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Time trends towards earlier puberty in boys and girls with type 1 diabetes: Insights from the German Diabetes Prospective Follow-up (DPV) registry, 2000 to 2021

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Abstract

Aim: To examine the time trends and factors associated with the onset of puberty in children with type 1 diabetes (T1D) using data from the German Diabetes Prospective Follow-up (*Diabetes-Patienten-Verlaufsdokumentation* [DPV]) registry.

Methods: A total of 13 127 children with T1D, aged 6 to 18 years, were included in the analysis. Regression analysis was performed to investigate the relationship between diabetes duration, body mass index (BMI) standard deviation score (SDS), glycated haemoglobin (HbA1c) level, migration background, and the onset of puberty, stratified by sex.

Results: Our findings revealed a significant trend towards earlier puberty in both girls and boys with T1D over the observed period (2000 to 2021). Puberty onset in girls (thelarche Tanner stage B2) decreased from 11.48 (11.35-11.65) years in 2000 to 10.93 (10.79-11.08) years in 2021 and gonadarche (Tanner stage G2/testicular volume >3 mL) decreased from 12.62 (12.42-12.82) years in 2000 to 11.98 (11.79-12.16) years in 2021 in boys (both $P < 0.001$). Longer diabetes duration, higher BMI SDS, and lower HbA1c level were associated with earlier puberty in both sexes ($P < 0.001$).

Conclusions: Our study highlights earlier puberty in children with T1D, influenced by BMI SDS, HbA1c level, and migration background. This has important implications for diabetes management and supporting healthy development. Further research is needed to understand the underlying mechanisms and develop potential interventions for this vulnerable population.

KEYWORDS
body composition, clinical physiology, cohort study, type 1 diabetes

Bettina Gohlke and Felix Reschke shared first authorship.

1 | INTRODUCTION

The onset of puberty is defined by the appearance of secondary sexual characteristics such as thelarche (Tanner stage B2) in girls and gonadarche (Tanner stage G2; testicular volume >3 mL) in boys, indicating activity of the hypothalamic-pituitary-gonadal axis. As early as 1997 a positive secular trend towards an earlier onset of puberty ("B2") in girls was reported in a US study.[1] Since then, several studies from different countries have confirmed this trend,[2–4] and a recent review article with a meta-analysis of all previously published studies on this topic showed that there had been a worldwide decrease in age at onset of puberty by 3 months/decade without a corresponding reduction for age at menarche in girls.[5] The trend is particularly pronounced in girls with obesity and those with Black African or Carribean ethnic backgrounds but is also detectable in other ethnicities and girls with normal weight.[3,4] Nutritional, stress-related and environmental/ socioeconomic factors have been associated with the earlier onset of puberty.[6–9] However, whether a similar trend can be observed in boys is still not confirmed, as previous studies have relied on self-reported markers of puberty rather than accurate clinical assessments.[10–13]

In addition, no information is available on whether there is a similar trend towards earlier puberty onset in children with type 1 diabetes (T1D). While it is known that girls with T1D experience delayed menarche compared to healthy individuals and that poor metabolic control exacerbates this delay, there is a gap in knowledge regarding puberty onset in this population.[14,15] This study aims to address this gap by analysing data from a large database of children and adolescents with T1D, investigating the onset of puberty from the year 2000 onwards.

2 | METHODS

2.1 | Data source

The data for this study were sourced from the German Diabetes Prospective Follow-up (*Diabetes-Patienten-Verlaufsdokumentation* [DPV]) registry database, a collaborative database where treatment centres from Germany, Austria, Switzerland and Luxembourg document information from diabetes-related visits for quality improvement and scientific research purposes. Twice a year, the registry transfers pseudonymized data to the Institute of Epidemiology and Medical Biometry at Ulm University, Germany, where data are validated and aggregated into a cumulative database. Data were retrieved from the DPV registry in December 2022.[16,17]

2.2 | Study design

This population-based cohort study used data collected from routine visits to participating diabetes treatment centres. The analysed data included information on pubertal stage according to Tanner,[18] testicular volume, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), height, weight, metabolic control (measured by glycated haemoglobin [HbA1c]), age, duration of diabetes, and sex.

Informed consent for participation in the DPV Initiative is typically obtained from patients or their parents, following approval by the respective internal review boards for data protection at each centre. The central analysis of anonymized data was approved by the Ethics Committee of the University of Ulm (ethic approval no. 314/21). It is important to note that, while obtaining informed consent is a common practice for a substantial number of participating centres, this is not uniformly collected due to variations in local protocols. This approach, however, did not affect the ethical feasibility of the study as per the Ethics Committee's assessment. This study complied with the ethical principles of the 1964 Declaration of Helsinki.

2.3 | Study population

Data from the DPV registry of children and adolescents between the ages of 6.0 and 17.9 years and with a clinical diagnosis of T1D were analysed. For each year from 2000 to 2021, the analysis was conducted in children with available data on the Tanner stage related to genital development/pubic hair in boys or breast development/pubic hair in girls. Female patients were asked about their age at menarche. Clinical data, such as HbA1c level and BMI, were collected for each patient. Patients with eating disorders, coeliac disease, or a birth weight <2500 g were excluded due to the known interference of these factors with the onset of puberty.[19] Patients were stratified based on three factors: (i) BMI; (ii) metabolic control; and (iii) duration of diabetes (below 2 years, between 2 and 6 years, above 6 years). Data analysis was performed after adjusting for these factors. In this study, metabolic control categories were divided into: HbA1c level <58 mmol/ml; HbA1c level 58 mmol/ml to 69 mmol/ml; and HbA1c level >69 mmol/ml. Although not aligned with current International Society for Pediatric and Adolescent Diabetes guidelines, this aligns with ongoing German DDG (Deutsche Diabetes Gesellschaft) guidelines.[20] As this DDG Guideline was the prevailing guideline in the region during the study period, we chose this categorization for our analysis.[21]

The dataset was stratified based on weight-class-determined BMI standard deviation score (SDS): those with a BMI < −1.29 SDS (<10th percentile) were classified as underweight, those with a BMI SDS between −1.29 and +1.29 (10th-90th percentile) as normal weight, and those with a BMI SDS ≥1.29 (above the 90th percentile) as overweight. SDS was calculated using reference data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGs) study.[22] HbA1c was standardized according to the Diabetes Control and Complications Trial (DCCT) reference range.[23] Three groups were defined according to their average HbA1c level during the documented period: Group 1: HbA1c average <7.5%; Group 2: HbA1c average 7.5% to 8.5%; and Group 3: HbA1c average >8.5%. The children and adolescents were considered as having a migratory background if the individual him/herself or at least one

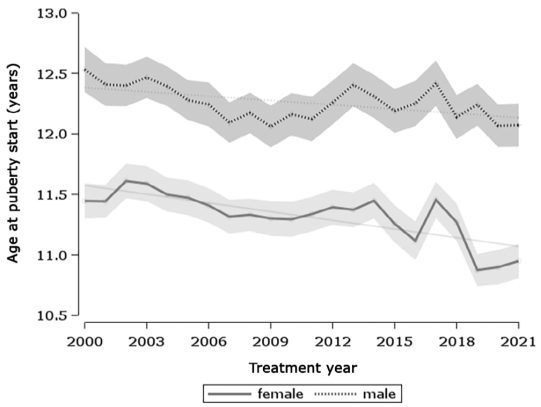

FIGURE 1 Mean age at onset of puberty in girls and boys between 2000 and 2021. Girls are represented by the solid line and light grey area. Boys are represented by the dotted line and dark grey area.

parent was not born in Germany, Austria, Luxembourg, or Switzerland. Although the primary focus of this analysis was not the participants' countries of origin, it is important to note that adolescents from African or Middle Eastern backgrounds tend to enter puberty earlier than those from Asian backgrounds. Given this knowledge, the data presented here are remarkably consistent with the findings of Prinz et al in 2019.[24]

2.4 | Statistical analysis

The study analysed the average ages of thelarche (Tanner stage B2) in girls, gonadarche (Tanner stage G2 and/or testis volume >3 mL in boys), and pubarche (Tanner stage P2) in both genders for each year between 2000 and 2021. Median, lower and upper quartiles were calculated for descriptive analyses. Linear regression models, adjusted for diabetes duration (categorized as ≤2 years, >2 to 6 years, and >6 years), BMI SDS (categorized as underweight, normal weight and overweight), HbA1c (categorized as good, moderate and poor metabolic control) and migratory background, were used to study time trends in age at onset of puberty from 2000 to 2021. All analyses were stratified by sex. In further analyses, we also stratified by BMI SDS and HbA1c categories. All statistical analyses were performed using SAS 9.4 (build TS1M7).

3 | RESULTS

3.1 | General findings

Puberty data from 13 127 children (migratory background documented in 20.57%) were analysed. For each year from 2000 to 2021, the analysis was conducted in children who had data available on Tanner stage 2, specifically related to pubic hair or genital development in boys (n = 6744 [51.38%]), or breast or pubic hair development in girls (n = 6383 [48.62%]). The overall median number of participants per year across the study period was 920 (interquartile range [IQR] 995.5; 865); in girls, it was 437 (IQR 450;421), and in boys it was 483 (IQR 510.2;470.1). The estimated age at B2/G2, adjusted for duration of diabetes (≤2 years, >2-6 years, >6 years), BMI SDS, HbA1c (as described above) and migration, is shown in Figure 1.

The mean age of puberty onset in girls exhibited a significant negative trend over time. The unadjusted mean age at Tanner stage B2 documentation decreased from mean 11.48 (range: 11.35-11.65) years in 2000 to 10.93 (10.79-11.08) years in 2021. This corresponds to an annual change of −0.028 years and a decrease of 3.2 months per decade ($P < 0.001$). Similarly to girls, boys also demonstrated a significant negative secular trend in the mean age of puberty onset. The mean age at Tanner stage G2 documentation or testicular volume >3 mL decreased from 12.62 (12.42-12.82) years in 2000 to 11.98 (11.79-12.16) years in 2021. Due to the greater variation during the whole observational period, this corresponds to an annual change of −0.015 per year and a decrease of 1.8 months per decade ($P < 0.001$). Table 1 shows the results of the regression analysis. Regression analysis, stratified by sex and adjusted for duration of diabetes, BMI SDS, HbA1c and migration background, showed similar results to those above: the mean age at B2 decreased from 11.45 (11.30-11.59) years in 2000 to 10.95 (10.81-10.95) years in 2021 in girls and from 12.53 (12.35-12.72) years in 2000 to 12.07 (11.89-12.25) years in 2021 in boys.

3.1.1 | Body mass index (BMI)

A mean of 5.1% of analysed girls (Range: 3.9% in 2010 to 8.2% in 2021) were categorized with a BMI-SDS < −1.28 (= underweight)

> Boys in this category represent a mean of 5.7% of analysed boys; range, 2.9% (in 2002) to 8.2% (in 2016) per year.

A mean of 85.8% of analysed girls (Range: 80.2% in 2021 to 89.1% in 2009) were categorized with a BMI-SDS between −1.28 ≤ and <1.28 (= normal weight).

> Boys in this category represent mean 82.9% of analysed boys; range, 76.0% (in 2020) to 86.9% (in 2011) per year.

A mean of 9.0% of analysed girls (Range: 7.1% in 2011 to 12.1% in 2017) were categorized with a BMI-SDS ≥ 1.28 (= overweight)

> Boys in this category represent amean of 11.3% of analysed boys; range, 8.7 (in 2000) to 17.8% (in 2020) per year.

TABLE 1 Regression analysis for puberty onset in children with type 1 diabetes

Girls				
Variable		**Coefficient**	**Standard error**	***P* value**
N	6382			
Diabetes duration	>6 years	0 (reference)		
	>2-6 years	−0.50	0.04	<0.001
	≤2 years	0.58	0.04	<0.001
BMI SDS	Overweight	0 (reference)		
	Normal weight	0.59	0.05	<0.001
	Underweight	1.45	0.09	<0.001
HbA1c	>8.5%	0 (reference)		
	7.5%-8.5%	−0.34	0.04	<0.001
	<7.5%	−0.45	0.04	<0.001
Migratory background	None	0 (reference)		
	Yes	−0.21	0.04	<0.001
Boys				
Variable		**Coefficient**	**Standard error**	***P* value**
N	6742			
Diabetes duration	>6 years	0 (reference)		
	>2-6 years	−0.79	0.046	<0.001
	≤2 years	−1.00	0.048	<0.001
BMI SDS	Overweight	0 (reference)		
	Normal weight	0.17	0.060	<0.001
	Underweight	0.82	0.098	<0.001
HbA1c	>8.5%	0 (reference)		
	7.5%-8.5%	−0.65	0.054	<0.001
	<7.5%	−0.96	0.049	<0.001
Migratory background	None	0 (reference)		
	Yes	−0.32	0.039	<0.001

Note: The table presents a regression analysis examining the factors associated with age at the onset of puberty in children with diabetes, stratified by sex. The analysis was adjusted for diabetes duration, BMI SDS, and migration background. The *P* value indicates the significance of each variable.
Abbreviations: BMI SDS, body mass index standard deviation score; HbA1c, glycated haemoglobin.

3.1.2 | Metabolic control

Group 1: HbA1c average during documented period <58 mmol/mol

Girls: mean 50.2% of analysed girls; range, 40.9% (in 2009) to 57.6% (in 2018) per year.
Boys: mean 48.2% of analysed boys; range, 42.6% (in 2000) to 55.5% (in 2021) per year

Group 2: HbA1c average during documented period >58mmol/mol to <69 mmol/mol

Girls: mean 28.2% of analysed girls; range, 22.9% (in 2004) to 36.1% (in 2009) per year.
Boys: mean 28.6% of analysed boys; range, 23.9% (in 2004) to 33.8% (in 2016) per year.

Group 3: HbA1c average in documented period >69 mmol/mol

Girls: mean 21.6% of analysed girls; range, 14.7% (in 2018) to 28.2% (in 2002) per year.
Boys: mean 23.2% of analysed boys; range, 17.3% (in 2021) to 26.8% (in 2007) per year.

3.2 | Study cohort stratified by BMI-SDS

In girls, a significant difference in the time of start of puberty was observed among the three weight groups (Figure 2). The group classified as overweight exhibited a pubertal onset more than 1 year earlier than the group with underweight: girls in the overweight category started puberty at a mean age of 10.60 (10.00-11.19) years in 2000 versus 10.22 (9.76-10.67) years in 2021, compared with girls in the

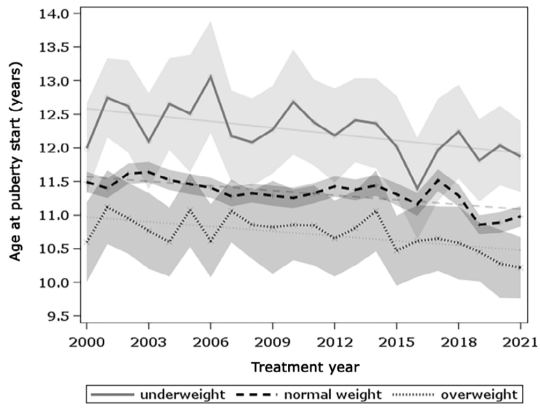

FIGURE 2 Comparison of age at onset of puberty in girls across weight groups between 2000 and 2021: underweight group, solid line; overweight group, dotted line; normal weight group, dashed line.

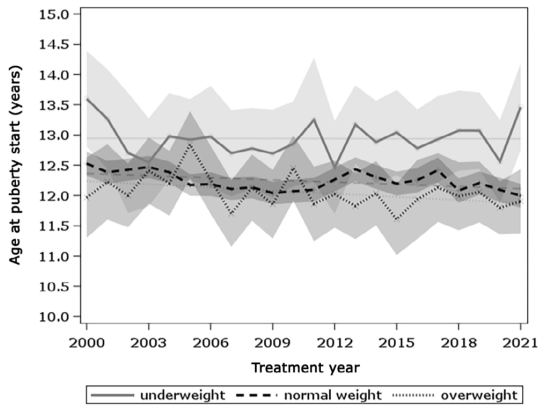

FIGURE 3 Comparison of age at the onset of puberty in boys across weight groups from 2000 to 2021: underweight group: below, dotted area; overweight group: above, grey-striped area; normal weight group: blank area.

underweight category, who started puberty at a mean age of 11.99 (11.32-12.67) years in 2000 versus 11.87 (11.34-12.4) years in 2021. Although a negative secular trend was observed in all BMI groups, this was much more pronounced in the normal weight and overweight groups ($P < 0.001$). Regression analysis stratified according to BMI SDS showed only a significant association with the duration of diabetes but not with HbA1c level for the whole group of girls. A significant association was shown for the underweight group's secular trend.

In boys, a significant but less distinct difference was observed among the three weight groups (Figure 3). The most pronounced time-trend for the start of puberty was observed in the normal weight group: puberty onset at mean age 12.53 (12.33-12.73) years in 2000 and 11.99 (11.79-12.19) years in 2021. Similarly

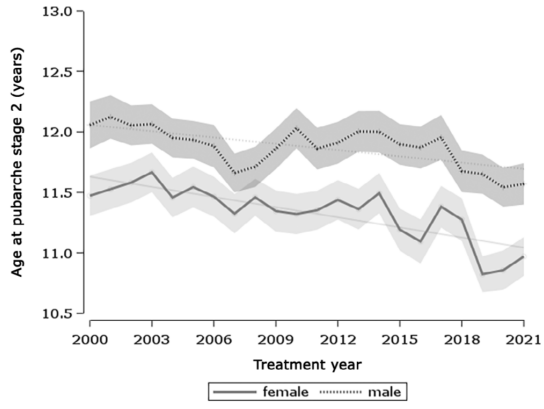

FIGURE 4 Mean age at pubarche in girls and boys with type 1 diabetes (T1D) adjusted for diabetes duration, body mass index standard deviation score (BMI SDS), glycated haemoglobin (HbA1c) and migration background (female sex: continuous line; male sex: dotted line).

to the observation in girls, the underweight boys started puberty more than 1 year later than the normal weight and the overweight groups: age 13.60 (12.81-14.39) years in 2000 and 13.46 (12.75–14.18) years in 2021.

3.3 | Study cohort stratified by HbA1c

In girls, a significant difference in age at start of puberty was seen between those with average HbA1c levels during the documented period of <7.5% (age 11.10 [10.89-11.31] years in 2000 vs.10.67 [10.48-10.85] years in 2021) in comparison to those with average HbA1c levels during the documented period of 7.5% to 8.5% (age 11.82 [11.54-12.09] years in 2000 vs. 10.92 [10.65-11.19] years in 2021), and those with average HbA1c levels in the documented period of >8.5% (age 11.73 [11.44-12-02] years in 2000 vs. 11.71 [10.86-11.51] years in 2021) was observed ($P < 0.001$). The change in age at the start of puberty was significant in Group 1 and Group 2, that is, those with good and moderate metabolic control, respectively (Figure S1).

Similarly to the cohort of girls, boys with average HbA1c levels during the documented period of <7.5% started puberty significantly earlier (age 12.42 [12.13-12.69] years in 2000 vs. 11.61 [11.37-11.85] years in 2021) than those with average HbA1c levels in the documented period of >8.5% (age 12.96 [12.61-13.32] years in 2000 vs. 12.55 [12.12-12.98] years in 2021) ($P < 0.001$; Figure S2).

3.4 | Pubarche

The mean age at pubarche, Tanner stage P2, adjusted for duration of diabetes, BMI SDS, HbA1c and migration background, is shown in Figure 4. The mean age at the documentation of Tanner P2 for girls decreased

from 11.52 (11.35-11.70) years in 2000 to 10.98 (10.82-11.15) years in 2021, which corresponds to a change of 0.02 years/year, according to a decrease of 2.72 months/decade ($P < 0.001$). The mean age at the onset of puberty in boys also showed a significant negative secular trend. The mean age at the documentation of Tanner P2 was 12.11 (11.91-12.31) years in 2000 and decreased to 11.49 (11.31-11.67) years in 2021, corresponding to a change of −0.0222 years/year, according to a decrease of 2.67 months/decade ($P < 0.001$).

A significant association with the start of pubarche could be demonstrated for the duration of diabetes, BMI-SDS and HbA1c.

4 | DISCUSSION

Our study examines the change in the timing of puberty onset over a period of more than 20 years in a large cohort of girls and boys with T1D. Our study is in line with previous reports on the timing of puberty in healthy girls,[1–5] but also provides new information on the onset of puberty in boys. While many studies document a time-trend towards the earlier onset of puberty in girls, information on boys is limited. Assessing information on boys' gonadarche and testicular volume is more challenging than evaluating data on girls' breast development (thelarche). Consequently, existing studies often rely on self-reporting, which is unreliable for puberty onset (Tanner stage 2).[25] Studying pubertal onset in children with T1D provides valuable insights into long-term outcomes and optimizing diabetes management. It sheds light on unique challenges and long-term health implications. Our study analysed data over 21 years and found a significant negative trend in the onset of puberty in both sexes. Girls demonstrated a significant decrease of over 3 months/decade, as reported by Eckert-Lind et al.[5] Boys exhibited a similar but slightly less pronounced secular trend, with a decrease of approximately 2 months/decade. Consequently, the average onset of puberty in boys is now expected to occur just before the age of 12 (11.98 years).

Since it is known that the hormonal changes of puberty can impact metabolic control in T1D and are connected to a decrease in insulin sensitivity,[26] it is essential to note that, compared to the year 2000, the onset of puberty is now expected more than half a year earlier in both sexes.

We observed that being overweight is associated with an earlier onset of puberty in girls with diabetes, similar to findings in healthy girls.[27–29] Girls who were classified as "overweight" (BMI SDS >1.25) began puberty at an average age of 10.22 years, which is more than 1 year earlier than girls who were classified as underweight or normal weight. There is growing evidence[30–32] that weight has a similar impact on pubertal development in boys. Boys classified as overweight started puberty earlier than normal-weight or underweight boys. In girls, the data on BMI-SDS and puberty onset were distinct, without overlap between the three groups (underweight, normal weight, overweight). However, in boys, only the underweight group showed a clear difference of more than a year in puberty onset compared to the normal or overweight groups. The normal weight and overweight groups had some overlap in puberty onset. While a significant difference in some years and over the entire period was observed, there were some years—for example, 2021—in which the average age at start of puberty was almost the same in both groups (11.99 years). Similarly to the findings in girls, albeit less pronounced, we could demonstrate a significant negative secular trend for the onset of puberty over the observation period.

Previous studies[14–16] have examined the impact of metabolic control on puberty in girls with T1D, primarily focusing on menarche, while research on puberty onset in both sexes is scarce. A single study in boys[33] found a correlation between mean HbA1c levels in the year before puberty and the onset of puberty in boys. This study showed that girls with average HbA1c levels of <7.5% experienced puberty onset approximately 1 year earlier than those with HbA1c levels >8.5%, and there was still a significant difference for those with moderate metabolic control (HbA1c >7.5 to <8.5%). In addition, we have now shown that the metabolic control of diabetes has a similar effect on the onset of puberty in boys. Those with optimal metabolic control started puberty earlier than those with suboptimal control. In adolescents with diabetes, obesity, which leads to an earlier start of puberty and poor metabolic control, which, by contrast, is associated with a later pubertal onset, often occur together. The observed less pronounced negative secular trend for pubertal onset in the boys with poor metabolic control might be due to the antagonistic influence of metabolic control and overweight on the onset of puberty.

Our patients with T1D showed not only a negative secular trend for gonadarche (thelarche in girls and increase of testicular volume in boys) as a sign of activation of the hypothalamic-pituitary-gonadal axis but also pubarche as a sign of earlier activation of the adrenarche. The mean age for documented Tanner stage P2, defining the start of pubarche, decreased significantly by more than 2.5 months/decade in both sexes. The same additional factors, namely, BMI-SDS, duration of diabetes, and metabolic control, were associated with the earlier onset of pubarche in both sexes.

Although many studies, especially in girls, confirm that puberty begins much earlier than it did 20 years ago, the reasons are still not fully understood. The influence of an increased weight/BMI on the earlier onset of puberty seems undisputed. The gonadotropin-releasing hormone (GnRH) neurons, which regulate the onset of puberty, are controlled by numerous stimulating metabolic hormones/adipokines, mainly leptin but also kisspeptin, neurokinin B and androgens.[34] Nevertheless, many studies show that the so-called negative secular trend for puberty is detectable even after BMI adjustment. This is in accordance with our finding that the normal weight and underweight patients with diabetes showed a similar secular trend to that in the overweight patients. The "gold standard" for the biochemical endocrinological diagnosis of centrally activated puberty is still the GnRH test, with the detection of a luteinizing hormone (LH) peak. Very little hormonal data demonstrate an earlier start of puberty because this test is difficult to perform in epidemiological studies in healthy children. One Dutch study[2] measured basal serum levels of LH, follicle-stimulating hormone and oestradiol and interpreted the earlier start as "true" central puberty due to hypothalamic-

pituitary-gonadal axis activation. In our large group of patients with diabetes, the start of puberty was established on clinical examination. However, we assume that the observed simultaneous onset and negative secular trend over 20 years of both gonadarche and adrenarche are indications of the central activation of the hypothalamic-pituitary-gonadal/adrenal axis.

Several studies[35,36] have recently reported that central precocious puberty occurred about three times more frequently during the COVID-19 pandemic in various countries. In particular, psychosocial stress during the lockdowns and changed lifestyle have been associated with this observation.[37] We did not observe an additional acceleration of the secular trend in puberty for patients with diabetes during the COVID-19 years.

In conclusion, we confirm a significant trend for an earlier start of puberty for girls with diabetes since 2000. In addition, we found a similar trend for boys with diabetes mellitus over the last 20 years. This is especially important to know because of the interaction of metabolic control in diabetes and puberty, which is connected to a decrease in insulin sensitivity. Furthermore, the impact of weight and metabolic control on the start of puberty was demonstrated.

One potential limitation of this study is that it was based on retrospective analyses of data, which may not have been collected systematically or with the specific aim of studying puberty in diabetic patients. Additionally, patients were seen because of their diabetes, not because of pubertal development, which may have influenced the selection of participants and the timing of assessments. Only a small percentage of documented visits included Tanner staging, which may limit the generalizability of the findings. Finally, the study was conducted in a specific geographical region and may not be representative of other populations.

AUTHOR CONTRIBUTIONS

B. G. and F. R. designed the study, created figures and tables, wrote the initial manuscript, and edited the manuscript. S. L. designed the study, performed data analyses, created figures, and edited the manuscript. C. B., G. G., S. T-S., D. D., L. B. and J. W. edited the manuscript. R. W. H. is the guarantor of the study and accepts full responsibility for the work and the conduct of the study, had access to the data, and controllated the decision to publish. All authors read and approved the final manuscript. G.G. and F. R. contributed equally to the study.

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CONFLICT OF INTEREST STATEMENT

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No authors reported disclosures.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15315.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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