Table 1a. Baseline Characteristics at the First Visit According to %dWC

variables	%dWC-Q1 (range: −21.3–−3.4)	%dWC-Q2 (range: −3.4–−0.1)	%dWC-Q3 (range: 0.0–3.3)	%dWC-Q4 (range: 3.3–33.4)	*p* value
Women					
n	348	202	223	426	
Age, years	53 (52-54)	53 (51-54)	51 (50-53)	51 (50-52)	0.066
Height, cm	156 (156-157)	157 (156-158)	157 (156-158)	157 (157-158)	0.037
Weight, kg	50 (51-52)	52 (52-54)	52 (52-55)	51 (51-53)	0.009
WC, cm	79 (78-80)	77 (77-80)	76 (76-78)	72 (73-74)	<0.001
BMI, kg/m^2	20.7 (20.7-21.3)	21.1 (21.2-22.2)	21.1 (21.2-22.1)	20.8 (20.8-21.3)	0.028
Systolic blood pressure, mmHg	115 (116-119)	118 (118-123)	114 (115-120)	113 (115-118)	0.129
Diastolic blood pressure, mmHg	72 (72-75)	73 (73-76)	72 (72-75)	71 (71-74)	0.198
Pulse rate, bpm	63 (63-64)	63 (62-65)	63 (63-65)	63 (63-64)	0.937
LDL-cholesterol, mg/dL	131 (127-134)	130 (125-134)	127 (124-133)	122 (121-127)	0.021
HDL-cholesterol, mg/dL	68 (68-71)	66 (66-70)	68 (67-70)	68 (68-70)	0.329
Trigryceride, mg/dL	77 (81-91)	77 (84-99)	77 (79-93)	69 (76-83)	0.026
Uric acid, mg/dL	4.5 (4.5-4.7)	4.5 (4.4-4.7)	4.6 (4.5-4.7)	4.4 (4.4-4.5)	0.076
Fasting glucose, mg/dL	87 (87-90)	89 (89-93)	88 (88-91)	88 (88-91)	0.149
Hemoglobin A1c, %	5.1 (5.1-5.2)	5.2 (5.1-5.2)	5.1 (5.1-5.2)	5.1 (5.1-5.2)	0.284
Blood urea nitrogen, mg/dL	13.0 (13.0-13.8)	13.0 (13.2-14.2)	13.0 (12.9-13.7)	13.0 (13.2-13.8)	0.705
Serum creatinine, mg/dL	0.60 (0.61-0.70)	0.60 (0.62-0.65)	0.60 (0.61-0.63)	0.60 (0.62-0.64)	0.408
Anti-dyslipidemic medication, *n* (%)	13 (3.7)	11 (5.4)	6 (2.7)	16 (3.8)	0.526
Anti-hypertensive medication, *n* (%)	27 (7.8)	18 (8.9)	9 (4.0)	17 (4.0)	0.022
Current smoker, *n* (%)	36 (10.3)	15 (7.4)	12 (5.4)	44 (10.3)	0.117
Men					
n	462	589	600	363	
Age, years	54 (53-55)	54 (53-54)	54 (53-54)	53 (51-53)	0.040
Height, cm	169 (169-170)	170 (169-170)	169 (169-170)	169 (169-170)	0.975
Weight, kg	68 (68-70)	68 (68-69)	67 (68-69)	67 (67-68)	0.328
WC, cm	88 (87-89)	87 (86-87)	85 (85-86)	82 (82-84)	<0.001
BMI, kg/m^2	23.8 (23.6-24.2)	23.7 (23.6-24.0)	23.6 (23.6-24.0)	23.3 (23.2-23.8)	0.150
Systolic blood pressure, mmHg	128 (127-131)	125 (127-130)	124 (125-127)	121 (121-124)	<0.001
Diastolic blood pressure, mmHg	81 (81-83)	80 (80-82)	79 (79-81)	77 (77-79)	<0.001
Pulse rate, bpm	62 (62-64)	62 (62-64)	62 (62-64)	61 (61-63)	0.347
LDL-cholesterol, mg/dL	132 (129-134)	130 (128-133)	129 (127-132)	125 (124-131)	0.225
HDL-cholesterol, mg/dL	54 (55-58)	54 (54-57)	53 (54-56)	55 (55-58)	0.328
Trigryceride, mg/dL	111 (122-136)	111 (123-134)	111 (126-140)	100 (115-133)	0.037
Uric acid, mg/dL	6.1 (6.0-6.2)	6.1 (6.1-6.3)	6.0 (6.0-6.2)	6.2 (6.0-6.2)	0.290
Fasting glucose, mg/dL	95 (97-100)	95 (97-99)	94 (95-97)	93 (94-97)	0.008
Hemoglobin A1c, %	5.3 (5.3-5.4)	5.3 (5.3-5.4)	5.2 (5.2-5.3)	5.2 (5.2-5.3)	0.005
Blood urea nitrogen, mg/dL	14.0 (14.3-15.0)	14.0 (14.4-14.9)	14.0 (14.0-14.6)	14.0 (14.1-14.7)	0.405
Serum creatinine, mg/dL	0.80 (0.83-0.92)	0.80 (0.85-0.87)	0.85 (0.85-0.87)	0.80 (0.84-0.86)	0.647
Anti-dyslipidemic medication, *n* (%)	18 (3.9)	25 (4.2)	28 (4.7)	16 (4.4)	0.942
Anti-hypertensive medication, *n* (%)	58 (12.6)	77 (13.1)	84 (14.0)	42 (11.6)	0.736
Current smoker, *n* (%)	137 (29.7)	194 (32.9)	175 (29.2)	121 (33.3)	0.352

Methods

Study Population

The study was approved by The Ethics Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11558 individuals underwent a general health screening at our institute. Of these, 3325 (2113 men, 1212 women) individuals

Table 1b. Baseline Characteristics at the First Visit According to %dBMI

variables	%dBMI-Q1 (range: −21.8–−1.9)	%dBMI-Q2 (range: −1.9–−0.2)	%dBMI-Q3 (range: −0.2–1.4)	%dBMI-Q4 (range: 1.4–15.7)	*p* value
Women					
n	284	268	305	342	
Age, years	53 (52-54)	54 (52-54)	52 (51-53)	49 (49-51)	0.002
Height, cm	156 (156-157)	157 (156-157)	158 (157-158)	157 (157-158)	0.005
Weight, kg	52 (52-54)	51 (52-53)	51 (51-53)	51 (51-53)	0.325
WC, cm	77 (76-78)	76 (76-78)	75 (75-77)	75 (75-77)	0.115
BMI, kg/m^2	21.3 (21.3-22.0)	20.9 (21.1-21.8)	20.5 (20.6-21.2)	20.7 (20.7-21.3)	0.002
Systolic blood pressure, mmHg	117 (118-123)	115 (115-119)	114 (115-119)	113 (115-118)	0.060
Diastolic blood pressure, mmHg	74 (73-76)	73 (72-75)	71 (72-74)	71 (71-74)	0.057
Pulse rate, bpm	63 (63-65)	64 (63-65)	61 (62-64)	63 (63-65)	0.106
LDL-cholesterol, mg/dL	133 (127-135)	132 (129-136)	125 (123-129)	117 (119-125)	<0.001
HDL-cholesterol, mg/dL	67 (66-70)	68 (67-71)	69 (68-71)	67 (67-70)	0.647
Trigryceride, mg/dL	79 (87-102)	76 (80-89)	74 (79-89)	68 (73-81)	0.002
Uric acid, mg/dL	4.5 (4.4-4.7)	4.4 (4.4-4.6)	4.6 (4.5-4.7)	4.4 (4.4-4.6)	0.408
Fasting glucose, mg/dL	88 (88-91)	88 (88-93)	88 (88-91)	88 (88-90)	0.933
Hemoglobin A1c, %	5.1 (5.1-5.2)	5.2 (5.1-5.3)	5.1 (5.1-5.2)	5.1 (5.0-5.1)	0.028
Blood urea nitrogen, mg/dL	13.0 (13.2-14.0)	13.0 (13.1-13.9)	13.0 (13.3-14.2)	13.0 (12.8-13.4)	0.174
Serum creatinine, mg/dL	0.60 (0.61-0.63)	0.60 (0.61-0.63)	0.60 (0.62-0.73)	0.60 (0.61-0.63)	0.002
Anti-dyslipidemic medication, *n* (%)	12 (4.2)	10 (3.7)	12 (3.9)	12 (3.5)	0.972
Anti-hypertensive medication, *n* (%)	23 (8.1)	15 (5.6)	16 (5.2)	17 (5.0)	0.352
Current smoker, *n* (%)	21 (7.4)	22 (8.2)	23 (7.5)	41 (12.0)	0.130
Men					
n	504	531	495	484	
Age, years	54 (53-55)	55 (54-55)	54 (53-54)	51 (51-52)	<0.001
Height, cm	169 (169-170)	169 (168-169)	170 (169-170)	170 (169-171)	0.012
Weight, kg	69 (68-70)	67 (67-68)	68 (68-69)	68 (67-69)	0.097
WC, cm	87 (86-87)	85 (85-86)	86 (85-87)	85 (85-86)	0.011
BMI, kg/m^2	24.0 (23.8-24.3)	23.4 (23.4-23.9)	23.7 (23.6-24.1)	23.5 (23.3-23.8)	0.012
Systolic blood pressure, mmHg	126 (127-130)	124 (125-128)	126 (125-129)	123 (123-126)	0.011
Diastolic blood pressure, mmHg	81 (81-83)	79 (79-81)	80 (80-82)	78 (78-80)	0.019
Pulse rate, bpm	62 (62-64)	62 (62-63)	62 (63-64)	62 (61-63)	0.106
LDL-cholesterol, mg/dL	133 (130-135)	129 (128-133)	130 (126-132)	125 (125-130)	0.014
HDL-cholesterol, mg/dL	54 (54-56)	54 (55-57)	54 (55-58)	54 (54-57)	0.437
Trigryceride, mg/dL	111 (126-141)	108 (123-136)	111 (120-135)	107 (118-132)	0.285
Uric acid, mg/dL	6.1 (6.1-6.3)	6.1 (6.0-6.2)	6.0 (6.0-6.2)	6.1 (6.0-6.3)	0.344
Fasting glucose, mg/dL	95 (97-100)	95 (97-100)	95 (95-97)	93 (94-96)	0.002
Hemoglobin A1c, %	5.3 (5.3-5.5)	5.3 (5.3-5.4)	5.2 (5.2-5.3)	5.2 (5.2-5.3)	<0.001
Blood urea nitrogen, mg/dL	14.0 (14.3-15.0)	14.0 (14.3-14.8)	14.0 (13.9-14.4)	14.0 (14.3-15.0)	0.130
Serum creatinine, mg/dL	0.80 (0.84-0.92)	0.80 (0.85-0.87)	0.80 (0.83-0.86)	0.90 (0.85-0.87)	0.303
Anti-dyslipidemic medication, *n* (%)	20 (4.0)	18 (3.4)	28 (5.7)	21 (4.3)	0.334
Anti-hypertensive medication, *n* (%)	72 (14.3)	81 (15.3)	47 (9.5)	61 (12.6)	0.035
Current smoker, *n* (%)	155 (30.8)	167 (31.5)	148 (29.9)	157 (32.4)	0.851

underwent a general health screening during this period (first visit) and again the following year (second visit). Among these 3325 individuals, 3213 (2014 men, 1199 women) who reported not taking antidiabetic drugs at either visit were enrolled in the current study. The mean ± standard deviation (SD) of the interval between the two visits of the individuals enrolled was 356 ± 51 days. The percent difference in

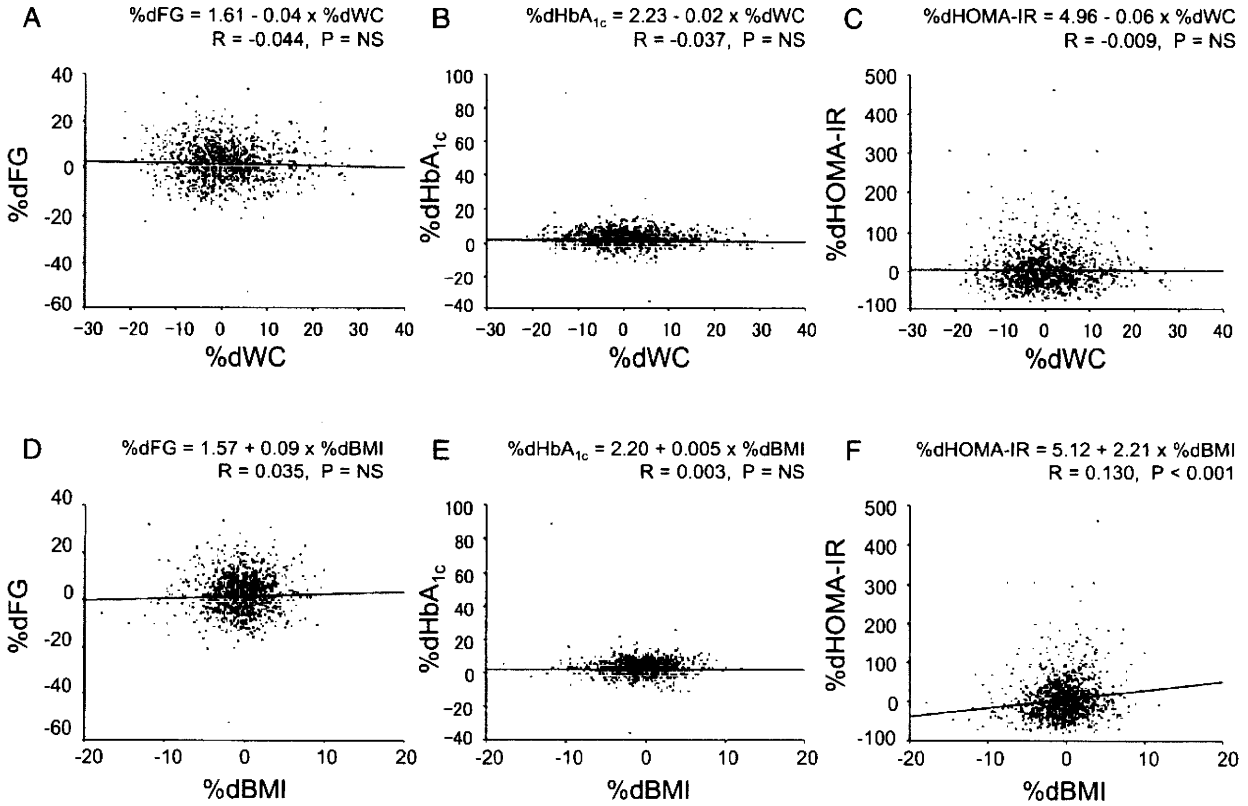

Fig. 1. Scatter plot and linear regression between %dWC and %dFG (A), %dHbA1c (B), and %dHOMA-IR (C) and between %dBMI and %dFG (D), %dHbA1c (E), and %dHOMA-IR (F) in women.

the value of WC, BMI, serum levels of fasting glucose (FG), HbA1c, and HOMA-IR between the first and second visits was designated %dWC, %dBMI, %dFG, %dHbA1c, and %dHOMA-IR, respectively. Blood samples were taken from all subjects after an overnight fast. BMI was expressed as weight (in kilograms) divided by the square of height (in meters). WC was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians[11].

Laboratory Analysis

Serum levels of TC, HDL-C, and TG were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method; hemoglobin A1c was determined by a latex agglutination immunoassay. Creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using a commercial kit. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the equation: HOMA-IR=(immunoreactive insulin (IRI)) × FBS/405. Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer.

Statistical Analysis

Data are expressed as the median (95% confidence interval (95%CI)) unless stated otherwise. The Kruskal-Wallis test, χ^2 test, logistic regression analysis, and multivariate linear regression analysis were applied as appropriate to assess the statistical significance of differences between groups using computer software, Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

We enrolled 1199 women and 2014 men in this study. The mean age of the individuals enrolled was 51.9 years in women and 53.4 years in men at the first visit. The sex-nonspecific range of the first to fourth %dWC quartiles was −21.3/−3.4, −3.4/−0.1, 0.0/3.3, and 3.3/33.4, respectively, and that of the first to fourth %dBMI quartiles was −21.8/−1.9, −1.9/−0.2, −0.2/1.4, and 1.4/15.7, respectively. Subject characteristics at the first visit are shown according to the

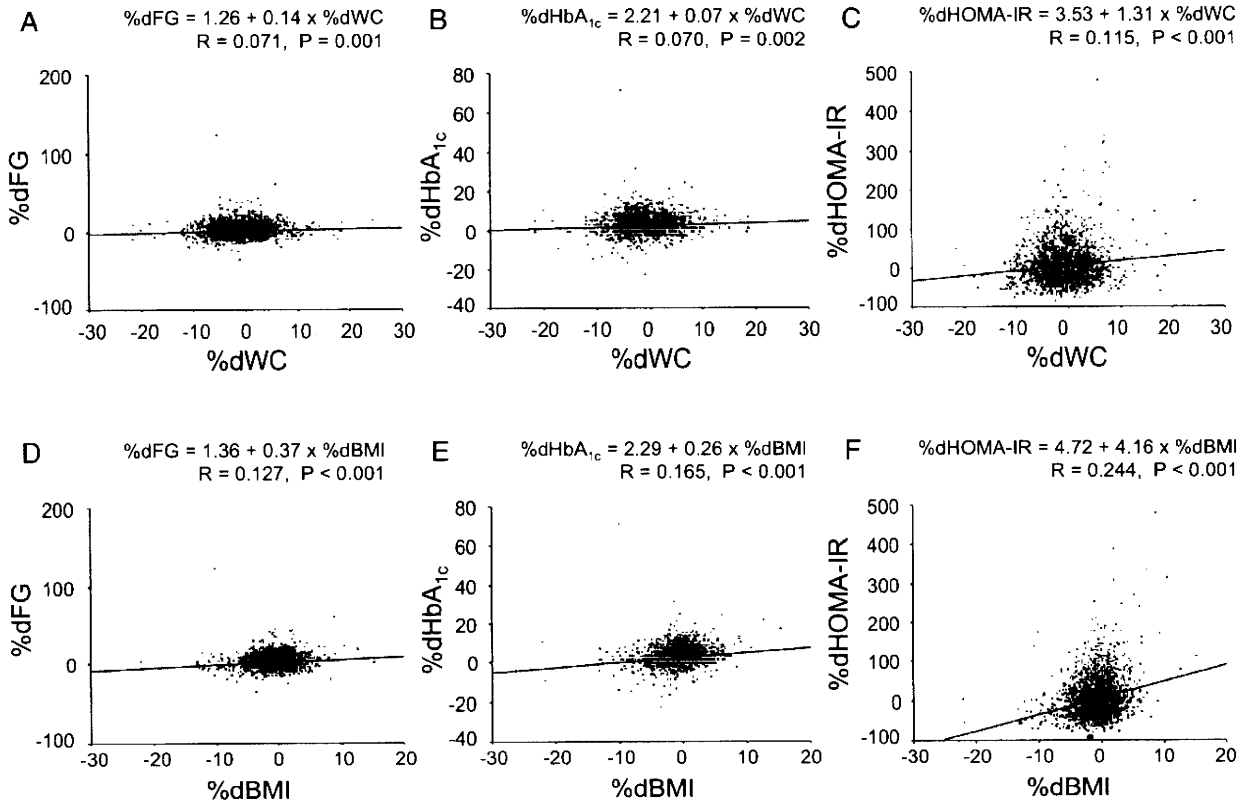

Fig. 2. Scatter plot and linear regression between %dWC and %dFG (A), %dHbA1c (B), and %dHOMA-IR (C) and between %dBMI and %dFG (D), %dHbA1c (E), and %dHOMA-IR (F) in men.

%dWC and %dBMI quartiles in **Table 1**. No statistically significant trends in the rate of anti-dyslipidemic medication or of current smoking were found across the four %dWC or %dBMI quartiles in either gender. The correlation coefficient between %dWC and %dBMI was 0.24 in women and 0.46 in men.

Association between Percent Changes in Obesity Parameters and Percent Changes in Diabetic Parameters

Scatter plots of %dWC and %dBMI versus %dFG, %dHbA1c and %dHOMA-IR, coupled with results of linear regression analyses, are shown in **Fig. 1** and **2**. In women, only the relationship between %dBMI and %dHOMA-IR was significant. In men, by contrast, the relationship was significant between both %dWC and %dBMI and the percent change in each of the diabetic parameters.

Fig. 3 and **4** show the percent changes in diabetic parameters according to the %dWC and %dBMI quartiles. In women, %dHOMA-IR increased with increasing %dBMI. In men, not only %dHOMA-IR but also %dFG and %dHbA1c increased with increasing %dWC and %dBMI.

Logistic Regression Analysis

A multivariate logistic regression analysis, adjusted for age at the first visit, of the second, third, and fourth %dBMI quartiles, showed that the first, second, third, and fourth %dBMI quartiles in men were associated with the highest %dHOMA-IR quartile (%dHOMA-IR >24.3%) with an odds ratio of 1.00 (reference), 1.47 (95%CI 1.08-2.01), 1.51 (95%CI 1.11-2.07), and 2.87 (95%CI 2.13-3.87), respectively. In women, on the other hand, the first, second, third, and fourth %dBMI quartiles were not significantly related to the highest %dHOMA-IR quartile (%dHOMA-IR >24.3%) with an odds ratio of 1.00 (reference), 1.23 (95%CI 0.82-1.85), 1.45 (95%CI 0.98-2.14), and 1.89 (95%CI 1.30-2.74), respectively.

Multivariate Linear Regression Analysis

In a multivariate linear regression analysis with age at the first visit and %dWC as independent vari-

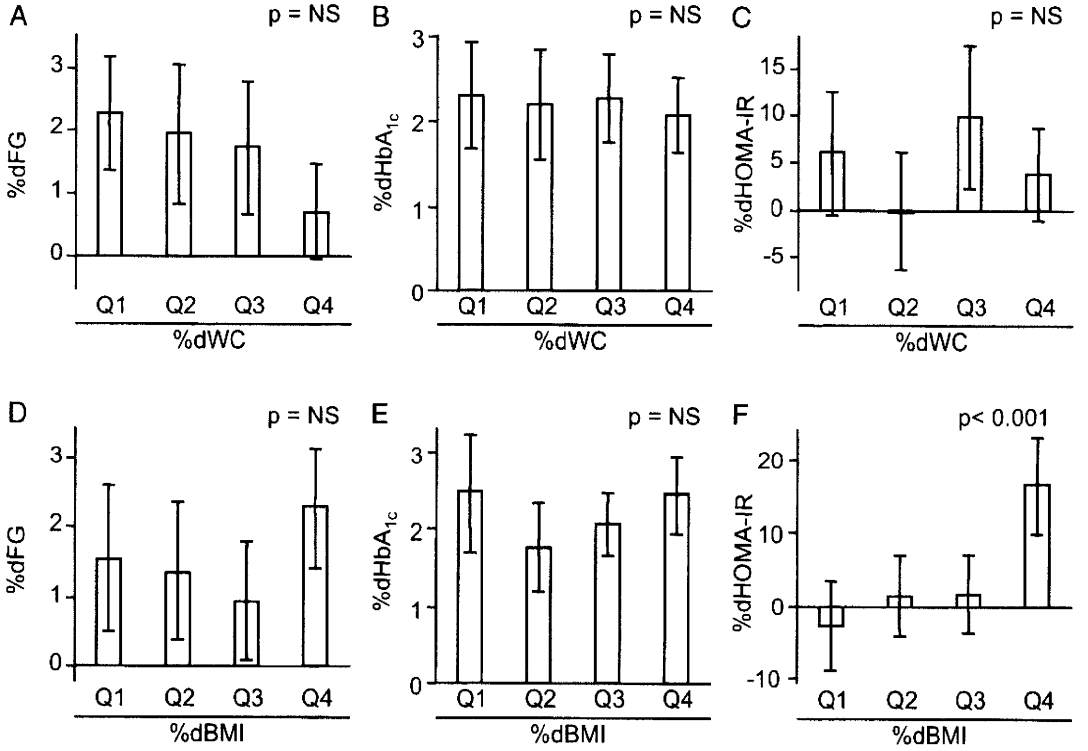

Fig. 3. %dFG (A), %dHbA$_{1c}$ (B), and %dHOMA-IR (C) according to %dWC quartiles, and %dFG (D), %dHbA$_{1c}$ (E), and %dHOMA-IR (F) according to %dBMI quartiles in women. The mean ± 95% confidence interval is shown in each group.

ables (**Table 2**, model 1), %dWC was an independent predictor for %dHOMA-IR in men, but not in women. However, when %dBMI was used as an additional covariate in the statistical model, %dWC did not remain significant (**Table 2**, model 2). In model 2, %dBMI was found to be an independent predictor for %dHOMA-IR, %dFG and %dHbA$_{1c}$ in men, but for only %dHOMA-IR in women.

Discussion

In the current study, we demonstrated that percent changes in obesity parameters (%dWC, %dBMI) were positively correlated with percent changes in glucose metabolism-related parameters (%dFG, %dHbA$_{1c}$, %dHOMA-IR) in men. In women, by contrast, there was no significant relationship between %dWC and percent changes in diabetic parameters, and %dBMI was not significantly associated with %dFG or %dHbA$_{1c}$. In the multivariate linear regression analysis, %dWC was a predictor for %dHOMA-IR in men, although it did not remain significant when %dBMI was used as an additional covariate in the statistical model, suggesting that changes in WC are not a predictor for changes in glucose-metabolism-related parameters independent of changes in BMI.

Obesity is associated with a cluster of specific metabolic abnormalities that may be related to cardiovascular risk factors[8, 12]. Wahrenberg *et al.* have reported that WC, which was found to be the strongest regressor among WC, BMI, log-plasma triglycerides, systolic blood pressure, and high-density lipoprotein cholesterol, is a risk factor for insulin resistance[13]. On the other hand, Onat *et al.* prospectively analyzed 1638 men and found that the age-adjusted waist-to-hip ratio (WHR) was significant in predicting diabetes mellitus[14]. Furthermore, Colditz *et al.* analyzed data from 114281 women who did not have diagnosis of diabetes mellitus, coronary heart disease, stroke, or cancer, and showed that BMI was the dominant predictor of risk for diabetes mellitus, although weight gain was also a risk factor for diabetes[15]. It has been shown that even small gains in weight during adulthood lead to a significantly increased risk of many chronic diseases[16]. Several studies showed that weight loss reduced regional depots of adipose tissue and

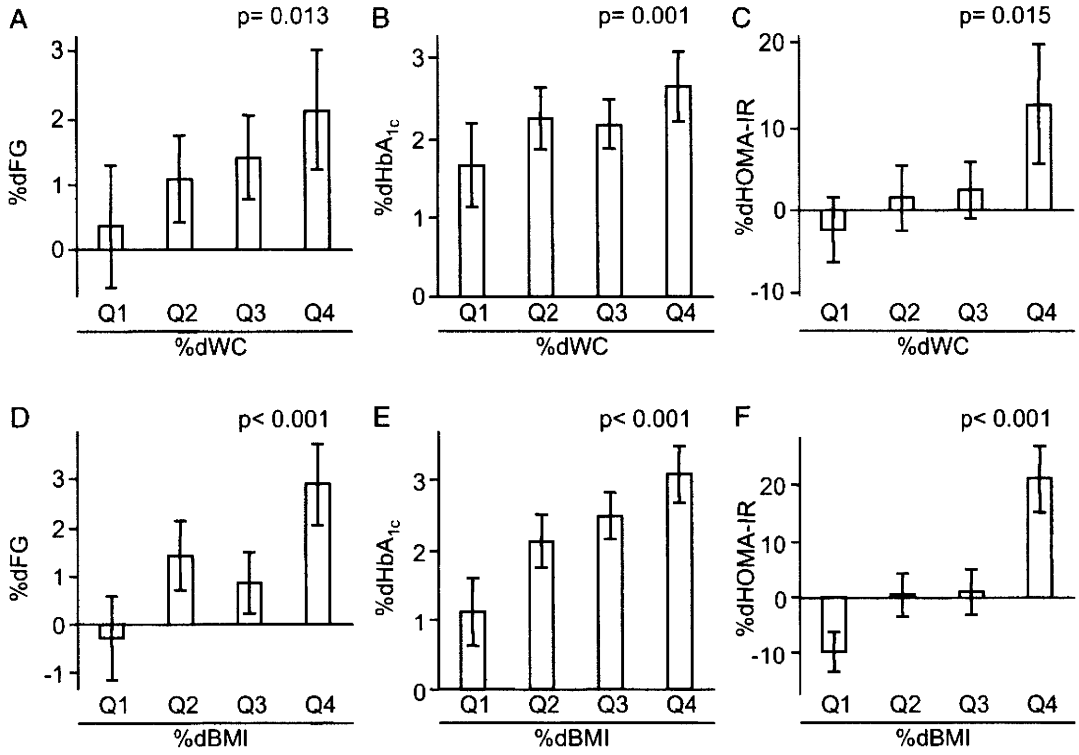

Fig. 4. %dFG (A), %dHbA$_{1c}$ (B), and %dHOMA-IR (C) according to %dWC quartiles, and %dFG (D), %dHbA$_{1c}$ (E), and %dHOMA-IR (F) according to %dBMI quartiles in men. The mean ± 95% confidence interval is shown in each group.

improved insulin sensitivity and cardiovascular risk factors[17, 18]. Pascale *et al.* analyzed 60 women and 33 men participating in a year-long weight loss program and concluded that improvements in FG, fasting insulin, and HbA$_{1c}$ were significantly related to weight loss[19].

Besides body weight, visceral fat has also been reported to be associated with β-cell function in individuals with impaired fasting glycemia and impaired glucose tolerance[9]. In general, BMI is strongly associated with subcutaneous fat area. As parameters of obesity, BMI and WC may have different meanings but similar associations. BMI may have a weaker association with visceral fat; by contrast, WC has a stronger correlation with visceral fat area in both genders[10]. It has been suggested that WC better reflects the accumulation of visceral fat than WHR[20, 21]. Therefore, it is possible that changes in WC have a stronger impact on changes in glucose metabolism as compared with changes in BMI.

In the current study, however, %dBMI was an independent factor predicting %dFG, %dHbA$_{1c}$, and %dHOMA-IR in men, and %dHOMA-IR in women. %dWC was an independent factor predicting %dHOMA-IR in men, only without adjustment for %dBMI. Why %dBMI had a stronger association with %dFG, %dHbA$_{1c}$ and %dHOMA-IR is not clear.

Because Asian women are relatively lean, subcutaneous fat may have a relatively greater influence on WC[22]. For example, Sakurai *et al.* analyzed 2935 men and 1622 women between 35 and 59 years of age: in a multiple logistic regression analysis, WC was associated with FG in both genders. However, the risk ratio of having two or more metabolic disorders was higher for BMI than for WC in women, suggesting WC to be a relatively poor discriminator of visceral fat, and BMI to be a more appropriate index of total and abdominal fat, especially in women[22, 23].

It has recently been demonstrated that the association between WC and cardiovascular risk markers, such as insulin resistance, weakens with age[24]. Janssen *et al.* reported that, although individuals with a moderate and high WC were likely to have elevated cardiometabolic risk markers irrespective of age, there seemed to be a significant correlation between age and WC, indicating that the relation between WC and insulin

Table 2. Multivariate linear regression analysis between percent changes in diabetic parameters and age, %dWC, and %dBMI

		β	95% CI		Standardized β	p value
Women	Model 1					
	Dependent variable, %dFG					
	age	−0.02	−0.06	0.03	−0.02	0.494
	%dWC	−0.05	−0.10	0.01	−0.05	0.118
	Dependent variable, %dHbA$_{1c}$					
	age	−0.01	−0.04	0.01	−0.03	0.353
	%dWC	−0.02	−0.06	0.01	−0.04	0.181
	Dependent variable, %dHOMA-IR					
	age	0.00	−0.30	0.31	0.00	0.993
	%dWC	−0.06	−0.44	0.32	−0.01	0.753
	Model 2					
	Dependent variable, %dFG					
	age	−0.01	−0.06	0.03	−0.02	0.605
	%dWC	−0.06	−0.12	0.00	−0.06	0.059
	%dBMI	0.12	−0.03	0.27	0.05	0.119
	Dependent variable, %dHbA$_{1c}$					
	age	−0.01	−0.04	0.02	−0.03	0.374
	%dWC	−0.03	−0.06	0.01	−0.04	0.168
	%dBMI	0.02	−0.08	0.11	0.01	0.741
	Dependent variable, %dHOMA-IR					
	age	0.08	−0.22	0.38	0.01	0.610
	%dWC	−0.28	−0.67	0.10	−0.04	0.152
	%dBMI	2.41	1.42	3.40	0.14	<0.001
Men	Model 1					
	Dependent variable, %dFG					
	age	−0.02	−0.06	0.01	−0.03	0.223
	%dWC	0.14	0.05	0.22	0.07	0.002
	Dependent variable, %dHbA$_{1c}$					
	age	−0.01	−0.03	0.01	−0.03	0.250
	%dWC	0.07	0.03	0.12	0.07	0.002
	Dependent variable, %dHOMA-IR					
	age	−0.08	−0.29	0.14	−0.02	0.479
	%dWC	1.30	0.80	1.80	0.11	<0.001
	Model 2					
	Dependent variable, %dFG					
	age	−0.01	−0.05	0.02	−0.02	0.434
	%dWC	0.03	−0.07	0.13	0.02	0.544
	%dBMI	0.35	0.20	0.49	0.12	<0.001
	Dependent variable, %dHbA$_{1c}$					
	age	−0.01	−0.03	0.01	−0.01	0.592
	%dWC	−0.01	−0.06	0.04	−0.01	0.740
	%dBMI	0.26	0.18	0.34	0.17	<0.001
	Dependent variable, %dHOMA-IR					
	age	0.02	−0.19	0.23	0.00	0.840
	%dWC	0.02	−0.52	0.57	0.00	0.932
	%dBMI	4.15	3.33	4.97	0.24	<0.001

For model 1, independent variables include age at the first visit and %dWC. For model 2, independent variables include age at the first visit, %dWC, and %dBMI.

resistance was attenuated in the elderly[24]. With regard to our study, the mean age of the individuals enrolled was 51.9 years in women and 53.4 years in men at the first visit. We may have to analyze the relationship between %dWC or %dBMI and changes in glucose metabolism in a younger population in future studies. In addition, WC measurements may be less reliable or reproducible than weight and height measurements, which might relate to the finding that although %dWC is a predictor for the change in diabetic parameters, the correlation between %dWC and %dBMI was weaker in women, the latter of which is a predictor for the changes in diabetic parameters also in women.

In the current study, interestingly, there was a gender difference in the relationship between %dWC and changes in diabetic parameters. Wing *et al.* reported that the relationship between changes in WHR and changes in lipid parameters differed between women and men: they showed that changes in WHR were associated with changes in total cholesterol and triglycerides levels in men, but not in women[18].

Although we did not look into the mechanisms that may explain the differences in the association of changes in obesity indexes and those in glucose metabolism-related markers between men and women, several explanations may exist. Adipose tissue has been recognized as a significant endocrine organ that releases biologically important cytokines, such as adiponectin, leptin, and vaspin[25, 26]. In several clinical studies, certain gender differences have existed in the serum levels of such adipokines (adiponectin[27, 28], leptin[29], and vaspin[30]), which may account, in part, for the difference in the association between changes in obesity indexes and those in glucose metabolism-related parameters in the current study. Such sexual dimorphism in adipocytokines may be related to the difference in the levels of sex hormones, such as dehydro-epiandrosterone-sulphate (DHEAS), oestradiol, and testosterone[27, 31, 32].

We previously analyzed the relationship between percent changes in obesity parameters and percent changes in serum lipid parameters, uric acid, and systolic blood pressure[33-35]. We found that, as in the current study, the impact of %dBMI was greater than that of %dWC from the viewpoint of changes in serum uric acid and blood pressure.

Our study has several potential limitations. First, we enrolled only individuals who underwent a general health screening at our institute for 2 consecutive years. Second, we analyzed data from participants without considering alcohol consumption or the number of cigarettes smoked. Third, we excluded individuals who were taking antidiabetic drugs at either visit. It has been suggested that these individuals are generally more motivated to improve their own health than those who are not taking such drugs. In addition, a longer follow-up would be required to draw more convincing conclusions in future studies.

In summary, over a one-year period, %dBMI was found to be an independent predictor for %dHOMA-IR in both genders and for %dFG and %dHbA$_{1c}$ only in men. Although %dWC was also associated with percent changes in these diabetic parameters, this relationship did not remain significant after controlling for %dBMI. Conversely, the relationship between %dBMI and percent changes in glucose-related metabolism parameters, especially in men, was independent of %dWC. These findings collectively suggest that controlling body weight, rather than WC, may be the primary target for improving glucose metabolism at least over a one-year period.

Acknowledgements

The work was supported in part by a grant from the Smoking Research Foundation, by Chiyoda Mutual Life Foundation, by a St Luke's Grant for Epidemiological Research, by Daiwa Securities Health Foundation, by a Gerontology Research Grant from Kowa Life Science Foundation, by the Foundation for Total Health Promotion, by the Himawari Welfare Foundation, and by the Gout Research Foundation of Japan.

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Original Article

Association between Gamma-Glutamyltransferase Levels and Insulin Resistance According to Alcohol Consumption and Number of Cigarettes Smoked

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Aim: Alcohol intake may increase serum gamma-glutamyltransferase (GGT) but reduce insulin resistance. We analyzed the association between GGT and a marker of insulin resistance, homeostasis model assessment for insulin resistance (HOMA-IR), according to the drinking and smoking status.
Methods: After excluding former smokers and/or former drinkers, the data of 10,482 men who underwent general health screening were analyzed.
Results: Alcohol consumption showed a graded association with GGT. In men with current alcohol consumption of ≥40 g per day, ≥20 cigarettes per day further increased GGT levels. Alcohol consumption showed a U-shaped association with HOMA-IR. In contrast, smoking 20–39 and ≥40 cigarettes per day increased HOMA-IR as compared with never smokers. An interaction between alcohol consumption and smoking was present for GGT ($p<0.001$) and HOMA-IR ($p=0.059$). GGT was not a significant negative predictive value for HOMA-IR regardless of the drinking or smoking status.
Conclusions: Although alcohol intake showed a graded association with GGT and a U-shaped association with HOMA-IR, serum GGT can be utilized as a predictor of insulin resistance in current drinkers.

J Atheroscler Thromb, 2010; 17:476-485.

Key words; Drinking, Cigarette smoking, Epidemiology, Insulin resistance, Liver function

Introduction

Recent epidemiological studies have shown that, besides being a biomarker of alcohol intake[1-4], elevated gamma-glutamyltransferase (GGT) may be a predictor of cardiovascular events[5], stroke[6], liver cancer[7], metabolic syndrome and type 2 diabetes[8], associations that may also be present in nondrinkers[9]. Several factors other than alcohol are known to affect serum GGT levels, including coffee consumption[10, 11] and obesity[12]. In addition, a recent study has demonstrated that cigarette smoking may also increase serum GGT levels, especially in men with moderate to heavy alcohol consumption[13]. Furthermore, alcohol consumption may improve insulin sensitivity and lower the incidence of metabolic syndrome[14-19]; therefore, drinking may increase GGT and decrease insulin resistance. On the other hand, it has been reported that serum GGT has a positive association with insulin resistance[20, 21]. To this end, we investigated the effect of drinking and smoking on GGT and HOMA-IR values, and whether the mode of association between GGT and insulin resistance was affected by drinking and smoking in Japanese men who underwent general health screening.

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Received: May 22, 2009
Accepted for publication: October 27, 2009

Methods

Study Population

The study was approved by the Ethics Commit-

tee of Mitsui Memorial Hospital and the Faculty of Medicine, University of Tokyo. Between January 2004 and April 2007, 33914 individuals underwent general health screening, among which information on alcohol consumption was available in 26952. Of these 26952 individuals, information on smoking behavior was further available in 24811, of which 15183 were male individuals and were enrolled in the current study. We were unable to identify any specific reasons to explain why some subjects failed to complete the questionnaire about their smoking and drinking status. Among 15183 individuals enrolled in the current study, data on hepatitis C core antigen (HCcAg) and hepatitis B surface antigen (HBsAg) were available in 14829 individuals (98%), of which 71 were positive for HCcAg and 175 were positive for HBsAg. Individuals who were positive for either type of chronic hepatitis virus infection were significantly older (56 ± 10 years) than hepatitis-negative subjects (53 ± 10 years), although GGT levels were not different between hepatitis-positive (52 ± 52 IU/L) and -negative (58 ± 84 IU/L) individuals. We did not exclude individuals who were taking antihypertensive, antidiabetic, or antidyslipidemic drugs, which might have affected insulin resistance and serum GGT levels, from the current study population.

In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employee's company (about two thirds of individuals attending our institute) or by the subject themselves (about one third of individuals attending our institute). Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer. Individuals were judged to be former smokers and/or former drinkers, if they had stopped cigarette smoking and/or alcohol drinking, respectively, more than one month before their attendance.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum GGT levels were measured enzymatically. Hemoglobin A1c was determined by latex agglutination immunoassay. Plasma glucose was measured by the hexokinase method and serum insulin by enzyme immunoassay. Homeostasis model assessment for insulin resistance (HOMA-IR) was calculated according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μU/mL) × fasting plasma glucose (FPG; mg/dL)]/405.

Statistical Analysis

Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis, Dunnett's post-hoc analysis and multiple linear regression analysis were appropriate to assess the statistical significance of differences between groups using computer software, StatView ver. 5.0 (SAS Institute, NC) and Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was significant.

Results

Baseline Characteristics

The baseline characteristics of the study subjects are described in **Table 1**. Among 15183 men, 4534 were former smokers and 416 were former drinkers. Individuals who were former smokers and/or drinkers ($n = 4701$) were significantly older than the remaining 10482 individuals.

GGT and HOMA-IR According to Smoking and Drinking Status

Current smokers who smoked 1-9, 10-19, and 20-39 cigarettes per day were significantly younger than never smokers (**Fig. 1A**). The daily amount of alcohol consumption showed a negative graded association with age. The number of cigarettes smoked showed a positive graded association with GGT (**Fig. 1B**) and, as compared with never smokers, individuals who currently smoked 1-9, 10-19, 20-39, and ≥40 cigarettes per day had significantly higher GGT levels (by Dunnett's post-hoc analysis). Similarly, the daily amount of alcohol consumption showed a graded association with GGT, and individuals who drank 1-19, 20-39, 40-59, and ≥60 g per day had significantly higher GGT levels than never drinkers (by Dunnett's post-hoc analysis). Individuals who smoked 20-39 and ≥40 cigarettes per day had significantly higher HOMA-IR than never-smokers (**Fig. 1C**). On the other hand, as compared with never drinkers, individuals who drank 1-19, 20-39, and 40-59 g alcohol per day had significantly lower HOMA-IR levels (by Dunnett's post-hoc analysis), demonstrating a U-shaped association.

GGT and HOMA-IR According to Cross Strata of Number of Cigarettes Smoked and Alcohol Consumption

In the following analysis, we analyzed the data from 10482 individuals after excluding former smokers and/or former drinkers. The mean GGT levels and HOMA-IR values according to the smoking and drinking category are shown in **Table 2**. Current

Table 1. Baseline characteristics

Variables	Whole	Former smokers and/or drinkers [A]	Except former smokers and drinkers [B]	*p* value ([A] vs. [B])
N	15,183	4,701	10,482	
Age, years	52.9 ± 10.4	55.6 ± 9.9	51.7 ± 10.4	<0.001
Height, cm	169.6 ± 6.0	169.1 ± 5.9	169.7 ± 6.0	<0.001
Weight, kg	68.3 ± 9.5	68.5 ± 8.9	68.2 ± 9.7	0.117
Body mass index, kg/m^2	23.7 ± 2.8	23.9 ± 2.7	23.6 ± 2.9	<0.001
Systolic blood pressure, mmHg	124.7 ± 18.6	127.6 ± 18.5	123.3 ± 18.4	<0.001
Diastolic blood pressure, mmHg	79.0 ± 11.3	81.0 ± 11.0	78.2 ± 11.3	<0.001
Heart rate, bpm	63.3 ± 9.5	63.4 ± 9.6	63.2 ± 9.5	0.373
LDL-cholesterol, mg/dL	126.7 ± 30.5	127.3 ± 30.0	126.5 ± 30.8	0.112
HDL-cholesterol, mg/dL	55.3 ± 13.4	56.9 ± 13.4	54.6 ± 13.3	<0.001
Triglycerides, mg/dL	133.7 ± 94.2	129.8 ± 83.9	135.5 ± 98.4	0.001
AST, IU/L	23.8 ± 12.1	24.0 ± 10.5	23.7 ± 12.7	0.208
ALT, IU/L	27.3 ± 19.4	26.5 ± 18.8	27.6 ± 19.6	0.001
GGT, IU/L	58.2 ± 82.9	58.3 ± 67.0	58.1 ± 89.1	0.926
Fasting glucose, mg/dL	100.3 ± 20.5	101.7 ± 20.8	99.7 ± 20.4	<0.001
Hemoglobin A1c, %	5.38 ± 0.74	5.41 ± 0.72	5.36 ± 0.75	<0.001
HOMA-IR	1.69 ± 1.52	1.74 ± 1.31	1.67 ± 1.60	0.007
Antihypertensive medication, N (%)	1,909 (12.6)	831 (17.7)	1,078 (10.3)	<0.001
Antidiabetic medication, N (%)	474 (3.1)	169 (3.6)	305 (2.9)	0.026
Antidyslipidemic medication, N (%)	674 (4.4)	276 (5.9)	398 (3.8)	<0.001
Smoking and drinking status				
Never smoker				
Never drinker, N (%)	791 (14.1)	0 (0)	791 (14.3)	
Former drinker, N (%)	90 (1.6)	90 (100)	0 (0)	
Current drinker, N (%)	4,744 (84.3)	0 (0)	4,744 (85.7)	
Former smoker				
Never drinker, N (%)	263 (1.7)	263 (1.7)	0 (0)	
Former drinker, N (%)	249 (1.6)	249 (1.6)	0 (0)	
Current drinker, N (%)	4,022 (26.5)	4,022 (26.5)	0 (0)	
Current smoker				
Never drinker, N (%)	416 (8.3)	0 (0)	416 (8.4)	
Former drinker, N (%)	77 (1.5)	77 (100)	0 (0)	
Current drinker, N (%)	4,531 (90.2)	0 (0)	4,531 (91.6)	

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance

drinking showed a graded association with GGT regardless of the smoking status. Cigarette smoking was also positively associated with GGT in some drinking categories: smoking 10–19 ($p<0.01$), 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank 40–59 g/day, and smoking 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day was associated with greater GGT values than never smoking in individuals who drank ≥60 g/day.

Individuals with alcohol consumption of 1–19, 20–39, or 40–59 g/day had lower HOMA-IR value than never drinkers, showing a U-shaped association between current drinking and HOMA-IR. This U-shaped relationship was absent or not significant in current smoking of 20–39 or ≥40 cigarettes per day (**Table 2**). Individuals who smoked 20–39 ($p<0.001$) and ≥40 ($p<0.001$) cigarettes per day had higher HOMA-IR than never smokers (**Table 2**).

Multiple Linear Regression Analysis

Next, multiple linear regression analysis using GGT and HOMA-IR as a dependent variable and age, BMI, amount of smoking, and alcohol consump-

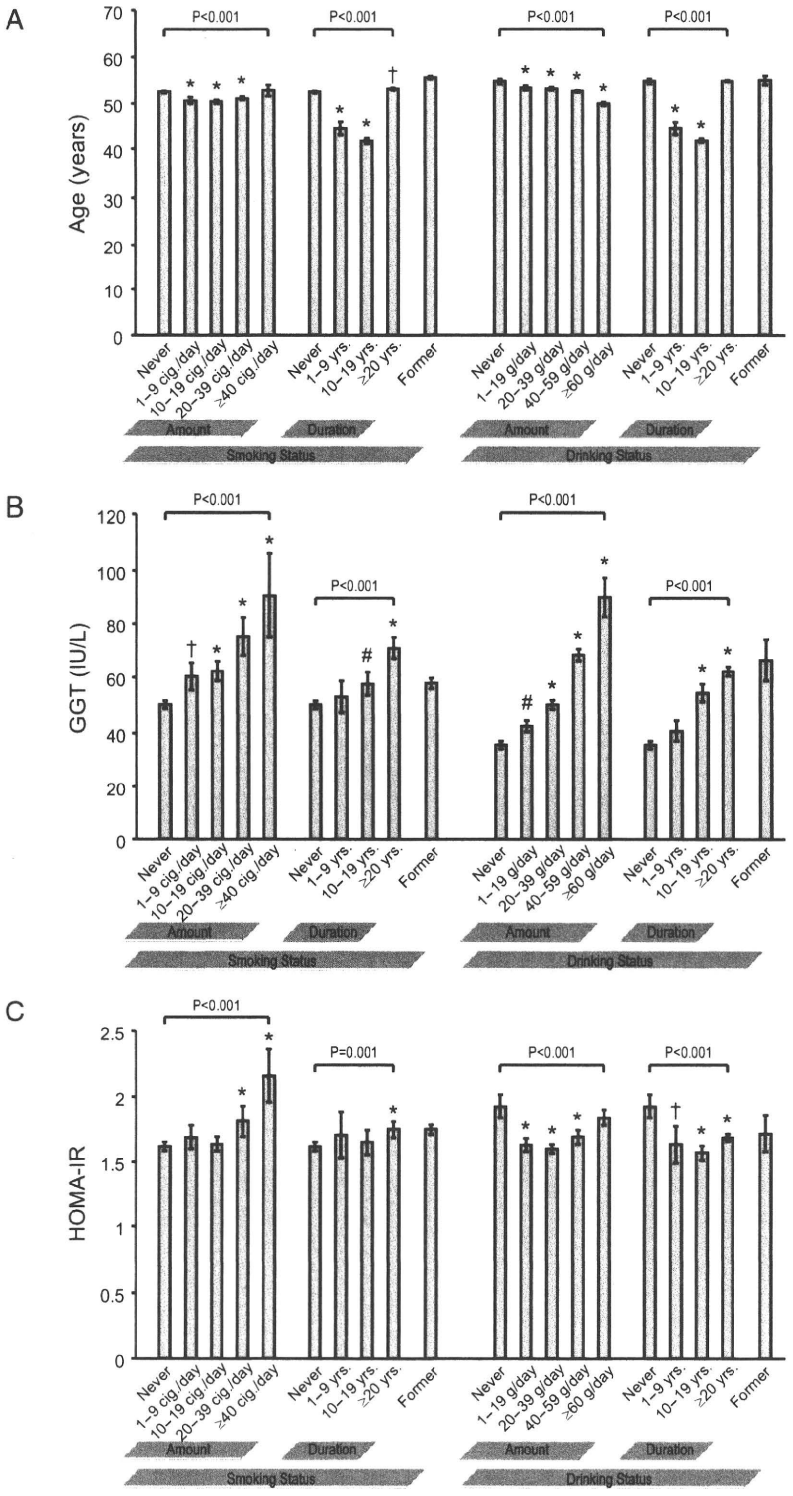

Fig. 1. Age, GGT, and HOMA-IR according to smoking and drinking status.

Bar graphs indicate the mean and 95% CI of age (A), GGT (B), and HOMA-IR. *P* values are for ANOVA trend tests. #, †, and * indicate $p<0.05$, $p<0.01$, and $p<0.001$, respectively, versus never smokers or never drinkers by Dunnett's post-hoc analysis.

Table 2. GGT and HOMA-IR according to smoking and drinking status

Smoking category (cig./day)	Drinking category																				
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				†p value
	N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			N	GGT			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	58.1	56.4	59.8	1,207	35.5	33.9	37.2	1,872	41.7	39.8	43.6	3,062	50.1	48.0	52.1	2,957	68,7	65.9	71.6	1,384	95.2	85.4	104.9	<0.001
									*p=	0.156			*p<	0.001			*p<	0.001			*p<	0.001			
0 (never smoker)	5,535	49.5	48.2	50.9	791	35.6	33.4	37.8	1,222	43.2	40.6	45.8	1,812	47.2	45.3	49.1	1,258	60.7	57.3	64.2	452	69.3	62.0	76.6	<0.001
									*p=	0.004			*p<	0.001			*p<	0.001			*p<	0.001			
1-9	771	59.8	54.7	64.9	48	44.0	32.4	55.6	147	39.0	33.8	44.1	207	51.1	45.4	56.8	253	69.5	57.8	81.2	116	87.1	70.3	103.9	<0.001
									*p=	0.950			*p=	0.845			*p=	0.055			*p=	0.001			
10-19	2,201	61.9	58.3	65.5	196	32.9	30.0	35.7	322	39.0	35.3	42.7	616	55.4	47.7	63.2	758	72.9	66.3	79.6	309	89.9	79.9	100.0	<0.001
									*p=	0.764			*p=	0.003			*p<	0.001			*p<	0.001			
20-39	1,748	75.6	68.1	83.0	151	35.4	32.1	38.7	158	37.0	33.1	40.9	399	55.1	50.3	59.8	623	77.0	71.4	82.6	417	122.1	93.0	151.3	<0.001
									*p=	1.000			*p=	0.413			*p=	0.010			*p<	0.001			
≥40	227	91.1	75.3	107.0	21	39.0	27.0	51.0	23	47.4	36.5	58.4	28	40.9	32.1	49.8	65	93.4	62.1	124.7	90	128.5	97.3	159.6	<0.001
									*p=	0.996			*p=	1.000			*p=	0.171			*p=	0.006			

Smoking category (cig./day)	Drinking category																								†p value
	#Overall				0 g/day (never drinker)				1-19 g/day				20-39 g/day				40-59 g/day				≥60g/day				
	N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			N	HOMA-IR			
		Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI			Mean	95%CI		
§Overall	10,482	1.67	1.64	1.70	1,207	1.89	1.79	1.99	1,872	1.57	1.51	1.63	3,062	1.5	1.51	1.59	2,957	1.7	1.62	1.77	1,384	1.8	1.78	1.92	<0.001
									*p<	0.001			*p<	0.001			*p=	0.001			*p=	0.878			
0 (never smoker)	5,535	1.62	1.58	1.65	791	1.83	1.70	1.96	1,222	1.58	1.50	1.66	1,812	1.54	1.49	1.59	1,258	1.57	1.51	1.64	452	1.80	1.67	1.94	<0.001
									*p<	0.001			*p<	0.001			*p<	0.001			*p=	0.995			
1-9	771	1.67	1.58	1.77	48	2.20	1.52	2.89	147	1.50	1.31	1.69	207	1.54	1.41	1.67	253	1.68	1.53	1.84	116	1.90	1.64	2.15	0.002
									*p=	0.003			*p=	0.004			*p=	0.026			*p=	0.338			
10-19	2,201	1.64	1.58	1.69	196	1.96	1.77	2.16	322	1.52	1.38	1.66	616	1.43	1.34	1.51	758	1.70	1.60	1.80	309	1.80	1.65	1.96	<0.001
									*p<	0.001			*p<	0.001			*p=	0.030			*p=	0.385			
20-39	1,748	1.82	1.70	1.94	151	2.03	1.74	2.32	158	1.49	1.31	1.66	399	1.74	1.61	1.87	623	1.92	1.62	2.22	417	1.80	1.68	1.92	0.274
≥40	227	2.17	1.97	2.37	21	1.91	1.29	2.52	23	2.71	1.98	3.45	28	1.96	1.46	2.46	65	1.84	1.52	2.16	90	2.39	2.02	2.76	0.068

†*p* values were for ANOVA trend tests. **p* values are versus never drinkers by Dunnett's post-hoc analysis. #Overall indicates all never or current drinkers, and §Overall indicates all never or current smokers. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

Table 3. Linear regression analysis using GGT and HOMA-IR as dependent variable

	β	95%CI		Standardized β	p value
Dependent variable: GGT					
Age	-0.57	-1.82	0.68	-0.01	0.372
BMI	2.25	1.79	2.71	0.08	<0.001
Smoking	3.18	2.17	4.19	0.05	<0.001
Alcohol consumption	12.34	11.19	13.49	0.17	<0.001
Dependent variable: HOMA-IR					
Age	0.04	0.01	0.06	0.02	0.001
BMI	0.23	0.22	0.24	0.43	<0.001
Smoking	0.04	0.03	0.06	0.04	<0.001
Alcohol consumption	-0.08	-0.10	-0.06	-0.06	<0.001

For the calculation of β values, age was subdivided into 10-year increments. Alcohol consumption (g/day) corresponding to 0 (never drinker), 1-19, 20-39, 40-59, and ≥60 was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1-9, 10-19, 20-39, and ≥40 was coded as 0, 1, 2, 3, and 4, respectively. GGT, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment for insulin resistance.

tion as independent variables was performed in 10482 individuals (**Table 3**). In this model, alcohol consumption (g/day) corresponding to 0 (never drinker); 1-19, 20-39, 40-59, and 60 or more was coded as 0, 1, 2, 3, and 4, respectively, and smoking (cigarettes/day) corresponding to 1-9, 10-19, 20-39, and 40 or more were defined as 0, 1, 2, 3, and 4, respectively. Alcohol consumption was associated positively with GGT, but negatively with HOMA-IR. On the other hand, smoking was found to be associated positively with both GGT and HOMA-IR. When an interaction term between alcohol consumption and smoking was used as additional independent variable, the interaction term was found to be significantly associated with GGT ($p<0.001$), and showed a borderline significant association with HOMA-IR ($p=0.059$). The variance inflation factor (VIF) scores of all independent variables tested were less than 10 (data not shown).

Association between GGT and HOMA-IR According to Alcohol Consumption

Next, we investigated whether the mode of association between GGT and HOMA-IR differs according to the amount of alcohol consumption. For this purpose, multiple regression analysis was performed in which age, BMI, and GGT were used as independent variables and HOMA-IR was used as a dependent variable after subdividing individuals according to alcohol consumption (**Table 4**). GGT was found be a positive predictive value for HOMA-IR in 19 out of the 25 drinking × smoking categories. In some combinations of drinking and smoking, such as drinking 0 g/day and smoking 1-9 cig./day, GGT was not a statistically significant predictor of HOMA-IR. This may be in part because the number of subjects with specific drinking and smoking conditions was relatively small.

Discussion

In the current study, by analyzing the data of men who underwent general health screening, except former smokers and/or former drinkers, we observed several points: (1) Alcohol consumption showed a graded association with GGT; (2) In individuals who drank 40 g or more per day, smoking 20 cigarettes or more per day further increased GGT levels (**Table 2**); (3) alcohol consumption showed a U-shaped association with HOMA-IR, when the daily number of cigarettes smoked was less than 20 per day; (4) Individuals who smoked 20-39 and ≥40 cigarette per day had higher HOMA-IR than never smokers (**Table 2**); (5) GGT was found be a positive predictive value of HOMA-IR in 19 out of the 25 drinking × smoking categories, and GGT was not a significant negative predictor of HOMA-IR regardless of the drinking or smoking status. These data collectively indicate that, although current drinking may increase GGT and reduce insulin resistance, GGT can be utilized as a marker of insulin resistance regardless of the drinking status.

Many studies have shown that serum GGT is a biomarker of increased alcohol consumption[1-4, 22]; however, GGT is known to be affected by other con-

Table 4. Linear regression analysis using HOMA-IR as dependent variable

		β	95%CI		Standardized β	p value
Current smoking - 0 cig./day (never smoker)						
0 g/day (never drinker)	BMI	0.20	0.16	0.24	0.33	<0.001
	GGT	0.07	0.03	0.11	0.12	0.001
1-19 g/day	BMI	0.22	0.19	0.24	0.42	<0.001
	GGT	0.04	0.02	0.05	0.12	<0.001
20-39 g/day	BMI	0.21	0.19	0.22	0.49	<0.001
	GGT	0.03	0.02	0.05	0.13	<0.001
40-59 g/day	BMI	0.18	0.16	0.20	0.47	<0.001
	GGT	0.04	0.03	0.04	0.20	<0.001
≥60 g/day	BMI	0.26	0.23	0.30	0.57	<0.001
	GGT	0.02	0.01	0.04	0.13	0.001
Current smoking - 1-9 cig./day						
0 g/day (never drinker)	BMI	0.44	0.21	0.67	0.49	<0.001
	GGT	0.13	−0.02	0.28	0.22	0.084
1-19 g/day	BMI	0.24	0.17	0.32	0.47	<0.001
	GGT	0.07	0.01	0.12	0.18	0.016
20-39 g/day	BMI	0.18	0.13	0.23	0.42	<0.001
	GGT	0.01	−0.02	0.04	0.05	0.396
40-59 g/day	BMI	0.23	0.18	0.27	0.50	<0.001
	GGT	0.01	0.00	0.03	0.11	0.049
≥60 g/day	BMI	0.27	0.20	0.34	0.57	<0.001
	GGT	0.04	0.02	0.06	0.26	<0.001
Current smoking - 10-19 cig./day						
0 g/day (never drinker)	BMI	0.16	0.10	0.22	0.34	<0.001
	GGT	0.27	0.19	0.36	0.40	<0.001
1-19 g/day	BMI	0.22	0.18	0.26	0.49	<0.001
	GGT	0.08	0.05	0.12	0.22	<0.001
20-39 g/day	BMI	0.18	0.15	0.21	0.44	<0.001
	GGT	0.00	−0.01	0.01	0.02	0.583
40-59 g/day	BMI	0.25	0.22	0.27	0.57	<0.001
	GGT	0.02	0.01	0.03	0.16	<0.001
≥60 g/day	BMI	0.22	0.18	0.26	0.54	<0.001
	GGT	0.03	0.01	0.04	0.17	<0.001
Current smoking - 20-39 cig./day						
0 g/day (never drinker)	BMI	0.27	0.18	0.37	0.42	<0.001
	GGT	0.17	0.04	0.30	0.20	0.010
1-19 g/day	BMI	0.12	0.06	0.18	0.30	<0.001
	GGT	0.07	0.00	0.14	0.16	0.036
20-39 g/day	BMI	0.22	0.18	0.26	0.47	<0.001
	GGT	0.04	0.02	0.07	0.16	<0.001
40-59 g/day	BMI	0.28	0.18	0.37	0.22	<0.001
	GGT	0.02	−0.02	0.06	0.03	0.395
≥60 g/day	BMI	0.22	0.19	0.26	0.57	<0.001
	GGT	0.01	0.00	0.01	0.15	<0.001
Current smoking - ≥40 cig./day						
0 g/day (never drinker)	BMI	−0.07	−0.29	0.16	−0.12	0.551
	GGT	0.41	0.18	0.64	0.80	0.002
1-19 g/day	BMI	−0.07	−0.29	0.16	−0.12	0.551
	GGT	0.41	0.18	0.64	0.80	0.002
20-39 g/day	BMI	0.15	0.02	0.28	0.42	0.028
	GGT	0.10	−0.15	0.34	0.17	0.425
40-59 g/day	BMI	0.18	0.06	0.30	0.37	0.003
	GGT	0.01	−0.02	0.03	0.07	0.559
≥60 g/day	BMI	0.28	0.18	0.38	0.47	<0.001
	GGT	0.05	0.03	0.07	0.42	<0.001

Standardized β values are estimates resulting from analysis performed on into standardized variables. For the calculation of β values, BMI was subdivided into 1 kg/m^2 increments, and GGT into 10 IU/L increments. Age, BMI, and GGT were used as independent variables. BMI, body mass index; GGT, gamma-glutamyl transpeptidase.

ditions, such as smoking, obesity, and hepatic steatosis[23, 24]. Evidence is accumulating that higher serum GGT levels may be associated with an increased incidence of cardiovascular events[5], metabolic syndrome and diabetes[8, 25, 26]; therefore, more attention has been paid recently to this liver enzyme. It is possible that the association between GGT and various disorders observed in previous studies may be mediated, in part, by enhanced insulin resistance in subjects with increased GGT levels.

Although mild to moderate alcohol consumption may increase GGT, it may improve insulin sensitivity[18, 27], leading to a reduction in the prevalence of metabolic syndrome[17]. This finding is in contrast to the observation that cigarette smoking will not improve insulin resistance, even in light smokers[14]. As alcohol consumption has opposite effects on GGT and insulin resistance, the mode of association between GGT and HOMA-IR might differ according to the drinking status; however, only a few studies have analyzed the relationship between GGT and insulin resistance in various drinking conditions. Yokoyama and colleagues reported that GGT is associated with increased insulin resistance in non-drinkers[28] and light drinkers, but not in heavy drinkers[29], a finding that supports the notion that the mode of association between GGT and HOMA-IR differs according to the drinking status. Yamada *et al.* have reported that HOMA-IR rose with increasing serum GGT in both alcohol consumers and non-consumers, and HOMA-IR values corresponding to all serum GGT levels were lower in alcohol consumers than in non-consumers[30]. A recent study indicated that cigarette smoking may also affect both GGT and insulin resistance independent of the drinking status, and cigarette smoking and alcohol intake may have a synergistic impact on GGT[13]. Smoking status should also be considered when assessing the impact of alcohol intake on the association between GGT and insulin resistance; however, to our knowledge, no previous studies have investigated the relationship between GGT and insulin resistance after stratifying both the drinking status and smoking status, as in the current study.

We found that in 19 of the 25 subgroups divided according to smoking and drinking status, GGT was found to be a positive predictive value of HOMA-IR, which indicates that increased GGT is associated with enhanced insulin resistance regardless of the smoking and drinking status. From this type of cross-sectional study, we cannot conclude whether there is any causal or resultant relationship between GGT and HOMA-IR. A recent study showed that GGT may play a causal role in promoting insulin resistance, presumably by enhancing oxidative stress[31, 32] and hepatic steatosis[33]. Whether a change in HOMA-IR would result in a predicted change in GGT should be investigated in future longitudinal studies.

Our study has some limitations. First, we did not take into account coffee intake, which might affect GGT level[2]. Second, as the prevalence of smokers was low, we did not analyze the data of female subjects. Third, the number of daily cigarettes and alcohol consumption solely reflected the amount that was being consumed at one time, and disregarded the frequency of smoking or drinking consumption. Therefore, this estimation of smoking and drinking quantity was not equal to the mean daily number of cigarettes smoked and the amount of alcohol consumption, except in every-day smokers and drinkers, respectively. We performed such an analysis because the frequency of smoking (or drinking) was reported as a category, two or three times per week, for example; therefore, it was technically difficult to estimate the mean daily number of cigarettes smoked or the alcohol consumption. In the future, however, the frequency of drinking and smoking should also be considered in such an analysis. Fourth, we did not exclude individuals who were taking antihypertensive and/or antidiabetic drugs, which may have affected serum GGT and HOMA-IR values.

In summary, alcohol consumption showed a graded positive association with GGT and a U-shaped negative association with HOMA-IR. Cigarette smoking may further increase GGT levels in individuals who are current drinkers and drink 20 g or more per day. In 19 of the 25 drinking × smoking categories, GGT was found be a positive predictive value of HOMA-IR, and GGT was not a significant negative predictor of HOMA-IR, regardless of the drinking or smoking status. These data indicate a positive association between GGT and insulin resistance also in current drinkers.

Acknowledgements

The work was supported in part by a grant from the Smoking Research Foundation, Chiyoda Mutual Life Foundation, a St Luke's Grant for the Epidemiological Research, Daiwa Securities Health Foundation, a Gerontology Research Grant from Kowa Life Science Foundation, the Foundation for Total Health Promotion, and the Gout Research Foundation of Japan.

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The Journal of Rheumatology

The Journal of Rheumatology Volume 37, no. 2

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J Rheumatol 2010;37;410-416
http://www.jrheum.org/content/37/2/410