

Association between variability in body mass index and development of type 2 diabetes: Panasonic cohort study

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To cite: Okada H, Hamaguchi M, Habu M, *et al.* Association between variability in body mass index and development of type 2 diabetes: Panasonic cohort study. *BMJ Open Diab Res Care* 2021;**9**:e002123. doi:10.1136/bmjdr-2021-002123

Received 9 January 2021
Revised 26 February 2021
Accepted 28 March 2021

ABSTRACT

Introduction Contrasting results have been reported for the association between the variability in body weight and development of diabetes. In the present study, we evaluated the association between the variability in body mass index (BMI) and development of type 2 diabetes in 19 412 Japanese participants without obesity and without body weight gain or loss during the study period.

Research design and methods We recorded body weight of the participants consecutively each year in Panasonic Corporation, Osaka, Japan from 2008 to 2014 to evaluate the variability of BMI. The participants with obesity (BMI ≥ 25 kg/m²) at baseline and body weight gain or loss from 2008 to 2014 (delta BMI $\geq \pm 1$ kg/m²) were excluded from the study. In total, 416 participants developed type 2 diabetes from 2015 to 2018. We used coefficient of variation (CV) to represent the variability in BMI during 6 years of the study period.

Results Cox regression analyses revealed that the risk of developing type 2 diabetes was higher in the fourth quartile (HR 1.33; 95% CI 1.01 to 1.75) of CV of BMI than that in the first quartile (lowest quartile) of CV of BMI after adjusting for multiple confounding factors. The risk for developing diabetes increased by 11.1% per 1% increase in CV of BMI.

Conclusions In conclusion, the variability in BMI is a risk factor for the development of diabetes in the Japanese population without obesity and without body weight gain or loss.

INTRODUCTION

In recent years, the prevalence of diabetes has increased globally and the medical costs have shown a similar trend. Therefore, the prevention of the development of diabetes is a common concern in clinical care settings. It has been well established that several risk factors including obesity accelerate the development of diabetes. Several studies have investigated the association between variability in body weight and development of diabetes.^{1–7} Some studies have reported that the presence of obesity and variability in body weight is a risk factor for the development of diabetes.^{3–6,7} In contrast, several studies have suggested that instead of variability in body weight, baseline body mass index (BMI) is

Significance of this study

What is already known about this subject?

- ▶ Obesity or body weight gain accelerate the development of diabetes.
- ▶ The association between the variability in body weight and development of diabetes is controversial.

What are the new findings?

- ▶ The risk for developing diabetes increased by 11.1% per 1% increase in coefficient of variation of body mass index (BMI).
- ▶ The risk for developing diabetes increased by 15.0% per 1% increase in coefficient of variation of BMI in participants without impaired fasting glucose at baseline.
- ▶ The variability in BMI is a risk factor for the development of diabetes in population without obesity and without body weight gain or loss.

How might these results change the focus of research or clinical practice?

- ▶ The variability in BMI is noteworthy to reduce the risk of the development of diabetes in population without obesity and without weight gain or loss.

a strong risk factor for the development of diabetes.^{1,4,5} The association between the variability in body weight and development of diabetes is controversial. One of the underlying reasons for contrasting results among the studies is the difference in definition of the variability in body weight. Other underlying reasons may be the differences in the duration of study, cohort size and/or accuracy of recording body weight. Moreover, we consider two significant reasons for the contrasting associations reported between variability in body weight and development of diabetes. First, the presence of obesity at baseline and body weight gain during the study period can lead to the development of diabetes. Body weight loss during study period can prevent for the development of diabetes. Although body weight at baseline and body weight gain or loss during the study period



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can affect the development of diabetes, many studies have not elucidated these effects. Second, the difference in race can influence the development of diabetes. The BMI of Japanese patients with diabetes is similar to that of the Japanese population as a whole.⁸ Variability in body weight may be more significant than the body weight at baseline in the Japanese population without obesity.

To the best of our knowledge, no study has elucidated the association between the variability in body weight and the development of type 2 diabetes in a population without obesity and without body weight gain or loss during the study period. Therefore, the present study, for the first time, investigated the association between the variability in BMI and the development of type 2 diabetes in the Japanese population without obesity and without body weight gain or loss during the study period.

MATERIALS AND METHODS

Study design and data collection

The present long-term retrospective cohort study comprised participants from a medical health check-up program, which was conducted in Panasonic Corporation, Osaka, Japan. The purpose of this program was to promote public health through the early detection of chronic diseases including metabolic disorders and the evaluation of their underlying risk factors. All employees participate in this program every year. The employer shall, as provided for by the Ordinance of the Ministry of Health, Labor and Welfare, have medical examinations of workers conducted by a physician. The present study used the data collected between 2008 and

2018, which were retrieved from the database named Panasonic cohort study.

The blood samples were collected after >10 hours of fasting. Body weight and height were recorded using an automatic weight and height machine. The participants wore only underwear when their body weight and height were recorded. The baseline characteristics were assessed using the self-administered questionnaire, which was standardized and has been previously validated. Forty-one items were included in the questionnaire. The participants were classified as non-smokers, past smokers and current smokers. Eating speed was classified as fast, normal and slow. The participants were asked about their habit of breakfast. The participants who consumed alcohol daily were classified as alcohol drinkers. The participants who played any sport twice a week regularly were classified as regular exercisers. Type 2 diabetes was defined by fasting plasma glucose level ≥ 126 mg/dL, having a self-reported history of diabetes and/or the use of antidiabetic medication. Impaired fasting glucose (IFG) was defined by the fasting plasma glucose level of 110–125 mg/dL. The variability in BMI was assessed from 2008 to 2014. The development of type 2 diabetes was assessed every year from 2015 to 2018.

Exclusion criteria

In total, 140 590 employees underwent a medical health check-up in 2008. The participants who did not undergo health check-up consecutively from 2008 to 2018 were excluded (n=65 256) from the study. The participants

Table 1 Characteristics of participants at baseline

	All	Development of diabetes (-)	Development of diabetes (+)	P value
N	19 412	18 996	416	-
Age (years)	42.16 (6.05)	42.1 (6.06)	44.8 (4.97)	<0.0001
Sex (male/female)	15 909/3503	15 513/3483	396/20	<0.0001
BMI at baseline (kg/m ²)	21.54 (2.04)	21.52 (2.04)	22.50 (1.81)	<0.0001
SBP (mm Hg)	116.11 (13.16)	115.98 (13.1)	121.63 (14.50)	<0.0001
DBP (mm Hg)	72.49 (10.15)	72.39 (10.12)	76.84 (10.55)	<0.0001
LDL cholesterol (mg/dL)	119.58 (29.93)	119.36 (29.758)	129.72 (34.64)	<0.0001
HDL cholesterol (mg/dL)	62.19 (15.13)	62.3 (15.14)	57.43 (14.18)	<0.0001
Triglycerides (mg/dL)	101.13 (76.79)	100.5 (76.58)	131.94 (80.08)	<0.0001
Glucose (mg/dL)	91.57 (8.17)	91.30 (7.93)	103.65 (9.762)	<0.0001
Uric acid (mg/dL)	5.69 (1.33)	5.68 (1.33)	6.21 (1.39)	<0.0001
Smoking (none/past/current)	10 363/2579/6470	10 205/2530/6261	158/49/209	<0.0001
Eating speed (fast/normal/slow)	5660/12 163/1589	5504/11 932/1570	156/241/19	<0.0001
Skipping breakfast (+/-)	4133/15 279	4018/14 978	115/301	0.001
Alcohol drinker (+/-)	5192/14 220	5039/13 957	153/263	<0.0001
Physical exercise (+/-)	2958/16 454	2889/16 107	69/347	0.44
CV of BMI (%)	2.22 (0.96)	2.21 (0.96)	2.30 (1.04)	0.037

Data are presented as mean (SD) or absolute number.

BMI, body mass index; CV, coefficient of variation; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

with diabetes at baseline and the participants who developed diabetes during the data collection for variability in BMI were excluded (n=5614) from the study. We excluded participants with obesity at baseline and with body weight gain or loss from 2008 to 2014. We defined body weight gain or loss as an increase or decrease of >1 kg/m² of BMI based on previous studies.^{9–11} The participants with obesity (BMI ≥ 25 kg/m²) at baseline and body weight gain or loss from 2008 to 2014 (delta BMI $\geq \pm 1$ kg/m²) were excluded (n=26 321) from the study. The participants with missing data were also excluded (n=23 987).

Variability in BMI

We collected BMI data consecutively from 2008 to 2014 to evaluate the variability in BMI. We calculated the coefficient of variation (CV) of BMI to assess the variability of BMI from 2008 to 2014. The CV was calculated as follows: CV=SD \times 100/average BMI.¹² Because we need to consider the effect of change in BMI after data collection of CV of BMI, we assessed change in BMI from 2015 to the end of the study. We defined change in BMI after data collection as the difference between BMI at the end of the study and that in 2015.

Statistical analyses

The means and frequencies of potential confounding variables were calculated. The differences in general characteristics at baseline according to the development of diabetes at follow-up were assessed by the t-test and χ^2 test as appropriate. The CV of BMI were divided into quartiles: <1.56 , 1.56–2.03, 2.04–2.65 and $>2.65\%$ in all participants

or <1.56 , 1.56–2.03, 2.04–2.66 and $>2.67\%$ in the participants without IFG at baseline. The association between the variability in BMI and the development of type 2 diabetes was evaluated by Cox regression analyses using multivariate models. Quartiles of CV of BMI and continuous variable of CV of BMI were added in model 1 and model 2, respectively. Covariates included in the multivariate model are the factors associated with the development of type 2 diabetes. Multivariate model was adjusted for age, sex, BMI at baseline, change in BMI after data collection, systolic blood pressure (SBP), levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose at baseline, smoking status, eating speed, skipping breakfast, alcohol consumption and physical exercise. We also assessed the association between the variability in BMI and the development of type 2 diabetes in patients without IFG at baseline who were likely to develop diabetes. All continuous variables are presented as mean \pm SD or absolute number. The differences with p value <0.05 were considered statistically significant. The associations are presented as HRs with 95% CI. The statistical analyses were performed using JMP software, V.10 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The baseline characteristics of the participants enrolled in this study are shown in table 1. Table 2 shows the baseline characteristics of the participants without IFG at baseline. In total, 416 participants among all participants

Table 2 Characteristics of the participants without impaired fasting glucose at baseline

	All	Development of diabetes (–)	Development of diabetes (+)	P value
N	19 031	18 716	315	–
Age (years)	42.11 (6.06)	42.07 (6.06)	44.54 (5.14)	<0.0001
Sex (male/female)	15 542/3489	15 245/3471	297/18	<0.0001
BMI at baseline (kg/m ²)	21.53 (2.04)	21.52 (2.04)	22.56 (1.79)	<0.0001
SBP (mm Hg)	115.92 (13.06)	115.84 (13.02)	120.76 (14.40)	<0.0001
DBP (mm Hg)	72.35 (10.10)	72.28 (10.07)	76.71 (10.92)	<0.0001
LDL cholesterol (mg/dL)	119.45 (29.85)	119.28 (29.73)	129.21 (35.17)	<0.0001
HDL cholesterol (mg/dL)	62.23 (15.13)	62.30 (15.14)	57.70 (14.21)	<0.0001
Triglycerides (mg/dL)	100.36 (73.45)	99.83 (73.26)	131.73 (78.32)	<0.0001
Glucose (mg/dL)	91.10 (7.53)	90.96 (7.45)	99.77 (7.45)	<0.0001
Uric acid (mg/dL)	5.68 (1.33)	5.67 (1.33)	6.21 (1.37)	<0.0001
Smoking (non/past/current)	10 183/2518/6330	10 071/2477/6168	112/41/162	<0.0001
Eating speed (fast/normal/slow)	5543/11 917/1571	5429/11 730/1557	114/187/14	0.003
Skipping breakfast (+/–)	4046/14 985	3957/14 759	89/226	0.002
Alcohol drinker (+/–)	5040/13 991	4928/13 788	112/203	0.002
Physical exercise (+/–)	2892/16 139	2838/15 878	54/261	0.34
CV of BMI (%)	2.22 (0.96)	2.21 (0.96)	2.35 (1.08)	0.016

Data are presented as mean (SD) or absolute number.

BMI, body mass index; CV, coefficient of variation; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Table 3 Multivariate adjusted HRs for development of diabetes in all participants

	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.04 (1.02 to 1.06)	<0.0001	1.04 (1.02 to 1.06)	<0.0001
Sex (male)	1.08 (0.68 to 1.79)	0.77	1.08 (0.69 to 1.80)	0.75
BMI at baseline	1.12 (1.06 to 1.19)	0.0002	1.12 (1.06 to 1.19)	0.0002
Change in BMI after data collection	0.99 (0.90 to 1.09)	0.87	0.99 (0.90 to 1.09)	0.85
CV of BMI quartile 1 (ref)	1	–	–	–
Quartile 2	1.10 (0.83 to 1.46)	0.50	–	–
Quartile 3	1.06 (0.80 to 1.42)	0.67	–	–
Quartile 4	1.33 (1.01 to 1.75)	0.03	–	–
CV of BMI	–	–	1.11 (1.01 to 1.22)	0.03
Systolic blood pressure	1.003 (0.996 to 1.01)	0.39	1.003 (0.996 to 1.01)	0.36
LDL cholesterol	1.002 (0.999 to 1.005)	0.17	1.002 (0.999 to 1.006)	0.16
HDL cholesterol	0.99 (0.98 to 0.999)	0.02	0.99 (0.98 to 0.999)	0.02
Triglycerides	0.9999 (0.999 to 1.0009)	0.93	0.9999 (0.999 to 1.0009)	0.89
Glucose	1.14 (1.13 to 1.16)	<0.0001	1.14 (1.13 to 1.16)	<0.0001
Smoking (past) (ref: none)	0.88 (0.63 to 1.21)	0.42	0.87 (0.62 to 1.20)	0.42
Smoking (current) (ref: none)	1.81 (1.45 to 2.25)	<0.0001	1.81 (1.45 to 2.25)	<0.0001
Eating speed (slow) (ref: normal)	0.83 (0.50 to 1.28)	0.41	0.83 (0.50 to 1.29)	0.42
Eating speed (fast) (ref: normal)	1.27 (1.04 to 1.56)	0.02	1.27 (1.03 to 1.55)	0.02
Skipping breakfast (yes) (ref: no)	1.17 (0.93 to 1.46)	0.17	1.17 (0.93 to 1.46)	0.17
Alcohol drinker (yes) (ref: no)	1.03 (0.83 to 1.27)	0.77	1.04 (0.84 to 1.28)	0.72
Physical exercise (yes) (ref: no)	1.08 (0.82 to 1.39)	0.59	1.08 (0.82 to 1.39)	0.60

BMI, body mass index; CV, coefficient of variation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ref, reference.

(315 participants among those without IFG at baseline) developed type 2 diabetes from 2015 to 2018.

Tables 3 and 4 show the adjusted HRs in multivariate models for the development of diabetes in all participants or in the participants without IFG at baseline. The risk of developing type 2 diabetes was higher in the fourth quartile of CV of BMI than that in the lowest quartile (first quartile) of CV of BMI in all participants and in those without IFG at baseline (model 1; HR 1.33; 95% CI 1.01 to 1.75 and HR 1.51; 95% CI 1.10 to 2.08, respectively). The risk for developing diabetes increased by 11.1% and 15.0% per 1% increase in CV of BMI in all participants and in those without IFG at baseline, respectively (model 2). Age, BMI at baseline, HDL cholesterol, glucose, current smoking habit and fast eaters were also associated with the increased odds of developing type 2 diabetes in all participants. Age, BMI at baseline, glucose and current smoking habit were associated with the increased odds of developing type 2 diabetes in the participants without IFG at baseline. If we change the combination of period for data collection of CV of BMI and follow-up as follows: 2008–2012 and 2013–2018, 2008–2013 and 2014–2018 or 2008–2015 and 2016–2018 respectively, the HR per

1% increase in CV of BMI was 1.04 (95% CI 0.93 to 1.15, $p=0.50$), 1.13 (95% CI 1.03 to 1.24, $p=0.013$) or 1.15 (95% CI 1.03 to 1.37, $p=0.0086$) in all participants.

DISCUSSION

The CV of BMI was associated with the increased odds of the development of type 2 diabetes. The main results were identified if the participants with IFG at baseline were excluded. The major finding of the present study is that the variability in BMI is an independent risk factor for the development of type 2 diabetes in a Japanese population. When CV of BMI and the development of type 2 diabetes were assessed from 2008 to 2012 and from 2013 to 2018, we found no association between CV of BMI and the development of type 2 diabetes because the period for data collection for CV of BMI might be short.

The association between the variability in body weight and the development of diabetes is still controversial. Although many studies have evaluated the effect of body weight or BMI at baseline on the development of diabetes, few studies have evaluated the effect of body weight gain or loss. A study evaluated the association

Table 4 Multivariate adjusted HRs for the development of diabetes in the participants without impaired fasting glucose at baseline

	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.04 (1.01 to 1.06)	0.002	1.04 (1.01 to 1.06)	0.002
Sex (male)	0.98 (0.60 to 1.68)	0.92	0.98 (0.61 to 1.69)	0.95
BMI at baseline	1.15 (1.07 to 1.23)	0.0002	1.15 (1.07 to 1.23)	0.0002
Change in BMI after data collection	0.97 (0.87 to 1.08)	0.59	0.97 (0.87 to 1.08)	0.57
CV of BMI quartile 1 (ref)	1	–	–	–
Quartile 2	1.16 (0.83 to 1.62)	0.50	–	–
Quartile 3	1.17 (0.84 to 1.64)	0.67	–	–
Quartile 4	1.51 (1.10 to 2.08)	0.01	–	–
CV of BMI	–	–	1.15 (1.04 to 1.28)	0.006
Systolic blood pressure	1.005 (0.997 to 1.01)	0.23	1.005 (0.997 to 1.01)	0.22
LDL cholesterol	1.003 (0.999 to 1.007)	0.10	1.003 (0.999 to 1.007)	0.10
HDL cholesterol	0.997 (0.99 to 1.006)	0.50	0.997 (0.99 to 1.006)	0.49
Triglycerides	1.0008 (0.9997 to 1.002)	0.16	1.0008 (0.9997 to 1.002)	0.16
Glucose	1.16 (1.14 to 1.18)	<0.0001	1.16 (1.14 to 1.18)	<0.0001
Smoking (past) (ref: none)	1.11 (0.77 to 1.59)	0.56	1.11 (0.76 to 1.58)	0.58
Smoking (current) (ref: none)	2.12 (1.64 to 2.75)	<0.0001	2.12 (1.64 to 2.74)	<0.0001
Eating speed (slow) (ref: normal)	0.70 (0.39 to 1.17)	0.18	0.70 (0.39 to 1.17)	0.19
Eating speed (fast) (ref: normal)	1.19 (0.94 to 1.50)	0.15	1.19 (0.94 to 1.50)	0.15
Skipping breakfast (yes) (ref: no)	1.22 (0.94 to 1.56)	0.14	1.21 (0.93 to 1.56)	0.15
Alcohol drinker (yes) (ref: no)	0.98 (0.76 to 1.25)	0.86	0.98 (0.77 to 1.25)	0.88
Physical exercise (yes) (ref: no)	1.16 (0.86 to 1.55)	0.33	1.16 (0.86 to 1.55)	0.33

BMI, body mass index; CV, coefficient of variation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ref, reference.

between variability in body weight and body weight gain or loss and reported the association between the variability in body weight and the development of diabetes.¹³ However, the duration of this study was very short and the variability in body weight was calculated for the data of only 2–3 years.¹³ The authors defined the weight-stable group with the change in body weight $<\pm 5\%$.¹³ However, we consider that the $\pm 5\%$ change in body weight during 2–3 years was large and unstable. Therefore, the exact effect of body weight gain or loss was not assessed. In the present analysis, we excluded the participants with obesity (BMI ≥ 25 kg/m²) at baseline and body weight gain or loss during 6 years period (delta BMI $\geq \pm 1$ kg/m²). Body weight was recorded in accuracy using an automatic weight and height machine in this study. Moreover, we have added change in BMI after data collection of the variability of BMI to multivariate models in order to exclude the effect of change in BMI after data collection of the variability of BMI.

It is unclear how the variability in body weight causes the development of diabetes. There were several reports which assess the association between the variability in body weight and glucose tolerance. A study reported the association between the variability in body weight and fatty acid metabolism.¹⁴ It was found that the variability in body weight was associated with an increase in the

size of adipocytes and the amount of lipogenic enzymes, including fatty acid synthase, acetyl-CoA carboxylase, malic enzyme, pyruvate kinase and lipoprotein lipase in an animal model.¹⁴ Additionally, it has been reported that the variability in body weight is associated with the increase in the amounts of myristic acid, palmitic acid, palmitoleic acid and stearic acid, which leads to the impairment in glucose metabolism.¹⁵ In contrast, the variability in body weight has been associated with the decrease in the amounts of linoleic acid and α -linolenic acid, which leads to the improvement in glucose metabolism.^{16 17} Tamakoshi *et al*¹⁸ have reported that the variability in body weight is associated with elevated C reactive protein among Japanese population. Elevated C reactive protein is known as the predictor of the development of diabetes.¹⁹ Chronic inflammation, which is caused by variability in body weight, might be associated with the development of diabetes. We should also consider the differences among races while accounting for the association between variability in body weight and the development of diabetes. The prevalence of obesity is lower in Asian populations than in the Western populations. The BMI of Japanese patients with diabetes is similar to that in the general Japanese population.⁸ This characteristic finding is important to be considered when evaluating the association between the variability in body weight

and the development of diabetes. Asian populations may be more susceptible to variations in body weight than Western populations. It has been reported that the variability in body weight can cause hyperinsulinemia.²⁰ The disturbance of insulin secretion, which is characteristic in Asian patients with diabetes, might be related to vulnerability to variability in body weight.

The strengths of our study are long study duration and large sample size. Moreover, the data of body weight are accurate. However, this study has several limitations. First, hemoglobin A1c (HbA1c) level was not included for the diagnosis of diabetes. Because we have no data on HbA1c, however a previous study had reported that the correlation coefficient between fasting glucose level and HbA1c level was 0.85,²¹ we considered that it was acceptable to assess the development of diabetes through fasting glucose levels and a self-reported history of diabetes. Second, the use of diuretics and psychoactive drugs could affect the variability in BMI. Unfortunately, however, we have no data about the use of diuretics and psychoactive drugs. Third, the study population consisted of Japanese men and women and they are relatively young. Therefore, it is uncertain whether the findings of this study are generalized to other ethnic groups and other generations.

It is important to focus on the variability in BMI in the Japanese population without obesity and without body weight gain or loss in clinical scene to reduce the risk of the development of diabetes. In conclusion, the variability in BMI is a risk factor for the development of diabetes in the Japanese population.

Contributors All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content. HO researched data and wrote manuscript. MaH, MOH, KK and HM contributed to discussion. MI researched data and contributed to discussion. MF reviewed and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests HO has received honoraria from Kissei Pharmaceutical, Daiichi Sankyo, Sanofi, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Kyowa Kirin, MSD, Sumitomo Dainippon Pharma, Novo Nordisk Pharma, Ono Pharmaceutical and Eli Lilly Japan. MaH has received grant support from Asahi Kasei Pharma, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Sanofi, Daiichi Sankyo, Takeda Pharmaceutical, Kyowa Kirin, Sumitomo Dainippon Pharma, Astellas Pharma, Novo Nordisk Pharma and Eli Lilly Japan. MF has received grants from Nippon Boehringer Ingelheim, Kissei Pharmaceutical, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Takeda Pharmaceutical, Sanofi, Astellas Pharma, MSD, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Novo Nordisk Pharma, Kowa Pharmaceutical, Eli Lilly Japan, Sanwa Kagaku Kenkyusho, Taisho Pharmaceutical, Ono Pharmaceutical, Terumo, Teijin Pharma, Nippon Chemiphar and Johnson & Johnson and received honoraria from Nippon Boehringer Ingelheim, Kissei Pharmaceutical, Daiichi Sankyo, Sanofi, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Astellas Pharma, Kyowa Kirin, MSD, Sumitomo Dainippon Pharma, Kowa Pharmaceutical, Novo Nordisk Pharma, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, Eli Lilly Japan, Taisho Pharmaceutical, Bayer Yakuin, AstraZeneca, Mochida Pharmaceutical and Combi.

Patient consent for publication Not required.

Ethics approval This study was approved by the local ethics committee of Panasonic Health Insurance Organization and was conducted in accordance with the principles of Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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