Is there an obesity paradox in the Japanese elderly population? A community-based cohort study of 13,280 men and women

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Running title: Obesity paradox in elderly Japanese

Abstract

Aim: Despite increased interest in an obesity paradox (i.e., a survival advantage of being obese), evidence remains sparse in Japanese populations. We aimed to verify this phenomenon among community-dwelling elderly people in Japan.

Methods: Subjects aged 65–84 years randomly chosen from all 74 municipalities in Shizuoka Prefecture completed questionnaires including body mass index information. Participants were followed from 1999 to 2009. Following World Health Organization guidelines, participants were classified using an appropriate body mass index for Asian populations as follows: <18.5 kg/m^2 (underweight), 18.5–23.0 kg/m^2 (normal weight), 23.0–27.5 kg/m^2 (overweight), and >27.5 kg/m^2 (obesity). We estimated hazard ratios and their 95% confidence intervals for all-cause mortality, controlling for sex, age, smoking status, alcohol consumption, physical activity, hypertension and diabetes mellitus.

Results: Compared with normal-weight subjects, overweight/obese subjects tended to have lower hazard ratios; the multivariate hazard ratios (95% confidence interval) were 0.86 (0.62–1.19) for obesity, 0.83 (0.73–0.94) for overweight, and 1.60 (1.40–1.82) for underweight. In subgroup analyses by sex and age, the hazard ratios tended to be lower among obese men, albeit not significantly; hazard ratios (95% confidence interval) were 0.56 (0.25–1.27) in men aged 65–74 and 0.78 (0.41–1.45) in men aged 75–84.

Conclusions: The present study provides evidence of a conservative obesity paradox among elderly Japanese people, using the appropriate body mass index cut-off points for Asian populations. In particular, obese elderly men tend to have a lower risk of all-cause mortality.

Key words: Body Mass Index, Elderly, Japanese, Mortality, Obesity

Introduction

Obesity is one of the major public health problems worldwide. Excess weight is related to several diseases including diabetes mellitus, hypertension, and coronary artery disease.[1] However, obesity in elderly people has been reported to be paradoxically associated with a lower, not higher, risk of adverse health outcomes.[2–5] These seemingly counterintuitive observations have been referred to as an “obesity paradox”,[6] and this phenomenon has received much academic attention. Additionally, it has a strong implication for clinicians as well as public health practitioners because, if the phenomenon reflects a causal relationship, the need of intervention for obese elderly people should be carefully scrutinized.[7]

It is well known that Asian populations have different associations between BMI, percentage of body fat, and health risks than that of Western populations.[8] For example, among Asian people, the prevalence of type 2 diabetes and cardiovascular disease is high, even among those who are categorized as normal weight according to international standards. To address this problem, a World Health Organization (WHO) consultation report recently proposed appropriate BMI cut-off points for Asian populations and redefined obesity as BMI greater than 27.5 kg/m^2.[8,9]

Japan is now undergoing a rapid ageing of the population at an unprecedented rate; related to this are several studies examining the association between body mass index (BMI) and mortality among elderly people.[10–12] For example, Tamakoshi et al., using a dataset of a large population-based cohort study of elderly Japanese aged 65–79 years, found no increased risk among overweight/obese subjects, except among obese women (i.e., BMI: ≥30 kg/m^2).[10] Conversely, Takata et al. reported that, among the Japanese elderly aged 80 years or older, those with BMI of 22.5–23.8 kg/m^2 had the lowest all-cause mortality rate, and that there was no association among those with BMI higher than that group.[11] However, these previous studies used a variety of BMI cut-off points and reference categories and did not use recently proposed appropriate BMI cut-off points for Asian populations.

From the perspective of exploring an obesity paradox, it is vital to clearly define "obesity". To our knowledge, however, there has been no study from Asia that examined an obesity paradox using the newly defined obesity measure. We therefore aim to verify an obesity paradox in elderly Japanese using the appropriate BMI cut-off points for Asian populations. The use of internationally comparable obesity criteria would be valuable when comparing with findings from Western countries.

Methods

Individual data were collected from participants in the Shizuoka Elderly Cohort Study, a population-based study conducted in Shizuoka Prefecture, Japan.[13–15] The primary purpose of the original cohort study was to evaluate the longitudinal associations between clinical, environmental and behavioral factors and health conditions. After stratifying the sample according to sex and age groups (65–74 and 75–84 years), we randomly selected 300 residents from each of the 74 municipalities in Shizuoka Prefecture. A total of 22,200 people were selected. In December 1999, 14,001 individuals completed and returned a questionnaire that had been sent to them by mail (response rate: 63%). The self-administered questionnaire inquired about age, sex, body weight, height, smoking habits, alcohol consumption habits, socio-economic status, working status, and disease conditions. Repeat surveys were then mailed to the same participants in December 2002, March 2006, and March 2009.

The 14,001 baseline respondents were defined as the Shizuoka cohort (Figure 1). 721 subjects whose BMI was missing at baseline were excluded. Among the rest of the 13,280 subjects, 1,301, 2,423, and 3,849 subjects were lost to follow-up in 2002, 2006, and 2009, respectively. The subjects who were lost to follow-up in 2006 and 2009 were treated as 3-year (1999-2002) and 6.25-year (1999-2006) survival cases, respectively.

BMI was calculated as weight (kg) divided by the square of height (m) at baseline. Participants were classified into appropriate BMI categories for Asian populations as follows[8]: <18.5 kg/m^2 for underweight, 18.5–23.0 kg/m^2 for normal weight, 23.0–27.5 kg/m^2 for overweight and >27.5 kg/m^2 for obesity. These cut-off points proved appropriate in an earlier study that examined the prevalence of obesity and type 2 diabetes.[16] Moreover, the pooled analysis by Sasazuki et al.[17] showed the risk of excess weight (BMI >27.0 kg/m^2) on mortality among middle-aged Japanese (>40 years) and concluded that a BMI of >27.0 kg/m^2 should be defined as a high-risk group for all-cause mortality. This result is consistent with the newly defined obesity in the Asian population.

The primary outcome in this study was all-cause mortality. We considered the following variables to be potential confounders: sex, age at baseline (continuous), smoking status (never, former, or current), alcohol consumption (none or rarely, 1–3 times/week, 4–6 times/week, or everyday), frequency of physical activity of more than 30 min (none, 1–2 times/week, 3–4 times/week, 5 or more times/week), hypertension, and diabetes mellitus. With respect to disease status, participants were asked whether they had been diagnosed with hypertension or diabetes mellitus at baseline.

Statistical analysis

Initially, a descriptive analysis was conducted for the demographic characteristics and lifestyles according to the follow-up status and baseline BMI categories. Next, person-years were counted for each subject from baseline to the date of death, the date of censorship, or the last follow-up, whichever occurred first. To account for potential reverse causation in the relationship between BMI and serious illness, those who died within the first year of follow-up were excluded. Then, the crude hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality according to the baseline BMI categories were estimated using Cox's proportional hazards model. Subsequently, we estimated age and sex-adjusted HRs and multivariate HRs.

To examine possible heterogeneity, we performed subgroup analyses by sex and age groups (65–74 and 75–84 years). Furthermore, we conducted a sensitivity analysis using WHO international cut-off points (<18.5 kg/m^2 for underweight, 18.5–25.0 kg/m^2 for normal weight, 25.0–30.0 kg/m^2 for overweight and >30.0 kg/m^2 for obesity). In addition, because the presence of pre-existing carcinoma at baseline may influence the effect of BMI, we reanalyzed the data excluding the participants with carcinoma at baseline.

All statistical analyses were performed with EZR ver.1.24 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.[18]

Approval for this study was obtained from the Institutional Review Board of the Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University on September 3, 2013 (No. 712).

Results

The baseline characteristics of the eligible 13,280 subjects, according to their follow-up status, are shown in Table 1. The deceased subjects tended to be slightly older and were likely to be men who were underweight, who were current or former smokers and who had sedentary lifestyles. Over the 9 years of follow-up, after excluding 189 deaths that occurred during the first year of follow-up, 1,507 deaths were identified with a known date of death among the 73,935 person-years with a mean follow-up of 5.65 years. Table 2 shows the baseline characteristics of participants according to BMI categories. Obese people were more likely to be women who never smoked, and who had a sedentary lifestyle.

The crude and adjusted HRs for all-cause mortality are shown in Table 3. The multivariate HR was 0.86 (95% CI 0.62–1.19) for obesity and 0.83 (95% CI 0.73–0.94) for overweight. For underweight and all-cause mortality, a positive association was observed (HR 1.60, 95% CI 1.40–1.82). In the subgroup analyses by sex and age groups, the HRs tended to be lower among obese men in both age groups, albeit not significantly. Among women in the younger age group, there was a positive association between obesity and all-cause mortality, but no association among women in the older age group.

When excluding those who had carcinoma at baseline, no substantial change was observed (Table 4). In addition, when using the WHO standard BMI cut-off values, no clear association was found between obesity and all-cause mortality, which was likely owing to the small number of obese people (data not shown).

Discussion

In our cohort study of 13,280 elderly Japanese people, we found that obese people, using the appropriate BMI cut-off points for Asian populations, tended to have a lower risk of all-cause mortality compared with individuals of a normal weight, which implies the presence of an obesity paradox in elderly Japanese. Notably, when stratifying by age and sex groups, the pattern was more prominent among men, and overweight male subjects had a significantly lower risk of all-cause mortality. Among 65–74-year-old women, we even found a positive association between obesity and all-cause mortality, albeit not significantly.

Although our finding is consistent with several other studies of Japanese elderly populations,[10,11] Matsuo et al.[12] showed that the risk of all-cause mortality among those aged 60–79 years is higher in obese people (i.e., BMI ≥27.0 kg/m^2) except in slightly obese men (i.e., BMI 27.0–29.9 kg/m^2). Although the reason for this inconsistent finding is unclear, there are two possible explanations. First, their study participants were relatively younger. As a meta-analysis by Wang[19] showed age-dependent decline of the association between obesity and all-cause mortality, this difference of age distribution may lead to the inconsistent finding. Second, whereas our reference category is broad (i.e., BMI 18.5–23.0 kg/m^2), Matsuo et al.[12] defined the reference category as 20.0–22.9 kg/m^2, which is a relatively narrow group with more survival advantage. For the lower normal-range group (i.e., BMI 18.5–19.9 kg/m^2), their multivariate HRs were 1.12 (95% CI 1.04–1.22) and 1.22 (95% CI 1.11–1.35) in men and women, respectively. Their choice of reference group may have led to overestimation of the risk among obese people.

We observed different patterns between the sexes, and overweight/obese men tended to have lower HRs for all-cause mortality. A similar pattern was reported in a previous study from Japan,[10] and we infer that this is partly explained by a difference in average life expectancy between men (80.5 years) and women (86.8 years).[20] Notably, the positive association between obesity and all-cause mortality in women was only observed among those aged 65–74 years, and it disappeared in those aged 75–84 years. Although this may imply that an obesity paradox emerges among Japanese women aged 85 years or older, further studies are warranted to test this hypothesis.

There are some limitations in our study. First, 57.0% of the participants were lost to follow-up, and we treated the 2,423 and 3,849 subjects who were censored in 2006 and 2009 as 3-year and 6.25-year survivors, respectively (Figure 1). Although accurate reasons of loss to follow-up are unknown, it is possible that the participants with lower BMI were more likely to be lost to follow-up. Given that those who were lost to follow-up tended to be smokers, even when we restricted the analysis to men, this may have resulted in underestimation of an obesity paradox. Furthermore, because those who were lost to follow-up tended to be older, this might have underestimated the findings of an obesity paradox. Second, we could not obtain information about the changes in smoking status during follow-up, so there is a possibility of residual confounding. Andrew et al.[21] postulated that obesity paradox in cardiovascular disease may be elucidated by smoking and reverse causation. Third, self-reported height and weight was used in this study, and it is possible that the accuracy of the data are associated with the age and sex of the subjects. However, self-reported height and weight are known to be generally reliable from elderly Japanese populations,[22] and this procedure has been employed in large cohort studies. Finally, because BMI was only recorded at baseline, we did not examine possible weight change during the study period. A recent study by Murayama et al.[23] examined the relationship between the trajectories of BMI and all-cause mortality among elderly Japanese. Even when their BMI decreased during the study period, higher BMI at baseline was associated with a lower mortality, which is consistent with our findings.

In conclusion, our study provides evidence of a conservative obesity paradox among elderly Japanese, when using the appropriate BMI cut-off points for Asian populations. Specifically, we found an inverse association only in overweight elderly people. Although no clear association was found between obesity and all-cause mortality, obese elderly men tended to have a lower risk of all-cause mortality. A variety of intervention programs for losing weight are now available for obese elderly people.[24] However, even if elderly people are able to lose weight successfully, our findings imply that weight loss interventions cannot be strongly recommended for elderly Japanese, particularly for men.

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Disclosure statement:

The authors declare no conflict of interest.

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Figure legend

Figure 1. Participants flow

Table 1 Baseline characteristics of all participants according to follow-up status (Shizuoka, Japan, 1999–2009).

				Loss to follow-up		
	All subjects	Survivors	Decedents	Censored during 2006–2009	Censored during 2002–2006	Censored during 1999–2002
Baseline characteristics	N=13280	N=4011	N=1696	N=3849	N=2423	N=1301
Mean age, years (SD)	73.92 (5.42)	72.32 (5.04)	76.65 (5.14)	73.56 (5.28)	74.54 (5.47)	75.16 (5.39)
Sex (%)						
Male	6860 (51.7)	1984 (49.5)	1163 (68.6)	1866 (48.5)	1177 (48.6)	670 (51.5)
Female	6420 (48.3)	2027 (50.5)	533 (31.4)	1983 (51.5)	1246 (51.4)	631 (48.5)
BMI (%)						
Underweight: <18.5 kg/m^2	1799 (13.5)	374 (9.3)	385 (22.7)	434 (11.3)	366 (15.1)	240 (18.4)
Normal weight: 18.5 to <23 kg/m^2	6991 (52.6)	2117 (52.8)	893 (52.7)	2046 (53.2)	1286 (53.1)	649 (49.9)
Overweight: 23 to <27.5 kg/m^2	4010 (30.2)	1370 (34.2)	375 (22.1)	1240 (32.2)	681 (28.1)	344 (26.4)
Obesity: ≧27.5 kg/m^2	480 (3.6)	150 (3.7)	43 (2.5)	129 (3.4)	90 (3.7)	68 (5.2)
Smoking status (%)						

Never	9031 (68.0)	2867 (71.5)	995 (58.7)	2687 (69.8)	1658 (68.4)	824 (63.3)
Former	1548 (11.7)	481 (12.0)	279 (16.5)	390 (10.1)	266 (11.0)	132 (10.1)
Current	2180 (16.4)	570 (14.2)	347 (20.5)	583 (15.1)	414 (17.1)	266 (20.4)
Missing	521 (3.9)	93 (2.3)	75 (4.4)	189 (4.9)	85 (3.5)	79 (6.1)
Daily alcohol intake (%)						
None/rarely	8633 (65.0)	2538 (63.3)	1092 (64.4)	2459 (63.9)	1679 (69.3)	865 (66.5)
1–3 times/week	1161 (8.7)	386 (9.6)	142 (8.4)	354 (9.2)	181 (7.5)	98 (7.5)
4–6 times/week	678 (5.1)	245 (6.1)	75 (4.4)	192 (5.0)	114 (4.7)	52 (4.0)
Everyday	2367 (17.8)	753 (18.8)	331 (19.5)	686 (17.8)	378 (15.6)	219 (16.8)
Missing	441 (3.3)	89 (2.2)	56 (3.3)	158 (4.1)	71 (2.9)	67 (5.1)
Physical activity (%)						
None/rarely	6157 (46.4)	1756 (43.8)	921 (54.3)	1667 (43.3)	1167 (48.2)	646 (49.7)
1–2 times/week	2323 (17.5)	769 (19.2)	243 (14.3)	707 (18.4)	402 (16.6)	202 (15.5)
3–4 times/week	1696 (12.8)	571 (14.2)	189 (11.1)	479 (12.4)	313 (12.9)	144 (11.1)
≧5 times/week	2310 (17.4)	763 (19.0)	238 (14.0)	725 (18.8)	401 (16.5)	183 (14.1)
Missing	794 (6.0)	152 (3.8)	105 (6.2)	271 (7.0)	140 (5.8)	126 (9.7)

Hypertension (%)						
Absent	8113 (61.1)	61.7 (61.7)	62.9 (62.9)	59 (59.0)	61.1 (61.1)	63.2 (63.2)
Present	4117 (31.0)	32 (32.0)	29.4 (29.4)	31.6 (31.6)	31.6 (31.6)	27.1 (27.1)
Missing	1050 (7.9)	6.3 (6.3)	7.7 (7.7)	9.4 (9.4)	7.3 (7.3)	9.7 (9.7)
Diabetes mellitus (%)						
Absent	11194 (84.3)	3511 (87.5)	1373 (81.0)	3225 (83.8)	2033 (83.9)	1052 (80.9)
Present	1036 (7.8)	247 (6.2)	192 (11.3)	262 (6.8)	212 (8.7)	123 (9.5)
Missing	1050 (7.9)	253 (6.3)	131 (7.7)	362 (9.4)	178 (7.3)	126 (9.7)

Abbreviations: BMI, body mass index; SD, standard deviation

Table 2. Baseline characteristics of participants according to BMI category (Shizuoka, Japan, 1999–2009).

	Body Mass Index (kg/m^2)			
	Underweight	Normal weight	Overweight	Obesity
	<18.5	18.5 to <23.0	23.0 to <27.5	≧27.5
Baseline characteristics	N=1799	N=6991	N=4010	N=480
Mean age, years (SD)	76.07 (5.08)	74.04 (5.40)	72.85 (5.32)	72.90 (5.35)
Sex (%)				
Male	882 (49.0)	3710 (53.1)	2088 (52.1)	180 (37.5)
Female	917 (51.0)	3281 (46.9)	1922 (47.9)	300 (62.5)
Smoking status (%)				
Never	1183 (65.8)	4632 (66.3)	2853 (71.1)	363 (75.6)
Former	199 (11.1)	856 (12.2)	450 (11.2)	43 (9.0)
Current	333 (18.5)	1231 (17.6)	562 (14.0)	54 (11.2)
Missing	84 (4.7)	272 (3.9)	145 (3.6)	20 (4.2)
Daily alcohol intake (%)				
None/rarely	1275 (70.9)	4442 (63.5)	2569 (64.1)	347 (72.3)

1–3 times/week	145 (8.1)	612 (8.8)	365 (9.1)	39 (8.1)
4–6 times/week	74 (4.1)	389 (5.6)	198 (4.9)	17 (3.5)
Everyday	239 (13.3)	1319 (18.9)	753 (18.8)	56 (11.7)
Missing	66 (3.7)	229 (3.3)	125 (3.1)	21 (4.4)
Physical activity (%)				
None/rarely	987 (54.9)	3158 (45.2)	1753 (43.7)	259 (54.0)
1–2 times/week	239 (13.3)	1240 (17.7)	757 (18.9)	87 (18.1)
3–4 times/week	216 (12.0)	874 (12.5)	554 (13.8)	52 (10.8)
≧5 times/week	241 (13.4)	1279 (18.3)	739 (18.4)	51 (10.6)
Missing	116 (6.4)	440 (6.3)	207 (5.2)	31 (6.5)
Hypertension (%)				
Absent	1315 (73.1)	4453 (63.7)	2141 (53.4)	204 (42.5)
Present	340 (18.9)	1934 (27.7)	1602 (40.0)	241 (50.2)
Missing	144 (8.0)	604 (8.6)	267 (6.7)	35 (7.3)
Diabetes mellitus (%)				
Absent	1547 (86.0)	5850 (83.7)	3412 (85.1)	385 (80.2)

Present	108 (6.0)	537 (7.7)	331 (8.3)	60 (12.5)
Missing	144 (8.0)	604 (8.6)	267 (6.7)	35 (7.3)

Abbreviations: BMI, body mass index; SD, standard deviation

Table 3. Number of deaths, person-years and hazard ratios for all-cause mortality by appropriate BMI category for Asian population (Shizuoka, Japan, 1999–2009).

	Body Mass Index (kg/m^2)			
	Underweight	Normal weight	Overweight	Obesity
	<18.5	18.5 to <23.0	23.0 to <27.5	≧27.5
All participants				
Person-years	8420.91	39246.58	23665.01	2602.58
Deaths (n) †	319	805	346	37
Crude HR (95% CI)	1.88 (1.65–2.14) *	1.00	0.71 (0.62–0.80)*	0.68 (0.49–0.95)*
Age–sex adjusted HR (95% CI)	1.66 (1.46–1.89) *	1.00	0.81 (0.72–0.92) *	0.85 (0.61–1.18)
Multivariate HR (95% CI) ‡	1.60 (1.40–1.82) *	1.00	0.83 (0.73–0.94) *	0.86 (0.62–1.19)
Men				
65–74 years old				
Person-years	1501.36	11093.71	7647.20	638.47
Deaths (n) †	45	197	96	6
Crude HR (95% CI)	1.74 (1.26–2.41) *	1.00	0.70 (0.55–0.90) *	0.53 (0.23–1.19)

Age-adjusted HR (95% CI)	1.61 (1.17–2.23) *	1.00	0.74 (0.58–0.94) *	0.55 (0.25–1.25)
Multivariate HR (95% CI) ‡	1.54 (1.11–2.13) *	1.00	0.76 (0.60–0.98) *	0.56 (0.25–1.27)
75–84 years old				
Person-years	2347.74	9416.68	4468.43	340.04
Deaths (n) †	165	369	134	10
Crude HR (95% CI)	1.82 (1.51–2.18) *	1.00	0.76 (0.62–0.92) *	0.75 (0.40–1.41)
Age-adjusted HR (95% CI)	1.79 (1.49–2.15) *	1.00	0.80 (0.65–0.97) *	0.75 (0.40–1.40)
Multivariate HR (95% CI) ‡	1.71 (1.42–2.06) *	1.00	0.81 (0.67–0.99) *	0.78 (0.41–1.45)
Women				
65–74 years old				
Person-years	1961.49	10734.59	7476.78	979.00
Deaths (n) †	20	65	48	8
Crude HR (95% CI)	1.68 (1.02–2.77) *	1.00	1.06 (0.73–1.54)	1.34 (0.64–2.78)
Age-adjusted HR (95% CI)	1.55 (0.94–2.56)	1.00	1.11 (0.76–1.61)	1.37 (0.66–2.86)
Multivariate HR (95% CI) ‡	1.52 (0.92–2.52)	1.00	1.20 (0.82–1.74)	1.53 (0.73–3.20)
75–84 years old				

Person-years	2610.32	8001.61	4072.61	645.07
Deaths (n) †	89	174	68	13
Crude HR (95% CI)	1.61 (1.25–2.08) *	1.00	0.76 (0.57–1.01)	0.88 (0.50–1.55)
Age-adjusted HR (95% CI)	1.53 (1.19–1.98) *	1.00	0.82 (0.62–1.08)	0.95 (0.54–1.68)
Multivariate HR (95% CI) ‡	1.50 (1.16–1.95) *	1.00	0.82 (0.61–1.08)	0.93 (0.53–1.64)

Abbreviations: HR, hazard ratio; CI, confidence interval

* $P<0.05$

† Deaths: died within the first year of follow-up was excluded.

‡ Smoking status, daily alcohol intake, physical activity, hypertension and diabetes mellitus were also adjusted for age and sex.

Table 4. Number of deaths excluding with cancer at baseline, person-years, hazard ratios for all-cause mortality by appropriate BMI category for Asian population, (Shizuoka, Japan, 1999-2009).

	Body Mass Index (kg/m^2)			
	Underweight	Normal weight	Overweight	Obesity
	<18.5	18.5 to <23.0	23.0 to <27.5	≧27.5
All participants				
Person-years	8421	39247	23665	2603
Deaths (n) †	278	710	322	55
Crude HR (95% CI)	1.87 (1.63–2.15) *	1.00	0.73 (0.64–0.83) *	0.72 (0.51–1.01)
Age–sex adjusted HR (95% CI)	1.65 (1.43–1.90) *	1.00	0.84 (0.74–0.96) *	0.88 (0.63–1.24)
Multivariate HR (95% CI) ‡	1.62 (1.41–1.87) *	1.00	0.84 (0.74–0.96) *	0.86 (0.61–1.21)
Men				
65–74 years old				
Person-years	1501	11094	7647	638
Deaths (n) †	35	166	91	5
Crude HR (95% CI)	1.63 (1.13–2.35) *	1.00	0.77 (0.60–1.00)	0.51 (0.21–1.23)

Age-adjusted HR (95% CI)	1.50 (1.04–2.17) *	1.00	0.81 (0.63–1.05)	0.54 (0.22–1.32)
Multivariate HR (95% CI) ‡	1.48 (1.02–2.14) *	1.00	0.82 (0.63–1.06)	0.52 (0.21–1.27)
75–84 years old				
Person-years	2348	9417	4468	340
Deaths (n) †	145	330	122	10
Crude HR (95% CI)	1.77 (1.46–2.16) *	1.00	0.76 (0.62–0.93) *	0.83 (0.44–1.56)
Age-adjusted HR (95% CI)	1.75 (1.44–2.13) *	1.00	0.80 (0.65–0.99) *	0.82 (0.44–1.53)
Multivariate HR (95% CI) ‡	1.68 (1.38–2.05) *	1.00	0.81 (0.66–1.00)	0.85 (0.45–1.59)
Women				
65–74 years old				
Person-years	1961	10735	7477	979
Deaths (n) †	17	55	45	8
Crude HR (95% CI)	1.65 (0.96–2.84)	1.00	1.14 (0.77–1.69)	1.55 (0.74–3.25)
Age-adjusted HR (95% CI)	1.54 (0.89–2.65)	1.00	1.18 (0.79–1.75)	1.58 (0.75–3.31)
Multivariate HR (95% CI) ‡	1.69 (0.97–2.92)	1.00	1.20 (0.81–1.79)	1.40 (0.65–2.99)
75–84 years old				

Person-years	2610	8002	4073	645
Deaths (n) †	81	159	64	12
Crude HR (95% CI)	1.68 (1.29–2.20) *	1.00	0.76 (0.57–1.02)	0.86 (0.48–1.54)
Age-adjusted HR (95% CI)	1.61 (1.23–2.11) *	1.00	0.82 (0.61–1.10)	0.93 (0.52–1.68)
Multivariate HR (95% CI) ‡	1.63 (1.24–2.14) *	1.00	0.81 (0.60–1.08)	0.88 (0.49–1.60)

Abbreviations: HR, hazard ratio; CI, confidence interval

* $P<0.05$

† Deaths: died within the first year of follow-up was excluded.

‡ Smoking status, daily alcohol intake, physical activity, hypertension and diabetes mellitus were also adjusted for age and sex.