number of deaths in parentheses. 2·2 pounds = 1 kg.

and were often rounded to the nearest half pound or pound. We therefore used the original units. Where forenames were missing or other data required for tracing were incomplete, we sought additional information from the national birth index, which lists all births in the country, and from local registers of baptisms. For 7613 men identification data were sufficient for submission to the National Health Service Central Register at Southport: 5654 (74%) were traced, of whom 1186 died at age 20–74 years between Jan 1, 1951, and Dec 31, 1987. The average birthweight of men who were not traced was 0·1 pounds less than those who were traced, and the weight at one year was 0·2 pounds less.

We analysed cause of death in relation to birthweight, weight at one year, and infant feeding. The numbers of deaths were compared with those expected from national rates for men of corresponding age and year of birth.[7] Death rates were expressed as standardised mortality ratios (SMRs), with the national average as 100. Ischaemic heart disease was defined by *International Classification of Diseases* (9th revision) numbers 410–414, chronic obstructive lung disease by 491–493 and 496, and lung cancer by 162–164. The social class of all except 22 of the men who died was derived from the occupation recorded on the death certificate.

Results

434 of the 1186 deaths were due to ischaemic heart disease; 328 occurred below the age of sixty-five years. The overall death rate from this condition (SMR 82) was below the national average.

The average weight of the men when they were one year old was 22·4 pounds (SD 2·6). SMRs for ischaemic heart disease fell steeply with increasing weight at age one (table I). This downward trend was significant ($p < 0.002$, χ^2 for trend). Of the other leading causes of death only chronic obstructive lung disease showed a similar trend (table I).

TABLE II—SMRS FOR ISCHAEMIC HEART DISEASE ACCORDING TO WEIGHT AT ONE YEAR AND METHOD OF FEEDING

Weight (pounds)	Breast fed	Bottle fed
≤18	112 (33)	105 (4)
19–20	81 (71)	79 (5)
21–22	100 (154)	72 (9)
23–24	69 (85)	97 (13)
25–26	61 (40)	144 (9)
≥27	38 (9)	89 (2)
Total	81 (392)	94 (42)

TABLE III—SMRS FOR ISCHAEMIC HEART DISEASE ACCORDING TO BIRTHWEIGHT AND WEIGHT AT ONE YEAR IN MEN WHO WERE BREAST FED

Weight at one year (pounds)	Weight at birth (pounds)			
	Below average (≤7)	Average 7·5–8·5	Above average (≥9)	Total
Below average (≤21)	100 (80)	100 (77)	58 (17)	93 (174)
Average (22–23)	86 (34)	87 (67)	80 (29)	85 (130)
Above average (≥24)	53 (14)	65 (42)	59 (32)	60 (88)
Total	88 (128)	85 (186)	65 (78)	81 (392)

There were only 43 deaths from this cause and the trend was not significant. There was no trend in death rates from lung cancer in relation to weight at one year (table I). Death rates from all causes showed a significant downward trend with increasing weight ($p < 0.001$). Exclusion of deaths from ischaemic heart disease and chronic obstructive lung disease abolished this trend.

The men's average birthweight was 7·9 pounds (SD 1·3). Men who weighed 5·5 pounds or less had the highest SMR for ischaemic heart disease at 104 (table I). The downward trend in SMRs with increasing birthweight was not significant. Men who weighed 5·5 pounds or less also had the highest SMRs for obstructive lung disease, and for all causes of death (trend not significant). There was no trend in SMRs for lung cancer.

429 (7·6%) of the men were bottle fed. On average they gained 0·4 pounds more between birth and one year than did those who were breast fed ($p < 0.001$, two-sample t-test). Among the bottle fed men death rates from ischaemic heart disease did not fall with increasing weight at one year (table II). This difference in trend between men who were breast and bottle fed was not significant. Because of the different weight gain of men who were bottle fed and the suggestion of a different association with ischaemic heart disease, we

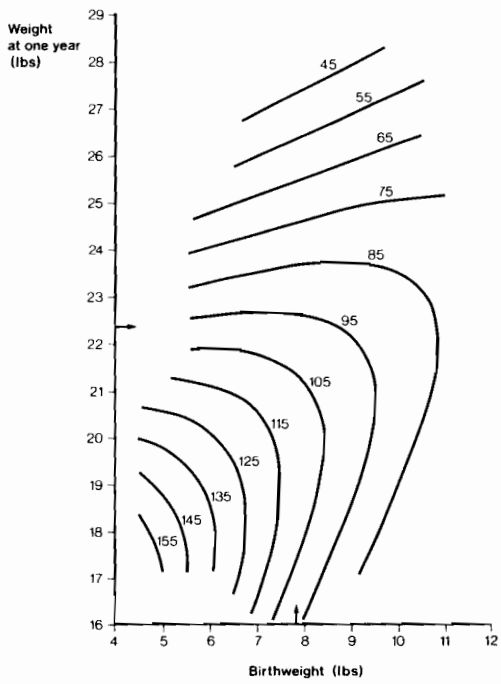

Fig 1—Relative risks for ischaemic heart disease in men who were breast fed according to birthweight and weight at one year.

Lines join points with equal risk. Arrows = mean weights.

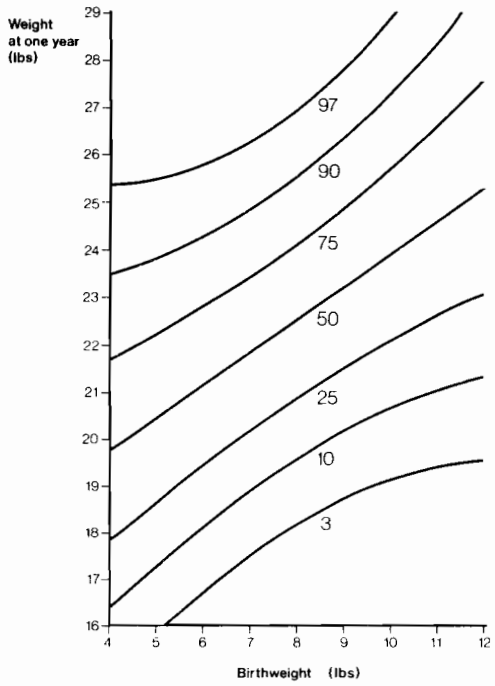

Fig 2—Percentiles of weight at one year according to birthweight in men who were breast fed.

restricted analysis of the inter-relation of birthweight and weight at one to the 5225 men who were breast fed. The lowest SMRs occurred in men who had above average birthweight or weight at one year (table III). The highest SMR (100) was in men for whom both weights were below average. Men for whom both weights were lowest, 5·5 pounds or less and 18 pounds or less, respectively, had an SMR of 220 (12 deaths, 95% confidence interval 114–384).

The simultaneous effect of birthweight and weight at one on SMRs is shown in fig 1, derived with Cox's proportional hazards method.[8] The lines join points with equal risk of ischaemic heart disease and are truncated to define an area within which lie 95% of the weights. The values are risks relative to the value of 100 for those with averge birthweight and weight at one. Fig 2 shows the percentiles of weight at one year according to birthweight.[9] Fewer men with lower birthweights attained the heaviest weights at one year and hence the lowest risks of ischaemic heart disease (fig 1). For example, only 10% of men whose birthweight was 5 pounds attained the median weight at one for those whose birthweight was 10 pounds.

Among the men who died mean birthweight was not related to social class at death (table IV). There was no downward trend in mean weight at one year with lower social class, but men in social class V had a lower than average mean weight ($p < 0·05$). The standard deviations in each social class were similar.

TABLE IV—MEAN BIRTHWEIGHT AND WEIGHT AT ONE YEAR ACCORDING TO SOCIAL CLASS AT DEATH

Social class	Mean weight at birth (pounds)	Mean weight at one year (pounds)
I (n = 38)	7·7	21·9
II (n = 177)	7·8	22·2
III non-manual (n = 125)	7·8	22·4
III manual (n = 430)	7·9	22·3
IV (n = 264)	7·8	21·9
V (n = 130)	7·8	21·6
Total (n = 1164)	7·9 (SD 1·3)	22·1 (SD 2·7)

Discussion

We have traced a population of men born in one part of Hertfordshire during 1911–30 whose weights in infancy were recorded. Hertfordshire is a prosperous part of England, and rates of ischaemic heart disease in the population are 18% below the national average. Weight at one year of age predicted death from ischaemic heart disease. Among those whose weights were 18 pounds or less death rates were almost three times greater than those who attained 27 pounds or more. These large differences were reflected in differences in deaths from all causes and hence life expectancy. 92·4% of the men were breast fed and so these results cannot be extrapolated to bottle fed populations.

7991 of all 15 664 singleton boys born in the area during the study period were weighed both at birth and at one year. Those who were not weighed at these ages may have differed from those who were. However, our analysis was based on internal comparisons and bias would be introduced only if the relation between infant growth and death from ischaemic heart disease differed in the two groups; this is unlikely. We traced 71% of the 7991 boys, despite the lapse of more than sixty years. Again bias from exclusion of those untraced is unlikely because the comparisons were internal. The variation within the data enabled us to make comparisons across a wide range of weights. 251 men had birthweights below 5·5 pounds. They had the highest death rates from ischaemic heart disease and chronic obstructive lung disease, and from all causes combined. Other evidence linking child growth with ischaemic heart disease comes from the inverse relation between adult height and cardiovascular mortality in England,[10] Norway,[11] and Finland.[12] Also average height is inversely related to cardiovascular mortality in the counties of England and Wales and in social classes.[13]

From our findings it could be argued that an environment which produces poor fetal and infant growth is followed by an adult environment that determines high risk of ischaemic heart disease. The adult influence is a matter of speculation. It is unlikely to be cigarette smoking, since early growth is unrelated to death from lung cancer; nor is growth related to any other leading cause of death except obstructive airways disease. We have information on social class only for a selected group of men, namely those who died. Among these men birthweight was unrelated to social class at death. Although average weight at one year was lower in men in social class V, the difference was small and there was no downward trend through all the social classes. These results argue against persistence of an adverse environment from intrauterine life to death.

The relation between weight at one year and death from ischaemic heart disease is strong: it spans more than sixty years, and it is graded. Among other leading causes of death only chronic obstructive lung disease shows a similar relation. Both prenatal and postnatal growth were important in determining weight at one year, since few infants with below average birthweights reached the heaviest weights at one. The combination of poor prenatal and postnatal growth led to the highest death rates from ischaemic heart disease. We conclude that processes linked to growth and acting in prenatal or early postnatal life strongly influence risk of ischaemic heart disease. Birthweight is inversely related to

adult blood pressure, and fetal growth can therefore be linked with hypertension, a known risk factor.[14] Experiments on animals have shown that infant feeding programmes lipid metabolism throughout life.[15]

Our results suggest that greater early growth will reduce deaths from ischaemic heart disease. In England and Wales past trends in infant mortality, an indicator of infant growth and health, correlate with subsequent trends in ischaemic heart disease in the same generations.[16] The large falls in cardiovascular mortality in the United States, Canada, Australia, and New Zealand during the past twenty years may also have resulted from improved child growth and health, reflected in the fall in infant mortality sixty and more years ago.[17]

The benefits associated with postnatal growth are greatest for babies with below average birthweight (fig 1): heavier weight at one year is accompanied by large reductions in death rates. Promotion of infant growth in babies of below average birthweight may therefore be a priority. Among babies with above average birthweight the risk of ischaemic heart disease is below average, irrespective of infant growth. Measures that promote infant growth may have additional benefit. Birthweight is strongly influenced by maternal height,[18] which is itself largely determined by growth in early childhood.[19] Increased growth of infant girls may lead to improved prenatal growth in their babies and may further reduce deaths from ischaemic heart disease.

We are grateful to Hertfordshire County Archives, who preserved the records and allowed us to use them; to the University of Southampton Archives, who stored the records during data abstraction; and to the staff at the NHSCR, Southport, and OPCS, London, who traced the men. Maire Dudleston, Carol Mincher, Sunita Parhar, and Julie Stevens computerised the data. The Milk Marketing Board gave a grant to assist tracing.

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GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR TO HARVEST CIRCULATING HAEMOPOIETIC STEM CELLS FOR AUTOTRANSPLANTATION

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Summary Granulocyte-macrophage colony-stimulating factor (GM-CSF), given to accelerate recovery from cytopenia induced by high-dose (7 g/m^2) cyclophosphamide, reproducibly brought about a dramatic increase (up to 1000-fold) in the number of peripheral blood granulocyte-macrophage colony-forming units (CFU-GM). These circulating progenitors were harvested by leucapheresis and reinfused, together with autologous bone marrow cells, in seven patients with cancer after total body irradiation and melphalan. Complete haemopoietic recovery occurred in all seven transplanted patients in a very short time: mean (SD) 9·1 (0·9) days (range 8–11) to achieve more than $0·5 \times 10^9$/l neutrophils, 9·9 (1·7) days (range 8–13) to over 1×10^9/l neutrophils, 10·7 (2·6) days (range 9–16) to over $0·5 \times 10^{11}$/l platelets, and 13·6 (4·2) days (range 13–21) to over $1·0 \times 10^{11}$/l platelets. A reduction in the severity of mucositis was also observed. The rapid haematological recovery made possible by this approach promises to increase the therapeutic index of high-dose chemoradiotherapy regimens and to widen their role as treatment for chemoradiosensitive tumours.

Introduction

THE availability for clinical use of haemopoietic growth factors will profoundly affect chemotherapy-induced cytopenia, which is the main factor contributing to morbidity, mortality, and underdosing in cancer treatment. Several clinical trials have shown beneficial effects of granulocyte-macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF) on bone marrow function in patients who had received standard-dose chemotherapy for tumours[1–4] and subjects accidentally exposed to caesium-137 radiation.[5] Cancer patients treated with high-dose combination chemotherapy and autologous bone marrow support who received GM-CSF showed faster myeloid recovery than similarly treated historical controls.[6,7] Although the time to achieve a granulocyte count of $0·5 \times 10^9$/l, was shorter in patients receiving GM-CSF, the effect was most pronounced during GM-CSF infusion. After discontinuation of the growth factor leucocyte counts in treated patients fell to control levels,[6] suggesting that an important component of the observed response was probably due to demargination of cells and mobilisation of mature cells from the bone marrow.[1,6] Moreover, no consistent effect on platelet count was noted.[6,7]

GM-CSF could be useful in the setting of autologous bone marrow transplantation in a different, indirect way. Socinski and colleagues[8] showed that GM-CSF, given alone or after cytotoxic chemotherapy, expands the circulating pool of haemopoietic progenitor cells by approximately