Observations on age at diagnosis of type 1 diabetes and family history in a small population: the Winchester cohort

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Abstract
Clinical and demographic data from the records of 694 white Caucasian patients with type 1 diabetes attending a secondary care diabetes clinic between 1983 and 2010 have been audited to give information on age at diagnosis of type 1 diabetes and frequency of a family history of diabetes in their first degree relatives over five chronological decades between 1961 and 2010.

All patients in the cohort lived in 12 postcode areas (six urban and six rural) in west Hampshire, and, although ascertainment is thought to be at least 90%, the exact at-risk populations are not accurately known, so no incidence nor prevalence figures can be given.

Mean age at diagnosis rose from 18.5 years in the decade 1961–70 to 26.7 years in 1991–2000, falling again to 21.9 in 2001–10. The ranges of ages at diagnosis were 0.7–53.5 years in the decade 1961–70, and 0.7–73.1 in the decade 1991–2000. Sixty-three of the 694 patients (9.1%) were diagnosed over the age of 45 years. This is important in the initial management of people presenting with new-onset diabetes at any age and for screening programmes to consider. Eighty-eight patients had a first degree relative with diagnosed diabetes, giving an overall risk of 1 in 8 (12.7%). Possible genetic mechanisms operating in this group, and their investigation, are put forward on a hypothetical basis. Copyright © 2014 John Wiley & Sons.

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Key words
type 1 diabetes; age at diagnosis; family history; cohort study

Introduction
Population studies may be used to give information about various aspects of the natural history of a disease. How meaningful that information will depend on the completeness of the ascertainment of cases and the knowledge of the exact size of the population at risk if incidence and prevalence are being considered. If a disease is notifiable on a prospective basis, as some infectious diseases are and have been, then the most accurate figures can be given. If ascertainment is likely to be incomplete and the at-risk population not accurately known, then observations on other aspects of the natural history of the disease are better regarded as cohort studies, but useful information can still be obtained as long as the limitations are accepted regarding extrapolation.

Type 1 diabetes is not a notifiable disease. There is little information on incidence or prevalence outside Scandinavia.\(^1\) Even in Norway, not all new cases of type 1 diabetes are notified, but any child diagnosed under the age of 15 years must be referred to a paediatric department, which has led to the formation of the Norwegian Childhood Diabetes Registry. This has given accurate data on changes in the incidence of type 1 diabetes when age at diagnosis is under 15 years. Changes in the delivery of diabetes care in the NHS – particularly by whom and in what clinical setting – and deteriorating communication\(^2\) have led to the extinction of the ‘Dinosaur Diabetic Clinic’; nevertheless, specialists still have the opportunity to collect and audit important clinical information and trends on large numbers of people with diabetes over a wide age range.

This article presents some facts about age at diagnosis of type 1 diabetes and family history of diabetes from a cohort of white Caucasian patients diagnosed and followed up by such a clinical service serving a defined population. It is not, however, possible even from these careful records to be accurate about incidence and prevalence. These data have in part been presented elsewhere.\(^3\) The opinions...
expressed, particularly in the interpretation of the family history data, may be conjecture.

Patients and methods
A secondary care (specialist) diabetes clinic was set up by one of us (APB) in 1983 to serve the population of Winchester, Eastleigh, and Andover over 12 postcode areas – six urban and six rural – in west Hampshire, UK; 1983 was the year of ‘U100 conversion’ in which the insulin preparations and syringes in use by every type 1 diabetes patient were changed over to uniform 100 unit strength. It is likely that all type 1 diabetes patients in this population were seen either at the new hospital diabetes clinics or on visits to general practices, and subsequently 95% attended regular clinics. These patients formed the parts of the cohort diagnosed in the decades 1961–70 and 1971–80 and followed up from 1983 onwards. There were also 29 patients diagnosed between 1941 and 1960 not included in this study. Thereafter, 90% or more of the practices continued to refer all newly-diagnosed patients to the hospital clinics up to 2010.

From 1995 onwards, clinical, demographic, laboratory and medication data from attendance at the diabetes clinics (follow-up visits usually twice a year including an annual review) were captured in the Diamond system (HiCom Technology) to use as the basis for letter writing and audit. The Specialist Paediatric Diabetes Clinic has used the ‘Twinkle’ version of the Diamond system for the last 10 years.

A retrospective audit of 694 Diamond and Twinkle patient records using a census date of 2010 was begun in 2012; the cohort was made up of those patients diagnosed in the five calendar decades 1961–70, 1971–80, 1981–90, 1991–2000, and 2001–10 whatever their age at diagnosis. These records are felt to be accurate because of the way in which they have been collected by a small number of professionals over a long period of time. All cases have been followed up, many for over 20 years, and represent true cases of type 1 diabetes, usually diagnosed with the classical triad of (osmotic) symptoms, glycosuria and ketonuria, with fasting blood glucose >7.0mmol/L and/or random blood glucose >11.1mmol/L. Insulin was started at diagnosis, or within six weeks to six months (‘primary or secondary failure’) and was in all cases appropriate, i.e. not followed by excessive weight gain or hypoglycaemia. There may be three patients with latent autoimmune diabetes of adults (LADA) in the series.

Population figures were obtained from the Hampshire Records Office, the Office of Population Censuses and Surveys (OPCS) and the online Office for National Statistics Census for 2001. All observations are presented numerically. There is no mathematical statistical analysis, but the possible biological significance of changes is discussed.

Results
Three aspects of the natural history of this cohort of patients with type 1 diabetes have been analysed in this study: overall demographics (Table 1); age at diagnosis (Table 1 and Table 2); and the presence of a family history of diabetes in one or more first degree relatives (Table 3).

Table 1 shows there were 694 (365 males and 329 females, sex ratio 1.11) patients with type 1 diabetes ascertained into the cohort living in the 12 postcode areas and diagnosed over the five chronological decades 1961–70, 1971–80, 1981–90, 1991–2000, and 2001–10. The youngest patient was diagnosed at 0.2 years and the oldest at 73.1 years of age, so the at-risk population corresponds to the

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<tbody>
<tr>
<td>Total patients diagnosed</td>
<td>66</td>
<td>114</td>
<td>156</td>
<td>164</td>
<td>194</td>
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<tr>
<td>Males/females</td>
<td>28/38</td>
<td>62/52</td>
<td>78/78</td>
<td>79/85</td>
<td>118/76</td>
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<tr>
<td>Sex ratio</td>
<td>0.74</td>
<td>1.19</td>
<td>1.00</td>
<td>0.93</td>
<td>1.55</td>
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<tr>
<td>Mean age at diagnosis (yrs)</td>
<td>18.5</td>
<td>18.2</td>
<td>23.6</td>
<td>26.7</td>
<td>21.9</td>
</tr>
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<td>Males (yrs)</td>
<td>18.2</td>
<td>20.6</td>
<td>24.9</td>
<td>25.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Females (yrs)</td>
<td>18.7</td>
<td>15.4</td>
<td>22.4</td>
<td>27.7</td>
<td>20.8</td>
</tr>
<tr>
<td>Ranges of age at diagnosis</td>
<td>0.7–53.5</td>
<td>1.3–52.5</td>
<td>0.2–62.1</td>
<td>0.7–73.1</td>
<td>1.3–68.3</td>
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<td>At-risk population aged 0.0–74.0 years</td>
<td>139 000</td>
<td>175 000</td>
<td>253 000</td>
<td>206 000</td>
<td>308 000</td>
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Table 1. Demographics of the Winchester cohort by calendar decade of diagnosis between 1961 and 2010

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</tr>
<tr>
<td>Age 0.0–14.9, % of total</td>
<td>51.5%</td>
<td>54.4%</td>
<td>32.7%</td>
<td>27.3%</td>
<td>45.4%</td>
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<tr>
<td>Age 15–29.9, % of total</td>
<td>27.3%</td>
<td>30.7%</td>
<td>34.0%</td>
<td>35.2%</td>
<td>25.8%</td>
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<tr>
<td>Age 30–44.9, % of total</td>
<td>15.2%</td>
<td>10.5%</td>
<td>24.4%</td>
<td>23.0%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Age 45–59.9, % of total</td>
<td>6.0%</td>
<td>4.4%</td>
<td>8.3%</td>
<td>12.1%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Age 60–74.9, % of total</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.6%</td>
<td>2.4%</td>
<td>1.5%</td>
</tr>
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Table 2. Percentages of patients in 15-year quintiles of age at diagnosis for each chronological decade between 1961 and 2010

Original article
Age at diagnosis and family history of type 1 diabetes
age range 0–74 years used by the OPCS. The population figures have been taken from the relevant Census for Hampshire for each decade, but, as will be discussed, are approximations.

Table 1 also shows the mean ages at diagnosis of all patients, and males and females separately, for each of the five calendar decades in which the patients are known to have been diagnosed and a range of the ages at diagnosis. Age at diagnosis is not normally distributed; there is no reason why it should be. Consequently, no statistical analysis has been done, but there appears to be an increase over the first four decades from in males 18.2 and females 18.7 years in decade 1961–70 to 25.5 and 27.7 respectively in decade 1991–2000, falling back to 22.6 and 20.8 in decade 2001–10. The mean ages at diagnosis for all patients was 22.5 years, for young males were diagnosed and referred. Likewise, there appears to be an increase in the frequency percentage for all the older quintiles (15.0–29.9 to 60.0–74.9 years) from the 1961–70 to 1991–2000 decades. Overall, 63 of the 694 patients (9.1%) were diagnosed with true type 1 diabetes over the age of 45 years.

Table 3 shows the numbers of patients with a first degree relative (parent, child, sibling, or in one pair twin) with diabetes (usually type 1 but some apparent type 2) by chronological decade of diagnosis. Overall, 88 of 694 patients (12.7%) had a first degree relative with diagnosed diabetes. The maximum risk (27/156, or 17.3%) was in those diagnosed in the decade 1981–90. Many diagnosed in the decade 2001–10 have not yet reached reproductive age, hence nil entries in the ‘parent of’ rows.

**Discussion**

Referring back to the title of this article, is this a population study or a cohort study? Population studies can give useful information about the incidence and prevalence of a disease only if the numerator (the number of new cases for incidence and the total number of cases for prevalence) and denominator (the size of the at-risk population for a given time interval) are known accurately. This is clearly not the case here, since although ascertainment (in this instance referral) of new cases is thought to be at least 90% from the beginning of the Clinic in 1983 at the time of U100 insulin changeover when all local patients were seen by one of us, it is probably not 100% and will not be until new cases of diabetes are notified in some way. The same is true for the denominator of population size which has had to be estimated since in none of the census material used is population counted by the same geographical areas of postcodes. The total at-risk populations given are probably over-estimates for decades 1981–90 and 2001–10, when the geographical area used for the population census was bigger than the postcode area, but an underestimate for 1991–2000 when it was physically smaller. If nothing else, this article demonstrates how difficult accurate population studies are, despite good record keeping, and will be. This then should be regarded as a cohort study, but with good enough ascertainment to make meaningful observations on those aspects of the natural history of type 1 diabetes relating to age at diagnosis and family history.

The difficulties with not having a register or notification system for new cases of (type 1) diabetes and no necessity to refer at least initially to a specialist centre are highlighted by the paucity of good information on age at diagnosis. The best information comes from Scandinavia and particularly Norway 1 with the Norwegian Childhood Diabetes Registry, but is limited to the age range 0–14.9 years. Valid comments can therefore be made on the trends in reduction in incidence rate in this age group, but perhaps it could be explained by an increase in other age groups as we have observed, as is shown in our Table 2. This is why we used the 15-year quintile analysis in the absence of other agreed methods of analysis. The Oxford study using the old regional health authority boundaries 4 showed an increase in the numbers of children.
diagnosed before age 15 years and particularly in the 0–4 years old group. Globally, an earlier study looked at the incidence of type 1 diabetes in children up to 14 years of age from 114 populations in 112 centres in 57 countries. Wide variations were found from 0.1 per 100,000 in China and Venezuela to 40.9 per 100,000 in Finland, suggesting difficulties in diagnosis and ascertainment in some areas as well as biological ones. The conclusion was that: ‘there was the need for continuous monitoring by using standardised methods in order to plan or assess prevention strategies.’

These previous studies have given useful information but only for a limited age group. Type 1 diabetes is no longer called ‘Juvenile Onset Diabetes’, nor a disease with maximum incidence in the 7–17-year-old age group as suggested by textbooks. This our observations show, and we are sure the clinical experience of many will support this finding. The wide range in age at diagnosis was recognised in the initial publication of Klein of the Wisconsin Epidemiologic Study of Diabetic Retinopathy when people with diabetes were considered in three categories: those diagnosed under 30 years of age (all on insulin); those diagnosed over 30 years of age on insulin; and those diagnosed over 30 years of age and not on insulin.6

Why might these changes in age at diagnosis have occurred? If the pathogenesis of type 1 diabetes usually invokes autoimmune mechanisms, then could there have been changes in the populations’ exposure to antigens? Among those usually linked with type 1 diabetes were the milk protein antigens and the common virus and their vaccines’ antigens. Certainly there have been changes in these areas, with those diagnosed in the earlier decades of this study likely to have had ‘free school milk’ whereas those in the later not. There will have been changes in the patterns of commonly encountered viruses and vaccine compositions in that time. In the decades 1961–70 and 1971–80, many women with type 1 diabetes lost pregnancies, or were grateful for one healthy child and uncomplicated pregnancy and limited their family size, which would again alter the demographics and how patterns of inheritance looked.

Type 1 diabetes should not be regarded as a disease of children only; therefore, due clinical care and judgement must be used in managing all newly-presenting cases of diabetes, in whom the type and need for insulin may not be apparent at first presentation. This is also important in screening programmes. In this cohort, 1 in 11 new cases were over 45 years of age, and from 1981 we began to see patients over 60 years of age, albeit still rarely. Age therefore should not be used as the sole diagnostic criterion for type of diabetes or insulin need at onset.

We stress that all cases were followed up by the specialist clinic and the older patients do not represent type 2 diabetes patients who required insulin at presentation (e.g. with foot disease or a myocardial infarction) and then did not when they were well. Accepting that type 1 diabetes patients have a wide range of age at diagnosis leads to the concept of people with diabetes having two ages: their chronological age, and a ‘diabetes age’ or duration of diabetes. The health and risk of a 55 year old diagnosed with type 1 diabetes at age 10 will be very different from that of a 55 year old diagnosed at age 45 with 10 years’ diabetes duration.

The observations on family history of diabetes in first degree relatives summarised in Table 3 are of interest, not only because of the findings, but also because they allow some hypotheses to be put forward regarding possible inheritance mechanisms in diabetes. In this cohort, 88 index cases (48 males and 40 females) had a first degree relative (i.e. sib or twin, child or children, or parent) with diabetes, usually also apparently type 1 diabetes and in the cohort. In some cases, a parent was diagnosed before the child. The overall risk was 1 in 8 (88 in 694 or 12.7%) for a person with type 1 diabetes to have a first degree relative with diabetes, but as high as 1 in 6 (27/156, or 17.3%) in the decade 1981–90. When there is vertical transmission (parent to child) of an inherited disease then autosomal dominance is the most common form of inheritance (e.g. an inherited peripheral neuropathy), and when horizontal (two children/sibs from unaffected parents) then inheritance is said to be by an autosomal recessive mechanism (e.g. albinism or cystic fibrosis). These may be the genetic mechanisms here.

The genetics of the whole range of clinical forms of diabetes are complex, and probably made more so because there is more heterogeneity or variation in diabetes than the two clinical types we label 1 and 2. If the genetics of diabetes were simple, then type 1 diabetes would be due to an enzyme deficiency in the insulin production chain, the affected individual having two abnormal recessive genes coding for the abnormal enzymes, and the parents only one each as in classical autosomal recessive inheritance. This is not the case for classical type 1 diabetes which has an autoimmune basis. However, the inheritance of the human leucocyte antigen (HLA) system, which plays a strong part in autoimmune reactions, is on a similar genetic mechanism to autosomal recessive inheritance, each unaffected parent having one of the HLA haplotypes linked to (i.e. more frequent in) diabetes, and the affected child or children having both to increase their susceptibility.

If type 1 diabetes were an autosomal recessive condition in simple genetics, then type 2 diabetes should be an autosomal dominant condition with single mutant gene effects on various parts of the insulin action or receptor mechanisms. There is of course good evidence for autosomal dominant inheritance in type 2
We conclude that, whatever the hypotheses, the observations from this cohort suggest that all new cases of apparent type 1 diabetes who have a first degree relative with diabetes should have full investigation of HLA haplotypes, autoantibodies related to diabetes, and the profile of tests used to investigate potential MODY cases and mitochondrial inheritance when the mother has diabetes. This applies whether it is child following parent or parent following child in diagnosis; this is in view of the wide range of age at diagnosis of what we currently call a single type of diabetes, i.e. type 1 diabetes, and the changes in age at diagnosis over five decades which we observed in the Winchester cohort.

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Declaration of interests

There are no conflicts of interest declared.

References