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Lazy Sunday afternoons: the negative impact of interruptions in patients' daily routine on adherence to oral antidiabetic medication. A multilevel analysis of electronic monitoring data

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ABSTRACT

Purpose

Considerable variability in adherence over time exists. The aim of this study was to investigate to what extent deviations from the prescribed regimen in type 2 diabetes patients can be explained by characteristics of the individual 'medication intake moments' and the patient.

Methods

Medication intake of 104 non-adherent type 2 diabetes patients from 37 community pharmacies was electronically monitored for 6 months. The primary outcome measures were: (1) whether or not the intake occurred and (2) whether or not the intake occurred within the agreed-upon time period (correct timing). Multilevel logistic regression analyses were performed to account for the nested structure of the data.

Results

Medication intakes in the evening and during weekends and holidays were more likely to be incorrectly timed and also more likely to be completely missed. Irrespective of timing, most intakes occurred in the mornings of Monday through Thursday (96 %), and least intakes occurred on Saturday evening (82 %). Correctly timed intakes most often occurred on Monday and Tuesday mornings (61 %) in contrast to Sunday evenings (33 %). A patient's medication regimen was significantly associated with adherence.

Conclusion

Based on our results, among patients who already have difficulties in taking their oral antidiabetic medication, interruptions in the daily routine negatively influence the intake of their medication. Professionals need to be aware of this variation in adherence within patients. As regular medication intake is important to maintain glycaemic control, healthcare professionals and patients should work together to find strategies that prevent deviations from the prescribed regimen at these problematic dosing times.

INTRODUCTION

Patients' adherence to medication is a dynamic behaviour that can change over time. Previous studies have reported significant variability in adherence over time, both between and within patients [1–5]. Most patients with type 2 diabetes need regular intake of oral antidiabetic medication to maintain glycaemic control. Good glycaemic control reduces the incidence of diabetes-related complications [6–8]. However, many patients experience difficulties in regularly taking their medication. A study following diabetes patients for 6 months showed that the first daily dose, often taken in the morning, was mostly taken very regularly. For patients with multiple doses per day, it was shown that the second and especially the third dose were taken irregularly [9]. The complexity of the medication regimen thus has an impact on adherence. Several studies involving patients with various chronic illnesses, including diabetes, have shown that increasing number of prescribed daily doses is associated with lower adherence [9–14].

Individual adherence may vary due to interruptions in patients' daily routine, for example, during weekends and holidays. Furthermore, the day of the week and the moment of intake during the day may influence the regularity with which patients take their medication. Dosing times may interfere with patients' work schedule or social life. Two studies, one involving patients on antihypertensive treatment and one involving patients infected with human immunodeficiency virus, showed that patients were more likely to miss weekend doses than weekday doses and that a morning dose was more likely to be taken correctly than an evening dose [15, 16]. A small seasonal impact was found in one of these studies as patients had more difficulty following their respective medication regimen between April and September [16]. All of these studies used logistic models to analyse patients' daily dosing adherence—that is whether or not the prescribed number of doses was taken on a day—and included patients' intake on the previous days to adjust for dependence. However, multilevel modelling can take clustering of intakes within patients into account in a relatively more powerful and efficient way [17]. In addition, it allows for characteristics of the individual intake moment (i.e. the exact moment at which the patient takes the medication) and those of the patient to be included in one analysis, thereby enabling their association with adherence to be accurately estimated. Finally, both between- and within-patient variation can be examined simultaneously.

Therefore, the aim of this study was to use multilevel modelling to investigate the extent to which deviations from the prescribed regimen in type 2 diabetes patients can be explained by specific characteristics of the individual patient and individual intake moment.

METHODS

Design and participants

In this observational study, the intake of oral antidiabetic medication of 104 type 2 diabetes patients was monitored using a real time medication monitoring (RTMM) system for a period of 6 months. The RTMM system uses an electronic medication dispenser that registers the date and time of each opening in real time at a central server, providing accurate and detailed information on patients' medication use. The RTMM dispenser can be fit for one type of medication, in this case the oral antidiabetic medication. Possible co-medications were not monitored. Data for this study were retrieved from a larger intervention study [18, 19]. Selection criteria for patient inclusion in this intervention study were: (1) use of oral antidiabetic medication for at least 1 year; (2) when combined with oral medication: use of insulin for at least 6 months; (3) a refill adherence to oral antidiabetic medication of <80 % in the year preceding the intervention [calculated as the total days' supply of medication collected at the pharmacy during that year divided by the total number of days (365), multiplied by 100 %]; (4) age between 18 and 65 years; (5) the last prescription for oral antidiabetics collected within 2 months prior to the intervention; (6) knowledge of the Dutch language; 7) access to a mobile phone. Thus, the intervention was aimed at patients who had difficulties in taking their medication. Eligible patients were selected from 37 community pharmacies based on pharmacy data. Further details on the design can be found in the study protocol [18]. This study protocol was approved by the Medical Ethics Committee of the Utrecht Academic Medical Centre and registered in the Primary Registry of the Netherlands (trial register number NTR1882).

Outcome measures

In agreement with their pharmacist and in accordance with their prescribed medication regimen, patients chose one, two or three daily time periods within which they would take their oral antidiabetic medication. For example, a patient who is prescribed a two-daily dose regimen might choose to take the medication between 8:00 and 9:00 hours and 17:00 and 18:00 hours, respectively. Patients could themselves decide upon the length of the time period. A 1-h period was most often chosen by patients, followed by a period between 1 and 2 h.
The two outcome variables were: (1) whether or not the medication intake occurred at all (taken or missed) and (2) whether or not the medication intake occurred within the agreed time period (correct or incorrect timing).

Statistical analyses

Data collected with the RTMM system have a hierarchical structure: the medication intakes are clustered within patients, i.e. the intakes are not independent observations, they are correlated with one patient. In turn, patients are clustered within pharmacies. Multilevel analyses were performed to account for this clustering [17]. Accordingly, the multilevel model consisted of three levels, namely, the pharmacy, patient, and medication intake. Because of the dichotomous nature of the two dependent variables, multilevel logistic regression models were used. Two models were estimated for both dependent variables: (1) a model with characteristics of the intake and (2) a model with both intake and patient characteristics. Variables included in the first model were the moment of intake (morning, afternoon or evening), the day of the week, and whether or not the intake was during a school

holiday (defined according to the advised holiday dates set by the Dutch government). Because the length of monitoring might have an effect on adherence, we included the number of elapsed days (range 1–183) as a control variable. Variables added in the second model were age, gender, whether or not insulin was used in combination with oral antidiabetics and the medication regimen (one, two or three doses per day). Due to the limited number of patients and missing values on other variables at the patient level (educational level, ethnicity, work status, household composition, duration of diabetes and the presence of complications), the association between these variables and the outcome measures was first tested in a bivariate analysis and only then included in the model if a significant association ($p < 0.05$) was found. Our data were retrieved from an intervention study in which the intervention group received SMS reminders when they forgot to take their medication in time. 'Whether or not receiving SMS reminders' was included as a control variable because we expected patients receiving alerts to have a more regular adherence pattern. Variables were centred around their means for interpretation purposes.

Due to the small numbers of patients per pharmacy in our study (one in 12 pharmacies, with up to nine in one pharmacy), we estimated between-pharmacy variance, but included no pharmacy-level variables in the model. The moment of intake was also included as random variable at the patient level because patients could have one, two or three intake moments per day.

The results of the analysis are presented as odds ratios (OR) with a 95 % confidence intervals (CI) for the fixed effects and as the variance with standard error (SE) and intra-class correlation (ICC) for random effects. The ICC at the patient and pharmacy level is an indication of the correlation between the medication intake of one patient and that between patients refilling their prescription at one pharmacy, respectively. All analyses were performed with MLwiN 2.25 [20].

RESULTS

More than half of the patients were male and their average age was 55 years (Table 1). Almost one-third of patients had a non-Western ethnicity. About three in ten patients combined their oral antidiabetics with insulin. Nearly all patients used co-medication(s), of which cardiovascular medication was the most common. On average, patients had been diagnosed with diabetes for 9.5 years. Half of the patients were prescribed two doses a day.

[TABLE 1]

In total, 36,199 medication intake moments were expected according to the medication regimen of all patients during the 6-month monitoring period. Intakes were more often scheduled by patients for the morning than for the afternoon and evening (Table 2). About two in ten intakes coincided with a school holiday. As the majority of patients entered the study between October and December 2008, most intakes were scheduled during the winter.

[TABLE 2]

Proportion of medication intakes occurring irrespective of timing

On average, 96, 88 and 85 % of intakes in the morning, afternoon and evening, respectively, occurred irrespective of timing. The morning intake was least often missed, both during weekdays and the weekend (Fig. 1). Most intakes occurred on the mornings of Monday through Thursday (96 %), and the least occurred on Saturday evenings (82 %).

[FIGURE 1]

Proportion of correctly timed medication intakes

The average percentages of intakes occurring within the agreed time period were 57, 47 and 43 % in the morning, afternoon and evening, respectively. Figure 2 shows that an intake scheduled for the morning and on a weekday was more often correctly timed than an intake scheduled for the afternoon or evening or during the weekend. The percentage of correctly timed intakes was lowest on Sunday evening (33 %) and highest on Tuesday morning (61 %).

[FIGURE 2]

Variation in intakes occurring irrespective of timing

Results of the multilevel analyses showed that the odds of an intake occurring in the morning was about 70 % higher than one occurring in the afternoon or evening and that the odds of an intake occurring on a weekday was 20–40 % higher than one on Sundays (Table 3, model 1). Furthermore, intakes during school holidays were more likely to be missed. Intakes during the autumn were less likely to be missed than those during the winter. The afternoon intake varied most between patients. Bivariate analyses showed that educational level, ethnicity, work status, household composition, duration of diabetes and complications were not associated with occurrence of intakes irrespective of timing nor with intakes occurring within the agreed time period; these variables were therefore not included in model 2. The impact of the moment of intake, day of the week, school holidays and seasons remained significant following the addition of the remaining patient characteristics to the model (Table 3, model 2). In addition, compared to older patients and patients using one or three doses a day, younger patients and patients on a twice-daily dose regimen were more likely to miss their medication intake. The variance between patients as well as between pharmacies decreased slightly after patient characteristics were included in the model, indicating that these characteristics accounted for only a small amount of variation.

[TABLE 3]

Variation in correctly timed intakes

The moment of intake, day of the week, and school holidays also had a significant impact on whether or not the intake was correctly timed (Table 3, model 1). Intakes in the evening, during the weekend and on a day during school holidays were less likely to occur within the agreed time period. No seasonal impact was found. Between-patient variance was slightly larger for the afternoon intake than for the morning and evening intake. Between-pharmacy variance accounted for 13 % of the

total variance. The medication intake characteristics remained significantly associated with the correct timing of intakes after the addition of patient characteristics to the model (Table 3, model 2). Patients taking medication once a day were more likely to take their dose within the agreed time period than those taking two or three doses a day. Adding these characteristics to the model only slightly reduced the variance between patients in the correct timing of the morning and afternoon intake—not the evening intake.

DISCUSSION

Our study shows that intakes during the weekend and during holidays were more often taken outside of the agreed time period, or even completely missed, indicating that interruptions in patients' daily routine have a negative impact on their medication intake . A morning intake was most often correctly timed, whereas an evening intake was most often incorrectly timed. More doses were missed by patients on a twice-daily regimen. These patients were, together with patients taking three doses a day, also more likely to take their medication outside of the hours they had agreed upon with their pharmacist.

Our results confirm the findings of previous studies examining the impact of the day of the week and moment of intake on adherence in other patient populations [15, 16]. By performing multilevel analyses, and as such taking into account clustering of intakes within patients, we were able to estimate these associations in a more powerful way than in previous studies. We found stronger effects of these characteristics on adherence in type 2 diabetes patients. In addition, we found a negative impact of school holidays on adherence, supporting the conclusion that interruptions in patients' daily routine have a negative influence on adherence. This holiday effect might be the reason that we did not find an effect of summer on adherence, thereby contradicting the seasonal impact found by Vrijens et al. [16]. It should be noted that the effect of school holidays might be stronger for patients with school-going children or for patients who work at schools. On the other hand, the effect of holidays might be underestimated for patients who go on vacation outside the official school holidays. That the evening intake was most often incorrectly timed was supported by results from interviews with type 2 diabetes patients, who highlighted that forgetting to take the medication with them when they ate out for dinner was a reason for non-adherence [21]. With respect to the medication regimen, our results partly conflict with those of Paes et al. who showed that a once-daily dose regimen provided the highest levels of both drug intake and timing adherence compared to a multiple dose regimen per day [9]. This was confirmed in our study for adherence with respect to timing. For intakes occurring irrespective of timing, however, we found that not three doses a day but two daily doses led to the highest proportion of missed intakes. In line with other studies, our results show that most socio-demographic characteristics were not associated with adherence [22, 23]. The association of increasing age and higher adherence (irrespective of timing) was also found in a study among patients with rheumatoid arthritis, in which it was suggested that older patients made fewer adherence errors due to having a more regular daily routine [24].

Strengths and weaknesses

With electronic monitoring (EM) it is possible to observe each single intake and subsequently each single deviation from the prescribed regimen. EM provides the

means to include the exact intake moment into adherence analyses. Our study is, to our knowledge, the first to analyse EM data with multilevel models. As such, we were able to take the clustering of intakes within patients into account, simultaneously explore the influence of intake and patient characteristics on adherence and analyse between- and within-patient variation. A common critique of EM is that it does not allow confirmation that a dose is actually taken and/or that no more or no less than the prescribed amount is taken. However, evidence for the validity of EM devices is provided by studies showing that mismatches between medication events and actual dosing were too rare to create substantial differences between projected and actual drug concentrations in the plasma [25–27].

Our limited sample comprised a select group of type 2 diabetes patients. Data were retrieved from a larger randomized controlled trial. For this trial, we selected patients who had a refill adherence of <80 % based on pharmacy data, i.e. patients who experienced problems in taking their medication. This may have led to an overestimation of the effects, as there is already a larger variation in medication intake in these patients than in adherent patients. Moreover, about half of the patients in this study received SMS reminders if they did not take their medication within the agreed time period. Our previous study showed that SMS reminders in particular improved the regularity with which patients adhere to their prescribed regimen [19]. The sending of SMS reminders, therefore, in the present study may have resulted in an underestimation of the effects. Consequently, our results can not be generalized to the whole type 2 diabetes population.

The primary aim of our study was to provide insight into the patterns of medication intake of type 2 diabetes patients. We did not include data on blood glucose levels in our study. Therefore, we could not study whether deviations from the agreed time period were translated in a less adequate control of blood glucose levels. Patients are usually advised to take their oral antidiabetics with their meals, which may not be consumed at the usual times during weekends and holidays. However, during these periods, medication is not only more often incorrectly timed, but also more often completely forgotten. Nevertheless, further research to investigate the clinical impact of these deviations is recommended.

As expected in our study population, all but six patients used co-medication. This number of patients is too small to reliably study the effect of co-medication (other than insulin) on adherence and was therefore not included in the multilevel model. For future studies, it would be interesting to include the number of co-medications into the model, as adherence has been shown to decrease with increasing number of co-medications [13].

Clinical implications

Regularity in medication intake is important in type 2 diabetes patients to obtain optimal blood glucose levels. However, our study suggests that irregularities are common. Physicians need to be aware of the fact that adherence of any individual patient can be irregular, especially when that patient's daily routine is interrupted. Physicians should discuss these problematic dosing times with patients in a collaborative effect to integrate medication intake on these days. For example, it has been shown that providing individualized recommendations via cues helps patients remember to take their medication and consequently improves adherence [28].

Future research

This study shows the possibilities of multilevel modelling for evaluating adherence behaviour from EM data. We therefore recommend using this technique in future adherence studies. Due to our limited sample size we have only explored patient variance at the moment of intake. Other intake characteristics or patient characteristics, such as social or psychological factors, may also contribute to differences between patients.

CONCLUSION

For patients who already have difficulties taking their oral antidiabetic medication, their medication intake appears to be negatively impacted when their daily routine is interrupted. During weekends and holidays patients more often take their medication outside the agreed time period or even completely miss their dose. Our findings suggest that healthcare professionals need to discuss with patients how to prevent deviations from the prescribed regimen, especially when their daily routine is broken.

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Conflict of interest

None.

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TABLES AND FIGURES

Table 1: Characteristics of patients at baseline

Patient characteristics	Values
Total no. patients	104 (100)
Age (years), mean (SD)	54.8 (6.7)
Male	57 (54.8)
Educational level[a] ($n = 85$)	
Low	34 (40.0)
Medium	28 (32.9)
High	23 (27.1)
Ethnicity ($n = 87$)	
Western population	60 (69.0)
Non-Western population	27 (31.0)
Work status ($n = 84$)	
Self-employed, paid or volunteer work	48 (57.1)
Unemployed (looking for job, disabled, housewife/-man, retired)	36 (42.9)
Household composition ($n = 83$)	
Living alone	12 (14.5)
Living with partner, children or others	71 (85.5)
Insulin use[b]	32 (30.8)
Use of co-medication (excl. insulin)[b]	98 (94.2)
Cardiovascular co-medication	90 (86.5)
Duration disease (years) ($n = 82$), mean (SD)	9.5 (9.8)
Complications of diabetes ($n = 84$)	13 (15.5)
Medication regimen	
Once daily	23 (22.1)

Patient characteristics	Values
Twice daily	52 (50.0)
Three times daily	29 (27.9)
Receiving SMS reminders	56 (53.8)

Data are presented as numbers with the percentage in parenthesis, unless indicated otherwise
[a] Classification: low = primary education, lower secondary education and lower vocational education; medium = intermediate secondary and intermediate vocational education; high = higher vocational education and university
[b] Use of insulin or other co-medication was identified from pharmacy data

Table 2
Characteristics of medication intakes that were expected in the 6-month monitoring period according to the medication regimen of the patients
*

Characteristics of medication intakes	Expected intakes (*n* = 36,199)
Moment of intake	
Morning	16,757 (46.3)
Afternoon	11,218 (31.0)
Evening	8,224 (22.7)
Day of the week	
Monday	5,148 (14.2)
Tuesday	5,163 (14.3)
Wednesday	5,171 (14.3)
Thursday	5,179 (14.3)
Friday	5.177 (14.3)
Saturday	5,187 (14.3)
Sunday	5,174 (14.3)

Characteristics of medication intakes	Expected intakes (*n* = 36,199)
During school holiday	7,114 (19.7)
Seasons	
Winter	13,494 (37.3)
Spring	9,000 (24.9)
Summer	4,250 (11.7)
Autumn	9,455 (26.1)

Data are presented as numbers with the percentage given in parenthesis

Fig. 1 The percentage of intakes occurring irrespective of timing by day of the week, categorized by moment of intake (clustering within patients taken into account). Note: the *vertical axis* ranges from 50 to 100 %

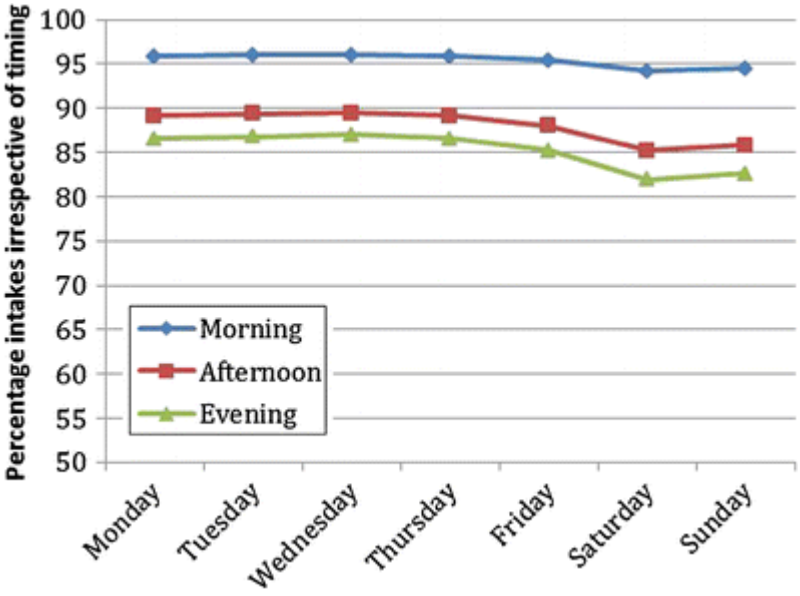

Fig. 2 The percentage of correctly timed medication intakes by day of the week, categorized by moment of intake (clustering within patients taken into account)

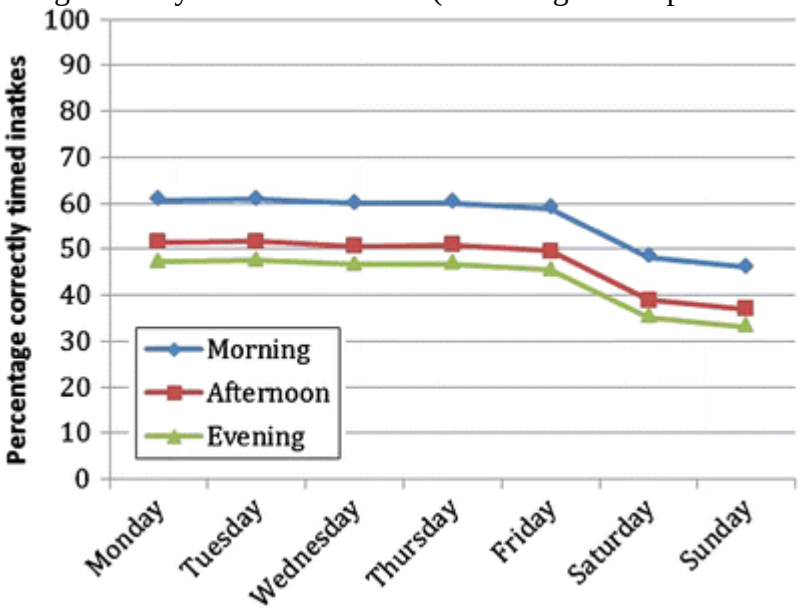

Table 3

Results of multilevel logistic regression analyses with the 'medication intake occurring irrespective of timing' and the 'intake occurring within the agreed time period' as dependent variables and characteristics of the medication intake and patient as independent variables

Variables	**Intake occurred irrespective of timing**		**Intake within agreed time period**	
	Model 1a	**Model 2b**	**Model 1a**	**Model 2b**
Characteristics intake level	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Moment of intake (ref = morning)				
Afternoon	0.35 (0.20–0.62)***	0.30 (0.18–0.51)***	0.69 (0.41–1.15)	0.68 (0.42–1.09)
Evening	0.28 (0.17–0.44)***	0.27 (0.17–0.42)***	0.58 (0.36–0.94)*	0.62 (0.39–1.00)*
Day of the week (reference = Sunday)				
Monday	1.36 (1.22–1.52)***	1.36 (1.22–1.52)***	1.81 (1.65–1.99)***	1.81 (1.65–1.99)***
Tuesday	1.39 (1.24–1.55)***	1.39 (1.24–1.55)***	1.83 (1.66–2.01)***	1.83 (1.66–2.00)***
Wednesday	1.41 (1.26–1.57)***	1.41 (1.26–1.57)***	1.75 (1.60–1.93)***	1.75 (1.60–1.93)***
Thursday	1.36 (1.21–1.52)***	1.36 (1.21–1.52)***	1.77 (1.62–1.95)***	1.77 (1.62–1.95)***
Friday	1.21 (1.09–	1.21 (1.09–	1.68 (1.53–	1.68 (1.53–

Variables	Intake occurred irrespective of timing		Intake within agreed time period	
	Model 1a	Model 2b	Model 1a	Model 2b
	1.36)***	1.36)**	1.84)***	1.84)***
Saturday	0.95 (0.86–1.06)	0.95 (0.86–1.06)	1.09 (1.00–1.20)	1.09 (0.99–1.20)
Day in school holiday (reference = no)	0.91 (0.84–0.98)*	0.91 (0.84–0.98)*	0.92 (0.86–0.98)*	0.92 (0.86–0.98)*
Seasons (reference = winter)				
Spring	1.00 (1.00–1.00)*	1.00 (1.00–1.00)*	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Summer	0.90 (0.78–1.04)	0.90 (0.78–1.03)	0.98 (0.88–1.09)	0.98 (0.88–1.08)
Autumn	1.18 (1.07–1.30)***	1.17 (1.06–1.30)**	1.02 (0.95–1.10)	1.02 (0.95–1.10)
Characteristics patient level				
Age		1.03 (1.00–1.07)*		1.03 (0.99–1.06)
Gender (reference = male)		1.38 (0.89–2.14)		1.52 (0.97–2.38)
Insulin use (reference = no)		0.86 (0.53–1.40)		1.07 (0.65–1.76)
Medication regimen (reference = once)				

Variables	Intake occurred irrespective of timing		Intake within agreed time period	
	Model 1a	Model 2b	Model 1a	Model 2b
Twice daily		0.41 (0.21–0.82)*		0.35 (0.18–0.68)**
Three times daily		1.10 (0.52–2.35)		0.40 (0.19–0.83)*
Random part				
Between-patient variance	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Morning intake	2.20 (0.37)	2.02 (0.34)	2.00 (0.33)	1.63 (0.27)
Afternoon intake	3.21 (0.66)	2.25 (0.47)	2.41 (0.51)	2.00 (0.43)
Evening intake	1.81 (0.37)	1.59 (0.32)	2.20 (0.45)	2.23 (0.45)
Between-pharmacy variance	0.42 (0.21)	0.28 (0.16)	0.49 (0.22)	0.49 (0.21)
ICCc (%)				
Patient level by moment of intake	40.1 % morning	38.1 % morning	37.8 % morning	33.1 % morning
	49.4 % afternoon	40.6 % afternoon	42.3 % afternoon	37.8 % afternoon
	35.5 % evening	32.6 % evening	40.1 % evening	40.4 % evening
Pharmacy level	11.3 %	7.9 %	13.0 %	13.0 %

*p < 0.05; **p < 0.01; ***p < 0.001
OR, Odds ratio; CI, confidence interval
aModel 1 included medication intake characteristics; the analysis was adjusted for the length of monitoring
bModel 2 included both intake and patient characteristics; the analysis was adjusted for the length of monitoring and whether or not patients received reminders for their medication intake
cIntra-class correlation (ICC). This is the ratio of the between-group variance and the total variance