RESEARCH ARTICLE

Relationships of habitual daily alcohol consumption with all-day and time-specific average glucose levels among non-diabetic population samples

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Abstract

Background: Alcohol consumption is a prevalent behavior that is bi-directionally related to the risk of type 2 diabetes. However, the effect of daily alcohol consumption on glucose levels in real-world situations in the general population has not been well elucidated. This study aimed to clarify the relationship between alcohol consumption and all-day and time-specific glucose levels among non-diabetic individuals.

Methods: We investigated 913 non-diabetic males and females, aged 40–69 years, during 2018–2020 from four communities across Japan. The daily alcohol consumption was assessed using a self-report questionnaire. All-day and time-specific average glucose levels were estimated from the interstitial glucose concentrations measured using the Flash glucose monitoring system for a median duration of 13 days. Furthermore, we investigated the association between all-day and time-specific average glucose levels and habitual daily alcohol consumption levels, using never drinkers as the reference, and performed multiple linear regression analyses after adjusting for age, community, and other diabetes risk factors for males and females separately.

Results: All-day average glucose levels did not vary according to alcohol consumption categories in both males and females. However, for males, the average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h were higher in moderate and heavy drinkers than in never drinkers, with the difference values of 4.6 and 4.7 mg/dL for moderate drinkers, and 5.7 and 6.8 mg/dL for heavy drinkers. Conversely, the average glucose levels between 17:00 and 24:00 h were lower in male moderate and heavy drinkers and female current drinkers than in never drinkers; the difference values of mean glucose levels were −5.8 for moderate drinkers, and −6.1 mg/dL for heavy drinkers in males and −2.7 mg/dL for female current drinkers.

Conclusions: Alcohol consumption was associated with glucose levels in a time-dependent biphasic pattern.

Keywords: Glucose levels, Alcohol consumption, Time-specific, Community-based samples, Non-diabetic, Flash glucose monitoring system

Background

The prevalence of diabetes mellitus (DM) and impaired glucose tolerance is rapidly increasing worldwide. According to the International Diabetes Federation (IDF), the worldwide diabetic population reached 537 million in 2021, indicating that one in ten adults has diabetes mellitus [1]. Longstanding high blood glucose levels can damage blood vessels, leading to various health problems, such as retinopathy, renal disease, peripheral neuropathy [2], coronary heart disease, stroke [3, 4], and deaths attributable to diabetes mellitus. Healthcare expenditure due to diabetes mellitus is also on the rise, creating a significant social, financial, and healthcare system burden worldwide [5, 6]. Therefore, establishing evidence-based preventive measures against diabetes mellitus is an urgent issue.

Alcohol consumption is a prevalent behavior that is bi-directionally related to the risk of type 2 diabetes. Light drinking could lower this risk, whereas heavy drinking could increase it [7–9]. However, the effect of alcohol
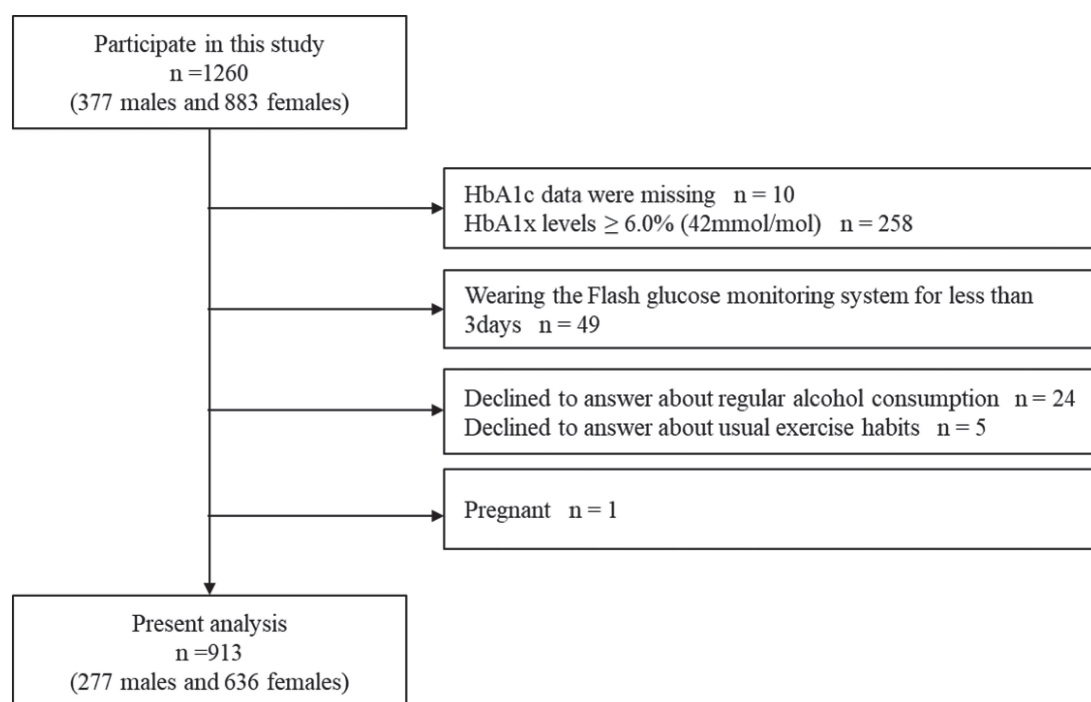
Fig. 1 Flowchart of study participants of the present study

consumption on glucose metabolism in daily life has not been well elucidated. A clinical experimental study of five non-diabetic young adult males showed that the ingestion of 48 g ethanol reduced glycogenesis by 45%, although plasma glucose concentrations did not change [10]. A randomized controlled trial of 51 non-diabetic postmenopausal females demonstrated that the ingestion of 30 g/day ethanol for eight weeks lowered fasting serum insulin concentrations by 20% but did not affect fasting plasma glucose levels compared with those in the placebo group [11]. However, these previous experimental studies did not capture the impact of daily alcohol consumption on glucose levels in real-world situations in the general population. Therefore, we aimed to clarify the relationship between habitual daily alcohol consumption and all-day and time-specific glucose levels in daily life using a Flash glucose monitoring system in community-based non-diabetic samples.

Methods

Study subjects

We included 1260 non-diabetic individuals (377 males and 883 females) who provided consent to participate in this study, were aged 40–69 years, and hailed from four communities, namely Ikawa town, Akita Prefecture (a northwestern rural community); Minami-Takayasu district, Yao City, Osaka Prefecture (a midwestern suburb); Kyowa district, Chikusei City, Ibaraki Prefecture (a mideastern rural community); and Kamisu City, Ibaraki Prefecture (an industrial area), in Japan. The first three communities

were sub-cohorts of the Circulatory Risk in Communities Study (CIRCS), an ongoing dynamic cohort study on lifestyle-related diseases involving approximately 12000 [12]. In Kamisu City, approximately 8000 adults receive health checkups annually, and the subjects were selected from among them. Surveys of daily glucose monitoring were conducted in 2019 in Ikawa, 2018–2019 in Minami-Takayasu, 2018–2020 in Kyowa, and 2019–2020 in Kamisu.

We excluded those participants whose hemoglobin A1c (HbA1c) data were missing (n = 10), whose HbA1c levels were ≥6.0% (42 mmol/mol) (n = 258), who were wearing the Flash glucose monitoring system for less than 3 days (n = 49), who declined to answer about regular alcohol consumption (n = 24), who declined to answer about usual exercise habits (n = 5), or who were pregnant (n = 1). In total, 913 participants (277 males and 636 females) were included in the present analysis (Fig. 1).

Measurements

Each participant's habitual daily alcohol consumption was assessed using a questionnaire. Participants were asked combined questions 1. whether they drank alcohol, and for current drinkers, 2. the amount of alcohol consumed per day in *go*-units (a Japanese traditional unit of volume equivalent to 23 g of ethanol). Alcohol consumption was categorized into five groups (never, former, Light; current <23, Moderate; 23–45, and Heavy; ≥46 g/day ethanol) for males and into three groups (never, former, and Current) for females.

The following covariates were also elicited by the ques-

tionnaire: the number of cigarettes smoked per day, their medical history, family history of diabetes mellitus, frequency and duration per occasion of physical activity during the past year (namely, for frequency: <1 /month, 1–3 /month, 1–2 /week, 3–4 /week, and every day; for time, <30 minutes, 30–59 minutes, 1–2 hours, 2–3 hours, and ≥4 hours), and skipping breakfast (yes or no).

Blood was collected from the participants in plastic serum separator gel tubes. The serum was allowed to stand for 15–20 minutes after collection and centrifuged for 15 minutes at 3000 rpm in a centrifuge with a turning radius of 16 to 18 cm within 30 minutes. In Ikawa and Minami-Takayasu, serum samples were transported to the Osaka Center for Cancer and Cardiovascular Disease Prevention, and serum glucose levels were measured using the hexokinase and glucose-6-phosphate dehydrogenase methods and an automatic analyzer (TBA-2000FR; Toshiba, Otawara, Tochigi, Japan), whereas HbA1c levels were measured using high-performance liquid chromatography with an HLC-723 G8 (Tosoh, Minato-ku, Tokyo, Japan). In kyowa and Kamisu, serum samples were transported to the Ibaraki Health Service Association, and serum glucose levels were measured using the hexokinase and ultraviolet absorption spectrophotometric methods, while HbA1c levels were assessed via enzymatic methods using an automatic analyzer (JCA-BM9130; JEOL Ltd, Tokyo, Japan). The body mass index (BMI) was calculated as weight in light clothing (kg) divided by height squared in stocking feet (m^2). The systolic and diastolic blood pressure levels were measured in the right arm by trained observers according to the unified epidemiological method, using automatic sphygmomanometers, except for participants in Minami-Takayasu in 2019, for whom standard mercury sphygmomanometers were used.

Measurement of the daily glucose levels

Glucose concentrations in the interstitial fluid were measured every 15 min for up to 15 days using a Flash glucose monitoring system (FGM; FreeStyle Libre Pro System, Abbott Diabetes Care, Inc. Alameda, CA, USA) in the upper left arm. We monitored glucose continuously, and analyzed date from day 2 through to the second-to-last day of recording. This was done because Freestyle Libre Pro is reported to be less accurate on the first day of measurement [13]. In addition, fewer data could be collected on the first and last days; hence, the average glucose values could not be calculated reliably. Finally, because of differences in the number of days of measurement among participants, the analyzed data amounted to one day in the shortest case and 13 days in the longest case. The distribution of the participants who had worn the FGM sensor for each span of days is shown in Table 1. For time-of-day classifications, because the nadirs of the daily glucose levels were found at 0:00, 5:00, 11:00, and 17:00 h (Fig. 2), we categorized the time range as follows: all-day, 0:00 to 5:00, 5:00 to 11:00, 11:00 to 17:00, and 17:00 to 24:00 h. The time-specific average glucose levels in each alcohol con-

Table 1 The distribution of the number of days participants wore the FGM sensor.

	Alcohol consumption				
	Never	Former	Light <23	Moderate 23–45	Heavy ≥46
Males					
No. of participants, n	77	13	77	51	59
Days wearing FGM sensor					
1 day, %	2.6	0.0	1.3	2.0	1.7
2 to 3 days, %	9.1	15.4	3.9	7.8	6.8
4 to 6 days, %	5.2	0.0	2.6	3.9	5.1
7 to 12 days, %	13.0	38.5	14.3	15.7	23.7
13 days (full days), %	70.1	46.2	77.9	70.6	62.7

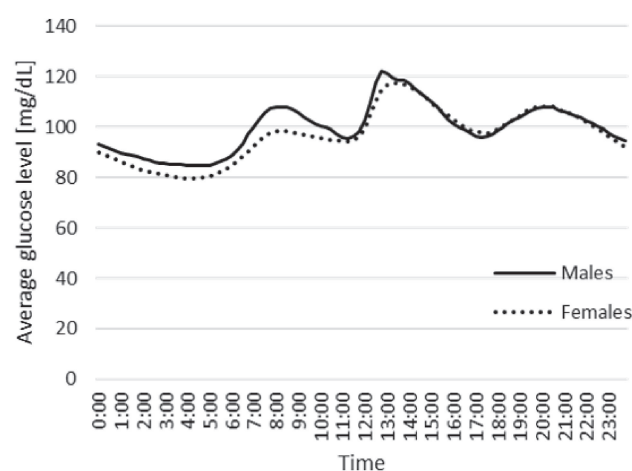|	Never	Former	Current
Females			
No. of participants, n	399	42	195
Days wearing FGM sensor			
1 day, %	2.0	2.4	1.0
2 to 3 days, %	1.8	4.8	3.6
4 to 6 days, %	3.8	4.8	5.1
7 to 12 days, %	18.1	19.1	14.4
13 days (full days), %	74.4	69.1	75.9

Fig. 2 Time-specific glucose levels among males and females.

sumption category were defined as the averaged values of individual mean glucose levels, which were calculated by averaging the measurement data of each participant in each time range without adjustment for sex, age, and community.

Statistical analysis

We compared the time-specific average glucose levels according to usual alcohol consumption with reference to never drinking, using multiple linear regression for males and females separately. The adjustment values included age (continuous), community (Ikawa, Minami-Takayasu, Chikusei, Kamisu), and other confounding variables, such as habitual smoking (never, former, current), the BMI (continuous), habitual physical activity (exercise at least 30 minutes a day at least once a week, yes or no), family

history of diabetes mellitus (yes or no), and skipping breakfast (yes or no). We conducted further adjustment for HbA1c levels at screening, after which HbA1c was categorized into two groups (≤ 5.5 and 5.6–5.9%, ≤ 37 and 38–41 mmol/mol) and stratified the HbA1c groups.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). P-values < 0.05 were considered to indicate statistical significance in two-tailed analyses.

Results

Of all participants, 667 (73%) wore the FGM sensor for full days. Table 2 shows the baseline characteristics according to the habitual alcohol consumption category among males and females. In males who were moderate and heavy alcohol consumers, the systolic and diastolic blood pressure, fasting and nonfasting blood glucose levels at screening, and the average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h were higher than those in others. Male heavy drinkers smoked more than others. Similarly, females who were current drinkers had higher fasting and nonfasting blood glucose levels as well as increased proportions of current smoking and skipping breakfast.

Figure 3 shows the time-specific variations of average glucose levels among alcohol consumption categories, and Table 3 shows the time-specific predicted differences in average glucose levels according to alcohol consumption categories among males and females. The all-day average glucose levels did not vary among alcohol consumption categories in either males or females. Among males, the time-specific average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h were approximately 5 to 7 mg/dL higher in moderate and heavy drinkers than in never drinkers, according to model 3 of the multivariable models. Contrastingly, the time-specific average glucose levels between 17:00 and 24:00 h were 6 mg/dL lower in male moderate and heavy drinkers and 3 mg/dL lower in female drinkers than in never drinkers, according to model 3.

Table 4 shows the results stratified by HbA1c levels at screening. The higher time-specific average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h in male heavy drinkers were more evident among males with 5.6–5.9% (38–41 mmol/mol) HbA1c levels. The lower time-specific average glucose levels between 17:00 and 24:00 h in male moderate and heavy drinkers and female drinkers were more evident among individuals with HbA1c $\leq 5.5\%$ (≤ 37 mmol/mol). The lower time-specific average glucose levels between 17:00 and 24:00 h in male light drinkers were more evident among males with HbA1c levels of 5.6–5.9% (38–41 mmol/mol).

Discussion

This is the first study to show an association between habitual daily alcohol consumption and time-specific glucose levels in daily life. Among males, the time-specific average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h were higher in moderate and heavy drinkers than in never drinkers. The time-specific average glucose levels between 17:00 and 24:00 h were lower in male moderate and heavy drinkers than in never drinkers and female current drinkers.

Possible mechanisms for the lowering of time-specific average glucose levels between 17:00 and 24:00 h among current drinkers could be the suppression of gluconeogenesis, caused by a decrease in the ratio of NAD to NADH [14] and the suppression of growth hormone secretion caused by the acute effect of alcohol consumption. The first mechanism can be explained as follows. Ethanol is oxidized by alcohol dehydrogenase to acetaldehyde and then metabolized to acetic acid by acetaldehyde dehydrogenase. NAD is consumed when ethanol is metabolized to acetaldehyde and acetic acid and thus reduced to NADH in the redox cycles. In an experimental study of five healthy adult males in fasting state, 48 g of ethanol consumption reduced gluconeogenesis by 45% after 5 h compared to no ethanol ingestion [10]. Japanese people generally consume alcohol only at dinner or night; hence, it is speculated that the acute effects of alcohol intake are those that appear between 17:00 and 24:00 h.

As the second mechanism, the acute suppression of growth hormone secretion by alcohol consumption re-
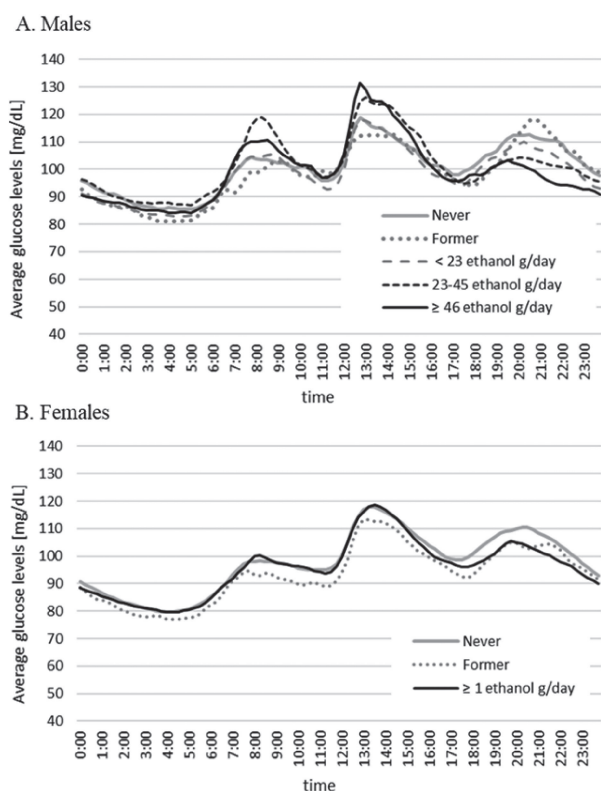

Fig. 3 Time-specific glucose levels according to alcohol consumption category among males and females.

Table 2 Characteristics of study subjects at baseline according to alcohol consumption.

	Alcohol consumption				
	Never	**Former**	**Light <23**	**Moderate 23–45**	**Heavy ≥46**
Males					
No. of participants, n	77	13	77	51	59
Age, years	55.7 (9.1)	58.4 (8.9)	56.5 (9.1)	58.7 (8.0)	56.3 (9.1)
Average glucose level, mg/dL					
All-day	100.5 (10.6)	98.6 (13.4)	98.2 (10.7)	101.5 (9.4)	99.3 (12.2)
0:00 to 5:00 h	88.9 (11.6)	85.1 (12.3)	85.6 (12.1)	89.8 (11.6)	86.7 (12.6)
5:00 to 11:00 h	97.6 (11.9)	94.7 (14.0)	97.1 (11.7)	102.7 (11.3)	100.3 (15.2)
11:00 to 17:00 h	106.9 (12.1)	106.2 (16.7)	105.3 (12.5)	112.0 (10.5)	114.4 (14.7)
17:00 to 24:00 h	105.9 (12.1)	105.0 (14.4)	101.9 (13.1)	99.9 (10.3)	97.2 (12.2)
HbA1c at screening, %	5.5 (0.2)	5.6 (0.2)	5.6 (0.2)	5.6 (0.2)	5.5 (0.3)
HbA1c at screening, mmol/mol	37 (2.6)	38 (2.4)	38 (2.5)	38 (2.2)	37 (2.6)
≤5.5 (≤37 mmol/mol), %	48.1	38.5	45.5	52.5	60.0
5.6–5.9 (38–41 mmol/mol), %	52.0	61.5	54.6	47.5	40.0
Fasting glucose at screening*, mg/dL	94.2 (6.9)	93.2 (8.1)	93.7 (6.8)	96.4 (9.5)	97.3 (9.1)
Non-fasting glucose at screening*, mg/dL	95.4 (12.6)	94.0 (11.6)	99.0 (16.1)	97.9 (16.6)	107.1 (28.7)
Body mass index, kg/m^2	23.7 (3.3)	23.9 (2.4)	23.8 (3.2)	24.1 (2.6)	23.5 (3.1)
Waist Circumstance, cm	84.2 (9.6)	84.1 (7.6)	84.4 (9.3)	85.6 (7.4)	84.5 (8.6)
Systolic blood pressure, mmHg	122.8 (14.0)	122.2 (13.4)	124.6 (13.5)	130.6 (15.0)	130.9 (14.9)
Diastolic blood pressure, mmHg	77.1 (9.9)	79.5 (9.9)	78.0 (9.6)	83.4 (9.0)	83.1 (9.6)
Antihypertensive medication, %	18.2	23.1	24.7	29.4	27.1
Smoking habit, %					
never	32.5	15.4	29.9	13.7	6.8
past	44.2	76.9	52.0	66.7	61.0
current	23.4	7.7	18.2	19.6	32.2
Exercise, %	39.0	61.5	41.6	47.1	37.3
Family history of diabetes mellitus, %	6.5	15.4	6.5	2.0	13.6
Skipping breakfast, %	26.0	7.7	18.2	15.7	22.0

	Never	**Former**	**Current**		
Females					
No. of participants, n	399	42	195		
Age, years	56.5 (8.4)	53.1 (8.3)	54.7 (8.0)		
Average glucose level, mg/dL					
All-day	97.6 (10.8)	93.5 (12.7)	95.9 (10.6)		
0:00 to 5:00 h	83.4 (11.5)	80.7 (14.2)	82.9 (11.4)		
5:00 to 11:00 h	92.8 (11.6)	88.6 (13.1)	92.7 (11.8)		
11:00 to 17:00 h	107.4 (13.0)	102.6 (13.4)	106.6 (13.7)		
17:00 to 24:00 h	103.5 (12.4)	98.9 (14.2)	98.7 (12.1)		
HbA1c at screening, %	5.6 (0.2)	5.6 (0.2)	5.5 (0.3)		
HbA1c at screening, mmol/mol	37 (2.5)	38 (2.1)	37 (2.9)		
≤5.5 (≤37 mmol/mol), %	41.6	30.2	48.2		
5.6–5.9 (38–41 mmol/mol), %	58.4	69.8	51.8		
Fasting glucose at screening*, mg/dL	91.4 (6.8)	92.0 (6.6)	93.6 (9.1)		
Non-fasting glucose at screening*, mg/dL	92.5 (13.2)	90.8 (10.1)	96.4 (17.1)		
Body mass index, kg/m^2	22.3 (3.6)	22.8 (4.5)	22.4 (3.7)		
Waist Circumstance, cm	79.0 (10.2)	80.5 (11.3)	79.7 (11.1)		
Systolic blood pressure, mmHg	120.9 (17.3)	116.6 (16.4)	119.8 (15.3)		
Diastolic blood pressure, mmHg	73.1 (10.5)	71.6 (9.9)	74.1 (10.4)		
Antihypertensive medication, %	10.3	7.0	5.1		
Smoking habit, %					
never	83.7	60.5	62.6		
past	10.3	30.2	22.6		
current	6.0	9.3	14.9		
Exercise, %	45.4	34.9	40.0		
Family history of diabetes mellitus, %	9.0	32.6	12.8		
Skipping breakfast, %	13.5	7.0	19.0		

In parentheses: standard deviations.

Table 3 Associations of time-specific average glucose levels (mg/dL) with alcohol consumption category.

	Never	Former		Light <23		Moderate 23–45		Heavy ≥46		
		β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value	
Males										
No. of participants, n	77	13		77		51		59		
all-day										
model 1	Ref.	3.4(−2.8,9.5)	.281	−1.8(−5.0,1.4)	.258	1.8(−1.8,5.4)	.336	0.8(−2.7.4.3)	.647	
model 2	Ref.	2.9(−3.2,9.1)	.348	−1.9(−5.1,1.3)	.236	1.0(−2.7,4.7)	.596	0.4(−3.2,3.9)	.832	
model 3	Ref.	3.0(−3.0,9.0)	.322	−2.0(−5.1,1.1)	.200	0.9(−2.7,4.5)	.613	1.4(−2.1,4.8)	.444	
0:00 to 5:00 h										
model 1	Ref.	1.4(−5.5,8.3)	.697	−2.6(−6.2,1.0)	.152	2.5(−1.6,6.6)	.236	−0.3(−4.2,3.6)	.879	
model 2	Ref.	1.6(−5.2,8.3)	.644	−2.5(−6.0,1.0)	.155	1.4(−2.6,5.5)	.486	−0.7(−4.6,3.1)	.706	
model 3	Ref.	1.7(−4.9,8.2)	.621	−2.6(−6.0,0.8)	.131	1.4(−2.6,5.3)	.498	0.2(−3.6,4.0)	.910	
5:00 to 11:00 h										
model 1	Ref.	2.4(−4.7,9.5)	.508	0.0(−3.7,3.7)	.997	5.7(1.5,10.0)	.008 †	4.8(0.7,8.8)	.021 *	
model 2	Ref.	1.8(−5.4,9.0)	.620	−0.3(−4.0,3.5)	.888	4.7(0.4,9.0)	.031 *	4.3(0.2,8.5)	.039 *	
model 3	Ref.	1.9(−5.0,8.8)	.587	−0.4(−4.0,3.2)	.826	4.6(0.5,8.8)	.028 *	5.7(1.6,9.7)	.006 †	
11:00 to 17:00 h										
model 1	Ref.	4.5(−2.8,11.8)	.225	−1.2(−4.9,2.6)	.550	5.5(1.2,9.8)	.013 *	6.5(2.4,10.7)	.002 †	
model 2	Ref.	3.4(−3.9,10.8)	.360	−1.4(−5.2,2.4)	.465	4.8(0.4,9.2)	.034 *	6.0(1.8,10.2)	.006 †	
model 3	Ref.	3.5(−3.8,10.8)	.346	−1.5(−5.3,2.3)	.436	4.7(0.4,9.1)	.034 *	6.8(2.5,11.0)	.002 †	
17:00 to 24:00 h										
model 1	Ref.	4.6(−2.3,11.5)	.193	−3.4(−7.0,0.1)	.060	−5.4(−9.4,−1.3)	.010 *	−6.7(−10.6,−2.7)	.001 †	
model 2	Ref.	4.5(−2.5,11.4)	.210	−3.4(−7.0,0.2)	.066	−5.8(−10.0,−1.6)	.007 †	−7.0(−11.0,−3.0)	.001 †	
model 3	Ref.	4.5(−2.4,11.4)	.196	−3.5(−7.0,0.1)	.056	−5.8(−10.0,−1.7)	.006 †	−6.1(−10.1,−2.1)	.003 †	

	Never	Former		Current		
		β (95%CI)	P-value	β (95%CI)	P-value	
Females						
No. of participants, n	399	42		195		
all-day						
model 1	Ref.	1.2(−2.0,4.4)	.454	−0.3(−1.9,1.4)	.762	
model 2	Ref.	1.2(−2.1,4.4)	.479	−0.2(−1.9,1.5)	.791	
model 3	Ref.	0.6(−2.6,3.7)	.710	−0.1(−1.7,1.6)	.937	
0:00 to 5:00 h						
model 1	Ref.	1.0(−2.7,4.7)	.588	0.3(−1.7,2.2)	.790	
model 2	Ref.	0.8(−2.8,4.4)	.655	−0.2(−2.0,1.7)	.874	
model 3	Ref.	0.3(−3.2,3.9)	.852	0.0(−1.9,1.9)	.987	
5:00 to 11:00 h						
model 1	Ref.	1.0(−2.5,4.4)	.583	1.3(−0.5,3.1)	.162	
model 2	Ref.	0.7(−2.9,4.2)	.705	1.4(−0.4,3.3)	.130	
model 3	Ref.	0.2(−3.3,3.7)	.920	1.6(−0.2,3.4)	.090	
11:00 to 17:00 h						
model 1	Ref.	1.6(−2.2,5.5)	.406	1.0(−1.1,3.0)	.356	
model 2	Ref.	1.7(−2.3,5.6)	.412	1.2(−0.9,3.3)	.259	
model 3	Ref.	1.1(−2.8,5.0)	.590	1.4(−0.7,3.4)	.189	
17:00 to 24:00 h						
model 1	Ref.	1.2(−2.4,4.8)	.518	−3.0(−4.9,−1.1)	.002 †	
model 2	Ref.	1.4(−2.3,5.1)	.450	−2.9(−4.9,−1.0)	.003 †	
model 3	Ref.	0.7(−2.8,4.3)	.683	−2.7(−4.6,−0.9)	.005 †	

β, partial regression coefficient; CI, confidence Intervals;

Model 1 was adjusted for age and community. Model 2 was adjusted further for smoking habit, BMI, family history of diabetes mellitus, exercise habits, skipping breakfast. Model 3 was adjusted further for HbA1c.

* P < 0.05, † P < 0.01, ‡ P < 0.001

Table 4 Associations of time-specific average glucose levels with alcohol consumption category, stratified by HbA1c levels.

		Alcohol consumption									
	Never	Former		Light <23		Moderate 23–45		Heavy ≥46			
		β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value		
Males											
No. of participants, n	37	5		35		20		31			
HbA1c ≤ 5.5%											
all-day											
model 1	Ref.	1.8(−8.2,11.8)	.718	0.1(−4.4,4.6)	.952	−0.2(−5.8,5.4)	.943	−0.9(−5.7,3.9)	.724		
model 2	Ref.	−0.2(−10.4,10.0)	.965	−0.4(−4.9,4.1)	.863	−2.5(−8.2,3.3)	.396	−3.0(−8.1,2.1)	.246		
model 3	Ref.	−0.8(−10.8,9.2)	.880	−1.0(−5.4,3.5)	.665	−2.9(−8.5,2.7)	.313	−2.1(−7.2,2.9)	.398		
0:00 to 5:00 h											
model 1	Ref.	−3.6(−14.7,7.6)	.531	−2.2(−7.3,2.8)	.384	−4.7(−11.0,1.5)	.138	−2.9(−8.2,2.5)	.296		
model 2	Ref.	−5.7(−16.8,5.4)	.313	−2.4(−7.4,2.5)	.328	−7.3(−13.5,−1.1)	.022	*	−4.9(−10.4,0.6)	.083	
model 3	Ref.	−6.4(−17.1,4.4)	.244	−3.2(−8.0,1.6)	.191	−7.8(−13.9,−1.8)	.012	*	−3.8(−9.2,1.6)	.166	
5:00 to 11:00 h											
model 1	Ref.	2.6(−9.0,14.2)	.660	1.7(−3.5,7.0)	.511	4.6(−1.9,11.0)	.168	3.9(−1.8,9.5)	.176		
model 2	Ref.	−0.2(−12.2,11.8)	.974	0.7(−4.6,6.0)	.799	2.1(−4.7,8.8)	.544	1.6(−4.3,7.6)	.585		
model 3	Ref.	−0.8(−12.6,11.0)	.895	0.0(−5.2,5.3)	.988	1.6(−5.0,8.2)	.629	2.6(−3.3,8.5)	.388		
11:00 to 17:00 h											
model 1	Ref.	3.4(−9.0,15.8)	.591	1.6(−4.0,7.2)	.564	5.6(−1.3,12.6)	.112	4.6(−1.4,10.6)	.128		
model 2	Ref.	1.1(−11.5,13.8)	.859	0.9(−4.7,6.5)	.758	3.5(−3.6,10.5)	.336	2.1(−4.1,8.4)	.503		
model 3	Ref.	0.8(−11.8,13.4)	.904	0.5(−5.2,6.1)	.868	3.2(−3.9,10.3)	.376	2.7(−3.6,9.0)	.397		
17:00 to 24:00 h											
model 1	Ref.	3.6(−7.4,14.5)	.519	−0.9(−5.8,4.1)	.727	−6.1(−12.2,0.0)	.051	−8.1(−13.4,−2.9)	.003	†	
model 2	Ref.	2.4(−8.8,13.5)	.676	−1.0(−5.9,4.0)	.702	−8.0(−14.3,−1.7)	.013	*	−10.0(−15.5,−4.4)	.001	‡
model 3	Ref.	1.9(−9.2,12.9)	.740	−1.5(−6.4,3.4)	.541	−8.4(−14.6,−2.2)	.008	†	−9.1(−14.7,−3.6)	.001	†
Hb A1c 5.6%–5.9%											
No. of participants, n	40	8		42		31		28			
all-day											
model 1	Ref.	3.6(−4.3,11.6)	.368	−3.8(−8.3,0.7)	.094	2.3(−2.7,7.2)	.364	2.9(−2.2,7.9)	.267		
model 2	Ref.	3.6(−4.6,11.9)	.387	−3.8(−8.4,0.8)	.108	2.2(−2.9,7.2)	.397	2.9(−2.4,8.1)	.281		
model 3	Ref.	3.3(−4.9,11.6)	.426	−3.7(−8.3,0.9)	.113	2.0(−3.0,7.1)	.425	2.9(−2.3,8.1)	.270		
0:00 to 5:00 h											
model 1	Ref.	4.2(−4.8,13.1)	.358	−3.0(−8.1,2.0)	.236	6.7(1.2,12.2)	.018	*	2.3(−3.3,8.0)	.418	
model 2	Ref.	4.4(−4.5,13.3)	.331	−3.0(−7.9,2.0)	.234	6.3(0.9,11.8)	.023	*	1.8(−3.8,7.5)	.520	
model 3	Ref.	4.2(−4.7,13.1)	.354	−2.9(−7.9,2.0)	.242	6.3(0.8,11.7)	.025	*	1.9(−3.8,7.5)	.512	
5:00 to 11:00 h											
model 1	Ref.	2.2(−7.1,11.5)	.643	1.8(−7.1,3.4)	.488	5.9(0.2,11.6)	.044	*	6.8(0.9,12.7)	.025	*
model 2	Ref.	2.2(−7.4,11.8)	.652	−1.6(−6.9,3.8)	.564	5.8(−0.1,11.7)	.054		7.2(1.1,13.2)	.021	*
model 3	Ref.	1.7(−7.8,11.1)	.725	−1.4(−6.7,3.8)	.590	5.6(−0.2,11.3)	.060		7.3(1.3,13.2)	.018	*
11:00 to 17:00 h											
model 1	Ref.	4.3(−5.1,13.7)	.368	−3.9(−9.2,1.4)	.144	4.5(−1.2,10.3)	.122	8.8(2.8,14.7)	.004	†	
model 2	Ref.	3.8(−5.9,13.6)	.438	−4.0(−9.4,1.4)	.147	4.2(−1.7,10.2)	.162	9.1(3.0,15.3)	.004	†	
model 3	Ref.	3.6(−6.1,13.3)	.467	−3.9(−9.3,1.5)	.153	4.1(−1.8,10.1)	.172	9.2(3.0,15.3)	.004	†	
17:00 to 24:00 h											
model 1	Ref.	3.9(−5.4,13.2)	.403	−6.1(−11.3,−0.8)	.023	*	−6.0(−11.7,−0.2)	.041	*	−5.2(−11.1,0.7)	.083
model 2	Ref.	4.1(−5.5,13.8)	.402	−6.1(−11.4,−0.7)	.027	*	−5.7(−11.6,0.2)	.058		−5.4(−11.5,0.7)	.080
model 3	Ref.	3.8(−5.8,13.5)	.432	−6.0(−11.3,−0.6)	.028	*	−5.8(−11.7,0.1)	.053		−5.4(−11.5,0.7)	.082

Table 4 (Continued.)

	Never	Former		Current	
		β (95%CI)	P-value	β (95%CI)	P-value
Females					
No. of participants, n	166	13		94	
HbA1c ≤ 5.5%					
all-day					
model 1	Ref.	2.4(−2.6,7.3)	.352	0.3(−1.8,2.5)	.771
model 2	Ref.	2.5(−2.6,7.6)	.333	0.2(−2.0,2.5)	.841
model 3	Ref.	2.2(−2.9,7.3)	.391	0.4(−1.8,2.6)	.708
0:00 to 5:00 h					
model 1	Ref.	0.5(−5.4,6.4)	.871	1.8(−0.7,4.4)	.156
model 2	Ref.	0.3(−5.6,6.2)	.922	1.4(−1.2,4.0)	.278
model 3	Ref.	0.1(−5.8,6.0)	.974	1.6(−1.0,4.2)	.239
5:00 to 11:00 h					
model 1	Ref.	1.7(−3.9,7.3)	.559	1.3(−1.2,3.7)	.310
model 2	Ref.	1.7(−4.1,7.4)	.565	1.4(−1.1,3.9)	.259
model 3	Ref.	1.5(−4.3,7.2)	.616	1.6(−0.9,4.1)	.216
11:00 to 17:00 h					
model 1	Ref.	4.0(−2.2,10.3)	.208	2.0(−0.8,4.7)	.158
model 2	Ref.	4.4(−2.0,10.8)	.176	2.1(−0.7,4.9)	.142
model 3	Ref.	4.1(−2.3,10.4)	.206	2.3(−0.5,5.0)	.108
17:00 to 24:00 h					
model 1	Ref.	2.9(−2.8,8.6)	.320	−3.0(−5.5,−0.5)	.019 *
model 2	Ref.	3.2(−2.6,9.0)	.282	−3.3(−5.8,−0.7)	.013 *
model 3	Ref.	2.8(−3.0,8.5)	.348	−3.0(−5.5,−0.4)	.021 *
HbA1c 5.6%–5.9%					
No. of participants, n	233	29		101	
all-day					
model 1	Ref.	0.2(−3.8,4.2)	.917	−0.2(−2.6,2.2)	.896
model 2	Ref.	0.0(−4.2,4.2)	.999	−0.1(−2.5,2.3)	.931
model 3	Ref.	−0.2(−4.4,4.0)	.925	−0.2(−2.6,2.2)	.867
0:00 to 5:00 h					
model 1	Ref.	0.7(−4.0,5.4)	.782	−0.5(−3.3,2.3)	.735
model 2	Ref.	−0.4(−5.0,4.2)	.868	−0.9(−3.6,1.8)	.513
model 3	Ref.	−0.5(−5.1,4.1)	.821	−1.0(−3.6,1.7)	.480
5:00 to 11:00 h					
model 1	Ref.	0.4(−4.0,4.8)	.858	2.0(−0.6,4.6)	.136
model 2	Ref.	−0.4(−4.9,4.1)	.866	1.9(−0.8,4.5)	.164
model 3	Ref.	−0.5(−5.1,4.0)	.812	1.8(−0.8,4.4)	.183
11:00 to 17:00 h					
model 1	Ref.	0.0(−4.9,4.9)	.998	0.6(−2.3,3.6)	.664
model 2	Ref.	0.2(−4.9,5.3)	.939	0.8(−2.2,3.8)	.600
model 3	Ref.	−0.1(−5.2,5.1)	.984	0.7(−2.3,3.7)	.659
17:00 to 24:00 h					
model 1	Ref.	−0.1(−4.7,4.5)	.974	−2.4(−5.2,0.3)	.081
model 2	Ref.	0.4(−4.3,5.2)	.857	−2.0(−4.8,0.8)	.155
model 3	Ref.	0.2(−4.5,4.9)	.930	−2.1(−4.9,0.6)	.132

β, partial regression coefficient; CI, confidence Intervals;
Model 1 was adjusted for age and community. Model 2 was adjusted further for smoking habit, BMI, family history of diabetes mellitus, exercise habits, skipping breakfast. Model 3 was adjusted further for HbA1c.
* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$

sulted in increased insulin sensitivity and reduced blood glucose levels [15, 16]. Ingestion of 0.8 g/kg of alcohol reduces plasma growth hormone secretion at night by 70–75% of non-drinking baseline levels among healthy males aged 21–26 years [15]. A randomized double-blinded trial demonstrated that consuming gin alone or both gin and tonic, but not tonic alone, results in a marked reduction in plasma growth hormone levels and hypoglycemia within 5 h of drinking [17]. Thus, the abovementioned mechanisms may explain the lower average glucose levels between 17:00 and 24:00 h in current drinkers than in never drinkers in our study.

Contrastingly, the average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h were higher in male moderate and heavy drinkers than in non-drinkers. This can be explained by different physiological processes during the 17:00 to 24:00 post-drinking interval, i.e., increased glucocorticoid levels and sympathetic excitation. Alcohol activates the hypothalamic-pituitary-adrenal axis, resulting in a dose-dependent increase in adrenocorticotropic hormone and glucocorticoid levels [18, 19]. In addition, acetaldehyde, a metabolite of alcohol, acts on the adrenal medulla and sympathetic ganglia to release catecholamines, resulting in sympathetic nerve excitation [20]. In a previous study of 539 Japanese males aged 35–65 years, heavy drinkers ($\geq$46 g ethanol/day) had higher salivary cortisol concentrations and a higher prevalence of blood pressure surge in the morning and higher sympathetic nervous activity and an increased heart rate during both daytime and sleep, than non-drinkers [21]. Since the amount of alcohol metabolized per hour is approximately 100 mg/kg of body weight [22], these hormonal and sympathetic nervous effects can last for 8 h after heavy drinking. Indeed, the long-lasting effects of heavy drinking may become more apparent after the aforementioned acute effects of heavy drinking are attenuated. The higher average glucose levels between 5:00 and 11:00 h and between 11:00 and 17:00 h observed in male moderate and heavy drinkers were probably due to the alcohol-induced increase in glucocorticoid levels and sympathetic nervous system activity.

Furthermore, suppressed glucose levels between 17:00 and 24:00 h were more pronounced in the individual with HbA1c $\leq$ 5.5% ($\leq$37 mmol/mol), while increased glucose levels between 5:00 and 11:00 h, between 11:00 and 17:00 h were more pronounced in those with HbA1c of 5.6–5.9% (38–41 mmol/mol). The reason may be due to differences in the basal insulin secretory capacity of the pancreas and the insulin resistance of skeletal muscle and liver.

Strengths and limitations

Our study has several strengths. First, the large sample size enabled us to conduct stratified analyses based on sex and HbA1c levels. Second, our study population was community-dwelling, which ensured the generalizability of our findings. Third, we monitored the daily variation of glu-

cose levels for many days consecutively, which reduced the impact of inter-day variations in glucose levels on the observed association.

The limitations of this study should also be discussed. First, our investigation was cross-sectional; hence, we could not determine the causality between drinking behavior and glucose levels or whether glucose levels affect drinking behavior. However, because our subjects were non-diabetic persons, it is unlikely that glucose levels could affect drinking behavior. Second, we could not examine the association between moderate and heavy drinking in females because of the limited sample size. Third, we did not have the data on alcohol beverage types and time of alcohol consumption, which warrant future studies. Forth, participants in our study may be more health conscious than non-participants, and thus selection bias may exist. Therefore, our results were likely to be generalizable, but not representative of the general population.

Conclusions

Alcohol consumption was associated with glucose levels in a time-dependent biphasic pattern. It remained uncertain how a time-dependent biphasic patterns of glucose levels by alcohol consumption lead to the development of diabetes mellitus, which will be examined in the future. Circadian changes in glucose levels among nondiabetic persons would provide useful information for the modification of lifestyle in the prevention of diabetes mellitus.

Abbreviations
BMI: body mass index; DM: diabetes mellitus; FGM: Flash glucose monitoring system; IDF: International Diabetes Federation.

Declarations
Ethics approval and consent to participate
The study protocol was approved by the ethics committees of Osaka University, the University of Tsukuba, and the Osaka Center for Cancer and Cardiovascular Disease Prevention. Written and oral explanations were provided to the participants and written informed consent was obtained.

Consent for publication
Not applicable.

Availability of data and material
Data cannot be shared for privacy or ethical reasons.

Competing interests
All authors declare no conflict of interest.

Authors' contributions
M.I.: Designed the study, wrote original draft preparation, initial statistical analysis, investigation, and data curation H.Imano: Reviewed, editing, revised statistical analysis, revised the manuscript, conceptualization, and supervised. I.M.: Revised the manuscript and investigation. K.Y.: Revised the manuscript and investigation.

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