Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

The Association Between Anion Gap and Albumin-Corrected Anion Gap with Sun Sensitivity: A National Retrospective Cross-Sectional Study

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Background: Sun sensitivity is a significant factor influencing the risk of sunburn and skin cancer. Given that current assessments mainly depend on self-reported information, exploring objective biochemical indicators may provide complementary insights. The purpose of this research was to determine whether anion gap and albumin-corrected anion gap can function as objective and easily accessible biomarkers for sun sensitivity in US adults.

Methods: We conducted a cross-sectional study utilizing data from the National Health and Nutrition Examination Survey collected between 2003–2006 and 2009–2018. Weighted logistic regression, restricted cubic splines, and subgroup analyses were conducted to examine the association between AG and ACAG and sun sensitivity.

Results: The analysis was conducted on a total of 17,739 participants. We found a positive correlation between both AG and ACAG with increased sun sensitivity (AG: OR = 1.04, 95% CI = 1.01–1.07, P = 0.012; ACAG: OR = 1.04, 95% CI = 1.01–1.07, P = 0.004). It was observed that participants in the highest quartile (Q4) of AG and ACAG presented with heightened sensitivity to sunlight (AG: OR = 1.23, 95% CI = 1.02–1.50, P = 0.034; ACAG: OR = 1.29, 95% CI = 1.07–1.57, P = 0.01). Subgroup analyses indicated a consistent trend across various subgroups.

Conclusion: Our study demonstrates that heightened levels of AG and ACAG are related to an elevated degree of sun sensitivity.

Keywords: sun sensitivity, skin protection, AG, ACAG, NHANES, skin photosensitivity

Introduction

Sun sensitivity, defined as an abnormal sensitivity of the skin to ultraviolet (UV) radiation, is a significant clinical and public health issue.[1] Individuals with high sun sensitivity—often characterized by traits such as fair skin and blonde hair—are more prone to sunburn and face a heightened risk of skin cancer.[2] Additionally, sun sensitivity is an important manifestation of various diseases and a common adverse reaction to certain medications.[3–5] Assessing an individual's sun sensitivity is crucial for developing effective sun protection strategies and preventing related skin damage. However, current clinical practices and epidemiological studies primarily rely on subjective indicators (such as self-reported history of sunburn) or relatively static characteristics (such as baseline skin color or ethnicity).[6] These methods struggle to sensitively and objectively reflect the dynamic changes in sun sensitivity. Therefore, identifying biomarkers that can objectively reflect the state of sun sensitivity, particularly its potential fluctuations, holds significant value.

Serum anion gap (AG) is a routine parameter for clinical assessment of acid-base balance and identification of types of metabolic acidosis, with elevated AG typically indicating the accumulation of unmeasured anions (such as lactate, ketoacids, and certain organic acids) in the body.[7] Notably, hypoalbuminemia can affect the accuracy of AG, leading to the introduction of albumin-corrected anion gap (ACAG) to enhance its reliability.[8] Recent studies have observed an association between elevated AG and ACAG levels and poor prognosis in various chronic diseases.[9–11] These associations are hypothesized to be related to the underlying pathophysiological states reflected by elevated AG or ACAG, such as metabolic derangements

Received: 12 July 2025
Accepted: 11 November 2025
Published: 17 November 2025

(organic acid accumulation), systemic inflammatory responses, or increased oxidative stress levels.[12] Because inflammatory activity and oxidative stress are known to impair skin barrier function and increase vulnerability to UV-induced damage, biochemical indicators that reflect systemic inflammatory or oxidative states may also correlate with sun sensitivity.[13,14] Given that AG and ACAG are biochemical indicators that reflect systemic metabolic acidosis, inflammation, and oxidative stress, their elevation might serve as indirect markers of a physiological milieu predisposing to higher skin sensitivity to sunlight. As a parameter based on routine biochemical testing that is easily accessible and cost-effective, ACAG has garnered researchers' interest due to its potential pathophysiological implications. However, whether AG and ACAG can serve as convenient biomarkers to indicate or reflect skin sensitivity to sunlight in the general population without a diagnosis of sun sensitivity remains an unexplored question. Given the accessibility of ACAG in clinical practice and its potential links to systemic pathological states, exploring its relationship with skin sun sensitivity holds potential application value. The objective of this study is to utilise a nationally representative large dataset, namely the National Health and Nutrition Examination Survey (NHANES), to examine the statistical correlation between AG and ACAG levels with sun sensitivity, with a view to providing a foundation for further in-depth research.

Methods

Study Design

In this retrospective cross-sectional study, we utilized publicly available data from NHANES collected during the periods of 2003–2006 and 2009–2018. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] Data collection for NHANES participants was conducted at mobile examination centers (MEC) specifically designed and located across the United States. NHANES is a continuous, national representative survey program that collects data every two years to determine the public's health and nutrition status, employing a complicated multistage probability sampling design along with specific sample weights tailored to different demographic groups. This program is administered by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The data collection cycle includes self-reported standard biochemical markers, blood cell count metrics, demographic characteristics of participants, and disease-related information. The NHANES study protocol has been approved by the NCHS Institutional Review Board. These surveys are carried out in compliance with local legislation and local institutional provisions. For more details, please visit https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Figure 1 illustrates the flowchart of this study. Among the 70,163 participants over a 7-year period, we excluded 44,848 participants who lacked data on sun sensitivity, 2,490 participants who were missing ACAG data, and 5,005 participants with incomplete data on covariates. The final sample comprised 17,820 participants.

Measurement of Sun Sensitivity

Sun sensitivity was the outcome measure of this study, and this assessment was applicable only to participants aged 20 to 59, in accordance with the NHANES survey design. It was determined using the dermatological questionnaire DED031. Participants were asked,

> If you have not been exposed to sunlight for several months and then spend half an hour in the sun without sunscreen or protective clothing, what happens to your skin?

Those who responded with "severe sunburn with blisters" or "severe sunburn for several days followed by peeling" were classified as "sun sensitive", while all others were categorized as "insensitive."

Measurement of AG and ACAG

The AG and ACAG was calculated using data from NHANES. The AG was determined using the following formula: AG (mmol/L) = [Sodium (mmol/L) + Potassium (mmol/L)] - [Chloride (mmol/L) + Bicarbonate (mmol/L)]. ACAG was assessed using the formula: ACAG (mmol/L) = [4.4 - Albumin (g/dL)] × 2.5 + AG.[7] For detailed information regarding the specific analytical instruments and laboratory methods, please refer to the NHANES Laboratory Procedures Manual. To further elucidate the relationship between AG and ACAG with sun sensitivity, quartile values of AG and ACAG were

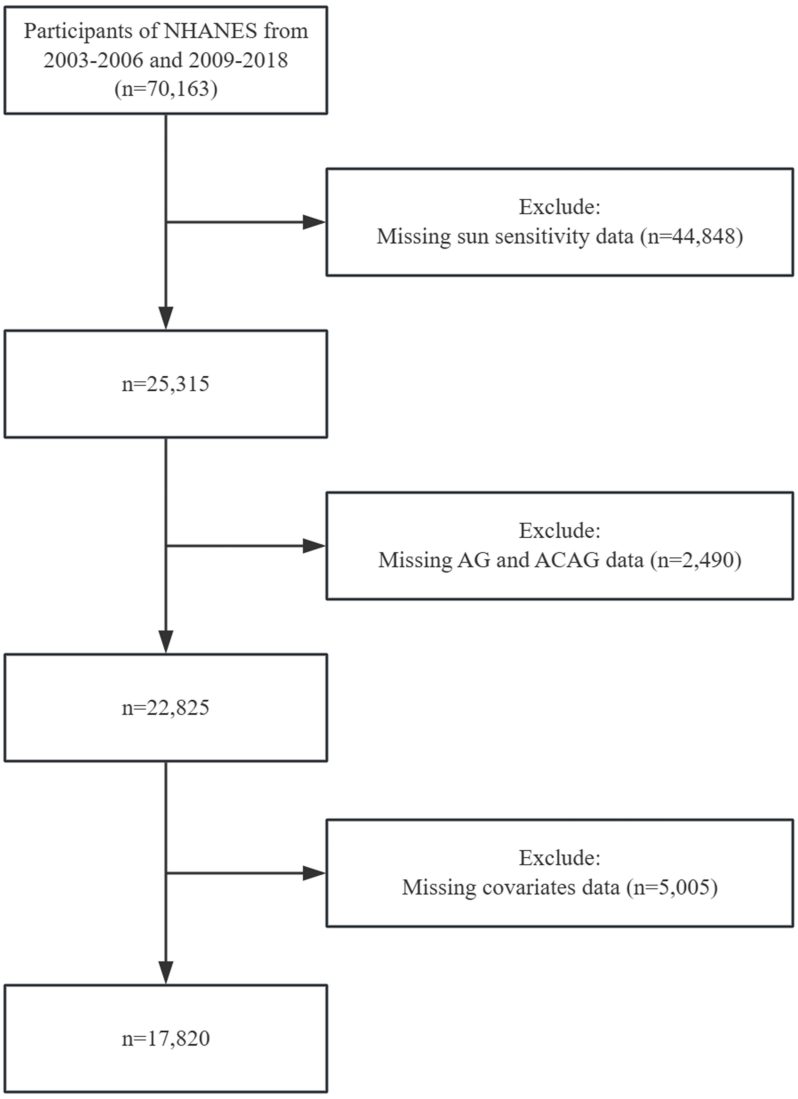

Figure 1 Flow chart of study participants.

used to categorise participants into four groups. For AG, the groups were defined as follows: Q1 (≤ 13.01), Q2 (13.02–14.34), Q3 (14.35–15.86), and Q4 (≥ 15.87). For ACAG, the groups were defined as: Q1 (≤ 13.40), Q2 (13.41–14.69), Q3 (14.70–16.24), and Q4 (≥ 16.25).

Covariates

Covariates included demographic information, lifestyle habits, medical history, and routine laboratory parameters. The demographic information comprised age, sex, race, educational level, marital status, and poverty income ratio (PIR). Lifestyle habits included smoking status, alcohol consumption, time spent in the shade, wearing long-sleeved shirts, and the application of sunscreen. Medical history considered the presence of hypertension, diabetes, chronic kidney disease (CKD), cardiovascular disease, and cancer. Routine laboratory parameters included body mass index (BMI) and estimated glomerular filtration rate (eGFR). Participants were categorized according to their educational attainment as follows: less than high school, high school or GED, and more than high school. Marital status was classified into three categories: married and living with partner, widowed and divorced and separated, and never married. Racial categories followed the classification method used by NHANES (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race). Participants were categorised as smokers if they had smoked at least 100 cigarettes in their

lifetime. Participants were asked whether they had drunk at least 12 alcoholic beverages in the past year, in order to assess their alcohol consumption. The variables for time spent in the shade, wearing long-sleeved shirts, and applying sunscreen were determined based on responses to the question, "On a sunny day, when you are outside for more than one hour, how often do you stay in the shade?" with answers of "always" or "most of the time." Disease status except CKD were established based on information provided by a physician or other healthcare professional. CKD is characterized by an eGFR of less than 60 mL/min/1.73 m^2, albuminuria levels of 30 mg/g or higher, or the presence of both criteria concurrently.[16] The formula for estimating eGFR is as follows: estimated eGFR = 175 × standardized serum creatinine $(Scr)^{-1.154}$ × $age^{-2.03}$ × 1.212 [if Black] * 0.742 [if female].[17] Albuminuria is calculated using the urinary albumin-to-creatinine ratio. Participants were categorised as having cardiovascular disease if they exhibited one or more of the following conditions: congestive heart failure, angina pectoris, myocardial infarction, coronary heart disease, stroke, or heart attack.[18]

Statistical Analysis

Data analysis was conducted in accordance with established standards and recommendations for survey weights related to the NHANES data. For calculating the sampling weights for the periods 2003 to 2006 and 2009 to 2018, the formula employed was: Sample 2-Year MEC Exam Weight (WTMEC4YR) divided by 7. In line with the requirements of complex survey design, all analyses incorporated sampling weights to produce population-level estimates. Continuous variables were expressed as weighted means ± standard deviations, while categorical variables were presented as frequency counts with adjusted proportions. Comparative analyses employed both parametric (Student's *t*-test) and non-parametric methods (Mann–Whitney *U*-test) for continuous measures, alongside χ^2-tests for categorical comparisons.

Weighted multivariable logistic regression models were employed to investigate the associations between AG and ACAG with the risk of sun sensitivity, while adjusting for various confounding factors. This method is suitable for a cross-sectional study with a binary outcome, allowing simultaneous control for potential confounders. Sequential models (Model 1-Model 4) were constructed to assess how progressive adjustment for covariates influenced the associations. Model 1 served as a baseline crude model, which did not adjust for any covariates. Model 2 adjusted for sociodemographic characteristics, including age, race, sex, educational level, marital status, and PIR. Model 3 further adjusted for lifestyle factors (smoking, alcohol consumption, time spent in the shade, wearing long-sleeved clothing, and applying sunscreen). Model 4 additionally adjusted for health conditions (such as hypertension, diabetes, cardiovascular disease, CKD, and cancer or malignant tumors) and laboratory parameters (BMI and eGFR). We applied restricted cubic spline (RCS) analysis to model potential non-linear relationships between AG and ACAG with sun sensitivity. This method allows the data itself to determine the shape of the relationship, providing a flexible way to explore possible curvilinear trends without imposing a specific model assumption.

Subgroup analyses were conducted to assess the consistency of AG and ACAG associations with sun sensitivity across demographic and health-related factors, ensuring robustness of the findings. Interaction tests were also conducted to evaluate the differences in associations across various subgroups. Furthermore, sensitivity analyses were performed using a dataset subjected to five imputations to estimate the stability of the results.

All data were analyzed using the software program Free Statistics (version 2.1.1). Statistically, a P-value of less than 0.05 (two-tailed) was considered significant.

Result

Baseline Characteristics

Table 1 presents the weighted baseline characteristics of participants categorized by sun sensitivity status. Among the 17,820 participants, the average age was 40 years, with 50.17% identified as male and 10.4% categorized as having skin sensitivity. Compared to individuals without skin sensitivity, those with skin sensitivity were more likely to exhibit the following characteristics: being female, identifying as non-Hispanic White, having a higher level of education, being married or cohabiting, possessing a higher PIR, consuming alcohol, preferring to spend time in the shade on sunny days,

Table 1 Weighted Demographic Characteristics of All Participants Stratified by Sun Sensitivity

Characteristic	Overall, N = 17,739	Sun Sensitivity		*P-value*
		Not Sensitive, N = 15,965	Sun Sensitive, N = 1,855	
Age, years	40.00 (29.00, 49.00)	40.00 (29.00, 49.00)	40.00 (30.00, 49.00)	0.41
Sex, n (%)				<0.001
Male	8,696 (50.17%)	7,998 (51.85%)	698 (39.47%)	
Female	9,124 (49.83%)	7,967 (48.15%)	1,157 (60.53%)	
Race, n (%)				<0.001
Mexican American	2,980 (9.33%)	2,779 (10.06%)	201 (4.64%)	
Other Hispanic	1,423 (5.50%)	1,319 (5.87%)	104 (3.09%)	
Non-Hispanic White	7,601 (66.78%)	6,222 (63.54%)	1,379 (87.50%)	
Non-Hispanic Black	3,748 (11.08%)	3,681 (12.57%)	67 (1.55%)	
Other Race	2,068 (7.32%)	1,964 (7.96%)	104 (3.23%)	
Education level, n (%)				<0.001
Less than high school	3,420 (12.87%)	3,113 (13.20%)	307 (10.76%)	
High school or GED	3,983 (22.33%)	3,600 (22.88%)	383 (18.85%)	
More than high school	10,417 (64.80%)	9,252 (63.93%)	1,165 (70.39%)	
Marital status, n (%)				0.024
Married & Living with Partner	10,928 (64.46%)	9,722 (63.98%)	1,206 (67.54%)	
Widowed & Divorced & Separated	2,561 (13.49%)	2,289 (13.51%)	272 (13.32%)	
Never married	4,331 (22.05%)	3,954 (22.51%)	377 (19.14%)	
PIR	3.13 (1.50, 5.00)	3.09 (1.47, 5.00)	3.38 (1.65, 5.00)	0.002
Smoking, n (%)				0.36
No	10,272 (56.23%)	9,276 (56.42%)	996 (55.02%)	
Yes	7,548 (43.77%)	6,689 (43.58%)	859 (44.98%)	
Drinking, n (%)				0.041
No	4,008 (17.78%)	3,651 (18.07%)	357 (15.90%)	
Yes	13,812 (82.22%)	12,314 (81.93%)	1,498 (84.10%)	
Stay in shade, n (%)				<0.001
No	11,737 (70.61%)	10,776 (72.99%)	961 (55.37%)	
Yes	6,083 (29.39%)	5,189 (27.01%)	894 (44.63%)	
Wear long sleeves, n (%)				<0.001
No	15,978 (91.49%)	14,356 (91.92%)	1,622 (88.72%)	
Yes	1,842 (8.51%)	1,609 (8.08%)	233 (11.28%)	
Use sunscreen, n (%)				<0.001
No	13,735 (71.88%)	12,649 (74.63%)	1,086 (54.29%)	
Yes	4,085 (28.12%)	3,316 (25.37%)	769 (45.71%)	
Hypertension, n (%)				0.12
No	13,831 (77.98%)	12,414 (78.23%)	1,417 (76.39%)	
Yes	3,989 (22.02%)	3,551 (21.77%)	438 (23.61%)	
Diabetes, n (%)				<0.001
No	16,610 (94.34%)	14,910 (94.67%)	1,700 (92.24%)	
Yes	1,210 (5.66%)	1,055 (5.33%)	155 (7.76%)	
CVD, n (%)				0.065
No	17,146 (96.65%)	15,394 (96.78%)	1,752 (95.82%)	
Yes	674 (3.35%)	571 (3.22%)	103 (4.18%)	
CKD, n (%)				0.51
No	16,147 (91.24%)	14,473 (91.31%)	1,674 (90.80%)	
Yes	1,673 (8.76%)	1,492 (8.69%)	181 (9.20%)	
Cancer & Malignancy, n (%)				<0.001
No	17,133 (95.05%)	15,406 (95.43%)	1,727 (92.61%)	
Yes	687 (4.95%)	559 (4.57%)	128 (7.39%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall, N = 17,739	Sun Sensitivity		*P-value*
		Not Sensitive, N = 15,965	Sun Sensitive, N = 1,855	
BMI, kg/m^2	27.70 (23.99, 32.45)	27.60 (23.90, 32.22)	28.08 (24.22, 33.50)	<0.001
eGFR, mL/min/1.73m^2	90.43 (78.69, 104.17)	90.55 (78.94, 104.57)	88.66 (76.97, 102.59)	0.001
AG	14.60 (13.20, 16.00)	14.55 (13.10, 16.00)	14.80 (13.50, 16.20)	<0.001
ACAG	14.75 (13.45, 16.30)	14.70 (13.40, 16.25)	15.00 (13.75, 16.60)	<0.001

Abbreviations: PIR, poverty–income ratio; CVD, cardiovascular disease; CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; AG, anion gap; ACAG, albumin-corrected anion gap.

wearing long sleeves, and applying sunscreen. Additionally, these individuals exhibited a higher risk of diabetes and cancer, along with elevated BMI, AG, ACAG, and lower eGFR.

Associations of AG and ACAG with Sun Sensitivity

A weighted logistic regression model was employed to determine the correlation between sun sensitivity and AG and ACAG (Table 2). In the analysis of the relationship between AG and sun sensitivity, the unadjusted model (Model 1) indicated that for every one-unit rise in AG, the risk of sun sensitivity among participants increased by 5% (OR = 1.05, 95% CI = 1.02–1.08, P < 0.001). Additionally, when AG was treated as a categorical variable, participants in the highest AG quartile (Q4) exhibited a higher risk of sun sensitivity (OR = 1.34, 95% CI = 1.13–1.59, P < 0.001). After adjusting for confounding variables including demographic characteristics, sun protection behaviors, lifestyle habits, and health conditions, each one-unit rise in AG was related to a 4% increase in the risk of sun sensitivity (OR = 1.04, 95% CI = 1.01–1.07, P = 0.016). Furthermore, participants in the highest AG quartile (Q4) had a 1.23-fold higher risk of sun sensitivity than those in the lowest quartile (Q1) (OR = 1.23, 95% CI = 1.02–1.50, P = 0.034). A similar pattern was observed in the analysis of ACAG and its association with sun sensitivity. After all covariates had been taken into account, it was found that each one-unit rise in ACAG was related to a 4% increase in the risk of sun sensitivity (OR = 1.04, 95% CI = 1.01–1.07, P = 0.004), and participants in the highest ACAG

Table 2 Weighted Associations of AG and ACAG with Sunlight Sensitivity

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
AG*	1.05(1.02, 1.08)	<0.001	1.05(1.02, 1.08)	<0.001	1.05(1.02, 1.08)	0.001	1.04(1.01, 1.07)	0.016
AG**								
Q1 (<=13.01)	Reference		Reference		Reference		Reference	
Q2 (13.02–14.34)	1.02(0.87, 1.21)	0.781	1.02(0.87, 1.21)	0.774	1.02(0.86, 1.21)	0.826	1(0.84, 1.20)	0.967
Q3 (14.35–15.86)	1.26(1.08, 1.46)	0.003	1.21(1.04, 1.41)	0.016	1.23(1.05, 1.44)	0.012	1.21(1.03, 1.43)	0.023
Q4 (≥15.87)	1.34(1.13, 1.59)	<0.001	1.33(1.11, 1.59)	0.002	1.33(1.10, 1.60)	0.004	1.23(1.02, 1.50)	0.034
P for trend		<0.001		<0.001		<0.001		0.006
ACAG*	1.06(1.03, 1.09)	<0.001	1.06(1.04, 1.09)	<0.001	1.06(1.04, 1.09)	<0.001	1.04(1.01, 1.07)	0.004
ACAG**								
Q1 (<=13.40)	Reference		Reference		Reference		Reference	
Q2 (13.41–14.69)	1.26(1.03, 1.54)	0.022	1.27(1.03, 1.56)	0.026	1.24(1.00, 1.54)	0.05	1.19(0.96, 1.48)	0.107
Q3 (14.70–16.24)	1.42(1.21, 1.67)	<0.001	1.39(1.17, 1.65)	<0.001	1.42(1.19, 1.69)	<0.001	1.35(1.12, 1.61)	0.002
Q4 (≥16.25)	1.49(1.27, 1.76)	<0.001	1.48(1.24, 1.76)	<0.001	1.47(1.21, 1.77)	<0.001	1.29(1.07, 1.57)	0.01
P for trend		<0.001		<0.001		<0.001		0.002

Notes: Model 1: No covariate was adjusted.Model 2: Adjust for model 1 + age, sex, race, marital status, education level and PIR.Model 3: Adjust for model 2 + smoking, drinking, stay in shade, wear long sleeves and use sunscreen.Model 4: Adjust for model 3 + hypertension, diabetes, CVD, cancerand malignancy, CKD, BMI and eGFR.

Abbreviations: AG*, AG as a continuous variable; AG**, AG as a categorical variable; ACAG*, ACAG as a continuous variable; ACAG**, ACAG as a categorical variable; OR, odds ratio; CI, confidence interval.

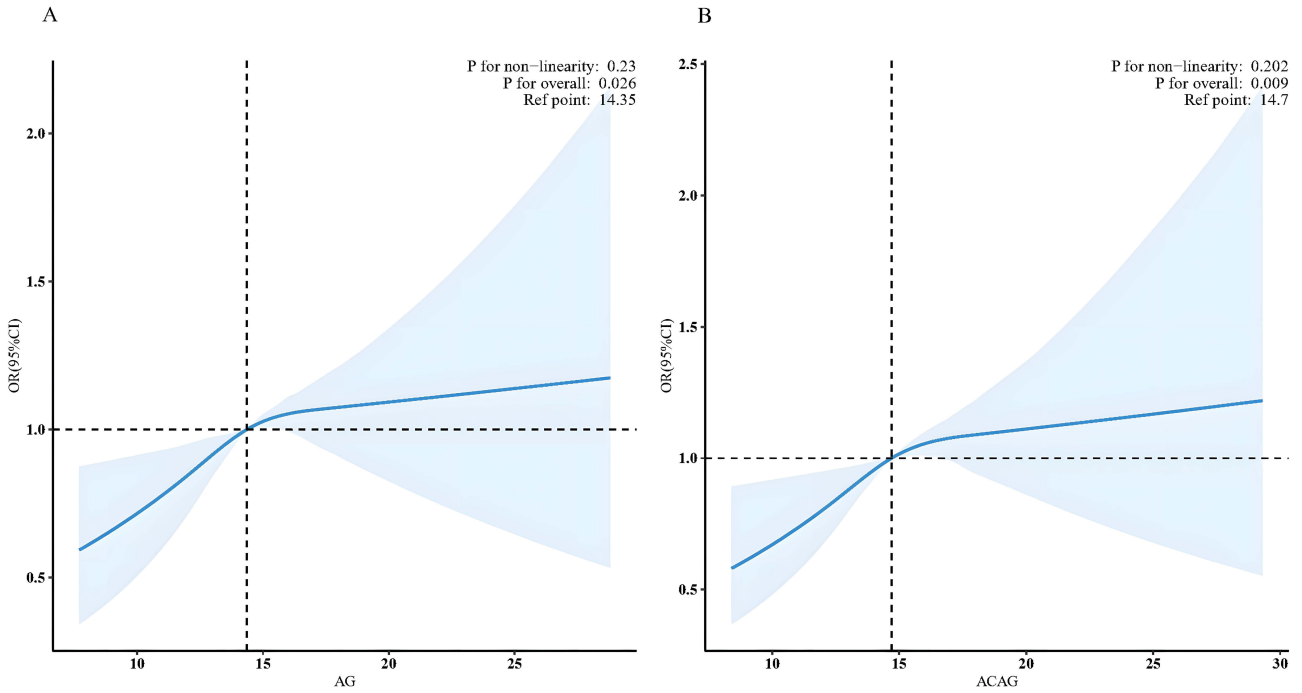

Figure 2 Weighted associations of AG (**A**) and ACAG (**B**) with sun sensitivity.

quartile (Q4) had a higher risk of sun sensitivity (OR = 1.29, 95% CI = 1.07–1.57, P = 0.01). The results of the RCS curve analysis showed that both AG and ACAG exhibited a linear association with sun sensitivity (Figure 2).

Subgroup Analyses

To evaluate the reliability of the associations between AG and ACAG with sun sensitivity within specific populations and to determine potential differences among various subgroups, we conducted a series of subgroup analyses and interaction tests. These analyses were stratified by sex, race, lifestyles habits, medical history, and three types of sun protection behaviors. After adjusting for all potential confounding variables, a positively correlated relationship was observed in both AG and ACAG with sun sensitivity risk, as illustrated in Figure 3. Notably, no significant statistical interactions were found between AG and ACAG with the risk of sun sensitivity among the participants across these subgroups.

Sensitivity Analyses

To assess the reliability and stability of the results, we performed five rounds of multiple imputations for the missing values of the covariates. The newly generated datasets were analyzed separately, and their cumulative effects were calculated. In the sensitivity analysis, the associations between AG and ACAG with the risk of sun sensitivity among participants remained consistent ($p < 0.05$) (Table 3).

Discussion

This study utilized comprehensive and representative data from the NHANES, covering the US population aged 20 to 59 from 2003 to 2006 and 2009 to 2018. The results suggest a positively correlated relationship between AG and ACAG levels and sun sensitivity risk among participants. Logistic regression analysis indicated that every unit increase in AG or ACAG was associated with a 4% increase of sun sensitivity. These findings were validated through subgroup analyses. These results underscore the potential value of AG and ACAG as biomarkers for sun sensitivity in the general population, suggesting that elevated levels of AG and ACAG may increase the risk of sun sensitivity. Therefore, monitoring AG and ACAG levels in participants is crucial for assessing skin sun sensitivity and mitigating the associated risks.

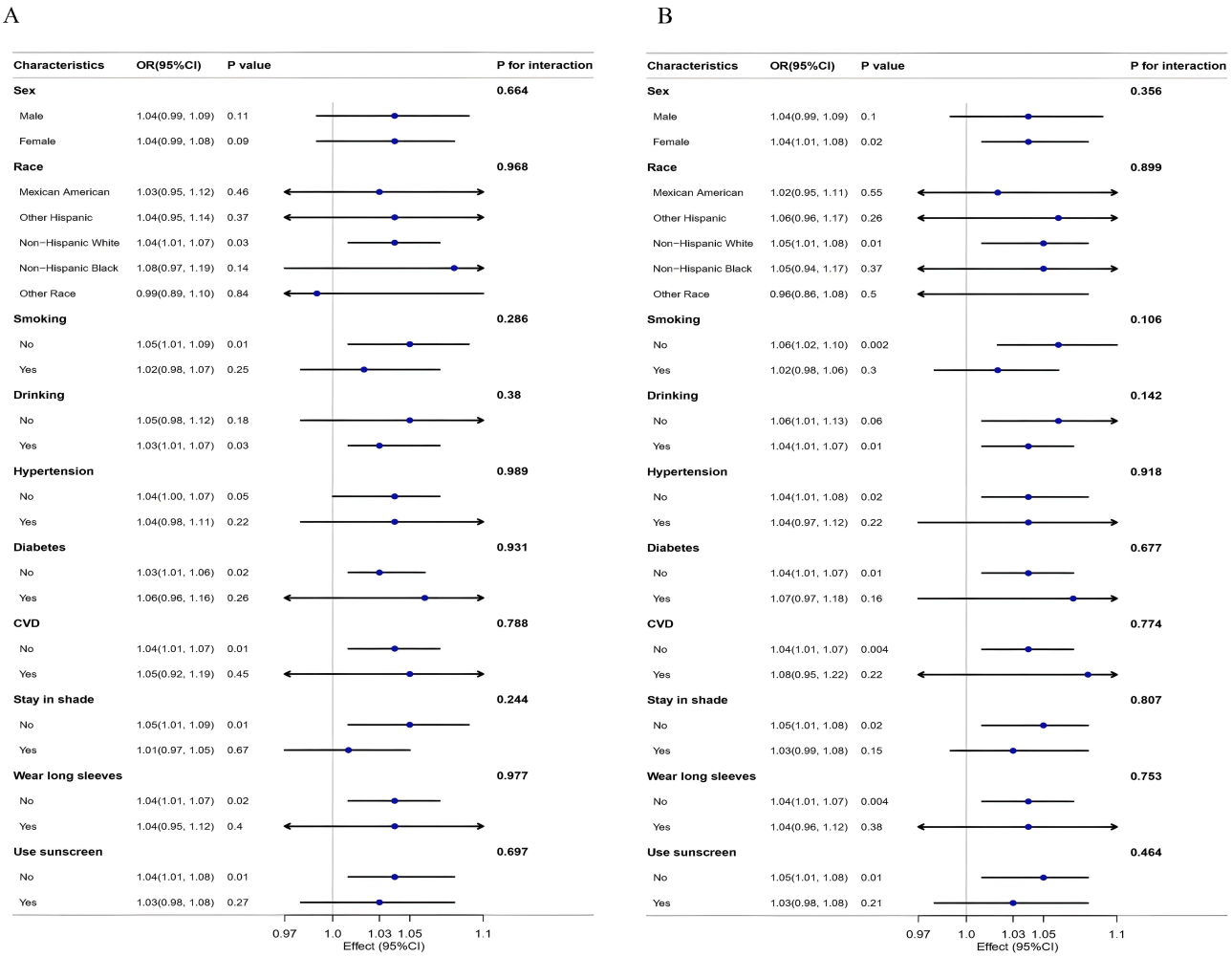

Figure 3 Weighted subgroup analysis for the associations of AG (**A**) and ACAG (**B**) with sun sensitivity.
Notes: Bold text highlights stratified variables and p-values for interaction.

Individuals with high sun sensitivity often exhibit characteristics such as fair skin and blonde hair, making them more susceptible to sunburn and skin cancer.[2,19] Consequently, this population should enhance their sun protection awareness and adhere to stricter photoprotection measures. Among sun protection strategies, wearing long-sleeved clothing and seeking shade are considered the most effective.[20] In contrast, the use of sunscreen may not provide adequate protection due to factors such as skin discomfort, improper application, or insufficient sun protection factor (SPF).[21] It is noteworthy that natural skin color may serve as a more reliable indicator of sun sensitivity, thus experts recommend avoiding artificial tanning methods to prevent sunburn.[22] In addition to inherent factors such as race and skin color, certain medical conditions can significantly impact skin photosensitivity. For instance, in patients with systemic lupus erythematosus (SLE), UV radiation can induce keratinocyte necrosis/apoptosis and trigger the release of nucleic acids; these nucleic acids can bind with autoantibodies, activating plasmacytoid dendritic cells, which in turn lead to a substantial increase in interferon-alpha (IFN-α) production and the activation of autoreactive T cells, ultimately amplifying the skin inflammatory cascade.[12] Erythropoietic protoporphyria (EPP), caused by mutations in the FECH gene, leads to the accumulation of protoporphyrin IX, a photosensitive compound that generates reactive oxygen species upon exposure to light, resulting in skin cell damage and enhanced pain response.[23] Additionally, certain medications can induce or exacerbate photosensitivity; for example, the risk of photosensitivity increases in hypertensive patients taking hydrochlorothiazide, and those on glibenclamide or chlorpropamide may also experience photosensitivity and nonspecific allergic reactions.[24,25] Therefore, individuals with fair skin or those living in regions with high UV exposure should be cautious when using

Table 3 Sensitivity Analyses

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	***P-value***	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***	**OR (95% CI)**	***P-value***
AG*	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001
AG**								
Q1 (<=13.01)	Reference		Reference		Reference		Reference	
Q2 (13.02–14.34)	1.13 (1.07, 1.2)	<0.001	1.08 (1.02, 1.15)	0.01	1.07 (1, 1.13)	0.039	1.05 (0.98, 1.11)	0.142
Q3 (14.35–15.86)	1.39 (1.31, 1.47)	<0.001	1.28 (1.21, 1.35)	<0.001	1.28 (1.21, 1.36)	<0.001	1.25 (1.18, 1.33)	<0.001
Q4 (≥15.87)	1.4 (1.32, 1.48)	<0.001	1.35 (1.28, 1.44)	<0.001	1.33 (1.25, 1.41)	<0.001	1.24 (1.17, 1.32)	<0.001
P for trend	1.13 (1.11, 1.15)	<0.001	1.11 (1.09, 1.13)	<0.001	1.11 (1.09, 1.13)	<0.001	1.09 (1.07, 1.11)	<0.001
ACAG*	1.06 (1.05, 1.07)	<0.001	1.06 (1.05, 1.07)	<0.001	1.06 (1.05, 1.06)	<0.001	1.04 (1.03, 1.04)	<0.001
ACAG**								
Q1 (<=13.40)	Reference		Reference		Reference		Reference	
Q2 (13.41–14.69)	1.26 (1.19, 1.34)	<0.001	1.24 (1.17, 1.31)	<0.001	1.22 (1.15, 1.3)	<0.001	1.18 (1.11, 1.26)	<0.001
Q3 (14.70–16.24)	1.37 (1.29, 1.45)	<0.001	1.29 (1.22, 1.37)	<0.001	1.3 (1.23, 1.38)	<0.001	1.22 (1.15, 1.3)	<0.001
Q4 (≥16.25)	1.51 (1.42, 1.59)	<0.001	1.46 (1.37, 1.54)	<0.001	1.44 (1.35, 1.52)	<0.001	1.27 (1.19, 1.35)	<0.001
P for trend	1.14 (1.12, 1.16)	<0.001	1.12 (1.1, 1.14)	<0.001	1.12 (1.1, 1.14)	<0.001	1.07 (1.05, 1.1)	<0.001

Notes: Model 1: No covariate was adjusted.Model 2: Adjust for model 1 + age, sex, race, marital status, education level and PIR.Model 3: Adjust for model 2 + smoking, drinking, stay in shade, wear long sleeves and use sunscreen.Model 4: Adjust for model 3 + hypertension, diabetes, CVD, cancerand malignancy, CKD, BMI and eGFR.

Abbreviations: AG*, AG as a continuous variable; AG**, AG as a categorical variable; ACAG*, ACAG as a continuous variable; ACAG**, ACAG as a categorical variable; OR, odds ratio; CI, confidence interval.

such medications to reduce the risk of skin damage. In conclusion, skin sun sensitivity is not static; it can fluctuate due to underlying health conditions or the use of specific medications. This highlights the importance of identifying indicators that can sensitively reflect changes in sun sensitivity.

Serum AG is an important indicator of the body's acid-base balance, with elevated levels typically reflecting the accumulation of lactate, ketone bodies, and unmeasured organic acid anions.[7] Given that some patients may present with hypoalbuminemia, and albumin is the principal unmeasured anion, variations in its concentration can significantly influence the accuracy of AG measurements.[26] To address this limitation, researchers introduced the ACAG, which markedly improves accuracy in populations with hypoalbuminemia, thereby expanding the research and clinical application value of this metric across a broader patient demographic.[27] ACAG not only aids in the diagnosis of types of metabolic acidosis but also reflects trends that indirectly indicate levels of oxidative stress and the degree of inflammatory response in the body.[7] The calculation of ACAG is based on routine biochemical parameters, offering the advantages of simplicity and low cost. Current studies demonstrate that elevated ACAG levels are closely associated with the severity of various diseases and are independent risk factors for predicting adverse clinical outcomes. A cohort study involving 2,121 patients with chronic obstructive pulmonary disease showed that patients with high ACAG levels had a greater risk of all-cause mortality.[28] A NHANES database cross-sectional study confirmed that ACAG effectively reflects renal function in hypertensive patients, with higher ACAG identified as an independently significant risk factor for a poor renal function.[29] Our findings further indicate that increased levels of AG and ACAG are associated with heightened sun sensitivity. This association reflects patterns observed in the general population, based on standardized self-reported assessments of sun sensitivity, rather than mechanisms specific to disease-related or medication-induced photosensitivity. However, the precise mechanisms underlying this association remain incompletely elucidated. A plausible explanation involves the heightened inflammatory and oxidative stress status reflected by elevated ACAG, which may ultimately enhance sun sensitivity. Specifically, glutathione (GSH), an important non-enzymatic antioxidant in the skin, detoxifies hydrogen peroxide through the glutathione peroxidase (GPx) pathway, inhibiting its conversion to highly reactive hydroxyl radicals via the Fenton reaction, thus protecting skin cells from oxidative damage induced by reactive oxygen species during light exposure.[30] When ACAG levels rise, this suggests an increase in oxidative stress and inflammatory response, potentially leading to GSH depletion or reduced GPx activity, thereby weakening the skin's

antioxidant capacity. This could result in exacerbated lipid peroxidation following light exposure, promoting inflammatory responses and photodamage.[31] Moreover, a chronic inflammatory environment can lead to the aberrant activation of the type I interferon (IFN) pathway, increased exposure to autoantigens, infiltration of inflammatory cells, and the formation of neutrophil extracellular traps (NETs), all while being accompanied by impaired clearance of apoptotic cells and suppression of regulatory T cell (Treg) function. These factors collectively amplify UV-induced skin damage and abnormal immune responses.[32]

This study has several significant advantages. First, it identifies ACAG as a potential important indicator for assessing the risk of sun sensitivity. Second, the size of the sample improves the statistical reliability and power of the results. The comprehensive approach of this study evaluated various factors, including demographic characteristics, lifestyle habits, health conditions, and biochemical tests, which further supports the validity of the research conclusions. Finally, we utilized a population cohort constructed from the NHANES database, which, considering its sampling design and weighting, includes diverse samples representing multiple ethnicities and age groups. This significantly enhances the applicability of our conclusions to the adult population in the US. However, this study also has several limitations. First, self-reported variables may introduce potential recall bias. Second, due to the cross-sectional design of the study, we cannot draw conclusions regarding the causal relationship between ACAG and sun sensitivity. Third, since the NHANES database only surveyed individuals aged 20 to 59 regarding sun sensitivity, we are unable to establish associations between AG and ACAG with sun sensitivity in populations younger than 20 or older than 59. Future studies including broader age ranges would be helpful to further validate these findings. Fourth, the applicability of findings from the NHANES dataset to populations in other regions may be limited due to differing genetic and environmental factors. In addition, the dataset does not capture detailed clinical information on photosensitivity-related conditions, which could be further explored in future research to enhance the generalizability of the findings.

Future research should validate the predictive role of ACAG in sun sensitivity through multi-center prospective cohort studies and explore intervention studies based on dynamic monitoring to elucidate its clinical translational potential.

Conclusion

This large-scale population-based study provides new evidence that elevated AG and ACAG are related to an increased sensitivity to sunlight in the general adult population. Utilizing AG and ACAG as biomarkers for sun sensitivity may facilitate the timely initiation of personalized intervention strategies for individuals at risk of heightened sun sensitivity.

Data Sharing Statement

The datasets generated for this study can be found in the CDC National Center for Health Statistics NHANES database at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics Approval and Consent to Participate

The data collection for the NHANES was approved by the Research Ethics Review Board (ERB) of the National Center for Health Statistics (NCHS), and written informed consent was obtained from all participants. The NHANES datasets are publicly available and fully de-identified; therefore, no separate ethical approval was required for this secondary analysis. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023, Article 32, Items 1 and 2), research that utilizes only publicly available and anonymized data is exempt from obtaining additional approval from an Institutional Review Board (IRB).

Acknowledgments

We express our gratitude to the participants and staff of the NHANES. We also appreciate the efforts of all the reviewers who took part in the review process.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not–for – profit sectors.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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