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Microalbuminuria and retinopathy in adolescents and young adults with type 1 and type 2 diabetes

Anna E. Ek^{1,2}  | Ulf Samuelsson³ | Annika Janson^{2,4,5} | Annelie Carlsson⁶ |
Amira Elimam^{1,2} | Claude Marcus¹

¹Division of Pediatrics, Department of Clinical Science, Intervention, and Technology, Karolinska Institute, Stockholm, Sweden

²Pediatric Endocrinology and Metabolic Diseases, Karolinska University Hospital, Stockholm, Sweden

³Division of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

⁴National Childhood Obesity Centre, Karolinska University Hospital, Stockholm, Sweden

⁵Division of Pediatric Endocrinology, Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

⁶Pediatrics, Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden

Correspondence

Anna E. Ek, Division of Pediatrics, Department of Clinical Science, Intervention, and Technology, Blickagången 6A Novum, Karolinska Institutet Karolinska University Hospital Huddinge, SE-141 57 Stockholm, Sweden.
Email: anna.ek.1@ki.se

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Abstract

Aim: To estimate the occurrence of complications related to early-onset type 2 diabetes compared with type 1 diabetes.

Methods: All individuals registered in the Swedish Pediatric Quality Diabetes Register and the Swedish National Diabetes Register with type 2 diabetes diagnosis at 10 to 25 years of age between 1996 and 2014 ($n = 1413$) were included. As controls, individuals with type 1 diabetes were randomly selected from the same registers and were matched for age, sex, and year-of-onset ($n = 3748$).

Results: Of the adolescents with type 2 diabetes in the pediatric register, 7.7% had microalbuminuria and 24.6% had signs of retinopathy 5 years after diagnosis, whereas the adolescents with type 1 diabetes 3.8% had microalbuminuria and 19.2% had retinopathy. Among the young adults with type 2 diabetes from the adult diabetes register 10 years after diagnosis 15.2% had microalbuminuria and 39.7% retinopathy, whereas the young adults with type 1 diabetes 4.8% had microalbuminuria and 43.8% retinopathy. After adjustment for established risk factors measured over time in the whole combined cohort, individuals with type 2 diabetes had significantly higher risk of microalbuminuria with a hazard ratio (HR) of 3.32 (95% confidence interval, CI 2.86-3.85, $P < .001$), and retinopathy with a HR of 1.17 (95% CI 1.06-1.30, $P 0.04$).

Conclusions: The prevalence of complications and comorbidities was higher among those with type 2 diabetes compared with type 1 diabetes, although prevalent in both groups. Early monitoring and more active treatment of type 2 diabetes in young individuals is required.

KEYWORDS

adolescents, microalbuminuria, retinopathy, type 2 diabetes

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1 | INTRODUCTION

The prevalence of type 2 diabetes among children and adolescents is increasing in several parts of the world. In the United States, the overall incidence of type 2 diabetes in youth has increased from 9 to 12.5 cases per 100 000 youth per year from 2002-2003 to 2011-2012.^{1,2} Large international variations of prediabetes and type 2 diabetes are apparent, with higher rates among certain ethnicities and populations, and the lowest incidence rate and prevalence in European countries. Austria have reported among the lowest incidence rates with 0.29 per 100 000 person-years,³ compared with the highest incidence rates among Pima Indians in the United States with 330 per 100 000 person-years.⁴ In Germany, the prevalence of type 2 diabetes in children is low with a prevalence rate of 2.42 per 100.000 youth under 20 years of age, and has remained unchanged over the past decade.^{5,6} The differences in prevalence and incidence are caused by both population characteristics and methodological differences,⁷ which make comparisons between countries rather difficult. The prevalence of early-onset type 2 diabetes in Sweden is not fully known, the overall incidence rate of diabetes was estimated in Kronoberg region in the south of Sweden between 1998 and 2001, and among children 0 to 19 years of age the incidence rate for type 2 diabetes was 3.1 per 100 000 person-years.⁸ Previous screening studies in Sweden have found no cases of silent type 2 diabetes in healthy school children 11 to 13 years of age, nor in children with severe obesity treated at obesity clinic.^{9,10} In contrast the prevalence of prediabetes is observed to be rather high among obese children in Sweden, three times higher than in a cohort of obese children in Germany.^{10,11} Impaired fasting glucose among obese Swedish children has an association with the development of type 2 diabetes in young adulthood and there are also indications of a rapid increase in type 2 diabetes in young adults.¹²

Individuals with early-onset type 2 diabetes have a worse risk factor profile at diagnosis, and the disease seems to be more progressive and pathogenic the earlier the onset of type 2 diabetes.¹³⁻¹⁷ The pattern of complications is similar for both type 1 and type 2 diabetes, both are associated with an increased risk of micro- and macrovascular complications,^{13,17,18} although recent studies have suggested that young adults with type 2 diabetes onset below 30 years of age have a higher metabolic risk compared with young adults with type 1 diabetes in both Australia and United States.^{14,19}

Given those findings, this study was designed to estimate the incidence of reported cases of type 2 diabetes among adolescents and young adults in Sweden and to evaluate the risk of developing complications related to early-onset type 2 diabetes, such as microalbuminuria and retinopathy, among adolescents and young adults with type 2 diabetes, as compared to patients with type 1 diabetes.

2 | RESEARCH DESIGN AND METHOD

We used data from two National Diabetes Quality Registries; the Swedish Pediatric Diabetes Quality Registry (SWEDIABKIDS) and the Swedish National Diabetes Register (NDR) from 1996 until 2014.

2.1 | Data sources

2.1.1 | The Swedish Pediatric Quality Registry, SWEDIABKIDS

The SWEDIABKIDS (SWE) database was established in 2000 as a Swedish national clinical quality register that aims to support and monitor diabetes care in children. Outpatient attendance data from all Swedish pediatric diabetes centers are registered in SWE, and from 2007 all Swedish pediatric diabetes centers ($n = 43$) report to the register and include data on almost all (approximately 99%) children and adolescents with diabetes in Sweden.²⁰ In Sweden, pediatric diabetes centers treat all children aged 0 to 18 years with diabetes of all types within their area. According to Swedish guidelines, which are based on ISPAD guidelines, children with diabetes visit a pediatric diabetes center at least four times annually and patient clinical data are reported into the SWE by trained nurses or physician^{21,22} (<http://www.ndr.nu/SWE>).

2.1.2 | The Swedish National Diabetes Register, NDR

The Swedish National Diabetes Register (NDR) was initiated in 1996 as a nationwide clinical quality register for monitoring and supporting diabetes care in Sweden, it includes patients with diabetes (both type 1 and 2) aged >18 years. As with SWE, more and more clinics have over the years commenced participating in the NDR and in 2012 more than 90% of all adult patients with diabetes were included.^{23,24} The data is collected by trained nurses and physicians and include information obtained in primary care and hospital outpatient clinics. Patient data is either continuously reported approximately annually via electronic patient clinical records or registered directly into the NDR, and it contains clinical data on about 90% of all adults with type 1 or 2 diabetes in Sweden (NDR year report 2019, <https://www.ndr.nu>).

Both SWE and the NDR are financially supported by the association of Local Authorities and Regions, SALAR, which represents the governmental, professional, and employer-related interests of Sweden's municipalities, country councils, and regions and the data is continuously validated.^{25,26} None of the registries collect data on ethnicity, socioeconomic status, or educational level. Each patient provides informed consent (verbal or written) before participation in the registers. The study was designed by two of the authors (A.E.E., C.M.) and ethical approval to conduct this study was approved by the Regional Ethics Committee in Stockholm, Sweden.

2.1.3 | Study population

Adolescents and young adults aged 10 to 25 years with newly diagnosed type 2 diabetes between 1996 until 2014 were identified in the SWEDIABKIDS and the NDR. At baseline, defined as the first entry in the SWE or NDR, each patient with type 2 diabetes was

matched for age, sex, and year-of-onset with approximately four individuals with type 1 diabetes who were randomly selected from the SWE/NDR. Type 2 diabetes was defined by the reporting physician, in Sweden the World Health Organization (WHO) diagnostic criteria is used to diagnose diabetes,²⁷ aided by determination of C-peptide, autoantibodies, and fasting levels of insulin that is part of standard care in Sweden.²⁸ Eight patients changed diagnosis when referred from the childhood register (SWE) to the register for adults (NDR) and they were subsequently excluded due to risk of misclassification. A subset of patients was not included in analysis of incidence but were analyzed for outcome measures in the multivariable analysis, since they were diagnosed with diabetes before SWE started in 2000

(n = 165). A flowchart depicting included and excluded participants is shown in Figure 1.

Since the data is collected from two separate registers, the details from the separate registers are further described below.

2.1.4 | Adolescents from SWE

Data on all patients diagnosed with type 2 diabetes with an age of 10 to 17.9 years at onset of diabetes, with at least one entry in SWE between 1 January 2000 until 31 December 2014, were obtained from the register and included in the study. One hundred fifty-three

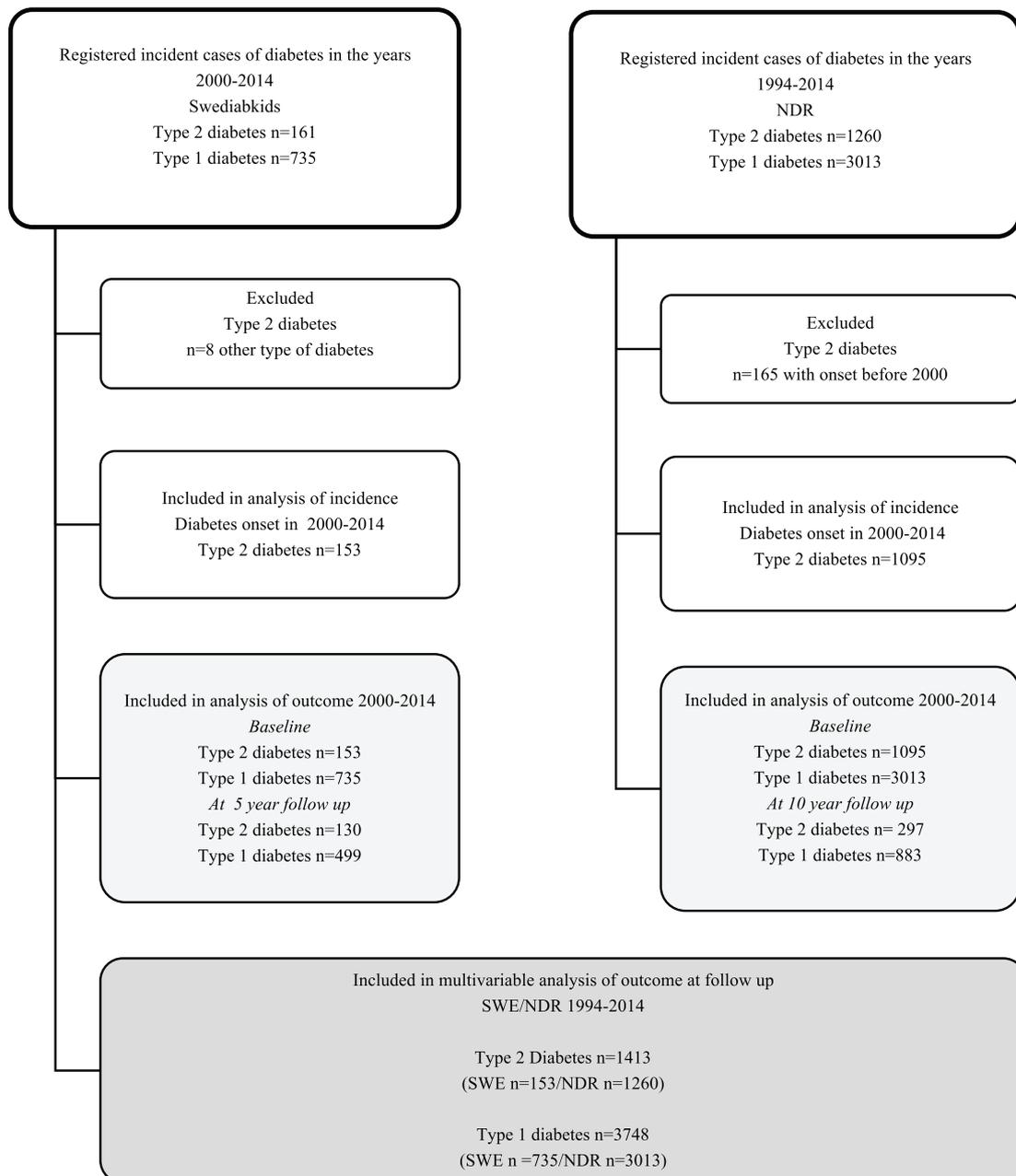


FIGURE 1 Flow chart of analyses of adolescents and young adults with diabetes registered in SWEDIABKIDS and the National Diabetes Register

patients with type 2 diabetes were reported during this time period, and 735 age, sex, and diabetes duration-matched patients with type 1 diabetes were found and will, for simplicity, be referred to as adolescents although a small number still are children. The adolescents with type 2 diabetes from SWE and the age-matched patients with type 1 diabetes with available data at follow up at 5 years of follow up, were analyzed for the outcomes.

2.1.5 | Young adults from NDR

Data on all patients diagnosed with type 2 diabetes aged 18 to 25 years at onset of diabetes, with at least one entry in NDR from 1 January 1996 until 31 December 2014 were included in the study. About 1260 patients with type 2 diabetes were reported during this time period, and 3013 matched patients with type 1 diabetes were found and will all be referred to as young adults.

The young adults with type 2 diabetes from NDR and the age-matched patients with type 1 diabetes with available data at follow up at 10 years of follow up, were analyzed for the outcomes.

2.1.6 | Combined cohort

We constructed one cohort out of the two cohorts from SWE and NDR. During the years 1996 to 2014, 1421 patients with type 2 diabetes with an age of 10 to 25 years at diabetes onset were reported in the registers combined, and 3748 patients with type 1 diabetes with a similar age of onset were identified. Since eight patients changed diagnose in transition from SWE to NDR, 1413 individuals with type 2 diabetes were therefore analyzed in the main cohort. All patients together from both registers had a median time to follow up of 3.5 years (range 0-14 years, mean 4 years). Thus, we studied individuals who were enrolled in SWE and NDR in the same year they were diagnosed with diabetes and we followed them for up to 14 years, but with varying time to follow up due to different year of diabetes onset. Outcome measures for all with available data at follow up were analyzed. Our final cohort consisted of 5161 individuals contributing to 40 663 observations. From both registers we have collected data on diabetes type, hemoglobin A1c (HbA1c), weight, height, body mass index (BMI), age at onset, gender, diabetes duration, systolic and diastolic blood pressure, micro- and macro-albuminuria, results from retinal photograph, and type of treatment from all registered outpatient visits from diagnosis until December 2014.

2.1.7 | HbA1c analysis and clinical parameters

All laboratory methods used in Sweden are standardized through the External Quality Assurance in Laboratory Medicine in Sweden (EQUALIS). The data on HbA1c was derived from capillary blood samples taken in connection with visits to the diabetes center or primary care health care center and analyzed with Bayer/Siemens DCA-2000

or using local laboratory methods and presented as HbA1c Mono S (%) method and converted to mmol/mol according to International Federation of Clinical Chemistry (IFCC). The IFCC reference method has been adopted in Sweden, and HbA1c levels will be presented as IFCC (mmol/mol). Body mass index was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Overweight and obesity was defined by international age- and gender-specific BMI cut-offs, corresponding to adult BMI cut-offs of 25 and 30 kg/m^2 at 18 years of age (ISO-BMI ≥ 25 and ISO-BMI ≥ 30).²⁹ Systolic and diastolic blood pressure were measured in mm Hg.

2.2 | Outcome measures

2.2.1 | Diabetic kidney disease

Microalbuminuria was defined as two positive results out of three samples obtained within 1 year, measured with the use of urinary albumin-to-creatinine ratio (ACR) ≥ 3.5 mg/mmol (in SI units which corresponds to >30 mg/g) in a spot urine collection.^{30,31}

2.2.2 | Diabetic retinopathy

Retinal status is assessed locally, that is, through fundus photography performed by ophthalmologist and reported to the register. Retinopathy was categorized as "yes" or "no," stage of retinopathy was not reported in the registry.

2.2.3 | Hypertension

Hypertension was defined as blood pressure levels 95th or greater centile for age (<18 years), 140/90 mm Hg or higher (>18 years), or documented use of antihypertensive therapy.³²

2.3 | Statistical methods

Descriptive analyses calculated the mean \pm SD for continuous variables and the number and percentage for categorical variables. When analyzing differences between the two independent groups the Student *t* test, the Mann-Whitney *U* (for non-parametric ordinal data), and χ^2 test (for differences in frequencies of complications) were used. A sensitivity analysis, receiver operating characteristic (ROC) curve, on the variables BMI, HbA1c, and blood pressure was made to explore the associations with the outcomes; microalbuminuria and retinopathy. The Kaplan-Meier analysis was used to calculate probability of complication-free survival, and differences between groups were tested by the log-rank test. A Cox regression analysis was used to assess the influence of different variables on the occurrence of complications. To understand which factors were associated with the risk of outcome, hazard ratios, and 95% CIs for the associations

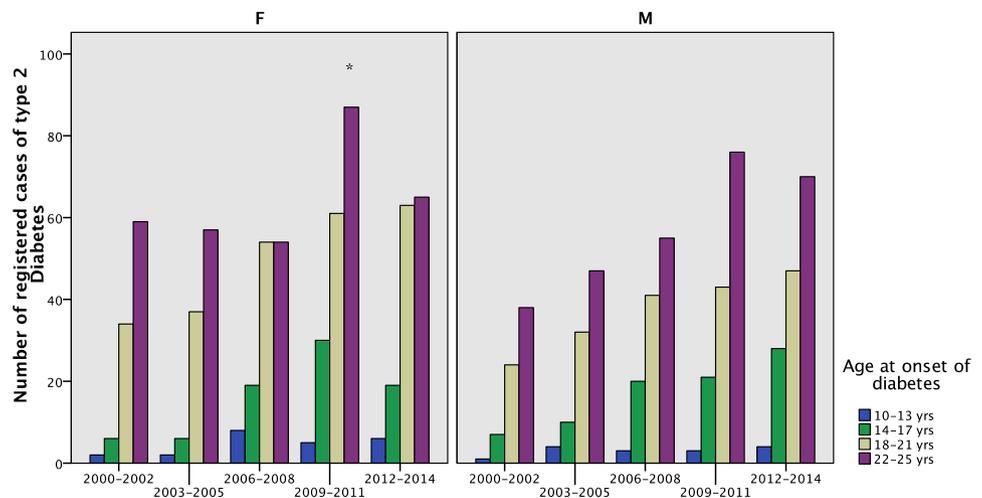
between diabetes type and each outcome were computed in sequentially adjusted models. A base model was adjusted for age, gender, and time from diagnosis was constructed and additional models explored whether adjustment of the individual covariates reduced the strength of associations: HbA1c, BMI, and systolic and diastolic blood pressure. The significance of explanatory variables in the final multivariable models are expressed as hazard ratios (HRs) and 95% CIs. All analyses used two-sided $P < .05$ as statistically significant. Goodness of fit was tested by log-likelihood. All analyses were performed with IBM SPSS 23.0 and 25.0 for MacOS (SPSS Inc, Chicago, Illinois).

3 | RESULTS

3.1 | Annual change in type 2 diabetes incidence

The frequencies of newly reported patients with type 2 diabetes are shown in Figure 2, from the year 2000 when SWE was started as a registry. Between 2000 and 2014, $n = 1248$ patients with type 2 diabetes were registered in SWE and NDR together, 675 females and 573 males. The number of patients registered increased significantly every year, except for 2014, due to not fully covered registration since data was retrieved from the registries in 2014. The adolescents with type 2 diabetes had a median time of follow up of 6.7 ± 2.8 years, and the age-matched patients with type 1 diabetes had 5.5 ± 1.5 years. The young adults with type 2 diabetes and the age-matched patients with type 1 diabetes from the NDR with available data at follow up had a median time of follow up of 10.3 ± 1.1 years.

FIGURE 2 Frequencies of reported cases of type 2 diabetes in SWE and NDR, with an age of onset of 10 to 25 years, between 2000 and 2014. Females and males are displayed in separate histograms and the age at onset of diabetes is displayed in separate boxes. The column proportions differ significantly from each other, with an increasing number of reported cases ($P = .043$)* especially among females 14 to 17 and also 22 to 25 of age at onset of diabetes ($P = .034$)*, differences in frequencies are tested with Pearson chi-square. **Fifty-one individuals in NDR had a reported year of onset of diabetes just before 18 years of age; in NDR the year of onset is reported, not the date of onset. Data withdrawn from SWE/NDR in 2014, registration is probably lacking in 2014 due to not fully covered registration since data was withdrawn from the registries in 2014



3.2 | Clinical characteristics at baseline and follow up

Table 1 shows the baseline characteristics where both the adolescents and young adults with type 2 diabetes had a higher average BMI with a distribution of more overweight and obesity and a higher blood pressure at diabetes onset compared with the adolescents with type 1 diabetes. The adolescents with type 2 diabetes had a lower HbA1c at diagnosis compared with type 1 diabetes adolescents, although the degree of missing data was higher among the individuals with type 1 diabetes. In contrast from the adolescents, the young adults had similar HbA1c levels at onset irrespective of diabetes type. Data on treatment at baseline, that is, the first registration, show that the number of individuals with type 2 diabetes who had a treatment of diet only were higher among the young adults.

Table 2 shows the characteristics at follow up by diabetes type and age group. The adolescents with type 2 diabetes were more overweight or obese, had lower HbA1c and fewer visits; 2.8 visits per year compared with 4.1 visits per year for the adolescents with type 1 diabetes. At follow up, 24.6% of the adolescents with type 2 diabetes had signs of retinopathy and 7.7% had microalbuminuria. Despite higher HbA1c, the prevalence of complications was significantly lower among the adolescents with type 1 diabetes, 19.2% had retinopathy and 3.8% had microalbuminuria. The young adults with type 2 diabetes were more overweight or obese, had hypertension and microalbuminuria to a higher degree than the patients with type 1 diabetes. At follow up, 15.2% of the young adults with type 2 diabetes had microalbuminuria whereas 4.8% of the patients with type 1 diabetes had microalbuminuria. Neither HbA1c, number of visits nor

TABLE 1 Comparisons of clinical characteristics at first registration in adolescents and young adults with type 1 and 2 diabetes

	Adolescents with diabetes diagnosis at 10 to 7.9 years of age (SWEDIABKIDS)			Young adults with diabetes diagnosis at 18 to 25 years of age (NDR)		
	Type 1 diabetes	Type 2 diabetes	P-value	Type 1 diabetes	Type 2 diabetes	P-value
Baseline visit registered 2000-2014, n	735	153		3013	1095	
Female, n (%)	352 (48.2)	79 (51)	0.360	1317 (43.7)	596 (54.4)	<0.001
Age at diabetes onset (years)	14.8 ± 1.9	15.0 ± 1.9	0.139	20.9 ± 2.2	21.9 ± 2.2	0.631
BMI (kg/m ²)	21.0 ± 3.9	34.1 ± 7.5	<0.001	23.9 ± 4.2	34.4 ± 7.7	<0.001
ISO BMI, n	444/97/18/176	9/21/97/26	<0.001	1550/532/191/740	94/159/593/249	<0.001
Nw/ow/obese/unknown (%)	(60.4/13.2/2.4/23.9)	(5.8/13.6/63/17)		(51.4/17.7/6.3/24.6)	(8.6/14.5/54.2/22.7)	
HbA1c % (mmol/mol)	8.4 (68 ± 24)	6.9 (52 ± 14)	<0.001	7.6 (60 ± 21)	7.5 (58 ± 21)	0.203
Missing, n (%)	265 (35.5)	35 (22.9)		315 (10.5)	130 (11.9)	
Systolic blood pressure (mm Hg)	114.7 ± 11.5	122.7 ± 12.9	<0.001	118.1 ± 11.5	124.4 ± 13.5	<0.001
Diastolic blood pressure (mm Hg)	66.4 ± 8.9	74.1 ± 9.2	<0.001	71.2 ± 8.7	76.1 ± 9.9	<0.001
Missing, n (%)	566 (77)	91 (59.5)		543 (18.0)	195 (17.8)	
Treatment at onset, n (%)						
Diet only	-	11 (7.2)		-	316 (28.9)	
Oral medication only	-	59 (38.6)		34 (1.1)	457 (41.7)	
Insulin only	480 (65.3)	27 (17.6)		2658 (88.2)	145 (13.2)	
Insulin and oral medication	-	18 (11.8)		41 (1.4)	137 (12.5)	
GLP-1 and/or combined treatment						
Missing, n (%)	-	-		1 (0.1)	5 (0.4)	
	255 (34.7)	38 (24.8)		102 (3.4)	36 (3.3)	

Note: Values are displayed as mean ± SD in continuous variables and as frequencies (%) in categorical variables. P-values are derived from t test, ANOVA or Mann-W U test for continuous variables and χ^2 for categorical variables.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA1c, hemoglobin A1c. ISO-BMI as levels of obesity according to Cole. GLP-1, Glucagon-like peptide 1 agonist.

prevalence of retinopathy at follow up were significantly different among type 2 adults as the matched individuals with type 1 diabetes.

3.3 | Association between outcomes and variables

Figure 3 displays in a ROC curve the association between the variables BMI, systolic, and diastolic blood pressure, and HbA1c and the two separate outcomes microalbuminuria and retinopathy. BMI had the strongest association with microalbuminuria in both types of diabetes, and HbA1c had the strongest association with retinopathy in both types of diabetes.

3.4 | Association model for type 2 diabetes and outcomes

Table 3 includes sequentially adjusted models for the associations of diabetes type and each outcome to determine which risk factors contributed to the higher risk among those with type 2 diabetes vs type

1. The base model was adjusted for age, sex, and diabetes duration and showed significantly higher rates of microalbuminuria in type 2 diabetes, with further adjustment for HbA1c, BMI, and blood pressure the association was slightly weaker but still significant. The base model for the risk of retinopathy showed a small but significant increased risk associated with type 2 diabetes. In an analysis stratified for sex, the hazard for complications significantly increased in males both for microalbuminuria and retinopathy, whereas the risk of retinopathy was lower in females with type 2 diabetes compared with type 1 diabetes.

3.5 | Association model for the two separate diabetes types and outcomes

Table 4 shows the clinical and biochemical characteristics associated with the development of complications separately for the different diabetes types. Despite that the effect size is small, it reveals different risk patterns for the two diabetes types and also gender differences. The development of microalbuminuria in type 2 diabetes is associated

TABLE 2 Comparisons of clinical characteristics at follow up in two cohorts of adolescents and young adults with type 1 and 2 diabetes

	Five years follow up of adolescents with diabetes diagnosis at 10-17.9 years of age (SWEDIABKIDS)			10 years follow up in young adults with diabetes diagnosis at 18-25 years of age (NDR)		
	Type 1 diabetes	Type 2 diabetes	P-value	Type 1 diabetes	Type 2 diabetes	P-value
Evaluated at follow up, n	499	130		883	297	
Female, n (%)	241 (48.3)	68 (52.3)	<0.001	407 (46.1)	177 (59.6)	<0.001
Age (years)	21.3 ± 4.0	22.2 ± 3.7	0.02	32.2 ± 2.2	32.7 ± 2.0	0.465
Diabetes duration (years)	5.5 ± 1.5	6.7 ± 2.8	0.036	10.3 ± 1.1	10.3 ± 1.1	0.911
No. of registrations/year	4.1 ± 3.6	2.8 ± 3.3	<0.001	1.2 ± 1.2	1.3 ± 1.9	0.081
BMI (kg/m ²)	23.9 ± 3.8	32.7 ± 7.5	<0.001	26.0 ± 4.4	32.1 ± 6.6	<0.001
ISO BMI, n (%)	280/113/27/79	11/28/60/31	<0.001	336/281/112/154	30/69/142/56	<0.001
Nw/ow/obese/unknown	(56.1/22.6/5.4/15.8)	(8.5/21.5/46.2/23.8)	<0.001	(38.1/31.8/12.7/17.4)	(10.1/23.2/47.8/18.9)	<0.001
HbA1c % (mmol/mol)	8.2 (66 ± 18)	7.5 (59 ± 22)	<0.001	7.9 (63 ± 14)	7.8 (62 ± 19)	0.583
Systolic blood pressure > 95th percentile (%)	24/328 (7.3)	12/91 (13.2)	0.077	39/799 (4.9)	39/253 (15.4)	<0.001
Diastolic blood pressure > 95th percentile (%)	8/328 (2.4)	9/91 (9.9)	<0.001	35/799 (4.4)	32/253 (12.6)	<0.001
Retinopathy, n (%)	85/442 (19.2)	32/103 (24.6)	0.008	373/851 (43.8)	98/247 (39.7)	0.273
Microalbuminuria, n (%)	16/416 (3.8)	10/113 (7.7)	0.029	42/883 (4.8)	45/297 (15.2)	<0.001
Treatment at follow up, n (%)						
Diet only	-	23 (17.7)		5 (0.6)	38 (12.8)	
Oral medication only	-	49 (37.7)		1 (0.1)	100 (33.7)	
Insulin only	469 (94)	23 (17.9)		852 (96.5)	72 (24.2)	
Insulin and oral medication	2 (0.4)	22 (16.9)		16 (1.8)	80 (26.9)	
GLP-1 and/or combined treatment	-	9 (6.9)		1 (0.1)	3 (0.8)	
Missing, n (%)	28 (5.6)	4 (3.1)		8 (0.9)	4 (1.3)	

Note: Values are displayed as mean ± SD in continuous variables and as frequencies (%) in categorical variables. *p*-values are derived from *t* test, ANOVA or Mann-W *U* test for continuous variables and χ^2 for categorical variables.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA1c, hemoglobin A1c. ISO-BMI as levels of obesity according to Cole. GLP-1, Glucagon-like peptide 1 agonist.

with; male sex, BMI, systolic blood pressure and a significant but small association with HbA1c levels. Development of retinopathy in type 2 diabetes was associated with male sex, higher levels of HbA1c and higher systolic and diastolic blood pressure. In type 1 diabetes the development of microalbuminuria was associated with female sex and HbA1c levels. The development of retinopathy in type 1 diabetes was associated with female sex, BMI, HbA1c, and higher diastolic blood pressure.

3.6 | Kaplan-Meier curve of overall event-free probability

The probability of microalbuminuria-free cumulative survival, that is, developing signs of nephropathy related to diabetes duration, is

displayed in Figure 4A. Signs of diabetes related microalbuminuria occurs earlier ($P < .001$) in diabetes type 2 compared with type 1 diabetes. The probability of retinopathy-free cumulative survival is displayed in Figure 4B. Retinopathy occurred earlier in type 2 diabetes ($P = .029$) compared with type 1 diabetes, but there is no clinically relevant difference in time to event.

4 | DISCUSSION

In this population-based study with information from two national databases of diabetes in Sweden, SWE, and NDR, we found a successive increase in the number of reported cases of type 2 diabetes among adolescents and young adults from 2000 to 2014. The young patients were followed from diagnosis with repeated measures of risk

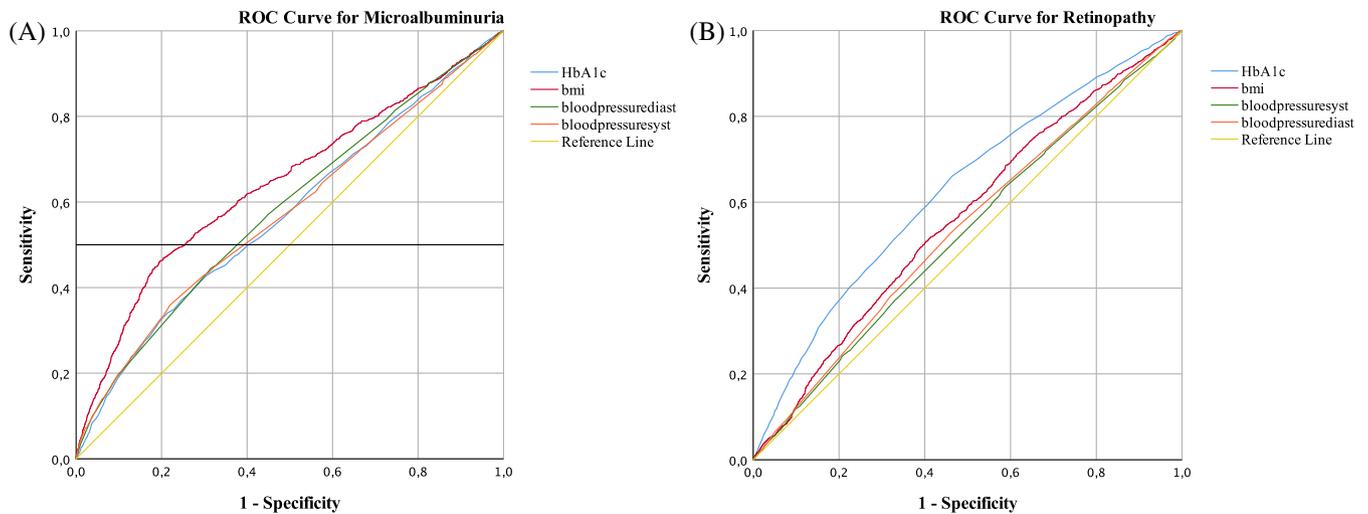


FIGURE 3 ROC curves for the association between variables and outcomes microalbuminuria and retinopathy in both type 1 and 2 diabetes

TABLE 3 Cox proportional hazard for the association between type 2 (vs 1) diabetes and outcomes

Outcome	No. of events/ no. of measurements	Model 1: Base	Model 2: 1 + BMI	Model 3: 1 + HbA1c	Model 4: 1 + BMI and HbA1c	Model 5: 1 + BMI, HbA1c and systolic and diastolic BP
All						
Microalbuminuria	986/16861					
HR (95% CI)		3.99 (3.49-4.36)	3.29 (2.80-3.85)	3.87 (3.45-4.34)	3.35 (2.91-3.86)	3.32 (2.86-3.85)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
Retinopathy	2428/14739					
HR (95% CI)		1.24 (1.14-1.35)	1.11 (1.00-1.23)	1.27 (1.17-1.39)	1.16 (1.04-1.28)	1.17 (1.06-1.30)
P-value		<0.001	0.045	<0.001	0.006	0.04
Males^a						
Microalbuminuria	460/8941					
HR (95% CI)		5.49 (4.68-6.24)	4.99 (4.10-6.07)	5.26 (4.67-6.20)	4.90 (4.01-5.98)	4.92 (3.99-6.07)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
Retinopathy	1236/7863					
HR (95% CI)		1.59 (1.42-1.78)	1.64 (1.43-1.88)	1.51 (1.34-1.70)	1.63 (1.41-1.87)	1.64 (1.42-1.89)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
Females^a						
Microalbuminuria	516/7800					
HR (95% CI)		2.89 (2.48-3.37)	2.24 (1.84-2.72)	2.38 (1.95-2.91)	2.47 (1.97-3.09)	2.36 (1.91-2.91)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001
Retinopathy	1158/6752					
HR (95% CI)		0.97 (0.83-1.1)	0.73 (0.62-0.85)	1.06 (0.94-1.21)	0.87 (0.67-0.81)	0.80 (0.68-0.95)
P-value		0.676	<0.001	0.323	0.002	0.008

Note: Base model adjusted for age, sex and diabetes duration. Goodness of fit was tested with quasi likelihood under independence criterion, and a *P*-value of <.05 for the model indicates good fit.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio.

^aSex was not included in models for the separate sexes.

factors and complications over time during 5 to 10 years, and 15% of individuals with type 2 diabetes had microalbuminuria and almost 40% developed retinopathy. The patients with type 2 diabetes

developed microalbuminuria earlier and also more frequently compared with the age-, sex-, and years-of-onset-matched patients with type 1 diabetes. Similar patterns have previously been demonstrated

TABLE 4 Cox proportional hazard analysis of clinical and biochemical characteristics that predict development of complications in the different diabetes types

	Type 1 diabetes			Type 2 diabetes		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Microalbuminuria						
Sex (male vs female)	0.620	0.517-0.743	<0.001	1.276	1.06-1.54	0.012
Age at onset	0.894	0.865-0.925	<0.001	0.988	0.947-1.030	0.560
BMI (kg/m ²)	1.001	0.982-1.020	0.898	1.025	1.012-1.039	<0.001
HbA1c (mmol/mol)	1.013	1.008-1.019	<0.001	1.005	1.001-1.010	0.028
Systolic blood pressure (mm Hg)	1.009	0.999-1.018	0.073	1.015	1.004-1.0017	<0.001
Diastolic blood pressure (mm Hg)	0.999	0.987-1.011	0.881	1.000	0.989-1.012	0.954
Retinopathy						
Sex (male vs female)	0.819	0.745-0.901	<0.001	1.443	1.211-1.718	<0.001
Age at onset	0.980	0.960-0.999	0.041	1.005	0.968-1.043	0.800
BMI	1.013	1.003-1.022	0.012	1.004	0.991-1.017	0.570
HbA1c	1.016	1.013-1.019	<0.001	1.009	1.005-1.013	<0.001
Systolic blood pressure	1.004	0.999-1.009	0.147	1.008	1.001-1.016	0.034
Diastolic blood pressure	0.991	0.984-0.997	0.004	0.980	0.970-0.991	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin A1c, HR, hazard ratio.

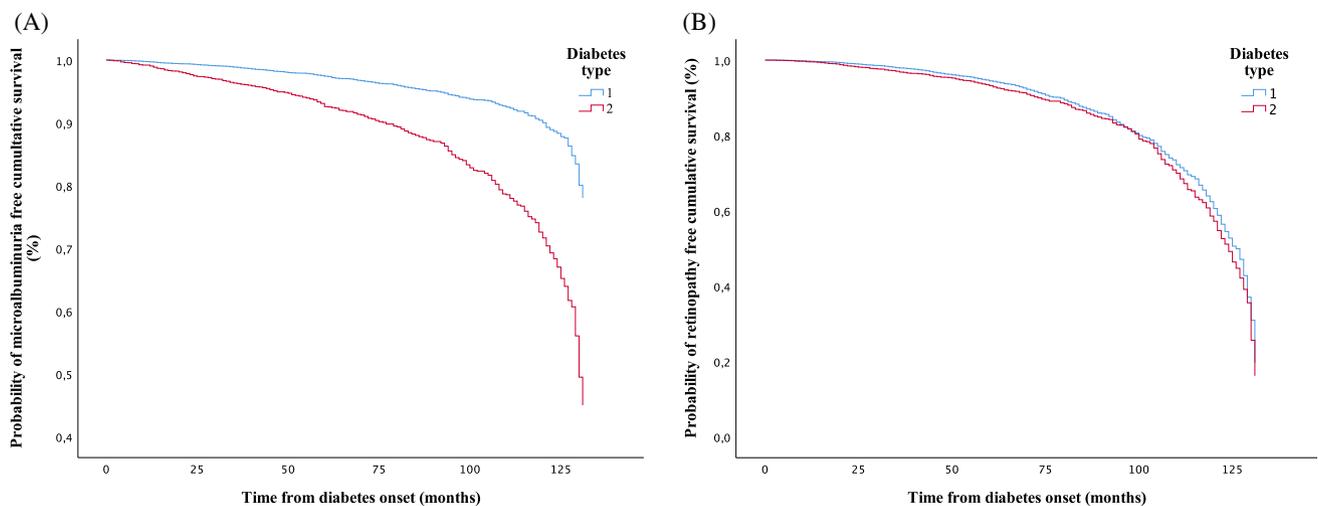


FIGURE 4 A, Kaplan-Meier survival curve displaying the probability of microalbuminuria free survival in type 1 and 2 diabetes at means of the covariates age, HbA1c, BMI, and blood pressure. Mean time to event in type 1 diabetes 123 months (with a 95% CI 122-124 months) and in type 2 diabetes 108 months (with a 95% CI 107-110 months). Log rank test showed significant differences between type 1 and 2 diabetes with a *P*-value of <0.001. B, Kaplan-Meier survival curve displaying the probability of retinopathy free survival in type 1 and 2 diabetes at means of covariates age, HbA1c, BMI, and blood pressure, cumulative hazard of developing signs of diabetes retinopathy in type 1 and 2 diabetes. Mean time to event in type 1 diabetes 113 months (with a 95% CI of 112-113 months) and in type 2 diabetes 108 months (with a 95% CI 109-112 months). Log rank test showed significant differences between type 1 and 2 diabetes with a *P*-value of 0.029

in other cultural settings as United States and Australia,^{13,14,16,19,33} and we can now confirm the same situation in Sweden. In the present study, the adolescents with type 2 diabetes were more frequently obese compared with the young adults and showed more signs of comorbidity. Despite lower HbA1c levels among the youngest patients with type 2 diabetes at follow up compared with type 1 diabetes, the presence of microalbuminuria was higher among the

adolescents and also young adults with type 2 diabetes. These findings, that are consistent with a report from a small number of type 2 diabetes patients from Australia,¹⁶ indicates that other factors than HbA1c levels are of importance for the risk of developing complications among young individuals with type 2 diabetes. We also found a small but significant difference in prevalence of retinopathy between type 1 and 2 diabetes, which is in accordance with some,¹⁴ but not all

previous studies.³⁴ Recently it has been suggested that type 2 diabetes can be divided into clusters with different clinical pictures and with different genetic patterns.³⁵ Our results suggest that type 2 diabetes onset in an early age is more progressive and pathogenic disease than type 1 diabetes and also more aggressive than type 2 diabetes later in life which is in accordance with previous studies.^{15,36} It is unclear to which extent children with type 2 diabetes develop a more aggressive type 2 diabetes due to their age or if young individuals primarily are to be found in a genetic cluster with a more severe type of diabetes. The multivariable analyses showed that in addition to the type 2 diabetes diagnosis; BMI, HbA1c, and systolic blood pressure were associated with the development of microalbuminuria but most probably other factors not measured in this study also contribute. There was a markedly higher prevalence of both microalbuminuria and retinopathy in males compared with females with type 2 diabetes, despite same degree of obesity, this is in accordance with a few earlier studies that suggests that men are more at risk for microvascular complications compared with women.³⁷⁻³⁹ It is well known that intensive treatment and frequent follow ups delays the onset of long-term complications in both type 1 and 2 diabetes.⁴⁰⁻⁴² The fundamental treatment of type 2 diabetes is diet and physical exercise, and to achieve effective weight treatment, several studies have shown that early and intensive lifestyle treatment with frequent contact and support from the health care providers is required.⁴³⁻⁴⁵ In the present study, adolescents with type 2 diabetes had fewer visits compared with the patients with type 1 diabetes, and we can also suspect that some are lost to follow up. The majority of the patients required pharmacological therapies, and this reflects the challenge for medical care to encourage and maintain changes of lifestyle.

This study has several strengths. The study population was drawn from two population-based quality registries of diabetes in Sweden and has clinical characteristics similar to those of the overall population from which it draws. The risk factors were measured longitudinally, with repeated measurements over time, during a long time in real-life diabetes management. However, this study has some limitations. First, the classification of diabetes type in the registers is based by the physician's opinion and experience, and although routine check-up at diabetes diagnosis in Sweden includes testing of autoantibodies and C-peptide according to ISPAD guidelines,²⁸ we cannot certify that the diagnosis of diabetes type is correct. In NDR, individuals with MODY (Maturity Onset of Diabetes in the Young) were at the time of the study included in the type 2 diabetes cohort. Although a very small group of patients, 1% to 2% of the diabetes population,⁴⁶ this might affect the results regarding complications due to diabetes as the most common variant (the glucokinase mutation) is not associated with complications.⁴⁷⁻⁴⁹ Third, the shorter time from diagnosis to signs of microalbuminuria in the individuals with type 2 diabetes compared with type 1 diabetes in the present study might be due to the unclear duration of diabetes type 2. However, we have not found any evidence of silent type 2 diabetes in Swedish children, neither at screening for type 2 diabetes in school children,⁹ nor screening among severely obese adolescents found any individuals with silent type 2 diabetes^{9,20,50,51} which contradicts a long preclinical course in early-

onset type 2 diabetes. Fourth, the patients, that is, the adolescents and the young adults are from two separate registers and differ in numbers of controls and female/male ratio. The withdrawal of data from the registers revealed an unexpectedly high number of cases of type 2 diabetes in the adult cohort in relation to the matched individuals with type 1 diabetes. It was therefore not possible to match according to study plan. Also, the time between visits were more variable among the adolescents with type 2 diabetes, and fewer compared with the controls with type 1 diabetes. This explains the differences in numbers of females and males, and also numbers of controls between the adolescents and young adults. Furthermore, as presented in the Section 2 the registers have developed over time and it is possible that some patients were not registered initially which might affect the prevalence data. Patients who were diagnosed with diabetes and registered in SWE or NDR from 1996 until 2014 were included and subsequently followed over time retrospectively, thus long-term data was limited for some patients. However, the marked increased prevalence of complications was mainly observed for type 2 diabetes and not for type 1 and we have no reason to believe that there is a registration bias between the two types of diabetes. Another limitation is that there is missing data, especially concerning microalbuminuria, but there was no significant difference in missing data between the two diabetes types that can explain the differences. We did not have any data on whether the degree of physical activity or type of treatment could affect the differences between type 1 and 2 diabetes, nor did we have data on the ethnic background or educational level, since this type of information is not allowed in the registers, so we could not analyze whether the ethnic background differed between type 1 and 2 diabetes.

In conclusion, in this longitudinal study of adolescents and young adults with type 2 diabetes a high prevalence of diabetes-related complications was found. Compared with type 1 diabetes and despite lower HbA1c levels, the prevalence of microalbuminuria and hypertension, 5 to 10 years after diagnosis was much higher. Together with previous long-term data,¹⁹ this clearly indicates that these patients are at higher risk for cardiovascular events. It is therefore important to intensify the behavioral support and the pharmacological treatment of comorbidities.^{52,53} Other treatment strategies aimed to improve both metabolic control, weight loss, and cardiovascular fitness, such as bariatric surgery⁵⁴ should also be considered to reduce the future health hazard, which both society and individual patients will benefit from.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.E.E. and C.M. contributed to the study concept. A.E.E. conducted the research, led the statistical analyses and wrote the manuscript. C. M. contributed to the statistical analysis, the discussion, and reviewed and edited the manuscript. U.S., A.C., A.E., and A.J. contributed to the discussion and reviewed and edited the manuscript. C.M. reviewed and supervised the revisions. All authors gave approval of the final version to be published. C.M. is the guarantor of this work.

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ORCID

Anna E. Ek  <https://orcid.org/0000-0002-1321-5073>

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