Fasting glucose levels and the risk of type 2 diabetes mellitus in participants with or without cardiovascular diseases

学　位　論　文

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Fasting glucose levels and the risk of type 2 diabetes mellitus in participants with or without cardiovascular diseases

（心血管疾患既往の有無でみた空腹時血糖レベルと２型糖尿病発症リスク）

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概要

【背景】空腹時血糖値 70mg/dL 未満では心血管疾患（CVD）発症が増加すると報告されている。しかし、空腹時血糖値 70mg/dL 未満での糖尿病発症リスクは不明である。我々は、空腹時血糖値レベルと糖尿病発症リスクの関係を CVD の有無別に検討した。

【方法】2008 年特定健診受診者において、①空腹時血糖値 ≧126mg/dL、②HbA1c ≧6.5%、③血糖降下薬内服、の何れも満たさない者（40-74 才、男女計 88,422 人）を非糖尿病者と定義し対象とした。2008 年時点で CVD の既往あり 81,639 名、既往なし 6,783 名だった。2009 年から 2011 年の再受診時、①②③のいずれかを満たす場合、糖尿病発症と定義した。2008 年空腹時血糖値を <70mg/dL、70～79mg/dL、80～84mg/dL、85～89mg/dL、90～94mg/dL、95～99mg/dL、100～109mg/dL、110～125mg/dL の 8 群に分類し、糖尿病発症オッズ比（reference 85～89mg/dL）をロジスティック多重回帰分析で求めた。$p<0.05$ を有意水準とした。

【結果】性、年齢、BMI、喫煙、高血圧症、脂質異常症、飲酒習慣で調整した補正オッズ比は、全症例対象で空腹時血糖値 <70mg/dL と 95-125mg/dL で上昇した。CVD なし群では空腹時血糖値 95-125mg/dL で補正オッズ比が上昇した。CVD あり群では、空腹時血糖値 <70mg/dL と 100-125mg/dL で補正オッズ比が上昇した。

【結語】CVD の既往のある群では、空腹時血糖値 <70mg/dL で糖尿病発症リスクが上昇することが示された。

Introduction

The risk of new-onset diabetes mellitus increases as fasting plasma glucose levels increase within normoglycemic levels between 80 mg/dL and 125 mg/dL [1-3]. However, the incidence of diabetes mellitus in those with fasting plasma glucose levels lower than 80 mg/dL has not been clarified.

Participants with fasting plasma glucose levels below 70 mg/dL have a high susceptibility to cardiovascular diseases (CVD) [4-6]. Thus, the correlation between fasting plasma glucose levels and CVD risk shows a J shape curve [4, 5]. The underlying mechanism(s) of the CVD risk in low fasting glucose levels is not clear [7]. Wei et al. hypothesized that long-term exposure to low fasting plasma glucose levels may serve as a risk factor for CVD mortality, due to the resulting abnormal cardiac activity and thrombosis, particularly in patients with atherosclerosis [6]. Tanne et al. suggested that hypoglycaemia or rapid changes in plasma glucose may lead to elevated counter-regulatory hormone levels, such as epinephrine and norepinephrine, which induce vasoconstriction and platelet aggregation [8]. Although such changes observed at low fasting plasma glucose levels (<70 mg/dL) may also impair glucose metabolism, no study has evaluated the incidence of new-onset diabetes mellitus at this range of fasting plasma glucose.

The purpose of this study was to examine whether the incidence of new-onset

diabetes mellitus increases when fasting plasma glucose levels are below 70 mg/dL, and if so, whether this may be correlated to CVD history.

Methods

Study population

This cohort study was performed as a part of the prospective ongoing project "Design of the comprehensive healthcare system for CKD based on the individual risk assessment by Specific Health Checkups." The Annual health check program, "The Specific Health Check and Guidance System" (SHCG) in Japan, was initiated by the Japanese government in 2008, to target the Japanese general population (40-74 years), with 3 subsequent follow-up visits in 2009, 2010 and 2011 [9, 10].

We obtained data for 226,021 participants who did not have diabetes mellitus in 2008; this data had already been recorded and were available for the whole study period of 2008-2011. We excluded participants who visited for only 1 year (n=39,168) and those with incomplete information recorded in the database, such as data about sex, age, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose levels, high-density lipoprotein-cholesterol (HDL-C) levels, low-density lipoprotein-cholesterol (LDL-C) levels, triglyceride (TG) levels, smoking habits, history of heart disease, and history of stroke (n=98,431).

Covariates

Height, body weight, blood pressure, and waist circumference of each subject were measured by trained staff. Questionnaires recording data on smoking status (current smoker or not), drinking habits (everyday, sometimes, rarely or never, regular exercise (exercise resulting in light sweating, walking >1 h/day), anti-hypertensive drug use, anti-hyperglycemic drug use, lipid lowering drug use, history of heart disease, and history of stroke were administered. Blood samples were collected after an overnight fast and were assayed within 24 hours with automatic clinical chemical analyzers. When needed, the HbA_{1c} value was corrected as a National Glycohemoglobin Standardization Program equivalent value, calculated with the following formula: HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) +0.4% [10-12].

Definition of Diabetes Mellitus, Hypertension, Dyslipidemia, and History of CVD

For this study, a participant was considered to have diabetes mellitus when the fasting plasma glucose level was ≥126 mg/dL, when the hemoglobin A_{1c} levels were ≥6.5% (48 mmol/mol), or if the participant had self-reported the use of anti-hyperglycemic drugs in 2008. Participants were considered to have new-onset diabetes mellitus if they met the above diabetes criteria in 2009, 2010, or 2011. Participants were considered hypertensive if their SBP was ≥140 mmHg, if their DBP was ≥90 mmHg, or if they had self-reported the use of antihypertensive drugs. Participants were considered dyslipidemia if HDL-C levels were ≤39 mg/dL, if LDL-C

levels were ≥140 mg/dL, if TG levels were ≥150 mg/dL, or if they had self-reported the use of lipid lowering drugs. Participants were considered to have a history of CVD if they had a self-reported history of heart disease or stroke.

Statistical analyses

To study the association between new-onset diabetes mellitus and low fasting plasma glucose levels, we analyzed 8 categories of fasting plasma glucose levels: <70 mg/dL, 70-79 mg/dL, 80-84 mg/dL, 85-89 mg/dL, 90-94 mg/dL, 95-99 mg/dL, 100-109 mg/dL, and 110-125 mg/dL. The group with fasting plasma glucose level of 85-89 mg/dL was used as the reference category.

Unadjusted and multivariable-adjusted logistic regression models were used to estimate the association between fasting plasma glucose concentration and the risk of new-onset diabetes mellitus in 1-3 year follow-ups. In the first step, we carried out unadjusted analyses (Model 1). In the second step, we adjusted for age, sex, and BMI (Model 2). In the third step, we further adjusted for current smokers (Model 3). In the fourth step, we further adjusted for hypertension and dyslipidemia (Model 4). In the last step, we finally adjusted for drinking habits (Model 5). All analyses were performed using SPSS software (version 24.0; SPSS, Chicago, IL, USA).

Results

The characteristics of all the participants are shown in Table 1. The average age

was 62.6 years; 40.2% of participants were men, and the average BMI was 23.4 kg/m^2. Compared to the reference group (category 85-89 mg/dL), except for those with fasting plasma glucose levels <70 mg/dL, patients in all other groups showed an increase in mean age, BMI, waist circumference, SBP, DBP, TG. HDL-C levels were decreased in all patients, except those with fasting plasma glucose levels <70 mg/dL. In the category of fasting plasma glucose levels <70 mg/dL, prevalence of hypertension (p<0.01) and current smoker condition was increased (p<0.001) as compared to the reference 85-89 mg/dL category. The percentage of participants with the habit of daily drinking was also high in the group of glucose level <70 mg/dL (statistically significant versus 85-89 mg/dL, p<0.001).

The characteristics of the participants without or with a history of CVD are shown in Table 2. The number of participants without a history of CVD was 81,639 with an average age of 62.3 years; 39.3% were male, and their average BMI was 23.3 kg/m^2. The proportion of hypertension (p<0.01), current smoking (p<0.001), and habit of drinking daily (p<0.001) were higher in the group of fasting plasma glucose <70 mg/dL. The number of participants with a CVD history was 6,783 with an average age of 66.1 years; 50.6% were males, and the average BMI was 23.9 kg/m^2. The prevalence of current smoking (p<0.001) and everyday drinking habit (p<0.001) was higher in the group with low fasting plasma glucose (<70 mg/dL).

Unadjusted and multivariable-adjusted logistic regression models of all participants in Table 3 show the association between fasting plasma glucose levels and the risk of new-onset diabetes mellitus. In all participants, the unadjusted OR increased when fasting plasma glucose levels were <70 mg/dL or >90 mg/dL. The OR for fasting plasma glucose levels <70 mg/dL remained elevated after adjustments for sex, age, BMI, current smoking status, hypertension, dyslipidemia and drinking habit (model 5) (OR 2.14, 95% CI 1.25-3.65), whereas after the adjustments (model 2-5), the OR increased for fasting plasma glucose levels of ≥95 mg/dL.

In participants without a history of CVD, the unadjusted OR increased for low fasting plasma glucose levels (<70 mg/dL) (model 1) (OR 1.87, 95% CI 1.01-3.46), but it was not significantly altered after the above-mentioned adjustments (model 3-5). In participants with a CVD history, the unadjusted ORs were significantly changed at fasting plasma glucose levels <70 mg/dL or ≥100 mg/dL. The association remained similar after adjustments for sex, age, BMI, current smoking condition, hypertension, dyslipidemia, drinking habit (model 5): <70 mg/dL (OR 5.24, 95% CI 1.71-16.11). The multivariable-adjusted ORs steadily increased for fasting plasma glucose levels of 100-109 mg/dL (OR 3.05, 95% CI 1.98-4.69) and 110-125 mg/dL (OR 10.17, 95% CI 6.64-15.57). **Figure 1** shows the unadjusted (Model 1, left) and adjusted (Model 5, right) ORs of new-onset diabetes mellitus for 8 fasting plasma glucose categories in

participants with or without a history of CVD.

Discussion

The current study presents two major findings regarding the association between normal ranges of fasting plasma glucose and the incidence of diabetes mellitus in a Japanese nation-wide general population. First, when fasting plasma glucose levels were categorized from <70 mg/dL to a maximum of 125 mg/dL in 8 groups, the OR for new-onset diabetes mellitus showed a J-shape curve; the OR increased when fasting plasma glucose levels were<70 mg/dL or ≥100 mg/dL. Second, the OR for new-onset diabetes mellitus increased for the category of fasting plasma glucose levels <70 mg/dL, for participants with a history of CVD but not for those without a history of CVD. This is the first study to evaluate the OR for new-onset diabetes mellitus in participants with fasting plasma glucose levels <70 mg/dL, showing a significant independent risk in participants with CVD history.

Previous studies showed that the risk of new-onset diabetes mellitus exhibited a linear increase with fasting plasma glucose levels of 80-125 mg/dL [1-3] consistent with our study findings. The OR adjusted for sex, age, and BMI (model 2) was the lowest for fasting plasma glucose levels of 80-84 mg/dL and gradually increased for levels of 85-89 mg/dL, 90-94 mg/dL, 95-99 mg/dL, 100-109 mg/dL, and 110-125 mg/dL. This can be explained by the possibility that an increase in fasting glucose

levels along with impairment in insulin sensitivity and/or secretion may start 3-6 years before the onset of diabetes mellitus [1, 13]. Our study, the first to investigate the OR for new-onset diabetes mellitus for fasting plasma glucose levels categorized from <70 mg/dL up to 125 mg/dL, showed an increase in OR for fasting plasma glucose levels <70 mg/dL. In a previous study [4], although the risk for diabetes onset was not investigated, participants with fasting glucose levels <70 mg/dL showed a low level of total serum cholesterol, low proportion of hypertension and low percentage of physical activity. Male individuals, whose fasting glucose levels were <70 mg/dL, showed a low frequency of regular alcohol intake while a high percentage of them were current smokers [4].

In our study, participants with low levels of fasting plasma glucose (<70 mg/dL) showed high SBP, high triglyceride levels and low LDL-cholesterol levels. A large number of them were current smokers, developed hypertension, and were reported to consume alcohol every day. Because this study is based on a nation-wide survey in 40-74 year-old Japanese, it is considered as an average study for all Japanese. The characteristics, which were observed in our participants with fasting plasma glucose <70 mg/dL, such as high blood pressure and high proportion of hypertension [14], low LDL-C level [15], high TG level [16, 17], current smoking [18, 19], have been reported as risk factors for the onset of diabetes mellitus. These characteristics could increase,

at least partly, the risk for new-onset diabetes. It has been reported that moderate levels of alcohol intake decreased the risk for new-onset diabetes mellitus [20, 21], whereas high levels increased it [22]. A higher proportion of participants with fasting plasma glucose <70 mg/dL were consuming alcohol every day. The increased alcohol consumption could be associated with low plasma glucose levels and an increase in new-onset diabetes mellitus [22]. However, fasting plasma glucose <70 mg/dL remained an independent risk factor for new-onset diabetes mellitus after adjustments for alcohol drinking habit (model 5).

Wei et al. reported that the relation between fasting plasma glucose and the risk for CVD showed a J shape curve: the onset of CVD increased in those with fasting plasma glucose levels <70 mg/dL compared to that in those with levels of 85-109 mg/dL [6]. The possible mechanism for this link is that long-term exposure to low fasting plasma glucose may serve as a risk factor for CVD, possibly through abnormal cardiac activity and thrombosis, particularly in patients with atherosclerosis [6, 7]. Another hypothesis is that hypoglycaemia or rapid changes in plasma glucose may lead to elevations of counter-regulatory hormones [8]. We therefore assessed the ORs for new-onset diabetes mellitus separately in participants with or without history of CVD. The OR of the group of fasting plasma glucose level <70 mg/dL increased in those with a history of CVD, but not in those without a history of CVD. In our subjects

with a history of CVD, among those with fasting plasma glucose level <70 mg/dL, there was a high proportion of current smokers and those who consumed alcohol daily.

Among participants with a history of CVD, the OR of the group with fasting plasma glucose levels <70 mg/dL increased after adjustments for sex, age, BMI, current smoking, hypertension, dyslipidemia and drinking habit (model 5), whereas among participants without a history of CVD, the OR was not significantly different among the categories with levels less than 90 mg/dL (model 3). Previous studies showed that current smoking patterns increased the risk for diabetes mellitus [18, 19], but the mechanism involved was not clear. Wu et al. reported that nicotine, a major constitute of cigarette smoke, increases lipolysis, which causes body weight reduction, elevates the levels of circulating free fatty acids and thus causes insulin resistance in insulin sensitive tissues [23]. In the group of participants with a history of CVD, BMIs of those with fasting plasma glucose levels <70 mg/dL and 85-89 mg/dL were not different. Considering that the proportion of current smokers was remarkably high in the group with fasting plasma glucose <70 mg/dL compared to 85-89 mg/dL (38.9% vs 11.3%), it can be assumed that participants with levels <70 mg/dL escape from obesity due to the lipolysis by smoking. Taken together, new-onset diabetes mellitus in participants with levels <70 mg/dL could be caused by insulin resistance

due to elevation of circulating free fatty acids [24, 25] induced by smoking-induced lipolysis.

The proportion of everyday drinking was high in the group of fasting plasma glucose <70 mg/dL regardless of CVD history. Alcohol consumption and incidence of diabetes mellitus showed a U-shaped relationship in a previous study [20, 26]. Drinking habits may lead to an increase in the onset of diabetes mellitus in participants with fasting plasma glucose levels <70 mg/dL. Although regular drinking and incidence of diabetes mellitus could be linked, the OR change remained significant after adjustments for drinking, suggesting that fasting plasma glucose <70 mg/dL in participants with CVD history is associated with a risk of new-onset diabetes mellitus independent of drinking habits.

Our study has several limitations. First, we evaluated only fasting plasma glucose level. Neither oral glucose tolerance test data, nor postprandial plasma glucose level measurements of the participants were available to us; hence we could not consider post-challenge or postprandial glucose levels, which are better markers for the onset of diabetes mellitus. Second, conditions of blood sampling were self-reported. Third, history of CVD and drug medication use was based on data from a self-administered questionnaire. When the participants were uncertain about the response, medical staff provided assistance; hence, the responses were considered accurate. Fourth,

insulin resistance could not be assessed in our study, because we did not measure insulin levels. Fifth, our participants consisted of a Japanese population; hence, our findings cannot be generalized to other race/ethnic groups. Last, some participants were excluded because of missing information.

In conclusion, the risk for new-onset diabetes mellitus was high when fasting glucose levels were <70 mg/dL in participants with history of CVD, indicating that this range of fasting glucose is a new and significant risk factor for diabetes mellitus within the general community. Considering that this range is also a risk factor for CVD, it is important to elucidate the relation between CVD and diabetes mellitus in cases of low fasting glucose levels (<70 mg/dL).

Compliance with ethical standards

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Duality of interest

The authors declare that there is no duality of inter- est associated with this manuscript.

Contribution statement

MS and EO developed the concept, researched the data, and wrote the manuscript. KA, HS, KI, TM, KY, KT, SF, IN, TK, MK, YS, MK, and TW contributed to discussion and reviewed the manuscript. KA, KI and TW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table1. Baseline characteristics of total subjects

Fasting plasma glucose	Total	ANOVA	<70 mg/dL	70-79 mg/dL	80-84 mg/dL	85-89 mg/dL	90-94 mg/dL	95-99 mg/dL	100-109 mg/dL	110-125 mg/dL
n	88422		528	3268	8327	16298	19894	16784	16947	6376
Age, years	62.6 (8.3)	<0.001	61.7 (8.4)	60.8 (9.2)‡	61.6 (8.9)†	62.1 (8.6)	62.5 (8.3)‡	62.9 (8.2)‡	63.2 (7.8)‡	63.9 (7.3)‡
% Male	40.2%		36.0%	26.1%	26.7%	31.8%	37.6%	43.6%	51.0%	57.2%
BMI, kg/m^2	23.4 (3.2)	<0.001	22.7 (3.5)	22.1 (3.0)‡	22.4 (3.1)‡	22.9 (3.1)	23.3 (3.1)‡	23.6 (3.2)‡	24.1 (3.2)‡	24.5 (3.5)‡
Waist circumference, cm	83.7 (9.0)	<0.001	82.1 (9.8)	79.8 (9.1)‡	81.0 (9.0)‡	82.2 (8.8)	83.4 (8.7)‡	84.4 (8.7)‡	85.6 (8.7)‡	86.8 (9.0)‡
Systolic blood pressure, mmHg	129 (18)	<0.001	129 (19)*	123 (17)‡	124 (17)‡	126 (17)	128 (17)‡	130 (17)‡	133 (18)‡	136 (18)‡
Diastolic blood pressure, mmHg	77 (11)	<0.001	74 (10)	73 (11)‡	74 (10)‡	75 (11)	76 (10)‡	77 (10)‡	79 (11)‡	80 (11)‡
HDL cholesterol, mg/dL	62 (15)	<0.001	61 (16)*	66 (16)‡	65 (16)‡	63 (16)	62 (15)‡	61 (15)‡	60 (15)‡	59 (15)‡
LDL cholesterol, mg/dL	126 (30)	<0.001	121 (31)*	122 (30)‡	124 (30)*	125 (29)	126 (29)*	127 (29)‡	127 (30)‡	127 (31)
Triglycerides, mg/dL	114 (73)	<0.001	127 (105)†	97 (63)‡	100 (61)‡	107 (66)	112 (69)‡	117 (73)‡	124 (80)‡	133 (91)‡
AST,U/L	24 (9)	<0.001	24 (9)	24 (10)	23 (9)	23 (9)	24 (9)	24 (9)‡	24 (10)‡	26 (13)‡
ALT, U/L	21 (12)	<0.001	20 (16)	20 (12)	19 (10)‡	20 (11)	21 (12)‡	22 (12)‡	23 (14)‡	25 (16)‡
ɤGTP, U/L	34 (41)	<0.001	30 (50)	27 (33)	27 (30)‡	29 (34)	32 (38)‡	34 (42)‡	39 (47)‡	46 (55)‡
Hypertension, %	44.30%		43.90%	31.40%	34.10%	38.10%	41.90%	45.90%	52.80%	61.60%
Dyslipidemia, %	53.3%		52.1%	46.1%	48.0%	49.9%	52.3%	55.0%	57.4%	60.1%
Current smoking, %	14.5%		42.6%	16.8%	12.8%	13.1%	13.4%	14.7%	15.7%	16.8%
Drinking habit, %										
everyday	19.1%		22.9%	13.3%	12.6%	14.4%	16.9%	20.2%	25.1%	29.8%
sometimes	21.6%		19.8%	21.3%	21.6%	21.1%	21.2%	21.5%	22.6%	21.8%
rarely or never	59.3%		57.3%	65.4%	65.7%	64.5%	61.9%	58.4%	52.3%	48.4%
Exercise, %										
exercise resulting in light sweating	41.9%		37.9%	40.2%	41.2%	41.3%	41.9%	42.2%	42.5%	43.8%
walking>1 hour/day	55.4%		52.5%	52.6%	54.4%	55.0%	56.0%	55.4%	55.8%	56.9%

Values are mean (SD) or %. *p<0.05, †p<0.01, and ‡p<0.001 vs. 85-89 mg/dL. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

Table 2. Baseline characteristics of participants without or with cardiovascular disease

Without cardiovascular disease (n=81,639)

Fasting plasma glucose	Total	ANOVA	<70 mg/dL	70-79 mg/dL	80-84 mg/dL	85-89 mg/dL	90-94 mg/dL	95-99 mg/dL	100-109 mg/dL	110-125 mg/dL
n	81639		492	3036	7693	15064	18462	15538	15609	5745
Age, years	62.3 (8.4)	<0.001	61.4 (8.4)	60.5 (9.2)‡	61.3 (9.0)†	61.8 (8.7)	62.2 (8.4)‡	62.6 (8.3)‡	62.9 (7.9)‡	63.7 (7.4)‡
% Male	39.3%		35.8%	25.6%	26.0%	30.8%	36.6%	42.8%	50.4%	56.2%
BMI, kg/m^2	23.3 (3.2)	<0.001	22.6 (3.5)	22.0 (3.0)‡	22.4 (3.1)‡	22.8 (3.1)	23.2 (3.1)‡	23.6 (3.2)‡	24.0 (3.2)‡	24.5 (3.5)‡
Waist circumference, cm	83.5 (9.0)	<0.001	81.8 (9.9)	79.7 (9.0)‡	80.8 (9.0)‡	82.0 (8.8)	83.2 (8.8)‡	84.3 (8.7)‡	85.5 (8.7)‡	86.7 (9.0)‡
Systolic blood pressure, mmHg	129 (18)	<0.001	129 (19)*	122 (17)‡	124 (17)‡	126 (17)	128 (17)‡	130 (17)‡	133 (18)‡	135 (18)‡
Diastolic blood pressure, mmHg	77 (11)	<0.001	75 (10)	73 (11)‡	74 (10)‡	75 (10)	76 (10)‡	77 (10)‡	79 (11)‡	80 (11)‡
HDL cholesterol, mg/dL	62 (15)	<0.001	61 (16)*	66 (16)‡	65 (16)‡	63 (16)	62 (15)‡	61 (15)‡	60 (15)‡	59 (15)‡
LDL cholesterol, mg/dL	126 (30)	<0.001	121 (31)*	123 (30)‡	124 (30)†	126 (29)	127 (30)	127 (29)‡	128 (30)‡	127 (31)
Triglycerides, mg/dL	114 (74)	<0.001	126 (106)†	97 (62)‡	100 (61)‡	107 (66)	111 (70)‡	117 (74)‡	124 (80)‡	134 (92)‡
AST,U/L	24 (9.2)	<0.001	23 (8.8)	24 (9.6)	23 (8.2)	23 (8.5)	23 (8.5)	24 (9.1)‡	24 (9.5)‡	26 (12.7)‡
ALT, U/L	21 (12)	<0.001	20 (15)	19 (11)	19 (10)‡	20 (11)	21 (11)‡	22 (13)‡	23 (14)‡	25 (16)‡
γ-GTP, U/L	33 (41)	<0.001	30 (51)	27 (30)*	27 (29)‡	29 (33)	31 (38)‡	34 (42)‡	39 (47)‡	45 (55)‡
Hypertension, %	42.2%		42.5%	29.7%	31.8%	35.6%	39.8%	43.9%	50.8%	59.2%
Dyslipidemia, %	52.9%		51.4%	46.0%	47.3%	49.6%	51.7%	54.7%	57.1%	60.1%
Current smoker, %	14.7%		42.9%	17.3%	12.9%	13.3%	13.6%	14.9%	16.0%	16.9%
Drinking habit, %										
everyday	19.0%		21.9%	13.4%	12.5%	14.4%	16.8%	20.1%	25.1%	29.9%
sometimes	21.7%		20.4%	21.8%	21.7%	21.2%	21.2%	21.6%	22.6%	21.9%
rarely or never	59.3%		57.7%	64.7%	65.8%	64.5%	61.9%	58.3%	52.2%	48.3%
Exercise, %										
exercise resulting in light sweating	41.6%		37.7%	40.1%	41.1%	40.9%	41.3%	41.8%	42.2%	43.3%
walking>1 hour/day	55.5%		51.5%	53.0%	54.4%	55.2%	56.0%	55.4%	55.9%	56.7%

With cardiovascular disease (n=6,783) (continued)

Fasting plasma glucose	Total	ANOVA	<70 mg/dL	70-79 mg/dL	80-84 mg/dL	85-89 mg/dL	90-94 mg/dL	95-99 mg/dL	100-109 mg/dL	110-125 mg/dL
n	6783		36	232	634	1234	1432	1246	1338	631
Age, years	66.1 (6.2)	0.058	66.2 (6.4)	65.2 (7.2)	65.4 (6.9)	66.0 (6.2)	66.2 (6.0)	66.3 (6.1)	66.2 (6.0)	66.2 (5.7)
% Male	50.6%		38.9%	32.8%	35.0%	43.7%	50.3%	53.1%	58.5%	66.2%
BMI, kg/m^2	23.9 (3.2)	<0.001	23.5 (3.2)	22.7 (3.3)*	23.1 (3.0)	23.5 (3.1)	23.8 (3.1)	23.9 (3.1)†	24.4 (3.2)‡	24.9 (3.2)‡
Waist circumference, cm	85.3 (8.7)	<0.001	86.1 (8.6)	81.2 (9.2)‡	83.2 (8.6)	84.0 (8.7)	85.2 (8.5)†	85.5 (8.4)‡	86.8 (8.5)‡	88.0 (8.9)‡
Systolic blood pressure, mmHg	132 (17)	<0.001	131 (19)	127 (17)	128 (16)	130 (16)	131 (16)	132 (16)†	134 (17)‡	137 (16)‡
Diastolic blood pressure, mmHg	77 (10)	<0.001	72 (11)	74 (11)	76 (10)	76 (10)	77 (10)	78 (10)	78 (10)‡	79 (10)‡
HDL cholesterol, mg/dL	60 (15)	<0.001	59 (16)	63 (16)	62 (16)	61 (15)	59 (15)*	59 (15)	58 (16)†	57 (14)‡
LDL cholesterol, mg/dL	121 (29)	0.053	115 (35)	116 (28)	120 (28)	120 (29)	122 (28)	122 (29)	121 (29)	121 (30)
Triglycerides, mg/dL	117 (66)	<0.001	135 (87)	101 (74)	106 (59)	110 (63)	118 (65)*	117 (61)	123 (70)‡	129 (78)‡
AST,U/L	25 (10)	<0.001	27 (11)	26 (15)	25 (12)	24 (8)	24 (9)	24 (7)	25 (13)	26 (13)†
ALT, U/L	22 (13)	<0.001	23 (19)	21 (20)	20 (10)	21 (12)	22 (12)	22 (11)	24 (14)‡	25 (14)‡
ɤ-GTP, U/L	37 (45)	<0.001	34 (27)	32 (56)	30 (37)	33 (40)	36 (41)	35 (40)	42 (50)‡	49 (56)‡
Hypertension, %	70.4%		63.9%	54.3%	62.1%	67.8%	68.9%	70.4%	75.0%	83.7%
Dyslipidemia, %	57.9%		61.1%	47.8%	55.7%	54.0%	59.4%	58.0%	61.1%	60.9%
Current smoking, %	12.3%		38.9%	11.2%	11.7%	11.3%	11.3%	12.3%	12.6%	15.4%
Drinking habit, %										
everyday	19.6%		36.1%	11.7%	14.0%	14.4%	17.3%	20.7%	24.6%	29.2%
sometimes	20.6%		11.1%	14.1%	20.8%	20.7%	20.8%	19.7%	22.5%	20.9%
rarely or never	59.8%		52.8%	74.2%	65.2%	64.9%	62.0%	59.6%	52.9%	49.8%
Exercise, %										
exercise resulting in light sweating	46.6%		41.9%	42.5%	42.5%	45.9%	48.8%	47.7%	45.8%	48.4%
walking>1 hour/day	54.8%		67.7%	47.2%	54.4%	52.7%	56.2%	55.1%	54.4%	58.5%

Values are mean (SD) or %. *p<0.05, †p<0.01, and ‡p<0.001 vs. 85-89 mg/dL. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

Table 3. Unadjusted and multivariable-adjused ORs (95% CI) for the risk of new-onset diabetes mellitus

Total subjects (n=88,422)

Fasting plasma glucose	Model 1 (Unadjusted)		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<70 mg/dL	2.17 (1.28-3.68)	<0.01	2.17 (1.28-3.69)	<0.01	2.03 (1.19-3.46)	<0.01	1.98 (1.16-3.37)	<0.05	2.14 (1.25-3.65)	<0.01
70-79 mg/dL	0.87 (0.62-1.23)	0.44	0.94 (0.66-1.33)	0.73	0.93 (0.66-1.32)	0.70	0.95 (0.67-1.34)	0.77	0.88 (0.60-1.30)	0.53
80-84 mg/dL	0.73 (0.56-0.94)	<0.05	0.75 (0.58-0.97)	<0.05	0.75 (0.58-0.97)	<0.05	0.76 (0.59-0.98)	<0.05	0.77 (0.58-1.01)	0.06
85-89 mg/dL	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
90-94 mg/dL	1.21 (1.02-1.44)	<0.05	1.16 (0.98-1.39)	0.09	1.17 (0.98-1.39)	0.09	1.15 (0.97-1.37)	0.12	1.18 (0.98-1.42)	0.07
95-99 mg/dL	2.04 (1.73-2.40)	<0.001	1.88 (1.60-2.23)	<0.001	1.89 (1.61-2.23)	<0.001	1.84 (1.56-2.17)	<0.001	1.88 (1.58-2.23)	<0.001
100-109 mg/dL	4.91 (4.23-5.69)	<0.001	4.37 (3.76-5.07)	<0.001	4.37 (3.76-5.07)	<0.001	4.19 (3.61-4.86)	<0.001	4.37 (3.73-5.12)	<0.001
110-125 mg/dL	22.26 (19.24-25.77)	<0.001	19.14 (16.51-22.18)	<0.001	19.14 (16.51-22.18)	<0.001	18.01 (15.53-20.88)	<0.001	19.15 (16.35-22.42)	<0.001

Without cardiovascular disease (n=81,639)

Fasting plasma glucose	Model 1 (Unadjusted)		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<70 mg/dL	1.87 (1.01-3.46)	<0.05	1.87 (1.01-3.47)	<0.05	1.73 (0.93-3.21)	0.08	1.68 (0.91-3.12)	0.10	1.79 (0.96-3.33)	0.07
70-79 mg/dL	0.84 (0.58-1.24)	0.38	0.91 (0.62-1.33)	0.62	0.90 (0.61-1.32)	0.58	0.91 (0.62-1.34)	0.63	0.79 (0.51-1.22)	0.29
80-84 mg/dL	0.76 (0.58-1.00)	0.05	0.79 (0.60-1.03)	0.09	0.79 (0.60-1.03)	0.09	0.79 (0.60-1.04)	0.10	0.80 (0.59-1.07)	0.13
85-89 mg/dL	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
90-94 mg/dL	1.26 (1.05-1.53)	<0.05	1.22 (1.01-1.47)	<0.05	1.22 (1.01-1.48)	<0.05	1.21 (1.00-1.46)	<0.05	1.22 (1.00-1.48)	0.05
95-99 mg/dL	2.14 (1.80-2.56)	<0.001	1.99 (1.67-2.38)	<0.001	1.99 (1.67-2.38)	<0.001	1.94 (1.63-2.32)	<0.001	1.95 (1.62-2.35)	<0.001
100-109 mg/dL	5.23 (4.46-6.14)	<0.001	4.68 (3.99-5.51)	<0.001	4.68 (3.98-5.50)	<0.001	4.49 (3.82-5.28)	<0.001	4.62 (3.89-5.48)	<0.001
110-125 mg/dL	24.42 (20.84-28.61)	<0.001	21.18 (18.04-24.86)	<0.001	21.18 (18.04-24.86)	<0.001	19.97 (17.00-23.45)	<0.001	20.93 (17.66-24.82)	<0.001

With cardiovascular disease (n=6,783)

Fasting plasma glucose	Model 1 (Unadjusted)		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<70 mg/dL	4.28 (1.44-12.77)	<0.01	4.31 (1.44-12.95)	<0.01	4.46 (1.48-13.44)	<0.01	4.40 (1.45-13.33)	<0.01	5.24 (1.71-16.11)	<0.01
70-79 mg/dL	1.07 (0.47-2.43)	0.88	1.19 (0.52-2.71)	0.68	1.19 (0.52-2.71)	0.68	1.24 (0.54-2.84)	0.61	1.53 (0.66-3.56)	0.32
80-84 mg/dL	0.55 (0.27-1.12)	0.10	0.59 (0.29-1.20)	0.14	0.59 (0.29-1.20)	0.14	0.59 (0.29-1.20)	0.15	0.60 (0.27-1.32)	0.20
85-89 mg/dL	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
90-94 mg/dL	0.93 (0.59-1.49)	0.77	0.88 (0.55-1.40)	0.59	0.88 (0.55-1.40)	0.59	0.86 (0.54-1.38)	0.54	0.99 (0.60-1.64)	0.98
95-99 mg/dL	1.49 (0.97-2.31)	0.07	1.39 (0.90-2.15)	0.14	1.39 (0.90-2.15)	0.14	1.37 (0.89-2.12)	0.16	1.52 (0.94-2.45)	0.09
100-109 mg/dL	3.16 (2.15-4.66)	<0.001	2.78 (1.88-4.11)	<0.001	2.78 (1.88-4.11)	<0.001	2.70 (1.83-3.99)	<0.001	3.05 (1.98-4.69)	<0.001
110-125 mg/dL	10.87 (7.42-15.94)	<0.001	9.15 (6.21-13.47)	<0.001	9.16 (6.22-13.49)	<0.001	8.81 (5.98-12.99)	<0.001	10.17 (6.64-15.57)	<0.001

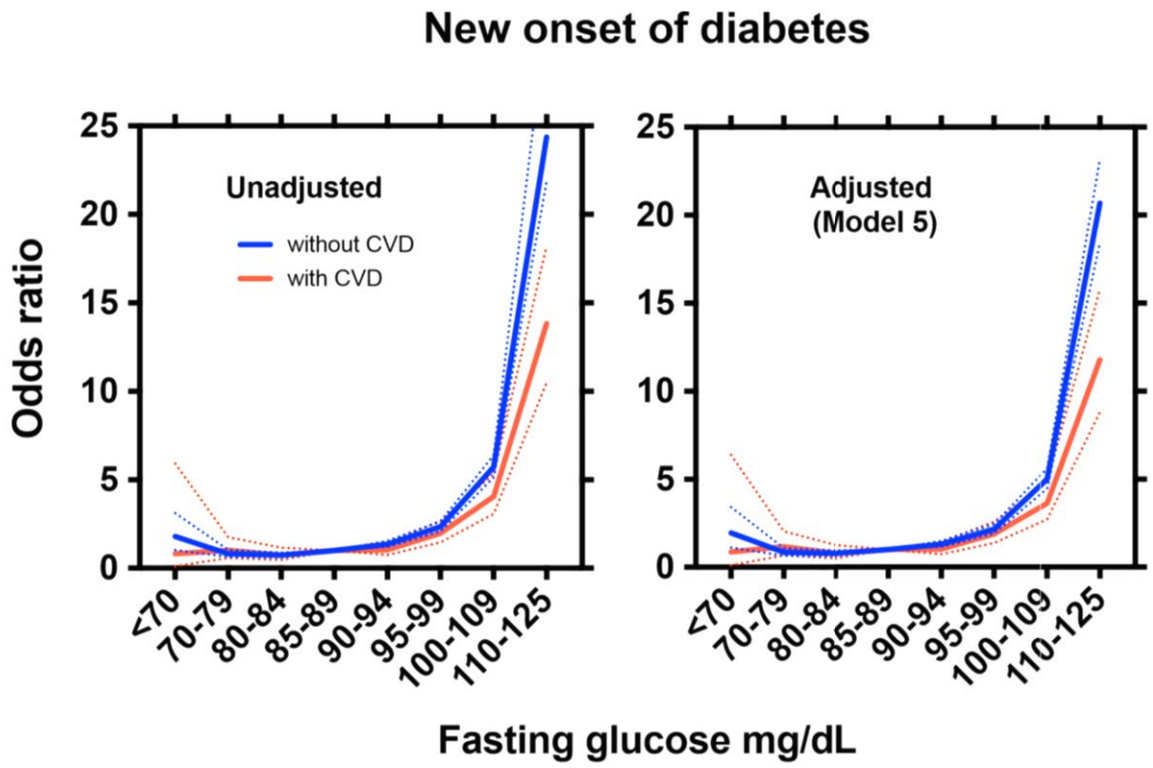
Values are odds ratios (95% confidential intervals). Model 2 (sex, age, BMI), Model 3 (sex, age, BMI, current smoking), Model 4 (sex, age, BMI, current smoking, hypertension, dyslipidemia), and Model 5 (sex, age, BMI, current smoking, drinking habit, hypertension, dyslipidemia). For Model 1 and Model 5 in participants with or without cardiovascular disease, see also Figure 1. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

Figure legend

Figure 1. Unadjusted and adjusted odds ratio for new-onset diabetes mellitus

Among participants who underwent Japanese nation-wide annual health check program, The Specific Health Check and Guidance System (SHCG) in 2008, non-diabetic participants without (n=81,639, blue line) or with (n=6783, red line) a history of cardiovascular diseases (CVD), between the age of 40 and 74 years, were selected and divided to 8 categories according to the fasting plasma glucose levels: less than 70 mg/dL, 70 to 79 mg/dL, 80 to 84 mg/dL, 85 to 89 mg/dL, 90 to 94 mg/dL, 95 to 99 mg/dL, 100 to 109 mg/dL, and 110 to 125 mg/dL. The odds ratios for new-onset diabetes mellitus in the 3-year follow up were calculated with 85 to 89 mg/dL as the reference category. Unadjusted and adjusted (Model 5, adjusted for sex, age, BMI, current smoking, drinking habit, hypertension, dyslipidemia) odds ratios are shown as solid (ORs) and dotted lines (95% confidential intervals). To convert glucose from mg/dL to mmol/L, multiply by 0.0555. P values vs the reference category, see Table 3.

Figure 1.


New onset of diabetes
Odds ratio
25
20
15
10
5
0
Unadjusted
without CVD
with CVD
Adjusted
(Model 5)
<70
70-79
80-84
85-89
90-94
95-99
100-109
110-125
Fasting glucose mg/dL