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## Calcium, magnesium and potassium intake and mortality in women with heart failure: the Women's Health Initiative

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### Abstract

Although diet is thought to affect the natural history of heart failure (HF), nutrient intake in HF patients has not been well studied. Based on prior research linking high intake of Ca, Mg and K to improved cardiovascular health, we hypothesised that these nutrients would be inversely associated with mortality in people with HF. Of the 161 808 participants in the Women's Health Initiative (WHI), we studied 3340 who experienced a HF hospitalisation. These participants were followed for post-hospitalisation all-cause mortality. Intake was assessed using questionnaires on food and supplement intake. Hazard ratios (HR) and 95% CI were calculated using Cox proportional hazards models adjusted for demographics, physical function, co-morbidities and dietary covariates. Over a median of 4.6 years of follow-up, 1433 (42.9%) of the women died. HR across quartiles of dietary Ca intake were 1.00 (referent), 0.86 (95% CI 0.73, 1.00), 0.88 (95% CI 0.75, 1.04) and 0.92 (95% CI 0.76, 1.11) (*P* for trend=0.63). Corresponding HR were 1.00 (referent), 0.86 (95% CI 0.71, 1.04), 0.88 (95% CI 0.69, 1.11) and 0.84 (95% CI 0.63, 1.12) (*P* for trend=0.29), across quartiles of dietary Mg intake, and 1.00 (referent), 1.20 (95% CI 1.01, 1.43), 1.06 (95% CI 0.86, 1.32) and 1.16 (95% CI 0.90, 1.51) (*P* for trend=0.35), across quartiles of dietary K intake. Results were similar when total (dietary plus supplemental) nutrient intakes were examined. In summary, among WHI participants with incident HF hospitalisation, intakes of Ca, Mg and K were not significantly associated with subsequent mortality.

**Key words:** Heart failure: Mortality: Calcium: Magnesium: Potassium

Although diet is thought to affect the natural history of heart failure (HF)<sup>(1)</sup>, only a few studies have sought to determine the effect of nutritional intake in patients with HF<sup>(2–7)</sup>. Many of these studies were small and examined the effect of dietary supplements, rather than nutrient intake from food. The intake of Ca, Mg and K could influence the course of HF through effects on blood pressure, inflammation, endothelial function and other pathways<sup>(8–16)</sup>. In one small study, high-dose supplementation with multiple micronutrients, including Ca and Mg, improved left ventricular function and quality of life among HF patients with reduced ejection fraction<sup>(6)</sup>. However, the effect of Ca, Mg and K intake on survival in patients with HF is not known. We therefore examined the associations of Ca, Mg and K intake from foods, as well as total intake from

diet and supplements, with all-cause mortality among Women's Health Initiative (WHI) participants who had a HF hospitalisation. We hypothesised that higher intake of Ca, Mg and K would be associated with lower rates of all-cause mortality in women with HF.

### Methods

#### Study population

The WHI has been previously described in depth<sup>(17,18)</sup>. Briefly, the WHI consisted of a clinical trial component with 68 132 post-menopausal women aged 50–79 years at the study entry and an observational study component with

**Abbreviations:** DM, dietary modification; HF, heart failure; WHI, Women's Health Initiative.

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93 676 post-menopausal women aged 50–79 years at the study entry, recruited between 1993 and 1998 through forty clinical centres. The WHI clinical trial included trials of hormone therapy, dietary modification (DM) and Ca plus vitamin D. The clinical trial and observational study were closed in 2004–05, and participants were invited to continue in the WHI extension study, which started in 2005. For the present analysis, we focused on the 4043 participants who had an adjudicated hospitalisation for HF between study entry and 2005. HF hospitalisations were locally adjudicated with central adjudication for quality control and were defined as hospitalisations with a final diagnosis of HF accompanied by medical treatment for HF, including diuretics, digitalis, vasodilators or angiotensin-converting enzyme inhibitors. Supporting evidence of HF from imaging was also noted. We excluded twenty-nine participants who did not survive at least 1 d past HF hospitalisation, 480 participants missing information on Ca, Mg, K or covariates and 194 participants with implausible energy intake ( $<2510$  or  $>20920$  kJ/d) producing a final sample size of 3340 women. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the institutional review boards at all the participating centres. Written informed consent was obtained from all the participants.

### Nutrient intake

A modified block FFQ<sup>(19)</sup> was administered during a screening visit for all the participants and additionally at year 1 for all participants in the DM trial, yearly thereafter for a proportion of the DM participants and at year 3 for the observational study participants. The most recent diet assessment prior to HF hospitalisation was selected for each participant. The FFQ contained 122 questions about the frequency of consumption of foods and beverages over the previous 3 months, nineteen adjustment items and four summary questions<sup>(19)</sup>. The frequency questions included predefined responses up to '2+ times per d' for foods and '6+ times per d' for beverages. There were also questions on portion sizes (small, medium or large), as compared with the specified medium-size portion. Pictures were used to help with portion size estimations.

Dietary nutrient intake was calculated by multiplying the frequency of consumption of each food by the nutrient content for the specified portion size and then summing over foods. Dietary nutrient intake was adjusted for energy intake using the residuals method<sup>(20)</sup>. To calculate total nutrient intake, the nutrient intake from supplements was added to the energy-adjusted dietary nutrient intake. In a study of the measurement characteristics of the FFQ, deattenuated correlation coefficients comparing 8 d of dietary intake (four 24-h recalls and 4 d of diet records) with the FFQ were 0.73 for dietary Ca, 0.78 for total Ca, 0.72 for dietary Mg, 0.69 for total Mg, 0.67 for total K and 0.67 for total K<sup>(19)</sup>. The test–retest intraclass correlation coefficient was 0.84 for Mg, and all correlations were  $\geq 0.67$ <sup>(19)</sup>.

### Covariates

Covariates were assessed by questionnaires and physical measurement (blood pressure and height and weight used to calculate BMI). As with the dietary assessment, the most recent assessment of covariates prior to HF hospitalisation was selected for each individual. For co-morbidities, such as myocardial infarction and revascularisation, self-reported conditions existing at the WHI baseline and occurring during the WHI follow-up prior to HF hospitalisation were combined.

### Mortality follow-up

The outcome of interest was all-cause mortality. Follow-up for these analyses started on the date of HF hospitalisation and continued through to the date of death or the last contact with the participant prior to August 2009. Deaths were ascertained by family, friends or health-care providers directly reporting the death to the WHI; family, friends or the US Postal Service responding to mailings; Internet searches (e.g. obituary search engines); the social security death index; or the National Death Index searches<sup>(21)</sup>.

### Statistical analysis

We summarised covariates using means for continuous variables and percentages for categorical variables by mortality status. We calculated Pearson's correlations among Ca, Mg and K intakes. In the subset of women with FFQ completed both before and after HF hospitalisation, we compared intakes from pre- and post-HF questionnaires to assess diet stability.

Cox proportional hazards models were used to estimate the hazard ratios and 95% CI of mortality associated with quartiles of the dietary intake of Ca, Mg and K as well as total intake from diet and supplements. Model 1 adjusted for age at HF hospitalisation (linear) and total energy intake (linear). Model 2 further adjusted for race/ethnicity (white, black or other), education (less than high school, high school graduate including some college, college graduate or graduate school), income ( $< \$20\,000$ ,  $\$20\,000$ – $34\,999$ ,  $\$35\,000$ – $49\,999$  or  $\geq \$50\,000$ ), married (yes or no), current smoking (yes or no), BMI (linear term), total exercise (metabolic equivalents h/week, linear term), physical function score (linear term), systolic blood pressure (linear term), diastolic blood pressure (linear term), history of high cholesterol, high blood pressure, diabetes, myocardial infarction, coronary revascularisation and atrial fibrillation, use of off-study post-menopausal hormone therapy, use of diuretics,  $\beta$ -blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and WHI study arm. Model 3 additionally adjusted for alcohol intake (none, 0–10 g/d or  $>10$  g/d) and quartiles of Na, Ca (Mg and K models), Mg (Ca and K models), K (Ca and Mg models), protein, saturated fat, monounsaturated fat, polyunsaturated fat and fibre. Because intake of Ca, Mg and K may reduce blood pressure, adjusting for factors related to blood pressure may be an over-adjustment. We therefore constructed a final model adjusted for all of the factors in model 3, except for systolic and diastolic blood

pressure, history of high blood pressure and use of diuretics,  $\beta$ -blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Collinearity was examined using the variance inflation factor. None of the variance inflation factors exceeded 4.1, below the threshold of 10, which has been proposed as an indicator of important collinearity<sup>(22)</sup>. Tests for linear trend were performed by including the median of each quartile as a continuous variable in the models. Potentially non-linear associations were explored using penalised splines<sup>(23)</sup>.

In sensitivity analyses, we excluded participants with self-reported HF at study entry because pre-existing HF may alter diet (*n* 303), participants with a history of cancer at baseline or during follow-up because of the cardiotoxic effects of some chemotherapeutic agents (*n* 654) and participants in the DM or Ca plus vitamin D trials because these participants may have altered their intake in ways not fully captured by the FFQ (*n* 1215). Finally, we excluded participants who did not have a physician diagnosis of HF at the index hospitalisation, because of the potential for misclassification of disease (*n* 251).

**Table 1.** Characteristics of 3340 Women's Health Initiative (WHI) participants with heart failure hospitalisation by mortality

(Mean values and standard deviations or percentages)

	Died during follow-up ( <i>n</i> 1433)		Survived follow-up ( <i>n</i> 1907)	
	Mean	SD	Mean	SD
Age at heart failure hospitalisation (years)	73.8	6.7	71.9	7.2
Race/ethnicity (%)				
American Indian/Alaskan native		0.8		0.3
Asian/Pacific Islander		1.3		0.6
Black		10.1		10.9
Hispanic		1.4		2.4
White not of Hispanic origin		85.6		84.8
Not one of above		0.9		1.0
Education (%)				
Less than high school		9.1		8.3
High school graduate/some college		62.3		60.4
College graduate		8.2		8.3
Graduate school		20.5		22.9
Income (%)				
< \$20 000		36.0		28.3
\$20 000–34 999		29.2		31.5
\$35 000–49 999		17.6		17.7
≥ \$50 000		17.2		22.5
Married (%)		48.3		51.7
Current cigarette smoking (%)		24.2		21.1
BMI (kg/m <sup>2</sup> )	29.9	7.3	30.9	7.4
Physical activity (MET-h/week)	8.1	10.9	9.4	11.5
Physical function score	54.2	27.0	63.2	25.8
Systolic blood pressure (mmHg)	135	21	134	19
Diastolic blood pressure (mmHg)	71	11	73	11
History of high cholesterol (%)		24.2		21.1
History of hypertension (%)		59.6		57.4
History of diabetes (%)		31.6		25.2
History of myocardial infarction (%)		21.6		14.9
History of revascularisation (%)		18.7		16.1
History of atrial fibrillation (%)		16.9		12.8
Off-study post-menopausal hormone use (%)		22.2		29.0
Use of diuretics (%)		46.2		38.3
Use of $\beta$ -blockers (%)		23.0		23.9
Use of ACE inhibitor or ARB (%)		33.5		30.9
Total energy (kJ/d)	6397	2648	6565	2536
Ca (mg/d)	802	346	807	330
Mg (mg/d)	247	54	248	53
K (mg/d)	2611	639	2598	622
WHI arm (%)				
Oestrogen alone intervention		5.0		5.1
Oestrogen alone control		4.8		5.5
Oestrogen plus progestin intervention		4.3		4.8
Oestrogen plus progestin control		4.6		4.6
Diet modification intervention		10.7		12.6
Diet modification control		14.9		19.4
Ca/vitamin D intervention		8.6		11.5
Ca/vitamin D control		8.9		11.2

MET, metabolic equivalents; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

We stratified results by whether the participants had a history of IHD prior to the index HF hospitalisation (history of myocardial infarction or revascularisation) and tested whether the associations between the micronutrients and mortality varied by history of IHD by including the product of an indicator variable for IHD and the median values of the micronutrient quartiles.

We tested the proportional hazards assumption by including the product of micronutrients and the natural logarithm of time as a term in the models; there was no evidence of violation of the proportional hazards assumption. Statistical analyses were conducted using SAS version 9.2 and R version 2.12.1. Two-sided *P* values < 0.05 were considered statistically significant.

## Results

Over a median of 4.6 years of follow-up (interquartile range 1.5–6.9 years) after HF hospitalisation, 1433 women died (42.9%). Characteristics of the study population are described in Table 1. The women who died were older, had lower physical activity, were more likely to use diuretics, and were more likely to have diabetes, hypertension, myocardial infarction, coronary revascularisation and atrial fibrillation. Dietary Ca intake was moderately correlated with dietary Mg (*r* 0.48) and K (*r* 0.54). Dietary intake of Mg and K were highly correlated (*r* 0.84). Among the 929 women with diet assessment before and after HF hospitalisation, correlations between

**Table 2.** Calcium, magnesium and potassium from foods and survival among women with heart failure (Hazard ratios (HR) and 95 % confidence intervals)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>P</i> -trend
<b>Ca</b>					
Median (mg/d)	476	655	833	1175	
Deaths	373	346	341	373	
Person-years	3589	4034	3884	3778	
Model 1*					0.29
HR	1	0.82	0.82	0.89	
95 % CI	Referent	0.71, 0.95	0.71, 0.95	0.77, 1.03	
Model 2†					0.79
HR	1	0.88	0.90	0.95	
95 % CI	Referent	0.76, 1.02	0.78, 1.05	0.82, 1.10	
Model 3‡					0.63
HR	1	0.86	0.88	0.92	
95 % CI	Referent	0.73, 1.00	0.75, 1.04	0.76, 1.11	
<b>Mg</b>					
Median (mg/d)	187	227	262	309	
Deaths	370	343	364	356	
Person-years	3721	3688	3845	4030	
Model 1*					0.002
HR	1	0.88	0.87	0.79	
95 % CI	Referent	0.76, 1.01	0.75, 1.00	0.68, 0.91	
Model 2†					0.09
HR	1	0.93	0.92	0.87	
95 % CI	Referent	0.80, 1.08	0.79, 1.07	0.75, 1.02	
Model 3‡					0.29
HR	1	0.86	0.88	0.84	
95 % CI	Referent	0.71, 1.04	0.69, 1.11	0.63, 1.12	
<b>K</b>					
Median (mg/d)	1895	2360	2754	3325	
Deaths	341	373	348	371	
Person-years	3754	3582	3965	3982	
Model 1*					0.03
HR	1	1.07	0.87	0.90	
95 % CI	Referent	0.93, 1.24	0.75, 1.02	0.78, 1.04	
Model 2†					0.57
HR	1	1.11	0.95	1.00	
95 % CI	Referent	0.95, 1.29	0.81, 1.11	0.85, 1.17	
Model 3‡					0.35
HR	1	1.20	1.06	1.16	
95 % CI	Referent	1.01, 1.43	0.86, 1.32	0.90, 1.51	

\* Model 1 adjusted for age at heart failure hospitalisation (linear) and total energy intake (linear).

† Model 2 adjusted for variables in model 1 and race/ethnicity (white, black or other), education (less than high school, high school graduate/some college, college graduate or graduate school), income (<\$20 000, \$20 000–34 999, \$35 000–49 999 or ≥\$50 000), married (yes or no), current smoking (yes or no), BMI (linear term), total exercise (metabolic equivalents h/week, linear term), physical function score (linear term), systolic blood pressure (linear term), diastolic blood pressure (linear term), history of high cholesterol, high blood pressure, diabetes, myocardial infarction, coronary revascularisation and atrial fibrillation, use of off-study post-menopausal hormone therapy, use of diuretics, β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and Women's Health Initiative study arm.

‡ Model 3 adjusted for variables in model 2 and alcohol intake (none, 0–10 g/d or > 10 g/d), and quartiles of Na, Ca (Mg and K models), Mg (Ca and K models), K (Ca and Mg models), protein, saturated fat, monounsaturated fat, polyunsaturated fat and fibre.

pre- and post-HF hospitalisation nutrient intakes were moderate ( $r$  0.49 for Ca, 0.56 for Mg and 0.54 for K).

In age- and energy-adjusted models, dietary intake of Mg and K were inversely associated with mortality (Table 2). However, after further multivariable adjustment, there was no significant association between any of the micronutrients and mortality. When dietary Ca, Mg and K were considered as continuous variables using penalised splines, there was no significant linear or non-linear association. Total intake (from foods and supplements) of Ca, Mg and K was associated with mortality in age- and energy-adjusted models, but the associations were not evident

after multivariable adjustment (Table 3). The findings were the same when we did not adjust for blood pressure-related variables. Results after excluding participants with baseline self-reported HF, participants with a history of cancer, participants in the DM or Ca plus vitamin D trials or participants who did not have a physician diagnosis of HF at the index hospitalisation were not materially different. No significant associations of Ca, Mg or K with mortality were observed among the women with a history of IHD ( $n$  860) or those without a history of IHD ( $n$  2480), and tests for interaction between the nutrients and history of IHD were not statistically significant.

**Table 3.** Calcium, magnesium and potassium from foods and supplements and survival among women with heart failure

(Hazard ratios (HR) and 95% confidence intervals)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>P</i> -trend
<b>Ca</b>					
Median (mg/d)	555	830	1206	1844	
Deaths	357	367	367	342	
Person-years	3802	3649	3725	4108	
Model 1*					0.002
HR	1	1.00	0.96	0.80	
95% CI	Referent	0.86, 1.15	0.83, 1.11	0.69, 0.93	
Model 2†					0.17
HR	1	1.07	1.07	0.92	
95% CI	Referent	0.92, 1.25	0.92, 1.24	0.78, 1.08	
Model 3‡					0.16
HR	1	1.08	1.07	0.91	
95% CI	Referent	0.93, 1.26	0.91, 1.26	0.77, 1.09	
<b>Mg</b>					
Median (mg/d)	199	259	320	408	
Deaths	350	354	373	356	
Person-years	3725	3784	3748	4027	
Model 1*					0.03
HR	1	0.91	0.94	0.84	
95% CI	Referent	0.79, 1.06	0.82, 1.09	0.72, 0.97	
Model 2†					0.98
HR	1	0.99	1.07	0.98	
95% CI	Referent	0.85, 1.15	0.92, 1.25	0.84, 1.15	
Model 3‡					0.46
HR	1	1.05	1.12	1.07	
95% CI	Referent	0.89, 1.24	0.94, 1.32	0.88, 1.30	
<b>K</b>					
Median (mg/d)	1907	2378	2771	3346	
Deaths	342	377	346	368	
Person-years	3762	3566	3952	4005	
Model 1*					0.02
HR	1	1.09	0.87	0.89	
95% CI	Referent	0.95, 1.27	0.75, 1.01	0.77, 1.03	
Model 2†					0.47
HR	1	1.14	0.94	1.00	
95% CI	Referent	0.98, 1.32	0.81, 1.10	0.85, 1.17	
Model 3‡					0.51
HR	1	1.23	1.04	1.14	
95% CI	Referent	1.03, 1.46	0.84, 1.29	0.88, 1.47	

\* Model 1 adjusted for age at heart failure hospitalisation (linear) and total energy intake (linear).

† Model 2 adjusted for variables in model 1 and race/ethnicity (white, black or other), education (less than high school, high school graduate/some college, college graduate or graduate school), income (<\$20 000, \$20 000–34 999, \$35 000–49 999 or ≥\$50 000), married (yes or no), current smoking (yes or no), BMI (linear term), total exercise (metabolic equivalents h/week, linear term), physical function score (linear term), systolic blood pressure (linear term), diastolic blood pressure (linear term), history of high cholesterol, high blood pressure, diabetes, myocardial infarction, coronary revascularisation and atrial fibrillation, use of off-study post-menopausal hormone therapy, use of diuretics, β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and Women's Health Initiative study arm.

‡ Model 3 adjusted for variables in model 2 and alcohol intake (none, 0–10 g/d or >10 g/d), and quartiles of Na, Ca (Mg and K models), Mg (Ca and K models), K (Ca and Mg models), protein, saturated fat, monounsaturated fat, polyunsaturated fat and fibre.

## Discussion

We did not find significant associations between dietary or total intake of Ca, Mg and K and mortality in WHI participants with HF. We had hypothesised that these nutrients would be associated with mortality based on previous research on HF and other CVD. For example, supplementation with Ca, Mg and K may reduce blood pressure, a risk factor for HF<sup>(11–14)</sup>. Extremely low Ca levels can cause HF in rare instances<sup>(24)</sup>. However, Ca supplements have been associated with increased risk of myocardial infarction and stroke in some studies<sup>(16)</sup>. High dietary intake of Mg has been inversely associated with the development of hypertension and type 2 diabetes<sup>(25,26)</sup>, risk factors for HF and with markers of inflammation and endothelial function<sup>(9,10)</sup>. Patients with HF are more likely to have low serum Mg than other older individuals, and low serum Mg has been associated with all-cause mortality in HF patients<sup>(27,28)</sup>. Higher K excretion, which in part reflects greater intake, is associated with a lower rate of CVD<sup>(15)</sup>. Low serum K has been associated with mortality in the context of HF<sup>(29,30)</sup>. In addition, diet patterns and foods with high Ca, Mg and K content have been associated with incident HF<sup>(31–34)</sup>.

There are a number of potential explanations for the lack of associations observed in the present study. The present hypothesis that intake of Ca, Mg and K are associated with all-cause mortality in women with HF relied on the assumption that availability of these nutrients in the body is related to dietary consumption. HF patients are often aggressively treated with multiple medications, which could confound or mask any influence of diet. Diuretics, which are a mainstay of HF treatment, can directly make an impact on circulating levels of K and Mg through urinary excretion<sup>(35)</sup>. We did not have data to examine how dietary intake influences serum levels of Ca, Mg and K in the present population. Prior to HF hospitalisation, 42% of the population were treated with diuretics. The use of diuretics could weaken the relationship between intake of the micronutrients and the effective exposure to them. In fact, the women who died following hospitalisation for HF were more likely to have hypertension and to use diuretics. We adjusted for diuretic use and other medication use prior to hospitalisation, but we were not able to capture medication use following hospitalisation. Additionally, kidney dysfunction is very common in HF and may influence the retention and availability of Ca, Mg and K. We did not have measures of kidney function in the present population.

The present dietary assessment was not ideal. FFQ are known to have substantial errors, which reduces the power to detect modest effects of diet. In addition, we used dietary assessment prior to HF hospitalisation rather than dietary assessment at the time of HF hospitalisation, and the correlations between pre- and post-HF hospitalisation intake of nutrients were moderate. This could lead to misclassification of diet during the relevant time period, biasing results towards no association if the misclassification is not related to mortality. However, in the present study, the errors in exposure assessment may be related to mortality, and the resulting bias would depend on the relationship between the error and underlying likelihood of death. We were

not able to rule out unmeasured or residual confounding, for example, by severity of HF or kidney function, which were not assessed. We did not have information on left ventricular systolic function or adjudicated HF aetiology; the relationship between diet and mortality in patients with HF could plausibly differ by these characteristics. We did examine the relationship between the micronutrients and mortality in women with and without evidence of ischaemic disease prior to HF hospitalisation, and we did not find associations of Ca, Mg or K in women with or without history of IHD. Finally, dietary intake of these nutrients, rather than serum levels, simply may not affect mortality in HF patients. In addition to the limitations of the present study, there were important strengths. These included the racially and ethnically diverse population, the extensive information collected on the WHI participants, the large number of HF hospitalisations among these participants and the relatively long follow-up for post-HF hospitalisation mortality.

In summary, we did not find significant associations between intake of Ca, Mg or K and post-HF hospitalisation mortality in WHI participants. These results do not challenge the present dietary recommendation for HF patients. Further research is needed to conclusively determine whether nutrient intake can reduce mortality in HF patients.

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