Running head: BMI, Smoking, Alcohol and multiple myeloma

Association of BMI, smoking and alcohol with multiple myeloma mortality in Asians: a pooled analysis of more than 800,000 participants in the Asia Cohort Consortium

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Abstract:

Background.

To date, few epidemiological studies have been conducted to elucidate lifestyle-related risk factors for multiple myeloma (MM) in Asia. We investigated the association of body mass index (BMI), smoking, and alcohol intake with the risk of MM mortality through a pooled analysis of more than 800,000 participants in the Asia Cohort Consortium.

Methods.

The analysis included 805,309 participants contributing 10,221,623 person-years of accumulated follow-up across Asia Cohort Consortium cohorts. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between BMI, smoking and alcohol at baseline and the risk of MM mortality were assessed using a Cox proportional hazards model with shared frailty.

Results.

We observed a statistically significant dose-dependent association between BMI categories and the risk of MM mortality (<18.5 kg/m^2: HR=0.80, 95% CI: 0.52–1.24; 18.5 to 24.9 kg/m^2: reference; 25.0 to 29.9 kg/m^2: HR=1.17, 0.94–1.47; ≥30 kg/m^2: HR=1.61, 0.99-2.64, p for trend=0.014). By sex, this association was more apparent in women than in men (P for heterogeneity between sexes=0.150). We observed no significant associations between

smoking or alcohol consumption and risk of MM mortality.

Conclusion.

This study showed that excess body mass is associated with an increased risk of MM mortality among Asian populations. In contrast, our results do not support an association between smoking or alcohol consumption and the risk of MM mortality in Asian populations.

Impact.

This study provides important evidence on the association of BMI, smoking and alcohol with the risk of MM mortality in Asian populations.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and is characterized by the neoplastic proliferation of plasma cells producing monoclonal immunoglobulins (1). Despite recent progress in treatment, MM is still an incurable disease associated with substantial mortality. MM occurs in people of all races and from all geographic locations but its incidence varies greatly across regions and countries (2). In general, Western countries show a higher incidence than Asian countries. For example, in the US, the age-standardized rates (ASRs) were 4.3 and 3.0 per 100,000 for males and females, respectively. In contrast, the ASRs in Asia were reported to be 1.0 and 0.7 per 100,000 for males and females, respectively (3). The difference in incidence suggests a substantial difference in risk-factor exposure between Western and Asian populations.

To date, several epidemiological studies have been conducted to elucidate lifestyle-related risk factors for MM. Body mass index (BMI), smoking, and alcohol intake are the most intensively examined factors. However, most epidemiological evidence on these factors has been obtained from studies in Western populations (4-6), whereas evidence from Asian populations is very limited. Because there are large differences in the prevalence of obesity, smoking, and drinking habits (7), as well as of MM incidence between the Western and Asian populations (3), large prospective studies of the associations between these factors and MM

risk in Asian populations are, therefore, needed. Given the limited statistical power due to the small number of MM cases in each cohort in Asia, a pooled analysis of the existing cohorts from the Asian Cohort Consortium is one of the ideal approaches to evaluate these relationships.

Here, we investigated the association of body mass index, smoking, and alcohol intake with the risk of MM mortality through a pooled analysis of more than 800,000 participants from the Asian Cohort Consortium.

Materials and Methods

Study population

Details of the Asian Cohort Consortium have been described elsewhere (8,9). Briefly, it is a consortium of cohorts in Asian countries developed to explore the association between genetics, environmental exposure, and the etiology of disease, with sufficient statistical power. Among the cohorts participating in the Asian Cohort Consortium, 16 provided information on MM-related deaths during follow-up, as well as data on BMI, smoking, alcohol intake, and potential confounders (sex, age, and education) at baseline. We excluded one cohort with missing data on vital status. Thus, we included 15 cohorts (9 in Japan, 2 in China, 1 in Taiwan, 1 in Korea, 1 in India, and 1 in Singapore) in this pooled analysis. We excluded participants who met any of the following criteria: 1) invalid or missing data on

vital status (n=1,565); 2) missing data on age or sex (n=3,163); 3) invalid or missing data on height or weight (n=2,290); or 4) BMI <15 kg/m^2 or >40 kg/m^2 (n=16,006). We included a total of 805,309 participants (384,927 men and 420,382 women) in this analysis. The Asian Cohort Consortium coordinating center at the National Cancer Center Japan obtained de-identified individual participant data from all participating cohorts and harmonized it for the statistical analysis.

Pooled analysis of the Asian Cohort Consortium cohorts was approved by the ethical committee of the National Cancer Center Japan (number 2014-041) and each study was approved by respective ethic committees overseeing the participating studies. This analysis was also approved by the Institutional Review Board of Aichi Cancer Center Research Institute.

Exposure data and study outcome

Height and weight at baseline were directly measured in 5 cohorts and obtained via self-report in 10 cohorts. Information on smoking, alcohol intake, and potential confounders was obtained through baseline questionnaires. BMI was calculated as weight [kg]/(height [m])^2. We categorized BMI according to the guidelines of the World Health Organization (10) as follows : <18.5 (underweight); 18.5–24.9 (normal weight); 25.0–29.9 (overweight); and ≥30 kg/m^2 (obese). We also applied a five-category BMI classification [<20.0, 20.0–22.4, 22.5–

171 24.9 (reference), 25.0–27.4, and ≥27.5 kg/m^2] as used in our previous report of a pooled
172 analysis of BMI and overall mortality in the Asian Cohort Consortium (9). Regarding
173 smoking, participants were classified as never, former, or current smokers, as well as by the
174 cumulative exposure to smoking in pack-years (never smokers; <20 pack-years; and ≥20
175 pack-years). Alcohol intake was calculated as grams per week to unify data on alcohol intake
176 across the cohorts and then the participants were classified into the following three groups:
177 nondrinkers; intake of 1–149 g/week of ethanol; and intake of ≥150 g/week of ethanol. The
178 exposure period for alcohol intake was the year prior to baseline for SMHS, SWHS,
179 Takayama, KMCC and SCHS, and it was not specified for other cohorts.
180 Study outcome was defined as death due to MM (ICD-9: 203 and ICD-10: C90) during
181 follow-up; cause of death was extracted from death certificates.
182
183 *Statistical analysis*
184 To determine the relative risk of MM mortality associated with BMI, smoking, and alcohol
185 intake, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) by a Cox
186 proportional hazards model with shared frailty (STATA command *stcox, shared*) (11) using
187 pooled individual participant data. An individual cohort was considered as the shared frailty
188 variable to account for between-study heterogeneity. The details of this statistical model were
189 described in previous articles (11, 12). We estimated two types of HR: model 1, which was

adjusted for age at baseline (continuous) and sex (men or women); and model 2, which was adjusted for age at baseline, sex, education (none, primary, secondary, trade or technical, university, post university, and missing) and exposures of interest including body mass index (<18.5, 18.5–24.9, 25.0-29.9, ≥30 kg/m^2); smoking (never-smoker, <20 pack-years, ≥20 pack-years); and alcohol intake (non-drinker, <150 g/week of ethanol, ≥150 g/week of ethanol). Missing values for covariates were treated as dummy variables in the models. We calculated P values for trend using ordinal variables across each exposure category. We also performed stratified analyses based on geographic regions (East Asia: cohorts from China, Japan, Korea, Singapore, and Taiwan; South Asia: cohorts from India) and countries. Likelihood-based methods were used to test for heterogeneity: between sexes; by smoking status; and across geographic regions and countries. The proportional hazards assumptions were tested using scaled Schoenfeld residuals and were found to be justified. All statistical analyses were performed using Stata version 14.1 software (Stata Corp., College Station, TX, USA), and P <0.05 was considered to be statistically significant.

Results

Table 1 shows the main characteristics of the participating cohorts in the Asian Cohort Consortium. The final analysis included 805,309 participants accounting for 10,221,623 person-years of accumulated follow-up. Mean age at baseline was approximately 54 years in

209 both men and women. Mean BMI ranged from 21.8 to 24.0 kg/m^2 in men and from 21.9 to
210 24.1 in women. The proportion of ever smokers was 63.7% in men and 6.8% in women,
211 respectively. Mean alcohol intake was 130 g/week in men and 9 g/week in women. During
212 the follow-up period (12.7 years on average), we identified a total of 428 MM-related deaths,
213 accounting for 0.33% of deaths from all causes.
214 Table 2 shows the adjusted HRs for MM mortality based on BMI. We observed a
215 statistically significant dose-dependent association between BMI categories and the risk of
216 MM mortality (<18.5 kg/m^2: HR=0.80, 95% CI: 0.52-1.24; 18.5 to 24.9 kg/ m^2: reference;
217 25.0 to 29.9 kg/m^2: HR=1.17, 0.94-1.47; ≥30 kg/m^2: HR=1.61, 0.99-2.64, p for trend=0.014,
218 per 1 kg/m^2: HR=1.04, 1.01-1.07, model 2). By sex, we also observed this significant
219 association among women, but observed no clear association among men (P for heterogeneity
220 between sexes=0.150, Supplementary Table 1). When we applied a five-category BMI
221 classification, we observed similar results (Table 1 and Supplementary Table 1).
222 Table 3 shows results of the stratified analysis by region and country. Similar findings
223 were observed when the analysis was restricted to East Asia, but evaluation for data from
224 South Asia was difficult because the number of MM-related deaths was low. We did not
225 observe significant heterogeneity of association across countries. To evaluate whether
226 smoking modified the association between BMI and the risk of MM mortality, we performed
227 stratified analysis by smoking status. The association between BMI and MM mortality was

more apparent in never-smokers than ever-smokers, although no formal evidence of heterogeneity was observed by smoking status (Supplementary Table 2).

Supplementary Table 3 shows the adjusted HRs for MM mortality based on smoking and alcohol intake categories. We observed no association between smoking or alcohol intake and risk of MM mortality. However, these associations were difficult to evaluate in women because the proportions of female smokers and drinkers were low and the number of the female cases who were smokers and drinkers was small.

Finally, we performed several sensitivity analyses as follows: 1) excluding the first 3 and 5 years of follow-up, 2) excluding participants with a past history of cancer to avoid the possibility of reverse causality and 3) excluding female participants in the analysis of smoking and alcohol. These analyses did not change our main results substantially (Supplementary Table 4, 5 and 6). We also conducted another sensitivity analysis by excluding one cohort at a time and ensured that our finding was not driven by any single cohort (Supplementary Table 7).

Discussion

In this pooled analysis of more than 800,000 Asian participants, we found a statistically significant dose-dependent association between BMI and MM mortality among Asian populations. By sex, this association this association was more apparent in women than in

men. We observed no significant association between smoking or alcohol intake and the risk of MM mortality.

A positive association between higher BMI and the risk of MM incidence and mortality has been previously reported (4,12). The 2016 IARC update on body fatness and cancer concluded that excess BMI is a risk factor for MM (13). However, although there is sufficient evidence in Western populations, only a few studies have been conducted in Asia. A prospective cohort study, which involved 781,283 Korean men and 103 MM cases, did not show a significant association between higher BMI and MM incidence, among both sexes combined, with an HR of 0.98 (95% CI: 0.30–3.32) for the BMI category of 27.0–29.9 kg/m^2 relative to the reference category of 18.5–22.9 kg/m^2 (14). The JPHC study in Japan, which is one of the 15 cohort studies in this pooled analysis, also did not report a statistically significant association between BMI and MM incidence among both sexes combined (23.0–29.9 kg/m2: reference; 25.0–29.9 kg/m2: HR=0.79, 0.45–1.38; ≥30 kg/m2: HR=0.76, 0.45–1.38) (15). Parr et al. conducted a pooled analysis of 424,519 participants in the Asia-Pacific Cohort Collaboration and did not observe a statistically significant association between obesity and MM mortality for both sexes combined, with an HR of 1.20 (95% CI: 0.59–2.43) for the BMI category of ≥30 kg/m^2 relative to the reference category of 18.5–22.9 kg/m^2 (16). In contrast, the JACC study in Japan, another cohort study included in this pooled analysis, showed a statistically significant association between obesity and MM mortality only among

266 women (18.5–25.0 kg/m2: reference; ≥30 kg/m^2: HR=4.11, 1.45–11.64) (17). The current
267 study observed a statistically significant dose-dependent association between BMI and MM
268 mortality also only among women. A recent meta-analysis suggests no sex difference in the
269 association between BMI and MM risk in mainly Western populations (4). This discrepancy
270 could be explained by the differences in body fat distribution (18) and metabolic profiles or
271 in genetic susceptibility to obesity (19) between Western and Asian populations. The possible
272 sex difference in Asian populations should be elucidated in future studies.
273 Different mechanistic pathways for the effect of excess BMI on the development of MM
274 have been proposed (20). Adiponectin, an adipocyte-derived cytokine that is inversely
275 correlated with BMI, has been shown to inhibit proliferation of MM cells and reduce
276 tumorigenic angiogenesis (21,22). In support of this hypothesis, Hofmann et al reported that
277 low levels of circulating adiponectin were associated with MM risk in overweight and obese
278 individuals (23). They also reported that adiponectin levels were significantly lower among
279 MM patients than among patients with monoclonal gammopathy of undetermined
280 significance (MGUS) – the MM precursor – suggesting that reduced expression of
281 adiponectin may be associated with progression from MGUS to MM (24). A recent analysis
282 showed that there is a large variation in adiponectin levels between the sexes and different
283 ethnic groups (25-28); in general, women have higher levels than men and Western
284 populations have higher levels than Asian populations. This difference may explain the sex

differences in BMI-associated MM risk, that we report here.

BMI is most commonly used to determine adiposity. However, in recent years, it has been reported to be an imprecise measure of body composition, including visceral and subcutaneous adiposity and muscle mass (29). This misclassification might mask true associations. Future researches with direct measures of body composition by computed tomography or dual energy x-ray absorptiometry could better characterize the association between adiposity and subsequent MM incidence and mortality.

Most studies have not found an association between smoking and MM risk and a recent meta-analysis of 40 observational studies confirmed this (6). The International Multiple Myeloma Consortium conducted a pooled analysis of nine case-control studies, including 2,670 cases and 11,913 controls, and also did not observe an association with smoking (30). Two studies in Japan were similarly null (31,32). Consistent with these studies, our results do not support an association between smoking and MM risk in Asian populations.

A pooled analysis of 59 case-control studies, including 1,567 cases and 7,296 controls, reported that ever-drinking was associated with reduced risk of MM (men: OR=0.72, 95% CI: 0.59–0.89; women: OR=0.81, 95% CI: 0.68–0.95) (33). A recent meta-analysis of 26 observational studies reported similar findings (pooled relative risk [RR] =0.88, 95% CI: 0.79–0.99) (34). However, most of this evidence has been accumulated in Western populations, whereas evidence in Asian populations remains inconclusive. The JACC study

304 (35) and the JPHC study (36), which are participating Japanese cohorts in the Asian Cohort
305 Consortium, did not find an association with alcohol. In the pooled analysis reported here, we
306 found no evidence that alcohol consumption was associated with the risk of MM mortality.
307 The present study has several strengths, most importantly the analysis of
308 individual-level data from a large multi-site, multi-country cohort, allowing better detection
309 of possible associations and the calculation of more precise estimates. Further, the
310 prospective design is less susceptible to recall bias than case-control studies. Several
311 limitations also warrant consideration. First, some cohorts collected anthropometric data that
312 were self-reported, although the validation of the self-reported height, weight, and BMI was
313 high among these cohorts (37,38). Second, as our analyses were conducted using information
314 at a single time point (baseline), we were unable to consider subsequent changes in BMI,
315 smoking habit, and alcohol intake over time. Third, we were unable to consider the effect of
316 other potential confounding factors, including physical activity, MGUS status and family
317 history of hematological malignancies. Fourth, the study outcome of this analysis was
318 mortality, rather than incidence, and we could not distinguish the possible difference in
319 associations with incidence and survival. However, recent analyses have reported that a
320 higher BMI was associated with longer survival among MM patients (39,40), suggesting that
321 the strength of the association we report here with higher BMI is more likely to be under-
322 than over-estimated. In addition, MM was a highly fatal disease during the follow-up period

of this study; therefore, the observed associations with MM mortality are a fair representation of the association with MM incidence. Finally, another potential limitation is the accuracy of diagnosis based on death-certificate data. Some fatal MM cases might not have been reported correctly due to the lack of diagnostic precision in some areas; nonetheless, it seems probable that any misclassification occurred independently of body size, smoking and alcohol intake.

In conclusion, this study showed that excess body mass is associated with an increased risk of MM mortality among Asian populations. In contrast, our results do not support an association between smoking or alcohol consumption and the risk of MM mortality in Asian populations.

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Table 1. Characteristics of the cohort studies in the present pooled analysis.

Country and Study	No. of subjects	Enrollment period	Mean Follow-up, years (SD)	Person-Years	Mean Age at Baseline, years (SD)		Mean BMI at Baseline (SD)		Method of Height and Weight Ascertained	% of Ever Smokers		Mean Alcohol Intake at Baseline, g/week (SD)		No. of Deaths	No. of myeloma Deaths	% of myeloma Deaths
					Men	Women	Men	Women		Men	Women	Men	Women			
China																
SMHS	61,426	2001-2006	9.5 (1.8)	581,041	55.4 (9.7)	NA	23.7 (3.1)	NA	DM	69.6	NA	82 (175)	NA	5,423	22	0.41%
SWHS	74,862	1997-2000	14.9 (2.3)	1,115,384	NA	52.6 (9.1)	NA	24.0 (3.4)	DM	NA	2.8	NA	1 (17)	7,618	35	0.46%
India																
Mumbai	145,093	1991-1997	5.2 (1.5)	755,039	52.6 (10.9)	48.0 (11.0)	22.1 (3.7)	22.8 (4.5)	DM	31.3	0.4	NA	NA	12,456	10	0.08%
Japan																
3pref. Aichi	32,142	1985	11.5 (5.1)	372,220	55.6 (11.0)	56.6 (11.4)	22.3 (2.8)	22.0 (3.0)	SA	82.6	15.2	NA	NA	5,404	14	0.26%
JPHC1	42,728	1990-1992	21.0 (4.3)	897,432	49.5 (5.9)	49.7 (5.9)	23.6 (2.8)	23.6 (3.1)	SA	75.7	7.5	237 (314)	16 (101)	7,392	37	0.50%
JPHC2	55,675	1992-1995	17.7 (4.2)	986,710	54.0 (8.8)	54.4 (8.8)	23.5 (2.9)	23.4 (3.2)	SA	75.5	7.7	211 (289)	15 (79)	12,517	66	0.53%
JACC	86,566	1988-1990	12.7 (3.4)	1,097,249	57.6 (10.2)	57.6 (9.9)	22.6 (2.8)	22.9 (3.1)	SA	76.2	6.0	NA	NA	12,851	72	0.56%
Miyagi	44,842	1990	16.2 (3.7)	725,882	51.7 (7.6)	52.2 (7.4)	23.5 (2.8)	23.7 (3.1)	SA	79.6	8.3	186 (185)	13 (53)	5,233	26	0.50%
Ohsaki	47,607	1995	10.8 (4.3)	513,397	59.5 (10.6)	60.7 (9.9)	23.3 (2.9)	23.7 (3.2)	SA	77.5	8.8	187 (186)	16 (68)	7,993	39	0.49%
RERF	49,424	1963-1993	21.9 (10.3)	1,084,701	52.4 (11.1)	51.9 (15.0)	21.8 (3.0)	21.9 (3.3)	SA	85.4	14.7	204 (262)	15 (63)	25,530	34	0.13%
3pref. Miyagi	29,443	1984	11.6 (5.0)	340,376	56.5 (11.0)	52.2 (7.4)	23.0 (2.9)	23.3 (3.4)	SA	59.3	8.7	NA	NA	5,848	8	0.14%
Takayama	29,640	1992	13.7 (4.0)	405,102	54.9 (12.2)	55.8 (13.0)	22.5 (2.8)	22.0 (2.9)	SA	81.8	15.9	288 (287)	54 (118)	5,465	17	0.31%
Korea																
KMCC	18,962	1994-2004	13.8 (4.7)	261,165	53.5 (14.5)	53.9 (14.3)	23.1 (3.0)	23.9 (3.4)	DM	78.3	8.3	12 (40)	3 (5)	3,477	8	0.23%
Singapore																
SCHS	63,147	1993-1999	11.5 (3.0)	723,862	56.7 (8.0)	56.3 (8.0)	23.0 (3.1)	23.2 (3.2)	SA	58.0	8.8	25 (80)	3 (17)	10,657	33	0.31%
Taiwan																
CBCSP	23,752	1991-1992	15.2 (2.6)	362,062	48.0 (10.2)	46.6 (9.8)	24.0 (3.2)	24.1 (3.5)	DM	56.2	0.9	NA	NA	2,755	7	0.25%
Total	805,309		12.7 (6.3)	10,221,623	54.3 (10.4)	53.6 (10.9)	23.0 (3.2)	23.2 (3.5)		63.7	6.8	130 (222)	9 (55)	130,619	428	0.33%

Abbreviations: BMI, body mass index; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; Mumbai, Mumbai Cohort Study; 3-Pref Aichi, Three-Prefecture

Cohort Study Aichi; JPHC, Japan Public Health Center-based prospective Study (1 and 2) ; JACC, The Japan Collaborative Cohort Study; Miyagi, The Miyagi Cohort Study; Ohsaki: Ohsaki Cohort Study; RERF, Radiation Effects Research Foundation; 3-Pref Miyagi, Three-Prefecture Cohort Study; Miyagi; Takayama, Takayama Cohort Study; KMCC, Korea Multi-Center Cancer Cohort; SCHS; Singapore Chinese Health Study; CBCSP, Community-Based Cancer Screening Project; NA, not available.

Table 2. Risk of multiple myeloma mortality according to body mass index

	Body Mass Index					P trend[1]	Per 1 kg/m^2
	<18.5	18.5–24.9	25.0–29.9	≥30			
Person-years	619,504	6,961,719	2,356,839	283,561			
No. of cases	22	280	109	17			
HR (model 1)	0.81 (0.52-1.25)	1.00 (Reference)	1.17 (0.93-1.46)	1.60 (0.98-2.61)		0.016	1.04 (1.01-1.07)
HR (model 2)	0.80 (0.52-1.24)	1.00 (Reference)	1.17 (0.94-1.47)	1.61 (0.99-2.64)		0.014	1.04 (1.01-1.07)
	<20.0	20.0–22.4	22.5–24.9	25.0–27.4	≥27.5		
Person-years	1,590,661	2,894,330	3,096,232	1,706,921	933,479		
No. of cases	58	121	123	76	50		
HR (model 1)	0.89 (0.65-1.22)	1.06 (0.82-1.36)	1.00 (Reference)	1.14 (0.85-1.51)	1.41 (1.01-1.96)	0.035	
HR (model 2)	0.88 (0.64-1.21)	1.06 (0.82-1.36)	1.00 (Reference)	1.14 (0.85-1.51)	1.42 (1.02-1.98)	0.030	

model 1: HRs are adjusted for age and sex.

model 2: HRs are adjusted for age, sex, smoking, alcohol intake and education.

1 P-values for trends were calculated by assigning scores for categories of body mass index.

Table 3. Risk of multiple myeloma mortality according to body mass index by region and country

	Body Mass Index				P trend[1]	Per 1 kg/m^2	P for heterogeneity[2]
	<18.5	18.5–24.9	25.0–29.9	≥30			
East Asia							
Person-years	490,945	6,521,799	2,203,889	249,951			
No. of cases	21	274	106	17			
HR (model 1)	0.86 (0.55-1.35)	1.00 (Reference)	1.14 (0.91-1.43)	1.59 (0.97-2.61)	0.039	1.03 (1.00-1.06)	0.544
HR (model 2)	0.86 (0.55-1.34)	1.00 (Reference)	1.15 (0.92-1.45)	1.64 (1.00-2.67)	0.028	1.03 (1.00-1.07)	0.545
South Asia (India)							
Person-years	128,559	439,921	152,950	33,610			
No. of cases	1	6	3	0			
HR (model 1)	0.49 (0.06-4.10)	1.00 (Reference)	1.59 (0.40-6.40)	NA	0.551	1.06 (0.92-1.23)	
HR (model 2)	0.54 (0.07-4.63)	1.00 (Reference)	1.54 (0.38-6.21)	NA	0.639	1.05 (0.90-1.23)	
China							
Person-years	61,477	1,053,353	512,047	69,548			
No. of cases	1	24	24	8			
HR (model 1)	0.70 (0.09-5.14)	1.00 (Reference)	1.71 (0.97-3.02)	3.85 (1.71-8.69)	0.001	1.14 (1.06-1.22)	0.206
HR (model 2)	0.68 (0.09-5.04)	1.00 (Reference)	1.72 (0.97-3.05)	3.85 (1.69-8.74)	0.001	1.14 (1.06-1.22)	0.196
Japan							
Person-years	362,488	4,559,859	1,367,655	133,067			
No. of cases	18	217	70	8			
HR (model 1)	0.88 (0.54-1.44)	1.00 (Reference)	1.05 (0.80-1.37)	1.20 (0.59-2.43)	0.451	1.01 (0.97-1.05)	
HR (model 2)	0.89 (0.55-1.45)	1.00 (Reference)	1.05 (0.80-1.38)	1.23 (0.61-2.49)	0.422	1.02 (0.98-1.05)	
Korea							
Person-years	11,414	168,680	72,043	9,028			
No. of cases	0	7	1	0			
HR (model 1)	NA	1.00 (Reference)	0.36 (0.04-2.90)	NA	0.473	0.90 (0.71-1.13)	
HR (model 2)	NA	1.00 (Reference)	0.38 (0.05-3.12)	NA	0.361	0.91 (0.72-1.16)	

Singapore						
Person-years	44,396	518,521	139,586	21,360		
No. of cases	2	21	10	0		
HR (model 1)	1.06 (0.25-4.54)	1.00 (Reference)	1.89 (0.89-4.02)	NA	0.482	1.05 (0.95-1.17)
HR (model 2)	1.06 (0.25-4.54)	1.00 (Reference)	1.91 (0.90-4.06)	NA	0.480	1.05 (0.95-1.17)
Taiwan						
Person-years	11,170	221,386	112,558	16,949		
No. of cases	0	5	1	1		
HR (model 1)	NA	1.00 (Reference)	0.33 (0.04-2.82)	2.22 (0.26-19.0)	0.994	1.04 (0.84-1.30)
HR (model 2)	NA	1.00 (Reference)	0.33 (0.04-2.84)	2.25 (0.26-19.6)	0.985	1.04 (0.84-1.30)

model 1: HRs are adjusted for age and sex.

model 2: HRs are adjusted for age, sex, smoking, alcohol intake and education.

1 P-values for trends were calculated by assigning scores for categories of body mass index, with 1 for <18.5, 2 for 18.5-24.9, 3 for 25.0–29.9, 4 for ≥30 kg/m2.

2 Heterogeneity for trend among regions or among countries.

Abbreviations: NA, not available.

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