RESEARCH ARTICLE

WILEY

A U-shaped association between serum albumin with total triiodothyronine in adults

Ya Zhang[1] | Ruijie Xie[2] | Jun Ou[3]

[1]Department of Breast and Thyroid Surgery, The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang, China

[2]Department of Hand & Microsurgery, The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang, China

[3]Department of Spine Surgery, The Affiliated Nanhua Hospital, Hengyang Medical school, University of South China, Hengyang, China

Correspondence
Jun Ou, Department of Spine Surgery, The Affiliated Nanhua Hospital, Hengyang Medical school, University of South China Hengyang 421002, China.
Email: 1976449789@qq.com

Abstract

Background: Thyroid dysfunction is a common thyroid disorder in our life and its symptoms are non-specific, therefore the diagnosis of thyroid dysfunction is important for patients. Albumin (ALB) can carry thyroid hormones to their sites of action as a way to achieve rapid delivery of thyroid hormones to the tissues. The purpose of this study was to investigate the relationship between serum ALB levels and total triiodothyronine (TT3) in adults.

Methods: Data from the 2007–2012 National Health and Nutrition Examination Survey (NHANES) were used to examine the association between ALB and TT3 using multivariate logistic regression models. Fitting smoothed curves and generalized weighted models were also used.

Results: The analysis included a total of 7933 participants that we found an independent positive relationship between ALB and TT3 among participants [0.006 (0.003, 0.009)]. In men, there was a significant positive correlation between ALB and TT3, whereas in women ALB and TT3 suggested a significant negative correlation. Moreover, our study revealed that the independent association between the levels of ALB and TT3 was significant in Non-Hispanic White, but not in Non-Hispanic Black. Notably, we found a U-shaped association between ALB and serum TT3 in total participants (inflection point for ALB: 41 g/L) and females after adjusted covariates (inflection point for ALB: 46 g/L).

Conclusions: We found a U-shaped relationship between serum ALB and TT3 with infection point at 41 g/L for ALB, which may provide a reference for future screening in adults with thyroid dysfunction.

KEYWORDS
cross-sectional study, NHANES, serum albumin, thyroid dysfunction, total triiodothyronine

Ya Zhang and Ruijie Xie have contributed equally to this work.

1 | INTRODUCTION

Thyroid dysfunction is a common thyroid disorder in our lives, and the symptoms are nonspecific therefore thyroid function testing is one of the most common tests to be requested by doctors.[1,2] The prevalence of autoimmune thyroid disease is the most common thyroid disease with Graves' disease and Hashimoto's thyroiditis being the most common forms, affecting approximately 1%–5% of the population.[3,4] The diagnosis of thyroid dysfunction has important implications for the patient, especially in pregnant women, as hypothyroidism requires lifelong treatment, while hyperthyroidism requires months or years of treatment.[5-7] Screening for diseases related to thyroid function is also becoming increasingly important. Diagnosed patients with suspected thyroid dysfunction by measurement of thyroid function through quantifying concentrations of circulating thyroid hormones and thyroid-stimulating hormone (TSH) is deemed to be the most accurate and reliable approach to confirming the disease.[8,9] The prevalence and incidence of hypothyroidism are growing, as more increasing patients with borderline disease are being treated. One study reported that approximately 30% of patients with mild hypothyroidism were treated despite having normal free thyroxine levels.[10,11]

Albumin (ALB) is known to be a protein produced by the liver, accounting for half of the total plasma protein content, and most importantly used to maintain plasma colloid osmotic pressure.[12-14] In addition, ALB is a transporter of many hormones such as thyroxine, cortisol, and testosterone. ALB which is the most abundant thyroxine-binding protein together with thyroid-binding globulin (TBG) and transthyretin (TTR) are the three main binding proteins that transport thyroid hormones (T3 and T4) to various sites throughout the body.[15,16] A comparative study from China found that low ALB levels showed a direct correlation with free triiodothyronine.[17] However, some scholars believe that ALB has a much lower affinity for thyroid hormones than TBG, such that changes in serum ALB levels do not result in a significant change in thyroid hormones levels, so most studies have examined the relationship between TBG and thyroid hormones, while few studies have examined the relationship between serum ALB and serum total T3 (TT3).[18] This study aimed to investigate if there is an association between serum ALB levels and TT3 in adults.

2 | MATERIALS AND METHODS

### 2.1 | Data source and analysis sample

The National Health and Nutrition Examination Survey (NHANES) database uses a multistage stratified sample to collect detailed information on a nationally representative study population as a means of providing a cross-sectional picture of the nutrition and health of the U.S. population. Its data are collected every 2 years by the NCHS.

A total of 30,442 people took part in the 2007–2012 NHANES data survey in our present study. We eliminated 11,229 subjects who lacked serum ALB data. In addition, after excluding 19,213 participants lacking thyroid hormone data, 841 with cancer, 1818 under 20 years of age, and only 7933 participants remained for the final analysis (Figure 1). The NCHS Research Ethics Review Board authorized the NHANES survey procedure, and all participants completed an informed consent form.

2.2 | Study variables

For the exposure variables in this investigation, serum ALB levels were measured. A Beckman UniCel® DxC800 Synchron was used to measure all of the techniques. Please see the laboratory techniques paper for further information on the analytical methods, concepts, and operational procedures. Bromcresol Purple reagent reacts with the ALB to form a detectable complex product during this process. The change of complex product in absorbance at 600 nm is directly proportional to the concentration of ALB in the sample. Serum TT3 levels were the study's outcome factor. The NHANES database uses the Access immunoassay system to quantify triiodothyronine levels in human serum and plasma. You can find more additional information on the NHANES website.
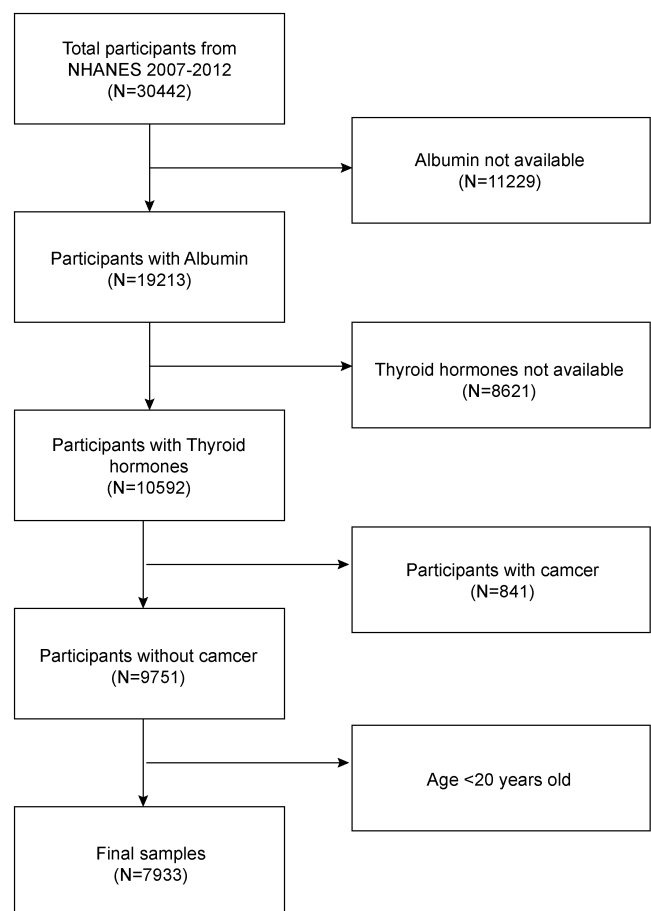
FIGURE 1 Flow chart of sample selection from the NHANES 2007–2012. NHANES, National Health and Nutrition Examination Survey

2.3 | Laboratory tests and clinical data

NHANES personnel took body measures of these participants, including weight, height, body mass index (BMI), and waist circumference. Self-reporting was used to collect data on age, gender, race, the ratio of family income to poverty, and educational level.

The laboratory measurements methods of total thyroxine (TT4), total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, total protein, globulin, free thyroxine, thyroglobulin, thyroglobulin antibodies, TSH, thyroid peroxidase antibodies, urinary iodine, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, urinary creatinine, urinary ALB, and serum uric acid were all clarified in detail at the NHANES website.

2.4 | Statistical analysis

We used package R (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com) to analyze, with $p < 0.05$ considered statistically significant. The link between ALB and TT3 was studied using a weighted multivariate logistic regression model. Stratified multivariate regression analysis was used to do the subgroup analysis. The nonlinear link between ALB and TT3 was addressed using smooth curve fits and generalized additive models.

3 | RESULTS

A total of 7933 subjects aged 20 years and above were included in Table 1. The individuals' weighted characteristics were divided into quartiles based on their ALB levels (Q1: <39 g/L; Q2: 39–42 g/L; Q3: 43–45 g/L; and Q4: >45 g/L). Between the ALB quartiles, there were substantial variations in baseline characteristics except for thyroglobulin antibodies, TSH, urine creatinine, and urine iodine. Individuals in the bottom quartile were more likely to be older, male, and Non-Hispanic Black. Compared to the other groups, participants in the bottom quartile have higher BMI, waist circumference, thyroxine free, thyroglobulin, thyroid peroxidase antibodies, TT4, globulin, ALP, and urine ALB, and lower education levels, income to poverty ratio, total cholesterol, LDL-cholesterol, HDL-cholesterol, TT3, total protein, ALT, AST, serum creatinine, serum uric acid, and triglyceride ($p < 0.05$).

We found a significant independent positive relationship between ALB and serum TT3 [0.006 (0.003, 0.009)]. However, after adjusting for covariates this significant correlation becomes insignificant (Table 2). Notably, a relationship between ALB with serum TT3 was a U-shaped curve with an infection point at 41 g/L for ALB (Figure 2).

The detailed findings of the multivariate regression analysis stratified by gender and race are shown in Table 2. There was a different significant relationship between ALB and TT3 in subgroup analysis stratified by gender. For males, there is a significant positive

association with ALB and TT3 in Model 1 [0.022 (0.018, 0.026)], Model 2 [0.012 (0.008, 0.016)], and Model 3 [0.017 (0.009, 0.024)]. For females, there is a significant negative association with ALB and TT3 in Model 1 [−0.010 (−0.015, −0.006)], Model 2 [−0.011 (−0.016, −0.006)], but become insignificant in fully adjusted Model [−0.008 (−0.017, 0.002)]. Of note, the relationship between ALB and serum TT3 in females was a U-shaped curve with an infection point of 46 g/L for ALB (Table 3). The relationship between ALB and TT3 was not completely identical in subgroup analysis stratified by race. For Non-Hispanic White, the significant positive association with ALB and TT3 was only in Model 1 [0.008 (0.004, 0.013)]. For Non-Hispanic Black, we did not find a significant correlation between ALB with TT3 in all three regression models. For Mexican Americans, we only found a strong negative relationship between ALB and TT3 in Model 2 (Table 2).

Figures 2-4 depict smooth curve fits and generalized additive models that were utilized to define the nonlinear connection between ALB and serum TT3.

4 | DISCUSSION

The aim of this study was to explore whether there are independent correlations between serum ALB and TT3 among adults older than 20 years. The results showed that the relationship of ALB with TT3 assumed a U-shaped (inflection point: 41 g/L for ALB).

According to statistics, including subclinical symptoms, the prevalence of hypothyroidism and hyperthyroidism in adults ranges from 5% to 15% and 0.5% to 2%, respectively.[5] However, there have been few studies on the association between ALB and TT3 serum levels in adults currently. The most common form of thyroid dysfunctional disease is autoimmune thyroid disease, which is usually associated with the presence of anti-thyroid peroxidase, anti-thyroglobulin, and anti-thyroid-stimulating hormone receptor antibodies.[19] Familial dysalbuminemic hyperthyroxinemia, which causes an increase in serum thyroid hormone levels by altering the affinity of ALB for thyroid hormones, is an autosomal dominant inherited disorder first reported in 1979.[20] Subsequently, Lalloz MR et al. identified a new, unique variant of ALB with increased affinity for T3, which binds excessively to T3 resulting in hyperthyroidism.[21] Hollander CS et al. found that increased TBG and thyroxine-binding prealbumin binding capacity was associated with a major deficiency in serum ALB concentration, which may be related to the fact that reduced serum ALB concentration may lead to the release of free fatty acids, which interfere with thyroxine binding.[22] An interesting finding in our study was that TT3 levels decreased with increasing ALB levels when ALB was less than 41 g/L, and increased with increasing ALB levels when ALB levels were greater than 41 g/L. In addition to this, the inflection point for ALB levels in females is 46 g/L.

Although there has been much research into the pathogenesis of thyroid disease, the more accepted cause is autoimmunity,[23] which will be only presented in a cursory way in this. One molecule with similar effects to TSH, due to its long duration of action was

TABLE 1 Weighted characteristics of the study population based on serum albumin quartiles

Serum albumin (g/L)	Q1	Q2	Q3	Q4	P value
Age (years)	49.273 ± 17.017	47.625 ± 16.092	46.408 ± 15.625	40.991 ± 14.998	<0.00001
Gender (%)					
Males	24.518	38.145	51.463	68.211	<0.00001
Females	75.482	61.855	48.537	31.789	
Race/Ethnicity (%)					
Non-Hispanic White	61.481	65.381	68.543	71.771	<0.00001
Non-Hispanic Black	18.836	13.338	8.572	6.434	
Mexican American	8.106	8.138	9.682	8.808	
Other race	11.578	13.143	13.203	12.987	
Educational level (%)					
Less than high school	24.23	20.327	19.326	15.865	<0.00001
High school	22.487	23.179	24.487	23.878	
More than high school	53.283	56.494	56.186	60.257	
Ratio of family income to poverty	2.709 ± 1.698	2.944 ± 1.643	3.069 ± 1.612	3.064 ± 1.662	<0.00001
Body mass index (Kg/m^2)	32.174 ± 8.565	29.403 ± 6.867	28.126 ± 5.600	26.411. ±4.998	<0.00001
Waist circumference (cm)	104.729 ± 18.418	99.526 ± 16.631	97.608 ± 14.781	93.099 ± 13.783	<0.00001
Laboratory features					
Total cholesterol (mmol/L)	4.995 ± 1.076	5.023 ± 1.031	5.111 ± 1.045	5.184 ± 1.097	<0.00001
Triglyceride (mmol/L)	1.509 ± 1.273	1.407 ± 1.051	1.601 ± 1.141	1.565 ± 1.600	0.00252
LDL-cholesterol (mmol/L)	2.857 ± 0.887	2.991 ± 0.883	3.025 ± 0.855	3.061 ± 0.934	0.00007
HDL-cholesterol (mmol/L)	1.362 ± 0.398	1.334 ± 0.400	1.340 ± 0.419	1.383 ± 0.431	0.00020
Thyroxine free (pmol/L)	10.505 ± 3.157	10.190 ± 1.985	10.165 ± 1.828	10.222 ± 1.805	0.00007
Thyroglobulin (ug/L)	18.092 ± 37.071	16.848 ± 50.855	16.243 ± 35.658	14.088 ± 37.348	0.02672
Thyroglobulin antibodies (IU/mL)	12.811 ± 89.817	13.855 ± 119.711	8.129 ± 64.118	10.811 ± 97.784	0.25791
Thyroid-stimulating hormone (mIU/L)	2.039 ± 2.421	2.032 ± 3.174	1.961 ± 2.251	2.160 ± 4.312	0.23820
Thyroid peroxidase antibodies (IU/mL)	28.684 ± 113.434	22.211 ± 91.523	24.053 ± 101.318	16.698 ± 72.747	0.00188
Total triiodothyronine (nmol/L)	1.783 ± 0.645	1.768 ± 0.464	1.801 ± 0.465	1.828 ± 0.396	0.00013
Total thyroxine (μg/dL)	8.484 ± 1.946	7.907 ± 1.553	7.728 ± 1.522	7.562 ± 1.474	<0.00001
Urine iodine (μg/L)	1093.881 ± 24651.561	251.485 ± 1004.280	280.950 ± 1520.570	210.927 ± 491.296	0.05112
Total protein(g/L)	68.633 ± 5.537	70.133 ± 4.039	71.797 ± 3.798	73.663 ± 3.990	<0.00001
Globulin(g/L)	31.336 ± 5.284	29.009 ± 4.058	28.315 ± 3.786	27.156 ± 3.845	<0.00001
Alanine aminotransferase (U/L)	23.090 ± 18.673	24.929 ± 24.568	26.460 ± 16.339	28.243 ± 17.962	<0.00001
Aspartate aminotransferase (U/L)	25.086 ± 15.634	25.491 ± 20.276	26.066 ± 13.144	27.228 ± 14.345	0.00021
Alkaline phosphatase (IU/L)	72.561 ± 26.305	67.256 ± 22.013	65.838 ± 20.228	64.372 ± 18.594	<0.00001
Serum creatinine (umol/L)	75.667 ± 36.728	74.625 ± 25.157	76.859 ± 21.923	79.191 ± 22.221	<0.00001
Urine creatinine (umol/L)	10667.119 ± 6728.212	10368.871 ± 6873.102	10744.755 ± 6822.765	10807.601 ± 6937.365	0.13513
Urine albumin (umol/L)	88.699 ± 622.811	23.259 ± 119.437	24.311 ± 131.626	18.394 ± 75.153	<0.00001
Serum uric acid (umol/L)	319.490 ± 91.431	311.905 ± 79.585	328.209 ± 83.080	334.889 ± 81.963	< 0.00001

Note: Mean ± SD for continuous variables: P-value was calculated by weighted linear regression model. % for categorical variables: *p*-value was calculated by weighted chi-square test.

TABLE 2 The association between serum albumin (g/L) and total triiodothyronine (nmol/L)

	Model 1: β (95% CI), p	Model 2: β (95% CI), p	Model 3: β (95% CI), p
Serum albumin (g/L)	0.006 (0.003, 0.009) 0.00006	−0.002 (−0.005, 0.001) 0.19429	0.003 (−0.004, 0.009) 0.40825
Gender			
Males	0.022 (0.018, 0.026) <0.00001	0.012 (0.008, 0.016) <0.00001	0.017 (0.009, 0.024) 0.00002
Females	−0.010 (−0.015, −0.006) 0.00003	−0.011 (−0.016, −0.006) <0.00001	−0.008 (−0.017, 0.002) 0.11244
Race/Ethnicity (%)			
Non-Hispanic White	0.008 (0.004, 0.013) 0.00032	−0.002 (−0.006, 0.003) 0.52158	0.004 (−0.004, 0.012) 0.32420
Non-Hispanic Black	−0.003 (−0.010, 0.005) 0.49628	−0.004 (−0.012, 0.003) 0.27374	0.002 (−0.013, 0.017) 0.77803
Mexican American	−0.002 (−0.008, 0.005) 0.56976	−0.013 (−0.020, −0.006) 0.00025	−0.003 (−0.014, 0.009) 0.62288
Other Race	0.010 (0.002, 0.018) 0.01798	0.003 (−0.006, 0.011) 0.51316	0.010 (−0.010, 0.030) 0.30724

Note: Model 1: No covariates were adjusted. Model 2: Age and race were adjusted.

Model 3: Age, gender, race, body mass index, ratio of family income to poverty, educational level, waist circumference, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total protein, globulin, thyroxine free, thyroglobulin, thyroglobulin antibodies, thyroid-stimulating hormone, thyroid peroxidase antibodies, total triiodothyronine, total thyroxine, urine iodine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum creatinine, urine creatinine, urine albumin, and serum uric acid were adjusted.

In the subgroup analysis stratified by gender or race, the model is not adjusted for the stratification variable itself.
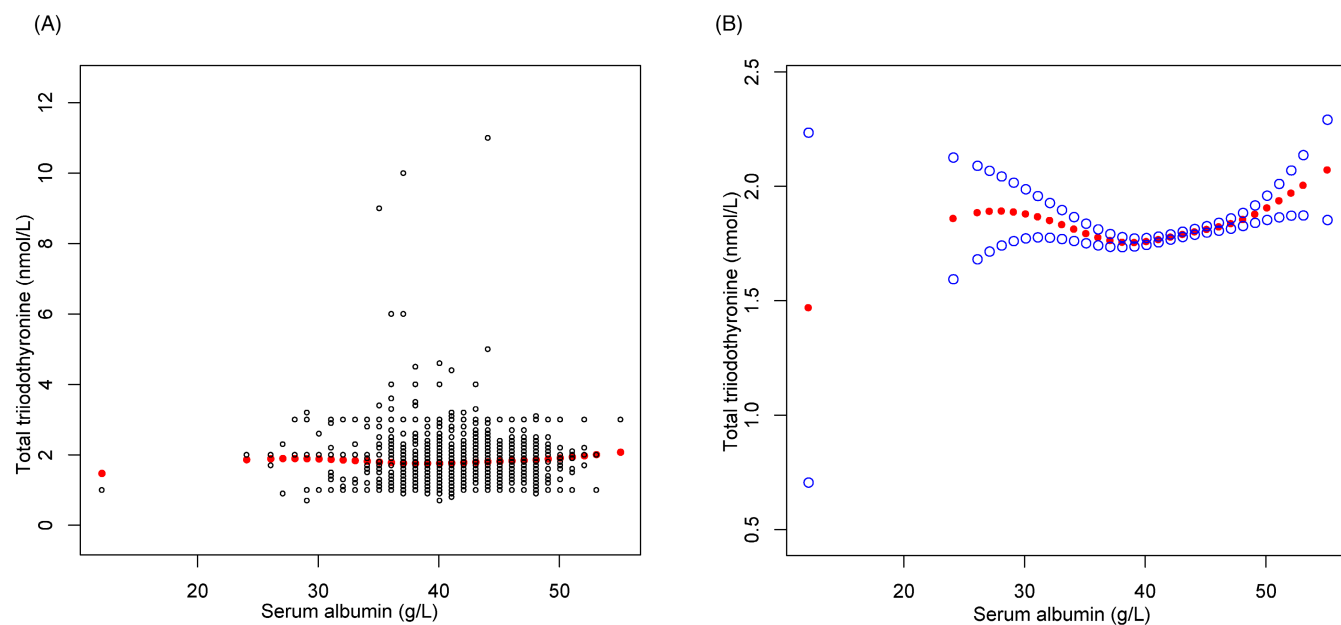

FIGURE 2 The association between serum albumin and total triiodothyronine. (A) Each Black point represents a sample. (B) The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Age, gender, race, body mass index, ratio of family income to poverty, educational level, waist circumference, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total protein, globulin, thyroxine free, thyroglobulin, thyroglobulin antibodies, thyroid-stimulating hormone, thyroid peroxidase antibodies, total thyroxine, urine iodine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum creatinine, urine creatinine, urine albumin, and serum uric acid were adjusted

called long-acting thyroid stimulator and was later identified as immunoglobulin G and found to be an antibody against the thyroid-stimulating hormone receptor (TSHR).[19,24,25] Anti-TSHR antibodies were found in 90% of Graves' disease patients and 0%–20% of Hashimotos thyroiditis, 10%–75% of patients with atrophic thyroiditis.[8] A study found that macro-TSH was the result of anti-TSH antibodies binding to TSH, and leading to a high molecular protein complex with low TSH bioactivity. Incidence increases with age, and altered TSH antigenicity or reduced autoimmune tolerance is thought to be the causative mechanism.[26] In addition to this, there

are anti-thyroid peroxidase (TPO) antibodies and anti-thyroglobulin (Tg) antibodies. One study proposed that anti-TPO antibodies in patients with autoimmune thyroid disease can destroy thyroid cells and act as competitive inhibitors of enzyme activity.[27] Another study concluded that anti-TPO antibodies are more common than anti-Tg antibodies and more indicative of thyroid disease.[28]

Data for participants in NHANES are nationally representative, hence our findings are extremely relevant to the entire population. We were also able to undertake subgroup analyses of ALB and TT3 across gender and ethnicity, to evaluate the relationship between

TABLE 3 Threshold effect analysis of serum albumin on total triiodothyronine using the two-piecewise linear regression model

| Total triiodothyronine	Adjusted β(95%CI) P value
Total	
Fitting by the standard linear model	0.006 (0.003, 0.009) <0.0001
Fitting by the two-piecewise linear model	
Inflection point	41
Direct serum albumin <41 (g/L)	−0.009 (−0.016, −0.002) 0.0169
Direct serum albumin >41 (g/L)	0.014 (0.010, 0.019) <0.0001
Log likelihood ratio	<0.001
Females	
Fitting by the standard linear model	−0.010 −(0.015, −0.006) <0.0001
Fitting by the two-piecewise linear model	
Inflection point	46
Direct serum albumin <46 (g/L)	−0.015 (−0.021, −0.010) <0.0001
Direct serum albumin >46(g/L)	0.045 (0.016, 0.075) 0.0027
Log likelihood ratio	<0.001

Note: Age, gender, race, body mass index, ratio of family income to poverty, educational level, waist circumference, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total protein, globulin, thyroxine free, thyroglobulin, thyroglobulin antibodies, thyroid-stimulating hormone, thyroid peroxidase antibodies, total triiodothyronine, total thyroxine, urine iodine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum creatinine, urine creatinine, urine albumin, and serum uric acid were adjusted.

Threshold effect analysis of serum albumin on total triiodothyronine in females using the two-piecewise linear regression model, the model is adjusted for all, but gender.

the serum levels of ALB and TT3 in our large sample size. However, there were some limitations or flaws in our research. First, the cross-sectional aspect of this study confined the results to a correlation rather than causality. To understand the specific mechanism of the relationship between ALB and TT3, further fundamental mechanistic research and large sample prospective studies are required. Second, environmental and dietary variables such as iodine and protein intake, which may impact the levels of serum ALB and TT3, were not taken into account. Third, our sample excluded participants with cancer, and our results may not apply to individuals with tumors.

5 | CONCLUSION

We found a U-shaped relationship between serum ALB and TT3 with infection point at 41 g/L for ALB, which may provide a reference for future screening in adults with thyroid dysfunction.
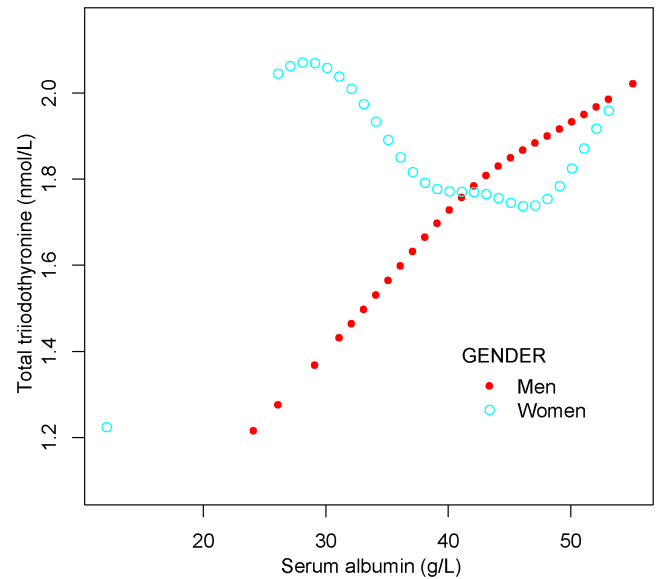
FIGURE 3 The association between serum albumin and total triiodothyronine is stratified by gender. Age, race, body mass index, ratio of family income to poverty, educational level, waist circumference, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total protein, globulin, thyroxine free, thyroglobulin, thyroglobulin antibodies, thyroid-stimulating hormone, thyroid peroxidase antibodies, total thyroxine, urine iodine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum creatinine, urine creatinine, urine albumin, and serum uric acid were adjusted
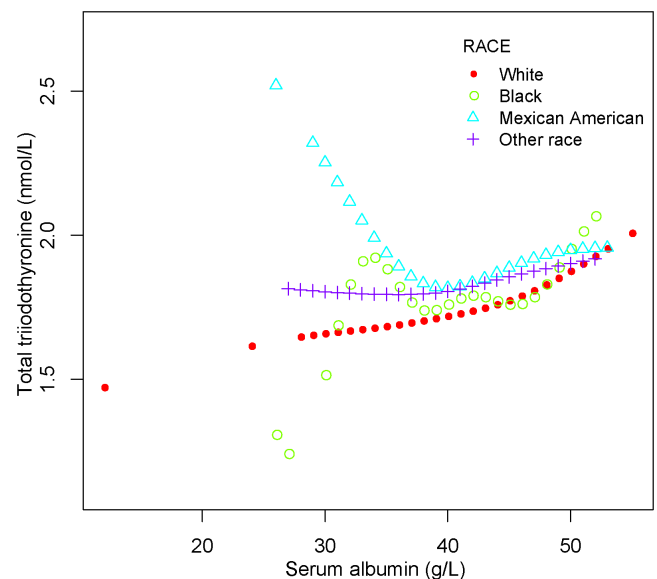
FIGURE 4 The association between serum albumin and total triiodothyronine is stratified by race. Age, gender, body mass index, ratio of family income to poverty, educational level, waist circumference, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total protein, globulin, thyroxine free, thyroglobulin, thyroglobulin antibodies, thyroid-stimulating hormone, thyroid peroxidase antibodies, total thyroxine, urine iodine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, serum creatinine, urine creatinine, urine albumin, and serum uric acid was adjusted

AUTHOR CONTRIBUTIONS

YZ, RX, and JO designed the research. YZ and RX collected, analyzed the data, and drafted the manuscript. YZ, RX, and JO revised the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

The survey data are publicly available on the internet for data users and researchers throughout the world (www.cdc.gov/nchs/nhanes/).

ORCID

Ya Zhang https://orcid.org/0000-0002-6013-0785
Ruijie Xie https://orcid.org/0000-0002-1635-962X

REFERENCES

1. Garmendia Madariaga A, et al. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(3):923-931.
2. Hollowell JG, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489-499.
3. Tomer Y. Mechanisms of autoimmune thyroid diseases: from genetics to epigenetics. *Annu Rev Pathol*. 2014;9:147-156.
4. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012;42(2):252-265.
5. Jonklaas J, Razvi S. Reference intervals in the diagnosis of thyroid dysfunction: treating patients not numbers. *Lancet Diabetes Endocrinol*. 2019;7(6):473-483.
6. Lee SY, Pearce EN. Testing, monitoring, and treatment of thyroid dysfunction in pregnancy. *J Clin Endocrinol Metab*. 2021;106(3):883-892.
7. Khadilkar S. Thyroid-stimulating hormone values in pregnancy: cutoff controversy continues? *J Obstet Gynaecol India*. 2019;69(5):389-394.
8. Carvalho GA, Perez CL, Ward LS. The clinical use of thyroid function tests. *Arq Bras Endocrinol Metabol*. 2013;57(3):193-204.
9. Pirahanchi Y, Toro F, Jialal I. *Physiology, Thyroid Stimulating Hormone, in StatPearls*. 2022, StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
10. Taylor PN, et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med*. 2014;174(1):32-39.
11. Taylor PN, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14(5):301-316.
12. Gounden V, Vashisht R, Jialal I. *Hypoalbuminemia, in StatPearls*. 2022, StatPearls Publishing. Copyright © 2022, StatPearls Publishing LLC.: Treasure Island (FL).
13. Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. *Int J Gen Med*. 2016;9:229-255.
14. Rozga J, Piątek T, Małkowski P. Human albumin: old, new, and emerging applications. *Ann Transplant*. 2013;18:205-217.
15. Schussler GC. Thyroxine-binding proteins. *Thyroid*. 1990;1(1):25-34.
16. Oppenheimer JH. Role of plasma proteins in the binding, distribution and metabolism of the thyroid hormones. *N Engl J Med*. 1968;278(21):1153-1162.
17. Quispe EÁ, Li XM, Yi H. Comparison and relationship of thyroid hormones, IL-6, IL-10 and albumin as mortality predictors in case-mix critically ill patients. *Cytokine*. 2016;81:94-100.
18. Pappa T, Ferrara AM, Refetoff S. Inherited defects of thyroxine-binding proteins. *Best Pract Res Clin Endocrinol Metab*. 2015;29(5):735-747.
19. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. *Front Immunol*. 2017;8:521.
20. Hennemann G, et al. Raised total thyroxine and free thyroxine index but normal free thyroxine. A serum abnormality due to inherited increased affinity of iodothyronines for serum binding protein. *Lancet*. 1979;1(8117):639-642.
21. Lalloz MR, Byfield PG, Himsworth RL. A new and distinctive albumin variant with increased affinities for both triiodothyronines and causing hyperthyroxinaemia. *Clin Endocrinol (Oxf)*. 1985;22(4):521-529.
22. Hollander CS, Bernstein G, Oppenheimer JH. Abnormalities of thyroxine binding in analbuminemia. *J Clin Endocrinol Metab*. 1968;28(7):1064-1066.
23. Swain M, Swain T, Mohanty BK. Autoimmune thyroid disorders-An update. *Indian J Clin Biochem*. 2005;20(1):9-17.
24. Rapoport B, McLachlan SM. TSH receptor cleavage into subunits and shedding of the A-Subunit; A molecular and clinical perspective. *Endocr Rev*. 2016;37(2):114-134.
25. Tomer Y, et al. Fine mapping of loci linked to autoimmune thyroid disease identifies novel susceptibility genes. *J Clin Endocrinol Metab*. 2013;98(1):E144-E152.
26. Hattori N, et al. Anti-thyrotropin autoantibodies in patients with macro-thyrotropin and long-term changes in macro-thyrotropin and serum thyrotropin levels. *Thyroid*. 2017;27(2):138-146.
27. Kaczur V, et al. Effect of anti-thyroid peroxidase (TPO) antibodies on TPO activity measured by chemiluminescence assay. *Clin Chem*. 1997;43(8 Pt 1):1392-1396.
28. Balucan FS, Morshed SA, Davies TF. Thyroid autoantibodies in pregnancy: their role, regulation and clinical relevance. *J Thyroid Res*. 2013;2013: 182472.