

Influence of the COVID-19 pandemic on regular clinic visits and medication prescriptions among people with diabetes

Retrospective cohort analysis of health care claims

Toshiki Maeda, MD, PhD, MPHa* (D, Takumi Nishi, PhD, MPHab, Masataka Harada, PhDc, Kozo Tanno, MD, PhD^{d,e}, Naoyuki Nishiya, PhD^{e,f}, Kei Asayama, MD, PhD^{g,h,i}, Nagako Okuda, MD, PhD^j, Daisuke Sugiyama, MD, PhD^k, Hiroshi Yatsuya, MD, PhD^I, Akira Okayama, MD, PhD^m, Hisatomi Arima, MD, PhD^a

Abstract

The aim of this study was to investigate the effect of the COVID-19 pandemic on regular clinic visits among people with diabetes and to elucidate the factors related to visit patterns among these patients during the pandemic.

This was a longitudinal study using anonymized insurance claims data from the Joint Health Insurance Society in Tokyo from October 2017 to September 2020. First, we identified patients with diabetes who were fully enrolled in the health plan from fiscal year 2017 until September 2020 and who were regularly receiving glucose-lowering medications (every 1–3 months) from October 2017 to September 2018. We divided follow-up into the pre-pandemic period (October 2018 to March 2020) and the pandemic period (April 2020 to September 2020). A multilevel logistic regression model was used to determine the risks of delayed clinic visits/medication prescriptions (i.e., >3 months after a previous visit/prescription) during the pandemic period.

We identified 1118 study participants. The number of delayed clinic visits/medication prescriptions during the pre-pandemic and pandemic periods was 188/3354 (5.6%) and 125/1118 (11.2%), respectively. There was a significant increase in delayed clinic visits during the pandemic (adjusted odds ratio 3.68 (95% confidence interval 2.24 to 6.04, P < .001), even after controlling for confounding factors. We also found a significant interaction between sex and delayed visits; women had significantly fewer clinic visits during the COVID-19 pandemic than men.

We clarified the relationship of the COVID-19 pandemic with delays in regular clinic visits and medication prescriptions among people with diabetes. The response to the COVID-19 pandemic differed between men and women.

Abbreviations: CI = confidence interval, COVID-19 = coronavirus disease 2019, DPP-4-I = dipeptidyl peptidase 4 inhibitors, FY = fiscal year, α GI = alpha-glucosidase inhibitors, GLP-1RA = glucagon-like peptide 1 receptor agonists, JPY = Japanese yen, OR = odds ratio, SD = standard deviation, SGLT2-I = sodium-glucose cotransporter-2 inhibitors, SU = sulfonyl urea.

Keywords: COVID-19, diabetes mellitus, disease management

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This study was approved by the institutional review board of Fukuoka University Clinical Research and Ethics Center (U21-01-010). All methods were carried out in accordance with the Declaration of Helsinki. Informed consent was waived according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects and ethics committee. Fukuoka University Clinical Research & Ethics Centre (FU-CREC) also granted the exemption. The members of FU-CREC involved in the decision were as follows: Fumihito Hirai, Shinichiro Yasunaga, Teruaki Izaki, Ryoko Sakurna, Satoshi Imaizumi, Kohichiro Kawashima, Toshiyasu Ikuta, Maho Oishi, and Yuri Kusunose. The authors have no conflicts of interest to disclose.

The datasets generated and/or analyzed during the current study are not publicly available owing to privacy policy of the data provider but are available from the corresponding author on reasonable request.

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^aDepartment of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan, ^bDepartment of Research Planning and Information Management, Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan, Department of Industrial Economics, Faculty of Economics, Fukuoka University, Fukuoka, Japan, "Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Iwate, Japan, "Iwate Tohoku Medical Megabank Organization, Iwate Medical University, Morioka Iwate, Japan, Division of Integrated Information for Pharmaceutical Sciences, Department of Clinical Pharmacy, Iwate Medical University School of Pharmacy, Iwate, Japan, "Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan, "KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium, Tohoku Institute for Management of Blood Pressure, Sendai, Japan, iDepartment of Health Science, Kyoto Prefectural University, Kyoto, Japan, "Faculty of Nursing And Medical Care, Keio University, Tokyo, Japan, 'Department of Public Health and Health Systems, Graduate School of Medicine, Nagoya University, Aichi, Japan, "Research Institute of Strategy for Prevention, Tokyo, Japan.

*Correspondence: Toshiki Maeda, Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan (e-mail: tmaeda@fukuoka-u.ac.jp).

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1. Introduction

Since the novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China on 31 December, 2019,^[1,2] the outbreak has rapidly spread all over the world. As of 29 September, 2021, the cumulative number of infected people stood at over 232 million, and nearly 5 million people have died worldwide.^[3] In Japan as of the same date in 2021, approximately 1.7 million people have been infected and there have been approximately 17,000 deaths attributed to COVID-19.[4] In the United States, excess deaths attributed to COVID-19 are estimated to be as high as 72.4%.^[5] As effective vaccines have become available, the prevalence of infection in highly vaccinated areas appears to be declining.^[3] However, COVID-19 remains a serious threat to people around the world and continues to disrupt the normal lives of people globally. The pandemic has also seriously damaged the global economy, social solidarity, and people's daily life. Owing to fear of catching and spreading the infection, people have stopped meeting with family and close friends, traveling, and enjoying entertainment. As for health care, the COVID-19 pandemic has had impacts on elective surgery^[6,7] and routine health care,^[8] as well as medical care for COVID-19 itself. According to a report from the United States, one-third of people surveyed said that they have avoided routine health care during the COVID-19 pandemic.^[8] However, such avoidance of routine care could lead to poor control of diseases and especially chronic, lifestyle-related diseases like diabetes mellitus.

Diabetes is prevalent worldwide, with an estimated 422 million people diagnosed with diabetes. The disease has directly caused 1.5 million deaths.^[9] Diabetes is also prevalent in Japan, where approximately 19.7% of men and 10.8% of women have diagnosed or suspected diabetes.^[10] Diabetes causes serious health complications,^[9,11] which lead to not only premature mortality $^{[12,13]}$ but also a heavy economic burden. $^{[\bar{1}4,15]}$ To prevent the progression of diabetes, strict disease management and regular follow-up are essential.[16-18] Indeed, several studies have reported that regular or a high frequency of health care visits^[17-19] is related to well-controlled diabetes. However, the COVID-19 pandemic might have affected the behavior of patients with diabetes, causing them to avoid routine care, especially during the first wave of the pandemic when there was insufficient information and vaccines were not yet available. This is concerning because diabetes mellitus is a primary risk factor for complications and death owing to COVID-19.[20-22] Although it is understandable that these patients might postpone routine care, delays in care can lead to a poor or deteriorating health condition. However, few studies have investigated the effects of the COVID-19 pandemic on the pattern of health care visits among patients with diabetes during the period before vaccines were available. Studies examining the behavior patterns of these patients would contribute to preparation for a similar crisis in the future.

The aim of this study was to investigate the effect of the COVID-19 pandemic on patterns of clinic visits among people with diabetes and to elucidate those factors related to these patterns among patients with diabetes during the pandemic, especially during the period when vaccines were unavailable.

2. Methods

2.1. Study design and participants

This was a retrospective cohort study conducted from October 2017 to September 2020, as part of a project aiming to elucidate the effect of COVID-19 on patients with diabetes during the first wave of the pandemic in Japan. The main objectives of that project were as follows: firstly, to investigate the effect of the COVID-19 pandemic on patterns of clinic visits, and finally to determine the starting point of delayed regular visits and patients' behavioral reactions to COVID-19. The present

study was related to the first objective and another study^[23] involved the second objective. We used anonymized insurance claim data from the Joint Health Insurance Society, which comprises several freight transportation service companies located in Tokyo. The Japanese government has established universal health insurance coverage that is generally divided into employee-based plans (Employee's Health Insurance), community-based plans (National Health Insurance), and Late Elders' Health Insurance.^[24,25] The Health Insurance Society is a type of employee-based plan. All insured are under 75 years old because those aged more than 75 years old are mandated to join the Late Elders' Health Insurance, according to Japanese law.^[25] We used monthly data for clinic visits and prescriptions because insurance claims are submitted each month. The Health Insurance Society included 84,907 people in fiscal year (FY) 2019 (from April 1, 2019 to March 31, 2020). Patients with diabetes were first identified using International Classification of Diseases, Tenth Revision (ICD-10) codes that correspond to diabetes (E10,11,12,13 and 14) and/or prescriptions for diabetes medications (N = 3753). From among these patients, we selected those fully enrolled in the health plan from FY 2017 until September 2020 (N = 3014). Consequently, we included patients who completed regular visits and those who were prescribed glucose-lowering medications every 1–3 months or more than four times within 1 year from October 2017 to September 2018 as study participants (N = 1118) (Supplemental Digital Content 1, http://links.lww.com/MD/G760). We divided the follow-up into pre-pandemic period 1 (October 2018 to March 2019), pre-pandemic period 2 (April 2019 to September 2019), pre-pandemic period 3 (October 2019 to March 2020), and the pandemic period (April 2020 to September 2020). We defined the pandemic period as starting from April 2020 because the government declared a State of Emergency for some large prefectures on 7 April 2020, which was then extended to all of Japan on 16 April, 2020.^[26] A patient was defined as having delayed clinic visits/medication prescriptions during any period when they failed to receive a medication prescription for more than 3 consecutive months; the interval of prescriptions in Japan is largely within 3 months.^[18] We compared the number of delayed clinic visits and/or medication prescriptions during the pandemic period with those during the pre-pandemic period. Details of the study design are depicted in Figure 1. We also changed the definition of delayed clinic visits/medication prescriptions from more than 3 to 4 months, to check robustness. COVID-19 vaccines became available in February 2021 in Japan;^[27] the data used in the study were prior to the period when vaccines against COVID-19 became available.

This study was approved by the institutional review board of Fukuoka University Clinical Research and Ethics Center (U21-01-010). Informed consent was waived according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

2.2. Definition of variables

Medications included brand-name as well as generic medications. Medications were categorized into alpha-glucosidase inhibitors (α GI), biguanide, dipeptidyl peptidase 4 inhibitors (DPP-4-I), glinide, glucagon-like peptide 1 receptor agonists (GLP-1RA), insulin, sodium-glucose cotransporter-2 inhibitors (SGLT2-I), sulfonyl urea (SU), thiazolidine, and compounding agents. Participants' age was the age at the end of each FY. We obtained standard monthly income data, used for the payment of insurance premiums in the final year because this was reported to have an association with clinic visits among patients with diabetes.^[18] We used these data, unchanged, throughout the study period because of limited data; income was considered not to have changed dramatically. Health insurance can apply to employees as well as dependent family members. We considered

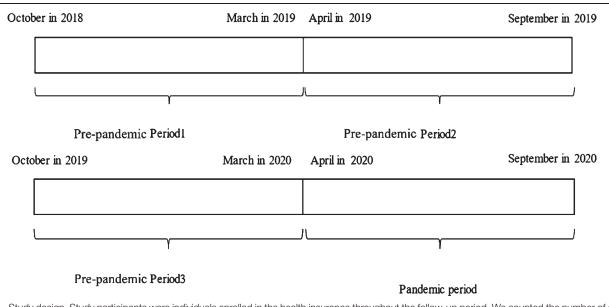


Figure 1. Study design. Study participants were individuals enrolled in the health insurance throughout the follow-up period. We counted the number of discontinuities in each period. We also adjusted for biannual variation (from October and March vs. from April to September) in multivariable analysis.

that each could react differently to a threat such as a pandemic; therefore, we created a variable of qualification (employees and dependents) and used them for adjustment.

2.3. Statistical analysis

We performed chi-square tests for categorical variables. The data had a person-period data structure and we analyzed outcome (*T*) using explanatory variables of the previous period (*T* – 1) to maintain temporality.^[28] For instance, when we analyzed delayed visits in pre-pandemic period 3, we used the explanatory variables of pre-pandemic period 2. We used a multilevel logistic regression model to examine the effect of the COVID-19 pandemic on regular visits by patients with diabetes using person-period data, with four periods per person. Variables used for adjustment were age, sex, income, qualification, biannual variation (October to March vs April to September), and medications (α GI, biguanide, DPP-4-I, glinide, GLP-1RA, insulin, SGLT2-I, SU, thiazolidine, and compounding agents).

We investigated the relationships between the impact of the COVID-19 pandemic on delayed clinic visits/medication prescriptions and age, sex, income, qualification (employee, dependent), biannual variation (October to March, April to September), and medication, using interaction terms. We treated age and income as continuous variables in the main analysis. To examine interaction, we treated continuous variables as binary at the mean value (age: <57, ≥ 57 years; income: $\langle 370, \geq 370$ ($\times 10^3$) JPY). We then conducted further analysis to check robustness by: firstly, changing the definition of delayed clinic visits/medication prescriptions from an interval of more than 3 months to one of 4 months; secondly, replacing 160 missing data points for standard monthly income with mean imputation; and finally, performing panel data analysis with a random-effects model rather than multilevel analysis. Furthermore, the rate of delayed visits was expected to be increased in accordance with a patient's diabetes history. Therefore, we used difference-in-differences analvsis under the hypothesis that the trend of delayed visits was constant. We compared delayed visits between pre-pandemic period 3 (October 2019 to March 2020) and the pandemic period (April 2020 to September 2020) ("exposure arm") with delayed visits between pre-pandemic period 1 (October 2018 to March 2019) and pre-pandemic period 2 (April 2019

to September 2019) ("control arm"). We used a multilevel linear model with adjustment for age, sex, income, qualification, and medications. Stata release 16 (StataCorp LLC, College Station, TX) was used for the statistical analyses. All reported p values were two-tailed, and the level of significance was set at P < .05.

3. Results

3.1. Participant characteristics

We identified 1118 study participants; the characteristics of participants are presented in Table 1. Participants' mean age (standard deviation; SD) in 2018 was 56.2 (8.6) years, and 77.7% were men (n = 869). Employees visited a health care facility more often than their dependents. Mean standard monthly income $\times 10^3$) JPY was 370.0 (SD 18.7). Table 2 shows the number of prescribed medications per period. Biguanide, DPP-4, glinide, insulin, SGLT2-I, SU, and compounding agents were more frequently used than other medicines. The frequency of prescription for each medication did not vary significantly through the study period, except for DPP-4-I.

3.2. Effect of the COVID-19 pandemic on delayed clinic visits/medication prescriptions

Figure 2 shows the rate of delayed clinic visits/medication prescriptions in each period. The number of delayed clinic visits/ medication prescriptions among the total 1118 participants was 52 in pre-pandemic period 1, 63 in pre-pandemic period 2, 73 in pre-pandemic period 3, and 125 during the pandemic period. There was a significant association between delayed clinic visits/ medication prescriptions and period (P < 0.001). Table 3 shows the results of univariate and multivariate analyses. The number (percentage) of delayed clinic visits/medication prescriptions in the pre-pandemic and pandemic periods was 188/3354 (5.6%) and 125/1118 (11.2%), respectively. There was a significant increase in delayed clinic visits/medication prescriptions during the pandemic period compared with the pre-pandemic period (adjusted odds ratio [OR] 3.68, 95% confidence interval [CI] 2.24 to 6.04; P < .001), even when controlling for sex, age, qualification (employee or dependent), standard monthly income, biannual variation (October to March, April to September), and medication.

3.3. Interaction between variables and the COVID-19 pandemic

We examined the interaction between the period of the COVID-19 pandemic and each variable (Fig. 3). Women had significantly fewer clinic visits during the COVID-19 pandemic than men (men: adjusted OR 2.65, 95% CI 1.55 to 4.52; women: adjusted OR 19.31, 95% CI 5.24 to 71.15; P = .013 for interaction). Furthermore, older people and dependents tended to delay routine care visits, although this was not statistically significant. There was no significant interaction for income or for each medication.

3.4. Analysis of robustness

We also changed the interval of irregular medication from more than 3 months to 4 months for further analysis and obtained similar results. The number (percentage) of gaps in each period was 28 (2.5%) in pre-pandemic period 1, 49 (4.4%) in pre-pandemic period 2, 50 (4.5%) in pre-pandemic period 3, and 102 (9.1%) during the pandemic period (P < .001); the adjusted OR for irregular visits in the pandemic period was 4.95 (95% CI 2.54 to 9.66; P < .001). When we imputed the mean value of income (369.876 [x10³] JPY) for missing data (adjusted OR 3.79, 95% CI 2.32 to 6.18; P < .001), the results did not change. The results of panel data analysis using a random-effects model showed an adjusted OR for irregular visits in the pandemic period of 3.45 (95% CI 2.21 to 5.40; P < .001), which was similar to the main results. Regarding the results for difference in differences, there was a significant difference between the control arm and the exposure arm (β .035, 95% CI .012 to .057; P=.002) (Fig. 4); this result was consistent with our other findings.

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Participant characteristics at the start of the study period (October 2018).

N or mean	
869 (77.7)	
249 (22.3)	
56.2 (8.6)	
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934 (83.5)	
184 (16.5)	
370.0 (18.7)	

JPY =	= Japanese	yen, SD	= standard	deviation.
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Prescribed medications in each period.

Rate of delayed visits over the period

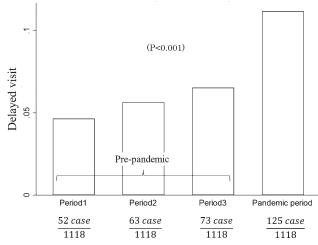


Figure 2. Rate of delayed clinic visits/medication prescriptions over the study period. The denominator is the population at risk (N = 1118). The numerator is the number of cases of irregular medication prescriptions (P < .001).

4. Discussion

In this study, we revealed that the COVID-19 pandemic had a negative impact on regular health care visits and medication prescriptions among people with diabetes during the first wave of the pandemic in Japan. We also found that the response to the pandemic was significantly different by sex.

Diabetes mellitus is a main risk factor for complications and death owing to COVID-19;[20-22] thus, it has been proposed that people with diabetes have avoided routine health care for fear of severe COVID-19 infection, especially during the period before vaccines were available. Some studies have reported decreased diagnosis rates among individuals with stroke,^[29] acute heart failure,^[30] and pulmonary embolism^[31] during the COVID-19 pandemic, probably because of a decline in consultations.^[32] However, those reports are mainly related to acute care. Furthermore, those studies have only compared the diagnosis rates between the periods before and during the COVID-19 pandemic. In contrast, we defined delayed visits and longitudinally followed individuals with chronic diseases such as diabetes, consequently demonstrating that routine health care declined among people with diabetes in Japan owing to the COVID-19 pandemic.

Some studies have reported that irregular clinic visits have a negative impact on several health outcomes. Research

	Pre-pandemic period 1 (Oct 2018 to Mar 2019)	Pre-pandemic period 2 (Apr 2019 to Sep 2019)	Pre-pandemic period 3 (Oct 2019 to Mar 2020)	Pandemic period (Apr 2020 to Sep 2020)	P *
aGI, <i>n</i> (%)	169 (15.1)	160 (14.3)	167 (14.9)	156 (14.0)	.852
Biguanide, n (%)	489 (43.7)	494 (44.2)	493 (44.1)	511 (45.7)	.794
DPP-4-I, n (%)	651 (58.2)	616 (55.1)	576 (51.5)	551 (49.3)	<.001
Glinide, n (%)	408 (4.4)	52 (4.7)	54 (4.8)	52 (4.7)	.968
GLP-1RA, n (%)	57 (5.1)	59 (5.3)	66 (5.9)	68 (6.1)	.696
Insulin, n (%)	183 (16.4)	186 (16.6)	194 (17.4)	193 (17.3)	.908
SGLT2-I, n (%)	331 (29.6)	344 (30.8)	355 (31.8)	377 (33.7)	.193
SU, n (%)	311 (27.8)	314 (28.1)	303 (27.1)	288 (25.8)	.607
Thiazolidine, n (%)	104 (9.3)	103 (9.2)	105 (9.4)	108 (9.7)	.986
Compounding agents, n (%)	425 (38.0)	422 (37.8)	402 (36.0)	394 (35.2)	.450

aGI = alpha-glucosidase inhibitor, DPP-4-I = dipeptidyl peptidase IV inhibitor, GLP-1RA = glucagon-like peptide 1 receptor agonist, SGLT2-I = sodium-glucose cotransporter-2 inhibitor, SU = sulfonyl urea. *Pearson's chi-square test.

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Effects of the coronavirus disease 2019 pandemic on irregular medication and visit	s.
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	Cases/total (%)	Crude OR (95% CI)	Р	Adjusted OR (95% CI)	Р
Period					
Pre-pandemic period	188/3354 (5.6)	1.00 (Reference)		1.00 (Reference)	
Pandemic period	125/1118 (11.2)	4.64 (2.96 to 7.28)	<.001	3.68 (2.24 to 6.04)	<.001

Multilevel logistic regression model was used for person-period data, with four periods per person. Variables used for adjustment included sex, age, qualification, standard monthly income, biannual variation, and medication.

CI = confidence interval, OR = odds ratio.

investigating the impact of irregular visits on diabetes outcomes using propensity score matching suggests that people with irregular health care visits tend to have poor glycemic control^[18] and a higher risk of hospitalization for ischemic heart disease and stroke.^[17] Other research has revealed a strong dose-response relationship between encounter frequency and metabolic outcomes, including glycemic control.^[19] These findings could be because frequent visits make it possible to adjust the medication dose and provide lifestyle coaching or other health education, which leads to better diabetes control.^[19] More frequent health care encounters are also associated with better medication adherence.[33,34] This study revealed that delayed clinic visits/medication prescriptions occurred during the COVID-19 pandemic in Japan. Such behavior could lead to poorer control of diabetes; however, we did not investigate delayed clinic visits/medication prescriptions in terms of clinical outcome. Further research is needed to investigate the effects of the COVID-19 pandemic on health outcomes in patients with diabetes.

Our study also revealed that older people tended to delay routine care visits. Older age is a risk factor for severe COVID-19 infection,^[20] so it is not surprising that older people have tended to avoid routine care for fear of infection. Interestingly, the response to the COVID-19 pandemic differed between men and women. Although the reason for this is unknown, one underlying mechanism could be sex differences in response to a threat. It has been reported that women are generally more risk-averse than men,[35,36] although these results are mainly derived from studies addressing financial risk. Another reason is that the data used in this study were claims data derived from an employee-based plan. Nearly all the men in this study were employees (99%) and only 30% of women were employees; the remaining 70% of women were classified as dependents. Thus, workers might be more strongly encouraged by occupational physicians to attend regular health care visits and receive their medication. Dependents, such as homemakers, might have postponed visits to a health care facility during the COVID-19 pandemic. However, when we analyzed only employees, there was still a significant interaction between response to the pandemic and patient sex (P = .037 for interaction; data not shown). Further research is needed to investigate sex differences in the response to threats such as a pandemic.

Some studies have reported that telehealth is effective for chronic disease management, such as diabetes management.^[37-39] The importance of telehealth was especially emphasized during the COVID-19 pandemic.^[40] There was a sharp increase in

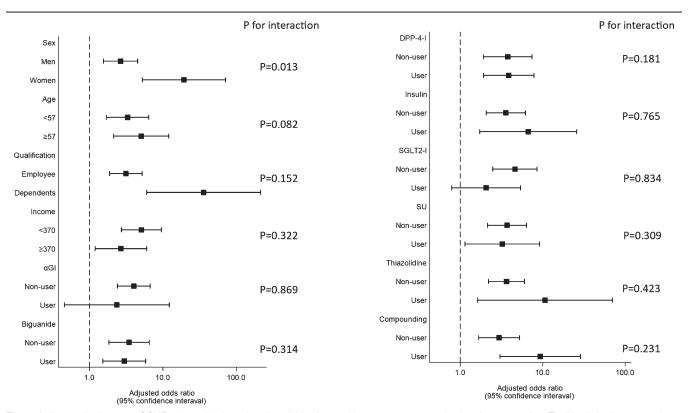


Figure 3. Interaction between COVID-19 pandemic and each variable. Age and income were categorized at the mean value. The X-axis is shown on a logarithmic scale. Glinide and glucagon-like peptide 1 receptor agonist not shown in the figure. α GI = alpha-glucosidase inhibitor, DPP-4-I = dipeptidyl peptidase IV inhibitor, SGLT2-I = sodium-glucose cotransporter-2 inhibitor, SU = sulfonylurea, compounding: compounding agents. The unit of income was (×10³) JPY.

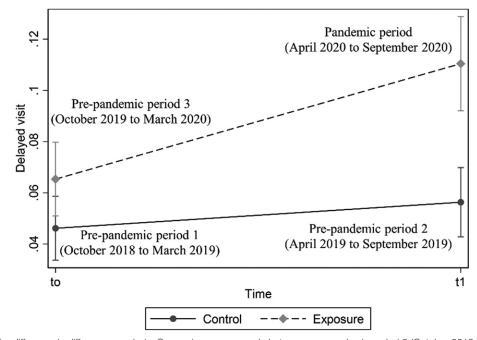


Figure 4. The results for difference in differences analysis. Comparisons were made between pre-pandemic period 3 (October 2019 to March 2020) and the pandemic period (April 2020 to September 2020) ("exposure arm") with delayed visits between pre-pandemic period 1 (October 2018 to March 2019) and pre-pandemic period 2 (April 2019 to September 2019) ("control arm"). Variables used for adjustment were age, sex, income, qualification, and medications.

the use of telehealth during the COVID-19 pandemic in many countries compared with before the pandemic.^[41-44] A similar trend was also observed in Japan, although the use of online consultation was limited to fewer than 10,000 at the peak in May 2020; that number has decreased and plateaued at approximately 5000–7000 during the following period in Japan as a whole.^[45,46] The reason for the limited use of telehealth might be owing to regulations,^[44,47] reimbursement,^[44,47,48] patients' or provider's literacy or preference, as well as the availability of technology.^[44,48,49] Evidence regarding telehealth is scarce in Japan; therefore, further research to evaluate the effect of telehealth is essential.

Although this study revealed the effect of the COVID-19 pandemic on delayed clinic visits/medication prescriptions for diabetes in practice, there are some limitations. We did not differentiate type 1 and type 2 diabetes in the analysis, which is an important limitation. The reason why we did not differentiate the type of diabetes is that it is not necessary that a provider differentiate type 1 and type 2 diabetes for reimbursement. In addition, disease coding is not sufficient for differentiating type 1 and type 2 diabetes because of its low sensitivity;^[50] thus, there could be some cases in which it is unknown whether the patient had type 1 or type 2 diabetes. As a side note, we excluded diagnoses of type 1 diabetes (ICD10:E10) at least once (N = 66), and a similar result was obtained (adjusted OR 4.11, 95% CI 2.43 to 6.95, P < .001). However, differentiation between type 1 and type 2 diabetes remained somewhat incomplete; further investigations are needed. The data were obtained prior to the period when vaccines against COVID-19 became available; therefore, the findings of this study are not necessarily relevant to the situation in the post-vaccine era. Study participants were limited to a single health insurance society for a specific transportation industry. Therefore, the results may not be generalizable to other populations because our participants might be more careful about their health so as to be able to drive safely. Additionally, there was a notable imbalance with respect to participants' sex, which could also be owing to characteristics of the transportation industry. We could not use critical influential factors such as physiologic data (for example, body mass index, blood sugar, and glycated hemoglobin), level of education, and period of treatment because these data were limited. Although we defined delayed clinic visits/medication prescriptions as patients who failed to receive a medication prescription for more than 3 consecutive months, it would be more accurate to use the discrepancy between prescription intervals and the time between visits; however, this information was unavailable.

5. Conclusion

We revealed a negative impact on regular health care visits and medication prescriptions among people with diabetes during the first wave of the COVID-19 pandemic in Japan. The response to the COVID-19 pandemic differed between men and women.

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Author contributions

Akira Okayama contributed to acquisition of the data. Kei Asayama, Nagako Okuda, Akira Okayama, Daisuke Sugiyama, Hiroshi Yatsuya, Akira Okayama, Hisatomi Arima contributed to conception of the work. Toshiki Maeda, Takumi Nishi, Masataka Harada contributed to analysis and interpretation of the data and drafting the manuscript. All authors critically revised the draft for important intellectual content, approved the final version of the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- Conceptualization: Akira Okayama, Daisuke Sugiyama, Hiroshi Yatsuya, Kei Asayama, Nagako Okuda
- Data curation: Kozo Tanno, Masataka Harada, Naoyuki Nishiya, Takumi Nishi

- Formal analysis: Masataka Harada, Takumi Nishi, Toshiki Maeda
- Funding acquisition: Akira Okayama
- Investigation: Toshiki Maeda
- Methodology: Akira Okayama
- Project administration: Akira Okayama, Toshiki Maeda
- Resources: Kozo Tanno, Naoyuki Nishiya
- Supervision: Akira Okayama, Hisatomi Arima
- Writing original draft: Toshiki Maeda
- Writing review & editing: Akira Okayama, Daisuke Sugiyama, Hiroshi Yatsuya, Hisatomi Arima, Kei Asayama, Kozo Tanno, Masataka Harada, Nagako Okuda, Naoyuki Nishiya, Takumi Nishi

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