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Original research

Skipping breakfast, late-night eating and current smoking are associated with medication adherence in Japanese patients with diabetes

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ABSTRACT

Aims: Little is known about the relationship between medication adherence for oral hypoglycemic agents (OHAs) and glycemic control after adjusting healthy adherer effect in large scale study. Thus, adjusting for health-related behaviors, we investigated the clinical variables associated with medication adherence and the relationship between medication adherence and glycemic control using a large claims database.
Methods: Analyzed were 8805 patients with diabetes whose medication records for OHA were available for at least 1 year. Medication adherence was evaluated by the proportion of days covered (PDC). Multivariate logistic regression model was used to identify clinical variables significantly associated with non-adherence. Multiple regression analysis evaluated the relationship between PDC and HbA1c after adjusting for health-related behaviors.
Results: Mean PDC was 80.1% and 32.8% of patients were non-adherence. Logistic analysis indicated that older age and taking concomitant medications were significantly associated with adherence while skipping breakfast (odds ratio 0.66 [95% CI 0.57–0.76]), late-night eating (0.86 [0.75–0.98]), and current smoking (0.89 [0.80–0.99]) were significantly associated with non-adherence.
Conclusions: Skipping breakfast, late-night eating and current smoking were significantly associated with medication adherence, suggesting that clinicians pay attention to those health-related behaviors to achieve good medication adherence.

1. Introduction

Poor adherence to medication among individuals with diabetes is relevant and urgent, not only leading to an attenuation of drug effects but to increases in medical costs [1]. According to a report of the World Health Organization, approximately 50% of patients with chronic diseases are non-adherent to their medical regimens, including medications [2], and in the United States direct and indirect costs of non-adherence were estimated to be $337 billion (approximately 1/9 of medical costs) [3].

Previous studies showed that adherence is associated with good glycemic control in patients with diabetes [4–6]. Although this relationship is affected by the healthy adherer effect, in which patients who are more adherent to their medications also have other generally healthy behaviors [4], few reports have evaluated the relationship between adherence to oral hypoglycemic agents (OHAs) and health-related behaviors such as smoking, drinking, exercise and eating habits in a large scale. In addition, little is known about the quantitative relationship between medication adherence for OHAs and glycemic control after adjusting for health-related behaviors.

Thus, we investigated clinical variables including health-related behaviors associated with medication adherence in patients with diabetes using a large claims database. Furthermore, after adjusting for the health-related behaviors for which information was available, we evaluated the quantitative

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relationship between medication adherence and glycemic control.

2. Material and methods

2.1. Overview

For this retrospective study, we reviewed data on employees and their dependents in Japan derived from health insurance claims provided by the Japan Medical Data Center Co., Ltd. (JMDC). The JMDC database contains monthly claims submitted to health insurance societies from medical institutions since January 2005. This database includes patient characteristics, medical diagnoses, drug prescription, and medical procedures. Details of the claim data and classifications were described elsewhere [7–9].

2.2. Study participants

The index date was defined as the earliest annual check-up day from 1 April 2008 to 31 March 2014 (index period).

We included patients with diabetes aged 18–74 years who were prescribed OHA from 365 days to 340 days before the index date. Patients were excluded following reasons: no diabetes mellitus diagnosis; patients who were not prescribed OHA from 365 days to 340 days before the index date; missing values for age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), laboratory data such as HbA1c (Fig. 1).

2.3. Definitions

The diagnosis of diabetes was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L or HbA1c ≥6.5% or both and no OHA prescription or with an OHA prescription regardless of FPG or HbA1c. Data on age, sex, BMI, BP, laboratory values, and information on questionnaires were acquired on the earliest annual check-up day (index date).

The use of OHA, antihypertensive medications, dyslipidemia medications, and antiplatelet agents were defined according to use status during the baseline period based on claims data. The number of concomitant medications was defined as the total number of antihypertensive medications, dyslipidemia medications and antiplatelet agents [10,11]. Information on current smoking, alcohol consumption frequency, exercising more than 30 min ≥2 times weekly for over a year, walking or equivalent physical activity for 1 h per day, habitually skipping breakfast ≥3 times weekly, eating dinner within 2 h before sleeping ≥3 times weekly, eating speed, having a snack after dinner ≥3 times weekly, and sleep adequacy was obtained from questionnaire surveys taken at health checkups. Current smoking, exercising more than 30 min ≥2 times weekly for over a year, walking or equivalent physical activity for 1 h per day, habitually skipping breakfast ≥3 times weekly, eating dinner within 2 h before sleeping ≥3 times weekly, having a snack after dinner ≥3 times weekly, and sleep adequacy were analyzed according to two categories (yes and no). Alcohol consumption frequency was analyzed as three categories (rarely, sometimes, and every day) as was eating speed (high, normal, and slow). Histories of coronary artery disease and/or cerebrovascular disease were defined according to claims using International Classification of Disease 10th revision (ICD-10) codes for cardiac events and related medical procedures, cerebrovascular events and related medical procedures, and questionnaire surveys during health check-ups.

2.4. Adherence assessment

We assessed adherence to only OHAs that were prescribed from 365 days to 340 days before the index date without distinguishing between prevalent users and new users. The observation period for medication adherence was one year (365 days) before the index date. Medication adherence was evaluated by the proportion of days covered (PDC). The PDC was calculated as the number of days with the drug on-hand during the observation period divided by 365 days. For fixed-dose combinations, the PDC was calculated for each component. In these calculations, inpatient and outpatient prescriptions were not differentiated. Patients were considered non-adherent if their PDC was <80%.

2.5. Statistical analysis

Categorical variables were expressed as numerals and percentages and were compared with the χ^2 test. Continuous variables were expressed as means and standard deviations and compared using ANOVA tests. A multivariate logistic regression model was used to identify clinical variables including health-related behaviors significantly associated with non-adherence. Multiple regression analysis was used to evaluate the relationship between PDC and HbA1c. We constructed 4 multivariate linear regression models with HbA1c as the dependent variable, adding sequentially clusters of variables. Clusters were added to the model in the following order: (1) PDC; (2) clinical variables of LDL-cholesterol (LDL-C), triglycerides (TG), HDL-cholesterol (HDL-C), BMI, and SBP; (3) baseline characteristics of age, sex, use of insulin, number of OHAs, history of coronary artery disease, history of cerebrovascular disease, and number of concomitant medications; and (4) health-related behaviors of current smoking, frequency of alcohol consumption, exercising more than 30 min two or more times weekly for over a year, walking or equivalent physical activity for 1 h per day, habitually skipping breakfast three or more times weekly, eating dinner within 2 h before sleeping for three times or more times weekly, eating speed, having a snack after dinner three or more times weekly, and sleep adequacy. We performed multiple imputation for questionnaires with missing values, which were smoking (n = 467), skipping breakfast (n = 1254), snacking after dinner (n = 2044), eating dinner late (n = 2533), eating speed (n = 2556), drinking alcohol (n = 1100), exercise habits (n = 1248), walking or equivalent physical activity (n = 2052), history of coronary artery disease (n = 1172), history of cerebrovascular disease (n = 1172), and adequate sleep (n = 1892). We replaced each missing value with a set of substituted plausible values by creating 20 filled-in complete data sets using multiple imputation by chained equation method. Analyses were performed using SPSS (version 21.0, Chicago, IL, USA). Statistical significance was considered for $P < 0.05$. The Ethics Committee of the Niigata University approved this study.

3. Results

We included patients with diabetes aged 18–74 years who were prescribed OHA from 365 days to 340 days before the index date. Initially, 371,536 patients were enrolled; however, 362,731 patients were excluded because they had no diabetes mellitus diagnosis (n = 341,805), not prescribed OHA from 365 days to 340 days before the index date (n = 18,632), missing value of age, BMI (n = 5), SBP (n = 10), DBP (n = 10), laboratory data, which was HDL-C (n = 6), LDL-C (n = 19), TG (n = 16), and HbA1c (n = 2267) (Fig. 1).

Fig. 2 shows the distribution of six groups of participants according to PDC (PDC < 20%; 20% ≤ PDC < 40%; 40% ≤ PDC < 60%; 60% ≤ PDC < 80%; 80% ≤ PDC < 100%; PDC = 100%).

Table 1 shows baseline characteristics of the study patients as a whole and the six groups divided according to the PDC. Of the study population 84% were men, and the mean age at index was 53 years. The mean PDC was 80.1%, and 32.8% of patients were non-adherent.

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Table 1
Baseline characteristics of the total study patients and six groups divided according to PDC.

	n = 8805	0% ≤ PDC < 20% n = 288	20% ≤ PDC < 40% n = 341	40% ≤ PDC < 60% n = 721	60% ≤ PDC < 80% n = 1566	80% ≤ PDC < 100% n = 5362	PDC = 100% n = 527	P trend
Age (years)	53 (8)	50 (9)	50 (9)	51 (8)	52 (8)	54 (8)	54 (8)	<0.01
Sex (Men, %)	7414 (84.2)	248 (86.1)	293 (85.9)	645 (89.5)	1358 (86.7)	4436 (82.7)	434 (82.4)	<0.01
BMI (kg/m^2)	26.4 (4.7)	25.9 (4.4)	27.0 (5.1)	26.6 (4.6)	26.7 (4.7)	26.2 (4.7)	26.1 (5.1)	<0.01
SBP (mmHg)	130 (16)	129 (19)	131 (17)	130 (17)	130 (16)	130 (16)	130 (16)	0.41
DBP (mmHg)	79 (11)	80 (12)	82 (11)	81 (11)	80 (10)	79 (11)	79 (11)	<0.01
HbA1c (%)	7.3 (1.4)	7.7 (2.1)	7.7 (1.8)	7.6 (1.7)	7.4 (1.4)	7.1 (1.2)	7.1 (1.1)	<0.01
TG (mmol/L)	1.3 (0.9–1.9)	1.4 (0.9–2.2)	1.4 (1.0–2.2)	1.4 (1.0–2.0)	1.4 (1.0–2.0)	1.3 (0.9–1.9)	1.3 (0.8–1.8)	<0.01
LDL-C (mmol/L)	3.1 (0.8)	3.3 (1.0)	3.2 (0.8)	3.2 (0.8)	3.1 (0.8)	3.0 (0.8)	3.0 (0.8)	<0.01
HDL-C (mmol/L)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	<0.01
Use of insulin (%)	833 (9.5)	25 (8.7)	44 (12.9)	69 (9.6)	168 (10.7)	457 (8.5)	70 (13.3)	<0.01
Current smoking (%)	2942 (33.4)	108 (37.5)	137 (40.2)	283 (39.3)	581 (37.1)	1688 (31.5)	145 (27.5)	<0.01
Missing (%)	467(5.3)	26(9.0)	11 (3.2)	36 (5.0)	81 (5.2)	284 (5.3)	29 (5.5)	
Skipping breakfast ≥3 times weekly (%)	850 (9.7)	41 (14.2)	72 (21.1)	101 (14.0)	179 (11.4)	414 (7.7)	43 (8.2)	<0.01
Missing (%)	1254 (14.2)	52 (18.1)	48 (14.1)	113 (15.7)	221 (14.1)	752 (14.0)	68 (12.9)	
Late night eating ≥3 times weekly (%)	2044 (23.2)	73 (25.3)	92 (27.0)	192 (26.6)	428 (27.3)	1145 (21.4)	114 (21.6)	<0.01
Missing (%)	2533 (28.8)	110 (38.2)	104 (30.5)	208 (28.8)	484 (30.9)	1485 (27.7)	142 (26.9)	
Snacking after dinner ≥3 times weekly (%)	910 (10.3)	28 (9.7)	36 (10.6)	78 (10.8)	166 (10.6)	549 (10.2)	53 (10.1)	0.90
Missing (%)	2044 (23.2)	90 (31.3)	83 (24.3)	173 (24.0)	405 (25.9)	1173 (21.9)	120 (22.8)	
Drinking alcohol (%)								0.16
Rarely	3410 (38.7)	117 (40.6)	139 (40.8)	266 (36.9)	587 (37.5)	2063 (38.5)	238 (45.2)	
Sometimes	2371 (26.9)	71 (24.7)	92 (27.0)	203 (28.2)	434 (27.7)	1446 (27.0)	125 (23.7)	
Every day	1924 (21.9)	56 (19.4)	72 (21.1)	155 (21.5)	358 (22.9)	1183 (22.1)	100 (19.0)	
Missing (%)	1100 (12.5)	44 (15.3)	38 (11.1)	97 (13.5)	187 (11.9)	670 (12.5)	64 (12.1)	
Eating speed (%)								0.06
High	2473 (28.1)	58 (20.1)	98 (28.7)	206 (28.6)	448 (28.6)	1521 (28.4)	142 (26.9)	
Normal	3379 (38.4)	105 (36.5)	122 (35.8)	260 (36.1)	568 (36.3)	2109 (39.3)	215 (40.8)	
Slow	397 (4.5)	17 (5.9)	17 (5.0)	46 (6.4)	63 (4.0)	228 (4.3)	26 (4.9)	
Missing (%)	2556 (29.0)	108 (37.5)	104 (30.5)	209 (29.0)	487 (31.1)	1504 (28.0)	144 (27.3)	
Habitual exercise >30 min ≥ 2 times weekly (%)	2271 (25.8)	62 (21.5)	82 (24.0)	149 (20.7)	372 (23.8)	1436 (26.8)	170 (32.3)	<0.01
Missing (%)	1248 (14.2)	51 (17.7)	48 (14.1)	113 (15.7)	221 (14.1)	748 (14.0)	67 (12.7)	
Walking or equivalent physical activity for 1 h or more per day (%)	2101 (23.9)	59 (20.5)	61 (17.9)	158 (21.9)	341 (21.8)	1332 (24.8)	150 (28.5)	<0.01
Missing (%)	2052 (23.3)	90 (31.3)	84 (24.6)	174 (24.1)	408 (26.1)	1176 (21.9)	120 (22.8)	
Adequate sleep	4465 (50.7)	128 (44.4)	157 (46.0)	341 (47.3)	783 (50.0)	2776 (51.8)	280 (53.1)	0.02
Missing (%)	1892 (21.5)	76 (26.4)	73 (21.4)	160 (22.2)	337 (21.5)	1150 (21.4)	96 (18.2)	
History of coronary artery disease (%)	552 (6.3)	13 (4.5)	14 (4.1)	29 (4.0)	92 (5.9)	335 (6.2)	69 (13.1)	<0.01
Missing (%)	1172 (13.3)	51 (17.7)	44 (12.9)	103 (14.3)	204 (13.0)	712 (13.3)	58 (11.0)	
History of cerebrovascular disease (%)	251 (2.9)	7 (2.4)	10 (2.9)	12 (1.7)	33 (2.1)	163 (3.0)	26 (4.9)	0.01
Missing (%)	1172 (13.3)	51 (17.7)	44 (12.9)	102 (14.1)	204 (13.0)	712 (13.3)	59 (11.2)	
Use of antihypertensive medications (%)	4275 (48.6)	108 (37.5)	132 (38.7)	308 (42.7)	742 (47.4)	2713 (50.6)	272 (51.6)	<0.01
Use of dyslipidemia medications (%)	4598 (52.2)	108 (37.5)	159 (46.6)	366 (50.8)	813 (51.9)	2863 (53.4)	289 (54.8)	<0.01
Use of antiplatelet agents (%)	846 (9.6)	23 (8.0)	21 (6.2)	54 (7.5)	133 (8.5)	530 (9.9)	85 (16.1)	<0.01
Number of OHAs (%)								<0.01
1	3972 (45.1)	212 (73.6)	203 (59.5)	302 (41.9)	586 (37.4)	2409 (44.9)	260 (49.3)	
2	2937 (33.4)	63 (21.9)	100 (29.3)	292 (40.5)	553 (35.3)	1786 (33.3)	143 (27.1)	
3	1462 (16.6)	12 (4.2)	33 (9.7)	106 (14.7)	313 (20.0)	905 (16.9)	93 (17.6)	
4	390 (4.4)	1 (0.3)	5 (1.5)	18 (2.5)	106 (6.8)	229 (4.3)	31 (5.9)	
5	44 (0.5)	0 (0)	0 (0)	3 (0.4)	8 (0.5)	33 (0.6)	0 (0)	
Number of concomitant medications (%)								<0.01
0	2403 (27.3)	135 (46.9)	129 (37.8)	224 (31.1)	430 (27.5)	1357 (25.3)	128 (24.3)	
1	2682 (30.5)	59 (20.5)	97 (28.4)	226 (31.3)	496 (31.7)	1648 (30.7)	156 (29.6)	
2	1824 (20.7)	48 (16.7)	59 (17.3)	146 (20.2)	329 (21.0)	1147 (21.4)	95 (18.0)	
3 or more	1896 (21.5)	46 (16.0)	56 (16.4)	125 (17.3)	311 (19.9)	1210 (22.6)	148 (28.1)	

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OHA, oral hypoglycemic agents; PDC, proportion of days covered; SBP, systolic blood pressure; TG, triglycerides.
Data are presented as mean (standard deviation) and n(%).

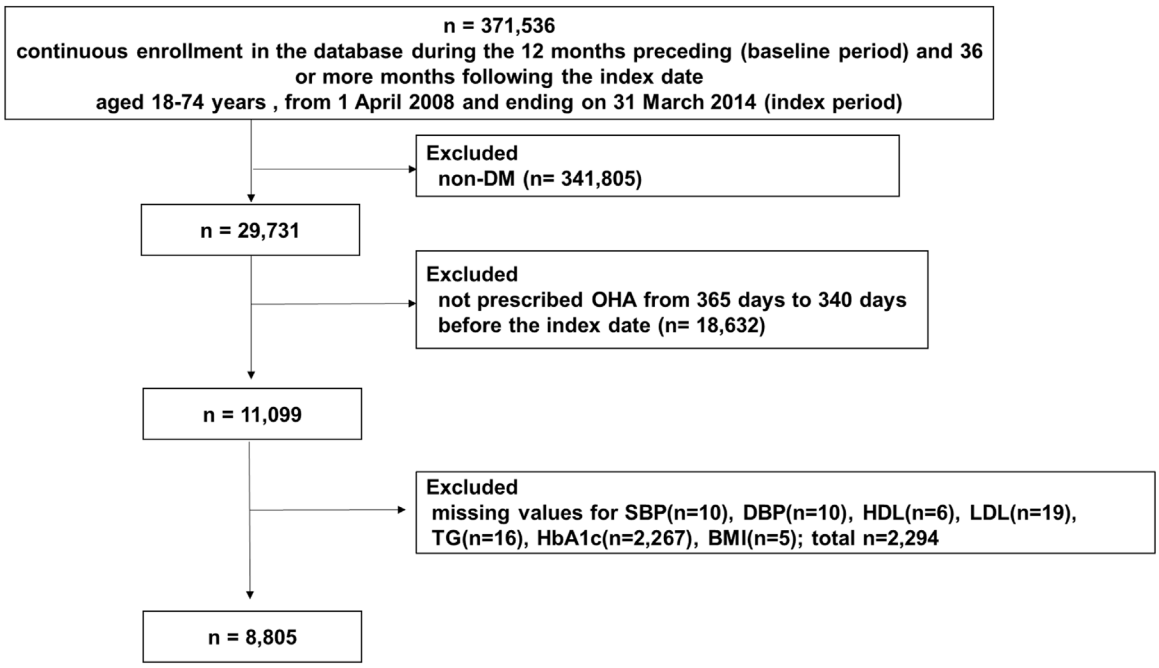

Fig. 1. Inclusion–exclusion criteria and sample size.

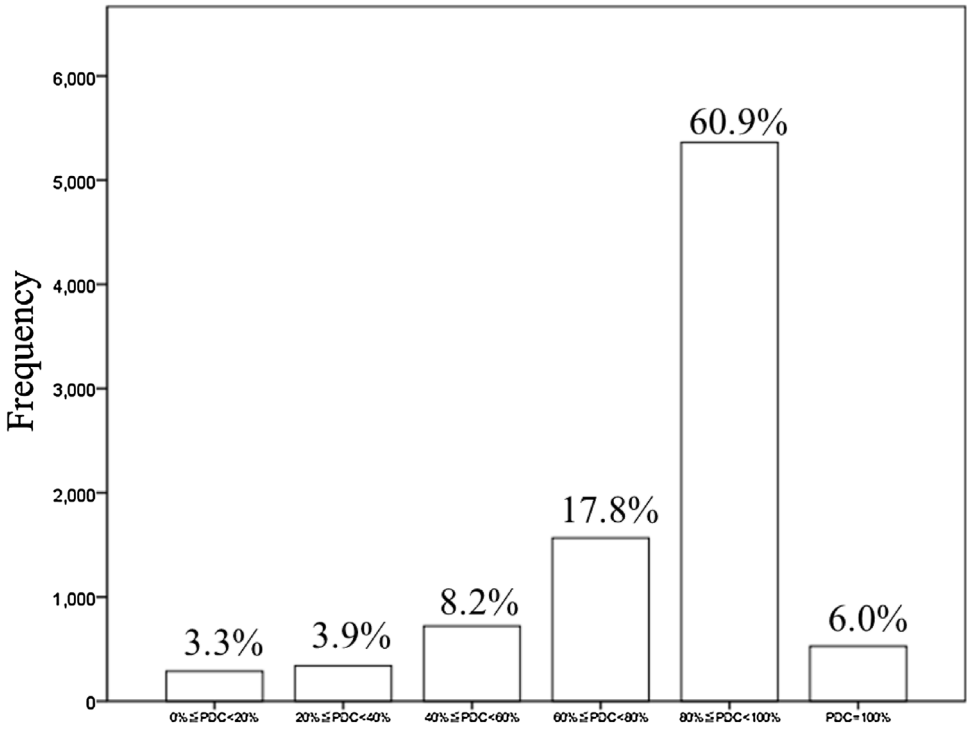

Fig. 2. Distribution of six groups of study participants with diabetes according to PDC (PDC < 20%; 20% ≤ PDC < 40%; 40% ≤ PDC < 60%; 60% ≤ PDC < 80%; 80% ≤ PDC < 100%; PDC = 100%). PDC, proportion of days covered.

The mean PDC increased with increased age and decreased rate of current smoking. For patients with the higher PDC, HbA1c, LDL-C, and TG tended to be lower.

The PDC and percent non-adherence for each OHA are shown in Supplemental Table 1. The PDC for sulfonylureas, biguanides, thiazolidines, α-glucosidase inhibitors, glinides, and DPP-4 inhibitors were 82%, 82%, 79%, 79%, 73%, and 85%, respectively, and the percent non-adherence for these OHAs were 27%, 29%, 33%, 34%, 42%, and 23%, respectively.

The results of the multivariate logistic regression model for baseline characteristics associated with non-adherence are shown in Fig. 3. Older age, taking 1 concomitant medication, 2 concomitant medications, and ≥3 concomitant medications were significantly associated with adherence and had odds ratios (95% CI) of 1.32 (1.24–1.41), 1.16 (1.03–1.31), 1.19 (1.03–1.37), and 1.28 (1.10–1.49), respectively. Skipping breakfast three or more times a week, eating dinner within 2 h before sleeping for three times or more times weekly and smoking were significantly associated with

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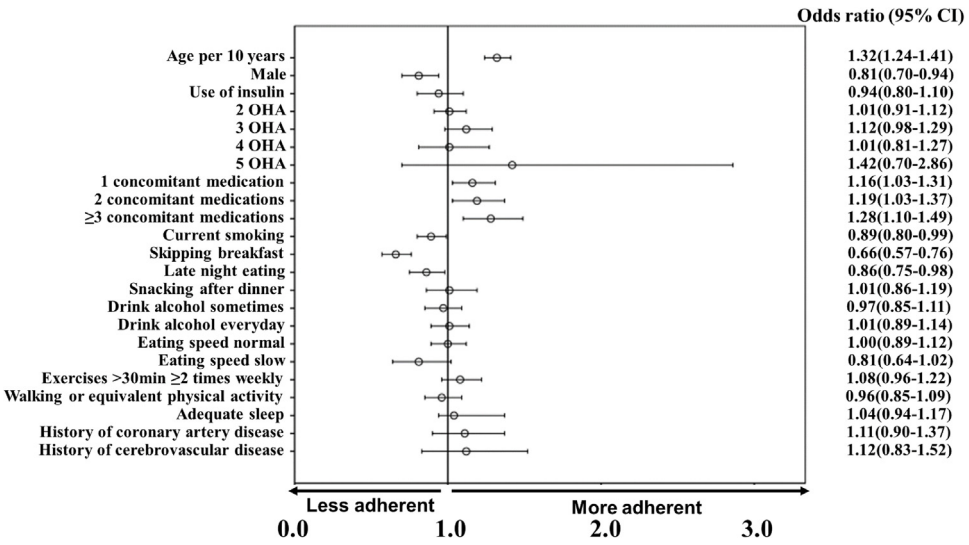

Fig. 3. Adjusted odds ratios (95%CI) for logistic regression models of factors associated with adherence (multiple imputation for questionnaires).

non-adherence with odds ratios (95% CI) of 0.66 (0.57–0.76), 0.86 (0.75–0.98), and 0.89 (0.80–0.99), respectively.

The correlation between HbA1c and PDC evaluated by multiple regression analysis is shown in Table 2.

HbA1c was negatively correlated with PDC (model 1), and the relationship between HbA1c and PDC was maintained after adjusting for clinical outcomes (model 2), baseline characteristics (model 3), and health-related behaviors (model 4). The coefficients of model 1, model 2, model 3, and model 4 were −0.97 (P < 0.01), 0.80 (P 0.01).–0.77 (P < 0.01), and −0.71 (P < 0.01), respectively. With 25% increases in PDC, HbA1c decreased by 0.2% in model 4. We performed the same analysis on 5967 patients who have all data of questionnaires survey, and the results were very similar to the previous results (Supplemental Fig. 1 and Supplemental Table 2).

4. Discussion

In this study, we clarified the status of medication adherence during the study period and determined clinical variables including health-related behaviors associated with it. Skipping breakfast, late-night eating and current smoking were significantly associated with non-adherence.

Our result showing a mean PDC of 80.1% was similar to the 75% reported by Tunceli et al.; however, they reported that 41% of patients were non-adherence vs. the 31.8% non-adherence shown in our study [10]. Kirkman et al. assessed medication adherence using the medication possession ratio (MPR) and reported that 30.9% of patients were non-adherence (MPR < 80%) [12]. Since the MPR represents the sum of medication supplies available to a patient within a given time period, it may overestimate adherence compared to PDC, suggesting that medication adherence in persons with diabetes in Japan is better than or comparable to that overseas.

As to the individual OHAs, DPP-4 inhibitors had the highest mean PDC and the lowest percent non-adherence. In fact, good medication adherence for DPP-4 inhibitors was reported [13–15]. On the other hand, the percent non-adherence for α-glucosidase inhibitors and glinides were 33.2% and 40.7%, respectively, which were higher than those for other OHAs, suggesting that dosage frequency influenced adherence to α-glucosidase inhibitors and glinides [16]. Unfortunately, we do not have data on frequency and timing of dosages. Future study is needed to investigate to the impact of these factors on medication adherence.

Current smoking was associated with non-adherence, which is consistent with previous reports [17,18]. Since smokers can be considered to have less interest in their health and treatment than non-smokers, adherence to medications might be poor in these patients. Skipping breakfast and eating supper within 2 h of bedtime were also associated with being non-adherent. It can be speculated that individuals who skipped breakfast do not take their medicines in the morning. Alternatively, meal times are often determined by social factors rather than biological needs [19], suggesting that lack of health awareness or the social and environmental background leading to skipping breakfast and eating supper within 2 h of bedtime may reduce medication adherence. Also, those health-related actions might reflect socioeconomic status. Therefore, no conclusions can be drawn on the relationships between those health-related actions and non-adherence from our findings.

We found that older age and the use of concomitant medications were significantly associated with adherence, which was consistent with previous reports [10,20,21]. Older patients or patients with multimorbidities may be more adherent because the severity of their medical condition makes them highly motivated to comply with treatment [10].

According to a study using receiver operating characteristic (ROC) curves to analyze the relationship between medication adherence for chronic diseases and any-cause hospitalization, the optimal cut-off value for the PDC indicating adherence was reported to be 80% [22]. Thus, our definition of non-adherence according to PDC of <80% has been supported by previous research.

Farmer et al. reported that non-adherent patients had a poorer HbA1c decline after 1 year compared with adherent patients [6]. Rozenfeld et al. showed that HbA1c decreased by 0.1 with 10% increases in medication adherence [5], which is consistent with our results. In a meta-analysis that examined the relationship between medication adherence and glycemic control, 10 out of 23 articles reported negative findings for glycemic control [4]. In 9 of these reports patient-reported adherence measures were used and the study populations were small. Most of these reports (6 out of 9) investigated the relationship between medication adherence and glycemic control after adjusting for health-related behaviors. On the other hand, 8 of the 13 reports that found an association between medication adherence and glycemic control surveyed for adherence using pharmacy data and had larger study populations than reports that surveyed using patient-reported adherence

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Table 2
Correlation between HbA1c and PDC evaluated by multiple regression analysis with multiple imputations for questionnaires.

Predictor	Model 1: PDC		Model 2: model 1 + clinical outcome		Model 3: model 2 + baseline characteristics		Model 4: model 3 + health-related behaviors	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
PDC	−0.97	<0.01	−0.80	<0.01	−0.77	<0001	−0.71	<0.01
LDL	NA	NA	0.01	<0.01	0.01	<0.01	0.01	<0.01
HDL	NA	NA	−0.003	0.02	−0.002	0.02	−0.001	0.37
TG	NA	NA	0.001	<0.01	0.002	<0.01	0.002	<0.01
BMI	NA	NA	0.01	<0.01	0.01	0.09	0.01	0.10
SBP	NA	NA	0.01	<0.01	0.01	<0.01	0.01	<0.01
Men vs. women	NA	NA	NA	NA	−0.05	0.17	−0.06	0.13
Age	NA	NA	NA	NA	−0.01	<0.01	−0.01	0.01
Use of Insulin	NA	NA	NA	NA	0.78	<0.01	0.78	<0.01
Number of OHAs	NA	NA	NA	NA	0.23	<0.01	0.23	<0.01
History of coronary artery disease	NA	NA	NA	NA	0.05	0.41	0.06	0.32
History of cerebrovascular disease	NA	NA	NA	NA	−0.03	0.72	−0.03	0.72
Number of concomitant medications	NA	NA	NA	NA	−0.09	<0.01	−0.09	<0.01
Current smoking	NA	NA	NA	NA	NA	NA	0.13	<0.01
Drinking alcohol	NA	NA	NA	NA	NA	NA	0.08	<0.01
Habitual exercise >30 min ≥ 2 times weekly	NA	NA	NA	NA	NA	NA	0.05	0.20
Skipping breakfast ≥3 times weekly	NA	NA	NA	NA	NA	NA	0.11	0.03
Snacking after dinner ≥3 times weekly	NA	NA	NA	NA	NA	NA	0.11	0.03
Late night eating	NA	NA	NA	NA	NA	NA	0.20	<0.01
Eating speed	NA	NA	NA	NA	NA	NA	0.08	0.01
Walking or equivalent physical activity for 1 h or more	NA	NA	NA	NA	NA	NA	−0.05	0.14
Adequate sleep	NA	NA	NA	NA	NA	NA	−0.03	0.36

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; OHA, oral hypoglycemic agents; PDC, proportion of days covered; SBP, systolic blood pressure; TG, triglycerides.

measures, but all but one evaluated the association without adjustment for health-related behaviors. Therefore, in that meta-analysis results on the relationship between medication adherence and glycemic control were considered to be controversial [4]. In our study, we found a negative correlation between PDC and HbA1c even after adjusting for health-related behaviors using large-scale data, suggesting that clinicians need to make an effort to help their patients better adhere to medication. Mobile applications improved medication adherence in patients with chronic disease [23]. Future studies are needed to clarify the fact that improved medication adherence lead to achieve improved glycemic control in Japanese patients with diabetes.

Several limitations should be considered. First, we do not have more recent data at this time. Thus, our findings should be confirmed with the latest data. Also, the impacts of new OHA such as SGLT2 inhibitors should be confirmed with an adequate sample size. Second, we cannot perform validity studies on questionnaires used in this study at this time. Previous reports using questionnaires in the JMDC database reported the utility of a specific health checkup database containing lifestyle behaviors and lifestyle diseases [24], as well as the association between eating habits and glycemic control or obesity [25]. Third, although medication adherence was significantly associated with glycemic control after adjusting for health-related behaviors, the analysis did not adjust for all possible healthy behaviors. Thus, our findings should be interpreted with caution since residual confounding must be considered. Fourth, PDC, which was calculated based on pharmacy records, measured only refill behavior and not actual consumption of the medications. We evaluated the PDC for OHAs only that was taken 340–365 days before the index date. Thus, PDC was underestimated in those who discontinued OHAs in the presence of improving glycemic control or side effects. Although we automatically removed duplicate prescriptions during hospitalization, the PDC might be overestimated since we do not know whether the patients actually took the OHAs. Fifth, because of the nature of employer-sponsored healthcare plans, patients over the age of 75 were not included and the study population was largely male. The results of this study cannot be applied to patients with diabetes over the age of 75 and caution must be used in applying these results to women with diabetes. Sixth, in this study, the PDC for fixed-dose combinations was calculated for each component, so the PDC of the actual fixed-dose combinations could not be examined. However, since only about 0.5% of this study population took fixed-dose combinations at the time of index, results would not be highly influenced.

In conclusion, skipping breakfast late-night eating and current smoking were significantly associated with medication adherence, suggesting that clinicians may need to pay attention to those health-related behaviors to achieve good medication adherence.

Disclosure summary

JMDC, Inc. created a nationwide claims-based database for our group without payment. Although members of this organization participated in the preparation of this manuscript, they did not contribute to analysis of data or the conclusions made. Thus, we feel there is no potential conflict of interest relevant to this report.

Authors' contributions

K.F, and H.So contributed to the conception and the design of the study and supervised this research. K.F, N.Y and H.Se contributed to acquisition of date. Y.Y, M.HY, Y.M, M.K, T.O, M.Y, M.K and S.K contributed analysis and interpretation of the date. Y.Y wrote the manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pcd.2020.05.002.

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Supplemental Table 1. PDC and percent non-adherence for each OHA

	n(%)	PDC	non-adherence(%)
Sulfonylureas	4161(47.3)	0.82(0.21)	1128(27.1)
Biguanides	3220(36.6)	0.82(0.21)	931(28.9)
Thiazolidines	2415(27.4)	0.79(0.24)	785(32.5)
α-glucosidase inhibitors	2979(33.8)	0.79(0.24)	1026(34.4)
Glinides	646(7.3)	0.73(0.28)	270(41.8)
DPP-4 inhibitors	2591(29.4)	0.85(0.19)	598(23.1)

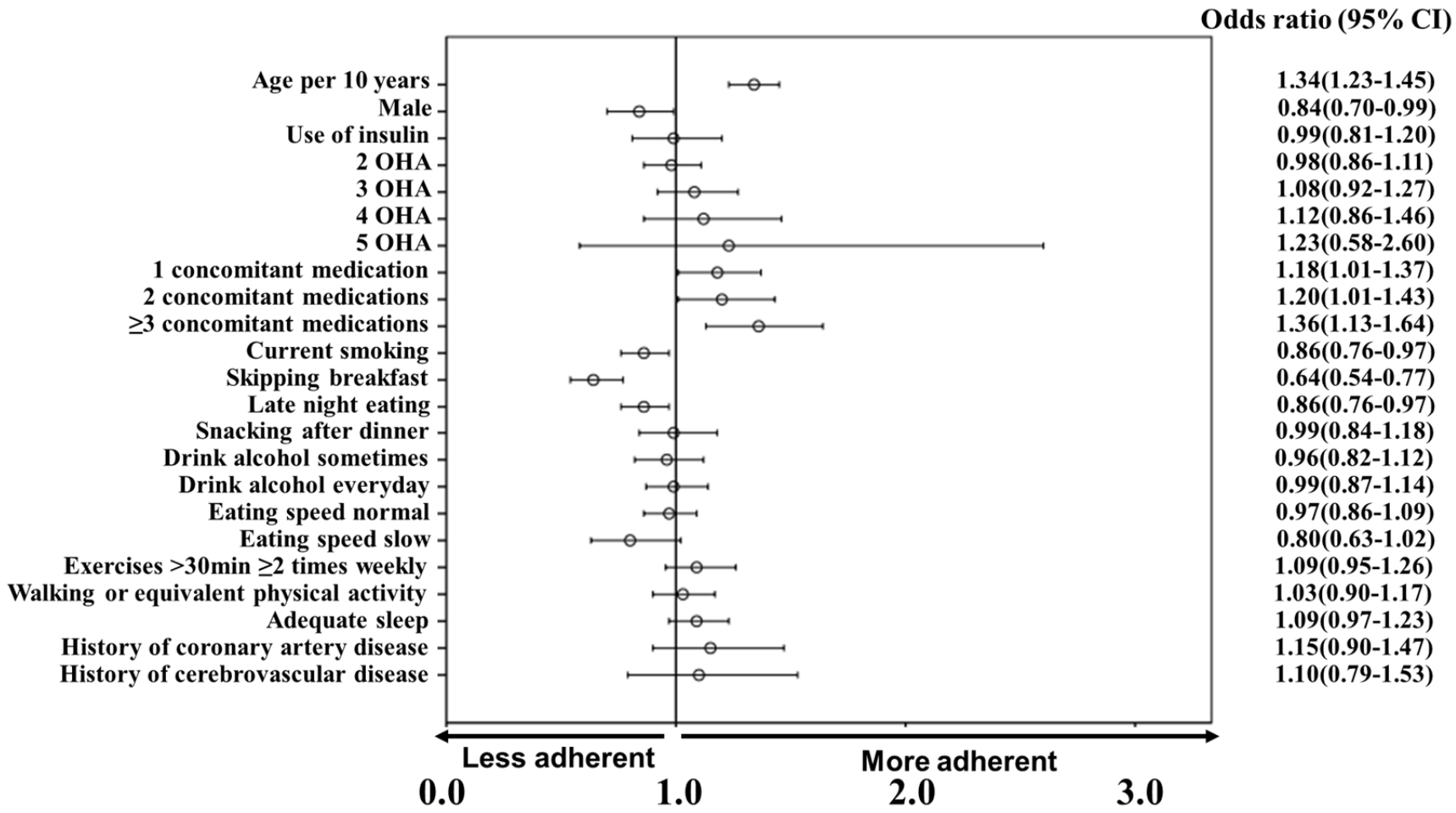
OHA, oral hypoglycemic agents; PDC, proportion of days covered.

Data are presented as mean (standard deviation) and n (%).

Supplemental table 2. Correlation between HbA1c and PDC evaluated by multiple regression analysis excluding missing values in questionnaires

	Model 1: PDC		Model 2: Model 1+ Clinical Outcome		Model 3: Model 2+ Baseline Characteristics		Model 4: Model 3+ Health-related Behaviors	
predictor	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
PDC	-0.99	<0.01	-0.84	<0.01	-0.82	<0.01	-0.75	<0.01
LDL	NA	NA	0.01	<0.01	0.01	<0.01	0.004	<0.01
HDL	NA	NA	-0.003	0.04	-0.003	0.03	-0.002	0.21
TG	NA	NA	0.001	<0.01	0.002	<0.01	0.002	<0.01
BMI	NA	NA	0.01	0.02	0.01	0.11	0.01	0.17
SBP	NA	NA	0.01	<0.01	0.01	<0.01	0.01	<0.01
men vs. women	NA	NA	NA	NA	-0.09	0.04	-0.09	0.06
Age	NA	NA	NA	NA	-0.01	0.02	-0.02	0.48
Use of Insulin	NA	NA	NA	NA	0.74	<0.01	0.73	<0.01
Number of OHA	NA	NA	NA	NA	0.18	<0.01	0.18	<0.01
History of coronary artery disease	NA	NA	NA	NA	0.03	0.69	0.03	0.67
History of cerebrovascular disease	NA	NA	NA	NA	0.04	0.69	0.03	0.70
Number of concomitant medications	NA	NA	NA	NA	-0.10	<0.01	-0.10	<0.01
Current Smoking	NA	NA	NA	NA	NA	NA	0.08	0.03
Drinking alcohol	NA	NA	NA	NA	NA	NA	0.11	0.04
Habitual exercise >30 min ≥2 times weekly	NA	NA	NA	NA	NA	NA	0.00	1.00
Skipping breakfast ≥3 times weekly	NA	NA	NA	NA	NA	NA	0.11	0.04
Snacking after dinner ≥3 times weekly	NA	NA	NA	NA	NA	NA	0.12	0.01
Late night eating	NA	NA	NA	NA	NA	NA	0.20	<0.01
Eating speed	NA	NA	NA	NA	NA	NA	0.08	0.01
Walking or equivalent physical activity for 1 hour or more	NA	NA	NA	NA	NA	NA	-0.003	0.95
Adequate sleep	NA	NA	NA	NA	NA	NA	-0.09	0.01

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; OHA, oral hypoglycemic agents; PDC, proportion of days covered; SBP, systolic blood pressure; TG, triglycerides.



Supplemental Figure 1. Adjusted odds ratios (95%CI) for logistic regression models of factors associated with adherence (excluded missing values in questionnaires).

Adjusted for HbA1c, LDL, HDL, TG, BMI, and SBP.

Reference categories: female, no use of insulin, 1 OHA, no concomitant medication, no smoking, have breakfast, no late night eating, no snacking after dinner, no exercise habit, no walking or equivalent activity, rarely drinking alcohol, eating speed high, inadequate sleep, no history of coronary artery disease, and no history of cerebrovascular disease.