

Urinary Iodine Concentration, Glycated Hemoglobin, and Thyroid Autoantibodies in US Adults: A Complex Survey-Weighted Cross-Sectional Analysis of NHANES 2007-2012

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Abstract

Objective: To examine cross-sectional associations of spot urinary iodine concentration (UIC) with glycated hemoglobin (HbA1c) and thyroid autoantibodies in US adults, and to assess the robustness of the estimates across analytic specifications. **Methods:** We combined three National Health and Nutrition Examination Survey (NHANES) cycles (2007-2012). The principal common sample comprised 8,278 adults aged ≥ 20 years, excluding known pregnancies, with required measurements. Survey weights, strata, and primary sampling units were incorporated. Log2-transformed UIC was related to HbA1c, thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and positivity for either antibody. Weighted quartiles, natural splines, interaction tests, jackknife replicate weights, and sensitivity analyses were used. Selected secondary tests were corrected for false discovery rate. **Results:** Weighted median UIC was 141.5 $\mu\text{g/L}$; 15.26% were positive for at least one antibody. After full adjustment, each doubling of UIC corresponded to an HbA1c difference of -0.0127 percentage points (95% CI -0.0316 to 0.0061 ; $P = 0.180$). Geometric mean ratios were 0.972 (95% CI 0.926 - 1.020) for TPOAb and 0.982 (0.959 - 1.005) for TgAb; the odds ratio for either antibody positivity was 0.972 (0.895 - 1.055). For the three UIC-antibody outcomes, all Benjamini-Hochberg-adjusted P values were ≥ 0.368 . The four-degree-of-freedom spline yielded an overall $P = 0.0218$ and a nonlinearity $P = 0.2967$; corresponding values in the stricter diabetes- and glucose-lowering-medication-exclusion sample ($n = 7,084$) were 0.1389 and 0.2025. Adjustment for urinary creatinine changed the magnitude or direction of the linear coefficient. **Conclusions:** Spot UIC showed no clearly supported adjusted linear association with HbA1c or thyroid

autoantibodies under the prespecified cross-sectional models. Exploratory signals were not consistent across analytic specifications. Interpretation should therefore remain limited to cross-sectional associations rather than clinical equivalence, long-term iodine effects, or causal mediation.

Keywords

Urinary Iodine Concentration, HbA1c, Thyroid Autoantibodies, NHANES, Complex Survey, Sensitivity Analysis

1. Introduction

Iodine is essential for thyroid hormone synthesis. Spot UIC is useful for characterizing recent iodine nutrition at the population level, but one random specimen cannot reliably characterize an individual's long-term intake [1]. Long-term regional iodine intake has been associated with thyroid disease [2]; such observations cannot be directly extrapolated to associations of a single UIC measurement with thyroid antibodies or glycemic biomarkers. A previous NHANES 2007-2012 analysis examined UIC, selenium intake, and thyroid antibody positivity [3]. The present study additionally evaluated HbA1c and continuous antibody concentrations under a different analytic framework.

Thyroid function has also been associated with incident type 2 diabetes in a prospective cohort [4]. Thyroid dysfunction, antibody positivity, and clinically diagnosed autoimmune thyroid disease are distinct phenotypes, however, and cross-sectional HbA1c is not equivalent to future diabetes incidence. We therefore separately investigated UIC-HbA1c, UIC-antibody, and antibody-HbA1c associations, emphasizing confidence intervals rather than statistical significance alone [5]. Exploratory indirect statistical associations were not interpreted as causal mediation [6].

2. Materials and Methods

2.1. Study Design and Participants

This secondary cross-sectional analysis linked demographic, examination, laboratory, smoking, diabetes questionnaire, and prescription-drug files by participant identifier (SEQN) within each cycle and pooled three cycles. Prescription records were first summarized at the participant level. Of 30,442 participants, 15,233 had valid design information; 9519 were aged ≥ 20 years. After excluding 98 known pregnancies, 9421 remained. Sequential exclusions for invalid UIC (476), both antibodies invalid (550), invalid HbA1c (14), and incomplete covariates (103) yielded 8278 participants. Unknown pregnancy status was not treated as known pregnancy. The TPOAb, TgAb, and either-antibody positivity models included 8207, 8230, and 8159 participants, respectively. An expanded HbA1c sample ($n = 8,344$), requiring valid UIC, valid HbA1c, and complete M3 covariates but not requiring

valid antibody measurements, was used as a sensitivity analysis.

2.2. Exposure and Outcomes

Urinary iodine concentration (UIC; URXUIO, $\mu\text{g/L}$) was measured in spot urine by inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) according to cycle-specific NHANES laboratory protocols [7]–[9]. Thyroid peroxidase antibodies (TPOAb; LBXTPO) and thyroglobulin antibodies (TgAb; LBXATG) were obtained from the NHANES thyroid profile laboratory datasets [10]–[12]. Serum TPOAb and TgAb were measured using Beckman Coulter Access/Access 2 sequential two-step immunoenzymatic assays according to the corresponding cycle- and laboratory-specific NHANES laboratory procedure manuals [10]–[18]. Because laboratory protocols and performing laboratories varied across survey cycles, low-end assay performance was reported using protocol-specific terminology. The University of Washington protocols reported approximate lowest detectable/reportable concentrations of 0.3 IU/mL for TPOAb and 0.9 IU/mL for TgAb, whereas the Collaborative Laboratory Services Access 2 protocols reported analytical sensitivities of 0.25 IU/mL for TPOAb and 0.9 IU/mL for TgAb [13]–[18]. Assay performance limits were distinct from both the minimum values in the released NHANES datasets and the reference cutoffs used to define antibody positivity. The publicly released NHANES LBXTPO and LBXATG concentration values were analyzed as provided, without additional substitution or censoring based on these assay-performance limits. TPOAb and TgAb concentrations were analyzed on the natural-log scale because of their skewed distributions. Antibody positivity was defined as TPOAb ≥ 9 IU/mL and TgAb ≥ 4 IU/mL, respectively, consistent with the NHANES laboratory reference cutoffs [10]–[18]. Either-antibody positivity was defined as positivity for at least one antibody. For formal binary analyses, participants were included only when both TPOAb and TgAb measurements were valid. HbA1c (LBXGH, %) was measured in whole blood by ion-exchange high-performance liquid chromatography (HPLC) [19]–[21]. NHANES 2007–2010 used the Tosoh A1C G7 automated HPLC glycohemoglobin analyzer; during the 2011–2012 cycle, the laboratory method changed from the Tosoh G7 to the Tosoh HLC-723G8 analyzer [19]–[22]. The original NHANES-released HbA1c values were retained as the primary continuous glycemic outcome. Linear coefficients are absolute HbA1c percentage-point differences, not relative percentage changes or incident diabetes risks.

2.3. Covariates and Medication Classification

Smoking status was defined using NHANES smoking questionnaire variables SMQ020 and SMQ040 and categorized as never smoker, former smoker, or current smoker. Never smokers were participants with SMQ020 = 2 (did not report smoking at least 100 cigarettes during their lifetime); former smokers were participants with SMQ020 = 1 and SMQ040 = 3 (had smoked at least 100 cigarettes during their lifetime but currently smoked not at all); and current smokers were

participants with SMQ020 = 1 and SMQ040 = 1 or 2 (currently smoked every day or some days). Refused, unknown, or missing responses were treated as missing [23]-[25]. Diabetes and glucose-lowering-treatment sensitivity analyses used DIQ010, DIQ050, and the cycle-specific oral-diabetes-pill item (DID070 in 2007-2008 and DIQ070 in 2009-2012) [26]-[28]. For sensitivity analyses excluding diagnosed diabetes, DIQ010 = 1 was classified as diagnosed diabetes; DIQ010 = 2 or 3 (no or borderline diabetes) was retained, whereas refused, unknown, or missing responses were treated as indeterminate [26]-[28]. Questionnaire-reported current glucose-lowering treatment combined current insulin use (DIQ050) and the cycle-specific diabetes-pill item. At the participant level, current treatment was classified as present if either component was coded 1; non-use required both components to be coded 2; and other combinations were classified as unknown. When the diabetes-pill item was missing, pill non-use was assigned only when DIQ010 = 2 and DIQ160 = 2; otherwise, treatment status remained unknown, consistent with the prespecified analytic coding [26]-[28]. Prescription-medication records from RXQ_RX were summarized at the participant level and linked by RXDDRGID to the NHANES RXQ_DRUG therapeutic-class file [29]-[31]. Only records with RXDUSE = 1 were treated as evidence of prescription medication use. Prescriptions were classified as glucose-lowering when the therapeutic class was ANTIDIABETIC AGENTS, ANTIDIABETIC COMBINATIONS, or INSULIN, and as thyroid medication when the therapeutic class was THYROID HORMONES or ANTITHYROID AGENTS. At the participant level, medication use was classified as present if at least one qualifying medication record was identified. Non-use was assigned only when no qualifying medication was identified and the available prescription-use and therapeutic-class information was fully resolved. Participants with unresolved therapeutic classifications, unspecified medications, or otherwise indeterminate prescription-use information were classified as having unknown medication status and were excluded from the corresponding medication sensitivity analyses.

2.4. Survey Design and Statistical Analysis

The 2007-2008 cycle used WTMEC2YR/3 and the 2009-2010 and 2011-2012 cycles used WTSA2YR/3, reflecting the relevant examination and one-third subsample designs when pooling three 2-year cycles [7]-[9] [32]. SDMVSTRA and SDMVPSU specified strata and primary sampling units, with cycle-nested strata. Analytic subpopulations were handled as survey domains. Taylor linearization was used for conventional models, and isolated PSUs were handled with the survey package adjust option; analyses were implemented with the R survey package [33]. Continuous outcomes were modeled by survey-weighted linear regression; antibody positivity by survey-weighted quasibinomial logistic regression.

Models were M1 (unadjusted), M2 (age, sex, race/ethnicity, cycle), and M3 (M2 plus BMI, smoking, serum creatinine). Natural splines of log₂ UIC used four degrees of freedom primarily and three as a sensitivity analysis; overall Wald and

nested nonlinearity tests were distinguished. Sex, continuous age, and antibody status were tested as effect modifiers. Exploratory path coefficients a , b , c , and c' were estimated in identical antibody-specific samples, and $a \times b$ was summarized using stratified jackknife replicate weights and approximate t -based 95% confidence intervals with 49 design degrees of freedom. These are statistical paths, not identified causal mediation effects [6]. Benjamini-Hochberg adjustment was applied separately to three families of three secondary tests [34]. Spline and sensitivity P values remained exploratory and unadjusted. No equivalence margins, equivalence tests, or multiple imputation were specified.

2.5. Quality Checks and Sensitivity Analyses

Analyses evaluated missingness, extreme UIC values, weighted 1st/99th-percentile winsorization, removal of the maximum UIC, alternative adjustment using waist circumference, urinary iodine-to-creatinine ratio, additional log₂ urinary creatinine, diabetes and medication exclusions, and survey-cycle differences. The expanded HbA_{1c} sample assessed sensitivity to antibody-measurement selection. Missingness categories in the participant flow are sequential, not mutually independent missingness estimates. Additional details are provided in Supplementary **Table S1** (interaction contrasts), Supplementary **Table S2** (derived analytic variables), Supplementary **Table S3** (participant selection), Supplementary **Table S4** (missingness), Supplementary **Table S5** (antibody lower-value piling), Supplementary **Table S6** (sensitivity analyses), Supplementary **Table S7** (natural-spline analyses), Supplementary **Table S8** (cycle-specific associations), Supplementary **Table S9** (UIC quartile analyses), Supplementary **Table S10** (antibody-specific path coefficients), and Supplementary **Table S11** (jackknife path estimates).

2.6. Ethics Statement

The NHANES 2007-2008 and 2009-2010 protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board under continuation of Protocol #2005-06, and the NHANES 2011-2012 protocol was approved under Protocol #2011-17. Written informed consent was obtained from all participants according to NHANES procedures [35]. The present study was a secondary analysis of publicly available, de-identified NHANES datasets and involved no direct participant contact. Therefore, additional ethical approval was not required for this secondary analysis according to applicable institutional policies.

3. Results

3.1. Sample Characteristics

The characteristics of the 8278 participants are presented in **Table 1**. The 8278 participants included 4867, 1875, and 1536 participants across the three successive cycles. Weighted mean age was 47.15 years; 51.2% were women, 68.7% were non-Hispanic White, mean BMI was 28.61 kg/m², and mean HbA_{1c} was 5.62%. Median UIC was 141.5 µg/L (interquartile range 78.3 - 247.1). Median TPOAb and

Table 1. Participant characteristics by weighted UIC quartile.

Variable	Overall n = 8278	Q1 n = 1840	Q2 n = 2113	Q3 n = 2141	Q4 n = 2184
UIC µg/L	141.5 (78.3, 247.1)	50.4 (34.3, 63.9)	108.4 (93.4, 124.9)	184.6 (162.8, 212.5)	364.6 (295.2, 497.5)
Age years	47.15 (0.43)	45.11 (0.67)	46.42 (0.59)	47.91 (0.68)	49.17 (0.66)
Male	48.8	39.4	48.7	51.6	55.6
Female	51.2	60.6	51.3	48.4	44.4
Mexican American	8.0	6.8	8.7	8.7	7.8
Other Hispanic	5.7	5.7	5.4	6.1	5.8
Non-Hispanic White	68.7	68.5	67.2	69.6	69.6
Non-Hispanic Black	10.6	11.1	12.2	10.1	9.1
Other/multiracial	6.9	8.0	6.5	5.6	7.7
2007-2008	31.7	25.8	31.3	33.2	36.4
2009-2010	34.0	34.4	35.7	34.1	32.0
2011-2012	34.3	39.7	33.0	32.7	31.6
BMI kg/m ²	28.61 (0.13)	27.55 (0.23)	28.61 (0.25)	29.06 (0.34)	29.22 (0.22)
Never smoker	54.5	52.5	54.3	54.8	56.1
Former smoker	24.6	23.5	23.6	25.0	26.3
Current smoker	20.9	23.9	22.1	20.2	17.5
Serum creatinine mg/dL	0.875 (0.004)	0.834 (0.008)	0.876 (0.007)	0.885 (0.005)	0.906 (0.008)
HbA1c %	5.62 (0.01)	5.55 (0.02)	5.65 (0.03)	5.65 (0.03)	5.64 (0.02)
TPOAb IU/mL	0.60 (0.30, 1.70)	0.70 (0.30, 1.90)	0.60 (0.30, 1.60)	0.60 (0.30, 1.50)	0.70 (0.30, 1.80)
TgAb IU/mL	0.60 (0.60, 0.60)	0.60 (0.60, 0.60)	0.60 (0.60, 0.60)	0.60 (0.60, 0.60)	0.60 (0.60, 0.60)
TPOAb positive %	12.02	13.26	11.97	11.15	11.72
TgAb positive %	7.89	9.35	7.40	8.07	6.72
Either antibody positive %	15.26	16.24	15.37	14.58	14.88

Note: Values are survey-weighted estimates. UIC, TPOAb, and TgAb are presented as median (interquartile range); age, BMI, serum creatinine, and HbA1c as mean (standard error); and categorical variables as weighted percentages. Q1 - Q4 are weighted UIC quartiles. Antibody estimates use outcome-specific available samples: n = 8,207 for TPOAb, n = 8,230 for TgAb, and n = 8,159 for either-antibody positivity.

TgAb were both 0.60 IU/mL. Weighted positivity prevalences were 12.02% (95% CI 10.69 - 13.49) for TPOAb, 7.89% (6.83 - 9.09) for TgAb, and 15.26% (13.87 - 16.78) for either antibody.

3.2. Primary Associations

Associations between UIC and HbA1c and thyroid autoantibodies are summarized

in **Table 2**, **Table 3**, and **Figure 1**. The unadjusted HbA1c difference per UIC doubling was 0.0229 percentage points (95% CI 0.0041 - 0.0417; $P = 0.018$), decreasing to -0.0004 ($P = 0.966$) in M2 and -0.0127 (95% CI -0.0316 - 0.0061 ; $P = 0.180$) in M3. Fully adjusted geometric mean ratios were 0.972 (0.926 - 1.020) for TPOAb and 0.982 (0.959 - 1.005) for TgAb; the OR for either-antibody positivity was 0.972 (0.895 - 1.055). The respective BH-adjusted P values were 0.368, 0.368, and 0.481. UIC quartile analyses did not show a clear monotonic pattern (overall $P = 0.500$ for HbA1c; $P = 0.831$ for either-antibody positivity; Supplementary **Table S9**).

3.3. Antibody Associations and Exploratory Paths

Associations between thyroid autoantibodies and HbA1c are summarized in **Table 3**. Exploratory statistical pathways linking urinary iodine concentration,

Table 2. UIC and thyroid antibody associations.

Outcome	Model	n	Effect estimate, 95% CI	P	BH P
TPOAb	M1	8207	0.974 (0.925, 1.025)	0.303	—
TPOAb	M2	8207	0.978 (0.929, 1.029)	0.378	—
TPOAb	M3	8207	0.972 (0.926, 1.020)	0.245	0.368
TgAb	M1	8230	0.986 (0.962, 1.012)	0.280	—
TgAb	M2	8230	0.985 (0.962, 1.008)	0.187	—
TgAb	M3	8230	0.982 (0.959, 1.005)	0.124	0.368
Either antibody positive	M1	8159	0.977 (0.900, 1.060)	0.571	—
Either antibody positive	M2	8159	0.976 (0.899, 1.060)	0.561	—
Either antibody positive	M3	8159	0.972 (0.895, 1.055)	0.481	0.481

Note: TPOAb and TgAb effect estimates are geometric mean ratios per doubling of UIC; either-antibody positivity is an odds ratio per doubling of UIC. M1 is unadjusted; M2 adjusts for age, sex, race/ethnicity, and survey cycle; M3 additionally adjusts for BMI, smoking, and serum creatinine. BH P denotes the Benjamini-Hochberg adjusted P value for the three M3 secondary tests.

Table 3. Associations of UIC and thyroid autoantibodies with HbA1c.

Exposure/comparison	Model	n	β , 95% CI	P	BH P
UIC per doubling	M1	8278	0.0229 (0.0041, 0.0417)	0.018	—
UIC per doubling	M2	8278	-0.0004 (-0.0192 , 0.0184)	0.966	—
UIC per doubling	M3	8278	-0.0127 (-0.0316 , 0.0061)	0.180	—
TPOAb per doubling	M3 + UIC	8207	0.0091 (-0.0011 , 0.0192)	0.078	0.120
TgAb per doubling	M3 + UIC	8230	0.0117 (-0.0032 , 0.0267)	0.120	0.120
Either antibody positive vs negative	M3 + UIC	8159	0.0441 (-0.0103 , 0.0986)	0.109	0.120

Note: β values are absolute HbA1c percentage-point differences. UIC, TPOAb, and TgAb comparisons are per doubling; either-antibody positivity compares positive with negative. M1 - M3 are as defined in the Methods; antibody models additionally include UIC. BH P denotes the Benjamini-Hochberg adjusted P value for the three antibody-HbA1c secondary tests.

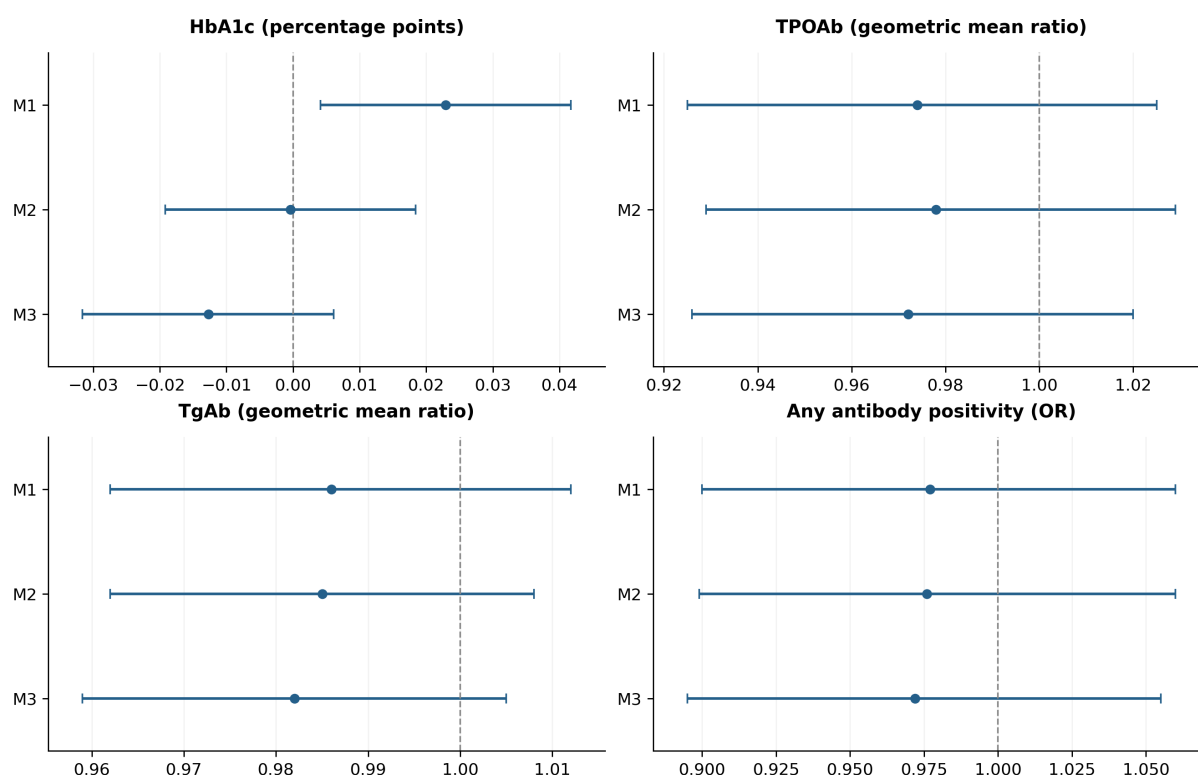


Figure 1. Associations per doubling of urinary iodine concentration with HbA1c and thyroid autoantibodies. Estimates and 95% confidence intervals are displayed on outcome-specific scales. M1 - M3 are as defined in the Methods.

thyroid autoantibodies, and HbA1c are presented in **Figure 2**. After adjusting for UIC and M3 covariates, each doubling of TPOAb and TgAb corresponded to HbA1c differences of 0.0091 (95% CI -0.0011 - 0.0192 ; $P = 0.078$) and 0.0117 (-0.0032 - 0.0267 ; $P = 0.120$) percentage points. Either-antibody positivity corresponded to 0.0441 (-0.0103 - 0.0986 ; $P = 0.109$) percentage points. All three BH-adjusted P values were 0.120. TPOAb path coefficients (a , b , c , and c') were -0.0282 , 0.0131 , -0.0125 , and -0.0122 , respectively; the corresponding TgAb coefficients were -0.0183 , 0.0169 , -0.0130 , and -0.0127 (Supplementary **Table S10**). The jackknife $a \times b$ estimates were -0.000368 (95% CI -0.001053 to 0.000318) for TPOAb and -0.000309 (95% CI -0.000767 to 0.000148) for TgAb (Supplementary **Table S11**). For both antibodies, the 95% CIs for the indirect estimates included zero.

3.4. Splines and Cycle Differences

The adjusted natural spline analysis is shown in **Figure 3**. In the main sample, the four-degree-of-freedom spline had an overall $P = 0.0218$ and a nonlinearity $P = 0.2967$; the corresponding three-degree-of-freedom values were 0.0255 and 0.1775. In the stricter diabetes- and glucose-lowering-medication-exclusion sample ($n = 7084$), the corresponding four-degree-of-freedom values were 0.1389 and 0.2025 (Supplementary **Table S7**). Cycle-specific M3 slopes were 0.0071, -0.0379 , and -0.0061 for 2007-2008, 2009-2010, and 2011-2012, respectively. The interaction

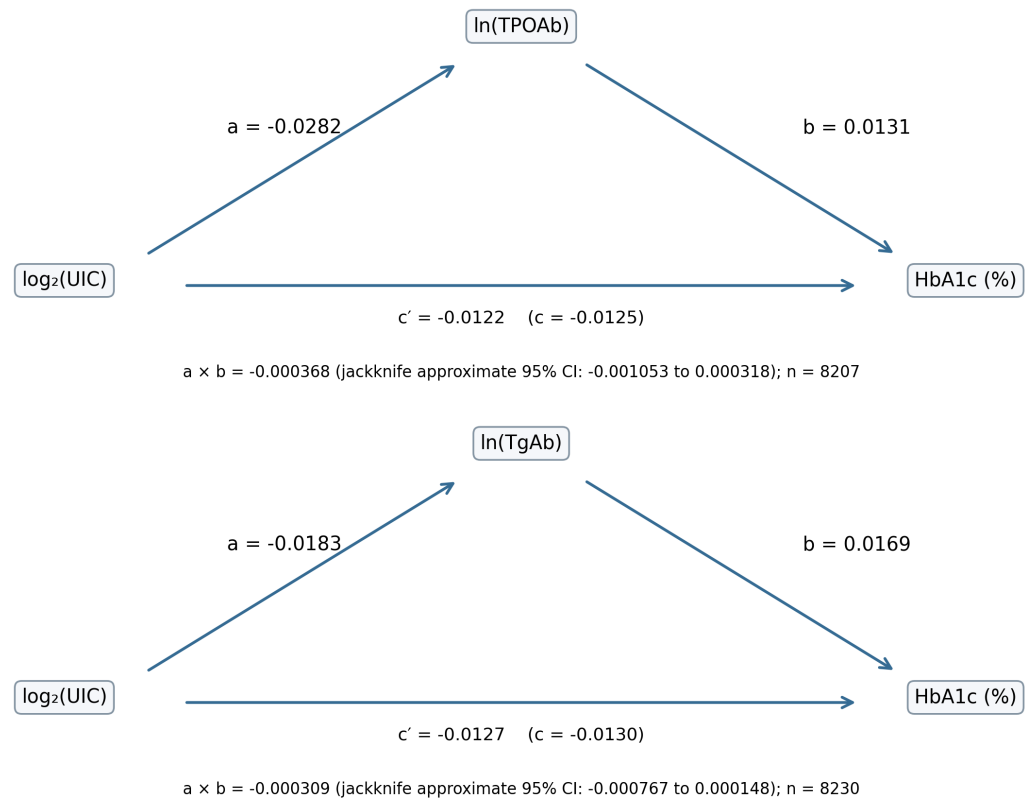


Figure 2. Exploratory statistical pathways relating urinary iodine concentration, thyroid autoantibodies, and HbA1c. UIC was log2-transformed and antibody concentrations were ln-transformed; therefore, b coefficients represent HbA1c differences per one-unit increase in ln(antibody), whereas **Table 3** reports associations per doubling.

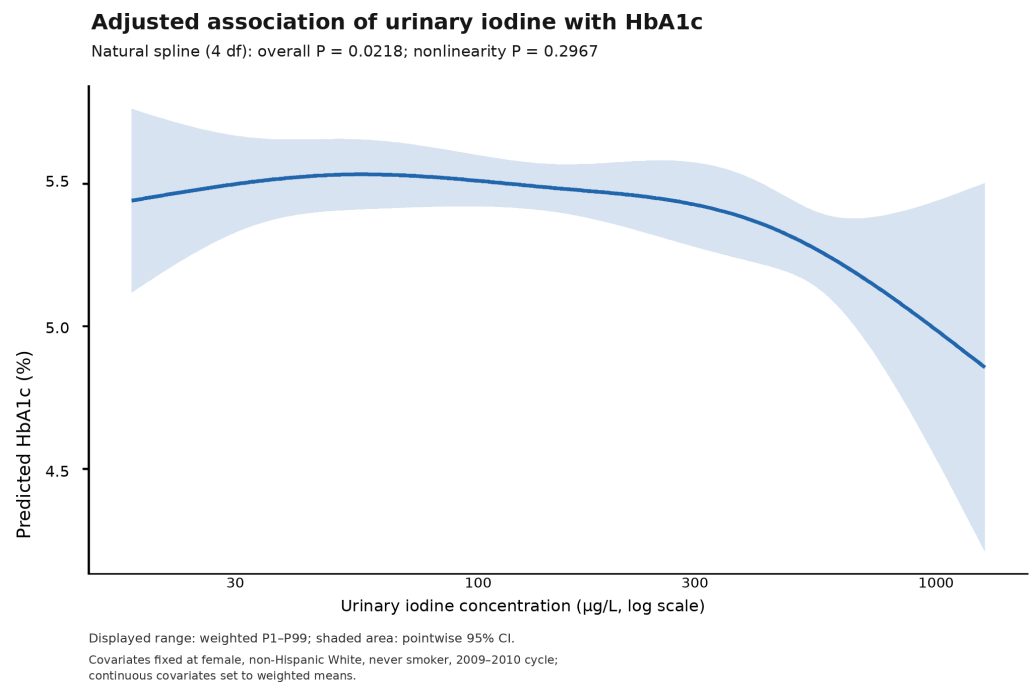


Figure 3. Adjusted natural spline (4 degrees of freedom) for urinary iodine concentration and predicted HbA1c.

P across survey cycles was 0.0235 in the primary sample and 0.1706 in the stricter diabetes- and glucose-lowering-medication-exclusion sample (Supplementary **Table S8**). The nominal spline and cycle-specific signals attenuated after sensitivity exclusions, while the tests for nonlinearity remained non-significant.

3.5. Interactions and Sensitivity Analyses

Conditional slopes and interaction tests are presented in **Table 4**, with corresponding interaction contrasts provided in Supplementary **Table S1**. Conditional HbA1c slopes were -0.0299 (95% CI -0.0531 to -0.0067) in men and 0.0015 (-0.0278 to 0.0308) in women; the sex interaction P was 0.0996 (BH-adjusted P = 0.2989). The interaction P values for age and antibody status were 0.6291 and 0.8693, respectively. In the expanded HbA1c sample ($n = 8,344$), M3 β was -0.0116 (95% CI -0.0300 to 0.0069 ; $P = 0.213$). Winsorization and exclusion of the maximum UIC yielded $\beta = -0.0115$ and -0.0125 , respectively. With iodine-to-creatinine ratio as exposure, $\beta = 0.00569$ (95% CI -0.01470 to 0.02608); adding log₂ urinary creatinine to the UIC model yielded $\beta = 0.00006$ (-0.02152 to 0.02164). Excluding diagnosed diabetes and reported glucose-lowering treatment ($n = 7190$) yielded $\beta = -0.0050$; progressively stricter medication exclusions yielded $\beta = -0.0040$ ($n = 7084$) and -0.0039 ($n = 6662$). All corresponding 95% CIs included zero (Supplementary **Table S6**). Approximately 85% of weighted TgAb observations were concentrated at the lowest observed value of 0.6 IU/mL, potentially limiting discrimination among low antibody concentrations (Supplementary **Table S5**). Of 9,421 eligible nonpregnant adults, 1143 were excluded from the main sample.

Table 4. Conditional slopes and interaction tests.

Modifier	Group or age	n	β 95% CI	Interaction P	BH P
Sex	Male	4132	-0.0299 (-0.0531 , -0.0067)	0.100	0.299
Sex	Female	4146	0.0015 (-0.0278 , 0.0308)	0.100	0.299
Antibody status	Negative	7007	-0.0135 (-0.0296 , 0.0026)	0.869	0.869
Antibody status	Positive	1152	-0.0074 (-0.0847 , 0.0699)	0.869	0.869
Continuous age	30 years	—	-0.0100 (-0.0314 , 0.0113)	0.629	0.869
Continuous age	50 years	—	-0.0131 (-0.0321 , 0.0059)	0.629	0.869
Continuous age	70 years	—	-0.0162 (-0.0407 , 0.0083)	0.629	0.869

Note: β is the conditional HbA1c percentage-point difference per doubling of UIC within the specified subgroup or at the specified age. Interaction P tests the UIC $\times$ modifier interaction; BH P is the Benjamini-Hochberg adjusted interaction P value.

4. Discussion

In this survey-weighted analysis, the fully adjusted linear association between spot UIC and HbA1c was small and imprecisely estimated. Its confidence interval permits small positive or negative associations and should not be interpreted as evidence of no association [5]. Similarly, antibody results differed in precision, and

the data do not establish that antibodies and HbA1c are unrelated. Single spot UIC cannot represent long-term individual iodine intake [1].

These findings address a different estimand from the regional long-term iodine study of Teng *et al.* [2] and the longitudinal thyroid-function/diabetes study of Chaker *et al.* [4]. Zhang *et al.* reported elevated antibody-positivity odds at UIC 500 - 800 versus 100 - 200 $\mu\text{g/L}$ in 6,612 NHANES participants [3]. Their restricted UIC range, categorized exposure, covariate selection, and selenium analyses differ from our continuous UIC slope and HbA1c outcome. Because the exposure definitions and analytic models differed substantially, the two estimates are not directly comparable.

Exploratory spline and cycle tests produced some nominally significant findings, but the spline nonlinearity tests did not demonstrate improved fit over a linear model. Results changed with exclusions and urinary dilution treatment. Thus, a U-shaped association, optimal iodine range, or subgroup-specific causal effect cannot be inferred. The marked accumulation of TgAb values at the same low value may have limited discrimination at low concentrations. Laboratory procedures also varied across survey cycles [10]-[18], which may have affected sensitivity to subtle between-participant differences; the magnitude and direction of any resulting bias are unknown.

Strengths include three NHANES cycles, design-based variance estimation, explicit outcome-specific samples, confidence intervals, and diverse sensitivity checks. Limitations include cross-sectional temporality, within-person UIC variability, complete-case selection, low-end antibody value accumulation, possible residual confounding by diet, selenium, supplementation, socioeconomic factors, and thyroid function, linear covariate specifications, and uncertain medication classification. The jackknife paths account for sampling variability but do not satisfy assumptions required for causal mediation [6].

5. Conclusion

Among US adults in NHANES 2007-2012, spot UIC was not clearly associated with HbA1c or thyroid autoantibodies after full adjustment in the primary linear models. Exploratory findings were sensitive to sample restrictions and model specification. Repeated UIC measurements, improved confounder control, and longitudinal designs are needed. These observational findings should not guide individual iodine diagnosis or supplementation decisions.

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Author Contributions

Conceptualization, J.P. and C.S.; methodology, C.C.; software, C.C.; validation, T.J. and C.S.; formal analysis, C.C.; investigation, T.J.; resources, J.P.; data curation, C.C.; writing, C.C.; visualization, C.C.; supervision, C.S.; project administration, C.S. All authors have read and agreed to the published version of the manuscript.

Data Availability

The NHANES datasets and accompanying documentation used in this study are publicly available from the Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS). The analysis code and supporting materials for this study are available on Zenodo at <https://doi.org/10.5281/zenodo.23397166>.

Ethics Approval and Consent to Participate

NHANES was conducted under protocols approved by the National Center for Health Statistics Research Ethics Review Board. The present study used publicly available, de-identified NHANES data and therefore did not require additional institutional ethical approval.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Tables

Table S1. Interaction contrasts corresponding to conditional UIC-HbA1c slopes.

Comparison	β 95% CI	Interaction P	BH P
Slope difference for female vs male	0.0314 (−0.0063, 0.0692)	0.100	0.299
Slope change per 10-year increase in age	−0.0016 (−0.0080, 0.0049)	0.629	0.869
Slope difference for antibody-positive vs antibody-negative	0.0061 (−0.0689, 0.0811)	0.869	0.869

Table S2. Definitions of derived analytic variables.

Role	Variable	Definition
Weight	wt_core	2007-2008: WTMEC2YR/3; the latter two cycles: WTSA2YR/3
UIC	log2_uic	log2(URXUIO), finite and >0
Antibodies	log_tpo/log_tgab	ln(LBXTPO)/ln(LBXATG), finite and >0
Positivity	tpo_pos/tgab_pos	≥9 and ≥4 IU/mL, respectively
Combined antibody status	auto_pos	Any positive = 1; both valid negative = 0; otherwise missing. Analyses required both antibodies valid.
UIC/creatinine ratio	log2_uic_cr	log2 (100 × URXUIO/URXUCR); original ratio in µg/g
Age interaction	age10	(RIDAGEYR−50)/10

Table S3. Sequential participant selection for the primary analysis.

Stage	n	Excluded at this step
Three cycles combined	30,442	—
Valid weights and survey design information	15,233	15,209
Age ≥ 20 years	9519	5714
Excluding known pregnancy	9421	98
Valid UIC	8945	476
At least one valid antibody measure	8395	550
Valid HbA1c	8381	14
Complete covariates	8278	103

Table S4. Missingness among adults remaining after age and pregnancy exclusions.

Variable	n missing/9421	Unweighted missing %	Weighted missing %
UIC	476	5.05	3.22
Urinary creatinine	222	2.36	1.56
TPOAb	808	8.58	7.03
TgAb	784	8.32	7.07
HbA1c	502	5.33	3.90

Continued

BMI	153	1.62	1.24
Smoking	7	0.074	0.035

Note: Variable-specific missingness is assessed independently among the 9,421 adults remaining after age and pregnancy exclusions. The 103 participants sequentially excluded for incomplete M3 covariates after the preceding UIC, antibody, and HbA1c eligibility criteria are reported in Supplementary **Table S3** and are not the number with any M3 covariate missing in the full $n = 9,421$ sample.

Table S5. Antibody lower-value piling by NHANES cycle.

Antibody and cycle	Lowest observed value	Sample n	Weighted piling proportion %
TPOAb 2007-2008	0.10	4827	4.87
TPOAb 2009-2010	0.18	1855	7.13
TPOAb 2011-2012	0.18	1525	24.21
TgAb 2007-2008	0.60	4857	85.95
TgAb 2009-2010	0.60	1846	85.39
TgAb 2011-2012	0.60	1527	84.77

Note: The lowest observed values are the minimum numeric values present in the publicly released NHANES datasets and should not be interpreted as assay limits of detection or analytical sensitivities.

Table S6. Sensitivity analyses for the UIC-HbA1c association.

Model or sample	n	β 95% CI	P
Primary model	8278	-0.0127 (-0.0316, 0.0061)	0.180
Original UIC in the same sample	8277	-0.0128 (-0.0317, 0.0061)	0.178
UIC/urinary creatinine ratio	8277	0.0057 (-0.0147, 0.0261)	0.575
Additional adjustment for log2 urinary creatinine	8277	0.0001 (-0.0215, 0.0216)	0.996
Waist-circumference complete sample, adjusted for BMI	8054	-0.0107 (-0.0306, 0.0092)	0.282
Waist-circumference complete sample, adjusted for waist circumference	8054	-0.0105 (-0.0314, 0.0104)	0.316
Weighted P1/P99 winsorization	8278	-0.0115 (-0.0316, 0.0086)	0.254
Excluding the maximum UIC value	8277	-0.0125 (-0.0313, 0.0063)	0.190
Excluding diagnosed diabetes and questionnaire-reported glucose-lowering treatment	7190	-0.0050 (-0.0249, 0.0148)	0.617
Further excluding prescription glucose-lowering drugs and unknown medication status	7084	-0.0040 (-0.0236, 0.0156)	0.684
Further excluding glucose-lowering drugs, thyroid drugs, and unknown medication status	6662	-0.0039 (-0.0241, 0.0162)	0.697
Excluding thyroid drugs and unknown medication status only	7620	-0.0164 (-0.0352, 0.0024)	0.086
Expanded HbA1c sample without the antibody-validity inclusion restriction	8344	-0.0116 (-0.0300, 0.0069)	0.213

Table S7. Natural-spline sensitivity analyses.

Sample	Degrees of freedom	n	Overall P	Nonlinearity P
Primary analysis	4	8278	0.0218	0.2967
Primary analysis	3	8278	0.0255	0.1775

Continued

Stricter diabetes- and glucose-lowering-medication-exclusion sample	4	7084	0.1389	0.2025
Stricter diabetes- and glucose-lowering-medication-exclusion sample	3	7084	0.1336	0.1723

Table S8. Cycle-specific UIC-HbA1c associations.

Analytic sample and cycle	n	β 95% CI	P
Primary analysis 2007-2008	4867	0.0071 (−0.0229, 0.0371)	0.571
Primary analysis 2009-2010	1875	−0.0379 (−0.0701, −0.0057)	0.029
Primary analysis 2011-2012	1536	−0.0061 (−0.0583, 0.0461)	0.785
Stricter diabetes- and glucose-lowering-medication-exclusion sample 2007-2008	4170	0.0068 (−0.0150, 0.0285)	0.460
Stricter diabetes- and glucose-lowering-medication-exclusion sample 2009-2010	1616	−0.0211 (−0.0489, 0.0066)	0.107
Stricter diabetes- and glucose-lowering-medication-exclusion sample 2011-2012	1298	0.0032 (−0.0231, 0.0295)	0.779

Interaction P across survey cycles was 0.0235 in the primary sample and 0.1706 after diabetes/glucose-lowering-treatment exclusion.

Table S9. Weighted UIC quartile associations with HbA1c and antibody positivity.

Outcome and comparison	Effect 95% CI	P
HbA1c Q2 vs Q1	0.0418 (−0.0383, 0.1220)	0.296
HbA1c Q3 vs Q1	0.0069 (−0.0530, 0.0669)	0.816
HbA1c Q4 vs Q1	−0.0179 (−0.0901, 0.0543)	0.617
Antibody positivity Q2 vs Q1	0.978 (0.724, 1.322)	0.883
Antibody positivity Q3 vs Q1	0.884 (0.658, 1.188)	0.403
Antibody positivity Q4 vs Q1	0.903 (0.661, 1.233)	0.509

Table S10. Exploratory antibody-specific path coefficients.

Antibody	Path	n	β 95% CI	P
TPOAb	a	8207	−0.0282 (−0.0765, 0.0202)	0.245
TPOAb	b	8207	0.0131 (−0.0015, 0.0277)	0.078
TPOAb	c	8207	−0.0125 (−0.0316, 0.0065)	0.191
TPOAb	c'	8207	−0.0122 (−0.0311, 0.0068)	0.201
TgAb	a	8230	−0.0183 (−0.0418, 0.0052)	0.124
TgAb	b	8230	0.0169 (−0.0046, 0.0385)	0.120
TgAb	c	8230	−0.0130 (−0.0322, 0.0062)	0.177
TgAb	c'	8230	−0.0127 (−0.0321, 0.0066)	0.191

Table S11. Jackknife estimates of indirect, direct, and total associations.

Antibody and effect	Estimate	SE	95% CI
TPOAb indirect	−0.0003677444	0.0003412119	−0.0010534354 to 0.0003179465
TPOAb direct	−0.0121685233	0.0093381338	−0.0309342057 to 0.0065971590
TPOAb total association	−0.0125362678	0.0094042959	−0.0314349079 to 0.0063623723
TgAb indirect	−0.0003094849	0.0002277314	−0.0007671283 to 0.0001481585
TgAb direct	−0.0127223929	0.0095316650	−0.0318769909 to 0.0064322051
TgAb total association	−0.0130318778	0.0094551160	−0.0320326448 to 0.0059688893