Published in final edited form as:

Ann Rheum Dis. 2012 June ; 71(6): 924–928. doi:10.1136/ard.2011.200523.

Mortality due to coronary heart disease and kidney disease among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study

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Abstract

Objectives—Whether the link between gout and mortality is causal or confounded by lifestyle factors or comorbidities remains unclear. Studies in Asia are warranted due to the rapid modernisation of the locale and ageing of the population.

Methods—The association between gout and mortality was examined in a prospective cohort, the Singapore Chinese Health Study, comprising 63 257 Singapore Chinese individuals, aged 45–74 years during the enrolment period of 1993–8. All enrollees were interviewed in person on lifestyle factors, current diet and medical histories. All surviving cohort members were contacted by telephone during 1999–2004 to update selected exposure and medical histories (follow-up I interview), including the history of physician-diagnosed gout. Cause-specific mortality in the cohort was identified via record linkage with the nationwide death registry, up to 31 December 2009.

Results—Out of 52 322 participants in the follow-up I interview, 2117 (4.1%) self-reported a history of physician-diagnosed gout, with a mean age at diagnosis of 54.7 years. After a mean follow-up period of 8.1 years, there were 6660 deaths. Relative to non-gout subjects, subjects with gout had a higher risk of death (HR 1.18; 95% CI 1.06 to 1.32), and specifically from death due to coronary heart disease (CHD) (HR 1.38, 95% CI 1.10 to 1.73) and kidney disease (HR 5.81, 95%

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Competing interests None.

Ethics approval The study was approved by the the institutional review boards of the National University of Singapore and the University of Minnesota.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

CI 3.61 to 9.37). All gout–mortality risk associations were present in both genders but the risk estimates appeared higher for women.

Conclusion—Gout is an independent risk factor for mortality, and specifically for death due to CHD and kidney disease.

There has been a rise in the prevalence of gout worldwide in recent decades,¹ attributed to increased longevity and trends in lifestyles leading to an increase in gout-related risk factors, including obesity, metabolic syndrome, hypertension and alcohol consumption. Studies in China,² Taiwan³ and Japan⁴ have reported that the prevalence of gout is increasing in Asian countries and approaching that seen in western populations.⁵ In addition, the age of onset of gout appears to be decreasing in several Asian societies,⁶ with a prevalence of 3.5% among men as young as in their twenties from a hospital-based study in Taiwan.⁷ Therefore, gout poses a rapidly growing public health burden in Asia.

Epidemiological studies have shown that hyperuricaemia and gout is associated with various comorbidities such as diabetes mellitus, obesity, metabolic syndrome, hypertension, stroke, cardiovascular and kidney diseases, all of which are established risk factors related to increased mortality.^{8–11} Two large-scale prospective studies in the USA have recently shown that gout is an independent risk factor for increased total mortality and mortality due to cardiovascular diseases, in particular, coronary heart disease (CHD).^{12,13} While both studies had at least a decade of follow-up and accounted for numerous potential confounders, the studies were performed in Caucasian men only, and thus the results may not be generalised to women or to Asian individuals who may have different genetic predispositions and adopt lifestyle and dietary patterns distinct from their western counterparts. Another cohort study evaluated approximately 61 000 Chinese men and women recruited in a health screening programme in Taiwan and reported that compared with normouricaemic subjects, subjects with gout had an increased risk of death due to total and cardiovascular diseases.¹⁴ However, that study had a relatively short mean follow-up time of 56 months and did not adequately adjust for significant confounders in the gout–mortality association such as smoking, body mass index, diet and history of CHD or stroke. Therefore, the full magnitude of disease burden from mortality due to gout warrants further evaluation in other Asian populations.

In the present study, we examined the association between the history of a diagnosis of gout and mortality risk within a prospective cohort of 52 322 Chinese men and women (the Singapore Chinese Health Study). In particular, we were interested in mortality due to cardiovascular and kidney diseases.

MATERIALS AND METHODS

Study population

The Singapore Chinese Health Study is a population-based, prospective study established between April 1993 and December 1998 by the recruitment of 63 257 Chinese individuals in Singapore, aged between 45 and 74 years, and who were residents in government-built housing estates, where 86% of the Singapore population lived during that period. Study subjects were restricted to the two major dialect groups of Chinese in Singapore, the Hokkien and Cantonese, who originated from the contiguous provinces of Fujian and Guangdong, respectively, in the southern part of China. At recruitment, each subject was interviewed face to face in their home by a trained interviewer using a structured, scanner-readable questionnaire that requested information on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, familial history of cancer and dietary intake. Information about usual diet in the

preceding 1 year was captured using a structured questionnaire that included a 165-item food frequency questionnaire that was subsequently validated against a series of 24 h dietary recall interviews conducted on random subsets of cohort participants.¹⁵ The study was approved by the institutional review boards of the National University of Singapore and the University of Minnesota, and all subjects who were enrolled gave informed consent.

Participants were re-contacted for a telephone interview between July 1999 and October 2004 (the follow-up I interview).¹⁶ After excluding those who had died, were not contactable, or who were no longer able to participate due to physical inability, 52 322 participants (82.7%) were re-interviewed for an update of lifestyle factors such as height, weight, use of tobacco and medical history. In particular, at this follow-up interview, the following question was asked in the spoken language of the subject, 'Have you been told by a doctor that you have gout?' If the response was 'yes', subjects were also asked, 'Please also tell me the age at which you were first diagnosed?' The interviewers were trained to confirm that the participants had gout and not other arthritis by checking if blood uric acid was reported to be elevated or dietary advice (avoidance of alcohol, red meat and other purine-rich foods) was given by their physicians. If the subject responded 'yes' to both questions, a case of gout would be ascribed. All the interviews were tape-recorded and subjected to quality checks by the managers of the study.

Ascertainment of mortality

Deaths were identified through record linkage with the Singapore Registry of Births and Deaths. For the current analysis, we updated mortality data to 31 December 2009. As of June 2011, only 47 subjects were known to be lost to follow-up due to migration out of Singapore or for other reasons. This suggests that emigration among participants is negligible in this cohort and that vital statistics in follow-up are virtually complete.

Underlying causes of death were coded according to the International Classification of Diseases, 9th revision; codes 390–449 were used for cardiovascular deaths, codes 410–414 for CHD deaths, codes 430–438 for stroke deaths and codes 585–586 for kidney disease deaths. Codes for cardiovascular deaths include all CHD and other heart disease, stroke, hypertension, diseases of arteries, arterioles and capillaries.

Statistical analysis

The study included 52 322 participants who were interviewed during the follow-up I interview. The differences between baseline characteristics by physician-diagnosed gout were examined using the χ^2 test for categorical variables and Student's *t* test for continuous variables. Person-years were counted from the date of follow-up I interview to date of death, date of last contact (for the few participants who migrated out of Singapore), or 31 December 2009, whichever occurred first. Proportional hazards (Cox) regression methods¹⁷ were used to examine the associations between gout and mortality risk. All Cox regression models included the following covariates: age at follow-up I interview, years between baseline and follow-up I interviews, gender, dialect (Hokkien, Cantonese), education (non-formal education, primary school, secondary school or higher), body mass index (<20, 20–<24, 24–<28, 28+ kg/m²), alcohol drinking (none/monthly, weekly, daily), smoking (never, former, current), moderate activity (none, 0.5–3 h/week, 4+ h/week), dietary intakes of saturated fat density (g/1000 kcal per day, quartiles) and cholesterol (mg/1000 kcal per day, quartiles). We further adjusted for physician-diagnosed hypertension and diabetes mellitus reported at baseline or follow-up I interview in model 2. Finally, we re-analysed the data limited only to subjects who did not report having physician-diagnosed CHD or stroke at baseline or follow-up I interview (model 3). For the analysis by duration of gout diagnosis, we performed tests for trend by entering ordinal categorical variables as continuous

variables in the Cox regression models. Statistical computing was conducted using SAS version 9.1 statistical software package. All p values quoted were two-sided and those less than 0.05 were considered statistically significant.

RESULTS

A total of 2117 (4.1%) subjects reported a history of physician-diagnosed gout. Table 1 shows the baseline characteristics of cohort members by the history of gout. The mean age at diagnosis of gout was 54.7 years (SD 10.0), with an IQR of 49–62 years. After a mean of 8.1 years in follow-up (SD 1.9) among 52 322 participants, there were 6660 deaths. Men were more likely to have gout than women. Compared with those without gout, participants with self-reported gout had a higher level of education, were more likely to have ever smoked, and consumed more alcohol, dietary saturated fat and cholesterol. People with gout were also more likely to report histories of stroke, diabetes mellitus, hypertension or CHD (table 1).

Table 2 shows the mortality risk by the history of physician-diagnosed gout. In this cohort, cardiovascular deaths accounted for 33% of all mortality and the majority of cardiovascular deaths were specifically caused by CHD (59% of total cardiovascular deaths). After adjusting for demographics and lifestyle factors in model 1, compared with participants without gout, those with gout had a significant 23% increase in the risk of all-cause mortality (HR 1.23; 95% CI 1.10 to 1.38). For cause-specific mortality, there was a 54% increase in the risk of CHD mortality (HR 1.54, 95% CI 1.23 to 1.93) and a sevenfold increase in mortality due to kidney disease (HR 7.21, 95% CI 4.48 to 11.60; table 2). As subjects with gout were more likely to report histories of diabetes mellitus and hypertension, which are in turn well-established risk factors for cardiovascular mortality, we adjusted for these two comorbidities as potential confounders in model 2. As expected, these risk estimates were attenuated after further adjustment for these comorbidity factors, but the risk estimates associated with gout for all-cause (HR 1.18, 95% CI 1.06 to 1.32), cardiovascular (HR 1.32, 95% CI 1.11 to 1.58), CHD (HR 1.38, 95% CI 1.10 to 1.73) and kidney disease mortalities (HR 5.81, 95% CI 3.61 to 9.37) remained statistically significant (table 2).

Gout may be a risk factor for mortality from CHD or stroke due to its association with the incidence of CHD and stroke. Furthermore, for subjects who also reported physician-diagnosed CHD or stroke at recruitment, we are unable to differentiate accurately if these diseases had occurred before or after the diagnosis of gout. Therefore, in model 3, we included only subjects without a history of stroke or CHD to avoid the potential confounding effect of these two diseases on the association between gout and cardiovascular mortality. Among subjects without a history of CHD or stroke, the gout–mortality associations for total deaths, CHD deaths and kidney disease deaths remained essentially unchanged (table 2).

In all the models, all the risk estimates were higher in women compared with men, but these differences by gender were not statistically significant (table 2). As incident gout is common as renal function declines, it is also possible that chronic renal disease preceded gout among the subjects who eventually died from kidney disease. We therefore only included subjects with more than 5 years of follow-up and still found a strong association between gout and kidney disease mortality (HR 4.92, 95% CI 2.39 to 10.13). Finally, we wanted to examine if a history of CHD or stroke modified the association between gout and kidney disease death. The association between gout and the risk of kidney disease mortality in the subpopulation with a history of CHD or stroke (HR 9.42, 95% CI 4.40 to 20.19) (see supplementary table S2, available online only) was approximately twice that observed in the subpopulation without a history of CHD or stroke (HR 4.35, 95% CI 2.29 to 8.24; table 2).

Table 3 shows the gout–mortality association according to the duration of physician-diagnosed gout at the time of the follow-up I interview. As most subjects with a longer duration of disease might be older than subjects with a shorter duration, we adjusted for age at interview in these analyses. The risk of cardiovascular mortalities increased with increasing duration of gout. While the hazard ratio (95% CI) for cardiovascular mortality among patients with gout diagnosed less than 10 years before the follow-up I interview was 1.28 (1.04 to 1.59) compared with those without a history of gout, the risk increased to 1.41 (1.05 to 1.90) for patients with gout whose initial diagnosis was 10 or more years before the interview (table 3). Similar results were observed in the subpopulation without a history of CHD or stroke (see supplementary table S3, available online only). Due to the relatively small number of fatal kidney disease cases, the dose-response association between the duration of gout diagnosis and fatal kidney disease was not as clear.

DISCUSSION

In this large, population-based cohort of middle-aged and older Chinese adults in Singapore, we found that gout was significantly associated with CHD and kidney disease mortalities. These associations were independent of major confounders in lifestyle and comorbidity factors, and were present in both men and women. However, all gout–mortality risk estimates were higher in women than in men.

The strengths of the present study include its population-based design, the large number of genetically homogenous subjects, detailed information on lifestyle factors such as tobacco smoking and alcohol intake, semiquantitative food frequency data on current diet, and medical history obtained through in-person interviews. All exposure information, including the self-reported history of physician-diagnosed gout, was collected before outcome (death) and thus it is free of recall bias. We had virtually complete data on mortality given that, to date, the number of subjects lost to follow-up was negligible.

A potential limitation of the present study is the self-reported nature of the gout, and lack of information on the treatment and control of the disease, as measured by the serum urate level. In this study, we had adopted the same methodology used in other cohort studies¹³¹⁸ whereby gout was defined by affirmative answer to the question, ‘Have you been told by a doctor that you have gout?’ In addition, we had trained our interviewers to confirm that the participants had gout and not other arthritis by checking if blood uric acid was reported to be elevated and dietary advice (avoidance of alcohol, red meat and other purine-rich foods) was given by their physicians in order to increase the accuracy of self-reported physician-diagnosed gout. Although gout is not life threatening, it is an extremely painful arthritis that debilitates the activities of daily living. Singapore is a small city-state with a system for easy access to specialised medical care, thus it is unlikely for affected individuals not to have consulted a physician and obtained a diagnosis of gout. Study participants were at a mean age of 61.5 years at the time of the follow-up I interview, and the prevalence of 4.1% for gout was consistent with the prevalence reported for similar age groups in other populations.⁵

As incident gout is common as renal function declines, it is possible that chronic renal disease preceded gout among the subjects who eventually died from kidney disease. To overcome this reverse causality bias, we excluded those with 5 years or fewer of follow-up, and the risk estimate for the association between gout and kidney disease mortality remained essentially unchanged. A published study comprising patients with end-stage renal diseases reported that such patients with incident gout exhibited an increased risk of mortality compared with those without (HR 1.49; 95% CI 1.43 to 1.55).¹⁹ Our findings thus have

external data corroboration and together they suggest that gout is an independent risk factor for mortality apart from advanced kidney disease.

Two large Caucasian cohort studies among US men, the Health Professional Follow-up Study¹² and the Multiple Risk Factor Intervention Trial,¹³ and a cohort study in Taiwan¹⁴ have reported on the risk of death, all cause and cause specific, in people with gout compared with those without. Our findings are remarkably comparable to the published results. All studies indicate an increase in overall mortality that is largely driven by an increase in CHD deaths.

Several biological mechanisms have been proposed to explain the relationship between hyperuricaemia and gout and cardiovascular disease. Hyperuricaemia and gout have been linked to several biomarkers of early disease, including carotid intima-media thickness, coronary calcium score, highly sensitive C-reactive protein and endothelial dysfunction. In a young cohort (Coronary Artery Risk Development in Young Adults) free of clinical heart disease, diabetes and renal impairment, increased serum urate level conferred a significant risk of subclinical atherosclerosis, as determined by the presence of coronary artery calcification.²⁰ Endothelial dysfunction is the earliest stage of atherosclerosis,²¹ and reduced compliance of large artery and peripheral arterial bed in endothelial dysfunction can be measured by endothelial-dependent flow-mediated dilation. A recent study showed that gout patients with elevated serum urate levels had significantly lower endothelial-dependent flow-mediated dilation compared with matched healthy controls, possibly due to decreased nitric oxide bioavailability.²² Other proposed mechanisms for the deleterious effects of uric acid on endothelial function include the induction of lipid oxidation and oxidative stress, and the stimulation of smooth muscle cell proliferation.²³ Conversely, allopurinol, a xanthine oxidase inhibitor that reduces the serum urate level, has been shown to improve endothelial dysfunction, reduce oxidative stress burden and improve myocardial efficiency by reducing oxygen consumption in patients after coronary artery bypass grafting.²³ Finally, gout attacks are associated with intense inflammation triggered by monosodium urate crystals, with the release of C-reactive protein, interleukin (IL)-1 β , IL-18 and tumour necrosis factor alpha.²⁴ Such recurrent episodic bursts and possible chronic low-grade inflammation may be another underlying mechanism for the link between gout and atherosclerosis.

Few studies have reported the risk of death due to kidney disease in gout patients. A Taiwanese study comparing 6631 subjects with gout with the general population reported standardised mortality ratios for fatal renal disease of 3.54 and 3.10 in women and men, respectively.²⁵ These figures are comparable to our risk estimates from the subpopulation without a self-reported history of physician-diagnosed CHD or stroke. It is difficult to ascertain if hyperuricaemia preceded chronic kidney disease or the reverse. As the kidneys are the main excretors of urate, chronic kidney disease has been strongly associated with hyperuricaemia and gout since antiquity, and 30–60% of gout patients have renal dysfunction of variable degree.²⁶ On the other hand, prolonged hyperuricaemia is associated with the development of hypertension, renal arteriosclerosis, glomerulosclerosis and tubulo-interstitial injury.²⁷ In a randomised trial of 113 chronic kidney disease patients who did not have gout, patients randomly assigned to receive allopurinol had slower progression of kidney disease and reduced cardiovascular events,²⁸ suggesting that reducing the urate level has beneficial effects on kidney and cardiovascular diseases. Our study suggests that cardiovascular disease and gout may act synergistically to increase the risk of kidney disease mortality, and this finding needs to be validated in other studies.

In conclusion, our study strengthens the evidence for gout as an independent risk factor for CHD and kidney disease mortalities. Patients with gout should be screened and managed for

CHD and kidney disease. Further research is needed to investigate whether optimising care for gout, especially for patients with a younger age of onset, may improve survival.

Acknowledgments

The authors would like to thank Siew-Hong Low of the National University of Singapore for supervising the field work of the Singapore Chinese Health Study, and Kazuko Arakawa and Renwei Wang for the development and maintenance of the cohort study database. The authors also thank the Ministry of Health in Singapore for assistance with the identification of mortality via database linkages.

Funding This study was supported by the National Institutes of Health (grant numbers R01-CA55069, R35-CA53890, R01-CA80205 and R01-CA98497).

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Table 1

Baseline characteristics of cohort members by history of gout (percentage or mean and SD) in the Singapore Chinese Health Study (1999–2009)

	Gout(n=2117)	No gout (n=50 205)	p Value
Age (years) at follow-up I interview	61.5 ± 7.7	61.6 ± 8.0	0.686
Body mass index (kg/m ²)	24.6 ± 3.5	23.1 ± 3.5	<0.0001
Gender (%)			<0.0001
Men	65.7	41.5	
Women	34.3	58.5	
Dialect (%)			0.035
Cantonese	46.2	48.5	
Hokkien	53.8	51.5	
Level of education (%)			<0.0001
No formal education	15.4	26.2	
Primary school (1–6 years)	42.9	44.7	
Secondary and above	41.7	29.1	
History of stroke (%)	5.1	3.5	0.0003
History of diabetes mellitus (%)	17.1	14.3	0.0003
History of hypertension (%)	62.8	38.2	<0.0001
History of CHD (%)	14.3	6.9	<0.0001
Cigarette smoking (%)			<0.0001
Never smokers	59.5	69.2	
Former smoker	26.1	14.8	
Current smokers	14.4	15.9	
Alcohol (%)			<0.0001
None/monthly	86.4	89.9	
Weekly	10.1	7.3	
Daily	3.5	2.8	
Weekly moderate activity (%)			<0.0001
No	71.8	77.8	
0.5–3 h/week	17.4	14.1	
4+ h/week	10.8	8.1	
Diet saturated fat density (g/day)	16.4 ± 7.9	15.7 ± 8.1	<0.0001
Diet cholesterol density (g/day)	186.6 ± 104.1	173.8 ± 104.7	<0.0001

CHD, coronary heart disease.

Table 2

Mortality risk by history of physician-diagnosed gout in the Singapore Chinese Health Study (1999–2009)

Models 1* and 2† (n=52 322)							Model 3‡ (n=47 035)		
		No of deaths		HR (95% CI)		No of deaths			
		No gout	Gout	Model 1	Model 2	No gout	Gout	HR (95% CI)	
Deaths from all causes									
All	6329	331	1.23 (1.10 to 1.38)	1.18 (1.06 to 1.32)	5005	213	1.11 (0.97 to 1.28)		
Men	3462	239	1.16 (1.02 to 1.33)	1.12 (0.98 to 1.28)	2722	150	1.04 (0.88 to 1.23)		
Women	2867	92	1.42 (1.15 to 1.75)	1.36 (1.10 to 1.67)	2283	63	1.30 (1.01 to 1.67)		
All cardiovascular deaths									
All	2063	134	1.49 (1.25 to 1.78)	1.32 (1.11 to 1.58)	1451	75	1.23 (0.97 to 1.56)		
Men	1109	98	1.40 (1.14 to 1.73)	1.23 (1.00 to 1.52)	757	52	1.10 (0.82 to 1.46)		
Women	954	36	1.70 (1.22 to 2.38)	1.52 (1.08 to 2.12)	694	23	1.51 (1.00 to 2.30)		
CHD deaths									
All	1213	85	1.54 (1.23 to 1.93)	1.38 (1.10 to 1.73)	808	47	1.35 (1.00 to 1.82)		
Men	686	62	1.41 (1.08 to 1.83)	1.26 (1.00 to 1.64)	439	32	1.16 (0.81 to 1.67)		
Women	527	23	1.92 (1.26 to 2.92)	1.71 (1.12 to 2.60)	369	15	1.81 (1.07 to 3.05)		
Fatal stroke									
All	526	26	1.28 (0.86 to 1.90)	1.12 (0.75 to 1.67)	384	15	1.06 (0.63 to 1.78)		
Men	245	16	1.06 (0.64 to 1.77)	0.93 (0.55 to 1.54)	177	9	0.85 (0.43 to 1.68)		
Women	281	10	1.71 (0.90 to 3.23)	1.52 (0.80 to 2.86)	207	6	1.45 (0.64 to 3.29)		
Fatal kidney disease									
All	98	23	7.21 (4.48 to 11.60)	5.81 (3.61 to 9.37)	73	12	4.35 (2.29 to 8.24)		
Men	32	9	4.45 (2.08 to 9.53)	3.89 (1.80 to 8.40)	24	7	4.76 (1.96 to 11.58)		
Women	66	14	10.02 (5.55 to 18.11)	7.72 (4.27 to 13.95)	49	5	3.78 (1.48 to 9.66)		

All risk estimates are relative to those without a history of gout.

* Model 1, adjusted for age at follow-up 1, years between baseline and follow-up 1, body mass index group (<20, 20–<24, 24–<28, 28+), gender, dialect group (Hokkien, Cantonese), education (non-formal education, primary school, secondary school or higher), alcohol drinking (none/monthly, weekly, daily), moderate physical activity (no, 0.5–3 h/week, 4+ h/week), cigarette smoking (never, former, current), dietary saturated fat density (g/day, quartiles), dietary cholesterol density (mg/day, quartiles).

† Model 2, further adjusted for physician-diagnosed hypertension and diabetes mellitus reported at baseline or follow-up 1 interview.

‡ Model 3 only includes subjects without a history of stroke or coronary heart disease (CHD) reported at baseline or follow-up 1 interview.

Table 3

Risk of all-cause and cause-specific mortality according to the duration of physician-diagnosed gout at follow-up I interview, the Singapore Chinese Health Study (1999–2009)

		HR (95% CI)	
	Cases	Model 1[*]	Model 2[†]
Deaths from all causes			
No gout	6329	1.00	1.00
0–9 Years of gout	226	1.19 (1.04 to 1.36)	1.17 (1.02 to 1.34)
10+ Years of gout	105	1.33 (1.10 to 1.62)	1.22 (1.00 to 1.48)
p Value for trend		0.0001	0.004
All cardiovascular deaths			
No gout	2064	1.00	1.00
0–9 Years of gout	89	1.41 (1.14 to 1.74)	1.28 (1.04 to 1.59)
10+ Years of gout	45	1.70 (1.26 to 2.29)	1.41 (1.05 to 1.90)
p Value for trend		<0.0001	0.002
CHD deaths			
No gout	1213	1.00	1.00
0–9 Years of gout	58	1.50 (1.15 to 1.96)	1.40 (1.07 to 1.82)
10+ Years of gout	27	1.64 (1.12 to 2.41)	1.34 (0.91 to 1.97)
p Value for trend		0.0002	0.010

^{*} Model 1, adjusted for age at follow-up I, years between baseline and follow-up I, body mass index group (<20, 20–<24, 24–<28, 28+), gender, dialect group (Hokkien, Cantonese), education (non-formal education, primary school, secondary school or higher), alcohol drinking (none/monthly, weekly, daily), moderate physical activity (none, 0.5–3 h/week, 4+ h/week), cigarette smoking (never, former, current), dietary saturated fat density (g/day, quartiles), dietary cholesterol density (mg/day, quartiles).

[†] Model 2, further adjusted for physician-diagnosed hypertension and diabetes mellitus reported at baseline or follow-up I interview.