AGE AT ONSET OF TYPE 1 DIABETES IN PARENTS AND RECURRENCE RISK IN OFFSPRING

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Objectives - Our aim was to study the recurrence risk of type 1 diabetes in the offspring of parents with adult onset (15-39 years) type 1 diabetes and to evaluate the transmission of diabetes within a continuum of parental age at onset of diabetes from childhood to adulthood.

Research Design and Methods - Diabetes status of all offspring (n=9,715) of two Finnish cohorts of parents with type 1 diabetes was defined until the end of year 2007. Cumulative incidences of type 1 diabetes among the offspring were estimated and several factors contributing the risk were assessed.

Results - During 137,455 person-years a total of 413 offspring were diagnosed with type 1 diabetes. The cumulative incidence by 20 years was 4.0% (95% CI 3.1-4.8) for the offspring of parents with adult onset diabetes. The risk was equal according to the sex of the parents. The cumulative incidence decreased in parallel with the increase in age at onset of diabetes in the fathers. In the offspring of diabetic mothers the risk was equal regardless of the age at onset of diabetes. However, the reduced risk in the maternal offspring was most pronounced in the daughters of the mothers with diagnosis age less than 10 years.

Conclusions - Type 1 diabetes transmission ratio distortion is strongly related to the sex and age at onset of diabetes in the diabetic parents.
Type 1 diabetes can occur at any age, although it is predominantly seen in children and young adults. Therefore, the majority of studies have been conducted in children below 15 years. The recurrence risk in the offspring ranges from 3-6% depending on the study design, follow-up time, and the population where the study has been conducted (1-3). Little is known about the recurrence risk in first-degree relatives of cases diagnosed with type 1 diabetes above 15 years. The incidence of type 1 diabetes is much lower in young adults than in children (4-6). Consequently, the risk of family members may also be different among the diabetic subjects affected after childhood. Sex-related factors seem to be involved in the transmission of diabetes from one generation to the next (7). By 20 years of age, 5-8% of the offspring of diabetic men, while only 2-5% of the offspring of diabetic women have been found to be affected (1-3; 8). We have previously shown that the recurrence risk of diabetes in the offspring of parents diagnosed between 0-17 years was higher the younger the father was when diagnosed with type 1 diabetes. This pattern was not present in the offspring of the mothers (8). We have enlarged our study to include also the offspring of parents diagnosed with diabetes between 15-39 years. This gives us an opportunity to determine the risk in the offspring of parents with a broad age span at diagnosis, and to elucidate whether there are differences in risk between the offspring of diabetic mothers and fathers.

METHODS
All offspring of Finnish population-based cohorts of probands with late onset type 1 diabetes diagnosed between 15-39 years were identified and followed regarding a diagnosis of type 1 diabetes until the end of year 2007. This cohort comprised 3,389 cases diagnosed during 1992-2001. This cohort was originally used for the study of incidence rates of type 1 and type 2 diabetes in Finland, and the ascertainment procedure has been described earlier (4; 5). Moreover, we used the same cohort of patients with early-onset diabetes diagnosed below 18 years between 1965-1979 (n=5,144) as in our previous publication in order to re-examine if the recurrence risk of type 1 diabetes in the offspring of mothers occurs in a sex-specific manner, the observation that was only suggestive in our previous publication. The analysis was conducted by means of increasing statistical power and taking into consideration parental age at onset. We identified all new offspring born between 2002-06 (n=520) and updated the diabetes status of the offspring until the year 2007.

The early-onset cohort was also used in order to provide a holistic view on the effect of parental onset of diabetes on the recurrence risk of type 1 diabetes in the offspring. All offspring were identified through the Central Population Register, and linked to the National Hospital Discharge Register, the Drug Reimbursement Register and the nationwide Finnish Diabetes Register of the Institute of Health and Welfare.

Statistical methods. The analyses were first carried out in the late onset cohort. Cox regression analysis was used to assess factors associated with the risk of progression to type 1 diabetes and the following potential predictors were included in the analyses: sex of the parent, sex of the offspring, age at the onset of parental diabetes as continuous variable, year of the birth of the offspring and the parental age at delivery. At the first stage, univariate analyses were performed. At the second stage, standard backward selection as well as stepwise selection techniques were used to identify possible significant variables.
All variables were included in the full model irrespective of statistical significance in the univariate analysis. A likelihood ratio test was used as test statistic in the comparison of the models at each step. Interactions between the variables were also tested. The risk of diabetes in the offspring of the mothers diagnosed before (n=875) and after (n=642) the offspring’s birth was also tested. In this analysis, the offspring of the mothers diagnosed between 20 and 39 were included. The effect of the parental age at diagnosis on the risk of diabetes in the offspring was evaluated by pooling the data on the early and late onset cohorts. Kaplan-Meier analyses provided long-term cumulative risk for the development of type 1 diabetes in the offspring. In order to find out whether the risk, associated with the age at onset of the fathers, levels off at some stage, the offspring were stratified into 5-year groups by paternal age at onset, and hazard ratios (HRs) were calculated using the last group as reference. Finally, since there were conspicuously less affected girls in the two lowest age at onset groups among the mothers the data were divided into two groups: mothers diagnosis age less than 10 years and more than 10 year and sex of the offspring was tested.

RESULTS
There were altogether 9,696 offspring in the two cohorts, 3,881 in the late-onset cohort and 5,821 in the early-onset cohort (13 overlapped) (Table 1). The offspring in the late onset cohort were approximately 5.2 years younger than those in the early onset cohort. During 137,455 person-years of observation a total of 413 offspring were diagnosed with type 1 diabetes; 318 offspring of parents from the early onset cohort and 97 offspring of parents from the late-onset cohort (2 overlapped). The overall incidence rate was 241.6 /100 000 person years (95% CI 201.5-287.2) in the offspring of parents diagnosed between 15-39 years. The cumulative risk by 20 years was 4.0% (95% CI 3.1-4.8) for the offspring of parents with late onset diabetes. The risk in the offspring did not differ by sex of the parents (p=0.30); the 20-year cumulative incidence was 4.2% (95% CI 3.0-5.4) for the offspring of mothers and 3.8% (95% CI 2.6-5.0) for the offspring of fathers (Figure 1A).

Cox proportional hazard modelling revealed that none of the tested variables was associated within the recurrence risk in the offspring of the parents with late onset diabetes, neither in univariate nor in any step in multivariate analyses (Table 2). There was no difference between the recurrence risk in the offspring of the mothers when pregnancy occurred before versus after the diagnosis of the maternal diabetes (p=0.22). The HR was 1.5 (95% CI 0.8-3.0) for the offspring born to the mothers with diabetes compared with those born before the mother’s diabetes. The HR for the offspring of the fathers diagnosed 15-19 years was 2.9 (95% CI 1.3-6.7) compared with those diagnosed 35-39 years. The risk in the diagnosis groups 20-24, 25-29 and 30-34 years was similar as in the reference group. Thus in the Kaplan-Meier analyses the offspring with paternal diagnosis age 20-39 were pooled. When the offspring of the two cohorts were pooled and analysed according to age at onset of diabetes in the parents, the risk of the offspring of the fathers showed a decreasing risk trend by the increase in the father’s age at onset (Figure 1B). In contrast to the offspring of fathers, the risk was equal in the offspring of the mothers in all age at onset groups. In the offspring of the mothers the 20-year cumulative risk was 4.7% (95% CI 3.9-5.4) irrespective of the age at onset of the mothers (Figure 1B).

However, a closer examination revealed that the risk in the sons of the mothers affected below 10 years was 2.0 times (95% CI 1.0-3.6, p=0.008) higher compared with the risk
in the girls (Figure 2). Until 20 years 2.7% (95% CI 1.0-4.2) of the girls were affected, while 6.9% (95% CI 4.2-9.6) of the boys. There was no difference between the gender of offspring when mothers’ age at diagnosis was more than 10 years (p=0.51), or overall in the offspring of the fathers (p=0.92).

**DISCUSSION**
This study shows that in contrast to the data from early onset type 1 diabetes, the recurrence risk is similar in the offspring of mothers and fathers with late onset type 1 diabetes. The cumulative incidence decreased in parallel with the increase in age at onset of diabetes in the fathers. However, there was no such pattern in the offspring of the mothers, although age at onset less than 10 years in the mothers also had an enhancing impact on the recurrence risk in the sons. On the contrary, the daughters of the mothers with diabetes and young age at onset, seems to be protected from diabetes.

This is the first longitudinal population-based study of the recurrence risk in offspring of parents with type 1 diabetes that takes into account the broad continuum of age at onset of diabetes in the parents from early childhood into adulthood. In general, most studies have focussed on diabetes in the children and there are very few studies including adult onset type 1 diabetes. However, it is obvious that in order to obtain a comprehensive picture of the risk pattern a broad age span is essential.

In many chronic diseases age at onset is an indicator of genetic susceptibility and the stronger the genetic component the earlier the onset of the disease and the greater the risk in the first-degree relatives (11; 12). The present study supports such an age-related relationship. There are great genetic, autoimmune, and clinical differences between childhood-onset and adult-onset type 1 diabetes (13). These differences seem to be reflected in the heterogeneity of the transmission pattern of type 1 diabetes according to age at onset. It can be hypothesized that the risk pattern observed in the offspring of the diabetic fathers is the anticipated one, but that the reduced risk of the offspring of the diabetic mothers is unexpected.

There are at least two explanations for the reduced risk in the offspring of diabetic mothers. The offspring may either be protected from diabetes or may be selectively lost during pregnancy (14). Accumulating evidence indicates that the intrauterine environment affects health later in life (15). The phenomenon is referred to as fetal programming or epigenetic modification (16; 17). Several studies have shown that a number of gestational events may contribute to the risk of type 1 diabetes (18-21). Boys seem to be more vulnerable to certain gestational events suggesting that perinatal determinants may influence the risk of diabetes in a sex-specific manner (22). It is noteworthy that an abnormal intrauterine environment may also protect the fetus through modification of gene expression of susceptibility genes for type 1 diabetes, and a fetus, exposed to maternal type 1 diabetes, could as a result be protected from the development of diabetes. Autoantibodies transmitted from the mother to the child have been reported to confer protection from the development of autoantibodies and type 1 diabetes later in life among children born to mothers with type 1 diabetes (23). It is, however, unclear whether these autoantibodies per se protect the offspring from diabetes or whether they are mere markers of other protective factors or mechanisms.

It has been suggested that one way to test the hypothesis that pregnancy may protect from diabetes is to compare the manifestation of diabetes in the offspring between those born before and after the mother has been diagnosed with diabetes (14; 24). We did not
find any differences between the two groups and our results are thus consistent with those by Lorenzen at al. (2). However, it has to be acknowledged that a possible protection, if there is one, may only occur in the mothers with childhood and adolescent diabetes and possibly with certain combination of susceptibility genes and antibodies, since the risk in the offspring of fathers and mothers affected with diabetes in adulthood is no different. Thus it is not possible to conclude anything about the possible protective effect with this kind of comparison. Although the capture years (1965-79 and 1992-2001) at first glance seem very different, the age distribution of the parents in the two included cohorts was in fact similar and also the birth year distributions of the offspring. In the early onset cohort offspring were born between 1969 and 2006 and in the late onset cohort between 1973 and 2006. The mean birth year in the first was thus 1990 and in the latter 1995. Therefore, the lower risk of diabetes in the offspring in the late onset cohort is probably due to other factors than the birth year. A limitation is the lack of precise information about type of diabetes in the offspring. Although type 2 diabetes has become increasingly common in children, it has to be emphasized, that type 2 diabetes under the age of 20 years has been very rare in Finland during the past decades (4; 5). The majority of the affected children was diagnosed below 20 and type 1 diabetes was thus the most likely diagnosis. In conclusion, the transmission ratio distortion is strongly related to the age at onset of diabetes in the diabetic parent. However, the recurrence risk is equal in the offspring of mothers and fathers with adult onset diabetes.

ACKNOWLEDGMENTS
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**Figure legends**

Figure 1. Cumulative incidence of type 1 diabetes in the offspring of fathers and mothers with late onset type 1 diabetes (p=0.30, log-rank test) (A) and in the offspring of fathers in the combined cohorts according to age at onset of diabetes in the fathers (p<0.0001, log-rank test) and in the offspring of mothers in the combined cohorts (p=0.69, log-rank test) (B).

Figure 2. Cumulative incidence of type 1 diabetes in the boys and girls of the diabetic mothers with diabetes onset less than 10 years (p=0.008, log-rank test) (A) and 10 years or more (p=0.75, log-rank test) (B).
Table 1. Descriptive data on the study population.

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<th>Female Probands 0-17</th>
<th>Male Probands 0-17</th>
<th>All Probands 0-17</th>
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<tr>
<td>Girls</td>
<td>2,501*</td>
<td>3,333*</td>
<td>5,821*</td>
<td>1,667</td>
<td>2,214</td>
<td>3,881</td>
<td>9,696**</td>
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<tr>
<td>Boys</td>
<td>1,248</td>
<td>1,615</td>
<td>2,857</td>
<td>809</td>
<td>1,108</td>
<td>1,961</td>
<td>4,771</td>
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<tr>
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<tr>
<td>Girls</td>
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<td>218</td>
<td>318</td>
<td>50</td>
<td>47</td>
<td>97</td>
<td>413***</td>
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<tr>
<td>Boys</td>
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<td>174</td>
<td>29</td>
<td>18</td>
<td>45</td>
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</table>

* 13 offspring had both parents from the early onset cohort
** 6 overlapped offspring with 2 diabetics
*** 2 overlapped offspring with type 1 diabetes
14 offspring with type 1 diabetes excluded from the analyses, because they had both parents with type 1 diabetes.

Table 2. Multivariate Cox regression analysis including factors that influence the recurrence risk in offspring of parents with late onset type 1 diabetes.

<table>
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<th>Variable</th>
<th>Univariate analyses</th>
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<tr>
<td></td>
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<tr>
<td>Male</td>
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<tr>
<td>Sex of offspring</td>
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<tr>
<td>Girls</td>
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<td>0.88</td>
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<td>Year of birth of offspring</td>
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<td>1.00-1.08</td>
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<tr>
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<td>Parental age at delivery</td>
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<td>0.96-1.05</td>
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No significant interaction terms.
REFERENCES
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Figure 2. Cumulative incidence of type 1 diabetes in the boys and girls of the diabetic mothers with diabetes onset less than 10 years (p=0.008, log-rank test) (A) and 10 years or more (p=0.51, log-rank test) (B).