HHS Public Access

Author manuscript

J Epidemiol Community Health. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

J Epidemiol Community Health. 2023 May ; 77(5): 315–321. doi:10.1136/jech-2022-219772.

Association of infection with *Toxoplasma gondii* and *Toxocara* on cognitive function among US adults aged 60 and over, NHANES 2011–2014

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Abstract

Background—*Toxoplasma gondii* and *Toxocara* are common parasites that infect humans globally. Our aim was to examine the relationship between *T. gondii* and *Toxocara* infection and cognition.

Methods—Multivariate logistic regression was used to test the association of *T. gondii* and *Toxocara* seropositivity on indices of cognitive function (a word list learning trial with delayed recall from the Consortium to Establish a Registry for Alzheimer's Disease, an animal fluency test (AFT) and a digit symbol substitution test (DSST)) among 2643 adults aged 60 years and older in the 2011–2014 National Health and Nutrition Examination Survey.

Results—Seropositivity to *T. gondii* or *Toxocara* were both associated with lower scores in all three cognitive function measures examined in univariate analyses. Except for the DSST, these associations were not significant after adjustment for age, gender, race and Hispanic origin, poverty level, education, US birth status, depression and hypertension. On stratification to account for significant interactions, *Toxocara* seropositivity was associated with worse scores on the AFT among those born outside the USA, worse scores on the DSST among those aged 60–69 years, female, Hispanic and with a high school diploma or less. Lower DSST scores with *Toxocara* infection was greater for adults living below compared with at or above the poverty level.

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Contributors DK-M performed analysis and interpretation of data, wrote first draft, reviewed and edited all drafts of manuscript; primary guarantor of content. DB and BP contributed to interpretation of the results, drafted original sections of the manuscript, performed critical review, substantive feedback, and editing. DK-M, DB and DP all provided input in the concept design and approved the final manuscript.

Competing interests None declared.

Disclaimer The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of [the Centers for Disease Control and Prevention

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by NCHS Ethics Review Board https://www.cdc.gov/nchs/nhanes/irba98.htm. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Conclusions—Seropositivity to these parasites, particularly to *Toxocara*, may be associated with diminished cognitive performance in certain subgroups of older adults.

INTRODUCTION

Toxocara and *Toxoplasma gondii* are two of the most common parasites that infect humans globally and are spread by faecal contamination of the environment or undercooked meat. Of the US population age 6 and over, approximately 5% have been infected with *Toxocara*[1] and 11% with *T… gondii*.[2] Those infected with one had almost twice the odds of infection with the other.[3] Most infected persons with normal immune systems exhibit no symptoms and remain undiagnosed. Infections are non-reportable and there are no recommendations for treating asymptomatic patients with positive serological tests.[4] However, both organisms can migrate to various body organs, including the central nervous system, causing both mechanical and immune-mediated damage.[5 6] Congenital transmission or infection among those immune suppressed can result in more severe symptoms.

Studies in animal models have shown that *T. gondii* and *Toxocara* cause behavioural alterations.[6 7] Substantial indirect evidence has implicated *T. gondii* infection in serious mental illnesses, including schizophrenia, bipolar disorder and suicidality.[8 9] Despite some evidence of an association of *Toxocara* with cognition, the relationship between cognition and infection has not been clearly defined.[10] Because the life cycle of these parasites entails migration through multiple tissues, infection could induce cognitive dysfunction by altering neurocircuitry, which could even occur through indirect mechanisms (eg, brain immune interactions) that do not require the organism to enter the bran parenchyma.[8 10 11]

Several studies have observed an association between *T. gondii* infection and cognitive function, varying in effect and by study population. Pearce *et al* found a relationship between *T. gondii* infection and reduced cognitive function, after adjusting for sociodemographic cofactors among young-aged to middle-aged adults with lower socioeconomic status or born outside the USA.[12] Gale *et al*[13] found an interaction between the effect of *T. gondii* infection on cognition in adults with multiple demographic and socioeconomic measures. In another study of asymptomatic older adults, seropositivity to *T. gondii* was associated with lower scores on tests of memory but not executive function.[14] Higher prevalence of *T. gondii* antibodies and higher IgG levels were found in patients with Alzheimer's disease compared with controls.[15] The association between cognitive functioning and seropositivity for *Toxocara* varied by age, gender and educational attainment in young-aged to middle-aged adults in an earlier nationally representative survey (NHANES III 1988–1994).[16] Similarly, Gale *et al* found lower cognitive scores for processing speed, learning and memory but not reaction time.[17] Both increased prevalence of *Toxocara* and *T. gondii* seropositivity and lower cognitive performance have been shown to vary by demographic factors and to have disproportionately affected socioeconomically disadvantaged populations.[1 2 18]

Cognitive health is an important public health concern for the ageing US population and there is growing interest in the possible role of these parasites in human cognition. Cognitive measures related to working memory, language and processing speed measured in the

National Health and Nutrition Examination Survey (NHANES) during 2011–2014 allowed us to examine the association between infection with *T. gondii* and *Toxocara* and cognitive functioning in a nationally representative sample of older adults.

METHODS

Study population

Analyses were conducted using data from NHANES 2011–2012 and 2013–2014. The NHANES is a cross-sectional survey that uses a complex sampling design to obtain a nationally representative sample of the civilian, non-institutionalised US population. Conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, NHANES includes an in-home interview and a physical examination with collection of laboratory specimens at a mobile examination centre (MEC). The overall examination response rate in 2011–2014 was 69.0% for all ages and 57.3% for adults aged 60 years and older. Data for the demographic, questionnaire, laboratory and physical examination measures are available from the NHANES website.[19] Detailed information about the NHANES survey design and sampling methods has been published elsewhere.[20]

Laboratory testing

Sera were tested for *T. gondii* and *Toxocara* IgG antibodies among participants ≥6 years of age who consented separately for specimen storage for future research during the interview and had surplus sera available after completion of all laboratory tests in the original NHANES protocol. *T. gondii* IgG antibodies were measured with the *Toxoplasma* IgG EIA (Bio-Rad, Redmond, Washington, USA)[21]; results ≥33 IU/mL were considered positive, <27 IU/mL negative and ≥27 IU/mL and <33 IU/mL equivocal. Equivocal and negative results were grouped together for analytic purposes. A multiplex bead-based assay (Tc-CTL-1MBA) with purified *Toxocara canis* antigen was used to measure *Toxocara* antibody. Details have been described previously.[1 22]

Cognitive function measures

Cognitive function was measured on adult participants aged 60 and older in the MEC to control situational variation or distraction. The instruments chosen were brief, easy to administer and score, and understandable to a diverse population. The assessments included (1) three-word list learning trials with a delayed recall from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) to assess new verbal learning and both immediate and delayed memory[23]; (2) an animal flluency test (AFT) to examine verbal semantic fluency, a component of executive function[24] and (3) a digit symbol substitution test (DSST), a performance module from the Wechsler Adult Intelligence Scale to evaluate attention, working memory and processing speed.[25]

The CERAD subtest consisted of 3 repeat recall trials of 10 words and a delayed recall which was administered after the AFT and DSST. Scores from all 4 trials (1 point per word recalled) were combined to create the variable CERAD4 (range 0–40, n=3123). In the AFT, participants were asked to name as many animals as possible in 1 min and scored one point for each animal named (n=3128). The DSST required the pairing of 9 numbers with their

correct symbols; scores were based on the total number of correct matches completed in 2 min (n=3127). Those who did not pass the practice tests for the AFT (n=18) or DSST (n=113) were given a score of zero in our analyses.

Covariates

Covariates associated with seroprevalence to *T. gondii*, *Toxocara* or cognitive function examined in both univariate analyses and multivariate regression models included age group (60–69 years and 70 and over), gender and race and Hispanic origin (self-identified as non-Hispanic white, non-Hispanic black, non-Hispanic Asian, Hispanic and other, including multiple races). Due to small sample sizes, non-Hispanic Asian and 'other' adults were combined for all multivariate analyses and included in the total population. Other demographic and socioeconomic cofactors included birthplace (defined as US born (50 US states or DC) or non-US born (all others, including those born in the US territories)), poverty level (family income divided by a poverty threshold specific for family size and categorised as below or at or above the poverty level)[26] and education level (less than high school, high school or a general equivalency diploma, or more than high school). Additional covariates associated with lower cognitive function in prior studies[12] that were examined included smoking status (never or former vs current cigarette use); alcohol use (never or any use); measured weight status defined as weight in metres squared divided by height in centimetres (body mass index (BMI)) and categorised as normal/underweight (BMI <25 kg/m^2), overweight (BMI >25 kg/m^2 and <30 kg/m^2) or obesity (BMI ≥30 kg/m^2)); diabetes (yes/no) defined as high glycohaemoglobin A1C (≥6.5) or self-reported diagnosis of diabetes; hypertension (yes/no) defined as measured mean high blood pressure (systolic >130 mm Hg or diastolic >80 mm Hg), self-reported hypertension diagnosis, or current use of hypertension medication; depression (yes/no) defined as a score >10 from the Patient Health Questionnaire-9.[27] Detailed information is available in the NHANES file documentation.[28]

Statistical analysis

All analyses were conducted using the NHANES examination weights to represent the total civilian non-institutionalised US population and account for oversampling and non-response.[29] SEs and test statistics were calculated using Taylor series linearisation with SUDAAN statistical software[30] to account for the complex sample design. Scores on the three cognitive function measures (AFT, DSST and CERAD4) were examined as continuous variables. Confidence intervals (CIs) for *T. gondii* or *Toxocara* prevalence estimates were constructed using the approach developed by Korn and Graubard.[31] All proportions met the NCHS standards for presentation except where noted.[32]

Univariate associations were evaluated using a t-statistic from a linear contrast procedure in SUDAAN. For each of the three cognitive measures, a multivariate regression model was created to examine the association of seropositivity to *T. gondii* and *Toxocara* with the cognitive score, adjusting for all cofactors significantly associated with the outcome.

Individual interactions of *T. gondii* or *Toxocara* seropositivity with each cofactor were evaluated. Our primary question was whether *T. gondii* or *Toxocara* seropositivity was

related to a decrease in any cognitive function measure in the overall population or in any subgroup for variables with a significant interaction. P values <0.05 were considered significant. No adjustments were made for multiple comparisons.

RESULTS

Study sample

Of the 3472 persons aged 60 years and older examined in the MEC, 2964 (85.4%) had test results for both *T. gondii* and *Toxocara* and 3042 (87.6%) completed all 3 cognitive measures. Our final sample consisted of 2643 persons (76.1% of those examined) with both antibody results and cognitive function measures. Among those examined, persons included in the final sample differed from those who were missing cognitive function, *Toxocara* or *T. gondii* data by race and Hispanic origin, education, and US birth status. After adjusting the sample weights, similar conclusions were reached so results using the original publicly available examination weights were presented here.

Univariate analyses

Mean scores and 95% CIs for each measure of cognitive function are provided, by *T. gondii* and *Toxocara* serological status, and by level of each cofactor in table 1.

Overall mean cognitive scores were AFT: 17.9 (95% CI 17.6 to 18.3), DSST: 51.2 (95% CI 50.0 to 52.4) CERAD4: 25.7 (95% CI 25.0 to 26.3). Seropositivity to either parasite was associated with lower scores for all three outcomes. Mean *AFT* score for persons who were *T. gondii* seropositive was 17.2 (95% CI 16.4 to 18.0) compared with 18.1 (95% CI 17.7 to 18.5) for those who were seronegative (p=0.049). DSST and CERAD4 scores were also lower among persons who were *T. gondii* seropositive compared with seronegative (46.8 (95% CI 44.8 to 48.9) v 52.3 (95% CI 50.9 to 53.6) and 25.0 (95% CI 24.1 to 26.0) v 25.8 (95% CI 25.2 to 26.5), p<0.001 and p=0.031, respectively). Similarly, mean scores were lower among persons who were seropositive to *Toxocara* (*AFT*:16.0 (95% CI 15.0 to 17.0), DSST:40.8 (95% CI 37.9 to 43.6), CERAD4:23.1 (95% CI 21.8 to 24.5)) compared with those seronegative (18.0 (95% CI 17.7 to 18.4), 51.8 (95% CI 50.5 to 53.0), 25.8 (95% CI 25.1 to 26.5), p≤0.001 for all 3 comparisons).

For all cognitive measures, persons aged 70 and older had significantly lower mean scores than those aged 60–69 years. Results varied by gender; males scored lower than females on DSST and CERAD4 measures. Non-Hispanic white adults scored higher on all three measures than non-Hispanic black or Hispanic adults, and higher than non-Hispanic Asian adults on the *AFT* and DSST but not on the CERAD4. Persons living below the poverty level, persons with less than or completed a high school education, those born outside the USA, those who drank alcohol in the past or never, those with hypertension, and those with diabetes all had lower scores on all three measures. Lower scores were associated with current smoking for the DSST only, and with depression for the AFT and DSST (table 1).

Associations between the seroprevalence of *T. gondii* and *Toxocara* by levels of these same cofactors were also examined (table 2).

Overall, 19.9% (95% CI 17.8 to 22.1) of adults were infected with *T. gondii* and 5.1% (95% CI 3.8 to 6.4) were infected with *Toxocara.,* Among adults with *T. gondii* seropositivity, 31.2% were seropositive for *Toxocara*. Higher seroprevalence was significantly associated with older age (*T. gondii* only), male gender, non-Hispanic black (*Toxocara* only) or Hispanic origin, living below the poverty level, less than a high school education, and birth outside the USA. Lower prevalence of *T. gondii* and higher prevalence of *Toxocara* was observed among non-Hispanic Asian compared with non-Hispanic white adults. There was no difference in the prevalence of either *T. gondii* or *Toxocara* with respect to alcohol use, smoking history, hypertension, diabetes, weight status or depression.

Multivariate analyses

After adjustment for all cofactors, neither *T. gondii* nor *Toxocara* were associated with mean AFT score (p=0.647 and p=0.898, respectively) or CERAD4 scores p=0.715 and p=0.159, respectively). However, lower DSST scores for those infected with *T. gondii* approached statistical significance (beta=−1.75 (95% CI −3.50 to 0.01), p=0.051) and with *Toxocara* reached statistical significance (beta=−3.54 (95% CI −5.74 to −1.34), p=0.003) (table 3).

Interactions and stratified models

There were no significant interactions with *T. gondii* seropositivity for any cognitive measure. However, the association of *Toxocara* status varied by age and US birth status for the *AFT* score; by age, gender, poverty level and education for the DSST score; and by hypertension status for the CERAD4 score (table 4).

The association of *Toxocara* infection with *AFT* scores varied by age group. Scores were lower for those *Toxocara* positive among those age 60–69 (beta=−1.12 (95% CI (−2.28 to −0.03), p=0.057) but were no longer significant for those age 70 and older (beta=1.07 (95% CI (−0.51 to 2.66), p=0.177). *Toxocara* infection was also associated with lower *AFT* scores among persons born outside the USA (beta=−1.83 (95% CI −3.16 to −0.51), p=0.008) but not US born (beta=0.80 (95% CI −0.43 to 2.03), p=0.194).

Toxocara infection was associated with significantly lower DSST scores among persons aged 60–69 years (beta=−5.39 (95% CI −8.15 to −2.63), p<0.001), women (beta=−6.82 (95% CI −10.40 to −3.21), p=0.001) and those with less than a high school education (beta=−6.24 (95% CI −10.00 to −2.48), p=0.002) and only a high school education (beta=−7.02 (95% CI −11.90 to −2.18), p=0.006). In addition, the association of *Toxocara* seropositivity and lower DSST scores was greater among those living below (beta=−7.29 (95% CI −11.3 to −3.25), p=0.001) compared with at or above the poverty level (beta=−2.79 (95% CI −5.13 to −0.45), p=0.021). Toxocara infection was also associated with significantly lower CERAD4 scores among persons without hypertension (beta=−4.20 (95% CI −6.74 to −1.67, p=0.002).

DISCUSSION

In this report, we analysed data from a nationally representative sample of older adults to gain insight on the potential role of *T. gondii* and *Toxocara* infection in the reduction of cognitive function. Although we found that both parasitic infections were associated with

decrements in attention, working memory and processing speed, as objectively measured by the DSST, only the association with *Toxocara* reached statistical significance.

The mechanisms and cofactors responsible for the association of these infections with distinct cognitive alterations may differ between older and younger adults. The findings of *T. gondii's* relationship to memory function in older adults has been less consistent than for younger individuals, with Gajewski *et al* finding worse memory among infected seniors, but Wyman *et al* finding no such association.[14 33] In another analysis of older adults (2013–2014 NHANES), the working memory scores were lower for persons who were *T. gondii* seropositive compared with those seronegative.[34] Both infections are more common among persons living in poverty, and poverty is associated with lower DSST scores (1,2,18). Thus, it is important to consider the relationship between poverty, infection and lower DSST scores. A study of younger adults revealed that *T. gondii* was associated with worse scores on a similar test of working memory and attention among those in the lowest income strata.[12] This was confirmed by an analysis showing a stronger association of *Toxoplasma* on this cognitive test among those in lower income and education strata.[13] Despite our current result of lower working memory among *Toxoplasma*-infected seniors in unadjusted analyses, we did not find a significant association in fully adjusted models (p=0.072) and no interactions were found between socioeconomic indicators and *Toxoplasma* on working memory as reported by Weiner *et al*.[34]

Our models detected worse DSST scores with *Toxocara* infection especially among adults living below the poverty level. Thus, poverty may not only increase a person's vulnerability to higher *Toxocara* exposure but may amplify the possible adverse effects of infection with this parasite on attention, working memory and processing speed. There are a variety of exposures associated with poverty and poor education that could partially explain the greater effect of *Toxocara* on cognition in this subgroup, including poor nutrition, other infections and increased inflammatory allostatic load.[35–37] Moreover, educational resources and a healthy environment may increase brain plasticity, compensating for the adverse effects of this parasite on cognition.[35] Nevertheless, a relationship between lower cognitive performance and *Toxocara* seropositivity has also been observed in children and young-aged to middle-aged adults, independent of socioeconomic status.[11 16]

Because we used *Toxocara* seroprevalence as an indicator of prior infection, we cannot determine when the adults were initially infected, one limitation of this study. Socioeconomic and seropositivity data were collected contemporaneously so we cannot know the socioeconomic trajectory of these participants, but lower socioeconomic status linked to *Toxocara* infection could have led to higher *Toxocara* exposure earlier in life. In our study, and a prior study of younger adults, *Toxocara* seroprevalence was not associated with age.[16] Nevertheless, lower socioeconomic status among the seniors in our study could have arisen earlier in life and led to higher *Toxocara* exposure at a younger age and possibly multiple times throughout their lifespan. Another limitation is our inability to demonstrate a biological gradient since we do not have data on the severity of the *Toxocara* infection. A recent paper suggesting that higher *Toxocara* serointensity may be associated with worse performance on the DSST[38] provides indirect support for a dose-response effect at least

with respect to the antibody response. Finally, due to the cross-sectional NHANES design, a reverse causality association between cognitive decline and infection cannot be ruled out.

Delineating the mechanism by which *Toxocara* may cause cognitive difficulties is complicated by the ambiguous relationship between serology and current infection.[10] The growing recognition that *Toxocara* seropositivity may be linked to mild or non-specific symptoms ('covert toxocariasis'), and that larval invasion of the brain may not produce overt neurological signs[39] provides additional support for its causative role in subtle cognitive alterations. Moreover, infection confined to the periphery could alter brain function and cognition, either through bloodborne cytokines, disruption of the blood–brain barrier, or via signalling from the gut or other viscera.[40] An animal model study suggests that *Toxocara* could disrupt the brain's ubiquitin-proteasome system, which clears aggregated and toxic proteins.[39]

This study found that *Toxocara* seropositivity may be associated with diminished cognitive function in older adults. With our ageing population, insight into the role of parasitic infections in altering any level of brain function is critical for understanding variation in cognitive performance later in life.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Data availability statement

Data are available in a public, open access repository. Original study protocol and survey documents can be found online at https://www.cdc.gov/nchs/nhanes/index.htm. Access to the NHANES survey data and documentation is available from: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *Toxocara* and *Toxoplasma gondii* are common parasites worldwide that can migrate to various organs including the central nervous system. Indirect evidence has implicated *T. gondii* in serious mental illness as well as cognitive impairment, but less is known about the effects of *Toxocara* infection.

WHAT THIS STUDY ADDS

⇒ The effects of *T. gondii* and *Toxocara* infection on three measures of cognitive function were examined among older adults in a nationally representative sample.

⇒ Both *T. gondii* and *Toxocara* seroprevalence were associated with a cognitive measure of working memory and processing speed, even after adjustment for sociodemographic and health factors. Only *Toxocara* was associated with other measures of lower cognitive function, especially in subgroups of lower socioeconomic status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research is needed to demonstrate a biological gradient and to confirm direction of causality. In addition, individuals should be instructed to practice measures to prevent infection.

Table 1

Mean cognitive functioning scores and 95% CI: US adults aged 60 and older, National Health and Nutrition Examination Survey 2011–2014

Cofactor	Level	AFT		DSST		CERAD4	
		Mean (95% CI)	P value	Mean (95% CI)	P value	Mean (95% CI)	P value
All		17.9 (17.6 to 18.3)		51.2 (50.0 to 52.4)		25.7 (25.0 to 26.3)	
Toxoplasma gondii	Positive	17.2 (16.4 to 18.0)	0.049	46.8 (44.8 to 48.9)	<0.001	25.0 (24.1 to 26.0)	0.031
	Negative	18.1 (17.7 to 18.5)	Ref	52.3 (50.9 to 53.6)	Ref	25.8 (25.2 to 26.5)	Ref
Toxocara	Positive	16.0 (15.0 to 17.0)	0.001	40.8 (37.9 to 43.6)	<0.001	23.1 (21.8 to 24.5)	0.001
	Negative	18.0 (17.7 to 18.4)	Ref	51.8 (50.5 to 53.0)	Ref	25.8 (25.1 to 26.5)	Ref
Age in years	60–69	19.4 (19.0 to 19.9)	Ref	56.8 (55.3 to 58.3)	Ref	27.5 (26.7 to 28.3)	Ref
	70 and over	16.1 (15.8 to 16.4)	<0.001	44.3 (43.0 to 45.5)	<0.001	23.4 (22.8 to 24.1)	<0.001
Gender	Male	18.2 (17.7 to 18.7)	Ref	48.9 (47.5 to 50.3)	Ref	24.6 (23.8 to 25.4)	Ref
	Female	17.7 (17.3 to 18.1)	0.090	53.1 (51.8 to 54.5)	<0.001	26.6 (26.0 to 27.2)	<0.001
Race	NH white	18.6 (18.1 to 19.1)	Ref	54.1 (52.6 to 55.6)	Ref	26.1 (25.2 to 26.9)	Ref
Hispanic origin	NH black	14.6 (13.9 to 15.2)	<0.001	37.6 (34.9 to 40.3)	<0.001	24.2 (23.4 to 25.1)	0.006
	NH Asian	14.9 (14.2 to 15.5)	<0.001	49.3 (45.6 to 52.9)	0.010	25.6 (24.0 to 27.3)	0.616
	Hispanic	15.8 (15.2 to 16.4)	<0.001	35.8 (33.8 to 37.7)	<0.001	23.1 (22.3 to 24.0)	<0.001
Poverty index	Below	15.2 (14.3 to 16.0)	<0.001	37.1 (33.5 to 40.6)	<0.001	22.8 (21.9 to 23.7)	<0.001
	At or above	18.3 (17.9 to 18.7)	Ref	52.7 (51.4 to 54.0)	Ref	26.0 (25.3 to 26.7)	Ref
Education	< High School	14.4 (13.8 to 15.1)	<0.001	34.5 (32.1 to 36.8)	<0.001	22.3 (21.4 to 23.1)	<0.001
	High School	16.2 (15.8 to 16.6)	<0.001	47.7 (45.6 to 49.8)	<0.001	24.7 (23.8 to 25.6)	<0.001
	> High School	19.5 (19.0 to 20.0)	Ref	57.0 (55.7 to 58.3)	Ref	26.9 (26.2 to 27.6)	Ref
Birth status	Non-US born	14.8 (14.2 to 15.4)	<0.001	38.8 (36.5 to 41.2)	<0.001	23.7 (22.9 to 24.4)	<0.001
	US born	18.3 (17.9 to 18.7)	Ref	52.7 (51.4 to 53.9)	Ref	25.9 (25.2 to 26.6)	Ref
Alcohol use	Current user	18.9 (18.4 to 19.5)	<0.001	55.5 (54.0 to 56.9)	<0.001	26.5 (25.8 to 27.2)	<0.001
	Not using	16.3 (15.9 to 16.7)	Ref	44.4 (42.8 to 46.0)	Ref	24.4 (23.8 to 25.0)	Ref
Smoking	Current	17.4 (16.5 to 18.3)	0.272	46.7 (43.6 to 49.7)	0.001	25.4 (24.0 to 26.8)	0.551
	Never or past	18.0 (17.6 to 18.4)	Ref	51.8 (50.6 to 53.0)	Ref	25.7 (25.1 to 26.3)	Ref
Hypertension	Yes	17.5 (17.1 to 17.9)	<0.001	49.7 (48.3 to 51.1)	<0.001	25.2 (24.4 to 25.9)	<0.001
	No	19.3 (18.6 to 20.0)	Ref	56.1 (54.4 to 57.8)	Ref	27.3 (26.5 to 28.1)	Ref

J Epidemiol Community Health. Author manuscript; available in PMC 2024 May 01.

Cofactor	Level	AFT		DSST		CERAD4	
		Mean (95% CI)	P value	Mean (95% CI)	P value	Mean (95% CI)	P value
Diabetes	Yes	16.5 (15.9 to 17.1)	<0.001	43.9 (41.5 to 46.4)	<0.001	24.4 (23.7 to 25.1)	0.001
	No	18.3 (17.8 to 18.8)	Ref	53.3 (51.8 to 54.8)	Ref	26.0 (25.3 to 26.8)	Ref
Weight status	Obesity	18.0 (17.6 to 18.4)	0.943	51.4 (49.9 to 52.8)	0.680	26.1 (25.4 to 26.8)	0.212
	Overweight	18.0 (17.4 to 18.6)	0.984	52.0 (50.3 to 53.6)	0.398	25.4 (24.7 to 26.1)	0.801
	Normal/under	18.0 (17.1 to 18.8)	Ref	50.8 (48.1 to 53.4)	Ref	25.5 (24.5 to 26.6)	Ref
Depression	Yes	15.7 (14.7 to 16.6)	<0.001	43.8 (39.2 to 48.3)	0.001	24.7 (23.6 to 25.9)	0.106
	No	18.1 (17.8 to 18.5)	Ref	52.0 (50.7 to 53.2)	Ref	25.8 (25.1 to 26.5)	Ref

AFT, animal fluency test; CERAD4, Consortium to Establish a Registry for Alzheimer's Disease; DSST, digit symbol substitution test; NH, non-Hispanic.

Table 2

Seroprevalence of *Toxoplasma gondii* and *Toxocara* (95% CI) by cofactors: US adults aged 60 and older, National Health and Nutrition Examination Survey 2011–2014

Cofactor	Level	Sample size	*T. gondii*		*Toxocara*	
			Percent (95% CI)	P value	Percent (95% CI)	P value
All		2643	19.9 (17.8 to 22.1)	—	5.1 (3.8 to 6.4)	—
Toxoplasma gondii	Positive	602	—	—	8.0 (4.8 to 11.2)	0.019
	Negative	2041	—	—	4.4 (3.2 to 5.5)	Ref
Toxocara	Positive	219	31.2 (23.1 to 39.4)	0.008	—	—
	Negative	2424	19.3 (17.1 to 21.6)	Ref	—	—
Age in years	60–69	1386	16.6 (14.5 to 18.6)	Ref	4.3 (2.6 to 6.0)	Ref
	70 and over	1257	24.1 (20.5 to 27.6)	<0.001	6.0 (4.6 to 7.5)	0.056
Gender	Male	1297	22.2 (19.7 to 24.8)	Ref	6.9 (4.8 to 8.9)	Ref
	Female	1346	18.0 (15.1 to 20.8)	0.014	3.6 (2.5 to 4.7)	0.001
Race	NH white	1306	19.1 (16.5 to 21.6)	Ref	3.6 (2.2 to 5.0)	Ref
Hispanic origin	NH black	581	23.9 (18.8 to 29.0)	0.078	10.0 (7.4 to 12.7)	<0.001
	NH Asian	211	9.6 (3.7 to 15.4) *	0.006	18.3 (12.3 to 24.2)	<0.001
	Hispanic	509	29.5 (23.9 to 35.1)	0.003	9.3 (4.7 to 13.8)	0.018
	Other	36	20.8 (11.3 to 30.3) *	—	6.6 (0.7 to 12.5) *	—
Poverty index	Below	411	27.2 (21.9 to 32.6)	0.005	10.7 (7.7 to 13.8)	<0.001
	At or above	2028	18.8 (16.7 to 21.0)	Ref	4.4 (3.0 to 5.7)	Ref
Education	< High school	693	26.0 (21.6 to 30.3)	0.001	9.7 (7.4 to 11.9)	<0.001
	High school	614	21.6 (17.0 to 26.2)	0.104	5.2 (3.1 to 7.3)	0.251
	> High school	1334	17.7 (15.6 to 19.8)	Ref	3.8 (2.4 to 5.3)	Ref
Birth status	Non-US born	640	29.0 (24.6 to 33.5)	0.001	15.0 (10.7 to 19.3)	<0.001
	US born	2002	18.8 (16.4 to 21.2)	Ref	3.9 (2.5 to 5.3)	Ref
Alcohol use	Current user	1454	19.0 (15.8 to 22.2)	0.395	4.3 (2.7 to 6.0)	0.080
	Not using	1136	21.5 (17.3 to 25.6)	Ref	6.0 (4.5 to 7.6)	Ref
Smoking	Current	348	21.9 (16.8 to 27.0)	0.436	7.2 (2.4 to 12.0) *	0.311

J Epidemiol Community Health. Author manuscript; available in PMC 2024 May 01.

Cofactor	Level	Sample size	*T. gondii*		*Toxocara*	
			Percent (95% CI)	**P value**	**Percent (95% CI)**	**P value**
	Never or past	2294	19.7 (17.2 to 22.1)	Ref	4.8 (3.6 to 6.0)	Ref
Hypertension	Yes	2099	19.1 (16.7 to 21.4)	0.159	5.4 (3.9 to 6.9)	0.173
	No	544	22.6 (18.0 to 27.3)	Ref	4.2 (2.6 to 5.7)	Ref
Diabetes	Yes	725	20.9 (17.5 to 24.3)	0.568	4.7 (3.8 to 5.7)	0.612
	No	1918	19.6 (17.0 to 22.3)	Ref	5.2 (3.6 to 6.8)	Ref
Weight status	Obesity	971	20.4 (17.2 to 23.6)	0.436	4.4 (2.4 to 6.4)	0.445
	Overweight	924	20.6 (17.1 to 24.1)	0.414	5.9 (4.1 to 7.7)	0.393
	Normal/under	709	18.5 (14.5 to 22.6)	Ref	5.0 (3.4 to 6.6)	Ref
Depression	Yes	247	15.9 (9.8 to 22.1)	0.133	7.6 (3.7 to 11.5)	0.090
	No	2349	20.2 (18.0 to 22.4)	Ref	4.7 (3.5 to 5.9)	Ref

*Relative CI width >130, does not meet National Center for Health Statistics presentation standards. Interpret with caution.

NH, non-Hispanic.

Table 3

Multivariate models for cognitive function scores, adjusted for *Toxoplasma gondii* and *Toxocara* seropositivity and cofactors: US adults aged 60 and older, National Health and Nutrition Examination Survey 2011–2014

Cofactor	Level	AFT		DSST		CERAD4	
		Beta*	P value	Beta*	P value	Beta*	P value
Toxoplasma gondii	Positive	−0.17 (−0.91, 0.57)	0.647	−1.75 (−3.50, 0.01)	0.051	0.12 (−0.56, 0.81)	0.715
	Negative	Ref		Ref		Ref	
Toxocara	Positive	0.06 (−0.94, 1.07)	0.898	−3.54 (−5.74, −1.34)	0.003	−0.89 (−2.15, 0.37)	0.159
	Negative	Ref		Ref		Ref	
Age in years	60–69†‡	Ref		Ref		Ref	
	70 and over	−2.86 (−3.46, −2.27)	<0.001	−11.20 (−12.58, −9.82)	<0.001	−3.67 (−4.46, −2.87)	<0.001
Gender	Male‡	Ref		Ref		Ref	
	Female	−0.12 (−0.72, 0.49)	0.694	5.51 (4.17, 6.84)	<0.001	2.31 (1.81, 2.82)	<0.001
Race and	NH white	Ref		Ref		Ref	
Hispanic origin	NH black	−2.73 (−3.28, −2.18)	<0.001	−9.62 (−11.38, −7.87)	<0.001	−0.55 (−1.57, 0.47)	0.282
	All Hispanic	−0.23 (−1.03, 0.58)	0.569	−7.23 (−9.50, −4.97)	<0.001	−1.31 (−2.34, −0.27)	0.015
	NH Asian/other	−1.23 (−2.60, 0.14)	0.077	2.62 (−1.05, 6.29)	0.156	0.31 (−1.04, 1.67)	0.641
Poverty index	Below‡	−0.46 (−1.10, 0.19)	0.160	−4.46 (−6.67, −2.25)	<0.001	−1.48 (−2.33, −0.63)	0.001
	At or above	Ref		Ref		Ref	
Education	< High school‡	−3.05 (−3.64, −2.45)	<0.001	−12.84 (−14.81, −10.88)	<0.001	−2.55 (−3.72, −1.39)	<0.001
	High school	−2.44 (−3.09, −1.78)	<0.001	−5.98 (−8.45, −3.51)	<0.001	−1.47 (−2.32, −0.63)	0.001
	> High school	Ref		Ref		Ref	
Birth status	Non-US born†	−2.39 (−3.35, −1.43)	<0.001	−6.17 (−8.72, −3.62)	<0.001	−0.66 (−1.74, 0.43)	0.226
	US born	Ref		Ref		Ref	
Alcohol use	Current use	1.15 (0.55, 1.75)	0.001	5.64 (4.02, 7.25)	<0.001	1.07 (0.60, 1.55)	<0.001
	Not using	Ref		Ref		Ref	
Smoking	Current	−0.80 (−1.69, 0.08)	0.074	−4.88 (−7.43, −2.33)	0.001	−0.45 (−1.54, 0.65)	0.411
	Never or past	Ref		Ref		Ref	

J Epidemiol Community Health. Author manuscript; available in PMC 2024 May 01.

Cofactor	Level	AFT		DSST		CERAD4	
		Beta*	**P value**	**Beta***	**P value**	**Beta***	**P value**
Hypertension	Yes§	−0.87 (−1.63,−0.11)	0.026	−2.78 (−4.62, −0.93)	0.004	−1.46 (−2.36, −0.56)	0.002
	No	Ref		Ref		Ref	
Diabetes	Yes	−0.50 (−1.14, 0.13)	0.115	−4.32 (−6.15, −2.50)	<0.001	−0.63 (−1.33, 0.07)	0.074
	No	Ref		Ref		Ref	
Weight status	Obesity	−0.07 (−0.99, 0.85)	0.878	2.02 (0.05, 3.99)	0.045	0.83 (0.11, 1.54)	0.024
	Overweight	−0.18 (−1.07, 0.70)	0.676	2.29 (0.60, 3.98)	0.010	0.25 (−0.46, 0.97)	0.474
	Normal/under	Ref		Ref		Ref	
Depression	Yes	−1.77 (−2.57, −0.98)	<0.001	−4.39 (−7.77, −1.00)	0.013	−0.77 (−1.91, 0.37)	0.178
	No	Ref		Ref		Ref	

*Beta from model adjusting for all covariates.

†Significant interaction between *Toxocara* and cofactor on AFT score.

‡Significant interaction between *Toxocara* and cofactor on DSST score.

§Significant interaction between *Toxocara* and cofactor on CERAD4 score.

AFT, animal fluency test; CERAD4, Consortium to Establish a Registry for Alzheimer's Disease; DSST, digit symbol substitution test.

Table 4

Adjusted stratified models evaluating interactions with *Toxocara* on cognitive function: US adults aged 60 and older, National Health and Nutrition Examination Survey 2011–2014*

Outcome	P value Interaction	Cofactor strata	Beta	95% CI		P value Beta
AFT	0.022	Age 60–69 years	−1.12	−2.28	0.03	0.057
		Age 70+ years	1.07	−0.51	2.66	0.177
	0.007	Non-US born	−1.83	−3.16	−0.51	0.008
		US born	0.80	−0.43	2.03	0.194
DSST	0.032	Age 60–69 years	−5.39	−8.15	−2.63	0.000
		Age 70+ years	−1.89	−5.13	1.35	0.244
		Males	−1.47	−3.81	0.88	0.211
	0.004	Females	−6.82	−10.40	−3.21	0.001
	0.048	Below poverty	−7.29	−11.3	−3.25	0.001
		At or above poverty	−2.79	−5.13	−0.45	0.021
	0.029	< High school education	−6.24	−10.00	−2.48	0.002
		High school education	−7.02	−11.90	−2.18	0.006
		> High school education	−0.83	−4.55	2.89	0.652
CERAD4	0.014	Hypertension	−0.36	−1.66	0.95	0.583
		No hypertension	−4.20	−6.74	−1.67	0.002

*Models adjusted for all cofactors—*Toxoplasma gondii, Toxocara,* age, gender, race and Hispanic origin, poverty index, education, US birth status, alcohol use, smoking, hypertension, diabetes, obesity and depression.

AFT, animal fluency test; CERAD4, Consortium to Establish a Registry for Alzheimer's Disease; DSST, digit symbol substitution test.