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Epidemiology

Patterns of trajectories of glycated hemoglobin, fasting plasma glucose, and body mass index until the first clinic visit: the real-world history of type 2 diabetes using repeated health checkup data of Japanese workers

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Abstract

Background. There is a lack of evidence regarding the trajectories of type 2 diabetes until the first clinic visit, including the untreated period after diagnosis.

Objective. We aimed to determine the real-world history of type 2 diabetes until the first clinic visit, including the untreated duration, and to assess the effective timing of the therapeutic intervention.

Methods. A total of 23,622 nondiabetic Japanese workers with a mean (SD) age of 38.8 (11.5) years were retrospectively followed from 2008 to 2022 for annual health checkups. The trajectories of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and body mass index (BMI) until the first clinic visit in diabetes individuals were determined. ROC analysis was performed to assess the contribution of each measure to the first visit.

Results. During a median follow-up of 12.0 years, 1,725 individuals developed type 2 diabetes, of whom 532 individuals visited clinics. HbA1c and FPG trajectories steeply rose in the year before the first clinic visit after their progressive upward trends. ROC analysis showed cutoff values for each measure. As the untreated duration increased, glycemia increased and BMI decreased among individuals who visited clinics.

Conclusions. To prevent the initial worsening of diabetes, early therapeutic intervention is necessary during the increasing trends before the steep rise in glycemia, regardless of the degree of obesity. HbA1c ≥6.5% (47.5 mmol/mol) and an HbA1c ≥0.2% (2.2 mmol/mol)/year increase may be an effective timing for therapeutic intervention.

Keywords: trajectory; first clinic visit; HbA1c; fasting plasma glucose; body mass index; type 2 diabetes

Introduction

Type 2 diabetes (T2D) and obesity are increasing worldwide, particularly in Asia [1–3]. Asian populations tend to develop diabetes at younger ages with lower body mass index (BMI) [2, 3]. There is pronounced dysfunction in early insulin secretion and a higher predisposition to insulin resistance at a lower degree of obesity in Asian populations than in Western populations [4–7]. The risk of diabetes is primarily associated with increased BMI in adulthood close to the time of diagnosis [8] and with the duration of obesity [9]. The effect of obesity on the risk of diabetes is greater in middle-aged adults than in older adults [10]. Weight gain in early adulthood plays a more important role than that in middle-to-late adulthood [11]. The trajectories of glycemia, BMI, insulin secretion, and sensitivity until the onset of T2D have been studied domestically and internationally [12–23]. However, there is a lack of evidence regarding the course of T2D until the first clinic visit, including the untreated period.

A cross-sectional time-series study of obesity and glycemic control at the first clinic visit for T2D in Japan showed that BMI increased and glycemic control worsened as time progressed [24]. However, the diabetes status in the untreated period before the first clinic visit is not well understood.

Therefore, we aimed to determine the real-world history of T2D until the first clinic visit, including the untreated period after the diagnosis of diabetes, and the effective timing of the therapeutic intervention was assessed. We traced the trajectories of glycated hemoglobin (HbA1c) values, fasting plasma glucose (FPG) concentrations, and BMI until diagnosing T2D and until the first clinic visit in healthy Japanese young to middle adulthood employees.

Key message

- HbA1c and FPG trajectories steeply rise the year before the first clinic visit.
- BMI becomes lower and glycemia worsens as the untreated duration increases.
- Early intervention is necessary to prevent the initial worsening of diabetes.
- A clinic should be visited at an upward trend before a steep rise in glycemia.
- A clinic visit is recommended if HbA1c ≥6.5% and an increase in HbA1c ≥0.2%/year.

Research design and methods

Study participants

A flow diagram of the participants included in the analyses is shown in Fig. 1. The cohort of 28,124 individuals consisted of the railway company employees who underwent annual health checkups between April 1, 2008 and March 31, 2009. Of these individuals, 4,502 were excluded owing to a follow-up <1 year (n = 2,851), diagnosis of diabetes at baseline (n = 1,634), and age >70 years at baseline (n = 1). Moreover, 16 individuals whose baseline glycemic data were missing and who had only one HbA1c or blood glucose measurement during follow-up and met the criteria for diabetes were excluded. Subsequently, 23,622 individuals without diabetes (21,492 men, 2,130 women), aged 18–67 years, were eligible for the present study and retrospectively followed up annually to March 31, 2022.

Annual health checkups and clinical measurements

Japanese workers are obliged to undergo annual health checkups. We collected the results of annual routine health checkups. In all participants, body weight, height, blood pressure, and urinalysis were determined at baseline and at each annual health checkup, and BMI was calculated as kg/m^2.

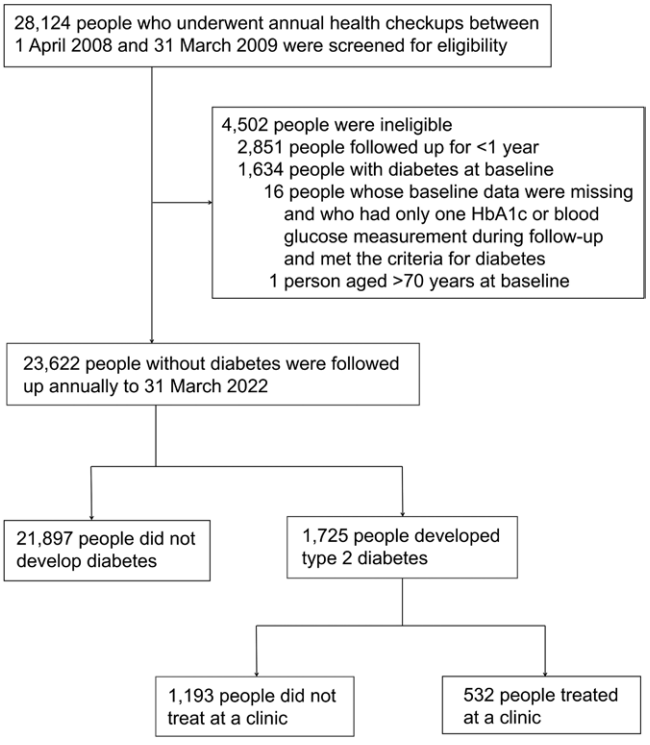


Figure 1. Flow diagram of participants included in the study.

After filling out a questionnaire before a health checkup, the current and past medical history, subjective symptoms, and lifestyle factors were ascertained during a medical interview by a public health nurse. A medical interview also ascertained the time when the last meal started. All new employees had blood tests performed during their initial health checkups, including measurement of plasma glucose concentrations and HbA1c values. Blood samples, including those for plasma glucose concentrations, were collected from individuals aged 20, 25, 30, and 35 years, and annually from individuals aged 39 years and older as of 1 April. HbA1c was measured in individuals aged 35 and 39 years and older as of 1 April, and in individuals of all ages with urinary glucose 1+ or higher from each annual urinalysis. Urinary glucose 1+ corresponds to a urine glucose concentration of 1 g/L. Blood tests were automatically performed in individuals of all ages who had abnormal values at the previous year's health checkup and were determined to require follow-up or reexamination, and in those who had not complied with a request for a doctor's consultation for their abnormalities. Further blood tests were added at the discretion of the managing physician for those of all ages who complained of any disease-related symptoms at the time of the examination. Furthermore, approximately 70% of those who were 35 years or older underwent complete medical checkups that included FPG and HbA1c measurements.

Plasma glucose concentrations were measured using an enzymatic method (Hexokinase UV method) (ARCHITECT plus C16000, TBA-FX8; Canon, Tokyo, Japan), and HbA1c was assayed using high-performance liquid chromatography (HLC-723G11; Tosoh, Tokyo, Japan). HbA1c values were measured as the National Glycohemoglobin Standardization Program (NGSP) values from 1 April 2013, and HbA1c (Japan Diabetes Society [JDS]) values up to 31 March 2013 were converted to the NGSP equivalent values using the following formula: (NGSP [%] = 1.02 × JDS [%] + 0.25) [25].

Diagnosis of T2D

T2D was identified using data from annual health checkups. Diabetes was diagnosed as FPG concentrations ≥7.0 mmol/L, random plasma glucose concentrations ≥11.1 mmol/L, HbA1c values ≥6.5% (48 mmol/mol), or self-reported clinician-diagnosed diabetes. Fasting was defined as no caloric intake for at least 10 hours. "Random" was regarded as less than 10 hours after initiating dietary intake. Individuals without diabetes at baseline who subsequently met any of the above-mentioned criteria were decided to be an incident case of T2D.

Confirmation of the first clinic visit

The date of the first visit to a clinic for each participant was confirmed by an interview with a public health nurse during

a health checkup the following year, self-reporting, and replying to a referral letter. Among individuals who developed diabetes, those who visited a clinic were classified as the treated group, and those who did not were classified as the untreated group.

Statistical analysis

Baseline clinical characteristics between incident diabetes and non-diabetes groups and between untreated and treated groups were compared using the Student's *t*-test and χ^2 test. All participants were divided according to whether they had developed T2D during the follow-up. The year of diagnosing T2D or the end of follow-up was expressed as year 0. The trajectories for HbA1c, FPG, and BMI from year 0 were traced back to baseline. In individuals who developed T2D, the trajectories for these measurements were then traced back to baseline, starting with the year of the first clinic visit or the end of follow-up as year 0. Additionally, we assessed the contribution of each measure to the first clinic visit at years –1 and –2 and the contribution of the difference between each measure at years –1 and –2 in the diabetes group, using the area under the receiver operating characteristic (ROC) curve (AUC). If the values were prediabetic when going backward from year 0, they were included in the analysis. Individuals with missing measurements at these time points were excluded from the analysis. DeLong's method was used to compare AUCs. The respective cutoff values were obtained. Furthermore, in the treated group, the time from diagnosing diabetes until the year of the first clinic visit was divided into the following five groups: <2 years, ≥2 and <3 years, ≥3 and <4 years, ≥4 and <5 years, and ≥5 years. The trajectories of these five groups for each measurement were similarly drawn as complete cases. Repeated measurements of HbA1c, FPG, and BMI were analyzed with the linear mixed-effects model to investigate time-dependent changes in HbA1c, FPG, and BMI. Contrasts were used for comparisons at each time point of the trajectories. A complete case analysis with a sensitivity analysis was performed to check whether our results were robust.

All statistical analyses were carried out using SAS package version 9.4 (SAS Institute, Cary, NC, USA). Two-tailed $P < 0.05$ was regarded as statistically significant.

Results

Baseline characteristics

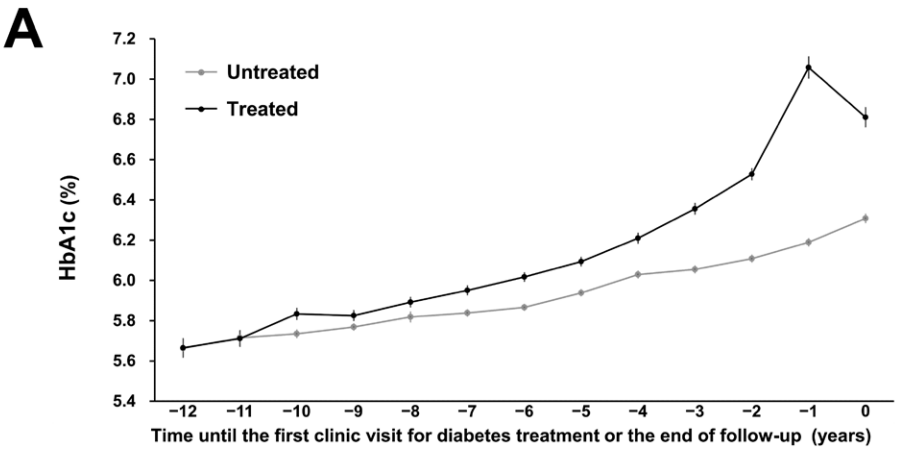
During the follow-up, 1,725 individuals developed T2D. Of them, 532 individuals attended clinics (Fig. 1). The total follow-up was a median (interquartile range) of 12.0 (6.3–13.0) years. In the diabetic group, the follow-up until onset was 5.4 (3.0–8.9) years, that after onset was 3.8 (1.0–6.1) years, that from baseline to the first clinic visit was 8.0 (5.9–10.2) years, and that from onset to the first clinic visit was 2.1 (1.3–4.0) years.

Table 1 shows the baseline clinical characteristics of total cases, incident diabetes and non-diabetes cases, and untreated and treated cases. The diabetes group was older, had more men, had higher HbA1c, FPG, BMI, and blood pressure values, and had a higher percentage of current smokers (all $P < 0.0001$) than the non-diabetes group. The treated group was younger ($P < 0.0001$) and had higher HbA1c, BMI (both

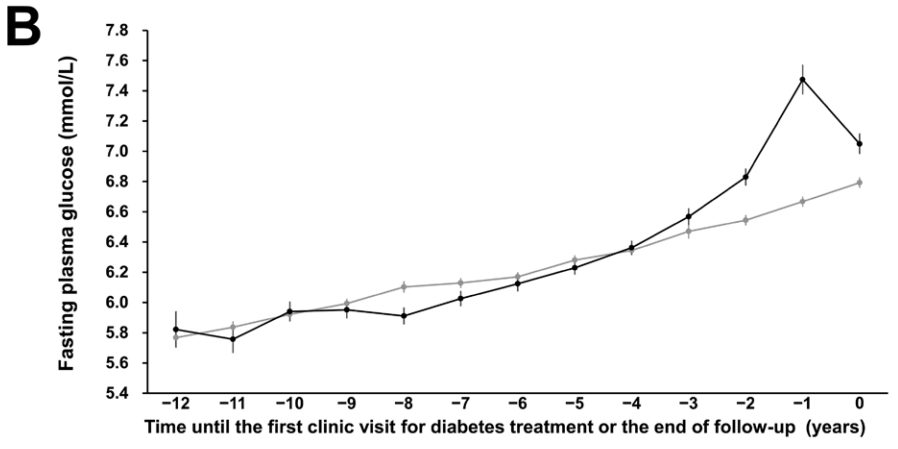
Table 1. Baseline clinical characteristics of the total participants, individuals who did or did not develop diabetes, and individuals treated or untreated for diabetes.

	Total (*n* = 23,622)	Non-diabetes (*n* = 21,897)	Diabetes (*n* = 1,725)	*P* value ¶	Untreated diabetes (*n* = 1,193)	Treated diabetes (*n* = 532)	*P* value #
Age (years)	38.8 ± 11.5	38.4 ± 11.6	44.2 ± 8.8	<0.0001	45.4 ± 8.5	41.5 ± 9.0	<0.0001
<20 years	322 (1.36)	315 (1.44)	7 (0.41)		3 (0.25)	4 (0.75)	
20–29 years	6,940 (29.38)	6,790 (31.01)	150 (8.70)		89 (7.46)	61 (11.47)	
30–39 years	5,515 (23.35)	5,169 (23.61)	346 (20.06)		187 (15.67)	159 (29.89)	
40–49 years	5,419 (22.94)	4,701 (21.47)	718 (41.62)		505 (42.33)	213 (40.04)	
50–59 years	5,403 (22.87)	4,899 (22.37)	504 (29.22)		409 (34.28)	95 (17.86)	
≥60 years	23 (0.10)	23 (0.11)	0 (0.00)		0 (0.00)	0 (0.00)	
Male sex	21,492 (91.0)	19,783 (90.4)	1,708 (99.0)	<0.0001	1,179 (98.8)	529 (99.4)	0.24
BMI (kg/m^2)	23.2 ± 3.4	22.9 ± 3.2	25.9 ± 4.2	<0.0001	25.2 ± 3.9	27.4 ± 4.4	<0.0001
Systolic BP (mmHg)	124 ± 14	124 ± 14	131 ± 15	<0.0001	131 ± 15	130 ± 13	0.66
Diastolic BP (mmHg)	78 ± 10	77 ± 10	83 ± 10	<0.0001	83 ± 11	83 ± 10	0.16
HbA1c (%) (mmol/mol) †	5.4 ± 0.3 (36 ± 4)	5.4 ± 0.3 (35 ± 3)	5.8 ± 0.4 (40 ± 5)	<0.0001	5.7 ± 0.4 (39 ± 4)	5.9 ± 0.6 (41 ± 6)	<0.0001
Fasting plasma glucose (mmol/mol) ‡	5.37 ± 0.52	5.32 ± 0.45	6.02 ± 0.78	<0.0001	5.97 ± 0.72	6.11 ± 0.91	0.002
Current smoker §	8,894 (38.4)	8,034 (37.4)	860 (51.0)	<0.0001	589 (50.6)	271 (51.9)	0.62

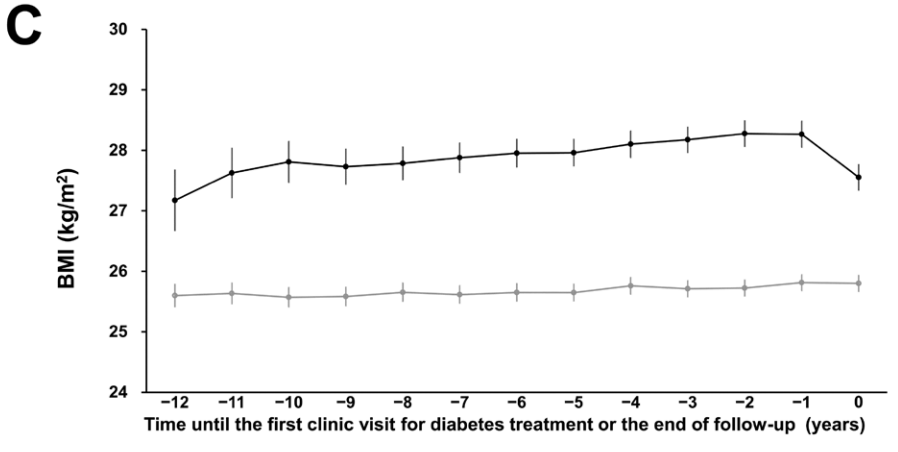
Values are *n* (%) or the mean ± standard deviation.
†Participants whose HbA1c values were measured: total (*n* = 21,995), non-diabetes (*n* = 20,270), diabetes (*n* = 1,725), untreated diabetes (*n* = 1,193), and treated diabetes (*n* = 532).
‡Participants whose fasting plasma glucose values were measured: total (*n* = 21,109), non-diabetes (*n* = 19,456), diabetes (*n* = 1,653), untreated diabetes (*n* = 1,147), and treated diabetes (*n* = 506).
§Participants whose current smoking status was confirmed by a questionnaire: total (*n* = 23,146), nondiabetes (*n* = 21,460), diabetes (*n* = 1,686), untreated diabetes (*n* = 1,164), and treated diabetes (*n* = 522).
¶Non-diabetes vs. diabetes.
#Untreated diabetes vs. treated diabetes.
BP, blood pressure; HbA1c, glycated hemoglobin.



Untreated (n)	349	435	545	609	685	780	862	930	995	1062	1109	1143	1193
(Incident diabetes [n])	(6)	(12)	(37)	(62)	(110)	(156)	(212)	(298)	(410)	(549)	(675)	(878)	(1193)
Treated (n)	34	68	109	163	198	265	312	362	427	434	471	483	532
(Incident diabetes [n])	(1)	(3)	(5)	(11)	(21)	(37)	(54)	(86)	(147)	(225)	(333)	(464)	(532)



Untreated (n)	233	290	369	454	488	576	647	692	750	838	856	866	1147
(Incident diabetes [n])	(19)	(25)	(46)	(78)	(105)	(153)	(209)	(269)	(329)	(469)	(547)	(679)	(1147)
Treated (n)	25	47	76	111	138	182	216	239	284	324	317	340	487
(Incident diabetes [n])	(2)	(4)	(8)	(15)	(24)	(39)	(56)	(80)	(122)	(200)	(231)	(327)	(487)



Untreated (n)	482	562	649	723	773	855	923	977	1038	1100	1136	1167	1193
(Incident diabetes [n])	(3)	(11)	(36)	(66)	(111)	(160)	(215)	(307)	(421)	(558)	(688)	(889)	(1193)
Treated (n)	74	118	179	230	273	339	382	425	469	496	506	500	532
(Incident diabetes [n])	(0)	(1)	(5)	(9)	(19)	(35)	(52)	(88)	(149)	(236)	(338)	(476)	(532)

Figure 2. Trajectories of HbA1c (A), FPG (B), and BMI (C) until the first clinic visit for diabetes treatment or at the end of follow-up among individuals who developed type 2 diabetes. Year 0 is the year of the first clinic visit (treated case) or the end of follow-up (untreated case). Data of the trajectories are shown as mean values. Error bars show standard errors.

$P < 0.0001$), and FPG ($P = 0.002$) values than the untreated group (Table 1).

Trajectories until diagnosing T2D

The trajectories of HbA1c, FPG, and BMI until the diagnosis of diabetes in all study participants were drawn from years −10 to 0 (Supplementary Figure 1). HbA1c and FPG trajectories rapidly increased in the year of diagnosing T2D. These results were similar to those reported previously.

Trajectories until the first clinic visit in the diabetes group

The trajectories of HbA1c, FPG, and BMI were drawn from years −12 to 0 (Fig. 2A–C). In the treated group's trajectories, after long-term gradual and moderate increases, a rapid increase in the lsmean (SE) of 0.538% (0.028%) for HbA1c and 0.656 (0.059) mmol/L for FPG occurred from years −2 to −1, reaching 7.087% (0.027%) and 7.471 (0.049) mmol/L, respectively. This pattern was followed by a steep decrease in the lsmean (SE) of 0.276% (0.027%) for HbA1c and 0.422 (0.054) mmol/L for FPG from years −1 to 0. In contrast, the untreated group's trajectories of HbA1c and FPG showed a gradual and steady progressive increase throughout the period. The lsmean (SE) of HbA1c and FPG in the untreated group was 5.599% (0.027%) and 5.695 (0.053) mmol/L at year −12, and 6.308% (0.017%) and 6.792 (0.027) mmol/L at year 0, respectively. The slope differences were 0.463% (0.033%) for HbA1c and 0.525 (0.069) mmol/L for FPG from years −2 to −1, and were−0.396% (0.032%) for HbA1c and −0.557 (0.063) mmol/L for FPG from years−1 to 0. However, the treated group's trajectory of BMI slowly increased from year−12 (26.758 [0.229] kg/m^2) to −1 (28.275 [0.190] kg/m^2), and then sharply decreased from years −1 to 0 (27.552 [0.190] kg/m^2, slope: −0.723 [0.071] kg/m^2). The untreated group's trajectory of BMI remained almost constant throughout the period. The slope differences in BMI were −0.110 (0.086) kg/m^2 from years −2 to −1, and were −0.697 (0.085) kg/m^2 from years −1 to 0. The lsmean (SE) of HbA1c, FPG, and BMI from years −12 to 0 was 6.146% (0.021%), 6.220 (0.034) mmol/L, and 27.586 (0.184) kg/m^2 in the treated group, and 5.909% (0.013%), 6.198 (0.020) mmol/L, and 25.509 (0.123) kg/m^2 in the untreated group, respectively. There were significant differences in the trajectories of HbA1c and BMI between the treated and untreated groups (both $P < 0.0001$). In addition, significant differences were observed at each corresponding time point for the trajectories of HbA1c from years −7 to 0 (all $P < 0.05$), those of FPG from years −3 to 0 (all $P < 0.05$), and those of BMI from years −12 to 0 (all $P < 0.0001$) between the treated and untreated groups.

The ROC analysis of HbA1c and FPG values at years −1 and −2 and the difference between each measure at years −1 and −2 for detecting the first clinic visit in the diabetes group are shown in Table 2 and Supplementary Figure 2. The AUC for the HbA1c value at year −1 was 0.813 (95% CI, 0.790–0.836), which was the most discriminatory to detect the first clinic visit, followed by year −2, then the difference between year −1 and year −2. The AUC for the FPG concentration at year −1 was 0.680 (0.643–0.718), followed by the difference between year −1 and year −2, then year −2. The cutoff values, sensitivity, and specificity of the HbA1c and FPG values at each time point were shown in Table 2.

Treated group's trajectories in the five groups classified by the time from diagnosis to the year of the first clinic visit

A complete case analysis from years −7 to 0 was performed. The lsmean (SE) of HbA1c, FPG, and BMI in each of the five groups are shown in Supplementary Table 1. As the untreated duration increased, the trajectories of HbA1c and FPG became higher. (Fig. 3A and B). There were significant differences in HbA1c (all $P < 0.01$) and FPG (all $P < 0.05$) values between the ≥5 years group and the other groups, and between the <2 years group and the other groups. In contrast, the BMI trajectories became lower with an increase in the untreated duration (Fig. 3C). There was a significant difference in BMI between the ≥5 years group and the <2 years group ($P = 0.024$). The patterns of the trajectories of HbA1c and FPG in the five groups showed similar trends. All trajectories of HbA1c and FPG showed peaks at year −1 and a decline at year 0. Regarding the patterns of the trajectories of BMI in all other groups excluding the ≥5 years group, the increasing tendency appeared to slow down and tended to decrease after the onset of diabetes, but there was no obvious change in the ≥5 years group. The <2 years group showed a peak BMI at year −1. All five trajectories of BMI showed a decline from years −1 to 0.

Table 2. The ROC analysis of HbA1c and FPG values at years −1 and −2 and the difference between each measure at years −1 and −2 for detecting the first clinic visit in the diabetes group.

	Events / *n* [†]	The time point in the trajectory [‡]	AUC (95% CI)	*P*-value	*P*-value	Cutoff point [§]	Sensitivity (%)	Specificity (%)
HbA1c (%) (mmol/mol)	451 / 1,537	Year −1	0.813 (0.790–0.836)	Reference		6.501 (47.53)	69.2	80.8
		Year −2	0.728 (0.701–0.755)	<0.0001	Reference	6.201 (44.27)	71.2	63.2
		(year −1)–(year −2)	0.686 (0.654–0.719)	<0.0001	0.0824	0.201 (2.19)	58.3	75.0
FPG (mmol/L)	279 / 1,035	year − 1	0.680 (0.643–0.718)	Reference		7.161	49.8	77.3
		Year −2	0.595 (0.557–0.634)	<0.0001	Reference	6.717	49.1	65.2
		(year −1)–(year −2)	0.631 (0.592–0.671)	0.0043	0.2578	0.334	56.3	66.4

[†]Individuals with missing measurements at years −1 and −2 were excluded from the analysis.
[‡]Year 0 was defined as the year of the first clinic visit or end of follow-up, year −1 was defined as the time point 1 year back from year 0, and year −2 was defined as the time point 2 years back from year 0.
[§]Cutoff points were determined by maximizing sensitivity plus specificity.
AUC, area under the ROC curve; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

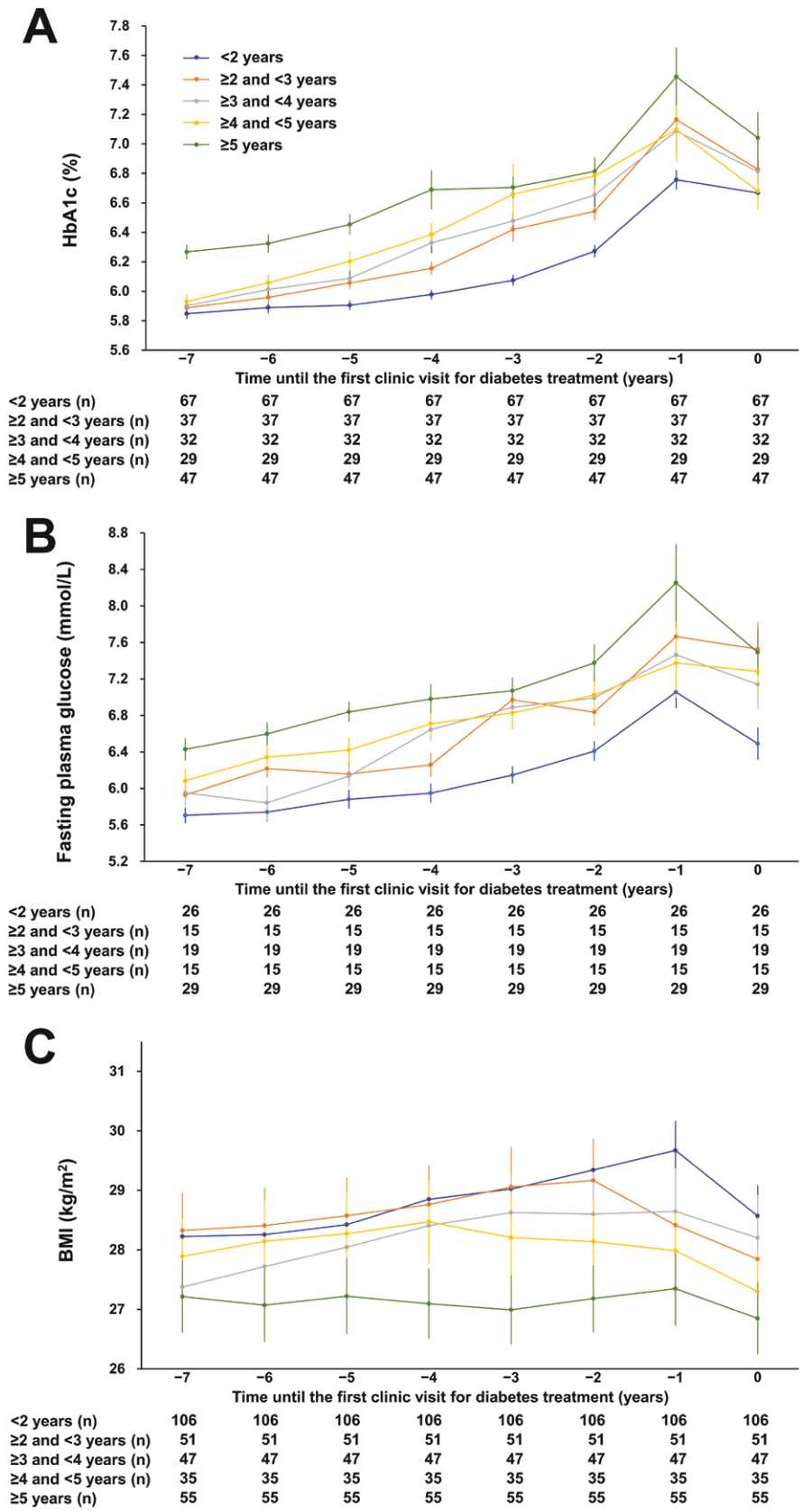


Figure 3. The treated group's trajectories of HbA1c (A), FPG (B), and BMI (C) classified by the untreated duration. Patients were divided into the five groups of <2 years, ≥2 and <3 years, ≥3 and <4 years, ≥4 and <5 years, and ≥5 years. Data of the trajectories are shown as mean values. Error bars show standard errors.

Discussion

In this study, the trajectories of HbA1c and FPG steeply increased in the year before the first clinic visit after their progressive upward trends, and these were identified as discriminatory for the first visit. The trajectory slope between years −1 and −2 could also be used to identify the first visit. As the untreated duration increased, glycemia increased and BMI decreased. A prolonged untreated duration in individuals may have greatly contributed to the rapid rise in glycemia. Notably, the HbA1c and FPG trajectories in the untreated group showed upward trends, whereas the BMI trajectory only slightly changed. This progressive upward trend in glycemia is particularly noteworthy, and could eventually lead to a steep rise in glycemia. Evaluating glycemic trends, as well as hyperglycemia is important. To prevent the initial worsening of diabetes, early therapeutic intervention is necessary during the upward trend before the steep rise in the glycemic trajectory, regardless of the degree of obesity. Periodic examinations and careful observation of an increasing trend in glycemia are required to identify the ideal timing for therapeutic intervention. The HbA1c value ≥6.5% (47.5 mmol/mol), which is also a diagnostic criterion, and an increase in HbA1c value ≥0.2% (2.2 mmol/mol) /year from the previous year may be an effective timing of therapeutic intervention.

There is limited evidence regarding the trajectories of biomarkers from the diagnosis of diabetes to the first clinic visit. According to a population-based longitudinal study between 1965 and 2000, BMI showed an increasing trend until the time of diagnosing diabetes, peaking at the time of the diagnosis or immediately after the diagnosis (0–2 years), and then gradually decreasing as the duration of diabetes increased [26]. This previous study generally supports our results, but the untreated duration was not evaluated.

The history from the diagnosis of diabetes to the first clinic visit is strictly different from the history until the diagnosis of diabetes. This is because, once people know that they have diabetes, they can receive guidance after health checkups and take various self-care measures such as diet and exercise even without visiting a clinic. As a result, weight loss or cessation of weight gain may occur in real life. In our study, the trajectory of HbA1c in the treated and untreated groups gradually diverged, with the difference reaching a maximum at year −1, followed by a decrease in the treated group and a further constant increase in the untreated group. In the treated group, the rapid rise in glycemia at year −1 may have led to a clinic visit through strong encouragement and guidance from healthcare providers. The decrease in glycemia at year 0 is probably due to therapeutic intervention of the clinic visits because these measurements were taken after the first clinic visit. BMI also decreased at year 0. In the untreated group, a deterioration in glycemia might occur after approximately 3 years, regardless of BMI.

Clinic-visiting behavior appears to be influenced by the apparent degree of obesity. Individuals with diabetes and a lower degree of obesity had delayed clinic visits and worse glycemia than those with a higher degree of obesity. This finding may be partially due to the fact that people with a lower BMI are less likely to receive advice or guidance from healthcare providers than those with a higher BMI. This possibility is consistent with health checkups focusing on metabolic syndrome, which are implemented as a national policy in the Japanese health insurance system. In addition, the natural course of losing weight as diabetes progresses by leaving it untreated may also have partly contributed to this finding. Particular attention should be paid to mild obesity in middle-aged individuals with diabetes who tend to delay clinic visits.

Lowering HbA1c immediately after the diagnosis of T2D reduces the risk of all-cause mortality and myocardial infarction 10–20 years later by several fold compared with delayed HbA1c lowering [27]. Preventing early exacerbation of diabetes may ultimately lead to prevention of complications and longer life expectancy.

A strength of our study included large-scale and long-term observations with repeated measurements over a wide age range. Notably, this study had a novel research design for evaluating the untreated duration after developing T2D. However, this study has several limitations. First, our study lacked data on insulin concentrations and oral glucose tolerance tests. Therefore, we could not assess insulin secretion or resistance, and we could not use plasma glucose concentrations at 2 hours postload to diagnose diabetes. Second, there was a limited frequency of blood sampling for participants aged younger than 39 years (see Methods). Additionally, a variation in the blood sampling time reduced the collection of fasting plasma glucose concentrations. To validate our results, we performed a complete case analysis using individuals with no missing time series data, and the results were similar (Supplementary Figure 3). Third, our study participants primarily consisted of young to middle-aged adults, predominantly men with a minority of women. The assessment of sex differences and older people in the study of such trajectories remains an issue to be further examined. Finally, our study participants were employed by a single large Japanese company. There are ethnic differences in the natural history of diabetes [12]. Therefore, generalizability to other ethnicities and the general population may be limited.

In conclusion, HbA1c and FPG trajectories steeply rise the year before the first clinic visit after their progressive upward trends. BMI becomes lower and glycemia worsens as the untreated duration increases. To prevent the initial deterioration of diabetes, early therapeutic intervention is necessary during the increasing trends before the steep rise in glycemia, regardless of the degree of obesity. When patients have HbA1c values ≥6.5% (47.5 mmol/mol) and an increase in HbA1c values ≥0.2% (2.2 mmol/mol) each year, this may be an effective time for therapeutic intervention.

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Supplementary data

Supplementary material is available at *Family Practice* online.

Author contributions

All authors contributed to the study and were involved in the manuscript. T.T. contributed to the study concept and design, data acquisition, data analysis and interpretation, and writing of the manuscript. M.S. contributed to the data interpretation and discussion of the implications of this work. M.N. contributed to

the study design and data analysis. H.Y. contributed to the discussion of the implications of this work. T.I. contributed to data acquisition. T.T. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript and have agreed to the publication of the manuscript.

Conflict of interest statement

All the authors declare no conflict of interest in this work.

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Ethical approval

The study protocol was approved by the Ethics Committee of the JR East Health Promotion Center, with an approval number of 2022-2 and an approval date of November 10, 2022. Informed consent was obtained from all participants by opt-out method. The protocol complied with the Japanese government's Ethical Guidelines for Medical and Health Research Involving Human Subjects, which conform to the provisions of the Declaration of Helsinki.

Data availability

The datasets generated and analyzed during the current study are not publicly available because the Ethical Guidelines prohibit researchers from providing their research data to other third-party individuals.

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