Original Article

# Serum albumin and hypertension: The mediating roles of BMI, C-reactive protein and extracellular fluid

Yan Wang BM[1], Huaiyu Hao BM[2], Qiang Lu MM[1], Lei Zhang MM[1]

[1]*Clinical Nutrition Department, Liangxiang Hospital of Beijing Fangshan District, Beijing, China*
[2]*Neurosurgery Department, Liangxiang Hospital of Beijing Fangshan District, Beijing, China*

**Background and Objectives:** The relationship between serum albumin and hypertension has attracted much attention. We sought to further validate these findings and explore the underlying mediators. **Methods and Study Design:** This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES 1999-2004), including 19,507 participants. Multivariable weighted logistic were employed to investigate the association of serum albumin with hypertension. The potential mediating role of body mass index (BMI), C-reactive protein (CRP), and extracellular fluid (ECF) was explored. Secondary analyses included subgroup analyses and restricted cubic spline (RCS). **Results:** Serum albumin per 1 g/L increase was associated with 10% lower hypertension prevalence (OR=0.90, 95%CI:0.89–0.91, $p$<0.001). This remained significant after full adjustment (including age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, total saturated fatty acids [TSFA] intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, alanine aminotransferase [ALT], and NHANES cycle)(OR = 0.98, 95%CI: 0.96–1.00, $p$ = 0.031). No evidence of non-linearity was observed in the RCS analysis ($p$ for non-linearity = 0.708). BMI mediated 42.75% (95%CI: 38.19%–48.33%), CRP 12.24% (95%CI: 9.29%–15.43%), and ECF 4.05% (95%CI: 2.74%–5.43%) of the association (all $p$ <0.001). Results were robust in sensitivity analyses. **Conclusions:** The serum albumin levels were negatively associated with the prevalence of hypertension. Mediation analyses demonstrated a significant mediating effect of BMI, CRP and ECF, suggesting that serum albumin might be related to hypertension, potentially mediated by BMI, ECF, and CRP.

**Key Words: serum albumin, hypertension, body mass index, C-reactive protein, extracellular fluid**

## INTRODUCTION

Hypertension is a major global health challenge and the leading modifiable risk factor for cardiovascular diseases and related disabilities worldwide.[1] It is estimated that 10% of global healthcare expenditures are directly attributable to hypertension and its complications.[2] Therefore, the prevention and treatment strategies for hypertension deserve primary attention. Serum albumin is a multifunctional protein that maintains human physiology.[3] It plays a primary role in maintaining osmotic pressure[4] and is involved in the transport of numerous small molecules, including fatty acids, hormones, and drugs.[5-8] Furthermore, it has emerged as a crucial factor in the body's defense mechanisms against oxidative stress.[9-11]

A study showed an inverse association between worsening circadian blood pressure and the serum albumin concentration in patients with essential hypertension.[12] Another survey of people undergoing health screening in Japan found that low serum albumin levels were a significant predictor of new-onset hypertension.[13] Moreover, a cohort study in China demonstrated that elevated serum albumin concentration was significantly associated with a reduced risk of hypertension.[14] These studies suggest a relationship between serum albumin and blood pressure, necessitating further exploration of the underlying factors contributing to this association to better understand this relationship.

Body mass index (BMI), is a simple anthropometric measure interrelating height and weight that is commonly used to identify the presence and severity of excess body fat.[15] Extracellular fluid (ECF) has been proposed as a potential preclinical disease marker, as early alterations in body water distribution may occur in the initial stages of disease progression.[16] C-reactive protein (CRP) is a widely recognized sensitive biomarker for inflammation, with elevated levels typically signaling the presence of inflammatory processes within the body.[17] Prior investigations established associations between BMI, ECF volume, and CRP concentration with hypertension.[18-20] Furthermore, serum albumin levels have been shown to be related to BMI,

**Corresponding Author:** Dr Huaiyu Hao, Liangxiang Hospital of Beijing Fangshan District, 45 Gongchen Avenue, Fangshan District, Beijing 102488, China
Tel: +86-13621116501
Email: yingyangfs@sina.com
Electronic supplementary information available. See apjcn.qdu.edu.cn/35_1_60_supp.pdf
Manuscript received 25 May 2025. Initial review completed 03 August 2025. Revision accepted 17 November 2025.
doi: 10.6133/apjcn.202602_35(1).0006

ECF volume, and CRP concentration.[21-23] Thus, we hypothesize that higher serum albumin levels may be associated with lower risk of hypertension, potentially mediated by BMI, ECF, and CRP.

Therefore, the objective of this study was to investigate the association between serum albumin and hypertension by analyzing data from the National Health and Nutrition Examination Survey (NHANES). Additionally, the study aimed to explore the potential mediating role of BMI, ECF and CRP in this association, thereby providing a more comprehensive understanding of the underlying factors contributing to this relationship.

## METHODS

### *Data sources*

Data analysis was conducted from November 1, 2024 to February 28, 2025. Data were collected from public files for 3 consecutive NHANES data cycles from 1999 to 2004. NHANES is a continuous cross-sectional observational study that collects health data from a representative sample of the non-institutionalized population in the United States. The NHANES study protocol (#98-12) received approval from the Institutional Review Board of the National Center for Health Statistics (NCHS), with all participants providing consent. Utilizing a sophisticated multistage probability cluster design for data collection and study methodology, NHANES ensures the acquisition of comprehensive and reliable information. Our secondary analysis followed the STROBE guidelines for studies, and did not require additional institutional review board approval. Detailed information regarding NHANES' methodology and ethics is available on the Centers for Disease Control and Prevention (CDC) and NCHS website (https://www.cdc.gov/nchs/nhanes/about/erb.html).

### *Study design and population*

For this cross-sectional study, we included participants with hypertension data and excluded individuals with missing data for serum albumin. Of the 31,126 participants, 11,619 were excluded due to lack of data on hypertension (n = 6,082) and albumin (n = 4,817). Thus, the final analysis comprised 19,507 eligible participants. Figure 1 illustrates the detailed participant enrollment process and the final analytic sample.

### *Hypertension*

As blood pressure measurements taken during a single visit may yield false-positive results, guidelines recommend confirming a hypertension diagnosis across two or more separate visits.[24] In this study, we therefore evaluated hypertension in two ways: (1) We determined whether participants had hypertension based on their responses to specific questions in the Blood Pressure and Cholesterol Questionnaire.[25] Participants were asked: "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure? (Question 1) " and "Were you told on two or more different visits that you had hypertension, also called high blood pressure? (Question 2)" Individuals were classified as having hypertension if they answered "yes" to both questions. (2) In the mobile examination center (MEC) blood pressures were measured by trained physician examiners using a mercury sphygmomanometer. The mean of all available measurements was used to calculate systolic blood pressure (SBP) and diastolic blood pressure (DBP). Individuals with SBP level of 140 mmHg or higher, DBP level of 90 mmHg or higher, were classified as having hypertension if they answered "yes" to Question 1.

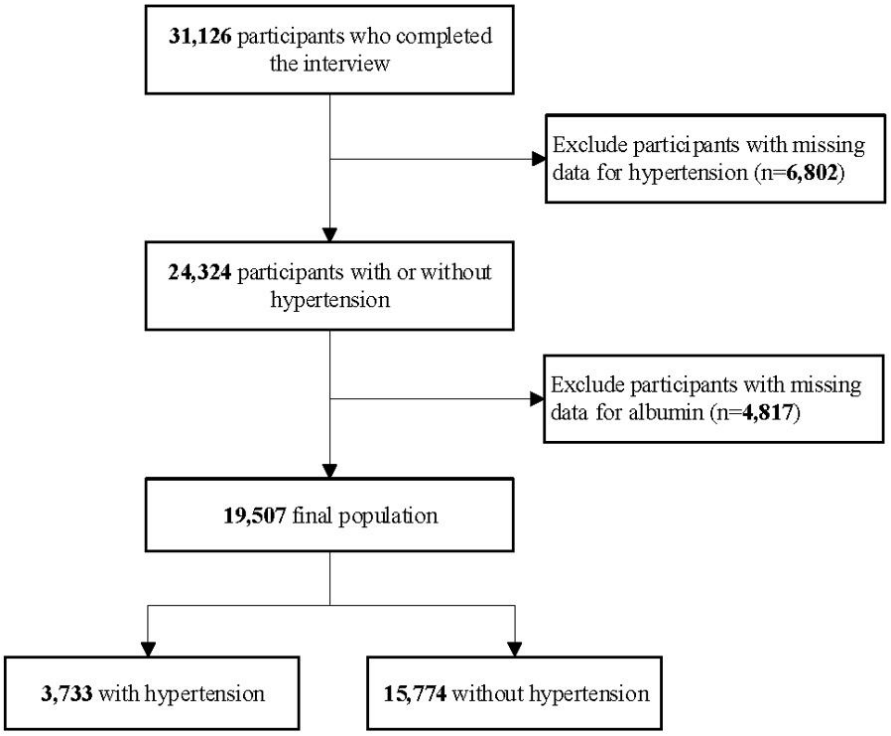


**Figure 1.** The study's flow diagram.

***Serum albumin***

The samples were always stored at an appropriate freezing temperature of -30 °C before being sent to the National Environmental Health Center for testing. After processing and storage, the serum samples were shipped to a collaborating laboratory for analysis.[26] Analyzed using a Hitachi Model 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN).[27] The DcX800 method was used as the standard for measuring the concentration of albumin. In this reaction, albumin reacts with bromocresol purple reagent to form a complex, and the absorbance at 600 nm is tested and monitored with respect to the albumin concentration. The change in absorbance is proportional to the concentration of albumin in the sample. Detailed procedures regarding sample collection and processing can be obtained through the NHANES Laboratory or Medical Technologist Procedures Manual.[26]

***Body mass index***

Body mass index was calculated as weight (kg) / height $(m)^2$.

***C-reactive protein***

C-reactive protein levels were measured by latex-enhanced nephelometry on a Dade Behring Nephelometer II Analyzer (BNII).[28]

***Extracellular fluid***

Extracellular fluid data was collected using the HYDRA ECF/ICF Bio-Impedance Spectrum Analyzer (Model 4200) manufactured by Xitron Technologies, Inc. (San Diego, California) during MEC testing.[29] Bioelectrical impedance analysis (BIA) enables a noninvasive measurement of body composition, as well as derived measurements of extra-/intracellular fluid, and total body water.[30-34]

***Covariates***

The covariates in this analysis were as follows: Sociodemographic factors included age, sex, race/ethnicity (non-Hispanic White, or other races), and educational level (<9 years, 9–12 years, or >12 years).[35] Lifestyle factors included smoking status (never, defined as fewer than 100 cigarettes smoked in a lifetime; former, defined as having quit smoking after smoking ≥100 cigarettes; and current)[35] and drinking status, which was defined by consuming ≥12 alcoholic drinks in any given year.[36] Dietary intake was obtained through a 24-hour dietary recall interview administered before the examination at the MEC and included sodium, potassium, fat, total saturated fatty acids (TSFA), carbohydrate, protein and energy intake.[35] Clinical conditions included diabetes, and coronary heart disease, each determined by self-report of a physician's prior diagnosis. Laboratory measurements included alanine aminotransferase (ALT), which was analyzed using a Beckman Synchron LX20 (Beckman Coulter)[37] and Creatinine, which was analyzed using a Hitachi Model 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN).[27]

***Statistical analysis***

Following NHANES analytic guidelines, we incorporated the complex sampling design and dietary sample weights into our study. The sampling weights were computed as follows: weights for 1999–2002 were assigned as two-thirds of the four-year dietary weight, and weights for 2003–2004 were one-third of the two-year dietary weight. Characteristics related to hypertension were delineated. Continuous variable data were presented using mean (standard deviation, SD) or median (interquartile range, IQR), while categorical variables were conveyed through numerical counts and percentage frequencies (%). Chi-squared test with Rao & Scott's second-order correction was applied to analyze categorical data, whereas the Wilcoxon rank-sum test for complex survey samples was employed for continuous variables to evaluate divergent disparities. The variance inflation factor (VIF) was used to assess potential multicollinearity among covariates, with a VIF value ≥ 5 indicating the presence of significant multicollinearity. Furthermore, multiple imputation was performed on covariates with missing values.

We utilized multivariable weighted logistic regression models to investigate the association between serum albumin and hypertension. Three models were constructed: Model 1 adjusted for age, sex, race/ethnicity, education level, smoking status, drinking status, and NHANES cycle. Model 2 additionally adjusted for sodium intake, potassium intake, fat intake, TSFA intake, energy intake, protein intake, and carbohydrate intake. Model 3 further included diabetes, coronary heart disease, creatinine, and ALT.

We employed restricted cubic spline (RCS) analysis with 3 knots, dividing the range of the albumin at the 10th, 50th, and 90th quantiles to fit curves and evaluate potential non-linear association between serum albumin and hypertension. Additionally, we further explored potential mediators of BMI, ECF and CRP in the association between serum albumin and hypertension. Mediation analyses were conducted using the Sobel test, Bootstrap, and the quasi-Bayesian Monte Carlo method with 1000 simulations based on normal approximation.[38]

Furthermore, potential modifications of the relationship between serum albumin and hypertension were assessed, including the following variables: age (<20 vs. 20-45 vs. 45-65 vs. ≥65 years), sex, race/ethnicity (non-Hispanic white vs. others), education level (<9 vs. 9-12 vs. >12 years), smoking status (never smoker vs. former smoker vs. current smoker), drinking status (drinker vs. non-drinker), sodium intake (<2300 vs. ≥2300 mg/d), potassium intake (3500 vs. ≥3500 mg/d), fat intake (<70 vs. ≥70 g/d), TSFA intake (<20 vs. ≥20 g/d), protein intake (<80 vs. ≥80 g/d), carbohydrate intake (<280 vs. ≥280 g/d), energy intake (2200 vs. ≥2200 kcal/d), diabetes (yes vs. no), coronary heart disease (yes vs. no), creatinine (<70.0 vs. ≥70.0 umol/L), and ALT (<20.0 vs. ≥20.0 U/L). Heterogeneity among subgroups was assessed by multivariate logistic regression, and interactions between subgroups and serum albumin were examined by likelihood ratio testing, and results were visualized using a forest plot. To evaluate the robustness of our results, we excluded participants with hypoproteinemia, serum albumin <30.0g/L, for sensitivity analyses.

Statistical analyses were conducted using R software (v4.2.2; http://www.Rproject.org), along with the R survey package (v4.1-1) and Free Statistics software (v2.1; Beijing Free Clinical Medical Technology Co., Ltd.). A two-tailed *p*-value of less than 0.05 was considered statistically significant.

## RESULTS

### *Characteristics of the participants*

Table 1 presents the baseline characteristics of the 19,507 study participants. The mean (SD) age of the study participants was 42.3 (19) years, with 3,733 cases (21.1%) identified as hypertension. Notably, individuals with hypertension were more likely to be older, women, non-Hispanic white, have lower educational attainment, be former smokers and non-drinkers, have lower nutrient intakes (sodium, fat, TSFA, energy, protein, and carbohydrate), have a higher incidence of diabetes and coronary heart disease, have higher creatinine, ALT, BMI, CRP and ECF, and have lower serum albumin. The statistical results of dietary intake by cycle indicated the consumption of sodium, fat, TSFA, protein and energy showed an increasing trend (Supplementary Table 1). Extrapolated to the national level, these results represent approximately 219 million individuals in the U.S.

### *Association between serum albumin and hypertension*

As shown in Table 2, each 1 g/L increase in serum albumin was associated with a 10% decrease in the prevalence of hypertension (OR = 0.90, 95%CI: 0.89–0.91, $p < 0.001$). When adjusting for all covariates including age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, ALT, and NHANES cycle, the above associations remained significant (OR = 0.98, 95%CI: 0.96–1.00, $p = 0.031$). After grouping serum albumin, in the fully adjusted model, participants with Q3 (44-46g/L), and Q4 (≥ 46g/L) were significantly negatively associated with the prevalence of hypertension (OR = 0.79, 95%CI: 0.64-0.96; OR = 0.8, 95%CI: 0.65–0.99). Meanwhile, no evidence of non-linearity was observed in the RCS analysis ($p$ for non-linearity = 0.708) (Figure 2).

### *Stratified analyses based on variables*

Stratified analyses were conducted to evaluate potential effect modifiers in the relationship between serum albumin and hypertension (Figure 3, Supplementary Figure 1). Subgroup analyses were conducted on samples categorized by age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, and ALT. No significant interactions were detected across any subgroups ($p > 0.05$), indicating that the negative association between serum albumin and hypertension was largely consistent across these factors. Additionally, when accounting for multiple testing, a *p*-value of less than 0.05 for the interaction with potassium intake may not represent statistical significance.

### *Sensitivity analysis*

Sensitivity analyses were performed to test the stability of association results. After excluding participants with hypoproteinemia (serum albumin <30.0g/L), the associations between serum albumin and hypertension (crude model: OR = 0.9, 95%CI: 0.89–0.91; adjusted model: OR = 0.98, 95%CI: 0.96–1.00. After grouping serum albumin, crude model: OR = 0.5, 95%CI: 0.42–0.60; OR = 0.35, 95%CI: 0.29–0.41; adjusted model: OR = 0.78, 95%CI: 0.64–0.96; OR = 0.8, 95%CI: 0.65–0.99) remained stable (Supplementary Table 2).

### *Mediation and additional analysis*

Figure 4 illustrates the potential mediating roles of BMI, CRP and ECF in the association between serum albumin and hypertension. We found that higher serum albumin was associated with lower BMI (β= -0.42, 95%CI: -0.44 – -0.39, $p < 0.001$), CRP (β= -0.06, 95%CI: -0.06 – -0.05, $p < 0.001$) and ECF (β= -0.11, 95%CI: -0.12 – -0.09, $p < 0.001$). Meanwhile, higher BMI (OR = 1.09, 95%CI: 1.08–1.10, $p < 0.001$), CRP (OR = 1.11, 95%CI: 1.07–1.16, $p < 0.001$) and ECF (OR = 1.09, 95%CI: 1.08–1.10, $p < 0.001$) were significantly associated with a higher risk of hypertension. Furthermore, significant mediating effects of BMI (proportion of mediation: 42.75%, 95%CI: 38.19%–48.33%, $p < 0.001$), CRP (proportion of mediation: 12.24%, 95%CI: 9.29%–15.43%, $p < 0.001$) and ECF (proportion of mediation: 4.05%, 95%CI: 2.74%–5.43%, $p < 0.001$) in the association between serum albumin and hypertension were observed.

## DISCUSSION

In this cross-sectional study, we demonstrated that serum albumin levels were significantly and negatively associated with the prevalence of hypertension. Sensitivity analyses supported the robustness of this relationship, underscoring the importance of serum albumin as a potential protective indicator for hypertension. Furthermore, a significant mediating effect of BMI, ECF, and CRP in the association between serum albumin and hypertension was observed.

The association between serum albumin and hypertension has been confirmed by previous studies. For instance, Eiji Oda conducted a 4-year longitudinal study of 855 women and 1,385 men within a Japanese health screening population, a decreased serum albumin level was found to be a significant predictor of hypertension. The incidence of hypertension significantly decreased with increasing albumin levels.[13] Yinxing Liu et al. conducted a cohort study in China involving 11,946 non-hypertensive adults aged 30 to 60 years with an average follow-up period of 4.3 years. They found that a moderate increase in serum albumin concentration was significantly associated with a reduced risk of hypertension in individuals aged ≥45 years with normal weight.[14] These findings align with our results, where we observed that high serum albumin levels were associated with low hypertension prevalence, suggesting that serum albumin may play a protective role in the occurrence and development of hypertension. Notably, our findings also indicate that BMI, ECF, and CRP mediate the relationship between serum

**Table 1.** Characteristics of participants

| Characteristics | Total | Without hypertension | Hypertension | *p* value |
|---|---|---|---|---|
| Unweighted sample size, n | 19507 | 15774 | 3733 | |
| Weighted sample size, n (in millions, %) | 219 | 173 (78.9) | 46 (21.1) | |
| Age (years), Mean (SD) | 42.3 (19.0) | 38.2 (17.7) | 57.7 (15.6) | <0.001*** |
| Sex, n (%) | | | | 0.046* |
| Men | 9474 (48.7) | 7739 (49.4) | 1735 (46.3) | |
| Women | 10033 (51.3) | 8035 (50.6) | 1998 (53.7) | |
| Race/ethnicity, n (%) | | | | <0.001*** |
| Non-Hispanic white | 8304 (71.1) | 6364 (70.2) | 1940 (74.6) | |
| Others | 11203 (28.9) | 9410 (29.8) | 1793 (25.4) | |
| Education level (years), n (%) | | | | <0.001*** |
| < 9 | 2516 (6.3) | 1795 (5.3) | 721 (10.0) | |
| 9–12 | 8306 (39.2) | 6722 (38.1) | 1584 (43.3) | |
| >12 | 8685 (54.5) | 7257 (56.6) | 1428 (46.7) | |
| Smoking status, n (%) | | | | <0.001*** |
| Never | 10087 (50.0) | 8277 (50.7) | 1810 (47.6) | |
| Former | 4040 (23.5) | 2739 (20.6) | 1301 (34.3) | |
| Current | 5380 (26.5) | 4758 (28.8) | 622 (18.1) | |
| Drinking status, n (%) | 13592 (71.6) | 11250 (73.5) | 2342 (64.5) | <0.001*** |
| Sodium intake (mg/d), Mean (SD) | 3467 (1874) | 3537 (1899) | 3207 (1753) | <0.001*** |
| Potassium intake (mg/d), Mean (SD) | 2727 (1368) | 2742 (1385) | 2668 (1297) | 0.059 |
| Fat intake (g/d), Mean (SD) | 83.0 (47.2) | 84.7 (47.7) | 76.7 (44.9) | <0.001*** |
| TSFA intake (g/d), Mean (SD) | 27.5 (17.2) | 28.2 (17.4) | 24.5 (15.8) | <0.001*** |
| Carbohydrate intake (g/d), Mean (SD) | 278 (139) | 288 (142) | 242 (121) | <0.001*** |
| Protein intake (g/d), Mean (SD) | 82.0 (42.7) | 83.5 (43.3) | 76.5 (39.9) | <0.001*** |
| Energy intake (kcal/d), Mean (SD) | 2222 (1044) | 2283 (1059) | 1994 (952) | <0.001*** |
| Diabetes, n (%) | 79 (6.3) | 80 (3.4) | 72 (17.0) | <0.001*** |
| Coronary Heart Disease, n (%) | 277 (3.4) | 288 (1.6) | 232 (10.4) | <0.001*** |
| Creatinine (umol/L), Mean (SD) | 73.9 (34.4) | 71.0 (20.9) | 84.8 (61.7) | <0.001*** |
| ALT (U/L), Median (IQR) | 21(16, 28) | 20 (15, 28) | 22 (17, 30) | <0.001*** |
| BMI (kg/m$^2$), Mean (SD) | 27.5 (6.41) | 26.6 (5.98) | 30.7 (6.93) | <0.001*** |
| CRP (mg/dL), Median (IQR) | 0.18 (0.06, 0.42) | 0.15 (0.06, 0.36) | 0.30 (0.14, 0.69) | <0.001*** |
| ECF (L), Mean (SD) | 16.3 (3.74) | 16.1 (3.69) | 17.1 (3.84) | <0.001*** |
| Serum albumin (g/L), Mean (SD) | 43.6 (3.49) | 43.9 (3.46) | 42.6 (3.39) | <0.001*** |

ALT, alanine aminotransferase; ECF, extracellular fluid; CRP, C-reactive protein; TSFA, total saturated fatty acids.
[†]Data were presented as unweighted number (weighted percentage) for categorical variables, mean (SD, standard deviation) or median (IQR, interquartile range) for continuous variables. Differences in baseline characteristics were compared using the $\chi^2$ test for categorical variables and the t-test or Wilcoxon rank-sum test for continuous variables.
*$p$<0.05, **$p$<0.01, ***$p$<0.001.

**Table 1.** Characteristics of participants (cont.)

| Characteristics | Total | Without hypertension | Hypertension | *p* value |
|---|---|---|---|---|
| Serum albumin, n (%) | | | | <0.001*** |
| Q1 (<41) | 3814 (16.8) | 2726 (14.5) | 1088 (25.0) | |
| Q2 (41-44) | 5815 (30.1) | 4485 (28.9) | 1330 (34.7) | |
| Q3 (44-46) | 4498 (24.0) | 3734 (24.7) | 764 (21.3) | |
| Q4 (≥46) | 5380 (29.2) | 4829 (31.9) | 551 (19.0) | |

ALT, alanine aminotransferase; ECF, extracellular fluid; CRP, C-reactive protein; TSFA, total saturated fatty acids.
†Data were presented as unweighted number (weighted percentage) for categorical variables, mean (SD, standard deviation) or median (IQR, interquartile range) for continuous variables. Differences in baseline characteristics were compared using the $\chi^2$ test for categorical variables and the t-test or Wilcoxon rank-sum test for continuous variables.
*$p$<0.05, **$p$<0.01, ***$p$<0.001.

**Table 2.** Association between serum albumin and hypertension

| Variable | Total | Event (%) | Non_adjusted model | | Model 1 | |
|---|---|---|---|---|---|---|
| | | | OR (95%CI) | *p* value | OR (95%CI) | *p* value |
| Albumin | 19507 | 3733 (19.1) | 0.90 (0.89,0.91) | <0.001*** | 0.96 (0.95,0.98) | <0.001*** |
| Albumin (Quartiles) | | | | | | |
| Q1 (<41) | 3814 | 1088 (28.5) | 1(Ref) | | 1 (Ref) | |
| Q2 (41-44) | 5815 | 1330 (22.9) | 0.70 (0.61,0.80) | <0.001*** | 0.77 (0.64,0.92) | 0.006** |
| Q3 (44-46) | 4498 | 764 (17.0) | 0.50 (0.42,0.60) | <0.001*** | 0.70 (0.58,0.85) | <0.001*** |
| Q4 (≥46) | 5380 | 551 (10.2) | 0.35 (0.29,0.41) | <0.001*** | 0.69 (0.56,0.86) | 0.001** |
| Trend.test | | | | <0.001*** | | 0.002** |

| Variable | Model 2 | | Model 3 | |
|---|---|---|---|---|
| | OR (95%CI) | *p* value | OR (95%CI) | *p* value |
| Albumin | 0.96 (0.95,0.98) | <0.001*** | 0.98 (0.96,1.00) | 0.031* |
| Albumin (Quartiles) | | | | |
| Q1 (<41) | 1 (Ref) | | 1 (Ref) | |
| Q2 (41-44) | 0.76 (0.63,0.92) | 0.007** | 0.84 (0.69,1.02) | 0.075 |
| Q3 (44-46) | 0.70 (0.57,0.85) | 0.001** | 0.79 (0.64,0.96) | 0.021* |
| Q4 (≥46) | 0.69 (0.56,0.86) | 0.002** | 0.80 (0.65,0.99) | 0.039* |
| Trend.test | | 0.002** | | 0.039* |

ALT, alanine aminotransferase; TSFA, total saturated fatty acids.
†Model 1 was adjusted for age, sex, race/ethnicity, education level, smoking status, drinking status, and NHANES cycle.
‡Model 2 was adjusted for age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, and NHANES cycle.
§Model 3 was adjusted for age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, ALT, and NHANES cycle.
*$p$<0.05, **$p$<0.01, ***$p$<0.001.

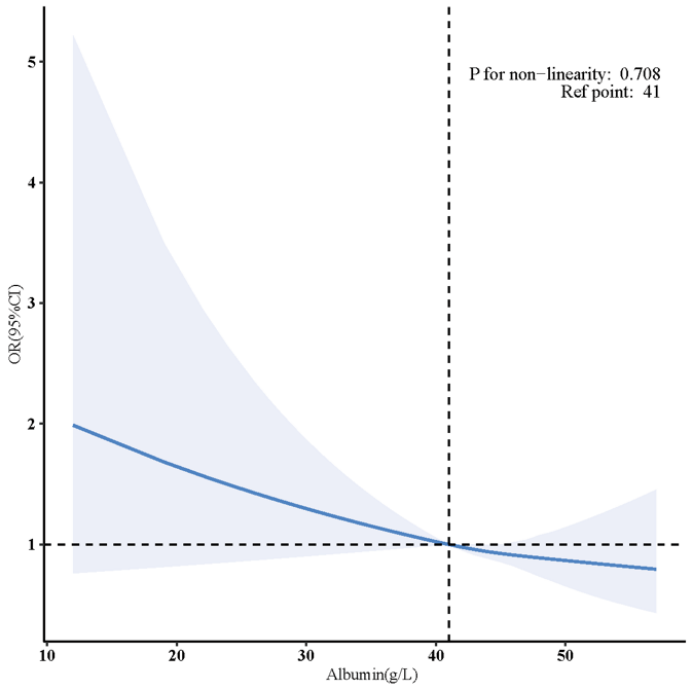


**Figure 2.** Association between serum albumin and hypertension odds ratio after full adjustment. The solid line represents the smoothed odds ratio (OR) for hypertension risk as albumin changes, and the shaded area indicates the 95% confidence interval (CI). Statistical analysis revealed a linear relationship between albumin and hypertension risk ($p$ for non-linearity = 0.708). Adjusted for age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, ALT, and NHANES cycle. ALT, alanine aminotransferase; TSFA, total saturated fatty acids

albumin and hypertension. This discovery provides a more comprehensive and novel perspective.

Prior studies have demonstrated that BMI, ECF and CRP were not only related to serum albumin levels, but also to hypertension prevalence. Serum albumin serves as a key biochemical marker of nutritional status and is synthesized exclusively in the liver.[39,40] An appropriately elevated level of serum albumin may be a positive sign of adequate nutritional status and healthy liver function. Through metabolic regulation, it mitigates adipose tissue accumulation (resulting in lower BMI),[41] helps maintain plasma osmotic pressure (reducing ECF expansion),[42] and suppresses inflammatory responses (decreasing CRP concentrations).[43] Meanwhile, the relationship between hypertension and overweight or obesity has been well documented across most racial, ethnic, and socioeconomic groups, although the association between blood pressure values and BMI depends on age, sex, type of obesity, and racial variations.[44,45] Growing evidence suggests that fluid overload, or increased ECF volume, plays a pivotal role in the pathophysiology of hypertension. The impact of ECF on blood pressure in patients with chronic kidney disease (CKD) has been reported, demonstrating that reducing ECF is key to controlling hypertension.[46,47] Hypertension was closely associated with the activation of the immune system, with the inflammatory response playing a pivotal role.[48] The NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome played a key role in the development and progression of several cardiovascular diseases.[49] Experimental investigations have revealed that CRP actively and directly participates in the development of elevated blood pressure.[50] These findings are consistent with our conclusions, emphasizing the importance of incorporating BMI, ECF, and CRP into strategies for the early prevention and management of hypertension.

While this investigation possesses several merits, such as a thorough assessment of a nationally representative population sample, mediation analysis, and meticulous control for multiple confounders, certain limitations warrant acknowledgment. First, the cross-sectional design does not permit establishing a causal relationship between serum albumin and hypertension. Mediation analysis based on cross-sectional data could lead to unreliable results. Our conclusions are based on observed associations only. The identified mediation effects should be interpreted as associations consistent with a hypothesized causal model, rather than definitive evidence of causation. The observed patterns represent statistical mediation within the constraints of the study design. Further randomized longitudinal studies or controlled trials are needed to establish causality. Second, despite utilizing multivariable logistic regression models and performing thorough sensitivity testing across subgroups, persistent confounding effects may persist. While NHANES datasets encompass numerous variables, unmeasured confounders could remain. Third, the current analysis centers on an American sample. Assessing serum albumin-hypertension relationships in diverse populations would enhance the generalizability of these outcomes.

### *Conclusion*

This study revealed the association between serum albumin and the onset of hypertension. Mediation analyses

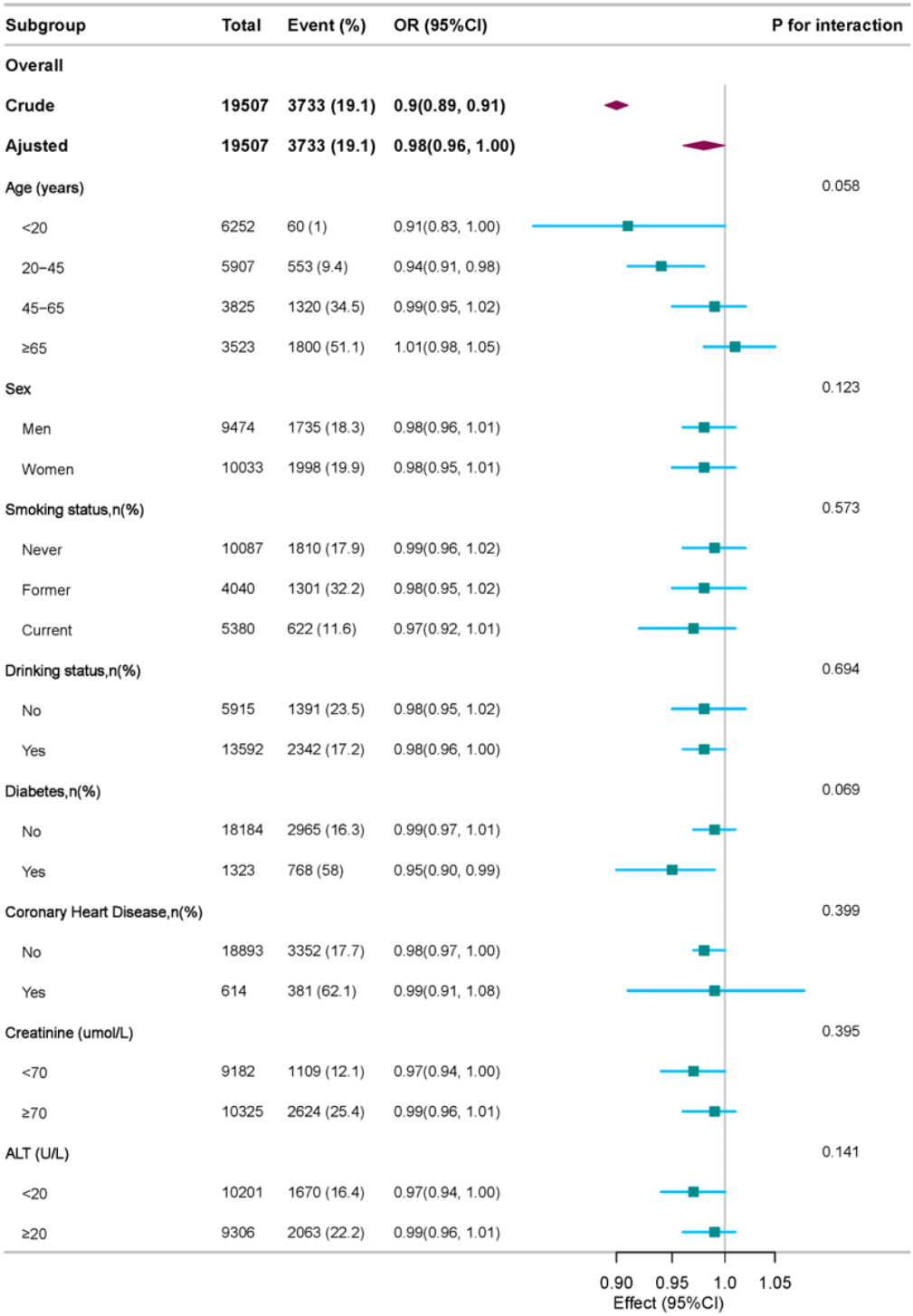


**Figure 3.** Association between albumin and hypertension according to basic features. †Except for the stratification component itself, each stratification factor was adjusted for all other variables, including age, sex, race/ethnicity, education level, smoking status, drinking status, sodium intake, potassium intake, fat intake, TSFA intake, carbohydrate intake, protein intake, energy intake, diabetes, coronary heart disease, creatinine, and ALT. ALT, alanine aminotransferase; TSFA, total saturated fatty acids

further explored the mediating role of BMI, CRP and ECF, which suggested that serum albumin might indirectly reduce the risk of hypertension by regulating obesity, inflammatory status and fluid balance. This finding provided a new perspective on the prevention and treatment of hypertension.

**ACKNOWLEDGEMENTS**

The authors would like to thank Dr Jie Liu and Dr Haibo Li for statistical support and study design consultations. Thank all staff for helping with the instruction of data analysis and writing. Additionally, the authors would like to thank the National Center for Health Statistics (NCHS) and the Centers for Disease Control and Prevention (CDC) for making NHANES data publicly available. The authors also acknowledge the efforts of NHANES participants and data collection staff.

**CONFLICT OF INTEREST AND FUNDING DISCLOSURES**

The authors declare no conflicts of interest.

No financial support was received from any institution or person for this study.

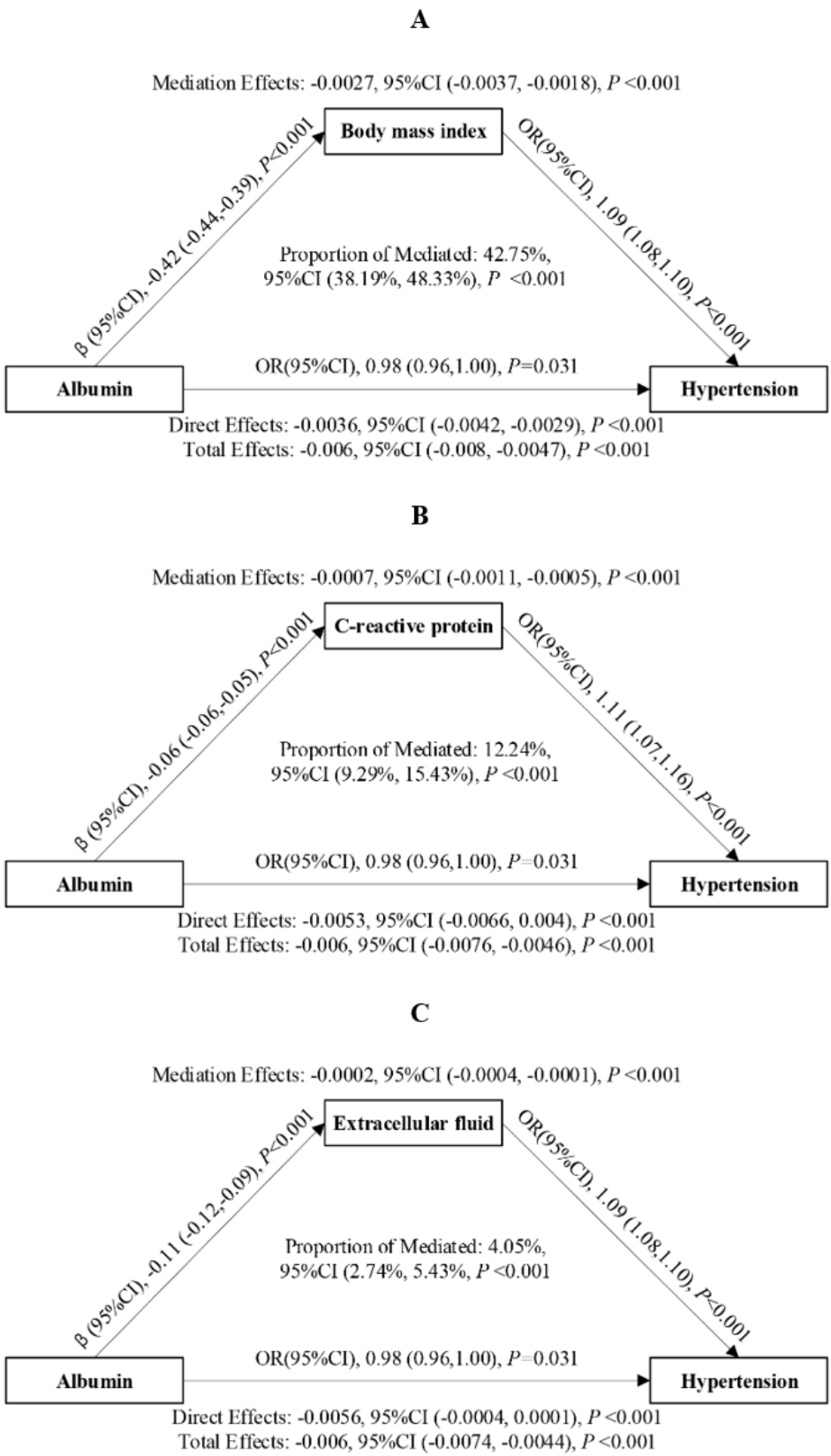


**Figure 4.** Mediation analysis of (A) Body mass index, (B) C-reactive protein, and (C) Extracellular fluid in the association between serum albumin and hypertension

**REFERENCES**


1. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol. 2021;18:785-802. doi:10.1038/s41569-021-00559-8
2. Campbell NRC, Schutte AE, Varghese CV, Ordunez P, Zhang XH, Khan T et al. São Paulo call to action for the prevention and control of high blood pressure: 2020. J Clin Hypertens (Greenwich). 2019;21:1744-52. doi:10.1111/jch.13741
3. Watanabe K, Kinoshita H, Okamoto T, Sugiura K, Kawashima S, Kimura T. Antioxidant Properties of Albumin and Diseases Related to Obstetrics and Gynecology. Antioxidants (Basel). 2025;14:55. doi:10.3390/antiox14010055
4. Evans TW. Review article: albumin as a drug--biological effects of albumin unrelated to oncotic pressure. Aliment Pharmacol Ther. 2002;16:6-11. doi:10.1046/j.1365-2036.16.s5.2.x
5. Mendez CM, McClain CJ, Marsano LS. Albumin therapy in clinical practice. Nutr Clin Pract. 2005;20:314-20. doi:10.1177/0115426505020003314
6. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol Aspects Med. 2012;33:209-90. doi:10.1016/j.mam.2011.12.002
7. di Masi A, Trezza V, Leboffe L, Ascenzi P. Human plasma lipocalins and serum albumin: Plasma alternative carriers?. J Control Release. 2016;228:191-205. doi:10.1016/j.jconrel.2016.02.049
8. Pstras L, Waniewski J, Lindholm B. Transcapillary transport of water, small solutes and proteins during hemodialysis. Sci Rep. 2020;10:18736. doi:10.1038/s41598-020-75687-1
9. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. FEBS Lett. 2008;582:1783-7. doi:10.1016/j.febslet.2008.04.057
10. Colombo G, Clerici M, Giustarini D, Rossi R, Milzani A, Dalle-Donne I. Redox albuminomics: oxidized albumin in human diseases. Antioxid Redox Signal. 2012;17:1515-27. doi:10.1089/ars.2012.4702
11. Anraku M, Chuang VT, Maruyama T, Otagiri M. Redox properties of serum albumin. Biochim Biophys Acta. 2013;1830:5465-72. doi:10.1016/j.bbagen.2013.04.036
12. Ahbap E, Sakaci T, Kara E, Sahutoglu T, Koc Y, Basturk T et al. The relationship between serum albumin levels and 24-h ambulatory blood pressure monitoring recordings in non-diabetic essential hypertensive patients. Clinics (Sao Paulo). 2016;71:257-63. doi:10.6061/clinics/2016(05)03
13. Oda E. Decreased serum albumin predicts hypertension in a Japanese health screening population. Intern Med. 2014;53:655-60. doi:10.2169/internalmedicine.53.1894
14. Liu Y, Xu S, Chen H, Dai S, Hao J, Chen X et al. Association between serum albumin concentration change trajectory and risk of hypertension: a cohort study in China. Front Cardiovasc Med. 2024;11:1325899. doi:10.3389/fcvm.2024.1325899
15. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev. 2016;17:95-107. doi:10.1111/obr.12334
16. Wang Y, Liu J, Hao H, Lu Q, Zhang L, Wei G et al. Nonlinear association between extracellular water/total body water ratio and all-cause mortality: a population-based cohort study. Sci Rep. 2025;15:19032. doi:10.1038/s41598-025-04202-1
17. Rizo-Téllez SA, Sekheri M, Filep JG. C-reactive protein: a target for therapy to reduce inflammation. Front Immunol. 2023;14:1237729. doi:10.3389/fimmu.2023.1237729
18. Pei J, Wang X, Zheng K, Su W, Hu X. Effect of body size and intensive blood pressure management on cardiovascular and serious adverse events. J Hypertens. 2022;40:878-87. doi:10.1097/HJH.0000000000003088
19. Wolff CB, Green DW, Paton JFR, Collier DJ. New understanding of circulatory blood flow and arterial blood pressure mechanisms. Cardiovasc Res. 2022;118:e29-e31. doi:10.1093/cvr/cvab363
20. Tsioufis P, Theofilis P, Dimitriadis K, Vlachakis PK, Iliakis P, Tsiachris D et al. Inflammatory Biomarkers in Hypertension. Curr Med Chem. Published online July 15, 2025. doi:10.2174/0109298673348789250604113545
21. Basolo A, Ando T, Chang DC, Hollstein T, Krakoff J, Piaggi P et al. Reduced Albumin Concentration Predicts Weight Gain and Higher Ad Libitum Energy Intake in Humans. Front Endocrinol (Lausanne). 2021;12:642568. doi:10.3389/fendo.2021.642568
22. Campos Munoz A, Jain NK, Gupta M. Albumin Colloid. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024
23. Sheinenzon A, Shehadeh M, Michelis R, Shaoul E, Ronen O. Serum albumin levels and inflammation. Int J Biol Macromol. 2021;184:857-62. doi:10.1016/j.ijbiomac.2021.06.140
24. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912-4018. doi:10.1093/eurheartj/ehae178
25. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Data Documentation, Codebook, and Frequencies. Blood Pressure & Cholesterol. 2006/4/1 [cited 2024/12/15]; Available from: https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/2003/DataFiles/BPQ_C.htm
26. Tang Y, Fan Y, Su J, Yang Z, Liu Z. The association between serum albumin levels and metabolic syndrome based on the NHANES and two sample Mendelian randomization study. Sci Rep. 2025;15:2861. doi:10.1038/s41598-025-86859-2
27. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Laboratory Procedure Manual, Analyte: Biochemistry Profile; Matrix: Serum; Method: Hitachi Model 917 Multichannel Analyzer. 1999/1/1 [cited 2024/12/15]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/public/1999/labmethods/lab18_met_biochemistry_profile.pdf
28. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Laboratory Procedure Manual, Analyte: C-Reactive Protein; Matrix: Serum; Method: Nephelometry. 2000/2/18 [cited 2024/12/15]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/public/2003/labmethods/l11_c_met_c_reactive_protein.pdf
29. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Procedure Manuals, BODY COMPOSITION PROCEDURES MANUAL. 2000/12/1 [cited 2024/12/15]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/public/1999/manuals/bc.pdf
30. Armstrong LE. Hydration assessment techniques. Nutr Rev. 2005;63:S40-S54. doi:10.1111/j.1753-4887.2005.tb00153.x
31. Basso F, Berdin G, Virzì GM, Mason G, Piccinni P, Day S et al. Fluid management in the intensive care unit: bioelectrical impedance vector analysis as a tool to assess hydration status and optimal fluid balance in critically ill patients. Blood Purif. 2013;36:192-9. doi:10.1159/000356366

32. Lee YH, Lee JD, Kang DR, Hong J, Lee JM. Bioelectrical impedance analysis values as markers to predict severity in critically ill patients. J Crit Care. 2017;40:103-7. doi:10.1016/j.jcrc.2017.03.013
33. Yılmaz Z, Yıldırım Y, Aydın FY, Aydın E, Kadiroğlu AK, Yılmaz ME et al. Evaluation of fluid status related parameters in hemodialysis and peritoneal dialysis patients: Clinical usefulness of bioimpedance analysis. Medicina (Kaunas). 2014;50:269-74. doi:10.1016/j.medici.2014.10.007
34. Malbrain ML, Huygh J, Dabrowski W, De Waele JJ, Staelens A, Wauters J. The use of bio-electrical impedance analysis (BIA) to guide fluid management, resuscitation and deresuscitation in critically ill patients: a bench-to-bedside review. Anaesthesiol Intensive Ther. 2014;46:381-91. doi:10.5603/AIT.2014.0061
35. Liu H, Wang L, Chen C, Dong Z, Yu S. Association between Dietary Niacin Intake and Migraine among American Adults: National Health and Nutrition Examination Survey. Nutrients. 2022;14:3052. doi:10.3390/nu14153052
36. Zhang TY, Chen HL, Shi Y, Jin Y, Zhang Y, Chen Y. The relationship between system inflammation response index and coronary heart disease: a cross-sectional study (NHANES 2007-2016). Front Cardiovasc Med. 2024;11:1439913. doi:10.3389/fcvm.2024.1439913
37. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Laboratory Procedure Manual. Analyte: Alanine Amino Transferase (ALT); Matrix: Refrigerated Serum; Method: Beckman Synchron LX20. 2003/1/1 [cited 2024/12/15]; Available from: https://wwwn.cdc.gov/nchs/data/nhanes/public/2003/labmethods/l40_c_met_alanine_amino_transferase.pdf
38. Zhang X, Yang Q, Huang J, Lin H, Luo N, Tang H. Association of the newly proposed dietary index for gut microbiota and depression: the mediation effect of phenotypic age and body mass index. Eur Arch Psychiatry Clin Neurosci. 2025;275:1037-48. doi:10.1007/s00406-024-01912-x
39. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Serum albumin and health in older people: Review and meta analysis. Maturitas. 2015;81:17-27. doi:10.1016/j.maturitas.2015.02.009
40. Moman RN, Gupta N, Varacallo MA. Physiology, Albumin. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022
41. Powers Carson J, Arora J. Glycated serum proteins and albumin but not glycated albumin show negative correlation with BMI in an overweight/obese, diabetic population from the United States. Clin Biochem. 2023;120:110654. doi:10.1016/j.clinbiochem.2023.110654
42. Jones CH, Smye SW, Newstead CG, Will EJ, Davison AM. Extracellular fluid volume determined by bioelectric impedance and serum albumin in CAPD patients. Nephrol Dial Transplant. 1998;13:393-7. doi:10.1093/oxfordjournals.ndt.a027836
43. Eckart A, Struja T, Kutz A, Baumgartner A, Baumgartner T, Zurfluh S et al. Relationship of Nutritional Status, Inflammation, and Serum Albumin Levels During Acute Illness: A Prospective Study. Am J Med. 2020;133:713-22.e7. doi:10.1016/j.amjmed.2019.10.031
44. Kotruchin P, Hoshide S, Kanegae H, Pongchaiyakul C, Kario K. Disparities in the impact of overweight on hypertension among Asians: a Japanese and Thai population-based study. J Hum Hypertens. 2019;33:123-30. doi:10.1038/s41371-018-0118-2
45. Redon J. Hypertension in obesity. Nutr Metab Cardiovasc Dis. 2001;11:344-53.
46. Vidal-Petiot E, Metzger M, Faucon AL, Boffa JJ, Haymann JP, Thervet E et al. Extracellular Fluid Volume Is an Independent Determinant of Uncontrolled and Resistant Hypertension in Chronic Kidney Disease: A NephroTest Cohort Study. J Am Heart Assoc. 2018;7:e010278. doi:10.1161/JAHA.118.010278
47. Theofilis P, Vordoni A, Kalaitzidis RG. Epidemiology, Pathophysiology, and Clinical Perspectives of Intradialytic Hypertension. Am J Nephrol. 2023;54:200-7. doi:10.1159/000531047
48. Guzik TJ, Nosalski R, Maffia P, Drummond GR. Immune and inflammatory mechanisms in hypertension. Nat Rev Cardiol. 2024;21:396-416. doi:10.1038/s41569-023-00964-1
49. Mo B, Ding Y, Ji Q. NLRP3 inflammasome in cardiovascular diseases: an update. Front Immunol. 2025;16:1550226. doi:10.3389/fimmu.2025.1550226
50. Hage FG. C-reactive protein and hypertension. J Hum Hypertens. 2014;28:410-5. doi:10.1038/jhh.2013.111.