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well-documented but is increasingly recognized as significant in maintaining cardiovascular health [4].

Copper, a trace mineral found in foods such as shellfish, nuts, seeds, and whole grains, is essential for numerous bodily functions, including angiogenesis, heart muscle contraction, and antioxidant defense [5]. Despite its critical roles, the specific mechanisms by which copper intake influences cardiovascular health remain under-explored [6]. Copper contributes to the function of important enzymes like superoxide dismutase, which protects cells from oxidative damage, and plays a role in maintaining endothelial and myocardial health [7]. Preliminary studies suggest that copper deficiency may be associated with increased heart disease risk due to its role in maintaining myocardial tissue integrity and vascular elasticity [6]. However, gaps remain in understanding the optimal intake levels and the direct e ects of copper on cardiovascular morbidity and mortality, particularly among those already at risk, such as hypertensive patients [8].

Previous studies exploring the association between copper and CVDs often su er from limitations like small sample sizes and cross-sectional designs [7]. e primary objective of this study is to explore the relationship between dietary copper intake and cardiovascular outcomes in hypertensive patients [9]. We aim to quantify copper intake among hypertensive individuals and investigate its association with the incidence of major cardiovascular events, including myocardial infarctions and strokes [7]. Additionally, the study will adjust for confounders like age and gender to delineate any dose–response relationships [10]. e results are expected to inform dietary recommendations and potentially influence public health guidelines for reducing cardiovascular risk in this population by incorporating copper intake considerations into nutritional recommendations and hypertension management strategies [11].

Methods

Data collection

We utilized cross-sectional data from the National Health

participants whether a doctor or other health professional had ever informed them that they had su ered from heart-related conditions such as a heart attack, coronary heart disease, angina, congestive heart failure, or stroke. e response options provided were "Yes," "No," or "Don't know," with "Yes" indicating a diagnosis of CVD. Participants who responded "Don't know" were excluded from the analysis.For mortality data, we utilized the NHANES Public-Use Linked Mortality Files available up to December 31, 2019, which can be found at CDC's website. ese files are linked to the National Death Index (NDI) data using probabilistic matching algorithms to ascertain mortality status. Mortality outcomes were classified according to the International Classification of Diseases, 10th Revision (ICD-10). In ICD-10, cardiovascular-related deaths are identified by specific codes, such as I50 for congestive heart failure and I60-I69 for stroke or cerebrovascular accidents. e follow-up period for each participant extended from the baseline examination date to the date of last known alive status or the date of removal from the mortality archive due to death.

Covariates extraction

Covariates that could influence the relationship between dietary copper intake and the risk of cardiovascular disease (CVD) or CVD-related mortality in hypertensive patients were collected through interviews and medical examinations. ese include sociodemographic and life-

Table 1 The general characteristics of the population in NHANESE 2001–2018

Variable	Total	No-CVD	CVD	*P*
Age	54.66 ± 0.20	53.29 ± 0.21	62.46 ± 0.30	< 0.0001
Copper (mg/day)	1.26 ± 0.01	1.27 ± 0.01	1.17 ± 0.02	< 0.0001
BMI	31.20 ± 0.09	31.10 ± 0.10	31.75 ± 0.20	0.002
Sex				0.002
Female	7255(49.46)	6119(50.08)	1136(45.95)	
Male	7422(50.54)	5981(49.92)	1441(54.05)	
Ethic				0.01
Black	4051(13.87)	3317(13.68)	734(14.94)	
Mexican	2078 (5.69)	1795(5.97)	283(4.12)	
Other	2217 (9.93)	1893(10.02)	324 (9.42)	
White	6331 (70.51)	5095(70.33)	1236(71.52)	
Education				< 0.0001
Less than 9th grade	1808 (6.01)	1422(5.47)	386(9.07)	
9-11th grade (Includes 12th grade with no diploma)	2275(11.57)	1779(10.92)	496(15.28)	
High school graduate/GED or equivalent	3591(25.68)	2940(25.26)	651(28.04)	
Some college or AA degree	4233(32.14)	3502(32.25)	731(31.48)	
College graduate or above	2770(24.61)	2457(26.10)	313(16.13)	
Diabetes				< 0.0001
DM	4328(24.00)	3152(20.83)	1176(42.01)	
IFG	814 (6.28)	676(6.17)	138(6.92)	
IGT	521 (3.41)	438(3.48)	83(3.00)	
No	9014(66.31)	7834(69.53)	1180(48.07)	
Smoke				< 0.0001
Former	4382(30.68)	3367(29.05)	1015(39.91)	
Never	7217(48.98)	6281(51.35)	936(35.57)	
Now	3078(20.34)	2452(19.61)	626(24.52)	
Alcohol user				< 0.0001
Former	3176(18.17)	2341(16.21)	835(29.28)	
Heavy	2441(17.77)	2130(18.61)	311(13.01)	
Mild	4971(37.54)	4155(37.93)	816(35.33)	
Moderate	1978(15.40)	1732(16.26)	246(10.56)	
Never	2111(11.11)	1742(10.99)	369(11.82)	
Stroke				< 0.0001
No	13748(95.01)	12100(100.00)	1648 (66.71)	
Yes	929 (4.99)	0 (0.00)	929(33.29)	
Coronary heart disease				< 0.0001
No	13719(93.89)	12100(100.00)	1619 (59.28)	
Yes	958 (6.11)	0 (0.00)	958(40.72)	
Angina				< 0.0001
No	14013(95.61)	12100(100.00)	1913 (70.76)	
Yes	664 (4.39)	0(0.00)	664(29.24)	
Congestive heart failure				< 0.0001
No	13903(95.77)	12100(100.00)	1803 (71.77)	
Yes	774 (4.23)	0 (0.00)	774(28.23)	
Heart attack				< 0.0001
No	13667(94.05)	12100(100.00)	1567 (60.30)	
Yes	1010 (5.95)	0 (0.00)	1010(39.70)	
CopperQ (mg/day)				< 0.0001
Q1 [0,0.754]	3509(20.42)	2758(19.53)	751(25.46)	
Q2(0.75,1.06]	3586(23.64)	2947(23.45)	639(24.67)	
Q3(1.06,1.46]	3758(27.09)	3129(27.26)	629(26.13)	
Q4(1.46,46.24]	3824(28.85)	3266(29.75)	558(23.74)	

heart failure (28.23% vs. 0%), and heart attack (39.70% vs. 0%) (*P*

and 0.66 ($P < 0.001$). After further adjustments in Model

Subgroup analysis

In analyzing the relationship between dietary copper intake and cardiovascular mortality among hyperten-

CI -0.39 to -0.13, $P < 0.001$) showed significant decreases in cardiovascular mortality, while no significant reductions were observed in Blacks ($P = 0.43$), possibly due to underlying genetic or environmental factors, or a smaller sample size in this group. Other ethnicities showed a marginally significant reduction (-0.20, 95% CI -0.40 to 0.00, $P = 0.05$). Education level was another critical factor, with individuals holding higher education degrees (college and above) demonstrating stronger protective e ects (-0.22, 95% CI -0.40 to -0.05, $P = 0.01$), likely reflecting healthier lifestyles and nutritional habits associated with higher educational attainment. For diabetes status, individuals without diabetes (-0.14, 95% CI -0.22 to -0.06, $P < 0.001$) and those with diabetes (-0.17, 95% CI -0.27 to -0.07, $P < 0.001$) both experienced significant reductions in cardiovascular mortality. Furthermore, a significant trend was observed among individuals with impaired fasting glucose (IFG; -0.16, 95% CI -0.30 to -0.01, $P = 0.03$), while no significant changes were found in those with impaired glucose tolerance (IGT; $P =$

Table 4 Subgroup analysis of the association between dietary copper intake and cardiovascular mortality rate

Abbreviations: *DM* Diabetes Mellitus, *IFG* Impaired Fasting Glucose, *IGT* Impaired Glucose Tolerance, *BMI* Body Mass Index

stress regulation, and inflammation. As a cofactor for nitric oxide synthase (NOS), copper is essential for NO production, which promotes vasodilation and blood pressure regulation [6].Copper deficiency has been linked to impaired NO synthesis and increased cardiovascular risk, while excess copper may lead to oxidative stress and endothelial dysfunction [22]. Additionally, copper influences mitochondrial energy metabolism and inflammatory pathways, both of which are involved in cardiovascular disease progression [23] Given these interactions, maintaining optimal copper intake is crucial for cardiovascular health, and further research is needed to clarify the safe upper limit of copper consumption and its long-term e ects on cardiovascular outcomes [24].

ese findings carry significant clinical implications. Given that both copper deficiency and excess may contribute to cardiovascular risk, it is essential to maintain an optimal dietary intake (~2.85 mg/day). Health professionals should prioritize natural food sources such as shellfish, nuts, whole grains, and legumes, while

cardiovascular health, addressing the limitations of previous observational studies. Well-designed prospective cohort studies are needed to validate the long-term e ects of moderate copper intake on CVD outcomes, incorporating biomarker-based copper status assessments (e.g., serum copper, ceruloplasmin levels) rather than relying solely on self-reported dietary recall. Additionally, randomized controlled trials (RCTs) should be conducted to establish a causal relationship between copper intake and cardiovascular health by testing dietary copper supplementation among high-risk populations, such as hypertensive patients with low baseline copper levels. ese trials should assess key cardiovascular indicators, including blood pressure, lipid profiles, oxidative stress markers (e.g., superoxide dismutase, malondialdehyde), and endothelial function (e.g., flow-mediated dilation, FMD), to elucidate the mechanistic pathways linking copper and CVD risk. Furthermore, genetic and metabolic studies should explore how variations in copper transport genes (e.g., ATP7A, ATP7B) modulate cardiovascular responses to dietary copper intake, as understanding these gene-nutrient interactions could help identify subpopulations that may benefit most from copper interventions. Finally, given the non-linear relationship observed between copper intake and cardiovascular outcomes, future studies should focus on determining the upper safe intake limit and evaluating the potential risks associated with excessive long-term copper consumption to refine dietary recommendations and public health guidelines.

Conclusions

is longitudinal study from the NHANES database (2001–2018) has significantly enhanced our understanding of the relationship between dietary copper intake and cardiovascular outcomes in hypertensive patients. We observed that higher copper intake is associated with reduced rates of cardiovascular morbidity and mortality. Specifically, patients with higher copper intake showed lower prevalence and better prognostic outcomes in cardiovascular health compared to those with lower intake levels. ese findings suggest that dietary copper may play a crucial role in cardiovascular protection among hypertensive individuals. erefore, incorporating copper into dietary recommendations could potentially improve cardiovascular health outcomes in this high-

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