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The association of *Toxoplasma gondii* IgG and cognitive function scores: NHANES 2013–2014

R. Constance Wiener^{a,*}, Christopher Waters^b, Ruchi Bhandari^c

^aWest Virginia University, Department of Dental Practice and Rural Health, School of Dentistry, 104a Health Sciences Addition, PO Box 9415, Morgantown, WV 26506, United States of America

^bWest Virginia University, Department of Dental Research, School of Dentistry, 106a Health Sciences Addition, PO Box 9448, Morgantown, WV 26506, United States of America

^cWest Virginia University, Department of Epidemiology, School of Public Health, Robert C Byrd Health Sciences Center North, Room G104C, Morgantown, WV 26506, United States of America

Abstract

Toxoplasma gondii (*T. gondii*) causes chronic, latent infections of global concern. Its subclinical influence on behavior and cognition are poorly understood. The objective of this research is to determine the relationship of *T. gondii* IgG with cognition using National Health and Nutrition Examination Survey data, 2013–2014 in older adults ≥ 60 years. A composite cognitive function score was created by adding the scores of the memory test, language/verbal fluency, and working memory test. *T. gondii* IgG was dichotomized at < 33 IU/mL (negative) and ≥ 33 IU/mL (positive). There were 19.2% of the participants who were *T. gondii* IgG⁺. The memory function and language/verbal fluency subtests failed to reach significance; however, the difference in the working memory test was significant. In the multivariable ordinal logistic regression analysis, controlling for potential confounders, the odds of cognitive function scores decreasing in quartiles among people with positive vs. negative *T. gondii* IgG are 1.55 (95% CI: 1.08, 2.21; *p* = .0170). Establishing an evidence base for the association of *T. gondii* IgG and cognition is complex, but essential.

Keywords

Toxoplasma gondii; Cognition; NHANES

1. Introduction

Toxoplasma gondii (*T. gondii*), a single-celled, eukaryotic, protozoan parasite, has a definitive host in cats and many intermediate hosts [1]. Approximately 11% of the U.S.

*Corresponding author. rwiener2@hsc.wvu.edu (R.C. Wiener).

Data Availability

The data used to support the findings of this study are available from the NHANES 2013–2014 website at <https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013>

Declaration of Competing Interest

The authors have no conflicts of interest to report.

population is infected [2]. In certain areas of the world, the prevalence is 80% [3]. Although mental/cognitive implications of *T. gondii* infection were suspected since the 1950s, researchers are reporting the association may be stronger than originally suspected [4].

Toxoplasma gondii exposure occurs from eating undercooked contaminated meat/shellfish; eating food that contacted contaminated utensils/surfaces; drinking contaminated water or unpasteurized goat's milk; eating contaminated soil on unwashed fruits/vegetables; exposure after working in contaminated soil or cleaning a cat's contaminated litter box; receiving contaminated organ transplants/blood transfusions; and via congenital transmission [2]. Once a *Toxoplasma gondii* oocyst is shed from a cat and infects a person, the parasite becomes a tachyzoite and can cross the intestinal barrier. From there, it enters blood cells (e.g. macrophages). The cells act as "Trojan horses" [5] to cross the blood-brain barrier, and enter neurons, astrocytes, microglial and Purkinje cells [6].

Toxoplasmosis is often sub-clinical. In a healthy hosts, the immune system holds it in a latent, chronic state, balancing immune responses against the intracellular tachyzoites' ability to manipulate immune cell maturation, apoptosis, and functions [5]. Behavioral changes have been noted in infected animals. Researchers theorize behavior manipulation increases the parasites likelihood for transmission by manipulating the host to engage in risky behaviors so that the host is likely to be preyed upon, particularly by a feline. For example, rats are typically neophobic and avoid predators, but infected rats are more active, and are *attracted* to cat urine [6]. As other mammals, including primates, remain significant prey for large felines, *T. gondii* is suspected to increase their risk-taking behavior [3].

Evidence suggests *T. gondii* can synthesize dopamine, harvest folate from host neural cells, damage cells, and impair cognitive function [7]. Such manipulation may occur in disorders such as bipolar disease, personality disorder, Parkinson's disease, Alzheimer's disease, obsessive-compulsive disorder, cryptic epilepsy, recurrent migraines, autism, and some brain tumors, some homicides, and some suicides [4,8]. However, the association between *T. gondii* and generalized cognitive function has not been fully determined [9,10]. Cognitive function can be measured in many domains with many tests. One series is the NHANES cognitive functioning series of 1) Consortium to Establish a Registry for Alzheimer's disease Delayed Word List Learning Test (DWRT)—a memory test; 2) Animal Fluency Test—a language/verbal fluency test; and, 3) Digit Symbol Substitution Test—a processing speed and working memory test. For the DWRT, participants read ten words and recalled them after 8–10 min (maximum score = 10). For the Animal Fluency Test, participants named as many animals as possible in 60 s (score = number of correct responses). The Digit Symbol Substitution Test involved placing symbols next to a number based on a key in 120 s (maximum score = 133).

The purpose of this research is to evaluate the relationship of *T. gondii* IgG and cognition in older adults based upon the manipulation hypothesis [11,12]. The research hypothesis is that there is an association of poorer cognitive function and *T. gondii* IgG.

2. Materials and methods

The West Virginia University Institutional Review Board acknowledged this research. The data source was the National Health and Nutrition Examination Survey (NHANES) 2013–14 [13]. NHANES is a complex, multistage survey. Cognitive function data were extracted from it. Cognitive tests were presented to individuals ≥ 60 years ($n = 1785$). *T. gondii* IgG was determined using surplus serum ($n = 1558$). *T. gondii* IgG analyses were not conducted from 2001 to 2012 or after 2014. The sample with available data was limited to NHANES 2013–2014.

The variable, composite cognitive function score, was created by adding the scores of the memory test, language/verbal fluency, and working memory test. The variable, composite cognitive function score, was categorized into quartiles: scores 0 to ≤ 53 (low cognitive function); scores > 53 to ≤ 69 ; scores > 69 to ≤ 85 ; and, scores > 85 , (high cognitive function). Quartiles for the scores were also created for each of the three subtests. The memory score quartiles were: 0 to < 5 correct; 5 to < 7 correct; 7 to < 9 correct; and > 9 correct. The language/verbal fluency score quartiles were: 0 to < 12 recalled and verbalized animal names; 12 to < 16 recalled and verbalized animal names; 16 to < 20 recalled and verbalized animal names; and > 20 verbalized and recalled animal names. The working memory score quartiles were: 0 to < 33 ; 33 to < 46 ; 46 to < 58 ; and > 58 . Separate analyses were conducted with each of these.

T. gondii IgG levels were determined by enzyme immunoassay. Details are available elsewhere [13]. The IgG levels were measured in IU/ml with results from 0 to 239 IU/mL. *T. gondii* IgG was dichotomized to a negative/positive variable (< 33 IU/ml, ≥ 33 IU/ml as indicated in the NHANES Analytical Guidelines) [13]. Use of the IgG concentration as a continuous variable was precluded by the skewed distribution of IgG concentration which could not be normalized with logarithmic, exponential, or inverse transformations.

Other variables are known to influence cognitive function. Analyses were adjusted for the following potential confounders: sex (female, male); age (60 to < 66 years and ≥ 66 years); race (non-Hispanic white, non-Hispanic black, Mexican-American, other); poverty level (poor/low income $< 200\%$ on the federal poverty level, moderate/high income $\geq 200\%$ on the federal poverty level); education (less than high school, high school graduate, some college, college and above); smoking (current, former, never); alcohol use (non-drinker, moderate use, heavy use); and, history of stroke (yes, no).

The data were analyzed using SAS® version 9.4 (SAS Institute Inc., Cary, NC). Sample descriptive statistics were calculated as frequencies and weighted percentages. Rho Scott Chi square bivariate analyses were used for associations between *T. gondii* IgG and cognitive function quartiles. Cumulative logit model for the response variable categorized in ordinal quartiles was used for ordinal logistic regression. Analyses included considerations for the complex survey design of the NHANES, including the use of survey weights provided by NHANES [13].

3. Results

There were 1382 participants; 53% were female; and 35.5% were ages 60 to < 66 years. Most were non-Hispanic white (81.2%), and were at 200% or above the federal poverty level (67.3%). There were 80.8% who had *T. gondii* IgG levels below 33 IU/mL (*T. Gondii* IgG⁻). The mean IgG was 17.29 IU/mL (standard deviation, 1.45; range 239; unweighted skewness, 2.03). Additional details are in Table 1. There were many significant associations in bivariate analyses on the association of variables with the composite cognitive function score quartile. Cognition was associated with *T. gondii* IgG, age, sex, race/ethnicity, federal poverty level, alcohol use, and stroke (Table 1).

In the unadjusted ordinal logistic regression analyses, participants *T. gondii* IgG⁺ were more likely to be in the lower cognitive function composite score quartile than participants *T. gondii* IgG⁻ (unadjusted odds ratio [UOR] = 1.61 (95% CI: 1.06, 2.44; $p = .0293$). Controlling for the other variables, the odds of cognitive function scores decreasing in quartiles among people *T. gondii* IgG⁺ compared to people *T. gondii* IgG⁻ are 1.55 (95% CI: 1.08, 2.21; $p = .0170$) (Table 2). Separate analyses excluding stroke and age did not affect the significance of the association between *T. gondii* IgG and composite cognitive function score (IgG AOR_{without stroke} = 1.52 [1.05, 2.18]; $p = .0254$ and IgG AOR_{without age} = 1.69 [1.17, 2.44]; $p = .0048$).

There were differences in the likelihood of cognitive function scores being low when examining interactions of *T. gondii* IgG with various factors. With individuals *T. gondii* IgG⁻ and no stroke as the reference, individuals *T. gondii* IgG⁺ who had a stroke had a UOR = 4.68 (95% CI: 2.69, 8.14; $p < .001$); individuals *T. gondii* IgG⁺ who did not have a stroke had a UOR = 1.23 (95% CI: 0.45, 3.34; $p = .6660$); and, individuals *T. gondii* IgG⁻ who had a stroke had a UOR = 3.11 (95% CI: 2.06, 4.69; $p < .001$). Other interactions are presented in Table 2.

The association of *T. gondii* IgG and the memory function and language/verbal fluency subtests failed to reach significance (IgG UOR_{memory} = 0.99; 95% CI: 0.67, 1.56; $p = .9445$ and IgG UOR_{language} = 1.18; 95% CI: 0.75, 1.87; $p = .4406$). In the interaction *T. gondii* IgG and sex on language/verbal fluency, men were less likely to score in the lower quartiles (UOR_{language} = 0.85; 95% CI: 0.51, 1.40; $p = .4923$); however the relationship failed to reach significance.

For the working memory test, *T. gondii* IgG⁺ individuals were more likely to be in the lower score quartile (UOR = 1.79 [95% CI: 1.30, 2.46; $p = .0014$; and AOR = 1.84 [1.25, 2.70; $p = .0019$]. Separate analyses excluding stroke and age did not affect the significance of the association between *T. gondii* IgG and working memory (IgG AOR_{without stroke} = 1.79 [95% CI: 1.22, 2.63; $p = .0028$]) and IgG AOR_{without age} = 1.95 [95% CI: 1.37, 2.77; $p = .0002$]).

4. Discussion

This study provides evidence of an association between *T. gondii* IgG⁺ and the prevalence of impaired cognitive function. In this sample of over 1300 participants, 19.2% were *T. gondii* IgG⁺, similar to the analysis of an NHANES III study [7], where approximately 20% of

participants were *T. gondii* IgG⁺. These estimates were reported to be higher than some previously found estimates, but within the expected range [7,14].

The ordinal logistic regression (adjusted) analyses of *T. gondii* IgG upon cognitive function scores indicated participants *T. gondii* IgG⁺ were more likely to have lower cognitive function scores than people *T. gondii* IgG⁻. The memory function and language/verbal fluency subtests failed to reach significance; however, the working memory was significant. Some researchers of *T. gondii* IgG⁺ older adults reported lower cognitive function, specifically in immediate memory, delayed recall and verbal learning [15,16]. However, researchers of 4620 younger adults did not find an association between cognitive performance and *T. gondii* IgG [17]. One difference among the studies is the cut-off for *T. gondii* IgG: 50 IU/ml was used by Tornai-Holm et al. [17] and Gajewski, et al. [15]; 6 IU/ml was used by Mendy, et al. [16]; and 35 IU/mL was used in this study as recommended by NHANES [13].

In a study of individuals aged 20–59 years, researchers found no main effects in neurocognitive function, nor in symbol-digit substitution, simple reaction time, and serial-digit learning test [18]. However, other researchers examining the same dataset found significant interactions (toxoplasmosis and poverty-to-income ratio; toxoplasmosis and education; toxoplasmosis and race/ethnicity) and indicated toxoplasmosis may adversely affect cognitive function in certain groups [10]. In this study, there were interactions in which lower income individuals, individuals with less than college education, and older individuals were more likely to have lower cognitive composite scores. Similar results were for stroke and race; however, the confidence intervals for stroke and race were wide and caution should be used in interpreting those results. The findings of Gale et al. (2014), were similar to the results of this study [10]. However, Wyman et al. (2017), failed to find any significance between interactions in the overall study sample of an older population [19]. In interactions by sex on nine cognitive tests, Flegr et al. (2012) reported men scored significantly better on verbal fluency, digit span-forward and the Stroop test I; whereas, women scored significantly better on digit span-backward [20]. In this study for the interaction *T. gondii* IgG and sex on language/verbal fluency, males were also less likely to score in the lower quartiles; however, the relationship failed to reach significance.

The findings of both positive and negative associations between cognitive function and people with *T. gondii* IgG⁺ could be the result of the many different tests to evaluate memory. The varying tests evaluate different aspects of memory function and they may have different interactions that could modify the association. The tests used in this study are valid within the NHANES Analytical Guidelines and available at the NHANES website [13].

5. Conclusion

This study is important as it is a large, nationally representative study of an association of *T. gondii* IgG and cognition. An objective biomarker, *T. gondii* IgG, and valid cognitive tests are study strengths. However, the sample was restricted to data that were available only in NHANES 2013–2014. The association of *T. gondii* IgG and human behavior, specifically cognition, is complex and requires further study. A relationship was found between the

lowest cognitive scores (lowest quartile) and *T. gondii* IgG versus the highest cognitive scores (highest quartile).

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Table 1
Composite Cognitive Function Score Quartiles and variables of interest, NHANES, 2013–2014 *N* = 1382.

Overall Sample Description		Quartiles of the cognitive function composite scores								
N	Weighted %	Q1	wt%	Q2	wt%	Q3	wt%	Q4	wt%	P-value
<i>Toxoplasmosis IgG</i>										
Positive	19.2%	97	21.5	80	24.3	66	26.9	47	27.1	0.0437
Negative	80.8%	252	13.7	269	21.4	279	27.9	292	37.0	
Age										
60 to less than 66	35.5%	84	8.2	87	12.9	118	25.5	181	53.4	< 0.0001
66 and above	64.5%	265	19.1	262	27.0	227	29.0	158	24.9	
Sex										
Female	53.0%	168	15.1	159	20.1	181	24.6	206	40.2	0.0016
Male	47.0%	181	15.4	190	24.1	164	31.2	133	29.3	
Race/ethnicity										
Non-Hispanic White	81.2%	118	10.9	186	21.3	197	28.4	242	39.4	< 0.0001
Non-Hispanic Black	7.3%	103	41.2	62	24.4	54	21.5	29	13.0	
Mexican American	7.0%	108	40.0	62	22.0	58	23.1	36	14.9	
Other	4.6%	20	13.0	39	30.3	36	32.3	32	24.4	
Federal Poverty Level										
< 200%	32.7%	217	29.0	159	27.5	119	23.7	82	19.9	< 0.0001
200% +	67.3%	98	7.9	166	19.8	209	30.3	234	42.0	
Smoking										
Current smoker	10.3%	58	21.8	43	23.5	41	27.1	30	27.5	0.1158
Former smoker	40.0%	120	13.6	144	25.6	130	26.4	132	34.3	
Never smoker	49.7%	170	15.1	162	18.7	174	28.9	177	37.3	
Alcohol use										
Non-drinker	31.9%	132	21.8	117	26.0	99	26.9	74	25.4	< 0.0001
Moderate	57.7%	82	8.5	117	16.1	161	30.1	196	45.3	
Heavy	10.4%	42	15.8	42	26.0	23	21.6	27	36.6	
Stroke										
Yes	7.1%	49	28.1	17	22.2	18	26.8	12	12.9	< 0.0001

Overall Sample Description		Quartiles of the cognitive function composite scores								
N	Weighted %	Q1	wt%	Q2	wt%	Q3	wt%	Q4	wt%	P-value
No	1283	94.4%	300	13.5	331	21.9	326	27.8	327	26.8
Cognitive function composite score										
Q1	349	15.2%								
Q2	349	22.0%								
Q3	345	27.7%								
Q4	339	35.0%								
Cognitive function memory score										
Q1	300	17.7%								
Q2	415	28.5%								
Q3	427	32.3%								
Q4	240	21.5%								
Cognitive function language score										
Q1	252	12.8%								
Q2	347	21.1%								
Q3	399	28.9%								
Q4	384	37.2%								
Executive function score										
Q1	311	13.7%								
Q2	351	20.5%								
Q3	347	28.4%								
Q4	373	37.4%								

Abbreviation: Q, quartile.

Toxoplasma gondii IgG cut-off was < 33 IU/ml for negativity. Cognitive function composite score quartiles: Quartile 1, 0 to 53 (low cognitive function); Quartile 2, (> 53 to 69; Quartile 3, > 69 to 85; and Quartile 4, > 85, (high cognitive function).

SAS® version 9.4 (SAS Institute Inc., Cary, NC) surveyfreq procedure used to determine Rho Scott Chi Square bivariate analyses. Weighted percentages were calculated with adjustments for primary sampling units, strata, and NHANES-provided weights.

Table 2

Ordinal Logistic Regression of *Toxoplasma gondii* IgG on composite cognitive function score quartiles in older adults, NHANES 2013–2014 N = 1382.

	Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
<i>Toxoplasmosis</i> IgG				
Positive	1.61(1.06, 2.44)	0.0293	1.55 (1.08, 2.21)	0.0170
Negative	reference		Reference	
Age				
66+			4.08 (2.97, 5.61)	< 0.0001
60–65			Reference	
Stroke				
Yes			3.69 (2.45, 5.56)	< 0.0001
No			Reference	
Sex				
Male			2.00 (1.41, 2.83)	< 0.0001
Female			Reference	
Race/ethnicity				
Non-Hispanic Black			4.42 (2.91, 6.71)	< 0.0001
Mexican American			4.36 (3.41, 5.57)	< 0.0001
Other			1.74 (1.00, 3.03)	0.0508
Non-Hispanic White			Reference	
Federal Poverty Level				
Low/poor			2.12 (1.79, 2.51)	< 0.0001
Mod/high			Reference	
Education				
< college degree v college			2.70 (1.48, 2.75)	< 0.0001
College degree			Reference	
Alcohol				
Non-drinker v moderate			2.02 (1.48, 2.75)	< 0.0001
Heavy v moderate			1.43 (0.99, 2.05)	0.0560
Moderate			Reference	

Interactions		
<i>T. gondii</i> IgG × stroke		
<i>T. gondii</i> IgG ⁻ and no stroke	reference	
<i>T. gondii</i> IgG ⁺ and a stroke	10.08 (4.76, 21.34)	< 0.001
<i>T. gondii</i> IgG ⁺ and no stroke	1.60 (1.03, 2.48)	0.0380
<i>T. gondii</i> IgG ⁻ and a stroke	3.19 (2.10, 4.8.6)	< 0.001
<i>T. gondii</i> IgG × age		
<i>T. gondii</i> IgG ⁻ and 60 to < 66	reference	
<i>T. gondii</i> IgG ⁺ and 66	4.68 (2.69, 8.14)	< 0.001
<i>T. gondii</i> ⁺ and 60 to < 66	1.23 (0.45, 3.34)	0.6660
<i>T. gondii</i> ⁻ and 66	3.11 (2.06, 4.69)	< 0.001
<i>T. gondii</i> IgG × race/ethnicity		
<i>T. gondii</i> IgG ⁻ and NHW	reference	
<i>T. gondii</i> IgG ⁺ and other	6.41 (4.08, 10.08)	< 0.001
<i>T. gondii</i> IgG ⁺ and NHW	1.55 (0.91, 2.65)	0.1020
<i>T. gondii</i> IgG ⁻ and other	3.29 (2.44, 4.46)	< 0.001
<i>T. gondii</i> IgG × income		
<i>T. gondii</i> IgG ⁻ and high income	reference	
<i>T. gondii</i> IgG ⁺ and low income	7.06 (5.47, 9.11)	0.001
<i>T. gondii</i> IgG ⁺ and high income	1.26 (0.80, 1.99)	0.2896
<i>T. gondii</i> IgG ⁻ and low income	3.05 (2.58, 3.60)	< 0.001
<i>T. gondii</i> IgG ⁻ and college	reference	
<i>T. gondii</i> IgG ⁺ and < college	5.84 (3.52, 9.70)	< 0.001
<i>T. gondii</i> IgG ⁺ and college	1.40 (0.87, 2.28)	0.1548
<i>T. gondii</i> IgG ⁻ and < college	3.15 (2.09, 4.74)	< 0.001
<i>Toxoplasma gondii</i> IgG × sex		
<i>T. gondii</i> IgG ⁻ females	reference	
<i>T. gondii</i> IgG ⁺ male	1.76 (1.04, 2.97)	0.0370
<i>T. gondii</i> IgG ⁺ female	2.18 (1.33, 2.56)	0.0041
<i>T. gondii</i> IgG ⁻ male	1.48 (1.19, 1.84)	0.0017
Interactions on cognitive subscore: DWRT		
<i>Toxoplasma gondii</i> IgG × sex		

Interactions	
<i>T. gondii</i> IgG ⁻ female	reference
<i>T. gondii</i> IgG ⁺ male	1.26 (0.73, 2.17) 0.3767
<i>T. gondii</i> IgG ⁺ female	1.27 (0.73, 2.18) 0.3660
<i>T. gondii</i> IgG ⁻ male	1.71 (1.30, 2.24) 0.0008
<i>Interactions on cognitive subscore: language/verbal fluency</i>	
<i>Toxoplasma gondii</i> IgG × sex	
<i>T. gondii</i> IgG ⁻ females	reference
<i>T. gondii</i> IgG ⁺ male	0.85 (0.51, 1.40) 0.4923
<i>T. gondii</i> IgG ⁺ female	1.48 (0.93, 2.35) 0.0908
<i>T. gondii</i> IgG ⁻ male	0.84 (0.65, 1.09) 0.1761
<i>Interactions on subscore: digit symbol substitution</i>	
<i>Toxoplasma gondii</i> IgG × sex	
<i>T. gondii</i> IgG ⁻ females	reference
<i>T. gondii</i> IgG ⁺ male	2.21 (1.46, 3.34) 0.0010
<i>T. gondii</i> IgG ⁺ female	2.43 (1.64, 3.60) 0.0002
<i>T. gondii</i> IgG ⁻ male	1.69 (1.35, 2.13) 0.0002

Abbreviations: OR, Odds Ratio; CI, Confidence interval; Q, quartile; v, versus; NHB, Non-Hispanic Black; NHW, Non-Hispanic White; MA, Mexican American; O, other; Low/poor, Federal poverty 2 or less; Mod/hi, Federal poverty level above 2; < HS, less than high school graduation; non-D, non-drinker; over, overweight; un/norm, under or normal weight; DWRT, Delayed Word List Learning Test, a cognitive function memory test.

Toxoplasma gondii IgG cut-off was < 33 IU/ml for negativity. Cognitive function composite score quartiles: Quartile 1, scores 0 to 53 (low cognitive function); Quartile 2, scores > 53 to 69; Quartile 3, scores > 69 to 85; and Quartile 4, scores > 85, (high cognitive function). The adjusted model includes sex (female, male); age (60 to less than 66 years, 66 years and above); race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other); poverty level (poor/low income less than 200% on the federal poverty level, moderate/high income 200% or above on the federal poverty level); education (less than high school, high school graduate, some college, college and above); alcohol use (non-drinker, moderate use, heavy use); and, history of stroke (yes, no).

SAS© version 9.4 (SAS Institute Inc., Cary, NC) surveylogistic procedure used to determine ordinal analyses. Analyses were calculated with adjustments for primary sampling units, strata, eligible population domain, and NHANES-provided weights.

Bold font indicates significant associations where p < 0.05