Key messages

- Individuals heterozygous for hereditary protein C deficiency have an increased risk of venous thrombotic events, including pulmonary embolism
- Anticoagulant prophylaxis may prevent such events, reducing morbidity
- Whether anticoagulant prophylaxis will also reduce mortality is not known
- This study shows that mortality is no higher in heterozygous individuals than in the general population
- Anticoagulant prophylaxis should not therefore be expected to improve the survival of heterozygous individuals

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Concordance rates of insulin dependent diabetes mellitus: a population based study of young Danish twins

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Abstract

Objective—To study the genetic contribution to the aetiology of insulin dependent diabetes mellitus.

Design—Historical cohort study of twins, with information on diabetes being gathered by questionnaire, verification of the diagnosis by the subject's diabetologist or general practitioner, and clinical examination in available twins.

Setting—Danish twin register and diabetic clinics and general practices throughout Denmark.

Subjects—20 888 twin pairs born during 1953-82, included in a population based nationwide register.

Main outcome measures—Crude and cumulative concordance rates and heritability in monozygotic and dizygotic twins.

Results—The crude probandwise concordance rate was 0.53 (95% confidence interval 0.33 to 0.73) for monozygotic twin pairs and 0.11 (0.05 to 0.21) for dizygotic twin pairs. When adjusted for age at onset of diabetes and age at last observation among unaffected twin partners the cumulative probandwise risk from birth to age 35 was estimated as 0.70 (0.45 to 0.95) for monozygotic twins and 0.13 (0.05 to 0.20) for dizygotic twins. The correlations of liability for monozygotic and dizygotic twin pairs were estimated as 0.96 (SE 0.09) and 0.58 (0.07), with a heritability estimate of 0.72 (0.21).

Conclusions—The risk of insulin dependent diabetes in monozygotic twins is higher than previously thought and for dizygotic twins is higher than in ordinary first degree relatives. Based on the findings of this study the genetic component to the disease seems more important than hitherto believed.

Introduction

Insulin dependent diabetes develops on the basis of genetic susceptibility interacting with environmental

factors. Research in twins represents unique opportunities for investigating the importance of genetic and non-genetic factors in the causation of insulin dependent diabetes mellitus. There are, however, difficulties with twin studies. Proband should be ascertained at random—that is, diabetic twins should be ascertained independently of the cotwin's disease status. Many twin studies have been based on ascertainment by advertising or sampling from diabetic clinics¹⁻⁶ with the inherent possibility of bias due to disproportionate sampling of concordant or monozygotic pairs, or both. Population based studies are preferred but have until now been carried out in the old twin registries in Scandinavia,^{7,8} which include many deceased twins as a consequence of study designs. The results of earlier twin studies of insulin dependent diabetes mellitus are inconsistent and in the earliest studies difficult to interpret because of the changing criteria for diagnosis and classification as well as lack of detailed clinical data.^{3,4,7,9}

In order to provide a framework for twin studies into disease aetiology we have established a new population based register of young Danish twins. This paper reports the concordance rates, recurrence risks for monozygotic and dizygotic twins, and an evaluation of the genetic contribution to insulin dependent diabetes as ascertained from the register.

Subjects and methods

TOTAL TWIN COHORT

We established a new Danish twin register comprising 20 888 twin pairs (41 776 subjects) born during 1953-82.¹⁰ The register includes 74.4% of twins born during 1953-67 and 97.4% of twins born during 1968-82. All twins who were alive and resident in Denmark in 1991 were sent a single page questionnaire asking about the presence of diabetes mellitus, their

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willingness to take part in other questionnaire studies, physical similarity, and mistaken identity.

All Danish death certificates are recorded in the register of causes of death, with actual and underlying causes of death noted. Through record linkage with the twin register we identified those twins who had died of diabetes before the study. Copies of death certificates were obtained from the National Board of Health and relevant clinical data about these patients obtained from the hospitals where they died.

Zygosity

Zygosity (classified as monozygotic, dizygotic, or unknown) was tentatively established based on the answers to questions about similarity. This method of determining zygosity is reportedly reliable in large twin populations.¹¹⁻¹³

DIABETIC TWIN COHORT

All twins who on the first questionnaire indicated that they had diabetes mellitus were sent a second, more detailed questionnaire. Additional information was sought from diabetologists and outpatient clinics. Based on this information the twins were classified as having insulin dependent or other types of diabetes. According to accepted genetic epidemiological principles,¹⁴ we defined a proband as a diabetic twin ascertained through the first questionnaire independently of disease status in the cotwin and with a verified diagnosis of diabetes. Twin partners who as a consequence of our study were examined and found to be affected were classified as secondary cases.¹⁵

Classification of diabetes mellitus

Criteria for insulin dependent diabetes in the questionnaire study were (a) age under 40; (b) start of insulin treatment within two years after diagnosis; and (c) (when information on weight was available) absence of overweight at the time of diagnosis. Age 40 was chosen as the cut off point because, though insulin dependent diabetes may be diagnosed at all ages, non-insulin dependent diabetes is predominantly diagnosed after 40.^{16,17}

Clinical examination

All twin pairs in whom one or both members were classified as having insulin dependent diabetes mellitus and in whom both were alive and willing to participate were invited for a clinical examination at Odense University Hospital. The aim was to investigate genetic and immunological markers for insulin dependent diabetes mellitus in the twins and to obtain baseline information for a follow up study of complications. The twins who took part in the clinical investigation had fasting C peptide concentrations measured and zygosity tested. The results indicated whether the questionnaire based diagnoses of zygosity and classification of diabetes were reliable.

All the non-diabetic cotwins were asked to have an oral glucose tolerance test immediately before or after the clinical examination. This was done at their local laboratory by using the WHO schedule—that is, they were given a glucose load of 1.75 g/kg body weight up to 75 g glucose and had their blood glucose concentration measured at zero, 60, and 120 minutes.

For the twin pairs participating in the clinical investigation zygosity was established by serological analysis of 11 blood and enzyme type systems, the same approach as in paternity testing. Twin pairs showing complete concordance for all systems are regarded as monozygotic, the frequency of misclassification of dizygotic twin pairs being less than 1%.¹²

Analysis of data

Concordance was assessed by probandwise

concordance rates,¹⁸ which are comparable to estimates of recurrence risk in other groups of relatives. To adjust for variable age at last observation probandwise concordance rates were estimated by Kaplan-Meier survival analysis.¹⁹ This approach is based on an analysis of partners of probands, a proband being defined as a person who has been ascertained independently of the cotwin (or other family members) and who points to the other affected members of his or her family. Twins enrolled as apparently healthy and subsequently found to have diabetes (in this case, on the basis of glucose tolerance) represented secondary cases. For the Kaplan-Meier life table this meant that twin pairs with two probands counted twice because the probands were pointing to each other. In pairs with a secondary case and a proband, only the secondary case counted, because secondary cases cannot point to the proband. In pairs with a proband and a healthy partner the healthy partner counted as being "at risk" and the proband did not count. The advantage of the probandwise rate is that it is independent of ascertainment.²⁰

The difference in concordance between monozygotic and dizygotic twin pairs was tested by χ^2 test with one degree of freedom on the basis of the pairwise concordance rates—that is, the proportion of concordance among all pairs affected. This is the accepted way of testing this difference.²¹ For a qualitative trait like diabetes there is no simple method by which to assess heritability. We used the procedures described by Neale and Cardon.²²

Results

QUESTIONNAIRE SURVEY

Of the 41 776 twin partners (20 888 pairs) registered, 38 506 (distributed among 20 131 pairs) were available for the initial questionnaire survey and 35 528 (92.3%), representing 19 180 pairs, replied (fig 1). In 225 twin pairs one or both partners indicated the presence of diabetes and were sent the diabetes questionnaire. Of these, 216 (96.0%) responded and in 88 pairs diabetes was excluded, the main reason being errors when filling in the initial questionnaire. This false positive rate corresponded to 0.3% of all responses. In nine pairs verification of diagnosis was impossible owing to non-response. These pairs were excluded from further consideration. Of five dead diabetic subjects identified by record linkage, four had had insulin dependent diabetes mellitus and one (from medical records) diabetes secondary to cystic fibrosis. The twin with cystic fibrosis was not considered further.

A total of 128 pairs with one or both partners having verified diabetes mellitus were ascertained from the

FIG 1—Distribution of respondents and non-respondents in initial questionnaire survey and numbers of diabetic pairs

questionnaire and record linkage survey (table I). Of these, 102 pairs were classified as having one or both partners affected with insulin dependent diabetes. Table II gives the characteristics of these twins.

CLINICAL EXAMINATION

Of the 102 twin pairs classified as having insulin dependent diabetes, 28 were unavailable for detailed examination. The reasons were death in one twin partner (seven pairs), emigration by one partner (five pairs), non-response by one twin partner (three pairs), and unwillingness to participate (13 pairs). Of the remaining 74 pairs, 55 (74.3%) participated. Thirty six of these pairs were of the same sex and had serological investigations performed. Two pairs (5.6%) initially classified as dizygotic had all serological markers in common and in each pair the partners looked strikingly similar. The two pairs were reclassified as monozygotic. No same sexed pairs initially classified as monozygotic were reclassified.

Fasting C peptide concentration has been recommended for use in epidemiological studies.^{23,24} Four diabetic twins had values between 200 and 500 pmol/l, providing no firm conclusion about the classification. None had values above 500 pmol/l, which is the limit for non-insulin requiring disease. In two monozygotic pairs the partners of the probands had glucose tolerance in the diabetic range and started insulin treatment shortly after the examination. As they did not fulfill the proband criteria in the ascertainment by questionnaire, these two twins were considered as secondary cases. In one dizygotic pair one twin had recently been diagnosed and the other twin was classified as diabetic by the general practitioner shortly afterwards. However, as both members of the pair were being managed by diet at the time of our investigation we could not with certainty establish the type of diabetes. This pair was excluded from further analysis. Six pairs with insulin dependent diabetes

TABLE IV—Pairwise discordance time from diagnosis of insulin dependent diabetes in first affected twin till diagnosis in second twin (concordant pairs) or duration till last observation (discordant pairs)

Time (years)	Monozygotic pairs		Dizygotic pairs	
	Concordant	Discordant	Concordant	Discordant
<1	2	1	0	0
1-	0	2	0	0
2-	1	0	0	6
3-	0	2	0	5
4-	2	0	0	4
5-	1	1	0	2
6-	0	2	1	2
7-	0	0	0	4
8-	0	2	0	2
9-	1	0	0	2
10-	1	0	0	2
11-	1	2	1	2
12-	0	0	1	5
13-	0	0	0	0
14-	0	1	0	3
≥15	0	3	0	24
Total	9	16	3	63

One monozygotic concordant, one dizygotic concordant, and two dizygotic discordant pairs were excluded owing to unavailability of discordance time.

FIG 2—Cumulative probandwise risk in twins estimated from time of birth. (As we did not have exact age at diagnosis we arbitrarily set this age at 20 for a 27 year old partner from a concordant, monozygotic pair and for both affected partners in a 25 year old concordant dizygotic pair. A further two discordant dizygotic pairs were excluded from analysis as they were uninformative with respect to age at diagnosis and discordance time respectively owing to death in one twin)

mellitus of unknown zygosity were unavailable for further study and were also excluded.

The final cohort of twin pairs affected with insulin dependent diabetes and ascertained through the questionnaire studies comprised 26 monozygotic and 69 dizygotic twin pairs.

CONCORDANCE RATES

The crude probandwise concordance rates were 0.53 (95% confidence interval 0.33 to 0.73) for monozygotic twin pairs and 0.11 (0.05 to 0.21) for dizygotic twin pairs (table III). The pairwise rates (0.38 and 0.06 for monozygotic and dizygotic pairs, respectively) were significantly different (χ^2 test 10.93, df=1; $P<0.001$), confirming the importance of genetic factors in the aetiology of insulin dependent diabetes mellitus. The age adjusted cumulative probandwise risk from birth to age 35 was estimated as 0.70 (0.45 to 0.95) for monozygotic twins and 0.13 (0.05 to 0.20) for dizygotic twins (fig 2). Table IV shows the pairwise discordance time from diagnosis in the first affected twin till diagnosis in the partner or end of follow up. For the concordant pairs the partners in two monozygotic pairs were diagnosed within one year. In the rest recurrence took place after more than nine years in three of nine

TABLE I—Distribution of all diabetic twins by initial zygosity and tentative diabetes classification as obtained from questionnaire survey.

Classification	No of pairs represented with diabetes			Total
	Monozygotic	Dizygotic	Unknown zygosity	
Insulin dependent diabetes mellitus	24	72	6	102
Non-insulin dependent diabetes mellitus	1	7	0	8
Maturity onset diabetes of youth	1	0	0	1
Impaired glucose tolerance	0	1	0	1
Gestational diabetes	2	4	0	6
Secondary diabetes	1	1	0	2
Mixed type†	0	2	0	2
Other‡	2	3	0	5
Unclassifiable	0	1	0	1
Total	31	91	6	128

†One pair with maturity onset diabetes of youth and non-insulin dependent diabetes mellitus and one pair with gestational diabetes and non-insulin dependent diabetes mellitus.

‡Transient glycosuria (one case), neonatal diabetes (one), transient diabetes during childhood (one), reported to have symptoms without verified diagnosis (two cases).

TABLE II—Characteristics of twins with insulin dependent diabetes

Zygosity	Mean age at study (years) (range)	Mean age at diagnosis (years) (range)
Monozygotic	27.9 (11-39)	18.3 (2-38)
Dizygotic	27.5 (11-38)	15.1 (1-35)

TABLE III—Crude concordance rates by zygosity in twin pairs with insulin dependent diabetes

Zygosity	No of pairs		Probandwise concordance rate (95% confidence interval)
	Concordant	Discordant	
Monozygotic	10 [18]†	16	0.53 (0.33 to 0.73)
Dizygotic	4 [8]†	65	0.11 (0.05 to 0.21)

Numbers of probands given in square brackets.

Key messages

- The recurrence risk for insulin dependent diabetes mellitus in monozygotic and dizygotic twins is higher than previously thought; this is important when counselling patients
- Though the concordance rate for monozygotic twins is high, it is below unity; this implies an environmental component to aetiology
- The risk to dizygotic twins is higher than to ordinary siblings, indicating shared environment as a possible contribution to aetiology
- The risk is higher in monozygotic twins than in HLA identical siblings, indicating that shared environment or genes outside the HLA region, or both, are important in the aetiology of diabetes

monozygotic pairs and two of three dizygotic pairs.

The correlations in liability for monozygotic and dizygotic twin pairs were estimated as 0.96 (SE 0.09) and 0.58 (0.07) respectively. We found that an aetiological model including additive genetic effects and shared and non-shared environmental effects fitted the data with a heritability estimate of 0.72 (SE 0.21).

Discussion

Diabetes in twins has been studied for years^{4,9} but results of the earliest studies are difficult to interpret owing to changes in the criteria for classifying diabetes mellitus. In contrast with some of the newer twin studies on insulin dependent diabetes mellitus,^{1,2} our study was population based and probands were ascertained independently of zygosity and diabetes status in the twin partner. In addition to a high response rate, the sample comprised the expected proportions of monozygotic and dizygotic twin pairs whereas the British series¹ comprised monozygotic pairs only and the American series² contained far more monozygotic than dizygotic pairs.

Reported concordance rates are difficult to compare because some studies do not distinguish between the various types of concordance rates (that is, probandwise, pairwise, or casewise). We prefer the probandwise rates, which are comparable to recurrence risks in other groups of relatives and are thus genetically interpretable.¹⁸ The great advantage of the probandwise rate is that it is independent of ascertainment. Thus it is not crucial that all twins should be studied, as long as there is no systematic bias in the ascertainment procedure.

Advertising for twins with specific diseases or studying clinic based cohorts might introduce systematic bias—for example, if concordant and monozygotic pairs were oversampled. Our twin cohort represented a population based twin sample and we had no reason to suspect any systematic bias in the ascertainment procedure: the proportions of monozygotic and dizygotic pairs were as expected in a population based sample of European origin (roughly one third monozygotic pairs), and the response rates to the first and second questionnaires were 92% and 96% respectively.

The deficit in the first half of the birth cohorts in the total twin register was most likely related to administrative factors rather than to major health events.¹⁰ The prevalence of insulin dependent diabetes in Denmark has been estimated as 0.3–0.4%,²⁵ so that the expected numbers of twins who would be ascertained were 73 in the birth cohort of 1953–67 and 48 in the birth cohort of 1968–82; the numbers actually ascertained were 74 and 43 respectively. The corresponding prevalence rates in monozygotic and dizygotic twins were 0.36% and 0.32%. Thus there was no evidence of overrepresentation of either zygosity class and no evidence of any selection bias.

The probandwise concordance rates for monozygotic twins in our study were substantially higher than the 0.23 estimated in a Finnish study using this methodology.⁸ The Finnish study was performed in an older twin register than ours. Twins had to be born before 1958, to be alive in 1967, and to respond to a questionnaire in 1975 in order to be included. This may have resulted in the lower than expected number of twins with insulin dependent diabetes in that study. Clustering in time of concordance has been suggested,⁷ but the pairwise discordance times in our study (table IV) do not support this.

ENVIRONMENT AND HERITABILITY

Based on zygosity testing and C peptide measurements we find that the classification of zygosity and diabetes is reliable in epidemiological studies. The fact that the concordance rate among monozygotic twins was less than unity confirms that environmental factors are of aetiological importance in insulin dependent diabetes. Furthermore, the recurrence risk for monozygotic twins is higher than the risk in HLA identical siblings²⁶ even when the large confidence interval around our estimates is considered. This indicates that shared environment or genes outside the HLA region, or both, may be important for disease aetiology. This is further supported by the observation that the concordance rate in dizygotic twins (in our study estimated as 0.13) is higher than the corresponding recurrence risk in non-twin siblings (estimated as 0.07 in a recent Danish family study).²⁷ Possibly the environmental exposure necessary to initiate the autoimmune process occurs early in life when twins share a common environment.

A model with additive genetic factors and shared and non-shared environmental factors seems to fit the data. Heritability was estimated as 0.72 (SE 0.21), which confirms the importance of genetic factors in insulin dependent diabetes. When interpreting genetic models and heritability estimates it is important to keep in mind that small twin samples do not have very much power. But as the best fitting model agreed with the results of comparing concordance rates and recurrence risk in siblings and HLA identical siblings, it is probably the best fitting model for these data.

It is also important to know that heritability estimates are based on calculating the genetic variation relative to the total phenotypic variation, both genetic and environmental, which does not take gene-environment interaction into account. Gene-environment interactions may be important in insulin dependent diabetes, making the results of heritability estimation based on quantitative genetic modelling difficult to interpret. For these reasons, calculations of genetic parameters like heritability from twin data should be interpreted with caution. Another approach is to use the twin data for in depth studies of concordance according to zygosity and the presence of immunological markers and susceptibility genes.

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Increasing prescription of drugs for secondary prevention after myocardial infarction

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Mortality from acute myocardial infarction is reduced after treatment in the recovery period by the selective use of aspirin, β blockers, warfarin, and angiotensin converting enzyme inhibitors.¹ Despite evidence from trials, the use of β blockers has not been translated into clinical practice.² Most patients with myocardial infarction are managed by general physicians and general practitioners, but immediate coronary care is increasingly complex and the choice of drug for secondary prevention has increased, adding to the confusion. Cardiologists need to guide management decisions without necessarily taking over complete care of patients with cardiovascular disease. We audited the use of drugs for secondary prevention before and after an intervention aimed at increasing their use.

Subjects, methods, and results

About 75% of patients with suspected myocardial infarction are admitted to the coronary care unit³ and managed by the admitting medical firm according to guidelines provided by the cardiologist. On a daily

ward round the consultant cardiologist supervises management, but on discharge patients return to the care of the admitting physician. The last time the cardiologist has direct contact with the patient may be less than 48 hours after admission.

We audited 170 consecutive admissions (128 men; average age 63 years, range 31-90) to the coronary care unit from 1 February 1992 to 31 July 1992 with a confirmed diagnosis of acute myocardial infarction.³ Readmitted patients were excluded. In 120 (71%) a thrombolytic drug was given, and 146 (86%) patients were discharged alive. Drugs prescribed for secondary prevention at discharge and at the first outpatient appointment, four to six weeks later, were noted. Notes were assessed for contraindications to the prescription of β blockers.

In December 1992 a stamp was introduced into the notes of patients with myocardial infarction on day 2 in the coronary care unit, which stated the cardiologist's recommended drug treatment for secondary prevention. Criteria for the choice of drug were derived from published trials.¹ The recommendation was for two drugs (aspirin plus another), since there are few published data on the efficacy of multiple drug combinations for secondary prevention. Following this a repeat audit of 185 consecutive patients (126 men; average age 66 years, range 25-90) admitted between 1 February 1993 and 31 July 1993 was performed. One hundred and twenty five (68%) were given thrombolysis, and 153 (83%) were discharged alive.

More patients were discharged taking β blockers and angiotensin converting enzyme inhibitors after the intervention (table). The number of patients not discharged on a β blocker in the absence of a documented contraindication fell from 20/66 (30%) to 7/72 (10%) ($P < 0.01$, Fisher's exact test). In 1992 only 29% (29/99) of case notes stated reasons why β blockers were not given and contraindications were not always clear; the reason for not prescribing an alternative was stated in only 3/55 (5%). In 1993 the stamp was identified in the notes of 117/153 (76%) patients and the recommendation was not followed in 25 (21%) patients. The reasons for this were numerous and detailed in 18/25 case notes, ranging from adverse drug reactions (8), development of contraindications after discharge from the coronary care unit (4), and choice of

Details of treatment used for secondary prevention after myocardial infarction before and after the intervention

Therapy		1992 No (%)	1993 No (%)	P value
Dual	Aspirin + another	74 (51)	115 (75)	$\chi^2=18.2$, $P < 0.0001$ Not significant $P < 0.0001$, Fisher's exact
	Other (no aspirin)	17 (12)	19 (12)	
	Aspirin only	51 (35)	17 (11)	
None	No treatment for prophylaxis	4 (3)	2 (1)	Not significant $\chi^2=3.8$, $P=0.05$ $\chi^2=8.1$, $P < 0.01$ Not significant Not significant Not significant
	β blocker	47 (32)	67 (44)	
	Angiotensin converting enzyme inhibitor	29 (20)	54 (35)	
	Calcium blocker	16 (11)	18 (12)	
	Oral anticoagulant	9 (6)	12 (7)	
	Aspirin	125 (86)	132 (86)	