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Relationship Between Dietary Magnesium Intake and Incident Heart Failure Among Older Women: The WHI

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Journal of the American Heart Association

ORIGINAL RESEARCH

Relationship Between Dietary Magnesium Intake and Incident Heart Failure Among Older Women: The WHI

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BACKGROUND: Women represent a large proportion of the growing heart failure (HF) epidemic, yet data are lacking regarding optimal dietary and lifestyle prevention strategies for them. Specifically, the association between magnesium intake and HF in a multiracial cohort of women is uncertain.

METHODS AND RESULTS: We included 97 725 postmenopausal women from the WHI (Women's Health Initiative) observational studies and placebo arms of the hormone trial. Magnesium intake was measured at baseline by a 122-item validated food-frequency questionnaire and stratified into quartiles based on diet only, total intake (diet with supplements), and residual intake (calibration by total energy). Incident hospitalized HF (2153 events, median follow-up 8.1 years) was adjudicated by medical record abstraction. In Cox proportional hazards models, we evaluated the association between magnesium intake and HF adjusting for potential confounders. Analyses were repeated on a subcohort (n=18 745; median-follow-up, 13.2 years) for whom HF cases were subclassified into preserved ejection fraction (526 events), reduced ejection fraction (291 events) or unknown (168 events). Most women were white (85%) with a mean age of 63. Compared with the highest quartile of magnesium intake, women in the lowest quartile had an increased risk of incident HF, with adjusted hazard ratios of 1.32 (95% CI, 1.02–1.71) for diet only (*P* trend=0.03), 1.26 (95% CI, 1.03–1.56) for total intake, and 1.31 (95% CI, 1.02–1.67) for residual intake. Results did not significantly vary by race. Subcohort analyses showed low residual magnesium intake was associated with HF with reduced ejection fraction (hazard ratio, 1.81, lowest versus highest quartile; 95% CI, 1.08–3.05) but not HF with preserved ejection fraction.

CONCLUSIONS: Low magnesium intake in a multiracial cohort of postmenopausal women was associated with a higher risk of incident HF, especially HF with reduced ejection fraction.

Key Words: heart failure with preserved ejection fraction ■ heart failure with reduced ejection fraction ■ residual method ■ total magnesium

In 2015, it was estimated that 5.7 million individuals over the age of 20 in the United States have been diagnosed with heart failure (HF).[1] Of those diagnosed with HF, 3 million were women. It is estimated that 455 000 new HF cases will be diagnosed in women older than 45 years each year.[1] However, data are lacking regarding optimal dietary and lifestyle prevention strategies for HF in this population.

Low serum and dietary magnesium have been associated with risk factors of HF, such as coronary heart disease,[2] insulin resistance,[3] type 2 diabetes mellitus,[4] hypertension,[5,6] and atrial fibrillation.[7] Dietary

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CLINICAL PERSPECTIVE

What Is New?

- The association between magnesium intake and heart failure in a multiracial cohort of women is unknown.
- This study showed that lower dietary intake of magnesium was associated with higher incidence rates of hospitalization for heart failure in postmenopausal women.
- In subgroup analyses, low dietary magnesium was associated with incident hospitalization for heart failure with reduced ejection fraction but not preserved ejection fraction.

What Are the Clinical Implications?

- These results suggest that ≈75% of postmenopausal women in this cohort have a median magnesium intake below US Recommended Daily Allowance levels, and a quarter of them are at increased risk of incident heart failure based on their dietary magnesium intake.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
JHS	Jackson Heart Study
LV	left ventricular
OS	observational study
WHI	Women's Health Initiative.

magnesium intake is also associated with HF hospitalizations in African-Americans in the Jackson Heart Study[8] and could potentially be a target for lifestyle modification and HF prevention, as >80% of older adults in the United States are not meeting dietary magnesium recommendations.[9] However, it is known that racial differences exist in magnesium intake,[9] and magnesium intake requirements are different for men and women.[10] Yet data are lacking on the relationship between dietary magnesium and HF in a multiracial cohort of women. Moreover, the relationship between magnesium intake and the type of HF (HF with preserved ejection fraction [HFpEF] or HF with reduced ejection fraction [HFrEF]) is unknown and would be important to understand potential mechanistic pathways of this relationship.

Because risk factors and the incidence and type of HF vary by women of different race,[11] understanding the association between magnesium intake and the risk of developing HF and its subtypes in a multiracial cohort of women represents a novel and potentially useful approach to identifying women at increased risk for target prevention. The purpose of this study is to examine the relationship between dietary magnesium and incident HF in the WHI (Women's Health Initiative) study. We hypothesize that low dietary magnesium intake will be associated with an increased risk of incident hospitalizations for HF. The prospective design of the WHI, the long follow-up, and availability of comprehensive dietary information and lifestyle factors in this clinically well-characterized multiracial population allow us the unique opportunity to rigorously test this hypothesis in postmenopausal women.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the WHI at https://www.whi.org/researchers/data/Pages/Home.aspx.

Study Population

The WHI recruited a total of 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the United States between 1993 and 1998, including a cohort of 93 676 women in a prospective observational study (OS) and 68 133 women in ≥1 of the following 3 clinical trials: hormone therapy, calcium and vitamin D, or dietary modification trial.[12] The calcium and vitamin D trial participants were recruited from the hormone therapy and dietary modification trials. The primary analysis included participants of the OS and control arm of the hormone therapy trial who completed baseline physical examination, demographic, medical history, and dietary questionnaires. Overall, baseline characteristics of participants from the OS and the hormone therapy trials were grossly similar except for college education (43% versus 32%), income <$20 000 per annum (14% versus 21%), mean body mass index (BMI; 27.2±5.8 versus 28.4±5.9), recreational physical activity (13.8±14.4 versus 11.9±13.8 metabolic equivalents/week), diabetes mellitus prevalence (3.8% versus 5.2%), and multivitamin use (42% versus 36.0%), respectively. Participants in the dietary modification trial were excluded from the analysis,

as baseline diet would not reflect a stable diet, and because of potential selection bias of a high percentage of dietary fat as an inclusion criterion for the dietary modification trial. Participants with HF at baseline were excluded as established by self-reporting on the eligibility screening and baseline medical history questionnaires, in which participants were asked to self-identify if they have ever been told by a doctor that they have HF or congestive HF. Participants were also excluded if they had a baseline energy intake outside the range of 600 kcal to 5000 kcal/day because of potential misclassification (Figure 1).[13] Given that this project used only deidentified data from the WHI, it met the criteria for exemption by the Providence Veterans Affairs Medical Center Institutional Review Board.

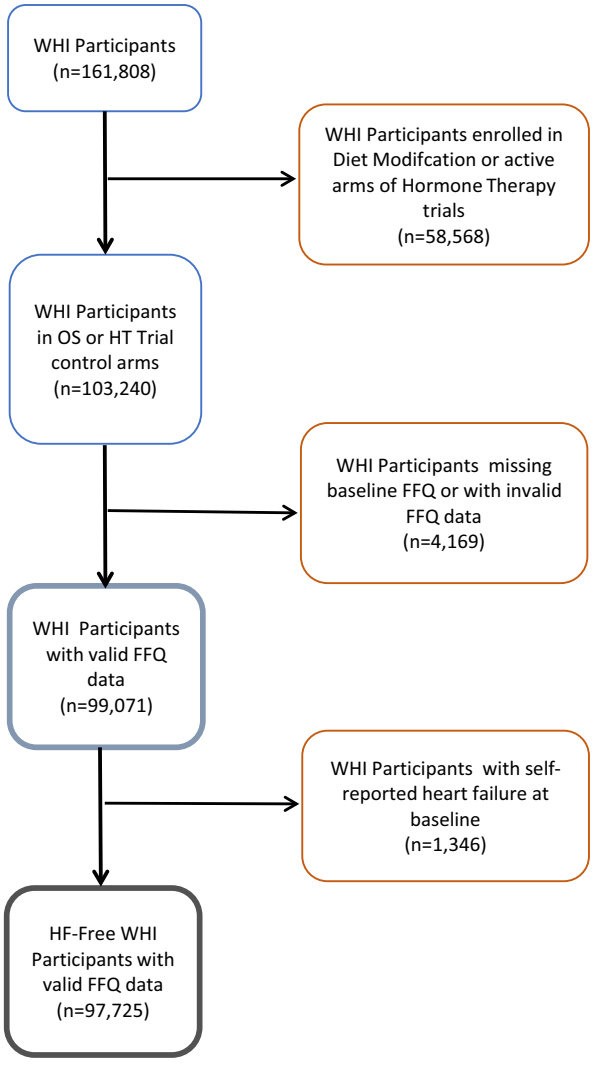

Figure 1. Flow diagram of WHI participants in the analysis. FFQ indicates food frequency questionnaire; OS, observational study; and WHI, Women's Health Initiative.

Exposure: Dietary Magnesium

Dietary magnesium intake was derived using a semiquantitative food frequency questionnaire that assessed nutrient intake over the past 3 months.[13–15] The nutrient database for the WHI food frequency questionnaire was adapted from the University of Minnesota Nutrition Coding Center (Minneapolis, MN) nutrient database.[16] The food frequency questionnaire was administered to all WHI participants at baseline. We used the baseline unadjusted measurements for dietary magnesium, as well as the residual method in which dietary magnesium was linearly regressed on calibrated total energy intake, and the residuals were used as the independent variable (exposure) in the subsequent analysis.[17] Total energy intake was calibrated using the equation derived from a study using recovery biomarkers previously in a subsample of the OS participants, accounting for age, race, and BMI.[18] Both dietary magnesium intake and residual magnesium intake were divided into quartiles.

Because participants could also ingest magnesium through oral supplementation, we constructed a total magnesium variable as a sensitivity analysis, which is the sum of dietary and supplemental magnesium. Data on magnesium supplement were obtained through the inventory of the patient's medication and supplement bottles brought in to the interviewer at baseline clinic visits and coded into a database through a standardized inventory procedure. In centers without direct access to a computer, a standardized interviewer-administered form was used to collect the information.[19,20] Because supplemental intake was measured by a separate methodology, we were not able to use the residual method for the total magnesium variable.

Outcome: Incident HF Hospitalizations

The primary outcome was incident hospitalization for HF, which was ascertained yearly in WHI by medical record abstraction of all self-report hospitalizations and classified by trained adjudicators using the standardized methodology as previously described.[21] Hospitalized HF requiring and/or occurring during hospitalization required physician diagnosis of new-onset or worsened HF on the reported hospital admission and ≥1 of the following 4 criteria: HF diagnosed by physician and receiving medical treatment for HF; symptoms plus documentation in the current medical record of a history of an imaging procedure showing impaired left ventricular (LV) systolic or diastolic LV function; pulmonary edema/congestion on chest radiograph on the current admission; or dilated ventricle(s) or "poor" LV or right ventricular function by echocardiography, radionuclide ventriculography,

or other contrast ventriculography or evidence of LV diastolic dysfunction. This method was found to have a 79% agreement rate comparing central adjudicated HF and local adjudication.[21]

In 2010, a subcohort of the WHI OS and hormone therapy trial oversampled for black and Hispanic participants, were retrospectively evaluated for HFpEF and HFrEF and then followed until March 31, 2018. Of the 44 174 participants in this subcohort, 18 745 were included in a subgroup analysis in this study to determine the etiology of HFpEF or HFrEF (secondary outcome) using the same exclusion criteria as the primary analysis (Figure S1).

Statistical Analysis

Descriptive statistics were generated for baseline covariates within quartiles of unadjusted dietary magnesium intake. Specifically, mean and SD were generated as descriptive statistics for each continuous covariate, while frequency and percentages were generated for each categorical covariate.

We used Cox proportional hazards models to estimate the hazard ratios (HRs) of HF for each quartile of magnesium intake, using the highest intake quartile as reference. Analyses were conducted first for quartiles of unadjusted magnesium intake adjusted for total energy intake, followed by quartiles of residual magnesium intake and then by quartiles of total magnesium intake accounting for supplemental magnesium. The time to HF event was calculated as the interval between baseline and incident HF, with censoring at last follow-up visit or death. Potential selection bias was accounted for by inverse probability weighting by membership in the OS or hormone therapy cohorts. The proportional hazard assumption was checked by visual examination of the survival curves. Potential confounders measured at baseline, determined on the basis of previous knowledge and prior literature, were included in the multivariable Cox proportional hazards models if the covariate was determined to be not on the causal pathway. As such, we used a sequential approach to analysis in which we constructed 5 submodels, each nested within the next (Table S1). In the final model, we adjusted for age; race; smoking status; BMI; dyslipidemia; systolic blood pressure; prior coronary heart disease; atrial fibrillation; heart rate; hypertension; diabetes mellitus; dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, and calibrated total energy, as these factors may influence body magnesium handling and storage)[22–24]; and medications, such as diuretics (hydrochlorothiazide, furosemide), mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, magnesium containing laxatives, proton pump inhibitors, or multivitamins, as these medications may affect magnesium exposure and potentially the outcome of HF. Sensitivity analyses were conducted, (1) excluding participants on diuretics and (2) excluding the first year of follow-up from the analysis to test the robustness of the findings. Stratified analyses were conducted by race (white versus nonwhite) and by using race-specific quartiles of magnesium intake.

We tested for the interaction on the multiplicative scale between dietary magnesium intake with age and race, as well as with comorbid diseases that predispose patients to hypomagnesemia (diabetes mellitus), respectively, and incident HF by including product terms for each interaction separately, in the full model. Trend testing across magnesium quartiles was conducted using the median magnesium value within each quartile. A subgroup analysis was conducted in the 18 745 participants from the 2010 subcohort to determine the subtype of HF (HFpEF or HFrEF).

All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Among 103 240 participants in the WHI OS or the placebo arm of the hormone therapy trials, 97 725 were included in the primary analysis. We observed 2153 HF cases over a median follow-up of 8.1 years. The median dietary magnesium intake across quartiles were 149 mg/day for women in the lowest quartile (mean 144.4±26.9), 212 mg/day (mean 212.3±17.1) for those in the second quartile, 272 mg/day (mean 273.3±19.3) for the third quartile, and 363 mg/day (mean 383.1±69.1) for the highest quartile of intake. Women in the lower quartiles of dietary magnesium intake were more likely to be aged 70 years or older, less likely to be white, had lower education and income, more likely to be current smokers, had lower recreational physical activity and slightly higher systolic blood pressure, and more likely to have hypertension, diabetes mellitus, dyslipidemia, and prior coronary heart disease. They also had lower dietary intake of alcohol, calcium, phosphorus, protein, potassium, sodium, vitamin D, and multivitamins and had lower total energy; and higher use of angiotensin-converting enzyme inhibitors, diuretics, and proton pump inhibitors (Table 1).

Compared with those in the highest quartile of unadjusted dietary magnesium intake, women in the lowest quartile had 1.32 times (95% CI, 1.02–1.71) the hazard of incident HF in a fully adjusted model (Table 2), the hazards of which decreased in a linear fashion with higher dietary magnesium intake (*P* value for linear trend=0.03). Results were similar using residual

Table 1. Demographic and Physiologic Characteristics (n=97 725)

	Uncalibrated Baseline Dietary Magnesium Intake Quartiles			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
N	21 869	25 002	25 475	25 379
Magnesium median, mg/d*	149	212	272	363
HF cases	522	558	551	522
HF incidence†	3.10 (3.09–3.12)	2.84 (2.83–2.86)	2.73 (2.72–2.74)	2.59 (2.57–2.60)
Age (y) continuous				
Mean (SD)	63.7 (7.4)	63.6 (7.3)	63.7 (7.3)	63.4 (7.3)
Age (y) categorical				
<50–59	6904 (31.6)	7920 (31.7)	7926 (31.1)	8299 (32.7)
60–69	9456 (43.2)	11 042 (44.2)	11 390 (44.7)	11 283 (44.5)
70 to ≥79	5509 (25.2)	6040 (24.2)	6159 (24.2)	5797 (22.8)
Race				
American Indian	143 (0.7)	95 (0.4)	88 (0.4)	85 (0.3)
Asian	870 (4.0)	727 (2.9)	553 (2.2)	514 (2.0)
Black	2903 (13.3)	1793 (7.2)	1322 (5.2)	1316 (5.2)
Hispanic	1258 (5.8)	935 (3.8)	690 (2.7)	746 (3.0)
White‡	16 403 (75.0)	21 181 (84.7)	22 577 (88.6)	22 447 (88.4)
Other	292 (1.3)	271 (1.1)	245 (1.0)	271 (1.1)
Education				
Less than high school	1844 (8.5)	1234 (5.0)	928 (3.7)	836 (3.3)
High school	7190 (33.2)	6873 (27.7)	6157 (24.4)	5281 (21.0)
Some college	6030 (27.8)	6864 (27.7)	6710 (26.5)	6390 (25.4)
College or greater	6625 (30.6)	9828 (39.6)	11 487 (45.4)	12 665 (50.3)
Income				
<20 000	4334 (19.8)	3684 (14.7)	3169 (12.4)	3295 (13.0)
20 000 to <35 000	5059 (23.1)	5518 (22.1)	5518 (21.7)	5383 (21.2)
35 000 to <50 000	3996 (18.3)	4669 (18.7)	4868 (19.1)	4947 (19.5)
50 000 to <75 000	3543 (16.2)	4675 (18.7)	5039 (19.8)	4959 (19.5)
>75 000	3257 (14.9)	4658 (18.6)	5155 (20.2)	5052 (19.9)
Missing	1680 (7.7)	1798 (7.2)	1726 (6.8)	1743 (6.9)
Smoking status				
Never	11 048 (51.3)	12 338 (50.1)	12 573 (50.0)	12 862 (51.4)
Past	8435 (39.2)	10 569 (42.9)	11 157 (44.4)	11 001 (43.9)
Current	2056 (9.6)	1729 (7.0)	1422 (5.7)	1172 (4.7)
Body mass index, kg/m^2				
Mean (SD)	27.5 (5.9)	27.2 (5.7)	27.2 (5.8)	27.4 (6.0)
Weight, kg				
Mean (SD)	71.5 (17.0)	71.3 (16.5)	71.7 (16.5)	72.9 (17.2)
Heart rate, beats per min				
Mean (SD)	70 (12.4)	69 (12.3)	69 (11.9)	69 (12.0)
Systolic blood pressure, mm Hg				
Mean (SD)	128 (18.2)	127 (17.9)	126 (17.8)	127 (17.7)
Diastolic blood pressure, mm Hg				
Mean (SD)	75 (9.4)	75 (9.2)	75 (9.3)	75 (9.2)
Waist/hip ratio				
Mean (SD)	0.81 (0.09)	0.81 (0.08)	0.80 (0.08)	0.81 (0.08)
Total energy expenditure from recreational physical activity (METS/wk)				
Mean (SD)	10.9 (13.1)	13.2 (14.0)	14.3 (14.4)	15.9 (15.2)

(*Continued*)

Table 1. Continued

	Uncalibrated Baseline Dietary Magnesium Intake Quartiles			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Dietary magnesium intake, mg/d				
Mean (SD)	144.4 (26.9)	212.3 (17.1)	273.3 (19.3)	383.1 (69.1)
Supplemental magnesium intake, mg/d				
Mean (SD)	63.0 (146.3)	71.4 (149.1)	75.0 (153.9)	78.0 (155.1)
Total magnesium intake, mg/d				
Mean (SD)	207.5 (149.6)	283.7 (150.4)	348.2 (155.3)	461.1 (170.8)
Dietary protein intake				
Mean (SD)	39.9 (12.1)	55.8 (14.1)	69.9 (16.5)	95.9 (27.5)
Dietary phosphorus intake				
Mean (SD)	642.6 (170.3)	939.4 (192.2)	1216.0 (233.4)	1745.7 (467.6)
Potassium, mg/d				
Mean (SD)	1553.1 (347.7)	2233.1 (321.8)	2823.3 (381.2)	3840.6 (790.2)
Calcium intake, mg/d				
Mean (SD)	434.5 (182.8)	661.1 (235.3)	877.9 (295.7)	1298.6 (504.2)
Vitamin D, µg/d				
Mean (SD)	2.3 (1.3)	3.4 (1.8)	4.6 (2.4)	6.9 (4.0)
Sodium intake, mg/d				
Mean (SD)	1632.5 (484.7)	2244.1 (583.7)	2775.4 (688.8)	3795.4 (1158.5)
Alcohol, servings/wk				
Mean (SD)	1.83 (4.13)	2.42 (4.66)	2.86 (5.29)	3.12 (6.38)
Calibrated total energy, kcal/d				
Mean (SD)	2220 (263.9)	2255 (261.0)	2282 (267.1)	2332 (282.7)
Hypertension				
Yes	7555 (35.4)	7993 (32.7)	7856 (31.6)	7835 (31.5)
Diabetes mellitus				
Yes	980 (4.5)	951 (3.8)	900 (3.5)	1033 (4.1)
Dyslipidemia				
Yes	2049 (9.4)	2374 (9.5)	2297 (9.0)	2138 (8.4)
Previous coronary heart disease				
Yes	1546 (7.1)	1625 (6.5)	1581 (6.2)	1535 (6.1)
Atrial fibrillation				
Yes	960 (4.4)	1031 (4.1)	1079 (4.2)	1092 (4.3)
Angiotensin receptor blockers				
Yes	155 (0.7)	196 (0.8)	160 (0.6)	190 (0.8)
Angiotensin-converting enzyme inhibitors				
Yes	1869 (8.6)	1960 (7.8)	1872 (7.4)	1745 (6.9)
Multivitamin				
Yes	7842 (35.9)	10 231 (40.9)	10 996 (43.2)	11 450 (45.1)
Diuretics				
Yes	3270 (15.0)	3379 (13.5)	3153 (12.4)	3042 (12.0)
Laxatives containing magnesium				
Yes	26 (0.1)	30 (0.1)	32 (0.1)	30 (0.1)
Proton pump inhibitors				
Yes	578 (2.6)	564 (2.3)	491 (1.9)	447 (1.8)

HF indicates heart failure.
*Range of dietary magnesium (mg/day) by quartiles: quartile 1: 0–181; quartile 2: 182–241; quartile 3: 242–309; quartile 4: 310–1004.
†Incidence rate per 1000 person-years' follow-up (95% CI).
‡266 participants with missing race/ethnicity information were allocated as white.

Table 2. Hazard Ratio of Incident Hospitalized HF (2005) by Quartiles of Magnesium Intake Using Unadjusted, Residual, and Total Intake Methods of Magnesium Intake Quantification

	Unadjusted Baseline Dietary Magnesium Intake Quartiles* (N=97 725)				
	Q1	Q2	Q3	Q4	
N	21 869	25 002	25 475	25 379	
HF cases	522	558	551	522	
HF incidence†	3.10 (3.09–3.12)	2.84 (2.83–2.86)	2.73 (2.72–2.74)	2.59 (2.57–2.60)	
	Hazard Ratio (95% CI)				
	Q1	Q2	Q3	Q4	*P* for Trend
Unadjusted	1.20 (1.06–1.36)	1.10 (0.98–1.24)	1.06 (0.94–1.19)	Referent	<0.01
Fully adjusted‡	1.32 (1.02–1.71)	1.17 (0.96–1.44)	1.08 (0.92–1.27)	Referent	0.03
Residual Baseline Dietary Magnesium Intake (Regression on Calibrated Total Energy Intake)§ (N=97 237)‖					
	Q1	Q2	Q3	Q4	
N	22 930	24 004	24 861	25 442	
HF cases	548	509	532	550	
HF incidence†	3.09 (3.08–3.11)	2.70 (2.68–2.71)	2.70 (2.69–2.72)	2.73 (2.72–2.74)	
	Hazard Ratio (95% CI)				
	Q1	Q2	Q3	Q4	*P* for Trend
Unadjusted	1.13 (1.01–1.27)	0.99 (0.88–1.11)	0.99 (0.88–1.12)	Referent	0.08
Fully adjusted‡	1.31 (1.02–1.67)	1.08 (0.89–1.32)	1.04 (0.89–1.22)	Referent	0.04
Unadjusted Baseline Total Magnesium Intake (Dietary and Supplemental Magnesium)¶ (N=97 725)					
	Q1	Q2	Q3	Q4	
N	21 683	24 368	25 555	26 119	
HF cases	556	558	514	525	
HF incidence†	3.32 (3.30–3.33)	2.91 (2.89–2.92)	2.54 (2.53–2.55)	2.54 (2.53–2.55)	
	Hazard Ratio (95% CI)				
	Q1	Q2	Q3	Q4	*P* for Trend
Unadjusted	1.30 (1.15–1.46)	1.14 (1.01–1.28)	1.00 (0.88–1.13)	Referent	<0.01
Fully adjusted‡	1.26 (1.03–1.56)	1.09 (0.93–1.29)	0.96 (0.84–1.11)	Referent	0.06

HF indicates heart failure; Q, Quartile.

*Range of dietary magnesium (mg/day) by quartiles: quartile 1: 0–181; quartile 2: 182–241; quartile 3: 242–309; quartile 4: 310–1004.

†Incidence rate per 1000 person-years' follow-up (95% CI).

‡Model stratified by observational study/hormone trial membership. Model adjusted for age, race, smoking status, body mass index, dyslipidemia, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, diabetes mellitus, dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy), medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, magnesium-containing laxatives, proton pump inhibitors), and multivitamins.

§Range of residual dietary magnesium by quartiles: quartile 1: –276 to –68; quartile 2: –67 to –12; quartile 3: –11 to 54; quartile 4: 55–750.

‖Sample size changed because of missingness in some variables used to calibrate total energy intake. Calibrated total energy as a variable was not included in the analysis using the residual method.

¶Range of total magnesium intake (mg/day) by quartiles: quartile 1: 0–211; quartile 2: 212–288; quartile 3: 289–382; quartile 4: 383–9275.

magnesium intake (HR, 1.31; 95% CI, 1.02–1.67, lowest versus highest quartile of intake; *P*-value for linear trend=0.04) and slightly attenuated in the total magnesium intake accounting for supplemental magnesium (HR, 1.26; 95% CI, 1.03, 1.56, lowest versus highest quartile of intake; *P* value for linear trend=0.06) (Table 2). Sensitivity analyses excluding participants on diuretic therapy (fully adjusted HR, 1.24; 95% CI, 0.92–1.67, lowest versus highest quartile of residual magnesium intake, n=84 449) or excluding the first year of follow-up (fully adjusted HR, 1.36; 95% CI, 1.05–1.76, lowest versus highest quartile of residual magnesium intake, n=97 077) showed similar HR trends, respectively.

In stratified analyses by race, results remained consistent among white women (n=82 608), with an adjusted hazard ratio of 1.43 (95% CI, 1.09–1.88, lowest versus highest quartile of intake; *P* value for linear trend=0.01) but attenuated and nonsignificant among nonwhite women (n=15 117; *P* value for linear trend=0.52 unadjusted, and *P*=0.67 using the

Table 3. Hazard Ratio of Incident Hospitalized HF (2005) by Race and by Quartiles of Magnesium Intake Using Unadjusted and Residual Intake Methods of Magnesium Intake Quantification

	Unadjusted Baseline Dietary Magnesium Intake Quartiles*				
	Q1	Q2	Q3	Q4	
	Number of HF cases (total number)				
White	412 (16 403)	487 (21 181)	497 (22 577)	472 (22 447)	
Nonwhite	110 (5466)	71 (3821)	54 (2898)	50 (2932)	
	HF incidence (95% CI)†				
White	3.22 (3.21–3.24)	2.90 (2.89–2.92)	2.76 (2.74–2.77)	2.62 (2.61–2.63)	
Nonwhite	2.72 (2.70–2.75)	2.49 (2.46–2.51)	2.50 (2.46–2.53)	2.29 (2.25–2.32)	
	Adjusted Hazard Ratios (95% CI)‡				*P* for Trend
	Q1	Q2	Q3	Q4	
White	1.43 (1.09–1.88)	1.25 (1.01–1.55)	1.13 (0.95–1.34)	Referent	0.01
Non-White	0.75 (0.35–1.62)	0.79 (0.43–1.46)	0.81 (0.48–1.38)	Referent	0.52
	Residual Baseline Dietary Magnesium Intake (Adjusted for Calibrated Energy)§				
	Q1	Q2	Q3	Q4	
	# HF cases (total #)				
White	432 (17 263)	440 (20 338)	486 (22 023)	501 (22 552)	
Non-White	116 (5667)	69 (3666)	46 (2838)	49 (2890)	
	HF incidence (95% CI)†				
White	3.19 (3.18–3.21)	2.73 (2.71–2.74)	2.77 (2.76–2.78)	2.78 (2.77–2.80)	
Non-White	2.77 (2.75–2.80)	2.51 (2.48–2.54)	2.16 (2.13–2.19)	2.28 (2.25–2.31)	
	Adjusted Hazard Ratios (95% CI)‡				*P* for Trend
	Q1	Q2	Q3	Q4	
White	1.42 (1.09–1.84)	1.14 (0.92–1.40)	1.10 (0.93–1.30)	Referent	0.01
Non-White	0.80 (0.37–1.69)	0.81 (0.45–1.48)	0.76 (0.45–1.30)	Referent	0.67

HF indicates heart failure; Q, Quartile.

*Range of dietary magnesium (mg/day) by quartiles: quartile 1: 0–181; quartile 2: 182–241; quartile 3: 242–309; quartile 4: 310–1004.

†Incidence rate per 1000 person-years' follow-up.

‡Model adjusted for age, smoking status, and traditional risk factors (body mass index, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, diabetes mellitus, dyslipidemia), dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy [not included in the analysis using the residual method]), medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, magnesium-containing laxatives, proton pump inhibitors), and multivitamins.

§Range of residual dietary magnesium by quartiles: quartile 1: −276 to −68; quartile 2: −67 to −12; quartile 3: −11 to 54; quartile 4: 55–750.

residual method; Table 3). The interaction terms between unadjusted magnesium intake (or residual magnesium) and race (*P*=0.84), age (*P*=0.37), and diabetes mellitus (*P*=0.65) were not statistically significant. Results remained similar when race-specific quartiles of magnesium intake were used.

For our subgroup analysis in the 2010 subcohort, we included 18 745 participants with 985 HF cases (526 HFpEF, 291 HFrEF, and 168 unknown HF type) over a median follow-up of 13.2 years (baseline characteristics, Table S2). Lower unadjusted dietary magnesium intake was significantly associated with higher hazards of HFrEF (HR=1.76 comparing lowest with highest quartile; 95% CI, 1.03–2.98; *P* value for linear trend=0.02) but not HFpEF (HR, 0.74 comparing lowest with highest quartile; 95% CI, 0.49–1.12; *P* value for linear trend=0.31; Table S3) in the fully adjusted model (Figure 2). Results were similar when residual dietary magnesium intake was used for both HFpEF (*P* value for linear trend=0.73 across quartiles) and HFrEF (*P* value for linear trend=0.01 across quartiles; Table S4). Results were no longer significant after accounting for total magnesium intake (adding magnesium supplements): *P* value for linear trend=0.24 across quartiles for HFpEF and 0.69 for HFrEF (Table S5). Sensitivity analyses excluding participants on diuretic therapy (fully adjusted HRs for HFpEF, 0.88; 95% CI, 0.54–1.41; and for HFrEF, 2.15; 95% CI, 1.19–3.87; lowest versus highest quartile of residual magnesium intake, n=15 593) or excluding the first year of follow-up (fully adjusted HRs for HFpEF, 0.99; 95% CI, 0.66–1.49; and for HFrEF, 1.76; 95% CI, 1.04–2.98; lowest versus highest quartile of residual magnesium intake, n=18 657) showed similar results, respectively.

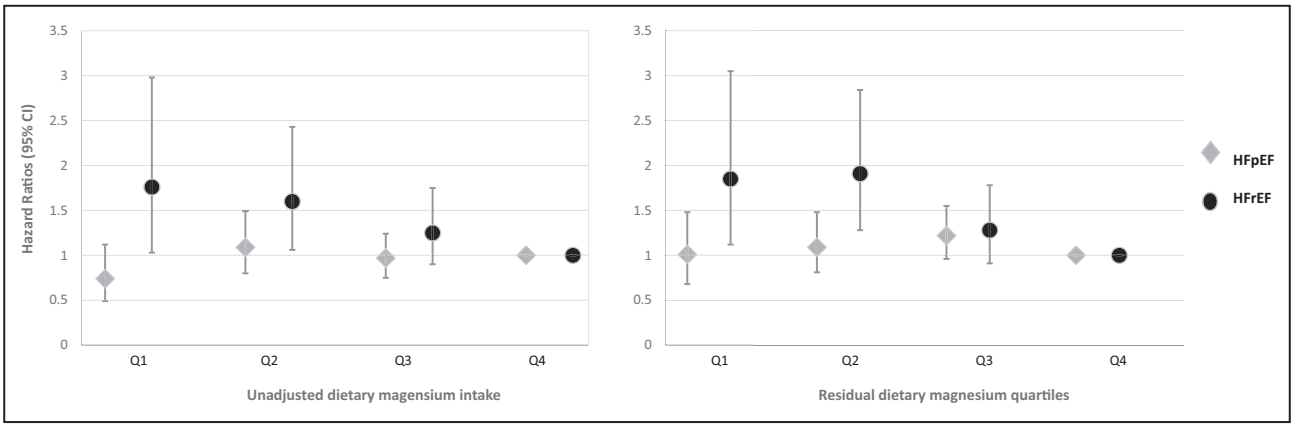

Figure 2. Hazard ratios (95% CI) of incident hospitalization for HFpEF) and HFrEF in 2010 subcohort by quartiles of unadjusted and residual magnesium intake, respectively.
Model adjusted for age, smoking status, and traditional risk factors (BMI, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, diabetes mellitus, dyslipidemia), dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy [not included in the analysis using the residual method]), medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, magnesium-containing laxatives, proton pump inhibitors), and multivitamins. BMI indicates body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

DISCUSSION

In this large, national, multiracial, prospective cohort study of postmenopausal women, lower dietary intake of magnesium was associated with higher incidence rates of hospitalization for HF. The relationship between quartiles of dietary magnesium and incident hospitalization for HF did not vary significantly by race, age, or presence of diabetes mellitus. In subgroup analyses, low dietary magnesium was associated only with incident hospitalized HFrEF but not HFpEF.

To our knowledge, this is one of the first studies that relates dietary magnesium in postmenopausal women to incident HF and its subtypes. Our results expand the previous findings that related higher magnesium intake to lower risk of hospitalizion for HF in black men and women from the JHS (Jackson Heart Study)[8] to women of other races. Although our results did not vary significantly by race, an attenuation of the association between dietary magnesium and HF to nonsignificant levels were found in the nonwhite women, which contrast the results in the JHS cohort. This discrepancy could be related to the differential dietary magnesium intake[9] and distinct risk of HF and its subtypes, which has been shown to vary by race.[11] Nonwhite women in our cohort had lower incidence rates of HF compared with whites, all of which remained under 1% and could have reduced our power to detect a statistically significant difference across quartiles of magnesium intake. In contrast, in the JHS cohort, despite a higher magnesium intake (mean of 181 and 474 mg in the lowest and highest quartiles of intake, respectively), a younger age (mean age, 55 years), and a shorter follow-up time (median, 1837 days), the rates of HF admission during follow-up remained high, at 1.1% per year. This is likely attributable to the high prevalence of diabetes mellitus (22%) and obesity (mean BMI, 31.8 kg/m^2) in the JHS, which conferred the cohort with a high risk for HF. Taken together, these findings do not show that the association between magnesium intake and incident HF significantly vary by race.

Potential mechanisms of the association between magnesium intake and HF hospitalizations can be several. Low serum and dietary magnesium have been associated with risk factors of HF, such as coronary disease,[2] left ventricular hypertrophy,[25] insulin resistance,[3] diabetes mellitus,[4] hypertension,[5,6] and atrial fibrillation,[7] which over time could lead to HF. The association between dietary magnesium with HFrEF but not HFpEF in our subgroup analysis is unique and requires further exploration of mechanisms. A 1-time infusion of elemental magnesium has been shown to acutely decreased LV filling pressures,[26] while the long-term effects of magnesium intake on the myocardium is not known. We postulate that the relationship between magnesium intake and HFrEF but not HFpEF may be in part explained by the vascular dilation effects of magnesium,[27] which mirrored the past vasodilator trials with angiotensin-converting enzyme inhibitors,[28] angiotensin receptor blockers,[29] and hydralazine and nitrates[30,31] and improved outcomes in patients with HFrEF but not HFpEF.[32,33] Hemodynamically, vasodilation using intravenous nitroprusside improved stroke volume in HFrEF but in much less magnitude in HFpEF.[34] Similarly, isosorbide did not significantly improve 6-minute walk distance or quality of life in participants with HFpEF.[33]

Based on the US Recommended Daily Allowance of dietary magnesium of 320 mg per day for nonpregnant women >30 years of age, the implications of our study are large, as ≈75% of postmenopausal women in this multicenter, multiracial cohort study have a magnesium intake (median, 272 mg for quartile 3) below Recommended Daily Allowances levels,[10] and our results suggest that a quarter of the postmenopausal women in this cohort are at increased risk of incident HF on the basis of their dietary magnesium intake. Our total magnesium intake analysis, which incorporated magnesium supplements, showed slight attenuation of the association between dietary magnesium and incident HF and could serve as preliminary data to explore how supplemental magnesium intake may attenuate the risk of HF. In addition, the ARIC (Atherosclerosis Risk in Communities) cohort demonstrated that low serum magnesium levels were associated with the development of incident HF.[35] It is plausible that habitually high intake of magnesium may eventually increase serum magnesium levels as a reflection of higher body stores to provide protective effects against HF.[36] Future studies are needed to further explore how magnesium supplementation may relate to HF risk.

Strengths of the current analysis include data from a large multiethnic prospective cohort of postmenopausal women that allowed for greater generalizability. The use of validated dietary data and a high-quality HF outcome adjudication process would facilitate future replication of our findings. The readjudication process in the WHI HF subtype cohort also allowed the secondary analysis examining HFpEF and HFrEF separately. We used inverse probability weighing to account for potential selection bias in the WHI cohort assembly subtypes. There were also limitations to this study. Despite our careful consideration of potential confounders, there is always the possibility of residual and/or unmeasured confounding. The dietary magnesium intake was only quantified at baseline and did not account for variations in magnesium intake over time and may have attenuated the results given the long duration of follow-up. The baseline HF criteria for exclusion into the study sample are based on self-report, which is low in sensitivity (28%–38%) but high in specificity (96%–97%)[37] and may lead to a nonselective misclassification bias and dilute the association between magnesium intake and incident HF hospitalizations. Additionally, data on kidney function were limited to only 10% of our study sample, for which adjustment for and interaction with kidney function in the analyses were not feasible. Finally, our analyses were restricted to women and thus not generalizable to men, but there has been no evidence that a clinically meaningful difference by sex exists on the association between dietary[8] or serum magnesium and cardiovascular end points.[35,38–40]

In conclusion, we demonstrated that low dietary magnesium in a multicenter, multiracial cohort of postmenopausal women was associated with a higher risk of incident HF, especially HFrEF.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S5
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Sub-models of Hazard ratio of incident hospitalized HF (2005) by quartiles (Q) of magnesium intake using unadjusted, residual and total intake methods of magnesium intake quantification

	Unadjusted baseline dietary magnesium intake quartiles* (N = 97,725)				
	Q1	**Q2**	**Q3**	**Q4**	
N	21,869	25,002	25,475	25,379	
HF cases	522	558	551	522	
HF incidence†	3.10 (3.09, 3.12)	2.84 (2.83, 2.86)	2.73 (2.72, 2.74)	2.59 (2.57, 2.60)	
		Hazard Ratio (95% CI)			p for trend
Unadjusted	1.20 (1.06, 1.36)	1.10 (0.98, 1.24)	1.06 (0.94, 1.19)	referent	<0.01
Model 1	1.15 (1.02, 1.30)	1.07 (0.95, 1.21)	1.02 (0.90, 1.15)	referent	0.02
Model 2	1.10 (0.97, 1.24)	1.04 (0.92, 1.18)	0.99 (0.88, 1.12)	referent	0.12
Model 3	1.14 (1.00, 1.29)	1.06 (0.94, 1.21)	1.01 (0.89, 1.14)	referent	0.04
Model 4	1.35 (1.04, 1.75)	1.19 (0.97, 1.46)	1.09 (0.92, 1.28)	referent	0.02
Model 5	1.32 (1.02, 1.71)	1.17 (0.96, 1.44)	1.08 (0.92, 1.27)	referent	0.03

	Residual baseline dietary magnesium intake (regression on calibrated total energy intake)‡ (N=97,237)§				
	Q1	**Q2**	**Q3**	**Q4**	
N	22,930	24,004	24,861	25,442	
HF cases	548	509	532	550	
HF incidence†	3.09 (3.08, 3.11)	2.70 (2.68, 2.71)	2.70 (2.69, 2.72)	2.73 (2.72, 2.74)	
		Hazard Ratio (95% CI)			p for trend
Unadjusted	1.13 (1.01, 1.27)	0.99 (0.88, 1.11)	0.99 (0.88, 1.12)	referent	0.08
Model 1	1.38 (1.23, 1.56)	1.08 (0.95, 1.21)	1.02 (0.90, 1.14)	referent	<0.01
Model 2	1.13 (1.00, 1.28)	0.99 (0.88, 1.12)	0.97 (0.86, 1.10)	referent	0.09
Model 3	1.18 (1.04, 1.33)	1.00 (0.88, 1.13)	0.98 (0.86, 1.10)	referent	0.02
Model 4	1.35 (1.06, 1.73)	1.10 (0.91, 1.35)	1.05 (0.90, 1.23)	referent	0.02
Model 5	1.31 (1.02, 1.67)	1.08 (0.89, 1.32)	1.04 (0.89, 1.22)	referent	0.04

Unadjusted baseline total magnesium intake (dietary and supplemental magnesium)‖ (N = 97,725)					
	Q1	**Q2**	**Q3**	**Q4**	
N	21,683	24,368	25,555	26,119	
HF cases	556	558	514	525	
HF incidence†	3.32 (3.30, 3.33)	2.91 (2.89, 2.92)	2.54 (2.53, 2.55)	2.54 (2.53, 2.55)	
		Hazard Ratio (95% CI)			p for trend
Unadjusted	1.30 (1.15, 1.46)	1.14 (1.01, 1.28)	1.00 (0.88, 1.13)	referent	<0.01
Model 1	1.29 (1.14, 1.45)	1.11 (0.98, 1.25)	0.97 (0.86, 1.10)	referent	<0.01
Model 2	1.19 (1.05, 1.34)	1.08 (0.95, 1.22)	0.95 (0.84, 1.07)	referent	<0.01
Model 3	1.19 (1.05, 1.35)	1.06 (0.93, 1.20)	0.94 (0.83, 1.07)	referent	0.01
Model 4	1.29 (1.08, 1.54)	1.11 (0.95, 1.29)	0.97 (0.85, 1.11)	referent	0.01
Model 5	1.26 (1.03, 1.56)	1.09 (0.93, 1.29)	0.96 (0.84, 1.11)	referent	0.06

Models stratified by Observational Study/Hormone Trial membership
Model 1 adjusted for age;

Model 2 adjusted for age, race, smoking status, BMI, and dyslipidemia;

Model 3 was model 2 + prior coronary heart disease, atrial fibrillation, heart rate, hypertension, and diabetes;

Model 4 was Model 3 + dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy); calibrated total energy as a variable was not included in the analysis using the Residual method

Model 5 (full model) was Model 4 + medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, Mg containing laxatives, proton pump inhibitors) and multivitamins.

** range of dietary magnesium (mg/day) by quartiles: Q1: 0 to 181; Q2: 182 to 241; Q3: 242 to 309; Q4: 310 to 1004*
† *incidence rate per 1000 person-years follow up (95% CI)*
‡ *range of residual dietary magnesium by quartiles: Q1: -276 to -68; Q2: -67 to -12; Q3: -11 to 54; Q4: 55 to 750*
§ Sample size changed due to missingness in some variables used to calibrate total energy intake.
|| *range of total magnesium intake (mg/day) by quartiles: Q1 0 to 211; Q2 212 to 288; Q3 289 to 382; Q4 383 to 9275*

Table S2. Baseline Characteristics of Heart Failure Type, 2010 Sub-cohort (n=18,745).

	Un-calibrated baseline dietary magnesium intake quartiles			
	Q1	**Q2**	**Q3**	**Q4**
N	5905	4755	4082	4003
Magnesium median (mg/day)	143	211	271	366
HF cases	250	280	233	222
HF incidence*	3.55 (3.53, 3.58)	4.60 (4.58, 4.63)	4.05 (4.03, 4.08)	4.09 (4.06, 4.11)
Age (years) continuous				
mean (SD)	62.4 (7.3)	62.7 (7.4)	63.0 (7.3)	62.8 (7.4)
Age (years) categorical				
<50 - 59	2218 (37.6)	1742 (36.6)	1434 (35.1)	1472 (36.8)
60 - 69	2584 (43.8)	2047 (43.1)	1764 (43.2)	1671 (41.7)
70 - ≥79	1103 (18.7)	966 (20.3)	884 (21.7)	860 (21.5)
Race				
American Indian	13 (0.2)	8 (0.2)	11 (0.3)	10 (0.3)
Asian	60 (1.0)	49 (1.0)	39 (1.0)	30 (0.8)
Black	2903 (49.2)	1793 (37.7)	1322 (32.4)	1316 (32.9)
Hispanic	1258 (21.3)	935 (19.7)	690 (16.9)	746 (18.7)
White	1635 (27.7)	1945 (40.9)	1992 (48.9)	1873 (46.8)
Other	27 (0.5)	22 (0.5)	22 (0.5)	26 (0.7)
Education				
<High School	954 (16.4)	533 (11.3)	390 (9.7)	375 (9.5)
High School	1932 (33.1)	1423 (30.3)	1128 (27.9)	945 (23.9)
Some College	1468 (25.2)	1253 (26.7)	1064 (26.3)	1029 (26.0)
≥College	1480 (25.4)	1490 (31.7)	1461 (36.1)	1605 (40.6)
Income				
<20,000	1817 (30.8)	1100 (23.1)	878 (21.5)	900 (22.5)
20,000 - <35,000	1325 (22.4)	1158 (24.4)	1011 (24.8)	960 (24.0)
35,000 - <50,000	986 (16.7)	890 (18.7)	713 (17.5)	777 (19.4)

50,000 - <75,000	791 (13.4)	719 (15.1)	671 (16.4)	617 (15.4)
>75,000	479 (8.1)	513 (10.8)	507 (12.4)	474 (11.8)
Missing	507 (8.6)	375 (7.9)	302 (7.4)	275 (6.9)
Smoking status				
Never	3050 (52.6)	2381 (51.0)	2034 (50.7)	2053 (52.4)
Past	1980 (34.2)	1808 (38.7)	1608 (40.1)	1574 (40.1)
Current	767 (13.2)	481 (10.3)	371 (9.2)	295 (7.5)
Body Mass Index (kg/m2)				
mean (SD)	29.4 (6.4)	29.0 (6.1)	29.0 (6.2)	29.4 (6.5)
Weight (kg)				
mean (SD)	76.3 (18.2)	75.6 (17.5)	76.0 (17.6)	77.3 (18.5)
Heart rate (beats per minute)				
mean (SD)	70 (12.5)		70 (12.6)	70 (11.5)
Systolic Blood Pressure (mm Hg)				
mean (SD)	130 (18.3)	129 (17.5)	129 (17.9)	129 (17.7)
Diastolic Blood pressure (mm Hg)				
mean (SD)	77 (9.6)	76 (9.2)	76 (9.5)	76 (9.4)
Waist/Hip Ratio				
mean (SD)	0.82 (0.08)	0.82 (0.08)	0.82 (0.08)	0.82 (0.08)
Total energy expenditure from recreational physical activity (METS/week)				
mean (SD)	9.2 (12.5)	11.6 (13.6)	12.2 (14.2)	14.0 (15.4)
Dietary magnesium intake (mg/day)				
mean (SD)	138.9 (29.0)	211.0 (16.9)	272.2 (19.1)	388.4 (75.4)
Total magnesium intake (mg/day)				
mean (SD)	182.1 (116.7)	265.1 (123.6)	329.3 (130.2)	447.2 (147.4)
Potassium (mg/day)				
mean (SD)	1462.2 (364.1)	2180.8 (334.5)	2775.9 (404.4)	3862.4 (880.5)
Calcium intake (mg/day)				
mean (SD)	400.3 (175.5)	632.1 (230.3)	838.9 (294.9)	1272.8 (530.7)
Dietary protein intake (grams)				
mean (SD)	39.56 (12.9)	56.9 (15.6)	72.0 (18.7)	101.9 (32.6)
Dietary phosphorus intake (mg)				
mean (SD)	624.6 (178.3)	941.1 (204.1)	1216.8 (249.2)	1791.7 (516.3)

Vitamin D (mcg/d)				
mean (SD)	2.1 (1.3)	3.4 (1.8)	4.4 (2.4)	6.8 (4.3)
Sodium intake (mg/day)				
mean (SD)	1618.5 (524.3)	2301.4 (644.4)	2875.0 (774.7)	4094.6 (1394.3)
Alcohol (servings/wk)				
mean (SD)	1.27 (3.66)	1.80 (4.28)	2.31 (5.43)	2.73 (7.04)
Calibrated total energy (kcal/day)				
mean (SD)	2272 (284.5)	2301 (280.0)	2326 (284.1)	2382 (313.5)
Hypertension				
Yes	2431 (43.1)	1772 (39.2)	1464 (37.9)	1452 (38.3)
Diabetes mellitus				
Yes	490 (8.3)	363 (7.7)	286 (7.0)	311 (7.8)
Dyslipidemia				
Yes	485 (8.2)	434 (9.1)	371 (9.1)	303 (7.6)
Previous coronary heart disease				
Yes	467 (7.9)	368 (7.7)	306 (7.5)	263 (6.6)
Atrial fibrillation				
Yes	249 (4.2)	161 (3.4)	149 (3.7)	158 (4.0)
Angiotensin receptor blockers				
Yes	41 (0.7)	36 (0.8)	20 (0.5)	20 (0.5)
Angiotensin converting enzyme inhibitors				
Yes	601 (10.2)	447 (9.4)	335 (8.2)	298 (7.4)
Multivitamin				
Yes	1607 (27.2)	1534 (32.3)	1398 (34.3)	1442 (36.0)
Diuretics				
Yes	1074 (18.2)	821 (17.3)	621 (15.2)	586 (14.6)
Laxatives containing magnesium				
Yes	15 (0.3)	8 (0.2)	5 (0.1)	3 (0.1)
Proton pump inhibitors				
Yes	129 (2.2)	112 (2.4)	70 (1.7)	60 (1.5)

** incidence rate per 1000 person-years follow up (95% CI)*
HF = heart failure, SD = Standard Deviation

Table S3. Hazard ratio of incident hospitalized preserved & reduced heart failure in 2010 sub-cohort by quartiles (Q) of unadjusted magnesium intake.

Heart Failure with preserved Ejection Fraction (HFpEF)

	Unadjusted baseline dietary magnesium intake				
	Q1	**Q2**	**Q3**	**Q4**	
N	5905	4755	4082	4003	
HFpEF cases	121	155	133	119	
HFpEF incidence*	1.81 (1.80, 1.82)	2.63 (2.61, 2.64)	2.30 (2.29, 2.32)	2.24 (2.23, 2.26)	
		HR (95% CI)			p for trend
Unadjusted	0.85 (0.70, 1.02)	1.19 (1.00, 1.42)	1.02 (0.86, 1.22)	referent	0.37
Fully-Adjusted	0.74 (0.49, 1.12)	1.09 (0.80, 1.49)	0.97 (0.75, 1.24)	referent	0.31

Heart Failure with reduced Ejection Fraction (HFrEF)

	Unadjusted baseline dietary magnesium intake				
	Q1	**Q2**	**Q3**	**Q4**	
N	5905	4755	4082	4003	
HFrEF cases	86	72	71	64	
HFrEF incidence*	1.18 (1.17, 1.19)	1.18 (1.17, 1.19)	1.28 (1.27, 1.28)	1.13 (1.13, 1.14)	
		HR (95% CI)			p for trend
Unadjusted	1.08 (0.84, 1.38)	1.06 (0.83, 1.36)	1.13 (0.88, 1.44)	referent	0.65
Fully-Adjusted	1.76 (1.03, 2.98)	1.60 (1.06, 2.43)	1.25 (0.88, 1.75)	referent	0.02

Model adjusted for age, race, smoking status, BMI, and dyslipidemia, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, and diabetes, dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy), medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, magnesium containing laxatives, proton pump inhibitors) and multivitamins.

** incidence rate per 1000 person-years follow up (95% CI)*

Table S4. Hazard ratio of incident hospitalized preserved & reduced heart failure in 2010 sub-cohort by quartiles (Q) of residual magnesium intake after regression on calibrated total energy intake

Heart Failure with preserved Ejection Fraction (HFpEF)

	Residual baseline dietary magnesium intake (adjusted for calibrated energy)				
	Q1	**Q2**	**Q3**	**Q4**	
N*	6337	4528	3951	3868	
HFpEF cases	140	129	148	109	
HFpEF incidence†	1.95 (1.94, 1.96)	2.24 (2.23, 2.25)	2.69 (2.67, 2.70)	2.14 (2.13, 2.16)	
		HR (95% CI)			p for trend
Unadjusted	0.94 (0.79, 1.13)	1.06 (0.88, 1.27)	1.25 (1.04, 1.49)	referent	0.30
Fully-Adjusted	0.97 (0.65, 1.46)	1.07 (0.78, 1.47)	1.21 (0.94, 1.55)	referent	0.73

Heart Failure with reduced Ejection Fraction HFrEF

	Residual baseline dietary magnesium intake (adjusted for calibrated energy)				
	Q1	**Q2**	**Q3**	**Q4**	
N*	6337	4528	3951	3868	
HFrEF cases	84	76	67	64	
HFrEF incidence†	1.07 (1.06, 1.07)	1.33 (1.32, 1.34)	1.23 (1.22, 1.24)	1.17 (1.17, 1.18)	
		HR (95% CI)			p for trend
Unadjusted	0.93 (0.73, 1.20)	1.15 (0.90, 1.46)	1.05 (0.82, 1.36)	referent	0.09
Fully-Adjusted	1.81 (1.08, 3.05)	1.90 (1.26, 2.86)	1.28 (0.91, 1.80)	referent	0.01

Model adjusted for age, race, smoking status, BMI, and dyslipidemia, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, and diabetes, dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy), medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, Mg containing laxatives, proton pump inhibitors) and multivitamins.

* Sample size changed due to missingness in some variables used to calibrate total energy intake.

† *incidence rate per 1000 person-years follow up (95% CI)*

Table S5. Hazard ratio of incident hospitalized preserved & reduced heart failure in 2010 sub-cohort by quartiles (Q) of total magnesium intake (accounting for magnesium supplements).

Heart Failure with preserved Ejection Fraction (HFpEF)

	Unadjusted total dietary magnesium intake				
	Q1	**Q2**	**Q3**	**Q4**	
N	6137	4819	4100	3689	
HFpEF cases	146	131	147	104	
HFpEF incidence*	2.13 (2.12, 2.14)	2.11 (2.10, 2.12)	2.66 (2.64, 2.68)	2.07 (2.06, 2.09)	
		HR (95% CI)			p for trend
Unadjusted	1.08 (0.90, 1.30)	1.03 (0.85, 1.24)	1.28 (1.07, 1.54)	referent	0.82
Fully-Adjusted	1.25 (0.89, 1.76)	1.11 (0.85, 1.45)	1.25 (1.01, 1.56)	referent	0.24

Heart Failure with reduced Ejection Fraction HFrEF

	Unadjusted total dietary magnesium intake				
	Q1	**Q2**	**Q3**	**Q4**	
N	6137	4819	4100	3689	
HFrEF cases	86	83	65	59	
HFrEF incidence*	1.11 (1.10, 1.12)	1.34 (1.33, 1.35)	1.15 (1.14, 1.16)	1.17 (1.16, 1.17)	
		HR (95% CI)			p for trend
Unadjusted	0.99 (0.77, 1.27)	1.16 (0.91, 1.47)	0.98 (0.76, 1.27)	referent	0.76
Fully-Adjusted	1.05 (0.67, 1.65)	1.13 (0.80, 1.60)	0.90 (0.67, 1.21)	referent	0.69

Model adjusted for age, race, smoking status, BMI, and dyslipidemia, systolic blood pressure, prior coronary heart disease, atrial fibrillation, heart rate, hypertension, and diabetes, dietary intake (sodium, potassium, calcium, alcohol, protein, phosphorus, calibrated total energy), medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, Mg containing laxatives, proton pump inhibitors) and multivitamins.

** incidence rate per 1000 person-years follow up (95% CI)*

Figure S1.