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Lower Serum Vitamin C Is Associated with Higher Systemic Immune Inflammation Index: A Population-Based Study

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Abstract **Background and Aims:** The significance of the systemic immune-inflammation index (SII) in assessing the inflammation condition has drawn considerable interest recently. Nevertheless, there has been no prior reporting on the correlation between serum vitamin C levels and SII. This study aimed to explore the relationship between serum vitamin C levels and SII score among adults in the United States. **Methods and Results:** The study utilized cross-sectional data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES). Multivariable linear regression models were employed to determine the independent relationship between serum vitamin C levels and SII score. Subgroup analysis and interaction test were carried out as well. Fitted smoothing curves were also used to describe the nonlinear relationship. 4408 participants were enrolled and those in the higher serum vitamin C quartile exhibited a tendency towards a lower mean SII score. In the fully adjusted model, a negative relationship between serum vitamin C levels and SII score emerged (β= -50.05, 95% CI -74.47 to -25.62). Notably, participants in the highest serum vitamin C quartile demonstrated a 73.79-unit reduction in SII score (β = -73.79, 95% CI -102.29 to -40.55) compared to those in the lowest serum vitamin C quartile. Subgroup analysis and interaction tests revealed no dependence for the association of serum vitamin C and SII. **Conclusion:** Our findings indicate that serum vitamin C levels are negatively associated with SII score.

Keywords: *vitamin c, systemic immune-inflammation index, cross-sectional study*

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1. Introduction

Numerous studies have underscored the pivotal role of inflammation in affecting human health, as elevated levels of inflammation are often observed in chronic diseases, including atherosclerosis, diabetes, systemic lupus erythematosus, rheumatoid arthritis, cirrhosis, and cancer. [1,2,3,4,5] [6,7,8,9,10] Consequently, managing inflammation levels is of great importance for controlling chronic diseases and improving national health.

The systemic immune-inflammation index (SII) stands out as an innovative and comprehensive biomarker which indicates inflammation levels within the human body. [11] Extensive research have the reliability and precision of SII prognostic marker for various neoplastic and chronic diseases, including non-alcoholic fatty liver disease, coronary heart disease, and hypertension, etc. [12,13,14] Furthermore, according to certain researchers, the SII carries a higher prognostic value than conventional inflammatory factors, including C-reactive protein (CRP), specifically for severe pancreatitis. [15]

Vitamin C (ascorbate) has long been acknowledged as a vital component of a human diet, and insufficiency of vitamin C can lead to scurvy. [16] Servicing as a water-soluble reducing agent and antioxidant, vitamin C exerts a significant influence on human immunity and inflammation. [16] Functioning as an antioxidant, it donates neutralizing free radicals and electrons, thereby protecting cells from harm. [16] Studies suggest that it has potential to reduce human inflammatory biomarkers like CRP and IL-6, but its effect on serum vitamin C and SII remains unreported. [17,18]

Thus, utilizing data from the National Health and Nutrition Examination Survey (NHANES), we aimed to ascertain the correlation between serum vitamin C and SII score.

2. Methods

Data Source

The authors obtained the data for this study from NHANES, a national survey administered by the National Center for Health Statistics (NCHS) in the United States. NHANES used a complex, multistage stratified

probability sampling method, ensuring sample representativeness. The detailed study data and design are publicly accessible via www.cdc.gov/nchs/nhanes/.

Study population

Data sourced from the 2003-2004 NHANES survey cycle was utilized, including adult participants (aged ≥ 20 years) who provided complete information on serum Vitamin C and SII. A total of 10,122 individuals were initially enrolled, but after excluding participants age < 20 years (n=2,839), those missing data on serum Vitamin C (n=2,845) or SII (n=30). The final analysis encompassed a cohort of 4,408 eligible participants age ≥ 20 years (see Figure 1).

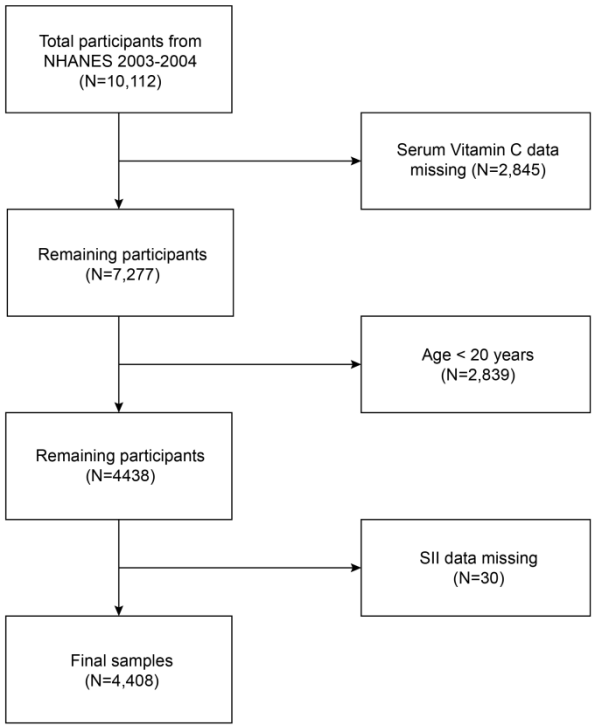

Figure 1. Flowchart of participant selection. NHANES, National Health and Nutrition Examination Survey; SII, systemic immune inflammation index

Measurement of Serum Vitamin C

Whole blood samples were collected using mobile examination clinics and then transported to the laboratory for analysis. Trained phlebotomists conducted the sample collection, following standard protocols.

The quantification of serum Vitamin C levels were conducted through isocratic ultra-high performance liquid chromatography. Peak area quantification was determined using a standard curve created from three distinct levels of an external standard (0.025, 0.150, and 0.500 md/dL).

Definition of systemic immunity-inflammation index (SII)

In our analysis, SII was designated as an exposure variable and is derived from blood samples. Technical term abbreviations are explained when first used. We measured lymphocyte, neutrophil, and platelet counts using automated hematology analyzing devices (Beckman Coulter DxH 800) and presented them as x1000 cells/μL. To maintain consistency in style, we follow a regular author and institution formatting and adhere to common academic sections. Additionally, we avoid biased language and favor clear, objective, and value-neutral language with high-level, standard vocabulary. The SII calculation is based on a precise formula: SII = platelet count x neutrophil count/lymphocyte count. [11]

Covariates

Covariates comprised gender (male/female), age (years), education levels (less than high school, high school or GED, above high school or unknown), race (Non-Hispanic Black, Mexican American, Non-Hispanic White, Other Hispanic, or Other Races), smoked at least 100 cigarettes in life (yes, no, or unknown), serum triglycerides (mg/dL), serum cholesterol (mg/dL), serum glucose (mmol/L), serum protein (g/dL), blood lymphocyte count (x1000 cells/μL), blood neutrophil count (x1000 cells/μL), blood platelet count (x1000 cells/μL), BMI (kg/m^2), waist circumference (cm), dietary protein (g), dietary energy (kcal), dietary fiber (g), dietary total fat (g), dietary carbohydrate (g), dietary vitamin A (μg), dietary vitamin B6 (mg), dietary B12 (μg).

Statistical analysis

The study was conducted with R (version 4.1.3) and EmpowerStats (version: 2.0) software for statistical computing and graphics. The baseline table of the study population was described statistically using subgroups of serum vitamin C quartile. Proportions are used to present categorical parameters, while mean and Standard Deviation (SD) summarize continuous variables. The beta value and 95% confidence intervals were calculated via multivariate linear regression analysis of serum vitamin C and SII. Simultaneously, smoothed curve fits were conducted by adjusting variables. $P < 0.05$ was considered statistically significant.

3. Results

Baseline characteristics

Table 1 demonstrated that 4,408 individuals participated in our study, meeting the inclusion and exclusion criteria and averaging an age of 50.45±19.43 years. Of this population, 51.41% were female and 48.59% were male. Quartile ranges for serum vitamin C were as follows: Quartile 1 (≤0.58) had a range of 0.01-0.58, Quartile 2 (≤0.95) had a range of 0.59-0.95, Quartile 3 (≤1.24) had a range of 0.96-1.24, and Quartile 4 (≤4.83) had a range of 1.25-4.83. The average SII score for all participants was 612.33±412.61 (1000 cells/μL). With higher levels of serum vitamin C, the score decreased as follows: Quartile 1: 637.07±443.60; Quartile 2: 641.75±398.30; Quartile 3: 583.02±314.85; Quartile 4: 577.71±372.80 (P<0.0001). Statistical significance showed differences among race, age, education level, gender, smoking, serum cholesterol, serum triglycerides, serum glucose, blood neutrophil count, blood platelet count, BMI, waist circumference, dietary energy, dietary carbohydrate, dietary fiber, dietary protein, dietary total fat, dietary vitamin A, dietary vitamin B6, and dietary vitamin B12 for the four serum vitamin C quartiles (all $p <$ 0.05). Participants in the decreased serum vitamin C group

had significantly higher levels of serum cholesterol, serum triglycerides, serum glucose, blood neutrophil number, blood platelet number, BMI, waist circumference, dietary fiber, dietary energy, dietary carbohydrate, dietary protein, dietary total fat, dietary vitamin A, and dietary vitamin B6 compared to those in the highest serum vitamin C group (all $p < 0.05$). The distinction in quartiles of serum protein, blood lymphocyte number, and dietary vitamin B12 did not achieve statistical significance (all $p > 0.05$).

Serum vitamin C and decreased SII

Table 2 displays the association between serum vitamin C and SII. The findings indicate that elevated serum vitamin C levels correlate with lower SII scores. The fully adjusted model displays a negative link between serum vitamin C and SII score (β = -50.05, 95% CI: -74.47 to -25.62), suggesting that each unit increase in serum vitamin C associates with 57.52 units decrease in SII score. The authors categorized serum vitamin C (previously a continuous variable) into quartiles for the sensitivity analysis. The highest quartile showed a decreased SII score compared to the lowest quartile. Specifically, the mean SII score of the highest serum vitamin C quartile was 73.79 units lower than that of the lowest quartile (β = -73.79, 95% CI: -102.29 to -40.55).

Table 1. Baseline characteristics of the study population according to Serum Vitamin C quartiles

Serum Vitamin C	Q1	Q2	Q3	Q4	*p*-Value
	N=1102	N=-1102	N=1102	N=1102	
Age (year)	44.11 ± 15.19	44.36 ± 16.13	46.54 ± 16.78	50.35 ± 18.42	<0.0001
Gender, %					<0.0001
Male	56.37	52.90	49.09	35.96	
Female	43.63	47.10	50.91	64.04	
Race, %					<0.0001
Mexican American	6.05	10.64	8.98	5.56	
Other Hispanic	2.97	4.18	4.62	2.81	
Non-Hispanic White	73.20	64.56	71.32	80.23	
Non-Hispanic Black	11.62	14.72	9.24	7.74	
Other Races	6.15	5.90	5.84	3.65	
Education level, %					<0.0001
Less than high school	24.39	19.69	14.97	14.16	
High school or GED	31.53	25.06	25.84	25.31	
Above high school	44.98	55.22	59.20	60.53	
Unknown	0.00	0.03	0.00	0.00	
Smoked at least 100 cigarettes in life, %					<0.0001
Yes	63.86	49.25	45.89	43.20	
No	36.12	50.72	54.09	56.79	
Unknown	0.02	0.03	0.02	0.01	
Serum cholesterol (mg/dL)	206.09 ± 45.45	199.05 ± 39.69	203.73 ± 40.83	204.34 ± 40.81	0.0010
Serum triglycerides (mg/dL)	154.17 ± 162.56	141.78 ± 113.45	130.90 ± 86.02	119.85 ± 81.88	<0.0001
Serum glucose (mmol/L)	5.37 ± 1.58	5.34 ± 1.55	5.16 ± 1.22	5.21 ± 1.62	0.0017
Serum protein (g/dL)	7.18 ± 0.49	7.21 ± 0.47	7.17 ± 0.46	7.17 ± 0.47	0.2391
Blood lymphocyte count (1000 cells/μL)	2.23 ± 1.07	2.10 ± 0.72	2.13 ± 1.21	2.12 ± 2.45	0.1776
Blood neutrophils count (1000 cells/ μL)	4.64 ± 1.84	4.58 ± 1.81	4.28 ± 1.52	4.11 ± 1.62	<0.0001
Blood platelets count (1000 cells/ μL)	272.71 ± 75.87	268.17 ± 64.20	263.16 ± 61.68	260.43 ± 64.15	<0.0001
SII (1000 cells/ μL)	637.07 ± 443.60	641.75 ± 398.30	583.02 ± 314.85	577.71 ± 372.80	<0.0001
BMI (kg/m^2)	29.22 ± 6.84	29.34 ± 6.43	27.60 ± 5.72	26.86 ± 5.61	<0.0001
Waist circumference (cm)	100.52 ± 15.69	100.00 ± 15.08	95.42 ± 14.62	93.93 ± 14.78	<0.0001
Dietary energy (kcal)	2213.13 ± 919.51	2279.93 ± 958.59	2171.04 ± 826.68	2080.58 ± 786.70	<0.0001
Dietary protein (g)	83.10 ± 36.75	88.52 ± 39.28	84.71 ± 35.31	80.58 ± 32.59	<0.0001
Dietary carbohydrate (g)	260.90 ± 119.61	273.60 ± 127.38	266.25 ± 106.45	256.46 ± 104.39	0.0082
Dietary fiber (g)	13.33 ± 7.10	15.90 ± 8.08	16.60 ± 8.33	17.74 ± 8.93	<0.0001
Dietary total fat (g)	86.07 ± 39.80	88.94 ± 41.16	81.06 ± 38.04	78.09 ± 35.86	<0.0001
Dietary vitamin A (μg)	511.22 ± 463.52	616.07 ± 468.16	673.55 ± 699.33	715.17 ± 560.68	<0.0001
Dietary vitamin B6 (mg)	1.72 ± 0.91	1.94 ± 1.01	2.00 ± 1.01	2.04 ± 1.04	<0.0001
Dietary vitamin B12 (μg)	5.28 ± 7.35	5.74 ± 6.23	5.63 ± 7.97	5.17 ± 4.39	0.1804
Dietary vitamin C (mg)	52.96 ± 52.70	84.78 ± 76.36	103.76 ± 84.14	113.23 ± 85.39	<0.0001

Mean ± SD for continuous variables: P value was calculated by weighted linear regression model.
% for categorical variables: P vale was calculated by weighted chi-square test.
Abbreviations: GED, General Educational Development; BMI, Body Mass Index.

Table 2. Association between serum Vitamin C and SII

Serum Vitamin C Groups	Crude model (Model 1) β (95% CI)	Minimally adjusted model (Model 2) β (95% CI)	Fully adjusted model (Model 3) β (95% CI)
	-41.32 (-62.62, -20.01)	-59.97 (-81.59, -38.35)	-50.05 (-74.47, -25.62)
p Value	0.0001	<0.0001	<0.0001
Q1 (0.01-0.58 mg/dL)	Reference	Reference	Reference
Q2 (0.59-0.95 mg/dL)	4.68 (-27.80-37.15)	8.90 (-23.32, 41.13)	23.95 (-10.86, 58.75)
Q3 (0.96-1.24 mg/dL)	-54.05 (-85.82, -22.28)	-61.68 (-93.23, -30.12)	-51.58 (-87.08, -16.53)
Q4 (1.25-4.83 mg/dL)	-58.36 (-91.11. -27.62)	-85.15 (-117.19, -53.10)	-73.79 (-102.29, -40.55)
p for trend	<0.0001	<0.0001	<0.0001

In sensitivity analysis, the serum vitamin C was converted from a continuous variable to a categorical variable (quartiles).
95% CI, 95% Confidence Interval; Model 1, no covariates were adjusted; Model 2, Adjusted for sex, age, race; Model 3, Adjusted for sex, age, race, education level, smoking, serum cholesterol, blood glucose, serum protein, serum triglycerides, BMI, waist circumference, dietary energy, dietary protein, dietary total fat, dietary carbohydrate, dietary fiber, dietary vitamin A, dietary vitamin B6, dietary vitamin B12.

Subgroup analysis

A significant association exists between serum vitamin C and SII score was detected in both male and female participants, age < 60 years, with normal weight, of non-Hispanic White ethnicity and smoking subjects (β = -39.67, -59.00, -42.41, -46.57, -57.83, -36.17, respectively) (Table. 3). Furthermore, the interaction test did not suggest a significant difference in the association between SII score and serum vitamin C across various stratifications, indicating no significant dependence on gender, BMI, age, race, and smoking for the negative relationship (all p > 0.05). The smooth curve fittings in Figure 2 also demonstrate the nonlinear relationship.

Table 3. Subgroup analysis for the association between serum Vitamin C and SII

SII	Beta (95% CI)	*p* for interaction
Gender		0.4130
Male	-39.67 (-75.19, -4.14)	
Female	-59.00 (-91.01, -26.99)	
Age (years)		0.5355
Age <60	-42.41 (-75.79. -9.03)	
Age ≥ 60	-26.50 (-64.75, 11.76)	
BMI		0.6011
Normal weight	-46.57 (-89.19, -3.94)	
Overweight	-20.81 (-63.38, 21.75)	
Obese	-19.05 (-63.17, 25.06)	
Race		0.9187
Mexican American	-62.64 (-189.16, 63.88)	
Other Hispanic	-1.94 (-155.98, 152.10)	
Non-Hispanic White	-57.83 (-84.95, -30.70)	
Non-Hispanic Black	-30.92 (-125.22, 63.38)	
Other Races	-24.71 (-173.95, 124.54)	
Smoked at least 100 cigarettes in life		0.6989
Yes	-36.17 (-69.18, -3.17)	
No	-26.78 (-63.30, 9.74)	
Unknown	-90.95 (-696.01, 514.10)	

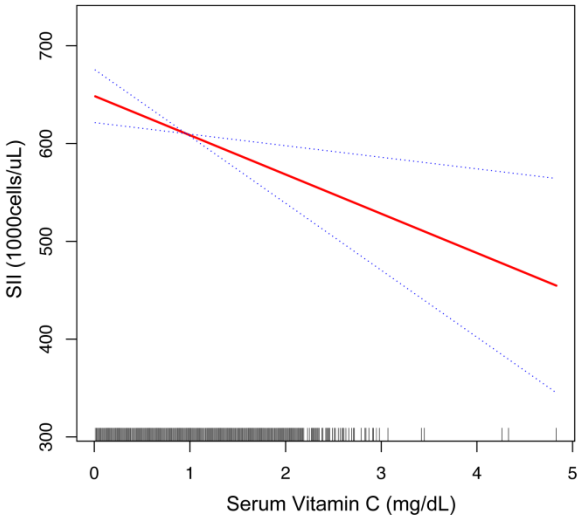

Figure 2. The association between serum vitamin C and SII. SII, systemic immune inflammation index

4. Discussion

In our cross-sectional study involving 4408 participants, we demonstrated a inverse correlation between SII score and serum vitamin C. We did not observe any significant link between sex, age, BMI, race, or smoking and the relationship between SII score and serum vitamin C, suggesting that reduced vitamin C levels in the serum might cause an increase in SII score. Our findings indicated that maintaining optimal serum vitamin C levels would potentially be a new approach to control SII score.

To date, this is the first study to assess the correlation between SII scores and serum vitamin C levels. Previous studies have demonstrated the correlation between vitamin C and inflammation. Ellulu et al. recruited 72 participants conducting a randomized controlled trial and discovered that a moderate quantity of vitamin C significantly suppressed inflammation with decreased plasma levels of IL-6 and CRP in hypertensive and/or diabetic patients. [19] Similarly, Righi et al. conducted a meta-analysis including 18 randomized clinical trials (RCTs) and 313 participants. The study showed that vitamin C reduced IL-6 levels and attenuated oxidative stress and inflammatory response. [20] Crook et al. conducted a cross-sectional study and confirmed that vitamin C deficiency was strongly linked

with acute and chronic inflammation, as well as plasma levels of CRP and red cell distribution width (RDW). [21] On the contrary, Colby et al. performed a double-blind, randomized, placebo-controlled trial and determined that vitamin C utilization did not significantly affect CRP levels in patients who underwent cardiothoracic surgery. [22] Nevertheless, the study included only 24 patients (13 received vitamin C, while 11 received placebo). The relatively small sample size could potentially affect the conclusions derived from the study conducted by Colby et al. Additionally, Zhang and colleagues conducted a two-week intervention study with 77 overweight/obese undergraduates (BMI $\geq$ 24 kg/m^2), revealing that vitamin C administration significantly reduced inflammation in these individuals even in the short term. [23] Vollbracht and colleagues conducted a long-term observational study in 71 patients experiencing allergy-related symptoms. They found that increased serum vitamin C levels related with a reduction in these symptoms. [24] Our study found a negative association between SII score and serum vitamin C levels, indicating that higher serum vitamin C levels are correlated with lower inflammation conditions in the human body. Given text already adheres to the principles. Considering SII score is a valuable indicator of the inflammation condition in the human body, the present results indicated that management of serum vitamin C levels may potentially attenuate inflammation status and prevent the progression of related chronic diseases.

Vitamin C is an essential exogenous vitamin, is renowned for its antioxidant and anti-inflammatory properties. Under normal physiological conditions, NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) linked to IκK (inhibitor of nuclear factor kappa-B) leading to inactivation of NFκB. Once IκK is phosphorylated by IKK (an inhibitor of nuclear factor kappa-B kinase), the active NFκB unit is released, resulting in the transcription of pro-inflammatory cytokines, like IL-6. Vitamin C reduces intracellular NFκB levels by decreasing reactive oxygen species (ROS) production. In addition, vitamin C activates related kinases involved in IκK phosphorylation resulting in decreased transcription of NFκB-dependent genes. Lower levels of pro-inflammatory factors were observed in the cells, which is consistent with our study that higher vitamin C levels are associated with lower inflammatory indicator, the SII score. In addition, some groups have reported that incubation of vitamin C with lymphocytes fosters their proliferation in their *in vitro* studies. [25,26] Additionally, vitamin C has been demonstrated to promote the differentiation and maturation of immature T-cells. [26,27] Furthermore, certain *in vitro* studies have shown that administering vitamin C may facilitate *Escherichia coli*-triggered apoptosis in neutrophils. [28] Attenuated apoptosis was noted in peritoneal neutrophils isolated from vitamin C-deficient Gulo mice. [29] These results suggest that increased levels of serum vitamin C may potentially enhance the maturation and proliferation of lymphocytes and the apoptosis of neutrophils, leading to an increase in the number of lymphocytes and a decrease in the number of neutrophils in circulation. Considering, Higher serum vitamin C levels result in a lower neutrophil count and a higher lymphocyte count, resulting in a lower SII score. This is consistent with the results from our analysis, as SII is calculated by platelet count x neutrophil count / lymphocyte count.

Our study possesses several strengths. Initially, the data was acquired from NHANES, a nationally representative database that utilized a standard protocol for population-based sampling, consequently making our analysis representative. Furthermore, the significant sample size enabled us to perform subgroup analyses. However, there are still limitations to our study. Primarily, this is a cross-sectional analysis, impeding the ability to determine a clear causal relationship. Additionally, while we adjusted for several relevant confounders, we cannot eliminate the influence of additional confounding factors. Thus, a cautious interpretation in needed. Moreover, the dataset used to generate our results was collected between 2003-2004, which is approximately 20 years ago. Thus, it might not accurately portray the present population's characteristics.

5. Conclusion

Our findings indicate that serum vitamin C levels are inversely associated with SII score.

Data Availability Statement

Publicly available databases were analyzed in this study. These data can be found at: www. cdc.gov/nchs/nhanes/.

Authors' Contribution

Yishi Shen: Conceptualization, investigation, methodology, writing-reviewing and editing.

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