Fetal and infant growth and cardiovascular risk factors in women

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Abstract

***Objective*—To examine whether cardiovascular risk factors in women are related to fetal and infant growth.**

***Design*—Follow up study of women born 1923-30 whose birth weights and weights at one year were recorded.**

***Setting*—Hertfordshire.**

***Subjects*—297 women born and still living in East Hertfordshire.**

***Main outcome measures*—Plasma glucose and insulin concentrations during a standard oral glucose tolerance test; fasting plasma proinsulin and 32-33 split proinsulin concentrations; blood pressure; fasting serum total, low density lipoprotein and high density lipoprotein cholesterol, triglyceride, and apolipoprotein A I and B concentrations; and plasma fibrinogen and factor VII concentrations.**

***Results*—Fasting plasma concentrations of glucose, insulin, and 32-33 split proinsulin fell with increasing birth weight (P=0·04, P=0·002, and P=0·0002 respectively, when current body mass index was allowed for). Glucose and insulin concentrations 120 minutes after an oral glucose load showed similar trends (P=0·03 and P=0·02). Systolic blood pressure, waist:hip ratio, and serum triglyceride concentrations also fell with increasing birth weight (P=0·08, P=0·07, and P=0·07 respectively), while serum high density lipoprotein cholesterol concentrations rose (P=0·04). At each birth weight women who currently had a higher body mass index had higher levels of risk factors.**

***Conclusion*—In women, as in men, reduced fetal growth leads to insulin resistance and the associated disorders: raised blood pressure and high serum triglyceride and low serum high density lipoprotein cholesterol concentrations. The highest values of these coronary risk factors occur in people who were small at birth and become obese. In contrast with men, low rates of infant growth did not predict levels of risk factors in women.**

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Introduction

Studies in men in Britain have shown that poor growth in fetal life and infancy is associated with higher rates of coronary heart disease in adult life. Studies of men born in Hertfordshire during 1911-30 have shown that low birth weight or low weight at one year, or both, are associated with increased death and prevalence rates of coronary heart disease,[1,2] and with raised levels of known cardiovascular risk factors including impaired glucose tolerance and diabetes,[3] hypertension,[3] high plasma clotting factor,[4] and serum apolipoprotein B concentrations,[5] and central obesity.[6] These findings have led to the hypothesis that cardiovascular disease in adults has its origins in impaired development during fetal life and infancy. Undernutrition during early life not only leads to reduced body size but also, depending on its timing, selectively changes an individual's body composition, hormonal axes, and metabolism.[7] This phenomenon is known as programming.[8]

Among the Hertfordshire men different patterns of early growth predicted different risk factors in adult life. High blood pressure was linked to low birth weight, but was not associated with low weight at one year.[3] High plasma fibrinogen and factor VII and serum apolipoprotein B concentrations were associated with low weight at one year, but were not related to birth weight.[4,5] High plasma glucose and insulin two hours after an oral glucose load were linked to both low birth weight and low weight at one year.[3] One possible explanation for these specific associations is that the timing of sensitive periods of development, which occur during phases of rapid cell replication, differs for different tissues and systems.

A recent study in Hertfordshire showed that low birth weight was associated with increased mortality from cardiovascular disease in women.[1] Death rates fell progressively between women with low and high birth weight. In contrast with men, mortality from cardiovascular disease was not related to weight at one year. We have traced a subsample of the women born in Hertfordshire during 1923-30 and still living in the county, and analysed levels of cardiovascular risk factors in relation to their birth weight and weight at one year.

Subjects and methods

From 1911 to 1948 each birth in Hertfordshire was notified by the attending midwife and the birth weight recorded. Health visitors also saw each child routinely during infancy and recorded its weight at the age of one year. They recorded whether infants were breast fed or bottle fed, or both, and whether or not they were weaned at one year. With the help of the NHS Central Registry, Southport, we traced 5585 women who were born in Hertfordshire during 1923-30.[1] Those who were unmarried in 1951 were identified from the NHS central register, which was established in that year. Those who were married and had therefore changed their names, were identified from the earlier, 1939 national register, in which changes of name were recorded throughout and immediately after the war for the purposes of food rationing. In all, 565 women were born in the six districts of East Hertfordshire and still lived there. We contacted them by letter, and 388 (69%) agreed to be interviewed at home. One of four trained fieldworkers, who had not seen the data on them as infants, visited the women. They obtained information on medical and social history and on smoking and drinking habits and measured height, weight, waist and hip circumference, and blood pressure, using the same methods as in our studies of men.[3] The father's occupation was used to define social class at birth, and current social class was derived from the women's occupation if she was single or the husband's occupation if she was married (most married women were housewives).[9]

After the interview the woman was asked if she would attend a local clinic to have blood samples taken; 12 women with diabetes, two receiving warfarin, and three who were housebound were excluded. Of the remaining 371, 309 (83%) agreed to attend. Blood was taken in the morning after a 12 hour overnight fast and 30 and 120 minutes after a standard (75 g) oral glucose load. Venepuncture was carried out with minimal haemostasis. Samples were analysed for plasma

glucose and insulin concentrations after fasting and at 30, and 120 minutes; fasting plasma proinsulin, 32-33 split proinsulin, fibrinogen, and factor VII concentrations; and fasting serum triglyceride, total cholesterol, high density lipoprotein cholesterol, and apolipoprotein A I and B concentrations. The laboratory methods were the same as those used in previous studies.[3 5] We analysed the data of the 297 women who completed the two hour glucose tolerance test.

STATISTICAL ANALYSIS

Birth weight and weight at one year had been measured by the health visitors in pounds (1 lb=0·45 kg), and as these measurements were often rounded to the nearest full or half pound we preserved the original units. Plasma concentrations of glucose, insulin, proinsulin, and 32-33 split proinsulin and serum concentrations of low density lipoprotein and high density lipoprotein cholesterol and triglycerides has skewed distributions. Values were transformed to normality with logarithms. The data were analysed with tabulation of means, multiple linear regression, and logistic regression; P values refer to analyses using the full range of continuously distributed variables.

Results

The 297 women were aged 60-71 (mean 64) years. Their mean birth weight was 7·6 lb and mean weight at one year 21·4 lb. Tables I and II show mean values for the risk factors examined, with the women divided into the six groups of birth weight and weight at one year used in the previous analyses of men. Body mass index (weight(kg)/height(m)^2) rose with increasing birth weight (P=0·05) and weight at one year (P=0·06).

GLUCOSE, INSULIN, PROINSULIN, 32-33 SPLIT PROINSULIN

Plasma glucose concentrations, fasting and 30 and 120 minutes after glucose, rose with increasing body mass index (P=0·003, 0·001, and 0·003 respectively), as did plasma insulin concentrations at 0, 30, and 120 minutes, and fasting plasma proinsulin and 32-33 split proinsulin concentrations (P=<0·0001 for all). We therefore allowed for body mass index when calculating the significance of trends with birth weight.

Plasma glucose and insulin concentrations fell between women of the lowest and highest birth weights (table I). The strongest trends were with fasting values. Table III shows that the lowest fasting insulin concentrations were in women who were heavy at birth and currently thin. The findings for glucose were similar. Concentrations of 32-33 split proinsulin fell with increasing birth weight (table I), the lowest concentrations being in women who were heavy at birth and currently thin (table IV). Plasma glucose and insulin concentrations at 120 minutes fell with increasing weight at one year (table II), though the trends were

TABLE I—*Mean body mass index; plasma glucose, insulin, and proinsulin concentrations; systolic blood pressure; serum triglyceride and cholesterol concentrations; plasma fibrinogen and factor VII concentrations; and waist:hip ratio, according to birth weight*

	Birth weight (lb)								
	≤5·5	-6·5	-7·5	-8·5	-9·5	>9·5	All	Standard deviation	Test for trend* (P value)
No of women	14	54	108	73	36	12	297		
Body mass index (kg/m^2)	27·3	26·0	27·1	27·1	27·6	28·3	27·0	4·6	
Glucose tolerance tests:									
Fasting:									
Glucose (mmol/l)	5·9	5·8	5·9	5·7	5·6	5·6	5·8	1·1†	0·04
Insulin (pmol/l)	55	55	49	47	45	48	49	1·7†	0·002
Proinsulin (pmol/)	3·7	3·9	3·6	3·8	3·5	4·2	3·7	1·8†	0·3
32-33 split proinsulin (pmol/l)	8·5	7·6	7·1	7·0	5·9	5·0	7·0	2·0†	0·0002
After 30 minutes:									
Glucose (mmol/l)	9·4	8·9	8·9	8·8	8·4	8·5	8·8	1·2†	0·09
Insulin (pmol/l)	272	286	261	257	240	290	263	1·7†	0·1
After 120 minutes:									
Glucose (mmol/l)	7·0	7·5	7·3	7·3	6·6	6·0	7·2	1·4†	0·03
Insulin (pmol/l)	217	274	248	245	201	204	242	2·0†	0·02
Systolic blood pressure (mm Hg)	164	160	161	160	151	156	159	24	0·08
Serum triglycerides (mmol/l)	1·6	1·4	1·3	1·4	1·3	1·2	1·3	1·6†	0·07
Serum cholesterol (mmol/l)	7·3	7·4	7·1	7·5	7·0	7·0	7·2	1·4	0·8
Serum high density lipoprotein cholesterol (mmol/l)	1·32	1·39	1·43	1·42	1·40	1·57	1·41	1·3†	0·04
Waist:hip ratio	0·80	0·81	0·80	0·80	0·80	0·80	0·80	0·06	0·07
Plasma fibrinogen (g/l)	3·18	2·92	2·98	3·06	2·89	3·35	3·00	0·50	0·4
Plasma factor VII (% of standard)	137	131	137	136	134	153	136	31	0·6

*Allowing for current body mass index. †Geometric standard deviation.

TABLE II—*Mean body mass index; plasma glucose, insulin, and proinsulin concentrations; systolic blood pressure; serum triglyceride and cholesterol concentrations; plasma fibrinogen and factor VII concentrations; and waist:hip ratio, according to weight at one year*

	Weight at one year (lb)								
	≤18	-20	-22	-24	-26	>26	All	Standard deviation	Test for trend* (P value)
No of women	36	89	89	57	17	9	297		
Body mass index (kg/m^2)	26·9	26·6	26·6	27·5	28·2	30·1	27·0	4·5	
Glucose tolerance tests:									
Fasting:									
Glucose (mmol/l)	5·7	5·8	5·7	5·7	6·1	6·0	5·8	1·1†	0·5
Insulin (pmol/l)	51	48	47	51	53	57	49	1·7†	0·9
Proinsulin (pmol/l)	3·7	3·6	3·8	3·4	5·3	4·7	3·7	1·8†	0·5
32-33 split proinsulin (pmol/l)	7·2	7·0	6·5	6·5	9·1	10·1	7·0	2·0†	0·8
After 30 minutes:									
Glucose (mmol/l)	8·5	8·9	8·8	8·7	9·4	9·1	8·8	1·2†	0·5
Insulin (pmol/l)	244	260	267	274	259	276	263	1·7†	0·9
After 120 minutes:									
Glucose (mmol/l)	7·4	7·4	7·2	6·8	7·3	6·6	7·2	1·4†	0·08
Insulin (pmol/l)	264	234	273	214	235	173	242	2·0†	0·01
Systolic blood pressure (mm Hg)	157	161	161	158	156	161	159	24	0·6
Serum triglycerides (mmol/l)	1·4	1·4	1·3	1·3	1·3	1·5	1·3	1·6†	0·5
Serum cholesterol (mmol/l)	7·3	7·3	7·3	7·1	6·7	7·6	7·2	1·4	0·9
Serum high density lipoprotein cholesterol (mmol/l)	1·42	1·45	1·41	1·40	1·33	1·39	1·41	1·3†	0·6
Waist:hip ratio	0·79	0·80	0·80	0·80	0·82	0·79	0·80	0·06	0·6
Plasma fibrinogen (g/l)	3·01	2·93	3·04	2·97	3·06	3·32	3·00	0·50	0·3
Plasma factor VII (% of standard)	136	135	134	142	129	147	136	31	0·8

*Allowing for current body mass index. †Geometric standard deviation.

TABLE III—*Geometric mean plasma fasting insulin concentration (pmol/l) according to birth weight and current body mass index. Figures in parentheses are numbers of women*

Birth weight (lb)	Adult body mass index (kg/m²)			
	≤24·5	-28	>28	All
≤7	44 (43)	48 (38)	72 (33)	52 (114)
-8	35 (36)	44 (33)	76 (33)	48 (102)
>8	34 (21)	42 (31)	66 (29)	47 (81)
All	38 (100)	45 (102)	71 (95)	49 (297)

TABLE IV—*Geometric mean plasma fasting 32-33 split proinsulin concentration (pmol/l) according to birth weight and current body mass index*

Birth weight (lb)	Adult body mass index (kg/m²)			
	≤24·5	-28	>28	All
≤7	6·0	7·0	10·3	7·4
-8	5·1	6·6	11·5	7·2
>8	3·9	5·5	9·4	6·1
All	5·2	6·4	10·4	7·0

not significant in a simultaneous regression with birth weight. Neither fasting glucose, insulin, proinsulin, or 32-33 split proinsulin concentrations, nor 30 minute glucose or insulin concentrations were related to weight at one year (table II).

In all, 21 women were found to have diabetes, defined by a 120 minute plasma glucose concentration of 11·1 mmol/l or more. They were older than the 186 women who had normal glucose tolerance (66 years *v* 64) and had a higher mean body mass index (29 *v* 27). Their mean birth weight was lower (7·2 lb *v* 7·6; P for difference 0·1). A further 90 women had impaired glucose tolerance, defined as a two hour plasma glucose concentration of 7·8-11·0 mmol/l. Table V shows the numbers of women with diabetes or impaired glucose tolerance according to birth weight. The prevalence of diabetes fell with increasing birth weight, although the trend was not significant (P=0·1). None of the 48 women weighing more than 8·5 lb at birth was diabetic. By combining the 12 women already known to have diabetes (in whom we did not perform any blood tests) with the 21 women found to be diabetic, we found that the numbers and percentages of women with diabetes in the six birth weight groups were: ≤5·5 lb, 2 (13%); 5·6-6·5 lb, 7 (13%); 6·6-7·5 lb, 13 (12%); 7·6-8·5 lb, 8 (11%); 8·6-9·5 lb, 2 (5%), and >9·5 lb, 1 (8%) (P value for trend 0·2). No trend occurred in prevalence of diabetes or impaired glucose tolerance with weight at one year.

TABLE V—*Numbers (percentages) of women with impaired glucose tolerance or diabetes according to birth weight*

Birth weight (lb)	Total of women	Two hour glucose (mmol/l)		
		7·8-11·0	≥11·1	≥7·8
≤5·5	14	2 (14)	1 (7)	3 (21)
-6·5	54	16 (30)	6 (11)	22 (41)
-7·5	108	35 (32)	9 (8)	44 (41)
-8·5	73	26 (36)	5 (7)	31 (42)
-9·5	36	10 (28)	0 (0)	10 (28)
>9·5	12	1 (8)	0 (0)	1 (8)
All	297	90 (30)	21 (7)	111 (37)

BLOOD PRESSURE

Systolic and diastolic blood pressures rose with increasing body mass index (P=0·005 and P=0·04 respectively). When body mass was allowed for, systolic pressures were highest in the women with the lowest birth weights and fell with increasing birth weight, though the trend was not significant (table I). Systolic pressures fell by 2·1 mm Hg (95% confidence interval -4·4 to 0·2) per pound increase in birth weight. Diastolic blood pressure was not related to birth weight. Neither systolic nor diastolic blood pressure was related to weight at one year (table II).

LIPIDS AND APOLIPOPROTEINS

Fasting serum concentrations of total and low density lipoprotein cholesterol, triglycerides, and apolipoprotein B rose with increasing body mass index (P=0·02, P=0·02, P<0·0001, and P=0·2 respectively), while serum high density lipoprotein cholesterol and apolipoprotein A I concentrations fell (P=0·0001 and P=0·0004 respectively). Independently of body mass index, high density lipoprotein cholesterol rose with increasing alcohol consumption (P=0·02). Triglyceride concentrations were highest in the women of lowest birth weight and fell with increasing birth weight (table I). High density lipoprotein cholesterol concentrations were lowest in the women of lowest birth weight and rose with increasing birth weight (table I). This trend was independent of alcohol consumption. Concentrations of total cholesterol (table I), low density lipoprotein cholesterol, apolipoprotein A I, and apolipoprotein B were not related to birth weight. None of the lipid or apolipoprotein concentrations were related to weight at one year (table II).

WAIST:HIP RATIO

The mean waist:hip ratio rose with increasing body mass index (P<0·0001). It was similar in all birth weight groups (table I), but when body mass index was allowed for, the ratio tended to be lower in the women with higher birth weight. Table VI shows that the women who were heavy at birth and had a low body mass index had the lowest waist:hip ratios. Waist:hip ratio was not related to weight at one year (table II).

FIBRINOGEN AND FACTOR VII

Fibrinogen concentration was not measured in 18 women, and factor VII concentration was not measured in 22, either because a sample could not be taken without haemostasis or because the specimen was haemolysed or clotted. Fibrinogen concentrations rose with increasing body mass index (P=0·0006) and age (P=0·04) and were higher (mean 3·21 g/l) in the 45 smokers than in the 234 non-smokers (2·96 g/l; P for difference 0·002). Factor VII concentrations rose with increasing body mass index P=0·03). Neither fibrinogen nor factor VII concentrations were related to birth weight (table I) or to weight at one year (table II).

TABLE VI—*Mean waist:hip ratio according to birth weight and current body mass index*

Birth weight (lb)	Adult body mass index (kg/m²)			
	≤24·5	-28	>28	All
≤7	0·78	0·81	0·83	0·80
-8	0·78	0·79	0·83	0·80
>8	0·76	0·79	0·82	0·80
All	0·78	0·80	0·83	0·80

INFANT FEEDING

Data on feeding were not recorded for seven of the women. Of the remaining 290 women, 208 were breast fed, 11 were bottle fed, and 71 received both breast milk and bottle feeds. No differences occurred between the three feeding groups in any of the risk factors measured. Among the women who were breast fed, either exclusively or in combination with bottle feeds, 65 had not been weaned at one year. Their cardiovascular risk factors were similar to those of the other women.

SOCIAL CLASS

No trends occurred in birth weight or weight at one year with current social class or social class at birth. Body mass index and waist:hip ratio were higher in women of lower current social class (P=0·0006 and P=0·006 respectively). Mean body mass index in

current social classes I, II and III (non-manual) was 26·0 compared with 27·5 in social class III (manual) and 27·7 in classes IV and V. Corresponding values for waist:hip ratio were 0·79, 0·80, and 0·82. Concentrations of 32-33 split proinsulin were higher in the women of lower current social class, but this was accounted for by their higher body mass index. None of the other risk factors was related to social class, either currently or at birth, and allowing for social class did not alter the trends of risk factors with birth weight.

Discussion

We have shown in a sample of women aged 60-71 years that those who had lower birth weight had higher plasma concentrations of glucose and insulin, higher systolic blood pressures, higher serum triglyceride concentrations, lower serum high density lipoprotein cholesterol concentrations, and higher waist:hip ratios. The associations between low birth weight and these cardiovascular risk factors factors are independent of social class, currently and at birth. The risk factors are strongly related to adult body mass index. Obesity in adult life adds to the disadvantage of low birth weight: the women who were light at birth and currently obese have the least favourable risk factor profile.

Our study sample comprised women who had complete health visitor records, who were traced and still lived in East Hertfordshire, and who were willing to take part in the study. No differences occurred in mean birth weight or weight at one year between women traced and not traced or between those who agreed to take part and those who did not. Our analysis was based on internal comparisons, and bias would be introduced only if the relation between early growth and risk factors differed between those traced and not traced, and between those who did and did not participate—such differences are unlikely to exist.

INSULIN RESISTANCE SYNDROME

Raised blood pressure, abnormal glucose and insulin metabolism, raised serum triglyceride concentrations, low serum high density lipoprotein cholesterol concentrations, and high waist:hip ratios are components of the insulin resistance syndrome, also known as syndrome X.[10] This syndrome is associated with coronary heart disease.[11] The link between low birth weight and syndrome X is consistent with the raised rates of death from coronary heart disease in women of low birth weight.[1] A relation between low birth weight and high blood pressure in women has been reported previously in Hertfordshire[12] and in three other studies.[13-15] An association between low birth weight and raised plasma glucose and insulin concentrations and syndrome X has been found in 50 year old women in Preston,[16,17] and in Mexican American women.[18]

PROGRAMMING

It has been argued that people whose growth was impaired in utero continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to programming.[19] We have previously summarised the reasons for rejecting this explanation.[1] Associations between reduced early growth and cardiovascular risk factors are being found in different populations.[20,21] As in the present study, the associations are independent of social class and other measures of adult lifestyle. The associations are statistically strong and graded. For these and other reasons,[1] we conclude that reduced early growth and cardiovascular disease are causally linked. This conclusion is strengthened by recent animal studies that show, for example, that experimentally induced low birth weight is followed by lifelong raised blood pressure.[22]

Key messages

- Men and women who had low birth weight are at increased risk of coronary heart disease
- They have increased levels of cardiovascular risk factors associated with insulin resistance
- The highest levels of these risk factors are in people who were small at birth and obese as adults
- Unlike in men, low rates of growth in infancy are not linked to coronary heart disease in women

MALE:FEMALE DIFFERENCES

We have found similarities and differences in the associations between early growth and cardiovascular risk factors in men and women in Hertfordshire. Low birth weight is associated with raised blood pressure in both men and women.[3] In both men and women plasma glucose and insulin concentrations two hours after a glucose load fall with increasing birth weight.[3] In contrast with men, however, fasting glucose and insulin concentrations in women were strongly related to birth weight, as was found in Mexican Americans.[18] An interpretation of this is that in women low birth weight is more strongly associated with insulin resistance than it is in men. This is consistent with the association in women between low birth weight and raised 32-33 split proinsulin concentrations (Table I and IV), a marker of insulin resistance in adults.[23] In men, but not in women, low weight at one year predicts raised plasma fibrinogen and factor VII concentrations,[4] raised serum apolipoprotein B concentrations,[5] and impaired glucose tolerance.[3] The absence of any association between weight at one year and cardiovascular risk factors in women is consistent with the lack of an association between low weight at one year and raised rates of death from coronary heart disease in women, in contrast with the strong association in men.[1] In men bottle feeding and prolonged breast feeding are associated with raised serum cholesterol concentrations and high rates of death from cardiovascular disease.[5] We have not found these associations in women.

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Mortality among twins after age 6: fetal origins hypothesis versus twin method

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Abstract

***Objective*—To test the validity of the fetal origins hypothesis and the classic twin method.**

***Design*—Follow up study of pairs of same sex twins in which both twins survived to age 6.**

***Setting*—Denmark.**

***Subjects*—8495 twin individuals born 1870-1900, followed through to 31 December 1991.**

***Main outcome measures*—Mortality calculated on a cohort basis.**

***Results*—Mortality among twins and the general population was not significantly different except among females aged 60-89, in whom mortality among twins was 1·14 times (SE 0·03) higher than in the general population. Mortality among female dizygotic twins was 1·77 times (0·18) higher than among monozygotic twins at age 30·59. Otherwise, mortality for monozygotic and dizygotic twins did not consistently differ after age 6.**

***Conclusion*—According to the fetal origins hypothesis the risk of adult morbidity and mortality is heightened by retardation in intrauterine growth. Twins, and in particular monozygotic twins, experience growth retardation in utero. The findings in the present study suggest that the fetal origins hypothesis is not true for the retardation in intrauterine growth experienced by twins. Furthermore, the data are inconsistent with the underlying assumption of a recent claim that the classic twin method is invalid for studies of adult diseases. The present study is, however, based on the one third of all pairs of twins in which both twins survived to age 6. The possible impact of this selection can be evaluated in future studies of cohorts of younger twins with lower perinatal and infant mortality.**

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Introduction

Classic studies of twins compare concordance or correlation for a given trait in monozygotic and dizygotic twins to estimate the relative importance of genes and environment in the aetiology of the trait. A twin study is of limited value if the aetiology of the trait differs in twins and singletons because the result from such a twin study might not be valid in the general population.

Usually, diseases with onset in adulthood have been thought to have the same aetiology in populations of both twins and singletons. This view has changed with the introduction of the fetal origins hypothesis, which states that retardation in intrauterine growth increases the risk for adult diseases such as diabetes mellitus, cardiovascular diseases, and hypertension.[1-3] Twins experience considerable retardation in intrauterine growth—for example, they are on average more than 900 g lighter than single children at birth.[4,5] Furthermore, monochorionic twins, who are exclusively monozygotic and comprise two thirds of all monozygotic twins, tend to have a lower birth weight than dichorionic twins,[6] which indicates that intrauterine conditions are even more adverse for monochorionic twins. Phillips has suggested, on the basis of the fetal origins hypothesis, that these factors could affect the validity of the classic twin method.[7,8]

A recent Swedish twin study, based on a 15 year follow up of twins surviving to age 46-65, showed that mortality from ischaemic heart disease was not higher among twins than in the general population.[9] This finding was taken as evidence against the fetal origins hypothesis. Concerns about the validity of this conclusion, however, have been raised because no distinction between mortality patterns among monozygotic and dizygotic twins was made. As monozygotic twins on average have lower birth weight than dizygotic twins[6] and as dizygotic twinning is positively correlated with higher socioeconomic status,[10] increased mortality from ischaemic heart disease might be found only among monozygotic twins.

Since the 1940s cardiovascular diseases and cancer have been the most common causes of death in Denmark, together comprising more than half of all causes of death.[11] Previous studies of Danish twins have shown no significant difference in the incidence of cancer between twins and the general population or between monozygotic and dizygotic twins.[12] If, as the fetal origins hypothesis predicts, twins experience a higher incidence of diabetes mellitus, cardiovascular disease, and hypertension than the general population then they should also experience higher mortality after childhood than the general population. Similarly, monozygotic twins should experience higher mortality after childhood than dizygotic twins.