Online-only Supplementary Data

The impact of overweight and obesity on the risk of hepatocellular carcinoma: prospective cohort study in over 14 million Korean adults

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- The National Health Insurance Service (NHIS) provides mandatory health insurance for 97% of the Korean population and nationwide biennial health screening.
- Clinical chemistry and anthropometric and blood pressure measurement were performed, and Information on smoking status, alcohol use, physical activity, and history of various diseases was collected via a questionnaire, during each biennial health screenings.
- The health examinations and data collection followed a standard protocol documented by the Ministry of Health and Welfare.

Study cohort
(N=15,163,545)
- Individuals aged 18-99 who participated in health screening by NHIS during 2003-2006.

Exclusion →

Missing information
(n=14,543)
- Risk factors and mediators (n=13,476)
  - Liver enzymes
    - Alanine transaminase, Aspartate transaminase
  - Cardiometabolic risk factors
    - Total cholesterol, fasting glucose, systolic blood pressure, body mass index, etc.
- Date of health examination (n=1,067)

Exclusion →

Known diseases
(n=883,180)
- Cancer (n=122,451)
  - History of cancer via a questionnaire at the time of health examinations
  - Hospitalization (C00-C97) due to cancer before health examination
- Liver diseases (n=760,729)
  - Clinical visits due to liver diseases (B15-B19, K70-K77) at least once within 12 months before, or two months after the baseline health examination

Final cohort analyzed
(n=14,265,822)

Figure S1. Study flow chart
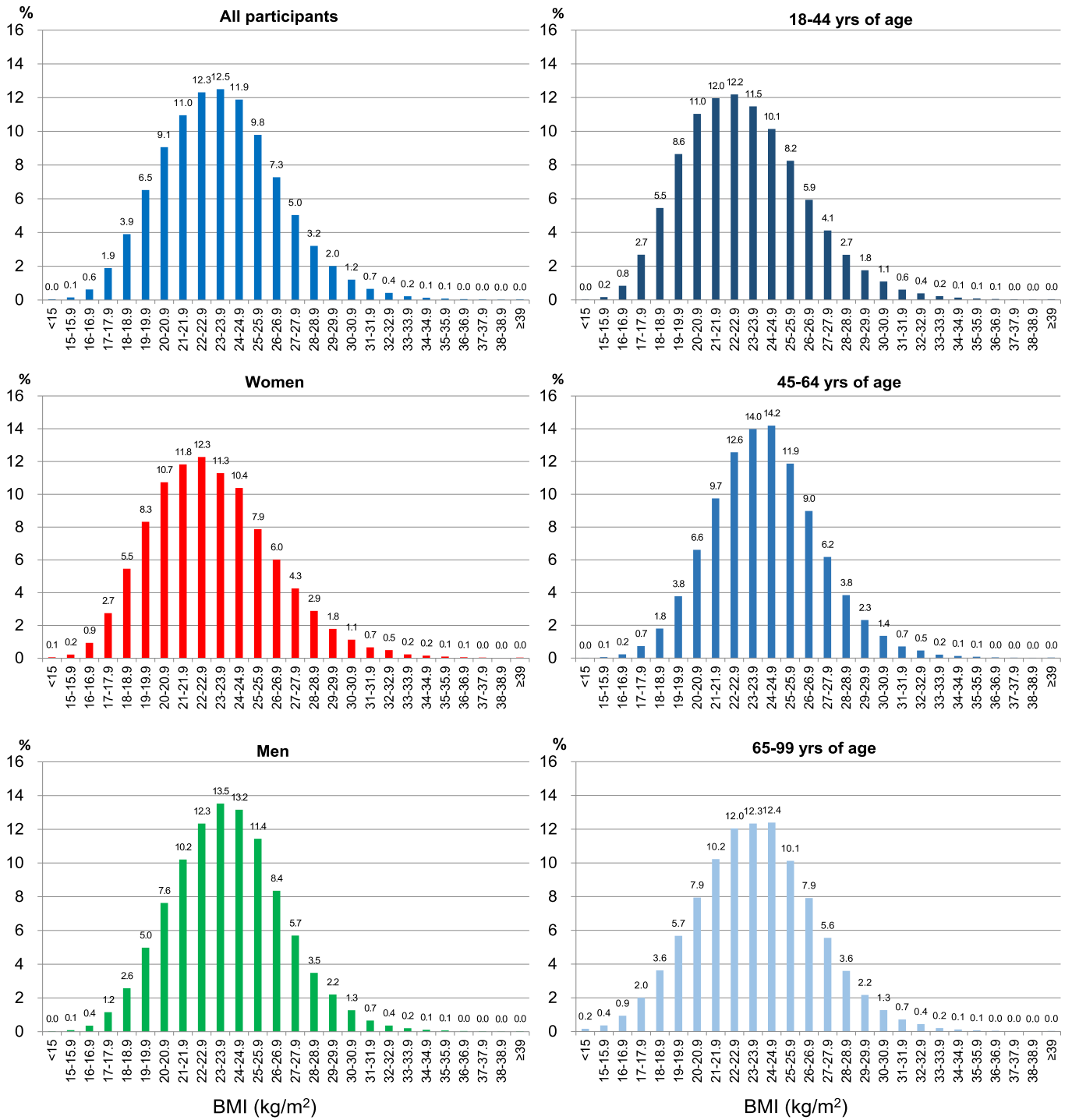
Figure S2. Distribution of body mass index (BMI) by sex and age.

All participants

Sex-specific analysis

Figure S3. HRs across 11 categories of BMI for HCC incidence.

BMI categories (kg/m^2, <17.5, 17.5-18.9 to 29.5-30.9 by 1.5, ≥31.0, 23.5-24.9 as reference). The midpoint was used as a representative value of each BMI category, except both ends (16.7 and 32.9) for which the median was used. HRs and 95% confidence intervals were calculated using Cox proportional hazard models with adjustment for sex (for all participants only), age at baseline, household income, smoking status, alcohol use, and physical activity. BMI, body mass index; HCC, hepatocellular carcinoma, HR, hazard ratio.

All participants

Sex-specific analysis

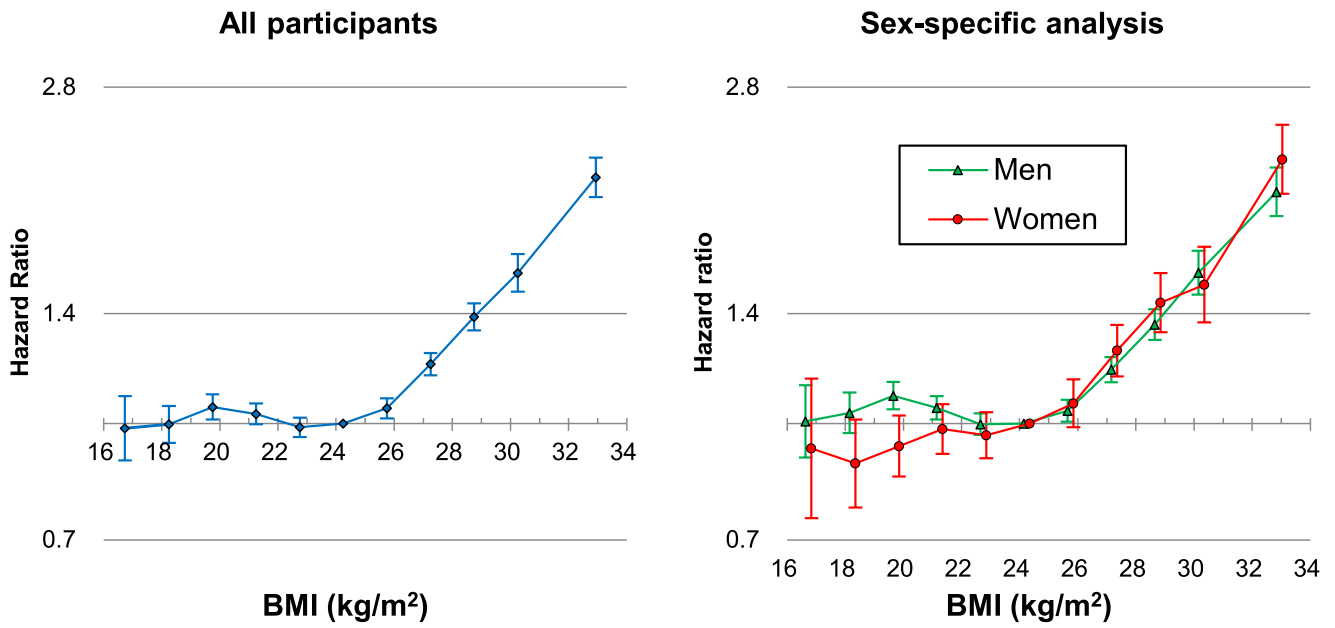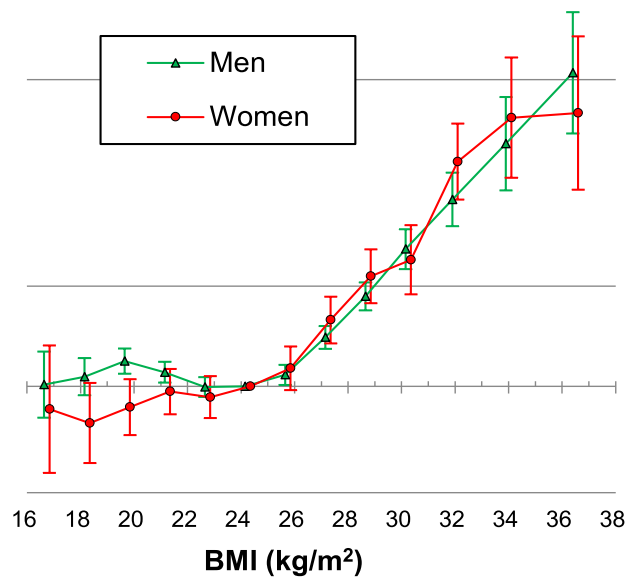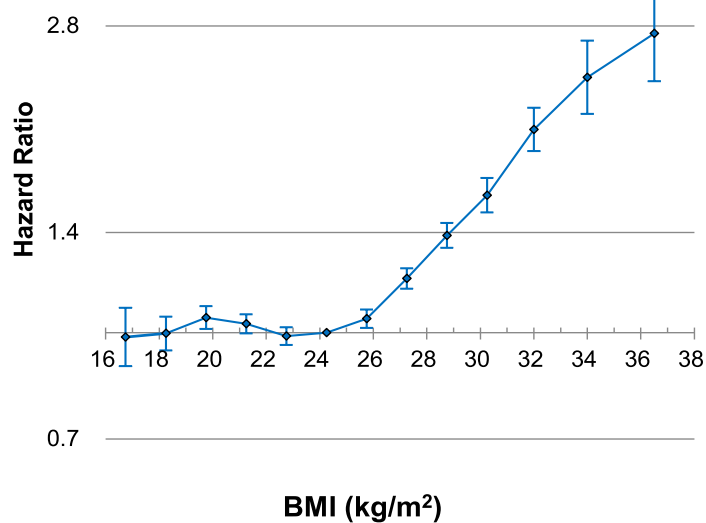**Figure S4. HRs across 13 categories of BMI for HCC incidence.**

BMI categories (kg/m², <17.5, 17.5-18.9 to 29.5-30.9 by 1.5, 31-32.9, 33-34.9, and ≥35.0, 23.5-24.9 as reference). The midpoint was used as a representative value of each BMI category, except both ends (16.7 and 36.5) for which the median was used. HRs and 95% confidence intervals were calculated using Cox proportional hazard models with adjustment for the same variables as in Figure S3. BMI, body mass index; HCC, hepatocellular carcinoma, HR, hazard ratio.
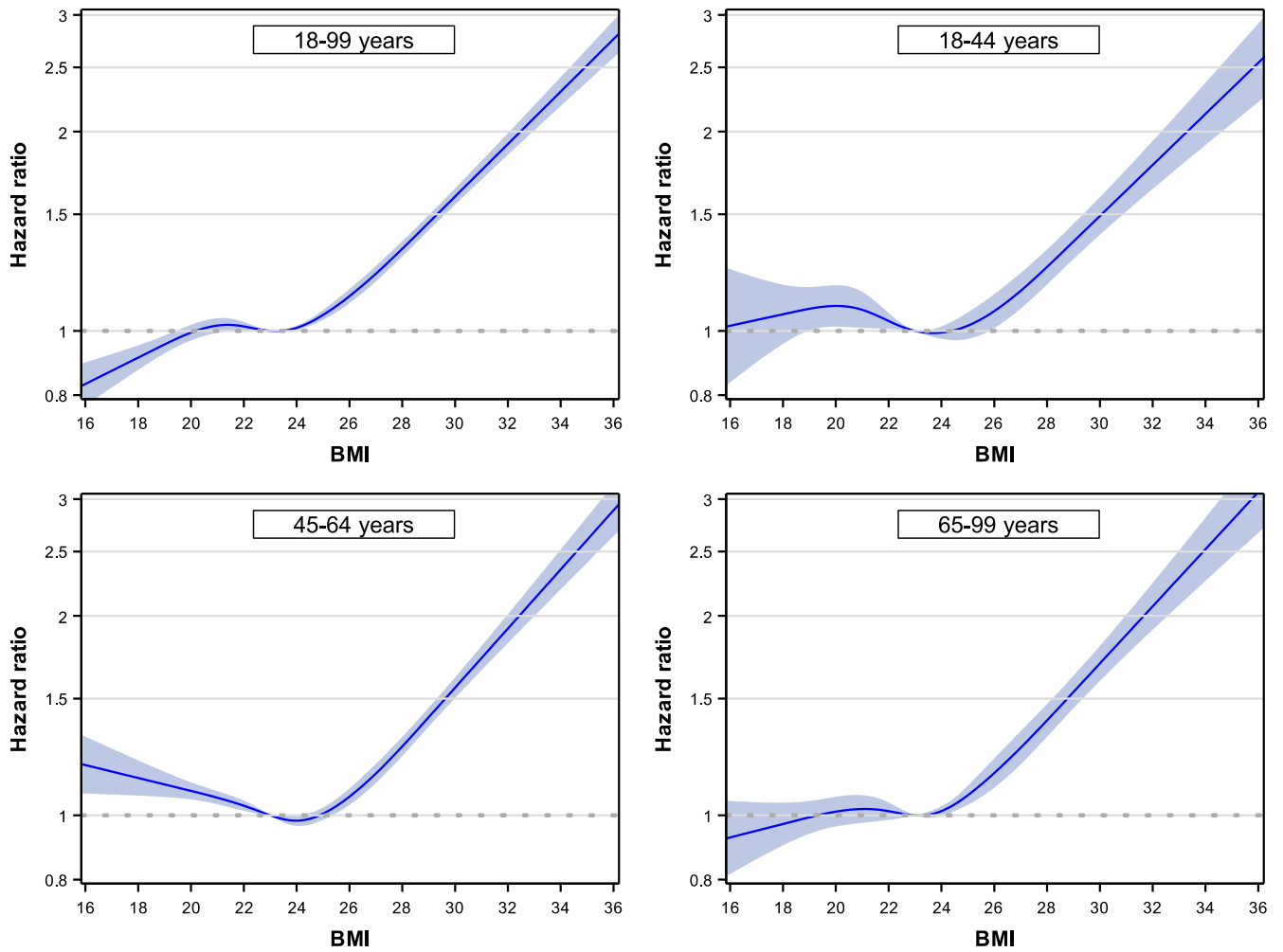
Figure S5. HRs* for HCC incidence by age using spline analysis (5 knots).
Restricted cubic splines of BMI with predefined 5 knots (5th, 27.5th, 50th, 72.5th, and 95th percentile) and 23 kg/m² as a reference were used. Hazard ratios and 95% CIs were calculated using Cox proportional hazards models after adjustment for the same variables as in Figure S3. BMI, body mass index; HCC, hepatocellular carcinoma, HR, hazard ratio. *P* for non-linearity <0.001 for all analyses.
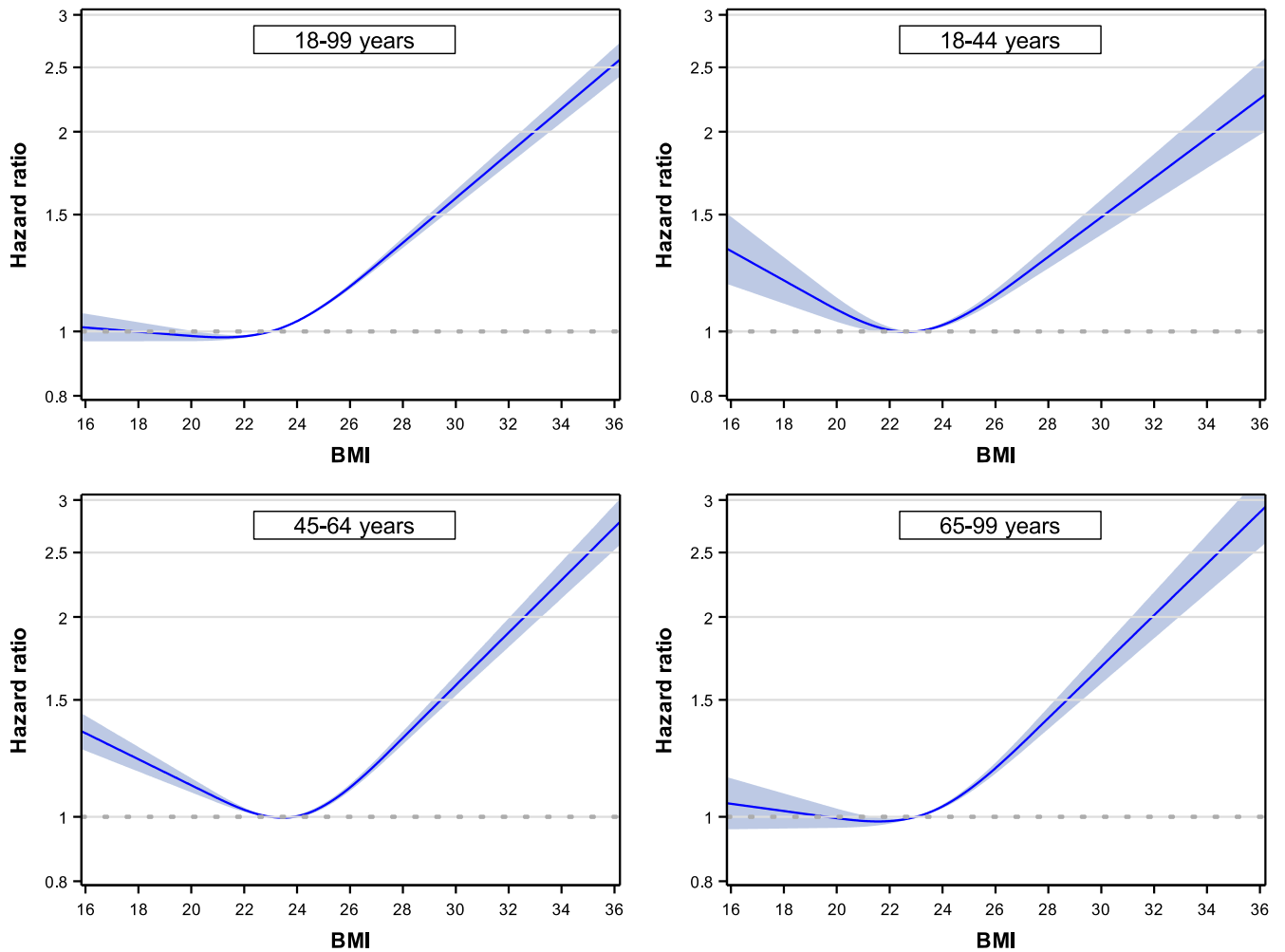
Figure S6. HRs* for HCC incidence by age using spline analysis (3 knots).
Restricted cubic splines of BMI with predefined 3 knots (10th, 50th, and 90th percentile) and 23 kg/m² as a reference were used. Hazard ratios and 95% CIs were calculated using Cox proportional hazards models after adjustment for the same variables as in Figure S3. BMI, body mass index; HCC, hepatocellular carcinoma, HR, hazard ratio. *P* for non-linearity <0.001 for all analyses.
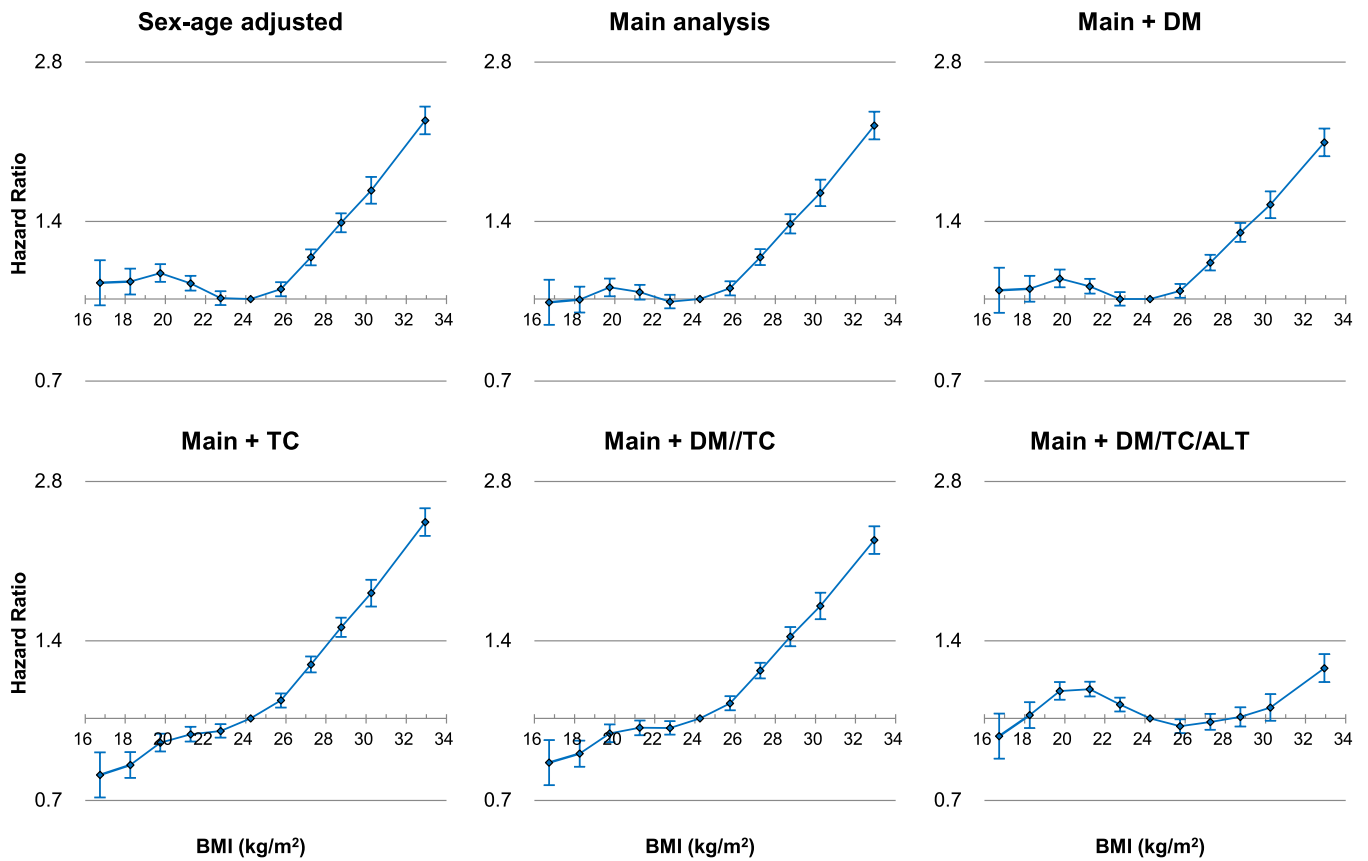
Figure S7. HRs* across 11 categories of BMI for HCC incidence according to adjusted variables.

BMI categories (kg/m², <17.5, 17.5-18.9 to 29.5-30.9 by 1.5, ≥31.0, 23.5-24.9 as reference). The midpoint was used as a representative value of each BMI category, except both ends (16.7 and 32.9) for which the median was used. *Hazard ratios and 95% confidence intervals were calculated using Cox models. Main analysis included sex, age, household income, smoking status, alcohol use, and physical activity. ALT, log-transformed alanine transaminase; BMI, body mass index; DM, diabetes status; HCC, hepatocellular carcinoma; TC, total cholesterol

HCC risks per each 5-unit increase in BMI by model

Adjustment	No. HCC		p-value	HR (95%CI)
Sex/Age	17992		<0.001	1.61 (1.56-1.67)
Main analysis	17992		<0.001	1.60 (1.55-1.66)
Main + DM	17992		<0.001	1.55 (1.50-1.60)
Main + TC	17992		<0.001	1.67 (1.62-1.73)
Main + DM/TC	17992		<0.001	1.61 (1.56-1.67)
Main + DM/TC/ALT	17992		<0.001	1.19 (1.15-1.24)

1.0   1.2   1.4   1.6   1.8
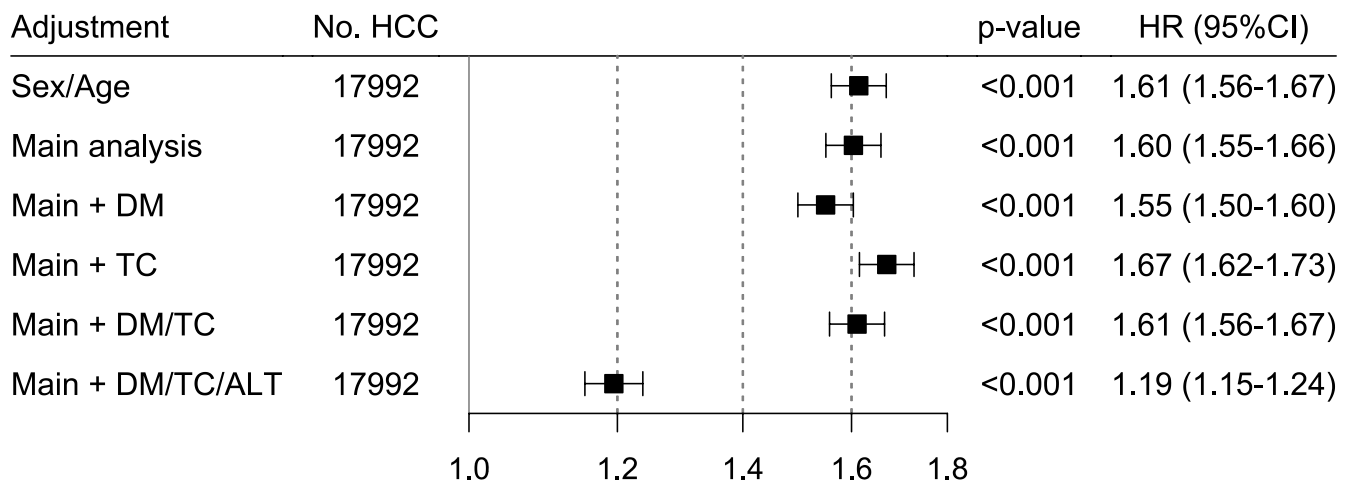
Figure S8. HRs[*] per each 5 kg/m^2 increase in BMI for HCC incidence according to adjusted variables in individuals with BMI ≥25 kg/m^2 (sensitivity analysis).

*Hazard ratios and 95% confidence intervals were calculated using Cox models. Main analysis included sex, age, household income, smoking status, alcohol use, and physical activity. ALT, log-transformed alanine transaminase; BMI, body mass index; DM, diabetes status; HCC, hepatocellular carcinoma; TC, total cholesterol.

Table S1. HRs[a] for HCC incidence across 11 BMI categories (Including numerical version of Figures 1 and S3).

Population	BMI kg/m²	No. of HCC	Crude rate per 10⁶	Sex, and age adjusted[b]		Multivariable adjusted[c]	
				p-value	HR (95% CI)	p-value	HR (95% CI)
All participants	<17.5	421	149	0.157	1.07 (0.97-1.18)	0.771	0.99 (0.89-1.09)
	17.5-18.9	1,417	144	0.008	1.08 (1.02-1.14)	0.919	1.00 (0.94-1.05)
	19.0-20.4	3,686	177	<0.001	1.12 (1.08-1.16)	0.010	1.05 (1.01-1.09)
	20.5-21.9	6,386	206	<0.001	1.07 (1.04-1.10)	0.073	1.03 (1.00-1.06)
	22.0-23.4	8,245	227	0.800	1.00 (0.97-1.03)	0.443	0.99 (0.96-1.02)
	23.5-24.9	9,161	255		1.00 (Reference)		1.00 (Reference)
	25.0-26.4	7,420	277	0.007	1.04 (1.01-1.08)	0.003	1.05 (1.02-1.08)
	26.5-27.9	5,104	313	<0.001	1.20 (1.16-1.24)	<0.001	1.20 (1.16-1.24)
	28.0-29.4	2,946	336	<0.001	1.39 (1.34-1.45)	<0.001	1.39 (1.33-1.44)
	29.5-30.9	1,315	344	<0.001	1.60 (1.51-1.70)	<0.001	1.59 (1.50-1.68)
	≥31.0	1,207	378	<0.001	2.17 (2.04-2.31)	<0.001	2.13 (2.00-2.26)
Men	<17.5	331	408	0.066	1.11 (0.99-1.24)	0.913	1.01 (0.90-1.12)
	17.5-18.9	1,165	346	<0.001	1.13 (1.07-1.21)	0.302	1.03 (0.97-1.10)
	19.0-20.4	3,063	350	<0.001	1.17 (1.12-1.22)	<0.001	1.09 (1.04-1.14)
	20.5-21.9	5,227	345	<0.001	1.10 (1.06-1.14)	0.008	1.05 (1.01-1.09)
	22.0-23.4	6,731	339	0.311	1.02 (0.98-1.05)	0.906	1.00 (0.97-1.03)
	23.5-24.9	7,577	349		1.00 (Reference)		1.00 (Reference)
	25.0-26.4	6,119	360	0.054	1.03 (1.00-1.07)	0.023	1.04 (1.01-1.08)
	26.5-27.9	4,081	405	<0.001	1.18 (1.13-1.22)	<0.001	1.18 (1.14-1.22)
	28.0-29.4	2,278	428	<0.001	1.36 (1.29-1.42)	<0.001	1.35 (1.29-1.42)
	29.5-30.9	967	463	<0.001	1.60 (1.50-1.71)	<0.001	1.59 (1.48-1.70)
	≥31.0	767	477	<0.001	2.07 (1.92-2.23)	<0.001	2.03 (1.89-2.19)
Women	<17.5	90	45	0.813	0.97 (0.79-1.21)	0.487	0.93 (0.75-1.15)
	17.5-18.9	252	39	0.174	0.91 (0.80-1.04)	0.074	0.88 (0.77-1.01)
	19.0-20.4	623	52	0.280	0.95 (0.86-1.04)	0.149	0.93 (0.85-1.02)
	20.5-21.9	1,159	73	0.807	0.99 (0.92-1.07)	0.659	0.98 (0.91-1.06)
	22.0-23.4	1,514	92	0.352	0.97 (0.90-1.04)	0.318	0.96 (0.90-1.04)
	23.5-24.9	1,584	111		1.00 (Reference)		1.00 (Reference)
	25.0-26.4	1,301	133	0.098	1.06 (0.99-1.14)	0.100	1.06 (0.99-1.14)
	26.5-27.9	1,023	163	<0.001	1.25 (1.16-1.36)	<0.001	1.25 (1.16-1.35)
	28.0-29.4	668	195	<0.001	1.46 (1.33-1.59)	<0.001	1.45 (1.32-1.59)
	29.5-30.9	348	201	<0.001	1.54 (1.38-1.73)	<0.001	1.53 (1.36-1.72)
	≥31.0	440	277	<0.001	2.28 (2.05-2.54)	<0.001	2.25 (2.02-2.50)

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio.
[a] HRs were calculated by Cox models after adjustment for risk factors.
[b] Adjustment for age at baseline, and sex
[c] Adjustment for age at baseline, sex, household income, smoking status, alcohol use, and physical activity.

Table S2. HRs[a] for HCC incidence across 7 BMI categories according to sex and age (Including numerical version of Figure 3).

Sex age group	BMI kg/m²	No. of HCC	Crude rate per 10⁶	Sex, and age adjusted[b]		Multivariable adjusted[c]	
				p-value	HR (95% CI)	p-value	HR (95% CI)
All participants	<18.5	1,212	147	<0.001	1.10 (1.04-1.17)	0.525	1.02 (0.96-1.08)
	18.5-20.9	6,218	178	<0.001	1.11 (1.08-1.15)	0.002	1.05 (1.02-1.08)
	21.0-22.9	9,869	217	0.034	1.03 (1.00-1.06)	0.701	1.01 (0.98-1.03)
	23.0-24.9	12,017	249		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	11,089	284	<0.001	1.08 (1.05-1.11)	<0.001	1.09 (1.06-1.12)
	27.5-29.9	4,862	338	<0.001	1.38 (1.34-1.43)	<0.001	1.38 (1.33-1.43)
	≥30.0	2,041	368	<0.001	1.92 (1.83-2.01)	<0.001	1.89 (1.80-1.98)
Participants aged 18-44 years	<18.5	205	33	0.471	1.05 (0.91-1.22)	0.903	0.99 (0.86-1.14)
	18.5-20.9	1,322	55	<0.001	1.12 (1.05-1.20)	0.046	1.07 (1.00-1.15)
	21.0-22.9	1,967	78	0.215	1.04 (0.98-1.10)	0.503	1.02 (0.96-1.09)
	23.0-24.9	2,218	97		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	2,017	116	0.101	1.05 (0.99-1.12)	0.142	1.05 (0.98-1.11)
	27.5-29.9	956	150	<0.001	1.41 (1.31-1.52)	<0.001	1.37 (1.27-1.48)
	≥30.0	411	148	<0.001	1.71 (1.54-1.91)	<0.001	1.64 (1.47-1.82)
Participants aged 45-64 years	<18.5	553	453	<0.001	1.28 (1.18-1.40)	<0.001	1.16 (1.06-1.26)
	18.5-20.9	3,254	395	<0.001	1.21 (1.16-1.26)	<0.001	1.13 (1.08-1.17)
	21.0-22.9	5,524	341	0.006	1.05 (1.01-1.09)	0.278	1.02 (0.98-1.06)
	23.0-24.9	7,103	344		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	6,708	382	<0.001	1.07 (1.04-1.11)	<0.001	1.09 (1.05-1.12)
	27.5-29.9	2,843	442	<0.001	1.34 (1.28-1.39)	<0.001	1.34 (1.28-1.40)
	≥30.0	1,196	540	<0.001	1.97 (1.85-2.09)	<0.001	1.95 (1.83-2.07)
Participants aged ≥65 years	<18.5	454	615	0.833	1.01 (0.91-1.12)	0.445	0.96 (0.87-1.06)
	18.5-20.9	1,642	620	0.935	1.00 (0.94-1.06)	0.169	0.96 (0.90-1.02)
	21.0-22.9	2,378	595	0.904	1.00 (0.94-1.05)	0.431	0.98 (0.93-1.03)
	23.0-24.9	2,696	583		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	2,364	594	<0.001	1.11 (1.05-1.17)	<0.001	1.11 (1.05-1.18)
	27.5-29.9	1,063	681	<0.001	1.45 (1.35-1.55)	<0.001	1.46 (1.36-1.57)
	≥30.0	434	780	<0.001	1.96 (1.77-2.17)	<0.001	1.97 (1.78-2.18)
Men	<18.5	985	377	<0.001	1.16 (1.08-1.24)	0.112	1.06 (0.99-1.13)
	18.5-20.9	5,129	348	<0.001	1.16 (1.12-1.20)	<0.001	1.08 (1.05-1.12)
	21.0-22.9	8,094	340	<0.001	1.05 (1.02-1.08)	0.141	1.02 (0.99-1.05)
	23.0-24.9	9,886	347		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	9,070	369	<0.001	1.07 (1.04-1.10)	<0.001	1.08 (1.05-1.11)
	27.5-29.9	3,744	438	<0.001	1.35 (1.30-1.40)	<0.001	1.35 (1.30-1.40)
	≥30.0	1,398	473	<0.001	1.85 (1.75-1.95)	<0.001	1.83 (1.73-1.93)
Men aged 18-44 years	<18.5	160	96	0.206	1.11 (0.94-1.30)	0.834	1.02 (0.87-1.20)
	18.5-20.9	1,086	113	<0.001	1.17 (1.09-1.26)	0.011	1.10 (1.02-1.19)

Sex age group	BMI kg/m^2	No. of HCC	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
				p-value	HR (95% CI)	p-value	HR (95% CI)
	21.0-22.9	1,688	116	0.160	1.05 (0.98-1.12)	0.457	1.02 (0.96-1.09)
	23.0-24.9	2,002	124		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	1,889	137	0.088	1.06 (0.99-1.12)	0.121	1.05 (0.99-1.12)
	27.5-29.9	891	177	<0.001	1.41 (1.30-1.53)	<0.001	1.38 (1.27-1.49)
	≥30.0	386	186	<0.001	1.77 (1.59-1.98)	<0.001	1.69 (1.52-1.89)
Men aged 45-64 years	<18.5	466	775	<0.001	1.31 (1.19-1.44)	0.001	1.17 (1.07-1.29)
	18.5-20.9	2,743	724	<0.001	1.26 (1.20-1.31)	<0.001	1.16 (1.10-1.21)
	21.0-22.9	4,592	615	<0.001	1.08 (1.04-1.12)	0.040	1.04 (1.00-1.08)
	23.0-24.9	5,876	566		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	5,555	598	<0.001	1.06 (1.03-1.10)	<0.001	1.08 (1.04-1.12)
	27.5-29.9	2,235	732	<0.001	1.31 (1.25-1.37)	<0.001	1.32 (1.25-1.38)
	≥30.0	813	1,038	<0.001	1.88 (1.75-2.02)	<0.001	1.88 (1.74-2.02)
Men aged ≥65 years	<18.5	359	1,023	0.456	1.04 (0.93-1.17)	0.838	0.99 (0.88-1.11)
	18.5-20.9	1,300	1,002	0.699	1.01 (0.95-1.09)	0.349	0.97 (0.90-1.04)
	21.0-22.9	1,814	994	0.902	1.00 (0.94-1.07)	0.561	0.98 (0.92-1.05)
	23.0-24.9	2,008	992		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	1,626	1,085	0.007	1.09 (1.03-1.17)	0.003	1.11 (1.04-1.18)
	27.5-29.9	618	1,386	<0.001	1.40 (1.28-1.53)	<0.001	1.42 (1.29-1.55)
	≥30.0	199	1,911	<0.001	1.94 (1.67-2.24)	<0.001	1.95 (1.69-2.26)
Women	<18.5	227	40	0.405	0.94 (0.82-1.08)	0.165	0.91 (0.79-1.04)
	18.5-20.9	1,089	54	0.385	0.97 (0.90-1.04)	0.198	0.95 (0.88-1.03)
	21.0-22.9	1,775	82	0.194	0.96 (0.90-1.02)	0.145	0.95 (0.90-1.02)
	23.0-24.9	2,131	108		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	2,019	140	<0.001	1.11 (1.04-1.18)	0.001	1.11 (1.04-1.18)
	27.5-29.9	1,118	192	<0.001	1.44 (1.34-1.55)	<0.001	1.44 (1.34-1.54)
	≥30.0	643	248	<0.001	2.00 (1.83-2.18)	<0.001	1.97 (1.80-2.15)
Women aged 18-44 years	<18.5	45	10	0.046	0.71 (0.51-0.99)	0.066	0.73 (0.53-1.02)
	18.5-20.9	236	16	0.064	0.84 (0.69-1.01)	0.093	0.85 (0.70-1.03)
	21.0-22.9	279	26	0.520	0.94 (0.79-1.13)	0.578	0.95 (0.80-1.14)
	23.0-24.9	216	32		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	128	35	0.736	1.04 (0.83-1.29)	0.815	1.03 (0.82-1.28)
	27.5-29.9	65	48	0.009	1.45 (1.10-1.91)	0.014	1.42 (1.07-1.87)
	≥30.0	25	35	0.444	1.18 (0.78-1.78)	0.557	1.13 (0.75-1.71)
Women aged 45-64 years	<18.5	87	141	0.105	1.20 (0.96-1.49)	0.226	1.14 (0.92-1.42)
	18.5-20.9	511	115	0.316	1.05 (0.95-1.17)	0.454	1.04 (0.94-1.15)
	21.0-22.9	932	107	0.266	0.95 (0.87-1.04)	0.244	0.95 (0.87-1.04)
	23.0-24.9	1,227	119		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	1,153	139	0.016	1.10 (1.02-1.20)	0.025	1.10 (1.01-1.19)

Sex age group	BMI kg/m^2	No. of HCC	Crude rate per 10^6	Sex, and age adjusted[b]		Multivariable adjusted[c]	
				p-value	HR (95% CI)	p-value	HR (95% CI)
	27.5-29.9	608	180	<0.001	1.39 (1.26-1.53)	<0.001	1.37 (1.24-1.51)
	≥30.0	383	267	<0.001	2.10 (1.87-2.35)	<0.001	2.03 (1.81-2.27)
Women aged ≥65 years	<18.5	95	245	0.336	0.90 (0.73-1.12)	0.197	0.87 (0.70-1.08)
	18.5-20.9	342	253	0.346	0.94 (0.82-1.07)	0.242	0.93 (0.81-1.05)
	21.0-22.9	564	260	0.633	0.97 (0.87-1.09)	0.574	0.97 (0.87-1.08)
	23.0-24.9	688	265		1.00 (Reference)		1.00 (Reference)
	25.0-27.4	738	298	0.022	1.13 (1.02-1.25)	0.019	1.13 (1.02-1.26)
	27.5-29.9	445	399	<0.001	1.52 (1.35-1.71)	<0.001	1.53 (1.36-1.72)
	≥30.0	235	519	<0.001	1.98 (1.71-2.30)	<0.001	2.00 (1.72-2.32)

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio.
[a] HRs were calculated by Cox models after adjustment for risk factors.
[b] Adjustment for age at baseline, and sex
[c] Adjustment for age at baseline, sex, household income, smoking status, alcohol use, and physical activity.

Table S3. HRs[a] per each 5 kg/m^2 increase in BMI for HCC incidence by BMI range, age, and sex (including Table 2).

Sex group	Age group, Years	BMI ≥25 kg/m^2 (n=4,284,559)					BMI <25 kg/m^2 (n=9,981,263)					BMI full range (n=14,265,822)				
		No. of HCC	p-value	HR (95% CI)	$P_{interaction}$ (age)	$P_{interaction}$ (sex)	No. of HCC	p-value	HR (95% CI)	$P_{interaction}$ (age)	$P_{interaction}$ (sex)	No. of death	p-value	HR (95% CI)	$P_{interaction}$ (age)	$P_{interaction}$ (sex)
All participants	18-99	17,992	<0.001	1.60 (1.55-1.66)			29,316	0.013	0.96 (0.93-0.99)			47,308	<0.001	1.21 (1.19-1.22)		
	18-44	3,384	<0.001	1.56 (1.45-1.68)	0.610		5,712	0.072	0.94 (0.87-1.01)	<0.001		9,096	<0.001	1.16 (1.12-1.20)	<0.001	
	45-64	10,747	<0.001	1.61 (1.54-1.68)			16,434	<0.001	0.90 (0.86-0.94)			27,181	<0.001	1.17 (1.15-1.20)		
	65-99	3,861	<0.001	1.64 (1.52-1.76)			7,170	0.192	1.04 (0.98-1.10)			11,031	<0.001	1.26 (1.22-1.30)		
Men	18-99	14,212	<0.001	1.60 (1.54-1.67)		0.853	24,094	<0.001	0.93 (0.90-0.96)		<0.001	38,306	<0.001	1.16 (1.14-1.18)		<0.001
	18-44	3,166	<0.001	1.59 (1.47-1.72)	0.485	0.085	4,936	0.012	0.91 (0.84-0.98)	0.001	0.001	8,102	<0.001	1.17 (1.12-1.21)	0.007	0.409
	45-64	8,603	<0.001	1.59 (1.51-1.68)		0.591	13,677	<0.001	0.88 (0.84-0.92)		0.211	22,280	<0.001	1.13 (1.10-1.16)		<0.001
	65-99	2,443	<0.001	1.70 (1.54-1.88)		0.322	5,481	0.522	1.02 (0.96-1.09)		0.287	7,924	<0.001	1.21 (1.17-1.26)		0.001
Women	18-99	3,780	<0.001	1.59 (1.50-1.70)			5,222	0.071	1.07 (0.99-1.15)			9,002	<0.001	1.32 (1.28-1.36)		
	18-44	218	0.118	1.24 (0.95-1.63)	0.166		776	0.012	1.28 (1.05-1.55)	0.016		994	<0.001	1.22 (1.10-1.35)	0.166	
	45-64	2,144	<0.001	1.63 (1.51-1.77)			2,757	0.311	0.95 (0.85-1.05)			4,901	<0.001	1.29 (1.24-1.35)		
	65-99	1,418	<0.001	1.58 (1.42-1.76)			1,689	0.114	1.10 (0.98-1.24)			3,107	<0.001	1.35 (1.28-1.42)		

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio.
[a] HRs were calculated by Cox models, after adjustment for age at baseline, sex, household income, smoking status, alcohol use, and physical activity