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Article

The association between serum α1-AGP and chronic kidney disease among US female ages 20 to 49 years: Results from the 2015-2018 National Health and Nutrition Survey

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Abstract: **Background:** Chronic kidney disease (CKD) affects over 35.5 million US adults. Serum α1-acid glycoprotein (α1-AGP), an acute-phase protein, exhibits anti-inflammatory properties in animal models, but its association with CKD in younger women remains underexplored. This study investigated the relationship between serum α1-AGP and CKD risk in US women aged 20–49 years. **Methods:** This nationally representative cross-sectional study used data on female adults in the US aged 20–49 years from the National Health and Nutrition Examination Survey 2015–2018 cycles. 2,137 individuals were included in the study after excluding individuals without serum α1-AGP, urine albumin, and creatinine data. Multivariate logistic regression models evaluated the association between serum α1-AGP and CKD. Moreover, we performed stratified and interaction analyses to see if the relationship was stable in different subgroups. **Results:** Among 2,137 participants (mean age 34.6 years, mean eGFR 111.7 mL/min/1.73 m^2), CKD prevalence was 8.8% (n=188). Higher serum α1-AGP levels were associated with lower CKD risk in the fully adjusted model (OR 0.37, 95% CI 0.16–0.84, P = 0.017), with a dose-response trend across quartiles (P = 0.041). The association was stronger in women aged 40–49 years (OR 0.20, 95% CI 0.05–0.76) and Mexican Americans (OR 0.07, 95% CI 0.01–0.56), though interaction terms were not significant (P > 0.05). **Conclusions:** Higher serum α1-AGP levels are associated with lower CKD prevalence in young women, suggesting a protective role. Longitudinal studies are needed to confirm causality and explore α1-AGP as a biomarker for CKD risk stratification.

Keywords: Serum α1-AGP; CKD; eGFR; NHANES; Cross-Sectional Study

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1. Introduction

Chronic Kidney Disease (CKD) is a global public health challenge, affecting over 10% of the world's population. In the United States alone, approximately 35.5 million adults are affected, with annual healthcare expenditures related to CKD reaching approximately $114 billion [1]. CKD is characterized by progressive loss of nephrons and abnormal accumulation of extracellular matrix (ECM), eventually leading to renal interstitial fibrosis and irreversible renal function decline [2]. Clinical studies indicate that approximately 38.2% of CKD patients exhibit significant proteinuria (>300 mg/g creatinine) [3], associated with a 3.7-fold increased risk of cardiovascular mortality [4] and a 2.9-fold increased risk of fractures compared to those without CKD [5]. While diabetes and hypertension remain the most prominent known risk factors for CKD [6], recent studies increasingly highlight the critical role of chronic low-grade inflammation in the development and progression of CKD [7]. In this context, acute-phase proteins, acting as key mediators in inflammatory responses, may significantly regulate the pathophysiological processes of CKD. However,

epidemiological evidence on the relationship between acute-phase proteins and CKD remains limited.

Alpha-1-acid glycoprotein (α1-AGP) is an acute-phase glycoprotein synthesized by the liver [8], with a molecular weight of approximately 45 kDa [9]. α1-AGP is extensively involved in various physiological processes, including immune regulation, drug transport, and inflammation suppression [10]. During inflammatory conditions, plasma α1-AGP concentrations can increase by two to five times above baseline levels [11]. Previous small-sample studies have reported significantly elevated α1-AGP levels in CKD patients, negatively correlated with renal function [12, 13]. However, most previous studies have focused on mixed-gender populations or patients with middle-to-late-stage CKD, leaving a gap in understanding the role of α1-AGP in younger populations with earlier-stage disease. Women, particularly premenopausal women, often exhibit slower CKD progression, which may due to the anti-inflammatory and renal protective effects of estrogen [14, 15]. This suggests that α1-AGP's role may vary by gender and age. To address this gap, this study utilized data from the 2015–2018 National Health and Nutrition Examination Survey (NHANES), focusing on women aged 20–49 years, and aimed to investigate the association between serum α1- AGP levels and the risk of CKD. We hypothesized that higher serum α1-AGP level would be associated with lower CKD prevalence in this population, potentially reflecting a protective role of α1-AGP. This study aims to provide novel epidemiological evidence to inform CKD risk stratification and guide future research on α1-AGP's role in renal health in different populations.

2. Methods

2.1. Inclusion and exclusion criteria

The data for this study were obtained from the NHANES, a nationally representative survey conducted by the National Center for Health Statistics (NCHS). NHANES employs a stratified, multi-stage probability cluster sampling design to monitor the nutritional status of the non-institutionalized U.S. population. Detailed information about NHANES is available on its official website (https://www.cdc.gov/nchs/nhanes/). The NCHS Ethics Review Board approved the NHANES study protocol, and all participants provided written informed consent upon enrollment. Since this study was a secondary analysis of publicly available de-identified data, an ethics statement was waived, and informed consent was not applicable. In this study, because α1-AGP data were only available for NHANES survey cycles 2015–2016 and 2017–2018, these cycles were selected. Only women aged 20 to 49 years were included for analysis to focus on premenopausal women with potentially distinct inflammatory and hormonal profiles relevant to α1-AGP regulation. Of 19,225 participants in these cycles, we excluded men, individuals without serum α1-AGP, urinary albumin, or creatinine data, and finally 2,137 participants were included in the analysis.

2.2. Definition of CKD

CKD was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as either an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or an albumin-to-creatinine ratio (ACR) ≥ 30 mg/g.

2.3. Measurement of serum α1-AGP

The Tina-quant Roche AAGP2 assay, which is based on the principle of immunological agglutination, was used to measure α1-AGP. Anti-α1-AGP antibodies react with antigen in the sample to form an antigen/antibody complex. Following agglutination, this is measured turbidimetrically (AAGP2 Tina-quant α1-AGP Gen.2 [package insert]). The laboratory and method were certified according to the Clinical Laboratory Improvement Amendment (1988) guidelines (Clinical Laboratory

Improvement Amendment, 1988). Either in-house prepared serum quality control (QC) pools at three levels or Roche QC pools at two levels were analyzed in every run in duplicate and evaluated for validity against pre-established means and control limits by use of a multi-rule quality control program (Caudill et al., 2008). Data were received after all the laboratory testing was complete. The data were not edited for extreme values. We accessed the NHANES database and extracted the pertinent data.

2.4. Covariates

Data on covariates were collected from questionnaires, physical examinations, and laboratory tests. The covariates included the following: age, race and ethnicity, educational level, marital status, physical activity, smoking status, hypertension, diabetes, body mass index (BMI, kg/m^2), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), white blood cell count (WBC,*10^9/L), hemoglobin (HGB, g/dL), Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m^2), Albumin-to-Creatinine Ratio (ACR, mg/g), serum 25-hydroxyvitamin D3 (vitamin D, nmol/L), albumin (ALB, g/L), uric acid (μmol/L), blood urea nitrogen (BUN, mmol/L), bicarbonate (mmol/L), serum calcium (mmol/L), serum phosphorus (mmol/L), total cholesterol (mmol/L), high-density lipoprotein (HDL, mmol/L), cholesterol (mmol/L), triglycerides (mmol/L), Hemoglobin A1c (HbA1c, %), folate (mmol/L), high-sensitivity C-reactive protein (hs-CRP, mg/L), and ferritin (ug/L).

2.5. Statistical Analysis

Participants were divided into four groups (Q1, Q2, Q3, and Q4) based on serum α1-AGP quartiles. For continuous variables, baseline characteristics of participants were presented as means with standard deviations (SD) for normally distributed data or as medians with interquartile ranges (IQR) for skewed distributions. For categorical variables, baseline characteristics were presented as frequencies with percentages (%). Differences in baseline characteristics between the four groups were assessed using one-way analysis of variance (ANOVA) for normally distributed continuous variables, the Kruskal-Wallis test for skewed continuous variables, and the chi-square test for categorical variables.

Univariate logistic regression was used to analyze the correlation between each variable and CKD. To evaluate the independent association between serum α1-AGP and CKD, multivariate logistic regression models were employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs). In multivariate analyses, different statistical models were used to verify the stability of the results. The covariates in the regression models were corrected according to two criteria: variables selected based on clinical constraints and variables with *P*-values < 0.05 in univariate analyses. Three models were constructed: Model 1 was adjusted for sociodemographic factors like age and educational level. Model 2 was further adjusted for physical measurement factors, including BMI, SBP, DBP, hypertension, diabetes, and physical activity. Model 3, a fully adjusted model, accounted for laboratory indicators and Model 2 variables, such as serum cholesterol, uric acid, hs-CRP, ferritin, vitamin D, HbA1c, folate, and HGB.

To examine whether the relationship between serum α1-AGP and CKD varied across subgroups based on age, race, educational level, marital status, physical activity, smoking status, hypertension, diabetes, and BMI, stratified analyses were performed. All statistical analyses were performed with R, version 4.3.1 (http://www.R-project. org, The R Foundation, Shanghai, China), and Free Statistics, version 2.0, p-value < 0.05 (two-sided) was declared statistically significant.

3. Results

3.1. Baseline demographic and clinical characteristics

Table 1 presents the baseline characteristics of the study participants categorized into quartiles (Q1–Q4) based on serum α1-AGP levels. The mean age of the participants was 34.6 ± 8.5 years. Mean eGFR was 111.7 ± 17.9 mL/min/1.73m^2, and median ACR was 7.4mg/g (IQR, 5.1-12.4). While most demographic factors, such as age, race, educational level, marital status, and physical activity, showed no significant differences across the quartiles ($p > 0.05$), several clinical parameters and biochemical markers varied significantly. Participants in Q4 (with the highest α1-AGP level) had the highest WBC count ($p < 0.001$) and hs-CRP level ($p < 0.001$). The lipid profiles also revealed significant differences across the four quartiles: participants in Q4 had the lowest HDL cholesterol levels ($p < 0.001$) and the highest triglyceride levels ($p < 0.001$). Interestingly, the eGFR showed a downward trend as serum α1-AGP levels increased, with significant differences observed across quartiles ($p < 0.001$). Additionally, the ACR was significantly lower in Q4 than in Q1, indicating improved renal function associated with higher serum α1-AGP levels ($p = 0.005$).

Table 1. Baseline characteristics of the study participants.

Characteristics	Total (n = 2137)	Serum Alpha-1-Acid Glycoprotein (g/L)				*p*
		Q1 (n = 534)	Q2 (n = 529)	Q3 (n = 538)	Q4 (n = 536)	
α1-AGP, g/L	0.82±0.2	0.50±0.1	0.70±0.0	0.80±0.0	1.10±0.2	< 0.001
Age, years	34.6 ± 8.5	34.3 ± 8.5	34.4 ± 8.8	34.8 ± 8.4	35.1 ± 8.5	0.381
Race, n (%)						0.219
Non-Hispanic White	686 (32.1)	156 (29.2)	166 (31.4)	172 (32.0)	192 (35.8)	
Non-Hispanic Black	431 (20.2)	115 (21.5)	105 (19.8)	99 (18.4)	112 (20.9)	
Mexican American	391 (18.3)	105 (19.7)	99 (18.7)	110 (20.4)	77 (14.4)	
Other Race	629 (29.4)	158 (29.6)	159 (30.1)	157 (29.2)	155 (28.9)	
Educational level, n (%)						0.308
High school or less	151 (7.1)	37 (6.9)	46 (8.7)	37 (6.9)	31 (5.8)	
Some College	615 (28.8)	153 (28.7)	154 (29.1)	167 (31.0)	141 (26.4)	
College or above	1370 (64.1)	344 (64.4)	329 (62.2)	334 (62.1)	363 (67.9)	
Marital status, n (%)						0.121
Married or living with partner	1271 (59.5)	322 (60.3)	298 (56.3)	340 (63.2)	311 (58.1)	
Living alone	865 (40.5)	212 (39.7)	231 (43.7)	198 (36.8)	224 (41.9)	
Hypertension, n (%)	339 (15.9)	72 (13.5)	84 (15.9)	92 (17.1)	91 (17.0)	0.333
Diabetes, n (%)	115 (5.4)	32 (6.0)	26 (4.9)	28 (5.2)	29 (5.4)	0.887
Physical activity, n (%)						0.060
Sedentary	1184 (55.5)	284 (53.2)	280 (52.9)	307 (57.1)	313 (58.6)	
Moderate	551 (25.8)	137 (25.7)	158 (29.9)	139 (25.8)	117 (21.9)	
Vigorous	400 (18.7)	113 (21.2)	91 (17.2)	92 (17.1)	104 (19.5)	
Smoking status, n (%)						0.251
Never	1491 (69.8)	381 (71.3)	381 (72.0)	368 (68.5)	361 (67.5)	
Former	258 (12.1)	60 (11.2)	63 (11.9)	75 (14.0)	60 (11.2)	
Current	386 (18.1)	93 (17.4)	85 (16.1)	94 (17.5)	114 (21.3)	
BMI, kg/m^2	30.0 ± 8.1	30.0 ± 7.8	30.0 ± 8.1	29.9 ± 8.2	30.0 ± 8.4	0.998
SBP, mmHg	114.7 ± 13.4	114.3 ± 12.6	115.2 ± 13.1	114.8 ± 13.4	114.5 ± 14.2	0.751
DBP, mmHg	69.9 ± 10.6	69.5 ± 10.4	69.4 ± 11.1	70.2 ± 10.0	70.3 ± 10.8	0.334
WBC, *10^9/L	7.7 ± 2.3	6.9 ± 2.0	7.6 ± 2.1	7.6 ± 2.0	8.8 ± 2.6	< 0.001
HGB, g/dL	13.0 ± 1.3	12.9 ± 1.2	13.0 ± 1.2	13.1 ± 1.3	13.0 ± 1.5	0.289

eGFR, mL/min/1.73m^2	111.7 ± 17.9	113.4 ± 18.2	112.5 ± 18.2	112.0 ± 17.5	109.1 ± 17.5	< 0.001
ACR, mg/g	7.4 (5.1, 12.4)	7.4 (5.4, 12.6)	7.8 (5.4, 13.5)	7.6 (5.1, 12.4)	7.0 (4.8, 10.9)	0.005
Vitamin D, nmol/L	56.3 ± 25.5	54.6 ± 24.3	56.4 ± 23.9	55.2 ± 26.7	59.1 ± 27.0	0.020
ALB, g/L	41.0 ± 3.7	41.2 ± 3.9	41.0 ± 3.8	41.0 ± 3.4	40.9 ± 3.9	0.711
Uric acid, umol/L	268.9 ± 67.9	245.9 ± 58.2	260.1 ± 58.0	274.2 ± 65.3	295.3 ± 78.1	< 0.001
BUN, mmol/L	4.2 ± 1.4	4.2 ± 1.3	4.1 ± 1.2	4.3 ± 1.7	4.2 ± 1.3	0.364
Bicarbonate, mmol/L	24.0 ± 2.3	24.1 ± 2.3	24.0 ± 2.1	23.9 ± 2.3	24.0 ± 2.2	0.448
Calcium, mmol/L	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.542
Phosphorus, mmol/L	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.006
Cholesterol, mmol/L	4.8 ± 1.0	4.8 ± 1.0	4.8 ± 1.0	4.8 ± 1.0	4.7 ± 0.9	0.103
HDL, mmol/L	1.5 ± 0.4	1.7 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	< 0.001
Triglycerides, mmol/L	1.4 ± 0.9	1.1 ± 0.8	1.3 ± 0.9	1.4 ± 0.9	1.6 ± 0.9	< 0.001
HbA1c, %	5.5 ± 0.9	5.3 ± 0.6	5.4 ± 0.8	5.6 ± 0.9	5.7 ± 1.0	< 0.001
Folate, nmol/L	1114.9 ± 459.1	1090.8 ± 417.6	1100.4 ± 438.5	1089.3 ± 427.2	1179.0 ± 537.9	0.003
hs-CRP, mg/L	2.4 (0.8, 5.4)	0.7 (0.4, 2.0)	1.4 (0.7, 3.4)	2.8 (1.4, 5.3)	6.3 (3.3, 11.6)	< 0.001
Ferritin, ug/L	41.0 (20.5, 75.5)	36.8 (19.4, 69.5)	39.6 (20.7, 72.7)	42.5 (21.5, 76.8)	48.0 (20.9, 83.0)	0.015

α1-AGP, Serum Alpha-1-Acid Glycoprotein; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell count; HGB, Hemoglobin; eGFR, Estimated Glomerular Filtration Rate; ACR, Albumin-to-Creatinine Ratio; ALB, Albumin; BUN, Blood Urea Nitrogen; HDL, High-Density Lipoprotein; HbA1c, Hemoglobin A1c; hs-CRP, High-Sensitivity C-Reactive Protein.

3.2. Univariate logistic regression analysis identified several significant risk factors associated with CKD.

Univariate logistic regression was performed to identify the risk factor related to CKD. We found that age was positively related to CKD risk, with each additional year increasing the odds by 3% [odd ratio (OR): 1.03, 95% confident interval (CI): 1.01–1.05, $p < 0.001$). Additionally, individuals with hypertension or diabetes had significantly higher risk of CKD (for hypertension, OR: 2.5, 95% CI: 1.78–3.5, $p < 0.001$; for diabetes, OR: 2.64, 95% CI: 1.62–4.32, $p < 0.001$). Interestingly, while elevated cholesterol level was associated CKD risk (OR: 1.44, 95% CI: 1.25–1.65, $p < 0.001$), increased triglycerides level was a protective factor for CKD (OR: 0.76, 95% CI: 0.62–0.94, $p = 0.009$). Among inflammatory markers, elevated ferritin (OR: 0.99, 95% CI: 0.99–1.0, $p < 0.001$) and serum α1-AGP levels (OR: 0.5, 95% CI: 0.26–0.96, $p = 0.038$) also showed negative associations with CKD risk (Table 2).

Table 2. Univariate logistic regression analysis of risk factors associated with CKD.

Variables	OR (95%CI)	*P*	Variables	OR (95%CI)	*P*
Age, years	1.03 (1.01~1.05)	<0.001	BMI, kg/m^2	0.97 (0.95~0.99)	0.002
Race, n (%)			SBP, mmHg	1.02 (1.01~1.03)	<0.001
Non-Hispanic White	1 (reference)		DBP, mmHg	1.03 (1.02~1.05)	<0.001
Non-Hispanic Black	1.25 (0.81~1.92)	0.315	WBC, *10^9/L	0.98 (0.92~1.05)	0.632
Mexican American	1.47 (0.96~2.25)	0.078	HGB, g/dL	0.72 (0.65~0.80)	<0.001
Other Race	1.15 (0.77~1.7)	0.504	eGFR, mL/min/1.73m^2	0.98 (0.98~0.99)	<0.001
Educational level, n (%)			ACR, mg/g	1.30 (1.25~1.36)	<0.001
High school or less	1 (reference)		Vitamin D, nmol/L	1.00 (1.00~1.01)	0.365
Some College	0.62 (0.37~1.04)	0.073	ALB, g/L	1.01 (0.97~1.05)	0.789
College or above	0.45 (0.28~0.74)	0.001	Uric acid, umol/L	0.99 (0.99~0.99)	<0.001
Marital status, n (%)			BUN, mmol/L	1.11 (1.02~1.22)	0.017
Married or living with partner	1 (reference)		Bicarbonate, mmol/L	1.02 (0.95~1.09)	0.547
Living alone	0.82 (0.60~1.12)	0.206	Calcium, mmol/L	0.60 (0.10~3.63)	0.575
Hypertension, n (%)	2.50 (1.78~3.50)	<0.001	Phosphorus, mmol/L	0.98 (0.40~2.41)	0.973

Diabetes, n (%)	2.64 (1.62~4.32)	<0.001	Cholesterol, mmol/L	1.44 (1.25~1.65)	<0.001
Physical activity, n (%)			HDL, mmol/L	1.26 (0.89~1.77)	0.197
Sedentary	1 (reference)		Triglycerides, mmol/L	0.76 (0.62~0.94)	0.009
Moderate	0.80 (0.56~1.15)	0.225	HbA1c, %	1.08 (0.92~1.26)	0.339
Vigorous	0.69 (0.45~1.06)	0.094	Folate, nmol/L	1.00 (1.00~1.00)	0.013
Smoking status, n (%)			hs-CRP, mg/L	1.01 (1.00~1.03)	0.129
Never	1 (reference)		Ferritin, ug/L	0.99 (0.99~1.00)	<0.001
Former	0.74 (0.44~1.22)	0.237	α1-AGP, g/L	0.50 (0.26~0.96)	0.038
Current	0.86 (0.57~1.29)	0.454			

OR: Odds Ratio; CI: Confidence Interval; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell count; HGB, Hemoglobin; eGFR, Estimated Glomerular Filtration Rate; ACR, Albumin-to-Creatinine Ratio; ALB, Albumin; BUN, Blood Urea Nitrogen; HDL, High-Density Lipoprotein; HbA1c, Hemoglobin A1c; hs-CRP, High-Sensitivity C-Reactive Protein; α1-AGP, Serum Alpha-1-Acid Glycoprotein.

3.3. The multiple logistic regression analysis revealed significant associations between serum α1-AGP levels and the risk of CKD subgroups across different models.

We further conducted multivariate logistic regression analysis to validate the association between α1-AGP and CKD after adjusting for the covariates. Adjustments for demographic factors (Model 1), clinical characteristics (Model 2), and biochemical variables (Model 3) bolstered these findings, showcasing the robustness of the negative association between serum α1-AGP level and CKD risk. These findings underscore the potential role of serum α1-AGP as an independent biomarker of CKD risk, particularly evident in the fully adjusted Model 3. In this model, the OR was 0.37 (95% CI: 0.16–0.84, p = 0.017), indicating a strong protective effect. When participants were stratified into quartiles, those in the highest serum α1-AGP quartile (Q4) showed a significantly lower risk of CKD compared to the reference group (Q1), with an OR of 0.58 (95% CI: 0.34–0.99, p = 0.045). A trend test confirmed a significant dose-response relationship across quartiles (p = 0.041), suggesting that higher serum α1-AGP levels consistently correlate with reduced CKD risk (Table 3).

Table 3. Association between serum α1-AGP and CKD in the multiple logistic regression model.

Variables	n.event%	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
CKD	188 (8.8)	0.50 (0.26~0.96) *	0.48 (0.25~0.94) *	0.39 (0.02~0.78) *	0.37 (0.16~0.84) *
α1-AGP Q1	54 (10.1)	1(Ref)	1(Ref)	1(Ref)	1(Ref)
α1-AGP Q2	53 (10.0)	0.99 (0.66~1.48)	0.97 (0.65~1.45)	0.97 (0.64~1.46)	1.08(0.7~1.67)
α1-AGP Q3	45 (8.4)	0.81 (0.54~1.23)	0.79 (0.52~1.20)	0.73 (0.47~1.12)	0.85(0.54~1.34)
α1-AGP Q4	36 (6.7)	0.64 (0.41~0.99) *	0.64 (0.41~0.99) *	0.58 (0.37~0.92) *	0.58(0.34~0.99) *
Trend test		0.031*	0.029*	0.009*	0.041*

*Model 1: Age, Educational level; Model 2: Model 1+ BMI, SBP, DBP, Hypertension, Diabetes, physical activity; Model 3: Model 2+ Cholesterol, uric acid, hs-CRP, Ferritin, Vitamin D, HbA1c, Folate, HGB; *p < 0.05*

OR, Odds Ratio; CI, Confidence Interval; CKD, Chronic Kidney Disease; α1-AGP, Serum Alpha-1-Acid Glycoprotein; Ref: Reference group (used to denote the group used as the baseline for comparison); Q1, Q2, Q3, Q4: Quartiles of Serum Alpha-1-Acid Glycoprotein (Q1 = lowest quartile, Q4 = highest quartile).

3.4. Subgroup analysis of serum α1-AGP and CKD prevalence

The multivariate regression model indicated a significant negative association between serum α1-AGP level and the CKD risk. To further explore this association, we conducted stratified and interaction analyses to determine whether the relationship between serum α1-AGP levels and CKD risk remained consistent across various subgroup. Notably, the protective effect of serum α1-AGP was more pronounced in women aged 40-49 years (adjusted OR: 0.20, 95% CI: 0.05–0.76), Mexican Americans (adjusted OR: 0.07, 95%

CI: 0.01–0.56), individuals classified as "Other Race" (adjusted OR: 0.17, 95% CI: 0.04–0.79), those with lower educational levels (adjusted OR: 0.03, 95% CI: 0.00–0.92), married individuals (adjusted OR: 0.22, 95% CI: 0.07–0.64), sedentary participants (adjusted OR: 0.32, 95% CI: 0.11–0.93), and never smokers (OR: 0.24, 95% CI:0.09–0.66). However, we did not find statistically significant interactions in the stratified analyses to investigate potential effect modification, indicating consistency across subgroups (Figure 1).

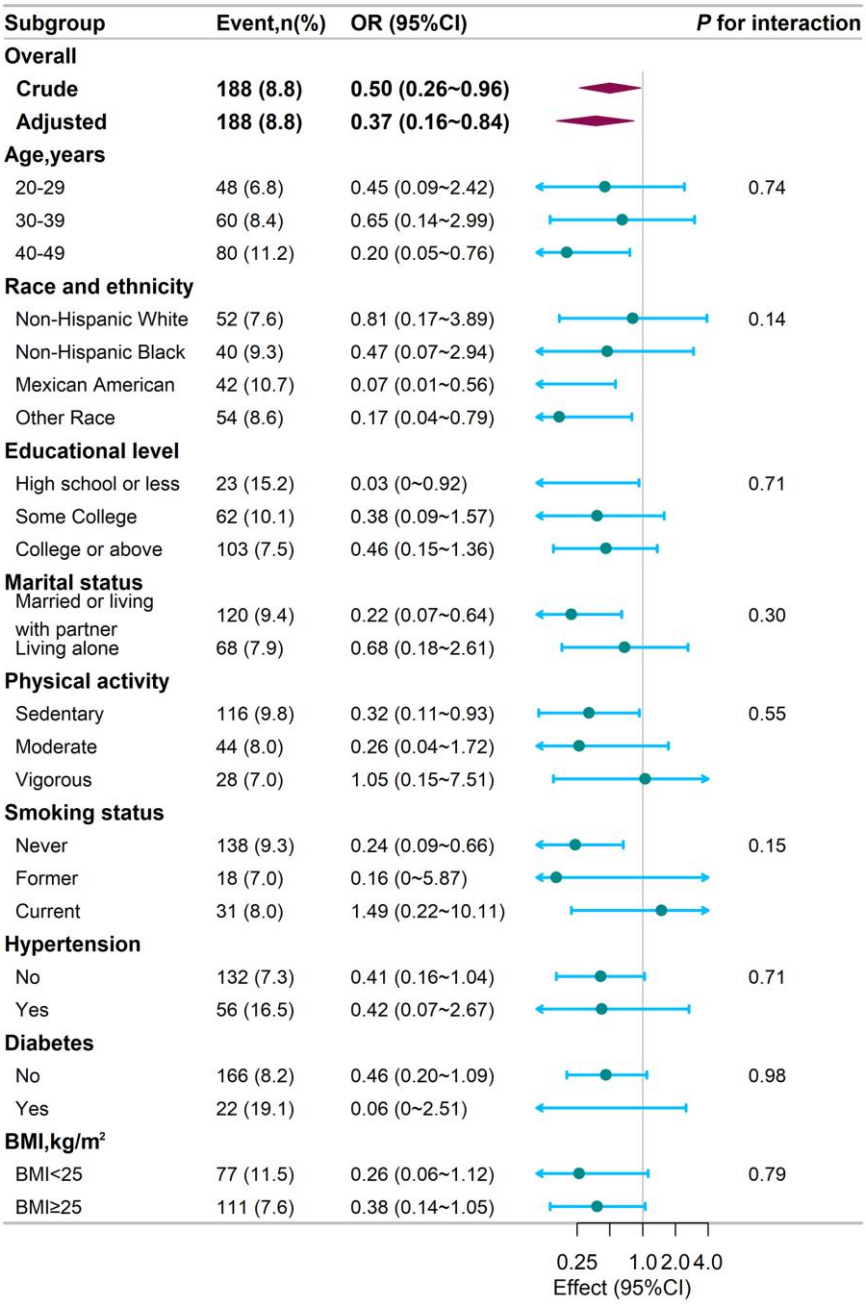

Figure 1. Associations between serum α1-AGP and CKD in different subgroups

4. Discussion

Based on data from the NHANES database, this study was the first to report a significant negative association between serum α1-AGP levels and the CKD risk in women aged 20–49 years at the population level. Higher α1-AGP levels were associated

with lower CKD risk, with a clear dose-response relationship across quartiles, even after adjusting for demographic factors (age, educational level), metabolic indicators (BMI, blood pressure, diabetes status, cholesterol levels), lifestyle factors (physical activity), and other inflammatory biomarkers. The robustness of this dose-response relationship across multiple model specifications suggested that α1-AGP may have a protective role in kidney function.

Notably, we observed that higher α1-AGP levels were associated with lower CKD prevalence, yet participants in the highest α1-AGP quartile also had elevated high-sensitivity C-reactive protein (hs-CRP) levels. This apparent paradox may be explained by the distinct biological roles and regulatory pathways of these two acute-phase proteins. hs-CRP primarily reflects acute systemic inflammation driven by interleukin-6 (IL-6) and other pro-inflammatory cytokines [16], whereas α1-AGP has demonstrated anti-inflammatory, antioxidant, and anti-fibrotic properties, particularly in the setting of chronic low-grade inflammation [17, 18]. Even in the presence of elevated hs-CRP, α1-AGP may exert renoprotective effects by modulating leukocyte activity, promoting anti-inflammatory macrophage polarization, and scavenging reactive oxygen species (ROS) [19, 20].

Our findings contrasted significantly with most previous research, which typically reported a positive association between α1-AGP levels and CKD risk, primarily focusing on elderly or mixed-gender populations [12, 13]. Most of the previous studies included populations with advanced CKD or high-risk individuals with comorbid diabetes or cardiovascular disease. In contrast, our study focused on younger female population with relatively preserved renal function and a lower proportion of diabetic nephropathy or hypertensive nephropathy, possibly involving autoimmune nephropathies such as lupus nephritis. This discrepancy may reflect population heterogeneity in the relationship between α1-AGP and CKD, potentially influenced by age, gender, and disease stage, and inflammatory profiles, highlighting the need for targeted research in younger women.

Mechanistically, evidence from animal and cellular models suggests that AGP possesses anti-inflammatory and anti-fibrotic properties, playing a crucial role in maintaining renal homeostasis. Studies in animal models have shown that exogenous AGP administration can significantly reduce renal inflammation and interstitial fibrosis during the progression from acute kidney injury (AKI) to CKD [21]. Conversely, AGP-knockout mice exhibit more severe structural and functional kidney damage [22]. AGP has also been identified as a downstream effector of the vitamin D signaling pathway; administration of exogenous AGP mimics the renoprotective effects of 1,25-dihydroxyvitamin D_3 by attenuating inflammation and fibrosis [23]. In models of proteinuric kidney disease, AGP promotes the polarization of anti-inflammatory $CD163^+$ macrophages while inhibiting the expression of pro-inflammatory cytokines, thereby alleviating glomerular injury [22, 24]. These findings collectively suggest that AGP may function as an endogenous protective factor in the early stages of kidney injury. However, in advanced CKD, persistent inflammation and oxidative stress may overwhelm AGP's protective capacity, causing it to act predominantly as an inflammatory marker. The role of α1-AGP may also be modulated by gender. Epidemiological and experimental evidence indicates that CKD progression is generally slower in women, particularly premenopausal women, compared to men [25]. This gender-based difference is largely attributed to the protective effects of estrogen, which include inhibition of the TGF-β signaling pathway [26], suppression of pro-inflammatory cytokines [27], and downregulation of the renin-angiotensin-aldosterone system (RAAS) [28]. Estrogen may enhance α1-AGP synthesis and glycosylation through activation of hepatic estrogen receptor α (ERα), thereby strengthening its anti-inflammatory and antioxidant properties [29]. Together, AGP and estrogen may synergistically stabilize the renal microenvironment, protect renal structures, and slow CKD progression.

From a clinical perspective, our findings carried several important implications for CKD prevention and management. The identification of α1-AGP as a potential protective factor provides new insights for risk stratification, particularly in high-risk populations such as women with metabolic syndrome or early-stage diabetic kidney disease. Despite these important implications, our study has several limitations that warrant consideration. First, due to its cross-sectional design, it is not possible to establish a temporal or causal relationship between α1-AGP and CKD. Future longitudinal cohort studies are needed to further validate the association between dynamic changes in α1-AGP and the rate of kidney function decline. Second, the NHANES database does not include data on sex hormones such as estrogen and progesterone, which limits the ability to directly investigate the mechanisms underlying the interaction between estrogen and α1-AGP. Additionally, this study focuses on women aged 20–49 years, and whether the findings can be generalized to other genders, age groups, or racial/ethnic populations requires further external validation through multicenter studies with large sample sizes.

5. Conclusions

Higher serum α1-AGP levels were associated with lower CKD prevalence in young women, suggesting a protective role. This study is the first to suggest at the population level that α1-AGP may not only serve as an inflammatory marker but may also play a protective role in kidney function, particularly among young women. This finding offers a new perspective for the individualized assessment of CKD risk. Longitudinal studies are needed to confirm causality and explore α1-AGP as a biomarker for CKD risk stratification.

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