Birthweight, early environment, and genetics: a study of twins discordant for acute myocardial infarction

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Summary

Background Epidemiological studies that used birthweight as a crude marker of fetal growth have suggested that low birthweight is associated with increased risk of coronary heart disease. Through investigation of this association within same-sexed twin pairs, confounding by genetic and early environmental factors can be greatly decreased. We undertook a case-control study in twins discordant for acute myocardial infarction (AMI).

Methods The case-control study was nested within the population-based Swedish Twin Registry and linked with the national cause-of-death and hospital-discharge registries. We manually retrieved birth records containing information on birth and maternal characteristics for 132 same-sexed twin pairs discordant for AMI and 118 individually matched control twin pairs.

Findings In comparisons between AMI cases and external matched control twins, cases had significantly lower birthweight (mean 2556 [SD 500] vs 2699 [530] g, p=0·04), birth length (47·1 [2·8] vs 47·9 [2·7] cm, p=0·04), and head circumference (33·0 [1·8] vs 33·5 [2·0] cm, p=0·03) than controls. In within-pair comparisons between AMI cases and healthy co-twins, no significant differences in birth measurements were found (birthweight 2458 [510] vs 2534 [530] g, p=0·73; birth length 47·1 [2·8] vs 47·2 [2·8] cm, p=0·91; head circumference 33·0 [1·7] vs 33·0 [1·8] cm, p=0·92).

Interpretation The lack of an association between birth characteristics and AMI within twin pairs suggests that previously reported associations may be influenced by genetic and early environmental factors, or possibly, by unmeasured maternal factors that operate independently of birthweight.

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Introduction

Restricted fetal growth has been associated with increased risk of coronary heart disease in adult life.[1–3] Studies in animals have shown that some features of intrauterine nutrition are important for cardiovascular and endocrine development,[4] but in human beings the underlying biological mechanisms are poorly understood.

Studies investigating the association between coronary heart disease and restricted fetal growth have used birthweight for gestational age as an indirect measure of fetal growth. However, both birthweight and adult risk of coronary heart disease are influenced by genetic and socioeconomic factors. Confounding by genetic differences or by early environmental influences linked to socioeconomic status could therefore at least partly account for the reported associations between fetal growth and risk of coronary heart disease.[5]

An alternative way to assess the aetiological role of retarded fetal growth is to study twins.[6] Twins are smaller, on average, than singletons of the same gestational age, and even within pairs of twins of the same sex there are commonly substantial differences in birthweight and other anthropometric measures. The risks of mortality from coronary heart disease[7] and overall mortality among twins are similar to those of the general population.[8] Through investigation of the association between birthweight and coronary heart disease within same-sexed twin pairs, confounding by genetic and early environmental factors can be substantially decreased.

In the population-based Swedish Twin Registry, linked with the registries of cause of death and hospital discharge, we investigated the association between birth characteristics and acute myocardial infarction (AMI) among same-sexed twins in Sweden. So that we could assess the impact of confounding by genetic factors and by early environmental influences other than fetal growth, we carried out a case-control study with two control groups. The first control group was unaffected external (unrelated) control twins, and the second was unaffected co-twins. This design enabled us to test two different hypotheses explaining the association between birth characteristics and AMI. First, the finding of an association between birth characteristics and AMI both among external control twins and among within-pair co-twin controls would strongly suggest a causal effect of birth characteristics on risk of AMI. Second, if the association were observed among external controls but not among co-twin controls, the likely explanation for the discrepant results is confounding by genetic or early environmental influences.

Methods

Study population
This case-control study was nested within the Swedish Twin Registry, which includes information on twins born in Sweden between 1886 and 1958.[9] Zygosity was determined by questionnaires posted in 1961 to all same-

sexed twin pairs born between 1886 and 1925, and in 1973 to all same-sexed twins born between 1926 and 1958. Zygosity was determined on the basis of self-reported childhood resemblance, which correctly classifies more than 95% of twin pairs.[10,11]

The Cause of Death Registry contains information on all deaths in Sweden between 1961 and 1997, including information about underlying and contributing causes of death. The reporting rate is 99·6%.[12] The Hospital Discharge Registry covers all public inpatient care in Sweden between 1987 and 1996, and includes information about main diagnosis and up to five additional diagnoses.[13] In these two registries, causes of death and diagnoses are coded according to the International Classification of Diseases (ICD).[14] The seventh revision (ICD7) was used during 1961 to 1968, the eighth revision (ICD8) during 1969 to 1986, the ninth revision (ICD9) during 1987 to 1996, and the tenth revision (ICD10) from 1997 onwards.

AMI was defined on the basis of the following ICD codes: 410–414 (ICD7 to ICD9) and I 21 (ICD10). We identified all cases of fatal AMI between 1961 and 1997 and all cases of non-fatal AMI between 1987 and 1996 among same-sexed twins born between 1886 and 1958 included in the twin registry. Through the ten-digit national registration number uniquely assigned to each Swedish resident,[15] fatal and non-fatal AMI could be identified by record linkage between the registries. The classification of fatal versus non-fatal AMI was based on the first registered AMI diagnosis.

The study population includes about 25 000 same-sexed twin pairs born between 1886 and 1958. Potentially eligible cases (n=2397) were defined as same-sexed twins diagnosed with fatal or non-fatal AMI, with a co-twin who was alive and without a history of AMI at the time when the case was diagnosed with AMI. To ensure correct identification of each twin in the pair at birth, the study was restricted to hospital births. Many infants delivered at hospitals were baptised, and their first names were generally registered in the delivery charts. The proportion of hospital deliveries among twins was 12·5% in 1910, 21·5% in 1920, and 32·1% in 1930; thereafter, the proportion has not been reported.[16] We further restricted the study to maternity hospitals that have filed delivery charts since the late 19th century: Stockholm, Göteborg, Malmö, Uppsala, Lund, Linköping, Borås, Sundsvall, Örnsköldsvik, and Gävle. These maternity hospitals were located in cities in densely populated counties, and in 1930 these cities and counties covered about 17% and 45% of the Swedish population, respectively.[17] Consequently, we estimated that of the 2397 potentially eligible cases the number of births at the included maternity hospitals would be between 130 (estimated births in the city population) to 346 (estimated births in the county population). We obtained hospital birth records from 189 cases.

Correct birth identification for each individual in the twin pair was confirmed by restriction to twins who were baptised (and named) at birth (n=118), or who reported birth order with mutual within-pair agreement in a telephone survey (n=14).[11] In the remaining 57 cases, identity for each twin within the pair could not be assessed with certainty.

The potentially eligible cases (n=2397) and those for whom we retrieved birth records (n=132) were similar in terms of proportions of fatal AMI (64% vs 57%), non-fatal AMI (36% vs 43%), zygosity (potentially eligible cases 28% monozygotic, 60% dizygotic, 12% unknown zygosity; included cases 30% monozygotic, 55% dizygotic, 15% unknown zygosity), and sex (62% male, 38% female vs 63% male, 37% female). Compared with the 2397 potentially eligible cases, the 132 study cases were slightly younger, owing to the inclusion criteria (hospital delivery, filed birth records, and correct birth identification). The range of birth years was 1895 to 1955 for the potentially eligible cases and 1902 to 1947 for the 132 included cases. The median year of birth and age at diagnosis were 1918 and 67 years for potentially eligible cases and 1925 and 63 years for included cases.

Recorded information about the mothers included age at the twins' birth, age at menarche, marital status, socioeconomic status (father's or single mother's profession), area of residence, parity, health status, pre-eclampsia/eclampsia or other pregnancy-related diseases, and the duration of stay in the maternity ward. Available information about the infants was first name, gestational age, birthweight, birth length, head circumference, birth order, presentation at birth, and mode of delivery (instrumental or not). Ponderal index was expressed as birthweight in grams as a percentage of birth length in cm.

Case-control study with external controls
In the first part of the study, we compared twins who were diagnosed with AMI (cases) with matched unrelated control twin pairs (external controls). Potentially eligible external controls were same-sexed twin pairs with registered gestational age in the hospital obstetric records. Both twins in the control twin pair had to be alive and without a history of AMI at the age when the case was diagnosed with AMI. A control pair was matched to each case for sex and person-years at risk of developing AMI. Information about control pairs was obtained from birth records of twin pairs born at the same hospital as the cases. On an alternating basis, we retrieved the records for the twin pair born closest before or after the case pair. In 29 cases, we were not able to retrieve controls from the same hospital, so we selected as controls same-sexed twin pairs who were born at hospitals of similar size to those where the cases were born. One of each external control twin pair was randomly selected. Of 132 AMI cases with correct birth identification, we excluded 14 without registered gestational age in the hospital birth record. The external case-control comparison is therefore based on 118 AMI cases and 118 external controls. The range of birth years for external control twins was 1904 to 1947. The differences in birth year were 2 years or less for 95% of all cases and their matched controls.

Case-control study of co-twin controls
The second part of the study was a within-pair comparison. Cases were defined as twins diagnosed with AMI. The co-twin control was alive and without a history of AMI at the time when the case was diagnosed with AMI. This comparison included all 132 cases and controls.

Statistical analysis
The paired *t* test was used to compare birth measurements between cases and external or co-twin controls. Odds ratios were estimated from conditional logistic regression. The odds ratio for continuous variables measures the change in risk per unit of the variable. In our analyses, odds ratios were calculated per 500 g increase in birthweight.

Results
Cases had significantly lower mean birthweight, birth length, and head circumference than the external controls (table 1). No significant difference in ponderal

Characteristic	Cases (n=118)	Controls (n=118)	p
Anthropometry			
Mean (SD) birthweight in g	2556 (500)	2699 (530)	0·04*
Mean (SD) birth length in cm†	47·1 (2·8)	47·9 (2·7)	0·04*
Mean (SD) head circumference in cm†	33·0 (1·8)	33·5 (2·0)	0·03*
Mean (SD) ponderal index	2·43 (0·27)	2·43 (0·26)	0·93*
Mean (SD) gestational age in weeks	37·6 (2·8)	38·0 (2·9)	0·27*
Maternal age (years)			
≤19	2 (2%)	2 (2%)	
20–29	52 (44%)	60 (51%)	
≥30	64 (54%)	56 (47%)	0·58‡
Parity†			
1	32 (28%)	39 (33%)	
≥2	84 (72%)	78 (67%)	0·34‡
Marital status			
Married	93 (79%)	105 (89%)	
Unmarried/separated	25 (21%)	13 (11%)	0·03‡
Occupational status†			
Manual worker	86 (79%)	71 (63%)	
Non-manual worker	15 (14%)	28 (25%)	
Self-employed	8 (7%)	13 (12%)	0·04‡
Area of residence			
Country	5 (4%)	7 (6%)	
Village	57 (48%)	54 (46%)	
City	56 (47%)	57 (48%)	0·81‡

Data are number of individuals unless otherwise stated. *Paired t test. †Birth length was missing for 2 cases and 2 external controls. Head circumference was missing for 26 cases and 26 external controls. Numbers for cases and controls do not add up to total study size because of missing information on some variables. Some percentages do not add up to 100 because of rounding. ‡Test for homogeneity.

Table 1: **Birth and maternal characteristics in twins with AMI and external control twins**

Variable	Adjusted odds ratio (95% CI)*
Increase in birthweight per 500 g	0·65 (0·45-0·95)
Maternal age (years)	
≤19	0·74 (0·08-6.77)
20–29	1·00†
≥30	0·88 (0·42–1·85)
Parity	
1	0·56 (0·23–1·37)
≥2	1·00†
Marital status	
Married	1·00†
Unmarried/separated	2·14 (0·74–6·17)
Occupational status	
Manual worker	1·00†
Non-manual worker	0·54 (0·22–1·33)
Self-employed	0·41 (0·08–1·99)
Area of residence	
Country	1·47 (0·16–13·09)
Village	1·00†
City	0·73 (0·33–1·61)

*Estimated by conditional logistic regression, adjusted for gestational age, maternal age, parity, marital status, occupational status, and area of residence. †Reference group.

Table 2: **Adjusted odds ratios for AMI according to birthweight and maternal characteristics**

index was found. Mean gestational age was lower among cases than controls, but not significantly so. A significantly higher proportion of cases than of external controls had unmarried mothers and parents with manual occupations. Cases and controls did not differ significantly in terms of maternal age, parity, or area of residence.

In the conditional logistic regression with birthweight as a continuous variable, a 500 g increase in birthweight corresponded to a 22% reduction in risk of AMI (crude odds ratio 0·78 [95% CI 0·61–1·00]). The association was even stronger after adjustment for gestational age, maternal age, parity, marital and occupational status, and area of residence (0·65 [0·45–0·95]; table 2). The risk of AMI was also associated with maternal characteristics, although none of the odds ratios for these variables reached statistical significance.

Both birth length and head circumference were also associated with the risk of AMI. After control for maternal factors, an increase of 3 cm in birth length corresponded to a 32% reduction in risk of AMI (odds ratio 0·65 [0·42–0·99]), and an increase in head circumference of 1 cm corresponded to a 23% reduction in risk of AMI (odds ratio 0·77 [0·59–1·01]).

In the comparison of cases and co-twin controls, no significant differences in birth characteristics were found (table 3). The stratified analyses included 40 monozygotic twin pairs and 72 dizygotic twin pairs (20 twin pairs were excluded because of unknown zygosity). There were no significant differences in birth measurements within monozygotic or dizygotic twin pairs.

In our main analyses, co-twin controls were alive and without a history of AMI at the time when the cases were diagnosed with AMI. To optimise the difference in risk of AMI between cases and co-twin controls, we also excluded twin pairs in which the co-twin control later developed AMI (n=17). In these analyses, mean birthweight was 2563 g among cases and 2540 g among co-twin controls (p=0·59). Similarly, no significant differences were found in mean birth length or head circumference (data not shown).

We then analysed only the data for fatal AMI cases and external controls (n=67). The results were similar to those for the total sample: mean birthweight of the cases was 2568 g and that of the external controls 2716 g (p=0·11), mean birth length 47·3 cm and 47·7 cm (p=0·32), and mean head circumference 32·9 cm and 33·3 cm (p=0·31). Mean gestational age was similar in cases and external controls (37·9 weeks; p=0·96). In analyses of fatal AMI cases and co-twin controls (n=75), mean birthweight was 2565 g and 2584 g (p=0·71), birth length 47·2 cm and 47·4 cm (p=0·62), and head circumference 32·9 cm and 33·1 cm (p=0·37).

Discussion

In the comparison of twins from different (external) pairs, mean birthweight, birth length, and head circumference were significantly lower among AMI cases than among

Variable	All twins (n=132)			Monozygotic twins (n=40)			Dizygotic twins (n=72)		
	Cases	Controls	p*	Cases	Controls	p*	Cases	Controls	p*
Birthweight (g)	2548 (510)	2534 (530)	0·73	2373 (470)	2417 (560)	0·54	2676 (510)	2620 (490)	0·29
Birth length (cm)†	47·1 (2·8)	47·2 (2·8)	0·91	45·9 (3·0)	46·6 (3·1)	0·09	47·9 (2·6)	47·6 (2·6)	0·30
Head circumference in cm†	33·0 (1·7)	33·0 (1·8)	0·92	32·3 (1·8)	32·3 (2·0)	0·72	33·4 (1·6)	33·3 (1·7)	0·73
Ponderal index	2·43 (0·28)	2·41 (0·27)	0·32	2·46 (0·32)	2·38 (0·27)	0·27	2·45 (0·27)	2·43 (0·27)	0·55

Data are mean (SD). *Paired t test. †Birth length was missing for nine cases and co-twin controls. Head circumference was missing for 30 pairs.

Table 3: **Differences in birth characteristics in twins with AMI and their co-twin controls**

controls. By contrast, the comparison within pairs discordant for AMI showed no differences in measurements between cases and controls, suggesting that previously reported associations between restricted fetal growth and AMI may have been influenced by genetic factors, postnatal environmental factors, or both.

The association between restricted fetal growth and adult risk of coronary heart disease has been reported from several independent studies[1-3] and has lent support to the fetal programming hypothesis.[1] However, whether this association is causal has been questioned.[18-21] Genetic factors are important for birthweight,[22-24] and coronary heart disease also has a substantial genetic component.[25,26] If the same set of genes is important for birthweight and for cardiovascular disease later in life, the association between birthweight and AMI might be explained by genetic influences rather than malnutrition in utero.[27] Factors associated with socioeconomic status and life-style, such as cigarette smoking, physical activity, diet, and stress, might also contribute to the associations between birthweight and coronary heart disease. Moreover, random misclassification of socioeconomic status and mobility may lead to residual confounding.[19] The results from our study support these concerns about causality, because we found an association when we used external controls but not when we used healthy co-twins as controls. Twins within a twin pair share similar environments in childhood and adolescence, which should lessen the impact of both known and unknown potential confounders. In monozygotic twins, differences in birth characteristics and in occurrence of AMI are independent of genetic factors.

However, we cannot exclude the possibility of fetal programming caused by unmeasured maternal factors, which could affect the susceptibility to AMI independently of birthweight or other birth characteristics for both members of a twin pair. Moreover, there have been suggestions that the fetus can be programmed by nutritional influences that do not affect body size at birth.[28]

This case-control study was nested in a well-defined cohort, the Swedish Twin Registry. Recall bias is not an issue, because birth information was recorded by the midwife at the time of birth. Inaccurately determined birth order is unlikely, because the included case twin-pairs were baptised at the maternity wards or were identified through telephone interviews of both twins. The statistical power of the within-pair comparisons to detect differences in birth measurements of similar magnitude to those detected in the external comparisons was 95%.

Our study population was restricted to births in maternity hospitals situated in densely populated counties. Lower mean birthweight has been reported among infants delivered in hospital than in infants delivered at home.[29] Our study therefore focused on the most vulnerable twin pairs (those born in hospital) according to the fetal programming hypothesis. Furthermore, we found 189 birth records of an estimated number ranging from 130 (potential births for the city populations) to 346 (potential births for the county populations). The probability of retrieving 346 birth records from the included maternity city hospital archives is low, because we could not retrieve birth records from all maternity hospitals in the included counties. Furthermore, some women may have given birth in maternity hospitals outside the county of origin. An association between birthweight and the ability to retrieve birth records 50–70 years later seems unlikely, however. The loss of unbaptised twins is probably due to differences in baptism practices between maternity hospitals and should be unrelated to birth characteristics of the twin

pairs. Since no significant differences were observed between data from the population-based Twin Registry and birth records of our study population in terms of proportions of fatal and non-fatal AMI, zygosity, and sex, selection bias should not be an important concern.

Four twin studies have assessed the association between birthweight and blood pressure, an established risk factor for AMI. A population-based cohort study in New Zealand reported significantly lower systolic blood pressure in term twins than in singletons at ages 9 and 18 years, but no differences in diastolic blood pressure at either age.[30] In a within-pair design, a UK hospital-based cohort study of 406 adult female twin pairs found significantly higher adult systolic blood pressure in lighter than in heavier co-twins; birthweight was self-reported during adulthood, however.[31] In a cohort study in Tasmania, Australia, among infants selected because of their high risk of the sudden infant death syndrome, at 8 years of age twins showed a non-significant inverse association between birthweight difference and systolic blood pressure, and in a comparison of twins with singletons a stronger association was found in twins.[32] A case-control study in the Netherlands used within-pair comparisons and found an inverse association between systolic blood pressure and birthweight within dizygotic twin pairs. However, there were no differences in systolic blood pressure within monozygotic twins.[33] Studies in Denmark and Italy have assessed the association between birthweight and non-insulin-dependent diabetes mellitus or impaired glucose tolerance. The Danish study showed significantly lower mean birthweight in both 14 mono-zygotic and 14 dizygotic twins diagnosed with non-insulin-dependent diabetes mellitus than in their healthy co-twins.[34] The Italian case-control study in 13 monozygotic twin pairs discordant for impaired glucose tolerance, hyper-insulinaemia, or both, reported significantly lower birthweights in monozygotic twins with abnormal oral glucose tolerance than in their healthy co-twins.[35] The reasons for differences in results between studies are not obvious, and their pertinence to coronary heart disease in general and AMI in particular remains unclear.

The results from twin studies may not necessarily be generalisable to singletons. Compared with singletons, twins have lower birthweight owing to slower fetal growth as well as shorter gestation. One previous Swedish study, however, found no differences in risk of mortality from ischaemic heart disease between twins and the general population.[7] Moreover, the overall mortality among Danish twins and the general population does not differ after 6 years of age.[8]

The generalisability has been particularly questioned in monozygotic twins, because two-thirds of monozygotic twins are monochorionic; they share a common placenta and thus also share many intrauterine environmental influences, not just the same genotype.[36] Our within-pair analysis showed no differences in anthropometric measurements in either monozygotic or dizygotic twins (no data were available on chorionicity). Most importantly, the results showed differences in these measurements between discordant external twins, results quite consistent with those previously reported in singletons. The fact that no such differences were seen in discordant within-pair twins suggests that these contrasting results cannot be attributed to the non-generalisability of evidence from twins overall, but rather to unknown genetic and early environmental differences associated with fetal growth in both singletons and twins.

In conclusion, our findings do not support a direct effect between fetal growth and AMI. The result suggests that genetic, maternal, and environmental factors during

childhood and adolescence associated with fetal growth may have influenced the previously reported associations between birthweight and AMI. Further studies with larger numbers of twins should help to elucidate further the associations between birth characteristics and subsequent risk of coronary heart disease.

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