Diabetes Technology and Therapeutics

DOI: 10.1089/dia.2023.0283

Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry

Authors

Torben Biester 1, Alexander Eckert 2,3, Marianne Becker 4, Claudia Boettcher 5, Sven Golembowski 6, Bettina Heidtmann 7, Christoph Klinkert 8, Silvia Müther 9, Birgit Rami-Merhar 10, Reinhard W. Holl 2,3 **for the DPV initiative**

Affiliations

1 AUF DER BULT, Diabetes Center for Children and Adolescents, Hannover, Germany

ORCID 0000-0001-8051-5562

2 University of Ulm, Institute for Epidemiology and Medical Biometry, ZIBMT, Ulm, Germany

Holl ORCID: 0000-0003-1395-4842

3 German Center for Diabetes Research e.V., Munich-Neuherberg, Germany

4 Centre hospitalier de Luxembourg, DECCP, Luxembourg, Luxembourg

ORCID 0000-0002-1643-1935

5 University of Bern, Bern University Hospital, Inselspital, Department of Paediatrics, Division of Paediatric Endocrinology, Diabetology & Metabolism

ORCID 0000-0001-5494-2616

6 Sana Klinikum Lichtenberg, Diabetes Center for Children and Adolescents, Berlin, Germany

7 Catholic Children`s Hospital Wilhelmstift, Hamburg, Germany

ORCID 0000-0001-6343-9000

8 Pediatric Practice, Herford, Germany

9 DRK Kliniken Berlin Westend, Diabetes Center for Children and Adolescents, Berlin, Germany

10 Dept. of Pediatric and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna

ORCID: 0000-0001-5575-5222

Corresponding Author

PD Dr. Torben Biester

AUF DER BULT, Diabetes-Center for Children and Adolescents

Janusz-Korczak-Allee 12

30173 Hannover

Germany

biester@hka.de

Key words

CSII, basal rate, insulin pump, AID, type1 diabetes

Parts of this analysis have been presented at the German Pediatric Diabetes and Endo meeting “JAPED” November 2022.

Diabetes Technology and Therapeutics

Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)

This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Abstract

Background

Since the introduction of insulin pumps into the therapy of paediatric subjects, different approaches have been taken to find optimal basal rates. Previously, the DPV registry provided circadian basal rate patterns for different age groups. As the number of pump users has increased recently and short-acting insulin analogues are now predominant, we performed a new analysis with a larger data pool.

Methods

We included all recent basal profiles from T1D patients between 1 and 25 years from the DPV 2021 data pool. We excluded night-time-only pump users, human regular insulin users, and daily basal rates < 0.05 U/kgBW/d and >1.0 U/kgBW/d.

Results

In the analysis of profiles from 25,718 young persons with T1D, differences in the daily pattern of basal rates were found between age groups. In addition, we saw significant ($p<0.001$) differences in total daily basal dose between genders in all age groups except adults. In addition, the shape of the expected basal-rate pattern differed by BMI, HbA1c and use of continuous glucose monitoring.

Discussion

This analysis demonstrates multiple factors influencing basal patterns and insulin requirement, including age group, gender, overweight, HbA1c, bolus frequency and sensor use. As circadian basal rates are still mandatory for initiating insulin pump therapy with or without automation, a multimodal approach is necessary to estimate optimal basal rates.

Background

In Germany, the use of CSII has been on the rise for children and adolescents with type 1 diabetes (T1D) across all age groups since 2000 [1]. By 2021, 56% of young individuals with type-1 diabetes in Germany, Austria, and Luxembourg had adopted CSII with 86% in the preschool age; it is therefore considered standard therapy within this age group. The utilization of continuous glucose monitoring (CGM) also increased significantly since 2016 [2].

Most studies on insulin pump therapy (CSII) for children have been conducted in Europe and the United States [3]. The first ideas of a circadian dawn-dusk profile for insulin pump basal rate patterns were described in the 1990s by Renner [4] for adult subjects. After that, differences in basal rates throughout the day were described according to age groups [5,6,7]. As a result, standard profiles have been developed and analyzed for various age groups [8].

A recent study showed that starting CSII with a circadian pattern could improve dose optimization. Optimal basal rate patterns were evaluated in a clinical setting with 150+ participants [9]. Some groups, however, have disputed the superiority of circadian profiles in adults [10], and there is evidence that variability of basal rates, as opposed to a more constant profile, may be associated with complications in adults [11].

In a German rehabilitation centre study, a clinical approach was taken with 339 adult patients to determine their basal insulin requirement through a 24-hour fasting process [12]. Due to metabolic and practical concerns, a 24-hour fasting test is unsuitable for children. Shorter fasting periods are advised to assess basal insulin requirements, avoiding hormonal reactions to fasting, which may interfere with the results.

For starting insulin pump therapy, some recommendations suggest starting with a flat basal rate (e.g. 50 % of total daily dose (TDD) equally distributed over 24 hours) [13]. Recommendations for children are comparable [14]. However, a more physiological approach is to adjust insulin delivery to a circadian insulin sensitivity pattern. Paediatric experts typically suggest a variable basal rate that includes two peaks: one in the early morning (dawn) and one in the late afternoon (dusk).

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Since September 2019, the first devices with automated insulin dosage (AID) have been available in Germany, Austria, and Luxembourg.

AID data evaluation shows that automated insulin delivery in paediatrics also follows circadian patterns [15]. Although insulin requirement varies throughout the day in association with the dawn phenomenon in adults, a study by Lindmeyer et al. showed that starting CSII with a constant infusion rate is safe [16].

Among the five currently (EU and US) marketed AID systems, two use a preset basal rate during the auto mode, and all five use a user-defined basal rate as a backup if the algorithm cannot implement automated mode or if the user switches this off. While using automated modes, routine basal rate adjustment in the outpatient clinic is more difficult because the traditional separation of basal and bolus insulin does not reflect the insulin dosing algorithms[17]. Therefore, when using AID systems, expected circadian profiles are still required as a basis for insulin pump settings at the start of therapy.

In Germany, available schemes based on the above mentioned publications are widely used to determine basal patterns, with subsequent individual adjustments. This routine and patient education on technical aspects, proved beneficial for overall glucose control during CSII use in an international comparison[18].

The DPV registry is a vast database on diabetes that has been collecting patient data since 1995 in Germany, Austria, Switzerland, and Luxembourg [19]. The currently recommended standard dosing schemes for paediatric subjects were published in 2008 and are based on the DPV data pool at that time [20]. A subsequent analysis was conducted in 2012 [21].

Methods

Study design and participants

We included data from the DPV registry between 2015 and 2021 on all individuals with type 1 diabetes using an insulin pump (CSII therapy), including AID between the ages of 1 and 25. The most up-to-date basal rate information for each person, regardless of SMBG or sensor monitoring, was used. We excluded patients on injection therapy, patients who used CSII only during nighttime, or patients with CSII but no available basal rate. We also

excluded basal rates that showed no insulin delivery for over 2 hours. In addition, we excluded users of human regular insulin and subjects with total daily basal rates < 0.05 U/kgBW/d or >1 U/kgBW/d due to suspected honeymoon phase, extreme insulin resistance or documentation errors. We did not consider profiles with >30 bolus administrations documented per day to analyse bolus frequency, assuming erroneous data entry. Individuals with missing BMI-SDS, HbA1c, or number of daily bolus administrations were only excluded from the analysis of the respective parameter.

Patient data

Our method for calculating body mass index (BMI) involved the use of standard deviation scores (SDS) derived from German reference values provided by the Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter (AGA)[22]. If an individual's BMI-SDS exceeded the 90th percentile for age and sex, they were classified as overweight. The HbA1c values were adjusted to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05%-6.05% (20.7-42.6 mmol/mol) by using the multiple of the mean transformation method to accommodate for the variations in laboratory methods. To meet the criteria of sensor use, the individual must have used the sensor for at least 80% of the days in the 90 days prior to their most recent visit.

Statistical analysis

To compare age groups (1-<6, 6-<12, 12-<18, 18-25 years), we utilized the most recent basal rate per patient and age group. Each person could therefore provide 1 to 2 basal rates for this analysis, as the analysis timespan is 6 years and therefore individuals' age group has changed in that period for all other comparisons, each subject's most recent basal rate was used, and each individual contributed one basal rate. Stratification was conducted by weight category (normal weight/overweight), HbA1c category (< 7.5 versus >7.5 %) and the number of boluses (<6 versus >=6) [23].

We compared unadjusted means, stratified by age group, to analyze differences in basal insulin dose between sexes. The analyses according to BMI category, HbA1c category, number of boluses and sensor use were conducted with multivariable linear regression models adjusted for age groups, sex and diabetes duration groups (<2/≥ 2 years) as well as

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

for interaction terms between age group and sex and between diabetes duration group and sex.

We calculated the absolute difference for each hourly interval using logistic regression models, again adjusted for the confounders mentioned above to analyze the differences in the basal rate trajectories between groups. An interaction term for the respective outcome variable and the hourly intervals as a time variable was additionally included. In order to determine if there were significant variations between the curves, the p-value of this interaction term was utilized. Further, the absolute differences of all hourly intervals were summed up, representing the area between the curves and, therefore, a standardized and comparable value for quantification.

All calculations were performed using SAS version 9.4 (build TS1M7) on a Windows server 2019 mainframe. Significance was determined using a two-sided p-value of less than 0.05.

Results

The registry contained records of 25,718 patients whose most recent profiles met the inclusion criteria (figure S1).

An “AGP-like” figure (including median and areas between the 10th, 25th, 75th, and 90th centile) shows a high variability over 24 h with a larger distance between the 10th and 90th centiles in the evening hours (Figure 1).

The median number of daily boluses administered was 6 [5;6] in all age groups without differences according to sex.

The analysis of sex differences was performed in 4 separate age groups (table1) based on the most recent basal rate per patient and age group: 1-<6 years, n=5 716; 6-<12 years, n=12 116, 12-<18years, n=15.494, 18-25years, n=4 472. Only 486 people (1.9 %) were current AID users.

Patterns

The basal rates showed different circadian patterns among age groups. Figure 1 shows a wider centile curve during the evening hours, mainly due to the pattern in the youngest

age group. This group has a different curve shape and a higher percentage of basal insulin in the evening than other age groups.

Comparing age groups, the proportion of insulin distribution differs most between the youngest and oldest age groups, with a difference of 19.6% of the total proportion (figure 2 a). Figure 2b quantifies hourly differences between the youngest and the oldest age group. Differences between sexes were smaller within the individual age groups (for quantification of other group comparisons, see supplement figure S2). The most negligible sex difference was observed in the preschooler age group (1.81 %).

Figure 3 shows the different shapes of basal patterns in the individual age groups (figure 3 a-d). As the hourly delivered basal rate depends on all the above factors, the basal rate patterns are expressed as a proportion of the total daily basal insulin requirement. Therefore, the sum of all hourly intervals is 100%. Figure 3e-h shows the corresponding absolute mean hourly insulin dose.

Discussion

We present patterns for expected basal insulin requirement during CSII therapy from a large multi-national diabetes registry. The number of subjects included in the current publication increased four times compared to the previous publication in 2012 [21]. The age groups are <6yr (n=837), 6 to <12 yr (n=1739), 12 to <18 yr (n=2985) and 18 to <25 yr (n=380). It is worth noting that the currently available basal rate recommendations only include data from 743 patients [20]. Furthermore, other advancements also support this recalculation: Use of CGM instead of SMBG[24], nearly exclusive use of rapid-acting analogs[25], new pump models[26], earlier switch to CSII from basal-bolus regimen[27], and lower targets for HbA1c [28].

It is worth noting that the basal patterns comparing the four age groups remained consistent with previous data. The shape and hourly proportion of CSII basal rate depends on age, sex, BMI, number of daily boluses, and quality of diabetes control. In addition to the circadian distribution, the total daily basal rate requirement differs among the groups, so both factors must be considered for recommended basal rate settings in an individual subject.

Studies have indicated that insulin regimens should be adjusted based on age [29] and the time of day [30]. In adults, age, sex, duration of insulin pump treatment, body mass index, HbA1c, and triglyceride concentrations essentially predicted the individual basal insulin requirement per day [7].

Karakus et al. studied 4193 daily AID profiles to demonstrate circadian insulin needs, which are comparable to our results. They analyzed the profiles separated into micro boluses and auto-corrections, both features of the device used in their study. Their mean participant's age was 12.3 years. Their findings indicate that a circadian profile requires two insulin peaks: one in the morning between 4:00-8:00 (corresponding to the dawn phenomenon [31]). The second peak they found was a steady increase from noon to bedtime (corresponding to the dusk phenomenon). Our data shows that the two insulin peaks are similar to the basal rate pattern of 12-18-year-olds in our study. Therefore, the data confirm that insulin requirement corresponds to the shape of the curve presented in our study.

Physicians' clinical approach to adjusting pump treatment settings based on sensor data shows a tremendous intra-individual variety that differs from computer-generated suggestions [32]. Using empirical data from a large population can facilitate the initiation of pump therapy. The shape of the basal rate distribution in adults is similar to the curve evaluated by Nauck et al. in their clinical fasting test with adult patients [12], but different compared to the distribution in adolescents. Thus, the profile presented reflects the need for a circadian adult basal rate, consistent with the results from Nauck et al.

Influencing factors – sex and age

The impact of sex varies depending on age. Boys and girls in the youngest age group require almost the same amount of insulin. In contrast, the 6-12-year-old group shows a higher total basal insulin dose in girls (figure 2) and a higher basal insulin dose per kg of BW (table 1). The sex difference is reversed in young adults. One possible explanation for this phenomenon is that girls experience puberty earlier, which results in a higher demand for insulin at a younger age. Males begin puberty later and continue to undergo changes

for a more extended period [33]. Furthermore, in the pubertal age groups, the circadian insulin distribution patterns differ most between the sexes (Figure 2 b+d).

During a lifetime with T1D, adolescence is the period that experiences the poorest metabolic control. In adolescence, most people with diabetes (PwD) are not meeting their metabolic targets [18], partly due to risk-taking behaviour. This group has the highest number of disruptors of glycaemic control: pubertal hormone surge, nocturnal growth hormone secretion, the highest amount of TDD and low adherence to treatment recommendations. All these factors contribute to unstable metabolic control.

Treatment result

When possible for the individual patient and resources are available, a treatment target for HbA1c below 7% is recommended[28]. Our data show that people meeting the target have different patterns than those who do not. Cross-sectional data cannot answer whether a more physiological basal rate supports better glycaemic control or whether worse metabolic control influences the 24-h-pattern of basal insulin requirement.

Implications for current and future therapy

All current AID systems on the market are using sensors, that need a “warming phase” of at least 1-2 hours (depending on the used model). That means, every AID user has breaks in AID use regularly. Furthermore, technical issues with sensor malfunction or just prematurely solution of adhesive might lead to suddenly interruptions in AID-mode. For all of these cases, an individual optimal basal rate, based on parameters described above, help the user to keep glycemic control until AID can be resumed.

Furthermore, depending on the AID system used, the pre-programmed basal rate is needed for the automated modus. All current systems use the total daily dose (TDD) of insulin as a parameter for the AID-algorithm. Some incorporate also the previous basal rate for AID calculation, some take the TDD from the past days to calculate ratios. In both cases, an optimal basal rate helps to provide an individual program with person’s individual insulin need.

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

In general, the concept of insulin delivery in AID mode is more “manual and automated” then “basal and bolus” as mentioned in the current ISPAD guidelines for insulin delivery.[34]

By today, one system also uses the programmed basal rate during automated therapy. For users of this system, an individual fitted basal rate is the base for automated therapy. There might be factors in the algorithm e.g. a maximum of hourly basal, calculated by the programmed patterns. In this case, an optimal rate is recommended. While in the past, fasting tests were used to find these optimums, pre-calculated patterns (Fig S3) based on these data can provide easy access to appropriate basal rates.

The first RCT with a so-called “open-source” AID system was recently published [35]. As these systems are not certified or approved by any authority or notified body, the risk of system failure might be more critical. Also, in these self-build systems, an applicable basal rate should be used as a backup system in case of a non-working AID.

In general, AI-powered systems are often seen as "the" promising treatment for Type 1 Diabetes, with potential benefits for users and care teams. However, a recent statement by EASD and ADA points out some issues that need to be solved with this technology, including regulatory aspects, data harmonization, and the use of various systems[36].

Our study revealed that the difference in AUC between the adolescent and young age groups was comparatively smaller than the sex differences observed in the adults’ group (2.57% versus 2.97% - see figure 2a). This finding suggests that insulin patterns are influenced by all the investigated factors independently. Therefore, a standardized backup basal rate considering all the factors discussed above, may provide support and safety for PwD and diabetes teams that have to adopt this new technology.

Strengths and weakness

Real-life data from PwD’s insulin pumps are entered into the prospective database. The current goals for therapy are to achieve an HbA1c level below 7.0% [37] and a time in range greater than 70% [38]. Nevertheless, diabetes teams can identify personalized goals with their patients; therefore, the aims might have differed in individual patients, and some documented basal rates might not be the optimal approach to achieve these glycemic

targets. This might be considered as a weakness of our study. However, compared to reports from other countries, the population in our study has fairly good diabetes control[39]. Therefore, the recommendations presented can be judged as adequate basal rates for our population.

Strength of our study is the large dataset from multiple centres in 4 countries, the standardized documentation using one single electronic health record software, and the centralized analysis.

Conclusion

Based on the data presented, the patterns of individual basal rates and the total amount of basal insulin needed vary depending on several factors, including age, sex, BMI, and the number of boluses administered per day. These factors have not been previously investigated, but they are crucial in determining personalized recommendations for basal insulin requirements. In addition, physical activity, body composition, nutrition choices, emotional stress and mental health are likely to affect basal rate patterns.

These multiple factors must be considered when estimating basal insulin requirement. For now, the sliding basal rate dosing schemes from the last publication have been updated (Figure S3). AID systems still require a programmed basal rate, either as a backup or as part of the algorithm. Therefore, a tool incorporating all these factors might be valuable in routine diabetes care.

Funding

The development of a new device to predict basal rates for CSII in children, adolescents and young adults with T1D was supported by three pediatric professional associations from German-speaking countries: the German AGPD (https://www.diabetes-kinder.de), the Austrian APEDÖ (https://www.paediatrie.at/arbeitsgruppen-und-referate/leiter-ag/ag-endokrinologie-und-diabetologie) and the Swiss SGPED (https://www.sgped-ssedp.ch).

The DPV registry is funded by the German Center for Diabetes Research (DZD), (grant number 82DZD14E03), by the German Diabetes Association (DDG) and by the Diabetes Surveillance of the Robert Koch Institute.

Acknowledgements

We would like to thank A. Hungele and R. Ranz for their support with data management and the development and continuous improvement of the DPV documentation software (both on the DPV team at Ulm University). Special thanks to Katharina Strehle for supporting the statistical analysis.We appreciate participation of all diabetes centers in Germany, Austria and Switzerland and Luxemburg: (see annex).

We like to thank DexCom Germany for development of the basal rate tool based on these results.

COI

TB reports speaker's honoraria from Insulet, NovoNordisk, Medtronic, Roche, Sanofi, Synlab and Ypsomed, Advisory board activity for Ascensia, Medtronic, Sanofi. Member of EMA Expamed panel.

BRM reports speaker's honoraria from Abbott, Insulet, Medtronic, Eli Lilly, Ypsomed.

AE, MB, CB, SG, BH, CK, SM, RWH report no conflict of interest

Contributions

TB and RWH planned the study. AE performed all statistical analyses and advised the author group on data analysis. All authors contributed to interpretation of results and discussion. The first draft of the manuscript was written by TB, read, revised and approved by all co-authors. The data was collected by all DPV centers.

Parts of this analysis have been presented at the German Pediatric Diabetes and Endo meeting "JAPED" November 2022.

Literature

1. Schöttler H, Auzanneau M, Best F, et al. Insulinpumpe, kontinuierliche und kapilläre Glukosemessung bei Kindern, Jugendlichen und Erwachsenen mit Diabetes mellitus: Daten des DPV-Registers zwischen 1995 und 2019. Diabetologie und Stoffwechsel 2020, doi:10.1055/a-1259-1190

2. van den Boom L, Auzanneau M, Woelfle J, et al. Use of Continuous Glucose Monitoring in Pump Therapy Sensor Augmented Pump or Automated Insulin Delivery in Different Age Groups (0.5 to <26 Years) With Type 1 Diabetes From 2018 to 2021: Analysis of the German/Austrian/Swiss/Luxemburg DPV Registry. J Diabetes Sci Technol 2023;19322968231156601, doi:10.1177/19322968231156601

3. Alvarenga CS, La Banca RO, Neris RR, et al. Use of continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes mellitus: a systematic mapping review. BMC Endocr Disord 2022;22(1):43, doi:10.1186/s12902-022-00950-7

4. Wizemann E RR, Hepp K. Prospective evaluation of a standardized basal rate distribution for CSII in type 1 diabetes over 6 months. Diabet Stoffw 2001;10(57):

5. Conrad SC, McGrath MT, Gitelman SE. Transition from multiple daily injections to continuous subcutaneous insulin infusion in type 1 diabetes mellitus. J Pediatr 2002;140(2):235-40, doi:10.1067/mpd.2002.120509

6. Danne T, Battelino T, Kordonouri O, et al. A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries. Pediatr Diabetes 2005;6(4):193-8, doi:10.1111/j.1399-543X.2005.00131.x

7. Nauck MA, Kahle-Stephan M, Lindmeyer AM, et al. Prediction of Individual Basal Rate Profiles From Patient Characteristics in Type 1 Diabetes on Insulin Pump Therapy. J Diabetes Sci Technol 2021;15(6):1273-1281, doi:10.1177/1932296820972691

8. Holterhus PM, Odendahl R, Oesingmann S, et al. Classification of distinct baseline insulin infusion patterns in children and adolescents with type 1 diabetes on continuous subcutaneous insulin infusion therapy. Diabetes Care 2007;30(3):568-73, doi:10.2337/dc06-2105

9. Demir G, Atik Altınok Y, Özen S, et al. Initial Basal and Bolus Rates and Basal Rate Variability During Pump Treatment in Children and Adolescents. J Clin Res Pediatr Endocrinol 2021;13(2):198-203, doi:10.4274/jcrpe.galenos.2020.2020.0171

10. Rilstone S, Reddy M, Oliver N. A Pilot Study of Flat and Circadian Insulin Infusion Rates in Continuous Subcutaneous Insulin Infusion (CSII) in Adults with Type 1 Diabetes (FIRST1D). J Diabetes Sci Technol 2021;15(3):666-671, doi:10.1177/1932296820906195

11. Laimer M, Melmer A, Mader JK, et al. Variability of Basal Rate Profiles in Insulin Pump Therapy and Association with Complications in Type 1 Diabetes Mellitus. PLoS One 2016;11(3):e0150604, doi:10.1371/journal.pone.0150604

12. Nauck MA, Lindmeyer AM, Mathieu C, et al. Twenty-Four Hour Fasting (Basal Rate) Tests to Achieve Custom-Tailored, Hour-by-Hour Basal Insulin Infusion Rates in Patients With Type 1 Diabetes Using Insulin Pumps (CSII). J Diabetes Sci Technol 2021;15(2):360-370, doi:10.1177/1932296819882752

13. Grunberger G, Abelseth JM, Bailey TS, et al. Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology insulin pump management task force. Endocrine Practice 2014;20(5):463-489

14. Phillip M, Battelino T, Rodriguez H, et al. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2007;30(6):1653-62, doi:10.2337/dc07-9922

15. Karakus KE, Yesiltepe Mutlu G, Gokce T, et al. Insulin Requirements for Basal and Auto-Correction Insulin Delivery in Advanced Hybrid Closed-Loop System: 4193 Days' Real-World Data of Children in Two Different Age Groups. J Diabetes Sci Technol 2022;19322968221106194, doi:10.1177/19322968221106194

16. Lindmeyer AM, Meier JJ, Nauck MA. Patients with Type 1 Diabetes Treated with Insulin Pumps Need Widely Heterogeneous Basal Rate Profiles Ranging from Negligible to Pronounced Diurnal Variability. Journal of Diabetes Science and Technology 2021;15(6):1262-1272, doi:10.1177/1932296820949939

17. Phillip M, Nimri R, Bergenstal RM, et al. Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice. Endocr Rev 2023;44(2):254-280, doi:10.1210/endrev/bnac022

18. Hermann JM, Miller KM, Hofer SE, et al. The Transatlantic HbA1c gap: differences in glycaemic control across the lifespan between people included in the US T1D Exchange Registry and those included in the German/Austrian DPV registry. Diabet Med 2019, doi:10.1111/dme.14148

19. Lanzinger S, Zimmermann A, Ranjan AG, et al. A collaborative comparison of international pediatric diabetes registries. Pediatr Diabetes 2022, doi:10.1111/pedi.13362

20. Klinkert C, Bachran R, Heidtmann B, et al. Age-specific characteristics of the basal insulin-rate for pediatric patients on CSII. Exp Clin Endocrinol Diabetes 2008;116(2):118-22, doi:10.1055/s-2007-990296

21. Bachran R, Beyer P, Klinkert C, et al. Basal rates and circadian profiles in continuous subcutaneous insulin infusion (CSII) differ for preschool children, prepubertal children, adolescents and young adults. Pediatr Diabetes 2012;13(1):1-5, doi:10.1111/j.1399-5448.2011.00777.x

22. Kromeyer-Hauschild K, Moss A, Wabitsch M. Referenzwerte für den Body-Mass-Index für Kinder, Jugendliche und Erwachsene in Deutschland. Anpassung der AGA-BMI-Referenz im Altersbereich von 15 bis 18 Jahren 2015;09(03):123-127, doi:10.1055/s-0037-1618928

Diabetes Technology and Therapeutics

Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

23. Forlenza GP, Pyle LL, Maahs DM, et al. Ambulatory glucose profile analysis of the juvenile diabetes research foundation continuous glucose monitoring dataset-Applications to the pediatric diabetes population. Pediatr Diabetes 2017;18(7):622-628, doi:10.1111/pedi.12474

24. van den Boom L, Karges B, Auzanneau M, et al. Temporal Trends and Contemporary Use of Insulin Pump Therapy and Glucose Monitoring Among Children, Adolescents, and Adults With Type 1 Diabetes Between 1995 and 2017. Diabetes Care 2019;42(11):2050-2056, doi:10.2337/dc19-0345

25. Eckert AJ, Bramlage P, Danne T, et al. The use of insulin preparations—an evaluation of the DPV registry. Deutsches Ärzteblatt international 2022, doi:10.3238/arztebl.m2022.0253

26. Heinemann L, Fleming GA, Petrie JR, et al. Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting, and research needs: a joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetes Care 2015;38(4):716-22, doi:10.2337/dc15-0168

27. Kamrath C, Tittel SR, Kapellen TM, et al. Early versus delayed insulin pump therapy in children with newly diagnosed type 1 diabetes: results from the multicentre, prospective diabetes follow-up DPV registry. The Lancet Child & Adolescent Health 2021;5(1):17-25, doi:10.1016/s2352-4642(20)30339-4

28. DiMeglio LA, Acerini CL, Codner E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. Pediatric Diabetes 2018;19(105-114, doi:10.1111/pedi.12737

29. Hanas R, Adolfsson P. Bolus Calculator Settings in Well-Controlled Prepubertal Children Using Insulin Pumps Are Characterized by Low Insulin to Carbohydrate Ratios and Short Duration of Insulin Action Time. J Diabetes Sci Technol 2017;11(2):247-252, doi:10.1177/1932296816661348

Diabetes Technology and Therapeutics

Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)

30. Hegab AM. Diurnal Variation of Real-Life Insulin Sensitivity Factor Among Children and Adolescents With Type 1 Diabetes Using Ultra-Long-Acting Basal Insulin Analogs. Front Pediatr 2022;10(854972, doi:10.3389/fped.2022.854972

31. Ostrovski I, Lovblom LE, Scarr D, et al. Analysis of Prevalence, Magnitude and Timing of the Dawn Phenomenon in Adults and Adolescents With Type 1 Diabetes: Descriptive Analysis of 2 Insulin Pump Trials. Can J Diabetes 2020;44(3):229-235, doi:10.1016/j.jcjd.2019.08.003

32. Nimri R, Battelino T, Laffel LM, et al. Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes. Nat Med 2020;26(9):1380-1384, doi:10.1038/s41591-020-1045-7

33. Rohrer T, Stierkorb E, Heger S, et al. Delayed pubertal onset and development in German children and adolescents with type 1 diabetes: cross-sectional analysis of recent data from the DPV diabetes documentation and quality management system. European journal of endocrinology 2007;157(5):647-53, doi:10.1530/EJE-07-0150

34. Sherr JL, Schoelwer M, Dos Santos TJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. Pediatr Diabetes 2022;23(8):1406-1431, doi:10.1111/pedi.13421

35. Burnside MJ, Lewis DM, Crocket HR, et al. Open-Source Automated Insulin Delivery in Type 1 Diabetes. N Engl J Med 2022;387(10):869-881, doi:10.1056/NEJMoa2203913

36. Sherr JL, Heinemann L, Fleming GA, et al. Automated insulin delivery: benefits, challenges, and recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association. Diabetologia 2023;66(1):3-22, doi:10.1007/s00125-022-05744-z

37. DiMeglio LA, Acerini CL, Codner E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. Pediatr Diabetes 2018;19 Suppl 27(105-114, doi:10.1111/pedi.12737

38. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care 2019;42(8):1593-1603, doi:10.2337/dci19-0028

39. Anderzén J, Hermann JM, Samuelsson U, et al. International benchmarking in type 1 diabetes: Large difference in childhood HbA1c between eight high-income countries but similar rise during adolescence—A quality registry study. Pediatric Diabetes 2020;21(4):621-627, doi:https://doi.org/10.1111/pedi.13014

40. Kromeyer-Hauschild K WMea. Perzentile f ü r den Bodymass-Index f ü r das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschrift Kinderheilkunde 2001;149(807 – 818

Table 1 . Demographic data and insulin doses; groups according to age and gender

group	Basal [U/kg/d]	TDD [IU/kgBW/d]	BMI-SDS [40]	Diabetes Duration [years]	HbA1c [%]
1-<6	N=2390				
F	0.24 [0.18;0.32]	0.67 [0.54;0.84]	0.61 [-0.01;1.19]	1.13 [0.42;2.21]	7.68 [7.01;8.48]
M	0.23** [0.16;0.30]	0.64** [0.51;0.80]	0.65 [0.04;1.19]	1.19 [0.39;2.26]	7.55 [6.98;8.47]
6-<12	N=6505				
F	0.34 [0.25;0.45]	0.71 [0.59;0.86]	0.39 [-0.19;1.05]	4.02 [2.21;6.05]	7.45 [6.91;8.08]
M	0.33*** [0.24;0.42]	0.67*** [0.56;0.81]	0.42 [-0.15;1.07]	4.31* [2.39;6.22]	7.39* [6.85;7.98]
12-<18	N=12351				
F	0.49 [0.38;0.62]	0.84 [0.71;1.00]	0.87 [0.17;1.50]	7.65 [4.93;10.60]	7.72 [7.14;8.44]
M	0.48 [0.37;0.62]	0.81*** [0.68;0.96]	0.44*** [-0.25;1.19]	7.69 [4.70;10.70]	7.69* [7.09;8.38]
18-<=25	N=4472				
F	0.43 [0.34;0.53]	0.83 [0.70;0.98]	0.69 [0.06;1.33]	10.78 [7.97;14.28]	7.77 [7.18;8.46]
M	0.45*** [0.36;0.57]	0.84 [0.71;0.98]	0.33*** [-0.36;1.08]	10.51 [7.31;14.27]	7.76 [7.12;8.46]

Data are presented as median [Q1; Q3]

Asterisk indicates statistically significant difference in individual age group according to sex (<0.05, **<0.01, ***<0.001)*

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Figure legends

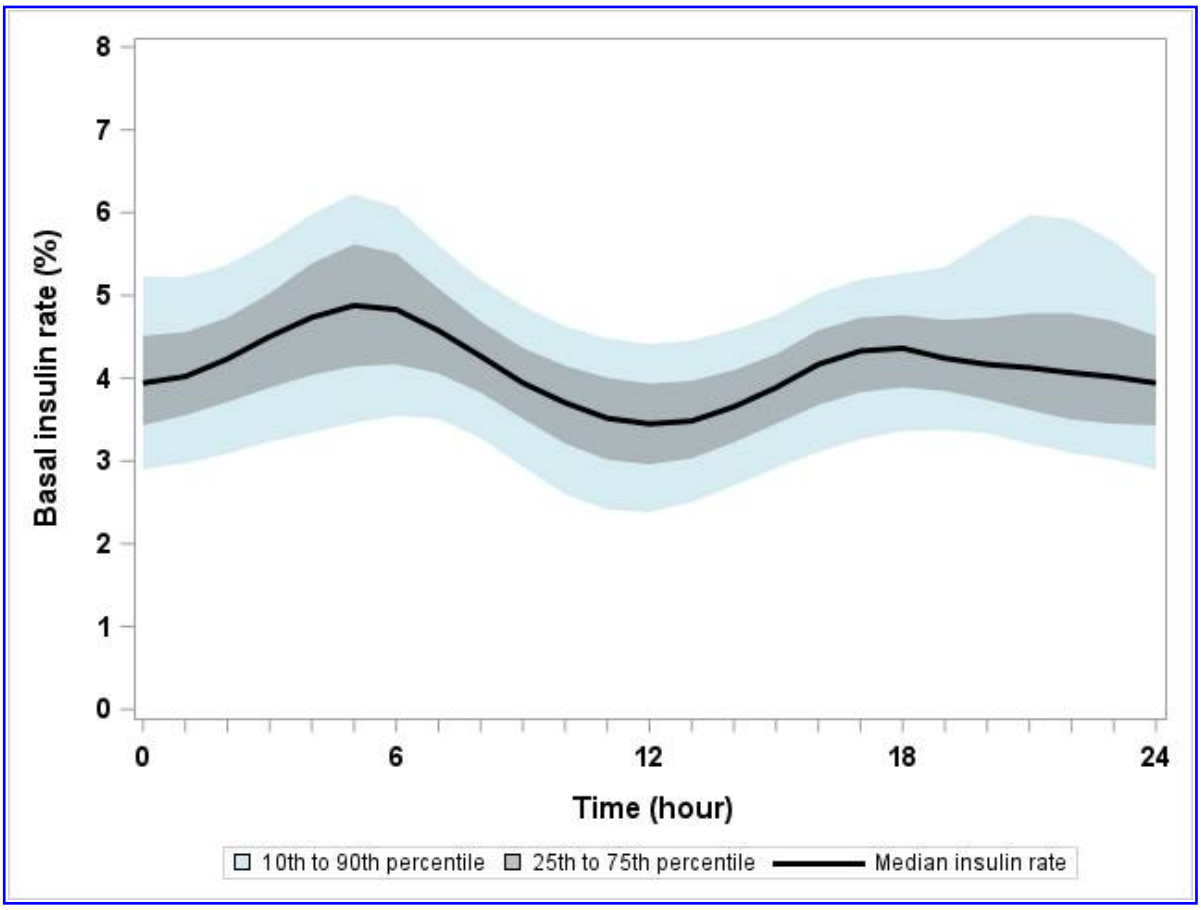

Figure 1

"AGP-like" overall patterns of basal rates (whole population)

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

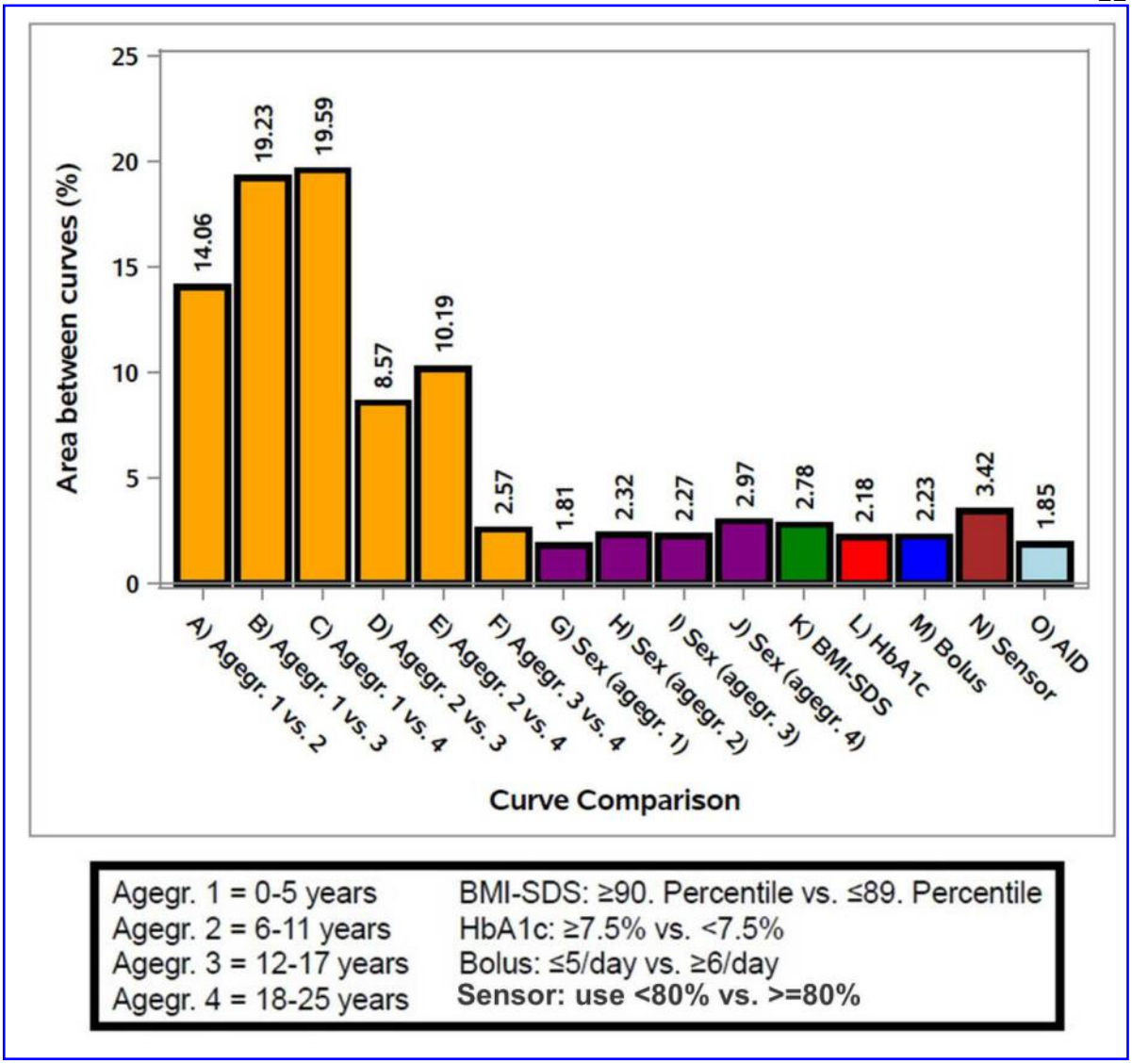

Figure 2

AUC differences between individual groups

For every paired comparison, the absolute number of AUC difference was calculated (Figure S2); results shown as bars

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

Diabetes Technology and Therapeutics
Expected Basal Insulin Requirement during CSII therapy by Age Group, Sex and BMI, based on 25,718 Young People with Type 1 Diabetes in the DPV Registry (DOI: 10.1089/dia.2023.0283)
This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

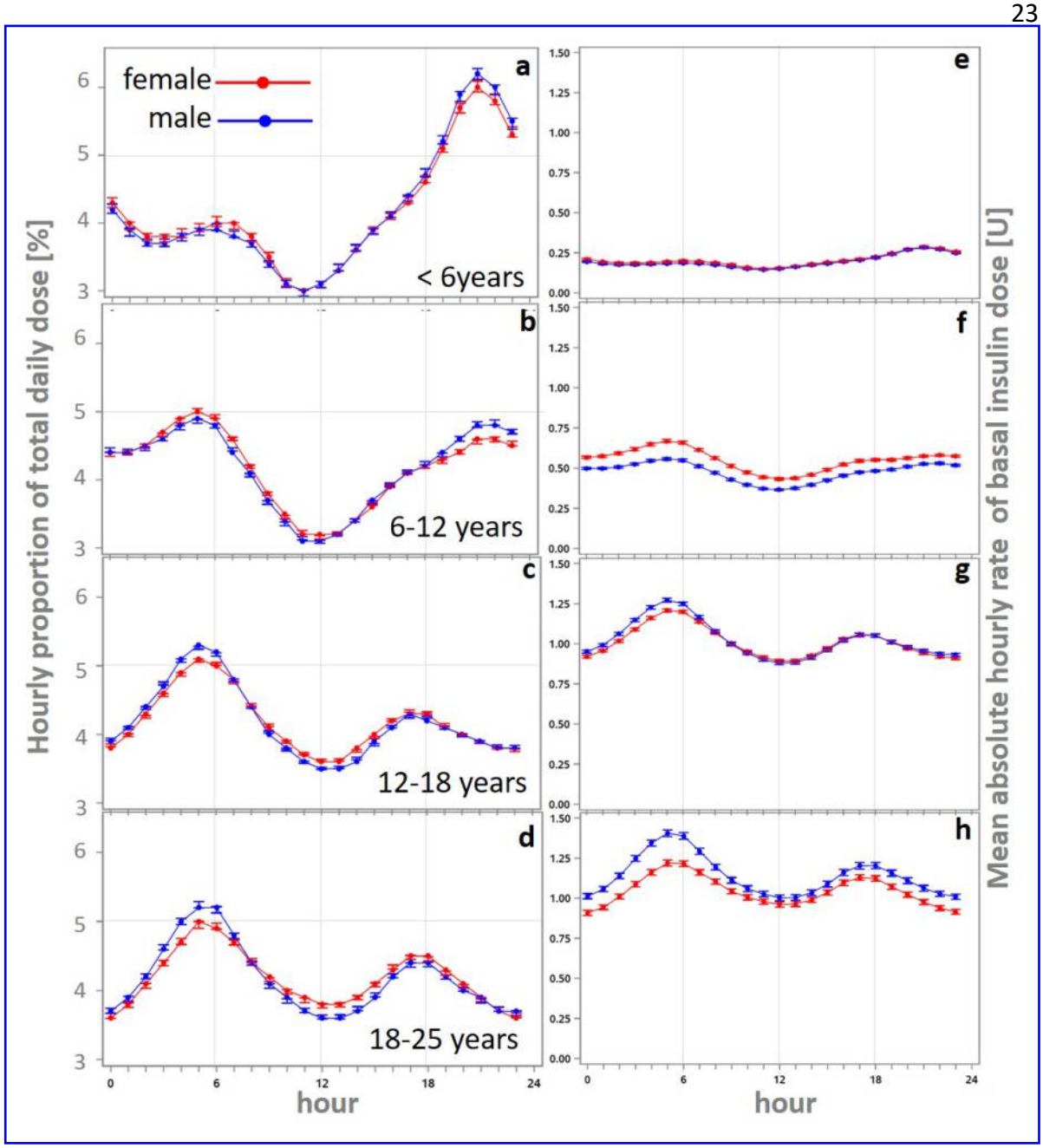

Figure 3

Basal patterns stratified by subgroups.

a-d: relative proportion of hourly basal rates: population by age group and gender (red: female, blue male);

e-g: absolute mean hourly basal rates: population by age group and gender (red: female, blue male);