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ORIGINAL ARTICLE

A Novel Insight into the Interplay between Serum Uric Acid and Blood Parameters: Unveiling a Complex Relationship

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SUMMARY

Background: **Serum uric acid (SUA), the end product of purine metabolism, is widely used in clinical and population health settings and is implicated in gout, cardiometabolic disorders, and kidney disease. Although SUA has been linked to routine hematological indices and inflammatory markers, population-level characterization of these relationships, especially potential non-linear patterns, and the extent to which routinely used renal biomarkers explain these associations remain insufficiently defined.**

Methods: **We conducted a cross-sectional analysis of 12,948 adults from NHANES 2015-March 2020 (pre-pandemic). Hematological parameters included red blood cell count (RBC), hemoglobin (HGB), white blood cell count (WBC), platelet count (PLT), C-reactive protein (CRP), and the hemoglobin-to-red cell distribution width ratio (HGB/RDW). Serum creatinine (Scr) and blood urea nitrogen (BUN) were evaluated as renal biomarkers potentially accounting for hematological-SUA associations. Survey-weighted generalized linear models (GLMs) estimated associations across nested adjustment sets; restricted cubic splines (RCS) assessed non-linearity; and mediation analyses decomposed associations into indirect (via Scr or BUN) and direct components; because available mediation methods do not fully incorporate the NHANES complex survey design, mediation results were conducted without sampling weights and interpreted as exploratory association decompositions.**

Results: **In fully adjusted survey-weighted models, RBC showed the most prominent positive association with SUA, while WBC and CRP exhibited smaller but statistically detectable positive associations; PLT showed no statistically significant association with SUA in the fully adjusted model. RCS analyses suggested non-linear exposure-response patterns for several indices: RBC demonstrated an U-shaped relationship with SUA, and HGB/RDW showed a non-linear pattern with peak SUA at intermediate levels. For WBC and CRP, spline curves were consistent with a saturating pattern (steeper increases at lower levels with plateauing at higher levels). Mediation analyses indicated that Scr and BUN accounted for a variable proportion of hematological-SUA associations, and for some indices the indirect and direct components operated in opposite directions, consistent with a suppression-type decomposition.**

Conclusions: **SUA was found to be correlated with a set of hematological and inflammatory markers measured routinely in a nationally representative sample of adults in the U.S., with RBC and a non-linear relationship between HGB/RDW standing out as notable features. Renal biomarkers (Scr and BUN) statistically explained part of these associations, supporting an integrated interpretation of blood and kidney markers when characterizing SUA-related risk profiles. Longitudinal studies are needed to evaluate temporal ordering and causal mechanisms.**
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KEYWORDS

serum uric acid, hematological parameters, renal biomarkers, mediation analysis, NHANES

LIST OF ABBREVIATIONS

BUN - Blood urea nitrogen
CI - Confidence interval
CRP - C-reactive protein
GLM - Generalized linear model
HGB - Hemoglobin
NHANES - National Health and Nutrition Examination Survey
PLT - Platelet count
RBC - Red blood cell count
RCS - Restricted cubic spline
RDW - Red cell distribution width
Scr - Serum creatinine
SUA - Serum uric acid
UA - Uric acid
WBC - White blood cell count

INTRODUCTION

The end result of purine metabolism, which is known as serum uric acid (SUA), is typically used clinically in assessing metabolic and renal status [1]. High levels of SUA have consistently been related to gout, hypertension, chronic kidney disease and cardiovascular outcomes in population-based studies [2]. In addition to being an indicator of disease, SUA indicates complex relationships between metabolic status, inflammation, and renal performance, which makes it relevant to assessing the public health risk [3-5].

SUA metabolism is a very complex process, which is controlled by a variety of systems and complex mechanisms [6]. One of them is the kidney, which plays a significant role in the process of uric acid metabolism. It works as an incredibly sensitive filtering mechanism, which plays the crucial role of filtering, reabsorbing, and secreting uric acid [7]. By these mechanisms, it successfully balances the concentration of SUA. Along with the kidney, hematological parameters, even less familiar in this regard, are also important. They are involved in the regulation of SUA either indirectly via inflammatory pathways, or directly via metabolic pathways. Xanthine oxidase activity has been linked to red blood cell (RBC) and hemoglobin (HGB) and the ratio of hemoglobin to red cell distribution width (HGB/RDW) by way of modulating tissue oxygen delivery. Xanthine oxidase is an essential enzyme in the purine metabolism pathway, which transforms hypoxanthine to xanthine and finally to SUA. Changes in the activity of this enzyme could be associated with the production of SUA [8]. Platelet (PLT) and white blood cell (WBC) counts, along with C-reactive protein (CRP), are positively associated with the systemic inflammatory state. Higher PLT, WBC counts, and elevated CRP levels generally indicate a more pronounced inflammatory state. Specifically, in an inflammatory environment, pro-inflammatory cytokines are released [9]. These cytokines, in turn, upregulate the hepatic enzymes related to SUA production [9,10]. As a result, there is a positive correlation between CRP and SUA [11]. Moreover, the cross-sectional nature of this study precludes inference of causal direction between hematological parameters and xanthine oxidase activity [12].

Currently, hematological parameters are increasingly recognized as routine clinical markers associated with SUA; however, the mechanisms and explanatory roles underlying these associations have not been clearly defined [13]. Previous studies have primarily focused on estimated Glomerular Filtration Rate (eGFR), but its calculation formulas have limitations. In contrast, serum creatinine (Scr) and blood urea nitrogen (BUN) are two widely used clinical biomarkers that can better reflect the changes in glomerular filtration and tubular reabsorption [14].

Experimental evidence suggests that inflammatory microenvironment would also tend to influence the efficiency of SUA excretion by increasing the renal tubular epithelial injuries; maybe all these factors are embodied in the Scr/BUN variation [12]. It is also necessary to provide a summation of these knowledge gaps as this may contribute to systematic testing of the functions of Scr and BUN to explain observed relationships between hematological parameters and SUA which have been comparatively understudied despite some experimental indications. In the light of existing ambiguity of how the inflammatory micro environments affect SUA excretion, we use the comprehensive data of the NHANES database and use techniques on elucidating this complex relationship.

The study takes the advantages of the NHANES database and creatively employs mediation analysis and other tools to examine the independent associations between RBC, PLT, and SUA. It further examines the roles of Scr and BUN in explaining observed associations, as well as the potential involvement of CRP, to explore relationships among hematological parameters, renal biomarkers, and SUA.

MATERIALS AND METHODS

Study framework

The National Health and Nutrition Examination Survey (NHANES) is a survey based on epidemiologically designed, cross-sectional studies that assess health and nutritional conditions in the U.S. population. The survey was established in 1999 by the Centers for Disease Control and Prevention (CDC) using a multi-stage cluster sampling method every two years. Access to all relevant data is provided as follows: https://www.cdc.gov/nchs/nhanes/.

This cross-sectional analysis used data from NHANES 2015-2020 cycles [15-17]. The NHANES applies a complicated multi-stage probability sampling design and can provide nationally representative estimates for the non-institutionalized population of the United States. The National Center for Health Statistics Research Ethics Review Board approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion criteria were adults aged ≥ 20 years with available SUA and at least one hematological parameter of interest (RBC, PLT, WBC, HGB, CRP, and HGB/RDW). Participants were required to have available serum creatinine (Scr) for the primary analytic dataset. For regression models, participants with missing values in variables required for a given model were excluded using model-level complete-case analysis. Diabetes mellitus and hyperlipidemia were defined using questionnaire and laboratory criteria. Missing covariate information was handled through model-level complete-case analysis. Ultimately, the application of these criteria retained 12,948 subjects for the analysis (Figure 1).

Data standardization

The laboratory protocols of the NHANES enabled standardized measurements of hematological, renal, and biochemical variables. SUA was determined by enzymatic colorimetry. Scr and BUN were obtained using the modified kinetic Jaffe and urease/glutamate dehydrogenase methods, respectively. Automated analyzers (Coulter DxH 800, Beckman Coulter) were used to estimate hematological parameters, such as RBC, PLT, WBC, HGB, and RDW. C-reactive protein (CRP) levels were determined using latex-enhanced nephelometry. Fasting glucose and lipid profiles, including total cholesterol, HDL, LDL, and triglycerides, were analyzed using CDC-standardized protocols.

Statistical analysis

All statistical procedures accounted for the complex, stratified, multistage sampling design of the National Health and Nutrition Examination Survey (NHANES) by incorporating sampling weights, primary sampling units (PSUs), and strata. Data from NHANES 2015 - 2016 (2-year cycle) and NHANES 2017 - March 2020 pre-pandemic (3.2-year cycle) were combined following National Center for Health Statistics analytic guidelines [15-17]. Specifically, MEC examination weights were used and appropriately recalibrated to account for the unequal survey cycle lengths, thereby producing nationally representative estimates of the non-institutionalized U.S. population [15-17]. Following NCHS analytic guidance, we used MEC examination weights from each cycle (WTMEC2YR for NHANES 2015 - 2016 and WTMECPRP for NHANES 2017 - March 2020 pre-pandemic) and re-scaled them to create a combined 5.2-year weight. Specifically, the combined weight was computed as WTMEC2YR × (2/5.2) for 2015 - 2016 and WTMECPRP × (3.2/5.2) for 2017 - March 2020 pre-pandemic. All survey-weighted analyses incorporated strata (SDMVSTRA) and primary sampling units (SDMVPSU).

Survey-weighted analyses were conducted using the survey package in R (version 4.3.1). Independent variables included RBC (10^6/μL), PLT (10^3/μL), WBC (10^3/μL), HGB (g/dL), CRP (mg/L), and HGB/RDW. Renal biomarkers included Scr (mg/dL) and BUN (mg/dL), which were evaluated as potential explanatory variables in mediation analyses. Covariates included age (continuous), gender (male/female), race/ethnicity (Mexican American, Non-Hispanic White, Non-Hispanic Black, Other), education level (< high school, high school, > high school), marital status (married/unmarried), hyperlipidemia (yes/no), and diabetes mellitus (yes/no). All continuous variables were standardized using z-scores to facilitate comparison across biomarkers.

The analytical process consisted of four stages: 1) The descriptive statistics present the demographics of the study population (gender, ethnicity, education, marital status, comorbidities) and laboratory measures (hematological indices, Scr, BUN, SUA). Continuous variables were summarized as median [Q1, Q3], and categorical variables as n (%). Baseline comparisons across SUA quartiles used unweighted Kruskal-Wallis tests (continuous) and Chi-squared tests (categorical), consistent with descriptive summaries. These unweighted tests were used solely for descriptive, distribution-based comparisons across quartiles, whereas population-representative inference relied on the survey-weighted regression and spline models. 2) Survey-weighted generalized linear models (svyglm; Gaussian family with log-link) were used to estimate associations between each hematological parameter and SUA. The log-link was chosen to ensure positive fitted SUA values and to allow exponentiated coefficients [exp(β)] to be interpreted as multiplicative changes in SUA per 1-SD increase in each standardized predictor. All predictors were standardized (z-scores), and exp(β) was interpreted as the multiplicative change in SUA per 1-SD increase in the predictor. Three nested models were fitted: Model 1 unadjusted; Model 2 adjusted for age, gender, and race/ethnicity; and Model 3 additionally adjusted for education, marital status, diabetes, and hyperlipidemia. All regression analyses incorporated NHANES weights, strata, and PSUs. 3) Restricted cubic splines with 3 - 5 knots were used to explore potential non-linear patterns; non-linearity was evaluated using design-based tests for spline terms of RBC, WBC, PLT, HGB, HGB/RDW, and CRP against SUA [18,19]. 4) Mediation analysis (R mediation package) measured the indirect effect of Scr and BUN and estimated average mediation effects (ACME: indirect effect through the specified mediator in the model), average direct effects (ADE: independent variable's direct effect), and total effects (sum of direct and indirect effects) [20]. p-values and 95% CIs were used to determine statistical significance. Because cur-

rently available mediation methods do not fully accommodate the complex NHANES survey design, mediation analyses were conducted without sampling weights and should be interpreted as exploratory, association-based decompositions. 5) The visualization of results was done in forest plots (β coefficients among models), in RCS curves with 95% CI bands (nonlinear trends) and through mediation diagrams (direct/indirect pathways). Lastly, adjusted 95% CIs and β coefficients of the hematological-SUA associations were plotted in the form of forest plots across the models. The trends are nonlinear in the RCS curves and the shaded areas indicate a 95% CIs. Direct and indirect pathways are summarized as the mediation diagrams. Since the design was cross-sectional in nature, the mediation findings were interpreted as a statistical breakdown of associations and not an indication of causal pathways. 6) Given the exploratory nature of this cross-sectional study, sensitivity analyses were performed to assess the robustness of the primary findings under different conditions. Specifically, we examined the associations between hematological parameters and SUA across the following scenarios: 1) CRP levels greater than 10 mg/L, indicating high inflammatory status, 2) CRP levels less than or equal to 10 mg/L, representing low to normal inflammation, 3) adjustment for serum creatinine (Scr), and 4) an unweighted analysis to assess the impact of sampling weights. The results from these sensitivity analyses were compared to the main models to evaluate the consistency of the associations.

RESULTS

Descriptive statistics and baseline characteristics

The final analytic sample included 12,948 adults from NHANES 2015 - March 2020, categorized into SUA quartiles (Q1 - Q4). Median age increased from 46.0 years in Q1 to 55.0 years in Q4 ($p < 0.001$), and the proportion of males increased from 18.4% to 74.1% ($p < 0.001$). Race/ethnicity composition differed across SUA quartiles, with Mexican American participants decreasing from 17.3% (Q1) to 11.2% (Q4) and Non-Hispanic Black participants increasing from 22.4% to 25.8% (all $p < 0.001$). The prevalence of diabetes increased from 16.0% in Q1 to 25.8% in Q4, and hyperlipidemia increased from 22.3% to 38.6% (both $p < 0.001$). Laboratory markers also varied across SUA quartiles: RBC increased from 4.51 to 4.87 × 10^6/μL, HGB increased from 13.4 to 14.6 g/dL, and Scr increased from 0.70 to 0.98 mg/dL (all $p < 0.001$), whereas PLT decreased from 242.0 to 229.0 × 10^3/μL ($p < 0.001$). Inflammatory and renal markers increased with higher SUA, including CRP (1.50 to 2.60 mg/L) and BUN (12.0 to 16.0 mg/dL) (both $p < 0.001$). HGB/RDW showed a modest increase from 0.99 to 1.07 ($p < 0.001$). Education level differed across quartiles ($p = 0.024$), whereas marital status did not ($p = 0.062$) (Tables 1, 2).

Survey-weighted associations between hematological parameters and serum uric acid

GLM models indicated unique relationships between hematological parameters and SUA at different levels of adjustment (Table 3).

Survey-weighted generalized linear models were used to examine associations between hematological parameters and SUA, with all predictors standardized (per SD) to facilitate comparison across biomarkers (Table 3). In the fully adjusted model (Model 3), RBC remained positively associated with SUA ($\exp(\beta) = 1.0267$, 95% CI: 1.0180 - 1.0356, $p < 0.001$). WBC and HGB showed statistically significant positive correlations with SUA but of small values (WBC: $\exp(\beta) = 1.0082$, 95% CI: 1.0008 - 1.0157, $p = 0.038$; HGB: $\exp(\beta) = 1.0151$, 95% CI: 1.0052 - 1.0251, $p = 0.006$).

In all the models, CRP exhibited a strong positive relationship with SUA, and a similar estimation of the effect was obtained post-adjustment (Model 3: $\exp(\beta) = 1.0225$, 95% CI: 1.0135 - 1.0316, $p < 0.001$). In comparison, the statistically significant linear relationship between SUA and PLT and HGB/RDW was not found statistically significant in the fully adjusted model (PLT: $p = 0.195$; HGB/RDW: $p = 0.793$). However, when limited cubic spline regression was done, it was discovered that there was a non-linear exposure-response pattern in the whole distribution of HGB/RDW (p non-linearity = 0.016), though this pattern was not manifested by a significant overall linear effect. Overall, the survey-weighted results indicate that while several hematological and inflammatory markers are statistically associated with SUA at the population level, the effect sizes are modest and close to unity, suggesting subtle changes in SUA per SD difference in each biomarker. Given the large sample size, statistical significance should be interpreted alongside effect magnitude and consistency across models.

Across the three models, adjustment for sociodemographic and metabolic covariates resulted in substantial attenuation of effect estimates, particularly for RBC and HGB, indicating that part of the crude associations may be attributable to shared demographic or metabolic factors. Nevertheless, the persistence of statistically significant associations after full adjustment suggests that these hematological parameters retain independent correlations with SUA at the population level.

Non-linear associations between hematological parameters and serum uric acid (Figure 2, 3; Table 4)

The restricted cubic spline (RCS) models were applied to estimate the potential non-linear exposure response patterns between the hematological values and SUA (Figures 2, 3; Table 4). In this instance of RBC, the test of non-linearity was significant (p of non-linearity < 0.001), the spline curve was showing U-shaped form, and the SUA is minimal at the centre of the distribution of RBC and maximum at the extremes. RCS analyses could also be used to justify the existence of non-linear associations (both p for non-linearity < 0.001) in the

Table 1. Baseline demographic characteristics of the study population by serum uric acid quartiles.

Variables	SUA Quartile Groups				p-value
	Q1 n = 3,237	Q2 n = 3,237	Q3 n = 3,237	Q4 n = 3,237	
Age	46.00 (33.00, 60.00)	50.00 (34.00, 63.00)	53.00 (37.00, 66.00)	55.00 (38.00, 67.00)	< 0.001
Race/ethnicity: mexican american	560 (17.3%)	484 (15.0%)	447 (13.8%)	364 (11.2%)	< 0.001
Race/ethnicity: non-hispanic white	1,043 (32.2%)	1,121 (34.6%)	1,136 (35.1%)	1,155 (35.7%)	< 0.001
Race/ethnicity: non-hispanic black	724 (22.4%)	708 (21.9%)	763 (23.6%)	836 (25.8%)	< 0.001
Race/ethnicity: other	910 (28.1%)	924 (28.5%)	891 (27.5%)	882 (27.2%)	< 0.001
Education level: below high school	350 (10.8%)	278 (8.6%)	317 (9.8%)	275 (8.5%)	0.024
Education level: completed high school	357 (11.0%)	371 (11.5%)	348 (10.8%)	374 (11.6%)	0.024
Education level: high school or above	2,527 (78.1%)	2,584 (79.8%)	2,571 (79.4%)	2,583 (79.8%)	0.024
Gender: male	597 (18.4%)	1,331 (41.1%)	1,916 (59.2%)	2,399 (74.1%)	< 0.001
Gender: female	2,640 (81.6%)	1,906 (58.9%)	1,321 (40.8%)	838 (25.9%)	< 0.001
Marital status: yes	1,849 (57.1%)	1,778 (54.9%)	1,834 (56.7%)	1,884 (58.2%)	0.062
Marital status: no	1,388 (42.9%)	1,459 (45.1%)	1,403 (43.3%)	1,353 (41.8%)	0.062

Data are presented as median [Q1, Q3] or n (%). p-values were calculated using Kruskal-Wallis test (continuous) or chi-squared test (categorical).

Table 2. Clinical characteristics and laboratory parameters of the study population by serum uric acid quartiles.

Variables	SUA Quartile Groups				p-value
	Q1 n = 3,237	Q2 n = 3,237	Q3 n = 3,237	Q4 n = 3,237	
RBC (× 10^6/μL)	4.51 (4.27, 4.79)	4.66 (4.37, 4.97)	4.81 (4.48, 5.12)	4.87 (4.54, 5.19)	< 0.001
PLT (× 10^3/μL)	242.00 (206.00, 287.00)	240.00 (202.00, 281.00)	234.00 (197.00, 278.00)	229.00 (196.00, 268.00)	< 0.001
WBC (× 10^3/μL)	6.80 (5.60, 8.20)	6.90 (5.70, 8.40)	6.90 (5.80, 8.40)	7.20 (5.90, 8.60)	< 0.001
HGB (g/dL)	13.40 (12.60, 14.20)	13.80 (12.90, 14.80)	14.30 (13.30, 15.20)	14.60 (13.40, 15.50)	< 0.001
CRP (mg/L)	1.50 (0.61, 3.90)	1.90 (0.74, 4.31)	2.02 (0.90, 4.60)	2.60 (1.10, 5.42)	< 0.001
HGB/RDW (unitless)	0.99 (0.90, 1.07)	1.03 (0.94, 1.11)	1.05 (0.95, 1.14)	1.07 (0.95, 1.16)	< 0.001
Scr (mg/dL)	0.70 (0.61, 0.81)	0.81 (0.68, 0.94)	0.89 (0.76, 1.03)	0.98 (0.84, 1.16)	< 0.001
SUA (mg/dL)	3.80 (3.40, 4.10)	4.80 (4.60, 5.10)	5.80 (5.50, 6.00)	7.10 (6.70, 7.80)	< 0.001
BUN (mg/dL)	12.00 (10.00, 15.00)	14.00 (11.00, 17.00)	14.00 (12.00, 17.00)	16.00 (13.00, 20.00)	< 0.001
DM: no	2,718 (84.0%)	2,673 (82.6%)	2,589 (80.0%)	2,403 (74.2%)	< 0.001
DM: yes	519 (16.0%)	564 (17.4%)	648 (20.0%)	834 (25.8%)	< 0.001
Hyperlipidemia: no	2,516 (77.7%)	2,395 (74.0%)	2,198 (67.9%)	1,988 (61.4%)	< 0.001
Hyperlipidemia: yes	721 (22.33%)	842 (26.0%)	1,039 (32.1%)	1,249 (38.6%)	< 0.001

Data are presented as median [Q1, Q3] or n (%). RBC red blood cell, HGB hemoglobin, PLT platelet, WBC white blood cell, CRP C-reactive protein, RDW red cell distribution width, Scr serum creatinine, BUN blood urea nitrogen, SUA serum uric acid, DM diabetes mellitus. Units are shown in the variable labels.

Table 3. Survey-weighted associations between hematological parameters and SUA (per SD), estimated by generalized linear models [exp (β)].

	Model 1		Model 2		Model 3	
	Exp (β) (95% CI)	p-value	Exp (β) (95% CI)	p-value	Exp (β) (95% CI)	p-value
RBC	1.0810 (1.0725, 1.0896)	< 0.001	1.0307 (1.0214, 1.0400)	< 0.001	1.0267 (1.0180, 1.0356)	< 0.001
PLT	0.9760 (0.9677, 0.9843)	< 0.001	1.0076 (0.9991, 1.0163)	0.090	1.0057 (0.9973, 1.0141)	0.195
WBC	1.0078 (1.0006, 1.0150)	0.040	1.0093 (1.0014, 1.0173)	0.028	1.0082 (1.0008, 1.0157)	0.038
HGB	1.0861 (1.0778, 1.0946)	< 0.001	1.0197 (1.0088, 1.0307)	0.001	1.0151 (1.0052, 1.0251)	0.006
CRP	1.0197 (1.0102, 1.0293)	< 0.001	1.0234 (1.0141, 1.0328)	< 0.001	1.0225 (1.0135, 1.0316)	< 0.001
HGB/RDW	1.0577 (1.0497, 1.0657)	< 0.001	1.0022 (0.9937, 1.0108)	0.619	0.9990 (0.9912, 1.0067)	0.793

Values are exponentiated regression coefficients [exp(β)] from generalized linear models. Values greater than 1 indicate positive associations with SUA, whereas values less than 1 indicate negative associations. Predictors were standardized (z-scores), and exp(β) represents the multiplicative change in SUA per 1-SD increase in the predictor.

Table 4. Comparison between Linear and Non-linear Relationships of Different Blood Cell Indices with SUA.

Variable	Linear_ Beta	Linear_ SE	Linear-_p	Linear_ AIC	Non Linear_ AIC	AIC_ Diff	Non Linear_ p	Spline visualiza-tion	Linear summary	Interpreta-tion note
RBC	0.05210	0.00861	< 0.001	29.447	39.202	9.8	< 0.001	non-linear	yes	complex non-linear relationship
WBC	0.00190	0.00089	0.038	36.655	28.546	-8.1	< 0.001	non-linear	no	complex non-linear relationship
PLT	0.00008	0.00007	0.195	30.948	30.948	0.0	0.195	linear	yes	consistent (non-linearity is not significant)
CRP	0.00258	0.00052	< 0.001	33.855	28.290	-5.6	< 0.001	non-linear	no	complex non-linear relationship
HGB	0.00958	0.00320	0.006	30.145	30.145	0.0	0.006	linear	yes	consistent (non-linearity is not significant)
HGB/ RDW	-0.00651	0.02456	0.793	28.742	31.615	2.9	0.021	non-linear	yes	complex non-linear relationship

Restricted cubic splines were used to visualize potential non-linear exposure-response patterns. Linear terms summarize average associations. AIC comparisons are reported descriptively; when AIC did not favor splines, spline curves were interpreted as exploratory visualization rather than superior model fit. Because AIC in survey-weighted svyglm models may not be directly comparable to conventional likelihood-based AIC, it is reported here as an approximation for descriptive model comparison.

Table 5a. Sensitivity analysis: CRP > 10 mg/L.

Variable	Estimate-exp (β) (95% CI)	p-value
RBC	0.9997 (0.9754, 1.0246)	0.983
PLT	0.9983 (0.9747, 1.0225)	0.889
WBC	1.0036 (0.9986, 1.0087)	0.168
HGB	0.9844 (0.9630, 1.0062)	0.169
CRP	0.9893 (0.9699, 1.0090)	0.292
HGB/RDW	0.9653 (0.9433, 0.9878)	0.005

Table 5b. Sensitivity analysis: CRP ≤ 10 mg/L.

Variable	Estimate-exp (β) (95% CI)	p-value
RBC	1.0292 (1.0201, 1.0383)	< 0.001
PLT	1.0028 (0.9938, 1.0119)	0.545
WBC	1.0136 (1.0044, 1.0230)	0.007
HGB	1.0217 (1.0114, 1.0321)	< 0.001
CRP	1.0418 (1.0349, 1.0486)	< 0.001
HGB/RDW	1.0077 (0.9999, 1.0155)	0.062

Table 5c. Sensitivity analysis: additional adjustment for Scr.

Variable	Model 3_plusScr	p_plusScr
RBC	1.0321 (1.0233, 1.0410)	< 0.001
PLT	1.0068 (0.9985, 1.0152)	0.121
WBC	1.0082 (1.0007, 1.0157)	0.04
HGB	1.0203 (1.0099, 1.0308)	< 0.001
CRP	1.0217 (1.0130, 1.0304)	< 0.001
HGB/RDW	1.0029 (0.9949, 1.0110)	0.481

Table 5d. Sensitivity analysis: survey-weighted vs. unweighted Model 3.

Variable	Unweighted_Model3	p_unweighted
RBC	1.0190 (1.0143, 1.0237)	< 0.001
PLT	1.0072 (1.0028, 1.0116)	0.001
WBC	1.0064 (1.0038, 1.0091)	< 0.001
HGB	1.0098 (1.0047, 1.0150)	< 0.001
CRP	1.0170 (1.0136, 1.0205)	< 0.001
HGB/RDW	0.9981 (0.9932, 1.0031)	0.459

case of WBC and CRP, as there was a sharp increase in SUA, followed by a plateau at higher concentrations in what may be termed a saturation-type pattern. Curves are centered at the weighted median of each biomarker (reference value).

In contrast, non-linearity was not confirmed in PLT, and the curve was generally consistent with a weak linear association. HGB showed a largely monotonic increasing pattern in the spline visualization; in model comparison, the linear specification was adequate for summarizing the association. Notably, HGB/RDW demonstrated a statistically significant non-linear pattern in RCS (p for non-linearity = 0.021), with fluctuations across the observed range rather than a simple monotonic trend. This indicates that the association may vary across the distribution of HGB/RDW and may not

Table 6. Mediation effect of Scr.

	Average Mediation Effect (ACME)		Average Direct Effect		Total Effect		Proportion Mediated	
	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
RBC	-0.0798 (-0.0974, -0.0638)	< 0.001	0.2942 (0.2417, 0.3520)	< 0.001	0.2154 (0.1609, 0.2746)	< 0.001	-0.3661 (-0.5497, -0.2593)	< 0.001
PLT	-0.0001 (-0.0002, 0.0000)	< 0.001	0.0008 (0.0004, 0.0012)	< 0.001	0.0007 (0.0003, 0.0010)	0.002	-0.2016 (-0.5619, -0.0882)	0.002
WBC	0.0002 (-0.0003, 0.0013)	0.214	0.0153 (0.0072, 0.0575)	< 0.001	0.0156 (0.0074, 0.0579)	< 0.001	0.0157 (-0.0101, 0.0438)	0.214
HGB	-0.0240 (-0.0303, -0.0191)	< 0.001	0.0608 (0.0426, 0.0792)	< 0.001	0.0368 (0.0180, 0.0561)	< 0.001	-0.6512 (-1.4349, -0.3878)	< 0.001
CRP	0.0011 (0.0005, 0.0021)	< 0.001	0.0142 (0.0097, 0.0195)	< 0.001	0.0153 (0.0108, 0.0208)	< 0.001	0.0724 (0.0304, 0.1360)	< 0.001
HGB/RDW	-0.1945 (-0.2486, -0.1558)	< 0.001	0.1517 (-0.0167, 0.3249)	0.074	-0.0428 (-0.2206, 0.1289)	0.630	4.5423 (-23.2573, 27.6785)	0.630

Table 7. Mediation effect of blood urea nitrogen (BUN).

	Average Mediation Effect (ACME)		Average Direct Effect		Total Effect		Proportion Mediated	
	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p	Estimate (95% CI)	p
RBC	-0.1105 (-0.1349, -0.0896)	< 0.001	0.3259 (0.2763, 0.3799)	< 0.001	0.2154 (0.1609, 0.2746)	< 0.001	-0.5130 (-0.7804, -0.3483)	< 0.001
PLT	-0.0003 (-0.0004, -0.0002)	< 0.001	0.0010 (0.0006, 0.0013)	< 0.001	0.0007 (0.0003, 0.0010)	0.002	-0.4821 (-1.2451, -0.2329)	0.002
WBC	0.0003 (-0.0013, 0.0018)	0.388	0.0152 (0.0071, 0.0573)	< 0.001	0.0156 (0.0074, 0.0579)	< 0.001	0.0217 (-0.0313, 0.0739)	0.388
HGB	-0.0439 (-0.0525, -0.0361)	< 0.001	0.0808 (0.0631, 0.0984)	< 0.001	0.0368 (0.0180, 0.0561)	< 0.001	-1.1921 (-2.7056, -0.7075)	< 0.001
CRP	0.0010 (-0.0000, 0.0022)	0.058	0.0142 (0.0099, 0.0194)	< 0.001	0.0153 (0.0108, 0.0208)	< 0.001	0.0684 (-0.0013, 0.1389)	0.058
HGB/RDW	-0.3080 (-0.3712, -0.2465)	< 0.001	0.2652 (0.1101, 0.4387)	0.002	-0.0428 (-0.2206, 0.1289)	0.630	7.1950 (-35.7287, 42.7026)	0.630

Negative proportion mediated may occur when indirect and direct effects have opposite signs (suppression-type decomposition).

be captured by a single average linear estimate.

Model comparison results (Table 4) indicated that the choice between linear and non-linear models was key to interpreting the results. Spline models were used to explore potential non-linear patterns; for some biomarkers the spline specification yielded lower AIC and a significant test for non-linearity, supporting the use of spline curves for visualization. When AIC did not favor splines, the spline curves were interpreted descriptively as visualization of localized patterns rather than evidence of superior model fit. For WBC and CRP, non-linear models offered a better fit, as indicated by lower AIC values, supporting the use of spline-based visualization. These variables showed a saturation-type pattern, with SUA rising sharply at lower levels and plateauing at higher levels. For RBC and HGB/RDW, the non-linear terms were statistically significant, but sometimes the model comparison was not in favor of the non-linear models, and so both the linear and non-linear models can be employed depending on the objective. Linear models offer a straightforward understanding of the average relationship with SUA, while RCS models capture localized non-linear features. Overall, while linear models provide average associations, RCS models excel in highlighting non-linear relationships that linear models may overlook. They are particularly useful for revealing complex patterns, although these non-linear trends may not always translate into significant linear

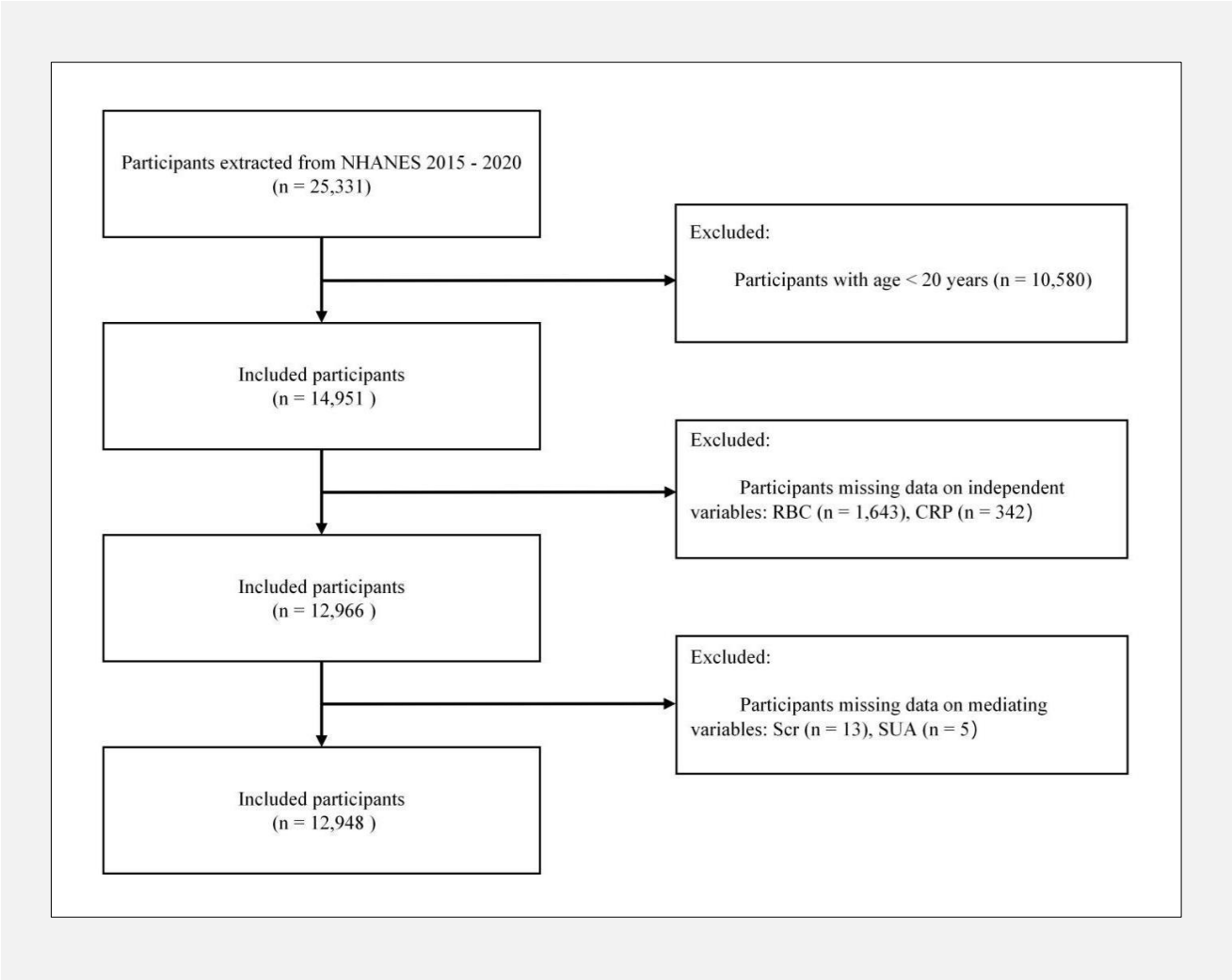

Figure 1. Flow chart of sample selection from NHANES 2015 - 2020.

associations in adjusted models. Therefore, RCS models complement linear approaches, particularly in complex datasets like ours.

Sensitivity analyses

Several sensitivity analyses were performed to evaluate the robustness of the main findings to alternative modeling choices and to potential effect modification by inflammatory status. It is shown in Table 5. First, given the non-linear pattern observed for CRP, we stratified analyses by CRP level among participants with available CRP measurements (> 10 mg/L vs. ≤ 10 mg/L). Among participants with CRP ≤ 10 mg/L, associations between SUA and RBC, WBC, HGB, and CRP remained statistically significant and directionally consistent with the primary survey-weighted results, while PLT and HGB/RDW remained non-significant. In contrast, among participants with CRP > 10 mg/L, most associations were attenuated and became non-significant, whereas HGB/RDW showed a modest inverse association with SUA, suggesting that associations may be less detectable in the high-CRP subgroup, although these subgroup analyses should be interpreted cautiously.

Second, to assess whether estimated associations were materially influenced by renal function, we refitted the fully adjusted model with additional adjustment for Scr. Effect estimates remained similar to the primary Model 3, indicating that inclusion of Scr did not substantially alter the observed associations. Finally, unweighted estimates were generally directionally consistent with the survey-weighted results, although effect sizes tended to be slightly larger, supporting the robustness of the primary findings while highlighting the importance of applying NHANES sampling weights for population-representative inference. Collectively, these sensitivity analyses indicate that the observed associations are not driven by extreme inflammatory states, renal function adjustment, or weighting strategy alone, but may vary

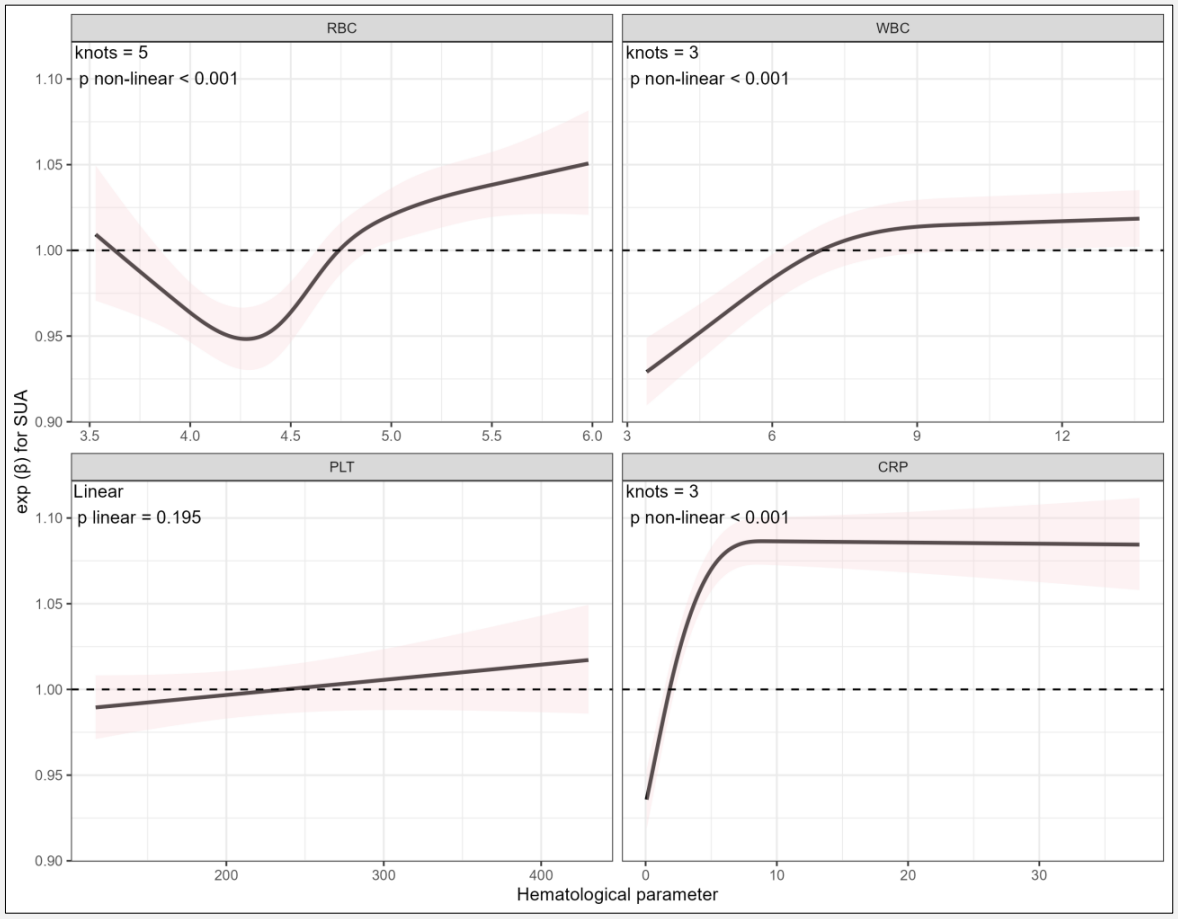

Figure 2. Restricted cubic spline analysis of the associations between blood cell counts, C-reactive protein, and serum uric acid.

in magnitude depending on inflammatory burden and analytic approach.

Mediation effects of Scr and BUN in the associations between hematological parameters and serum uric acid

We performed mediation analyses to explore the possibility of renal biomarkers explaining some (part) of the observed hematological-SUA associations using serum creatinine (Scr) and blood urea nitrogen (BUN) as ideal candidates (Tables 6, 7). Key results are summarized using estimated effects (ACME, ADE, total effect) with 95% CIs and p-values.

To further examine whether renal biomarkers may statistically account for part of the observed associations between hematological parameters and SUA, mediation analyses were conducted using Scr and BUN as candidate mediators (Tables 6, 7). The mediation framework decomposed the total association between each hematological parameter and SUA into an indirect component operating through the renal biomarker (average mediation effect, ACME) and a remaining direct component (average direct effect, ADE). Given the cross-sectional design of NHANES, these results are interpreted as an association-based decomposition rather than evidence of causal or temporal mediation. These mediation analyses were conducted without sampling weights and should be viewed as exploratory.

Overall, the mediation analyses revealed heterogeneous patterns across hematological parameters and renal biomarkers. It was observed that a statistically significant indirect variable was observed with the use of Scr or BUN in some parameters, and this implies that a marker of renal functioning may be reflecting an intermediate correlational association between hematological condition and SUA levels. In other instances, the indirect and the direct components were anti-correlated, which provided a suppression-like effect in which the appearance

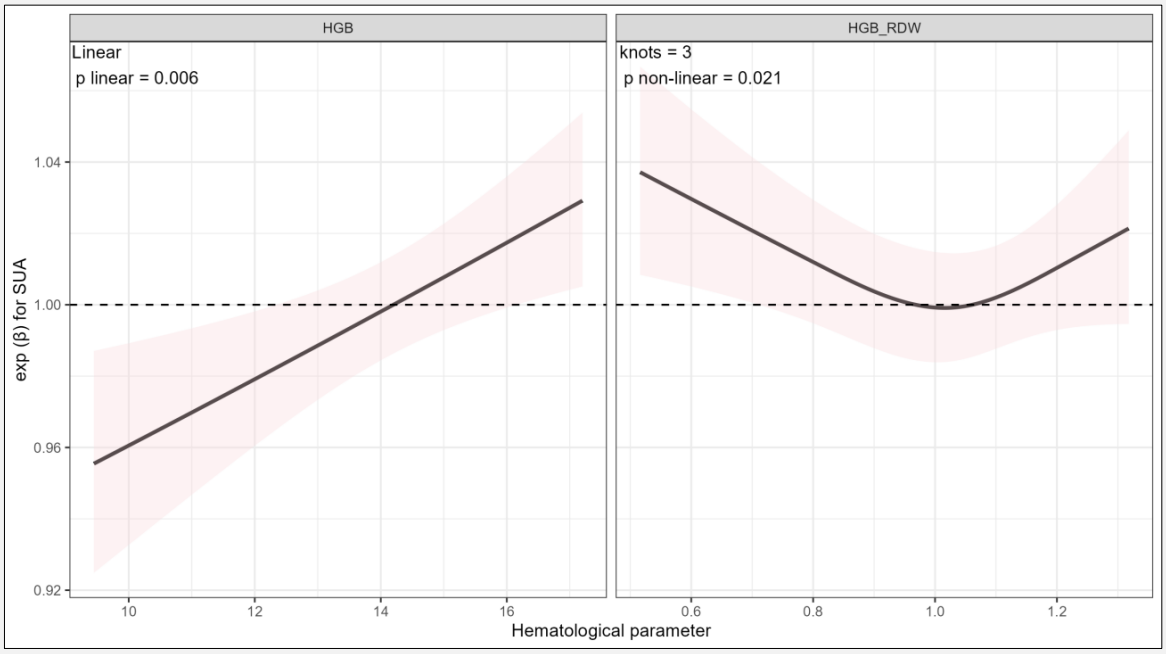

Figure 3. Restricted cubic spline analysis of the associations between hemoglobin-related parameters and serum uric acid.

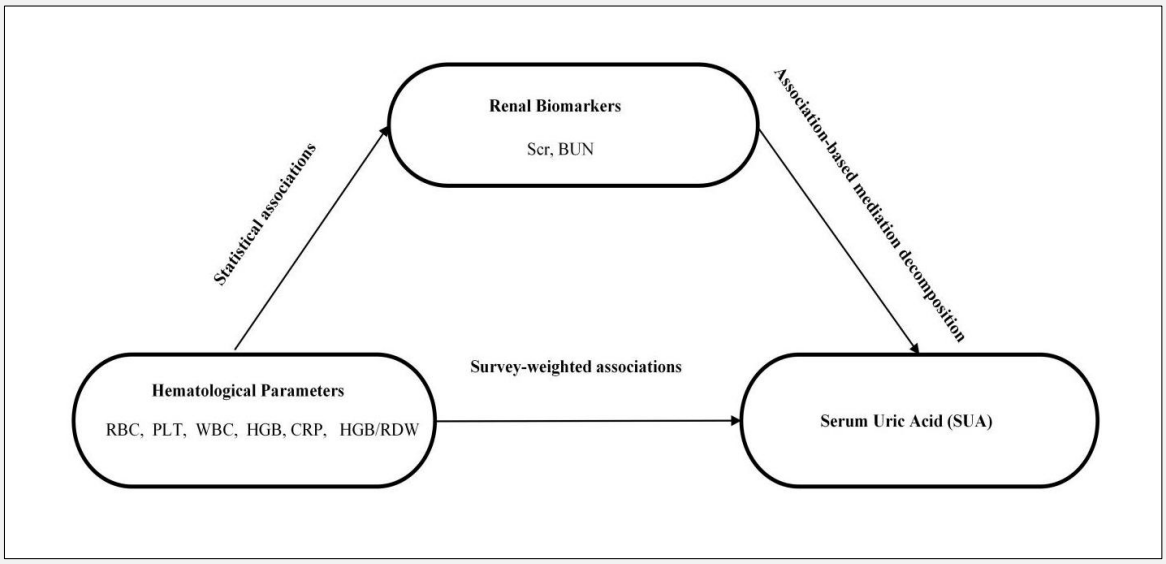

Figure 4. Conceptual framework illustrating associations between hematological parameters, renal biomarkers, and serum uric acid.

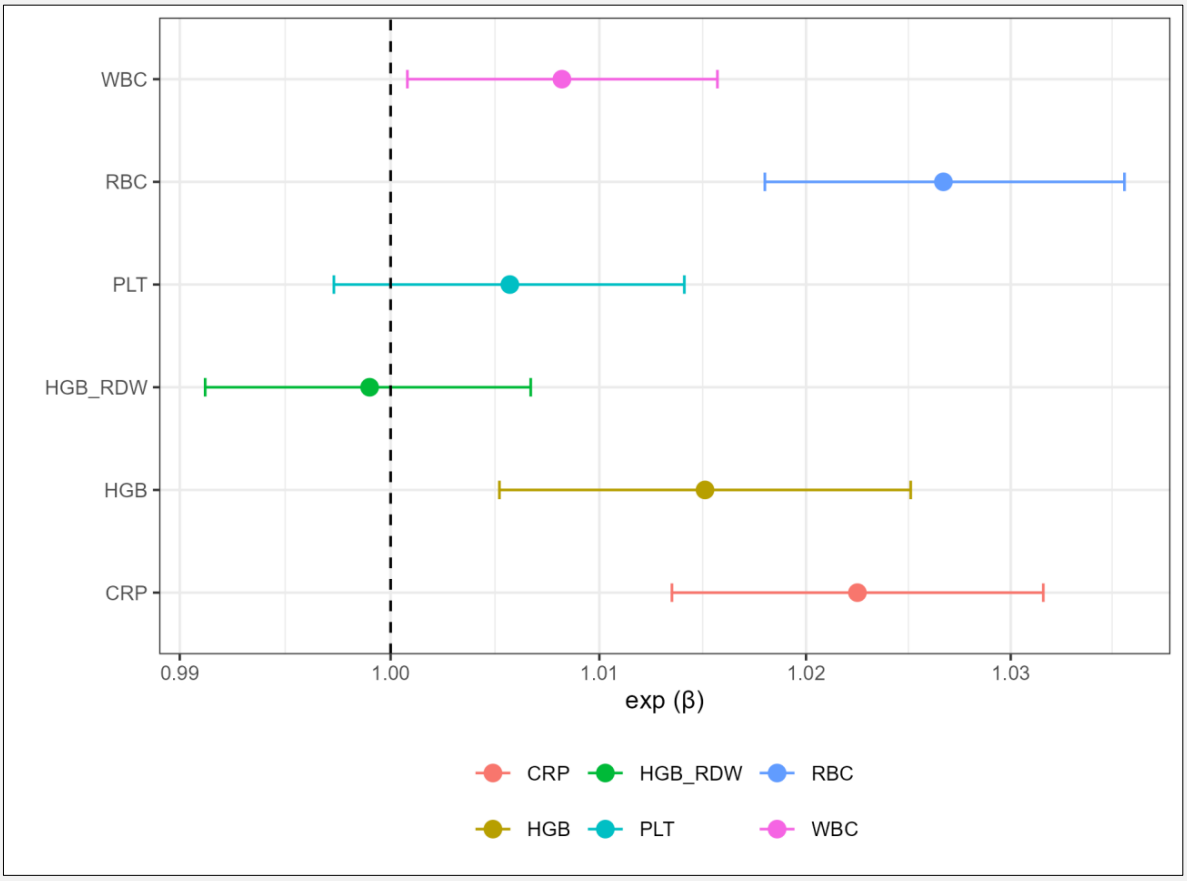

Figure 5. Associations between hematological parameters and serum uric acid.

The forest plot indicates the adjusted effect estimates with 95% confidence rating of each of the hematological parameters. The null association is represented by the vertical reference line. The estimated association of SUA with the modeled scale that is either a positive value or a negative one is depicted as an approximation towards the right or the left of this line.

of the renal biomarker led to the appearance of the apparent strength of the total correlation. This tendency is in line with the fact that renal biomarkers might neutralize or obscure the direct hematological-SUA correlation in this statistical framework.

Comparisons between Scr- and the BUN-based mediation models revealed that the two renal biomarkers might signify varying properties of the renal physiology, which might be of concern to the SUA variation. Though Scr related components were more eminent in comparison to others of the hematological indices the BUN related components were more eminent in comparison to others, again suggesting the potentiality of a disparity in glomerular and tubular related correlational constructs. Weak, non-significant indirect effects, however, through Scr or BUN in small amounts of hematological parameters indicated some statistical mediation in the present models.

Taken together, these findings indicate that renal biomarkers account for part, but not all, of the observed hematological-SUA associations, and that this contribution varies across biomarkers. The mediation results should therefore be viewed as descriptive and hypothesis-generating, highlighting potential interaction structures among hematological parameters, renal function indicators, and SUA that warrant further investigation in longitudinal or experimental studies.

The correlations between blood cell parameters (such as RBC, PLT, WBC, HGB, CRP, HGB/RDW), parameters of renal functions (Scr as Serum Creatinine and BUN as Blood Urea Nitrogen), and SUA are depicted by this figure. Arrows represent statistical associations observed in survey-weighted models and mediation-based decompositions. This conceptual framework does not imply causality. This framework is not a contributory model but a conceptual overview of perceived relation-

ships. This schematic gives the visual description of the complicated interactions within the blood, kidney, and SUA.

Summary of association patterns across hematological parameters

To provide a synthesized overview of correlations between hematological parameters and SUA, the adjusted estimates of the effects of these variables were summarised with the help of forest plots (Figure 5). The visualization assists in contrasting direction, relative strength, and accuracy of connection between parameters in the shared analytics architecture.

Effects were generally small in models and the intersection between confidence intervals of a mixture of hematological indices was extensive. Some of the parameters were more consistently related to SUA across ways of analysis, and some of the parameters were further revealed to have less stable or weaker relationships with SUA when adjusted. It is noteworthy that given NHANES was population-representative and had a large sample size, statistical significance should be viewed in comparison to effect size and consistency as compared to a strong biological impact.

Overall, the forest plot shows that a number of hematological parameters are correlated to SUA on the population level, but none of them is independent. Instead, the specified tendencies are reflective of a distributed association model, in which erythrocyte-associated, inflammatory, and renal-associated indicators interoperate to modulate SUA. These findings demonstrate the relevance of applying a mixture of routine hematological and renal markers to characterize SUA risk conditions and not single biomarkers.

DISCUSSION

In the present cross-sectional national representative study of relevant hematological parameters in the U.S., we examined the relationships between these parameters and SUA; we also investigated the extent to which commonly used renal biomarkers, including Scr and BUN, would be located to give a statistically significant contribution to the correlations. We found that population-wide changes in variability of SUA are complex with the utilization of erythrocyte-related indices, inflammatory markers, and the renal function index together.

A key observation was the presence of non-linear relationships between RBC count and SUA in limited cubic spline examinations. The association between RBC and SUA was curved rather than being linear across the spectrum of exposures, implying that average linear approximations might be insufficient to detect a localized change in the strength of the association. It was also observed that the same non-linear features occurred on the HGB/RDW. The given trends are consistent with previous experimental and epidemiological literature according to which the processes involving erythrocytes may be associated with the SUA metabolism under various physiological conditions. It is worth noting that the overall effects sizes obtained due to the use of linear models were low, which implies that the association is unlikely to be significant individual-level effects, but simple population-level trends.

Although the fully adjusted linear models did not show a statistically significant association between HGB/RDW and SUA, restricted cubic spline modeling indicated a non-linear pattern in their relationship. This suggests that HGB/RDW may exhibit changes in SUA across its distribution that are not captured by average linear estimates. Nevertheless, these non-linear features should be interpreted as exploratory rather than evidence of a consistent linear association and should be validated in future studies. Future longitudinal or mechanistic studies are needed to clarify whether these non-linear exposure-response patterns have biological significance. RDW has been widely regarded as an indicator of erythrocyte heterogeneity and has been linked to oxidative stress and systemic inflammation in previous studie [21]. In addition, previous work has reported associations between RDW-related indices and SUA levels or renal dysfunction, suggesting that erythrocyte heterogeneity may be linked to altered urate handling under certain physiological or pathological conditions [22]. Our findings extend this body of evidence by demonstrating population-level associations between HGB/RDW and SUA in a nationally representative sample. However, given the cross-sectional design, these associations should be interpreted as correlational rather than indicative of specific biological mechanisms or causal pathways. Inflammatory markers, including WBC count and CRP, demonstrated statistically significant but relatively weak associations with SUA. Restricted cubic spline analyses suggested the existence of non-linear or saturating relationships, particularly in the example of CRP, which suggests that the strength of the relationship may vary at various levels of systemic inflammation. These findings conform to earlier reports indicating that low-grade inflammatory conditions are associated with SUA change, and they also indicate that the contribution of markers that relate to inflammation can only explain a small proportion of SUA change at the population level.

Analyses through mediation also postulated that renal biomarkers partly explain the results of the observed relationships between hematological parameters and SUA. Both the Scr-based and BUN-based models presupposed that there might be middle associative factors of hematological conditioning and concentrations of SUA in renal functioning. In several instances, direct and indirect factors played contrary roles and contributed to the suppression-type tendencies instead of direct mediation. These findings suggest that Scr and BUN could reflect disparate renal physiological actions that are engaged in the change in SUA, and should not be viewed as the considerations of equality in a single

pathway. The results of mediation show, therefore, by no means more than an average relationship based on decomposing, but not a demonstration of causal associations or even time-statistical precedence. Methodologically, survey-weighted generalized linear models, constrained cubic spline analyses, sensitivity analyses, and mediation decomposition provide a wholesome way of defining the SUA-related correlates of the population-based data. This combined method enables the analysis of both average associations and the possible non-linear characteristics and takes due consideration of the complicated sampling structure of NHANES.

From a practical and research-oriented approach, we find that a combination of hematological and renal indicators used on a regular basis may bring in additional information insofar as the determination of change of the SUA is concerned in the realm of population health. This is because such indices are relatively inexpensive and widespread, and thus their combined study may help in the epidemiological stratification of risks and also the creation of hypotheses. Importantly, though, the existing results do not coincide with specific clinical interventions and threshold-related decision-making. Instead, they describe the fields of study that can be focused on by future research, such as the study of oxidative stress-related erythrocyte heterogeneity and urate transporter under different physiological conditions where urate is undergoing renal clearance. Such molecular evidence, together with the hematological and renal biomarkers regularly available today, can be better utilized to describe high-risk phenotypes of SUA in preclinical investigations of the future. These forms of integrative models may ultimately prove to be valuable to comprehend mechanistic knowledge, although their practical utility needs to be supported in longitudinal and interventional studies.

Overall, the present findings present the interplay of the hematologic status, renal function, and the inflammatory burden in the population in regulating SUA. While our analyses provide a comprehensive description of these associations, causal inference and therapeutic implications remain beyond the scope of this cross-sectional study.

Strength and limitations

This work has many strengths. To begin with, the mediation analysis was used to investigate association patterns with Scr and BUN that helped understand patterns of kidney issues related to the change in SUA. Moreover, with the use of the complex sampling design developed by NHANES, generalisable output over the whole population adds to a relevance in public health [23]. Moreover, the implementation of non-linear modeling provides the opportunity to explore potential non-linear patterns across biomarker distributions of hematological-SUA relationships and stratification of risk depending on individual parameters. Nevertheless, the study has its limitations. For one thing, the cross-sectional study design of the NHANES restricts the ability to infer conclusions of causal involvement since no temporal relationships between hematological changes, renal function, and SUA can be said to exist [24]. Longitudinal studies with repeated measurements of these same variables are warranted to confirm these pathways and evaluate their stability over time. Besides, residual confounding may remain (e.g., diet/purine intake, alcohol consumption, urate-lowering therapy or diuretics, and comorbidities), which are not fully captured in NHANES or were not included in the current models. For another, although major confounding effects were adjusted for, unmeasured factors such as genetic factors or dietary purine intake might partially explain the observed associations [25,26]. Moreover, given its short half-life, single-time-point assessments of CRP concentrations also underestimate the cumulative effect of chronic inflammation on SUA levels [27]. Irrespective of these shortcomings, this study gives a population-level account that can assist in giving a future study direction and highlights the need to carry out integrated research to unravel more intricate facets of the SUA regulation [28].

CONCLUSION

In this cross-sectional, nationally representative analysis of U.S. adults from NHANES 2015 - March 2020 (pre-pandemic), SUA exhibited coordinated associations with routinely measured hematological and inflammatory markers. RBC presented the highest positive relationship with SUA in adjusted models, and WBC and CRP remained positively associated with SUA in the fully adjusted model, although the effect sizes were modest. There is weak evidence of an independent relationship with PLT. It is interesting to note that spline-based analyses focused on non-linear trends - the principal one distinguishing a U-shaped correlation between RBC and SUA and a non-linear exposure response trend of the HGB/RDW, which implied that localized change in biomarker distributions could be obscured by the average linear estimates. The proposed roles of exploratory mediation include that renal biomarkers (Scr and BUN) provide a variable contribution to hematological-SUA relationships and may hide complex (including suppression-type) actions in favor of being uniform intermediaries.

Together with these findings, these findings advance reasons to consider routine blood indices alongside renal biomarkers as critical to elucidate the direction, not to mention causality, of the alteration of SUA in clinical and community settings and emphasize the importance of longitudinal and mechanistic studies.

Institutional Review Board Statement:

This study was a secondary analysis of publicly available, de-identified NHANES data. NHANES protocols were approved by the National Center for Health Sta-

tistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent.

Informed Consent Statement:
The NHANES study involved informed consent from the subjects who participated in the study.

Data Availability Statement:
NHANES data are publicly available from the National Center for Health Statistics website.

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Declaration of Generative AI in Scientific Writing:
The authors declare that no Generative AI or AI-assisted technologies were used in the writing of this manuscript.

Declaration of Interest:
The authors declare no conflict of interest.

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