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# Heterogeneity of Type I diabetes: analysis of monozygotic twins in Great Britain and the United States

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## Abstract

*Aims.* To determine the risk, hazard rate and factors affecting progression to diabetes in monozygotic twins of patients with Type I (insulin-dependent) diabetes mellitus.
*Methods.* Prospective analysis was done of two cohorts of non-diabetic monozygotic twins of patients with Type I diabetes from Great Britain ($n = 134$) and the United States ($n = 53$).
*Results.* The diabetes-free survival analysis was similar between both cohorts ($p = 0.6$). The combined survival analysis ($n = 187$, median follow-up = 17.7 years, range = 0.01–57) at 40 years of discordance estimated a 39 % probability of diabetes for the initially discordant twin. Survival analysis with left truncation of data estimated that probability to be 50 %. For twins who became concordant ($n = 47$), the median discordance time was 4.2 years (range 0.4 to 39), exceeding 15 years in 23.4 %. Twins of probands diagnosed at 24 years of age or younger had a 38 % probability of diabetes by 30 years of discordance, compared with 6 % for twins of probands diagnosed after 24 years of age ($p = 0.004$). The twins of probands diagnosed before 15 years of age had the highest diabetes hazard rate in the first discordance year, decreasing thereafter. By survival analysis, diabetes risk was higher in twins who were heterozygous for *DR3-DQ2* and *DR4-DQ8* than in twins with neither *DR3-DQ2* nor *DR4-DQ8* ($p < 0.05$).
*Conclusion/interpretation.* Monozygotic twins of patients with Type I diabetes from two different countries had similar rates of progression to diabetes. Whereas most twins did not develop diabetes, 25 % of the twins who progressed did so after more than 14 years of discordance. An age-related heterogeneity was observed, with higher progression to diabetes for twins of patients diagnosed at a younger age. [Diabetologia (2001) 44: 354–362]

**Keywords** Type I diabetes, genetics, twin study, age, gender, HLA, truncated data, survival analysis, progression.

Twin studies have helped to define the importance of genetic and environmental factors in the aetiology of disease [1–9]. By measuring concordance rates (both twins affected) in identical (monozygotic) and non-identical (dizygotic) twins, estimates of genetic influence can be obtained. In primarily genetic disorders, concordance rates should be higher in monozygotic than in dizygotic twins. Differences between monozygotic twins must be due to factors not coded in the germ line, i.e. non-germ-line genetic (e.g. somatic) or environmental factors. Monozygotic twins also show differences in genes that undergo random rearrangement such as immunoglobulin and T-cell receptor genes.

Comprehensive population-based studies of twins have only recently been initiated, so most of the information available on diabetic twins is from clinic-

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based studies. Although these clinic-based studies are liable to ascertainment bias, resulting in an overestimation of concordance for the disease, they have helped to define distinctions between Type I (insulin-dependent) and Type II (non-insulin-dependent) diabetes mellitus, and to identify metabolic and immune changes in the prediabetic period that predict progression to diabetes [10–22]. All studies to date have found that the concordance rate of monozygotic twins with Type I diabetes is higher than that of dizygotic twins, indicating that important genetic factors contribute to the disease [12, 17, 21, 23–25]. These concordance rates were, however, substantially less than 100% in line with a major role for non-germline genetic or environmental factors. Unfortunately, most studies involve only small numbers of twins followed for limited periods, the longest follow-up being 14 years [26]. There is also a lack of direct studies of initially discordant twins. We observed that some twins develop diabetes many years after the diagnosis of the index twin [16, 27].

In our analysis, two studies, from Britain and the United States, are combined to provide an estimate of the risk and rate of progression to diabetes in monozygotic twins of patients with Type I diabetes. The combined analysis provided a powerful database with 187 twin pairs, many followed for up to 40 years. As both of these are clinic-based studies, we attempted to reduce bias by including only those pairs that were discordant at referral, i.e. one twin was diabetic and the other was not. The purpose of this study was to determine the proportion of monozygotic twins of Type I diabetes patients, who had been initially non-diabetic but who later develop the disease, the rate at which they did so and the factors which influenced that rate.

## Subjects and methods

*Subjects.* A total of 187 initially non-diabetic monozygotic twins (including two sets of triplets) of patients with Type I diabetes were studied. Ascertainment of these twin pairs has been described previously [19, 26]. Only twins discordant when first studied were included. Of these, 53 twins were studied in the United States: 17 at the Barbara Davis Center and the remaining 36 twins or triplets initially at the Joslin Diabetes Center. A total of 134 twins were studied in the United Kingdom. Monozygosity was confirmed by parental report, same sex, histocompatibility antigen testing and blood group typing and recently, for the United States cohort, by DNA-based testing for 5 highly polymorphic microsatellite loci (LDLR, GYPA, HBGG, D7S8, GC (AmpliType PM. Perkin Elmer. Roche Molecular System, Branchburg, N.J, USA).

These studies were approved by the Institutional Review Boards of the University of Colorado and the Joslin Diabetes Center (United States cohort) and by the ethical committees of the Royal Hospitals Trust, London, United Kingdom (United Kingdom cohort). Written informed consent was obtained from the participants for the study.

*HLA typing.* For the series from the United States, *DQ beta* typing was carried out using oligonucleotide probes [28] and DQ alpha typing using AmpliType (PE Applied Biosystems, Branchburg, N.J., USA).

For the series from Great Britain, HLA typing was carried out using serologic assays with antibodies provided by the HLA Tissue Typing Xth Workshop. For DQ subtyping, the single-step allele specific polymerase chain reaction was used.

*Statistical analysis.* Time-to-event analytic methods included Kaplan-Meier estimates (with log-log confidence intervals), log-rank and generalized Wilcoxon test statistics, Cox's partial likelihood regression methods and smoothed (kernelled) hazard estimates [29]. All of the above methods were also undertaken assuming first, no left truncation of the data, and, second, assuming left truncation of the discordance time by discordance time at referral. Truncation analysis [29] was accomplished using the start-stop paradigm for which start time was discordance time at referral. Other statistical analysis included the Chi-squared test and Fisher's exact test where appropriate. A $p$ value of less than 0.05 was considered statistically significant.

## Results

We studied prospectively 53 and 134 non-diabetic twins or triplets of patients with Type I diabetes from the United States and Great Britain, respectively. For those twins or triplets progressing to diabetes ($n = 47$), follow-up ended at the onset of diabetes (Tables 1, 2).

### *Risk and rate of progression to diabetes*

A total of 13 out of 53 (24.5%) initially non-diabetic co-twins from the U.S. cohort and 34/134 (25.4%) from the British cohort developed diabetes on follow-up. Survival analysis for the development of diabetes showed no differences between the cohorts ($p = 0.6$) (Fig. 1). The probability of progression to diabetes for the initially non-diabetic twins at a follow-up of 10 years from the onset of diabetes in the index twin (discordance time), was 20.4% (SEM = 6.1%) and 19.1% (SEM = 3.4%), respectively, in the U.S. and the British series. At 25 years it was 28.8% (SEM = 7.9%) and 27.0% (SEM = 4.3%), respectively. Combining both cohorts ($n = 187$), the median follow-up was 17.7 years (range 0.01–57 years). The survival analysis of the combined series is shown in Figure 2. The probability of progression to diabetes at 10 years of discordance from the onset of diabetes in the index-twin was 19.4% (SEM = 2.8), and at 25 years, 27.4% (SEM = 3.6%). Altogether 12 twins were followed for 40 years or more from the time of diagnosis in the index twin and the probability of progression to diabetes at 40 years of discordance was 38.9% (SEM = 6.7%). A survival analysis correcting for left truncated data of the combined series was also done (data not shown). Because twin pairs were not

**Table 1.** Characteristics of initially discordant twins from the United States and Great Britain, by outcome and time of discordance

| | All twin pairs | | Concordant twin pairs | | | | Discordant twin pairs | |
|---|---|---|---|---|---|---|---|---|
| | | | Discordance ≤ 15 yrs | | Discordance > 15 yrs | | Discordance > 15 yrs | |
| | US | GB | US | GB | US | GB | US | GB |
| No. | 53 | 134 | 9 | 27 | 4 | 7 | 17 | 75 |
| Age of onset (proband)[a] | 11.7 (1.4–38.8) | 13.7 (1.6–70) | 11.1 (1.9–20.9) | 10.9 (2.1–31.8) | 11.8 (10.7–18.6) | 14.3 (1.6–37.3) | 13.9 (6.3–38.8) | 19 (2.2–70) |
| Age at 1st evaluation[a] | 13.6 (2.1–52.7) | 16.1 (2.2–77.5) | 12.7 (2.1–21.7) | 11.3 (2.3–32.1) | 20.4 (11.8–35.2) | 18.5 (8.6–44.8) | 29.4 (8.1–52.7) | 27.5 (2.8–77.5) |
| Discordance at 1st evaluation[a] | 1.9 (0–28.2) | 1.6 (0–35.4) | 0.7 (0–1.7) | 0.2 (0.0–2.5) | 5.8 (0.2–23.3) | 7.5 (0.7–15.4) | 11.6 (0.6–28.2) | 4 (0–35.4) |
| Sex (female/male) | 26/27 | 65/69 | 6/3 | 15/12 | 4/0 | 1/6 | 5/12 | 36/39 |

[a] Data are median (range) in years

**Table 2.** HLA of initially discordant twin from the United States and Great Britain, by outcome and time of discordance

| | All twin pairs | | Concordant twin pairs | | | | Discordant twin pairs | |
|---|---|---|---|---|---|---|---|---|
| | | | Discordance ≤ 15 years | | Discordance > 15 years | | Discordance > 15 years | |
| | US | GB | US | GB | US | GB | US | GB |
| DR3-DQ2 or DR4-DQ8 | 85.3 (29/34) | 88.2 (60/68) | 85.7 (6/7) | 100 (12/12) | 100 (4/4) | 100 (5/5) | 83.3 (10/12) | 85.0 (34/40) |
| DR3-DQ2 and DR4-DQ8 | 28.6 (10/35) | 15.4 (10/65) | 28.6 (2/7) | 15.4 (2/13) | 66.6 (2/3) | 40 (2/5) | 7.1 (1/14) | 16.7 (6/36) |
| Neither DR3-DQ2 nor DR4-DQ8 | 12.7 (13/102) | 11.8 (8/68) | 14.3 (1/7) | 0 (0/12) | 0 (0/4) | 0 (0/5) | 16.7 (2/12) | 15.0 (6/40) |

Data are percent (proportion)

necessarily referred at the time of diagnosis in the index twin, but often later on, left truncation of discordance time by discordance time at referral was included in this analysis. Up to 25 % of the twins developed diabetes by 3.6 years of discordance and 50 % by 40 years of discordance.

There were 47 twins who progressed to diabetes. For this group of twin pairs who became concordant on follow-up, the median discordance time was 4.2 years (range 0.4 to 39 years). For 13 (27.7 %) twin pairs, the discordance time until progression to diabetes was 10 years or longer and in 11 (23.4 %) pairs it exceeded 15 years. There were 10 twin pairs in which the second twin (non-index twin) developed diabetes after 30 years of age. All 10 non-index twins were positive for anti-islet autoantibodies, with 5 twins positive for ICA, 1 twin positive for IA-2/ICA512, and 9 twins positive for GAD (one twin did not have GAD measured). Anti-insulin was positive in 3 out of 4 twins measured.

In the first year after diagnosis of diabetes in the index twin, the hazard rate (or incidence) of progression to diabetes in the non-index twin was 3.4 % (CI = 2.1–5.0 %) (Fig. 3). The incidence of diabetes for each year decreased sharply during the following 9 years, then reached a plateau at an incidence of progression to diabetes per year of 1.0 % (CI = 0.7 to 1.4 %) for the next 30 years.

*Factors determining risk and rate of progression to diabetes*

*Age.* The age of diabetes onset in the index twin and the non-index twin were significantly correlated ($p < 0.0001$, $r = 0.66$, data not shown) for the 47 twin pairs who became concordant on follow-up.

A survival analysis of progression to diabetes by age at diagnosis in the index twin is shown in Figure 4. Progression to diabetes in monozygotic twins of index twins who were diagnosed with diabetes at 25 years of age or older ($n = 37$) was significantly less ($p = 0.004$) than the progression to diabetes for the twins of index twins who were diagnosed at a younger age ($n = 150$). The estimated probability of progressing to diabetes by 30 years of discordance was 38 % (SEM = 5.3 %) for the twins of index cases who were diagnosed with diabetes at younger than 25 years of age, compared with 6 % (SEM = 4.1 %) for the remaining co-twins of those index twins diagnosed at 25 years of age or older. The pairs in which the index twin was diagnosed at or after 25 were followed for a median time of 25.2 years (range 1.3 to 53) and only two twins (5 %) developed diabetes. For these two twins the age of onset in the index and non-index twin, respectively, were 31.8 and 37.9 years for one pair, and 37.3 and 54.7 years for the other pair. A total of 45 (30 %) twins developed diabetes in the

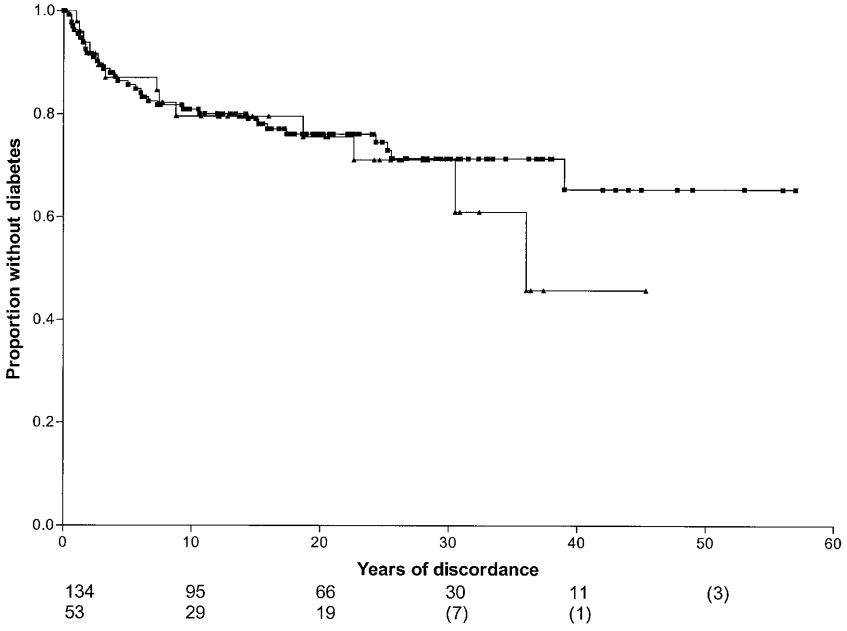
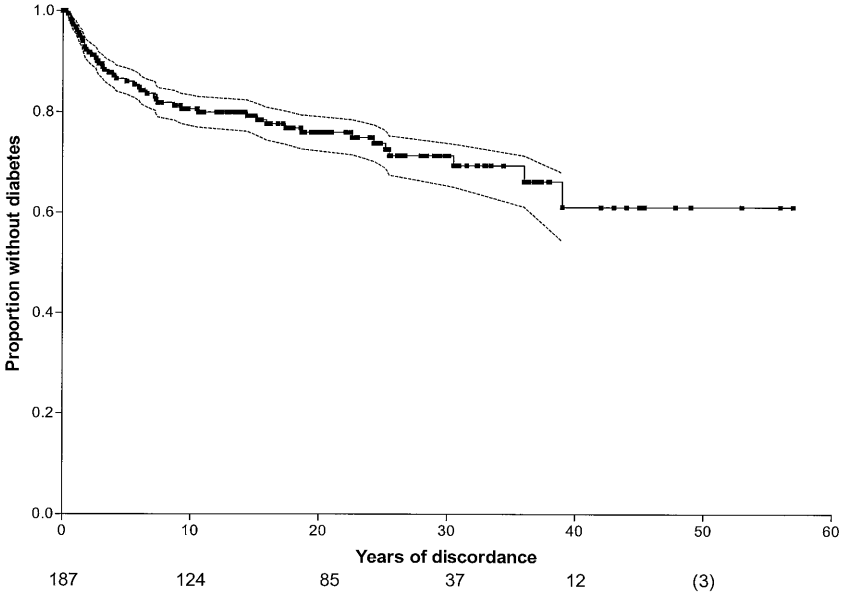



**Fig. 1.** Diabetes-free survival analysis of Great Britain (—■—) cohort versus United States (—▲—) cohort. Numbers at the bottom are the number of subjects still followed at each time point for each cohort. Numbers in brackets at the bottom table means that the number of subjects still followed at that time point is less than 10. *p* value (log-rank) = 0.6

subset of twin pairs in which the index twin was diagnosed at under 25 years of age. Using Cox's regression model we estimated that the twins of patients who were diagnosed at 25 years of age and older are at 0.54 (95% CI = 0.33–0.87) times the risk of the twins of patients who were diagnosed at 0 to 14 years of age. The twins of patients who were diagnosed at 15 to 25 years of age are at 0.7 (95% CI = 0.48–1) times the risk of the twins of patients diagnosed between 0 to 14 years of age. Stratified Kaplan-Meier analysis for truncated data estimated that twins of patients who were diagnosed at 9 years of age or younger have a 50% risk of developing Type I diabetes within 6 years (data not shown).

The distribution of diabetes-associated HLA types was similar between the group of twin mates of patients diagnosed before 25 years of age and the group

**Fig. 2.** Diabetes-free survival analysis of the combined Great Britain and United States cohorts. Interrupted lines denote 95% confidence interval. Numbers at the bottom are the number of subjects still followed at each time point for each cohort. Numbers in brackets at the bottom means that the number of subjects still followed at that time point is less than 10



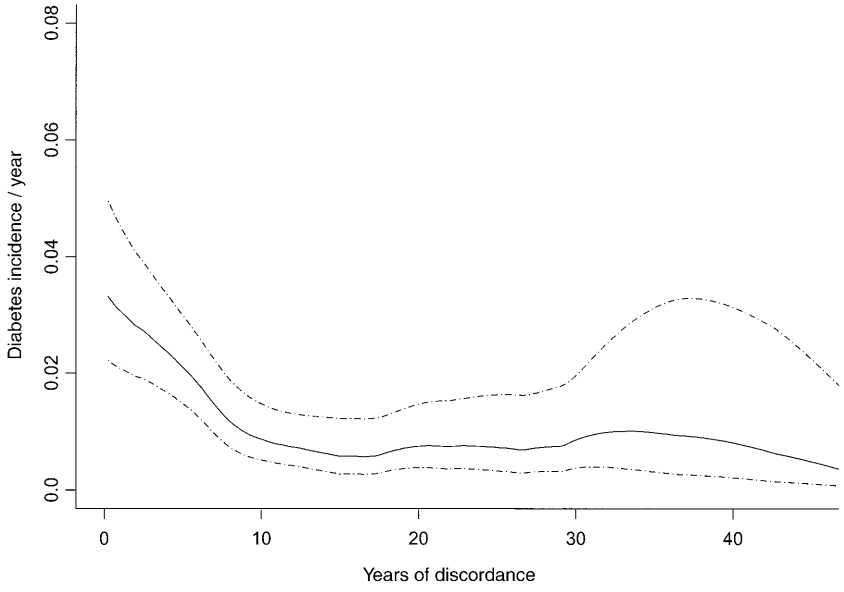
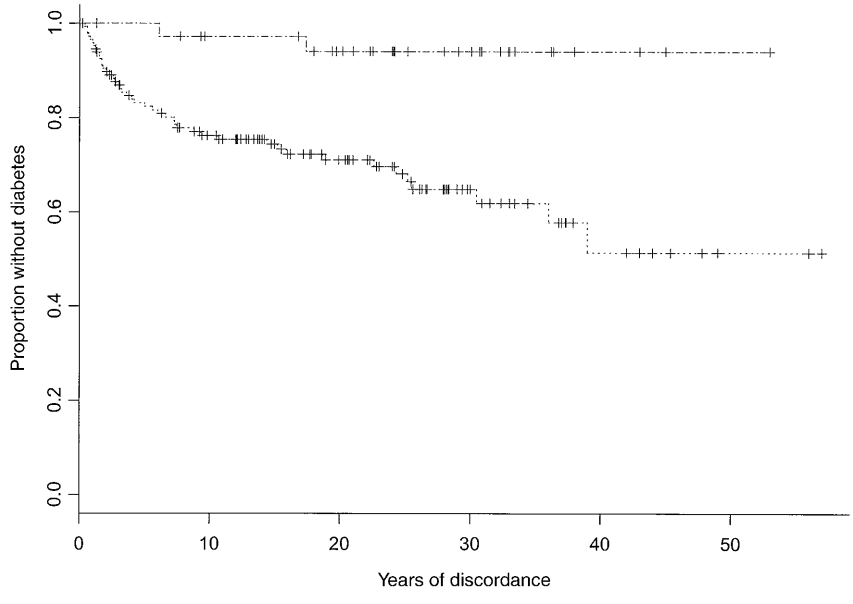



**Fig. 3.** Hazard rate of diagnosis of Type I diabetes per year for the combined Great Britain and United States cohorts

of twin mates of patients diagnosed at or after 25 years of age. In the former group, among the twins who had HLA typing, there were 15 of 79 twin pairs who were heterozygous for DR3-DQA1*0501-DQB1*0201 and DR4-DQA1*0301-DQB1*0302 (DQ2/DQ8 genotype), and 69 of 79 twins who had either DQ2 or DQ8. In the group of twin mates of patients diagnosed at 25 years of age or older, 5 of 21 twin pairs were heterozygous for DQ2 and DQ8 ($p = 0.76$), and 18 of 21 had either DQ2 or DQ8 ($p = 0.71$).

The incidence of diabetes for each year in the non-index twin by age at diagnosis of diabetes in the index twin are shown in Figure 5. Monozygotic twins of patients who were diagnosed with diabetes before the 15 years of age showed a hazard rate pattern similar to the one described for all the subjects (Fig. 5). Non-index twins of patients diagnosed with diabetes at 15 years of age or later, on the other hand, showed little variation in their incidence of diabetes with time.

**Fig. 4.** Diabetes-free survival analysis of the combined Great Britain and United States cohorts, by age at diagnosis in the index twin: Ages 0 to 24 years ($n = 150$) in dotted line ( · · · ), 25 years and older ($n = 37$) in dashed line ( · - · - ). Cross-lines represent censored subjects. $p$ value (log-rank) = 0.004



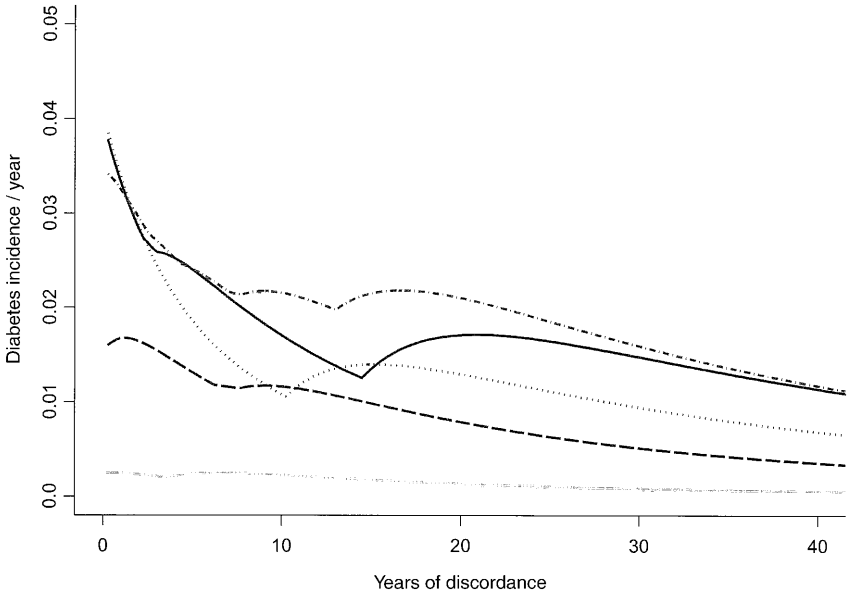
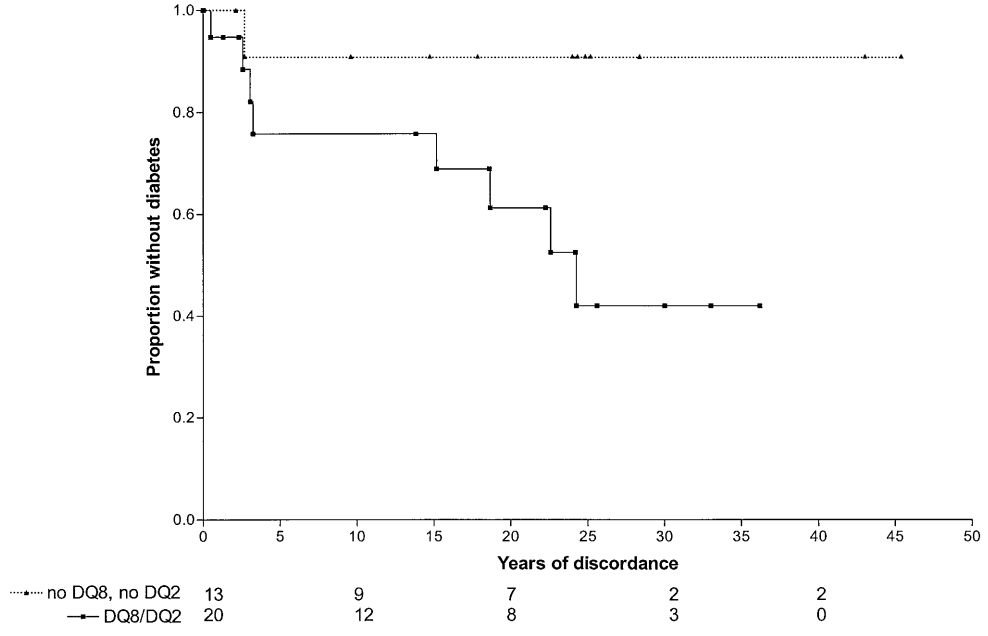



**Fig. 5.** Hazard rate of diagnosis of Type I diabetes per year for the combined Great Britain and United States cohorts, by age at diagnosis in the index twin: Ages 0 to 6 years ($n = 38$) in solid line (——), ages 7 to 10 years ($n = 33$) in dotted line (····), ages 11 to 15 ($n = 42$) in dashed line ( · – · –· –), ages 16 to 23 ($n = 34$) in dashed line (– – –), 24 years and older ($n = 40$) in dashed line (– ··· –)

*Sex.* In the combined series there were 96 females and 91 males. The survival analysis of progression to diabetes was not different between the sexes ($p = 0.24$, data not shown). The distribution of diabetes-associated HLA haplotypes was not different between males and females. Among those females for whom HLA information was available, 11 of 47 were heterozygous for DQ2 and DQ8, and 46 of 51 had DQ2 or DQ8. Among the males, there were 9 of 53 who were heterozygous ($p = 0.46$) and 41 of 49 had DQ2 or DQ8 ($p = 0.38$).

*HLA.* There were 20 twins who were heterozygous for HLA *DQ2* and *DQ8* ("high-risk" HLA). A total of 67 twins had either *DQ2* or *DQ8* but not both haplotypes ("moderate-risk" HLA). Another 13 twins had neither *DQ2* nor *DQ8* ("low-risk" HLA). The

**Fig. 6.** Diabetes-free survival analysis of the combined Great Britain and United States cohorts, by HLA type. Subjects who were heterozygous for DR3-DQ2 and DR4-DQ8, compared with subjects who had neither DR3-DQ2 nor DR4-DQ8. Numbers at the bottom are the number of subjects still followed at each time point for each cohort. $p$ value (log-rank) < 0.05. The curve for twins with either DQ8 or DQ2 but not both was between the curves shown in this figure



remaining twins did not have HLA typing to include them in any of these three groups. Survival analysis of progression to diabetes was significantly different ($p < 0.05$) between the high risk and the low-risk groups (Fig. 6). Progression to diabetes was greater but not statistically different between the twins with high-risk HLA ($n = 20$) and the remaining patients ($n = 80$) but the $p$ value was 0.08.

Out of these twins with available HLA typing, all 9 twin pairs who became concordant after 15 or more years of discordance in the index twin had either HLA DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*0301-DQB1*0302. This is similar to twin pairs who became concordant before 15 years of discordance (18 of 19) ($p = 1.0$) (Table 2). A total of 50 % (4 of 8) of the twin pairs who became concordant after 15 or more years of discordance were heterozygous for HLA *DQ2* and *DQ8*. This is not different from the twin pairs who became concordant before 15 years of discordance (4 of 20, $p = 0.17$) (Table 2).

The hazard rate for the twins who were not heterozygous for DR3-DQA1*0501-DQB1*0201 and DR4-DQB1*0301-DQB1*0302 was analysed after stratification by age. The results of this analysis were similar to those of the entire cohort, a steeply decreasing hazard among twin mates of probands who were diagnosed under 15 years of age and a flat hazard rate over time for twin mates of probands who were diagnosed at 15 years of age or older. Among the twins who were heterozygous for *DQ2* and *DQ8*, the same analysis with stratification by age was not possible due to their small numbers.

## Discussion

In order to assess whether non-germ-line genetic or environmental factors play a part in the aetiology of Type I diabetes, we examined two large series of monozygotic twins of patients with Type I diabetes from Great Britain and the United States. To avoid over-ascertainment of concordant pairs we excluded pairs who were concordant for diabetes on referral. We found that the proportion of non-diabetic twins progressing to diabetes was strikingly similar in the two series, as were their rates of developing diabetes. This remarkable similarity between British and American twins in their progression to diabetes enabled us to analyse the combined series of 187 pairs. Many twins were followed prospectively for over 40 years after the diagnosis in the index twin.

Our combined series indicated that most of the monozygotic twins of patients with Type I diabetes did not develop diabetes themselves. The probability of concordance for diabetes in the combined series was 27 % at 25 years and 39 % at 40 years from the diagnosis of the index twin. Previous reports of monozygotic twins, using smaller numbers and a much shorter follow-up, found concordance rates between 21 % and 70 % [16, 21, 23, 30]. We might have underestimated concordance for Type I diabetes because we excluded twins who were concordant at referral and there was often a time lapse between diagnosis in the first twin and referral. We, therefore, assumed our data was truncated and re-estimated the concordance rate to correct for this bias. This analysis estimated the risk of progression to diabetes in the non-diabetic twin was 50 % at 40 years of discordance from the diagnosis of the index twin. These observations show that about half of the twin pairs remain discordant and, by implication, non-germ-line genetic or environmental factors must play a major part in either causing or preventing Type I diabetes.

Of the 187 non-diabetic twins followed prospectively, 47 developed diabetes under observation. Several features distinguish those twin pairs who became concordant for diabetes from those who remain discordant. The age at diagnosis in the index twin was related to the risk of progression to diabetes in their twin. Twins of patients diagnosed at or over 25 years of age were much less likely to become concordant for diabetes (5 %) than the twins of those diagnosed at a younger age (27.3 %, $p < 0.004$). The survival analysis, with correction for truncated data, estimated that twins of patients who were diagnosed at 9 years of age or younger had a 50 % risk of developing diabetes within 6 years of diagnosis in the index twin. Similar observations have been made in smaller twin studies [21, 26]. It could be argued that these differences in diabetes risk for the non-index twin by age at diagnosis in the index twin are related to a different distribution of diabetes-associated HLA types. We did not, however, find any significant difference in HLA type distribution between those index twins who were diagnosed with diabetes at a young age and those were diagnosed later in life. Therefore, this age-related heterogeneity does not appear to be related to different HLA types. The increased concordance in twins of index cases diagnosed at a younger age could reflect either a greater genetic load, with greater disease penetration, or an increased non-genetic (e. g. environmental) effect. Without a comparable study of dizygotic twins we are not able to distinguish between these two possibilities.

The remarkable low rate of concordance in twins diagnosed at 25 years of age or older indicates that non-germ-line genetic or environmental factors probably play a major part in causing or preventing their diabetes. Such factors could include mutated or rearranged genes (for example, encoding T-cell receptors or immunoglobulins) or environmental factors. In either case, our observations indicate that there is heterogeneity in the contribution of non-germ-line genetic or environmental factors to diabetes. Because

the levels of concordance as well as the rates of progression in the British and the U. S. series are so similar, it seems likely that the genetic and non-genetic factors causing or preventing Type I diabetes in the two countries are similar. A study of concordant twin pairs suggested that they were more likely to have both HLA DR3 and DR4 antigens than discordant pairs but the numbers were too small to relate this difference to age at diagnosis [31]. In this study, we found that survival analysis of progression to diabetes was significantly different ($p < 0.05$) between the subset of twins who were heterozygous for the haplotypes DR4-DQA1*0301-DQB1*0302 and DR4-DQA1*0501-DQB1*0201 ("high-risk" HLA) and the subset of twins who did not have any of these haplotypes ("low-risk" HLA). In our previous report on the United States series, we found that, by life table analysis, the probability of developing positive autoantibodies at 10 years of discordance was higher among the monozygotic twins bearing the DR4-DQA1*0301-DQB1*0302/DR4-DQA1*0501-DQB1*0201 genotype ("high-risk" genotype) than in the monozygotic twins without this genotype, the latter group therefore included both "low-risk" and "moderate-risk" genotypes [19].

Monozygotic twins tend to develop Type I diabetes at a similar age. Family and twin studies suggest that the age at diagnosis is, to a substantial degree, genetically determined [32]. Our present study, however, indicates that non-genetic factors also play an important part in determining the age at diagnosis. We found clustering between twins for age at diagnosis, consistent with a genetic effect, despite the twin pairs being discordant at referral, and irrespective of their age at diagnosis. Our results confirm and are in line with a previous work reporting that diabetes risk decreases as discordance time increases [21]. Some twins, however, developed diabetes many years after the index twin. Indeed, over 23% of these initially discordant twins who developed diabetes did so more than 15 years after the diagnosis of the index twin. The risk of developing diabetes was highest in the first year after diagnosis of the index twin and fell sharply during the following 9 years to a level that remained relatively constant for the subsequent 30 or more years. This sharp decline in disease risk was found only in young twins. Such a decline in disease risk in young, but not adult onset twins, suggests that the non-genetic events leading to Type I diabetes in the young twins occur within a finite period. This loss of effect of non-genetic factors with age and time from diagnosis of the index twin could be due to lack of exposure or loss of susceptibility [33]. Given the similarity between British and the twins from the United States, in their pattern of disease progression it is likely that these non-genetic factors are ubiquitous. Some investigators have reported waxing and waning of autoimmunity in early childhood suggesting multiple "hits" promoting islet autoimmunity. Our observations that risk decreases with time argues strongly against multiple "hits" causing diabetes at least in the twins of patients diagnosed in childhood, because that would lead to an increase in disease risk over time. On the other hand, multiple hits protecting from diabetes would contribute to a decrease in risk. This hypothesis does not seem consistent, however, with our current ability to predict diabetes, unless these multiple hits happened early in life before assays which enable prediction are applied.

In summary, our observations indicate that non-germ-line genetic or environmental factors play an important part in both the development of Type I diabetes and in the rate of disease progression. Since the rates of progression to and level of concordance for diabetes in the British and the United States series are so similar, it seems likely that the genetic and non-genetic factors causing Type I diabetes in the two countries are also similar. Both the risks of developing diabetes and the rates of developing the disease differ between younger and older twins, suggesting an age-related heterogeneity in the contribution of factors causing or preventing diabetes.

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