OBJECTIVE
Worsening of glycemic control in type 1 diabetes during puberty is a common observation. However, HbA1c remains stable or even improves for some youths. The aim is to identify distinct patterns of glycemic control in type 1 diabetes from childhood to young adulthood.

RESEARCH DESIGN AND METHODS
A total of 6,433 patients with type 1 diabetes were selected from the prospective, multicenter diabetes patient registry Diabetes-Patienten-Verlaufsdokumentation (DPV) (follow-up from age 8 to 19 years, baseline diabetes duration ≥2 years, HbA1c aggregated per year of life). We used latent class growth modeling as the trajectory approach to determine distinct subgroups following a similar trajectory for HbA1c over time.

RESULTS
Five distinct longitudinal trajectories of HbA1c were determined, comprising group 1 = 40%, group 2 = 27%, group 3 = 15%, group 4 = 13%, and group 5 = 5% of patients. Groups 1–3 indicated stable glycemic control at different HbA1c levels. At baseline, similar HbA1c was observed in group 1 and group 4, but HbA1c deteriorated in group 4 from age 8 to 19 years. Similar patterns were present in group 3 and group 5. We observed differences in self-monitoring of blood glucose, insulin therapy, daily insulin dose, physical activity, BMI SD score, body-height SD score, and migration background across all HbA1c trajectories (all \( P \leq 0.001 \)). No sex differences were present.

Comparing groups with similar initial HbA1c but different patterns, groups with higher HbA1c increase were characterized by lower frequency of self-monitoring of blood glucose and physical activity and reduced height (all \( P < 0.01 \)).

CONCLUSIONS
Using a trajectory approach, we determined five distinct longitudinal patterns of glycemic control from childhood to early adulthood. Diabetes self-care, treatment differences, and demographics were related to different HbA1c courses.
Current estimates suggest that the number of children with type 1 diabetes exceeds half a million worldwide (1). In Germany, approximately 30,000 children and young adults are affected by type 1 diabetes (2). One main objective of medical treatment for individuals with type 1 diabetes is to maintain good metabolic control during puberty (3). The American Diabetes Association, International Society for Pediatric and Adolescent Diabetes, and national German diabetes guidelines for children and adolescents advise a target hemoglobin A1c (HbA1c) of less than 7.5% (58 mmol/mol) for all pediatric age-groups (3–5). Despite these recommendations, youths frequently fail to meet targets for metabolic control (6), with glycemic control often deteriorating during early adolescence (6–8) and HbA1c peaking at the age of 16 years (8.5% [69 mmol/mol]) (9).

Previous studies have examined the distribution of metabolic control by age among children and young adults with type 1 diabetes (6,9). Most studies focused on population averages for HbA1c at different ages, often over limited time periods. However, it is important to analyze longitudinal data in diabetes research (10,11). Modeling longitudinal trajectories of disease control can be used to identify subgroups of individuals exhibiting different patterns of change (12–15); multivariable analyses can then be leveraged to identify clinical care factors predicting unique patterns of change. Prior studies have used group-based modeling to identify patterns of metabolic control during adolescence (8,16–18), but their findings were limited by small sample sizes or restricted observation periods. Only one prior study analyzed within-patient trajectories but not group-based trajectories of glycemic control across the pediatric to adult transition in a non-European cohort (6).

Previous research has also revealed that deterioration in metabolic control occurs for many but not all adolescents (16). Identifying which individuals experience worsening metabolic control from childhood to early adulthood represents an important gap in knowledge. Increasing insulin requirements caused by hormonal changes associated with puberty, coping with sexual maturation, and changes in medical care are known to relate to the dynamics of metabolic control (19–21). Furthermore, treatment failure, lack of adherence, insulin purging, eating disorders, and depression (7,16), as well as demographic and socioeconomic variables (6,22), are associated with higher HbA1c. Exactly how these factors relate to trajectories of glycemic control remains to be determined. The established link between insufficient glycemic control in early adolescence and risks for diabetes-related complications in adulthood and the development of lifelong skills emphasizes the importance of establishing optimal metabolic control during this critical time (23).

The objective of the present study was to identify distinct trajectories of HbA1c from age 8 to 19 years among a large number of children, adolescents, and young adults with type 1 diabetes from the German/Austrian Diabetes-Patienten-Verlaufsdokumentation (DPV) registry using group-based modeling adapting the approach by Nagin (12). In addition, we also examined whether demographic and clinical variables discriminate between patterns of glycemic control.

### RESEARCH DESIGN AND METHODS

#### Subjects and Registry

Subjects for the current study were extracted from the multicenter diabetes patient registry DPV. Currently, 440 German/Austrian/Luxembourg/Swiss specialized centers prospectively document demographic and clinical data of patients with diabetes. Twice a year, locally collected data are anonymized and transferred to the University of Ulm, Ulm, Germany, for central analysis and quality assurance. Data are screened for inconsistency or improbability and reported back to centers for verification or correction.

Until September 2015, 421,676 patients with any type of diabetes were documented in the database. For the present analysis, patients with type 1 diabetes were longitudinally followed up from age 8 to 19 years. Subjects with duration of diabetes ≥ 2 years at the age of 8 years were included. Per year of life, data sets were aggregated for each patient (number of visits per individual was median 5.0 [3.0; 6.0] per year of life). Further selection criteria were a mandatory HbA1c value at the age of 8 years (baseline) and HbA1c values in at least another 6 years during follow-up. The final study population comprised 6,433 young patients with type 1 diabetes from 230 German and 15 Austrian centers (Fig. 1).

### Diabetes Outcome Variables

Glycemic control was assessed by HbA1c. The multiple of the mean method was used to mathematically standardize HbA1c to the reference range of the Diabetes Control and Complications Trial (DCCT) (4.05–6.05% [20.7–42.6 mmol/mol]) in order to adjust for differences between laboratories (24,25). Insulin treatment was categorized as insulin pump therapy or injection therapy. Daily insulin dose was calculated per kilogram body weight. The frequency of self-monitoring of blood glucose (SMBG) was recorded per day.

BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m²). Adjusting for age and sex, BMI SD score (BMI-SDS) and body height SD score (H-SDS) were computed using national reference data (KiGGS, Robert Koch Institute, Berlin, Germany) (26). The frequency of physical activity (PA) episodes (duration at least 45 min) was recorded per week. For a detailed description, see Bohn et al. (27). Migration background was defined as at least one parent not born in Germany or Austria.

#### Statistical Analysis

Covariates were analyzed for the age of 8, 12, and 16 years. Results of descriptive statistics are presented as medians with quartiles for continuous variables and as proportions for binary variables. Differences among groups were examined using Kruskal-Wallis or χ² tests. To adjust for multiple testing, P values were corrected by false discovery rate.

We applied latent class growth modeling (LCGM) based on Nagin (12) to identify distinct subgroups following a similar pattern of change over time for HbA1c. LCGM is a semiparametric statistical technique that is used to analyze longitudinal data (12). As the basic assumption is that there are latent clusters of trajectories in the population, the model is also called “latent class mixture model.”

In general, one assumes disease histories (in our case, HbA1c trajectories) of f(i = 1, . . . , N) subjects at T(t = 1, . . . , T) times. There are J (j = 1, . . . , J) latent clusters of different
Diabetes patients in DPV (09/15): 
\(n=421,676\)

- Type 1 diabetes: 
  \(n=104,956\)
- Other types of diabetes: 
  \(n=316,720\)
- 8 to 19 years: 
  \(n=63,538\)
- \(<8\) or \(>19\) years: 
  \(n=41,418\)
- Diabetes duration \(\geq 2\) years at age 8 years: 
  \(n=12,223\)
- Diabetes duration \(< 2\) years at age 8 years: 
  \(n=51,315\)
- No HbA1c at age 8 years and/or at least six HbA1c values missing between 8 and 19 years: 
  \(n=5,790\)

Study population: 
\(n=6,433\)

Figure 1—Flowchart for selection of the study population from the DPV registry.

_histories in the population. \(Y_i = \{y_{i1}, \ldots, y_{iT}\}\) describes the longitudinal sequence of measurements of subject \(i\) over \(T\) times. For convenience, \(Y_i\) describes the complete behavior of a subject \(i\). The probability of observing \(Y_i\) is \(P(Y_i = y_i) = \prod_{t=1}^{T} p(y_{it})\), where \(p(y_{it})\) denotes the probability distribution function of \(y_{it}\) at time \(t\) given membership in the latent cluster \(j\), and \(\pi_j\) is the probability of belonging to cluster \(j\). Each cluster \(j\) is modeled by

\[y_{it} \mid j = \beta_0 + \beta_1 \text{Age}_{it} + \beta_2 \text{Age}_{it}^2 + \beta_3 \text{Age}_{it}^3 + e_{it},\]

where \(\text{Age}_{it}\) denotes the age of subject \(i\) at time \(t\), \(\beta_0, \beta_1, \beta_2, \text{and } \beta_3\) are the parameters that determine the shape of the polynomial in cluster \(j\), and \(e_{it}\) is a normally distributed error term. A latent variable \(y_{it}\) presents the linkage between age and \(\text{HbA1c}\). Each function corresponds to a distinct trajectory. Parameters are estimated by maximum likelihood. For more details see Nagin, section 2.2.1 (12).

The aim of the LCGM is to select the model with optimal number of distinct patterns as well as the appropriate polynomial order that represents the heterogeneity in trajectories (12). The number of groups and orders of the polynomials were determined by the Bayes information criterion (BIC). As BIC does not always explicitly identify an optimal number of groups, the context of the study objectives and also clinical relevance should be considered (13,28). A further criterion discussed in literature is that each trajectory should include at least 5% of all patients (28). The search for the optimal number of groups was performed by a “forward” classifying approach, which starts with a one-class solution and then adds further classes.

Subsequently, multinomial logistic regression models were used to assess which parameters are associated with the membership in the respective classes. Sex, age at onset, baseline \(\text{HbA1c}\), baseline visit year, and SMBG, insulin pump therapy, insulin dose, BMI-SDS, H-SDS, PA, and migration background were included as covariates. Results are given as odds ratios (OR) with 95% CI.

SAS 9.4 (SAS Institute Inc., Cary, NC) was used. Trajectory analysis was performed using the PROC TRAJ macro (29). To validate the results of this macro, we also used PROC NLP. A two-sided \(P < 0.01\) was considered significant.

RESULTS

We analyzed 6,433 patients with type 1 diabetes followed from childhood to young adulthood. A total of 51.6% of the patients were male. At baseline, mean age was 8.5 years [8.4; 8.6] with a median duration of diabetes of 4.1 years [2.8; 5.6]. Median HbA1c was 7.3% [6.7; 8.0] (56 mmol/mol [50; 64]).

Trajectory Analysis

Using the LCGM, five classes with distinct trajectories of metabolic control were identified (Fig. 2). BIC continuously decreased from the one-class model to the five-class model (BIC1 = 96,313, BIC2 = 84,402, BIC3 = 80,129, BIC4 = 78,207, and BIC5 = 76,512). Adding a sixth class yielded a lower BIC (BIC6 = 75,440) but lowered one group size to below 5%. Polynomial functions were fitted using quadratic and cubic orders (BIC5opt = 76,246). Using the PROC NLP procedure, similar results were observed.

The largest class (\(n = 2,646\), 40% of patients, group 1) showed a stable pattern of good metabolic control and was therefore named “intermediate stable.” Group 2 (\(n = 1,709\), 26.9%), the “low stable” group, is a cluster of individuals with low initial HbA1c and slight increase in HbA1c. Individuals with stable, but high HbA1c were classified as “high stable” (\(n = 941\), 16.6%, group 3). The “intermediate increase” trajectory (\(n = 788\), 13.0%, group 4) was characterized by intermediate initial glycemic control and an increase of HbA1c. Subjects with high baseline HbA1c and an increase from age 8 to 19 years were classified as the “high increase” group (\(n = 349\), 5.4%, group 5).

Comparison of Baseline and Follow-up Characteristics

Patient characteristics of each group are depicted in Table 1. At the age of 8 (baseline), 12, and 16 years, we observed differences in HbA1c, SMBG frequency, mode of insulin therapy, daily insulin dose, BMI-SDS, H-SDS, PA, and migration background across all trajectories (all \(P \leq 0.001\)). Proportion of migration background was lowest in the low stable trajectory. There were no differences in sex distribution or age at diabetes onset across all groups.
HbA1c rose from childhood to young adulthood in all five groups, with a higher HbA1c increase in the intermediate increase and high increase groups, and a smaller increase in the three stable groups (Table 1). Frequency of SMBG decreased in all groups. At the age of 16 years, the lowest frequency of SMBG was observed in the intermediate increase and high increase groups. Across all groups, the number of subjects treated with insulin pump increased. At the age of 16 years, a lower proportion of insulin pump therapy was observed in the high stable, intermediate increase, and high increase trajectories. Daily insulin dosage rose across all groups, with the lowest dosage in the low stable and intermediate stable groups.

H-SDS decreased in all trajectory groups, except in the low stable group. Youths aged 16 years were shorter in the high stable, intermediate increase, and high increase trajectory groups.

Frequency of PA increased with age in the low stable and intermediate stable trajectories, while it decreased in the high increase group. At the age of 16 years, subjects in the low stable and intermediate stable groups were more physically active.

Unadjusted Comparison Between Different Trajectory Groups
Because of the similar initial metabolic control but higher increase over time, we compared the high stable and high increase groups and the intermediate stable and intermediate increase groups (Table 1).

No baseline differences were observed between the high stable and the high increase groups (all $P > 0.05$). At the age of 12 years, subjects in the high increase group had worse metabolic control, had lower body height, and were more often physically inactive (all $P < 0.01$). At the age of 16 years, patients in the high increase group had higher daily insulin requirement, whereas frequency of SMBG and PA and standardized height and weight were lower (all $P < 0.001$).

At baseline, no differences were present between the intermediate increase and the intermediate stable groups, except SMBG frequency was lower in the intermediate increase group ($P < 0.001$). The intermediate increase group was characterized by higher HbA1c and lower frequency of SMBG in patients aged 12 years and by higher daily insulin dose, lower frequency of SMBG, and less PA in patients aged 16 years (all $P < 0.001$). No differences were observed in standardized height and weight between groups.

Adjusted Regression Models at Age 16 Years
Results of multinomial regression models are presented in Table 2. At baseline, no differences between the high increase and the high stable trajectories were present. A higher BMI-SDS and H-SDS and more SMBG and PA at the age of 16 years were related to a lower risk of belonging to the high increase trajectory.

Comparing the intermediate increase and the intermediate stable trajectories at the age of 8 years, no differences were observed, except for the calendar year of baseline visit (OR [95% CI] 0.94 [0.91; 0.97]). Patients aged 16 years with more frequent SMBG and more PA as well as lower daily insulin dose were less likely to be in the intermediate increase trajectory.

Secondary Analysis of Treatment Center
No differences in center size were present across all trajectories. Distribution of center size was similar between the high stable and high increase groups and also between the intermediate stable and intermediate increase trajectories. In the multinomial regression models, similar findings were observed.

CONCLUSIONS
This longitudinal study aimed to investigate developmental courses of metabolic control during adolescence in a large cohort of German/Austrian patients with type 1 diabetes. Using a group-based modeling approach, we observed five groups with distinct trajectories of glycemic control. Three groups followed a relatively stable pattern at different HbA1c levels (approximately 80% of the patients), whereas two groups exhibited deterioration in metabolic control at different initial HbA1c levels (approximately 20%). Diabetes self-care, treatment differences, and demographics were related to differential development of HbA1c during the transition from childhood to young adulthood.

Subgroups with distinct longitudinal trajectories of metabolic control across the young adolescent–to–adult transition have not been reported for a large population with type 1 diabetes before. Although improvement in metabolic control in children and adolescents during the past decade was reported (25), many youths still fail to achieve targets (6). Even though previous research revealed deterioration in glycemic control up to age 16 years (6), not every child is equally susceptible to HbA1c deterioration (17). A previous study showed that metabolic control remained relatively stable in many
Table 1—Characteristics of the study population

<table>
<thead>
<tr>
<th>Group, group probability</th>
<th>Male, %</th>
<th>Age at type 1 diabetes onset, years</th>
<th>Migration, %</th>
<th>Age, years</th>
<th>HbA1c, % (mmol/mol)</th>
<th>SMBG, per day</th>
<th>Pump therapy, %</th>
<th>Daily insulin dose, IU/kg</th>
<th>BMI-SDS</th>
<th>H-SDS</th>
<th>PA, per week</th>
<th>Probability of diabetes onset, years</th>
<th>HbA1c, % (mmol/mol)</th>
<th>SMBG, per day</th>
<th>Pump therapy, %</th>
<th>Daily insulin dose, IU/kg</th>
<th>BMI-SDS</th>
<th>H-SDS</th>
<th>PA, per week</th>
<th>Probability of diabetes onset, years</th>
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</thead>
<tbody>
<tr>
<td>Low stable, 0.92</td>
<td>54</td>
<td>4.5 [3.0; 5.8]</td>
<td>14</td>
<td>8</td>
<td>6.6 [6.2; 7.1]</td>
<td>6.0</td>
<td>17</td>
<td>0.8</td>
<td>0.26</td>
<td>0.21</td>
<td>1.0 [0.0; 2.0]</td>
<td>2.0 [0.22; 0.73]</td>
<td>2.0 [0.43; 0.87]</td>
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<td>12</td>
<td>(49 [44; 54]) [5.0; 7.9]</td>
<td>[0.7; 0.9]</td>
<td>[0.44; 0.62]</td>
<td>[0.43; 0.91]</td>
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<td>Intermediate stable, 0.89</td>
<td>52</td>
<td>4.4 [2.9; 5.7]</td>
<td>18*</td>
<td>8</td>
<td>7.4 [7.0; 7.8]</td>
<td>6.0</td>
<td>19</td>
<td>0.8</td>
<td>0.30</td>
<td>0.13</td>
<td>1.0 [0.0; 2.0]</td>
<td>2.0 [0.19; 0.78]</td>
<td>2.0 [0.53; 0.80]</td>
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<td>12</td>
<td>(57 [53; 62]) [4.3; 7.1]</td>
<td>[0.7; 0.9]</td>
<td>[0.26; 0.84]</td>
<td>[0.45; 0.90]</td>
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<tr>
<td>High stable, 0.88</td>
<td>49*</td>
<td>4.2 [2.8; 5.6]</td>
<td>28*</td>
<td>8</td>
<td>8.4 [7.9; 9.0]</td>
<td>5.0</td>
<td>13*</td>
<td>0.8</td>
<td>0.38</td>
<td>0.01</td>
<td>1.0 [0.0; 2.0]</td>
<td>2.0 [0.16; 0.92]</td>
<td>2.0 [0.68; 0.68]</td>
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<td>12</td>
<td>(68 [63; 75]) [4.0; 7.0]</td>
<td>[0.7; 0.9]</td>
<td>[0.16; 0.92]</td>
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<td>Intermediate increase, 0.87</td>
<td>50</td>
<td>4.3 [2.9; 5.7]</td>
<td>21*</td>
<td>8</td>
<td>7.4 [7.3; 8.1]</td>
<td>6.0</td>
<td>35</td>
<td>0.9</td>
<td>0.18</td>
<td>0.10</td>
<td>2.0 [0.0; 3.0]</td>
<td>2.0 [0.37; 0.71]</td>
<td>2.0 [0.56; 0.78]</td>
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<td>12</td>
<td>(61 [57; 65]) [4.3; 7.0]</td>
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<td>[0.37; 0.71]</td>
<td>[0.56; 0.78]</td>
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<td>High increase, 0.95</td>
<td>48</td>
<td>4.3 [2.9; 5.7]</td>
<td>24*</td>
<td>8</td>
<td>9.0 [8.5; 9.6]</td>
<td>5.0</td>
<td>26*</td>
<td>0.9</td>
<td>0.72</td>
<td>2.0</td>
<td>1.0 [0.0; 3.0]</td>
<td>2.0 [0.28; 0.88]</td>
<td>2.0 [0.86; 0.56]</td>
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<td>16</td>
<td>(75 [69; 81]) [4.0; 6.5]</td>
<td>[0.8; 1.1]</td>
<td>[0.28; 0.88]</td>
<td>[0.86; 0.56]</td>
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Data are given as median with quartiles or proportions, unless otherwise stated. *Significant differences from the reference group low stable (P < 0.01).
individuals during adolescence (30). This stability over years despite dramatic changes underscores the importance of childhood determinants of diabetes-related outcomes in adulthood (31). Several studies examining this intragroup variability strengthen our finding of different patterns of HbA1c associated with diverse predictors (8,16–18).

Comparing trajectories with similar initial glycemic control but different HbA1c increase, groups differed by self-care with lower frequency of SMBG in subjects with HbA1c deterioration. This finding is in line with previous research pointing out that SMBG is related to longitudinal HbA1c trajectories (17). Furthermore, a longitudinal study indicated that individuals using insulin pumps were less likely to be in the deteriorating trajectory compared with patients with injection therapy (8). This corresponds to our finding and suggests that the established benefits of pump therapy, including the ability to adjust basal rates, may contribute to better HbA1c courses (37,38).

Research previously concluded that body height was negatively correlated with HbA1c (35). Retardation in growth after onset of disease has been reported in both cross-sectional and longitudinal studies (35,36). This is in accordance with our finding that deteriorating metabolic control trajectories are related to shorter body height. Hence, growth retardation might represent a potential long-term complication of poor glycemic control.

Furthermore, a longitudinal study indicated that different trajectories of HbA1c among patients with HbA1c increase in insulin-stimulated glucose uptake in muscles, improved well-being, and reduced risk of overweight, all of which might contribute to better HbA1c (27,33,34).

In contrast to previous studies (6,17), Helgeson et al. (8) corroborate our finding that sex and age at onset did not differ between trajectories. However, different results might be explained by diverse study populations or different numbers of trajectories. In stable good HbA1c courses, fewer youths with migration background were observed. Language barriers, communication problems, and heterogeneous health status among ethnicities might contribute to difficulties during routine care and result in suboptimal metabolic control (6,41).

Although not addressed in the current study as the information was not available, it is recognized that HbA1c patterns are also likely to be influenced by genetic or disease-specific factors (22), as well as by psychosocial factors (8,18,19,21).

The group-based modeling approach is a valuable tool to analyze longitudinal disease histories by identifying distinct clusters (12). Despite the advantages, the method is discussed controversially in literature (42). PROC TRAJ is not official SAS procedure, but rather a macro and is therefore not validated by the SAS Institute. However, we used the PROC NLP procedure as reported by Kuss et al. (14) to validate this macro and observed similar results. Furthermore, as the BIC often fails to find an optimal number of clusters, researchers have to apply additional criteria based on clinical relevance. Nevertheless, this is a common problem described in other publications (17). In a recent article, Twisk and Hoekstra (28) concluded that LCGM seems to be preferable above more simple methods.

A strength of this study is the huge number of pediatric patients and the long observation period of HbA1c during adolescence. The DPV database provides detailed information on patients’ characteristics that allows for the examination of multiple factors associated with HbA1c trajectories. One limitation of the current study might be that HbA1c was not measured in a central laboratory. However, HbA1c levels were mathematically standardized to reduce variation between laboratories. As in the group-based modeling approach missing data are assumed to be missing at random and LCGM are estimated by using all available observations, our data provide sufficient information. However, a considerable number of patients were
excluding due to the lack of observations in more than half of the years during follow-up. Although we observed similar baseline characteristics in both the study cohort and patients excluded, a selection bias cannot be excluded completely. Moreover, no differences across the groups were observed at baseline. Thus, future research should evaluate additional covariates that might predict these trajectories, including genetic and psychosocial factors. In particular, physicians should focus on preventive interventions to improve HbA1c and to reduce the risk of long-term diabetes-related complications in youths at risk for unfavorable trajectories of glycemic control.

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Sponsors were not involved in data acquisition or analysis.

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

Author Contributions. A.S. wrote the manuscript. A.S., J.M.H., and R.W.H. analyzed data. J.M.H., J.R., C.B., D.D., J.G.-H., O.K., B.R.-M., and C.V. researched data and reviewed and edited the manuscript. R.W.H. 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. Prior Presentation. Parts of the work were presented in the poster session of the International Society for Pediatric and Adolescent Diabetes annual meeting, Valencia, Spain, 26–29 October 2016.

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