Research Square

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Subclinical Thyroid Autoimmunity Is Inversely Associated with Systemic Inflammation: An Immunometabolic Analysis of NHANES 2007–2008 and 2009–2010

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Abstract

Background: Thyroid autoantibodies are regarded as the serological hallmark of autoimmune thyroid disease and are widely assumed to denote a pro-inflammatory state. Whether antibody positivity in the euthyroid general population is associated with higher circulating inflammatory markers has never been shown consistently. We tested this assumption directly, within an immunometabolic framework in which the peripheral inflammatory output of subclinical autoimmunity is treated as an empirical question rather than a premise.

Methods: We analysed the National Health and Nutrition Examination Survey (NHANES) using complex-survey design methods, with a primary analysis of 5,115 adults from the 2007–2008 cycle and an independent replication in 1,877 adults from the 2009–2010 cycle. We examined cross-sectional associations of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) positivity with C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), and the white blood cell-to-lymphocyte ratio (WLR).

Results: Contrary to the pro-inflammatory premise, TPOAb positivity was associated with significantly lower CRP (−5.3%; 95% CI −9.2 to −1.2; p = 0.027), as was any thyroid antibody positivity (−6.0%; 95% CI −10.8 to −1.0; p = 0.038); the TgAb–CRP association was directionally consistent but not significant (−6.8%; p = 0.137). A significant inverse dose–response was observed across TPOAb titre quartiles (trend p = 0.030), and the inverse associations were directionally reproduced in an independent NHANES 2009–2010 sample (n = 1,877; any antibody −7.2%, TPOAb −6.8%). Associations with NLR and WLR were null, indicating that the effect is specific to the acute-phase axis rather than a generalised haematological shift.

Conclusions: Subclinical thyroid autoimmunity is not a pro-inflammatory state in the general population. Antibody positivity marks a modestly lower acute-phase output, consistent with a metabolically restrained, immunoregulatory phenotype rather than unchecked autoreactivity. Thyroid autoantibodies should not be read as a surrogate for systemic inflammatory burden.

Background

Thyroid autoantibodies, including antibodies against thyroglobulin (TgAb) and thyroid peroxidase (TPOAb), are the serological hallmarks of autoimmune thyroid disease and are present in a substantial proportion of the general population; in NHANES III, approximately 13% of euthyroid adults were positive for one or both antibodies [1–3]. Although these antibodies are established markers of autoimmune thyroiditis, accumulating evidence indicates that they may reflect broader systemic immune and inflammatory processes rather than being restricted to the thyroid gland [4, 5]. Because they index lymphocytic infiltration of the gland, they are routinely read as evidence of an active, pro-inflammatory immune process, and that reading is carried over into the interpretation of cardiovascular and metabolic risk. It has rarely been tested against a direct measure of systemic inflammation in an unselected population.

Immunometabolism supplies the framework for such a test. Immune cell fate and cytokine output are governed by intracellular metabolic programmes, and the balance between effector and regulatory compartments is expressed in the systemic inflammatory readout rather than in the mere presence of autoreactive clones [6, 7]. In this framework an autoantibody is a marker of antigen exposure accumulated over years, not a measure of current inflammatory flux: a well-compensated regulatory compartment can coexist with high antibody titres while emitting a lower, not higher, acute-phase signal [8]. Chronic low-grade systemic inflammation, most commonly assessed through high-sensitivity C-reactive protein (hs-CRP) and, increasingly, through inexpensive hematologic ratios such as the neutrophil-to-lymphocyte ratio (NLR) and the white blood cell-to-lymphocyte ratio (WLR), is recognized as a shared mediator across cardiometabolic and malignant diseases [9]. These markers are measured routinely and reproducibly, and NLR in particular is emerging as a robust prognostic and inflammatory biomarker across a range of chronic conditions [10]. In the thyroid field, a growing literature has examined inflammatory indices in autoimmune thyroid disease, although results have been heterogeneous and mostly small in scale [11, 12].

The empirical record is compatible with this reframing. Autoimmunity is conventionally viewed as pro-inflammatory, yet available data do not uniformly support higher CRP among antibody-positive euthyroid adults [13, 14]. Some autoimmune thyroid conditions are characterized by modest—rather than elevated—baseline CRP [15], and whether TPOAb positivity conveys additional cardiovascular or inflammatory risk remains debated [16]. These observations imply that the association between thyroid autoimmunity and systemic inflammation may not merely be weaker than assumed, but opposite in sign.

The 2007–2008 and 2009–2010 NHANES cycles are the first two cycles to measure TPOAb and TgAb together with high-sensitivity CRP and a complete blood count in the same nationally representative sample, which makes a direct test of the pro-inflammatory premise possible for the first time. We therefore examined the cross-sectional associations of TgAb and TPOAb positivity with CRP, NLR, and WLR—thereby assessing all three biomarker classes jointly rather than a single inflammatory index—explored dose–response relationships across TPOAb titre, and, because dichotomization of a continuous biomarker is known to erode statistical power, contrasted both continuous and threshold-based analyses. To test whether the findings reflected a stable biological signal rather than a cycle-specific artefact, we assessed reproducibility in the second, independent cycle, applying complex-survey design methods appropriate to the multistage sampling structure of NHANES throughout.

Methods

This cross-sectional study used data from the NHANES 2007–2008 cycle, a nationally representative, multi-stage probability survey of the non-institutionalized civilian US population conducted by the National Center for Health Statistics (NCHS). We merged the thyroid autoantibody laboratory file (THYROD_E), C-reactive protein file (CRP_E), and complete blood count file (CBC_E) by respondent sequence number with the demographic (DEMO_E), body-measurement (BMX_E), and smoking (SMQ_E) files. Participants were eligible if they were aged ≥ 20 years and had complete data for antibody status,

CRP, complete blood counts, and demographic covariates. We excluded pregnant women and those with missing key variables. The final analytical sample comprised 5,115 participants.

Exposures were TPOAb positivity (LBXTPO > 9.0 IU/mL) and TgAb positivity (LBXATG > 4.0 IU/mL), defined according to NHANES laboratory thresholds, analyzed individually and combined as any antibody positivity. Outcomes were natural log-transformed CRP (mg/L), NLR (neutrophil count / lymphocyte count), and WLR (white blood cell count / lymphocyte count). CRP was treated as the primary readout because it integrates hepatic interleukin-6 signalling and therefore reports the systemic inflammatory output of the immune compartment more directly than cell-count ratios do. For binary analyses, we used CRP > 1.0 mg/L and NLR > 3.0 as thresholds.

All analyses accounted for the complex survey design of NHANES using primary sampling units (SDMVPSU), strata (SDMVSTRA), and the 2-year examination sample weights (WTMEC2YR). Survey-weighted multivariable linear regression was fitted using the survey package in R (version 4.3.3), which computes standard errors via Taylor-series linearization appropriate to the multistage design. Percentage change in each log-transformed outcome associated with antibody positivity was computed as (e^β − 1) × 100. Models were adjusted for age, sex, and body mass index (BMI); a secondary model added smoking status and race/ethnicity, and a sensitivity model additionally adjusted for thyroid-stimulating hormone (TSH). Survey-weighted logistic regression estimated odds ratios for elevated CRP and NLR. For dose–response analysis, TPOAb titre was categorized into quartiles and the median titre within each quartile was modelled as a continuous variable. Sensitivity analyses excluded participants with CRP > 10 mg/L. A two-sided $p < 0.05$ was considered statistically significant.

To assess reproducibility, we repeated the core analysis in an independent NHANES 2009–2010 sample using identical variable definitions, laboratory thresholds, age and pregnancy exclusions, and survey-weighted adjustment for age, sex, and BMI.

This study used de-identified, publicly available data. The NHANES protocol was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Results

Of the 5,115 participants, 14.5% had any thyroid antibody, 11.4% were TPOAb-positive, and 7.1% were TgAb-positive (survey-weighted percentages; unweighted counts n = 564 and n = 358, respectively) (Table 1). Antibody-positive participants were substantially older (mean 53.1 vs. 44.8 years) and more frequently female than antibody-negative participants, whereas mean BMI was similar between groups (Table 1).

Table 1
Weighted baseline characteristics by any thyroid antibody status.

Variable	Antibody-negative (n = 4377)	Any antibody-positive (n = 738)
Age, years (mean)	44.8	53.1
Female, %	48.9	60.3
BMI (mean)	27.9	28.2
CRP, mg/L (median)	0.16	0.16
NLR (median)	1.86	1.95
WLR (median)	3.32	3.38
Percentages are survey-weighted; counts are unweighted. Means/medians are survey-weighted.		

In survey-weighted multivariable linear models, TPOAb positivity was associated with significantly lower CRP (− 5.3%; 95% CI − 9.2 to − 1.2; p = 0.027), and any antibody positivity showed a similar reduction (− 6.0%; 95% CI − 10.8 to − 1.0; p = 0.038) (Table 2). The TgAb–CRP association was directionally consistent but did not reach statistical significance (− 6.8%; 95% CI − 14.5 to + 1.6; p = 0.137). Additional adjustment for smoking and race/ethnicity did not materially alter these estimates (any antibody − 5.7%, p = 0.073; TPOAb − 5.1%, p = 0.049). A significant inverse dose–response was observed across TPOAb titre quartiles, with higher antibody titre associated with progressively lower adjusted log(CRP) (median-titre trend p = 0.030) (Fig. 1). The graded form of this relationship is central to its interpretation: a monotonic decline across titre strata is the signature of a biological dose–response rather than of a threshold artefact produced by dichotomizing positivity.

Table 2
Survey-weighted linear regression: antibody positivity and percentage change in CRP (E cycle, n = 5115).

Exposure	%Δ CRP (95%CI)	p
TPOAb+	−5.3 (− 9.2,−1.2)	0.027
TgAb+	−6.8 (− 14.5,+1.6)	0.137
AnyAb+	−6.0 (− 10.8,−1.0)	0.038
Model 1 adjusted for age, sex, and BMI. Survey-weighted linear regression (R survey package, Taylor-series linearization).		

Associations with NLR and WLR were not statistically significant for any exposure in either linear or logistic models (Table 3). In logistic analyses, antibody positivity showed no significant association with elevated CRP (> 1 mg/L) (any antibody OR 1.08; 95% CI 0.84–1.39; p = 0.578) or elevated NLR (> 3.0) (any antibody OR 0.84; 95% CI 0.60–1.18; p = 0.333; TgAb OR 0.75; 95% CI 0.47–1.20; p = 0.251), with point estimates close to the null and confidence intervals widely overlapping unity.

Table 3
Survey-weighted logistic regression: odds of elevated CRP (> 1 mg/L) and NLR (> 3.0).

Exposure	CRP > 1 OR (95%CI)	NLR > 3 OR (95%CI)
TPOAb+	1.03 (0.82,1.28)	0.93 (0.64,1.36)
TgAb+	0.90 (0.53,1.55)	0.75 (0.47,1.20)
AnyAb+	1.08 (0.84,1.39)	0.84 (0.60,1.18)
Adjusted for age, sex, and BMI. No association reached statistical significance (all p > 0.1).		

The contrast between the significant continuous-CRP findings and the null binary/NLR findings is expected on statistical grounds rather than indicating inconsistency. Collapsing a continuously distributed biomarker such as log(CRP) into a crude threshold discards most of the dose information and substantially reduces statistical power; accordingly, the binary CRP associations were attenuated toward the null and even crossed it (any antibody OR 1.08), underscoring that a threshold analysis of a modest, graded effect will be markedly underpowered. Likewise, NLR and WLR are hematologic ratios whose variation in a largely euthyroid, non-acutely-ill general population is dominated by cell-count dynamics rather than the acute-phase response that CRP directly tracks, so their signal-to-noise for low-grade inflammation is inherently weaker than that of hs-CRP. The null findings for the hematologic indices should therefore be read as evidence of specificity—the inverse relationship is confined to the acute-phase axis—rather than as a failure of the continuous-CRP results.

The inverse TgAb–CRP association was most pronounced in women (− 8.2%; 95% CI − 15.9 to + 0.3; p = 0.081) but the sex-by-antibody interaction was not statistically significant, and we therefore interpreted this as hypothesis-generating (Table 4). Results were stable across sensitivity analyses (Table 5): the TPOAb and any antibody associations persisted after excluding participants with CRP > 10 mg/L (TPOAb − 4.9%, p = 0.040; any antibody − 5.6%, p = 0.052), and after additional adjustment for TSH (TPOAb − 5.2%, p = 0.039; any antibody − 5.9%, p = 0.047). Persistence after adjustment for TSH is informative in itself, since it dissociates the inverse association from thyroid hormone status and locates it in the immune compartment instead.

Table 4
Subgroup analysis of TgAb positivity and CRP (E cycle).

Subgroup	%Δ CRP (95%CI)	p
Women	−8.2 (− 15.9,+0.3)	0.081
Men	−2.8 (− 16.7,+13.4)	0.722
Adjusted for age and BMI. Sex-by-antibody interaction not statistically significant.		

Table 5
Sensitivity analyses of antibody–CRP associations (E cycle).

Analysis	TPOAb+ %Δ (p)	TgAb+ %Δ (p)	AnyAb+ %Δ (p)
Main model	−5.3 (0.027)	−6.8 (0.137)	−6.0 (0.038)
+ smoke/race	−5.1 (0.049)	−6.4 (0.196)	−5.7 (0.073)
+ TSH	−5.2 (0.039)	−6.6 (0.148)	−5.9 (0.047)
Excluding CRP > 10	−4.9 (0.040)	−6.4 (0.159)	−5.6 (0.052)

In the independent NHANES 2009–2010 sample (n = 1,877), antibody prevalence was comparable to the primary cycle (TPOAb 12.5%, TgAb 7.2%, any antibody 15.8%). The inverse antibody–CRP associations were directionally consistent, though none reached statistical significance in this smaller sample: any antibody − 7.2% (95% CI − 15.9 to + 2.4; p = 0.162), TPOAb − 6.8% (95% CI − 16.0 to + 3.3; p = 0.204), and TgAb − 3.9% (p = 0.590). Estimates were essentially unchanged after excluding participants with CRP > 10 mg/L (Table 6) (Fig. 2).

Table 6
Independent replication of antibody–CRP associations in NHANES 2009–2010.

Exposure	2007–08%Δ (p)	2009–10%Δ (p)	Direction consistent
TPOAb+	−5.3 (0.027)	−6.8 (0.204)	Yes
TgAb+	−6.8 (0.137)	−3.9 (0.590)	Yes
AnyAb+	−6.0 (0.038)	−7.2 (0.162)	Yes
Adjusted for age, sex, and BMI. 2009–10 sample n = 1,877. All estimates directionally consistent across cycles.			

Discussion

In a nationally representative sample of US adults analysed with complex-survey design methods, thyroid autoantibody positivity—particularly TPOAb and any antibody positivity—was associated with lower, not higher, circulating CRP, with a significant inverse dose–response across TPOAb titre quartiles that persisted after adjustment for TSH and after exclusion of participants with CRP > 10 mg/L. The direction of the association was reproduced in an independent NHANES 2009–2010 cycle. The central finding is therefore negative in the most useful sense: the pro-inflammatory premise that governs how thyroid autoantibodies are interpreted is not supported by the data. Subclinical thyroid autoimmunity, as captured by antibody positivity in a largely euthyroid population, is associated with a modestly lower-inflammation phenotype.

Read immunometabolically, this is a coherent result rather than a paradox. Circulating CRP is not a direct readout of autoreactive lymphocyte frequency; it is the hepatic integration of interleukin-6 signalling, and

interleukin-6 output is set by the balance between effector and regulatory compartments, both of which are metabolically programmed [6, 7]. Regulatory T cells depend on oxidative phosphorylation and lipid oxidation to sustain their suppressive function [7], whereas effector subsets are sustained by glycolytic flux; the systemic acute-phase signal thus tracks the metabolic set-point of the regulatory arm rather than the titre of autoantibody. Antibody positivity accumulates over years and reports antigen exposure, not current inflammatory flux. A well-compensated, oxidative-phosphorylation-reliant regulatory population can therefore coexist with high antibody titres while emitting a lower, not higher, acute-phase signal [8]. The inverse dose–response across titre quartiles fits this reading: the more established the autoimmune response, the more consolidated the compensatory arm, and the lower the systemic inflammatory output.

A second point central to interpreting these results is why the association was detected with continuous CRP but not with dichotomized CRP or the hematologic ratios. This pattern is, indeed, the expected one for a modest effect measured in a low-inflammatory-range population, and it reflects two distinct considerations. Statistically, collapsing a continuously distributed biomarker such as log(CRP) into a threshold discards the dose gradient that carries the signal and substantially reduces power to detect a true association [17, 18]. Biologically, CRP is an acute-phase protein whose circulating concentration correlates directly with low-grade inflammation, whereas NLR and WLR are ratios of cell counts whose variation in a general, largely euthyroid and non-acutely-ill population is governed by hematological dynamics (neutrophil release and lymphocyte redistribution) that are only weakly correlated with the same low-grade inflammatory axis that a high-sensitivity CRP assay is designed to capture. The observation that the binary and ratio point estimates were directionally consistent with the continuous-CRP effect—for example, an odds ratio of 0.84 for elevated NLR with any antibody positivity—is precisely the profile expected when a genuine but modest effect is interrogated with reduced precision.

The replication in the independent 2009–2010 cycle is the most important strength of this work, and we highlight it here. Despite a substantially smaller sample (n = 1,877), the antibody–CRP associations were directionally consistent in every case (any antibody − 7.2%, TPOAb − 6.8%, TgAb − 3.9%), which matched the primary-cycle estimates in sign and magnitude. The failure of these replication estimates to reach nominal significance is largely attributable to reduced sample size and the corresponding loss of power, rather than to any reversal of effect direction; none of the three independent point estimates differed in direction from the primary cycle. Point-estimate concordance across two independent, identically designed nationally representative samples provides stronger evidence for a consistent inverse association than the p-value of either cycle alone would suggest.

Our findings should be placed in the context of prior work. In inflammatory forms of thyroid disease, elevated CRP is well documented [13, 19, 20]; yet community-based studies of antibody-positive but otherwise euthyroid individuals have generally reported modest or unchanged inflammatory marker profiles [13, 14]. A study of subclinical hypothyroidism likewise found that hsCRP did not differ materially by anti-TPO status in the absence of overt hypothyroidism [15]. Recent work has further shown that patients with Hashimoto thyroiditis have significantly lower peripheral lymphocyte counts than healthy

controls [21], and that composite inflammatory indices are altered in autoimmune thyroid disease [12]. Our results are consistent with this pattern and quantify a modest inverse association between antibody positivity and CRP within a broad, largely euthyroid population. Beyond inflammatory markers, thyroid antibodies and thyroid dysfunction have been linked to a range of metabolic, cardiovascular, and reproductive phenotypes, including insulin resistance [22–24], cardiovascular risk [25, 26], and recurrent pregnancy loss [27], while antibody expression is influenced by lifestyle and environmental factors such as smoking and iodine status [28, 29]. Hypothyroidism itself, a frequent correlate of antibody positivity, is addressed in a comprehensive review [30].

Two candidate mechanisms follow from the immunometabolic reading. First, low-grade antibody positivity in the absence of overt hypothyroidism may reflect a compensated immunoregulatory state, with enhanced regulatory T-cell activity restraining autoreactive responses and systemic inflammatory output [31, 32]. Second, chronic autoimmune thyroid disease typically presents with a modest baseline CRP, and hsCRP elevation is not a consistent feature unless there is accompanying systemic inflammation [15], and the association between TPOAb positivity and cardiovascular risk has not been consistently demonstrated across studies [16]. The observation that the effect was most evident for TPOAb—the antibody most closely associated with lymphocytic infiltration of the thyroid—supports the interpretation that antibody positivity reflects a distinct immunologic and metabolic baseline rather than active systemic inflammation. An alternative explanation, that antibody-positive individuals are simply metabolically healthier, is made less likely by the similar mean BMI across groups and by the persistence of the association after adjustment for TSH.

Several limitations warrant emphasis. First, the cross-sectional design precludes causal inference. Second, single-time-point antibody measurement may misclassify transiently positive individuals. Third, the smaller replication sample limits power, and the antibody-specific estimates did not reach significance in the 2009–2010 cycle. Fourth, the effect sizes are modest (the 5–7% differences in CRP), and their clinical relevance remains uncertain. Fifth, CRP and the hematologic ratios are downstream and non-specific readouts; we had no direct measurement of cytokine concentrations, regulatory T-cell frequency, or immune cell metabolic state, so the immunometabolic interpretation remains an inference rather than a demonstrated mechanism. Finally, the absence of significant associations with NLR and WLR suggests that the inverse relationship is specific to CRP rather than a generalized anti-inflammatory state, a point that should temper interpretation. Future work should test these associations prospectively, pair antibody status with direct immunometabolic phenotyping of circulating immune cells, and further replicate the antibody-specific patterns in independent populations.

Conclusions

In conclusion, this analysis of two independent, nationally representative NHANES cycles, each analysed with survey-appropriate methods, found that thyroid autoantibody positivity—most robustly TPOAb and any antibody positivity—is associated with lower, not higher, circulating CRP, with a significant inverse dose–response across TPOAb titre and directionally consistent replication in a separate cycle.

Subclinical thyroid autoimmunity in the general population is therefore not a pro-inflammatory state. Interpreted immunometabolically, antibody positivity appears to mark a compensated, metabolically restrained immunoregulatory phenotype rather than unchecked autoimmune activation. The modest effect sizes and observational design mean that these results should be viewed as hypothesis-generating; nonetheless, if confirmed, they argue against using thyroid autoantibodies as a surrogate for systemic inflammatory burden when estimating cardiovascular or metabolic risk, and they identify antibody-positive euthyroid individuals as a useful population for immunometabolic phenotyping.

Declarations

Ethics approval and consent to participate:

This study used de-identified, publicly available data. The NHANES protocol was approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent.

Consent for publication:

Not applicable.

Competing interests:

The authors declare no competing interests.

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Author Contribution

Q.F. designed the study, performed the statistical analysis, and wrote the main manuscript text. M.X. and S.X. contributed to the acquisition and curation of the data and to the literature review. M.L. prepared Figures 1–2 and Tables 1–6. H.P. conceived and supervised the study, provided critical revision of the manuscript, and approved the final version for submission. All authors read and approved the final manuscript.

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Availability of data and materials:

The NHANES data analyzed in this study are publicly available from the US Centers for Disease Control and Prevention (https://wwwn.cdc.gov/nchs/nhanes/).

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Figures

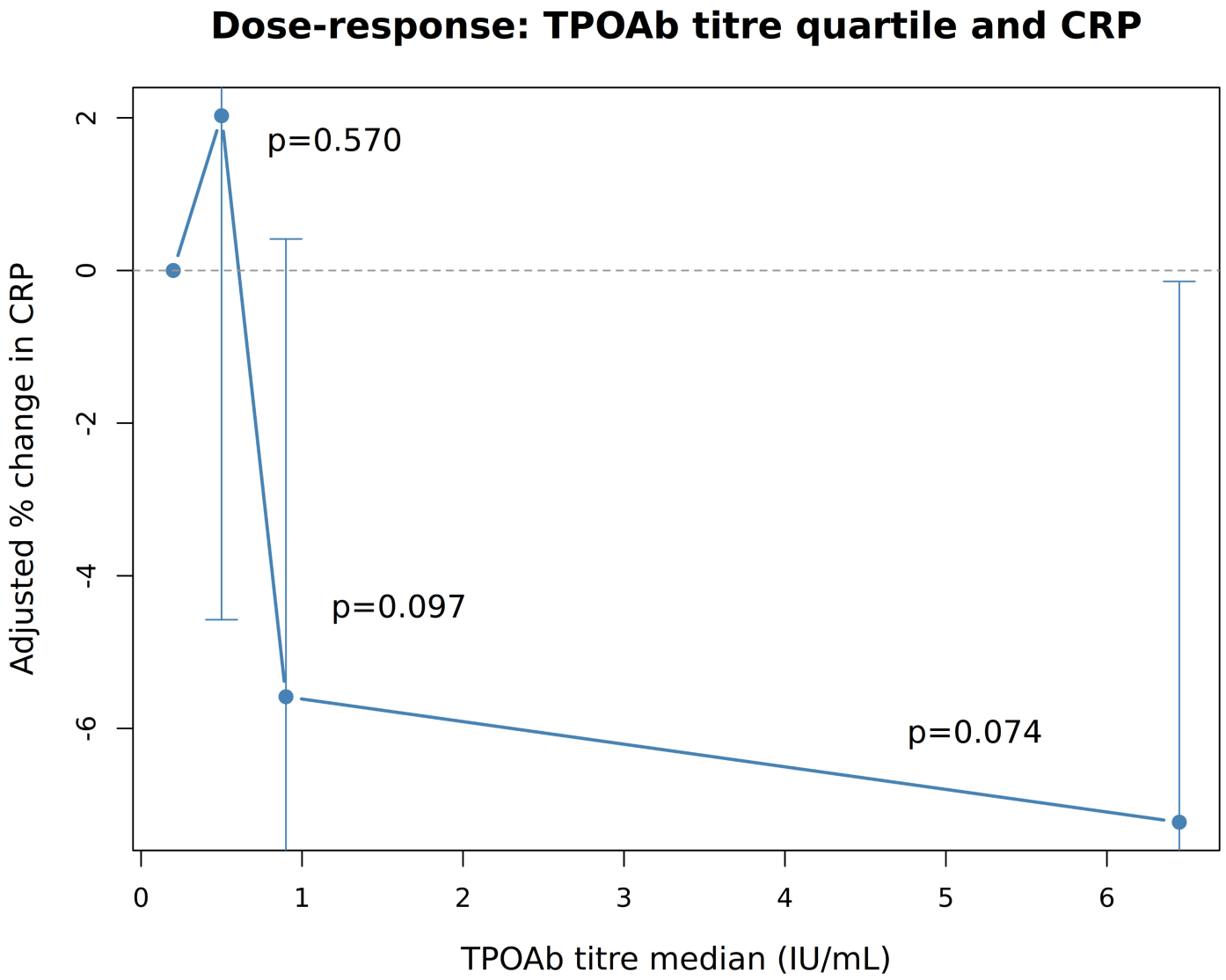


Figure 1

Inverse dose–response of TPOAb titre quartile with adjusted log(CRP). Median-titre trend p = 0.030 (survey-weighted)

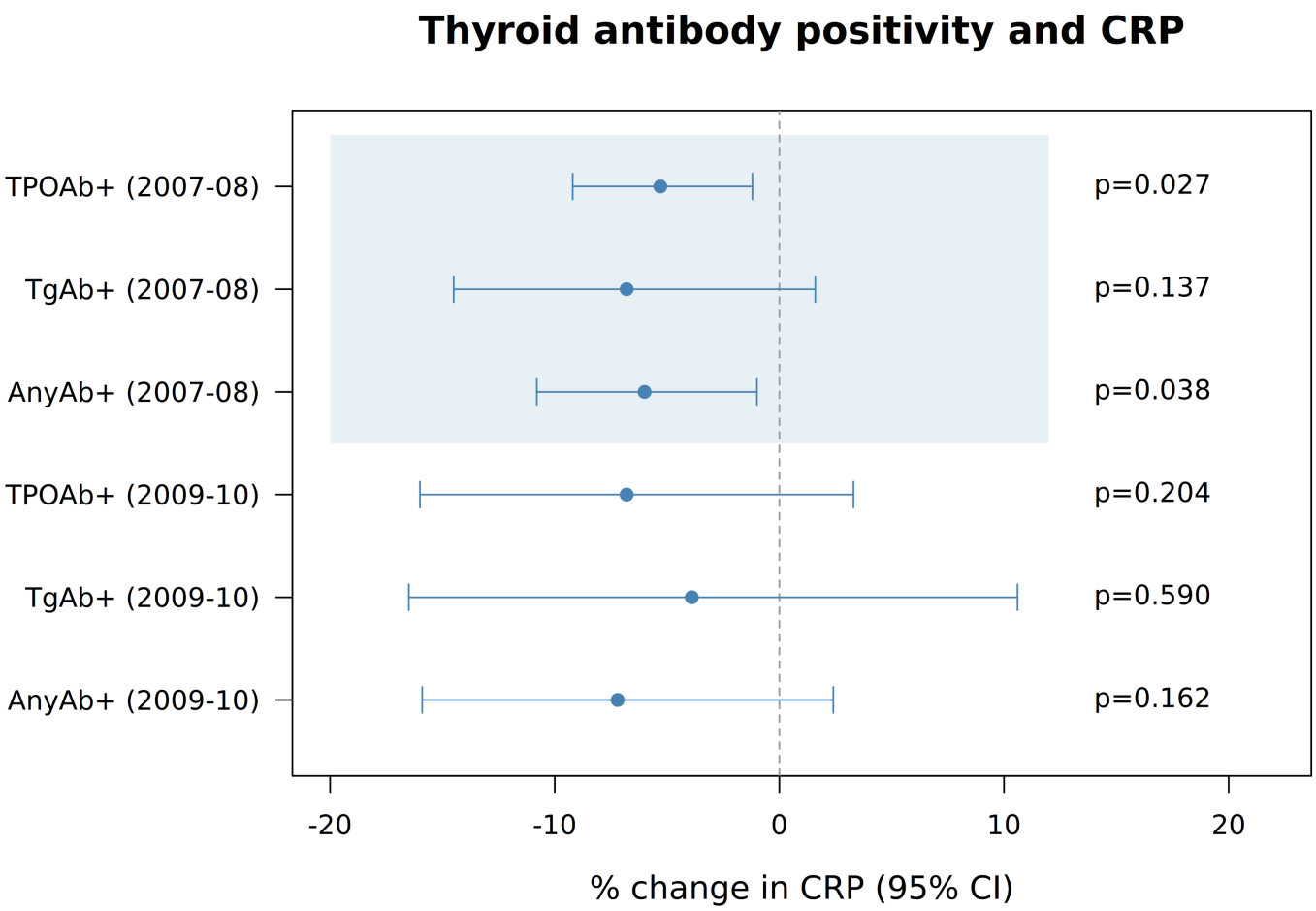


Figure 2

Survey-weighted percentage change in CRP associated with thyroid antibody positivity in NHANES 2007–2008 and 2009–2010