Preventive Medicine Reports 44 (2024) 102793

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Association between rheumatoid arthritis and serum vitamin C levels in Adults: Based on the National health and Nutrition Examination survey database

Jing Zhang [a], Pu Liu [b], Sirou Huang [b], Qingping Chen [a], Xiaoyuan Wang [c], Hua Liu [a,*]

[a] Department of Rheumatology and Immunology, Xi'an No. 5 Hospital, No.112 XiGuanZhengJie, LianHu District, Xi'an City, Shaanxi Province 710082, China
[b] Department of rheumatism and Immunology, The First Affiliated Hospital of Xian Medical University, Xi'an City, Shaanxi Province 710077, China
[c] Department of Rheumatism and Immunology, Second Hospital of Lanzhou University, Lanzhou City, Gansu Province 730030, China

ARTICLE INFO

Keywords:
Rheumatoid arthritis
serum vitamin C
Association
NHANES
Public health

ABSTRACT

This study attempted to investigate relationship between rheumatoid arthritis and serum vitamin C levels using data from National Health and Nutrition Examination Survey (NHANES).

The NHANES database aims to collect health, nutrition, biological, and behavioral data from a nationally representative sample of the population. This study utilizes NHANES data from three cycles: 2003–2004, 2005–2006, and 2017–2018, extracting data on the prevalence of rheumatoid arthritis and serum vitamin C levels. A generalized linear model is used to evaluate the association between the two.

A total of 12,665 participants were included in the final analysis. Serum vitamin C levels were significantly higher in the non-rheumatoid arthritis group compared to the rheumatoid arthritis group (0.63 vs. 0.59, $P = 0.042$). Generalized linear model analysis showed that higher serum vitamin C levels were associated with a decreased risk of rheumatoid arthritis (OR = 0.62, 95 %CI: 0.40–0.98, $P = 0.034$). Stratified analysis revealed a significant interaction between non-hypertensive individuals and rheumatoid arthritis with serum vitamin C levels ($P < 0.05$). After adjusting for confounding factors, serum vitamin C levels remained significantly associated with rheumatoid arthritis in all models ($P < 0.05$). Restricted cubic spline results indicated that serum vitamin C levels above 0.95 mg/dL could help prevent rheumatoid arthritis. Increasing dietary vitamin C intake through supplementation was found to raise serum vitamin C levels.

There was a significant association between rheumatoid arthritis and serum vitamin C levels, indicating that high levels of serum vitamin C may be a protective factor against rheumatoid arthritis.

1. Introduction

Chronic autoimmune disease rheumatoid arthritis with a hallmark of joint destruction can affect blood vessels, metabolism, bones, and psychology over time(McInnes and Schett, 2017). Currently, the global incidence of rheumatoid arthritis is about 1 %, and it is more common in women(Smolen et al., 2016), with women having a 2–3 times higher risk of developing rheumatoid arthritis than men(Jang and Kwon, 2022). Without appropriate treatment, the symptoms of rheumatoid arthritis worsen with exacerbations, and the joints gradually become irreversibly damaged, affecting physical and psychological function(Chaurasia et al., 2020), and shortening the patient's life expectancy(Lassere et al., 2013). Importantly, rheumatoid arthritis is still an incurable disease, and only the symptoms can be alleviated and pain relieved through treatment (Chaurasia et al., 2020). The prevention and treatment of rheumatoid arthritis is currently a serious public health problem that requires attention.

The etiology of rheumatoid arthritis is not yet clear, and earlier studies have reported that imbalance of oxidative stress regulation plays a crucial role in development and progression of rheumatoid arthritis (Mueller et al., 2021). Antioxidants have been suggested as prospective targets for the prevention and therapy of rheumatoid arthritis because they are significant scavengers of reactive oxygen species (ROS) (Ahmadinejad et al., 2017). Among them, vitamin C is one of the basic exogenous vitamins and is well known for its powerful antioxidant properties. Vitamin C also plays a role in physiological events, such as

* Corresponding author.
E-mail address: xaliuh@126.com (H. Liu).

https://doi.org/10.1016/j.pmedr.2024.102793
Received 3 July 2023; Received in revised form 6 June 2024; Accepted 6 June 2024
Available online 13 June 2024

maintaining redox homeostasis, immune regulation, collagen synthesis, and gene transcription(Vollbracht and Kraft, 2022; Mandl et al., 2009; Dosedel et al., 2021). Studies have reported that chronic lower respiratory illness mortality is enhanced by low blood vitamin C levels(Salo et al., 2022). A cross-sectional study manifested that serum vitamin C levels are significantly associated with fibrosis in male and overweight or obese non-alcoholic fatty liver disease patients(Cao et al., 2022). However, association between serum vitamin C levels and the risk of rheumatoid arthritis has not been fully studied. In this study, we used a large population-based survey dataset, namely National Health and Nutrition Examination Survey (NHANES), to investigate association of rheumatoid arthritis with serum vitamin C levels.

2. Methods

2.1. Study population

NHANES is a nationally representative survey of the civilian, non-institutionalized population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention in the United States. Detailed descriptions of the NHANES methods are available on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm). All study procedures were authorized by the NCHS ethical review board prior to data collection, and all participants gave their signed, informed consent. Due to the use of anonymized public data in this study, approval from the Institutional Review Board is not required. We downloaded NHANES data from three periods: 2003–2004, 2005–2006, and 2017–2018. A total of 29,724 participants were included in the survey. After excluding participants who did not meet diagnostic criteria for rheumatoid arthritis and serum vitamin C level data (n = 8,420) and demographic data (n = 8,639), a total of 12,665 participants were finally included (Fig. 1).

2.2. Rheumatoid arthritis

The diagnosis of rheumatoid arthritis was based on medical conditions questionnaire collected through interviews as part of the NHANES program. Participants who answered “yes” to the question “Doctor ever said you had arthritis” and answered “Rheumatoid arthritis” to the subsequent question “Which type of arthritis was it?” were defined as having rheumatoid arthritis.

2.3. Vitamin C measurement

Blood samples were collected by trained phlebotomists and stored under appropriate conditions. The samples were transported to the laboratory and analyzed by trained laboratory personnel using a standardized protocol. NHANES Quality Assurance and Quality Control protocols were authorized by Clinical Laboratory Improvement Amendments of 1988. Serum vitamin C levels were assessed by electrochemical detection using high-performance liquid chromatography at 650 mV (https://wwwn.cdc.gov/Nchs/Nhanes/2003–2004/L06VIT_C.htm). Serum vitamin C level values were logarithmically transformed to approximate normal distribution, and the logarithmically transformed values were used in subsequent analyses. Dietary data from NHANES, encompassing food components, nutritional elements, and energy information, are managed by the Food Surveys Research Group in the United States. The calculation of dietary vitamin C involved averaging the data obtained from two rounds of 24-hour dietary recall interviews.

2.4. Covariate assessment

Gender, age, race, body mass index (BMI), alcohol drinking, smoking, and hypertension were identified as likely covariates and confounding factors and were adjusted in analysis model. The age of the selected participants in this study was the age at screening, categorized as 20–45 years, 45–69 years, or > 69 years. Gender was categorized as male or female. Race was classified as Mexican American, non-Hispanic Black, non-Hispanic White, other Hispanic, or other races. BMI was classified as ≤ 25 kg/m^2, 25–30 kg/m^2, or > 30 kg/m^2 (Tian et al., 2022). Based on the question “Do you now smoke cigarettes” in the questionnaire, participants who answered “Every day” or “Some days” were defined as “current smokers”, and those who answered “Yes” to “Smoked at least 100 cigarettes in life” were defined as “ever smokers”, while others were defined as “never smokers”. Hypertension was defined as meeting one of the criteria: (a) ever been told they have hypertension; (b) ever been told to take hypertension prescription; (c) currently taking prescription medication to treat hypertension; (d) mean systolic blood pressure ≥ 130 mmHg or mean diastolic blood pressure ≥ 80 mmHg in the NHANES examination section(Whelton et al., 2018).

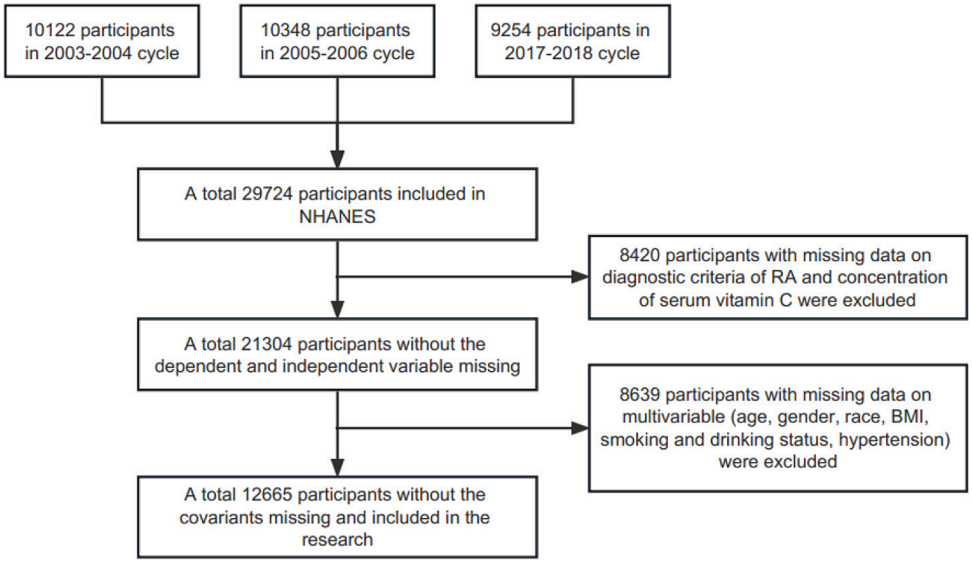

Fig. 1. Flowchart for Selecting Participants with and without Rheumatoid Arthritis from the NHANES Database across Three Cycles (2003–2004, 2005–2006, and 2017–2018).

2.5. Statistical analysis

All analyses were completed on R software (version 4.2.1, https://www.R-project.org). The 'tableone' package was used to draw the baseline table, which grouped adults with or without rheumatoid arthritis and reported sample sizes and proportions for categorical variables, and means and standard deviations for continuous variables (n not weighted, n(%), mean and standard deviation weighted). The 'survey' package was used to construct weighted generalized linear models of serum vitamin C levels and rheumatoid arthritis, with separate linear regressions performed for each variable type. The p-values of the interaction terms in the stratified linear regression were tested by chi-square test. Stratified on hypertension, the 'survey' package was used to construct weighted linear models of serum vitamin C levels and rheumatoid arthritis (Crude: unadjusted; Model I: adjusted for gender, age, race; Model II: adjusted for gender, age, race, BMI, hypertension, alcohol drinking, triglycerides, total cholesterol). Additionally, this study employed the 'rms' package to construct restricted cubic splines, investigating the optimal serum vitamin C levels for preventing the onset of rheumatoid arthritis. The 'svyglm' function was utilized to explore the linear relationship between dietary vitamin C intake and serum vitamin C levels. $P < 0.05$ meant statistically significant.

3. Results

A total of 12,665 participants were included in the final analysis, of whom 51.4 % were female. The majority of participants were aged 20–45 years, non-Hispanic White, never smokers, and drinkers, and the vast majority were non-rheumatoid arthritis patients. The mean serum vitamin C level for all participants was 0.63 mg/dL (Table 1). Subsequently, we grouped the 12,665 participants according to whether they had rheumatoid arthritis and compared the relevant characteristics between the two groups. Among them, 712 participants had rheumatoid arthritis, and 11,953 participants did not. Participants with rheumatoid arthritis were mostly aged 45–69 years (55.4 %), obese, had smoking and drinking habits, had hypertension, and had higher levels of serum vitamin C. Significant differences were seen between the two groups in age, race, BMI, smoking, drinking, hypertension, and serum vitamin C levels ($P < 0.05$).

After adjusting for all confounding factors (Table 2), we found that an increase in serum vitamin C level was linked with a decreased risk ratio of developing rheumatoid arthritis (OR = 0.62, 95 %CI: 0.40–0.98, $P = 0.034$).

We found significant differences ($P < 0.05$) in association of serum vitamin C levels with rheumatoid arthritis in female participants, participants aged below 69 years, participants with BMI $\leq$ 25 kg/m^2, drinkers, and non-hypertensive participants through stratified analysis (Table 3). Furthermore, we found that the interaction between serum vitamin C levels and hypertension had a significant difference (P for interaction = 0.027) in the analysis of rheumatoid arthritis, and this interaction was significant in non-hypertensive participants ($P = 0.002$).

In multiple linear regression (Table 4), we found that regardless of whether the confounding factors were adjusted or not, there was a significant negative association of serum vitamin C levels with the risk of rheumatoid arthritis (OR < 1, $P < 0.05$). In the subgroup of non-hypertensive participants, adjusted or not, serum vitamin C levels were significantly negatively correlated with the risk of rheumatoid arthritis (OR < 1, $P < 0.05$). Furthermore, we explored the optimal serum vitamin C levels for preventing rheumatoid arthritis through restricted cubic splines, and the results are depicted in Fig. 2. A linear association was observed between serum vitamin C levels and rheumatoid arthritis. When the serum vitamin C level exceeded 0.95 mg/dL, it was associated with a certain degree of reduction in the risk of developing rheumatoid arthritis.

Furthermore, a linear regression analysis was employed to investigate the relationship between dietary vitamin C intake and serum vitamin C levels (Supplementary Table 1). The results revealed that for each increase of 1 unit in dietary vitamin C intake, there was a corresponding increase of 0.0016 mg/dL in serum vitamin C levels. A

Table 1
Comparison of Characteristics between Adults with and without Rheumatoid Arthritis in the NHANES Database across Three Cycles (2003–2004, 2005–2006, and 2017–2018).

Characteristics	N(%) / Mean ± SD	non-rheumatoid arthritis	rheumatoid arthritis	P-value
Overall	12,665	11,953	712	
Gender				
Female	6500 (51.4)	6113 (51.3)	387 (53.1)	0.542
Male	6165 (48.6)	5840 (48.7)	325 (46.9)	
Age				<0.001*
20–45	5510 (48.2)	5404 (49.4)	106 (21.1)	
45–69	4806 (39.5)	4425 (38.8)	381 (55.4)	
>69	2349 (12.4)	2124 (11.9)	225 (23.5)	
Race				0.003*
Mexican American	2248 (8.1)	2141 (8.2)	107 (6.1)	
Other Hispanic	664 (4.6)	631 (4.7)	33 (3.7)	
Non-Hispanic White	5954 (70.0)	5653 (70.2)	301 (65.3)	
Non-Hispanic Black	2659 (10.5)	2447 (10.2)	212 (16.3)	
Other races	1140 (6.8)	1081 (6.7)	59 (8.6)	
BMI (kg/m^2)				0.021*
≤25	3646 (30.5)	3474 (30.7)	172 (26.1)	
25–30	4302 (32.6)	4088 (32.7)	214 (30.7)	
>30	4717 (36.9)	4391 (36.7)	326 (43.2)	
Smoking				<0.001*
Never smoking	6747 (52.6)	6436 (53.3)	311 (38.0)	
Former smoking	3300 (25.5)	3061 (25.1)	239 (34.5)	
Now Smoking	2618 (21.9)	4391 (21.7)	326 (27.5)	
Alcohol drinking				0.034*
No	2971 (19.5)	2790 (19.3)	181 (23.8)	
Yes	9694 (80.5)	9163 (80.7)	531 (74.6)	
Hypertension				<0.001*
No	5727 (49.0)	5543 (49.8)	184 (32.5)	
Yes	6938 (51.0)	6410 (50.2)	528 (67.5)	
Serum vitamin C (mg/dL)	0.93 (0.51)	0.96 (0.51)	0.89 (0.55)	0.097
Log-formed Serum vitamin C (mg/dL)	0.63 (0.26)	0.63 (0.26)	0.59 (0.28)	0.042*

Note: n is unweighted, n(%), mean, and SD are weighted.
* P < 0.05.

Table 2
Analysis of the Association between Serum Vitamin C Levels and Rheumatoid Arthritis in Adults Using Data from Three NHANES Cycles (2003–2004, 2005–2006, and 2017–2018).

Characteristics	OR	95 %CI	P-value
Log-formed Serum vitamin C (mg/dL)	0.62	0.40–0.98	0.034*

* $P < 0.05$.

Table 3
Relationship between Serum Vitamin C Levels in Adults from Different Population Groups and Rheumatoid Arthritis in the NHANES Database across Three Cycles (2003–2004, 2005–2006, and 2017–2018).

Participants	OR	95 %CI	P-value	P for interaction
Gender				0.592
Female	0.57	0.33–1.00	0.042*	
Male	0.65	0.35–1.20	0.200	
Age				0.113
20–45	0.23	0.11–0.45	<0.001*	
45–69	0.59	0.36–0.96	0.030*	
>69	0.50	0.21–1.17	0.100	
Race				0.697
Mexican American	0.48	0.16–1.41	0.200	
Other Hispanic	0.23	0.03–1.92	0.200	
Non-Hispanic White	0.76	0.45–1.29	0.300	
Non-Hispanic Black	0.50	0.22–1.16	0.100	
Other races	0.30	0.05–1.76	0.200	
BMI (kg/m^2)				0.154
≤25	0.05	0.00–0.58	0.012*	
25–30	0.76	0.33–1.74	0.500	
>30	1.09	0.62–1.93	0.800	
Smoking				0.556
Never smoking	1.05	0.49–2.27	0.900	
Former smoking	0.62	0.26–1.47	0.300	
Now Smoking	0.54	0.25–1.18	0.110	
Alcohol drinking				0.053
No	1.15	0.63–2.09	0.600	
Yes	0.50	0.30–0.86	0.009*	
Hypertension				0.027*
No	0.28	0.13–0.64	0.002*	
Yes	0.97	0.61–1.52	0.900	

Note: The interaction term P-value is adjusted for gender, age, race, BMI, smoking, drinking, and hypertension.
* $P < 0.05$.

Table 4
Exploration of the Relationship between Adult Serum Vitamin C Levels and Rheumatoid Arthritis across Three Cycles of the NHANES Database (2003–2004, 2005–2006, and 2017–2018) Using Different Models (Adjusting for Confounding Factors).

Participants	Models	OR	95 % CI	P-value
All participants	Crude	0.62	0.40–0.98	0.034*
	model I	0.48	0.31–0.73	<0.001*
	model II	0.63	0.40–1.00	0.039*
Hypertension				
No	Crude	0.28	0.13–0.64	0.002*
	model I	0.25	0.12–0.51	<0.001*
	model II	0.32	0.13–0.76	0.008*
Yes	Crude	0.97	0.61–1.52	0.900
	model I	0.70	0.43–1.15	0.150
	model II	0.87	0.53–1.43	0.600

Note: Crude is unadjusted; model I is adjusted for gender, age, and race; model II is adjusted for gender, age, race, BMI, smoking, drinking, and hypertension.
* $P < 0.05$.

significant positive association was observed between dietary vitamin C intake and serum vitamin C levels ($P < 0.001$).

4. Discussion

This study included a total of 12,665 participants from the NHANES database from three periods (2003–2004, 2005–2006, and 2017–2018), including 6,500 females and 6,165 males. Among them, 712 were rheumatoid arthritis patients, and compared with normal individuals, rheumatoid arthritis patients had lower levels of serum vitamin C. Furthermore, in all models adjusted or unadjusted for covariates, we disclosed a significant negative association of rheumatoid arthritis with serum vitamin C levels, and higher levels of vitamin C could lessen the risk of rheumatoid arthritis. When serum vitamin C levels exceeded 0.95 mg/dL, there was a certain degree of prevention against the occurrence of rheumatoid arthritis. Increasing the dietary intake of vitamin C through supplementation elevated serum vitamin C levels, demonstrating a significant positive association between the two.

This study reports a prevalence rate of 5.6 % for RA based on the NHANES database in the United States. This finding aligns with previous research using NHANES data, which estimated RA prevalence to be approximately 5–7 % (Liu et al., 2023; Chen et al., 2022; Lei et al., 2023; Sheng et al., 2023). However, according to the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) 2021 estimates, the RA patient population in the United States is about 1.46 million, with a prevalence rate of only 0.46 % [95 % Uncertainty Intervals (UI): 0.42 % − 0.50 %](IfHMa, 2024). Further research indicates that from 2004 to 2014, the prevalence of RA among insured adults in the United States ranged from 0.41 % to 0.54 % (Hunter et al., 2017; United States Bone and Joint Initiative, 2020). The discrepancies between prevalence estimates from NHANES and other studies can be attributed to several factors: (1) different diagnostic criteria across studies, with NHANES primarily using self-reported surveys, which introduce more subjective bias, whereas the GBD database relies on ICD codes for global disease classification; (2) differences in sample representativeness, distribution, study design, and data collection methods, with NHANES employing random sampling to represent the health status of the U.S. population at specific times, while GBD standardizes data from multiple sources and models for global comparisons, potentially introducing additional uncertainty and bias. These methodological differences highlight the significant variation in disease prevalence data collected by NHANES and GBD, explaining the inconsistencies observed.

This is the first to report that serum vitamin C levels in rheumatoid arthritis patients are higher than those in non-rheumatoid arthritis patients using NHANES database. Our findings are congruous with previous studies (Das et al., 2021). rheumatoid arthritis is a complex chronic systemic inflammatory disease (Conforti et al., 2021). Elevated levels of ROS in the synovial fluid of rheumatoid arthritis patients are believed to result from activated macrophages, monocytes, neutrophils, and possible hypoxia-reperfusion reactions during affected joint movement (Blake et al., 1989; Merry et al., 1991). ROS, through NF-κB activation, initiate a cascade of events, upregulating the gene expression of pro-inflammatory cytokines, mediating immune responses (Tas et al., 2005), and causing inflammation. Any form of inflammation is associated with ROS formation, leading to substantial antioxidant consumption (Vollbracht and Kraft, 2022). Antioxidants defend against oxidative damage by preventing lipid peroxidation and aiding in neutralizing oxygen free radicals. Vitamin C plays a supportive role in various enzyme-catalyzed reactions and possesses the ability to counteract inflammatory biomarkers (Mah et al., 2011). For example, critically ill patients with some forms of pneumonia, sepsis, or Coronavirus Disease 2019 have clinically relevant vitamin C deficiencies, which cannot be corrected by increasing vitamin C intake through the intestinal or gastric route (Carr et al., 2017; Arvinte et al., 2020; Carr et al., 2020; Chiscano-Camon et al., 2020). Therefore, we speculate that the reason for the decrease in serum vitamin C levels in rheumatoid arthritis patients may be that the sustained systemic inflammatory state of rheumatoid arthritis patients requires a large amount of vitamin C to clear ROS (Birben et al., 2012) and regulate immune function (Dosedel et al., 2021), leading to a decrease in the concentration of this antioxidant in rheumatoid arthritis patients. Das et al.'s study also revealed a negative association between serum malondialdehyde levels and vitamin C in rheumatoid arthritis patients, with lower vitamin C levels observed in rheumatoid arthritis patients (Das et al., 2021). This association may be attributed to the ability of vitamin C to counteract lipid peroxidation of cellular components to a greater extent, leading to the depletion of antioxidant levels (Das et al., 2021; Mah et al., 2011).

Simultaneously, according to the results of this study, when serum vitamin C levels exceeded 0.95 mg/dL, the risk of rheumatoid arthritis decreased. Further analysis of the relationship between dietary vitamin

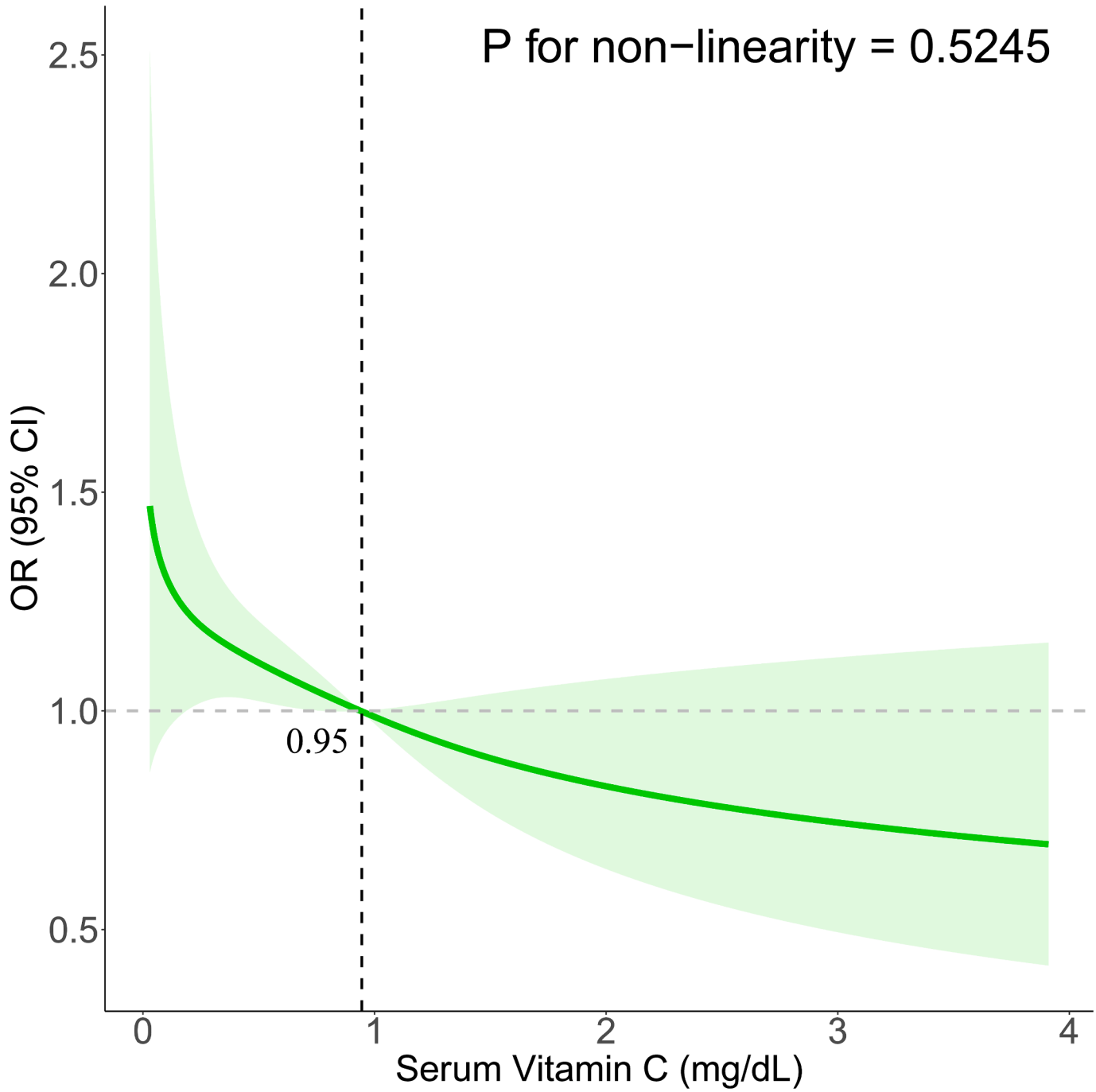

Fig. 2. Restricted Cubic Spline Analysis for Identifying Optimal Serum Vitamin C Levels for Preventing Rheumatoid Arthritis in Adults Using Data from Three NHANES Cycles (2003–2004, 2005–2006, and 2017–2018) (Adjusted for All Confounders).

C intake and serum vitamin C levels revealed a significant positive association, indicating that supplementing dietary vitamin C intake could increase serum vitamin C levels. Previous research has reported a decrease in the activity of red blood cell antioxidant enzymes in rheumatoid arthritis patients, primarily due to inadequate intake of serum antioxidant nutrients and a shift in the redox balance towards excessive ROS production (Sarban et al., 2005; Kamanli et al., 2004; Gambhir et al., 1997). *In vitro* studies suggested that dietary antioxidants effectively inhibit the release of inflammatory cytokines by reducing available ROS (Jung and Sung, 2004; Kowalski et al., 2005; Surh et al., 2005). Nutritional adjustments for rheumatoid arthritis patients have garnered widespread attention as a complementary therapy for disease management. A systematic review indicated that increased consumption of olive oil, oily fish rich in fats, fruits, and vegetables has a protective effect against the onset of rheumatoid arthritis (Pattison et al., 2004). This underscores the potential positive impact of dietary antioxidant supplementation on regulating blood inflammatory molecule levels in relatively stable rheumatoid arthritis patients already undergoing conventional treatment. By focusing on the low levels of serum vitamin C in rheumatoid arthritis patients, this study identified that supplementing dietary vitamin C intake could raise serum vitamin C levels, thereby reducing the risk of developing rheumatoid arthritis. This provides substantive guidance for public health policies and health education, emphasizing the importance of balanced dietary antioxidant supplementation. Furthermore, these study findings have practical implications for the early intervention and management of rheumatoid arthritis,

suggesting that monitoring serum vitamin C levels, a biomarker, could be employed for implementing earlier intervention measures to slow down or alleviate the progression of the disease.

Intriguingly, we found a significant interaction between hypertension and rheumatoid arthritis and serum vitamin C levels. Prevalence of hypertension is extremely high in rheumatoid arthritis patients (Panoulas et al., 2007), which may be due to the immune system dysfunction of rheumatoid arthritis affecting vascular function and renal hemodynamics (Wolf and Ryan, 2019), or the long-term use of glucocorticoids, nonsteroidal anti-inflammatory drugs, and some disease-modifying antirheumatic drugs increasing the risk of hypertension (Panoulas et al., 2008). Studies have shown that serum vitamin C levels of hypertensive patients are relatively low and are negatively correlated with systolic and diastolic blood pressure (Ran et al., 2020). Vitamin C has been shown to have cell-protection, anti-mutation, hemangiectasis, and anti-platelet aggregation effects. Das *et al.* (Das, 2019) therefore advocate for appropriate vitamin C supplementation in hypertensive patients to reduce blood pressure. Vitamin C supplementation is correct in the treatment of rheumatoid arthritis in multiple studies (Miggiano, 2005; Choi, 2005), but it is not recommended to use vitamin C alone to treat rheumatoid arthritis (Rosenbaum et al., 2010). Vitamin C as a dietary supplement for rheumatoid arthritis patients may be reasonable. However, we revealed that significant negative association of rheumatoid arthritis with serum vitamin C levels did not exist in the hypertensive population after stratified analysis, but in the non-hypertensive population. We speculated that the antihypertensive drugs taken by hypertensive participants may affect the relationship between serum vitamin C and rheumatoid arthritis. For example, diuretic antihypertensive drugs (Blowey, 2016) increase urine output to reduce blood volume and lower blood pressure, while vitamin C, as a water-soluble vitamin, is mainly excreted through kidneys (Lykkesfeldt and Tveden-Nyborg, 2019), and diuretic antihypertensive drugs may also affect the excretion of vitamin C. At the same time, this phenomenon may also be an indication that the treatment of comorbidities may significantly affect the study results, and it is worth considering as a stratification factor by researchers.

Limitations of our study should also be noted. First, our data came from questionnaire responses from participants, so there may be recall bias that could affect the estimation of link of serum vitamin C levels to risk of rheumatoid arthritis in cross-sectional studies. Second, cross-sectional studies did not allow us to infer causality, and all of our data came from the NHANES database, which may limit the applicability of our results in other populations. Given these limitations, it is particularly important to design scientifically reasonable multicenter randomized controlled trials to verify the results of this study.

Ethics approval and consent to participate.

Informed consent was waived by the committee of The First Affiliated Hospital of Xian Medical University [2023–67].

Funding

This work was supported by Xi'an Science and Technology Project (2021JH-03–0427); Natural Science Basic Research Program of Shaanxi (2021JZ-59); Project of Xi 'an Health Commission(2021qn06).

CRediT authorship contribution statement

Jing Zhang: Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pu Liu:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Sirou Huang:** Resources, Methodology, Investigation, Formal analysis. **Qingping Chen:** Writing – review & editing, Resources, Project administration, Methodology, Investigation. **Xiaoyuan Wang:** Writing – review & editing, Supervision, Project administration, Investigation. **Hua Liu:** Writing – review & editing, Visualization, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102793.

References

Ahmadinejad, F., Geir Moller, S., Hashemzadeh-Chaleshtori, M., Bidkhori, G., Jami, M.S., 2017. Molecular mechanisms behind free radical scavengers function against oxidative stress. Antioxidants (basel) 6.

Arvinte, C., Singh, M., Marik, P.E., 2020. Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American community hospital intensive care unit in may 2020: a pilot study. Med Drug Discov. 8, 100064.

Birben, E., Sahiner, U.M., Sackesen, C., Erzurum, S., Kalayci, O., 2012. Oxidative stress and antioxidant defense. World Allergy Organ J. 5, 9–19.

Blake, D.R., Merry, P., Unsworth, J., Kidd, B.L., Outhwaite, J.M., Ballard, R., et al., 1989. Hypoxic-reperfusion injury in the inflamed human joint. Lancet 1, 289–293.

Blowey, D.L., 2016. Diuretics in the treatment of hypertension. Pediatr Nephrol. 31, 2223–2233.

Cao, P., Li, F., Xiao, Y., Hu, S., Kong, K., Han, P., et al., 2022. Identification and validation of 7-lncRNA signature of epigenetic disorders by comprehensive epigenetic analysis. Disease Markers. 2022, 5118444.

Carr, A.C., Rosengrave, P.C., Bayer, S., Chambers, S., Mehrtens, J., Shaw, G.M., 2017. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care. 21, 300.

Carr, A.C., Spencer, E., Dixon, L., Chambers, S.T., 2020. Patients with community acquired pneumonia exhibit depleted vitamin C status and elevated oxidative stress. Nutrients. 12.

Chaurasia, N., Singh, A., Singh, I.L., Singh, T., Tiwari, T., 2020. Cognitive dysfunction in patients of rheumatoid arthritis. J Family Med Prim Care. 9, 2219–2225.

Chen, L., Sun, Q., Peng, S., Tan, T., Mei, G., Chen, H., et al., 2022. Associations of blood and urinary heavy metals with rheumatoid arthritis risk among adults in NHANES, 1999–2018. Chemosphere. 289, 133147.

Chiscano-Camon, L., Ruiz-Rodriguez, J.C., Ruiz-Sanmartin, A., Roca, O., Ferrer, R., 2020. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. Crit Care. 24, 522.

Choi, H.K., 2005. Dietary risk factors for rheumatic diseases. Curr Opin Rheumatol. 17, 141–146.

Conforti, A., Di Cola, I., Pavlych, V., Ruscitti, P., Berardicurti, O., Ursini, F., et al., 2021. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmun Rev. 20, 102735.

Das, U.N., 2019. Vitamin C for type 2 diabetes mellitus and hypertension. Arch Med Res. 50, 11–14.

Das, D.C., Jahan, I., Uddin, M.G., Hossain, M.M., Chowdhury, M.A.Z., Fardous, Z., et al., 2021. Serum CRP, MDA, vitamin C, and trace elements in Bangladeshi patients with rheumatoid arthritis. Biol Trace Elem Res. 199, 76–84.

Dosedel, M., Jirkovsky, E., Macakova, K., Krcmova, L.K., Javorska, L., Pourova, J., et al., 2021. Vitamin C-sources, physiological role, kinetics, deficiency, use, toxicity, and determination. Nutrients 13.

Gambhir, J.K., Lali, P., Jain, A.K., 1997. Correlation between blood antioxidant levels and lipid peroxidation in rheumatoid arthritis. Clin Biochem. 30, 351–355.

Hunter, T.M., Boytsov, N.N., Zhang, X., Schroeder, K., Michaud, K., Araujo, A.B., 2017. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004–2014. Rheumatol Int. 37, 1551–1557.

Evaluation IfHMa. GBD Results. Available from: https://vizhub.healthdata.org/gbd-results/.

Jang, S., Kwon, E.J., Lee, J.J., 2022. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. Int J Mol Sci 23.

Jung, W.J., Sung, M.K., 2004. Effects of major dietary antioxidants on inflammatory markers of RAW 264.7 macrophages. Biofactors. 21, 113–117.

Kamanli, A., Naziroglu, M., Aydilek, N., Hacievliyagil, C., 2004. Plasma lipid peroxidation and antioxidant levels in patients with rheumatoid arthritis. Cell Biochem Funct. 22, 53–57.

Kowalski, J., Samojedny, A., Paul, M., Pietsz, G., Wilczok, T., 2005. Effect of apigenin, kaempferol and resveratrol on the expression of interleukin-1beta and tumor necrosis factor-alpha genes in J774.2 macrophages. Pharmacol Rep. 57, 390–394.

Lassere, M.N., Rappo, J., Portek, I.J., Sturgess, A., Edmonds, J.P., 2013. How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. Intern Med J. 43, 66–72.

Lei, T., Qian, H., Yang, J., Hu, Y., 2023. The exposure to volatile organic chemicals associates positively with rheumatoid arthritis: a cross-sectional study from the NHANES program. Front Immunol. 14, 1098683.
Liu, B., Wang, J., Li, Y.Y., Li, K.P., Zhang, Q., 2023. The association between systemic immune-inflammation index and rheumatoid arthritis: evidence from NHANES 1999–2018. Arthritis Res Ther. 25, 34.
Lykkesfeldt, J., Tveden-Nyborg, P., 2019. The Pharmacokinetics of Vitamin C. Nutrients. 11.
Mah, E., Matos, M.D., Kawiecki, D., Ballard, K., Guo, Y., Volek, J.S., et al., 2011. Vitamin C status is related to proinflammatory responses and impaired vascular endothelial function in healthy, college-aged lean and obese men. J Am Diet Assoc. 111, 737–743.
Mandl, J., Szarka, A., Banhegyi, G., 2009. Vitamin C: update on physiology and pharmacology. Br J Pharmacol. 157, 1097–1110.
McInnes, I.B., Schett, G., 2017. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet. 389, 2328–2337.
Merry, P., Grootveld, M., Lunec, J., Blake, D.R., 1991. Oxidative damage to lipids within the inflamed human joint provides evidence of radical-mediated hypoxic-reperfusion injury. Am J Clin Nutr. 53, 362S–S369.
Miggiano, G.A., Gagliardi, L., 2005. Diet, nutrition and rheumatoid arthritis. Clin Ter 156, 115–123.
Mueller, A.L., Payandeh, Z., Mohammadkhani, N., Mubarak, S.M.H., Zakeri, A., Alagheband Bahrami, A., et al., 2021. Recent advances in understanding the pathogenesis of rheumatoid arthritis: new treatment strategies. Cells. 10.
Panoulas, V.F., Douglas, K.M., Milionis, H.J., Stavropoulos-Kalinglou, A., Nightingale, P., Kita, M.D., et al., 2007. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology (oxford). 46, 1477–1482.
Panoulas, V.F., Metsios, G.S., Pace, A.V., John, H., Treharne, G.J., Banks, M.J., et al., 2008. Hypertension in rheumatoid arthritis. Rheumatology (oxford). 47, 1286–1298.
Pattison, D.J., Harrison, R.A., Symmons, D.P., 2004. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. J Rheumatol. 31, 1310–1319.
Ran, L., Zhao, W., Tan, X., Wang, H., Mizuno, K., Takagi, K., et al., 2020. Association between Serum Vitamin C and the Blood Pressure: A Systematic Review and Meta-Analysis of Observational Studies. Cardiovasc Ther. 2020, 4940673.
Rosenbaum, C.C., O'Mathuna, D.P., Chavez, M., Shields, K., 2010. Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis. Altern Ther Health Med. 16, 32–40.
Salo, P.M., Mendy, A., Wilkerson, J., Molsberry, S.A., Feinstein, L., London, S.J., et al., 2022. Serum antioxidant vitamins and respiratory morbidity and mortality: a pooled analysis. Respir Res. 23, 150.
Sarban, S., Kocyigit, A., Yazar, M., Isikan, U.E., 2005. Plasma total antioxidant capacity, lipid peroxidation, and erythrocyte antioxidant enzyme activities in patients with rheumatoid arthritis and osteoarthritis. Clin Biochem. 38, 981–986.
Sheng, N., Wang, J., Xing, F., Duan, X., Xiang, Z., 2023. Associations between exposure to phthalates and rheumatoid arthritis risk among adults in NHANES, 2007–2016. Chemosphere. 338, 139472.
Smolen, J.S., Aletaha, D., McInnes, I.B., 2016. Rheumatoid arthritis. Lancet. 388, 2023–2038.
Surh, Y.J., Kundu, J.K., Na, H.K., Lee, J.S., 2005. Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals. J Nutr. 135, 2993S–3001S.
Tas, S.W., Remans, P.H., Reedquist, K.A., Tak, P.P., 2005. Signal transduction pathways and transcription factors as therapeutic targets in inflammatory disease: towards innovative antirheumatic therapy. Curr Pharm Des. 11, 581–611.
Tian, X., Xue, B., Wang, B., Lei, R., Shan, X., Niu, J., et al., 2022. Physical activity reduces the role of blood cadmium on depression: A cross-sectional analysis with NHANES data. Environ Pollut. 304, 119211.
United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS), Fourth Edition, 2020. Rosemont, IL. Available at http://www.boneandjointburden.org. Available from: https://www.boneandjointburden.org/fourth-edition/iiib21/rheumatoid-arthritis.
Vollbracht, C., Kraft, K., 2022. Oxidative Stress and Hyper-Inflammation as Major Drivers of Severe COVID-19 and Long COVID: Implications for the Benefit of High-Dose Intravenous Vitamin C. Front Pharmacol. 13, 899198.
Whelton, P.K., Carey, R.M., Aronow, W.S., Casey Jr., D.E., Collins, K.J., Dennison Himmelfarb, C., et al., 2018. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension 71, e13–e115.
Wolf, V.L., Ryan, M.J., 2019. Autoimmune Disease-Associated Hypertension. Curr Hypertens Rep. 21, 10.