Associations of dietary magnesium intake with mortality from cardiovascular disease: The JACC study

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ABSTRACT

The authors sought to investigate the relationship between dietary magnesium intake and mortality from cardiovascular disease in a population-based sample of Asian adults. Reported findings are based on dietary magnesium intake in 58,615 healthy Japanese aged 40–79 years, in the Japan Collaborative Cohort (JACC) Study. Dietary magnesium intake was assessed by a validated food frequency questionnaire administered between 1988 and 1990. During the median 14.7-year follow-up, we documented 2690 deaths from cardiovascular disease, comprising 1227 deaths from strokes and 557 deaths from coronary heart disease. Dietary magnesium intake was inversely associated with mortality from hemorrhagic stroke in men and with mortality from total and ischemic strokes, coronary heart disease, heart failure and total cardiovascular disease in women. The multivariable hazard ratio (95% CI) for the highest vs. the lowest quintiles of magnesium intake after adjustment for cardiovascular risk factor and sodium intake was 0.49 (0.26–0.95), P for trend = 0.074 for hemorrhagic stroke in men, 0.68 (0.48–0.96), P for trend = 0.010 for total stroke, 0.47 (0.29–0.77), P for trend < 0.001 for ischemic stroke, 0.50 (0.30–0.84), P for trend = 0.005 for coronary heart disease, 0.50 (0.28–0.87), P for trend = 0.002 for heart failure and 0.64 (0.51–0.80), P for trend < 0.001 for total cardiovascular disease in women. The adjustment for calcium and potassium intakes attenuated these associations. In conclusion, dietary magnesium intake was associated with reduced mortality from cardiovascular disease in Japanese, especially for women.

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1. Introduction

Magnesium is an essential trace element in the human body and is also hypothesized as a protective factor against cardiovascular disease [1]. A number of controlled clinical trials have examined the efficacy of magnesium in the secondary prevention of cardiovascular disease, but have yielded mixed results [2].

Magnesium intake has been associated with reduction of blood pressure levels [3], serum triglyceride levels [4] and lowered risk of diabetes mellitus [5] and of arrhythmia and in heart failure patients [6]. Two large-scale prospective studies of American women showed inverse associations between dietary magnesium intake and risks of total and ischemic strokes [7,8]. A more recent review indicated modestly reduced risk of coronary heart disease in women [9]. Therefore, we hypothesized inverse associations

between dietary magnesium intake and mortality from stroke, coronary heart disease and heart failure.

There is, however, limited evidence on the relationship between magnesium intake and the incidence of or mortality from cardiovascular disease. The aim of this study was to investigate the association between dietary magnesium and risk of mortality from cardiovascular disease, using the data from a large prospective study of Japanese men and women.

2. Methods

2.1. Study population

The Japan Collaborative Cohort (JACC) Study for the Evaluation of Cancer Risk, as sponsored by the Ministry of Education, Sports and Science, was conducted from 1988 to 1990. The population-based sample included 110,792 subjects (46,465 men and 64,327 women) from 45 communities. All subjects had been asked to complete self-administered questionnaires pertaining to lifestyle behaviors and cardiovascular risk factors such as hypertension, diabetes, stroke, myocardial infarction, and cancer. The sampling methods and protocols of the JACC study have been described in

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detail previously [10]. Subjects were excluded if they reported a history of stroke, coronary heart disease or cancer ($n = 5689$) at baseline, or if they were unable to provide data for the food frequency questionnaire ($n = 46{,}198$). Data from the remaining 58,615 subjects (23,083 men and 35,532 women) were subsequently used for the analysis. There was some difference in baseline characteristics between individuals who responded to food frequency questionnaire and those who did not, such as mean age (56.5 vs. 59.3 years old), college or higher education (12.6% vs. 5.7%) and higher perceived mental stress (20.7% vs. 7.7%).

In most communities, informed consent was obtained from each participant, except in a few study areas where informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders. The present study was approved by the institutional review board of Nagoya University, the University of Tsukuba and Osaka University.

2.2. Assessment of magnesium intake

Dietary magnesium intake was assessed by a baseline self-administered food frequency questionnaire, which included 33 food items. Participants were asked to estimate average consumption of certain foods over the previous years. Five frequency responses ranging from 'rarely' '1–2 days per month' '1–2 days per week' '3–4 days per week' to 'almost every day' were provided. Magnesium content per 100 g of each food from the fifth revised Japan Food Tables [11], and the portion size for each food was estimated by a previous validation study [11]. The intake of magnesium was calculated from the participants' frequency scores of consumption of each food 0, 0.38, 1.5, 3.5 and 7 per week. We did not have sufficient data to determine supplemental magnesium intake and water magnesium intake. In addition to magnesium, each nutrient was adjusted for total energy using the residual method.

To test the validity of this food frequency questionnaire as a measure of long-term average dietary intakes, four 3-day dietary records were collected over a one-year period ($n = 85$). The dietary records showed the average dietary magnesium intake was 301 mg/day, which was greater than the data of food frequency questionnaire (220 mg/day). Pearson's correlation coefficient between magnesium intake estimated by the food frequency questionnaire and the four 3-day dietary records was 0.34 after individual energy adjustment. Mean values ±standard deviations of magnesium intake estimated by 3-day dietary records were 302 ± 78.5 mg/day in spring, 300 ± 76.9 mg/day in summer, 304 ± 80.8 mg/day in autumn and 300 ± 87.3 mg/day in winter, indicating no seasonal variation. The supplement of magnesium was uncommon, and water magnesium intake composed of 2% of total magnesium intake in Japan [12]. To test reproducibility, two questionnaires were conducted in one year apart for 85 participants; Spearman correlation coefficients were 0.79. Major food sources of magnesium intake in Japanese persons were cereals, vegetables, soybeans and fishes, all of which were covered with dietary questionnaire of the current study [13].

2.3. Mortality surveillance

Investigators conducted a systematic review of death certificates as part of the mortality surveillance in each community. Death certificates were forwarded to the department of public health for each respective area, and mortality data were reported to the Ministry of Health and Welfare. We coded causes of death using the International Classification of Disease, 9th Revision from 1988 to 1994, and the 10th Revision from 1995 to 2003 for the National Vital Statistics where the comparability is diagnosis of cardiovascular disease between the two classifications was confirmed. The

consistency between ICD9 and ICD10 in terms of cardiovascular disease was investigated previously. When the Ministry of Health reclassified 1994 deaths coded by ICD9 using ICD10 rules, stroke increased by 13%, heart failure decreased by 1.6% and myocardial infarction decreased by 8.9% [14,15]. In Japan, registration of death is required by Family Registration Law and is assumed to be adhered to across Japan. Therefore, all deaths that occurred in the cohort were ascertained by means of a death certificate from a public health center, except for subjects who died after moving away from their original community, in which they were treated as censored cases. The subjects who moved out of the original communities were also treated as censored cases ($n = 2956$). The follow-up period was conducted until the end of 2006, except for four areas where follow-up was terminated in 1999, and four areas where follow-up was similarly terminated in 2003. The median follow-up period for participants was 14.7 years.

The primary end points for this analysis were death from cardiovascular disease (CVD) (International Classification of Disease, 9th revision, codes 390-459, and 10th revision, codes 101-199), including stroke (codes 430-438 and I50-I69), which was further subdivided into hemorrhagic stroke (430-431 and I60-I61) and ischemic stroke (433-434 and I63), coronary heart disease (CHD, 410-414 and I20-I25) and heart failure (428 and I50).

2.4. Data analysis

Data analysis was based on age-adjusted mortality rates of CVD during the follow-up period from 1989 to 2006 (up to 1999 in four areas and up to 2003 in four other areas). Years of follow-up were determined as the period from submission of the initial baseline questionnaire to death, termination of follow-up, or until moving out of the original community. Participants were divided into quintiles according to their estimated dietary intake of magnesium.

Age-adjusted mean values and proportions of selected CVD risk factors are presented based on these quintiles. We used Cox proportional-hazards models to estimate age-adjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CIs). We also tested for trends across the quintiles by assigning median values to each quintile. The confounding variables used for adjustment included body mass index (BMI, sex-specific quintiles), smoking status (never, ex-smoker and current smokers of 1–19, and ≥ 20 cigarettes per day), ethanol intake (never, ex-drinker, and current drinker 1–22, 23–45, 46–69 or ≥ 69 g per day), history of hypertension (yes or no), history of diabetes mellitus (yes or no), sports participation time (never, 1–2 h, 3–4 h or ≥ 5 h per day), walking time (never, about 30 min, 30–60 min and ≥ 60 min per day), educational status (educated until 12, 13–15, 16–18 or ≥ 19 years old), perceived mental stress (low, median, and high), menopausal status (yes or no), and hormone-replacement therapy (yes or no). We also utilized another multivariable model adjusted for dietary intake of sodium, calcium, and potassium to investigate the independent contribution of dietary magnesium to CVD mortality.

All statistical analyses for two-tailed tests were conducted using SAS version 9.13 (SAS Institute Inc., Cary). *P* values less than 0.05 were regarded as statistically significant.

3. Results

Table 1 shows the age-adjusted mean values and prevalence of cardiovascular risk factors at baseline according to quintiles of dietary magnesium intake. Dietary intakes of calcium, sodium and potassium were greater with increasing dietary magnesium intake. Compared with men and women in the lowest quintile of dietary magnesium intake, those in the higher quintiles were older, had

Table 1
Baseline characteristics according to quintiles of dietary magnesium intake.

	Quintile of magnesium intake					P for trend
	1 (low)	2	3	4	5 (high)	
Men						
No. of subjects	4616	4617	4617	4617	4616	
Median magnesium intake (mg/day)	173.0	206.8	231.5	256.6	293.7	
Mean age (SD) (years)	53.9 (9.6)	54.9 (9.6)	55.9 (9.5)	56.6 (10)	58.4 (10)	<0.001
Mean body mass index (kg/m^2)	22.7 (2.7)	22.7 (2.7)	22.7 (2.6)	22.6 (2.7)	22.7 (2.8)	0.496
Mean energy intake (SD) (kcal/day)	1701 (490)	1763 (482)	1798 (493)	1784 (500)	1667 (485)	<0.001
Mean calcium intake (SD) (mg/day)	333 (107)	439 (99)	508 (102)	574 (104)	684 (120)	<0.001
Mean sodium intake (SD) (mg/day)	1376 (476)	1895 (508)	2231 (528)	2539 (552)	3048 (671)	<0.001
Mean potassium intake (SD) (mg/day)	1591 (294)	2033 (220)	2332 (224)	2641 (243)	3168 (376)	<0.001
Mean total dietary fiber intake (SD) (mg/day)	6.8 (2.2)	9.0 (2.4)	10.5 (2.8)	11.9 (3.1)	13.4 (3.6)	<0.001
Current smokers (%)	57.5	53.8	51.8	50.9	47.0	<0.001
Mean alcohol intake (g/day of ethanol)	37.2	29.9	26.2	21.1	13.0	<0.001
History of hypertension (%)	19.8	19.4	20.0	18.3	17.5	0.007
History of diabetes mellitus (%)	6.2	5.4	6.0	6.0	7.1	0.023
Sports time ≥3 h/week (%)	28.4	30.3	31.8	36.2	38.1	<0.001
Walking time ≥30 min/day (%)	48.9	48.8	44.7	46.6	47.5	<0.001
College or higher education (%)	14.9	15.2	16.8	17.8	19.9	<0.001
High perveived mental stress (%)	24.2	23.2	22.2	22.7	21.1	<0.001
Women						
No. of subjects	7106	7107	7107	7107	7106	
Median magnesium intake (mg/day)	174.5	205.2	225.6	245.4	273.8	
Mean age (SD) (years)	55.7 (10.1)	55.5 (9.8)	55.8 (9.8)	56.8 (9.7)	57.6 (9.7)	<0.001
Mean body mass index (kg/m^2)	22.9 (3.1)	22.9 (3.0)	22.9 (3.0)	22.9 (3.0)	22.9 (3.0)	0.760
Mean energy intake (SD) (kcal/day)	1418 (409)	1446 (370)	1451 (346)	1468 (331)	1404 (360)	<0.001
Mean calcium intake (SD) (mg/day)	353 (111)	458 (100)	519 (101)	575 (100)	659 (114)	<0.001
Mean sodium intake (SD) (mg/day)	1338 (435)	1807 (466)	2057 (481)	2290 (494)	2697 (604)	<0.001
Mean potassium intake (SD) (mg/day)	1707 (290)	2134 (215)	2395 (209)	2647 (215)	3063 (318)	<0.001
Mean total dietary fiber intake (SD) (mg/day)	7.6 (2.3)	9.5 (2.4)	10.7 (2.6)	12.0 (2.7)	13.3 (3.2)	<0.001
Current smokers (%)	5.9	4.4	3.9	3.7	4.2	<0.001
Mean alcohol intake (g/day of ethanol)	3.0	1.7	1.2	1.1	0.8	<0.001
History of hypertension (%)	20.9	21.0	20.0	20.5	20.2	0.500
History of diabetes mellitus (%)	3.4	3.1	3.2	3.4	4.1	0.014
Sports time ≥3 h/week (%)	20.7	24.2	25.8	28.3	30.8	<0.001
Walking time ≥30 min/day (%)	47.0	45.2	44.8	43.2	45.1	<0.001
College or higher education (%)	7.6	8.8	9.8	10.7	11.8	<0.001
High perceived mental stress (%)	20.3	19.6	19.9	18.4	18.3	<0.001
Menopause (%)	60.7	61.7	62.8	67.0	67.9	<0.001
Hormone-replacement therapy (%)	4.3	4.1	4.2	4.7	4.8	<0.001

SD, standard deviation.

less current smokers, less alcohol intake, higher education, higher sport activity and less perceived mental stress. Magnesium intake was positively associated with history of diabetes mellitus for both sexes. Women in the higher quintiles of magnesium intake were more likely to have menopause and hormone replacement therapy.

As shown in Table 2, greater dietary magnesium intake was associated with lower age-adjusted risks of mortality from hemorrhagic stroke in men, and from total and ischemic strokes, coronary heart disease, heart failure and total cardiovascular disease in women. After further adjustment for known cardiovascular risk factors, these associations remained statistically significant for hemorrhagic strokes in men, and heart failure and total cardiovascular disease in women. The respective multivariable hazard ratios (95%) were for the highest vs. lowest quintiles of magnesium intake were 0.59 (0.35–0.99), P for trend = 0.03 in men, 0.69 (0.43–0.99), P for trend = 0.02, and 0.82 (0.69–0.97), P for trend = 0.01 in women.

Table 3 shows the results after further adjustment for dietary sodium, calcium and potassium intake. The inverse association between dietary magnesium intake and mortality from hemorrhagic stroke in men remained unchanged after adjustments for dietary sodium intake, with the multivariable hazard ratio (95%) being 0.49 (0.26–0.95), P for trend = 0.074. However, when adjusted for dietary potassium and calcium intake, the inverse association was lost. The adjustment for dietary sodium intake in women

strengthened the inverse association between dietary magnesium intake and mortality from total and ischemic stroke, coronary heart disease, heart failure and total cardiovascular disease, the corresponding multivariable hazard ratios were 0.68 (0.48–0.96), P for trend = 0.010, 0.47 (0.29–0.77), P for trend < 0.001, 0.50 (0.30–0.84), P for trend = 0.005, 0.50 (0.28–0.87), P for trend = 0.002, 0.64 (0.51–0.80), P for trend < 0.001. When adjusted for dietary calcium, these inverse associations were weakened but the associations with mortality from coronary heart disease, heart failure and total cardiovascular disease remained borderline significant. However, the further adjustment for potassium intake attenuated these inverse associations.

We investigated the joint impact of magnesium and calcium intakes by examining hazards ratios of mortality according to the combination of the lower and higher (≥median) of magnesium and calcium intakes with reference of the lower intakes in both cations. The multivariable hazard ratios of mortality from coronary heart disease were 0.74 (0.55–1.00) for women with the higher magnesium intake and calcium intake, 0.76 (0.52–1.11) for women with the higher magnesium and lower calcium intakes, 0.83 (0.54–1.27) for women with the lower magnesium and higher calcium intakes, compared with those with the lower intakes in both cations. The corresponding hazard ratio (95% CI) of mortality for heart failure were 0.74 (0.55–0.99), 0.74 (0.51–1.09) and 0.85 (0.56–1.30). Those of mortality from total cardiovascular disease were 0.82 (0.72–0.93), 0.90 (0.77–1.06) and 0.91 (0.76–1.09).

Table 2
Sex-specific hazard ratios (95% CI) of mortality from stroke, coronary heart disease, heart failure and total cardiovascular disease according to quintiles of dietary magnesium intake.

	Quintiles of dietary magnesium intake					
	1 (low)	2	3	4	5 (high)	P value
Men						
Number of subjects	4616	4617	4617	4617	4616	
Person year	65,763	66,430	67,256	67,409	65,663	
Total stroke						
n	103	92	124	130	158	
Age-adjusted HR	1.00	0.75 (0.57–0.99)	0.88 (0.68–1.15)	0.83 (0.64–1.08)	0.84 (0.65–1.08)	0.408
Multivariable HR[a]	1.00	0.79 (0.60–1.05)	0.96 (0.74–1.25)	0.94 (0.72–1.23)	1.03 (0.79–1.35)	0.435
Hemorrhagic stroke						
n	45	31	40	39	41	
Age-adjusted HR	1.00	1.01 (0.63–1.62)	0.64 (0.41–0.98)	0.70 (0.45–1.10)	0.67 (0.44–1.04)	0.042
Multivariable HR[a]	1.00	1.16 (0.66–2.04)	0.54 (0.33–0.88)	0.66 (0.40–1.08)	0.59 (0.35–0.99)	0.026
Ischemic stroke						
n	46	54	69	80	106	
Age-adjusted HR	1.00	0.94 (0.64–1.40)	1.03 (0.71–1.49)	1.04 (0.72–1.49)	1.08 (0.76–1.53)	0.498
Multivariable HR[a]	1.00	1.00 (0.68–1.49)	1.10 (0.75–1.60)	1.14 (0.78–1.65)	1.30 (0.90–1.88)	0.097
Coronary heart disease						
n	55	56	55	69	76	
Age-adjusted HR	1.00	0.87 (0.60–1.26)	0.76 (0.52–1.10)	0.87 (0.61–1.25)	0.83 (0.58–1.18)	0.405
Multivariable HR[a]	1.00	0.86 (0.59–1.26)	0.76 (0.52–1.11)	0.88 (0.61–1.27)	0.81 (0.56–1.18)	0.391
Heart failure						
n	29	32	36	45	44	
Age-adjusted HR	1.00	0.94 (0.57–1.55)	0.93 (0.57–1.52)	1.03 (0.65–1.65)	0.83 (0.51–1.33)	0.751
Multivariable HR[a]	1.00	0.96 (0.58–1.60)	1.00 (0.61–1.64)	1.12 (0.69–1.82)	0.88 (0.53–1.46)	0.371
Total cardiovascular disease						
n	215	222	264	293	349	
Age-adjusted HR	1.00	0.87 (0.72–1.05)	0.91 (0.76–1.09)	0.91 (0.76–1.09)	0.91 (0.76–1.08)	0.495
Multivariable HR[a]	1.00	0.90 (0.75–1.09)	0.96 (0.80–1.15)	0.98 (0.82–1.18)	1.02 (0.85–1.22)	0.514
Women						
Number of subjects	7106	7107	7106	7107	7106	
Person year	102,148	104,440	105,824	106,951	107,615	
Total stroke						
n	113	133	105	143	126	
Age-adjusted HR	1.00	1.20 (0.93–1.54)	0.87 (0.57–1.14)	1.06 (0.83–1.35)	0.83 (0.64–1.07)	0.079
Multivariable HR[a]	1.00	1.24 (0.96–1.59)	0.93 (0.71–1.21)	1.12 (0.87–1.44)	0.90 (0.69–1.16)	0.273
Hemorrhagic stroke						
n	47	55	47	56	58	
Age-adjusted HR	1.00	1.09 (0.74–1.62)	1.14 (0.75–1.71)	1.07 (0.72–1.59)	1.20 (0.81–1.77)	0.438
Multivariable HR[a]	1.00	1.12 (0.71–1.77)	1.39 (0.87–2.20)	1.22 (0.78–1.91)	1.22 (0.79–1.88)	0.345
Ischemic stroke						
n	55	65	48	69	59	
Age-adjusted HR	1.00	1.25 (0.88–1.80)	0.84 (0.57–1.23)	1.04 (0.73–1.48)	0.77 (0.54–1.12)	0.090
Multivariable HR[a]	1.00	1.32 (0.92–1.89)	0.89 (0.60–1.31)	1.10 (0.77–1.57)	0.84 (0.58–1.22)	0.205
Coronary heart disease						
n	63	48	36	41	58	
Age-adjusted HR	1.00	0.78 (0.54–1.14)	0.54 (0.36–0.81)	0.54 (0.36–0.80)	0.67 (0.47–0.96)	0.008
Multivariable HR[a]	1.00	0.85 (0.58–1.24)	0.59 (0.39–0.90)	0.60 (0.40–0.89)	0.77 (0.53–1.11)	0.058
Heart failure						
n	49	51	53	49	43	
Age-adjusted HR	1.00	1.09 (0.73–1.61)	1.02 (0.69–1.51)	0.82 (0.55–1.22)	0.63 (0.42–0.96)	0.011
Multivariable HR[a]	1.00	1.14 (0.77–1.69)	1.07 (0.72–1.58)	0.84 (0.57–1.26)	0.69 (0.43–0.99)	0.017
Total cardiovascular disease						
n	271	269	242	283	282	
Age-adjusted HR	1.00	1.02 (0.86–1.20)	0.84 (0.70–0.99)	0.86 (0.73–1.02)	0.76 (0.64–0.90)	<0.001
Multivariable HR[a]	1.00	1.05 (0.88–1.24)	0.88 (0.74–1.05)	0.91 (0.77–1.07)	0.82 (0.69–0.97)	0.006

[a] Adjusted further for body mass index, smoking status, ethanol intake, history of hypertension, history of diabetes mellitus, sports time, walking time, educational status and perceived mental stress, and for women, menopausal status and hormone replacement therapy.

4. Discussion

In this large prospective cohort study with a median follow-up of 14.7 years, we found that dietary magnesium intake was associated with lower risk of mortality from hemorrhagic stroke in men, and reduced mortality from coronary heart disease, heart failure and total cardiovascular disease in women.

Previous cohort studies have examined the relationship between dietary magnesium intake or serum magnesium with the incidence of and mortality from stroke [7,8,16–20]. The Nurses' Health study, a 14-year follow-up of 121,700 registered female nurses showed a hazard ratio of incident total stroke of 0.80 (95% CI,

0.63–1.01) for the highest vs. lowest quintiles of magnesium intake after adjusting for age and smoking status [8]. In that study, the hazard ratio (95% CI) of ischemic stroke was 0.74 (0.54–1.02), but weakened to 0.84 (0.60–1.19) after further adjustment for cardiovascular risk factors. Similarly, the ARIC Study, a prospective study of 13,560 American men and women aged 45–64 years reported an inverse association between serum magnesium levels and the risk of ischemic stroke. The age-, sex-, and race-adjusted hazard ratios (95% CI) of ischemic stroke for those with serum magnesium levels of, 1.6, 1.7, and ≥ 1.8 mEq/L compared with ≤ 1.5 mEq/L were 0.78 (0.62–0.96), 0.70 (0.56–0.88), and 0.75 (0.59–0.95), P for trend = 0.005 [16]. After adjusting for hypertension and diabetes,

Table 3
Hazard ratios (95% CI) of mortality from stroke, coronary heart disease, heart failure and total cardiovascular disease according to quintiles of dietary magnesium intake.

	Quintiles of dietary magnesium intake					
	1 (low)	2	3	4	5 (high)	P value
Men						
Hemorrhagic stroke						
Multivariable HR[a]	1.00	1.16 (0.66–2.04)	0.54 (0.33–0.88)	0.66 (0.40–1.08)	0.59 (0.35–0.99)	0.026
Multivariable HR[b]	1.00	0.56 (0.34–0.93)	0.62 (0.36–1.06)	0.54 (0.30–0.96)	0.49 (0.26–0.95)	0.074
Multivariable HR[c]	1.00	0.77 (0.47–1.26)	1.13 (0.66–1.95)	1.20 (0.67–2.15)	1.54 (0.81–2.93)	0.112
Multivariable HR[d]	1.00	0.70 (0.39–1.24)	1.03 (0.52–2.04)	1.34 (0.61–2.95)	1.76 (0.69–4.52)	0.190
Women						
Total stroke						
Multivariable HR[a]	1.00	1.24 (0.96–1.59)	0.93 (0.71–1.21)	1.12 (0.87–1.44)	0.90 (0.69–1.16)	0.273
Multivariable HR[b]	1.00	1.12 (0.85–1.48)	0.79 (0.58–1.08)	0.91 (0.67–1.24)	0.68 (0.48–0.96)	0.009
Multivariable HR[c]	1.00	1.27 (0.98–1.66)	0.98 (0.73–1.32)	1.22 (0.90–1.65)	1.03 (0.74–1.44)	0.952
Multivariable HR[d]	1.00	1.51 (1.12–2.04)	1.27 (0.87–1.85)	1.85 (1.22–2.80)	1.81 (1.12–2.94)	0.015
Ischemic stroke						
Multivariable HR[a]	1.00	1.32 (0.92–1.89)	0.89 (0.60–1.31)	1.10 (0.77–1.57)	0.84 (0.58–1.22)	0.205
Multivariable HR[b]	1.00	1.01 (0.68–1.52)	0.61 (0.39–0.97)	0.71 (0.46–1.11)	0.47 (0.29–0.77)	<0.001
Multivariable HR[c]	1.00	1.45 (0.99–2.11)	1.06 (0.69–1.63)	1.37 (0.88–2.14)	1.04 (0.64–1.70)	0.924
Multivariable HR[d]	1.00	1.68 (1.09–2.57)	1.29 (0.75–2.21)	1.94 (1.07–3.52)	1.83 (0.92–3.67)	0.081
Coronary heart disease						
Multivariable HR[a]	1.00	0.85 (0.58–1.24)	0.59 (0.39–0.90)	0.60 (0.40–0.89)	0.77 (0.53–1.11)	0.058
Multivariable HR[b]	1.00	0.73 (0.48–1.10)	0.47 (0.29–0.76)	0.45 (0.27–0.73)	0.50 (0.30–0.84)	0.005
Multivariable HR[c]	1.00	0.79 (0.53–1.17)	0.53 (0.34–0.84)	0.53 (0.33–0.85)	0.71 (0.44–1.15)	0.089
Multivariable HR[d]	1.00	1.20 (0.76–1.88)	0.97 (0.52–1.78)	0.98 (0.49–1.97)	1.52 (0.70–3.27)	0.267
Heart failure						
Multivariable HR[a]	1.00	1.14 (0.77–1.69)	1.07 (0.72–1.58)	0.84 (0.57–1.26)	0.69 (0.43–0.99)	0.017
Multivariable HR[b]	1.00	1.19 (0.76–1.85)	1.03 (0.64–1.66)	0.75 (0.45–1.25)	0.50 (0.28–0.87)	0.002
Multivariable HR[c]	1.00	1.11 (0.73–1.67)	1.02 (0.66–1.59)	0.81 (0.50–1.30)	0.65 (0.39–1.10)	0.063
Multivariable HR[d]	1.00	1.20 (0.74–1.95)	1.21 (0.68–2.15)	1.06 (0.54–2.05)	0.80 (0.36–1.76)	0.632
Total cardiovascular disease						
Multivariable HR[a]	1.00	1.05 (0.88–1.24)	0.88 (0.74–1.05)	0.91 (0.77–1.07)	0.82 (0.69–9.97)	0.006
Multivariable HR[b]	1.00	0.99 (0.82–1.19)	0.79 (0.64–0.97)	0.78 (0.63–0.96)	0.64 (0.51–0.80)	<0.001
Multivariable HR[c]	1.00	1.04 (0.87–1.24)	0.87 (0.72–1.06)	0.90 (0.74–1.11)	0.83 (0.66–1.03)	0.052
Multivariable HR[d]	1.00	1.25 (1.02–1.53)	1.16 (0.90–1.49)	1.31 (0.98–1.74)	1.26 (0.90–1.75)	0.178

[a] Adjusted further for body mass index, smoking status, ethanol intake, history of hypertension, history of diabetes mellitus, sports time, walking time, educational status and perceived mental stress, and for women, menopausal status and hormone replacement therapy.
[b] Adjusted for factors cited above and for dietary sodium intake.
[c] Adjusted for factors cited above and for dietary calcium intake.
[d] Adjusted for factors cited above and for dietary potassium intake.

however, the hazard ratios were attenuated to the non-significant level for that study. Dietary magnesium intake was marginally inversely associated with the risk of ischemic stroke [16]. The Women's Health Study, a 10-year follow-up of 39,876 female health professionals obtained a similar non-significant result, showing a relative risk of total stroke of 0.90 (95% CI, 0.65–2.00) for the highest vs. lowest quintiles of total (diet plus supplement) magnesium intake, while the corresponding hazard ratio (95% CI) for total stroke was 1.07 (0.49–2.31) for total stroke and 0.83 (0.57–1.21) for ischemic stroke [7]. Three other prospective studies of Americans, Taiwanese and Swedish also showed non-significant inverse associations between dietary magnesium intake and risk of total or ischemic strokes [17–19], whereas a prospective study of Finish male smokers reported that total (diet plus supplement) magnesium intake was inversely associated with risk of ischemic stroke [20].

The relationship between dietary magnesium intake and the risk of hemorrhagic stroke was examined in either the Nurses' Health Study [7] or the Women's Health Study [8]. They showed no significant associations between total magnesium (dietary plus supplement) intake and risk of hemorrhagic stroke. A prospective study of Finish male smokers also showed no association between magnesium intake and risk of intracerebral or subarachnoid hemorrhagic [20]. The present study demonstrated an inverse association between dietary magnesium intake and mortality from hemorrhagic stroke in men but not in women (Table 4).

The Honolulu Heart Study of 7172 male Japanese living in Hawaii showed an inverse association between dietary magnesium intake and risk of coronary heart disease

in the first 15 years of follow-up [22]. The Health Professionals Follow-up Study also showed an inverse but non-significant association between dietary magnesium intake and risk of coronary heart disease [22]. The present study similarly showed the non-significant but inverse association between dietary magnesium intake and mortality from coronary heart disease in both sexes.

The present study also observed reduced risk of mortality from congestive heart failure associated with dietary magnesium intake in women. The possible mechanism behind this has not been well studied, nor have there been any population-based studies to confirm this association. Our findings are consistent with results from a recent randomized controlled trial [23], in which patients with severe congestive heart failure who received 1-year supplementation with magnesium orotate (6000 mg for 1 month, 3000 mg for about 11 months) had a better survival rate (75.7%; compared with the placebo group (51.6%; P for trend = 0.05) [23].

Many of the associations found in this study (mortality from hemorrhagic stroke, heart failure and total cardiovascular disease) were attenuated or lost after adjusting for calcium and potassium intakes. This may be explained by the high correlations between dietary magnesium and calcium ($r = 0.78$ in men and 0.74 in women), and potassium ($r = 0.91$ in men and 0.93 in women). The major food sources for magnesium are milk and dairy products, rice, vegetables, meat, fish and rice in Japanese diets [13]. Milk and dairy products, vegetables and fish intakes have been inversely associated with the incidence of or mortality from cardiovascular disease in Japanese populations [24–27]. It was difficult to determine whether the cardioprotective effects observed in this

Table 4
Summary of associations between magnesium intake and cardiovascular disease in previous studies.

Source, cohort study, country	Cohort size, sex and age	Follow-up years	The highest vs. lowest categories of magnesium intake (mg/day)	Variables controlled	No. of outcomes	Hazard ratios (95% CIs)
Ascherio et al. [17], Health Professional Follow-up Study, USA	43,738 men aged 40–75	8.0	452 vs. 243 (median)	Age, smoking, profession, histories of hypertension and hypercholesterolemia, family history of MI, BMI, physical activity, and intakes of alcohol, dietary fiber, potassium and total energy	328 TS	0.92 (0.58–1.46)
Iso et al. [8], The Nurses' Health Study, USA	85,764 women aged 34–59	14.0	381 vs. 211 (median)	Age, smoking	690 TS 203 HS 386 IS	0.80 (0.63–1.01) 0.82 (0.53–1.26) 0.74 (0.54–1.02)
				Age, smoking, BMI, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, ω-3 fatty acid intake, histories of diabetes and hypercholesterolaemia	386 IS	0.84 (0.60–1.19)
Larsson et al. [20], Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland	26,556 smoking men aged 50–69	13.6	575 vs. 382 (median)	Age, supplementation group, smoking, BMI, physical activity, systolic and diastolic BP, serum total and HDL cholesterol, histories of diabetes and coronary heart disease and intakes of alcohol and total energy	2702 IS	0.85 (0.76–0.97)
Weng et al. [18], Cardiovascular Disease risk Factor Two-township Study, Taiwan	1772 men and women aged ≥40	10.6	>282.2 vs. <242.6	Age, sex, smoking, area, central obesity, BMI, diabetes mellitus, physical activity, hypertension, use of antihypertensive drug, self-report heart disease, hypercholesterolemia, hypertriglyceridemia, fibrinogen, apolipoprotein B, plasminogen and alcohol intake	132 IS	0.68 (0.45–1.04)
Ohira et al. [16], Atherosclerosis Risk in Communities Study, USA	13,560 men and women aged 45–64	15.0	>367 vs. <186	Age, sex, race-field center, smoking status, BMI, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fibrinogen, von Willebrand factor, educational level and energy intake	577 IS	0.80 (0.75–1.13)
Larsson et al. [19], Swedish Manmography Cohort, Sweden	34,670 women aged 49–83	10.4	373 vs. 267 (median)	Age, education, smoking, BMI, physical activity, history of diabetes, history of hypertension, aspirin use, family history of myocardial infarction, and intakes of alcohol, protein, cholesterol, total fiber, folate and total energy	1680 TS 1310 IS 154 ICH 79 SAH	1.02 (0.82–1.27) 0.98 (0.77–1.26) 1.02 (0.59–1.75) 0.68 (0.33–1.42)

Table 4 (*Continued*)

Source, cohort study, country	Cohort size, sex and age	Follow-up years	The highest vs. lowest categories of magnesium intake (mg/day)	Variables controlled	No. of outcomes	Hazard ratios (95% CIs)
Abbott et al. [21], Honolulu Heart Program, USA	7172 men aged 45-68	30.0	340–1138 vs. 50.3–186	Age, total cholesterol, hypertension, diabetes, BMI, physical activity index, smoking and daily alcohol intake	1431 CHD	0.59 (0.39–0.89)
Al-Delaimy et al. [22], The Health Professional Follow-up Study, USA	39,633 men aged 40–75	12.0	453 vs. 261 (median)	Age, time-period, energy intake, history of diabetes, history of high cholesterol, family history of MI, smoking, aspirin history, BMI, alcohol intake, physical activity and vitamin E intake	1449 CHD	0.86 (0.72–1.92)
Song et al. [7], Women's Health Study, USA	39,875 women aged 39–89	10.0	433 vs. 255 (median)	Age, randomized treatment, BMI, energy intake, smoking, exercise, alcohol, postmenopausal hormone use, multivitamin use, history of diabetes, hypertension, hypercholesterolemia and parents' history of MI at <60 years	368 TS 672 CHD 280 MI 1,037 CVD 120 CVD deaths	0.90 (0.65–1.26) 1.08 (0.84–1.38) 1.48 (1.01–2.18) 1.00 (0.82–1.23) 1.32 (0.71–2.47)
					282 IS 70 HS	0.83 (0.57–1.21) 1.07 (0.49–2.31)
Zhang et al., 2012. The Japan Collaborative Cohort Study, Japan (present study)	58,615 men and women aged 40–79	14.7	294 vs. 173 (median) for men 274 vs. 175 (median) for women	Body mass index, smoking status, ethanol intake, history of hypertension, history of diabetes, sports time, walking time, educational status and perceived mental stress, and for women, menopausal status and hormone replacement therapy	Men 607 TS deaths 196 HS deaths 355 IS deaths 308 CHD deaths 186 HF deaths 1,343 CVD deaths	1.03 (0.79–1.35) 0.59 (0.35–0.99) 1.30 (0.90–1.88) 0.81 (0.56–1.18) 0.88 (0.53–1.46) 1.02 (0.85–1.22)
					Women 620 TS deaths 263 HS deaths 296 IS deaths 246 CHD deaths 245 HF deaths 1,647 CVD deaths	0.90 (0.64–1.16) 1.22 (0.79–1.88) 0.84 (0.58–1.22) 0.77 (0.53–1.11) 0.69 (0.43–0.99) 0.82 (0.69–0.97)

Abbreviations: BMI, body mass index; TS, total stroke; ICH, intracerebral hemorrhagic; IS, ischemic stroke; HS, hemorrhagic stroke; SAH, subarachnoid hemorrhagic; CHD, coronary heart disease; MI, myocardial infarction; CVD, cardiovascular disease.

study were attributed repeatedly to dietary magnesium, calcium or potassium intake [28]. However, in the present study, reduced mortality from coronary heart disease, heart failure and total cardiovascular disease associated with dietary magnesium intake was maintained after dietary calcium intake was taken into account by the statistical adjustment and stratified analyses.

An inverse association between magnesium intake and mortality from cardiovascular disease is biologically plausible. Beneficial effects on cardiovascular outcomes may be explained by its effect in regulating blood pressure [29]. A recent meta-analysis of 20 clinical trials showed that magnesium supplementation led to a small overall reduction in blood pressure in a dose-dependent manner [30]. A double-blind, placebo-controlled study of 47 patients with acute myocardial infarction showed that magnesium supplementation over three months reduced serum triglyceride levels [4], a risk factor for coronary heart disease [13]. A recent meta-analysis showed that magnesium intake was inversely associated with incidence of type 2 diabetes [5]. However, we found a positive association between magnesium intake and history of diabetes mellitus in the present study. Clinical and experimental studies have shown that magnesium can suppress ventricular arrhythmia [31], which was found to increase risk of mortality in heart failure patients [32]. Thus, our finding of the association between magnesium intake and reduced mortality from heart failure is plausible. Magnesium may also reduce risk of cardiovascular disease through other pathways such as the improvement of endothelial function and the inhibition of inflammation and platelet aggregation [31].

The strengths of the present study included its large population-based sample from around Japan, as well as its prospective design. The measurement of exposure variable covariates and outcomes were standardized through the use of a uniform questionnaire and surveillance protocol. However, some limitations warrant consideration. First, approximately 53% of the total participants have responded to the food frequency questionnaire. They were 3 years younger, more educated and had more perceived mental stress compared with those who did not responded. We adjusted these variables to examine the associations between magnesium intake and mortality from cardiovascular disease. Second, stroke subtypes were classified according to ICD codes that may result in misclassification. The widely-used computerized tomography in local hospitals around Japan since the 1980s has made it possible to accurately diagnose and document stroke and its subtypes on a death certificate. A quarter to a half of heart failure deaths may have been sudden deaths of unknown origin or deaths occurring in the final stages of chronic disease. As a result, deaths from heart failure may have been over represented as Japanese physicians may have been inclined to diagnose some of these as 'unspecified heart failure' (I50.9 for ICD-10) [14,32,33]. A similar problem exists for the diagnosis of coronary heart disease because a quarter of this death certificate diagnoses may be contaminated by heart failure or non-heart diseases [32]. Another limitation was that we examined magnesium intake by food frequency questionnaire only. The association between serum and dietary magnesium is weak, and a previous study showed a stronger association between serum magnesium levels and risk of cardiovascular risk compared to dietary magnesium intake [16].

In conclusion, findings from the present prospective study suggest that a high dietary intake of magnesium may be beneficial to reduce risk of cardiovascular mortality in Japanese, especially for women.

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Disclosure

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