A Comparison of Familial and Sporadic Type 1 Diabetes Among Young Patients

Diabetes Care 2021;44:1116–1124 | https://doi.org/10.2337/dc20-1829

Beate Karges,[1,2] Nicole Prinz,[3,4] Kerstin Placzek,[5] Nicolin Datz,[6] Matthias Papsch,[7] Ursula Strier,[8] Dirk Agena,[9] Walter Bonfig,[10] Heiner Kentrup,[2] and Reinhard W. Holl[3,4]

OBJECTIVE

To investigate natural course, treatment, and outcomes in familial versus sporadic type 1 diabetes.

RESEARCH DESIGN AND METHODS

In a population-based study, we compared patients with onset of type 1 diabetes before the age of 20 years who had a first-degree relative with type 1 diabetes (familial diabetes) with patients with type 1 diabetes who had no first-degree relative with type 1 diabetes (sporadic diabetes) at diagnosis and over the first 10 treatment years, using multivariable regression and proportional hazards models. Patients were identified from the Diabetes Prospective Follow-up Registry (DPV) between 1995 and 2018.

RESULTS

Of 57,371 patients with type 1 diabetes, 53,606 (93.4%) had sporadic diabetes and 3,765 (6.6%) had familial diabetes. Familial diabetes, compared with sporadic diabetes, was associated with younger age (median 7.9 vs. 9.7 years, $P < 0.001$), lower prevalence of ketoacidosis (11.9% vs. 20.4%, $P < 0.001$), and lower HbA_{1c} levels (9.7% vs. 11.1%, $P < 0.001$) at onset and higher prevalence of associated autoimmune disease (16.7% vs. 13.6%, $P < 0.001$). Over 10 years, patients with familial diabetes, in comparison with sporadic diabetes, more often used insulin pumps ($P < 0.001$) and had a lower rate of severe hypoglycemia (12.97 vs. 14.44 per 100 patient-years, $P < 0.001$) but similar HbA_{1c} levels ($P \geq 0.08$) and ketoacidosis rates (1.85 vs. 2.06 per 100 patient-years, $P = 0.11$). In familial and sporadic diabetes, absence of ketoacidosis at onset predicted fewer events of severe hypoglycemia (hazard ratio [HR] 0.67, $P < 0.001$, and 0.91, $P < 0.001$, respectively) and of ketoacidosis (HR 0.64, $P = 0.007$, and 0.66, $P < 0.001$, respectively) after 10 years.

CONCLUSIONS

Familial type 1 diabetes, compared with sporadic type 1 diabetes, is characterized by earlier disease manifestation and higher autoimmune comorbidity as well as less metabolic decompensation at onset, likely related to higher disease awareness in affected families, while the course of disease is similar. These findings may have implications for the generalizability of results of diabetes prevention trials from patients with familial type 1 diabetes to patients with sporadic type 1 diabetes.

The prevalence of familial type 1 diabetes varies, with estimates ranging from 5% (1) to 12.2% (2) depending on the population investigated, the length of observation, and the study setting (3–6). Those with familial diabetes carry the risk haplotype

[1]Division of Endocrinology and Diabetes, Medical Faculty, RWTH Aachen University, Aachen, Germany
[2]Department of Pediatrics, Bethlehem Hospital Stolberg, Stolberg, Germany
[3]Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany
[4]German Center for Diabetes Research (DZD), Neuherberg, Germany
[5]Department of Pediatrics, Medical Faculty, Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany
[6]Diabetes Center for Children and Adolescents, Children's Hospital Auf der Bult, Hannover, Germany
[7]Department of Neonatology, Pediatric and Adolescent Medicine, Marienhospital Gelsenkirchen, Gelsenkirchen, Germany
[8]Department of Pediatrics, Elisabeth-Krankenhaus Rheydt, Mönchengladbach, Germany
[9]Practice of Pediatrics and Pediatric Diabetes, Hildesheim, Germany
[10]Department of Pediatrics, Klinikum Wels-Grieskirchen, Wels, Austria

Corresponding author: Beate Karges, bkarges@ukaachen.de

Received 21 July 2020 and accepted 23 February 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.14109854.

DR4-DQ8 more often than those with sporadic diabetes (2,4) indicating that HLA-associated genetic risk might play a role in familial clustering of the disease. Patients with familial and patients with sporadic diabetes have comparable autoantibody profiles suggesting similar immunologic disease mechanisms (2).

Individuals with a first-degree relative with type 1 diabetes have an increased lifetime risk of type 1 diabetes compared with the general population (1). Because of their high lifetime diabetes risk and easy identification, first-degree relatives are ideal candidates for type 1 diabetes prevention strategies and have been recruited for clinical intervention trials (7–9). However, it remains unclear whether familial diabetes and sporadic diabetes are distinct entities of type 1 diabetes, as the clinical course of familial type 1 diabetes has only been investigated in a few studies, including a small number of cases and with sparse outcome data (10–12).

The generalizability of results from diabetes prevention trials from familial to sporadic type 1 diabetes would be in question if these forms of diabetes were different. The aim of this study was to investigate the prevalence of familial type 1 diabetes at a population-based level and to examine whether natural course, comorbidities, insulin treatment, and outcomes differ in young patients with type 1 diabetes who have a first-degree relative with type 1 diabetes compared with patients with sporadic type 1 diabetes with use of a large database to identify participants.

RESEARCH DESIGN AND METHODS

Study Design

This was a population-based observational study with comparison of patients with type 1 diabetes who had a first-degree relative with type 1 diabetes (familial diabetes group) and patients with type 1 diabetes who had no first-degree relative with type 1 diabetes (sporadic diabetes group) between 1 January 1995 and 31 December 2018. In the familial type 1 diabetes group, we distinguished between patients who were diagnosed after their relative (relative-first group), patients who were diagnosed before their relative (patient-first group), and patients for whom the date of type 1 diabetes diagnosis in the relative was unknown (unknown-first group).

Patients included in the study were identified from the Diabetes Prospective Follow-up Registry (DPV) in September 2019 at Ulm University. A total of 495 diabetes centers documented treatment and outcome of diabetes care using the DPV Diabetes Documentation System in Germany, Austria, Switzerland, and Luxembourg, covering an estimated proportion of >90% of all pediatric patients with diabetes in Germany, Austria, and Luxembourg. The analysis of anonymized data was approved by the Ethics Committee of Ulm University, Ulm, Germany.

Study Population

Patients were eligible for inclusion in the study if they had a clinical diagnosis of type 1 diabetes. Exclusion criteria were age <6 months at diagnosis, age ≥20 years at diagnosis, onset of type 1 diabetes before 1995 or after 2018, and missing documentation of the first treatment year. Family history of diabetes was documented with the category of affected family member as parent, full sibling including twin or half-brother/half-sister, or child; diabetes type; and date of diagnosis in the affected first-degree relative.

For each patient, demographic data including age at onset of type 1 diabetes, sex, and migration background; metabolic decompensation at diagnosis comprising plasma glucose, HbA_{1c}, pH, and presence of ketoacidosis; and comorbid thyroid disease, celiac disease, or Addison disease were analyzed. Clinical data of the first treatment year included insulin injection therapy or pump therapy, daily insulin dose, HbA_{1c} level, BMI (calculated as weight in kilograms divided by the square of height in meters), and frequency of self-monitoring of blood glucose level. Over the first 10 treatment years, the proportion of patients with insulin pump therapy, of patients with at least one event of severe hypoglycemia, and of patients with at least one event of diabetic ketoacidosis; HbA_{1c} levels; BMI; and cumulative duration of hospital stay were calculated per year. Event rates of severe hypoglycemia, of hypoglycemic coma, and of ketoacidosis were assessed per 100 patient-years by summing up of all events.

Outcomes

Age at onset of type 1 diabetes was defined according to the day of diagnosis. Time between diagnosis in the first and second relative was calculated for all patients with familial type 1 diabetes and separately for the relative-first group and the patient-first group. Analysis of metabolic decompensation at onset included the first documented blood glucose level on day 1 and the first HbA_{1c} level within 10 days after diagnosis. The diagnosis of comorbid thyroid, celiac, or Addison disease was based on clinical diagnosis during the whole observation period.

Insulin treatment regimen was classified as one to three or four or more insulin injection time points per day or pump therapy. BMI values were transformed to SD scores based on German reference values as previously described (13,14). Glycated hemoglobin values were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range 4.05%–6.05% with the multiple-of-the-mean transformation method. Partial remission period was defined as insulin dose–adjusted HbA_{1c} ($IDAA_{1c}$) (calculated as HbA_{1c} (%) + [4 × insulin dose (units per kilogram per 24 h)]) at least once ≤9 (15).

Diabetic ketoacidosis was defined as blood pH <7.3 or bicarbonate <15 mmol/L (16). Ketoacidosis until day 10 after type 1 diabetes diagnosis was considered ketoacidosis at onset. Ketoacidosis later than 10 days after diagnosis of type 1 diabetes was considered as an event in established diabetes. Severe hypoglycemia was defined as requiring assistance from another person to actively administer carbohydrates, glucagon, or intravenous glucose consistent with guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (17) and the International Hypoglycemia Study Group (18). Hypoglycemic coma was defined as loss of consciousness or occurrence of seizures according to ISPAD classification (17).

Statistical Analyses

Clinical characteristics were compared between patients with familial diabetes and patients with sporadic diabetes as well as between different groups of familial diabetes (relative-first group, patient-first group, and unknown-first group) by Kruskal-Wallis test for nonparametric continuous variables and by χ^2 test for

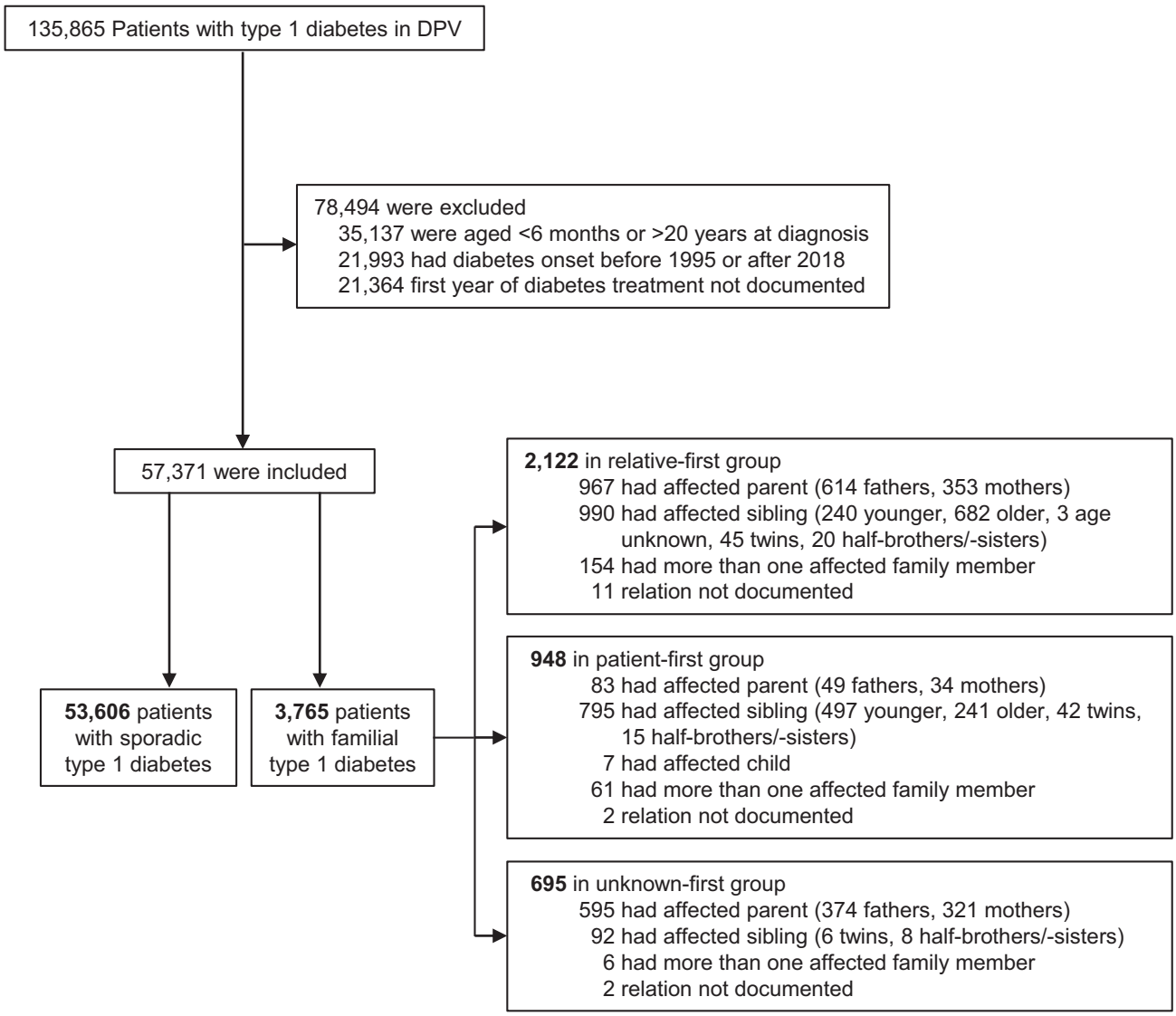

Figure 1—Selection of study population.

binomial distributed variables. *P* values were corrected for multiple comparisons with the Bonferroni-Holm method.

For analysis of insulin treatment regimen, metabolic control, rates of acute complications, and other outcomes, we conducted multivariable regression analyses with adjustment for age at diabetes onset (categorized as $<$10, 10–15, $>$15 years), sex, and migration background (defined as birthplace outside of Germany, Austria, Switzerland, or Luxembourg for the patient or for one or both parents) to account for relevant confounders. We used logistic regression analyses to estimate the percentage of patients with diabetic ketoacidosis at onset, with insulin pump therapy, with HbA_{1c} levels $<$7.5%, with $IDAA_{1c}$ at least once $\leq$9, and with at least one event of severe hypoglycemia, of coma, and of diabetic ketoacidosis; linear regression analyses to assess age at onset, glycated hemoglobin levels, and BMI SD score; negative binomial regression analyses to evaluate rates of severe hypoglycemia, of hypoglycemic coma, and of diabetic ketoacidosis after diagnosis with individual time at risk as offset; and Poisson regression analyses to examine cumulative duration of hospital stay. In regression models with comparison of more than two groups, *P* values were adjusted for multiple testing according to the Tukey-Kramer method. To evaluate outcomes over the first 10 treatment years, we calculated adjusted means per year using respective regression models. Outcomes were compared between groups per treatment year, and *P* values were corrected for multiple comparisons with the Bonferroni-Holm method. Repeated measurements per subject were taken into account with use of a first-order autoregressive covariance structure.

To compare the outcome glycemic control (defined as percentage of patients with HbA_{1c} $<$7.5%) in relation to baseline parameters age ($\geq$10 vs. $<$10 years), ketoacidosis (absence vs. presence), and HbA_{1c} ($\geq$9% vs. $<$9%) at onset, we estimated adjusted relative risks (aRRs) after treatment years 1 and 10 in sporadic and familial diabetes using logistic regression models with an interaction term. Time-to-event analyses for severe hypoglycemia and diabetic ketoacidosis

Table 1—Clinical characteristics of patients with familial versus sporadic type 1 diabetes

		Familial			
	Sporadic, *N* = 53,606	All, *N* = 3,765	Patient first, *N* = 948	Relative first, *N* = 2,122	Unknown first, *N* = 695
Demographics at onset of disease					
Age, years	9.7 (6.1; 12.8)	7.9 (4.3; 11.5)	6.5 (3.4; 10.0)	8.5 (4.9; 12.0)	8.1 (4.3; 11.5)
Time between onset in first and second relative, years	—	6.0 (2.3; 13.2)	3.3 (1.3; 6.5)	8.4 (3.3; 19.5)	—
Male sex	28,894 (53.9)	2,003 (53.2)	491 (51.8)	1,157 (54.5)	355 (51.1)
Migration background	10,405 (19.4)	806 (21.4)	244 (25.7)	446 (21.0)	116 (16.7)
Metabolism at onset of disease					
Blood glucose, mg/dL	417 (307; 544)	390 (281; 521)	442 (331; 568)	366 (267; 494)	393 (273; 520)
Blood glucose, mmol/L	23.1 (17.0; 30.2)	21.6 (15.6; 28.9)	24.5 (18.4; 31.5)	20.3 (14.8; 27.4)	21.8 (15.1; 28.8)
Blood pH	7.35 (7.26; 7.39)	7.38 (7.33; 7.40)	7.35 (7.24; 7.40)	7.38 (7.35; 7.41)	7.38 (7.34; 7.41)
Diabetic ketoacidosis	8,430 (20.4)	367 (11.9)	180 (24.1)	136 (7.5)	51 (9.6)
HbA_{1c}, %	11.1 (9.6; 12.8)	9.7 (8.3; 11.4)	10.7 (9.4; 12.4)	9.3 (8.0; 10.8)	9.6 (8.2; 11.3)
HbA_{1c}, mmol/mol	98 (81; 116)	83 (67; 101)	94 (79; 112)	78 (64; 95)	82 (66; 100)
Associated autoimmune diseases					
All	7,274 (13.6)	630 (16.7)	194 (20.5)	337 (15.9)	99 (14.2)
Thyroid disease	5,355 (10.0)	438 (11.6)	141 (14.9)	230 (10.8)	67 (9.6)
Celiac disease	2,246 (4.2)	235 (6.2)	63 (6.7)	133 (6.3)	39 (5.6)
Addison disease	27 (0.05)	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
Treatment regimen and metabolic control during the first treatment year					
1–3 insulin injections per day	10,276 (19.2)	578 (15.4)	217 (22.9)	257 (12.1)	104 (15.0)
≥4 insulin injections per day	33,541 (62.6)	2,024 (53.8)	510 (53.8)	1,141 (53.8)	373 (53.7)
Insulin pump therapy	9,788 (18.3)	1,163 (30.9)	221 (23.3)	724 (34.1)	218 (31.4)
Insulin dose, IU/kg/day	0.6 (0.4; 0.8)	0.5 (0.4; 0.7)	0.6 (0.4; 0.8)	0.5 (0.4; 0.7)	0.5 (0.4; 0.7)
HbA_{1c}, %	7.2 (6.5; 8.0)	7.1 (6.5; 7.9)	7.2 (6.5; 7.9)	7.1 (6.5; 7.9)	7.1 (6.5; 7.9)
HbA_{1c}, mmol/mol	55 (47; 64)	55 (48; 63)	55 (48; 63)	55 (48; 63)	55 (48; 63)
$IDAA_{1c}$*	9.7 (8.6; 11.0)	9.5 (8.5; 10.7)	9.7 (8.7; 10.9)	9.4 (8.5; 10.6)	9.5 (8.4; 10.7)
$IDAA_{1c}$ at least once ≤9	32,263 (61.2)	2,390 (64.1)	553 (59.0)	1,399 (66.5)	438 (64.0)
SMBG frequency per day, mean ± SD	5.5 ± 2.1	5.9 ± 2.2	5.8 ± 2.1	5.9 ± 2.3	6.0 ± 2.1
BMI, SD score	0.1 (–0.5; 0.8)	0.2 (–0.5; 0.8)	0.1 (–0.4; 0.8)	0.2 (–0.5; 0.8)	0.2 (–0.4; 0.9)

Data are median (quartiles) or *n* (%) unless otherwise indicated. SMBG, self-monitoring of blood glucose. *$IDAA_{1c}$ calculated as HbA_{1c} (%) + [4 × insulin dose (units/kg/24 h)]; a value ≤9 indicates partial remission period.

were carried out with use of Kaplan-Meier curves. Patients with severe hypoglycemia or diabetic ketoacidosis during their individual observation time were censored at first occurrence of the respective event. Cox proportional hazards models (with adjustment for age at onset [<10 and ≥10 years], sex, and migration background) were used for estimation of Kaplan-Meier curves and hazard ratios (HRs) with individual observation time as the underlying time metric to relate the baseline parameters (age, ketoacidosis, and HbA_{1c} at onset) to the occurrence of severe hypoglycemia and diabetic ketoacidosis in sporadic and familial diabetes after a disease duration of 1 and 10 years, respectively.

Results are presented as model-based estimates including 95% CIs. $P < 0.05$ (two sided) was considered statistically significant. All analyses were performed with SAS for Windows, version 9.4 (SAS Institute), on a Windows-server 16 mainframe computer.

RESULTS

Study Population

Of 135,865 patients with type 1 diabetes in the DPV, we identified 57,371 individuals who met the inclusion criteria (median age at onset 9.6 years, quartiles 5.9 and 12.8; 54% male) from 429 diabetes centers (Fig. 1). A total of 53,606 individuals had no first-degree relative with type 1 diabetes (sporadic diabetes [93.4%]), and 3,765 patients had a first-degree relative with type 1 diabetes (familial diabetes [6.6%]). Among 3,765 patients with familial diabetes, 2,122 patients had a relative earlier diagnosed with type 1 diabetes (relative-first group) and 948 patients were diagnosed with type 1 diabetes before their relative (patient-first group), while for 695 patients the age at diabetes onset in the relative was unknown (unknown-first group) (Table 1).

Among 3,765 patients with familial diabetes, 1,645 (44%) had a parent, 1,877 (50%) had a sibling including 93 twins and 43 half-brothers or half-sisters, 7 had a child, and 221 (6%) had >1 affected family member, and in 15 cases the relation was not documented. Overall, 3.2% and 3.6% of patients of the whole study population had at least one parent and at least one sibling with type 1 diabetes, respectively. Of 2,122 patients in the relative-first group, 967 (46%) had a parent and 990 (47%) had a

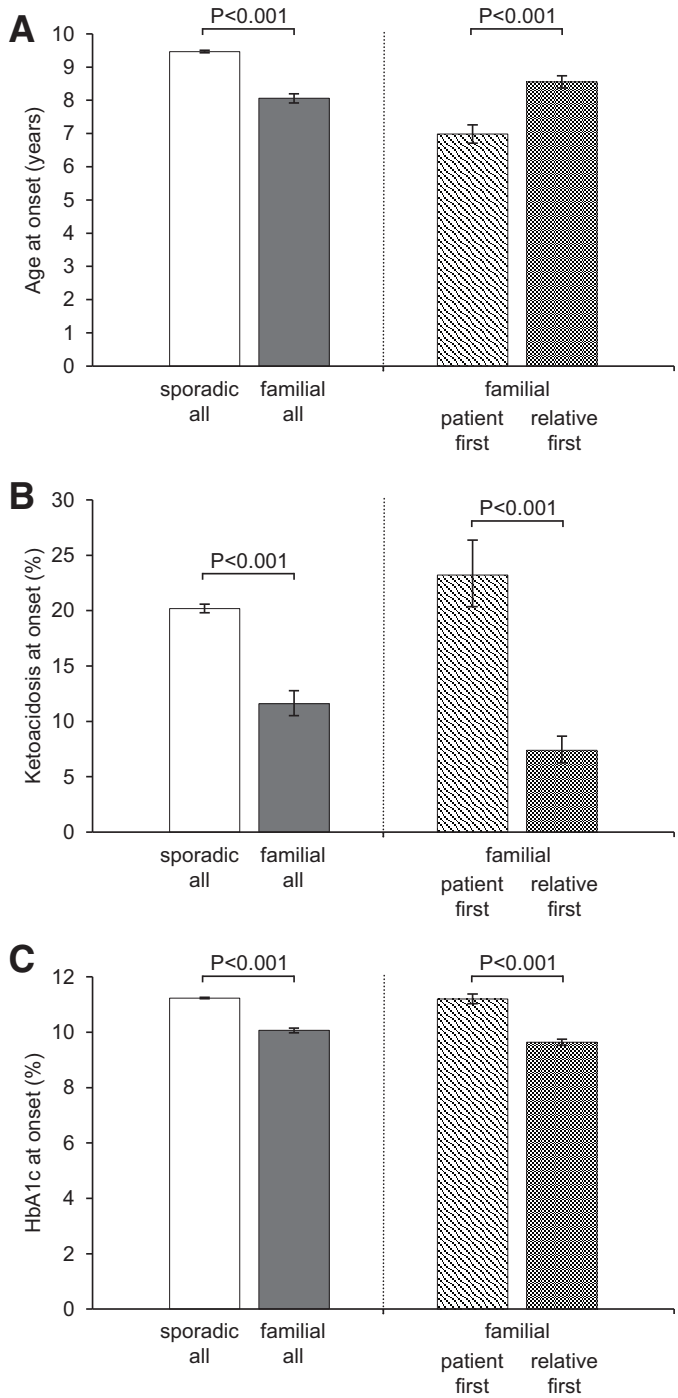

Figure 2—Familial vs. sporadic type 1 diabetes at onset of disease. Shown are the age at onset of type 1 diabetes (*A*), the percentage of patients with diabetic ketoacidosis (pH <7.3) at onset (*B*), and the HbA_{1c} level (%) at onset (*C*) in patients with sporadic type 1 diabetes (n = 53,606) and in all patients with familial type 1 diabetes (n = 3,765) (left) as well as in the patient-first group (n = 948) and in the relative-first group (n = 2,122) (right). Data are adjusted estimates with 95% CI.

sibling (Fig. 1). Of 948 patients in the patient-first group, 83 (9%) had a parent, 795 (84%) had a sibling, and 7 (1%) had a child (Fig. 1). Of 695 patients in the unknown-first group, 595 (86%) had a parent and 92 (13%) had a sibling (Fig. 1).

Characteristics of Patients With Familial Versus Sporadic Type 1 Diabetes

Age at onset of type 1 diabetes was lower in familial diabetes compared with sporadic diabetes (7.9 vs. 9.7 years, $P <$ 0.001), mainly attributable to the patient-first group (6.5 years) and to a lesser degree to the relative-first group (8.5 years) (Table 1 [both P for comparison with sporadic diabetes <0.001]). These differences persisted after adjustment for relevant confounders (Fig. 2*A*). Time between diagnoses in the first and second affected family member was longer in the relative-first group in comparison with the patient-first group (8.4 vs. 3.3 years, $P < 0.001$) (Table 1). The proportion of individuals with migration background was higher in the patient-first group (25.7%) in comparison with sporadic diabetes (19.4%, $P < 0.001$) (Table 1). Associated autoimmune diseases were more frequent in familial diabetes than in sporadic diabetes (16.7% vs. 13.6%, $P < 0.001$) with higher prevalence of celiac disease (6.2% vs. 4.2%, $P < 0.001$), which was highest in the patient-first group (6.7%) (Table 1).

Metabolic decompensation at diabetes onset was less severe in familial diabetes than in sporadic diabetes (Table 1), persisting in adjusted analyses with lower percentage of ketoacidosis (11.6% vs. 20.2% [Fig. 2*B*]) and lower HbA_{1c} levels (10.1% vs. 11.2% [Fig. 2*C*]). These differences were attributable to better metabolic control at onset in the relative-first group with lowest percentage of ketoacidosis (7.4%) and lowest HbA_{1c} levels (9.6%), both $P < 0.001$ for comparison with sporadic diabetes, while the patient-first group was similar to those with sporadic diabetes with highest percentage of ketoacidosis (23.2%) and comparable HbA_{1c} levels (11.2%) (both $P \geq 0.17$) (Fig. 2*B* and *C*). The patient-first group had slightly higher blood glucose in comparison with the sporadic diabetes group at onset of disease (442 vs. 417 mg/dL, $P = 0.03$) (Table 1).

Insulin Treatment and Glycemic Control in Familial Versus Sporadic Type 1 Diabetes

Insulin pump therapy was used more often in patients with familial diabetes than in patients with sporadic diabetes during the first year (30.9% vs. 18.3%, $P < 0.001$), with the highest proportion of pump use in the relative-first group (34.1%) (Table 1). This difference persisted in adjusted analyses (Supplementary Table 1). Over 10 years, patients with familial diabetes

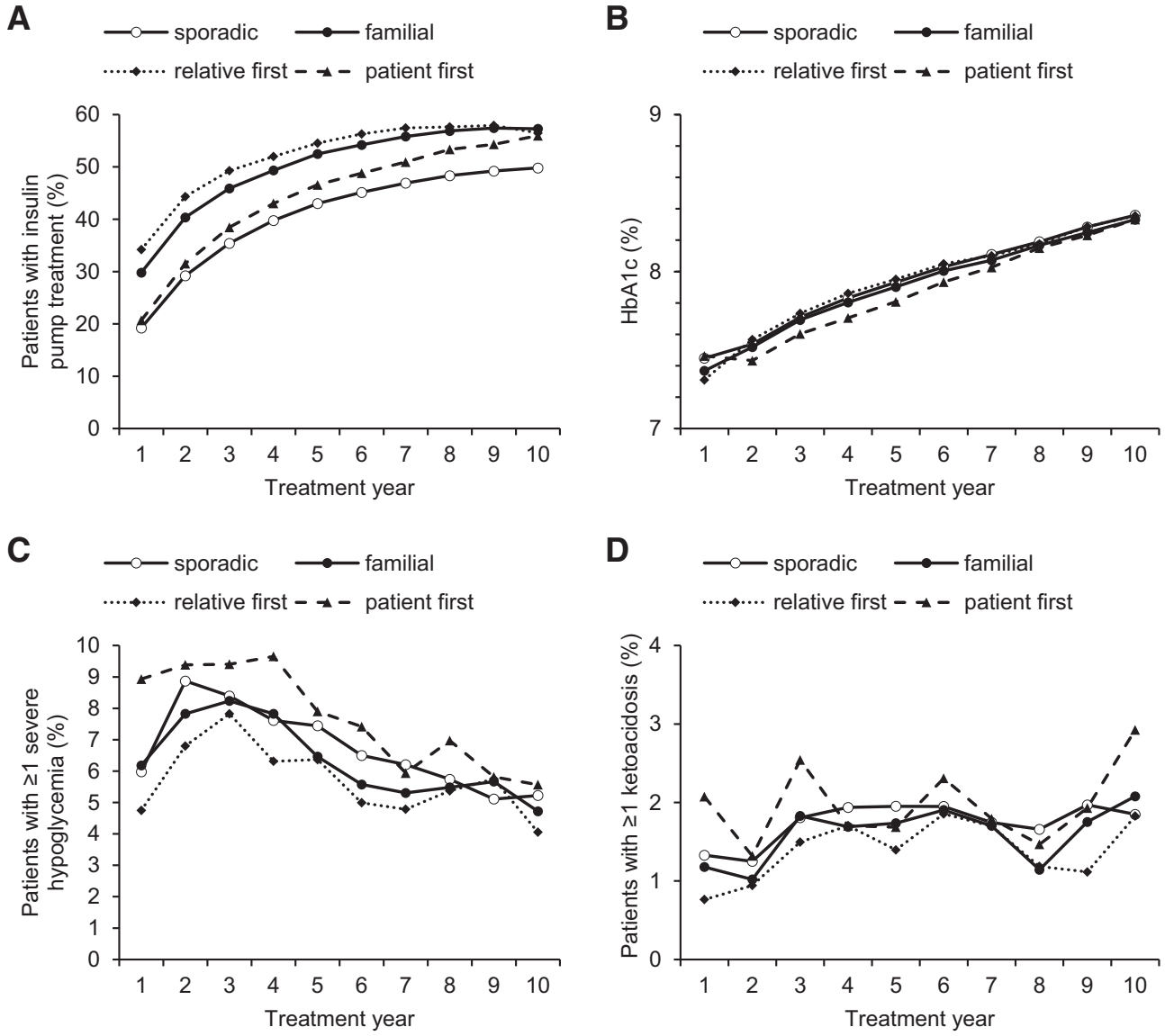

Figure 3—Familial vs. sporadic type 1 diabetes over the first 10 treatment years. Shown are the percentage of patients with insulin pump use (*A*), HbA_{1c} values (*B*), the percentage of patients with at least one episode of severe hypoglycemia (*C*), and the percentage of patients with at least one episode of diabetic ketoacidosis (*D*) among patients with sporadic type 1 diabetes and all patients with familial type 1 diabetes as well as the relative-first group and the patient-first group as adjusted estimates per year.

continued to use pump therapy more often than patients with sporadic diabetes (all $P < 0.001$) (Fig. 3*A*). Pump use remained higher in the relative-first group in comparison with the sporadic diabetes group until year 9 (all $P \leq 0.001$) but was similar in year 10 ($P = 0.40$). The relative-first group more often used pumps than the patient-first group until year 4 (all $P \leq 0.004$), while the two groups converged thereafter (all $P \geq 0.05$) (Fig. 3*A*).

Patients with familial diabetes had a slightly lower mean HbA_{1c} level in comparison with patients with sporadic diabetes during the first year (7.4% vs. 7.5%, $P < 0.001$) due to the low HbA_{1c} level in the relative-first group (7.3%) in adjusted analyses (Supplementary Table 1). From year 2 to year 10, mean HbA_{1c} levels did not differ between familial diabetes and sporadic diabetes (all $P \geq 0.08$) or between the relative-first and sporadic diabetes groups (all $P = 1.0$) (Fig. 3*B*). Median Insulin dose was lower in familial diabetes than in sporadic diabetes (0.5 vs. 0.6 IU/kg/day, $P < 0.001$) during the first year (Table 1). With use of the Hvidøre formula to estimate partial diabetes remission, familial diabetes compared with sporadic diabetes was associated with a lower $IDAA_{1c}$ value (9.5 vs. 9.7, $P < 0.001$) and a higher proportion of individuals with $IDAA_{1c}$ at least once ≤9 (64.1% vs. 61.2%, $P = 0.007$). This difference was due to the high percentage of IDAAC–based remission in the relative-first group (66.5%), while that in the patient-first group (59.0%) was similar to that in the sporadic diabetes group (Table 1), as confirmed in adjusted analyses (Supplementary Table 1).

Median BMI SD score was higher in familial diabetes than in sporadic diabetes during the first year (0.2 vs. 0.1, $P = 0.007$) (Table 1). Over 10 years, patients with familial diabetes had higher mean BMI SD score than patients with

sporadic diabetes in the first 2 years ($P \leq 0.005$), while BMI SD scores were similar thereafter (all $P = 1.0$). Total mean number of days in hospital was lower in familial diabetes than in sporadic diabetes during the first year (16.7 vs. 18.0 days, $P < 0.001$) and particularly low in the relative-first group (15.6 days) (Supplementary Table 1). Over 10 years, duration of hospital stay did not differ between the groups (all $P = 1.0$).

Severe Hypoglycemia and Ketoacidosis in Familial Versus Sporadic Type 1 Diabetes

Severe hypoglycemia rates were lower in the relative-first group in comparison with the sporadic diabetes group (11.1 vs. 15.8 per 100 patient-years, $P = 0.03$) during the first year (Supplementary Table 1). In the following years, the percentage of patients with at least one event of severe hypoglycemia did not differ between any groups (all $P = 1.0$) (Fig. 3*C*). Throughout 10 years, severe hypoglycemia rates were lower in familial diabetes (12.97 per 100 patient-years, 95% CI 11.98–14.04) compared with sporadic diabetes (14.44 per patient-year, 95% CI 14.13–14.76, $P = 0.01$), lowest in the relative-first group (11.29 per patient-year, 95% CI 10.11–12.60, $P < 0.001$ for comparison with sporadic diabetes), highest in the patient first-group (15.83 per 100 patient-years, 95% CI 13.66–18.35, $P = 0.002$ for comparison with the relative-first group), and in between in the unknown-first group (13.64 per 100 patient-years, 95% CI 11.33–16.41).

Hypoglycemic coma rates were similar in familial diabetes and sporadic diabetes (all $P \geq 0.27$) during the first year (Supplementary Table 1). Throughout 10 years, coma rates were similar in familial diabetes (2.95 per 100 patient-years, 95% CI 2.64–3.30) and sporadic diabetes (3.02 per patient-year, 95% CI 2.92–3.11, $P = 0.71$), in the relative-first group (2.70 per patient-year, 95% CI 2.31–3.16), the patient-first group (3.46 per 100-patient--years, 95% CI 2.84–4.22), and the unknown-first group (2.85 per 100 patient-years, 95% CI 2.20–3.68).

Ketoacidosis rates were lower in the relative-first group than in the patient-first group (0.9 vs. 2.7 per 100 patient-years, $P = 0.01$) during the first year (Supplementary Table 1). In the following years, the percentage of patients with at least one event of ketoacidosis did not differ between the groups (all $P = 1.0$) (Fig. 3*D*). Throughout 10 years, ketoacidosis rates were similar in familial diabetes (1.85 per 100 patient-years, 95% CI 1.63–2.10) and sporadic diabetes (2.06 per 100 patient-years, 95% CI 1.99–2.14, $P = 0.11$), in the relative-first group (1.63 per 100 patient-years, 95% CI 1.35–1.95, $P = 0.06$ for comparison with the sporadic diabetes group), in the patient-first group (2.27 per 100 patient-years, 95% CI 1.82–2.83), and in the unknown-first group (1.80 per 100 patient-years, 95% CI 1.34–2.42).

Clinical Outcomes Related to Baseline Parameters in Familial and Sporadic Type 1 Diabetes

Older age (≥10 vs. <10 years) at onset of type 1 diabetes was associated with fewer events of severe hypoglycemia in sporadic and familial diabetes after year 1 (HR 0.50 and 0.41, respectively [Supplementary Table 2]) and 10 years (HR 0.76 and 0.72 [Supplementary Fig. 1*A*]) and with fewer events of ketoacidosis after year 1 (HR 0.70 and 0.25 [Supplementary Table 2]). Absence versus presence of ketoacidosis at onset predicted better metabolic control in sporadic and familial diabetes after year 1 (6.6% and 11.3% more patients with HbA_{1c} <7.5%, aRR 1.12 and 1.22 [Supplementary Table 3]), fewer events of severe hypoglycemia after 10 years (HR 0.91 and 0.67 [Supplementary Fig. 1*C*]), and fewer events of ketoacidosis after year 1 (HR 0.57 and 0.27 [Supplementary Table 2]) and 10 years (HR 0.66 and 0.64 [Supplementary Fig. 1*D*]). Higher HbA_{1c} at onset (≥9% vs. <9%) was associated with inferior glycemic control in sporadic and familial diabetes after year 1 (10.4% and 15.0% less patients with HbA_{1c} <7.5%, aRR 0.85 and 0.78 [Supplementary Table 3]).

CONCLUSIONS

The population-based prevalence of familial type 1 diabetes was 6.6% in the current study and lower than that in smaller populations, ranging from 10.3 to 12.2% (2–5), but in line with estimates reported in American Diabetes Association (6) and ISPAD (19) guidelines. In the current study, 3.2% and 3.6% of patients with type 1 diabetes had at least one parent and at least one sibling with type 1 diabetes, respectively, corresponding to previous estimates (19). A lower prevalence of affected siblings of 1.9% was recently reported from Finland (4), only including full siblings and a family history at time of diagnosis in the index child, while the current study also considered half-brothers/half-sisters and provided longer observation of relatives: over more than two decades. Accordingly, a higher prevalence of affected siblings of 7.0% was reported from Sweden during a period of 43 years (3).

Familial type 1 diabetes in this study was characterized by younger age at onset and higher prevalence of associated autoimmune disease in comparison with sporadic type 1 diabetes. The results differ from earlier reports describing similar ages in sporadic and familial cases in smaller populations (2,4,5,20) but are in accordance with previous observations in twins and siblings identifying young age at onset in the first sibling as a major risk factor for type 1 diabetes in the second sibling (3,21–23). Higher autoimmune comorbidity, early disease manifestation, and short time between diagnoses in the first and second family member observed in the current study support the notion that patients with familial diabetes share higher HLA-associated and other genetic (21) and environmental (24) risks compared with patients with sporadic type 1 diabetes, leading to an accelerated immune-mediated disease.

Owing to the large study population, subgroup analyses in patient-first and relative-first individuals could be performed, allowing us to further dissect the observed differences between familial and sporadic diabetes. Youngest age at onset, highest ketoacidosis rate, and highest blood glucose at diabetes onset in the patient-first group point to more aggressive autoimmunity in familial diabetes. Of note, 84% of the second affected family members were siblings in the patient-first group. Still, less metabolic decompensation at onset, i.e., less ketoacidosis and lower HbA_{1c} levels, was overall noticed in patients with familial type 1 diabetes—a feature exclusively attributable to the patients in the relative-first group. It is likely that higher disease awareness in such families contributes to timely recognition and diagnosis and, hence, earlier initiation of therapy in the second family member. Earlier insulin treatment of autoimmune diabetes may favor

partial β-cell recovery (15), explaining a higher percentage of patients with partial remission in the relative-first group in comparison with the sporadic diabetes group. Familial expertise with type 1 diabetes therapy may further explain better glycemic control in the first year, higher acceptance of insulin pump use during initial treatment, and fewer events of severe hypoglycemia in the relative-first group.

Long-term metabolic control was not different in patients with familial and sporadic diabetes, with similar HbA_{1c} levels and similar rates of diabetic ketoacidosis and hypoglycemic coma, as observed in other populations (10–12). Furthermore, after the first year, no metabolic differences were found between the relative-first group and sporadic diabetes group over 10 treatment years. Ketoacidosis at diabetes onset predicted more events of acute complications after 10 years in sporadic and familial diabetes in the current study. Familial experience with diabetes treatment may prevent inferior clinical outcomes, but conversely, high disease burden in families coping with more than one affected individual might interfere with optimal metabolic control (10,11). Patients with familial diabetes might therefore benefit from dedicated education programs to be evaluated with a focus on sib-pairs and parent-child pairs.

Strengths of the current study include its large population-based data set, with >50,000 patients with type 1 diabetes; the prospective data collection over 10 treatment years; and a nationwide capture rate of >90% of pediatric patients. Results are representative of a Western European population but may not be applicable to populations with different type 1 diabetes prevalence, or different average family sizes and reproduction rates, as low numbers of siblings and offspring may contribute to underestimating the true prevalence of familial type 1 diabetes (25). Further limitations of this study are the sole use of clinical data, not including genetic and immunological information. Records on type 1 diabetes–specific antibodies for capturing early stages of diabetes in first-degree relatives were not available for this analysis.

The data from the current study may have implications in the context of type 1 diabetes prevention trials, since first-degree relatives of patients with type 1 diabetes are the primary source of recruitment (7–9). First-degree relatives have a 15-fold higher relative lifetime risk (1) and a higher annual incidence (5) of type 1 diabetes compared with the general population. In the current study, familial diabetes was distinct from sporadic diabetes in terms of earlier manifestation and higher prevalence of concomitant autoimmune disease, pointing to subtle differences in immunological disease mechanisms that may potentially affect immune-targeted diabetes prevention. While some differences observed between subgroups of familial and sporadic diabetes, including ketoacidosis rates and insulin therapy during the first year, were attributable to behavioral factors, the clinical course of disease including treatment-related outcomes and metabolic control was comparable during follow-up. Taken together, the study data provide evidence that familial and sporadic type 1 diabetes are overall similar, supporting the view that results from diabetes prevention trials conducted in familial type 1 diabetes may be generalized to sporadic type 1 diabetes comprising >90% of cases in the general population.

In conclusion, familial type 1 diabetes is characterized by younger age at disease manifestation and higher autoimmune comorbidity in comparison with sporadic type 1 diabetes, as well as less metabolic decompensation at onset, likely related to higher disease awareness in affected families. The clinical course and metabolic outcomes during follow-up in patients with familial type 1 diabetes and those with sporadic type 1 diabetes are similar. These findings may have implications for the generalizability of results of diabetes prevention trials from patients with familial type 1 diabetes to patients with sporadic type 1 diabetes.

Acknowledgments. The authors thank Esther Bollow for excellent help with data analysis. In addition, Andreas Hungele, Ramona Ranz, and Katharina Fink were responsible for data aggregation and development of the DPV documentation software. All are clinical case managers from the Institute of Epidemiology and Medical Biometry. The authors are grateful to all investigators participating in the DPV Initiative. A list of the institutions that contributed to this analysis is provided in Supplementary Material.

Funding. This work was supported by the German Center for Diabetes Research (DZD) (grant 82DZD14A02), funded by the Federal Ministry of Education and Research, Berlin, Germany; by the German Diabetes Association; and by the Robert Koch Institute, Berlin, Germany.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. B.K., K.P., N.D., M.P., U.S., D.A., W.B., H.K., and R.W.H. researched data. N.P. and R.W.H. contributed to statistical analysis. B.K. wrote the manuscript. All authors reviewed/edited the manuscript and contributed to discussion. R.W.H. is the coordinator for the DPV Initiative. N.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Couper JJ, Haller MJ, Greenbaum CJ, et al. ISPAD clinical practice consensus guidelines 2018: stages of type 1 diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl. 27):20–27
2. Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J; Finnish Pediatric Diabetes Register. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care 2013;36:348–354
3. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. Diabetologia 2009;52:1820–1828
4. Turtinen M, Härkönen T, Parkkola A, Ilonen J; Finnish Pediatric Diabetes Register. Characteristics of familial type 1 diabetes: effects of the relationship to the affected family member on phenotype and genotype at diagnosis. Diabetologia 2019;62:2025–2039
5. Zung A, Na'amnih W, Bluednikov Y, Mery N; Israel IDDM Registry Study Group (IRRSG). The proportion of familial cases of type 1 diabetes is increasing simultaneously with the disease incidence: eighteen years of the Israeli Pediatric Diabetes Registry. Pediatr Diabetes 2018;19:693–698
6. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. Diabetes Care 2018;41:2026–2044
7. Knip M, Åkerblom HK, Al Taji E, et al.; Writing Group for the TRIGR Study Group. Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes: the TRIGR randomized clinical trial. JAMA 2018;319:38–48
8. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the Diabetes Prevention Trial–Type 1. Diabetes Care 2005;28:1068–1076
9. Herold KC, Bundy BN, Long SA, et al.; Type 1 Diabetes TrialNet Study Group. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019; 381:603–613
10. Hietala K, Forsblom C, Summanen P; FinnDiane Study Group. The risk of proliferative

retinopathy in siblings with type 1 diabetes. Diabet Med 2012;29:1567–1573
11. Lebenthal Y, Shalitin S, Yackobovitch-Gavan M, Phillip M, Lazar L. Retrospective comparative analysis of metabolic control and early complications in familial and sporadic type 1 diabetes patients. J Diabetes Complications 2012;26:219–224
12. Fox LA, Mubasher M, Wolfsdorf JI, et al.; T1D Exchange Clinic Network. Characteristics of youth with type 1 diabetes (T1D) with and without a parent with T1D in the T1D exchange clinic registry. J Diabetes 2016;8:834–838
13. Rosenbauer J, Dost A, Karges B, et al.; DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes Care 2012;35:80–86
14. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA 2017;318:1358–1366
15. Mortensen HB, Hougaard P, Swift P, et al.; Hvidoere Study Group on Childhood Diabetes. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care 2009;32:1384–1390
16. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19(Suppl. 27):155–177
17. Abraham MB, Jones TW, Naranjo D, et al. ISPAD clinical practice consensus guidelines 2018: assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes 2018;19(Suppl. 27):178–192
18. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157
19. Mayer-Davis EJ, Kahkoska AR, Jefferies C, et al. ISPAD clinical practice consensus guidelines 2018: definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl. 27):7–19
20. Lebenthal Y, de Vries L, Phillip M, Lazar L. Familial type 1 diabetes mellitus - gender distribution and age at onset of diabetes distinguish between parent-offspring and sib-pair subgroups. Pediatr Diabetes 2010;11:403–411
21. Gillespie KM, Aitken RJ, Wilson I, Williams AJ, Bingley PJ. Early onset of diabetes in the proband is the major determinant of risk in HLA DR3-DQ2/DR4-DQ8 siblings. Diabetes 2014;63:1041–1047
22. Triolo TM, Fouts A, Pyle L, Yu L, Gottlieb PA; Type 1 Diabetes TrialNet Study Group. Identical and nonidentical twins: risk and factors involved in development of islet autoimmunity and type 1 diabetes. Diabetes Care 2019;42:192–199
23. Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. N Engl J Med 2008;359:2849–2850
24. Nisticò L, Iafusco D, Galderisi A, et al.; Study Group on Diabetes of the Italian Society of Pediatric Endocrinology and Diabetology. Emerging effects of early environmental factors over genetic background for type 1 diabetes susceptibility: evidence from a Nationwide Italian Twin Study. J Clin Endocrinol Metab 2012;97:E1483–E1491
25. Al-Chalabi A, Lewis CM. Modelling the effects of penetrance and family size on rates of sporadic and familial disease. Hum Hered 2011;71:281–288