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Association between dietary retinol intake and rheumatoid arthritis based on NHANES database

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Abstract

Objective This study focused on the investigation of the correlation between dietary retinol intake and rheumatoid arthritis (RA) using the National Health and Nutrition Examination Survey (NHANES) database.

Methods Data from five NHANES cycles from 2003 to 2012 were utilized for this study. Dietary retinol intake was considered as the independent variable, and RA was the dependent variable. A weighted logistic regression method was applied to construct the relational model of the two variables. Stratified analysis without adjusting for confounding factors and subgroup analysis with confounding factors adjusted were conducted to explore the association between dietary retinol intake and RA. The optimal intake of dietary retinol was determined by the restricted cubic splines (RCS) analysis.

Results 22,971 samples were included in this study. The weighted logistic regression model was employed to construct the relational model of dietary retinol intake and RA (OR: 0.95, 95% CI: 0.91–0.99, $p = 0.019$). Stratified analysis displayed a great influence on the relational model exerted by the interaction between gender and retinol intake (p for interaction = 0.014). A significant association between retinol intake and RA was also indicated in the model adjusted for demographic characteristics (OR: 0.95, 95% CI: 0.90-1.00, $p = 0.029$). Subgroup analysis by gender showed that in the female population, unadjusted model (OR: 0.90, 95% CI: 0.84–0.96, $p = 0.002$), model adjusted for demographic characteristics only (OR: 0.89, 95% CI: 0.83–0.96, $p = 0.002$), and model adjusted for all confounding factors (OR: 0.91, 95% CI: 0.85–0.99, $p = 0.019$) indicated dietary retinol intake as a protective factor against RA. RCS analysis demonstrated that in the female population, regardless of the model used (Crude, Model I, and Model II), an intake of dietary retinol > 354.86 mcg was associated with RA disease reduction (OR < 1.0, p-non-linear < 0.05, p-overall < 0.05).

Conclusion Increased dietary retinol intake was associated with RA disease reduction, particularly in the female population. Women are recommended to increase their dietary retinol intake (> 354.86 mcg) to reduce the risk of RA.

Keywords Dietary retinol, Rheumatoid arthritis, Logistic regression, Restricted cubic splines, National Health and Nutrition Examination Survey

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Introduction

As a systemic autoimmune disease, rheumatoid arthritis (RA) primarily affects the joints, often resulting in impaired joint function, restricted movement, and even permanent disability [1]. Globally, there were over 18 million RA patients in 2019, with 1.07 million new cases, resulting in 2.43 million years lived with disability (YLD) burden. It is projected that by 2040, the number of new RA cases worldwide will increase by 1.4-fold [2]. Furthermore, RA cannot be cured, and even current first and second-line treatment options only provide disease control and progression retarding. Once the treatment is discontinued, the patient's autoimmune response may relapse or worsen [3]. Additionally, a remarkable proportion of RA patients exhibit inadequate response to medications, with only 25–40% responding to methotrexate, for example [4]. Despite the significant advancements in RA treatment facilitated by the introduction of biologics, it is noteworthy that approximately two-thirds of patients show no response within the first six months of initial biologic therapy [5], and at least 12% of patients who receive retreatment with biologics still experience treatment failure [6]. Moreover, the increased burden on the economy due to RA-related healthcare, hospitalization, absenteeism, and work-related disability is substantial [7–9]. Therefore, early intervention targeting risk factors is crucial in delaying or preventing the onset of RA.

Diet has attracted significant interest among researchers as a modifiable factor in RA. Studies have shown that with rich antioxidants and anti-inflammatory food as content, the Mediterranean diet is welcomed for preventing the occurrence of RA and its complications [10]. By comparison, a Western diet with high saturated fatty acids in red meat may be linked to an increased risk of RA through direct induction of inflammation or indirect facilitation of insulin resistance and body mass index (BMI) [11–13]. Retinol, the active form of vitamin A, must be acquired through the diet and is primarily sourced from foods such as vegetables (carotenoids), meat, eggs, and milk [14, 15]. Convincing evidence suggests that retinol, as an antioxidant, exerts anti-inflammatory effects by inhibiting the expression of a variety of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-12) to mediate the inflammatory response [14, 16, 17]. Mendelian randomization studies have displayed a protective role of higher serum retinol and its metabolite levels against RA, while no such association has been found with other dietary antioxidants (vitamin C, vitamin E, lycopene, etc.) [18, 19]. Overall, there is a close relationship between retinol and RA. However, research on retinol intake guidelines has been lacking.

Therefore, based on the existing knowledge linking retinol intake to RA risk, this study aimed to explore the relationship between dietary retinol intake and RA using the National Health and Nutrition Examination Survey (NHANES) database from 2003 to 2012, comprising five cycles of participant information. A weighted logistic regression model was used to construct the relational model of dietary retinol intake and RA. Further analysis of the model was conducted by adjusting for confounding factors including gender, age, race, BMI, smoking, alcohol consumption, diabetes, and hypertension. Additionally, a restricted cubic spline (RCS) analysis was employed to determine the optimal dietary retinol intake in different populations.

Methods

Data source and study population

The NHANES database is a cross-sectional survey in the United States that assesses the health and nutritional status of the general population. All participants signed written informed consent and the study protocol was approved by the Institutional Review Board of the National Center for Health Statistics (NCHS). The questionnaires and relevant protocols can be found on the Centers for Disease Control and Prevention (CDC) website (http://www.cdc.gov/nchs/nhanes.htm). In this study, we collected data from five cycles of the NHANES database, spanning from 2003 to 2012, comprising a total of 50,912 individuals. After excluding 7,256 individuals with no records of RA diagnosis or dietary retinol intake, we obtained a final sample of 43,656 individuals. Subsequently, an additional 20,685 individuals with missing information on covariates (age, gender, race, BMI, smoking status, alcohol consumption, history of hypertension, and history of diabetes) were excluded, resulting in a final sample size of 22,971 individuals. Figure 1 displayed the criteria for inclusion and exclusion.

Dietary retinol intake

Dietary retinol intake was estimated based on a 24-hour dietary recall questionnaire, which assessed the types and amounts of food and beverages consumed within the 24 h before the interview. The dietary recall was conducted twice for each participant, with the first recall recorded at the Mobile Exam Center (MEC) and the second recall obtained through a telephone interview conducted 3 to 10 days later. Based on the aforementioned dietary recalls, the United States Department of Agriculture (USDA) food and nutrient database was used to assess the participants' dietary retinol intake [20, 21]. When data from both recalls were available, the average was taken. To approximate a normal distribution, the dietary retinol intake data were log-transformed, and the analysis in this study was performed using the natural logarithm of the dietary retinol intake.

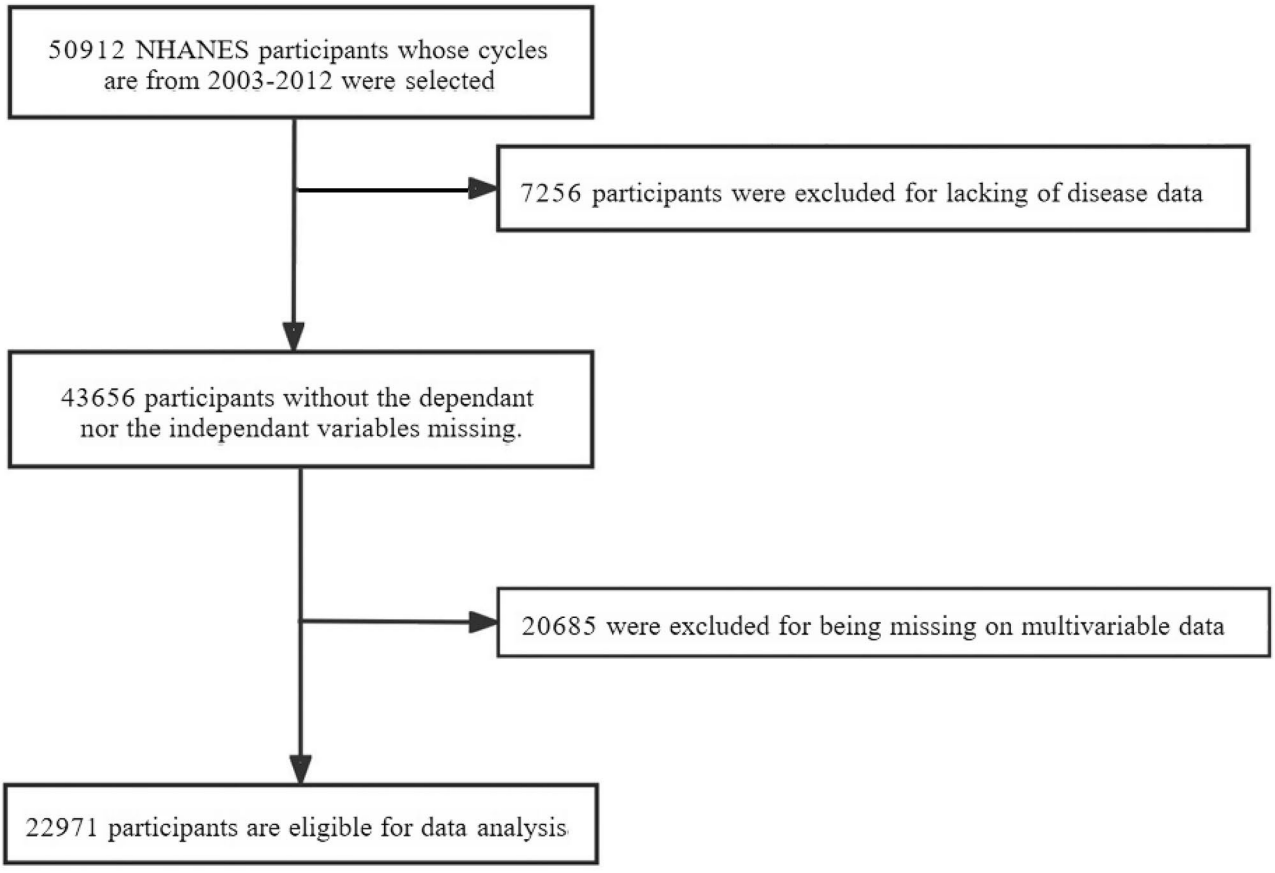

Fig. 1 Inclusion and Exclusion Flow Chart of NHANES Participants from 2003 to 2012

RA

In NHANES, the following sequential questions were used to make an RA diagnosis. If the participant responded the question "Doctor ever said you had arthritis?" with "yes", and the question "Which type of arthritis?" or "Which type of arthritis was it?" with "RA", they were diagnosed as having RA [22, 23].

Covariates

This study included several confounding factors related to dietary retinol intake and RA, including demographic characteristics (age, gender, and race), as well as BMI, alcohol consumption, smoking status, history of hypertension, and history of diabetes. In terms of age, three groups, 20–45 years, 45–69 years, and 69 years and older, were grouped [24]. Race was classified as Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic, and other race. BMI categories were defined as ≤25 kg/m², 25–30 kg/m², and >30 kg/m² [25]. Alcohol consumption was assessed based on questionnaire information indicating whether the individual consumed the equivalent of 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of spirits in a year. In the NHANES questionnaire, participants who responded "every day" or "some days" to the question "Do you currently smoke?" were placed into "current smokers" group, and those who answered "Smoked at least 100 cigarettes in life" were placed into "former smokers" group and other responses were placed into "never smoked" group [26]. The status of diabetes was determined based on the NHANES questionnaire responses, with individuals meeting any of the following criteria considered to have diabetes: being informed by a doctor about having diabetes, currently taking antidiabetic medications, having a glycated hemoglobin level>6.5%, or having a fasting blood glucose level>126 mg/dL [27]. Hypertension status was determined based on the NHANES questionnaire responses, with individuals meeting any of the following criteria considered to have hypertension: being informed by a doctor about having hypertension, being informed about taking prescription medication for hypertension, currently taking prescription medication for hypertension, or having an average systolic blood pressure≥130 mmHg or diastolic blood pressure≥80 mmHg in examination [28].

Statistical analysis

Data processing and analysis in this study were performed using the tableone package and the survey package in R software (v 4.2.1). Firstly, the baseline tables were generated using the tableone package to display the overall distribution of participant characteristics and the distribution of features stratified by the presence or absence of RA. Sample size and proportions were used to display categorical variables, whereas mean and standard deviation (sd) were used to show continuous variables. Sample size (n) was unweighted, proportions (%), mean, and sd were weighted. Secondly, the survey package was used to construct weighted logistic regression models of dietary retinol intake and RA to conduct stratified analysis. By adjusting for confounding factors, chi-square tests were employed to calculate the interaction *p*-values of dietary retinol intake and confounding factors. Subgroup analyses were conducted for confounding factors with significant interaction *p*-values. Three models were constructed in this study by adjusting for different confounding factors: Crude model (unadjusted for any confounding factors), Model I (adjusted for age, gender, and race), and Model II (adjusted for age, gender, race, BMI, smoking status, alcohol consumption, diabetes, and hypertension). The regression relationship model between dietary retinol intake and RA was expressed as odds ratios (ORs) with 95% confidence intervals (CIs), where $p<0.05$ suggested statistical significance.

Linear regression is often used to determine the relationship between independent and dependent variables in clinical trials. However, this linear relationship is not always easy to satisfy, especially when the independent variable is continuous. Converting continuous variables into categorical variables based on certain cutoff points can explore unknown nonlinear relationships. Restricted cubic spline (RCS) analysis, as a smoothing function, is well-suited for nonlinear relationships and preserves independent local structures. It is commonly used to handle nonlinear relationships between continuous variables and the dependent variable, and it can identify key points [29]. In this study, RCS was used to explore the optimal intake level of dietary retinol stratified by gender in different models.

Table 1 Baseline characteristics distribution of participants

Characteristics	*N* (%) / Mean ± SD
Overall	22,971
Gender (%)	
Female	11,656 (51.4)
Male	11,315 (48.6)
Age (%)	
20–45	10,269 (49.7)
45–69	8636 (38.8)
≥69	4066 (11.5)
Race (%)	
Mexican American	3886 (8.2)
Other Hispanic	1759 (4.4)
Non-Hispanic White	11,076 (70.4)
Non-Hispanic Black	4826 (11.4)
Other race	1424 (5.7)
BMI (%)	
≤25	6822 (32.2)
25–30	7836 (33.6)
>30	8313 (34.2)
Alcohol intake (%)	
No	6600 (23.9)
Yes	16,371 (76.1)
Smoke (%)	
Never smoked	12,143 (52.6)
Former smoker	5833 (24.7)
Current smoker	4995 (22.7)
Diabetes (%)	
No	19,564 (89.5)
Yes	3407 (10.5)
Hypertension (%)	
No	10,759 (50.8)
Yes	12,212 (49.2)
Retinol (mg)	439.78 (451.88)
Log Retinol (mg)	5.76 (1.08)
RA (%)	
No	21,756 (95.9)
Yes	1215 (4.1)

Note: n (%) represents the categorical variable and mean (sd) represents the continuous variable. n is unweighted; n (%), mean and sd are weighted

Results

Baseline characteristics

As demonstrated by Tables 1, 22 and 971 participants participated in this study, with males accounting for 48.6% and females accounting for 51.4%. The population aged 20–45 years accounted for 49.7%, and non-Hispanic white individuals accounted for 70.4%. Among the participants, 4.1% were diagnosed with RA. The clinical characteristics of the participants stratified by the presence or absence of RA were presented in Table 2, indicating remarkable differences in gender, age, race, BMI, alcohol consumption, smoking status, hypertension, and diabetes ($p<0.05$). The majority of RA patients were female (58.5%), aged 45–69 years (58.0%), non-Hispanic white (68.4%), obese (45.8%), had a history of alcohol consumption (70.1%) and smoking (63.4%), and had hypertension (68.6%) but no diabetes (76.5%). Furthermore, the dietary retinol intake of RA patients was considerably lower than that of non-RA individuals (405.00 mg vs. 441.26 mg, $p<0.05$).

Association between dietary Retinol Intake and RA

In the weighted logistic regression model without adjusting for confounding factors, the results shown in Table 3

Table 2 Baseline characteristics distribution of RA and Non-RA patients

Characteristics	Non-RA	RA	*p*-value
Overall	21,756	1215	
Gender (%)			0.003
Female	10,952 (51.1)	704 (58.5)	
Male	10,804 (48.9)	511 (41.5)	
Age (%)			< 0.001
20–45	10,089 (51.0)	180 (19.3)	
45–69	7967 (38.0)	669 (58.0)	
≥69	3700 (11.0)	366 (22.7)	
Race (%)			< 0.001
Mexican American	3714 (8.3)	172 (5.6)	
Other Hispanic	1670 (4.4)	89 (4.0)	
Non-Hispanic White	10,534 (70.4)	542 (68.4)	
Non-Hispanic Black	4457 (11.1)	369 (17.0)	
Other race	1381 (5.7)	43 (5.0)	
BMI (%)			< 0.001
≤25	6532 (32.4)	290 (26.8)	
25–30	7478 (33.9)	358 (27.4)	
>30	7746 (33.7)	567 (45.8)	
Alcohol intake (%)			0.001
No	6187 (23.6)	413 (29.9)	
Yes	15,569 (76.4)	802 (70.1)	
Smoke (%)			< 0.001
Never smoked	11,624 (53.2)	519 (36.6)	
Former smoker	5436 (24.3)	397 (34.0)	
Current smoker	4696 (22.4)	299 (29.4)	
Diabetes (%)			< 0.001
No	18,705 (90.1)	859 (76.5)	
Yes	3051 (9.9)	356 (23.5)	
Hypertension (%)			< 0.001
No	10,427 (51.6)	332 (31.4)	
Yes	11,329 (48.4)	883 (68.6)	
Retinol (mean (SD))	441.26 (454.68)	405.00 (378.37)	0.007
Log Retinol(mean(SD))	5.76 (1.08)	5.68 (1.00)	0.04

Note: n (%) represents the categorical variable and mean (sd) represents the continuous variable. n is unweighted; n (%), mean and sd are weighted

Table 3 The Relational Model of Dietary Retinol Intake and RA based on weighted logistic regression

Characteristic	OR	95%CI	*p*-value
Log Retinol (mg)	0.95	0.91–0.99	0.019

Note: No adjustment for any confounding factors

indicated that an increase in retinol intake considerably reduced the risk of RA (OR: 0.95, 95% CI: 0.91–0.99, $p=0.019$).

Subgroup analysis

Multivariable weighted logistic regression analysis for RA, as presented in Table 4, demonstrated that dietary retinol intake increased present negative correlation with the incidence of RA in females (OR: 0.90, 95% CI: 0.84–0.96, $p=0.002$), middle-aged individuals (45–69 years) (OR: 0.83, 95% CI: 0.87–0.99, $p=0.015$), obese individuals (BMI > 30 kg/m^2) (OR: 0.93, 95% CI: 0.87–0.99, $p=0.024$), non-smokers (OR: 0.90, 95% CI: 0.85–0.96, $p<0.001$), and diabetes patients (OR: 0.90, 95% CI: 0.82–0.99, $p=0.024$). The interaction p values, adjusting for all confounding factors, demonstrated that gender considerably influenced the correlation between dietary retinol intake and the risk of RA (p for interaction = 0.014), while other factors did not show remarkable effects (p for interaction > 0.05).

Table 4 Stratified analysis of multi-confounding factors

Participants	OR	95%CI1	*p*-value	*p* for interaction
Gender				0.014
Female	**0.90**	**0.84–0.96**	0.002	
Male	1.04	0.94–1.15	0.400	
Age				0.580
20–45	0.96	0.88–1.04	0.300	
45–69	0.83	0.87–0.99	0.015	
≥69	0.84	0.69–1.01	0.064	
Race				0.766
Mexican American	0.98	0.82–1.17	0.800	
Other Hispanic	0.89	0.76–1.04	0.140	
Non-Hispanic White	0.95	0.90–1.01	0.110	
Non-Hispanic Black	0.96	0.90–1.03	0.200	
Other race	0.94	0.77–1.15	0.600	
BMI				0.608
≤25	0.95	0.89–1.02	0.200	
25–30	0.98	0.88–1.10	0.700	
>30	0.93	0.87–0.99	0.024	
Alcohol intake				0.554
No	0.95	0.88–1.02	0.140	
Yes	0.95	0.90–1.01	0.091	
Smoke				0.074
Never smoked	0.90	0.85–0.96	< 0.001	
Former smoker	0.92	0.81–1.05	0.200	
Current smoker	1.04	0.94–1.15	0.400	
Diabetes				0.558
No	0.96	0.91–1.01	0.130	
Yes	0.90	0.82–0.99	0.024	
Hypertension				0.616
No	0.95	0.90–1.01	0.088	
Yes	0.94	0.87–1.02	0.120	

Note: Interaction p value adjusting for gender, age, race, BMI, smoking, alcohol consumption, diabetes, and hypertension

The results of the weighted logistic regression models, adjusted for various confounding factors, were presented in Table 5, indicating that the intake of dietary retinol increase presented negative correlation with the incidence of RA. The correlation was remarkable in both our Crude model (OR: 0.95, 95% CI: 0.91–0.99, $p=0.019$) and model I (OR: 0.95, 95% CI: 0.90-1.00, $p=0.029$). Subgroup analysis revealed consistent associations in females, after adjusting for different confounding factors, in the Crude model (OR: 0.90, 95% CI: 0.84–0.96, $p=0.002$), model

Table 5 Subgroup Analysis and Relational models with different confounding factors adjusted

Participants	Models	OR	95% CI	*p*-value
All participants	Crude	0.95	0.91–0.99	0.019
	model I	0.95	0.90-1.00	0.029
	model II	0.96	0.91–1.02	0.200
Gender				
Male	Crude	1.04	0.94–1.15	0.400
	model I	1.03	0.93–1.14	0.600
	model II	1.06	0.94–1.19	0.400
Female	Crude	0.90	0.84–0.96	0.002
	model I	0.89	0.83–0.96	0.002
	model II	0.91	0.85–0.99	0.019

Note: Crude is not adjusted; Model 1 adjusts for age, gender, and race; Model 2 adjusts for age, gender, race, BMI, smoking, alcohol consumption, diabetes, and high blood pressure

I (OR: 0.89, 95% CI: 0.83–0.96, $p=0.002$), and model II (OR: 0.91, 95% CI: 0.85–0.99, $p=0.019$). These findings indicated that increased dietary retinol intake was associated with a reduced risk of RA in female.

RCS analysis

Based on the results from the previous section, we conducted RCS analysis on the five statistically significant models (Crude-all, Crude-female, model I-all, model I-female, and model II-female) to explore the optimal dietary retinol intake for RA prevention in different populations (Fig. 2). The results showed that in the unstratified population, regardless of confounding factor adjustment (Crude, model I), the incidence of RA (OR < 1.0) was negatively correlated with the dietary retinol intake exceeding 354.86 mcg, but no remarkable non-linear association was found (p-non-linear > 0.05) (Fig. 2A and B). In the female population, significant non-linear relationships between the risk of RA and dietary retinol intake were observed in all models (Crude, model I, and model II) (p-non-linear < 0.05), and the incidence of RA (OR < 1.0) was negatively correlated with the dietary retinol intake exceeding 354.86 mcg (Fig. 2C, D and E).

Discussion

In this cross-sectional study, a negative correlation between dietary intake of retinol and the incidence of RA in the adult population of the United States was observed, with a more pronounced effect in women. Moreover, RCS analysis revealed a significant negative correlation between the incidence of RA adults with the

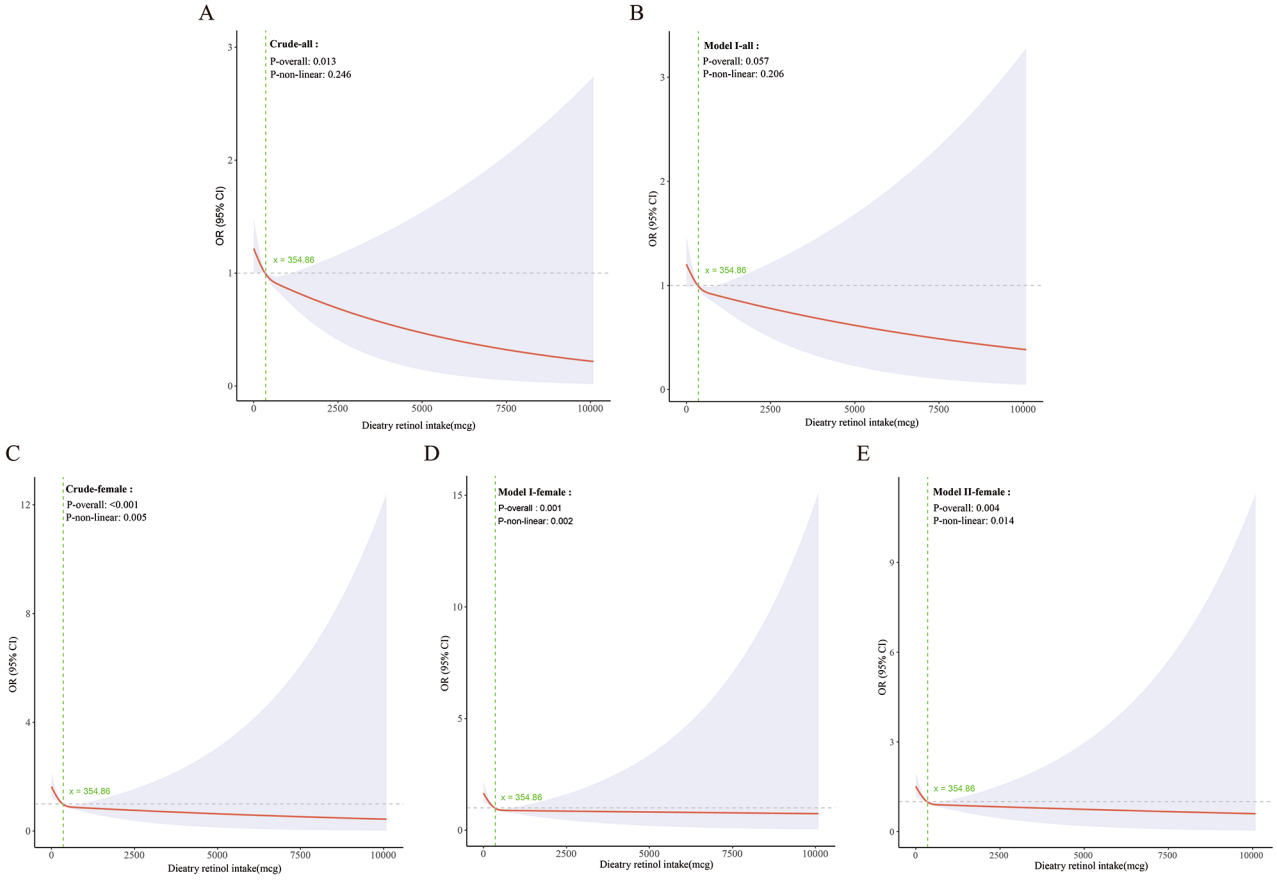

Fig. 2 RCS Analysis. **A**. Crude-all; **B**. Model I-all; **C**. Crude-female; **D**. Model I-female; **E**. Model II-female

dietary retinol intake exceeding 354.86 mcg. Our study could provide potential novel dietary guidance for RA prevention and treatment.

Although the etiology of RA remains unclear, a lot of studies have suggested that the pathogenesis of RA is complex. It is characterized by an imbalance between osteoblasts and osteoclasts, excessive growth of synovial cells, and impaired immune cell function at the cellular level [30]. The inflammatory arthritis of RA is activated and sustained by intricate interplays among different dendritic cell (DC) subsets, fibroblasts, osteoclasts, B cells, T cells, neutrophils, and macrophages [31]. Inflammatory cytokines such as TNF-α, Th17, and IFN-γ can also contribute to RA [32–34]. As an antioxidant, retinol can inhibit or treat cellular damage induced by oxidative stress and impede the development of various chronic diseases, including RA, induced by endogenous oxidative stress. [35]. Furthermore, retinol undergoes metabolism in the body, and its metabolites can, for one thing, bind to nuclear receptors to reduce inflammatory mediators, such as cytokines and chemokines, thereby attenuating the inflammatory response [36, 37]. For another, retinol metabolites can influence the differentiation of immune cells, such as T cells and B cells, and promote the generation of regulatory T cells (Tregs), exerting anti-inflammatory and immune tolerance-maintaining effects, which may alleviate the autoimmune processes involved in RA [36, 38]. In addition to immune modulation, retinol also affects the activity of osteoblasts and osteoclasts, participating in the process of bone remodeling [39]. Sufficient intake of retinol may contribute to the protection of joint structures and the prevention of joint damage in patients with RA. The results of this study further confirmed that increased dietary retinol intake is associated with a reduction in RA incidence.

This study also demonstrated that the negatively correlation between the reduction in the incidence of RA and dietary retinol intake is more remarkable in women than in men. From an epidemiological perspective, RA is more common in women, with a prevalence rate 2 to 3 times higher than in men [40]. The gender disparity in RA may be attributed to the sexual heterogeneity in immune responses. The sexual dimorphism in immune competence is studied in both innate and adaptive immunity [41]. Generally, testosterone has immunosuppressive effects, while estrogen has immunoenhancing effects on the immune system [42]. Estrogen modulates immune responses by reducing the negative selection of high-affinity autoreactive B cells, controlling B cell function, and resulting in Th2 responses [43, 44]. Early studies suggested that females may confer resistance to viral infections because of stronger antibody production capacity but excessive immune responses in females can lead to immune-mediated pathogenesis and autoimmune tendencies [42, 45, 46]. Although the current treatment for RA is not gender-specific, the gender differences in immune responses displayed that treatments tailored to gender may be optimal.

The recommended daily intake of retinol varies for different population groups, with 700 mcg/day for adult females and 900 mcg/day for adult males, according to the National Institutes of Health in the United States [47]. However, our research results indicated that females only need to consume more than 354.86 mcg to develop a significant negative correlation with reduction in RA incidence. In other words, as long as females meet the daily recommended intake of retinol, they can achieve a reduced risk of RA to some extent. However, data statistics show that almost half (52%) of the population in the United States does not meet the average retinol requirement [48]. The insufficient intake of retinol among the population is a key issue. Globally, public health priorities have shifted from nutritional methods to food-based methods. These methods offer various social, economic, and health benefits, and food can be obtained throughout the year, either through consumption or other means [49]. Bad dietary choices can lead to deficiencies in nutrient intake and contribute to malnutrition [50]. Considering that liver, egg yolks, and dairy products are major sources of dietary retinol [51], increasing the consumption of these foods may reduce the risk of RA. Additionally, enriching dietary diversity can offer sustainable options for controlling malnutrition [52], which should be considered, especially for young populations to develop lifelong healthy eating habits.

This study has strengths in using a large sample size and multiple cycles, which provides good representativeness. However, there are also some limitations in this study. Firstly, since most of the included data variables are based on questionnaire surveys, there may be subjective information bias, which could introduce recall bias and inaccuracies, affecting the accurate estimation of dietary retinol intake. Secondly, this study investigates the relationship between baseline dietary retinol intake data and the development of RA. As chronic disease RA typically develops over a long period of time, baseline data may not fully reflect changes in participants' dietary habits throughout the entire study period, potentially introducing some result biases. Additionally, although this study adjusted for some known confounding factors, the development of RA is influenced by multiple factors, and our study cannot comprehensively control for all these confounders, which may have some impact on the study results. Moreover, this study is a cross-sectional study and does not involve time series, therefore, further causal analysis cannot be conducted to examine the relationship between dietary retinol intake and RA.

In conclusion, among US adults, there is a negative correlation between dietary retinol intake and RA, and women may experience certain benefits when their intake exceeds 354.86 mcg. Further prospective trials and the inclusion of more diverse confounding factors are needed in the future to support our findings and gain a more comprehensive understanding of the impact of dietary retinol intake on RA risk.

Abbreviations

RA	Rheumatoid arthritis
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic splines
NCHS	National Center for Health Statistics
YLD	Years lived with disability
CDC	Centers for Disease Control and Prevention
MEC	Mobile Exam Center

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Author contributions
(I) Conception and design: Yuexin Ni. (II) Administrative support: Yating Cao. (III) Provision of study materials or patients: Yun Qiu. (IV) Collection and assembly of data: Yingyuan Li. (V) Data analysis and interpretation: Yating Cao, Yun Qiu. (VI) Manuscript writing: Yuexin Ni, Yating Cao. (VII) Final approval of manuscript: All authors.

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Data availability
Data from this study were included in the NHANES public database (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Su YJ, Chen HM, Chan TM, Cheng TT, Yu SF, Chen JF et al. Disease-modifying anti-rheumatic drugs associated with different diabetes risks in patients with rheumatoid arthritis. RMD Open 2023; 9.
2. Shi G, Liao X, Lin Z, Liu W, Luo X, Zhan H, et al. Estimation of the global prevalence, incidence, years lived with disability of rheumatoid arthritis in 2019 and forecasted incidence in 2040: results from the global burden of Disease Study 2019. Clin Rheumatol. 2023;42:2297–309.
3. Li C, Han Y, Luo X, Qian C, Li Y, Su H, et al. Immunomodulatory nano-preparations for rheumatoid arthritis. Drug Deliv. 2023;30:9–19.
4. Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis. 2014;73:75–85.
5. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010;62:22–32.
6. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. British Society for Rheumatology Biologics R. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum. 2007;56:13–20.
7. Hsieh PH, Wu O, Geue C, McIntosh E, McInnes IB, Siebert S. Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. Ann Rheum Dis. 2020;79:771–7.
8. Ukkola-Vuoti L, Karlsson A, Tuominen S, Lassenius MI, Aaltonen J, Ranta M, et al. Burden of idiopathic inflammatory rheumatic diseases in occupational healthcare: increased absenteeism and healthcare resource utilization. Scand J Work Environ Health. 2023;49:341–9.
9. Ruiz-Montesinos MD, Hernandez-Cruz B, Ariza-Ariza R, Carmona L, Ballina J, Navarro-Sarabia F, et al. [Cost analysis in a cohort of rheumatoid arthritis patients managed in rheumatology units in Spain]. Reumatol Clin. 2005;1:193–9.
10. Philippou E, Nikiphorou E. Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. Autoimmun Rev. 2018;17:1074–7.
11. Gioia C, Lucchino B, Tarsitano MG, Iannuccelli C, Di Franco M. Dietary habits and Nutrition in Rheumatoid Arthritis: can Diet Influence Disease Development and Clinical manifestations? Nutrients. 2020; 12.
12. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr. 2015;114:999–1012.
13. Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17:86.
14. Carazo A, Macakova K, Matousova K, Krcmova LK, Protti M, Mladenka P, Vitamin A, Update. Forms, sources, Kinetics, detection, function, Deficiency, therapeutic use and toxicity. Nutrients. 2021; 13.
15. Marie A, Darricau M, Touyarot K, Parr-Brownlie LC, Bosch-Bouju C. Role and mechanism of vitamin A metabolism in the pathophysiology of Parkinson's Disease. J Parkinsons Dis. 2021;11:949–70.
16. Kim SY, Koo JE, Song MR, Lee JY. Retinol suppresses the activation of toll-like receptors in MyD88- and STAT1-independent manners. Inflammation. 2013;36:426–33.
17. Cui Z, Lin Y, Liu Y, Cao L, Cui L. Retinoic acid-platinum (II) complex [RT-Pt(II)] protects against rheumatoid arthritis in mice via MEK/Nuclear factor kappa B (NF-kappaB) pathway downregulation. Med Sci Monit. 2020;26:e924787.
18. Zhou X, Mi J, Liu Z. Causal association of diet-derived circulating antioxidants with the risk of rheumatoid arthritis: a mendelian randomization study. Semin Arthritis Rheum. 2022;56:152079.
19. Huang L, Xie Y, Jin T, Wang M, Zeng Z, Zhang L, et al. Diet-derived circulating antioxidants and risk of knee osteoarthritis, hip osteoarthritis and rheumatoid arthritis: a two-sample mendelian randomization study. Front Med (Lausanne). 2023;10:1147365.
20. Cifelli CJ, Houchins JA, Demmer E, Fulgoni VL. Increasing Plant Based foods or dairy Foods differentially affects nutrient intakes: dietary scenarios using NHANES 2007–2010. Nutrients. 2016; 8.
21. Chen F, Du M, Blumberg JB, Ho Chui KK, Ruan M, Rogers G, et al. Association among Dietary Supplement Use, Nutrient Intake, and Mortality among U.S. adults: a Cohort Study. Ann Intern Med. 2019;170:604–13.
22. Matsunaga M, Lim E, Davis J, Chen JJ. Dietary Quality Associated with Self-reported diabetes, Osteoarthritis, and rheumatoid arthritis among younger and older US adults: a cross-sectional study using NHANES 2011–2016. Nutrients. 2021; 13.
23. Liu B, Wang J, Li YY, Li KP, Zhang Q. The association between systemic immune-inflammation index and rheumatoid arthritis: evidence from NHANES 1999–2018. Arthritis Res Ther. 2023;25:34.
24. Va P, Dodd KW, Zhao L, Thompson-Paul AM, Mercado CI, Terry AL, et al. Evaluation of measurement error in 24-hour dietary recall for assessing sodium and potassium intake among US adults - National Health and Nutrition Examination Survey (NHANES), 2014. Am J Clin Nutr. 2019;109:1672–82.
25. Tian X, Xue B, Wang B, Lei R, Shan X, Niu J, et al. Physical activity reduces the role of blood cadmium on depression: a cross-sectional analysis with NHANES data. Environ Pollut. 2022;304:119211.
26. Zhang Y, Liu W, Zhang W, Cheng R, Tan A, Shen S, et al. Association between blood lead levels and hyperlipidemiais: results from the NHANES (1999–2018). Front Public Health. 2022;10:981749.

27. Liu Y, Geng T, Wan Z, Lu Q, Zhang X, Qiu Z, et al. Associations of serum folate and vitamin B12 levels with Cardiovascular Disease Mortality among patients with type 2 diabetes. JAMA Netw Open. 2022;5:e2146124.
28. Shi W, Wang H, Zhou Y, Sun Y, Chen Y. Synergistic interaction of hypertension and diabetes on chronic kidney disease: insights from the National Health and Nutrition Examination Survey 1999–2006. J Diabetes Complications. 2020;34:107447.
29. Lu Z, Tao G, Sun X, Zhang Y, Jiang M, Liu Y, et al. Association of Blood Glucose Level and glycemic variability with mortality in Sepsis patients during ICU hospitalization. Front Public Health. 2022;10:857368.
30. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–19.
31. Lin YJ, Anzaghe M, Schulke S. Update on the Pathomechanism, diagnosis, and Treatment options for Rheumatoid Arthritis. Cells. 2020; 9.
32. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. J Clin Invest. 2008;118:3537–45.
33. Robert M, Miossec P. IL-17 in rheumatoid arthritis and Precision Medicine: from Synovitis expression to circulating bioactive levels. Front Med (Lausanne). 2018;5:364.
34. Kokkonen H, Soderstrom I, Rocklov J, Hallmans G, Lejon K, Rantapaa Dahlqvist S. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. Arthritis Rheum. 2010;62:383–91.
35. Rammohan A, Zyryanov GV, Bhagath YB, Manjula K, Antioxidants. Structure-activity of plant polyphenolics. Vitam Horm. 2023;121:395–411.
36. Oliveira LM, Teixeira FME, Sato MN. Impact of Retinoic Acid on Immune Cells and Inflammatory Diseases. Mediators Inflamm. 2018; 2018:3067126.
37. Spinas E, Saggini A, Kritas SK, Cerulli G, Caraffa A, Antinolfi P, et al. Can vitamin a mediate immunity and inflammation? J Biol Regul Homeost Agents. 2015;29:1–6.
38. Amimo JO, Michael H, Chepngeno J, Raev SA, Saif LJ, Vlasova AN. Immune Impairment Associated with Vitamin A Deficiency: Insights from Clinical Studies and Animal Model Research. Nutrients. 2022; 14.
39. Yee MMF, Chin KY, Ima-Nirwana S, Wong SK. Vitamin A and bone health: a review on current evidence. Molecules. 2021; 26.
40. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum. 2010;62:1576–82.
41. Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol. 2014;35:97–104.
42. Butterworth M, McClellan B, Allansmith M. Influence of sex in immunoglobulin levels. Nature. 1967;214:1224–5.
43. Cutolo M, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, et al. Estrogens and autoimmune diseases. Ann N Y Acad Sci. 2006;1089:538–47.
44. Grimaldi CM, Jeganathan V, Diamond B. Hormonal regulation of B cell development: 17 beta-estradiol impairs negative selection of high-affinity DNA-reactive B cells at more than one developmental checkpoint. J Immunol. 2006;176:2703–10.
45. Mangalam AK, Taneja V, David CS. HLA class II molecules influence susceptibility versus protection in inflammatory diseases by determining the cytokine profile. J Immunol. 2013;190:513–8.
46. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35:347–69.
47. Saji H, Okada M, Tsuboi M, Nakajima R, Suzuki K, Aokage K, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet. 2022;399:1607–17.
48. Bird JK, Murphy RA, Ciappio ED, McBurney MI. Risk of Deficiency in multiple concurrent micronutrients in children and adults in the United States. Nutrients. 2017; 9.
49. Gonzalez M, Federici S, Perentes J, Uniportal. VATS S9 segmentectomy: The ligamentum-based approach. Multimedia manual of cardiothoracic surgery: MMCTS. 2021; 2021.
50. Geng S, Ma J, Liu S, Zhang J, Sheng X. Lack of Dietary Diversity contributes to the gaps in Micronutrient Status and Physical Development between Urban and Rural infants. Iran J Public Health. 2018;47:958–66.
51. Bondi A, Sklan D. Vitamin A and carotene in animal nutrition. Prog Food Nutr Sci. 1984;8:165–91.
52. Jones AD. Critical review of the emerging research evidence on agricultural biodiversity, diet diversity, and nutritional status in low- and middle-income countries. Nutr Rev. 2017;75:769–82.

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