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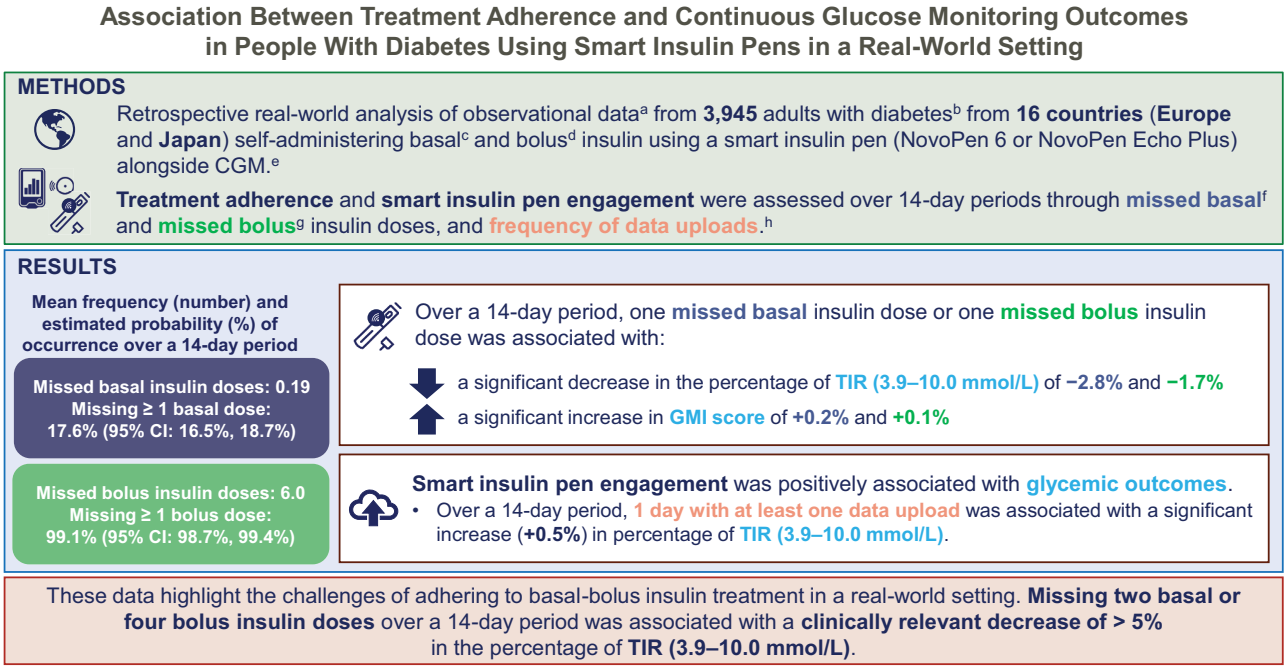

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Smart insulin pen data provide detailed insights into dosing frequency and treatment adherence.
- **What is the specific question(s) we wanted to answer?**
  To gather real-world insights, we investigated the association of basal-bolus insulin adherence, smart pen engagement, and glycemic outcomes using real-world data from adults with diabetes in 16 countries who were using a smart insulin pen and continuous glucose monitoring.
- **What did we find?**
  Treatment adherence and smart insulin pen engagement were positively associated with glycemic outcomes.
- **What are the implications of our findings?**
  Missing two basal or four bolus insulin doses over a 14-day period would be associated with a 5% decrease (a clinically relevant change) of time with glucose levels in target glycemic range (3.9–10.0 mmol/L).

Association Between Treatment Adherence and Continuous Glucose Monitoring Outcomes in People With Diabetes Using Smart Insulin Pens in a Real-World Setting

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ORIGINAL ARTICLE

OBJECTIVE

To evaluate the association of insulin injection adherence, smart insulin pen engagement, and glycemic control using real-world data from 16 countries from adults self-administering basal insulin degludec and bolus insulin with a smart insulin pen (NovoPen 6 or NovoPen Echo Plus) alongside continuous glucose monitoring (CGM).

RESEARCH DESIGN AND METHODS

Data were aggregated over 14-day periods. Treatment adherence was defined according to the number of missed basal and missed bolus insulin doses and smart pen engagement according to the number of days with data uploads.

RESULTS

Data from 3,945 adults, including 25,157 14-day periods with ≥70% CGM coverage, were analyzed. On average, 0.2 basal and 6.0 bolus insulin doses were missed over 14 days. The estimated probability of missing at least one basal insulin dose over a 14-day period was 17.6% (95% CI 16.5, 18.7). Missing one basal or bolus insulin dose per 14 days was associated with a significant decrease in percentage of time with glucose levels in range (TIR) (3.9–10.0 mmol/L), of −2.8% (95% CI −3.7, −1.8) and −1.7% (−1.8, −1.6), respectively; therefore, missing two basal or four bolus doses would decrease TIR by >5%. Smart pen engagement was associated positively with glycemic outcomes.

CONCLUSIONS

This combined analysis of real-world smart pen and CGM data showed that missing two basal or four bolus insulin doses over a 14-day period would be associated with a clinically relevant decrease in TIR. Smart insulin pens provide valuable insights into treatment injection behaviors.

Consistent glycemic control is necessary to prevent diabetes-related complications (1,2). Glycemic management in type 1 diabetes requires multiple daily injections (MDI) of basal and bolus insulin or continuous subcutaneous insulin infusion, ideally with an automated insulin delivery (AID) system, and in type 2 diabetes MDI may be required as the disease progresses (2).

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Challenges in managing MDI can reduce adherence to insulin therapy, leading to suboptimal glycemic control and increasing the risk of morbidity and early mortality (3). Nonadherence may arise owing to factors such as forgetfulness, fear of injections, concerns about insulin dose and risk of overdose, the risk and fear of hypoglycemia and weight gain, and difficulties in integrating insulin injections into daily routines (3,4).

Technological advancements have led to improved insulin delivery systems, including smart insulin pens, AID systems, and continuous glucose monitoring (CGM) devices (5). Smart insulin pens, like NovoPen 6, offer insights into insulin dosing frequency and treatment adherence patterns to health care professionals (HCPs) and people living with diabetes, whereas CGM provides glucose pattern data; collectively, these data could assist HCPs in tailoring treatment regimens to improve adherence and clinical outcomes (6–9).

The relationship between treatment adherence and glycemic outcomes has been documented in clinical trials, and results of a real-world Swedish study of adults with type 1 diabetes using NovoPen 6 demonstrated that missed insulin doses were negatively associated with glycemic parameters (10). There are limited additional real-world data on this topic for type 1 diabetes, and available real-world data for type 2 diabetes often rely on sources (e.g., insurance claims) where collection of glycemic data is not systematic (11,12). Thus, there is a need for global studies to comprehensively examine the broader impact of treatment adherence on glycemic outcomes in real-world settings.

In this study we investigated the association between adherence to a basal-bolus insulin treatment regimen and glycemic outcomes using real-world observational data collected via smart insulin pens and CGM for adults with diabetes across 16 countries. The association between engagement with a smart insulin pen and glycemic outcomes was also explored.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This was a retrospective, real-world analysis of observational data from individuals with diabetes who volunteered to share their data anonymously for research purposes. Users were included from all countries where the NovoPen 6 was launched at the time of this analysis, covering 15 European countries and Japan.

Adults (aged ≥18 years) included in this analysis were administering basal insulin degludec (degludec) and either bolus insulin aspart (aspart) or fast-acting insulin aspart (faster aspart) using a smart insulin pen (NovoPen 6 or NovoPen Echo Plus; Novo Nordisk) with CGM and were using a mobile app (diasend, Glooko; FreeStyle LibreLink, Abbott Laboratories; or Glooko, Glooko) to view the data.

When pairing each smart insulin pen with the mobile app, individuals also selected and recorded the insulin type administered with that pen. Smart insulin pens collected data regarding the dose and time of injections. Once these data had been uploaded to the app, knowledge of the insulin type linked to each smart insulin pen, as well as the differences in dosing patterns across smart insulin pens, could be used to differentiate basal and bolus doses that had been administered. The mobile apps also compiled data on the CGM values and individual's age and country of residence; the diabetes type of the individual was registered in the diasend and Glooko apps but not in the FreeStyle LibreLink app. A sensitivity analysis was performed for the subgroup of individuals eligible for inclusion with a recorded type 1 diabetes diagnosis (as registered in the mobile app). Smart insulin pen and CGM data were collected continuously through uploads to the apps between 23 March 2021 and 8 July 2023. Smart insulin pen data were uploaded by individuals to their mobile devices with use of near-field communication. CGM data were collected via intermittently scanned and real-time devices (brand and model details not available).

Outcomes and Statistical Analyses

Following clinical practice, we aggregated data into nonoverlapping 14-day periods, summarizing adherence statistics and CGM outcomes over each period. A 14-day period was included in the analysis if there were ≥10 days with CGM data of ≥70% coverage, at least two degludec injections, and at least one bolus injection (aspart or faster aspart).

The adherence to basal-bolus insulin therapy was quantified according to number of missed basal and missed bolus insulin doses (Fig. 1). A missed basal insulin dose was defined according to a window of >40 h between two consecutive doses, per the local degludec label (13). The number of missed basal doses was counted as the number of such windows in the 14-day period (Fig. 1). A missed bolus insulin dose was identified where there was a meal with no bolus injection in the window of 15 min before to 1 h after the start of a meal; meals were detected from the CGM signal with use of the clinically validated Glucose Rate Increase Detector (GRID) algorithm, which estimates the rate of change of glucose levels and identifies glucose excursions (defined as a gradient of ≥5.3 mmol/L/h for two consecutive readings [30 min] or ≥5.0 mmol/L/h for three consecutive readings [45 min]) at points when the CGM signal is ≥7.2 mmol/L (10,14) (Fig. 1). The number of bolus insulin doses over a 14-day period was also assessed. Given that participants had to actively engage with their smart insulin pen and mobile app to upload their data, the number of days with data uploads over a 14-day period was used as a proxy for engagement with the smart insulin pen data.

For assessment of glycemic control, the following CGM-derived parameters were aggregated for each 14-day period: percentage of time with glucose levels in target glycemic range (time in range [TIR]) (3.9–10.0 mmol/L), percentage of time above target glycemic range (TAR) (>10.0 and >13.9 mmol/L), and percentage of time below target glycemic range (TBR) (<3.9 and <3.0 mmol/L); mean plasma glucose; glycemic variability (coefficient of variation ([%CV]); and glucose management indicator (GMI) score (15). Adherence events were analyzed in terms of the probability of having at least one event in 14 days and the number of events per 14 days. The probabilities were estimated with a generalized linear mixed model based on the binomial distribution, with individual identifier (ID) as a random effect allowing for variation between individuals. The mean number per 14 days was estimated with a generalized linear mixed model based on the negative binomial distribution with individual identifier as a random effect. A linear mixed model was used to determine the relationship between basal-bolus adherence measures and glycemic outcomes, with the individual as a random effect. The model included covariates describing

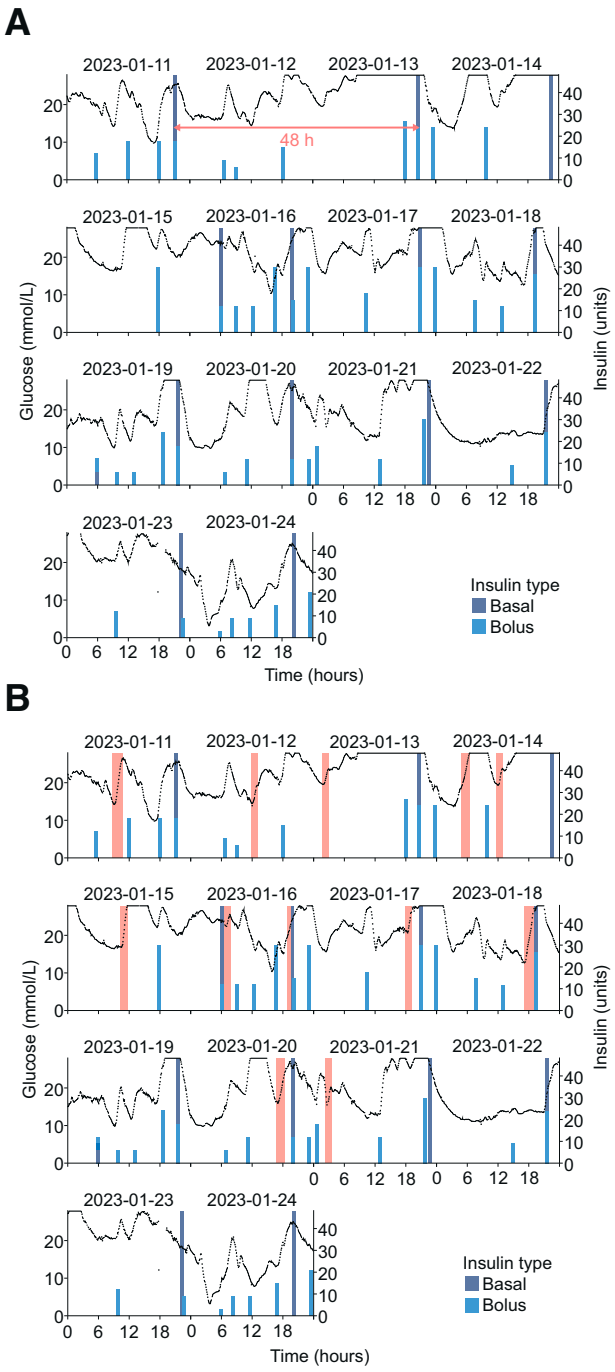

Figure 1—Definitions of basal-bolus adherence: missed basal insulin dose (*A*) and missed bolus insulin dose (*B*). Black lines (*A* and *B*) show CGM traces. Red horizontal arrows (*A*) indicate missed basal insulin doses. Red bars (*B*) show missed bolus insulin doses, with meals detected as large gradients in the CGM signal, where a bolus dose is not administered within a window of 15 min before to 60 min after the estimated onset of the meal. Dates data over the panels are presented as year-day-month.

between-individual and within-individual differences. Between-individual covariates comprised the average number of daily bolus injections, missed basal injections, missed bolus injections, and upload days over a 14-day period, as well as daily insulin dose (basal plus bolus insulin), age, and sex. Within-individual covariates comprised the difference between the 14-day value and the individual-level value in the number of daily bolus injections, missed basal injections, missed bolus injections, and upload days over a 14-day period, and the total daily insulin dose. All terms were included as first-order effects except for age, for which a second-order term was included. For verification, a model with second-order effects for the individual-level covariates was also implemented. The model was fitted with the software R (16) and the library lme4 (17). A significance level of 0.05 was predefined for all statistical comparisons. A sensitivity analysis was conducted to assess adherence and glycemic control, as outlined above, for the subgroup of individuals with a recorded type 1 diabetes diagnosis.

RESULTS

Study Population Characteristics

Among the 31,195 users of smart insulin pens and CGM devices who provided data-sharing consent, 4,922 adults had two smart insulin pens (one to administer basal insulin degludec and one to administer bolus insulin) and had ≥10 days with acceptable CGM data of ≥70% coverage over a 14-day period. Overall, 3,945 individuals (mean [SD] age 43.0 [15.6] years) met all the inclusion criteria for the basal-bolus analysis (Supplementary Fig. 1), with 332,967 acceptable CGM days and 25,157 14-day periods (Table 1). Of these, 670 individuals (39.6 [14.9] years) with a registered diabetes type met the inclusion criteria for the sensitivity analysis (Supplementary Fig. 1), with 85,707 acceptable CGM days and 6,380 14-day periods (Supplementary Table 1).

The study population characteristics and glycemic parameters for the basal-bolus analysis and the type 1 diabetes subgroup are shown in Table 1 and Supplementary Table 1, respectively. The number of daily bolus injections was similar across the basal-bolus group (mean [SD] 3.9 [1.6]) and the type 1 diabetes subgroup (4.5 [1.6]).

Frequency and Estimated Probability of Missed Insulin Doses

The mean number of missed basal insulin doses over a 14-day period was 0.19 (95% CI 0.18, 0.21) for the basal-bolus group; the estimated probability of missing at least one basal insulin dose over a 14-day period was 17.6% (16.5, 18.7) (Supplementary Table 2).

The mean number of missed bolus insulin doses over a 14-day period was 6.0 (95% CI 5.9, 6.1) for the basal-bolus group (Supplementary Table 2). For both the basal-bolus group and the type 1 diabetes subgroup, there was considerable variation between individuals, with some individuals having an estimated mean of

Table 1—Characteristics of the study population

	Basal-bolus cohort (*N* = 3,945)
14-day periods, *n* (*n* per individual)	25,157 (6.4)
CGM days, *n* (*n* per individual)	332,967 (84.4)
Days with degludec injections, *n* (*n* per individual)	302,068 (76.6)
Days with bolus insulin injections, *n* (*n* per individual)	320,924 (81.3)
Age, years	43.0 (15.6)
Mobile application use, *n* (%)	
Abbott FreeStyle LibreLink	3,131 (79.4)
Glooko/diasend	417 (10.6)
diasend	165 (4.2)
Glooko	232 (5.9)
Sex, *n* (%)*	
Female	307 (46.2)
Male	357 (53.8)
Country, *n* (%)	
U.K.	1,237 (31.4)
France	1,009 (25.6)
Sweden	429 (10.9)
Denmark	167 (4.2)
Finland	153 (3.9)
Japan	187 (4.7)
Austria	150 (3.8)
Czech Republic	194 (4.9)
Belgium	140 (3.5)
Other†	279 (7.1)
Diabetes type, *n* (%)	
Unknown	3,220 (81.6)
Type 1	670 (17.0)
Other	55 (1.4)
Bolus insulin, *n* (%)	
Faster aspart	1,958 (49.6)
Aspart	1,987 (50.4)
Basal insulin, degludec, *n* (%)	3,945 (100.0)
CGM interval, *n* (%)‡	
900 s	3,489 (88.4)
300 s	452 (11.5)
Other	4 (0.1)
CGM-derived metrics	
TIR 3.9–10.0 mmol/L, %	54.3 (20.1)
TAR >10.0 mmol/L, %	42.2 (21.1)
TAR >13.9 mmol/L, %	18.2 (17.0)
TBR <3.9 mmol/L, %	3.4 (3.6)
TBR <3.0 mmol/L, %	0.5 (0.9)
Mean glucose concentration, mmol/L	10.0 (2.4)
%CV	32.2 (6.2)
GMI score, %	7.6 (1.0)
Smart insulin pen data	
Upload days, *n*/14 days	4.8 (4.4)
Missed basal insulin doses, *n*/14 days	0.4 (0.6)
Missed bolus insulin doses, *n*/14 days	7.4 (5.1)
Bolus insulin doses, *n*/day	3.9 (1.6)
Bolus insulin doses, *n*/14 days	48.1 (23.1)
Basal insulin dose, units/day	26.2 (16.8)
Bolus insulin dose, units/day	30.0 (20.2)

Data are means (SD) unless otherwise indicated. *If data were available; not all apps recorded the sex of the participants. Data were available for 664 individuals (16.8%) of the basal-bolus cohort. †Other countries were Germany, the Netherlands, Norway, Poland, the Republic of Ireland, Spain, and Switzerland; if the country was missing, this was captured as "other."' ‡The brand and model details for CGM devices were unknown; the interval between readings was inferred from the CGM data.

>20 missed bolus doses (data not shown). The estimated probability of missing at least one bolus insulin dose was 99.1% (98.7, 99.4) for the basal-bolus group.

Overall, the frequency and estimated probability of missed insulin doses were similar across the basal-bolus group (Supplementary Table 2) and type 1 diabetes subgroup (Supplementary Table 3).

Association Between Insulin Doses and Glycemic Outcomes

The estimated associations between missed basal and missed bolus insulin doses and glycemic outcomes are summarized in Table 2 (basal-bolus analysis) and Supplementary Table 4 (type 1 diabetes subgroup analysis).

Missed Basal Insulin Doses

In the basal-bolus group and type 1 diabetes subgroup, one missed basal insulin dose per 14-day period was associated with a statistically significant decrease in percentage of TIR and increase in percentage of TAR >10.0 mmol/L, TAR >13.9 mmol/L, mean plasma glucose, and GMI score (Table 2, Fig. 2, and Supplementary Table 4). Across the basal-bolus group (Table 2) and the type 1 diabetes subgroup (Supplementary Table 4), missed basal insulin doses were not associated with significant changes in TBR <3.9 mmol/L, TBR <3.0 mmol/L, or %CV. The between-individual and within-individual effects were similar across all parameters (data not shown).

Missed Bolus Insulin Doses

In the basal-bolus group and type 1 diabetes subgroup, missed bolus insulin doses were associated with a statistically significant decrease in TIR and TBR <3.9 mmol/L and an increase in mean plasma glucose, TAR >10.0 and TAR >13.9 mmol/L, %CV, and GMI score (Fig. 2, Table 2, and Supplementary Table 4).

The between-individual and within-individual effects generally showed similar trends for all parameters; however, the associations were more pronounced between individuals than within individuals (data not shown). Some nonlinearity was detected: the associations between missed bolus insulin doses and the percentage of TIR were strongest among individuals with 0–15 missed bolus doses, tapering off for individuals with TIR <40% (data not shown).

Table 2—Associations of insulin doses and numbers of days with data uploads over a 14-day period with glycemic outcomes in the basal-bolus cohort

Response	Missed basal dose	Missed bolus dose	Daily bolus injection	Days with data uploads
TIR 3.9–10.0 mmol/L, %				
Slope (95% CI)	−2.76 (−3.73, −1.79)	−1.73 (−1.84, −1.62)	1.55 (1.21, 1.89)	0.47 (0.35, 0.60)
P	<0.0001	<0.0001	<0.0001	<0.0001
TAR >10.0 mmol/L, %				
Slope (95% CI)	2.90 (1.87, 3.93)	1.80 (1.68, 1.91)	−1.71 (−2.07, −1.34)	−0.41 (−0.54, −0.27)
P	<0.0001	<0.0001	<0.0001	<0.0001
TAR >13.9 mmol/L, %				
Slope (95% CI)	3.25 (2.43, 4.07)	1.40 (1.31, 1.49)	−1.55 (−1.84, −1.26)	−0.24 (−0.35, −0.13)
P	<0.0001	<0.0001	<0.0001	<0.0001
TBR <3.9 mmol/L, %				
Slope (95% CI)	−0.13 (−0.34, 0.08)	−0.07 (−0.09, −0.04)	0.16 (0.09, 0.23)	−0.06 (−0.09, −0.04)
P	0.2141	<0.0001	<0.0001	<0.0001
TBR <3.0 mmol/L, %				
Slope (95% CI)	0.01 (−0.05, 0.06)	0.00 (−0.00, 0.01)	0.01 (−0.00, 0.03)	−0.02 (−0.02, −0.01)
P	0.8276	0.8059	0.1420	<0.0001
Mean glucose concentration, mmol/L				
Slope (95% CI)	0.46 (0.34, 0.58)	0.20 (0.19, 0.21)	−0.22 (−0.26, −0.18)	−0.03 (−0.05, −0.02)
P	<0.0001	<0.0001	<0.0001	<0.0001
GMI score, %				
Slope (95% CI)	0.20 (0.15, 0.25)	0.09 (0.08, 0.09)	−0.10 (−0.11, −0.08)	−0.01 (−0.02, −0.01)
P	<0.0001	<0.0001	<0.0001	<0.0001
%CV				
Slope (95% CI)	−0.26 (−0.59, 0.07)	0.42 (0.38, 0.46)	0.28 (0.16, 0.39)	−0.22 (−0.26, −0.18)
P	0.1176	<0.0001	<0.0001	<0.0001

Between-individual effects (*N* = 3,945). The presented data include estimated regression coefficients (slope) with 95% CI. Headers show individual-level parameters, calculated as averages over the 14-day blocks for each individual. The regression coefficient shows that, for example, in comparison of two individuals with equal characteristics except one has on average one more missed basal insulin dose per 14 days, this individual would have a mean change in TIR of −2.76%.

Bolus Insulin Doses

In the basal-bolus group and type 1 diabetes subgroup, on average, each daily bolus insulin dose over a 14-day period was associated with a statistically significant increase in percentage of TIR and statistically significant decrease in percentage of TAR >10.0 mmol/L and TAR >13.9 mmol/L, mean plasma glucose, and GMI score. In the basal-bolus group, each daily bolus dose was associated with a statistically significant increase in %CV (Table 2) but was associated with a slight decrease, but not statistically significant, in %CV in the type 1 diabetes subgroup (Supplementary Table 4). In the basal-bolus group, daily bolus insulin doses were associated with a statistically significant increase in percentage of TBR <3.9 mmol/L but not with changes in TBR <3.0 mmol/L (Table 2). The within-individual effect had the opposite association for all parameters compared with the between-individual effects (data not shown). This suggests that periods during which an individual administered more bolus insulin doses than usual were also the periods during which it was difficult to maintain a stable glucose level.

Association Between Smart Insulin Pen Engagement and Glycemic Outcomes

The mean (SD) number of days with data uploads over a 14-day period was 4.8 (4.4) days in the basal-bolus group and 2.1 (2.8) days in the type 1 diabetes subgroup. Across both groups, over a 14-day period, the number of upload days was associated with a statistically significant increase in percentage of TIR and decrease in percentage of TAR >10.0 mmol/L, mean plasma glucose, GMI score, and %CV (Fig. 2, Table 2, and Supplementary Table 4). In the basal-bolus group, the number of upload days was associated with a statistically significant decrease in the percentage of TBR <3.9 mmol/L and TBR <3.0 mmol/L; however, in the type 1 diabetes subgroup, this was associated with a decrease, but not statistically significant, in the percentage of TBR <3.9 mmol/L and TBR <3.0 mmol/L. The between-individual and within-individual effects were similar across all parameters except for TBR <3.9 mmol/L and TBR <3.0 mmol/L, which increased rather than decreased within individuals (data not shown).

Glycemic Outcomes According to Age, Sex, and Total Daily Insulin Dose

Generally, glycemic control was statistically significantly better among older individuals than younger individuals in the basal-bolus group ($P < 0.0001$) (Supplementary Fig. 2); this trend, albeit not statistically significant, was also observed in the type 1 diabetes subgroup. Glycemic outcomes were not dependent on sex in either group. Furthermore, across groups, there was a negative association between the total daily (basal and bolus) insulin dose and percentage of TIR (data not shown).

CONCLUSIONS

This analysis of real-world multinational data collected through a smart insulin

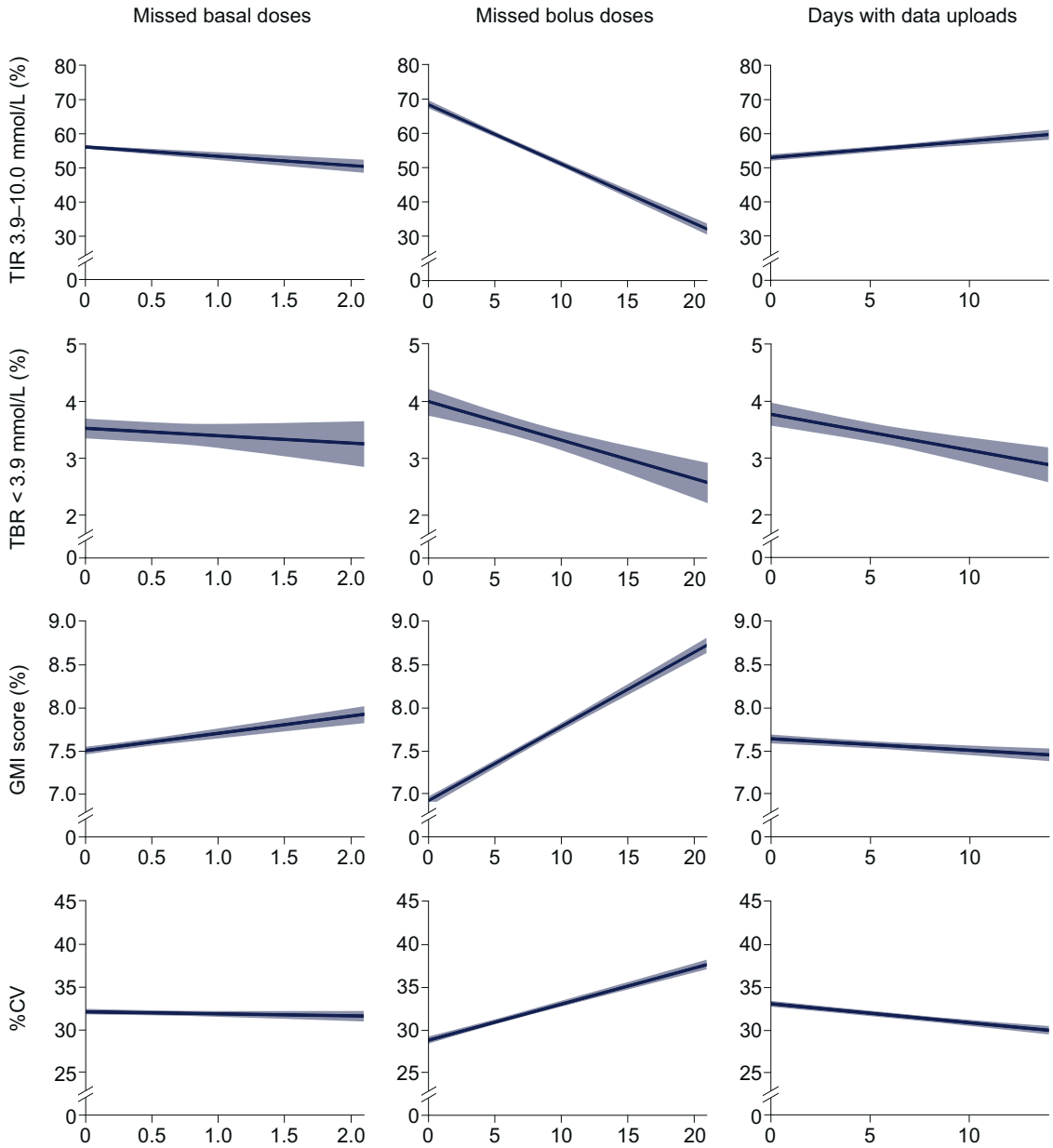

Figure 2—Associations of missed basal insulin doses, missed bolus insulin doses, and days with data uploads over a 14-day period with glycemic outcomes in the basal-bolus cohort. Between-individual effects (*N* = 3,945).

pen and CGM demonstrates that adherence to basal-bolus insulin treatment is challenging for individuals and that treatment adherence and engagement with a smart insulin pen are positively associated with glycemic outcomes. In the basal-bolus analysis, missed basal or bolus insulin doses were each associated with a decrease in the percentage of TIR and increased GMI scores, consistent with findings from a previous Swedish study (10). On average, over a 14-day period, one missed insulin dose was associated with a significant decrease in the percentage of TIR (−2.8% and −1.7% change in TIR with a missed basal dose and a missed bolus dose, respectively); therefore, missing two basal or four bolus insulin doses over a 14-day period would correspond to a clinically relevant reduction (≥5%) in the percentage of TIR, according to internationally accepted guidelines (18). Individuals in this study missed an average of 6.0 bolus insulin doses over a 14-day period, enough to cause a clinically relevant change in TIR. In another study, in individuals using a Bluetooth-enabled pen cap over a 1-month period, those who were most adherent (85% dose adherence) to insulin injections had lower HbA_{1c} than those who were least adherent (49% dose adherence) to treatment (HbA_{1c} 7.7% [60.7 mmol/mol] vs. 8.6% [70.5 mmol/mol]) (19), emphasizing the impact of missed insulin injections on glycemic control.

In our study, missing one basal insulin dose over 14 days was associated with a reduction in TIR of −2.8%, comparable with findings of a Swedish study (2022, Ekberg et al. [10]), where a −2.6% reduction in TIR was reported. Conversely, one missed bolus insulin dose was associated with a reduction in TIR, of −1.7%, greater than the reduction in TIR reported by Ekberg et al., −0.3%. This discrepancy could stem from

the smaller cohort and simpler modeling in the Swedish study. The present analysis was more comprehensive, accounting for additional effects and distinguishing between-individual and within-individual effects, unlike the study of Ekberg et al., which provided a single estimate. The within-individual estimate of the association between a missed bolus dose and TIR (−0.3%) in our study aligns with the overall estimate reported by Ekberg et al. The variation in missed bolus doses was likely less pronounced in the study by Ekberg et al. due to all participants being from Sweden, resulting in a more uniform study population than in our multinational study. The estimated probability of missing at least one basal insulin dose over a 14-day period was ∼18% for the basal-bolus group and 17% for the type 1 diabetes subgroup—somewhat similar to findings from individuals with type 1 diabetes in Sweden using smart insulin pens (22%) (10) but lower than the nonadherence rate reported by individuals with diabetes using a Bluetooth-enabled insulin pen cap (36%) (19). The lower rates in this analysis may reflect differences in populations and study designs. In this study, some individuals could have used disposable insulin pens instead of their smart insulin pen, which would not be discernible in these data; however, this would hypothetically increase rather than decrease the estimated probability of missing a basal insulin dose.

The number of days with a data upload from the smart insulin pen to the mobile app over a 14-day period served as a proxy for smart insulin pen engagement, consistent with previous studies. In the basal-bolus group, greater smart insulin pen engagement was associated with significantly better glycemic control, consistent with similar studies on connected insulin pen caps (20), mobile-based diabetes apps (21,22), and associations between FreeStyle scans and CGM parameters (23).

Basal-bolus insulin adherence measures were highly similar between the basal-bolus insulin group and the type 1 diabetes subgroup, although broader CIs were observed in the type 1 diabetes subgroup owing to the smaller sample size. These similarities could suggest that the basal-bolus group predominantly comprised individuals with type 1 diabetes or that adherence affects glycemic control similarly in individuals with type 1 and type 2 diabetes using MDI.

Glycemic control, as measured by TIR, was statistically significantly better in older versus younger individuals in this analysis. For better understanding of the potential factors contributing to this difference, in future studies researchers should investigate whether this stems from inherent distinctions in glycemic control achievement between younger and older individuals (24) or is linked to the reported higher level of interest among older individuals in adopting smart insulin pen technologies (25).

This analysis benefits from real-world data collection from a large multinational population using smart insulin pens in diverse health care settings. Smart insulin pens enabled accurate injection timing data collection under real-world conditions, offering valuable insights into treatment adherence its impact on glycemic outcomes. The study design minimized recollection bias, which is ideal for quantifying missed insulin doses.

Observational studies offer valuable insights, but their limitations should be acknowledged. This analysis only included participants who volunteered to share their data anonymously, potentially introducing selection bias. Our results may apply to other basal-bolus populations using regular insulin pens, but it is unclear how individuals using smart insulin pens differ from those who do not. Factors like baseline adherence, glycemic control, and country-level differences in clinical practice and reimbursement levels may influence the decision to use a smart insulin pen and are not discernible from the available data. Despite consideration of all available demographic variables, clinical characteristics information was limited; additionally, data for brand names or CGM device models were not collected.

Moreover, while the self-report nature of medication data may introduce the potential for misclassification, the quality and reliability of these data are generally high because they are typically entered only once, when the smart insulin pen is registered, minimizing the impact on study outcomes. The frequency of data uploads may not necessarily reflect engagement with smart insulin pen data. For example, we hypothesize that individuals or their HCPs review their data with upload to their mobile app, but we cannot assume that this occurs in clinical practice. Also, the proxy (days with data uploads) for smart insulin pen engagement could be influenced by various factors; nevertheless, it consistently provides data of clinical importance.

Since we lacked meal information in this study, we used the GRID algorithm, which has been clinically validated for use with both AID systems and MDI to detect meal-related glucose excursions. However, as the algorithm has only been validated in silico, it served as a surrogate measure of meal detection. The algorithm estimates the rate of glucose level changes to identify glucose excursions and was used in conjunction with injection data to identify missed bolus insulin doses (14). This method aligns with previous studies where the GRID algorithm (6,10,20) or similar methods (26,27) were used. Specifically, a meal identified with the algorithm without a corresponding bolus insulin injection was considered an indication of a missed bolus insulin dose. This approach is somewhat akin to that of Norlander et al. (27), where a meal was defined according to specific CGM signal criteria and the absence of an insulin dose within 2 h of this rise was considered as a missed bolus insulin dose. Nonetheless, future prospective studies that validate the GRID algorithm with use of concurrent CGM, insulin, and meal logging to assess its specificity, sensitivity, and predictive values would be advantageous. Despite potential limitations in detecting certain meals (e.g., low-carbohydrate meals or well-dosed meals owing to the absence of a glucose spike in the CGM signal), the GRID algorithm demonstrates high specificity, particularly for identifying inadequately dosed meals as shown in silico. It should be noted that the onset of the meal is an estimate, from the CGM signal, subject to uncertainty. Furthermore, late insulin doses, given >60 min after a meal, will, according to our definition, be classified as "missed bolus doses." We base our definition on the product information for faster aspart and aspart, which instructs individuals to take their bolus at most 2–10 min before the meal and at most 20 min after the meal (28,29). There may, however, be clinical scenarios where individuals may intentionally delay their bolus insulin dose, such as in the case of those with gastroparesis who delay their bolus dose to prevent vomiting and consequent hypoglycemia (30). Thus, it may be relevant to consider missed bolus insulin doses as "missed or delayed bolus

insulin doses" in interpreting these findings and in using the GRID algorithm in future studies. Finally, in other studies including data from both a CGM device and a Bluetooth-enabled pen cap (31), a smart insulin pen (32), or a sensor-augmented insulin pump (27), various methods have been used to define a missed bolus insulin dose (defined, respectively, as a rise in glucose of $\geq$2.8 mmol/L without a bolus dose within 2 h, a rise in glucose of $>$3.9 mmol/L without a bolus dose 2 h before to 4 h after the excursion, or a rise in glucose of $>$3.9 mmol/L without a bolus dose within 2 h from the start of the rise) (27,31,32). To our knowledge, there is currently no consensus definition for a missed bolus insulin dose.

We should also note that the primary results reflected between-individual differences in adherence, potentially affected by unobserved confounders. However, within-individual differences explored in this analysis showed similar tendencies. While these findings suggest associations, causality cannot be determined based solely on these data. In future studies researchers could investigate injection behavior patterns in individuals with type 2 diabetes or those using other basal insulins to explore whether the findings in this study also apply to different populations seen in real-world clinical practice.

In conclusion, these smart insulin pen data from a multinational population highlight challenges in adhering to basal and bolus insulin treatment in a real-world setting. Missing two basal and four bolus insulin doses within a 14-day period can adversely affect glycemic control, corresponding to a clinically relevant reduction in percentage of TIR. Leveraging smart insulin pen and CGM data in collaborative conversations between HCPs and individuals during routine consultations may facilitate the identification and implementation of personalized treatments to address adherence challenges, potentially improving treatment outcomes. Combining a smart insulin pen with additional support, e.g., app-based training, education, or artificial intelligence–derived insulin dosing suggestions (33), may further improve glycemic control and help bridge the gap observed between individuals treated with MDI therapy and those treated with AID systems.

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