Cumulative risk, age at onset and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes. A nationwide population based cohort study.

Running title: Age at onset and sex in end-stage renal disease.

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**Objective** - This study aimed to estimate the current cumulative risk of ESRD due to diabetic nephropathy in a large nationwide population-based prospective type 1 diabetes cohort and specifically study the effects of sex and age at onset.

**Research design and methods** - In Sweden, all incident cases of type 1 diabetes aged 0-14 years and 15-34 years are recorded in validated research registers since 1977 and 1983 respectively. These registers were linked to the Swedish Renal Registry that, since 1991, collects data on patients who receive active uremia treatment. Patients with ≥13 years duration of type 1 diabetes were included (n=11,681).

**Results** – During a median time of follow-up of 20 years 127 patients had developed ESRD due to diabetic nephropathy. The cumulative incidence at 30 years of type 1 diabetes duration was low with a male predominance, 4.1% (95%CI 3.1-5.3) vs. 2.5% (95%CI 1.7-3.5). In both males and females, onset of type 1 diabetes before 10 years of age was associated with the lowest risk of developing ESRD. The highest risk of ESRD was found in males diagnosed at 20-34 years, hazard ratio=3.0 (95% CI: 1.5-5.7). In females with onset 20-34 years the risk was similar to patients’ diagnosed before 10.

**Conclusions** - The cumulative incidence of ESRD is exceptionally low in young type 1 diabetes patients in Sweden. There is a striking difference in risk for male compared with female patients. The different patterns of risk by age at onset and sex suggest a role for puberty and sex hormones.
Diabetic nephropathy is one of the most severe complications in patients with type 1 diabetes, leading to end-stage renal disease (ESRD) and need for renal replacement therapy (dialysis and transplantation). Diabetic nephropathy is also a major predictor of cardiovascular morbidity and mortality in patients with type 1 diabetes(1). Although the incidence of type 1 diabetes has increased in children and onset of disease occurs at younger age(2; 3) a decrease in incidence of diabetic nephropathy and a longer duration from onset of diabetes to diabetic nephropathy and ESRD has been reported from dedicated centers(4). Recently a follow up of the DCCT intensive treated type 1 diabetes cases showed a cumulative incidence of nephropathy of 9% at 30 years of diabetes compared with 25% in the conventionally treated group(5). A Finnish population-based study showed a cumulative incidence of ESRD of 7.8% after 30 years of diabetes duration(6). Next to Finland, Sweden has the highest incidence of childhood onset diabetes reported worldwide(7) and since the 1980ies Sweden has a strict nationwide childhood diabetes care program including intensive insulin treatment and home blood glucose monitoring to counteract development of late complications.

Poor glycaemic control and high blood pressure are the two most important risk factors in the initiation and development of diabetic nephropathy(8; 9), but they are not sufficient for development of diabetic nephropathy and ESRD. Other factors, such as genetic susceptibility and growth- and sex-hormones, seem to contribute(10; 11). Some studies suggest that male sex is a risk factor for development of diabetic nephropathy and ESRD(12-14). Several studies indicate that young age at onset of diabetes can prolong the time until development of microalbuminuria, diabetic nephropathy, ESRD and other vascular complications(6; 15; 16). It has thus been suggested that puberty could promote the development of chronic diabetic complications due to deterioration of glycaemic control, rapid growth and hormonal changes(17; 18). An increased risk for both hospitalization due to severe vascular complications and a higher mortality rate have also been found in patients with pubertal onset of diabetes compared to those with younger age at onset(19; 20). If puberty is associated with increased risk of diabetic nephropathy, diabetes onset after that age would decrease diabetic nephropathy risk and approach the risk of pre-pubertal onset cases.

In the present study we used data from two large nationwide population-based cohorts of young patients with type 1 diabetes:
- to estimate the cumulative incidence and long-term risk of ESRD after 30 years of recommended intensive insulin treatment
- to study the effects of age at onset of diabetes and sex on these risks

**RESEARCH DESIGN AND METHODS**

**Study population.** Since 1 July, 1977 all incident cases of type 1 diabetes in the ages 0-14 years are recorded in the Swedish Childhood Diabetes Registry (SCDR). Only those who are insulin treated from diagnosis (approximately 99% of cases) are registered. Comparisons with external sources have shown that the level of ascertainment in the SCDR is 96-99%(21; 22). The Diabetes Incidence Study in Sweden (DISS) records incident cases of diabetes in the age-group 15-34 years since 1 January 1983. The completeness of the DISS-register has varied between 82% and 91% depending on the source of ascertainment(23) with no significant gender difference. The classification into type 1, type 2 and unclassified is based on the treating doctors’ clinical classification. During 1983-1991 the WHO classification was used and since 1992 the ADA classification criteria were used.
This change in diagnostic criteria would probably little affect the results since only clinically overt cases of type 1 diabetes were included. Of all patients less than 10% classified by clinical criteria as type 1 diabetes at diagnosis are misclassified when the diagnosis was checked using autoantibodies and C-peptide(24).

End-stage renal disease is defined as need to start active uremia treatment due to renal failure (glomerular filtration rate <10-15 ml/min). The Swedish Renal Registry (SRR) collects data on all patients with chronic renal failure who starts dialysis treatment or receives a kidney transplant. A validation study showed that more than 95% of the patients who started treatment for chronic renal failure had been reported to the SRR(25). The SRR started in 1991 and at that time none of the patients in the SCDR had diabetes duration longer than 13 years.

When type of diabetes differed between the two diabetes registries and the SRR, the classification reported to the SRR was used since this was made after a long clinical follow-up. Five patients were classified as having ESRD due to type 2 diabetes in the SRR and were therefore excluded from the analyses. Patients with ESRD due to other diagnoses than diabetes (N=11) were also excluded.

The present study covers the majority of all cases of ESRD due to type 1 diabetes at 13 years duration or longer, during 1991-2007, and should hereby represent the Swedish type 1 diabetes population at large. Patients with 13 years duration (i.e. diabetes onset 1 July 1977 – 31 December 1995 for the SCDR and 1 January 1983 – 31 December 1995 for the DISS) would have equal chance of entering the SRR, starting in 1991. Thus 6789 patients with onset before 15 years of age and 4892 patients with onset of diabetes between 15-34 years were included. Dates of death were obtained by linking the diabetes registers to the Swedish Cause of Death Register.

This study was approved by the regional research ethics committee in Umeå, according to the Swedish law on research ethics in line with the principles of the Helsinki declaration and the European convention on human rights and biomedicine. The study and the statistical analysis were designed and interpreted by the authors. The funding bodies had no role in the design and conduct of the study, in collection, management, analysis or interpretation of the data or in preparation and approval of the manuscript.

**Statistical analyses.** The age at onset was divided into three groups, 0-9, 10-19 and 20-34 years, hence the 10-19 group includes the pubertal years for the vast majority of the cohort. Incidence rates of ESRD were calculated as number of cases divided by number of years at risk in 6-year intervals, 13-18, 19-24 and 25-30 years of diabetes.

Kaplan-Meier analyses were used to calculate the cumulative incidences. Cox-regression analyses were performed to estimate the hazard ratio (HR) of developing ESRD, to compare the HR by age at onset groups and sex and to adjust for the potential confounding variables age at follow-up and sex. In these analyses the time at risk was calculated from onset of diabetes until ESRD (i.e. date of first treatment with renal replacement therapy), death or 31 December 2007.

Kaplan-Meier analyses may overestimate the cumulative incidence when the event of death is censored in the same way as when censoring for other reasons. Therefore we also computed the cumulative incidence when taking into account death as a competing risk event. This method accounts for death as an event that removes the risk of ESRD and hence provides a more accurate estimate of the risk(26). SPSS 16.0 for Windows was used for the Kaplan-Meier and Cox regression analyses while the R statistical software, 2.5.1, (The R foundation for statistical computing, available at: http://www.r-
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project.org/index.html), with the function “cuminc” from the “cmprsk” package, was used for calculations with death as a competing risk event.

RESULTS
Long term incidence rate and cumulative incidence of ESRD. The study included patients with at least 13 years duration of type 1 diabetes. In total 127 patients had developed ESRD due to type 1 diabetes, 79 in the SCDR and 48 in the DISS (Table 1). No patient had developed ESRD before 13 years duration of diabetes. Maximum follow-up was 30.0 years for the SCDR and 24.9 years for the DISS. The median follow-up time was 21.2 years for patients in the SCDR and 18.9 for patients in the DISS. The median time from onset of diabetes to ESRD was 21.7 (range; 14.7-28.2) and 18.5 (13.7-24.8) respectively.

The overall incidence rate of ESRD during 237,592 person-years of follow-up was 0.53 per 1000 person-years.

Effect of age at onset and sex on development of ESRD. Table 2 shows incidence rates of ESRD per 1000 person-years of diabetes duration, at 13-18, 19-24 and 25-30 years after diabetes onset. The incidence increased by increasing diabetes duration. The sharpest increase in incidence was seen between 13-18 and 19-24 years, while the increase between 19-24 and 25-30 years was modest partly due to that the 20-34 year onset group could not contribute as they had a maximum duration of 25 years.

The cumulative incidences in the different age at onset-groups with (table 4) and without (table 3) accounting for death as competing risk event. Only 224 out of 11,681 patients (1.9%) had died, 33 of them after having developed ESRD (Table 1). Therefore the analyses with death as competing risk did not change the results. The overall mortality in the study was 0.94 deaths per 1000 person-years of diabetes duration. There was 14 times higher risk of death among patients with ESRD, HR=14 (95% CI: 9.7-21), adjusted for sex and age at follow-up. Male patients had almost twice the risk of death due to any cause, compared with female patients, HR=1.9 (95% CI: 1.4-2.6) adjusted for ESRD and age at follow-up. Among patients developing type 1 diabetes before the age of 20 there was no difference between males and females as can be seen in the cumulative incidence curves (figure 1). Males who were 20-34 years old when diagnosed with type 1 diabetes had twice as high risk of ESRD as females, HR=2.3 (95% CI: 0.99-5.3). Taking death into account as competing risk reduced the male/female risk increase marginally, HR=2.2 (95% CI: 0.97-5.2).

The cumulative incidences of ESRD for males and females in the different age at onset-groups, 0-9, 10-19 and 20-34, are shown in figure 2. The lowest risk for ESRD was found in males and females with onset of type 1 diabetes before 10 years of age (figure 2). Among male patients the risk to develop ESRD was significantly increased in those developing diabetes at 20-34 years, HR=3.0 (95% CI: 1.5-5.7), as well as 10-19 years, HR=2.6 (95% CI: 1.5-4.7), compared with the youngest age at onset group (0-9 years). Taking death into account as a competing risk did not change the results.

In females there was no difference in the risk of developing ESRD with diagnosis of type 1 diabetes at 20-34 years compared with diagnosis at younger than 10 years of age, HR=1.4 (95% CI: 0.5-3.6). The highest risk was observed for the 10-19 years age-group, HR=2.8 (95% CI: 1.4-5.5), (figure 2). Taking death into account as a competing risk did not change the results. Using a grouping of age at onset 0-9, 10-14, 15-24, 25-34 did not change the overall pattern of difference seen by sex.

DISCUSSION
In this nationwide population-based study of patients with type 1 diabetes and at least 13
years duration, the cumulative incidence of ESRD due to diabetic nephropathy is surprisingly low, 3.3% at 30 years of duration. The Swedish Pediatric Association working group for diabetes in children in the nationwide diabetes in childhood care program already in 1982 (updated regularly) recommended intensive insulin treatment and home blood glucose monitoring. In adults, national guidelines for treatment of diabetes were issued by the Swedish Board of Health and Welfare in 1977 and since then regularly updated. These guidelines also involve intensive treatment of glucose and blood pressure, including ACE-inhibition, for type 1 diabetes patients. These active treatment programs may clearly contribute to the low rate of ESRD in Sweden and our findings accord with that of a decrease in incidence of albuminuria as reported from a dedicated centre in Sweden(4).

Since the study is based on incidence registers we have no access to individual HbA1c data but according to the Swedish National Diabetes Register (NDR) that since 1996 estimates markers of quality of care, the yearly mean HbA1c value have decreased from 8.5% (DCCT standard) to 8.1% during the time period 1996-2005.

Previous studies, from different populations with different years of onset of diabetes, have reported a cumulative incidence of ESRD of 7-13% at 20 years(27-29). The cumulative incidence seen in this study is also lower than reported in a recent Finnish nationwide population-based study where 2.2% at 20 years of follow-up and 7.8% at 30 years were found(6). The Finnish study also showed a time-period effect with a decline in cumulative incidence over time (1965-1999). In our cohort, however, there was no difference in risk of ESRD depending on year of diabetes onset, which may be explained by the later starting date of our study (1977) and more active treatment programs for both metabolic control and signs of incipient nephropathy. This difference between the cohorts may also contribute to the discrepancies in cumulative incidences. A decline in cumulative incidence of ESRD has been indicated by an unchanged reporting rate for type 1 diabetes in both the European Dialysis and Transplant Association (EDTA) registry including the SRR through the 1990-2000s despite an increase in prevalence of type 1 diabetes and longer survival in patients with type 1 diabetes(30).

The peak incidence of diabetic nephropathy has been found to occur 15-25 years after the onset of type 1 diabetes(27; 31) and the median duration from onset of diabetic nephropathy to ESRD is usually about 10 years(27). The development of ESRD due to diabetic nephropathy within 15 years of diabetes duration is rare; in this study only 3 patients had developed ESRD before this duration. The relatively constant incidence rates at 19-24 and 25-30 years of diabetes duration may indicate that the peak incidence of ESRD had been reached at 30 years of diabetes duration, or that the peak incidence has been delayed beyond 30 years of diabetes duration. Both alternatives suggest a favorable change in the natural history of diabetic nephropathy also in susceptible patients. These findings of a favorable time trend in diabetes nephropathy is in correspondence with the results of Pittsburg Epidemiology of Diabetes Complications Study(32).

Our study confirms previous findings of a reduced risk, or a delay, in development of ESRD in patients diagnosed with type 1 diabetes before the age of five (n=2) and 10 years(6; 14; 15; 33). A similar age dependency of risk has been found for severe retinopathy and blindness due to diabetes(33). The reasons for this age at onset effect could be for example genetic, endocrine or healthcare related. It could be argued that children and families who become used to insulin treatment at an early age might adhere
better to treatment and diet than those that are diagnosed with diabetes at an older age and especially during puberty. Previous studies have indicated that pre-pubertal years with diabetes involve a reduced risk or a longer time to development of diabetic nephropathy and retinopathy(17; 34). It has also since long been speculated that puberty, characterized by rapid growth, hormonal changes (especially in growth hormone and sex hormones) and worsening in glycaemic control, may accelerate the processes leading to chronic diabetic complications(35; 36). We speculated that if puberty was a strong determinant for development of diabetic nephropathy then diabetes onset after puberty would give a similar risk as pre-pubertal onset. In our study this was found in females only. In males the ESRD risk was increased also after puberty compared to onset of diabetes at 0-9 years of age. The group with age at onset at 10-19 years includes both pre-pubertal and post-pubertal cases which could dilute the actual effect of puberty, however, this group includes almost all with diabetes onset during the pubertal years.

Male sex has been reported to be a risk factor for development of diabetic nephropathy even though this relationship is not as strong as in non-diabetic renal diseases(12; 14). In this study males had an increased overall cumulative incidence of ESRD compared to females, but only in patients with age at onset of diabetes at 20 years or older. The higher male /female ratio of ESRD found in our study is further supported by data generated from the NDR (personal communication) showing that the mean prevalence of both micro- and macroalbuminuria was higher in men than in women in 2009; 15.6 vs. 11.6 % and 8.4 vs. 7.2 %, respectively.

The factors involved in this sex-specific difference could possibly include lifestyle, diet, kidney and glomerular size, differences in glomerular hemodynamics, and direct effects of sex-hormones(37; 38). When accounting for death as a competing risk event, males still had twice the risk of developing ESRD, however not statistically significant, which can be explained by the higher death rates in males. Experimental evidence from animal studies suggests that both estrogens and testosterone play a role in the development of renal disease(39), estrogens slow progression rate(40; 41) while testosterone exacerbates, and the absence of testosterone attenuates, the development of renal disease(42). The pattern of cumulative incidence by age and sex in the present study indicates different combinations of factors to play a role in post-pubertal development of ESRD and further studies are needed to confirm and understand these effects.

In conclusion, the cumulative incidence of ESRD in young patients with type 1 diabetes, with onset after 1977, is very low in Sweden. Pre-pubertal age at onset of diabetes seems to protect against, or prolong, the time to ESRD development, and the same may be true for post-pubertal onset in females (≥20 years at onset). The finding of a sex difference specifically in patients with diabetes onset after 20 is of clear interest and needs further exploration.

Author contributions: A.M. and M.S. researched data and wrote the manuscript. I.W. researched data and contributed to the manuscript. Y.B. reviewed/edited the manuscript. S.S., L.N. and H.A. supervised data collection and reviewed/edited the manuscript. G.D. supervised data collection and wrote the manuscript.

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### Table 1 – Number of patients with and without ESRD, median (range) time from diabetes onset to ESRD and number of deaths with and without ESRD, by age at diagnosis and sex, in patients with type 1 diabetes with at least 13 years duration.

| Age at diagnosis (years) | Number (%) | Median (range) time from diabetes onset to ESRD (years) | Number of deaths (%) | Number (%) | Median (range) time from diabetes onset to ESRD (years) | Number of deaths (%) |
|--------------------------|------------|--------------------------------------------------------|----------------------|------------|--------------------------------------------------------|----------------------|
|                          | Males      | With ESRD | Without ESRD | With ESRD | Without ESRD | With ESRD | Without ESRD | With ESRD | Without ESRD | With ESRD | Without ESRD | With ESRD | Without ESRD | With ESRD | Without ESRD |
| 0-9                      | 1984 (99.2)| 15 (0.8)  | 23.1 (18.2-26.2) | 23 (1.2)  | 4 (0.2)      | 1860 (99.4)| 11 (0.6) | 21.7 (16.2-27.8) | 10 (0.5) | 4 (0.2)      |
| 10-19                    | 2244 (98.2)| 41 (1.8)  | 20.8 (15.3-28.2) | 30 (1.3)  | 9 (0.4)      | 1796 (98.5)| 28 (1.5) | 18.9 (14.7-26.0) | 15 (0.8) | 5 (0.3)      |
| 20-34                    | 2267 (98.9)| 25 (1.1)  | 18.6 (13.7-24.8) | 86 (3.7)  | 10 (0.4)     | 1403 (99.5)| 7 (0.5)  | 17.9 (14.0-23.1) | 27 (1.9) | 1 (0.1)      |
| 0-34                     | 6495 (98.8)| 81 (1.2)  | 20.7 (13.7-28.2) | 139 (2.1) | 23 (0.3)     | 5059 (99.1)| 46 (0.9) | 19.5 (14.0-27.8) | 52 (1.0) | 10 (0.2)     |

### Table 2 – Incidence rates per 1000 person-years at six-year intervals of diabetes duration, 13-18, 19-24 and 25-30 years after diagnosis.

| Intervals of diabetes duration (years) | Males / Females 13-18 | Males / Females 19-24 | Males / Females 25-30 |
|---------------------------------------|------------------------|-----------------------|-----------------------|
| Age at diagnosis (years)              | Males / Females        | Males / Females       | Males / Females       |
| 0-9                                   | 0.1 (-0.1-0.3) / 0.2 (-0.1-0.5) | 1.9 (0.7-3.0) / 1.0 (0.1-1.9) | 2.8 (0.1-5.6) / 3.0 (0.1-5.9) |
| 10-19                                 | 1.0 (0.4-1.6) / 1.7 (0.8-2.6) | 4.3 (2.6-6.0) / 2.2 (0.8-3.6) | 4.6 (0.9-8.3) / 2.8 (-0.4-6.0) |
| 20-34                                 | 1.3 (0.6-2.0) / 0.8 (0.1-1.5) | 3.6 (1.6-5.6) / 0.9 (-0.4-2.2) | -                     |
| 0-34                                  | 0.8 (0.5-1.1) / 0.9 (0.5-1.3) | 3.2 (2.3-4.2) / 1.5 (0.8-2.2) | 3.7 (1.4-5.9) / 2.9 (0.8-5.1) |

95% confidence intervals in parenthesis.

### Table 3 – Cumulative incidences of ESRD, by age at onset and sex, at different diabetes durations.

| Duration of type 1 diabetes (years) | Males / Females 20 | Males / Females 25 | Males / Females 30 |
|------------------------------------|--------------------|--------------------|--------------------|
| Age at diagnosis (years)           | Males / Females    | Males / Females    | Males / Females    |
| 0-9                                | 0.1 (0.0-0.4) / 0.2 (0.1-0.7) | 1.4 (0.7-2.4) / 0.7 (0.3-1.4) | 2.3 (1.3-3.8) / 1.9 (0.9-3.6) |
| 10-19                              | 1.0 (0.6-1.7) / 1.3 (0.8-2.0) | 3.3 (2.3-4.6) / 2.4 (1.5-3.5) | 5.3 (3.5-7.5) / 3.2 (2.1-4.8) |
| 20-34                              | 1.0 (0.6-1.7) / 0.7 (0.3-1.5) | 6.1 (1.5-15.5) / 1.1 (0.4-2.5) | -                  |
| 0-34                               | 0.7 (0.5-1.0) / 0.7 (0.5-1.1) | 2.6 (2.0-3.3) / 1.4 (1.0-2.0) | 4.1 (3.1-5.3) / 2.5 (1.7-3.5) |

95% confidence intervals in parenthesis. The cumulative incidence is estimated using the Kaplan-Meier method and given as percent.
Table 4 – Cumulative incidences of ESRD with death as competing risk, by age at onset and sex, at different diabetes durations.

| Age at diagnosis (years) | Duration of type 1 diabetes (years) | 20 | 25 | 30 |
|--------------------------|-------------------------------------|----|----|----|
|                          | Males / Females                     |    |    |    |
| 0-9                      | 0.1 (0.0-0.4) / 0.2 (0.1-0.7)       |    |    |    |
| 10-19                    | 1.0 (0.6-1.6) / 1.3 (0.8-2.0)       |    |    |    |
| 20-34                    | 1.0 (0.6-1.7) / 0.7 (0.3-1.5)       |    |    |    |
| 0-34                     | 0.7 (0.5-1.0) / 0.7 (0.5-1.0)       |    |    |    |

95% confidence intervals in parentheses. The cumulative incidence with death as a competing risk takes into account that death is an event competing with the risk to develop ESRD.

Figure 1 – Cumulative incidences of developing ESRD in male and female patients with type 1 diabetes onset at 0-9, 10-19 and 20-34 years.
For patients with diabetes onset before 10 or 10-19 years of age there is no significant difference between males and females, $P=0.53$ and $P=0.50$, but with onset at 20-34 years there is a difference, borderline significant, between males and females in risk of developing ESRD, $P=0.05$. 
Figure 2 – Cumulative incidences of developing ESRD in male and female patients according to age at onset of type 1 diabetes.

When using age at onset 0-9 years as reference the risk of ESRD is significantly increased with age at onset 10-19 years and 20-34 years for males. For females the risk is significantly increased with age at onset 10-19 years, but not 20-34 years.