Article

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Association Between Daily Dietary Vitamin C Intake and Heart Failure in Hypertensive Individuals Aged 50 Years and Above: NHANES 2003–2020

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Background: Vitamin C, a dietary antioxidant, may influence the risk for cardiovascular disease. This investigation aimed to examine the association of daily dietary vitamin C intake with heart failure (HF) risk among hypertensive individuals aged ≥50 years.

Methods: We analyzed 7901 hypertensive individuals (aged ≥50 years) from the National Health and Nutrition Examination Survey (NHANES) (2003–2020). Dietary vitamin C intake was quantified via two 24-hour diet recalls and stratified into quintiles. Logistic regression models were utilized to examine the link between vitamin C intake and HF risk, yielding data in odds ratios (OR) and 95% confidence intervals (CI). Restricted cubic spline (RCS) and stratification were executed to evaluate dose-response relationships and heterogeneity.

Results: Individuals in the highest vitamin C quintile (≥127.15 mg/day) demonstrated 62% elevated OR versus the lowest quintile (<28.55 mg/day; OR = 1.62, 95% CI: 1.06–2.48, $p = 0.030$), with a significant linear trend across quintiles (trend test $p = 0.015$). RCS analysis confirmed a linear dose-response pattern of vitamin C intake with HF risk (p for overall = 0.002, p for nonlinear = 0.134). Exploratory subgroup analyses identified significant associations among males ($p = 0.027$), non-Hispanic Whites ($p = 0.029$), high school graduates ($p = 0.019$), married individuals ($p = 0.011$), never smokers ($p = 0.008$), non-alcohol consumers ($p = 0.005$), and those with diabetes mellitus (DM) ($p = 0.002$) or hyperlipidemia ($p = 0.035$). Associations were also significant for individuals in the highest body mass index (BMI) quintile ($p = 0.004$), the lowest age tertile ($p = 0.004$), the highest poverty-to-income ratio (PIR) quintile ($p = 0.021$), the highest urinary albumin-to-creatinine ratio (UACR) quintile ($p = 0.033$), and both the lowest ($p = 0.028$) and highest ($p = 0.014$) estimated glomerular filtration rate (eGFR) quintiles, with no significant interactions across these subgroups. After further adjustments to the micronutrients in the diet and the prescription of antihypertensive drugs, this clear association became no longer significant. However, the continuous model still has statistical significance.

Conclusion: Higher dietary vitamin C intake was positively linked to an increased probability of HF in hypertensive individuals aged 50 years and above. Our findings provide a foundational framework for recommending dietary vitamin C intake for HF prevention in high-risk groups ≥50 years.

Keywords: vitamin C; heart failure; hypertension; NHANES; oxidative stress

Introduction

Heart failure (HF) is a complex clinical condition characterized by impaired cardiac systolic/diastolic function, typically arising from structural or functional myocardial abnormalities. A prominent clinical manifestation of this pathophysiological condition is compromised cardiac output, despite compensatory neurohormonal activation and elevated left ventricular filling pressures. Based on epidemiological data documented in 2017, there were approximately 64.3 million HF cases globally [1]. The incidence of HF among adults is 0.1% to 4.3%, while the one-year HF mortality rate ranges from 4% to 45% [2]. Oxidative stress contributes to various pathophysiological processes in HF such as myocyte hypertrophy, apoptosis, myocardial ischemia, and reperfusion. Antioxidant administration has demonstrated efficacy in preventing these processes, underscoring oxidative stress as a critical mediator in HF development [3].

Vitamin C (also called ascorbic acid) is widely recognized as an antioxidant, but its paradoxical pro-oxidative effects become particularly pronounced at high concentrations. The role of vitamin C as an endogenous antioxidant, specifically in neutralizing reactive oxygen species (ROS), remains contentious. The capacity of vitamin C remains controversial, with *in vitro* efficacy well documented

but *in vivo* effects uncertain. In HF, vitamin C is thought to exert endothelial effects and improve autonomic nervous system control [4,5]. Elevated plasma vitamin C levels are linked to a reduced risk of coronary artery disease and cardiovascular mortality. However, this association is most pronounced when baseline plasma vitamin C levels are insufficient; in contrast, supplementation has minimal impact on cardiovascular risk when plasma vitamin C levels are already adequate [6,7]. Notably, a clinical trial demonstrated accelerated coronary progression (0.044 vs. 0.028 mm/year) in postmenopausal cardiovascular patients receiving combined vitamin C (500 mg twice daily) and E (400 IU twice daily) versus placebo [8]. Moreover, the prevalence and mortality rates of HF are significantly higher among older adults than among the total adult population [2]. Given the limited available evidence on the link between vitamin C intake and HF risk, especially in middle-aged and elderly individuals with cardiovascular risk, we intended to analyze data from the National Health and Nutrition Examination Survey (NHANES) to investigate the relationship between daily dietary vitamin C consumption and HF in hypertensive individuals aged 50 years and above.

Methods

Study Population

The analytical data for this investigation were acquired from the 2003–2020 National Health and Nutrition Examination Survey (NHANES), a nationally representative survey administered by the USA Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/nchs/nhanes/about/). NHANES includes examination, interview, and laboratory data. To ensure the representation of key demographic subgroups, NHANES applies a stratified multistage probability sampling method and an oversampling strategy. Inclusion criteria of this study comprise the following: (1) those participating in the 2003–2020 NHANES; (2) those aged ≥50 years; and (3) those diagnosed with hypertension, either through clinical diagnosis by physician or meeting diagnostic criteria for hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg). Exclusion criteria for this study are as follows: (1) those younger than 50 years; (2) those without hypertension or hypertension diagnosis data; (3) those without data on HF, dietary vitamin C intake at the time of the first and second interviews, age, sex, ethnicity, education, marital status, poverty-to-income ratio (PIR), smoking status, alcohol consumption, stroke history, body mass index (BMI), diabetes mellitus (DM), hyperlipidemia, urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and nutritional intake such as energy, dietary fiber, vitamin E, and sodium. Between 2003 and 2020, 86,618 individuals participated in NHANES. Following screening criteria, 7901 eligible individuals were enrolled in the analysis (Fig. 1). This study used de-identified, publicly available data from the NHANES.

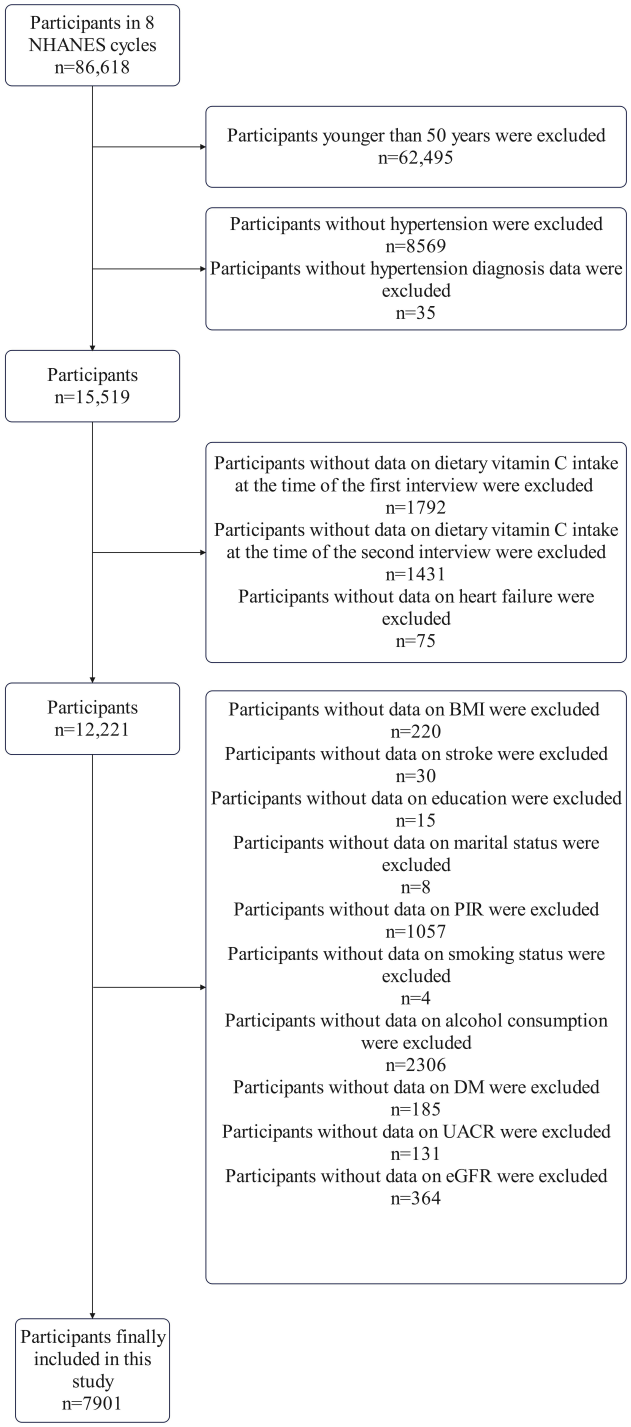

Fig. 1. Flowchart of the participants. Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PIR, poverty-to-income ratio; UACR, urinary albumin-to-creatinine ratio; NHANES, National Health and Nutrition Examination Survey. The figure was created using EdrawMax version 14.2.2 by Wondershare Technology Group Co., Ltd., Shenzhen, China.

Assessment of Hypertension

Hypertension was diagnosed through either clinical diagnosis by physician or fulfillment of the diagnostic criteria for hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) [9,10].

Assessment of HF

Diagnosis of HF was determined based on response to the question in the NHANES questionnaire (MCQ160b): "Has a doctor or other health professional ever told you that you had congestive heart failure". Participants who replied with "yes" to this question were assigned to the HF category. Given the fact that self-reported HF data from the NHANES are included in the American Heart Association's annual report on cardiovascular disease and stroke, such HF data were considered valid and reliable [11]. The specificity of self-reported HF exceeds 99%, and this result has been employed in various studies that utilized the NHANES database [11–13].

Weight Allocation

Given the NHANES sampling design, we incorporated primary sampling units, strata, and sample weights in data analysis. The "survey" package in R statistical software was applied to the weighted analysis to generate nationally representative estimates. This approach ensures the generalizability of results while avoiding overestimation of statistical significance. In accordance with NHANES guidelines, weight selection prioritized variables representative of small population subgroups, with appropriate weights applied accordingly [14,15].

Assessment of Daily Dietary Vitamin C Intake

Due to significant data missing on supplements, this study only analysed dietary sources of vitamin C. Daily dietary vitamin C intake was quantified through two 24-hour diet recalls. Since the 2003–2004 cycle, each participant has undergone two interviews: the first one was face-to-face and the second one was through phone call conducted 3–10 days after the first interview. The vitamin C intake was quantified as the mean of the two response data points. Nutrient intake was evaluated using the U.S. Department of Agriculture database. Further details are accessible at NHANES (https://www.cdc.gov/nchs/nhanes/).

Assessment of Covariates

The statistical analysis models incorporated sociodemographic and health-related variables to adjust for potential confounders. These variables comprised age, sex, history of stroke, ethnicity, PIR, BMI, DM, education, hyperlipidemia, UACR, smoking status, marital status, alcohol consumption, eGFR, daily dietary intake of energy, dietary fiber, vitamin E, and sodium [16,17]. The status of stroke was determined according to the MCQ160f question in the questionnaire [18]. DM was diagnosed based on the history of diabetes, insulin or hypoglycemic medication use, glycated hemoglobin levels ≥6.5%, fasting blood glucose levels ≥126 mg/dL, or postprandial blood glucose levels ≥200 mg/dL two hours after eating [19,20]. Participants were classified as having hyperlipidemia if they met any of the following criteria: (1) total cholesterol (TC) ≥200 mg/dL, (2) triglyceride (TG) ≥150 mg/dL, (3) low-density lipoprotein-cholesterol (LDL-C) ≥130 mg/dL, (4) high-density lipoprotein-cholesterol (HDL-C) ≤40 mg/dL for males or ≤50 mg/dL for females, or (5) history of using lipid-lowering medications [21]. The eGFR was calculated using equations reported in the previous study [22]. A detailed summary of the demographic data, questionnaires, and laboratory methods is accessible at NHANES database. Based on their data distribution, BMI and PIR were categorized into quintiles (Q1–Q5), where Q1 and Q5 represented the lowest and highest 20% of values, respectively. Similarly, age was grouped into tertiles based on its distribution.

Statistical Analysis

The 18-year survey weights were extracted and applied to all analyses to characterize the NHANES sampling design. The Kolmogorov–Smirnov test was used to assess whether the continuous variables were normally distributed. This test revealed that none of the continuous variables in Table 1 met the normality assumption. Consequently, characteristics of individuals were illustrated utilizing median and the first and third quartiles for continuous data and frequency and percentage for categorical data. The Kruskal–Wallis test was leveraged for the comparison of continuous variables, while the comparison of categorical variables was performed using the Rao–Scott Chi-square test.

To examine the link between vitamin C intake and HF, we conducted logistic regression analyses, which generated data in terms of odds ratios (OR) and 95% confidence intervals (CI). Data on Vitamin C levels were subjected to quintile stratification (the lowest quintile as a reference). In the logistic regression models, adjustments were made for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, and alcohol consumption (model 2), and then further adjustments were made for stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, and eGFR on the basis of model 2 (model 3); and then further adjustments were made for dietary intake of energy, dietary fiber, vitamin E, and sodium on the basis of model 3 (model 4). Trend test analyses were employed to assess the linear trend in HF risk across different categories of vitamin C intake. Furthermore, the restricted cubic spline (RCS) models with all covariates adjusted were leveraged to evaluate the dose-response link between vitamin C intake and HF risk. The reference value of the RCS model was set at the median intake, with knot positions determined following the mini-

Table 1. Characteristics of the study population categorized by levels of daily dietary vitamin C intake.

Variables	Total (n = 7901)	Vitamin C intake						
		Q1 (n = 1609)	Q2 (n = 1490)	Q3 (n = 1619)	Q4 (n = 1565)	Q5 (n = 1618)	Statistic	p
Energy (kCal), median (Q_1, Q_3)	1818.50 (1418.00, 2285.00)	1612.50 (1212.50, 2047.00)	1781.00 (1410.50, 2292.00)	1816.50 (1440.00, 2230.00)	1848.00 (1479.00, 2269.50)	2049.00 (1623.00, 2541.00)	χ^2# = 155.22	<0.001
Dietary fiber (g), median (Q_1, Q_3)	15.00 (10.90, 20.40)	10.30 (7.45, 13.50)	14.20 (10.65, 18.40)	14.95 (11.75, 20.40)	17.00 (12.70, 21.90)	19.65 (14.80, 25.60)	χ^2# = 912.81	<0.001
Vitamin E (mg), median (Q_1, Q_3)	6.80 (4.75, 9.82)	4.79 (3.40, 6.76)	6.29 (4.68, 8.76)	6.96 (5.04, 9.46)	7.79 (5.39, 11.61)	8.72 (6.30, 13.43)	χ^2# = 518.47	<0.001
Sodium (mg), median (Q_1, Q_3)	3035.50 (2288.00, 3883.00)	2653.00 (1992.50, 3478.50)	3126.00 (2330.00, 3903.50)	3075.50 (2347.50, 3891.00)	3054.00 (2338.00, 3877.00)	3238.00 (2519.00, 4212.50)	χ^2# = 73.60	<0.001
BMI (kg/m^2), median (Q_1, Q_3)	29.27 (25.70, 33.88)	29.75 (26.13, 34.85)	29.89 (26.20, 35.00)	29.20 (25.70, 33.55)	28.73 (25.54, 33.40)	28.34 (25.20, 33.05)	χ^2# = 16.17	0.004
Age (years), median (Q_1, Q_3)	64.00 (57.00, 72.00)	62.00 (56.00, 70.00)	63.00 (56.00, 71.00)	65.00 (57.00, 73.00)	65.00 (58.00, 74.00)	64.00 (57.00, 73.00)	χ^2# = 29.35	<0.001
UACR (mg/g), median (Q_1, Q_3)	8.73 (5.40, 19.29)	8.73 (5.35, 20.46)	8.41 (5.40, 19.29)	8.94 (5.50, 19.03)	9.14 (5.54, 18.71)	8.60 (5.26, 19.21)	χ^2# = 1.79	0.775
eGFR (mL/min/1.73 m^2), median (Q_1, Q_3)	82.42 (66.60, 96.73)	82.17 (65.66, 96.96)	83.00 (64.03, 97.78)	82.42 (65.77, 95.46)	81.40 (66.36, 94.69)	84.51 (69.96, 98.92)	χ^2# = 12.00	0.022
HF, n (%)							χ^2 = 1.09	0.979
Yes	594 (6.43)	131 (6.59)	121 (6.35)	114 (6.05)	104 (6.89)	124 (6.29)		
No	7307 (93.57)	1478 (93.41)	1369 (93.65)	1505 (93.95)	1461 (93.11)	1494 (93.71)		
Stroke, n (%)							χ^2 = 7.20	0.363
Yes	650 (6.77)	152 (8.01)	134 (7.27)	114 (5.97)	126 (6.26)	124 (6.35)		
No	7251 (93.23)	1457 (91.99)	1356 (92.73)	1505 (94.03)	1439 (93.74)	1494 (93.65)		
Sex, n (%)							χ^2 = 28.24	0.021
Male	3789 (45.54)	753 (43.45)	725 (47.34)	735 (41.70)	731 (44.98)	845 (50.19)		
Female	4112 (54.46)	856 (56.55)	765 (52.66)	884 (58.30)	834 (55.02)	773 (49.81)		
Ethnicity, n (%)							χ^2 = 32.53	0.049
Mexican American	1038 (4.25)	204 (4.32)	199 (3.86)	234 (4.84)	192 (3.80)	209 (4.43)		
Other Hispanic	594 (3.04)	120 (3.23)	121 (2.87)	113 (3.04)	131 (3.34)	109 (2.74)		
Non-Hispanic White	4105 (77.20)	810 (74.27)	794 (79.57)	836 (77.50)	843 (78.68)	822 (76.00)		
Non-Hispanic Black	1775 (10.61)	415 (13.05)	289 (8.33)	364 (10.74)	327 (9.71)	380 (11.22)		
Others	389 (4.89)	60 (5.12)	87 (5.37)	72 (3.89)	72 (4.47)	98 (5.61)		
Education, n (%)							χ^2 = 303.21	<0.001
Less than 9th grade	1125 (7.27)	286 (10.42)	238 (6.89)	231 (6.58)	191 (6.98)	179 (5.50)		
9–11th grade	1173 (11.58)	289 (15.13)	232 (12.15)	240 (11.47)	220 (10.38)	192 (8.80)		
High school graduate	2036 (26.90)	460 (32.74)	393 (30.65)	418 (25.80)	383 (24.22)	382 (21.08)		
Some college/AA degree	2085 (29.44)	403 (28.14)	386 (29.73)	451 (32.23)	413 (27.60)	432 (29.49)		
College graduate or higher	1482 (24.81)	171 (13.57)	241 (20.58)	279 (23.93)	358 (30.82)	433 (35.13)		

Table 1. Continued.

Variables	Total (n = 7901)	Vitamin C intake						
		Q1 (n = 1609)	Q2 (n = 1490)	Q3 (n = 1619)	Q4 (n = 1565)	Q5 (n = 1618)	Statistic	p
Marital status, n (%)							χ^2 = 90.62	0.003
Married	4470 (62.16)	835 (56.63)	842 (62.82)	948 (63.88)	920 (65.02)	925 (62.42)		
Widowed	1419 (14.34)	283 (15.18)	273 (12.72)	264 (13.28)	306 (16.67)	293 (13.83)		
Divorced	1085 (13.72)	276 (17.25)	205 (15.27)	214 (12.78)	184 (10.26)	206 (13.04)		
Separated	232 (2.03)	47 (3.20)	37 (1.21)	56 (2.80)	43 (1.34)	49 (1.59)		
Never married	477 (5.00)	109 (4.93)	96 (5.41)	89 (4.12)	83 (4.45)	100 (6.07)		
Living with partner	218 (2.76)	59 (2.81)	37 (2.57)	48 (3.14)	29 (2.26)	45 (3.05)		
Smoking status, n (%)							χ^2 = 214.74	<0.001
Never	3789 (47.47)	665 (41.03)	698 (45.76)	800 (48.85)	765 (49.26)	861 (52.43)		
Former	2962 (37.92)	569 (34.21)	558 (37.58)	609 (38.83)	641 (42.06)	585 (36.93)		
Current	1150 (14.61)	375 (24.75)	234 (16.66)	210 (12.32)	159 (8.68)	172 (10.64)		
Alcohol consumption, n (%)							χ^2 = 16.64	0.052
No	2670 (29.41)	532 (30.24)	528 (30.38)	573 (31.70)	526 (29.19)	511 (25.55)		
Yes	5231 (70.59)	1077 (69.76)	962 (69.62)	1046 (68.30)	1039 (70.81)	1107 (74.45)		
DM, n (%)							χ^2 = 34.41	0.009
No	5168 (70.61)	1015 (68.26)	940 (67.78)	1053 (71.82)	1043 (69.25)	1117 (75.93)		
Yes	2733 (29.39)	594 (31.74)	550 (32.22)	566 (28.18)	522 (30.75)	501 (24.07)		
Hyperlipidemia, n (%)							χ^2 = 16.26	0.150
No	1199 (14.00)	222 (11.78)	218 (13.84)	242 (14.48)	236 (13.32)	281 (16.60)		
Yes	6702 (86.00)	1387 (88.22)	1272 (86.16)	1377 (85.52)	1329 (86.68)	1337 (83.40)		
PIR, n (%)							χ^2 = 220.76	<0.001
Q1	2429 (19.92)	622 (27.47)	486 (20.02)	478 (18.53)	423 (16.83)	420 (16.75)		
Q2	1705 (20.03)	382 (26.30)	316 (18.67)	365 (19.70)	337 (19.79)	305 (15.69)		
Q3	1496 (19.89)	267 (17.82)	293 (19.56)	308 (21.09)	292 (20.36)	336 (20.60)		
Q4	889 (14.00)	161 (12.26)	163 (16.49)	179 (12.66)	192 (14.37)	194 (14.19)		
Q5	1382 (26.17)	177 (16.14)	232 (25.26)	289 (28.01)	321 (28.64)	363 (32.77)		

Notes: χ^2#, Kruskal–Wallis test; χ^2, Rao–Scott Chi-square test; Q_1, 1st Quartile; Q_3, 3st Quartile; Q1–Q5, variables grouped by quintiles.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; AA, associate in arts; PIR, poverty-to-income ratio; UACR, urinary albumin-to-creatinine ratio.

mum Akaike information criterion (AIC). Furthermore, stratified analyses were conducted, dividing UACR and eGFR into five equal groups (Q1–Q5). Additionally, a sensitivity analysis was conducted.

All analyses were completed by applying R software (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria), and the Zstats 1.0 platform (https://www.zstats.net) (version 1.0, Zhejiang Chinese Medicine University, Hangzhou, China) was applied to generate statistical tables and select graphical outputs [23,24]. A p-value $<$ 0.05 was regarded as statistically significant.

Results

Characteristics

Between 2003 and 2020, there were 86,618 participants in the NHANES. Following screening criteria, 7901 eligible individuals were enrolled in the analysis (Fig. 1). Characteristics stratified by vitamin C intake are detailed in Table 1. The enrolled individuals had a median age of 64 years, with women accounting for 54.46% of the entire cohort. HF was identified in 594 participants. Significant differences were noted across quintiles of daily dietary vitamin C intake in terms of energy, dietary fiber, vitamin E, sodium, BMI, age, eGFR, sex, ethnicity, education, marital status, smoking status, DM, and PIR ($p < 0.05$).

Association of Daily Dietary Vitamin C Intake With HF

Table 2 displays the association of vitamin C intake with HF. The highest quintile of daily vitamin C intake (≥127.15 mg/day) was linked to higher odds of HF in model 3 (OR [95% CI] = 1.50 [1.03–2.19], $p = 0.038$) and model 4 (OR [95% CI] = 1.62 [1.06–2.48], $p = 0.030$) versus the lowest quintile (<28.55 mg/day). There was a clear dose-response association between vitamin C intake and HF, as shown by trend testing across intake quintile medians in model 3 (p for trend = 0.016) and model 4 (p for trend = 0.015). In addition, higher vitamin C intake was associated with a higher odds of HF when daily dietary vitamin C intake was analyzed as a continuous variable in model 3 (OR [95% CI] = 1.0021 [1.0007–1.0036], $p = 0.0043$) and model 4 (OR [95% CI] = 1.0024 [1.0008–1.0041], $p = 0.0039$).

Moreover, the RCS model demonstrated a clear overall correlation between vitamin C intake and HF risk (p for overall = 0.002), while the nonlinearity test was not statistically significant (p for nonlinear = 0.134). These results are indicative of a potential linear association between vitamin C intake and HF risk (Fig. 2).

Association of Vitamin C Intake With HF Stratified by Participants' Characteristics

To examine whether there is population heterogeneity in the link between vitamin C consumption and HF,

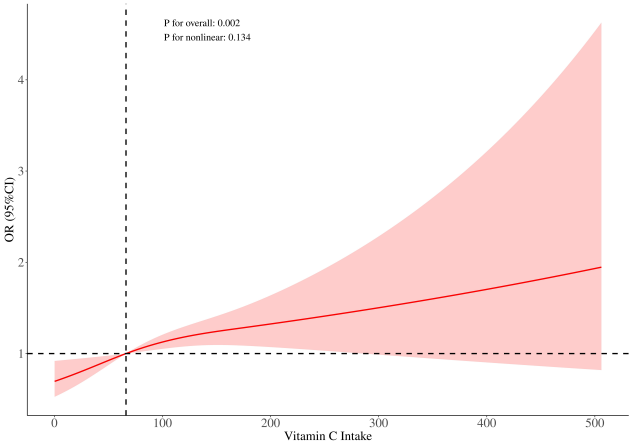

Fig. 2. The restricted cubic spline (RCS) analysis of daily dietary vitamin C intake (mg/day) and heart failure risk, adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, and dietary intake of energy, dietary fiber, vitamin E, and sodium. Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PIR, poverty-to-income ratio; UACR, urinary albumin-to-creatinine ratio. The figure was created using Zstats platform (https://www.zstats.net) version 1.0 by Zhejiang Chinese Medicine University, Hangzhou, China.

exploratory subgroup analyses according to baseline characteristics were further conducted, and modification effect was evaluated by means of interaction test (Fig. 3). In the subgroup analyses, vitamin C consumption was divided into lower median intake (LMI) (<66.25 mg/day) and upper median intake (UMI) (≥66.25 mg/day). No interaction was observed in any subgroup (p for interaction > 0.05). In males, vitamin C intake was associated with HF (OR = 1.62 [1.07–2.46], $p = 0.027$), whereas no correlation was detected in females (OR = 1.30 [0.82–2.06], $p = 0.267$). In the non-Hispanic White subgroup, vitamin C intake was linked to HF (OR = 1.56 [1.05–2.29], $p = 0.029$). In the subgroup of high school graduates, vitamin C intake was related to HF (OR = 1.70 [1.10–2.61], $p = 0.019$). In the married subgroup, vitamin C intake was correlated with HF (OR = 1.83 [1.16–2.89], $p = 0.011$). In the subgroup of never smokers, vitamin C intake was related to HF (OR = 1.94 [1.21–3.13], $p = 0.008$). In the subgroup of non-drinkers, vitamin C intake was also linked to HF (OR = 2.16 [1.27–3.66], $p = 0.005$). Vitamin C intake also had an association with HF in DM patients (OR = 1.83 [1.26–2.65], $p = 0.002$). Similarly, this phenomenon was detected in patients with hyperlipidemia (OR = 1.42 [1.03–1.95], $p = 0.035$). In the highest quintile of BMI, vitamin C consumption was related to HF (OR = 2.10 [1.28–3.43], $p = 0.004$). In the lowest tertile of age, vitamin C intake was correlated with HF (OR = 2.90

Table 2. Association between daily dietary vitamin C intake (mg) and heart failure.

Dietary vitamin C quintile	Model 1				Model 2				Model 3				Model 4			
	β	SE	OR (95% CI)	*p*	*β*	SE	OR (95% CI)	*p*	*β*	SE	OR (95% CI)	*p*	*β*	SE	OR (95% CI)	*p*
Q1			1.00 (Reference)				1.00 (Reference)				1.00 (Reference)				1.00 (Reference)	
Q2	–0.04	0.19	0.96 (0.66–1.40)	0.835	0.10	0.20	1.10 (0.74–1.64)	0.636	0.10	0.21	1.10 (0.72–1.68)	0.651	0.12	0.22	1.13 (0.74–1.74)	0.575
Q3	–0.09	0.22	0.91 (0.59–1.41)	0.678	0.03	0.21	1.03 (0.68–1.56)	0.888	0.22	0.22	1.25 (0.81–1.93)	0.325	0.26	0.23	1.29 (0.82–2.04)	0.269
Q4	0.05	0.24	1.05 (0.65–1.69)	0.842	0.22	0.24	1.25 (0.79–1.99)	0.343	0.35	0.25	1.42 (0.88–2.30)	0.159	0.41	0.25	1.51 (0.92–2.46)	0.107
Q5	–0.05	0.18	0.95 (0.68–1.34)	0.777	0.19	0.18	1.21 (0.85–1.73)	0.293	0.41	0.19	1.50 (1.03–2.19)	0.038	0.48	0.22	1.62 (1.06–2.48)	0.030
p for trend			0.969				0.220				0.016				0.015	
Dietary vitamin C (continuous)	0	0.0008	1.0000 (0.9983–1.0016)	0.9718	0.0009	0.0007	1.0009 (0.9995–1.0023)	0.2205	0.0021	0.0007	1.0021 (1.0007–1.0036)	0.0043	0.0024	0.0008	1.0024 (1.0008–1.0041)	0.0039

Notes: Q1–Q5, daily dietary vitamin C intake grouped by quintiles; *β*, regression coefficient;

Model 1, univariable logistic regression analysis;

Model 2, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, and alcohol consumption;

Model 3, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, and eGFR;

Model 4, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, and dietary intake of energy, dietary fiber, vitamin E, and sodium.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PIR, poverty-to-income ratio; UACR, urinary albumin-to-creatinine ratio; SE, standard error; OR, odds ratios; CI, confidence intervals.

Table 3. Sensitivity analysis.

Dietary vitamin C quintile	Model 5				Model 6				Model 7			
	β	SE	OR (95% CI)	*p*	*β*	SE	OR (95% CI)	*p*	*β*	SE	OR (95% CI)	*p*
Q1			1.00 (Reference)				1.00 (Reference)				1.00 (Reference)	
Q2	0.14	0.22	1.15 (0.74–1.78)	0.540	0.12	0.22	1.12 (0.73–1.74)	0.602	–0.12	0.21	0.89 (0.59–1.33)	0.564
Q3	0.27	0.23	1.31 (0.83–2.07)	0.246	0.25	0.23	1.28 (0.81–2.02)	0.290	–0.07	0.23	0.93 (0.60–1.45)	0.761
Q4	0.41	0.25	1.50 (0.92–2.46)	0.112	0.39	0.25	1.47 (0.89–2.43)	0.132	0.31	0.24	1.36 (0.84–2.20)	0.214
Q5	0.46	0.22	1.59 (1.03–2.44)	0.040	0.45	0.22	1.57 (1.02–2.42)	0.045	0.18	0.25	1.20 (0.74–1.94)	0.454
p for trend			0.021				0.024				0.163	
Dietary vitamin C (continuous)	0.0023	0.0008	1.0023 (1.0007–1.0040)	0.0061	0.0023	0.0008	1.0023 (1.0007–1.0040)	0.0068	0.0041	0.0014	1.0041 (1.0014–1.0068)	0.0040

Notes: *β*, regression coefficient; Q1–Q5, daily dietary vitamin C intake grouped by quintiles; SII is calculated by platelet count × neutrophil count/lymphocyte count.

Model 5, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, and dietary intake of energy, dietary fiber, vitamin E, sodium, and uric acid;

Model 6, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, energy, and dietary intake of dietary fiber, vitamin E, sodium, and SII.

Model 7, multivariable logistic regression analysis adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, energy, and dietary intake of dietary fiber, vitamin E, sodium, carotenoids, niacin, total folate, vitamin B2, vitamin B6, vitamin B12, magnesium, iron, potassium, and prescription for hypertension.

Abbreviations: SE, standard error; OR, odds ratios; CI, confidence intervals; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PIR, poverty-to-income ratio; SII, Systemic Immune-Inflammation Index; UACR, urinary albumin-to-creatinine ratio.

[1.45–5.82], $p = 0.004$). In the highest quintile of PIR, vitamin C consumption was related to HF (OR = 2.48 [1.17–5.27], $p = 0.021$). In the highest quintile of UACR, vitamin C intake was linked to HF (OR = 1.68 [1.05–2.67], $p = 0.033$). Similarly, in both the lowest and highest eGFR quintiles, vitamin C intake was associated with HF in both the lowest (OR = 1.55 [1.06–2.29], $p = 0.028$) and highest eGFR quintiles (OR = 2.88 [1.27–6.54], $p = 0.014$). These results showed that a higher daily intake of vitamin C through diet was associated with an increased OR of HF in men, non-Hispanic Whites, high school graduates, married individuals, never smokers, non-drinkers, DM patients, patients with hyperlipidemia, individuals in the highest BMI quintile, individuals in the lowest age tertile, individuals in the highest PIR quintile, individuals in the highest UACR quintile, and individuals in the lowest and highest eGFR quintiles. The positive association of vitamin C intake with HF in these populations suggests that there may be specific biological mechanisms or unknown confounding factors in these populations. Further validation of the association of vitamin C with HF in different populations is needed.

Sensitivity Analysis

To ensure the robustness of the logistic regression results, we performed sensitivity analyses (Table 3). After further adjustments to the micronutrients in the diet and the prescription of antihypertensive drugs, this clear association between daily dietary vitamin C intake and HF became no longer significant. However, the continuous model still has statistical significance.

Discussion

This study examined the association of dietary vitamin C intake with HF among hypertensive patients aged ≥50 years based on the 2003–2020 NHANES data. Our research indicated that higher vitamin C intake was associated with a higher OR of HF in hypertensive individuals aged 50 years and above. Individuals in the highest quintile of vitamin C intake (≥127.15 mg/day) displayed a 62% greater OR of HF versus those in the lowest quintile (<28.55 mg/day) in the model adjusted for all covariates (model 4). This relationship, however, may be influenced by the intake of unknown levels of specific nutrients. In addition, models 1 and 2 are not statistically significant, but models 3 and 4 show significance. This may be because health indicators such as BMI, DM, and hyperlipidemia impact the relationship between daily vitamin C intake and HF more than other factors do. The association between higher daily dietary vitamin C consumption and a higher OR of HF among hypertensive individuals aged 50 years and above persisted across exploratory subgroup analyses. However, there was no interaction among all subgroups. A study found that female sex is consistently associated with poorer reported health-related quality of life (HRQoL) in HF populations, patient groups affected by other chronic conditions, and the general community [25]. However, our subgroup analysis revealed a statistically significant correlation between daily vitamin C intake and HF in men only. This may be attributed to nitric oxide synthesis promoted by estrogen in women, which improves vasodilatory function. This function may attenuate cardiovascular damage caused by oxidative stress, masking the association between high vitamin C intake and HF in women. Additionally, the correlation detected in Settergren *et al.*'s study [25] could be attributed to the conspicuous gender differences in the Swedish population. After making further adjustments to micronutrients in the diet and prescribing antihypertensive drugs, the clear association was no longer significant. However, the continuous model remains statistically significant. These findings underscore the significant disparities in dietary habits and nutritional risks across different populations, underscoring the pressing need for more research involving ethnically diverse groups. In short, our findings revealed that the recommended dietary intake of vitamin C for hypertensive patients aged 50 and above should be carefully assessed.

Epidemiological studies examining vitamin C's connection with HF have yielded conflicting results. The heart-protective effects of vitamin C vary in clinical trials. Randomised controlled trials have shown that vitamin C supplementation can enhance endothelial function and lower blood pressure in patients with primary hypertension, particularly when combined with vitamin E; however, other studies have produced inconsistent results [26]. Some trials have indicated that vitamin C has no sustained cardiovascular benefits, particularly in critically ill patients or those receiving high-dose intravenous treatment without close monitoring [27,28]. Therefore, the therapeutic effect of vitamin C remains uncertain when used as a single drug, and the debate continues. One study reported that consumption of vitamin C supplements was connected with elevated cardiovascular mortality risk in diabetic postmenopausal women [29]. Besides, high red blood cell folate levels or folate deficiency may increase the risk of HF [11]. Recent research indicated that long-term daily multivitamin use exerts no beneficial effects on all-cause or heart disease mortality among U.S. adults without chronic conditions [30]. Additionally, a cohort study has failed to establish a connection between vitamin supplement consumption and overall mortality and cardiovascular mortality in populations without vitamin deficiencies. However, prolonged use of these supplements in women may lower the overall mortality risk while elevating the risk for coronary heart disease [31]. In a 2021 Mendelian randomisation study, Chen *et al.* [32] found that adequate vitamin C intake did not reduce the risk of HF. High doses of ascorbic acid can lead to an increased concentration of free radicals through oxidative reactions. These free radicals then enter cancerous cells and produce oxidative stress. In this case, ascorbic acid can induce the death of cancerous cells and cellular arrest through an in-

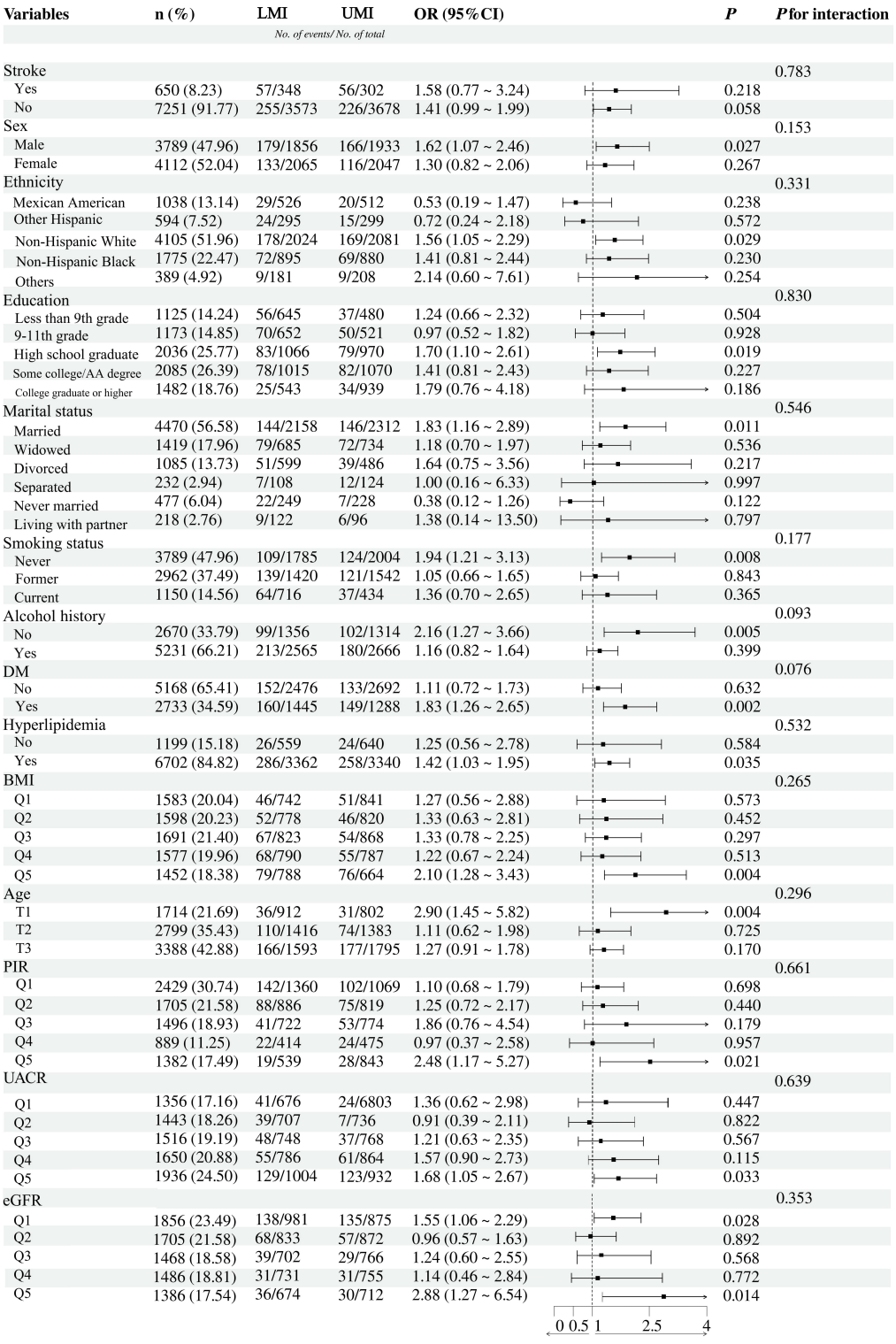

Fig. 3. Association of daily dietary vitamin C intake with heart failure stratified by participants' features, adjusted for age (categorized into tertiles), sex, ethnicity, education, marital status, PIR (categorized into quintiles), smoking status, alcohol consumption, stroke history, BMI (categorized into quintiles), DM, hyperlipidemia, UACR, eGFR, and dietary intake of energy, dietary fiber, vitamin E, and sodium. Notes: Q1–Q5, variables grouped by quintiles; T1–T3, variables grouped by tertiles. Abbreviations: LMI, lower median intake; UMI, upper median intake; OR, odds ratios; CI, confidence intervals; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PIR, poverty-to-income ratio; UACR, urinary albumin-to-creatinine ratio. The figure was created using Zstats platform (https://www.zstats.net) version 1.0 by Zhejiang Chinese Medicine University, Hangzhou, China.

tense process of oxidation [33]. This process may also occur in endothelial cells and cardiomyocytes, resulting in cell death, hypertension and HF. These indicate a range of potentially safe doses for vitamin C intake. Vitamin C deficiency may have adverse health effects, while excessive intake, especially in individuals with pre-existing conditions, may be harmful. Moreover, administering doses beyond the physiological needs of healthy individuals may not result in further benefits.

Oxidative stress denotes a biochemical imbalance where reactive species oxidatively modify cellular constituents, including nucleic acids, proteins, and membrane lipids [34]. Combining vitamin C with cisplatin in cervical cancer cells has been found to markedly elevate intracellular levels of ROS and hydrogen peroxide, demonstrating that vitamin C acts as an oxidizing agent at pharmacological doses [35].

The positive association of higher vitamin C intake with increased HF OR in hypertensive individuals aged 50 years and above may be explained by several biological mechanisms, particularly related to the dual role of vitamin C (antioxidant/pro-oxidant) [36]. The enediol part of ascorbic acid enables its dual functionality as an antioxidant and a pro-oxidant through redox cycling, a process influenced by dosage and context. At physiological concentrations ranging from 10 to 200 µM, it acts by donating electrons or hydrogen atoms to counteract reactive oxygen species (ROS) like superoxide and peroxyl radicals. This action results in the formation of a stable ascorbate radical (Asc- $^{-}$) that undergoes harmless dismutation, concurrently replenishing other antioxidants such as glutathione and vitamin E. Conversely, at elevated pharmacological levels exceeding 1–5 mM, it rapidly reduces transition metals like Fe^{3+} to Fe^{2+}, leading to the generation of H_2O_2 via an oxygen-mediated pathway. This process overwhelms cellular catalase, initiating Fenton chemistry and yielding highly toxic hydroxyl radicals (•OH). Consequently, this cascade triggers lipid peroxidation, DNA impairment, and selective apoptosis, particularly in cancer cells characterized by elevated labile iron levels and compromised defense mechanisms [36]. *In vitro* studies have shown that high pharmacological concentrations of vitamin C ($>$5 mM) can cause ROS-mediated cell death in sensitive cell lines [37,38]. The outcome hinges on the availability of metal ions, the activity of enzymes, and the cellular redox status, illustrating how the identical reducing property can shield normal cells while exerting cytotoxic effects on stressed cells. At high concentrations, vitamin C participates in the redox cycle, generating hydroxyl radicals via the Fenton reaction in the presence of transition metal, depleting intracellular glutathione (GSH) and nicotinamide adenine dinucleotide phosphate (NADPH) pools [39,40]. This process intensifies oxidative stress and lipid peroxidation, leading to myocardial cell damage and dysfunction, which elevates the OR for HF, especially in people with hypertension [41,42]. Alternatively, vitamin C effectively scavenges lipid peroxyl radicals; however, its activity against other oxidants, such as superoxide, peroxynitrite, and hypochlorite, is relatively limited. Collagen is essential for maintaining the structural integrity of blood vessels and connective tissues. Vitamin C plays a role in collagen synthesis by acting as a cofactor for prolyl and lysyl hydroxylases, which catalyze the formation of hydroxyproline and hydroxylysine. These hydroxylation reactions depend on vitamin C to maintain the redox state of iron [5]. Electrons derived from vitamin C have the capacity to reduce iron, which can lead to the formation of superoxide and hydrogen peroxide, subsequently resulting in the generation of reactive oxidant species [40]. Therefore, under certain conditions, vitamin C acts as a reducing agent that can produce oxidants. This may alter the normal antioxidant action of vitamin C, affecting collagen synthesis, leading to damage to the integrity of the blood vessels, inflammatory cell infiltration and atherosclerotic plaque formation, and ultimately inducing HF. Furthermore, *in vitro* studies using human colon cancer (HT29) cell models have demonstrated that enhanced hydrogen peroxide (H_2O_2) production cannot be offset by altered expression of antioxidant genes following vitamin C treatment. This suggests that increased preservation of H_2O_2, a type of ROS, may also lead to heart failure under the influence of vitamin C. Vitamin C exhibits dual roles as both an antioxidant and a pro-oxidant, highlighting the complexity of its function. In addition, ascorbic acid also has nephrotoxicity and hepatotoxicity. Despite being a potent antioxidant, ascorbic acid can lead to nephrotoxicity post-administration. Ascorbic acid is converted to Ascorbate ion by losing an electron, followed by conversion to DHA upon losing two more electrons. DHA is then transformed into Diketogluconic acid, an unstable compound. This compound irreversibly converts to Diketogluconic acid, which breaks down into L-erythrulose and Oxalic acid. The combination of Oxalic acid with calcium ions results in its deposition in renal tubules, leading to acute tubular necrosis and the development of "oxalate nephropathy". Additionally, the decrease in GSH levels enhances ROS production, triggering an increase in TGF-β and CTGF, ultimately promoting fibrosis [43]. This could eventually lead to irreversible end-stage renal failure [44]. Ascorbic acid also has a hepatotoxic effect similar to its nephrotoxic effect. Administering a high dose of ascorbic acid to liver cells can deplete NAD+ levels, damage DNA and cause apoptosis. The nephrotoxicity and hepatotoxicity of ascorbic acid could finally lead to the development of HF. Our research indicated that higher vitamin C consumption may elevate the probability for HF in hypertensive individuals aged 50 years and above. This finding emphasizes the need for large-scale clinical trials to pinpoint the safe daily vitamin C intake levels, especially in populations with comorbidities like hypertension, DM, or renal insufficiency.

Until now, there is still no consensus on the recommended dosage of Vitamin C for daily consumption. The conflicting guidelines on recommended vitamin C intake published by the World Health Organization (WHO) and the National Academy of Medicine (NAM) illustrate this disagreement. Panels writing for the WHO and countries such as the UK, Australia, New Zealand, and India have concluded that there is no consistent evidence indicating that vitamin C provides health benefits besides preventing scurvy. Writing panels from these countries have recommended a daily vitamin C intake in the range of 40–45 mg. On the contrary, writing panels for the NAM and countries such as Japan, Germany, Switzerland, and Austria have concluded that recommending higher vitamin C intake may help prevent certain pathological conditions in addition to scurvy. An average daily vitamin C intake of 75–110 mg is recommended by the writing panels for these countries [45]. Individuals aged 50 years and above with cardiovascular risk factors should strictly adhere to the recommended daily intake of vitamin C to minimize the HF risk. With more and more consumers showing an interest in health and wellness maintenance, incorporating vitamins into diet has become commonplace. In fact, it is estimated that 60% of consumers worldwide take vitamin supplements daily, with cardiovascular disease prevention cited as the prime motive in the majority of these people [46]. Based on our findings, individuals aged 50 years and above with hypertension may not benefit from high-dose vitamin C consumption in the context of HF prevention. Thus, rather than unnecessarily consuming higher-than-recommended dosages of vitamin C, this patient cohort should adopt other cardiovascular health-promoting behaviors, such as regular exercise and adequate rest, and should consume a balanced diet to achieve better health.

This investigation pioneers the application of NHANES data to appraise the association of dietary vitamin C consumption with HF. The usage of nationally representative data from NHANES enhances reliability of the current analysis. Nonetheless, several limitations warrant acknowledgment. The cross-sectional design precludes causal inference regarding association between vitamin C and HF. There is a possibility of reverse causality. For instance, patients with hypertension complicated by HF might be more likely to consume more vitamin C as part of their health management regimen. Thus, prospective studies are needed to determine the causality between daily dietary vitamin C intake and HF. Geographical restriction to U.S. participants may limit the external validity of our results. Therefore, more research in diverse populations is needed. Due to the limited availability of HF-related variables in the NHANES, HF was determined by means of self-report, which unfortunately elevated the risk of misclassification. Future studies should employ alternative definitions of HF, such as those based on hospitalization records, laboratory test results, or imaging confirmation. Furthermore, reliance on self-reported 24-hour diet recalls, which reflect only the short-term intake, may introduce measurement inaccuracies, potentially compromising their capacity to represent the long-term nutritional patterns. For assessing vitamin C intake in this study, the participants underwent a 24-hour diet recall process, which was consistent with the standardized process in the NHANES. However, there is still a risk of recall bias. The participants may have omitted or misreported food intake, or they may have adjusted their reporting due to social desirability bias (e.g., overstating their fruit intake). This type of bias can lead to misclassification of exposure, which may affect the true association between vitamin C intake and HF. Hence, the use of food frequency questionnaires (FFQs) in future studies is suggested. This study may also introduce selection bias. For example, the NHANES study design may have missed hypertensive patients who were hospitalized or in poor health, affecting the extrapolation of the results to the overall hypertensive population. Future studies need to include a broader hypertensive population, including hospitalized patients. Additionally, there may be unmeasured confounding factors, such as healthy dietary behaviors. For example, individuals who consume higher levels of vitamin C may also engage in other cardiovascular health-promoting practices, all of which are confounders that need to be controlled for in future studies.

Conclusion

Higher daily consumption of dietary vitamin C is associated with a higher probability of HF among hypertensive individuals aged 50 years and above. These findings underscore the significance of precision dietary interventions in preventing and managing HF. Further studies are essential to elucidate the role of vitamin C in HF among middle-aged and elderly hypertensive patients, for the purposes of exploring the causal relationship and establishing appropriate dietary recommendations.

Availability of Data and Materials

The research data analyzed in this investigation were sourced from the NHANES database (https://www.cdc.gov/nchs/nhanes/about/).

Author Contributions

Conceptualization, YZX; methodology, YZX and QC; software, YZX; validation, YZX and QC; formal analysis, YZX and QC; investigation, YZX and QC; resources, YZX and QC; data curation, YZX and QC; writing—original draft preparation, YZX; visualization, YZX; supervision, QC; project administration, QC. Both authors have been involved in revising it critically for important intellectual content. Both authors gave final approval of the version to be published. Both authors have participated sufficiently

in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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