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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.

The present study used a database on mortality of Danish twins and singletons born 1870-1900, which permitted assessment of mortality patterns among monozygotic and dizygotic twins separately. Pairs of twins in which both twins survived to age 6 were included, and all traced twins were followed through to 31 December 1991. The aim of the study was to examine whether (*a*) twins have higher mortality than the general population in adulthood and (*b*) monozygotic twins have higher mortality than dizygotic twins in adulthood.

Methods

The present study was based on two sources of data, the Danish twin registry and the Danish mortality database at Odense University.

DANISH TWIN REGISTRY

This registry was established in 1954 and was the first nationwide twin registry in the world.[13,14] The birth registers from all 2200 parishes of the relevant calendar years were manually scrutinised to identify all twin births. Through regional population registers (in operation since 1924) and other public sources, a search was made for the twins or, if needed, their closest relatives. As soon as a twin was traced a questionnaire was sent to him or her. If neither of a pair of twins was alive a questionnaire was sent to the closest relative. Specific questions about the degree of similarity between twins in a pair were included in the questionnaire to assess zygosity in twins of the same sex. For twins who had died or emigrated at an early age it was impossible to obtain reliable data for zygosity classification. Consequently, pairs were not followed up if one or both twins had died or emigrated before the age of 6. Nearly all the twins who survived to age 15 have been traced; untraced twins are almost all twins who died or emigrated in childhood, although the dates of death or emigration are unknown. The validity of zygosity classification based on answers to postal questionnaires has been evaluated by comparison with the results of later blood group determinants, and the misclassification rate has been found to be less than 5%.[14]

The validity of the Danish panel of cohorts of same sex twins born 1881-1920 has been evaluated and found to be very high.[12] Of special importance for mortality studies was the observation that year of death was correctly coded in 99% of the twins—that is, only 1% were coded as alive when in fact they were dead. During the past decade matching twins with the Danish person and death registers has reduced this 1% error rate to almost zero. At present the 1870-1900 cohorts of same sex twins have been followed up through to 1991 with regard to mortality.

THE DANISH MORTALITY DATABASE AT ODENSE UNIVERSITY

This database comprises age specific and sex specific death and population counts for Denmark for 1870-1900, based on information from the Danish vital statistics. Censuses were conducted in Denmark in 1870, 1880, 1890, and 1901, and the yearly number of live born infants and deaths has been recorded with accuracy by the Lutheran church since the beginning of the 19th century. As censuses were not conducted every year and death counts were reported in five year age groups before 1915 in the Danish vital statistics, linear interpolation was used to obtain estimates of death rates in one year age and calendar intervals for the general population.

On the basis of these two data sources, we calculated sex specific mortality from age 6 to 89 in the general population, all twins, the monozygotic twins, the dizygotic twins, and the twins of unknown zygosity for the three birth cohorts 1870-80, 1881-90, and 1891-1900, as well as in the combined birth cohorts 1870-1900. We expected the twins of unknown zygosity to have the highest mortality in the first part of life as early death is one reason for unknown zygosity. Hence, a grouping less favourable than the already disadvantaged monozygotic group would be a grouping in which all twins of unknown zygosity were regarded as monozygotic. We therefore analysed a group comprising monozygotic twins and twins of unknown zygosity.

Mortality was calculated on a cohort basis with central death rates as $m_x=D_x/(P_x-D_x/2)$, where D_x is the number of deaths at age x and P_x the population at risk. Sign tests based on m_x values for one year age intervals were used to test the significance of the differences between m_x for twins and the general population as well as between monozygotic and dizygotic twins for the age groups 6-29, 30-59, 60-89, and 6-89. Sign tests provide a robust non-parametric procedure for testing for differences in mortality patterns over an age interval. For those age intervals showing significant differences in mortality between two groups the excess mortality was calculated as the average of the ratios of one year m_x values in the interval.

Results

A total of 17 440 same sex pairs of twins were born during 1870-1900 in Denmark. Table I gives a summary of the data of the Danish twin registry. Table II shows the year of birth, status, and zygosity of the twins traced and followed through to 1991. In the general population 21·4% of the males and 18·9% of the females died before age 6 in these birth cohorts. Hence, about 36% (1-(1-20·2%)^2) of the pairs of twins would have experienced one or two deaths before age 6 if twins had the same mortality pattern as the general population. The actual mortality suffered by twins was much worse: in two thirds of the pairs of twins one or both died before age 6.

Figures 1 and 2 show the sex specific mortality trajectories among twins and the general population and among monozygotic twins, dizygotic twins, and the general population respectively. Table III shows

TABLE I—*Details from Danish twin registry on pairs of same sex twins born 1870-1900, by pairwise status on 31 December 1991. Values are numbers of pairs of twins (percentages of number of pairs born)*

Year of birth	No of pairs born	One or both twins		Both twins untraced	One twin untraced		Both twins traced		
		Dead before age 6	Emigrated		Cotwin dead	Cotwin alive	Both twins dead	One twin alive, cotwin dead	Both twins alive
1870-80	5635	3725 (66)	108 (2)	557 (10)	354 (6)	0	891 (16)	0	0
1881-90	5660	3831 (68)	173 (3)	319 (6)	148 (3)	0	1189 (21)	0	0
1891-1900	6145	4193 (68)	138 (2)	280 (5)	73 (1)	0	1385 (23)	68 (1)	8 (0·1)
Total	17 440	11 749 (67)	419* (2)	1156 (7)	575* (3)	0	3465* (20)	68* (0·3)	8* (0·0)

*Pairs of twins also included in table II.

TABLE II—*Details from Danish twin registry on pairs of same sex twins born 1870-1900 and followed through to 1991, by zygosity and individual status on 31 December 1991. Values are numbers of twin individuals*

	Alive			Dead			Emigrated			Total			
Year of birth	Monozygotic	Dizygotic	Unknown zygosity	Monozygotic	Dizygotic	Unknown zygosity	Monozygotic	Dizygotic	Unknown zygosity	Monozygotic	Dizygotic	Unknown zygosity	Total
1870-80	0	0	0	452	796	888	56	60	100	508	856	988	2352
1881-90	0	0	0	690	1214	622	74	176	96	764	1390	718	2872
1891-1900	29	51	4	879	1601	431	64	128	84	972	1780	519	3271
Total	29	51	4	2021	3611	1941	194	364	280	2244	4026	2225	8495

TABLE III—*Comparison of mortality trajectories by sign test for twins, twin zygosity group, and the general population, Denmark 1870-1900. Values are numbers of ages (P values) when first population had higher mortality than second*

	Age group (years)			
	6-29 (n=24)*	30-59 (n=30)*	60-89 (n=30)*	6-89 (n=84)*
Male:				
All twins combined *v* general population	11 (0·839)	10 (0·099)	15 (1·0)	36 (0·230)
Dizygotic twins *v* monozygotic twins	17 (0·064)	15 (1·0)	16 (0·856)	48 (0·230)
Dizygotic twins *v* monozygotic twins and twins of unknown zygosity	9 (0·307)	18 (0·362)	16 (0·856)	43 (0·913)
Female:				
All twins combined *v* general population	9 (0·307)	11 (0·200)	25 (0·000325)	45 (0·586)
Dizygotic twins *v* monozygotic twins	17 (0·064)	22 (0·0161)	17 (0·585)	56 (0·00299)
Dizygotic twins *v* monozygotic twins and twins of unknown zygosity	8 (0·152)	27 (0·00000843)	11 (0·200)	46 (0·445)

*Number of ages in age group.
P values were calculated from binomial distribution with 0·5 chance of success or failure—that is, under null hypothesis that both populations experienced same underlying mortality with random noise distributed with mean 0. In each case probability is two tailed probability that number of ages when first population had higher mortality than second would be as large as observed or larger. If Bonferroni's correction is applied to account for multiple comparisons then at 5% level only P values of $<0{\cdot}00208$ (0·05/24) are significant.

the significance of the differences between m_x among twins and the general population as well as among monozygotic twins and monozygotic twins combined with twins of unknown zygosity versus dizygotic twins.

The tables and figures show that the mortality among twins and the general population was not significantly different except among women aged 60-89. The average of the ratios of mortality among female twins versus the general population for one year age intervals was 1·14 (SE 0·03) in the 60-89 age group. The corresponding figure for female dizygotic twins compared with female monozygotic twins in the 30-59 age group was 1·77 (0·18). Otherwise, mortality among monozygotic and dizygotic twins did not consistently differ after age 6.

When the analysis was stratified by 10 year birth cohorts and zygosity groups two differences between mortality patterns in the population and in twins were observed: mortality was higher before adulthood among twins of unknown zygosity and lower among twins before age 60, especially in the older cohorts. In addition, higher mortality at very old ages was observed among twins of unknown zygosity in the cohorts of females born 1870-80 and 1891-1900 and males born 1891-1900.

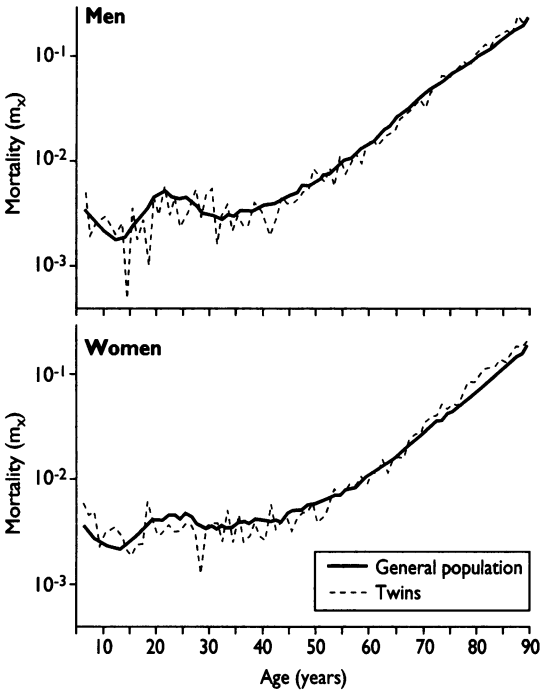

FIG 1—*Mortality among twins and in general population in Denmark, age 6-89 years. Mortality was calculated for cohorts born 1870-1900*

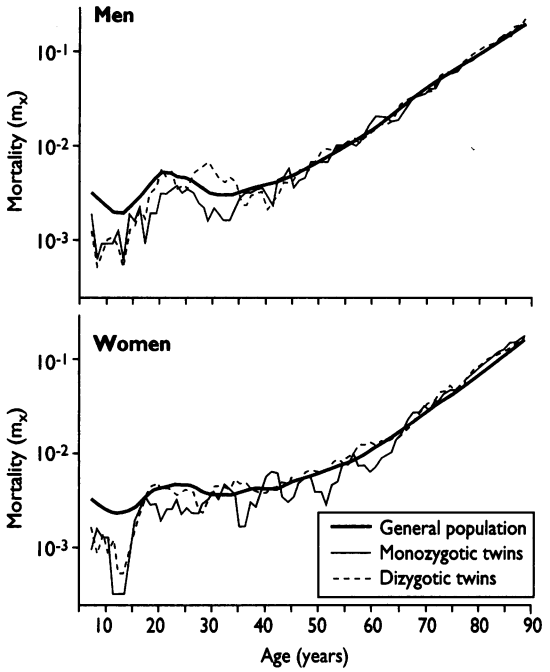

FIG 2—*Mortality (three year moving average) among monozygotic twins, dizygotic twins, and the general population in Denmark, age 6-89 years. Mortality was calculated for cohorts born 1870-1900*

Discussion

DO TWINS HAVE HIGHER MORTALITY THAN GENERAL POPULATION IN ADULTHOOD?

The literature on perinatal and infant mortality among twins is comprehensive, and the large excess risk to twins is well known.[15,16] Little information on

mortality among twins after childhood, however, is available. Hrubec and Neel found lower mortality among army veteran male twins than among American males.[17] This was expected as lower mortality is a general tendency among army veterans.[18] In a study of Mormons born before 1850 who survived to adulthood and married, male twins lived slightly less long than their singleton brothers, while no difference existed between female twins and their singleton sisters.[19]

Few mortality data are available on population based twin cohorts with known zygosity, and, indeed, mortality data covering the entire period of adulthood on a cohort basis are only available through the Danish twin registry.[12] The present study was based on follow up of 8495 twin individuals for at least 90 years, and no evidence was found that the mortality after age 6 among twins born 1870-1900 was different from mortality in the general Danish population, except among female twins age 60 and over, who had increased mortality.

When the analyses were stratified by 10 year birth cohorts a tendency towards lower mortality among twins before old age was observed, especially in the older cohorts. This observation could be a consequence of the death of frailer twin individuals during the period of very high mortality in the first six years of life. The survivors might be robust and perhaps more robust than singletons on average. The older cohorts also included a larger proportion of untraced invididuals. The group of untraced twins comprises mainly twins who died or emigrated very early in life, although the exact dates are unknown. Despite the inclusion of more than 8000 twins in the present study just a few missed cases of death among younger adults can greatly affect the low mortality in this age group.

On the basis of the multiple comparisons in the present study, the data show that mortality among twins after age 6 is similar to mortality in the general population. Hence, the data suggest that the fetal origins hypothesis is not true for the adverse intrauterine conditions experienced by twins. The type of retardation in intrauterine growth in twins, however, might be different from that in low birthweight singletons with regard to prediction of adult disease.

DO MONOZYGOTIC TWINS HAVE HIGHER MORTALITY THAN DIZYGOTIC TWINS IN ADULTHOOD?

Phillips has hypothesised that the greater concordance in monozygotic twins than in dizygotic twins for a number of adult diseases could simply reflect the shared adverse intrauterine condition of monochorionic monozygotic twins rather than common genetic factors.[7 8] The strong recommendation by Phillips to dismiss the classic twin method in studies of common diseases in adulthood is based on a theoretical framework with few data to support it. In addition, as pointed out by Macdonald,[20] the theory itself it inconsistent: as adverse intrauterine conditions are predictors of later diseases and monochorionic twins tend to differ most in birth weight a bias towards lower concordance rates should be expected among monozygotic twins and not in the opposite direction, as claimed by Phillips.[7] Furthermore, according to Phillips's hypothesis, monochorionic twins, and hence monozygotic twins, would have a higher incidence of a number of diseases, which conflicts with most previous investigations.[12 21]

In the present study the only evidence of differences in mortality between monozygotic and dizygotic twins after age 6 was a lower (not higher) mortality among female monozygotic twins than among female dizygotic twins at middle ages. Even grouping all twins of unknown zygosity with monozygotic twins failed to demonstrate any generally increased mortality among monozygotic twins in adulthood than among dizygotic twins.

Key messages

- Previous studies have suggested that morbidity and mortality in adults are linked to intrauterine development (the fetal origins hypothesis)
- It has been claimed that twin studies of adult diseases are invalid owing to the link between intrauterine development and adult diseases
- Contrary to the prediction from the fetal origins hypothesis this study found that mortality among twins and in the general population was similar after age 6
- Contrary to the underlying assumption of the claim that the twin method is invalid, this study found that mortality in monozygotic and dizygotic twins was similar after age 6
- This study suggests that the fetal origins hypothesis is not true for the retardation in intrauterine growth in these twin cohorts and that the hypothesis is no threat to the validity of the twin method

At older ages twins of unknown zygosity had a higher mortality in some cohorts (females born 1870-80 and 1891-1900 and males born 1891-1900). The reason for this and for the greater similarity in mortality between the general population and twins among males than among females remains unclear.

Because the incidence of disease and mortality among the different twin zygosity groups are closely similar to those in the general population we think that the burial of the classic twin method in studies of disease in adulthood should at least await a more consistent and well documented demonstration of the invalidity of the method. Not only does the similarity in mortality between monozygotic and dizygotic twins undermine Phillips's hypothesis, but the similar mortality after early childhood among twins and singletons casts doubt on the fetal origins hypothesis. 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 could be evaluated in younger twin cohorts—for example, 1901-30—with lower perinatal and infant mortality.

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Predictors of ratio of placental weight to fetal weight in multiethnic community

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Abstract

***Objective*—To determine whether placental ratio is influenced by maternal ethnic origin, obesity, hypertension, and haematological indices of iron deficiency anaemia.**

***Design*—Observational study.**

***Setting*—District general hospital in Birmingham.**

***Subjects*—692 healthy nulliparous pregnant women, of whom 367 were European, 213 Asian, 99 Afro-Caribbean, and 13 of other or undocumented ethnic origin.**

***Main outcome measures*—Placental ratio and maternal body mass index, blood pressure, and haematological indices.**

***Results*—Though birth weight and placental weight were lower in Asian women than in other groups, mean placental ratio was similar in Asian (19·5% (SD 3·3%)), European (20·0% (4·0%)), and Afro-Caribbean women (20·4% (5·3%)). Gestational age at birth was the main predictor of placental ratio in the univariate analysis ($r = -0·34$, $P < 0·001$) and multivariate analysis. The only other significant predictor of placental ratio in multivariate analysis was maternal body mass index, which was positively associated with placental ratio ($r = 0·1$, $P = 0·01$). Mean (SD) placental ratio was not significantly higher in women who developed gestational hypertension (20·4% (4·5%)) and pre-eclampsia (23·3% (7·3%)) than in normal women (19·8% (3·8%)). No evidence of a relation between placental ratio and first antenatal visit haemoglobin concentration or mean cell volume was detected, and placental ratio was not associated with change in mean cell volume during pregnancy or with third trimester serum ferritin concentration.**

***Conclusions*—These data do not support the proposed association between poor maternal nutrition and increased placental ratio. The association between high placental ratio and adult hypertension may be confounded by genetic and environmental factors associated with maternal obesity (and possibly maternal hypertension).**

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Introduction

Barker and colleagues have reported that the risk of essential hypertension in adult life falls with increasing birth weight and rises with increasing placental weight and that the people at highest risk are those with a high placental weight relative to birth weight—that is, a high placental ratio.[1] The group has stressed the likely dominant influence of maternal nutrition, and in particular maternal iron deficiency anaemia, on intrauterine growth.[2] Using data from the Oxford record linkage system, they described a specific association between low maternal haemoglobin combined with a fall in mean cell volume during pregnancy and a raised placental ratio.[3]

The maternal factors that lead to discordance between birth and placental weight are, however, poorly understood. The importance of maternal nutrition as a determinant of placental ratio is disputed.[4] The data from the Oxford record linkage system showed a strong positive association between maternal body mass index and placental ratio, an association which has received relatively little attention.[3] Obesity and hypertension are linked in pregnancy as in the non-pregnant state.[5] Though pre-eclampsia is known to be associated with increased placental ratio,[6] the relation between more common manifestations of hypertension in pregnancy, such as gestational hypertension, and placental ratio is unclear.

We studied maternal factors that influence the ratio of placental weight to birth weight (placental ratio) in women recruited for a study of early markers for pre-eclampsia. The women were from a multiethnic inner city community with a relatively high proportion of patients of Asian (mainly first generation from northern India, Pakistan, and Bangladesh) and Afro-Caribbean ethnic origin. There is evidence of poor maternal nutrition in pregnant Asian women relative to European women.[7,8] If nutrition is an important determinant of placental ratio the placental ratio would be expected to be higher in this group.

The aim of this study was to identify maternal factors which influence placental ratio in this population, with particular reference to the role of maternal ethnic origin, obesity, and hypertension and haematological indices of maternal iron deficiency anaemia.

Subjects and methods

We studied a group of 692 healthy nulliparous pregnant women referred for antenatal care to Dudley Road Hospital, Birmingham, before the 31st week of gestation. The median gestational age at referral was 16 weeks (interquartile range 13-18 weeks), and 85% of the women were referred at or before the 20th completed week of pregnancy. These women were recruited for a prospective study of early markers for pre-eclampsia.[9,10] Women with diabetes and twin births were excluded. Of the 692 women, 367 were European, 213 Asian, 99 Afro-Caribbean, and 13 of other or undocumented ethnic origin. This represents the usual ethnic distribution of nulliparous women referred to the hospital. Iron supplements were prescribed at the booking antenatal visit for women with a haemoglobin concentration below 11·0 g/l.

Proteinuric pre-eclampsia and gestational hypertension were defined according to current internationally agreed criteria.[11] Data on birth weight and