(Cont Table 1)

	Women					
	Fasting			Non-fasting		
	Non-DM	DM	*p* value	Non-DM	DM	*p* value
n	14993	878		68132	3977	
Age (y)	55.8 ± 9.6	58.2 ± 8.8	<0.01	58.4 ± 10.1	60.2 ± 8.8	<0.01
BMI (kg/m^2)	23.2 ± 3.0	24.6 ± 3.4	<0.01	23.5 ± 3.1	24.6 ± 3.6	<0.01
SBP (mmHg)	129 ± 18	136 ± 17	<0.01	132 ± 17	138 ± 17	<0.01
DBP (mmHg)	78 ± 11	81 ± 10	<0.01	78 ± 11	80 ± 10	<0.01
Hypertension treatment (%)	2235 (15)	233 (27)	<0.01	13306 (20)	1239 (31)	<0.01
Never smoker (%)	14068 (94)	836 (94)	0.15	65094 (96)	3764 (95)	0.049
ex-smoker (%)	116 (1)	2 (0)	-	346 (1)	28 (1)	-
20 cigarettes per day ≥ (%)	540 (4)	24 (3)	-	1878 (3)	131 (3)	-
≥ 20 cigarettes per day (%)	269 (2)	16 (2)	-	814 (1)	54 (1)	-
Never drinker (%)	13232 (88)	783 (89)	0.51	61900 (91)	3661 (92)	0.07
Sometimes (%)	1064 (7)	55 (6)	-	3887 (6)	190 (5)	-
66 g/day ≥ (%)	671 (4)	37 (4)	-	2303 (3)	123 (3)	-
≥ 66 g/day (%)	26 (0)	3 (0)	-	52 (0)	3 (0)	-
TC (mmol/L)	5.5 ± 0.9	5.6 ± 0.9	<0.01	5.4 ± 0.9	5.5 ± 0.9	<0.01
HDLC (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	<0.01	1.5 ± 0.4	1.4 ± 0.4	<0.01
TG (mmol/L)	1.0 (0.8-1.4)	1.2 (0.8-1.7)	<0.01	1.4 (1.0-1.9)	1.7 (1.2-2.4)	<0.01
Non-HDLC (mmol/L)	3.9 ± 0.9	4.2 ± 1.0	<0.01	3.9 ± 0.9	4.1 ± 0.9	<0.01
LDLC (mmol/L)	3.4 ± 0.8	3.5 ± 0.9	<0.01	-	-	
TC/HDLC	3.7 ± 1.1	4.0 ± 1.1	<0.01	3.9 ± 1.1	4.2 ± 1.2	<0.01
Non-HDL/HDLC	2.7 ± 1.1	3.0 ± 1.1	<0.01	2.9 ± 1.1	3.2 ± 1.2	<0.01
LDLC/HDLC	2.3 ± 0.9	2.5 ± 0.9	<0.01	-	-	
TG/HDLC	0.8 ± 0.7	1.1 ± 0.9	<0.01	1.2 ± 1.0	1.5 ± 1.2	<0.01
Dyslipidemia treatment (%)	561 (4)	51 (6)	<0.01	2247 (3)	186 (5)	<0.01
PG (mmol/L)	5.3 ± 0.6	6.0 ± 0.6	<0.01	5.8 ± 1.1	7.0 ± 1.6	<0.01

The data are presented as the mean ± SD or median (interquartile range).
BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HDLC, high-density lipoprotein cholesterol; LDLC, LDL-cholesterol; PG, plasma glucose, SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides

oped DM during a mean follow-up of 5.5 years (5.4 years for men and 5.9 years for women). The number of men who diagnosed as having DM based on blood glucose results, the initiation of treatment or both was 3,107 (77%), 779 (19%) and 126 (3%), respectively, while that for women was 3,742 (77%), 962 (20%) and 151 (3%), respectively. The sex-stratified baseline characteristics determined according to the fasting status are shown in **Table 1**. Approximately 17% of men and 18% of women were in a fasting state at baseline. The baseline data for the participants who dropped out and those were followed up are shown in **Supplemental Table 1**. The TG levels were not normally distributed (**Supplemental Fig. 1**). The men with a fasting status who developed DM had higher TG, TC/HDLC, non-HDLC/HDLC and TG/HDLC values and lower HDLC values than those who did not develop DM. In addition, the levels of TC, TG, non-HDLC, TC/HDLC, non-HDLC/HDLC and TG/HDLC in the non-fasting men were significantly higher among those who developed DM than those who did not. The women in a fasting state who developed DM had higher TC, TG, non-HDLC, LDLC, TC/HDLC, non-HDLC/HDLC, LDLC/HDLC and TG/HDLC values and lower HDLC values than those who did not. As to non-fasting women, the levels of TC, TG, non-HDLC, TC/HDLC, non-HDLC/HDLC and TG/HDLC were significantly higher among those who developed DM than those who did not. However, in the non-fasting women, the levels of HDLC were significantly lower among the participants who developed DM than in those who did not.

Following multivariate adjustment for covariates, the TG and TG/HDLC values were found to be sig-

Table 2. Age-adjusted and multivariable hazard ratios (HRs) for incident diabetes according to the quartiles (Q) of the serum lipid levels

	Ranges (mmol/L)	mg/dL	N	Person-years	No. of incidence	Incidence Rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting men										
TC										
Q1	<4.58	<177	1627	8481	144	17.0	1.00 (ref)	0.65	1.00 (ref)	0.71
Q2	4.58-5.11	177-197	1685	9430	126	13.4	0.80 (0.63-1.02)		0.78 (0.61-0.99)	
Q3	5.12-5.73	198-221	1686	9313	146	15.7	0.93 (0.74-1.18)		0.89 (0.70-1.12)	
Q4	5.74-	222-	1745	9293	156	16.9	1.00 (0.80-1.25)		0.91 (0.72-1.15)	
HDLC										
Q1	<1.14	<45	1628	8786	170	19.3	1.00 (ref)	<0.01	1.00 (ref)	0.07
Q2	1.14-1.34	45-51	1793	9644	153	15.8	0.82 (0.66-1.02)		0.84 (0.67-1.04)	
Q3	1.35-1.60	52-61	1641	9084	121	13.4	0.69 (0.55-0.87)**		0.75 (0.59-0.95)*	
Q4	1.61-	62-	1681	9003	128	14.1	0.72 (0.58-0.91)**		0.82 (0.64-1.06)	
TG										
Q1	<0.87	<77	1666	9089	107	11.7	1.00 (ref)	<0.01	1.00 (ref)	0.02
Q2	0.87-1.18	77-104	1681	9127	130	14.3	1.22 (0.94-1.57)		1.08 (0.84-1.40)	
Q3	1.19-1.68	105-149	1679	9287	155	16.8	1.44 (1.12-1.84)**		1.22 (0.95-1.57)	
Q4	1.69-	150-	1717	9014	180	20.2	1.75 (1.38-2.22)**		1.31 (1.02-1.69)*	
TG/HDLC										
Q1	<0.57		1638	8857	105	11.9	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	0.57-0.87		1714	9378	139	14.7	1.27 (0.99-1.64)		1.15 (0.89-1.48)	
Q3	0.88-1.40		1691	9313	142	15.3	1.32 (1.03-1.70)*		1.12 (0.86-1.45)	
Q4	1.41-		1700	8969	186	20.6	1.81 (1.42-2.30)**		1.45 (1.12-1.88)**	
Non-fasting men										
TC										
Q1	<4.37	<169	8037	39530	807	20.5	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	4.37-4.90	169-189	8175	42550	819	19.3	0.96 (0.87-1.06)		0.96 (0.87-1.06)	
Q3	4.91-5.47	190-211	8100	41939	866	20.6	1.03 (0.94-1.14)		1.01 (0.92-1.12)	
Q4	5.48-	212-	8141	42011	948	22.4	1.15 (1.04-1.26)**		1.12 (1.02-1.24)*	
HDLC										
Q1	<1.09	<42	7947	39697	880	22.1	1.00 (ref)	0.61	1.00 (ref)	0.29
Q2	1.09-1.29	42-49	8644	44493	896	20.3	0.91 (0.83-1.00)*		0.95 (0.86-1.04)	
Q3	1.30-1.55	50-59	7841	40515	743	18.2	0.83 (0.75-0.91)**		0.88 (0.79-0.97)*	
Q4	1.56-	60-	8021	41325	921	22.1	1.00 (0.91-1.10)		1.08 (0.98-1.20)	
TG										
Q1	<1.00	<89	8076	40839	796	19.3	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	1.00-1.41	89-125	8004	41047	758	18.6	0.97 (0.88-1.07)		0.93 (0.84-1.03)	
Q3	1.42-2.06	126-182	8171	42734	847	19.9	1.06 (0.96-1.17)		0.99 (0.90-1.10)	
Q4	2.07-	183-	8202	41410	1039	25.3	1.37 (1.25-1.50)**		1.22 (1.10-1.35)**	
TG/HDLC										
Q1	<0.69		8056	41056	833	20.3	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	0.69-1.09		7950	40712	736	18.2	0.90 (0.82-1.00)*		0.90 (0.81-0.998)*	
Q3	1.10-1.79		8312	43371	836	19.3	0.98 (0.89-1.08)		0.98 (0.89-1.08)	
Q4	1.80-		8135	40891	1035	25.4	1.31 (1.19-1.43)**		1.31 (1.19-1.43)**	

(Cont Table 2)

	Ranges (mmol/L)	mg/dL	N	Person-years	No. of incidence	Incidence Rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting women										
TC										
Q1	<4.86	<188	3878	23027	171	7.5	1.00 (ref)	<0.01	1.00 (ref)	0.17
Q2	4.86-5.45	188-210	3940	23635	208	8.8	1.08 (0.88-1.33)		1.03 (0.84-1.26)	
Q3	5.46-6.07	211-234	4027	24085	227	9.4	1.10 (0.90-1.34)		1.00 (0.82-1.23)	
Q4	6.08-	235-	4026	23523	272	11.6	1.29 (1.06-1.57)**		1.15 (0.95-1.40)	
HDLC										
Q1	<1.29	<50	3857	22495	269	12.0	1.00 (ref)	<0.01	1.00 (ref)	0.08
Q2	1.29-1.52	50-58	4059	24268	234	9.6	0.84 (0.70-1.00)*		0.89 (0.75-1.07)	
Q3	1.53-1.77	59-68	3965	23405	197	8.4	0.74 (0.62-0.89)**		0.86 (0.71-1.03)	
Q4	1.78-	69-	3990	24102	178	7.4	0.67 (0.55-0.81)**		0.86 (0.70-1.04)	
TG										
Q1	<0.76	<67	3830	23130	163	7.1	1.00 (ref)	<0.01	1.00 (ref)	0.02
Q2	0.76-1.02	67-90	4091	24732	182	7.4	0.95 (0.77-1.17)		0.86 (0.70-1.07)	
Q3	1.03-1.40	91-124	3918	23173	210	9.1	1.11 (0.90-1.37)		0.90 (0.73-1.11)	
Q4	1.41-	125-	4032	23235	323	13.8	1.63 (1.34-1.98)**		1.20 (0.98-1.46)	
TG/HDLC										
Q1	<0.46		4038	24598	173	7.0	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	0.46-0.68		3978	23947	166	7.0	0.91 (0.74-1.13)		0.82 (0.66-1.02)	
Q3	0.69-1.02		3880	22632	216	9.6	1.20 (0.98-1.47)		0.96 (0.78-1.18)	
Q4	1.03-		3975	22093	323	14.0	1.69 (1.40-2.04)**		1.22 (1.00-1.49)*	
Non-fasting women										
TC										
Q1	<4.73	<183	18059	105400	754	7.2	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	4.73-5.32	183-205	17864	104691	907	8.6	1.14 (1.03-1.25)**		1.07 (0.97-1.18)	
Q3	5.33-5.91	206-228	17805	103877	1021	9.9	1.25 (1.14-1.38)**		1.14 (1.04-1.26)**	
Q4	5.92-	229-	18381	104048	1295	12.4	1.54 (1.41-1.69)**		1.37 (1.23-1.48)**	
HDLC										
Q1	<1.21	<47	16200	90709	1125	12.4	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	1.21-1.41	47-54	18853	109371	1083	9.9	0.83 (0.76-0.90)**		0.90 (0.83-0.98)*	
Q3	1.42-1.69	55-65	18699	110269	928	8.4	0.72 (0.66-0.78)**		0.84 (0.77-0.92)**	
Q4	1.70-	66-	18357	107667	841	7.8	0.68 (0.62-0.74)**		0.86 (0.78-0.95)**	
TG										
Q1	<0.98	<87	18148	108551	633	5.8	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	0.98-1.37	87-121	17962	105641	824	7.8	1.25 (1.12-1.38)**		1.12 (1.01-1.24)*	
Q3	1.38-1.94	122-172	17893	102269	1024	10.0	1.55 (1.40-1.71)**		1.29 (1.17-1.43)**	
Q4	1.95-	173-	18106	101555	1496	14.8	2.23 (2.03-2.45)**		1.69 (1.53-1.86)**	
TG/HDLC										
Q1	<0.62		17429	104659	626	6.0	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	0.62-0.94		18150	106294	843	7.9	1.24 (1.12-1.38)**		1.11 (0.997-1.23)	
Q3	0.95-1.51		18256	105512	1005	9.5	1.45 (1.31-1.60)**		1.20 (1.08-1.33)**	
Q4	1.52-		18274	101551	1503	14.7	2.19 (1.99-2.40)**		1.62 (1.47-1.79)**	

HDLC, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides
Adjusted for age (years), body mass index, antihypertensive medication use (yes or no), antihyperlipidemic medication use (yes or no), systolic blood pressure, smoking status (never smoked; ex-smoker; current smoker, ≥20 cigarettes per day; and current smoker, ≥20 cigarettes per day) and alcohol intake (never, sometimes, ≥66 g/day, and ≥66 g/day). *$p<0.05$; **$p<0.01$ vs. Q1

Table 3. Age-adjusted and multivariable hazard ratios (HRs) of incident diabetes according to the quartiles (Q) of the serum lipid levels for each body mass index category

	Ranges mmol/L	mg/dL	N	Person-year	No. of incidence	Incidence rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting men										
BMI < 18.5										
TG										
Q1	< 0.65	< 58	69	308	4	12.9	1.00 (ref)	0.67	1.00 (ref)	0.28
Q2	0.65-0.81	58-72	71	330	8	24.5	1.97 (0.59-6.56)		1.36 (0.38-4.92)	
Q3	0.82-1.07	73-95	73	336	5	14.9	1.18 (0.32-4.38)		0.96 (0.25-3.73)	
Q4	1.08-	96-	72	347	4	11.6	0.93 (0.23-3.74)		0.55 (0.12-2.42)	
BMI 18.5-24.9										
TG										
Q1	< 0.84	< 74	1153	6396	66	10.4	1.00 (ref)	< 0.01	1.00 (ref)	0.02
Q2	0.84-1.12	74-99	1199	6574	76	11.5	1.13 (0.81-1.57)		1.12 (0.80-1.56)	
Q3	1.13-1.58	100-140	1181	6674	94	14.0	1.38 (1.01-1.90)*		1.31 (0.95-1.81)	
Q4	1.59-	141-	1186	6300	103	16.4	1.61 (1.18-2.20)**		1.44 (1.04-1.99)*	
BMI ≤ 25.0										
TG										
Q1	< 1.07	< 95	425	2254	46	20.4	1.00 (ref)	0.06	1.00 (ref)	0.20
Q2	1.07-1.46	95-129	441	2414	52	21.4	1.08 (0.72-1.60)		0.95 (0.64-1.42)	
Q3	1.47-2.06	130-182	433	2353	51	21.8	1.10 (0.74-1.64)		0.87 (0.58-1.30)	
Q4	2.07-	183-	440	2231	63	28.1	1.46 (1.00-2.15)*		1.32 (0.84-1.94)	
Non-fasting men										
BMI < 18.5										
TG										
Q1	< 0.73	< 65	333	1388	52	37.2	1.00 (ref)	0.07	1.00 (ref)	0.045
Q2	0.73-0.93	65-82	345	1591	32	20.2	0.55 (0.36-0.86)**		0.54 (0.35-0.85)**	
Q3	0.94-1.27	83-112	348	1512	40	26.7	0.73 (0.48-1.10)		0.71 (0.47-1.08)	
Q4	1.28-	113-	348	1626	36	22.0	0.62 (0.41-0.95)*		0.58 (0.38-0.90)*	
BMI 18.5-24.9										
TG										
Q1	< 0.95	< 84	5515	28209	535	19.0	1.00 (ref)	0.01	1.00 (ref)	< 0.01
Q2	0.95-1.30	84-115	5529	28681	512	17.8	0.96 (0.85-1.08)		0.94 (0.83-1.06)	
Q3	1.31-1.83	116-162	5664	29637	526	17.9	0.96 (0.85-1.09)		0.99 (0.87-1.12)	
Q4	1.84-	163-	5579	29156	607	20.9	1.17 (1.04-1.31)**		1.18 (1.05-1.34)**	
BMI ≤ 25.0										
TG										
Q1	< 1.34	< 119	2183	11213	199	17.9	1.00 (ref)	< 0.01	1.00 (ref)	< 0.01
Q2	1.34-1.88	119-166	2201	11380	269	23.5	1.35 (1.13-1.62)**		1.28 (1.06-1.54)*	
Q3	1.89-2.60	167-230	2204	10969	301	27.3	1.57 (1.32-1.88)**		1.38 (1.15-1.66)**	
Q4	2.61-	231-	2204	10668	331	31.3	1.80 (1.51-2.15)**		1.56 (1.30-1.87)**	

nificantly associated with incident DM in men in a fasting state (**Table 2**). As shown in **Table 2** and **Supplemental Table 2**, among men with a non-fasting status, the TC, non-HDLC, TG, TC/HDLC, non-HDL/HDLC and TG/HDLC values were significantly associated with incident DM. Meanwhile, the TG/HDLC values were significantly associated with incident DM after multivariate adjustment in women

(Cont Table 3)

	Ranges mmol/L	mg/dL	N	Person-year	No. of incidence	Incidence rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting women										
BMI < 18.5										
TG										
Q1	< 0.61	< 54	149	951	3	3.1	1.00 (ref)	0.62	1.00 (ref)	0.96
Q2	0.61-0.78	54-69	163	876	5	5.7	1.40 (0.33-5.89)		1.56 (0.34-7.18)	
Q3	0.79-1.02	70-90	162	935	4	4.3	0.80 (0.18-3.70)		1.13 (0.22-5.68)	
Q4	1.03-	91-	163	958	5	5.2	0.86 (0.20-3.75)		1.14 (0.25-5.18)	
BMI 18.5-24.9										
TG										
Q1	< 0.73	< 65	2709	16476	103	6.2	1.00 (ref)	0.09	1.00 (ref)	0.79
Q2	0.73-0.96	65-85	2673	16301	98	6.0	0.85 (0.64-1.12)		0.78 (0.59-1.04)	
Q3	0.97-1.32	86-117	2754	16697	122	7.3	0.98 (0.75-1.28)		0.82 (0.62-1.07)	
Q4	1.33-	118-	2771	16354	153	9.4	1.18 (0.91-1.52)		0.98 (0.75-1.28)	
BMI ≤ 25.0										
TG										
Q1	< 0.90	< 80	1040	6324	65	10.2	1.00 (ref)	< 0.01	1.00 (ref)	< 0.01
Q2	0.90-1.21	80-107	1094	6281	82	13.1	1.23 (0.89-1.70)		1.28 (0.92-1.78)	
Q3	1.22-1.66	108-147	1099	5898	115	19.4	1.77 (1.31-2.42)**		1.77 (1.31-2.42)**	
Q4	1.67-	148-	1094	6219	123	19.7	1.81 (1.33-2.45)**		1.69 (1.24-2.29)**	
Non-fasting women										
BMI < 18.5										
TG										
Q1	< 0.76	< 67	682	3837	24	6.3	1.00 (ref)	< 0.01	1.00 (ref)	< 0.01
Q2	0.76-0.97	67-86	690	3699	21	5.6	0.80 (0.44-1.44)		0.79 (0.44-1.44)	
Q3	0.98-1.32	87-117	718	3908	36	9.3	1.27 (0.75-2.13)		1.33 (0.79-2.24)	
Q4	1.33-	118-	698	3599	52	14.3	1.90 (1.17-3.11)*		1.83 (1.11-3.00)*	
BMI 18.5-24.9										
TG										
Q1	< 0.93	< 82	11725	70315	374	5.2	1.00 (ref)	< 0.01	1.00 (ref)	< 0.01
Q2	0.93-1.27	82-112	11573	70130	450	6.4	1.12 (0.98-1.29)		1.07 (0.94-1.23)	
Q3	1.28-1.80	113-159	12012	70781	546	7.7	1.28 (1.12-1.47)**		1.17 (1.03-1.34)*	
Q4	1.81-	160-	11870	69276	737	10.7	1.71 (1.51-1.94)**		1.48 (1.30-1.69)**	
BMI ≤ 25.0										
TG										
Q1	< 1.19	< 104	5394	30671	270	8.8	1.00 (ref)	< 0.01	1.00 (ref)	< 0.01
Q2	1.19-1.65	105-146	5639	31486	386	12.2	1.36 (1.17-1.59)**		1.23 (1.05-1.44)**	
Q3	1.66-2.29	147-203	5525	29959	461	15.5	1.69 (1.45-1.97)**		1.48 (1.27-1.72)**	
Q4	2.30-	204-	5583	29355	620	21.0	2.31 (2.00-2.66)**		1.88 (1.63-2.18)**	

BMI, body mass index; TG, triglycerides
Adjusted for age (years), BMI, antihypertensive medication use (yes or no), antihyperlipidemic medication use (yes or no), systolic blood pressure level, smoking status (never smoked; ex-smoker; current smoker, ≥ 20 cigarettes per day; and current smoker, ≥ 20 cigarettes per day) and alcohol intake (never, sometimes, ≥ 66 g/day, and ≥ 66 g/day). *$p < 0.05$; **$p < 0.01$ vs. Q

with a fasting status. As shown in **Table 2** and **Supplemental Table 2**, the TC, non-HDLC, TG, TC/HDLC, non-HDL/HDLC and TG/HDLC values were significantly associated with incident DM in women with a non-fasting status. In contrast, the HDLC levels were inversely associated with incident DM in the

Table 4. Area under the receiver operating characteristic curves for the incidence of diabetes mellitus based on conventional risk factors and the triglyceride values

	Men			
	Fasting		Non-fasting	
	Model 1: CRF	Model 2: CRF + TG	Model 1: CRF	Model 2: CRF + TG
AUCROC (95% CI)	0.616 (0.600, 0.632)	0.619 (0.603, 0.635)	0.592 (0.583, 0.600)	0.593 (0.585, 0.602)
Change in AUCROC, *p* value	Ref.	0.097	Ref.	0.100
	Women			
	Fasting		Non-fasting	
	Model 1: CRF	Model 2: CRF + TG	Model 1: CRF	Model 2: CRF + TG
AUCROC (95% CI)	0.636 (0.624, 0.647)	0.636 (0.624, 0.648)	0.623 (0.616, 0.630)	0.626 (0.612, 0.633)
Change in AUCROC, *p* value	Ref.	0.404	Ref.	<0.001

The data are presented as the AUCROC and 95% CI. AUCROC, Area under the receiver operating characteristic curve; CI, confidence interval; CRF, conventional risk factors; TG, triglycerides
Conventional risk factors: age, body mass index, antihypertensive medication use, antihyperlipidemic medication use, systolic blood pressure, smoking status and alcohol intake

non-fasting women.

Utility of TG for Predicting DM

Table 3 shows the sex- and fasting state-specific multivariate-adjusted HRs for DM according to the quartiles (Q) of TG in each BMI category. A dose-response relationship between DM and TG was present among men in a fasting state and women in a non-fasting state with a normal BMI (18.5-24.9) (**Table 3**). The multivariable-adjusted HRs for DM in TG Q2 (0.84-1.12 mmol/L), Q3 (1.13-1.58 mmol/L) and Q4 (≥1.59 mmol/L) compared with Q1 (<0.84 mmol/L) were 1.12 (95% confidence interval (CI): 0.80, 1.56), 1.31 (0.95, 1.81) and 1.44 (1.04, 1.99), respectively, in fasting men with a normal BMI (18.5-24.9) (**Table 3**). The multivariable-adjusted HR for DM for TG Q4 (≥1.84 mmol/L) compared with Q1 (<0.95 mmol/L) was 1.18 (1.05, 1.34) in men with a non-fasting status and a normal BMI (18.5-24.9). The following trends were observed in women with a non-fasting status and normal BMI. Specifically, the multivariable-adjusted HRs for DM for TG Q2 (0.93-1.27 mmol/L), Q3 (1.28-1.80 mmol/L) and Q4 (≥1.81 mmol/L) compared with Q1 (<0.93 mmol/L) were 1.07 (95%CI: 0.94, 1.23), 1.17 (1.03, 1.34) and 1.48 (1.30, 1.69), respectively (**Table 3**). The ability to predict the development of DM by adding TG to the model consisting of conventional risk factors significantly improved based on the area under the ROC curve in women in a non-fasting state (**Table 4**). In contrast, no significant differences were observed in discriminative ability among women in a fasting state (**Table 4**). However, a borderline significant difference was observed in discriminative ability among men in both a fasting and non-fasting state (**Table 4**).

Discussion

This study includes three major findings. First, in the current large cohort study, the TG and TG/HDL levels were found to be independent strong predictors of incident DM. Second, the TG level was found to be an independent predictor of incident DM in both fasting and non-fasting men and non-fasting women. Third, these relationships were observed in the subjects with a normal BMI (18.5-24.9). To our knowledge, this is the first investigation of the role of fasting and non-fasting lipid measurements within the same cohort in predicting future DM.

A limited number of studies have been performed to evaluate the effects of lipids on the incidence of DM[7, 8, 15]. For example, Hadaegh *et al.* showed the TG, TG/HDL-C and TC/HDL-C levels to be independent predictors of incident DM in both fasting men and women in an Iranian cohort[8]. Meanwhile, Ley *et al.* demonstrated that the fasting TG, non-HDLC and TC/HDL-C levels are associated with incident DM in Canadians[7]. Similar results were reported by He *et al.* in that the TG and TG/HDLC levels were found to be independent predictors of incident DM in Chinese subjects in a fasting state[15]. However, the authors did not separate men and

women in their analysis[7, 15]. In our study, the TG and TG/HDLC levels were identified to be significantly associated with incident DM in fasting men, whereas the TG/HDLC values were found to be significantly associated with incident DM in fasting women only after multivariate adjustment. These discrepancies in the ability to predict DM among lipid variables may result from inherent differences in the study samples. Another reason for the inconsistent results is that the individuals for whom samples were evaluated varied with regard to the baseline DM risk. For example, the subjects assessed by Hadaegh *et al.* were younger and had higher BMI values and TG levels than those evaluated in our study[8]. In addition, compared with our study subjects, the patients investigated in the report by Ley *et al.* were younger and had higher BMI values; there was also a higher prevalence of women[7]. In contrast, in the report by He *et al.*, the BMI values were similar to those noted in our study, although the subjects were younger, and there was a higher prevalence of women[15]. The apparent lack of an association between TG and DM in fasting women may be due to the fact that the non-fasting TG level is more greatly influenced by insulin impairment, resulting in an increased TG level via the following mechanisms. A relationship between insulin and the synthesis or dissimilation of TG-rich lipoproteins, such as very-low-density lipoproteins, has been described[6]. For example, the levels of insulin-regulated lipoprotein lipase (LPL) and the plasma LPL mass are decreased in patients with insulin resistance, such as those with DM or metabolic syndrome[23, 24]. In addition, the plasma TG values are negatively correlated with the plasma LPL mass and improve following insulin therapy in patients with DM[24]. Bansal *et al.* showed that the non-fasting TG level is associated with the incidence of cardiovascular disease, whereas the fasting TG level exhibits a slight independent relationship with cardiovascular disease in women, after adjusting for BMI[25]. Our findings are consistent with these results, suggesting that the impact of TG on the future development of DM is limited in women compared with men in a fasting state. However, Iso *et al.* showed that the level of TG is an independent predictor of coronary heart disease in both Japanese men and women[26]. These discrepancies may result from differences in the definitions of TG quartiles between these two studies. Further studies are therefore needed to clarify this issue.

Current guidelines recommend measuring the lipid levels in a fasting state[27, 28]. However, recent studies suggest the usefulness of non-fasting lipid measurements[18]. In community-based individuals, the mean TG level varies by less than 20% when the measurements are obtained over a range of one to 16 hours after a meal[18]. From the view of convenience for both patients and clinicians and the need to reduce the burden on laboratories, it would be practical to use non-fasting samples[29, 30]. In the current study, the non-fasting TG and TG/HDLC values were found to be associated with the incidence of DM in both men and women. In contrast, the non-fasting HDLC level was identified to be inversely associated with incident DM in women. Similarly, Njolstad *et al.* showed the non-fasting HDLC level to be inversely associated with incident DM in Norwegian women[31], and Perry *et al.* documented an association between the non-fasting TG level and incident DM in British men[14]. These findings are consistent with our results. Moreover, an elevated non-fasting TG level has been reported to be associated with an increased risk of cardiovascular disease[3, 4, 25, 26]. Therefore, our results are reasonable, given the findings of previous epidemiological studies[3, 4, 25, 26].

The effect of TG on the risk of DM has been examined[7-15]. An impaired insulin function, consisting of insulin resistance and β-cell damage, is a characteristic feature of incident DM[16]. Insulin resistance is associated with TG[6, 32]. In our study, TG was found to be an independent predictor of incident DM in both fasting and non-fasting men and non-fasting women. Meanwhile, fasting TG is associated with HOMA-IR in European, Australian Aboriginal, Chinese and Korean individuals[32, 33]. Moreover, a decrease in the effects of insulin has been shown to not only increase the TG level, but also decrease the HDLC level, resulting in an increased TG/HDL ratio[33]. In the present study, the TG/HDLC ratio was found to be an independent predictor of incident DM in both sexes in a fasting and non-fating state. Taken together, the TG/HDLC value is a useful predictor of incident DM, regardless of the fasting status, and TG is an independent predictor of DM in fasting and non-fasting men as well as non-fasting women. However, the TG and TG/HDLC values are not reliable markers of insulin resistance in African Americans or South Asians[33-35]. Further validation studies are needed to clarify the usefulness of TG and/or TG/HDL for predicting incident DM.

Insulin resistance results in decreased insulin effects and is related to obesity, which carries a very strong risk for DM[36, 37]. However, Asians typically have a lower mean BMI with a higher prevalence of DM, compared with Caucasians at similar BMI values[20, 21]. Therefore, other mechanisms, such as impaired insulin secretion, have been proposed to account for the development of DM[20, 21, 38, 39]. In our study, the

TG level was found to be an independent predictor of incident DM in both fasting and non-fasting men and non-fasting women with a normal BMI. Similar results were reported by Petty *et al.*, who showed a strong positive association between the TG concentration and the risk of DM after adjusting for age and BMI in British men in a fasting state[14]. The results of our quartile analysis showed that the levels of TG in fasting men (1.59 mmol/L), non-fasting men (1.84 mmol/L) and non-fasting women (1.28 mmol/L) found to be predictive of incident DM are similar to those identified in previous studies[8, 40]. For example, Mclaughlin *et al.* showed a cutoff point for TG for insulin resistance of 1.47 mmol/L in overweight volunteers in a fasting state[40]. In a report by Hadaegh *et al.*, the level of TG for incident DM was 1.61 mmol/L in fasting men and 1.54 mmol/L in fasting women[8]. These values are clearly lower than those recommended by the American Diabetes Association for DM screening[41] and those included in criteria for metabolic syndrome[42]. However, the TG level is not a reliable marker of insulin resistance in African Americans or South Asians[33-35]. Taken together, clinicians should pay attention to ethnicity when considering which patients are at high risk for DM. In addition, our results must be confirmed in prospective studies including subjects from various ethnic groups.

There are several possible mechanisms as to why TG elevation is related to the development of DM. First, as shown in patients with metabolic syndrome, the accumulation of intra-abdominal fat and a high level of free fatty acids play a role in insulin resistance[16, 17, 43, 44]. Second, a decrease in skeletal muscle mass can lead to peripheral tissue insulin resistance[45]. Third, the consumption of a high-fat diet is positively associated with insulin sensitivity[46]. Fourth, impaired insulin secretion influenced by a family history of DM may induce a decrease in the effects of insulin. The accumulation of TG in the skeletal muscle, liver and pancreas, resulting in increased insulin resistance and β-cell damage, cumulates in a vicious cycle of insulin impairment[16, 17]. Unfortunately, we have no data regarding the lifestyle factors or family history of our study patients. Further investigation is therefore needed to assess these issues.

In our study, the sex- and fasting state-specific multivariate-adjusted HRs for DM according to the quartiles of TG in each BMI category remained unchanged, even with adjustment of the baseline glucose levels (data not shown). These results may be due to the fact that a fasting state was defined as not having had a meal for the last eight hours, not necessarily an overnight fast. Since we were unable to assess the duration of fasting or composition of the subjects' diets, the effects of non-fasting plasma glucose on the development of DM may have been underestimated.

The present study is associated with several strengths and weaknesses. To the best of our knowledge, this is the first study to compare fasting and non-fasting lipid measurements within the same population-based cohort of Japanese men and women in predicting future DM. The large sample size allowed for the examination of relationships according to the BMI category. However, several limitations should also be considered. First, we were unable to assess the duration of fasting since we did not obtain data for the interval from the last meal and instead only determined whether the participant was in a fasting or non-fasting state. It has been shown that elevation in the TG level measured within two to four hours after food consumption is strongly associated with cardiovascular disease[25], and the plasma TG level has been reported to increase three hours after the ingestion of fat-containing test meals[47]. Therefore, the incidence of a non-fasting state may have been underestimated in our study. Moreover, non-fasting lipid measurements, especially those of TG, have been shown to be affected by the levels of dietary fat and exercise[6]. Therefore, further studies are needed to assess the association between non-fasting lipids and the incidence of DM taking into consideration dietary intake and exercise. Second, we did not diagnose DM using oral glucose tolerance tests, the most sensitive DM test for detecting glucose intolerance and insulin resistance. However, the prevalence of DM was similar to that observed in general population-based studies employing oral glucose tolerance tests in Japan[48]. We diagnosed DM according to the results of blood examinations and/or whether the subject was under treatment for DM. The criteria for a diagnosis of DM based on blood tests differ according to whether the individual is fasting. Third, we did not obtain both fasting and non-fasting measurements for the same individual during the same year, as our subjects only underwent annual health examinations once yearly. These issues may have introduced bias in the associations between the lipid levels and incident DM based on the fasting status. The percentage of subjects with incident DM in a fasting or non-fasting state differed in men (8.5% and 10.6%, respectively), whereas these values were similar in women (5.5% and 5.5%, respectively). Therefore, it is difficult to compare the strength of the association between fasting and non-fasting states in men. Fourth, the measurements of alcohol intake do not take into account the effects of binge drinking, which affects lipid variables, particularly TG. Fifth, an

observational study in principle can never prove causality. Therefore, our results should be confirmed in prospective interventional studies.

Conclusion

In conclusion, our data suggest that the fasting and non-fasting TG levels in men and non-fasting TG levels in women are predictive of future DM among those with a normal BMI. Clinicians must consider that these individuals may be at high risk for DM.

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Contribution Statement

K.F. developed the study design, collected the data, contributed to the discussions, wrote the report and reviewed and edited the final manuscript. A.S. and Y.H. planned and supervised the research, collected the data, contributed to the discussions, wrote the report and reviewed and edited the final manuscript. T.S. and F.I. collected the data, contributed to the discussions, wrote the report and reviewed and edited the final manuscript. H.I. and M.D. collected the data and reviewed and edited the final manuscript. H.W. and H.O. collected the data, contributed to the discussions and reviewed and edited the final manuscript. H.Sh. collected the data, contributed to the discussions and reviewed and edited the final manuscript. H.So. developed the study design, contributed to the discussions and reviewed and edited the final manuscript.

Duality of Interests

The authors declare that there is no duality of interests associated with this manuscript.

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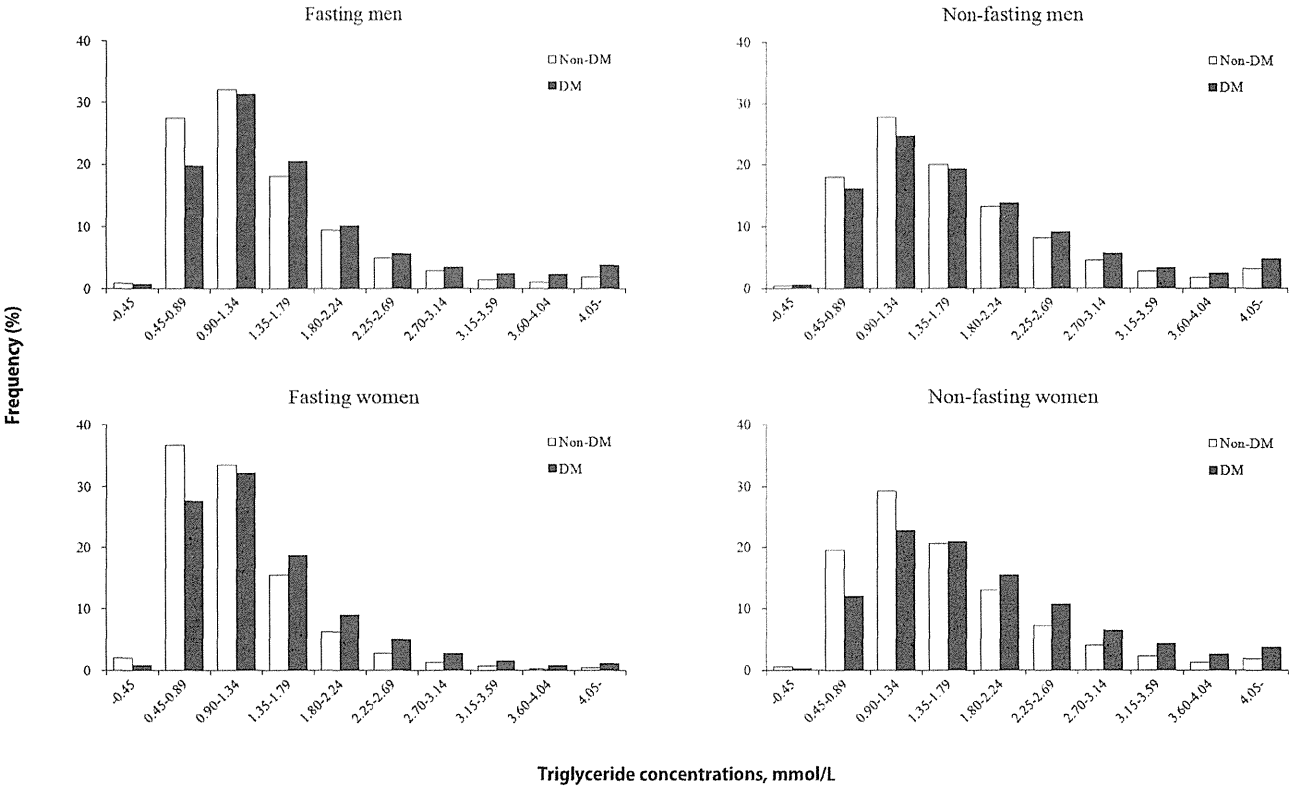
Supplemental Table 1. Characteristics of the study participants

	Men			Women		
	Follow up	Dropped out	*p* value	Follow up	Dropped out	*p* value
n	39196	19191		87980	35407	
Age (y)	61.4 ± 9.8	59.6 ± 10.8	<0.01	58.1 ± 10.0	57.4 ± 11.1	<0.01
BMI (kg/m^2)	23.2 ± 2.9	23.3 ± 3.0	<0.01	23.5 ± 3.1	23.6 ± 3.3	<0.01
SBP (mmHg)	136 ± 17	137 ± 18	0.39	132 ± 18	132 ± 19	<0.01
DBP (mmHg)	81 ± 11	81 ± 11	<0.01	78 ± 11	78 ± 11	<0.01
Hypertension treatment (%)	8386 (21)	3839 (20)	<0.01	17013 (19)	7179 (20)	<0.01
Never smoker (%)	8997 (23)	3897 (20)	<0.01	83762 (95)	32582 (92)	<0.01
ex-smoker (%)	11698 (30)	5170 (27)	–	492 (1)	326 (1)	–
20 cigarettes per day ≥ (%)	6212 (16)	3023 (17)	–	2573 (3)	1673 (5)	–
≥ 20 cigarettes per day (%)	12289 (31)	7101 (37)	–	1153 (1)	826 (2)	–
Never drinker (%)	13626 (35)	6716 (35)	<0.01	79576 (90)	31273 (88)	<0.01
Sometimes (%)	5025 (13)	2395 (12)	–	5186 (6)	2537 (7)	–
66 g/day ≥ (%)	18240 (47)	8491 (44)	–	3134 (4)	1523 (4)	–
≥ 66 g/day (%)	2305 (6)	1589 (8)	–	84 (0)	74 (0)	–
TC (mmol/L)	5.0 ± 0.9	5.0 ± 0.9	0.07	5.4 ± 0.9	5.4 ± 0.9	<0.01
HDLC (mmol/L)	1.4 ± 0.4	1.3 ± 0.4	<0.01	1.5 ± 0.4	1.5 ± 0.4	0.18
TG (mmol/L)	1.4 (1.0-2.0)	1.4 (1.0-2.1)	<0.01	1.3 (0.9-1.9)	1.4 (0.9-1.8)	0.04
Non-HDLC (mmol/L)	3.6 ± 0.9	3.7 ± 0.9	<0.01	3.9 ± 0.9	3.9 ± 0.9	<0.01
TC/HDLC	3.9 ± 1.2	4.0 ± 1.3	<0.01	3.9 ± 1.1	3.8 ± 1.1	0.01
Non-HDL/HDLC	2.9 ± 1.2	3.0 ± 1.3	<0.01	2.9 ± 1.1	2.8 ± 1.1	0.01
TG/HDLC	1.4 ± 1.2	1.5 ± 1.3	<0.01	1.2 ± 1.0	1.2 ± 1.0	0.22
Dyslipidemia treatment (%)	573 (1)	246 (1)	0.08	3045 (3)	1024 (3)	<0.01
PG (mmol/L)	6.1 ± 1.3	6.1 ± 1.3	<0.01	5.8 ± 1.1	5.8 ± 1.1	0.17

The data are presented as the mean ± SD or median (interquartile range).
BMI, body mass index; DBP, diastolic blood pressure; HDLC, high-density lipoprotein cholesterol; PG, plasma glucose, SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides



Supplemental Fig. 1. Sex- and fasting status-specific distributions of the baseline triglyceride levels according to the presence or absence of diabetes mellitus.

Supplemental Table 2. Age-adjusted and multivariable hazard ratios (HRs) for incident diabetes according to the quartiles (Q) of the serum lipid levels

	Ranges mmol/L	mg/dL	N	Person-years	No. of incidence	Incidence Rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting men										
Non-HDLC										
Q1	<3.15	<122	1694	8848	142	16.1	1.00 (ref)	0.32	1.00 (ref)	0.70
Q2	3.15-3.73	122-144	1677	9361	125	13.3	0.85 (0.67-1.08)		0.76 (0.60-0.97)*	
Q3	3.74-4.36	145-168	1666	9152	153	16.7	1.06 (0.85-1.33)		0.96 (0.76-1.21)	
Q4	4.37-	169-	1706	9156	152	16.5	1.05 (0.84-1.32)		0.87 (0.69-1.11)	
LDLC										
Q1	<2.58	<100	1651	8556	152	17.7	1.00 (ref)	0.42	1.00 (ref)	0.12
Q2	2.58-3.09	100-119	1664	9175	124	13.5	0.76 (0.60-0.97)*		0.75 (0.59-0.95)	
Q3	3.10-3.66	120-141	1659	9287	141	15.2	0.87 (0.69-1.09)		0.82 (0.65-1.03)	
Q4	3.67-	142-	1679	9066	140	15.4	0.87 (0.69-1.10)		0.80 (0.63-1.01)	
TC/HDLC										
Q1	<3.07		1641	8656	121	13.9	1.00 (ref)	<0.01	1.00 (ref)	0.09
Q2	3.07-3.74		1693	9426	129	13.6	0.99 (0.77-1.27)		0.89 (0.69-1.15)	
Q3	3.75-4.61		1707	9374	144	15.3	1.12 (0.88-1.43)		0.98 (0.76-1.27)	
Q4	4.62		1702	9061	178	19.7	1.43 (1.13-1.80)**		1.19 (0.92-1.54)	
Non-HDLC/HDLC										
Q1	<2.07		1664	8802	122	13.8	1.00 (ref)	<0.01	1.00 (ref)	0.11
Q2	2.07-2.75		1697	9393	133	14.2	1.03 (0.81-1.32)		0.93 (0.72-1.20)	
Q3	2.76-3.62		1691	9335	140	15.1	1.10 (0.87-1.41)		0.97 (0.75-1.25)	
Q4	3.63-		1691	8987	177	19.7	1.44 (1.14-1.82)**		1.20 (0.93-1.55)	
LDLC/HDLC										
Q1	<1.72		1639	8735	125	14.4	1.00 (ref)	0.26	1.00 (ref)	0.82
Q2	1.72-2.29		1675	8996	144	15.9	1.12 (0.88-1.42)		0.96 (0.78-1.18)	
Q3	2.30-2.94		1667	9346	136	14.6	1.03 (0.81-1.32)		1.09 (0.89-1.34)	
Q4	2.95-		1672	9007	152	16.8	1.19 (0.94-1.50)		1.16 (0.94-1.43)	
Non-fasting men										
Non-HDL										
Q1	<2.98	<115	8171	40136	837	20.9	1.00 (ref)	<0.01	1.00 (ref)	0.046
Q2	2.98-3.53	115-136	7825	40838	765	18.8	0.92 (0.83-1.01)		0.90 (0.81-0.99)*	
Q3	3.54-4.13	137-159	8154	42584	881	20.8	1.02 (0.93-1.12)		0.99 (0.90-1.09)	
Q4	4.14-	160-	8303	42472	957	22.6	1.12 (1.02-1.23)*		1.07 (0.97-1.19)	
TC/HDLC										
Q1	<3.03		8056	40558	859	21.3	1.00 (ref)	0.01	1.00 (ref)	0.33
Q2	3.03-3.73		8074	41647	802	19.1	0.92 (0.84-1.01)		0.91 (0.82-0.998)*	
Q3	3.74-4.61		8098	42278	813	19.3	0.93 (0.85-1.03)		0.90 (0.81-0.99)	
Q4	4.62-		8225	41547	966	23.0	1.13 (1.03-1.23)*		1.05 (0.95-1.17)	
Non-HDLC/HDLC										
Q1	<2.03		8048	40532	860	21.4	1.00 (ref)	0.01	1.00 (ref)	0.33
Q2	2.03-2.73		8073	41676	798	19.0	0.91 (0.83-1.01)		0.90 (0.81-0.99)*	
Q3	2.74-3.62		8185	42657	825	19.4	0.94 (0.85-1.03)		0.90 (0.81-0.995)*	
Q4	3.63-		8147	41165	957	23.0	1.12 (1.02-1.23)*		1.05 (0.95-1.17)	

(Cont Supplemental Table 2)

	Ranges mmol/L	mg/dL	N	Person-years	No. of incidence	Incidence Rate/1,000 person-years	Age-adjusted HR (95% CI)	*p* for trend	Multivariable HR (95% CI)	*p* for trend
Fasting women										
Non-HDLC										
Q1	<2.82	<109	3889	23157	161	6.9	1.00 (ref)	<0.01	1.00 (ref)	0.06
Q2	2.82-3.34	109-129	4068	24490	205	8.4	1.09 (0.88-1.34)		0.98 (0.80-1.21)	
Q3	3.35-3.93	130-151	3897	23273	209	8.9	1.11 (0.90-1.36)		0.92 (0.75-1.14)	
Q4	3.94-	152-	4017	23350	303	13.0	1.53 (1.25-1.86)**		1.20 (0.98-1.46)	
LDLC										
Q1	<2.82	<109	3884	22991	183	8.0	1.00 (ref)	0.04	1.00 (ref)	0.68
Q2	2.82-3.34	109-129	3951	24065	203	8.4	0.97 (0.80-1.19)		0.91 (0.74-1.11)	
Q3	3.35-3.93	130-151	3993	23544	212	9.0	0.98 (0.80-1.20)		0.88 (0.72-1.07)	
Q4	3.94-	152-	3984	23307	271	11.5	1.21 (1.00-1.47)		1.03 (0.85-1.25)	
TC/HDLC										
Q1	<2.96		3908	23468	162	6.9	1.00 (ref)	<0.01	1.00 (ref)	0.03
Q2	2.96-3.54		3976	24129	171	7.1	0.96 (0.78-1.19)		0.85 (0.68-1.06)	
Q3	3.55-4.29		3965	23168	246	10.7	1.36 (1.11-1.66)**		1.09 (0.89-1.34)	
Q4	4.30-		4022	23505	299	12.8	1.56 (1.29-1.90)**		1.13 (0.93-1.39)	
Non-HDLC/HDLC										
Q1	<1.97		3963	23811	167	7.0	1.00 (ref)	<0.01	1.00 (ref)	0.03
Q2	1.97-2.54		3924	23819	165	6.9	0.93 (0.75-1.15)		0.82 (0.66-1.02)	
Q3	2.55-3.31		3988	23319	246	10.6	1.33 (1.09-1.63)**		1.07 (0.87-1.31)	
Q4	3.32-		3996	23321	300	12.9	1.56 (1.28-1.89)**		1.13 (0.93-1.38)	
LDLC/HDLC										
Q1	<1.72		3904	23315	160	6.8	1.00 (ref)	<0.01	1.00 (ref)	0.13
Q2	1.72-2.20		3946	23811	190	8.0	1.09 (0.88-1.34)		0.97 (0.78-1.19)	
Q3	2.21-2.81		3996	23641	237	10.1	1.30 (1.07-1.60)*		1.05 (0.86-1.29)	
Q4	2.82-		3966	23140	282	12.3	1.51 (1.24-1.84)**		1.13 (0.92-1.39)	
Non-fasting women										
Non-HDLC										
Q1	<3.26	<126	17753	104814	697	6.7	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	3.26-3.84	126-148	18240	106747	875	8.1	1.15 (1.04-1.27)**		1.05 (0.95-1.16)	
Q3	3.85-4.49	149-173	18075	105167	1058	10.1	1.36 (1.23-1.49)**		1.16 (1.05-1.28)**	
Q4	4.50-	174-	18041	101288	1347	13.3	1.74 (1.59-1.91)**		1.39 (1.27-1.53)**	
TC/HDLC										
Q1	<3.06		17715	104702	693	6.6	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	3.06-3.69		18215	107313	829	7.7	1.10 (1.00-1.22)		0.99 (0.90-1.10)	
Q3	3.70-4.50		17908	104448	1095	10.5	1.45 (1.32-1.59)**		1.20 (1.10-1.33)**	
Q4	4.51-		18271	101553	1360	13.3	1.78 (1.62-1.95)**		1.33 (1.21-1.47)**	
Non-HDLC/HDLC										
Q1	<2.07		17989	106245	699	6.6	1.00 (ref)	<0.01	1.00 (ref)	<0.01
Q2	2.07-2.69		17929	105651	825	7.8	1.12 (1.02-1.24)*		1.01 (0.92-1.12)	
Q3	2.70-3.51		18107	105618	1109	10.6	1.46 (1.33-1.61)**		1.22 (1.10-1.34)**	
Q4	3.52-		18084	100502	1344	13.3	1.79 (1.63-1.96)**		1.34 (1.22-1.48)**	

HDLC, high-density lipoprotein cholesterol; LDLC, LDL-cholesterol; TC, total cholesterol
Adjusted for age (years), body mass index, antihypertensive medication use (yes or no), antihyperlipidemic medication use (yes or no), systolic blood pressure, smoking status (never smoked; ex-smoker; current smoker, ≥20 cigarettes per day; and current smoker, ≥20 cigarettes per day) and alcohol intake (never, sometimes, ≥66 g/day, and ≥66 g/day). *$p<0.05$; **$p<0.01$ vs. Q1

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Original Article

The Dose-Response Relationship Between Body Mass Index and the Risk of Incident Stage ≥3 Chronic Kidney Disease in a General Japanese Population: The Ibaraki Prefectural Health Study (IPHS)

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ABSTRACT

Purpose: To examine the relationship between body mass index (BMI) and the risk of stage ≥3 chronic kidney disease (CKD) in a general Japanese population.

Methods: A total of 105 611 participants aged 40–79 years who completed health checkups in Ibaraki Prefecture, Japan, and were free of CKD in 1993 were followed-up through 2006. Stage ≥3 CKD was defined by an estimated glomerular filtration rate <60 mL/min/1.73 m^2 reported during at least 2 successive annual surveys or as treatment for kidney disease. Hazard ratios (HRs) for the development of stage ≥3 CKD relative to the BMI categories were calculated using the Cox proportional hazards regression model, which was adjusted for possible confounders and mediators.

Results: During a mean follow-up of 5 years, 19 384 participants (18.4%) developed stage ≥3 CKD. Compared to a BMI of 21.0–22.9 kg/m^2, elevated multivariable-adjusted HRs were observed among men with a BMI ≥23.0 kg/m^2 and women with a BMI ≥27.0 kg/m^2. Significant dose-response relationships between BMI and the incidence of stage ≥3 CKD were observed in both sexes (*P* for trend <0.001).

Conclusions: Obesity was associated with the risk of developing stage ≥3 CKD among men and women.

Key words: chronic kidney disease; body mass index; obesity; dose-response relationship; epidemiology

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem. In Japan, CKD affects 13.3 million adults.[1] With the increasing incidence of hypertension and type 2 diabetes and the aging of the Japanese population, the number of individuals with CKD will likely continue to increase. CKD is recognized as an independent risk factor for myocardial infarction and cardiovascular mortality and can result in significant morbidity, mortality, and increased medical costs.[2]

Obesity is also a major public health issue, and its prevalence has been increasing worldwide. Obesity is associated with the development of many cardiovascular disease (CVD) risk factors, including type 2 diabetes mellitus,[3,4] hypertension,[5,6] dyslipidemia,[7] and CKD.[8] Prospective cohort studies have revealed the longitudinal relation between body mass index (BMI) and the risk of moderate CKD. A greater baseline BMI was associated with an increased risk of stage ≥3 CKD in the Physician's Health Study,[9] the Hypertension Detection and Follow-Up Program,[10] and the Framingham Heart Study.[11] Because treatment of long-term CKD is costly, the best approach is to reduce the incidence of stage ≥3 CKD or prevent it entirely. Examining the modifiable risk factors for stage ≥3 CKD,

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such as obesity, is important because of the public health implications.

A relationship between obesity and the risk of stage ≥3 CKD in Japanese participants has been reported.[12] However, not enough information was presented to examine the dose-response relationship between obesity and the risk of CKD (ie obesity was only considered as dichotomous data); consequently, the dose-response relationship in Japanese individuals remains unclear. An examination of the CKD risk using more-detailed BMI categories in a large cohort is warranted. Additionally, no studies have considered the age-specific relationship between BMI and the development of stage ≥3 CKD. Further research on this issue may help officials implement more effective public health and clinical efforts aimed at the primary prevention of CKD. The purpose of our study was to examine the dose-response relationship between BMI and the development of stage ≥3 CKD in a general Japanese population.

METHODS AND PROCEDURES

Study population

The study population consisted of 194 333 individuals (63 865 men and 130 468 women) aged 40–79 years who were living in Ibaraki Prefecture, Japan. These individuals had participated in community-based annual health checkups in 1993 (as part of the Ibaraki Prefectural Health Study), which were conducted by the local governments in accordance with the Law of Health and Medical Services for the Elderly. The Ibaraki prefectural government collected data from the local governments, and personal information was removed to ensure anonymity. We excluded 18 939 patients (2367 men and 16 572 women) because of incomplete data, 10 075 individuals (4101 men and 5974 women) because of a history of CVD, and 10 491 individuals (3615 men and 6876 women) because of the presence of stage ≥3 CKD and/or ongoing treatment for CKD. We further excluded 48 864 individuals (17 999 men and 30 865 women) who failed to participate in the 1994 survey, thereby ensuring that all of the participants were followed for at least one year.

Ultimately, the study included 105 611 participants (35 738 men and 69 873 women). These participants were followed by annual examinations until a diagnosis of stage ≥3 CKD, withdrawal from the repeated examinations, or the end of 2006, whichever occurred first. The Ibaraki Epidemiology Study Union Ethics Review Committee approved the protocol for this cohort study.

Measurements

Kidney function was assessed using the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the new Japanese abbreviated prediction equation,[13] modified from the Modification of Diet in Renal Disease (MDRD) Study,[14] as recommended by the Japanese Society of Nephrology:

$$\text{eGFR (mL/[min·1.73 m}^2\text{])} = [194 \times (\text{serum creatinine [mg/dL]})]^{-1.094} \times (\text{age})^{-0.287} \times 0.739 \text{ (for women only)}$$

According to Levey et al, stage ≥3 CKD is defined as the presence of kidney damage or an eGFR <60 mL/min/1.73 m^2 reported at least twice in successive annual surveys.[15]

Serum creatinine level was measured using the Jaffe method with an automated analyzer (Hitachi 7350; Hitachi, Tokyo, Japan, or RX-30; Nihon Denshi, Tokyo, Japan) in 1993–2003; in 2004–2006, it was measured using the enzyme method with an automated analyzer (Hitachi 7770; Hitachi). The coefficient of validation for creatinine value was 0.61%. Serum creatinine measurements from 1993–2003 were converted to the value obtained in the enzyme method using the following equation:

$$\text{serum creatinine by enzyme method (mg/dL)} = 0.9915 \times \text{serum creatinine by the Jaffe method (mg/dL)} - 0.211$$

The serum creatinine values measured using the enzyme method and the serum creatinine values measured using the Jaffe method were then converted to the enzyme method from the same subjects at the same point in time, and the comparability between them was found to be excellent ($r = 0.99$, $P < 0.001$). Proteinuria was defined as a urinary protein excretion of 1+ or more by dipstick test (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan).

The patients' height in sock feet and weight in light clothing were measured at baseline. BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2).

We measured the following cardiovascular risk factors: serum total cholesterol, serum high-density-lipoprotein (HDL) cholesterol, serum triglyceride, plasma glucose, blood pressure, use of medications, cigarette smoking, and typical alcohol intake. Blood samples were drawn into two polyethylene terephthalate tubes from seated participants; one tube contained an accelerator, while the other contained sodium fluoride and ethylenediaminetetraacetic acid. Overnight fasting (≥8 h) was not mandatory. The serum total cholesterol and serum triglyceride levels were measured using the enzyme method with the RX-30 device in 1993–1995, the H7350 device in 1996–2003, and the H7700 device in 2004–2006. The HDL cholesterol levels were measured using the phosphotungstic acid magnesium method with an MTP-32 device (Corona Electric, Ibaraki, Japan) in 1993–1995, the selective inhibition method with the H7350 device in 1996–2003, and the H7700 device in 2004–2006. Dyslipidemia was defined as triglycerides ≥1.7 mmol/L, HDL cholesterol <1.036 mmol/L, or as the patient being prescribed medication for dyslipidemia treatment.

The blood glucose level was measured using the glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan) in 1993–1996, the enzyme method with a H7170 device (Hitachi) in 1997–2003, and

the H7700 device in 1994–2006. The participants were considered diabetic if they had a plasma glucose of ≥6.1 mmol/L in a fasted state or ≥7.8 mmol/L in a non-fasted state, or if they were being treated for diabetes mellitus. The laboratory participated in external standardization and successfully met the criteria for precision accuracy for the measurement of blood samples, as established by the Japan Medical Association, the Japanese Association of Medical Technologists, and the Japan Society of Health Evaluation and Promotion.

Blood pressure was measured on the right arm of seated participants who had rested for more than 5 min; trained observers obtained these measurements using a standard mercury sphygmomanometer in 1993–2004 and an automated sphygmomanometer in 2005–2006. When the systolic blood pressure was >150 mm Hg or the diastolic blood pressure was >90 mm Hg, a second measurement was obtained after the subject took several deep breaths. The lower values, which were almost always observed during the second measurement, were used for the analyses. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. CVD risk factors were defined as hypertension, dyslipidemia, and diabetes.

Lastly, we conducted an interview to ascertain the number of cigarettes smoked per day, the typical weekly alcohol intake (converted to grams of ethanol per day), and the history of CVD and CKD.

Statistical analysis

The participants were classified into the following categories with regard to their BMI (kg/m^2): <18.5; 18.5–20.9; 21.0–22.9; 23.0–24.9; 25.0–26.9; 27.0–29.9; or ≥30.0. To compare the participants' physical characteristics according to the BMI categories, one-way analysis of variance was used for continuous variables, and a χ^2-test was used for categorical variables. The Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs) of risk of development of stage ≥3 CKD relative to the BMI categories in comparison to the reference group, 21.0–22.9 kg/m^2. A BMI of 22 kg/m^2 is commonly set as the optimal body size in Japan.[16] The analyses were stratified by sex and age groups (40–59 and 60–79 years old).

We used two multivariate-adjusted models. In model one, covariates included age and the potential confounders of cigarette smoking (never, former, current [1–19 cigarettes/day or ≥20 cigarettes/day]) and typical alcohol intake (never, sometimes, everyday [<56 g/day or ≥56 g/day]). In model two, potential mediators were added to model one. Potential mediators included systolic blood pressure, the use of antihypertensive medication (yes or no), triglyceride level (log-transformed), serum total cholesterol, serum HDL cholesterol, the use of lipid medication (yes or no), blood glucose status (normal [<6.1 mmol/L in a fasted state or <7.8 mmol/L in a non-fasted state], borderline [6.1–7.0 mmol/L in a fasted state or 7.8–11.1 mmol/L in a non-fasted state], hyperglycemic [>7.0 mmol/L in a fasted state or >11.1 mmol/L in a non-fasted state]), the use of diabetes medication (yes or no), and proteinuria (yes or no). A P value <0.05 was regarded as statistically significant. The SAS System for Windows, release 9.3 (SAS Institute Inc., Cary, NC, USA), was used for all analyses.

RESULTS

Sex-stratified baseline characteristics of the cardiovascular risk factors according to our BMI categories are provided in Table 1. All of the factors, except diabetic medication use in men and lipid medication use in men and women, were associated with BMI in both sexes. A higher BMI was linked with a higher eGFR and a higher prevalence of proteinuria in both sexes.

Of the 105 611 participants (35 738 men and 69 873 women), 19 384 (18.4%) developed stage ≥3 CKD (5978 men and 13 406 women) over a mean follow-up of 5 years (4.9 years for men and 5.1 years for women). Table 2 and Figure show the sex-stratified HRs for the incidence of stage ≥3 CKD according to BMI category. In both sexes, compared to a BMI of 21.0–22.9 kg/m^2, the age- and potential confounder-adjusted HRs were higher for the higher BMI categories (model 1; P for trend <0.001; Table 2). Further, these results were similar even when adjusted for potential mediators (model 2; Figure). The HRs of BMI ≥30.0 kg/m^2 were markedly higher in men and women (HR 1.60, 95% CI 1.24–2.06 and HR 1.41, 95% CI 1.25–1.60, respectively).

Table 3 shows the sex-stratified HRs for stage ≥3 CKD by BMI categories among diabetes-free and CVD risk factor-free patients at baseline. In analyses limited to those free of either diabetes or of any CVD risk factors, the HRs were higher for the higher BMI categories (P for trend <0.001).

Table 4 shows the sex- and age-stratified HRs for the incidence of stage ≥3 CKD by BMI category compared with a BMI of 21.0–22.9 kg/m^2. In men aged 40–59 years, the multivariable HRs of BMI ≥30.0 kg/m^2 were significantly higher. In men aged 60–79 years, the multivariable HRs of BMI ≥23.0 kg/m^2 were significantly higher. In women aged 40–59 years, the multivariable HRs of the overall BMI categories were not significantly associated (P for trend = 0.291). In women aged 60–79 years, the multivariable HRs of BMI ≥27.0 kg/m^2 were significantly higher. In both sexes and age classes, except women aged 40–59 years, a significant dose-response relationship between BMI and the incidence of stage ≥3 CKD was observed.

DISCUSSION

To the best of our knowledge, this is the first cohort study to demonstrate a dose-response relationship between obesity and

Table 1. Baseline characteristics of participants by BMI categories

Gender and baseline variables	Body mass index, kg/m^2							*P* for difference
	<18.5	18.5–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	≥30.0	
Men (*n* = 35738)								
Number of participants	1570	6717	9044	9097	5928	2899	483	
Age, years	65.0 (8.8)	62.5 (9.5)	60.8 (9.7)	59.8 (9.7)	59.0 (9.6)	58.9 (9.4)	57.4 (9.4)	<0.001
eGFR, mL/(min·1.73 m^2)	89.9 (18.6)	90.2 (18.4)	88.6 (17.4)	87.1 (17.3)	86.4 (16.8)	85.3 (16.5)	84.4 (16.6)	<0.001
Proteinuria, %	2.2	1.7	1.4	1.8	2.2	3.7	6.4	<0.001
Total cholesterol, mmol/L	4.67 (0.81)	4.75 (0.82)	4.94 (0.85)	5.07 (0.86)	5.17 (0.86)	5.21 (0.86)	5.26 (0.86)	<0.001
HDL cholesterol, mmol/L	1.63 (0.43)	1.52 (0.40)	1.41 (0.38)	1.30 (0.34)	1.24 (0.31)	1.18 (0.29)	1.14 (0.28)	<0.001
Triacylglycerol, mmol/L	1.06 (0.59)	1.21 (0.71)	1.50 (0.91)	1.78 (1.05)	2.05 (1.22)	2.23 (1.31)	2.32 (1.31)	<0.001
Blood glucose, mmol/L	6.41 (2.15)	6.37 (2.09)	6.35 (1.98)	6.39 (2.03)	6.45 (2.01)	6.60 (2.26)	6.70 (2.23)	<0.001
Systolic blood pressure, mm Hg	131.4 (18.2)	133.5 (17.7)	135.1 (16.9)	136.9 (16.6)	138.2 (16.2)	140.8 (16.7)	142.6 (16.2)	<0.001
Diastolic blood pressure, mm Hg	76.9 (10.6)	78.1 (10.4)	79.7 (10.3)	81.3 (10.3)	82.9 (10.3)	84.6 (10.6)	86.9 (10.9)	<0.001
Lipid medication use, %	0.4	0.7	1.2	1.6	1.5	2.0	2.3	0.289
Diabetic medication use, %	3.2	2.6	2.7	3.6	3.7	4.0	3.1	0.361
Antihypertensive medication use, %	12.5	14.5	16.6	19.7	22.4	26.5	32.1	<0.001
Smoking status, %								<0.001
Never	18.1	18.7	22.3	24.1	24.4	25.1	28.6	
Former	22.2	23.5	27.3	30.3	32.0	33.3	28.8	
Current								
<20 cigarettes/day	26.4	21.0	16.2	13.8	12.0	10.7	9.7	
≥20 cigarettes/day	33.3	36.8	34.2	31.9	31.6	31.0	32.9	
Alcohol intake, %								<0.001
Never	44.8	35.6	31.9	31.1	31.0	33.4	37.7	
Sometimes	10.4	11.1	11.9	13.8	14.6	15.7	14.9	
Everyday								
<56 g/day	41.1	47.5	49.5	49.1	47.3	42.9	38.9	
≥56 g/day	3.6	5.8	6.7	6.1	7.1	8.1	8.5	
Women (*n* = 69873)								
Number of participants	2846	12052	17146	17122	11559	7229	1919	
Age, years	60.4 (10.3)	57.5 (9.8)	57.8 (9.3)	58.5 (8.8)	59.4 (8.6)	59.8 (8.4)	59.0 (8.5)	<0.001
eGFR, mL/(min·1.73 m^2)	94.5 (22.0)	96.1 (22.3)	94.2 (21.1)	93.4 (24.9)	91.8 (20.7)	91.4 (20.4)	91.3 (21.0)	<0.001
Proteinuria, %	0.9	0.7	0.8	0.9	1.2	1.7	3.3	<0.001
Total cholesterol, mmol/L	5.19 (0.88)	5.27 (0.87)	5.39 (0.89)	5.48 (0.89)	5.55 (0.88)	5.60 (0.91)	5.61 (0.92)	<0.001
HDL cholesterol, mmol/L	1.72 (0.40)	1.61 (0.38)	1.51 (0.36)	1.43 (0.34)	1.38 (0.33)	1.35 (0.31)	1.33 (0.31)	<0.001
Triacylglycerol, mmol/L	1.07 (0.50)	1.23 (0.65)	1.42 (0.79)	1.61 (0.90)	1.77 (0.96)	1.88 (1.04)	1.94 (0.99)	<0.001
Blood glucose, mmol/L	5.90 (1.61)	5.79 (1.40)	5.83 (1.40)	5.96 (1.50)	6.04 (1.52)	6.16 (1.71)	6.35 (2.03)	<0.001
Systolic blood pressure, mm Hg	126.5 (17.9)	127.2 (17.3)	130.1 (17.0)	132.7 (16.9)	135.4 (16.6)	138.6 (16.8)	141.7 (16.9)	<0.001
Diastolic blood pressure, mm Hg	73.5 (10.4)	74.7 (10.3)	76.4 (10.1)	78.3 (10.0)	79.9 (10.0)	82.0 (10.0)	84.1 (10.6)	<0.001
Lipid medication use, %	1.9	2.2	3.2	3.8	4.2	4.6	4.6	0.988
Diabetic medication use, %	1.3	1.5	1.5	1.9	2.3	2.7	3.2	<0.001
Antihypertensive medication use, %	8.7	10.4	13.8	19.0	23.9	30.6	38.0	<0.001
Smoking status, %								<0.001
Never	92.2	95.1	95.5	95.9	95.7	95.2	93.3	
Former	0.5	0.4	0.6	0.5	0.6	0.7	0.8	
Current								
<20 cigarettes/day	4.9	3.2	2.7	2.4	2.5	2.7	3.9	
≥20 cigarettes/day	2.3	1.3	1.1	1.3	1.3	1.5	2.1	
Alcohol intake, %								<0.001
Never	91.3	90.0	90.0	90.7	90.8	91.7	91.5	
Sometimes	4.8	5.8	6.3	5.7	5.9	5.1	4.8	
Everyday								
<56 g/day	3.9	4.1	3.6	3.5	3.2	3.1	3.4	
≥56 g/day	—	0.1	0.1	0.1	0.1	0.1	0.3	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SD, standard deviation.
Showing mean (SD) for continuous variables: age, fasting and non-fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and triglycerides.
SI conversion factors: to convert blood glucose values to mmol/L, multiply by 0.055 51; to convert cholesterols values to mmol/L, multiply by 0.025 86; to convert triglycerides values to mmol/L, multiply by 0.011 29.

the risk of stage ≥3 CKD in a Japanese population. The dose-response relationship was found in men aged 40–59 and 60–79 years and in women aged 60–79 years. In addition, this relationship was independent of diabetes and other CVD risk factors (ie hypertension and dyslipidemia). We also observed that the risk of stage ≥3 CKD was markedly higher in obese men and women with a BMI ≥30.0 kg/m^2 than in men and women with a BMI of 21.0–22.9 kg/m^2, except in women aged 40–59 years.

The significant relationship observed between BMI and the incidence of stage ≥3 CKD in our study was consistent with that observed in previous studies in Caucasian and Asian

Table 2. Sex-specific HRs and 95% CI for stage ≥3 CKD by BMI categories

Sex and body mass index category (kg/m^2)	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariate-adjusted HR[a] (model 1)	95% CI	*P* for trend
Men								
<18.5	1570	7061	20.1	**0.76**	**0.63, 0.90**	**0.73**	**0.69, 0.61**	
18.5–20.9	6717	33677	20.1	**0.90**	**0.82, 0.99**	**0.89**	**0.87, 0.81**	
21.0–22.9	9044	47022	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	9097	46973	23.1	**1.27**	**1.16, 1.38**	**1.27**	**1.09, 1.17**	<0.001
25.0–26.9	5928	30170	22.9	**1.38**	**1.25, 1.52**	**1.39**	**1.11, 1.26**	
27.0–29.9	2899	14091	23.6	**1.48**	**1.31, 1.68**	**1.48**	**1.08, 1.30**	
≥30.0	483	2252	28.4	**2.01**	**1.56, 2.59**	**1.98**	**1.24, 1.54**	
Women								
<18.5	2846	14223	19.8	**0.75**	**0.66, 0.85**	**0.74**	**0.72, 0.66**	
18.5–20.9	12052	65680	17.8	**0.86**	**0.80, 0.93**	**0.86**	**0.84, 0.80**	
21.0–22.9	17146	94954	20.1	1	(ref.)	1	(ref.)	
23.0–24.9	17122	92420	22.0	1.05	0.99, 1.12	1.05	0.95, 0.99	<0.001
25.0–26.9	11559	61186	24.7	**1.11**	**1.04, 1.19**	1.11	0.96, 1.04	
27.0–29.9	7229	36348	27.9	**1.23**	**1.14, 1.33**	**1.23**	**1.01, 1.14**	
≥30.0	1919	8760	34.5	**1.66**	**1.47, 1.87**	**1.64**	**1.25, 1.45**	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.
[a]Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day).

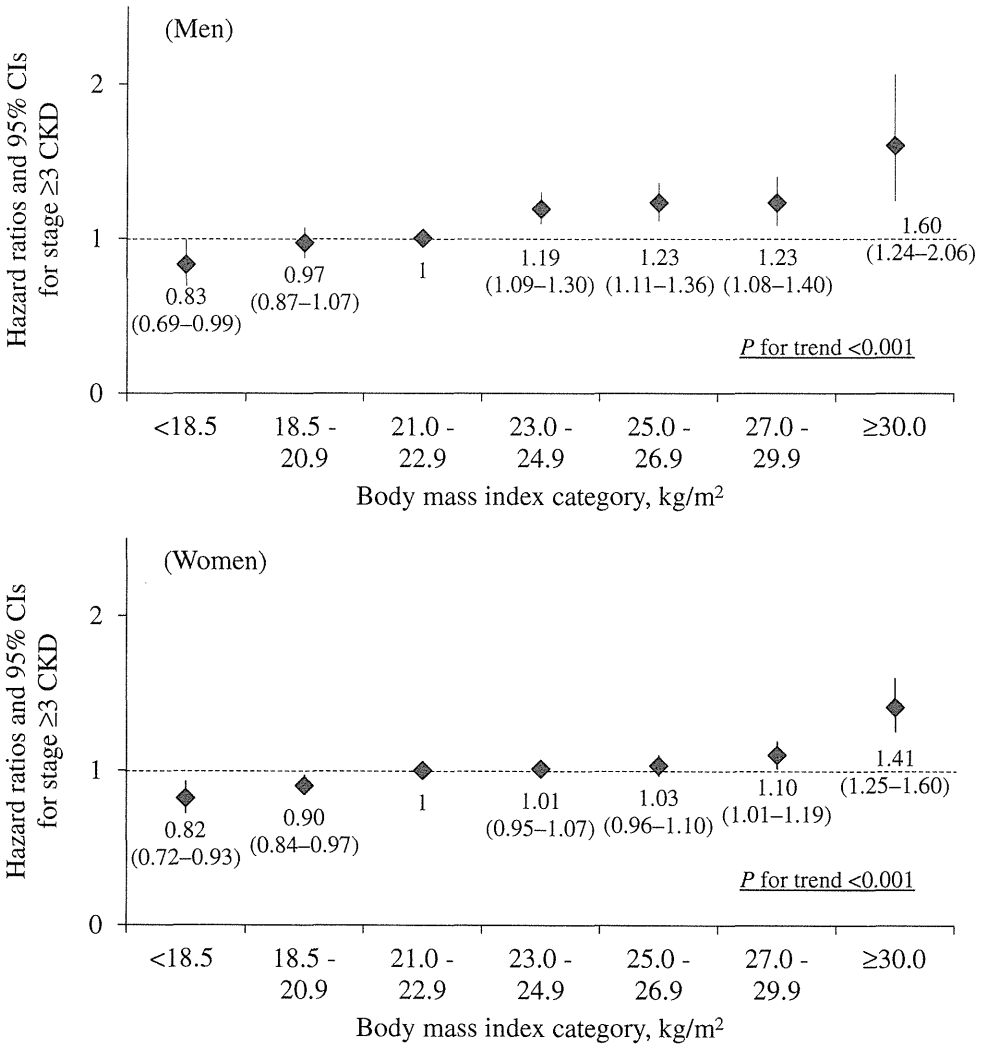

Figure. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of stage ≥3 chronic kidney disease (CKD) in men and women.