Balkan Med J 2025;42:452-63

The Associations of Dietary Copper and Magnesium Intake, Geriatric Nutritional Risk Index, and Systemic Inflammation Response Index with Stroke Risk in the Elderly

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Background: The effects of dietary copper and magnesium intake, the geriatric nutritional risk index (GNRI), and the systemic inflammation response index (SIRI) on stroke risk in the elderly remain unclear.

Aims: To examine the relationships between dietary copper and magnesium intake, GNRI, SIRI, and stroke risk in the elderly.

Study Design: Cross-sectional study.

Methods: Data from 7,157 elderly participants in National Health and Nutrition Examination Survey 2007-2016 were analyzed using multifactorial logistic regression, subgroup analysis, smooth curve fitting, threshold effect analysis, mediation analysis, and sensitivity analysis.

Results: Higher dietary copper and magnesium intake were significantly and linearly associated with lower stroke risk. SIRI was positively associated with stroke risk, while GNRI had a stable protective effect. In fully adjusted models, medium- and high-level copper and magnesium intake were positively associated with GNRI and negatively associated with SIRI. GNRI mediated 4.4% and 5.5% of the associations between copper and magnesium intake and stroke risk, respectively; SIRI mediated 3.4% and 2.9%, respectively.

Conclusion: Higher dietary copper and magnesium intake are associated with reduced stroke risk in the elderly, with GNRI and SIRI exerting modest mediating effects.

INTRODUCTION

Globally, stroke is a leading cause of mortality and long-term functional impairment. In the United States, approximately 800,000 people experience a stroke each year, accounting for about 5.2% of all deaths.[1] Compared with younger adults, older individuals face a higher risk of vascular events due to reduced vascular elasticity and atherosclerosis. Epidemiological data indicate that more than 75% of strokes occur in older adults, posing serious health threats and substantial economic burdens.[2] Furthermore, prognosis after stroke is generally poorer in this population, underscoring the need to identify risk factors and develop targeted intervention strategies.

The geriatric nutritional risk index (GNRI), which combines serum albumin levels with body weight changes, provides a comprehensive evaluation of nutritional status and has demonstrated significant prognostic value in various chronic diseases.[3] GNRI not only identifies individuals at risk of malnutrition but also predicts outcomes in stroke patients, with lower GNRI levels being closely linked to higher risks of cognitive decline, functional disability, and mortality after stroke.[4-6] The systemic inflammation response index (SIRI), calculated from monocyte, neutrophil, and lymphocyte counts, is a composite biomarker reflecting the balance between inflammation and immune function.[7] SIRI has shown strong predictive capacity in cardiovascular disease, cancer, and chronic kidney disease and plays an important role in prognostic evaluations across these conditions.[8-10]

Metal elements play an essential role in human physiological metabolism and disease pathogenesis. Magnesium, the fourth most abundant mineral in the body, regulates vasodilation, blood pressure, and platelet aggregation, potentially offering protection against stroke.[11,12] The effect of copper on stroke risk, however, remains controversial. As a key participant in redox reactions,

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Received: July 03, 2025 **Accepted:** August 14, 2025 **Available Online Date:** 01.09.2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-7-25

Available at www.balkanmedicaljournal.org

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Cite this article as: Luo B, Liu S, Zheng L, Zhang B, Zou W. The Associations of Dietary Copper and Magnesium Intake, Geriatric Nutritional Risk Index, and Systemic Inflammation Response Index with Stroke Risk in the Elderly. Balkan Med J.; 2025; 42(5):452-63.

adequate copper intake may help preserve vascular wall integrity and antioxidant defenses, whereas excessive copper exposure can promote oxidative stress and inflammation, potentially increasing stroke risk.[13,14]

Most prior research has focused on the individual relationships of dietary metal elements, nutritional indicators, and inflammatory markers with stroke, with limited attention to possible synergistic or antagonistic interactions among these factors-particularly in older adults. Elucidating these interactions could inform targeted dietary and nutritional interventions and improve stroke risk assessment in the elderly.

MATERIALS AND METHODS

Study population

This study used data from the National Health and Nutrition Examination Survey (NHANES), which is conducted biennially. All participants provided informed consent, and the study protocol was approved by the NHANES Institutional Review Board.[13] Detailed information is available at https://www.cdc.gov/nchs/nhanes/index.htm.

We combined data from NHANES cycles 2007–2016, encompassing 50,588 participants. individuals were excluded if they were younger than 60 years, lacked complete stroke data, or were missing data on GNRI, SIRI, or dietary copper or magnesium intake. The final analytic sample included 7,157 older adults (Figure 1).

Dietary copper and magnesium intake

Dietary intake estimates reflected participants' reported food and beverage consumption during the 24 h prior to the interview, including types and amounts consumed, and calculated energy, nutrient, and other dietary components. Each participant completed two 24-h dietary recalls: the first through face-to-face interviews conducted by trained interviewers and the second by telephone 3-10 days later. When both recalls were available, the average intake was used for analysis; if only the first recall was completed, those data were used.[13]

GNRI and SIRI

GNRI was calculated as follows[15]:

$$\text{GNRI} = (1.489 \times \text{serum albumin (g/L)}) + (41.7 \times \frac{\text{actual body weight (kg)}}{\text{ideal body weight (kg)}})$$

Ideal body weight was determined using the Lorentz equations: females, 0.60 × height (cm)-40; males, 0.75 × height (cm)-62.5. If the ratio of actual to ideal body weight was ≥ 1, the value was set to 1.[15]

SIRI was calculated as follows[16]:

$$\text{SIRI} = \frac{\text{neutrophil count} \times \text{monocyte count}}{\text{lymphocyte count}}$$

Based on previously established cut-offs[17], GNRI was classified as high-risk (< 98) or low-risk (≥ 98). SIRI was analyzed as a continuous variable.[16,18]

Stroke

Stroke history was determined from self-reported responses to the Medical Conditions Questionnaire. Participants who reported having been diagnosed with stroke by a physician or other healthcare professional were classified as having a stroke history; all others were classified as not having a stroke history.[19]

Covariates

Potential confounders affecting the relationship between dietary copper and magnesium intake and stroke were categorized into three groups: demographic characteristics, lifestyle factors, and comorbidities.

• **Demographic variables:** Gender, age (years), race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic Black, other race), education level (less than 9th grade, 9-11th grade, high school graduate/GED or equivalent, some college or associate degree, college graduate or above), and poverty income ratio (poverty-income ratio, ≤ 1 or > 1).

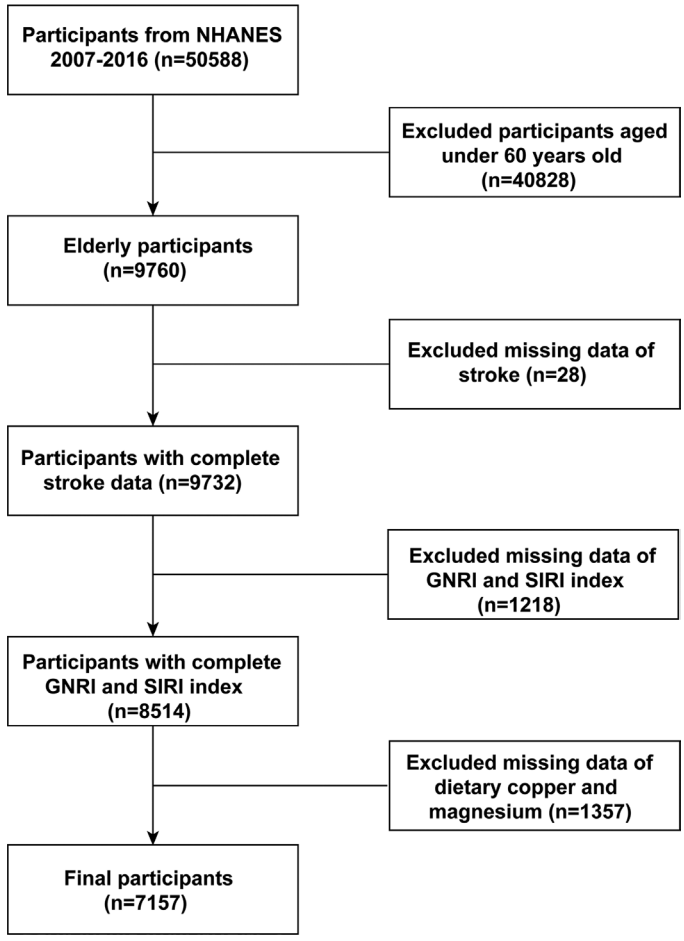

FIG. 1. Diagram of participant enrollment process.
GNRI, geriatric nutritional risk index; SIRI, systemic inflammation response index.

• **Lifestyle factors:** Body mass index categorized as normal weight (< 25 kg/m²), overweight (25- <30 kg/m²), or obese (≥ 30 kg/m²), physical activity duration [≤ 30 min (minimum)/day, 30-60 min/day, > 60 min/day], smoking status (ever smoked ≥ 100 cigarettes), and drinking status (≥ 12 drinks per year).

• **Comorbidities:** Physician-diagnosed diabetes, hypertension, hypercholesterolemia, and myocardial infarction.

Statistical analysis

All analyses were conducted using R software (version 4.2.1) and EmpowerStats (v4.2.0), incorporating sampling weights to account for the complex survey design of NHANES. Continuous variables are presented as mean ± standard deviation and categorical variables as percentages. Variance inflation factor (VIF) diagnostics were applied to all covariates to evaluate multicollinearity; all VIF values were < 5, indicating no significant collinearity issues (Supplementary Table S1). Because dietary copper and magnesium intake data were not normally distributed, logarithmic transformations were applied (denoted as Ln-copper and Ln-magnesium). These transformed variables were first analyzed as continuous measures. Subsequently, quartile-based analyses were conducted, using Quartile 1 (Q1) as the reference category. We applied four hierarchical regression models with progressive covariate adjustment:

Model 1: Unadjusted

Model 2: Adjusted for core demographic covariates

Model 3: Further adjusted for lifestyle factors

Model 4: Fully adjusted for demographic, lifestyle, and comorbidity variables

Baseline characteristics were compared between stroke and non-stroke groups using weighted chi-squared tests for categorical variables and weighted linear regression for continuous variables. Primary associations were evaluated using weighted multivariable logistic regression, yielding β coefficients, odds ratios (ORs), and 95% confidence intervals (CIs) for dietary copper, dietary magnesium, GNRI, and SIRI in relation to stroke outcomes. Subgroup analyses and interaction tests were performed to examine heterogeneity across population subgroups. Dose-response relationships and potential thresholds were evaluated using smooth curve fitting and threshold effect analysis. Mediation analysis was conducted to assess whether GNRI and SIRI mediated the associations between dietary copper and magnesium intake and stroke. To assess robustness, we performed two sensitivity analyses:

Adding covariates-total energy intake, prescription medication use, and dietary supplement use-to the fully adjusted model

Excluding participants with implausible dietary energy intake (< 600 or > 5,000 kcal/day)[20]

Missing data in categorical variables were imputed using the mode, while missing continuous variables were imputed using the median.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 7,157 participants. Among them, 567 reported a physician diagnosis of stroke. Stroke patients were generally older, with 58.16% aged over 70 years. Racial distribution differed between groups, with a higher proportion of non-Hispanic Black and other race participants in the stroke group. Stroke patients also had lower educational attainment and lower income levels. In terms of lifestyle factors, stroke patients engaged in less physical activity (lower proportion meeting high-intensity exercise criteria) and had higher smoking rates, while alcohol consumption was slightly lower. The prevalence of chronic diseases was markedly higher, including hypertension, diabetes, and prior myocardial infarction. Biomarker analysis indicated a higher prevalence of nutritional risk among stroke patients.

Multivariable logistic regression

Table 2 presents the associations of dietary copper intake, magnesium intake, GNRI, and SIRI with stroke risk in older adults,

TABLE 1. Weighted Comparison in Basic Characteristics.

Characteristics	No stroke, n = 6,590	Stroke, n = 567	Overall, n = 7,157	*p* -value
Gender (%)				0.561
Male	45.232	43.887	45.139	
Female	54.768	56.113	54.861	
Age (%)				< 0.001
≤ 70	59.723	41.844	58.482	
> 70	40.277	58.156	41.518	
Race (%)				< 0.001
Mexican American	3.709	3.181	3.672	
Other Hispanic	3.190	2.255	3.125	
Non-Hispanic White	81.563	77.019	81.247	
Non-Hispanic Black	7.521	10.311	7.715	
Other race	4.017	7.234	4.240	

TABLE 1. Continued

Characteristics	No stroke, n = 6,590	Stroke, n = 567	Overall, n = 7,157	*p* -value
Education level (%)				< 0.001
Less than 9th grade	6.861	11.081	7.154	
9-11th grade	10.294	16.353	10.715	
High school grad/GED or equivalent	23.739	29.677	24.152	
Some college or AA degree	29.874	25.348	29.560	
College graduate or above	29.232	17.542	28.420	
PIR (%)				< 0.001
≤ 1	8.212	13.076	8.550	
> 1	91.788	86.924	91.450	
BMI (%)				0.709
Normal weight	25.178	26.523	25.271	
Overweight	36.170	34.529	36.056	
Obese	38.652	38.948	38.673	
Weight (kg)	81.165 ± 19.627	79.890 ± 20.923	81.077 ± 19.722	0.836
Height (cm)	166.455 ± 10.028	164.671 ± 9.818	166.331 ± 10.024	0.100
Physical activity (min/day)				< 0.001
< 30	7.203	6.123	7.128	
≥ 30, < 60	72.871	82.101	73.512	
≥ 60	19.925	11.776	19.360	
Smoking (%)				< 0.001
Yes	50.424	58.164	50.962	
No	49.576	41.836	49.038	
Drinking (%)				0.006
Yes	70.895	65.086	70.492	
No	29.105	34.914	29.508	
Hypertension (%)				< 0.001
Yes	56.772	78.821	58.303	
No	43.228	21.179	41.697	
Hypercholesterolemia (%)				0.006
Yes	58.322	64.560	58.755	
No	41.678	35.440	41.245	
Diabetes (%)				< 0.001
Yes	18.164	31.585	19.096	
No	78.514	63.926	77.501	
Borderline	3.322	4.489	3.403	
Heart attack (%)				< 0.001
Yes	7.815	19.195	8.605	
No	92.185	80.805	91.395	
Magnesium (mg)	288.497 ± 122.301	265.697 ± 114.985	286.914 ± 121.945	1.000
Copper (mg)	1.274 ± 1.084	1.133 ± 0.628	1.264 ± 1.060	0.996
Albumin (g/L)	42.196 ± 2.957	41.418 ± 3.247	42.142 ± 2.985	1.000
SIRI (%)	1.434 ± 1.034	1.698 ± 1.422	1.452 ± 1.067	1.000
GNRI (%)				< 0.001
< 98	7.189	14.245	7.679	
≥ 98	92.811	85.755	92.321	

Mean ± SD for continuous variables. p value was calculated by weighted linear regression model.
% for categorical variables. p value was calculated by weighted chi-square test.
PIR, poverty-income ratio; BMI, body mass index; GNRI, geriatric nutritional risk index; SIRI, systemic inflammation response index; SD, standard deviation; Min, minimum.

TABLE 2. The Associations of Dietary Copper and Magnesium Intake, Along with GNRI and SIRI, with Stroke Risk.

	OR (95% CI), *p* -value			
Exposure	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Ln-copper	0.633 (0.524, 0.765) < 0.001	0.730 (0.598, 0.892) 0.002	0.752 (0.616, 0.918) 0.005	0.784 (0.640, 0.959) 0.018
Ln-copper quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.733 (0.581, 0.924) 0.009	0.797 (0.629, 1.010) 0.060	0.812 (0.641, 1.030) 0.086	0.816 (0.641, 1.039) 0.099
Q3	0.759 (0.603, 0.956) 0.019	0.850 (0.669, 1.079) 0.181	0.875 (0.689, 1.112) 0.276	0.912 (0.715, 1.163) 0.457
Q4	0.555 (0.433, 0.713) < 0.001	0.670 (0.515, 0.872) 0.003	0.689 (0.530, 0.897) 0.006	0.724 (0.554, 0.946) 0.018
p for trend	< 0.001	0.007	0.014	0.047
Ln-magnesium	0.564 (0.460, 0.691) < 0.001	0.677 (0.543, 0.845) 0.001	0.704 (0.564, 0.879) 0.002	0.749 (0.597, 0.939) 0.012
Ln-magnesium quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.688 (0.545, 0.868) 0.002	0.729 (0.575, 0.923) 0.009	0.744 (0.587, 0.943) 0.015	0.751 (0.590, 0.955) 0.020
Q3	0.737 (0.586, 0.927) 0.009	0.846 (0.667, 1.073) 0.169	0.872 (0.687, 1.107) 0.261	0.904 (0.709, 1.152) 0.413
Q4	0.545 (0.425, 0.698) < 0.001	0.676 (0.520, 0.880) 0.004	0.702 (0.539, 0.914) 0.009	0.755 (0.578, 0.988) 0.040
p for trend	< 0.001	0.012	0.028	0.110
SIRI	1.170 (1.104, 1.240) < 0.001	1.160 (1.093, 1.232) < 0.001	1.149 (1.082, 1.220) < 0.001	1.106 (1.040, 1.177) 0.001
GNRI	0.958 (0.942, 0.975) < 0.001	0.968 (0.951, 0.986) < 0.001	0.972 (0.954, 0.989) 0.002	0.976 (0.959, 0.994) 0.010
GNRI categorical				
< 98	Ref	Ref	Ref	Ref
≥ 98	0.556 (0.434, 0.713) < 0.001	0.637 (0.494, 0.820) < 0.001	0.670 (0.519, 0.866) 0.002	0.745 (0.574, 0.967) 0.027

OR, odds ratio; 95% CI, 95% confidence interval. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4. GNRI, geriatric nutritional risk index; SIRI, systemic inflammation response index. Model 1 adjust for: none. Model 2 adjust for: gender; age; race; education level; and PIR. Model 3 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status. Model 4 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status; diabetes; hypertension; hypercholesterolemia; heart attack.
PIR, poverty-income ratio; BMI, body mass index; GNRI, geriatric nutritional risk index; SIRI, systemic inflammation response index.

based on multivariable logistic regression analyses. Dietary copper intake was inversely associated with stroke risk; in model 4, each 1-ln unit increase corresponded to a 21.6% lower risk (OR = 0.784; 95% CI, 0.640-0.959; $p = 0.018$). Similarly, higher magnesium intake was protective, with each 1-ln unit increase associated with a 25.1% reduction in stroke risk (OR = 0.749; 95% CI, 0.597-0.939; $p = 0.012$) in model 4. GNRI showed a consistent protective effect, while SIRI was positively associated with stroke risk. Participants with GNRI ≥ 98 had 25.5% lower odds of stroke compared with those with GNRI < 98 (OR = 0.745; 95% CI, 0.574-0.967; $p = 0.027$) in model 4.

Table 3 presents the associations between dietary copper and magnesium intake and GNRI. Both copper and magnesium intake were positively correlated with GNRI across all models. In quartile analysis (model 4), compared with Q1, participants in Q4 showed higher GNRI values. Specifically, each 1-ln unit increase in copper intake was associated with a 0.450-unit increase in GNRI (β = 0.450; 95% CI, 0.132–0.767; $p = 0.005$). Similarly, each 1-ln unit increase in magnesium intake corresponded to a 0.625-unit increase in GNRI (β = 0.625; 95% CI, 0.305–0.945; $p < 0.001$).

Table 4 summarizes the associations between dietary copper and magnesium intake and SIRI. In model 4 quartile analysis, participants in Q4 had significantly lower SIRI values compared with Q1. Each 1-ln unit increase in copper intake was associated with a 0.094-unit decrease in SIRI (β = -0.094; 95% CI, -0.168 to -0.021; $p = 0.012$), indicating a significant inverse relationship between moderate to high copper intake and SIRI. Magnesium intake showed a similar negative association with SIRI.

Subgroup analysis

Based on model 4, subgroup analyses were conducted to assess potential effect modification in the associations between dietary copper and stroke (Figure 2) and between dietary magnesium and stroke (Figure 3). Significant protective associations for both metals were observed in subgroups of older women, individuals with higher educational attainment or higher income, those engaging in moderate physical activity, non-smokers, and participants without hypercholesterolemia or diabetes. Among drinkers, copper intake remained significantly protective, whereas magnesium intake was not significantly associated with stroke risk. Interaction *p* -values for all subgroups exceeded 0.05, indicating no statistically significant heterogeneity across strata.

TABLE 3. The Associations Between Dietary Copper and Magnesium Intake and GNRI.

	β (95% CI), *p* -value			
Exposure	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Ln-copper	1.072 (0.836, 1.307) < 0.001	0.588 (0.341, 0.835) < 0.001	0.545 (0.300, 0.790) < 0.001	0.499 (0.255, 0.743) < 0.001
Ln-copper quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.511 (0.202, 0.819) 0.001	0.240 (-0.067, 0.547) 0.126	0.251 (-0.053, 0.555) 0.106	0.217 (-0.087, 0.520) 0.161
Q3	0.928 (0.620, 1.237) < 0.001	0.495 (0.183, 0.808) 0.002	0.469 (0.160, 0.779) 0.003	0.424 (0.116, 0.733) 0.007
Q4	1.172 (0.864, 1.480) < 0.001	0.533 (0.212, 0.854) 0.001	0.504 (0.186, 0.822) 0.002	0.450 (0.132, 0.767) 0.005
***p* for trend**	< 0.001	< 0.001	< 0.001	0.003
Ln-magnesium	1.489 (1.225, 1.752) < 0.001	0.885 (0.605, 1.166) < 0.001	0.822 (0.544, 1.101) < 0.001	0.762 (0.484, 1.041) < 0.001
Ln-magnesium quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.606 (0.299, 0.914) < 0.001	0.366 (0.059, 0.672) 0.019	0.327 (0.024, 0.630) 0.034	0.296 (-0.006, 0.598) 0.055
Q3	1.150 (0.842, 1.459) < 0.001	0.704 (0.391, 1.017) < 0.001	0.638 (0.328, 0.948) < 0.001	0.588 (0.278, 0.897) < 0.001
Q4	1.441 (1.133, 1.749) < 0.001	0.763 (0.441, 1.086) < 0.001	0.683 (0.363, 1.004) < 0.001	0.625 (0.305, 0.945) < 0.001
***p* for trend**	< 0.001	< 0.001	< 0.001	< 0.001

β, β coefficients; 95% CI, 95% confidence interval. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4. Model 1 adjust for: none. Model 2 adjust for: gender; age; race; education level; and PIR. Model 3 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status. Model 4 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status; diabetes; hypertension; hypercholesterolemia; heart attack.
PIR, poverty-income ratio; BMI, body mass index; GNRI, geriatric nutritional risk index.

TABLE 4. The Associations Between Dietary Copper and Magnesium Intake and SIRI.

	β (95% CI), *p* -value			
Exposure	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Ln-copper	0.017 (-0.039, 0.073) 0.560	-0.104 (-0.161, -0.047) 0.00034	-0.093 (-0.150, -0.036) 0.001	-0.082 (-0.139, -0.025) 0.005
Ln-copper quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.030 (-0.044, 0.103) 0.425	-0.029 (-0.100, 0.042) 0.425	-0.024 (-0.095, 0.047) 0.511	-0.019 (-0.090, 0.051) 0.593
Q3	0.013 (-0.060, 0.087) 0.724	-0.102 (-0.175, -0.030) 0.005	-0.090 (-0.163, -0.018) 0.014	-0.082 (-0.153, -0.010) 0.026
Q4	0.019 (-0.054, 0.093) 0.606	-0.119 (-0.194, -0.045) 0.002	-0.108 (-0.182, -0.034) 0.004	-0.094 (-0.168, -0.021) 0.012
***p* for trend**	0.727	0.0003	0.001	0.004
Ln-magnesium	0.035 (-0.028, 0.098) 0.278	-0.117 (-0.182, -0.052) 0.0004	-0.101 (-0.166, -0.036) 0.002	-0.085 (-0.150, -0.020) 0.010
Ln-magnesium quartile				
Q1	Ref	Ref	Ref	Ref
Q2	0.034 (-0.039, 0.108) 0.362	-0.037 (-0.107, 0.034) 0.310	-0.029 (-0.100, 0.042) 0.420	-0.026 (-0.097, 0.044) 0.460
Q3	0.007 (-0.067, 0.080) 0.862	-0.114 (-0.186, -0.042) 0.002	-0.100 (-0.172, -0.028) 0.007	-0.091 (-0.162, -0.019) 0.014
Q4	0.050 (-0.023, 0.124) 0.182	-0.110 (-0.185, -0.036) 0.004	-0.093 (-0.168, -0.018) 0.015	-0.077 (-0.151, -0.002) 0.044
***p* for trend**	0.301	0.0007	0.004	0.015

β, β coefficients; 95% CI, 95% confidence interval. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4. Model 1 adjust for: none. Model 2 adjust for: gender; age; race; education level; and PIR. Model 3 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status. Model 4 adjust for: gender; age; race; education level; PIR; BMI; physical activity duration; smoking status; drinking status; diabetes; hypertension; hypercholesterolemia; heart attack.
PIR, poverty-income ratio; BMI, body mass index; SIRI, systemic inflammation response index.

Smooth curve fitting and threshold effect analysis

Figures 4 (a-d) illustrate the dose-response relationships between dietary copper intake and stroke risk across models 1-4, while Figures 4 (e-h) show the corresponding associations for dietary magnesium (Figure 4). Smooth curve models revealed significant linear inverse correlations between both dietary copper and magnesium intake and stroke risk in older adults. Threshold effect analyses (Table 5) supported these findings, and results for models 2-4 (Supplementary Tables 2-4) were consistent with those of model 1.

Mediation analysis

Although the cross-sectional design of this study precludes definitive causal inferences regarding mediation, we explored the potential mediating roles of GNRI and SIRI in the associations between dietary copper and magnesium intake and stroke risk (Figure 5). In fully adjusted models, GNRI mediated 4.4% of the association for copper and 5.5% for magnesium, while SIRI mediated 3.4% and 2.9%, respectively.

Sensitivity analysis

Sensitivity analyses confirmed the robustness of the findings. Additional adjustment for covariates (Supplementary Tables 5-10) and exclusion of participants with implausible dietary energy intake (Supplementary Tables 11-13) produced results consistent with the primary analysis.

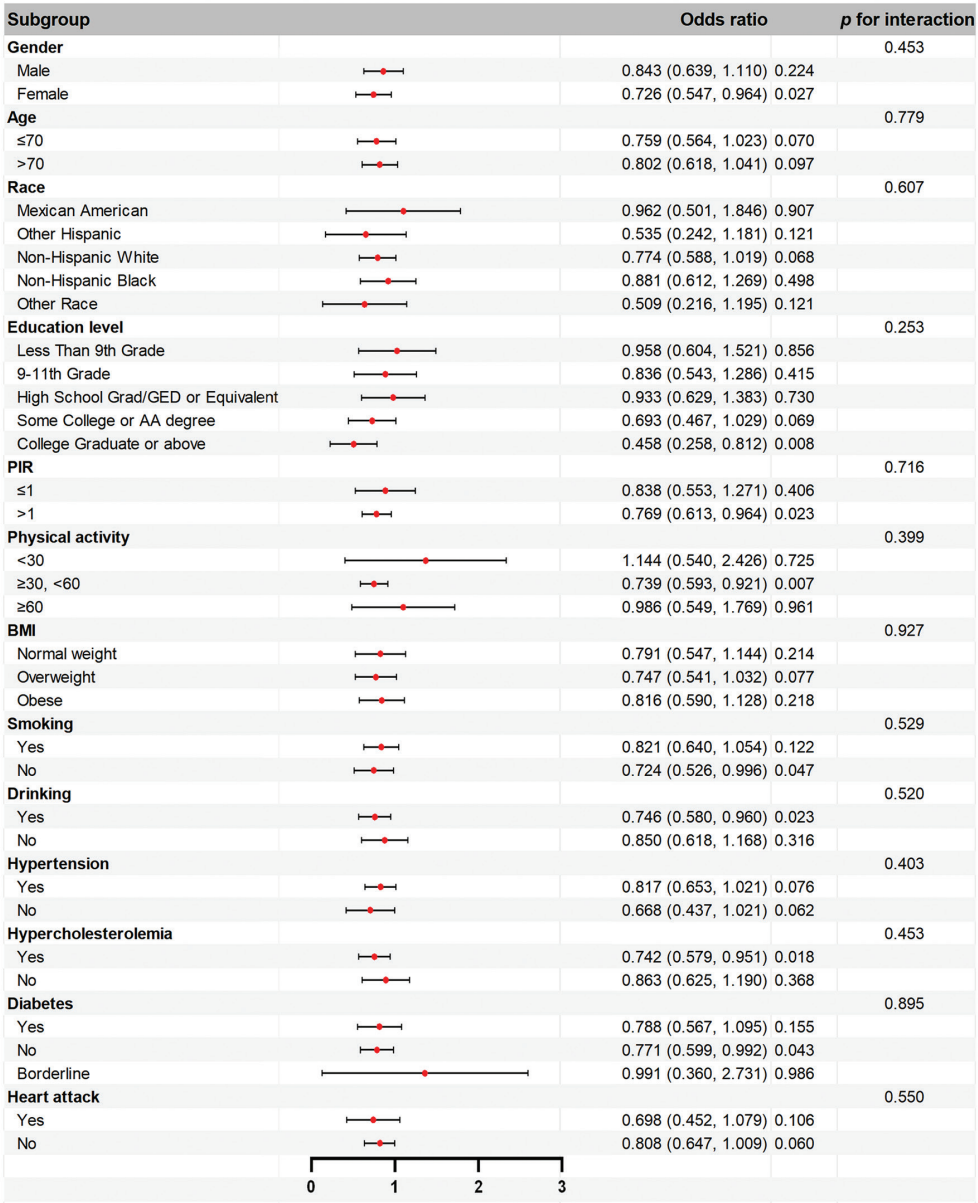

FIG. 2. Subgroup analysis for the relationship between dietary copper intake and stroke risk.
PIR, poverty-income ratio; BMI, body mass index.

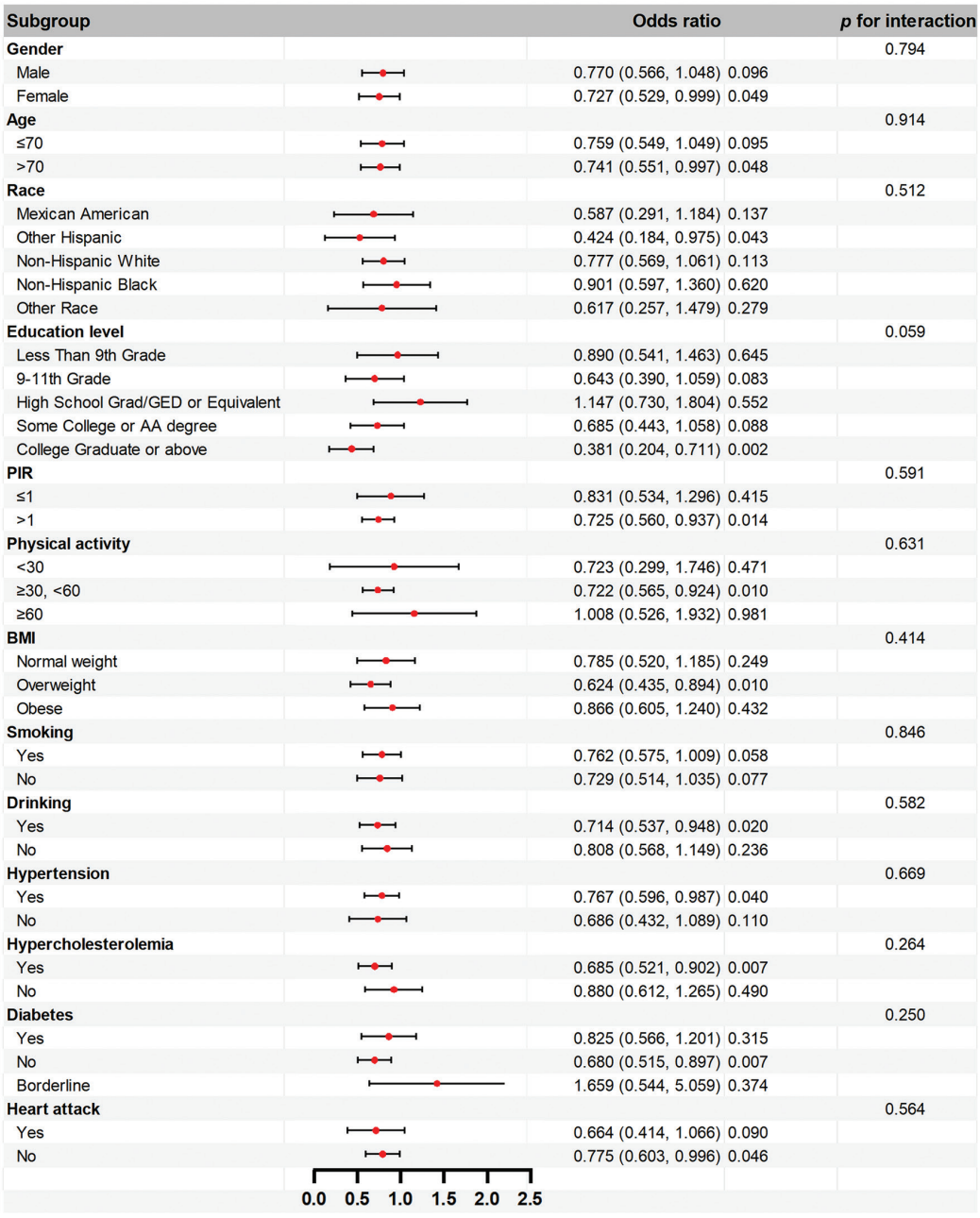

FIG. 3. Subgroup analysis for the relationship between dietary magnesium intake and stroke risk.
PIR, poverty-income ratio; BMI, body mass index.

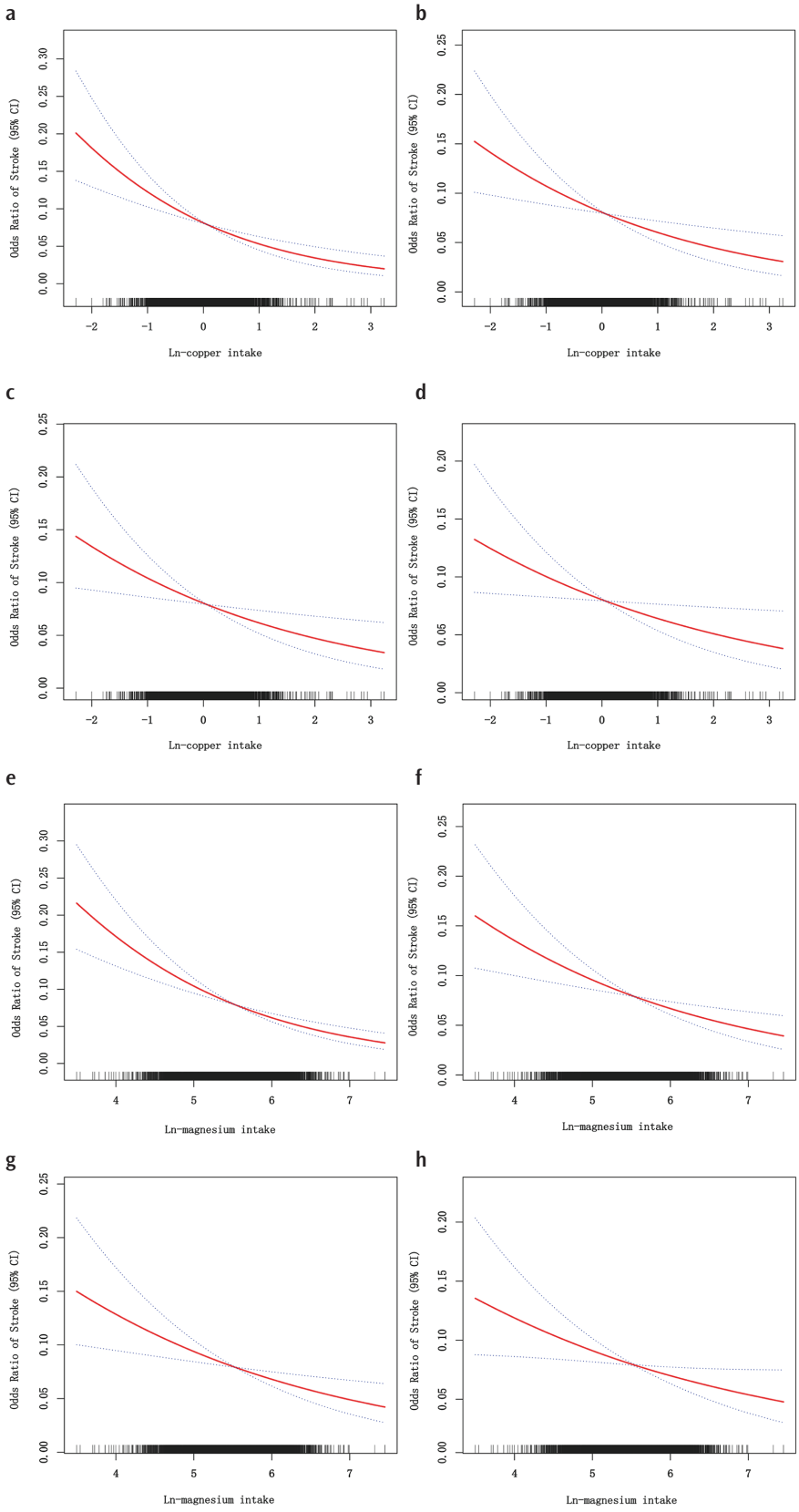

FIG. 4. The smooth curve model describing the dose-response relationship between dietary copper and magnesium intake and stroke risk. Figures (a-d) depict the dose–response relationships between dietary copper intake and stroke risk in elderly individuals across Models 1 to 4, while Figures (e-h) show the corresponding associations for dietary magnesium.

CI, confidence interval.

TABLE 5. Threshold Effect Analysis of Model 1.

	Ln-copper		Ln-magnesium	
Exposure	**OR (95% CI)**	***p* -value**	**OR (95% CI)**	***p* -value**
Model 1				
A straight-line effect	0.633 (0.524, 0.765)	< 0.0001	0.564 (0.460, 0.691)	< 0.0001
Model 2				
Fold points (K)	0.751		6.168	
Less than the K-segment effect 1	0.585 (0.478, 0.716)	< 0.0001	0.529 (0.427, 0.654)	< 0.0001
Greater than the K-segment effect 2	1.398 (0.694, 2.818)	0.348	2.724 (0.597, 12.422)	0.196
Effect size difference of 2 versus 1	2.390 (1.105, 5.171)	0.027	5.154 (1.058, 25.116)	0.042
Equation predicted values at break points	-2.859 (-3.041, -2.676)		-2.901 (-3.081, -2.720)	
Log likelihood ratio tests		0.051		0.068

OR, odds ratio; 95% CI, 95% confidence interval.
In model 1, the linear effect (Model I) indicates that each logarithmic unit increase in dietary copper or magnesium intake is associated with a 37% (OR = 0.633, 95% CI: 0.524-0.765, $p < 0.0001$) and 44% (OR = 0.564, 95% CI: 0.460-0.691, $p < 0.0001$) reduction in stroke risk, respectively. The fold points (k) in model 2 (threshold models) were identified at 0.751 for copper and 6.168 for magnesium. When intake levels were below these cutoff points, the risks decreased by 41% and 47%, respectively (both $p < 0.0001$). Conversely, above the thresholds, changes in risk were not statistically significant (copper: $p = 0.348$; magnesium: $p = 0.196$). Likelihood ratio tests showed that the threshold models were not significantly better than the linear models (copper: $p = 0.051$; magnesium: $p = 0.068$), further supporting a linear negative relationship between dietary copper and magnesium intake and stroke risk in the elderly.

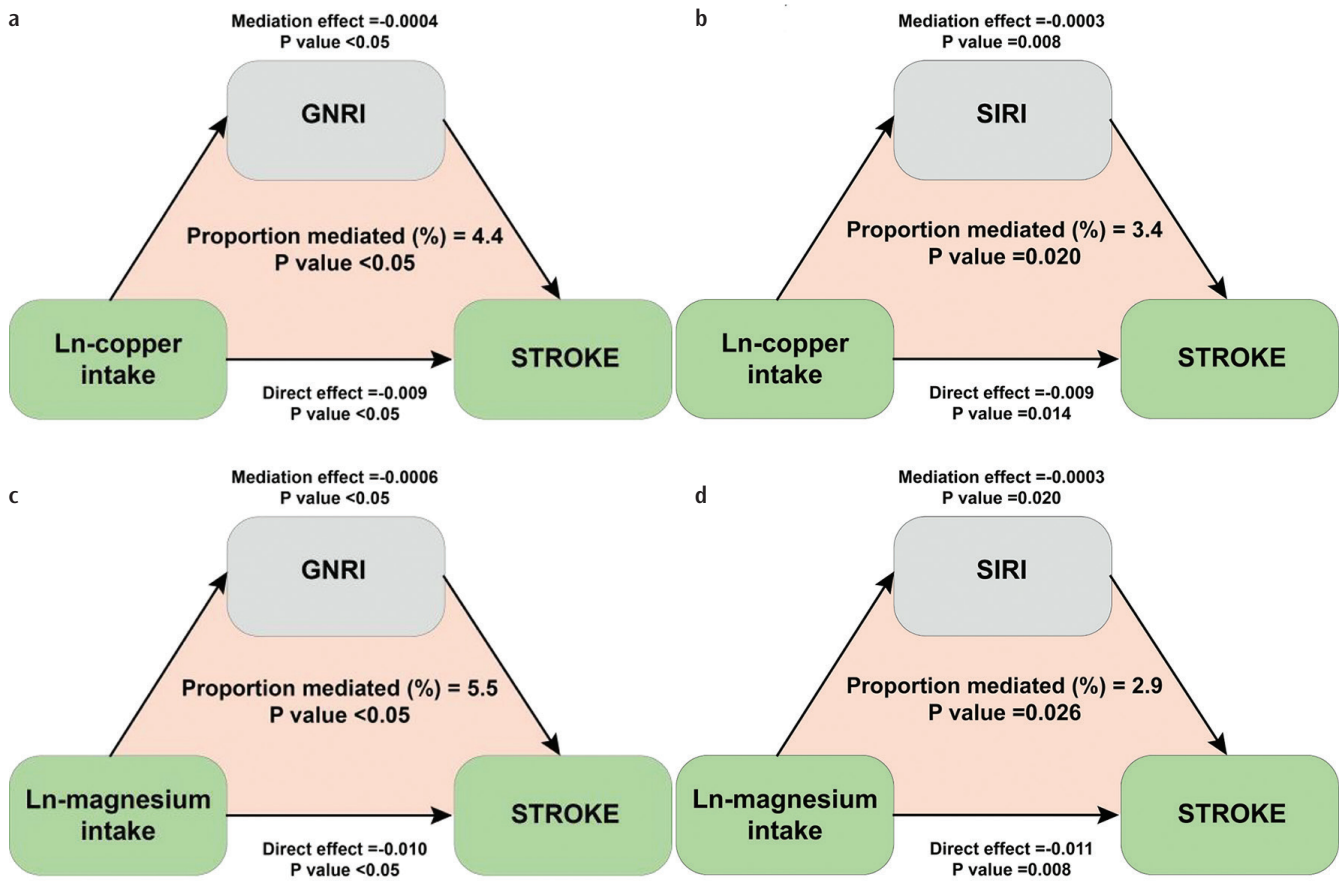

FIG. 5. Mediation analysis of the relationship between dietary copper and magnesium intake and stroke risk. Figures (a, b) illustrate the mediating role of GNRI and SIRI in stroke risk associated with copper intake in the fully adjusted model. Figures (c, d) illustrate the mediating role of GNRI and SIRI on stroke risk associated with magnesium intake in the fully adjusted model.
GNRI, geriatric nutritional risk index; SIRI, systemic inflammation response index.

DISCUSSION

To our knowledge, this is the first study to systematically investigate the associations of dietary copper and magnesium intake, GNRI, and SIRI with stroke risk in the elderly, providing novel insights for stroke prevention. Using data from 7,157 older adults, we found that higher dietary intake of copper and magnesium was significantly associated with lower stroke risk. Subgroup and interaction analyses showed that these protective associations were generally consistent across various population subgroups. Smooth curve modeling and threshold effect analyses demonstrated a significant, linear, inverse relationship between copper and magnesium intake and stroke risk. Mediation analysis further indicated that GNRI and SIRI may play modest mediating roles in these associations.

Previous studies on dietary copper and stroke risk have reported inconsistent findings. Li et al.[21] identified a nonlinear, L-shaped association, with stroke risk increasing significantly above a threshold of 2.45 mg/day. In contrast, a prospective cohort study in Japan reported a positive correlation between dietary copper intake and stroke-related mortality.[22] Evidence for dietary magnesium has been similarly mixed. Larsson et al.[23], in a dose-response meta-analysis, found that magnesium intake was inversely associated with ischemic stroke risk but showed no significant relationship with cerebral hemorrhage or subarachnoid hemorrhage. Conversely, a large prospective cohort study of Chinese adults reported no significant association between dietary magnesium intake and stroke risk.[24] In the present study, we observed a significant, linear, inverse association between dietary copper and magnesium intake and stroke risk in the elderly population. Discrepancies across studies may be attributable to differences in study design, stroke subtypes or stages, sample characteristics and sizes, and potential confounding factors.[25]

Current research has primarily focused on the direct association between dietary metal elements and stroke; however, few studies have investigated the pathways through which these elements may influence nutritional status and inflammation, and ultimately affect stroke risk-particularly in the elderly. In this study, GNRI and SIRI were employed as indicators of potential mediating pathways to examine the relationship between dietary copper and magnesium intake and stroke risk. GNRI, which incorporates serum albumin levels and body weight changes, is a key indicator for assessing nutritional risk in older adults.[26] Our findings indicate that moderate to high dietary copper and magnesium intake are positively associated with GNRI. Mechanistically, magnesium supports ATP production, while copper contributes to mitochondrial respiratory chain function-together enhancing energy metabolism, preserving muscle mass and body weight, and thereby improving GNRI scores and overall nutritional status.[27,28] SIRI, an inflammatory biomarker, reflects the degree of systemic inflammation. We observed that moderate to high dietary copper and magnesium intake were negatively associated with SIRI, suggesting that these metal elements may influence inflammation status. Mechanistically, copper, as an essential cofactor for superoxide dismutase and ceruloplasmin, exerts antioxidant effects by scavenging free radicals and inhibiting oxidative stress.[29] Ceruloplasmin also exhibits anti-inflammatory properties, reducing levels of pro-inflammatory cytokines such as interleukin-6 and C-reactive protein.[30] However, some studies suggest that excessive copper intake may exacerbate oxidative stress, disrupt the blood-brain barrier, and damage vascular structures, potentially leading to adverse health outcomes.[31] In the present study, no such adverse effects were observed; rather, higher dietary copper intake was associated with a reduced risk of stroke in the elderly. This beneficial association may be partly explained by the relatively low copper content in predominantly meat-based Western diets, as well as age-related declines in physiological functions, digestive efficiency, and metabolic capacity, which can limit nutrient absorption and utilization.[32] Furthermore, magnesium deficiency has been linked to chronic low-grade neuroinflammation, whereas adequate magnesium intake may help prevent such inflammation.[33] Mechanistically, magnesium has been shown to attenuate the production of reactive oxygen species and nitric oxide in the central nervous system, thereby mitigating oxidative damage and inflammation induced by hypoxia. It also suppresses NF-κB signaling, reducing pro-inflammatory cytokine release[34], and promotes M2 macrophage polarization, further alleviating neuroinflammation.[35]

This study found significant inverse associations between dietary copper and magnesium intake and stroke risk in the elderly. Mediation analysis suggested that these relationships might be partially mediated by GNRI and SIRI. Although the estimated mediating effects were modest (GNRI, 4.4% for copper, 5.5% for magnesium; SIRI, 3.4% for copper, 2.9% for magnesium), they point to potential indirect pathways. The relatively small mediation proportions indicate that copper and magnesium may influence stroke risk primarily through mechanisms beyond those captured by GNRI and SIRI.

Several limitations should be acknowledged. First, dietary intake data in NHANES were obtained from two 24-h recall interviews, a method that may not accurately reflect long-term dietary patterns and is prone to recall bias. Given that stroke develops over many years, such short-term measures may not adequately represent long-term exposure, which is more relevant to disease etiology. Second, stroke status was determined based on self-reported physician diagnoses. While common in large-scale surveys, this approach is vulnerable to misclassification bias, particularly among participants with cognitive impairments or limited healthcare access. Furthermore, due to data constraints, this analysis could not distinguish between ischemic and hemorrhagic stroke subtypes or disease stages, nor account for all potential covariates that may influence risk. Third, the cross-sectional design precludes establishing causality or verifying the temporal sequence required for robust mediation analysis (exposure → mediator → outcome). Moreover, some covariates included in our models (e.g., hypertension, diabetes, heart attack) may themselves lie on the causal pathway between metal intake and stroke-i.e., they could act as mediators rather than pure confounders. Adjusting for such variables could result in over-adjustment, potentially biasing the estimated direct associations between metal intake and stroke as well as the mediation effects. Consequently, the observed associations involving GNRI and SIRI should be interpreted as exploratory evidence of potential

pathways rather than definitive proof of mechanisms. Prospective longitudinal studies are needed to validate these findings and clarify the temporal relationships.

In conclusion, dietary copper and magnesium intake were associated with a reduced risk of stroke in the elderly. Appropriately increasing the intake of these metals may help lower stroke risk among older adults. Mediation analysis suggested that GNRI and SIRI may represent modest mediating pathways in this relationship. However, the relatively small mediation proportions indicate that most of the associations between metal intake and stroke likely operate through other biological mechanisms beyond those captured by GNRI and SIRI. Further research is warranted to elucidate these pathways.

Acknowledgements: We would like to express our thanks to the personnel at the National Center for Health Statistics of the Centers for Disease Control for their work in developing, gathering and organizing the NHANES data, as well as for establishing the publicly accessible database.

Ethics Committee Approval: This study used data from the National Health and Nutrition Examination Survey (NHANES), which is conducted biennially.

Informed Consent: All participants provided informed consent, and the study protocol was approved by the NHANES Institutional Review Board.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- B.L., S.L.; Design- B.L.; Supervision- W.Z.; Materials- B.L.; Data Collection or Processing- L.Z.; Analysis and/or Interpretation- L.Z.; Literature Review- B.Z.; Writing- B.L., S.L.; Critical Review- W.Z.

Conflict of Interest: The authors declare that they have no conflict of interest.

Supplementary: https://balkanmedicaljournal.org/img/files/2025-7-25-supp.pdf

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