ORIGINAL ARTICLE

Fasting plasma glucose level in the range of 90–99 mg/dL and the risk of the onset of type 2 diabetes: Population-based Panasonic cohort study 2

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ABSTRACT

Aim/Introduction: As the association between a fasting glucose concentration of 90–99 mg/dL and the onset of type 2 diabetes is still controversial, we aimed to assess it in 37,148 Japanese individuals with a normal plasma glucose concentration.

Materials and Methods: This long-term retrospective cohort study included individuals having a medical checkup at Panasonic Corporation from 2008 to 2018. In total, 1,028 participants developed type 2 diabetes.

Results: Cox regression analyses revealed that the risk for the onset of diabetes increased by 9.0% per 1 mg/dL increase in fasting plasma glucose concentration in subjects with the concentration ranging from 90 to 99 mg/dL. Compared with individuals with a fasting glucose concentration of ≤89 mg/dL, the adjusted hazard ratios for developing diabetes were 1.53 (95% CI; 1.22–1.91), 1.76 (95% CI; 1.41–2.18), 1.89 (95% CI; 1.52–2.35), 3.17 (95% CI; 2.61–3.84), and 3.41 (95% CI; 2.79–4.15) at fasting plasma glucose concentrations of 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL, respectively. In populations with obesity, the adjusted hazards ratios for developing diabetes were 1.56 (95% CI; 1.15–2.09), 1.82 (95% CI; 1.37–2.40), 2.05 (95% CI; 1.55–2.69), 3.53 (95% CI; 2.79–4.46), and 3.28 (95% CI; 2.53–4.22) at fasting plasma glucose concentrations of 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL, respectively.

Conclusions: This study demonstrates that the risk of type 2 diabetes among subjects having a fasting plasma glucose concentration of 90–99 mg/dL, is progressively higher with an increasing level of fasting plasma glucose concentration in a Japanese people.

INTRODUCTION

The presence of diabetes and the medical costs of diabetes have been increasing worldwide, recently. Therefore, one of the goals in clinical care is to prevent the onset of diabetes. In the Japanese population, several risk factors, for example, age, obesity, smoking history, hypertension, impaired glucose tolerance, impaired fasting glucose (IFG), hyperlipidemia, and family history are well known risks for the onset of diabetes[1–7].

Impaired fasting glucose is defined as a fasting glucose concentration of 100–125 mg/dL (5.6–6.9 mmol/L) in the United States[8–10]. On the other hand, the World Health Organization and the Japanese Diabetes Association define the cutoff for IFG as 110 mg/dL (6.1 mmol/L)[8,11]. The Japan Diabetes Society defined high-normal glycemia as a fasting glucose concentration of 100–109 mg/dL[11]. Several studies have assessed the association between normal plasma glucose and the onset of type 2 diabetes in the Japanese people. It has been reported that not only a concentration of fasting plasma glucose 100–109 mg/dL

but also 95–99 mg/dL represent a risk for developing diabetes[12]. Conversely, Kabeya *et al.*[13]. suggested that a fasting plasma glucose concentration of 90–99 mg/dL did not relate to the onset of diabetes. Thus, the association between a fasting plasma glucose concentration of 90–99 mg/dL and developing type 2 diabetes remains controversial. The underlying reasons for the conflicting results of previous studies are differences in sample size, study duration, age, and covariates. Previous studies were based on relatively small samples, had short follow-up periods, or were focused on the elderly population.

To our knowledge, the association between normal plasma glucose and the onset of type 2 diabetes in Japanese people is still controversial. Thus, this is the first study to investigate the association between a normal concentration of plasma glucose and developing type 2 diabetes in a large Japanese population and long follow-up periods.

MATERIALS AND METHODS
Study design and data collection
This is a retrospective cohort study including participants who worked at Panasonic Corporation, Osaka, Japan, and underwent a physical examination program. This study used the database of the Panasonic cohort study from 2008 to 2018. The Panasonic cohort study is described in detail elsewhere[14]. All participants received a blood examination every year. The baseline characteristics were assessed using a self-administered questionnaire, which was standardized and has been previously validated. 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 habits of breakfast and snacks after dinner. The participants who consumed alcohol daily were classified as alcohol drinkers. The participants who practiced any sport twice a week regularly were classified as regular exercisers. The definition of type 2 diabetes was followed as a fasting plasma glucose concentration of $\geq$ 126 mg/dL, taking an anti-diabetic medication, and/or having a self-reported history of diabetes.

The study was approved by the local ethics committee of Panasonic Health Insurance Organization (Approval number: 2021-001) and was conducted in accordance with the principles of the Declaration of Helsinki.

Exclusion criteria
In all, 140,590 employees underwent a physical examination program in 2008. We excluded participants from the study who did not undergo the physical examination program consecutively from 2008 to 2018 ($n = 65,256$), who had been diagnosed with diabetes at baseline ($n = 4,342$), who had a fasting plasma glucose concentration of $\geq$ 100–125 mg/dL at baseline ($n = 8,853$), and those with missing data ($n = 24,991$).

Statistical analyses
The differences in the general characteristics at baseline according to the onset of diabetes at follow-up and the glucose

concentration at baseline (glucose $\leq$ 89 mg/dL and $\geq$ 90 mg/dL) were evaluated by Mann–Whitney U test and chi-square test as appropriate. The fasting plasma glucose concentrations were divided into six groups to evaluate the relation between the onset of type 2 diabetes and fasting plasma glucose concentration: $\leq$ 89, 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL. The association between fasting plasma glucose concentration and the onset of type 2 diabetes was assessed by Cox regression analyses. The continuous variable of fasting plasma glucose concentration and the six groups according to fasting plasma glucose concentration were added to the multivariate models 1 and 2, respectively. The multivariate analysis was adjusted for the factors related to the onset of type 2 diabetes such as age, sex, BMI, levels of triglycerides, levels of high-density lipoprotein (HDL) cholesterol, levels of low-density lipoprotein (LDL) cholesterol, levels of uric acid, systolic blood pressure (SBP), smoking status, eating speed, the habit of snacks after dinner, the habit of breakfast, alcohol consumption, and the habit of physical exercise. We also assessed the association between fasting plasma glucose concentration and the onset of type 2 diabetes in patients with obesity (BMI $\geq$ 25 kg/m^2) at baseline who had a high risk of developing diabetes. A receiver operating characteristic curve analysis was performed for the fasting plasma glucose concentration to assess its ability to identify the onset of type 2 diabetes. Statistical analyses of this study were performed using JMP software (SAS Institute, NC, USA). The continuous variables are presented as the mean ± standard deviation or as absolute numbers. We defined differences with a P value < 0.05 as statistically significant. The associations are presented as hazard ratios with 95% confidence intervals (CI).

RESULTS
Tables 1 and 2 show the baseline characteristics of all participants in this study. In total, 1,028 participants developed type 2 diabetes in the study. Table 3 shows the unadjusted hazard ratios for the onset of diabetes.

Table 4 shows the adjusted hazard ratios in multivariate models for the onset of diabetes. For every 1 mg/dL increase in the concentration of fasting glucose, the risk of developing diabetes increased by 9.0% (model 1). The risk of developing type 2 diabetes was higher at fasting plasma glucose concentrations of 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL than at a concentration of $\leq$ 89 mg/dL. The adjusted hazard ratios for the onset of diabetes were 1.53 (95% CI; 1.22–1.91), 1.76 (95% CI; 1.41–2.18), 1.89 (95% CI; 1.52–2.35), 3.17 (95% CI; 2.61–3.84), and 3.41 (95% CI; 2.79–4.15) at fasting plasma glucose concentrations of 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL, respectively (model 2). Age, BMI, SBP, triglycerides, HDL cholesterol, LDL cholesterol, current smoking habits, alcohol consumption, eating speed, and skipping breakfast were also related with developing type 2 diabetes.

Tables 5 and 6 show the incidence rate (per 1000 person-year) and the adjusted hazard ratios for the onset of diabetes in multivariate models in all populations and in subjects with

Table 1 | Characteristics of participants at baseline

	ALL	Development of diabetes (−)	Development of diabetes (+)	P value
N	37,148	36,120	1,028	−
Age (year)	41.59 (6.17)	41.55 (6.18)	42.89 (5.80)	<0.0001
Sex (male/female)	30,262/6,886	29,336/6,784	926/102	<0.0001
BMI (kg/m^2)	22.80 (3.17)	22.72 (3.09)	25.84 (4.12)	<0.0001
SBP (mmHg)	117.14 (13.52)	116.95 (13.41)	124.06 (15.29)	<0.0001
DBP (mmHg)	73.13 (10.42)	72.99 (10.37)	78.0 (11.21)	<0.0001
LDL cholesterol (mg/dL)	122.13 (30.55)	121.81 (30.41)	133.39 (33.39)	<0.0001
HDL cholesterol (mg/dL)	59.82 (14.87)	60.04 (14.86)	51.96 (12.80)	<0.0001
Triglycerides (mg/dL)	108.93 (83.49)	107.61 (81.94)	155.42 (117.26)	<0.0001
Glucose (mg/dL)	89.44 (5.91)	89.35 (5.90)	92.69 (5.34)	<0.0001
Uric acid (mg/dL)	5.79 (1.37)	5.77 (1.37)	6.29 (1.33)	<0.0001
Smoking (none/past/current)	19,233/4,547/13,368	18,873/4,428/12,819	360/119/549	<0.0001
Eating speed (fast/normal/slow)	12,490/22,024/2,634	12,033/21,484/2,603	457/540/31	<0.0001
Snack after dinner (+/−)	6,513/30,635	6,339/29,781	174/854	0.62
Skipping breakfast (+/−)	8,353/28,795	8,038/28,082	315/713	<0.0001
Alcohol drinker (+/−)	8,432/28,716	8,243/27,877	189/839	0.001
Physical exercise (+/−)	5,543/31,605	5,388/3,0732	155/873	0.86

Data are presented as mean (standard deviation) or absolute number. BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Table 2 | Characteristics of participants at baseline according to glucose level

	Glucose ≤ 89 mg/dL	Glucose ≥ 90 mg/dL	P value
N	17,636	19,512	−
Age (year)	40.65 (6.40)	42.44 (5.83)	<0.0001
Sex (male/female)	13,345/4,291	16,917/2595	<0.0001
Body mass index (kg/m^2)	22.32 (3.07)	23.24 (3.19)	<0.0001
Systolic blood pressure (mmHg)	114.95 (13.14)	119.13 (13.54)	<0.0001
Diastolic blood pressure (mmHg)	71.48 (10.24)	74.62 (10.36)	<0.0001
LDL cholesterol (mg/dL)	118.84 (30.32)	125.11 (30.46)	<0.0001
HDL cholesterol (mg/dL)	61.13 (15.14)	58.63 (14.52)	<0.0001
Triglycerides (mg/dL)	100.63 (77.67)	116.43 (87.74)	<0.0001
Glucose (mg/dL)	84.39 (4.04)	94.01 (2.79)	<0.0001
Uric acid (mg/dL)	5.61 (1.37)	5.95 (1.35)	<0.0001
Smoking (none/past/current)	9,124/1,860/6,652	10,109/2,687/6,716	<0.0001
Eating speed (fast/normal/slow)	5,746/10,604/1,286	6,744/11,420/1,348	0.0003
Snack after dinner (+/−)	3,132/14,504	3,381/16,131	0.28
Skipping breakfast (+/−)	3,955/13,681	4,398/15,114	0.80
Alcohol drinker (+/−)	3,501/14,135	4,931/14,581	<0.0001
Physical exercise (+/−)	2,524/15,112	3,019/16,493	0.002

Data are presented as mean (standard deviation) or absolute number. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

obesity (BMI ≥ 25 kg/m^2). The adjusted hazard ratios for the onset of diabetes in subjects with obesity were 1.56 (95% CI; 1.15–2.09), 1.82 (95% CI; 1.37–2.40), 2.05 (95% CI; 1.55–2.69), 3.53 (95% CI; 2.79–4.46), and 3.28 (95% CI; 2.53–4.22) at fasting plasma glucose concentrations of 90–91, 92–93, 94–95, 96–97, and 98–99 mg/dL, respectively.

The cut-off value of fasting plasma glucose concentration to identify the onset of type 2 diabetes was 92 mg/dL or 90 mg/dL in all populations or in subjects with obesity (BMI ≥ 25 kg/m^2). When all subjects with a fasting plasma glucose concentration of 100–125 mg/dL at baseline were included, the cut-off value of fasting plasma glucose concentration was 99 mg/dL or 101 mg/dL in all the population or in subjects with obesity (BMI ≥ 25 kg/m^2).

DISCUSSION

In this study, a fasting plasma glucose in the range of 90–99 mg/dL was related with increased odds of developing type 2

Table 3 | Unadjusted hazard ratios for development of diabetes

	HR (95% CI)	*P* value
Age	1.04 (1.03–1.05)	<0.0001
Sex (male)	2.08 (1.71–2.57)	<0.0001
Body mass index	1.25 (1.23–1.27)	<0.0001
Systolic blood pressure	1.03 (1.03–1.04)	<0.0001
Low-density lipoprotein cholesterol	1.01 (1.009–1.01)	<0.0001
High-density lipoprotein cholesterol	0.96 (0.95–0.96)	<0.0001
Triglycerides	1.002 (1.002–1.003)	<0.0001
Uric acid	1.31 (1.25–1.37)	<0.0001
Glucose	1.12 (1.11–1.13)	<0.0001
Glucose ≤ 89 mg/dL	1	–
90–91 mg/dL	1.77 (1.42–2.20)	<0.0001
92–93 mg/dL	2.10 (1.69–2.58)	<0.0001
94–95 mg/dL	2.38 (1.93–2.93)	<0.0001
96–97 mg/dL	4.20 (3.49–5.05)	<0.0001
98–99 mg/dL	4.93 (4.08–5.95)	<0.0001
Smoking (past) (ref: none)	1.40 (1.14–1.72)	0.002
Smoking (current) (ref: none)	2.21 (1.94–2.53)	<0.0001
Eating speed (slow) (ref: normal)	0.48 (0.33–0.68)	<0.0001
Eating speed (fast) (ref: normal)	1.51 (1.33–1.71)	<0.0001
Snack after dinner (yes) (ref: no)	0.96 (0.81–1.12)	0.59
Skipping breakfast (yes) (ref: no)	1.53 (1.34–1.75)	<0.0001
Alcohol drinker (yes) (ref: no)	0.77 (0.65–0.90)	0.0008
Physical exercise (yes) (ref: no)	1.02 (0.85–1.20)	0.86

diabetes. The effects observed were almost the same as in subjects with obesity. Our study indicates that hazard ratios for the onset of type 2 diabetes, among the subjects having fasting plasma glucose concentration of 90–99 mg/dL with or without obesity, is progressively higher with an increasing level of fasting plasma glucose concentration.

The Japan Diabetes Society defined high-normal glycemia as a fasting glucose concentration of 100–109 mg/dL, and individuals with a concentration of glucose in this range have a high risk of diabetes[11]. There are few studies that have evaluated the relationship between fasting blood glucose concentration in the normal range and the onset of type 2 diabetes. The association between a fasting glucose concentration of 90–99 mg/dL and the onset of type 2 diabetes is still controversial. Kato *et al.*[12]. reported that a fasting glucose concentration of 100–109 mg/dL imposes a substantial risk for the onset of diabetes and a fasting glucose concentration of 95–99 mg/dL was found to be related with an increased hazard ratio only in women. Their study followed 11,369 subjects who were recruited from annual health examinations conducted in Omiya City during 7 years. In their study, the definition of type 2 diabetes was followed as a fasting plasma glucose concentration of ≥ 126 mg/dL, taking an anti-diabetic medication, and/or having a self-reported history of diabetes and they used the data including every socioeconomic status in the elderly population. Moreover, Noda *et al.*[5] also assessed the association between fasting glucose concentration in the normal range and the onset of diabetes. Their study

followed 2,207 subjects who were recruited from public health center annual health examinations during 5 years. In their study, type 2 diabetes was defined using the fasting plasma glucose concentration, HbA_{1c}, and self-reported history of diabetes and they used the data including every socioeconomic status in the elderly population. Considering that Japan's Ministry of Health, Labour and Welfare reported that the risk of diabetes gradually increases from the fourth decade of life, further studies in younger subjects are needed to prevent the onset of diabetes. We believe that the findings of our study may be useful to shed light on the association between fasting glucose concentration in the normal range and in developing diabetes.

It has been proposed that the onset of diabetes is triggered by insulin resistance, which eventually leads to the exhaustion of pancreatic β cells, as shown in studies conducted in Western populations[15]. However, pre-diabetes in a Japanese population is both characterized by lower insulin secretion and lower insulin resistance compared with Western populations[16]. Mitsui *et al.*[17]. reported that insulin secretory defects and decreased insulin sensitivity may occur even in patients with a fasting glucose concentration of 100–109 mg/dL. Moreover, type 2 diabetes is a disease with a very long, silent phase, during which time the plasma glucose is normal but already elevated in those destined to develop diabetes compared with those destined not. Hence, we hypothesize that insulin secretory defects may occur in individuals with a fasting glucose concentration of 90–99 mg/dL. It is important to note that a slight increase in insulin resistance due to body weight gain can easily lead to the onset of type 2 diabetes by disrupting the balance of insulin secretion capacity, which is commonly observed in East Asians.

We should consider the cost of interventions aimed to prevent diabetes in individuals with a fasting glucose concentration of 90–99 mg/dL. If the cutoff value of IFG is lowered, the costs derived from screening and health guidance for the prevention of diabetes would increase markedly. Therefore, we assessed patients with obesity (BMI ≥ 25 kg/m^2) at baseline who were likely to develop diabetes and identified subjects at high risk. Our study showed that subjects with a fasting glucose concentration of 90–99 mg/dL and a BMI of ≥ 25 kg/m^2 are also at risk of developing diabetes. It is considered that subjects with prediabetes often have some risk factors of cardiovascular disease, including dyslipidemia and hypertension[18], and are at increased risk for cardiovascular disease[19,20]. Therefore, we suggest that the cutoff value of high-normal glycemia might be reduced to less than 100 mg/dL in individuals with or without obesity.

The strengths of our study include its long follow-up period, large sample size, and consecutive enrolment because this cohort is based on corporation health examinations. However, there are several limitations in this study. First, hemoglobin A1c levels were not considered in the diagnosis of diabetes. Although we did not collect data on HbA1c, the correlation coefficient between HbA1c level and fasting glucose concentration was reported to be 0.85 in a previous study[21]; therefore,

Table 4 | Multivariate adjusted hazard ratios for development of diabetes

	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.03 (1.02–1.04)	<0.0001	1.03 (1.02–1.04)	<0.0001
Sex (male)	0.78 (0.61–0.999)	0.049	0.79 (0.62–1.008)	0.06
Body mass index	1.18 (1.16–1.20)	<0.0001	1.18 (1.16–1.20)	<0.0001
Systolic blood pressure	1.01 (1.008–1.02)	<0.0001	1.01 (1.008–1.02)	<0.0001
LDL cholesterol	1.003 (1.0006–1.005)	0.01	1.003 (1.0006–1.005)	0.01
HDL cholesterol	0.99 (0.98–0.99)	<0.0001	0.98 (0.98–0.99)	<0.0001
Triglycerides	1.0008 (1.0003–1.001)	0.002	1.0008 (1.0003–1.001)	0.002
Uric acid	1.02 (0.97–1.08)	0.45	1.02 (0.97–1.08)	0.48
Glucose	1.09 (1.08–1.11)	<0.0001	–	-
Glucose ≤ 89 mg/dL	–	-	1	-
90–91 mg/dL	–	-	1.53 (1.22–1.91)	0.0003
92–93 mg/dL	–	-	1.76 (1.41–2.18)	<0.0001
94–95 mg/dL	–	-	1.89 (1.52–2.35)	<0.0001
96–97 mg/dL	–	-	3.17 (2.61–3.84)	<0.0001
98–99 mg/dL	–	-	3.41 (2.79–4.15)	<0.0001
Smoking (past) (ref: none)	1.24 (0.99–1.53)	0.06	1.23 (0.99–1.53)	0.06
Smoking (current) (ref: none)	2.02 (1.74–2.33)	<0.0001	1.99 (1.72–2.31)	<0.0001
Eating speed (slow) (ref: normal)	0.66 (0.44–0.94)	0.02	0.67 (0.45–0.95)	0.02
Eating speed (fast) (ref: normal)	1.06 (0.93–1.21)	0.34	1.06 (0.93–1.21)	0.35
Snack after dinner (yes) (ref: no)	0.93 (0.78–1.10)	0.41	0.93 (0.78–1.10)	0.40
Skipping breakfast (yes) (ref: no)	1.35 (1.17–1.55)	<0.0001	1.34 (1.16–1.54)	<0.0001
Alcohol drinker (yes) (ref: no)	0.72 (0.61–0.86)	0.0001	0.73 (0.61–0.86)	0.0002
Physical exercise (yes) (ref: no)	1.09 (0.91–1.29)	0.35	1.10 (0.92–1.30)	0.31

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 5 | Incident cases and incident rate (per 1,000 person-year) for the development of diabetes in all population and obesity (BMI ≥ 25 kg/m^2)

Glucose	All population		Obesity (BMI ≥ 25 kg/m^2)	
	n	Incident cases (Incidence rate)	n	Incident cases (Incidence rate)
≤89 mg/dL	17636	249 (1.42)	3134	123 (3.97)
90–91 mg/dL	4655	116 (2.51)	999	60 (6.11)
92–93 mg/dL	4456	131 (2.97)	1040	74 (7.26)
94–95 mg/dL	4044	135 (3.37)	983	79 (8.21)
96–97 mg/dL	3529	205 (5.92)	869	126 (15.10)
98–99 mg/dL	2828	192 (6.94)	716	106 (15.48)

Incidence rate; per 1,000 person-year.

we thought that it was possible to evaluate the onset of diabetes using the fasting glucose concentration. Secondly, medication for hypertension could affect the onset of diabetes. Unfortunately, however, we have no data about the medication for hypertension. Thirdly, an oral glucose tolerance test and insulin level could be useful to diagnose diabetes and to indicate the potential risk for the onset of type 2 diabetes. Unfortunately, however, we have no data about oral glucose tolerance test and insulin level. Finally, the study population consisted of relatively young Japanese men and women with high socioeconomic status, and it is therefore unclear whether the findings of this study are generalizable to other ethnic groups and age categories.

It is important to focus on the fasting glucose concentration in the normal range in Japanese people in clinical settings to reduce the risk of the onset of diabetes. In conclusion, our data indicate that the risk of type 2 diabetes diagnosed by a fasting plasma glucose concentration of ≥ 126 mg/dL, within 10 years, among the subjects having a fasting plasma glucose concentration of 90–99 mg/dL, is progressively higher with increasing level of fasting plasma glucose concentration in a Japanese people.

Table 6 | Multivariate adjusted hazard ratios for development of diabetes in all population and obesity (BMI ≥ 25 kg/m^2)

Glucose	All population		Obesity (BMI ≥ 25 kg/m^2)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
≤89 mg/dL	1	–	1	–
90–91 mg/dL	1.53 (1.22–1.91)	0.0003	1.56 (1.15–2.09)	0.005
92–93 mg/dL	1.76 (1.41–2.18)	<0.0001	1.82 (1.37–2.40)	<0.0001
94–95 mg/dL	1.89 (1.52–2.35)	<0.0001	2.05 (1.55–2.69)	<0.0001
96–97 mg/dL	3.17 (2.61–3.84)	<0.0001	3.53 (2.79–4.46)	<0.0001
98–99 mg/dL	3.41 (2.79–4.15)	<0.0001	3.28 (2.53–4.22)	<0.0001

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