Longitudinal trajectories of metabolic control from childhood to young adulthood in type 1 diabetes from a large German/Austrian registry: A group-based modelling approach

Short running title: Trajectories of HbA1c during puberty

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Abstract

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

Research Design and Methods 6,433 type 1 diabetes-patients were selected from the prospective, multicenter diabetes patient registry DPV (follow up from 8-19 years, baseline diabetes duration ≥2 years, HbA1c aggregated per year of life). We used latent class growth modelling as trajectory approach to determine distinct subgroups following a similar trajectory for HbA1c over time.

Results Five distinct longitudinal trajectories of HbA1c were determined comprising g_1=40%, g_2=27%, g_3=15%, g_4=13%, and g_5=5% of patients. Groups 1-3 indicated stable glycemic control at different HbA1c-levels. At baseline similar HbA1c was observed in groups 1 and 4, but HbA1c deteriorated in group 4 from age 8 to 19 years. Similar patterns were present between groups 3 and 5. We observed differences in self-monitoring of blood glucose (SMBG), insulin therapy, daily insulin dose, physical activity (PA), BMI-SDS, body-height-SDS, and migration background across all HbA1c trajectories (all $p \leq 0.001$). No gender differences were present. Comparing groups with similar initial HbA1c but different patterns, groups with higher HbA1c increase were characterized by lower frequency of SMBG and PA, and reduced height (all $p<0.01$).

Conclusion 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.

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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 (ADA), international society for pediatric and adolescent diabetes (ISPAD), and national German diabetes guidelines for children and adolescents advise a target hemoglobin A1c (HbA1c) 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, and 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 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 as well as the development of lifelong skills emphasizes the importance of establishing optimal metabolic control during this critical time (23)(23).

The objective of this 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 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 present study were extracted from the multicenter diabetes patient registry DPV ("Diabetes-Patienten-Verlaufsdokumentation"). 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, 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, datasets were aggregated for each patient (median number of visits per individual was 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 six years during follow up. The final study population comprised 6,433 young patients with type 1 diabetes from 230 German and 15 Austrian centers (Figure 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.

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Adjusting for age and gender, BMI standard deviation score (BMI-SDS) and body height-SDS (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 minutes) was recorded per week. For detailed description see (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 χ^2-tests. To adjust for multiple testing, p-values were corrected by false discovery rate (FDR).

We applied latent class growth modelling (LCGM) based on Nagin (12) to identify distinct subgroups following a similar pattern of change over time for HbA1c. LCGM is a semi-parametric statistical technique which is used to analyze longitudinal data (12). Since 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 *I* (i=1,…,N) subjects at *T* (t=1,…,T) times. There are *J* (j=1,…,J) latent clusters of different 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_{it} describes the complete behavior of a subject i. The probability of observing Y_i is $P(Y_i=y_i)=\sum_{j=1}^{J}\pi_j\prod_{t=1}^{T}p(y_{it}|j)$, where $p(y_{it}|j)$ denotes the probability distribution function of y_{it} at time t given membership in the latent cluster j, and π_j is the probability of belonging to cluster j. Each cluster j is modeled by

$$y^*_{it\,|\,j}=\beta^j_0+\beta^j_1 Age_{it}+\beta^j_2 Age^2_{it}+\beta^j_3 Age^3_{it}+\varepsilon_{it}{}^j,$$

where Age_{it} denotes the age of subject i at time t, β^j_0, β^j_1, β^j_2, and β^j_3 are the parameters that determine the shape of the polynomial in cluster j, and ε^j_{it} is a normally distributed error term. A latent variable y^*_{it} presents the linkage between age and 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 five percent 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. Gender, age at onset, baseline HbA1c, baseline visit year as well as SMBG, insulin pump therapy, insulin dose, BMI-SDS, body height-SDS and PA at the age of 16 years were included as covariates. Results are given as odds ratios (OR) with 95% confidence intervals.

Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC, USA) 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-value <0.01 was considered significant.

Results

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

Trajectory analysis

Using the LCGM, five classes with distinct trajectories of metabolic control were identified (Figure 2). BIC continuously decreased from the one-class model to the five-class model (BIC_1=96,313, BIC_2=84,402, BIC_3=80,129, BIC_4=78,207, BIC_5=76,512). Adding a sixth

class yielded a lower BIC (BIC_6=75,440) but lowered one group size to below 5%. Polynomial functions were fitted using quadratic and cubic orders (BIC_{5opt}=76,246). Using the PROC NLP procedure, similar results were observed.

The largest class (n=2,646, 40% of patients, black short dashed line, group 1) showed a stable pattern of good metabolic control and was therefore named *intermediate stable*. Group 2 (n=1,709, 26.9%, red solid line), 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%, green long dashed line, group 3). The *intermediate increase* trajectory (n= 788, 13.0%, blue dash dotted line, 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 *high increase* group (n=349, 5.4%, orange dash dot dotted line, 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, self-monitoring frequency, mode of insulin therapy, daily insulin dose, BMI-SDS, height-SDS, physical activity, and migration background across all trajectories (all p≤0.001). Proportion of migration background was lowest in the *low stable* trajectory. There were no differences in gender 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.

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

Frequency of physical activity 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

Due to similar initial metabolic control but higher increase over time, we compared the *high stable* and the *high increase* groups, and also the *intermediate stable* and the *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, smaller 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, while frequency of SMBG and physical activity, 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 being 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 physical activity 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* trajectory were present. A higher BMI-SDS and height-SDS, more SMBG and more physical activity 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* trajectory at the age of 8 years, no differences were observed, except for the calendar year of baseline visit (OR with 95% confidence interval: 0.94 [0.91; 0.97]). Patients aged 16 years with more frequent SMBG and more physical activity 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 the *high increase* groups, and also between the *intermediate stable* and the *intermediate increase trajectories.* In the multinomial regression models, similar findings were observed.

Conclusion

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), while two groups exhibited deterioration in metabolic control at different initial HbA1c levels (approximately 20%). Diabetes self-care, treatment differences as well as 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 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 (17-19), and is also consistent with cross-sectional studies linking frequent SMBG to better metabolic control (32). Motivation and adhering to self-monitoring as well as improved self-care associated with frequent SMBG are possible explanations.

In the current study, subjects with stable good metabolic control were more physically active compared to patients with impaired glycemic control. Physical activity has many positive health benefits such as enhanced insulin sensitivity, lower blood glucose, an increase in insulin-stimulated glucose uptake in muscles as well as improve well-being and reduced risk of overweight, all of which might contribute to better HbA1c (27, 33, 34).

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 smaller body height. Hence, growth retardation might represent a potential long-term complication of poor glycemic control.

Furthermore, a longitudinal study indicated that individuals using insulin pumps were less likely to be in the deteriorating trajectory compared to 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). Moreover, our finding of higher insulin dose among patients with HbA1c increase is in line with previous research (39) and might be explained by increased insulin resistance, hormonal changes or reduced compliance during puberty (7, 40).

Furthermore, we examined demographic factors related to HbA1c patterns. In contrast to previous studies (6, 17) Helgeson et al. (8) corroborate our finding that gender 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 present study as 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 no official SAS procedure, but rather a macro and is therefore not validated by the SAS Institute. However, to validate this macro we used the PROC NLP procedure as reported by Kuss et al. (14), and observed similar results. Furthermore, since 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 as well (17). In a recent paper, 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 that allows analyzing patterns of HbA1c during adolescence. The DPV database provides detailed information on patients' characteristics that allow the

examination of multiple factors associated with HbA1c trajectories. One limitation of the present study might be that HbA1c was not measured in a central laboratory. However, to reduce variation between laboratories, HbA1c levels were mathematically standardized. Since 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 excluded due to 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, at baseline no differences across the groups were observed. Thus, future research should evaluate additional covariates that might predict these trajectories, including genetic and psychosocial factors. In particular, in youths at risk for unfavorable trajectories of glycemic control, physicians should focus on preventive interventions to improve HbA1c and to reduce the risk of long-term diabetes-related complications.

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Conflict of Interest

The authors report that they have no conflict of interest.

Author Contributions

R.W.H. is the principle investigator of the study, contributed to data analysis and interpretation, and reviewed/edited the manuscript. A.S. wrote the manuscript. J.M.H., C.B., D.D., J.G.-H., O.K., B.R.-M., J.R. and C.V. researched data und reviewed/edited the manuscript. Analyzed the data: A.S., J.M.H. and R.W.H. All co-authors approved the final version to be published.

Ethic

The Ethics Committee of the University of Ulm has authorized the DPV Initiative as well as analyses of anonymized data related to quality of care. The local review board of each participating center has approved the anonymized data collection.

Guarantor statement

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 accuracy of the data analysis.

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Table 1 Characteristics of the study population.

Group with group probability	Male, %	Age at type 1 diabetes onset, years	Migration, %	Age, years	HbA1c, % (HbA1c mmol/mol)	SMBG, per day	Pump therapy, %	Daily insulin dose, IU/kg	BMI-SDS	H-SDS	Physical activity, per week
Low stable	54	4.5 [3.0;5.8]	14	**8**	6.6 [6.2;7.1] (49 [44;54])	6.0 [5.0;7.9]	17	0.8 [0.7;0.9]	0.26 [-0.22;0.73]	0.21 [-0.43;0.87]	1.0 [0.0;2.0]
0.92				**12**	6.8 [6.5;7.2] (51 [48;55])	6.0 [5.0;8.0]	35	0.9 [0.7;1.0]	0.09 [-0.44;0.62]	0.21 [-0.43;0.91]	2.0 [1.0;3.0]
				16	7.0 [6.6;7.4] (53 [49;57])	5.4 [4.3;7.0]	40	0.9 [0.8;1.1]	0.30 [-0.26;0.84]	0.24 [-0.45;0.90]	2.0 [0.0;3.0]
Intermediate stable	52	4.4 [2.9;5.7]	18*	**8**	7.4 [7.0;7.8]* (57 [53;62])	6.0 [4.3;7.1]*	19	0.8 [0.7;0.9]	0.30 [-0.19;0.78]	0.13 [-0.53;0.80]	1.0 [0.0;2.0]
0.89				**12**	7.7 [7.4;8.1]* (61 [57;65])	6.0 [5.0;7.1]*	38	0.9 [0.7;1.0]	0.18 [-0.37;0.71]*	0.10 [-0.56;0.78]*	2.0 [1.0;3.0]
				16	8.1 [7.6;8.6]* (65 [60;70])	5.0 [4.0;6.0]*	43	0.9 [0.8;1.1]	0.41 [-0.13;0.91]*	0.00 [-0.69;0.70]*	2.0 [0.0;3.0]
High stable	49*	4.2 [2.8;5.6]*	28*	**8**	8.4 [7.9;9.0]* (68 [63;75])	5.0 [4.0;7.0]*	13*	0.8 [0.7;0.9]*	0.38 [-0.16;0.92]*	0.01 [-0.68;0.68]*	1.0 [0.0;2.0]*
0.88				**12**	9.0 [8.5;9.6]* (75 [69;81])	5.0 [4.0;6.5]*	26*	0.9 [0.8;1.1]*	0.72 [-0.28;0.88]*	-0.10 [-0.86;0.56]*	2.0 [0.0;3.0]*
				16	9.0 [8.4;9.5]* (75 [68;80])	5.0 [4.0;6.0]*	33*	1.0 [0.8;1.2]*	0.62 [0.14;1.14]*	-0.42 [-1.13;0.32]*	1.0 [0.0;3.0]*

Intermediate increase	50	4.3 [2.9;5.7]	21*	**8**	7.4 [6.9;7.9]* (57 [52;63])	5.0 [4.0;7.0]*	14	0.8 [0.7;0.9]	0.33 [-0.11;0.77]	0.11 [-0.52;0.70]	1.0 [0.0;2.0]
				12	8.4 [7.8;8.9]* (68 [62;74])	5.6 [4.3;7.0]*	35	0.9 [0.7;1.1]*	0.17 [-0.35;0.73]*	0.04 [-0.62;0.73]*	2.0 [0.0;3.0]*
0.87				**16**	10.3 [9.6;11.1]* (89 [81;98])	4.0 [3.7;5.0]*	38	1.0 [0.8;1.2]*	0.43 [-0.20;0.92]	-0.09 [-0.72;0.55]*	1.0 [0.0;2.0]*
High increase	48	4.3 [2.9;5.7]	24*	**8**	8.5 [7.9;9.4]* (69 [63;79])	5.0 [4.0;6.0]*	15	0.8 [0.7;1.0]*	0.36 [-0.14;0.87]*	-0.05 [-0.83;0.50]*	1.0 [0.0;2.0]*
				12	10.1 [9.3;11.0]* (87 [78;97])	5.0 [4.0;6.0]*	29	1.0 [0.8;1.1]*	0.18 [-0.33;0.77]*	-0.29 [-1.08;0.22]*	1.0 [0.0;2.0]*
0.95				**16**	11.8 [11.0;13.0]* (105 [97;119])	4.0 [3.0;5.0]*	28*	1.1 [0.9;1.3]*	0.34 [-0.47;0.84]	-0.67 [-1.49;-0.08]*	0.0 [0.0;2.0]*

Values are given as median with quartiles or proportions. Significant differences from the reference group *low stable* are marked with * ($p<0.01$).

HbA1c: Hemoglobin A1c, SMBG: self-monitoring of blood glucose, BMI-SDS: body mass index standard deviation score KIGGS, H-SDS: Body height–SDS KIGGS.

Table 2 Comparison between the *high increase* and *high stable* and between the *intermediate increase* and *intermediate stable* groups at age 16 years.

	High increase **versus** ***high stable*** *OR with 95% confidence intervals* (β coefficients with standard error)	***Intermediate increase*** **versus** ***intermediate stable*** *OR with 95% confidence intervals* (β coefficients with standard error)
Male versus female	**0.50 [0.30; 0.81]** (β= -0.34±0.13)	0.82 [0.63; 1.07] (β= -0.10±0.07)
Age at type 1 diabetes onset, years	1.06 [0.93; 1.21] (β= 0.06±0.07)	0.93 [0.87; 1.01] (β= -0.07±0.04)
Baseline HbA1c, %	0.94 [0.76; 1.16] (β= -0.06±0.11)	1.04 [0.89; 1.22] (β= 0.04±0.08)
SMBG, per day	**0.74 [0.64; 0.87]** (β= -0.30±0.08)	**0.76 [0.70; 0.83]** (β= -0.28±0.04)
Pump therapy versus injections	0.83 [0.50; 1.37] (β= -0.10±0.13)	1.19 [0.91; 1.56] (β= 0.09±0.07)
Daily insulin dose, IU/kg	1.90 [0.98; 3.72] (β= 0.64±0.34)	**2.80 [1.80; 4.37]** (β= 1.04±0.23)
BMI-SDS	**0.50 [0.38; 0.65]** (β= -0.70±0.14)	0.99 [0.85; 1.16] (β= -0.01±0.08)
H-SDS	**0.78 [0.63; 0.97]** (β= -0.25±0.11)	0.92 [0.81; 1.03] (β= -0.08±0.06)
Physical activity, per week	**0.85 [0.74; 0.98]** (β= -0.16±0.07)	**0.91 [0.85; 0.98]** (β= -0.09±0.03)
Baseline visit year, years	1.01 [0.95; 1.07] (β= 0.01±0.03)	0.99 [0.96; 1.03] (β= -0.01±0.02)

Multivariable models were fitted with co-variables gender, age at type 1 diabetes onset, baseline HbA1c, baseline visit year as well as SMBG, pump therapy, insulin dose, BMI-

SDS, body height-SDS, and physical activity at the age of 16 years. Estimates are odds ratios (OR) with 95% confidence intervals. ORs in bold depict statistical significance ($p<0.01$).

HbA1c: Hemoglobin A1c, SMBG: self-monitoring of blood glucose, BMI-SDS: body mass index standard deviation score KIGGS, H-SDS: Body height–SDS KIGGS.

Figure legends

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

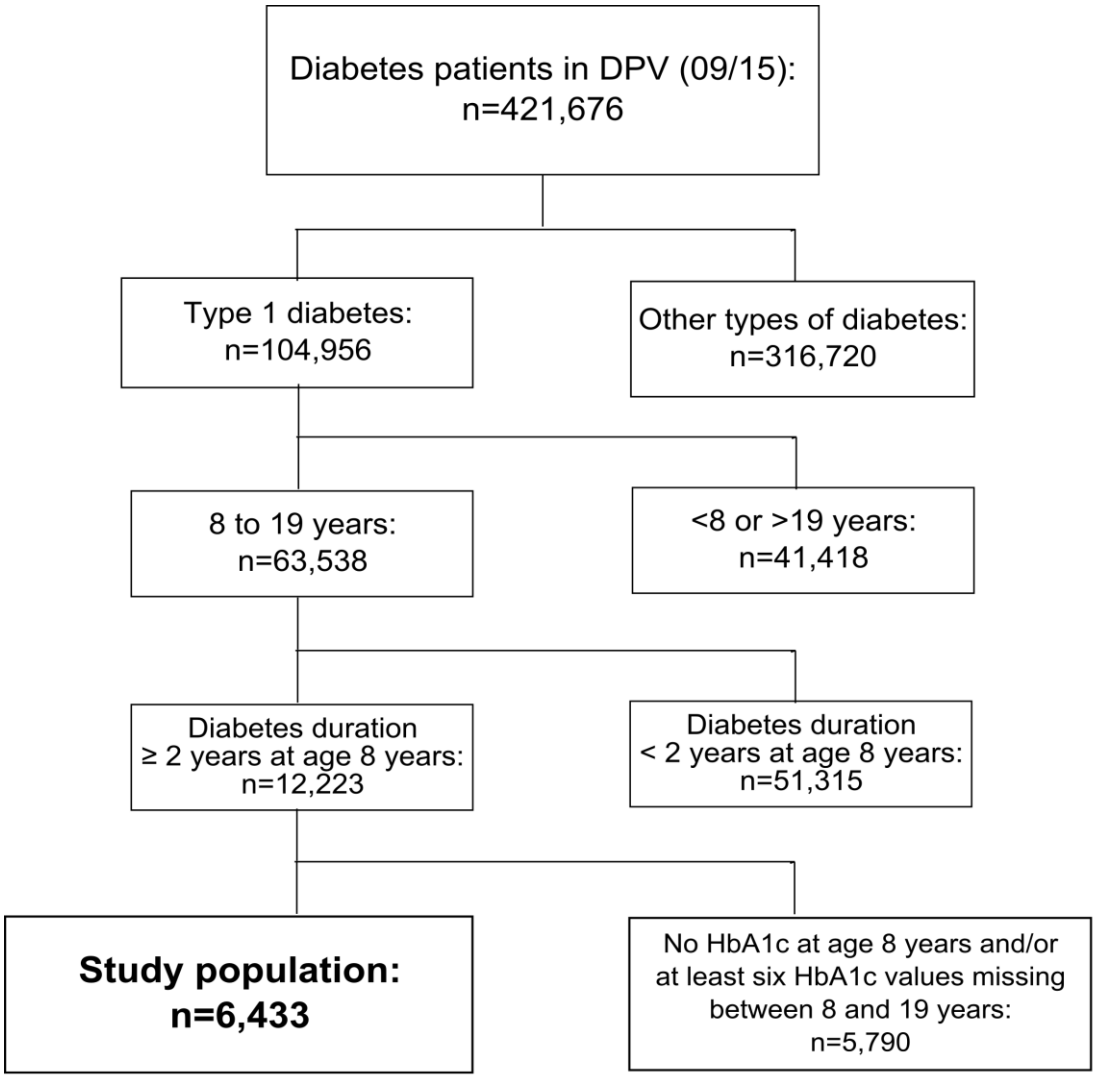

Figure 2 Figure depicts HbA1c trajectories with 99% confidence intervals for the five different cluster during puberty. The red curve (solid line, group 2, 26.9%) is categorized as *low stable*, the black curve (short dash line, group 1, 40.0%) as *intermediate stable*,

the green curve (long dash line, group 3, 14.6%) as *high stable*, the blue curve (dash dot line, group 4, 13.0%) as *intermediate increase*, and the orange curve (dash dot dot line, group 5, 5.4%) as *high increase*.