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Potassium Intake, Stroke, and Cardiovascular Disease

A Meta-Analysis of Prospective Studies

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Objectives The objective of this study was to assess the relation between the level of habitual potassium intake and the incidence of cardiovascular disease (CVD).

Background Prospective cohort studies have evaluated the relationship between habitual potassium intake and incidence of vascular disease, but their results have not been not entirely consistent.

Methods We performed a systematic search for prospective studies published, without language restrictions (1966 to December 2009). Criteria for inclusion were prospective adult population study, assessment of baseline potassium intake, assessment of vascular events as outcome, and follow-up of at least 4 years. For each study, relative risks (RRs) and 95% confidence intervals (CIs) were extracted and pooled using a random-effect model, weighted for the inverse of the variance. Heterogeneity, publication bias, subgroup, and meta-regression analyses were performed.

Results Eleven studies were identified, providing 15 cohort samples that included 247,510 male and female participants (follow-up 5 to 19 years), 7,066 strokes, 3,058 coronary heart disease (CHD) events, and 2,497 total CVD events. Potassium intake was assessed by 24-h dietary recall (n = 2), food frequency questionnaire (n = 6), or 24-h urinary excretion (n = 3). In the pooled analysis, a 1.64-g (42 mmol) per day higher potassium intake was associated with a 21% lower risk of stroke (RR: 0.79; 95% CI: 0.68 to 0.90; p = 0.0007), with a trend toward lower risk of CHD and total CVD that attained statistical significance after the exclusion of a single cohort, based on sensitivity analysis (RR: 0.93; 95% CI: 0.87 to 0.99; p = 0.03 and RR: 0.74; 95% CI: 0.60 to 0.91; p = 0.0037).

Conclusions Higher dietary potassium intake is associated with lower rates of stroke and might also reduce the risk of CHD and total CVD. These results support recommendations for higher consumption of potassium-rich foods to prevent vascular diseases. (J Am Coll Cardiol 2011;57:1210–9) © 2011 by the American College of Cardiology Foundation

The relationship between dietary potassium intake and blood pressure (BP) has been known for a long time (1). Many cross-sectional and longitudinal prospective studies have detected an inverse relationship between dietary potassium intake and BP (2,3). In the largest available meta-analysis of the randomized controlled trials of potassium supplementation, an increase in potassium intake of at least 20 mmol (0.78 g) per day was associated with significant average reductions of 4.9 mm Hg systolic BP and 2.7 mm Hg diastolic BP in hypertensive patients (4), although no significant effect was apparent in one large trial (5). The effect of potassium on BP was more pronounced in those having an elevated sodium intake and in black compared with white individuals. In a more recent meta-analysis (6), which included only 5 studies featuring a prolonged follow-up (at least 8 weeks), a favorable impact was also detected; however, the difference was not statistically significant after the exclusion of a single outlier study reporting an exceptionally large favorable effect (7).

In a different long-term randomized controlled trial that assessed the effects of increased potassium intake attained by natural foods, patients assigned to the potassium-rich diet achieved and maintained BP control at the end of a 1-year follow-up with less than half the amount of drugs needed by the control group (8).

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Because hypertension is the main cause of cardiovascular morbidity and mortality (9), it is reasonable to expect that higher potassium intake could favorably affect cardiovascular morbidity and mortality rates. Indeed, a high potassium intake dramatically reduces the elevated death rate associated with a high-salt diet in stroke-prone spontaneously hypertensive rats (10) and the extent of renal damage in Dahl salt-sensitive rats (11).

Randomized controlled trials of the effects of long-term increases in dietary potassium intake on morbidity and mortality from cardiovascular disease (CVD) are lacking, and indeed such a trial could hardly be carried out because of technical difficulties and ethical problems. Nevertheless, several prospective cohort studies over 3 decades have explored the possible association between habitual dietary potassium intake and incidence of vascular events. The results of these studies are not entirely consistent possibly because of, in some cases, insufficient statistical power.

The technique of meta-analysis allows the evaluation of the combined results of different studies, thus enhancing the overall statistical power, increasing precision of the estimates of effectiveness, evaluating consistency among studies, and exploring possible publication bias. Therefore, we performed a systematic review and meta-analysis to assess whether or not the overall evidence obtained in prospective studies supports the presence of a relationship between habitual levels of dietary potassium intake and stroke and cardiovascular outcomes and to obtain an estimate of the risk.

Methods

Data sources and searches. We performed a systematic search for publications using Medline (1966 to December 2009), Embase (from 1988), Allied and Complementary Database (from 1985), Cumulative Index to Nursing and Allied Health Literature (from 1982), Psychinfo (from 1985), and the Cochrane Library. The search strategy used the expressions potassium intake AND stroke, cerebrovascular disease, cardiovascular disease, coronary heart disease, cerebrovascular accident, cerebrovascular disorders, cardiovascular accident, cardiovascular disorders, cerebral infarction, cerebral hemorrhage or combinations thereof, either in medical subject headings or in the title/abstract, with no language restrictions. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies (12).

Study selection. Two reviewers (L.D. and G.B.) independently extracted the data. Discrepancies about inclusion of studies and interpretation of data were resolved by arbitration (P.S. or F.P.C.), and consensus was reached after discussion. In the case of missing data for potentially suitable studies, the authors were contacted and asked to provide the necessary information. To be included in the meta-analysis, a published study had to meet the following criteria: 1) original article; 2) prospective design; 3) adult population; 4) assessment of potassium intake as baseline exposure; 5) fatal or nonfatal stroke, CVD, and/or coronary heart disease (CHD) determined prospectively as outcome; 6) indication of the number of participants exposed and the rate or number of events in different categories of potassium intake; 7) assessment of relative risk (RR) or hazard ratio (HR) for different potassium intake categories, and 8) follow-up of at least 4 years (mean or median).

Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CHD = coronary heart disease
CVD = cardiovascular disease

Of a total of 3,271 publications retrieved (Fig. 1), 12 studies were identified that met the inclusion criteria. Because 2 studies referred to the same cohort (NHANES I [National Health and Nutrition Examination Survey I] [13,14]), we included the one that used more stringent inclusion criteria (14), excluding patients with positive history of CVD at baseline. Therefore, 11 studies were used for the meta-analysis, providing suitable data on 15 cohorts overall (Table 1) (14–24).

Data extraction. The following characteristics of the identified studies and respective populations were recorded: publication reference, total number of participants, country, sex, age (mean, median, or range), follow-up (years), outcome reported (fatal or nonfatal stroke, CHD, or CVD),

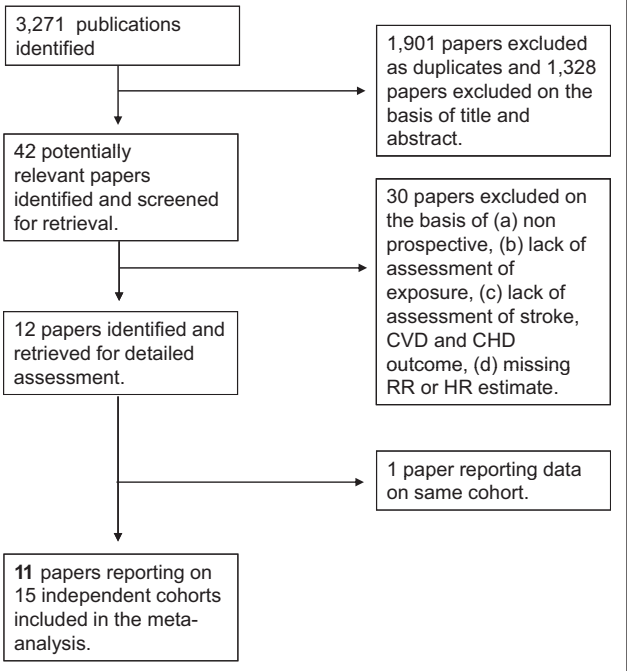

Figure 1 Stepwise Procedure for Selection of Studies

Flowchart indicating the results of the systematic review with inclusions and exclusions. CHD = coronary heart disease; CVD = cardiovascular disease; HR = hazard ratio; RR = relative risk.

Table 1 Characteristics of the Prospective Studies Included in the Meta-Analysis

First Author (Ref. #)	Year	Country	Age (yrs)	Sex	Recruitment Time	Study Population (n)	Follow-up (yrs)	Outcome(s)	Outcome Assessment	Potassium Intake Assessment	Quality Score
Khaw (15)	1987	United States	50–79	Men/women	1972–1974	859	12	Fatal stroke	Death certificates (ICDA 430–438) review by physicians and hospital records	24-h dietary recall	16
Tunstall-Pedoe (16)	1997	Scotland	40–59	Men/women	1984–1987	11,629	7.6	Fatal/nonfatal CHD	Case notes requested for all hospital episodes of MI and other emergency admissions for CHD, extracted and coded according to MONICA project criteria	24-h urine collection	15
Ascherio (17)	1998	United States	40–75	Men	1986	43,738	8	Fatal/nonfatal stroke	Nonfatal outcomes review conducted by physicians, fatal outcomes review by physicians plus National Death Index (medical records or autopsy reports)	FFQ	16
Iso (18)	1999	United States	34–59	Women	1980	85,764	14	Fatal/nonfatal stroke	Notification of outcomes, review by physicians plus National Death Index, documented by medical records and death certificates	FFQ	18
Bazzano (14)	2001	United States	25–74	Men/women	1971–1975	9,805	19	Fatal/nonfatal stroke and CHD	Death certificates (ICD-9: 430–434.9, 436, or 437.0–437.1, 410–414), hospital records, nursing home documentation	24-h dietary recall	18
Green (19)	2002	United States	73	Men/women	1989–1990	4,934	7.3	Fatal/nonfatal stroke	Hospital records (including admission and discharge notes), results of tests, cerebral imaging studies	FFQ	14
Geleijnse (20)	2007	the Netherlands	≥55	Men/women	1990–1993	1,448	5	Fatal CVD, fatal/nonfatal MI and stroke	Physician registries ICD-10 I20–I25, I46, I49, I50, I60–I67, I70–I74, R96 I60–I67	Overnight urine potassium, FFQ	15
Weng (21)	2008	Taiwan	57	Men/women	1990–1993	1,772	10.6	Fatal/nonfatal stroke	Death certificates, insurance claim records of NHI database, subject's self-reported disease history (ICD-9-CM: 430–438)	FFQ	15
Larsson (22)	2008	Finland	50–69	Men	1985–1988	26,556	13.6	Fatal/nonfatal stroke	Discharge diagnoses and death certificates (ICD-8, -9, -10)	FFQ	15
Umesawa (23)	2008	Japan	40–79	Men/women	1988–1990	58,730	12.7	Fatal CVD, CHD, and stroke	National Vital Statistics (ICD-9)	FFQ (4 × 3-day dietary records)	18
Cook (24)	2009	United States	30–54	Men/women	2000	2,275	5	Fatal/nonfatal CVD	Notification of outcomes in post-trial surveillance, review by physician plus National Death Index	24-h urine collection	17

CHD = coronary heart disease; CVD = cardiovascular disease; FFQ = food frequency questionnaire; ICDA = International Classification of Diseases, adapted for use in the United States; MI = myocardial infarction; MONICA = Multinational Monitoring of Trends and Determinants in Cardiovascular Disease.

outcome assessment method, number (rate) of events, potassium intake assessment method, and level of potassium intake in different categories. Categorization of potassium intake differed among studies: some of them reported the number of patients exposed and the rate (number) of events occurring across categories of potassium intake and some others reporting differences in the event rate for a given difference in potassium intake (15,16,20,24). Whereas in the latter case, the RR or HR reported by the authors was used for the analysis, for the studies that stratified participants by categories of potassium intake, the RR for the highest versus lowest intake was calculated by comparing the event rate in the 2 extreme categories (Table 2).

Statistical analysis. The quality of the studies included in the meta-analysis was evaluated by the Downs and Black score system. The adapted quality score system contained 4 sections: reporting, external validity, internal validity—bias, and internal validity—confounding. A higher score was considered to be an indicator of better quality, on a scale of 19 (25).

Relative risks or HRs were extracted from the selected publications, and their SEs were calculated from the respective confidence intervals (CIs). The value from each study and the corresponding SE were transformed into their natural logarithms to stabilize the variances and to normalize their distribution. The pooled RR (and 95% CI) was estimated using a random-effect or fixed-effect model, weighted for the inverse of the variance (26). The pooled estimate from the random-effects model was used if the test for heterogeneity was significant. The heterogeneity among studies was tested by Q statistic and quantified by H statistic and I^2 statistic (27). Funnel plot asymmetry was used to detect publication bias, and the Egger regression test was applied to measure funnel plot asymmetry. In the case of significant funnel plot asymmetry, suggesting a number of possibly "missing" publications, the pooled RR estimate was recalculated based on the estimated number of "missing" studies and their effect sizes and SEs, a method known as "trim and fill" (28,29).

The influence of individual cohorts, from which the meta-analysis estimates were derived, was examined by omitting one cohort at a time to see the extent to which inferences depend on a particular study or group of studies (sensitivity analysis).

Subgroup and meta-regression analyses were used to identify associations between risk of stroke, CHD, or CVD and relevant study characteristics (sex of participants, country of origin, duration of follow-up, method of potassium intake assessment, difference in potassium level, and quality score and control for baseline BP and body mass index [BMI]) as possible sources of heterogeneity.

All statistical analyses were performed using MIX software version 1.7 (30) and Stata version 9.1 (Stata Corp., College Station, Texas) for meta-regression analysis (31).

Results

Characteristics of the study cohorts. The relevant features of the 11 studies included in the meta-analysis are reported in Table 1. Overall, the meta-analysis involved 247,510 participants from 6 countries (6 studies from the United States and 1 each from Finland, Japan, the Netherlands, Scotland, and Taiwan). Eight studies recruited both male and female participants, whereas 2 studies recruited only men and 1 recruited only women. Six studies reported only stroke events (fatal or nonfatal), 1 only CVD outcomes, 1 only fatal and nonfatal CHD, and 3 reported combined outcomes. Potassium intake was assessed by food frequency questionnaire in 6 studies, 24-h urine excretion in 3 studies, and 24-h dietary recall in 2 studies. Average potassium intakes ranged between 45 and 85 mmol/day in all but 1 population, for which a very large average intake of 125 mmol/day was reported (22). The overall number of incident strokes was 7,066 and that of CHD events 3,058. The number of events reported simply as CVD events was 2,497. Of the 8 studies including both male and female participants, 3 reported outcomes separately for men and women (15,16,23). The study by Green et al. (19) also included 2 different cohorts, based on the use of diuretics.

Thus, overall there were 11 cohorts available for the relationship between potassium intake and stroke, 6 cohorts available for the relationship with CHD, and 4 cohorts for the relationship between potassium intake and CVD. The weighted average follow-up time was 12.2 years (range 5 to 19 years).

Potassium intake and stroke risk. Detailed figures on population size, incident strokes (when possible, total stroke incidence was used), and baseline levels of potassium intake of the 11 cohorts included in the meta-analysis are given in Table 2 (overall, 233,606 participants and 7,066 events) (14,15,17–23), and the results of the pooled analysis are shown in Figure 2. In the pooled analysis, higher potassium intake (average weighted difference: 1.64 g or 42.1 mmol/day) was significantly associated with lower risk of stroke (RR: 0.79; 95% CI: 0.68 to 0.90; $z = 3.38$; $p = 0.0007$). There was significant heterogeneity among studies ($Q = 22.0$; $p = 0.01$; $I^2 = 55\%$), and there was no evidence of publication bias by the Egger test ($p = 0.11$). As shown in Figure 2 for the individual cohorts included in the analysis, a trend toward an inverse association between potassium intake and stroke risk was detected in 9 cohorts and was statistically significant in 4 of them. A nonsignificant opposite trend was observed in only 2 cohorts (both small, and one involving diuretic therapy). Sensitivity analysis showed that the risk of stroke did not vary substantially with the exclusion of any individual study.

In addition, we carried out an analysis including the results of the NHANES I cohort as reported by Fang et al. (13) in place of the report on the same cohort by Bazzano et al. (14) (included in the main analysis). The pooled RR only changed from 0.79 to 0.75 (95% CI: 0.64 to 0.87; $z = 3.66$;

Table 2 Detailed Outcome of the Studies

First Author (Ref. #) (Year)	Participants	Cohort (n)	Events (n)			Comparison	Potassium Intake Difference, g (mmol)/day	Factors Controlled for in Multivariate Analysis
			Total Strokes (Ischemic/Hemorrhagic)	CVD	CHD			
Khaw (15) (1987)	Men	356	9 (—/—)	—	—	Continuous variable	0.39 (10.0)	Age, SBP or DBP, BMI, total cholesterol, fasting plasma glucose, smoking
	Women	503	15 (—/—)					
Tunstall-Pedoe (16) (1997)	Men	5,754	—	—	404	Interquintile difference	0.88 (22.7)	Age
	Women	5,875			177		0.74 (19.1)	
Ascherio (17) (1998)	Men	43,738	328 (210/70)	—	—	Quintile (V vs. I)	1.90 (48.7)	Age, hypertension, BMI, energy intake, smoking, alcohol, hypercholesterolemia, parental history of MI at age <65 yrs, profession, exercise, fiber and magnesium intake
Iso (18) (1999)	Women	85,764	690 (386/203)	—	—	Quintile (V vs. I)	1.54 (39.4)	Age, smoking, for ischemic stroke: time interval, hypertension, diabetes, hypercholesterolemia, BMI, alcohol, menopausal status and post-menopausal hormone use, exercise, aspirin/multivitamin/vitamin E use, ω-3/magnesium/calcium intake
Bazzano (14) (2001)	Men/women	9,805	927 (—/—)	—	1,847	Quartile (IV vs. I)	2.66 (68.2)	Age, race, sex, SBP, total cholesterol, BMI, diabetes, exercise, education, alcohol, smoking, vitamin supplement, saturated fat/energy/cholesterol/sodium/calcium/fiber/vitamin C and A intake
Green (19) (2002)	Nonusers of diuretics	3,595	268 (121/33)	—	—	Quintile (V vs. I)	**2.43 (62.3)**	Age, sex, diabetes, hypertension, CHD, congestive heart failure, atrial fibrillation, SBP, serum creatinine, potassium supplement
	Users of diuretics	1,339	165 (78/12)					
Geleijnse (20) (2007)	Men/women	1,448	181	217	206	Continuous variable	0.86 (22.0)	Age, sex, creatinine and sodium excretion, BMI, smoking, diabetes, diuretic use, education, energy intake, alcohol, calcium, saturated fat
Weng (21) (2008)	Men/women	1,772	— (132/—)	—	—	Quartile (IV+III vs. I)	**1.49 (38.2)**	Age, sex, BMI, hypertension, therapy, diabetes, central obesity, alcohol, smoking, sex–smoking interaction, CHD, hypercholesterolemia, hypertriglyceridemia, exercise, fibrinogen, apoB, plasminogen, geographic area
Larsson (22) (2008)	Men	26,556	3,365 (2,702/579)	—	—	Quintile (V vs. I)	1.95 (49.9)	Age, supplementation group, smoking, BMI, SBP and DBP, total cholesterol, HDL cholesterol, diabetes, CHD, exercise, alcohol, energy intake
Umesawa (23) (2008)	Men	23,119	986 (510/380)	1,066	233	Quintile (V vs. I)	1.29 (33.0)	Age, BMI, smoking, alcohol, hypertension, diabetes, menopause, hormone therapy, exercise, education, mental stress, calcium and sodium intake
	Women	35,611		1,021	191			
Cook (24) (2009)	Men/women	2,275	—	193	—	Continuous variable	1.95 (50.0)	Age, race, sex, clinic, treatment, education, baseline weight, changes in weight, smoking, alcohol, exercise, family history of CVD, sodium excretion

BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure; other abbreviations as in Table 1.

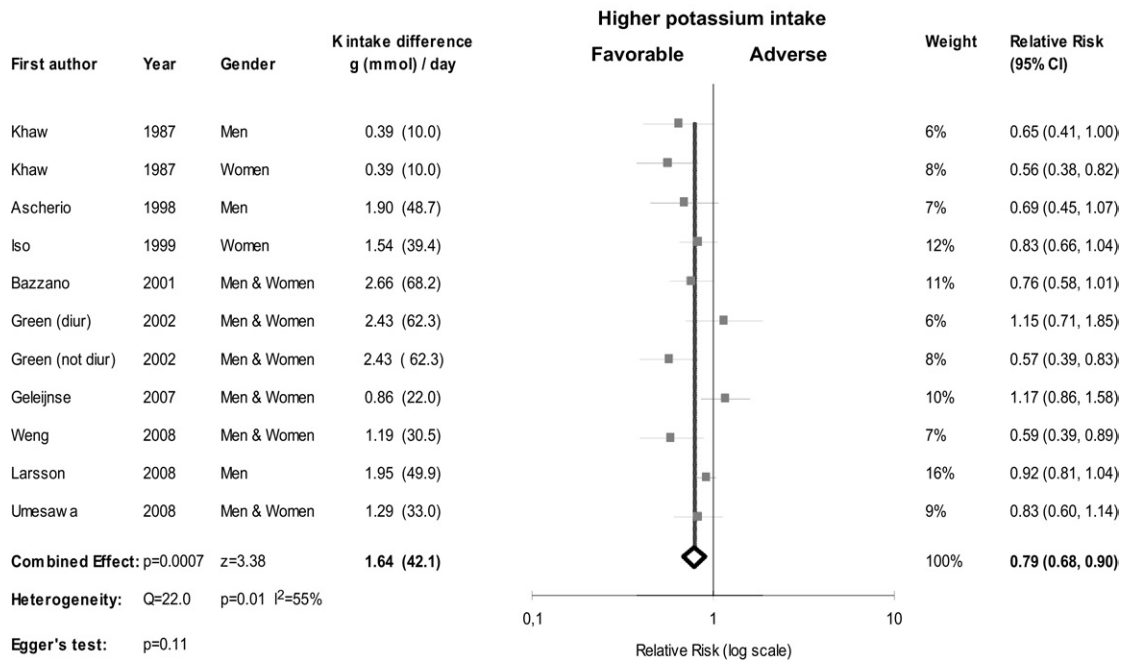

Figure 2 **Risk of Stroke**

Forest plot of the risk of incident stroke associated with higher potassium intake compared with lower potassium intake in 11 population cohorts from published prospective studies. Results are expressed as relative risk and 95% confidence intervals (CIs).

p = 0.0003). There was a significant heterogeneity among studies (Q = 39.3; p = 0.0002; I^2 = 67%) but no evidence of publication bias (Egger test; p = 0.13).

Potassium intake and CHD risk. Data on population size, incident CHD, and baseline levels of potassium intake of the 6 cohorts included in the analysis are given in Table 2 (overall 81,612 participants and 3,058 events) (14,16,20,23). In the pooled analysis, there was a trend toward an inverse association between higher potassium intake (average weighted difference: 1.38 g or 35.3 mmol/day) and risk of CHD (RR: 0.92; 95% CI: 0.81 to 1.04; z = 1.35), which was not statistically significant (p = 0.18) (Fig. 3). There was moderate nonstatistically significant heterogeneity among studies (Q = 9.1; p = 0.10; I^2 = 45%). There was no evidence of publication bias by the Egger test (p = 0.51), but the "trim and fill" method identified 1 possibly missing study, modifying the pooled estimate to an RR of 0.94, with 95% CI of 0.81 to 1.10. The evaluation of individual studies showed a trend toward an inverse association between potassium intake and CHD risk in 4 cohorts, with significantly lower risk in 2, whereas a nonsignificant opposite trend was observed in 2 small cohorts. Sensitivity analysis showed that the exclusion of a single study (23) led to a pooled estimate of RR of 0.93 (95% CI: 0.87 to 0.99), which was statistically significant (p = 0.03).

Potassium intake and CVD risk. Detailed figures on population size, incident CVD, and baseline levels of potassium intake of the 4 cohorts included in this analysis are given in Table 2 (overall 62,453 participants and 2,497 events) (20,23,24). In the pooled analysis, there was a trend toward an inverse relationship between higher potassium intake (average weighted difference: 1.30 g or 33.4 mmol/day) and CVD risk (RR: 0.85; 95% CI: 0.62 to 1.16; z = 1.01), which was not statistically significant (p = 0.31) (Fig. 4). There was significant heterogeneity among studies (Q = 10.3; p = 0.02; I^2 = 71%) and no evidence of publication bias (Egger test; p = 0.40). The evaluation of individual studies showed a trend toward an inverse association between potassium intake and CVD risk in 3 cohorts, with significantly lower relative risk in one of them. A nonsignificant opposite trend was observed in 1 small cohort. Sensitivity analysis showed that the exclusion of a single study (20) led to a pooled estimate of RR of 0.74 (95% CI: 0.60 to 0.91; p = 0.0037). After exclusion of this cohort, there was no study heterogeneity (Q = 1.51; p = 0.47; I^2 = 0%).

Source of heterogeneity. Further analyses were carried out to check for potential sources of heterogeneity that may have affected the association between dietary potassium and vascular outcomes. Subgroup analysis was used for categoric variables and meta-regression for continuous variables.

SUBGROUP ANALYSIS. We explored the influence of sex, method of potassium intake assessment, and population baseline BMI or BP. For all 3 types of vascular events, sex and potassium intake assessment (food frequency questionnaire/

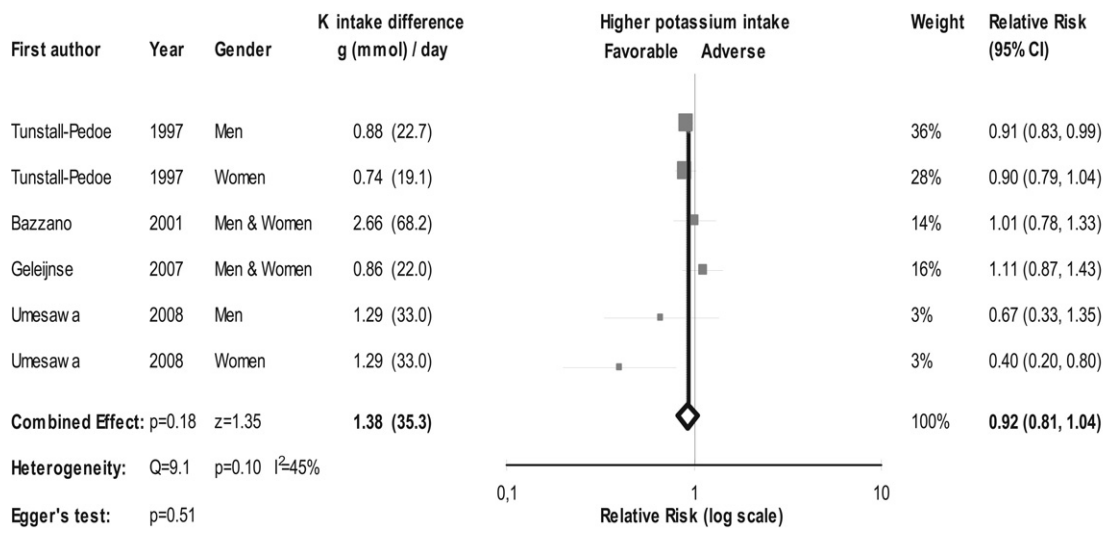

Figure 3 Risk of CHD

Forest plot of the risk of incident coronary heart disease (CHD) associated with higher potassium intake compared with lower potassium intake in 6 population cohorts from 4 published prospective studies. Results are expressed as relative risk and 95% confidence intervals (CIs).

24-h dietary recall or urine collection) were not significant sources of heterogeneity (Table 3). Separate analysis of the studies reporting RR estimates adjusted for baseline BP or hypertension status confirmed the inverse association between potassium intake and risk of stroke (10 cohorts; pooled RR: 0.76 [95% CI: 0.66 to 0.87]; p < 0.0001; Q = 16.9; p = 0.05; I^2 = 47%) (14,15,17–19,21–23); similar results were obtained from separate analysis of the studies that adjusted for baseline BMI or body weight (9 cohorts; RR: 0.79 [95% CI: 0.69 to 0.91]; p = 0.001; Q = 16.3; p = 0.04; I^2 = 51%) (14,15,17,18,20–23) (Online Appendix).

META-REGRESSION ANALYSIS: STROKE. Meta-regression analysis (Table 4) indicated no influence of the study quality score, length of follow-up, population potassium intake at baseline, recruitment year, and between-group difference in potassium intake on the inverse association between potassium intake and risk of stroke.

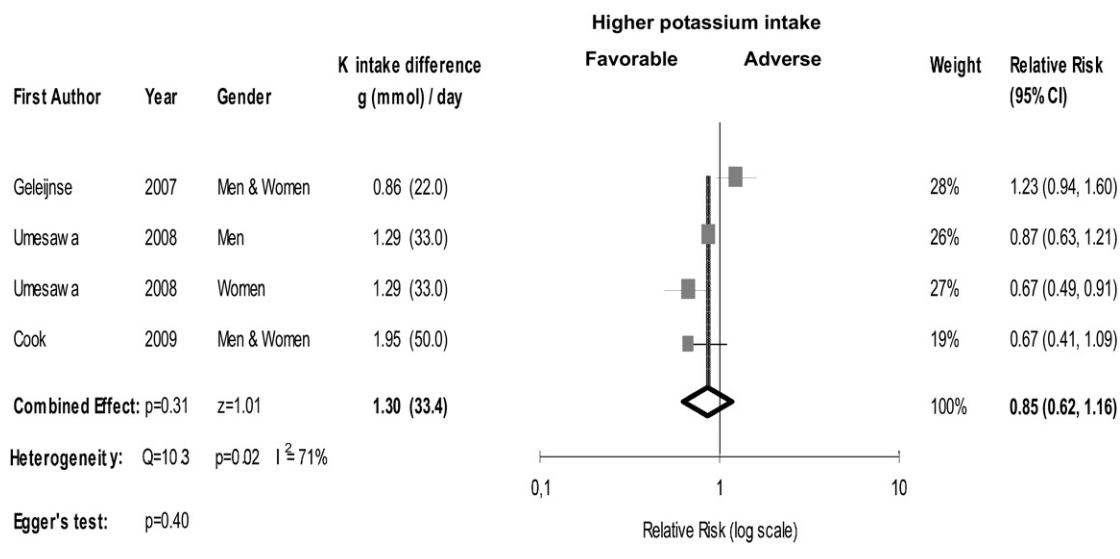

Figure 4 Risk of CVD

Forest plot of the risk of incident cardiovascular disease (CVD) associated with higher potassium intake compared with lower potassium intake in 4 population cohorts from 3 published prospective studies. Results are expressed as relative risk and 95% confidence intervals (CIs).

Table 3 Subgroup Analysis

	Variables (n cohorts)	Pooled RR	95% CI	Heterogeneity (p Value)
Stroke				
Sex	Men (3)	0.81	0.64–1.02	0.50
	Women (2)	0.70	0.48–1.02	
Potassium intake assessment	FFQ (7)	0.80	0.68–0.93	0.18
	Dietary recall (3)	0.68	0.55–0.83	
CHD				
Sex	Men (2)	0.91	0.83–0.99	0.39
	Women (2)	0.65	0.30–1.41	
Potassium intake assessment	FFQ/dietary recall (3)	0.69	0.39–1.23	0.31
	Urine collection (3)	0.93	0.85–1.00	

CI = confidence interval; RR = relative risk; other abbreviations as in Table 1.

META-REGRESSION ANALYSIS: CHD. The results of meta-regression analyses (Table 4) indicated that potassium intake difference, length of follow-up, quality score, recruitment year, and population potassium intake at baseline were not significant sources of heterogeneity in the relationship of the potassium intake effect on the risk of CHD.

META-REGRESSION ANALYSIS: CVD. Meta-regression analysis (Table 4) showed that the length of follow-up (coefficient: −0.064 [95% CI: −0.112 to −0.015]; p = 0.01) and quality score (coefficient: −0.165 [95% CI: −0.287 to −0.043]; p = 0.01) were significant sources of heterogeneity. The estimated between-study variance was reduced from 0.074 to 0.0035 (length of follow-up) and 0.0023 (quality score).

Discussion

The present meta-analysis assessed the effects of dietary potassium on cardiovascular end points in a sample of nearly 250,000 individuals, pooled from 11 published studies, the largest studied so far. The results indicated that an average increase of 1.64 g (42 mmol) of potassium per day is associated with a 21% reduced risk of stroke, suggesting an important protective role. This finding was strengthened by the detection of a significant protective effect in as many as 4 of the 11 individual cohorts included in the analysis and by the observation that a (not significant) opposite trend was reported in only 2 small cohorts. The protective effect of potassium against the risk of stroke may conceivably relate to its BP-lowering effect, particularly in hypertensive individuals and in those with elevated sodium intake. Nevertheless, because all of the studies included in the analysis reported an estimate of risk adjusted for baseline BP or hypertension status—and our subgroup analysis showed the independence of the effects of potassium from baseline BP and other confounders—it appears that at least part of the effect of potassium might be based on different mechanisms. High-potassium diets were reported to inhibit free radical formation and to reduce the production of vascular and plasma lipid peroxides in stroke-prone spontaneously hy-

Table 4 Meta-Regression Analysis

	Coefficient	SE	p Value	95% CI
Stroke (n = 11 for each)				
Potassium intake difference	0.001	0.004	0.72	−0.007 to 0.009
Average potassium intake	0.001	0.003	0.93	−0.006 to 0.006
Length of follow-up	−0.011	0.019	0.56	−0.050 to 0.027
Quality score	−0.010	0.052	0.84	−0.113 to 0.092
Recruitment time	0.012	0.010	0.23	−0.007 to 0.032
CHD (n = 6 for each)				
Potassium intake difference	0.037	0.078	0.64	−0.117 to 0.190
Average potassium intake	−0.002	0.003	0.55	−0.007 to 0.004
Length of follow-up	−0.002	0.011	0.84	−0.025 to 0.020
Quality score	−0.020	0.042	0.63	−0.102 to 0.061
Recruitment time	−0.003	0.009	0.76	−0.021 to 0.015
CVD (n = 4 for each)				
Potassium intake difference	−0.023	0.013	0.07	−0.048 to 0.002
Average potassium intake	−0.044	0.023	0.06	−0.089 to 0.001
Length of follow-up	−0.064	0.024	0.01	−0.112 to −0.015
Quality score	−0.165	0.062	0.01	−0.287 to −0.043
Recruitment time	−0.021	0.039	0.59	−0.098 to 0.056

Abbreviations as in Tables 1 and 3.

pertensive rats (32,33), to inhibit vascular smooth muscle cell proliferation in vitro (34), and to reduce aortic wall thickening in stroke-prone spontaneously hypertensive rats by increasing the release of growth-inhibiting agents (35). More recently, a high-potassium diet was shown to exert a protective effect against the development of vascular damage induced by salt loading, at least in part through suppression of the production of reactive oxygen species (36). This large body of evidence from experimental studies provides further biologic plausibility to the possible protective effect of dietary potassium against cardiovascular events.

Our study also showed a trend toward RR reduction for CHD and CVD in the pooled analysis for individuals consuming a higher-potassium diet: for both outcomes, this trend was not statistically significant. In both cases, however, statistical significance was achieved upon exclusion of a single cohort on the basis of sensitivity analysis, with reductions of 7% in the risk of CHD and 26% in the risk of total CVD being associated with differences in potassium intake of 1.4 and 1.3 g per day, respectively. Our findings add to the results of a recent intervention study using a potassium-enriched salt that detected a long-term positive effect of increased potassium intake on cardiovascular mortality in elderly men in northern Taiwan (37).

Potassium is particularly abundant in fruits and vegetables. A greater fruit and vegetable consumption has already been shown to protect against the occurrence of stroke. According to the meta-analysis by He et al. (38), 5 or more servings of fruit and vegetables per day are associated with a 26% lower rate of stroke compared with 3 or fewer servings. In that study, the association was similar for ischemic and hemorrhagic stroke. Thus, the present meta-analysis points to potassium as one of the factors responsible for the beneficial effect of high vegetable and fruit consumption, at least for ischemic stroke.

Study limitations. Our analysis showed a significant heterogeneity among the studies in terms of sample size, duration of observation, number of events, and difference in dietary potassium intake between the groups being compared. This heterogeneity led to a reduced statistical power in detecting a possible association between dietary potassium and CHD and CVD. For this reason, although statistical evidence in favor of an effect of higher potassium intake on risk of CHD and total cardiovascular events was actually obtained after the exclusion of outliers based on sensitivity analysis, we acknowledge that the evidence in favor of the protective effect of potassium against CHD and CVD is less robust and not conclusively proven.

A further limitation was given by the inaccurate estimates of habitual potassium intake that was available for all studies only at baseline. In addition, none of the methods available for the evaluation of potassium intake provided 100% accurate estimates, the best one being 24-h urine collection, which was adopted in only 3 studies. Inaccurate estimates of habitual potassium intake introduce a regression dilution bias, which is expected to reduce the probability to detect true biologic associations, and thus may have led to underestimating the reduction in the risk of stroke and other vascular events associated with a higher-potassium diet.

Also, the lack of potential confounders in the analyses presented in the single study reports is a limitation of our study. For instance, only 4 studies reported an estimate of risk adjusted for sodium intake (14,20,23,24), the most relevant confounding factor of the potassium effect.

Finally, although subgroup and meta-regression analysis failed to identify duration of exposure, sex, baseline BP or hypertensive status, or BMI or obesity status as factors contributing to heterogeneity of the study results, the number of studies included in the analysis, particularly for the CHD and CVD outcomes, may have been too small to allow a conclusive evaluation of the effect of these different factors.

Implications. According to a recently published meta-analysis of the relationship of sodium intake to the risk of stroke (39), a 5 g or 85 mmol/day lower dietary sodium intake is associated with a reduction in the risk of stroke of 23%. This value is similar to the risk reduction (21%) observed in the present analysis for a 1.64 g or 42 mmol/day higher potassium intake. This risk reduction would be translated into a reduction of as many as 1,155,000 stroke deaths per year on a worldwide scale and is expected to produce overall health benefits by reducing the impact of disability to an extent similar to that obtained by dietary salt reduction. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines recommended an intake of 100 mmol or more potassium per day (40). In all of the populations that were the object of the present meta-analysis, the average potassium intake was far lower than this. Potassium intake may be increased by well-described dietary changes, mainly an increase in fruit and vegetable consumption, as recommended by all guidelines for CVD prevention and treatment, as well as by national guidelines for healthy nutrition in the general population.

Conclusions

Increasing dietary potassium intake is expected to exert a protective effect against stroke and might also reduce the incidence of CHD and total CVD. These results apply to the general population, not only to specific subgroups at higher risk. The favorable effects of dietary potassium were documented at least to some extent independently of other factors. Efforts should therefore be made to favor the synergy with other nutritional- or lifestyle-related preventive measures.

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Key Words: cardiovascular disease ■ coronary heart disease ■ meta-analysis ■ potassium intake ■ stroke.

APPENDIX

For a table on the analysis of the stroke risk including the studies adjusted for baseline BP or hypertension status and baseline BMI or body weight, please see the online version of this article.