Received: 20 July 2020 | Revised: 27 September 2020 | Accepted: 30 November 2020

DOI: 10.1111/pedi.13177

ISPAD WILEY

Worse glycemic control, higher rates of diabetic ketoacidosis, and more hospitalizations in children, adolescents, and young adults with type 1 diabetes and anxiety disorders

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Funding information
Deutsche Diabetes Gesellschaft; German Centre for Diabetes Research, Grant/Award Number: 82DZD14A02

Abstract

The aim of the study was to explore the metabolic characteristics and outcome parameters in youth with type 1 diabetes and anxiety disorders. HbA1c levels, rates of severe hypoglycemia, diabetic ketoacidosis (DKA), and hospital admission in children, adolescents, and young adults with type 1 diabetes and an anxiety disorder from 431 diabetes-care-centers participating in the nationwide German/Austrian/Swiss/Luxembourgian diabetes survey DPV were analyzed and compared with youth without anxiety disorders. Children, adolescents, and young adults with type 1 diabetes and anxiety disorders (n = 1325) had significantly higher HbA1c (8.5% vs. 8.2%), higher rates of DKA (4.2 vs. 2.5 per 100 patient-years), and higher hospital admission rates (63.6 vs. 40.0 per 100 patient-years) than youth without anxiety disorders (all $p < 0.001$). Rates of severe hypoglycemia did not differ. Individuals with anxiety disorders other than needle phobia (n = 771) had higher rates of DKA compared to those without anxiety disorders (4.2 vs. 2.5 per 100 patient-years, $p = 0.003$) whereas

the rate of DKA in individuals with needle phobia (n = 555) was not significantly different compared to those without anxiety disorders. Children, adolescents, and young adults with anxiety disorders other than needle phobia had higher hospitalization rates (73.7 vs. 51.4 per 100 patient-years) and more inpatient days (13.2 vs. 10.1 days) compared to those with needle phobia (all p < 0.001). Children, adolescents, and young adults with type 1 diabetes and anxiety disorders had worse glycemic control, higher rates of DKA, and more hospitalizations compared to those without anxiety disorders. Because of the considerable consequences, clinicians should screen for comorbid anxiety disorders in youth with type 1 diabetes.

1 | INTRODUCTION

Children, adolescents, and young adults with type 1 diabetes appear to have a higher prevalence of emotional or behavioral problems and mental disorders compared to their peers without type 1 diabetes.[1-4] Symptoms of depression and anxiety and the corresponding disorders are the most frequently reported emotional problems and mental comorbidities in youth with type 1 diabetes.[2,4,5] A meta-analysis by Buchberger et al. shows that depressive symptoms are prevalent in up to 30% and symptoms of anxiety are present in up to 32% of children and adolescents with type 1 diabetes.[2] A recent population-based study from Denmark reports that anxiety disorders are the most common mental comorbidities in children and adolescents with type 1 diabetes.[5] There is conclusive evidence that the risk of poor metabolic outcome is highly increased in the presence of emotional or behavioral symptoms and mental disorders.[4-6] Numerous studies demonstrate that mental comorbidities in general are associated with worse glycemic control in pediatric and adolescent type 1 diabetes.[2,4-12] In addition, individuals with mental comorbidity have an increased risk of hospital admission due to diabetic ketoacidosis (DKA).[5] Moreover, higher rates of severe hypoglycemia are reported in children, adolescents, and young adults with emotional problems (e.g. depressive symptoms or depression).[13] Studies in youth with anxiety symptoms also demonstrate positive correlations between symptoms of anxiety and poor glycemic control.[6,7,12,14-17] Symptoms of anxiety often accompany poor diabetes self-management and insufficient coping strategies.[6,12] Furthermore, anxiety symptoms are associated with poor quality of life.[6,12] To our knowledge, no data about other outcome parameters (e.g. rates of severe hypoglycemia and DKA, and hospital admission rates) in children and adolescents with type 1 diabetes and anxiety disorders are available. Besides the lack of knowledge about outcome parameters in type 1 diabetes and anxiety disorders in general, only scarce data are available about the consequences and sequelae of different subgroups of anxiety disorders in youth with type 1 diabetes.[14] Diagnostic manuals like the International Statistical Classification of Diseases and Related Health Problems (ICD) describe the diagnostic criteria for the different anxiety disorders. Anxiety disorders according to ICD version 10 (ICD-10) are divided into the main categories 'phobias (i.e. agoraphobia, social phobia, and specific phobias including needle phobia)', 'panic disorders', and 'generalized anxiety disorder'. Despite the fact that fear of needles and needle phobia appear to be very common in children, adolescents, and young adults with type 1 diabetes, only sparse data are available about the impact of needle phobia on glycemic control and other outcome parameters in youth with type 1 diabetes.[14-20] The prevalence of fear of self-testing, fear of injections in multiple injection therapy or fear of changing infusion-sites in insulin pump therapy ranges from 10% to 30% in individuals with type 1 diabetes up to the age of 21 years.[14,19,20] In children with newly diagnosed type 1 diabetes, prevalence of fear with injections was even higher, with 41% exhibiting fear associated with insulin injections and 32% reporting fear associated with fingersticks.[18] In that study, Howe et al. described an improvement of fear and distress with needles after 6 to 9 months compared to the time at diagnosis of type 1 diabetes.[18] Extant literature of needle phobia and glycemic control is controversial.[14,18-20] Some studies fail to show significant associations between fear of self-testing or self-injecting and HbA1c levels.[18,19] In contrast, other studies report suboptimal glycemic control in youth with more intense fear of needles or in children with protest and poor cooperation with injections.[18,20]

Therefore, our objective was to describe the clinical and metabolic characteristics and outcome parameters in youth with type 1 diabetes and anxiety disorders, as well as in the subgroup of youth with needle phobia. We hypothesized that outcome parameters are worse, e.g. that HbA1c levels, rates of DKA and severe hypoglycemia, and hospital admission rates are higher in children, adolescents, and young adults with type 1 diabetes and an anxiety disorder compared to those without anxiety disorders. Furthermore, our hypothesis was that individuals with needle phobia have worse glycemic control, higher rates of DKA and more hospitalizations compared to those with other anxiety disorders. Therefore, we aimed to explore the associations between anxiety disorders, needle phobia and glycemic control, and also between the presence of anxiety disorders, needle phobia and diabetes-specific acute complications (e.g. rates of severe hypoglycemia and DKA, and hospital admission rates).

2 | METHODS

Within the prospective computer-based multicenter diabetes survey 'Diabetes Prospective Follow-up' (DPV), clinical and laboratory data of persons with type 1 diabetes were recorded in diabetes-care centers in Germany, Austria, Switzerland, and Luxembourg. Data were

provided by physicians and health care professionals and derived from inpatient and outpatient medical records. Approval from the ethics committee of Ulm University for data collection and anonymous analysis was obtained. Overall, 75,258 children, adolescents and young adults with type 1 diabetes aged ≤20 years with a diabetes duration of more than 1 year from 1995 until June 2019 from 431 participating diabetes-care centers were included in the analysis. Parameters age, sex, migratory background, diabetes duration, body mass index standard deviation score (BMI SDS), type of insulin therapy (multiple daily injections or insulin pump treatment), HbA1c, severe hypoglycaemias, episodes of DKA, number of hospital admissions, and length of hospital stay were recorded. Data were aggregated and analyzed in the patients' most recent treatment year. Migratory background was defined as the place of birth of the patient or one or both parents in a country other than Germany, Austria, Switzerland, or Luxembourg. BMI SDS was calculated using the national KiGGS (German Health Interview and Examination Survey for Children and Adolescents) reference data in Germany[21] and Cole's method.[22] HbA1c values were measured locally and standardized mathematically to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (21–43 mmol/mol) using the multiple of the mean (MOM) method.[23] Median HbA1c for each subject during the most recent treatment year were calculated. Severe hypoglycemia's (hypoglycemia with loss of consciousness or seizure or requiring assistance from another person to actively administer carbohydrates, glucagon, or intravenous glucose) and episodes of DKA (pH <7.3 and/or bicarbonate <15 mmol/mol) were defined according to the guidelines of International Society for Pediatric and Adolescent Diabetes (ISPAD).[24,25] Rates of severe hypoglycemia, DKA, and hospital admission rates were presented as events per 100 patient-years. Length of inpatient care was presented per patient-year. The database was searched for the diagnosis of anxiety disorders including generalized anxiety disorders, social phobias, panic disorders, specific phobias (including needle phobia), selective mutism, and obsessive–compulsive disorders according to the ICD-10 GM (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification) classification. Because of their overlapping symptoms, obsessive–compulsive disorders were also included into the search. Diagnosis of an anxiety disorder was based on ICD-10 GM codes and no additional surveys or questionnaires asking for symptoms or signs of anxiety or phobia were done. Needle phobia according to ICD-10 GM is defined as extreme or irrational fear or as avoidance of particular objects or situations, in this

TABLE 1 Characteristics of the children, adolescents, and young adults with type 1 diabetes with and without anxiety disorders

	total	with anxiety disorders	without anxiety disorders	p
Number	75,258	1325	73,932	-
Age (years)[a]	16.4 (13.1; 17.7)	16.4 (13.9; 17.6)	16.4 (13.1; 17.8)	0.61[b]
Sex ratio (male/female)	53% / 47%	**44% / 56%**	**53% / 47%**	**<0.001**[c]
Migratory background	17%	18%	17%	0.56[c]
Diabetes duration (years)[a]	6.0 (3.3; 9.4)	**6.8 (4.0; 10.1)**	**6.0 (3.3; 9.4)**	**<0.001**[b]
BMI SDS[a]	+0.36 (–0.25; +0.95)	+0.37 (–0.32; +1.02)	+0.36 (–0.25; +0.95)	0.75 [b]
Insulin pump treatment	41%	**60%**	**40%**	**<0.001**[c]
HbA1c (mmol/mol)[a] (%)[a]	62.7 (54.0; 74.7) 7.9 (7.1; 9.0)	**64.8 (56.0; 77.9)** **8.1 (7.3; 9.3)**	**62.7 (54.0; 74.7)** **7.9 (7.1; 9.0)**	**<0.001**[b]
Rate of episodes of DKA (per 100 patient-years)[d]	2.5 (2.4; 2.7)	**3.9 (2.9; 5.3)**	**2.5 (2.4; 2.6)**	**0.004**[e]
Rate of severe hypoglycemia (per 100 patient-years)[d]	12.8 (12.4; 13.3)	10.3 (8.0; 13.3)	12.9 (12.5; 13.3)	0.09 [e]
Hospital admission rate (per 100 patient-years)[d]	41.8 (41.4; 42.3)	**64.5 (60.5; 68.7)**	**41.4 (41.0; 41.9)**	**<0.001**[f]
Length of hospital stay (days per patient-year)[g]	11.9 (11.9; 12.0)	**13.8 (13.5; 14.1)**	**11.9 (11.8; 11.9)**	**<0.001**[f]
Mental comorbidities				
Depression	2%	**21%**	**2%**	**<0.001** [c]
Eating disorder	1%	**4%**	**1%**	**<0.001** [c]
ADHD[h]	3%	**9%**	**3%**	**<0.001** [c]

[a]Data expressed as median (lower quartile; upper quartile).
[b]Wilcoxon-test for comparison of subjects with versus without anxiety disorders, adjusted for multiple testing applying the Bonferroni stepdown method.
[c]X^2-test for comparison of subjects with versus without anxiety disorders, adjusted for multiple testing applying the Bonferroni stepdown method.
[d]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[e]Negative-binomial model for comparison of subjects with versus without anxiety disorders.
[f]Poisson model for comparison of subjects with versus without anxiety disorders.
[g]Data expressed as mean (95% confidence interval).
[h]Attention deficit hyperactivity disorder.
Bold values in the last column indicate that $p < 0.05$

TABLE 2 Comparison of children, adolescents, and young adults with type 1 diabetes with versus without anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year

	with anxiety disorders (*n* = 1325)	without anxiety disorders (*n* = 73,932)	p
BMI SDS [a]	+0.29 (+0.24; +0.34)	+0.33 (+0.32; +0.34)	0.09 [b]
HbA1c (mmol/mol) [a] (%) [a]	**69.7 (68.7; 70.7)** **8.5 (8.4; 8.6)**	**66.3 (66.2; 66.5)** **8.2 (8.2; 8.2)**	**<0.001** [b]
Rate of episodes of DKA (per 100 patient-years) [c]	**4.2 (3.1; 5.7)**	**2.5 (2.4; 2.6)**	**<0.001** [d]
Rate of severe hypoglycemia (per 100 patient-years) [c]	10.9 (8.4; 14.1)	12.4 (12.0; 12.8)	0.35 [d]
Hospital admission rate (per 100 patient-years) [c]	**63.6 (59.7; 67.9)**	**40.0 (39.6; 40.5)**	**<0.001** [e]
Length of hospital stay (days per patient-year) [a]	**13.6 (13.3; 13.9)**	**11.6 (11.6; 11.6)**	**<0.001** [e]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[c]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[d]Negative-binomial model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[e]Poisson model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
Bold values in the last column indicate that $p < 0.05$

TABLE 3 Comparison of children, adolescents, and young adults with type 1 diabetes with versus without anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression

	with anxiety disorders (*n* = 1325)	without anxiety disorders (*n* = 73,932)	p
BMI SDS[a]	+0.28 (+0.23; +0.33)	+0.33 (+0.32; +0.34)	0.06[b]
HbA1c (mmol/mol)[a] (%)[a]	**68.2 (67.2; 69.2)** **8.4 (8.3; 8.5)**	**66.4 (66.2; 66.5)** **8.2 (8.2; 8.2)**	**<0.001**[b]
Rate of episodes of DKA (per 100 patient-years)[c]	3.2 (2.4; 4.5)	2.4 (2.3; 2.6)	0.09[d]
Rate of severe hypoglycemia (per 100 patient-years)[c]	10.3 (8.0; 13.3)	12.3 (11.9; 12.8)	0.17[d]
Hospital admission rate (per 100 patient-years)[c]	**53.3 (49.8; 56.9)**	**39.8 (39.4; 40.3)**	**<0.001**[e]
Length of hospital stay (days per patient-year)[a]	**12.1 (11.9; 12.4)**	**11.5 (11.5; 11.5)**	**<0.001**[e]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
[c]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[d]Negative-binomial model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
[e]Poisson model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
Bold values in the last column indicate that $p < 0.05$

case needles, injections, or changing infusion-sites in insulin pump therapy. Needle phobia is associated with several anxiety symptoms, for example vegetative symptoms (like palpitations, sweating, or tremor), shortness of breath, nausea, dizziness, lightheadedness, or unsteadiness. The anxiety symptoms or the avoidance of the particular objects or situations result in intense emotional distress for the individual with needle phobia. Individuals with type 1 diabetes and anxiety disorders were subsequently divided into the group 'needle phobia' and the group 'anxiety disorder other than needle phobia'. Additionally, the database was searched for the diagnoses of depression, eating disorders, attention deficit hyperactivity disorders, autism spectrum disorders, and schizophrenia according to the ICD-10 GM classification.

3 | STATISTICAL ANALYSIS

We used SAS 9.4 statistic software for data evaluation and statistical analysis (SAS Institute, Cary, NC, USA). Descriptive and unadjusted data are presented as median with lower and upper quartiles, outcomes from regression models as least-square means with 95% confidence intervals. Wilcoxon's rank sum test was performed for unadjusted comparisons of age, diabetes duration, BMI SDS, and HbA1c between subjects with anxiety disorder and subjects without anxiety disorder. X^2-test was used to compare sex, migratory background, and use of insulin pump treatment between groups. Bonferroni stepdown method (Holm method) was used to adjust p-values for multiple testing in unadjusted comparisons. Negative-binomial models were applied to

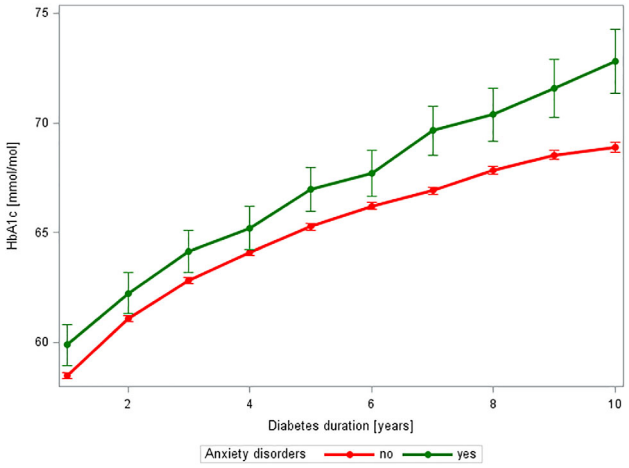

FIGURE 1 HbA1c levels (estimated mean of annual means, with 95% confidence interval) depicted over diabetes duration (divided into yearly intervals) in youth with type 1 diabetes and with anxiety disorders (green line) vs without anxiety disorders (red line), adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year. Mean HbA1c levels were significantly higher in the group of youth with anxiety disorders (green line) compared to the group of youth without anxiety disorders (red line) and increased with diabetes duration in both groups

calculate and compare rates of severe hypoglycemia and DKA, Poisson models for hospital admission rates and length of hospital stay in individuals with anxiety disorder vs. without anxiety disorder with individual time under risk as offset. Linear regression models for the adjusted comparison of HbA1c levels and BMI SDS between the groups 'with anxiety disorders', 'with needle phobia', 'with other anxiety disorders (needle phobia excluded)', and 'without anxiety disorders' were calculated. All models were adjusted for age group (≤/>16 years), sex, diabetes duration group (≤/>5 years), migratory background (yes, no), type of insulin therapy (insulin pump, multiple daily injections), and treatment year (5-year intervals). We calculated a trend model for the effect of diabetes duration on HbA1c in the group of children with and without anxiety disorder adjusting for repeated measurements of individuals. We used an autoregressive covariance structure considering measurements that are closer to each other more strongly correlated than measurements that are further apart. For the calculation of degrees of freedom, we used the between-within method. The model was adjusted for age group, sex, migratory background, type of insulin therapy, and treatment year. Further regression modeling was performed in a similar way but adjusting for depression as well. Additionally, sensitivity analysis was done, comparing youth with anxiety disorders and youth without mental disorders, i.e. without the diagnoses depression,

TABLE 4 Comparison of children, adolescents, and young adults with type 1 diabetes with either needle phobia or other anxiety disorders versus without anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year

	without anxiety disorders (*n* = 73,932)	with needle phobia (*n* = 555)	p	with other anxiety disorders (*n* = 771)	p
BMI SDS [a]	**+0.33 (+0.32; +0.34)**	**+0.24 (+0.17; +0.32)**	**0.03** [b]	+0.31 (+0.25; + 0.38)	0.58 [c]
HbA1c (mmol/mol) [a] (%) [a]	**66.3 (66.2; 66.5)** **8.2 (8.2; 8.2)**	**68.3 (66.7; 69.8)** **8.4 (8.3; 8.5)**	**0.01** [b]	**70.5 (69.2; 71.8)** **8.6 (8.5; 8.7)**	**<0.001** [c]
Rate of episodes of DKA (per 100 patient-years) [d]	**2.5 (2.4; 2.6)**	3.2 (1.9; 5.5)	0.35 [e]	**4.5 (3.1; 6.7)**	**0.003** [f]
Rate of severe hypoglycemia (per 100 patient-years) [d]	12.4 (12.0; 12.8)	9.8 (6.4; 14.9)	0.28 [e]	11.8 (8.4; 16.4)	0.76 [f]
Hospital admission rate (per 100 patient-years) [d]	**40.0 (39.5; 40.4)**	**46.8 (41.7; 52.5)**	**0.008** [g]	**74.6 (68.9; 80.8)**	**<0.001** [h]
Length of hospital stay (days per patient-year) [a]	**11.6 (11.6; 11.7)**	11.4 (11.0; 11.9)	0.38 [g]	**14.7 (14.4; 15.1)**	**<0.001** [h]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model for comparison of subjects with needle phobia versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[c]Linear regression model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[d]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[e]Negative-binomial model for comparison of subjects with needle phobia versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[f]Negative-binomial model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[g]Poisson model for comparison of subjects with needle phobia versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[h]Poisson model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
Bold values in the last column indicate that $p < 0.05$

TABLE 5 Comparison of children, adolescents, and young adults with type 1 diabetes with either needle phobia or other anxiety disorders versus without anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression

	without anxiety disorders (*n* = 73,932)	with other anxiety disorders (needle phobia excluded) (*n* = 771)	p
BMI SDS [a]	+0.33 (+0.32; +0.34)	+0.30 (+0.24; + 0.37)	0.46 [b]
HbA1c (mmol/mol) [a] (%) [a]	**66.4 (66.2; 66.5)** **8.2 (8.2; 8.2)**	**68.1 (66.8; 69.4)** **8.5 (8.3; 8.5)**	**0.01**[b]
Rate of episodes of DKA (per 100 patient-years) [c]	2.4 (2.3; 2.6)	3.1 (2.0; 4.6)	0.28 [d]
Rate of severe hypoglycemia (per 100 patient-years) [c]	12.4 (11.9; 12.8)	10.6 (7.6; 14.8)	0.38 [d]
Hospital admission rate (per 100 patient-years) [c]	**39.8 (39.3; 40.2)**	**57.1 (52.5; 62.0)**	**<0.001** [e]
Length of hospital stay (days per patient-year) [a]	**11.5 (11.5; 11.5)**	**12.5 (12.2; 12.9)**	**<0.001** [e]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
[c]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[d]Negative-binomial model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
[e]Poisson model for comparison of subjects with other anxiety disorders (needle phobia excluded) versus without anxiety disorders adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, treatment year, and depression.
Bold values in the last column indicate that $p < 0.05$

TABLE 6 Comparison of children, adolescents and young adults with type 1 diabetes with needle phobia versus with other anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year

	with needle phobia (*n* = 555)	with other anxiety disorders (*n* = 771)	p
BMI SDS[a]	+0.27 (+0.19; +0.35)	+0.36 (+0.29; +0.43)	0.10[b]
HbA1c (mmol/mol)[a] (%)[a]	68.4 (66.8; 70.0) 8.4 (8.3; 8.6)	69.3 (67.3; 70.6) 8.5 (8.4; 8.6)	0.40[b]
Rate of episodes of DKA (per 100 patient-years)[c]	3.2 (2.0; 5.2)	3.9 (2.6; 5.8)	0.53[d]
Rate of severe hypoglycemia (per 100 patient-years)[c]	7.7 (4.9; 12.0)	9.4 (6.5; 13.6)	0.49[d]
Hospital admission rate (per 100 patient-years)[c]	**51.4 (45.9; 57.4)**	**73.7 (68.0; 80.0)**	**<0.001**[e]
Length of hospital stay (days per patient-year)[a]	**10.1 (9.7; 10.5)**	**13.2 (12.9; 13.6)**	**<0.001**[e]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[c]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[d]Negative binomial model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[e]Poisson model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
Bold values in the last column indicate that $p < 0.05$

eating disorder, attention deficit hyperactivity disorder, autism spectrum disorder, or schizophrenia, in exactly the same way. Statistical significance was assumed if two-sided p-values were < 0.05.

4 | RESULTS

Characteristics of the children, adolescents and young adults with type 1 diabetes with and without anxiety disorders are depicted in Table 1. Due to significant differences between children, adolescents and young adults with anxiety disorders and those without anxiety disorders in respect to sex, diabetes duration, and frequency of insulin pump treatment (more females, longer diabetes duration and more insulin pumps in the group with anxiety disorder, see Table 1), we applied linear regression modeling for comparison of outcome parameters between these groups (see Table 2). After adjusting for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year, youth with anxiety disorders had significantly higher HbA1c levels (8.5% vs. 8.2%), higher rates of DKA (4.2 vs. 2.5 per 100 patient-years), and higher hospital admission rates (63.6 vs. 40.0

per 100 patient-years) than youth without anxiety disorders (see Table 2). Rates of severe hypoglycemia were not different (see Table 2). Given the comorbidity of depression in individuals with anxiety disorders (21% depression in individuals with anxiety disorders, see Table 1), we performed further regression modeling adjusting for depression as well (see Table 3). Results were similar for all outcome parameters except for the rates of DKA which did not differ significantly between the individuals with and those without anxiety disorders (see Table 3). In Figure 1, annual mean HbA1c levels are depicted in relation to diabetes duration. HbA1c levels increased with diabetes duration and were significantly higher in youth with anxiety disorders compared to youth without anxiety disorders throughout the course of diabetes (see Figure 1). Sensitivity analysis, comparing youth with anxiety disorders with those without mental disorders, revealed likewise significant results (see Appendix).

Out of all 1325 children, adolescents and young adults with anxiety disorders, 555 (42%) were diagnosed with needle phobia and 771 (58%) had other anxiety disorders (see Table 4). Youth with anxiety disorders other than needle phobia had significantly higher rates of DKA compared to youth without anxiety disorders (4.5 vs. 2.5 per 100 patient-years, $P < 0.003$), whereas the rate of DKA was not significantly different in youth with needle phobia compared to youth without anxiety disorders (see Table 4). Adjusting for depression as well showed that rates of DKA were not significantly different in children, adolescents, and young adults with anxiety disorders other than needle phobia compared to those without anxiety disorders (3.1 vs. 2.4 per 100 patient-years, $p = 0.28$). Results regarding the outcome parameters glycemic control and rates of severe hypoglycemia were unaffected after adjusting for depression (see Table 5). Comparing youth with needle phobia and those with other anxiety disorders, we found more hospitalizations and longer inpatient in youth with anxiety disorders other than needle phobia (see Table 6). Adjusting for depression, results remained unchanged (data not shown).

5 | DISCUSSION

In our survey, children, adolescents and young adults with type 1 diabetes and anxiety disorders had worse glycemic control compared to youth without anxiety disorders, as shown in other studies.[2,6,12,15,17] To our knowledge, studies published so far do not examine the frequency of DKA and severe hypoglycemia, nor the number of hospital admissions in youth with type 1 diabetes and anxiety disorders.[2,6,12,15,17] Only Garrison and co-authors demonstrate that internalizing disorders are associated with an increased risk of repeated hospitalizations in youth with type 1 diabetes.[26] We demonstrate for the first time that youth with anxiety disorders had - in addition to worse glycemic control - higher rates of DKA and higher hospital admission rates than individuals without anxiety disorders. Episodes of DKA are potentially life-threatening complications and may have a considerable impact on the individual in everyday life as well as over the lifelong course of diabetes. Moreover, episodes of DKA and hospital admissions account for a large amount of health services costs. Therefore, investigating the frequencies of DKA and hospital admissions is important to develop prevention strategies. Obtaining information about the rates of acute complications in youth with type 1 diabetes and anxiety disorders is crucial in public health research, considering that anxiety disorders are among the most common mental disorders in the general pediatric and adolescent population.[27]

Anxiety disorders in general may have a negative impact on several emotion-regulation strategies.[15,28] Dysfunctional strategies such as avoidance and suppression are positively associated with anxiety whereas problem solving is negatively associated with anxiety.[28] Therefore, dealing with diabetes-specific tasks, e.g. prevention and treatment of hyperglycemia, is probably impaired. Worse glycemic control results and DKA may develop because the person with type 1 diabetes does not recognize the symptoms and signs of DKA or does not follow the DKA prevention regime. Furthermore, anxiety-induced symptoms such as dizziness, shakiness, sweating, and heart palpitations could be misinterpreted as hypoglycaemia.[15] This misinterpretation may result in inadvertently causing hyperglycemia due to carbohydrate ingestions in the setting of euglycemia. If this happens repeatedly, higher HbA1c levels will result in the long term. However, the misinterpreted symptoms may also lead to checking the glucose level, revealing normal values.[15] Again, if this occurs frequently, the youth or the parent are frustrated and they will possibly decrease the number of glucose measurements, which in turn will cause higher HbA1c.[15] Lastly, anxiety disorders in general are often associated with other emotional or behavioral problems and mental disorders. Most mental comorbidities contribute to worse glycemic control as well as to a higher rate of DKA and hospital admissions.[5] In our analysis, we found that 21% of individuals with an anxiety disorder also suffered from depression (see Table 1). Adjusting for depression, we still found higher HbA1c and more hospital admissions in children, adolescents, and young adults with anxiety disorders. This indicates that anxiety is additionally contributing to worse glycemic control and more hospitalizations in youth with type 1 diabetes. Rates of DKA between individuals with and without anxiety disorders did not differ significantly after adjusting for depression. Hence, higher rates of DKA in youth with anxiety disorders, might for the most part refer to the assessed comorbidities rather than the anxiety disorder itself.

Interestingly, rates of severe hypoglycemia did not differ in youth with and without anxiety disorders in our survey. In contrast, youth with other mental comorbidities, for example depression or eating disorders, had higher rates of severe hypoglycaemia.[14,29] Youth with anxiety disorders may have an accompanying fear of severe hypoglycemia, leading to the avoidance and prevention of severe hypoglycaemia.[30,31] Although we were not able to assess and identify fear of hypoglycemia in individuals in the present study, deliberate and frequent decreased insulin doses due to fear of hypoglycemia may well lead to hyperglycemia and subsequently to less frequent severe hypoglycemia. Furthermore, youth with needle phobia often avoid insulin injections and this again results in hyperglycemia and less frequent severe hypoglycemia. Additionally, we closely examined youth

with needle phobia in more detail. In our survey, needle phobia accounted for more than 40% of anxiety disorders. Data regarding needle phobia in type 1 diabetes are limited but other studies note that needle phobia is very common in children with type 1 diabetes.[14,18-20] The most recent study about needle phobia shows that children with positive scores for fear of self-testing, fear of injections, or fear of changing infusion-sites had significantly higher HbA1c than those without.[20] We also observed worse glycemic control in youth with needle phobia compared to youth without anxiety disorders. Remarkably, youth with anxiety disorders other than needle phobia had higher rates of hospital admissions and a longer inpatient care compared to youth with needle phobia. The reason for this remains unclear. Probably, the group of youth with needle phobia comprised also individuals with only mild needle phobia or mild fear of injections. Fear associated with needles and injections is very common and prevalence of needle fear decreases with age.[32] A meta-analysis from 2019 reports that the majority of young children experience needle fear whereas the prevalence of needle fear is 20% to 50% in adolescents and 20% to 30% in young adults in the general population.[32] Mild needle phobia or mild fear of injections in youth with type 1 diabetes may be overcome in some individuals by 'self-treatment', i.e. exposure to self-testing and injections, especially if the diabetes care team provides suggestions, reassurance and encouragement in this process. In line with that, Howe et al. described an improvement of fear and distress with needles after 6 to 9 months compared to the time at diagnosis of type 1 diabetes.[18] In individuals with mild needle phobia or fear of injections the reduction of symptoms after 'self-treatment' and after getting older may lead to less and shorter hospitalizations over time. Moreover, it may be that individuals with needle phobia are frequently treated with psychological interventions because of the need of daily injections in multiple injections therapy or the frequent changing infusion sites in insulin pump therapy, respectively. Treatment of needle phobia consists of exposure therapy and cognitive behavioral therapy in children, adolescents as well as in adults. Regrettably, only limited data about psychological interventions in youth with type 1 diabetes and needle phobia is available.[33] A single study investigated the effect of an interactive computer game on distress of insulin injection in children and adolescents with type 1 diabetes.[33,34] In children and adolescents in general, a review from 2018 reports on different psychological interventions (i.e. distraction, hypnosis, combined cognitive behavioral therapy, and breathing interventions) being effective in reducing needle-related pain and distress.[33] With successful treatment of needle phobia in youth with type diabetes for example by exposure therapy and cognitive behavioral therapy the number of hospitalizations might decrease subsequently. Unfortunately, we do not have any data about psychological interventions offered to children, adolescents and young adults with needle phobia in our study.

In our survey, several limitations were encountered. Anxiety disorders were only recorded in a small group, i.e. in less than 2% of the total population. Given an expected prevalence of 10% to 30% of anxiety symptoms and anxiety disorders,[2,4,5] anxiety disorders are presumably underdiagnosed in this real-world setting. Diabetes care providers only identify 50% of individuals with needle phobia correctly, suggesting that only the more severe forms are being recognized.[13,18,22] Therefore, in our survey, only the more severe anxiety disorders may be reported. However, in our opinion this does not weaken the interpretation of the results. Moreover, we did not analyze the data with respect to the implementation of psychological interventions or pharmacotherapy. Finally, we did not examine the different subgroups of anxiety disorders separately, but focused on anxiety disorders in general and on needle phobia. Youth with either generalized anxiety disorder, social phobia, or panic disorder might have differences with regard to their clinical characteristics, glycemic control, and frequency of acute complications.

In summary, youth with type 1 diabetes and anxiety disorders had worse glycemic control, higher rates of DKA, and higher hospital admission rates compared to youth without anxiety disorders. Youth with anxiety disorders other than needle phobia had higher hospitalization rates and inpatient care was longer compared to those with needle phobia. Because of the considerable metabolic consequences clinicians should be aware of comorbid anxiety disorders in youth with type 1 diabetes and standardized screening should be considered.

ACKNOWLEDGMENTS

We thank all children, adolescents, young adults, and their families, and the diabetes-care-centers participating in the prospective diabetes survey (DPV, complete list see www.d-p-v.eu). DPV was supported by the German Centre for Diabetes Research (DZD, grant number 82DZD14A02), and the German Diabetes Association (DDG). We thank Ramona Ranz and Andreas Hungele for the development work of the DPV software, and Esther Bollow and Katharina Fink for the data management. In addition, we want to thank Julia Grimsmann for help with the preparation of the manuscript and Stefanie Lanzinger for checking the analysis. Open access funding enabled and organized by Projekt DEAL.

AUTHOR CONTRIBUTIONS

Angela Galler designed the research analysis, performed the research, wrote, edited, and reviewed the manuscript. Sascha R. Tittel designed the research analysis, performed the research, contributed to the discussion, and reviewed the manuscript. Harald Baumeister, Christina Reinauer, Burkhard Brosig, Marianne Becker, Holger Haberland, Dörte Hilgard, Marcelus Jivan, Joaquina Mirza, and Julia Schwab contributed to the discussion and reviewed the manuscript. Reinhard W. Holl designed the research analysis, performed the research, contributed to the discussion, and reviewed the manuscript. All authors have read and approved the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13177.

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How to cite this article: Galler A, Tittel SR, Baumeister H, et al. Worse glycemic control, higher rates of diabetic ketoacidosis, and more hospitalizations in children, adolescents, and young adults with type 1 diabetes and anxiety disorders. *Pediatr Diabetes*. 2021;22:519–528. https://doi.org/10.1111/pedi.13177

APPENDIX

TABLE A1 Comparison of children, adolescents and young adults with type 1 diabetes with anxiety disorders vs no mental disorders and vs without anxiety disorders, adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year

	with anxiety disorders (*n* = 1,326)	no mental disorders (*n* = 69,619)	without anxiety disorders (*n* = 73,932)	p with anxiety disorders vs no mental disorders	p with anxiety disorders vs without anxiety disorders
BMI SDS[a]	+0.29 (+0.24; +0.34)	+0.33 (+0.33; +0.34)	+0.33 (+0.32; +0.34)	0.07[b]	0.09[b]
HbA1c (mmol/mol)[a]	**69.7 (68.7; 70.7)**	**66.0 (65.8; 66.1)**	**66.3 (66.2; 66.5)**	**<0.001**[b]	**<0.001**[b]
Rate of episodes of DKA (per 100 patient-years)[c]	**4.2 (3.1; 5.7)**	**2.3 (2.2; 2.4)**	**2.5 (2.4; 2.6)**	**<0.001**[d]	**<0.001**[d]
Rate of severe hypoglycaemia (per 100 patient-years)[c]	10.9 (8.4; 14.1)	12.2 (11.7; 12.6)	12.4 (12.0; 12.8)	0.43[d]	0.35[d]
Hospital admission rate (per 100 patient-years)[c]	**63.6 (59.7; 67.9)**	**38.2 (37.8; 38.7)**	**40.0 (39.6; 40.5)**	**<0.001**[e]	**<0.001**[e]
Length of hospital stay (days per patient-year)[a]	**13.6 (13.3; 13.9)**	**11.2 (11.2; 11.3)**	**11.6 (11.6; 11.6)**	**<0.001**[e]	**<0.001**[e]

[a]Data expressed as estimated mean (95% confidence interval).
[b]Linear regression model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[c]Data expressed as estimated rate per 100 patient-years (95% confidence interval).
[d]Negative-binomial model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.
[e]Poisson model adjusted for age, sex, diabetes duration, migratory background, type of insulin therapy, and treatment year.