Development and Worsening of Diabetes Among Adults Aged Over 40 Years: A 6-Year Follow-Up Study of 140,000 People in Japan – The Shizuoka Study

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Abstract

Background

Hemoglobin A1c (HbA1c) levels are commonly measured during health check-ups and used as an indicator of diabetes. However, the contribution of screening tests to the prevention of the future development of diabetes is scarcely analyzed. We evaluated the relationship between HbA1c screening results and future risk of diabetes development and worsening.

Methods

We used the Shizuoka Kokuho Database, a Japanese administrative claims database of insured persons aged > 40 years. Individuals available for follow-up during 2012–2017 and who had not received any diabetes treatment before 2013 were considered. We constructed logistic regression models to evaluate the association of the likelihood of initiating diabetes treatment by 2017 with the number of health check-ups received after 2013, HbA1c levels, and trend changes at the 2013 health check-up and assess the likelihood of using injection drugs.

Results

Overall, 137,852 individuals were analyzed. Compared to the normal HbA1c Group (HbA1c < 6.5%) with no trend changes, the normal group with improving trends had higher odds (odds ratio 22.64; 95% confidence interval 14.66–34.99) of starting treatment within 4 years. Among people with diabetes treatment initiated by 2017, injection drugs were more likely used in the normal group than in the diabetes group (HbA1c ≥ 6.5%). Higher numbers of health check-ups were significantly associated with lower likelihoods of starting injection drugs.

Conclusions

Good control of HbA1c levels, as indicated by the results of the health check-ups, might have led to insufficient attention to lifestyle habits, which might have resulted in a deterioration of glycemic control.

Background

According to the latest 2019 Global Burden of Disease (GBD) study, diabetes mellitus is currently one of the leading causes of disease burden globally [1], with a prevalence of 9.0% in women and 9.6% in men in 2019 [2].

In Japan, the National Health and Nutrition Survey in 2018 demonstrated that the percentage of people who were strongly suspected of having diabetes was 9.3% in women and 18.7% in men, and that with respect to age group was higher for older people [3].

The healthcare cost for diabetes in Japan was USD 12 billion in 2018, of which USD 8 billion was for people aged 65 and older, rising by USD 70 million annually for this age group [4]. Diabetes is a major risk factor for various diseases such as acute myocardial infarction and chronic kidney disease. Healthy lifestyle and early interventions in patients with prediabetes to prevent the development or worse prognosis of diabetes appear to be the most cost-effective measures as severe cases of diabetes increase the development of these diseases and incur higher healthcare costs [5,6]. Various attempts have been made to estimate the risk of developing diabetes. For example, in Japanese populations, hypertension, fatty liver, body mass index (BMI), and percentage of weight gain since the age of 20 years have been shown to be predictive of diabetes incidence [7–9]. In 2018, Japan's National Center for Global Health and Medicine developed models for predicting the onset of diabetes within 3 years, which includes a history of treatment for hypertension and hyperlipidemia and BMI as predictive factors [10], although the accuracy of these models has not yet been fully evaluated.

In Japan, health check-ups are widely available to the general population aged ≥ 40 years and play a vital role in screening for diabetes and other lifestyle-related diseases. Fasting blood glucose and hemoglobin A1c (HbA1c) levels are measured during health check-ups to screen for diabetes; however, only few studies have empirically analyzed the extent to which these screening tests contribute to the prevention of the future development and worse prognosis of diabetes in clinical settings. Therefore, using health check-up data from 2012 to 2017 and related health insurance claims data, this study evaluated the relationship between HbA1c screening results and the future risk of type 2 diabetes development. We hypothesized that our findings would contribute to the evidence related to forestalling the increasing burden of diabetes globally.

Methods

Study population and data

We used the Shizuoka Kokuho Database for this study, which is an administrative claims database of insured persons of the National Health Insurance (NHI) and Late Elders' Health Insurance (LEHI) in the Shizuoka prefecture, Japan. The Shizuoka prefecture is located approximately at the center of Japan on the Pacific coast, with a population of approximately 3.6 million as of 2020; it is the tenth largest prefecture among the 47 prefectures in the country.

There are three main types of health insurances in Japan: the Employee's Health Insurance (EHI), NHI, and LEHI; the EHI and NHI are for those who are aged ≤ 74 years, while the LEHI is for those who are aged ≥ 75 years [11]. The EHI is provided to employed workers (company employees) and their dependents and insured by many insurers (number of insurers in Japan is more than 1,500), which is mostly dependent on the size of the company. Meanwhile, the NHI is designed for people who are not company employees (hence, not eligible to be members of the EHI), are aged < 74 years, and are insured by the prefectural and municipal governments (villages, towns, and cities). Those who are aged > 75 years, including self-

employed persons aged > 75 years, are enrolled in the LEHI, which is insured by the prefectures. The Shizuoka Kokuho Database does not contain insurance claims data from the EHI.

The Shizuoka Kokuho Database also contains data on health check-ups, which are performed annually as part of the NHI and LEHI systems on a voluntary basis for those aged > 40 years at designated community centers and medical institutions [11]. A health check-up notification is sent to each household every year, based on the city's family registry. The check-up comprises a physical examination, blood test, and self-reported medical history with a lifestyle survey.

In this study, we considered both the insurance claims data, which included data on prescribed medicines (detailing the year and month of prescription), and the health check-up data for all insured persons enrolled in the NHI and LEHI in the Shizuoka prefecture between April 2012 and March 2018 (2012–2017). These data were tied to individuals by anonymized individual identifiers for research purposes. More details about the database can be found elsewhere [12].

Eligibility criteria for analyses

In this study, we considered only individuals who had health check-up records (aged > 40 years) and could be followed up from 2012 to 2017. The database also included data on the dates when insured persons were enrolled into and withdrew from the NHI and LEHI schemes, and we included only those who were confirmed to have enrolled from 2012 to 2017. Insured persons who withdrew during this period were those who transferred their resident cards to another prefecture or those who transferred their insurance to the EHI scheme.

We included individuals who had health check-ups in both 2012 and 2013. We excluded individuals who self-reported undergoing diabetes treatment or dialysis therapy during the health check-ups between 2012 and 2013. In addition, we excluded those who were newly prescribed with diabetes medications, including injection drugs, between 2012 and 2013; we confirmed this from the insurance claims data [13]. We also excluded those without HbA1c data.

Statistical analyses

The specific objectives of this study were, among people without a history of diabetes, to assess the associations of HbA1c levels at the 2013 health check-up and transition trends in the HbA1c levels from the previous year with the likelihood of initiating diabetes treatment within the next 4 years (by 2017). Treatment initiation was defined as a case in which a drug was prescribed more than once every three months, and whether the treatment was an oral drug or injectable drug was based on the type of drug used in Japan [13].

To evaluate the associations, we constructed two logistic regression models: (1) the associations of the likelihood of initiating diabetes treatment by 2017 with (a) HbA1c levels at a health check-up in 2013, (b) trends in the HbA1c level changes from 2012 to 2013, and (c) number of health check-ups after 2013 and

(2) the associations of the likelihood of using injection drugs among those who began diabetes treatment by 2017 with (a), (b), and (c).

For (a), the HbA1c level was treated as a categorical variable, and upon considering the ease of clinical and policy decision-making as well as sample size, the two groups were as follows: normal group (< 6.5%, including the suspicious zone for prediabetes) and diabetes group (≥ 6.5%) [14,15]. For (b), the trends in HbA1c levels from 2012 to 2013 indicated changes in these groups and were defined as three categories: improving, no change, and worsening. Based on (a) and (b), we created the following categorical variables and included them in the regression models: normal group with no trend changes; normal group with improving trend; diabetes group with no trend changes; and diabetes group with a worsening trend (hereafter referred to as HbA1c Groups A, B, C, and D, respectively).

In the regression models, the selection of variables was based on the backward-stepwise method with a p-to-remove value of > 0.05. Covariates of primary interest, including the HbA1c levels and trends (represented by HbA1c Groups A–D) and number of health check-ups received after 2013 (c), were entered into the models, regardless of their significance and as long as stable models were obtained.

Results

Figure 1 shows the flowchart depicting the selection of the study participants. Between 2012 and 2017, a total of 463,506 individuals had health check-up records and were available for continuous follow-up. Finally, 137,852 participants met the eligibility criteria and were included in the analysis.

The demographic characteristics of the participants stratified by whether they initiated diabetes treatment (treatment group) or not (no-treatment group) by 2017 are presented in Table 1. The mean age was 68.57 years (standard deviation [SD] 9.89) and 69.13 (SD 8.85) years in the non-treatment and treatment group, respectively. The proportion of females was higher in the no-treatment group (females 57.57%; males 42.43%) and that of males was higher in the treatment group (females 43.89%; males 56.11%) (Table 1). Except for the low-density lipoprotein (LDL) cholesterol values and alcohol habits, there were statistically significant differences between the groups in all the clinical data and smoking status.

Table 1
Demographic characteristics of the study participants (n = 137,852)

	No-treatment group (n = 134,537)	Treatment group (n = 3,315)	Difference
Demographic features			
Age, years (mean, SD)	68.57 (9.89)	69.13 (8.85)	< 0.01
Sex (n, %)			< 0.001
Female	77,449 (57.57)	1,455 (43.89)	
Male	57,088 (42.43)	1,860 (56.11)	
Clinical characteristics			
BMI (mean, SD)	22.28 (3.10)	24.17 (3.69)	< 0.001
SBP, mmHg (mean, SD)	128.17 (16.26)	131.98 (15.90)	< 0.001
DBP, mmHg (mean, SD)	74.47 (10.56)	76.02 (10.66)	< 0.001
Triglycerides, mg/dL (mean, SD)	108.76 (65.34)	141.81 (100.28)	< 0.001
HDL, mg/dL (mean, SD)	63.52 (16.56)	56.70 (15.01)	< 0.001
LDL, mg/dL (mean, SD)	124.38 (29.39)	125.11 (31.03)	0.16
GOT, IU/L (mean, SD)	23.69 (9.06)	27.07 (14.74)	< 0.001
GPT, IU/L (mean, SD)	19.35 (11.80)	27.02 (20.18)	< 0.001
γ-GTP, IU/L (mean, SD)	30.18 (34.86)	46.64 (74.68)	< 0.001
HbA1c, % (mean, SD)	5.57 (0.35)	6.62 (0.87)	< 0.001
Hematocrit, % (mean, SD)	41.55 (3.89)	43.04 (4.06)	< 0.001
Hemoglobin, g/dL (mean, SD)	13.60 (1.40)	14.18 (1.48)	< 0.001
RBC, 10^4/μL (mean, SD)	441.68 (43.67)	458.94 (46.97)	< 0.001
Uric acid, mg/dL (mean, SD)	5.17 (1.34)	5.41 (1.31)	< 0.001
Serum creatinine, mg/dL (mean, SD)	0.76 (0.31)	0.78 (0.28)	< 0.001
eGFR, mL/min (mean, SD)	69.25 (14.74)	70.37 (15.64)	< 0.001

[a] Data were compared between groups using unpaired Student's t-test or chi-square test for continuous variables or categorical variables, respectively. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; RBC, red blood cell; eGFR, epidermal growth factor receptor.

	No-treatment group (n = 134,537)	Treatment group (n = 3,315)	Difference
Urine glucose (n, %)			< 0.001
Negative	132,761 (98.68)	2,925 (88.24)	
Trace	665 (0.49)	95 (2.87)	
1+	460 (0.34)	109 (3.29)	
2+	200 (0.15)	71 (2.14)	
3+	164 (0.12)	110 (3.32)	
Urine protein (n, %)			< 0.001
Negative	118,467 (88.06)	2,704 (81.57)	
Trace	10,272 (7.64)	333 (10.05)	
1+	4,172 (3.10)	187 (5.64)	
2+	1,086 (0.81)	64 (1.93)	
3+	250 (0.19)	23 (0.69)	
Anti-hypertensive drugs (n, %)	51,296 (38.13)	1,750 (52.79)	< 0.001
Lipid-lowering drugs (n, %)	32,496 (24.15)	1,090 (32.88)	< 0.001
Medical history (n, %)			
Cerebrovascular disease	5,471 (4.07)	196 (5.91)	< 0.001
Cardiovascular disease	8,384 (6.23)	277 (8.36)	< 0.001
Lifestyle			
Daily smoking (n, %)	11,875 (8.83)	420 (12.67)	< 0.001
Alcohol consumption (n, %)			0.07
Daily	26,793 (19.91)	719 (21.69)	
Sometimes	25,606 (19.03)	635 (19.16)	
Never	74,882 (55.66)	1,788 (53.94)	

[a] Data were compared between groups using unpaired Student's t-test or chi-square test for continuous variables or categorical variables, respectively. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; RBC, red blood cell; eGFR, epidermal growth factor receptor.

The treatment patterns for diabetes by 2017 for all ages and stratified by age groups are shown in Table 2. HbA1c Groups A–D accounted for 97.12%, 0.11%, 0.72%, and 2.05% of the study participants, respectively. In addition, among HbA1c Groups A–D, the proportions of those who initiated diabetes treatment by 2017 were 1.18%, 27.63%, 59.74%, and 39.10%, respectively. Among those who started treatment in 2017, the proportions of those who ended up using injection drugs were 2.85%, 7.14%, 3.23%, and 0.99% in HbA1c Groups A–D, respectively; these proportionate differences across HbA1c Groups A–D were statistically significant. Similar treatment patterns were also observed in the age subgroups.

Table 2
Diabetes treatment patterns by HbA1c levels that were evaluated at the health check-up in 2013 for all ages and by age groups

All ages	**HbA1c level/Trend**				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No trend change (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	133,885 (97.12)	152 (0.11)	986 (0.72)	2,829 (2.05)	137,852 (100.00)
No treatment (n, %)[a]	132,307 (98.82)	110 (72.37)	397 (40.26)	1,723 (60.90)	134,537 (97.60)
Treatment (n, %)	1,578 (1.18)	42 (27.63)	589 (59.74)	1,106 (39.10)	3,315 (2.40)
Oral drug only (n, %)[b]	1,533 (97.15)	39 (92.86)	570 (96.77)	1,095 (99.01)	3,237 (97.65)
Injection drug (n, %)	45 (2.85)	3 (7.14)	19 (3.23)	11 (0.99)	78 (2.35)
40–50 years old	HbA1c Level/Trend				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No trend change (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	5,759 (98.68)	4 (0.07)	26 (0.45)	47 (0.81)	5,836 (100.00)
No treatment (n, %)[a]	5,717 (99.27)	3 (75.00)	6 (23.08)	24 (51.06)	5,750 (98.53)
Treatment (n, %)	42 (0.73)	1 (25.00)	20 (76.92)	23 (48.94)	86 (1.47)

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; Chi-square or Fisher's exact test (when the number of observations was below 5) was used to compare the distributions of the HbA1c levels and trend changes between the no-treatment and treatment groups and between the oral drug only and injection drug groups; HbA1c, hemoglobin A1c.

All ages	HbA1c level/Trend				
Oral drug only (n, %)[b]	41 (97.62)	0 (0.00)	17 (85.00)	23 (100.00)	81 (94.19)
Injection drug (n, %)	1 (2.38)	1 (100.00)	3 (15.00)	0 (0.00)	5 (5.81)
50–60 years old	HbA1c Level/Trend				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No trend change (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	12,002 (97.96)	13 (0.11)	72 (0.59)	165 (1.35)	12,252 (100.00)
No treatment (n, %)[a]	118,79 (98.98)	9 (69.23)	24 (33.33)	96 (58.18)	12,008 (98.01)
Treatment (n, %)	123 (1.02)	4 (30.77)	48 (66.67)	69 (41.82)	244 (1.99)
Oral drug only (n, %)	119 (96.75)	4 (100.00)	44 (91.67)	69 (100.00)	236 (96.72)
Injection drug (n, %)	4 (3.25)	0 (0.00)	4 (8.33)	0 (0.00)	8 (3.28)
60–70 years old	HbA1c Level/Trend				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No trend change (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	65,307 (96.88)	93 (0.14)	509 (0.76)	1,504 (2.23)	67,413 (100.00)
No treatment (n, %)[a]	64,560 (98.86)	68 (73.12)	192 (37.72)	913 (60.70)	65,733 (97.51)

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; Chi-square or Fisher's exact test (when the number of observations was below 5) was used to compare the distributions of the HbA1c levels and trend changes between the no-treatment and treatment groups and between the oral drug only and injection drug groups; HbA1c, hemoglobin A1c.

All ages	HbA1c level/Trend				
Treatment (n, %)	747 (1.14)	25 (26.88)	317 (62.28)	591 (39.30)	1,680 (2.49)
Oral drug only (n, %)[c]	724 (96.92)	23 (92.00)	313 (98.74)	584 (98.82)	1,644 (97.86)
Injection drug (n, %)	23 (3.08)	2 (8.00)	4 (1.26)	7 (1.18)	36 (2.14)
70–80 years old	HbA1c Level/Trend				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No trend change (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	28,827 (96.71)	25 (0.08)	239 (0.80)	717 (2.41)	29,808 (100.00)
No treatment (n, %)[a]	28,417 (98.58)	17 (68.00)	115 (48.12)	444 (61.92)	28,993 (97.27)
Treatment (n, %)	410 (1.42)	8 (32.00)	124 (51.88)	273 (38.08)	815 (2.73)
Oral drug only (n, %)	399 (97.32)	8 (100.00)	121 (97.58)	272 (99.63)	800 (98.16)
Injection drug (n, %)	11 (2.68)	0 (0.00)	3 (2.42)	1 (0.37)	15 (1.84)
> 80 years old	HbA1c Level/Trend				
	Normal/No trend change (HbA1c Group A)	Normal/Improving trend (HbA1c Group B)	Diabetes/No change trend (HbA1c Group C)	Diabetes/Worsening trend (HbA1c Group D)	Total
Total (n, % in row)	21,990 (97.55)	17 (0.08)	140 (0.62)	396 (1.76)	22,543 (100.00)

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; Chi-square or Fisher's exact test (when the number of observations was below 5) was used to compare the distributions of the HbA1c levels and trend changes between the no-treatment and treatment groups and between the oral drug only and injection drug groups; HbA1c, hemoglobin A1c.

All ages	HbA1c level/Trend				
No treatment (n, %)[a]	21,734 (98.84)	13 (76.47)	60 (42.86)	246 (62.12)	22,053 (97.83)
Treatment (n, %)	256 (1.16)	4 (23.53)	80 (57.14)	150 (37.88)	490 (2.17)
Oral drug only (n, %)	250 (97.66)	4 (100.00)	75 (93.75)	147 (98.00)	476 (97.14)
Injection drug (n, %)	6 (2.34)	0 (0.00)	5 (6.25)	3 (2.00)	14 (2.86)

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$; Chi-square or Fisher's exact test (when the number of observations was below 5) was used to compare the distributions of the HbA1c levels and trend changes between the no-treatment and treatment groups and between the oral drug only and injection drug groups; HbA1c, hemoglobin A1c.

The results of the logistic regression analyses are shown in Table 3. After adjusting for covariates, the HbA1c levels and trend changes at a health check-up in 2013 were significantly associated with the likelihood of initiating diabetes treatment by 2017, with an odds ratio (OR) of 22.64 (95% confidence interval [CI] 14.66–34.99) for HbA1c Group B, 90.83 (95% CI 76.33–108.08) for HbA1c Group C, and 36.95 (95% CI 33.10–41.26) for HbA1c Group D compared to that for HbA1c Group A. The number of health check-ups received demonstrated no statistically significant association with the initiation of diabetes treatment.

Table 3
Adjusted odds ratios for diabetes treatment versus no treatment among all participants (Model 1) and for injection drug use versus only oral drug use among those treated for diabetes (Model 2)

	Model 1		Model 2	
Variables	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
HbA1c level/Trend				
Normal/No trend change (HbA1c Group A)	Ref.		3.62 (1.63–8.04)	< 0.01
Normal/Improving trend (HbA1c Group B)	22.64 (14.66–34.99)	< 0.001	10.93 (2.63–45.37)	< 0.01
Diabetes/No trend change (HbA1c Group C)	90.83 (76.33–108.08)	< 0.001	1.97 (0.77–5.07)	0.16
Diabetes/Worsening trend (HbA1c Group D)	36.95 (33.10–41.26)	< 0.001	Ref.	
Number of health check-ups after 2013				
0	Ref.		Ref.	
1	0.84 (0.66–1.08)	0.19	0.52 (0.20–1.38)	0.19
2	0.99 (0.79–1.25)	0.94	0.45 (0.18–1.14)	0.09
3	1.04 (0.84–1.29)	0.73	0.24 (0.09–0.61)	< 0.01
4	0.88 (0.72–1.07)	0.20	0.19 (0.09–0.42)	< 0.001
Age, years	1.01 (1.00–1.01)	0.08	0.98 (0.95–1.01)	0.17
Sex				
Female	1.05 (0.92–1.20)	0.48	1.13 (0.63–2.05)	0.68
Male	Ref.		Ref.	
BMI	1.08 (1.07–1.10)	< 0.001	–	

CI, confidence interval; HbA1c, hemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase; eGFR, epidermal growth factor receptor.

	Model 1		Model 2	
SBP, mmHg	1.01 (1.00–1.01)	< 0.001	–	
DBP, mmHg	0.99 (0.98–0.99)	< 0.001	–	
Triglyceride, mg/dL	1.00 (1.00–1.00)	< 0.01		
HDL, mg/dL	0.99 (0.99–0.99)	< 0.001	1.02 (1.00–1.03)	0.06
GOT, IU/L	0.99 (0.99–1.00)	0.06	–	
GPT, IU/L	1.01 (1.01–1.02)	< 0.001	–	
γ-GTP, IU/L	1.00 (1.00–1.00)	< 0.001	–	
Hemoglobin, g/dL	1.10 (1.05–1.14)	< 0.001	–	
Uric acid, mg/dL	–		–	
Serum creatinine, mg/dL	1.31 (0.99–1.71)	0.06	–	
eGFR, mL/min	1.01 (1.00–1.01)	< 0.001		
Urine glucose				
Negative	Ref.		Ref.	
Trace	1.19 (0.84–1.69)	0.33	3.18 (1.01–10.00)	< 0.05
1+	1.69 (1.20–2.37)	< 0.01	1.27 (0.29–5.64)	0.75
2+	2.47 (1.55–3.92)	< 0.001	4.72 (1.45–15.36)	< 0.05
3+	2.39 (1.58–3.63)	< 0.001	2.65 (0.83–8.44)	0.10
Urine protein (n, %)				

CI, confidence interval; HbA1c, hemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase; eGFR, epidermal growth factor receptor.

	Model 1		Model 2	
Negative	Ref.		Ref.	
Trace	1.14 (0.97–1.33)	0.10	1.39 (0.60–3.22)	0.44
1+	1.27 (1.02–1.57)	< 0.05	2.24 (0.92–5.47)	0.08
2+	1.21 (0.82–1.80)	0.34	1.89 (0.42–8.49)	0.41
3+	1.59 (0.85–2.98)	0.15	–	
Anti-hypertensive drugs	1.32 (1.19–1.47)	< 0.001	–	
Lipid-lowering drugs	1.37 (1.24–1.52)	< 0.001	0.37 (0.17–0.78)	< 0.01
Medical history				
Cerebrovascular disease	1.19 (0.97–1.46)	0.09	–	
Daily smoking	1.14 (0.98–1.33)	0.08	–	

CI, confidence interval; HbA1c, hemoglobin A1c; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase; γ-GTP, gamma-glutamyl transpeptidase; eGFR, epidermal growth factor receptor.

Among participants who initiated diabetes treatment by 2017, whether the treatment led to the use of injection drugs was significantly associated with HbA1c levels and trends at a health check-up in 2013, with an OR of 3.62 (95% CI 1.63–8.04) for the HbA1c Group A and 10.93 (95% CI 2.63–45.37) for the HbA1c Group B compared to the reference group HbA1c Group D. From 2014 to 2017, those who received three or more health check-ups had lower odds of using injection drugs as a treatment for diabetes than those who never received one; an OR of 0.24 (95% CI 0.09–0.61) when participants received three health check-ups and 0.19 (95% CI 0.09–0.42) when they received four health check-ups.

Discussion

Our study found that compared to the normal group with no changes in HbA1c levels (HbA1c Group A) detected at a health check-up in 2013, the normal group whose HbA1c levels improved (HbA1c Group B) was more likely to start treatment for diabetes within 4 years. This finding suggests that when HbA1c levels demonstrate an improving trend, physicians and patients might be less likely to pay sufficient attention to lifestyle habits and other factors related to diabetes, which could result in treatment initiation [16]. In addition, in the diabetes group with no trend changes (HbA1c Group C), the diabetes group with

worsening trend (HbA1c Group D) was less likely to start treatment within 4 years (OR 0.41; 95% CI 0.34–0.49) (data not shown).

In addition, among people who initiated diabetes treatment by 2017, diabetes treatment was significantly more likely to lead to the use of injection drugs in the normal group with both no HbA1c level changes and improving HbA1c level trends than the diabetes group with worsening trends. Similarly, good control of HbA1c levels, as indicated by the results of the health check-ups, might have led to insufficient attention to lifestyle habits, which might have resulted in a deterioration of glycemic control and led to the initiation of using injection drugs [17,18].

Our study also found that people who underwent health check-ups annually were less likely to start using injection drugs. This finding may not necessarily demonstrate a causal relationship between health screening specifically and diabetes incidence; it may be attributed to the fact that people who are more concerned about their health are more likely to undergo health check-ups more frequently [19]. However, previous studies have suggested that health check-ups might be useful in screening for lifestyle-related diseases to a certain extent [20–22], and it will continue to play a role in preventing the onset and worsening of diabetes if appropriate interventions are implemented.

To the best of our knowledge, this is the first study to empirically analyze the extent to which factors related to clinical practice and healthcare seeking (i.e., health check-ups) are associated with the future risk of diabetes development and worsening. However, our study had some limitations. Participating in annual health check-ups is voluntary; therefore, people who were concerned about their own health were more likely to be included in the study. Furthermore, the health check-up data were limited to those aged > 40 years, data of insured persons enrolled in the EHI scheme were not considered, and only participants in the Shizuoka prefecture were included in the study, which was not representative of the whole country. Therefore, our findings may not be generalizable to a wider population. Although glucagon-like peptide-1 (GLP-1) agonists were classified as injection drugs in the present analysis, GLP-1 agonists tend to be used as first-line agents in Japan; however, insulin, which is also classified as an injection drug, is used mainly for patients with severe diabetes. Thus, although GLP-1 agonists are injection drugs, they may not be appropriate indicators of the severity of diabetes. GLP-1 agonists were intentionally classified as an oral drug for sensitivity analysis; however, the results were unchanged. One possible reason for this may be that during the study period (2012–2017), the introduction of GLP-1 agonists was not yet widespread and only few patients were prescribed them in the Shizuoka prefecture. Finally, those with type 1 and 2 diabetes were not differentiated in our study. However, most of the people aged 40 and older who were diagnosed with diabetes were likely to have type 2 diabetes because of its higher prevalence in the general population (approximately 95%) [23,24]; hence, it can be assumed that most of the participants who initiated treatment in this study had type 2 diabetes.

Conclusions

Our study showed that people with normal HbA1c levels with an increasing trend were more likely to be at a higher risk of subsequent development of diabetes and initiate treatment with injection drugs than people of the other groups. These findings suggest that although current health check-ups provide health guidance for people at high risk of lifestyle diseases, this guidance may tend to focus only more on people who already have higher HbA1c levels, have worsening HbA1c level trend, or have poorly controlled HbA1c levels. Further guidance about preventive health behaviors and lifestyle measures to lower the risk of diabetes development should also be imparted to those who present with normal HbA1c levels during health check-ups.

Declarations

Ethical approval and consent to participate

The Research Ethics Committee of Shizuoka General Hospital approved this study (authorization number SGHIRB#2019100) and waived the need for informed consent as this study was a secondary analysis of anonymized data. All methods were carried out in accordance with STROBE Statement to report our observational study.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Shizuoka General Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Shizuoka General Hospital.

Authors' contributions

SN, HS, SK, HK, and HM conceived and designed the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. SN, KS, HY, SK, NI, HK, and HM acquired the data. SN conducted statistical analysis and all authors contributed to interpreting the results. SN, HS, and SKR drafted the article. All authors made critical revision of the manuscript for important intellectual content and gave final approval for the manuscript. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding bodies.

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Competing interests

None declared.

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Figures

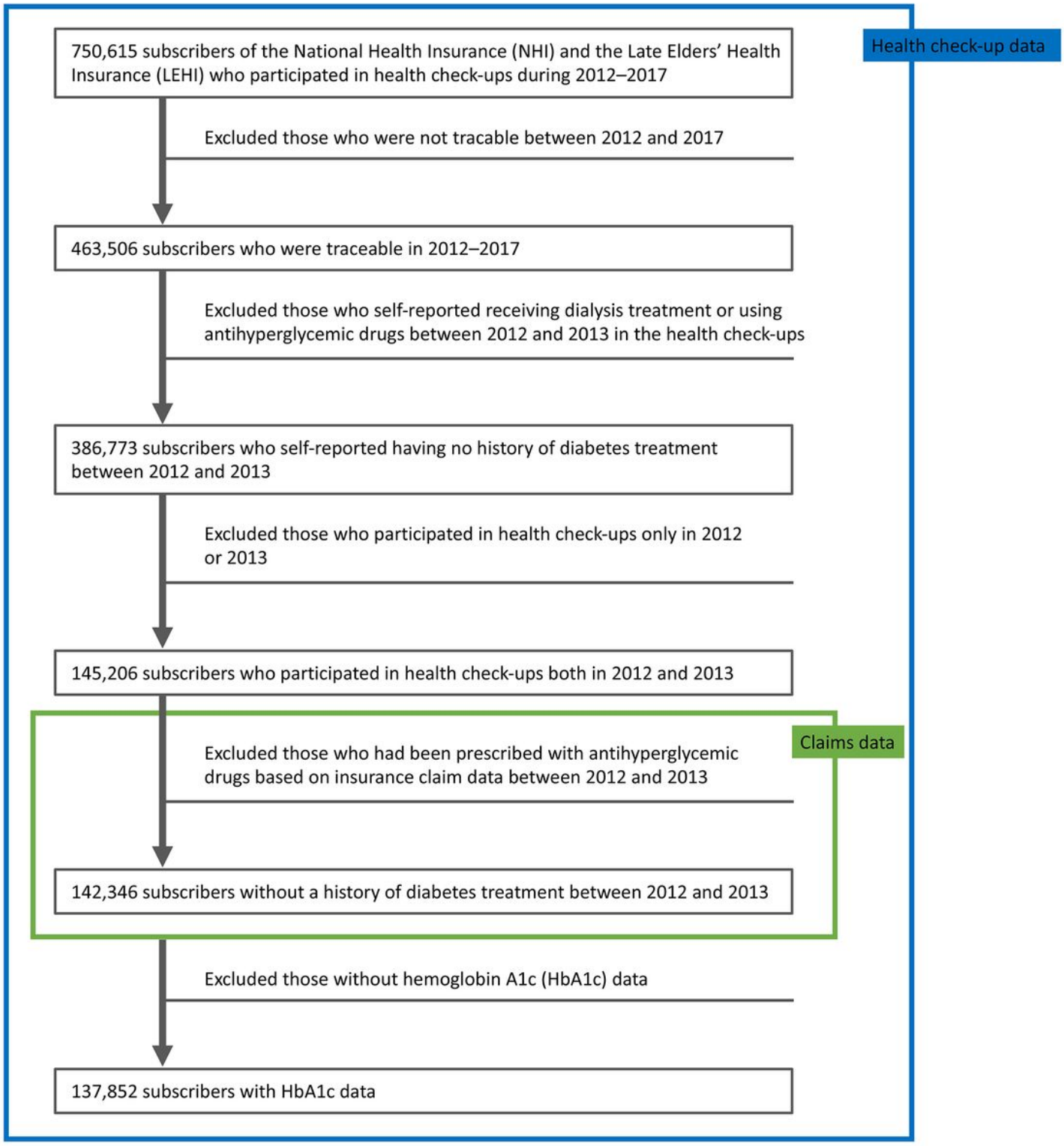

Figure 1

Flowchart of the participant selection process