



BMJ Open Association between seropositivity for toxocariasis and cognitive functioning in older adults: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (NHANES), 2011–2014

Ge Song ¹, Chao Yang,² Zhe Qu,³ Xuechun Lin,⁴ Minhui Liu ⁵, Yanhong Wang⁶

To cite: Song G, Yang C, Qu Z, *et al.* Association between seropositivity for toxocariasis and cognitive functioning in older adults: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (NHANES), 2011–2014. *BMJ Open* 2023;**13**:e068974. doi:10.1136/bmjopen-2022-068974

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-068974>).

Received 07 October 2022
Accepted 07 February 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Yanhong Wang;
yanhongwang@lzu.edu.cn

ABSTRACT

Objectives This study sought to examine the relationship between seropositivity for toxocariasis and cognitive functioning in a nationally representative sample of US older adults.

Design A cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) data collection took place in the US at participants' homes and mobile examination centres with specialised equipment.

Participants The study population consisted of 3188 community-dwelling US older adults aged 60 and above from the NHANES 2011 to 2014.

Outcome measures IgG antibody against *Toxocara* spp was tested by a Luminox assay using recombinant rTc-CTL-1 antigen. A value >23.1 mean fluorescence intensity (MFI) indicated positive for toxocariasis and a value ≤23.1 MFI as negative for toxocariasis. The Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest immediate and delayed memory, the Animal Fluency test and the Digit Symbol Substitution Test (DSST) were used to assess cognitive functioning. Cognitive test-specific and global cognitive z scores were computed using sample means and SD.

Results The study population consisted of 3188 participants who represented a total of 111 896 309 civilian citizens in the USA. The mean age of the participants was 69.6 years (standard deviation 6.8). The prevalence of toxocariasis in this population was 7.3% (95% confidence interval [CI] 6.1% to 8.5%). The survey-weighted linear regression model showed that compared with participants who were toxocariasis seronegative, those who were seropositive had lower DSST z score (beta [β] = -0.12, 95% CI -0.22 to -0.01) and global cognition z score (β = -0.11, 95% CI -0.22 to -0.01), after controlling for age, sex, race/ethnicity, education, depressive symptoms, smoking status, body mass index, prevalent coronary heart disease, prevalent stroke, and systolic blood pressure, physical activity, and total cholesterol.

Conclusions In our study, seropositive toxocariasis was independently and significantly associated with worse

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We used National Health and Nutrition Examination Survey data and the study population was nationally representative of older adults in the USA.
- ⇒ A wide range of sociodemographic, lifestyle, mental health and physical health covariates were adjusted for, reducing the possibility of residual confounding.
- ⇒ The cross-sectional study design prevents the assessment of longitudinal relationships.

working memory, sustained attention, processing speed and global cognition in older adults. If this association is causal, public health measures to prevent human toxocariasis might help protect older adults' cognitive function.

INTRODUCTION

Alzheimer's disease and related dementia (ADRD) pose a serious threat to families, communities and healthcare systems around the world. Between 1990 and 2016, the number of people living with dementia has more than doubled, primarily as a result of population ageing and increased life expectancy.¹ Given that ADRD is currently incurable, identifying modifiable risk factors associated with ADRD would be the major way to alleviate the burden of ADRD. Researchers in a recent study suggested that age-specific incidences of dementia in the USA have decreased as a result of intervening on modifiable risk factors.²

Many parasite infections have been linked to cognitive decline.^{3,4} Among them is human toxocariasis, an infection with *Toxocara* spp larvae which are common ascarid roundworms found in mammals.⁵ Toxocariasis is

an under-reported parasitic disease that affects a large number of people worldwide, especially those living in poverty. By hand-to-mouth contact with embryonated eggs of *Toxocara* spp larvae in the faeces of dogs and cats, respectively, humans can become infected through zoonotic transmission.⁶ An infection could also occur from humans ingesting contaminated, undercooked meat.⁷ In the USA, about 14% of people are seropositive for toxocariasis, and the prevalence varies across ethnicity and regions.⁸

Studies have shown that toxocariasis is associated with worse cognitive functioning in animals.^{9–11} However, surprisingly little evidence exists regarding this relationship in humans, despite the fact that toxocariasis is widely prevalent in humans and has been shown to affect the brain.¹² A few studies have examined the relationship between *Toxocara* spp seropositivity and cognitive functioning in children.^{3,8,13,14} To our knowledge, there is only one relevant study exclusively targeting older adults.¹⁵ However, the authors of that study failed to account for important confounders such as body mass index (BMI)¹⁶ and depressive symptoms¹⁷ and did not calculate global cognition. Thus, more studies are needed to examine the relationship between toxocariasis and cognitive functioning in older adults.

In this study, taking advantage of the National Health and Nutrition Examination Survey (NHANES)¹⁸ 2011–2014, we aimed to examine the relationship between seropositivity status for toxocariasis and cognitive functioning in a nationally representative sample of US older adults. The findings of this study will inform public health interventions to protect cognitive functioning in older adults.

METHODS

NHANES study design and recruitment

The National Center for Health Statistics of the Centers for Disease Control and Prevention conducts the NHANES, a continuous cross-sectional survey of US adults, children and youth who are not institutionalised in civilian settings. Every 2 years, a nationwide survey is conducted among about 5000 nationally representative participants. In-home interviews and physical examinations at mobile examination centres with specialised equipment are used to assess their sociodemographic, physical and nutritional conditions. Medical, dental and physiological examinations are included in health exams, in addition to laboratory testing of urine and blood samples. Participants' IgG antibodies against *Toxocara* spp and cognitive functioning was measured in the NHANES 2011–2014 cycles. To increase the sample size and power of this study, two survey cycles (2011–2012 and 2013–2014) were combined. A total of 19 151 people took part in the NHANES between 2011 and 2014. They were chosen from a group of census blocks or area segments within clusters of census blocks. The specific sampling strategy has been published somewhere else.¹⁹

Of the 19 151 individuals, we excluded individuals aged <60 (n=15 679) or had missing data on IgG antibodies against *Toxocara* spp. (n=284). Finally, a total of 3188 participants aged 60 and above were included in the analysis. The characteristics of the excluded participants due to missing data (n=284) were in online supplemental appendix table 1. People who were excluded from the study were more likely to be other than non-Hispanic white, overweight/obese, finished less education, had less severe depressive symptoms, had higher systolic blood pressure, and had worse performance on the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest (CERAD-WL) immediate recall, CERAD-WL delayed recall, animal fluency test (AFT) and digit symbol substitution test (DSST), compared with the included participants.

Independent variable: seropositivity for toxocariasis

IgG antibody against *Toxocara* spp was tested by a Luminex assay using recombinant rTc-CTL-1 antigen in the laboratory. The *Toxocara* assay procedure in the Luminex platform has been described elsewhere.²⁰ For quality control and assay validation, *Toxocara* 100, *Toxocara* 50 and *Toxocara* 0 were used as the three controls for each run. The controls should fall within the established value's mean±2 SD. The entire plate was retested if the controls on the plate had a value that was outside the acceptable range. The assay has been tested against reference serum sets and showed 90% sensitivity and 99% specificity. A value greater than the 23.1 mean fluorescence intensity (MFI) was categorised as positive for toxocariasis, ≤23.1 MFI as negative for toxocariasis.²¹ Then, we categorised the participants into 'negative' or 'positive' for toxocariasis in our analyses.

Dependent variables: cognitive functioning

The CERAD-WL, the AFT and the DSST were used to assess participants' cognitive function. The detailed methodology has been published elsewhere.¹⁸

1. The CERAD-WL evaluated participants' verbal learning abilities both immediately (immediate memory) and later (delayed memory).²² It was formed by a delayed recall following three learning trials. Participants must read aloud ten randomly chosen words that are displayed on a computer screen in large, bolded characters, one at a time, for each immediate learning trial. Participants were told to remember and recall as many words as they could after the words were presented. The placement of the 10 words was altered on each of the three trials. Each trial had a maximum score of 10 points. The total of a participant's three trial scores was their immediate memory score, which ranged from 0 to 30. The delayed recall test, which was given to participants after completing the AFT and the DSST, required them to recall as many words as they could from the same 10-word list. The number of accurately recalled words of a participant determined his/her delayed memory score, which ranged from 0 to 10.

- Participants' language proficiency and executive function were assessed by the AFT.²³ Participants had 1 min to name as many animals as they could, and each animal they named earned them one point. Prior to the AFT test, participants were asked to name three items of clothing as a warm-up.
- The DSST measured the participants' working memory, sustained attention and processing speed.²⁴ The test was administered using a paper form with a top-mounted key that had nine numbers and paired symbols on it. The 133 boxes that were placed next to the numbers gave participants 2 min to match the symptoms to the appropriate symbols. The total number of accurate matches served as the basis for the score.²⁵ The DSST had a possible score range of 0–133.²⁶ A sample practice test was given to participants before the actual test.

Covariates

Covariates were selected based on literature review and included age (years), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black or Hispanics and others), education (below high school, high school graduate or some college or above), depressive symptoms measured by the Patient Health Questionnaire-9 (PHQ-9),²⁷ smoking status (never, former or current smokers), BMI (<18.5 kg/m², 18.5–24.9 kg/m², 25–29.9 kg/m² or ≥30 kg/m²), prevalent coronary heart disease (CHD) (yes or no), prevalent stroke (yes or no), systolic blood pressure (mm Hg), physical activity (hours/week) and total cholesterol (mg/dL). The PHQ-9 was a nine-item screening tool with a total score ranging from 0 to 27 and measures the frequency of depressive symptoms during the previous 2 weeks, and a higher score denotes more severe depression symptoms. The total PHQ-9 score was used to represent the extent of depressive symptoms. The information was collected through either interviews or health examinations.

Statistical analysis

Since the NHANES was designed to represent the civilian, non-institutionalised US population using a complex multistage probability sampling,²⁸ we took into account survey analysis procedures by incorporating the sample weights for each participant into the analysis through the use of a survey package in R software, V.4.1–1.^{29 30} The weight-adjusted samples were better representative of the actual population. We summarised the characteristics of participants using weighted means and SD for continuous variables and weighted proportions for categorical variables. We used a design-based two-sample t-test and χ^2 test (with Rao-Scott correction) to examine between-group differences.

Since the cognitive tests used in this study are based on different scales, we calculated cognitive test-specific z scores to have a mean of 0 and a variance of 1. We also calculated an arithmetic mean of the four z-scores from different cognitive tests to represent a global cognitive

z-score. We used survey-weighted linear regression models to evaluate the association between toxocariasis seropositivity and cognitive function for each cognitive test z-score. Specifically, we built two models for each outcome. Model 1 was unadjusted, and model 2 was adjusted for the aforementioned covariates. We assessed whether there was a potential effect measure modification by key demographic variables for the association between seropositivity for toxocariasis and cognitive z scores by using the Rao-Scott likelihood ratio test comparing the model with interaction terms versus without the interaction term.

The statistical significance level was set at 5%. A 95% CI excluding zero was regarded as statistically significant. All analyses were performed using the R statistical package V.4.2.2.³¹

Patients and public involvement

None.

RESULTS

Participants' characteristics by toxocariasis seropositivity status were presented in [table 1](#). Of the 3188 participants, 1403 were from 2011 to 2012 cycle; 1785 were from 2013 to 2014 cycle. They represented a total of 111 896 309 civilian citizens in the USA. The mean age of the participants was 69.6 years (SD=6.8). The prevalence of toxocariasis in this population was 7.3% (95% CI 6.1% to 8.5%). About half of the participants were female (54.6%), non-Hispanic white (78.3%), completed some college or above (59.3%), were never smokers (49.9%) and had a BMI ≥30 (37.0%) and an average of 2.7 hours of physical activity per week. Their mean total cholesterol and systolic blood pressure were 190.2 mg/dL and 122.9 mm Hg, respectively. Their mean immediate memory, delayed memory, AFT and DSST scores were 19.5, 6.2, 17.9 and 52.0, respectively.

Compared with participants with seronegative for toxocariasis, those with seropositive for toxocariasis were more likely to be of other ethnicities than non-Hispanic white. The two groups of participants were similar in terms of the distribution of other covariates. The CERAD W-L immediate recall and the DSST score were lower in those who were seropositive for toxocariasis than those who were seronegative for toxocariasis (18.8 vs 19.5, p=0.03 and 48.8 vs 52.2, p=0.006, respectively).

[Table 2](#) showed survey-weighted means and SDs of the cognitive test-specific and global cognitive z scores by toxocariasis seropositivity status. The mean of CERAD W-L immediate call, CERAD W-L delayed recall, AFT and DSST was 0.20, 0.16, 0.27 and 0.37, respectively, among participants with seronegative for toxocariasis. Comparing with those who were seronegative for toxocariasis, the participants who were seropositive for toxocariasis tended to have lower z-scores in each cognitive test. Specifically, the mean of CERAD W-L immediate call, CERAD W-L delayed recall, AFT and DSST was 0.05, 0.05, 0.18 and 0.18, respectively. Similar pattern was seen

Table 1 Individual-level characteristics of participants by toxocariasis seropositivity

Variables	Total	Negative	Positive	Pvalue
Total, n (%)	3188 (100.0)	2900 (91.0)	288 (9.0)	
Age (years), mean (SD)	69.6 (6.8)	69.6 (6.8)	69.6 (6.8)	0.897
Sex, %				0.358
Male	45.4	45.1	48.7	
Female	54.6	54.9	51.3	
Race/ethnicity, %				<0.001
Non-Hispanic whites	78.3	79.0	68.7	
Non-Hispanic blacks	8.5	8.4	9.9	
Hispanics and others	13.2	12.6	21.4	
Education, %				0.134
Below high school	18.4	17.9	24.2	
High school graduate	22.3	22.2	23.7	
Some college or above	59.3	59.9	52.1	
Depressive symptoms (PHQ-9), mean (SD)	3.2 (4.6)	3.2 (4.6)	3.8 (5.2)	0.186
Smoking status, %				0.229
Never	49.9	50.3	44.9	
Former	38.4	38.4	38.7	
Current	11.6	11.2	16.4	
Body mass index (kg/m ²), %				0.694
<18.5	1.5	1.5	1.5	
18.5–24.9	25.3	25.5	22.2	
25.0–29.9	36.2	36.1	37.3	
≥30	37.0	36.9	39.0	
Prevalent CHD, %	10.0	10.1	8.9	0.666
Prevalent stroke, %	7.8	7.9	6.5	0.434
Systolic blood pressure (mm Hg), mean (SD)	122.9 (18.9)	122.9 (19.0)	122.0 (17.7)	0.299
Physical activity (hours/week), mean (SD)	2.7 (10.9)	2.7 (11.2)	2.4 (5.5)	0.351
Total cholesterol (mg/dL), mean (SD)	192.0 (42.1)	192.0 (42.1)	191.6 (42.2)	0.901
CERAD W-L immediate recall, mean (SD)	19.5 (4.8)	19.5 (4.7)	18.8 (5.3)	0.030
CERAD W-L delayed recall, mean (SD)	6.2 (2.4)	6.2 (2.3)	5.9 (2.4)	0.126
Animal fluency test, mean (SD)	17.9 (5.7)	17.9 (5.7)	17.4 (5.2)	0.364
Digit symbol substitution test, mean (SD)	52.0 (16.8)	52.2 (16.8)	48.8 (16.8)	0.006

Data were expressed as unweighted number of participants and corresponding proportions in the total column and weighted percentages for categorical variables, and weighted means and SDs for continuous variables.

Bolded values mean statistical significance ($p < 0.05$).

CERAD W-L, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; CHD, coronary heart disease; PHQ-9, Patient Health Questionnaire-9.

for the global cognition z-scores (0.23 and 0.08 for those who were seronegative and seropositive for toxocariasis, respectively).

Then, we evaluated the mean difference in cognitive test z scores between the seropositive versus seronegative for toxocariasis groups using survey-weighted linear regression models (table 3). In the unadjusted model 1, compared with participants who were seronegative for toxocariasis, those who were seropositive for toxocariasis had statistically significant lower CERAD W-L immediate

recall z score (beta (β) = -0.15 , 95% CI -0.28 to -0.02), lower DSST z score (beta = -0.20 , 95% CI -0.33 to -0.06) and global cognition z score (beta = -0.15 , 95% CI -0.27 to -0.04). After accounting for potential confounders (model 2), the mean difference in cognitive test z scores between the two groups attenuated. However, the mean difference remained statistically significant for DSST z scores and global cognition z scores in the adjusted model. Specifically, in the adjusted model 2, we found

Table 2 Survey-weighted means and SD of cognitive test-specific and global cognitive z scores by toxocariasis seropositivity

	Negative	Positive
CERAD W-L immediate recall	0.20 (0.94)	0.05 (1.05)
CERAD W-L delayed recall	0.16 (0.97)	0.05 (1.02)
Animal fluency test	0.27 (1.04)	0.18 (0.95)
Digit symbol substitution test	0.37 (0.97)	0.18 (0.97)
Global cognition	0.23 (0.81)	0.08 (0.84)

CERAD W-L, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest.

that participants who were seropositive for toxocariasis had lower DSST z scores (beta (β) = -0.12 , 95% CI -0.22 to -0.01) and lower global cognition z scores (β -0.11 , 95% CI -0.22 to -0.01) than those who were seronegative for toxocariasis.

We also evaluated whether the mean difference in cognitive test z scores (ie, DSST z scores and global cognition z scores) for those who were toxocariasis seropositive versus seronegative would differ by key demographic variables (online supplemental appendix figure 1). We did not observe statistical significance interactions between toxocariasis seropositivity status and demographic variables with respect to cognitive test z scores. In general, participants who were seropositive for toxocariasis tended to have lower global cognition z scores than those who were seronegative for toxocariasis in the subgroups of these demographic variables.

DISCUSSION

In this cross-sectional analysis of nationally representative older adults in the USA, being seropositive for toxocariasis is independently associated with worse working memory, sustained attention and processing speed as indicated by the DDST z scores (beta [β] -0.12 , 95% CI -0.22 to -0.01) as well as global cognition z scores (β -0.11 , 95% CI -0.22

to -0.01). This relationship is independent of age, sex, race/ethnicity, education, depressive symptoms, smoking status, BMI, prevalent CHD, prevalent stroke, systolic blood pressure, physical activity and total cholesterol. Our results suggest that although our findings need to be validated by longitudinal studies, given the escalating population ageing and high prevalence of toxocariasis in the USA, public health interventions that prevent toxocariasis may help protect cognitive function in older adults.

A limited number of studies have examined the associations of toxocariasis with cognitive outcomes in humans. Most of these studies targeted children whose developing brains are susceptible to *Toxocara* infection. In one early study of 333 children aged 5–7 years, no statistically significant association was found between *Toxocara* seropositivity and cognitive function.³² In a larger but early study of a nationally representative sample from the NHANES 1988–1994 cycle data, compared with children who were *Toxocara* negative, *Toxocara* seropositive children had worse attention, perceptual reasoning and academic achievement.⁸ In another study using the NHANES 1988–1994 cycle data on adults aged 21–59 years, researchers found that toxocariasis was associated with worse information processing speed measured by symbol-digit substitution. In addition, they found significant interactions between toxocariasis and age, which suggested that the susceptibility to toxocariasis-related cognitive dysfunction may vary among different age groups of adults.³³

Only one relevant previous study exclusively targeted older adults. In a cross-sectional study of 1350 elderly adults aged 60 years and above, *Toxocara* seropositivity was associated with worse executive function and processing speed measured by the AFT and the DSST, respectively, but not for verbal learning abilities measured by CERAD-WL.¹⁵ However, in that study, researchers did not evaluate global cognition, and several important covariates were not taken into account, such as depressive symptoms, prevalent CHD, prevalent stroke and systolic blood pressure. In our study, we included 3188 elderly participants from two NHANES cycles (2011–2012 and

Table 3 The mean difference in cognitive test-specific and global cognitive z-scores comparing seropositive versus seronegative for toxocariasis from survey-weighted linear regressions

	Coefficient* (95% CI)	
	Model 1	Model 2
Cognitive test z score		
CERAD W-L immediate recall	-0.15 (-0.28 to 0.02)	-0.12 (-0.26 to 0.01)
CERAD W-L delayed recall	-0.11 (-0.26 to 0.03)	-0.11 (-0.26 to 0.03)
Animal fluency test	-0.09 (-0.29 to 0.11)	-0.04 (-0.28 to 0.20)
Digit symbol substitution test	-0.20 (-0.33 to 0.06)	-0.12 (-0.22 to 0.01)
Global cognition	-0.15 (-0.27 to 0.04)	-0.11 (-0.22 to 0.01)

Model 1 was unadjusted; Model 2 was fully adjusted for age, sex, race/ethnicity, education, depressive symptoms, smoking status, body mass index, prevalent coronary heart disease, prevalent stroke, systolic blood pressure, physical activity and total cholesterol.

Bolded values mean statistical significance (95% CI excluding zero).

*Seropositive versus seronegative (reference).

CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest.



2013–2014), evaluated global cognition, and comprehensively adjusted for potential covariates, which added stronger evidence regarding the negative relationship between *Toxocara* infection and cognitive functioning.

The possible biological mechanisms that account for the association between *Toxocara* infection and worse cognitive functioning are complicated. *Toxocara* physically destroys brain tissue and causes pathohistological alterations in the brain.³⁴ Further, *Toxocara* larvae can cross the blood–brain barrier and increase the barrier permeability during infection.³⁵ In addition, as part of the cerebral immune response, *Toxocara* infection is shown to alter inflammatory mediators, such as proinflammatory cytokines and chemokines, which may result in brain dysfunction.³⁶ In particular, animal models demonstrated neurodegenerative changes related to cerebral *Toxocara* infections, such as accumulation of the amyloid beta and increased expression of the ubiquitin-proteasome system.¹⁰ Future studies are expected to clarify the underlying mechanism.

To the best of our knowledge, this is the first study on the relationship between toxocariasis and cognitive functioning in a relatively large, nationally representative sample of older adults in the USA. Thus, it makes a unique contribution to the literature. The rigorous evaluation of IgG antibodies against *Toxocara* spp infection and the three cognitive tests to assess cognitive functioning were just two of the stringent quality control and assurance measures that were put in place throughout the NHANES study, thus guaranteeing the quality of the data used in this study. Moreover, global cognition was calculated using a rigorous statistical method to represent participants' overall cognition. In addition, a wide range of sociodemographic, lifestyle and covariates related to mental and physical health were adjusted, reducing the possibility of residual confounding. The results of our study can, therefore, be generalised to older adults in the USA.

The major limitation of this study is the cross-sectional study design; thus, we did not know whether participants had long-term exposure to *Toxocara* spp or a recent exposure when the IgG immune response to *Toxocara* spp had just begun. Reverse causation is also possible. Moreover, with three cognitive tests, we may not comprehensively assess participants' cognitive functioning. Last but not least, the excluded people due to missing data (n=284) and the included participants (n=3188) had sociodemographic and health differences, raising the possibility of selection bias.³⁷ Future studies are expected to (A) use more advanced laboratory methods for identifying specific agents that caused toxocariasis and stages of the infection, (B) explore the pathophysiological mechanisms on the cognitive effects of toxocariasis, (C) target non-western populations, especially those from developing countries and (d) use longitudinal designs to assess the temporal relationship between toxocariasis and cognitive functioning. These studies could lead to the discovery of novel biomarkers for cognitive decline and shed light on the development of toxocariasis treatments and vaccines that would shield people from the disease's adverse effects.

In conclusion, seropositivity for toxocariasis is prevalent in US older adults and is associated with worse working

memory, sustained attention, processing speed as well as global cognition in this population. Public health interventions are needed to prevent toxocariasis, which may (if this association is causal) help preserve cognitive function in the growing proportion of older adults in the USA.

Author affiliations

¹Department of Natural Sciences, University of Houston-Downtown, Houston, Texas, USA

²The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

³School of Nursing, Xu Zhou Medical College, Xuzhou, Jiangsu, China

⁴Department of Nutrition and Food hygiene, Hubei Key Laboratory of Food Nutrition and Safety, Ministry of Education Key Laboratory of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

⁵Central South University Xiangya School of Nursing, Changsha, Hunan Sheng, China

⁶School of Nursing, Lanzhou University, Lanzhou, Gansu, China

Acknowledgements We thank all participants in the NHANES study. We thank the NHANES research team for providing the data.

Contributors CY and ZQ performed data analysis; SG and XL drafted the original manuscript. ML, YW and CY significantly provided feedback to the manuscript. SG is the guarantor of this manuscript.

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.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The NHANES was approved by the National Center for Health Statistics Research Ethics Review Board. Participants provided written informed consent before enrolling in the study. The present analysis was granted an exemption by the University of Houston-Downtown Committee for the Protection of Human Subjects because this study only used deidentified, publicly available data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ge Song <http://orcid.org/0000-0002-3109-6477>

Minhui Liu <http://orcid.org/0000-0002-4554-3135>

REFERENCES

- Nichols E, Szoek CE, Vollset SE, *et al*. Global, regional, and national burden of alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2019;18:88–106.
- Rocca WA, Petersen RC, Knopman DS, *et al*. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement* 2011;7:80–93.

- 3 Kvalsvig JD, Cooppan RM, Connolly KJ. The effects of parasite infections on cognitive processes in children. *Ann Trop Med Parasitol* 1991;85:551–68.
- 4 Jasti A, Ojha SC, Singh YI. Mental and behavioral effects of parasitic infections: a review. *Nepal Med Coll J* 2007;9:50–6.
- 5 Fan C-K, Holland CV, Loxton K, et al. Cerebral toxocariasis: silent progression to neurodegenerative disorders? *Clin Microbiol Rev* 2015;28:663–86.
- 6 Hotez PJ, Wilkins PP. Toxocariasis: america's most common neglected infection of poverty and a helminthiasis of global importance? *PLoS Negl Trop Dis* 2009;3:e400.
- 7 Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003;16:265–72.
- 8 Walsh MG, Haseeb MA. Reduced cognitive function in children with toxocariasis in a nationally representative sample of the united states. *Int J Parasitol* 2012;42:1159–63.
- 9 Hamilton CM, Stafford P, Pinelli E, et al. A murine model for cerebral toxocariasis: characterization of host susceptibility and behaviour. *Parasitology* 2006;132(Pt 6):791–801.
- 10 Chou C-M, Lee Y-L, Liao C-W, et al. Enhanced expressions of neurodegeneration-associated factors, UPS impairment, and excess A β accumulation in the hippocampus of mice with persistent cerebral toxocariasis. *Parasit Vectors* 2017;10:620.
- 11 Waindok P, Janecek-Erfurth E, Lindenwald DL, et al. Toxocara canis- and Toxocara cati-induced neurotoxocarosis is associated with comprehensive brain transcriptomic alterations. *Microorganisms* 2022;10:177.
- 12 Gale SD, Hedges DW. Neurocognitive and neuropsychiatric effects of toxocariasis. *Adv Parasitol* 2020;109:261–72.
- 13 Jones JL, Lopez B, Alvarez Mury M, et al. Toxoplasma gondii infection in rural Guatemalan children. *Am J Trop Med Hyg* 2005;72:295–300.
- 14 Mendy A, Vieira ER, Albatineh AN, et al. Toxoplasma gondii seropositivity and cognitive functions in school-aged children. *Parasitology* 2015;142:1221–7.
- 15 Erickson LD, Hedges D, Stone A, et al. Association between toxocariasis seropositivity and serointensity and cognitive function in older U.S. adults. *Folia Parasitol (Praha)* 2022;69:1–6.
- 16 Wang C, Chan JSY, Ren L, et al. Obesity reduces cognitive and motor functions across the lifespan. *Neural Plast* 2016;2016:2473081.
- 17 Ge S, Tang X, Wei Z, et al. Smoking and cognitive function among middle-aged adults in China: findings from the China health and retirement longitudinal study baseline survey. *J Addict Nurs* 2020;31:E5–12.
- 18 NHANES. Data documentation, codebook, and frequencies NHANES website2017. 2012. Available: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/CFQ_G.htm
- 19 Johnson CL, Paulose-Ram R, Ogden CL, et al. National health and nutrition examination survey. *Analytic Guidelines* 1999.
- 20 NHANES. Toxoplasma gondii antibody- serum (surplus) (sstoxo_g). 2016 Available: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/SSTOXO_G.htm
- 21 Anderson JP, Rascoe LN, Levert K, et al. Development of a luminex bead based assay for diagnosis of toxocariasis using recombinant antigens tc-CTL-1 and tc-TES-26. *PLoS Negl Trop Dis* 2015;9:e0004168.
- 22 Fillenbaum GG, van Belle G, Morris JC, et al. Consortium to establish a Registry for Alzheimer's disease (CERAD): the first twenty years. *Alzheimers Dement* 2008;4:96–109.
- 23 Carone DA. E. strauss, E. m. s. sherman, & o. spreen, a compendium of neuropsychological tests: administration, norms, and commentary. *Applied Neuropsychology* 2007;14:62–3.
- 24 Silva MA. Development of the WAIS-III: A brief overview, history, and description. *Graduate Journal of Counseling Psychology* 2008;1:11.
- 25 Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol* 2018;38:513–9.
- 26 Mirra SS, Heyman A, McKeel D, et al. The Consortium to establish a Registry for Alzheimer's disease (CERAD). Part II. standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991;41:479–86.
- 27 Kroenke K, Spitzer R, Williams J. The patient health questionnaire (phq-9)–overview. *J Gen Intern Med* 2001;16:606–16.
- 28 Control CfD, Prevention. National center for health statistics (NCHS). national health and nutrition examination survey questionnaire (or examination protocol, or laboratory protocol). 2006. Available: <http://www.cdc.gov/nchs/nhanes.htm>
- 29 Gu Y, Guo J, Moshfegh AJ. Race/ethnicity and gender modify the association between diet and cognition in U.S. older adults: National health and nutrition examination survey 2011–2014. *Alzheimers Dement (N Y)* 2021;7:e12128.
- 30 Lumley T. Analysis of complex survey samples. *J Stat Soft* 2004;9:1–19.
- 31 RC. R: A language and environment for statistical computing. R foundation for statistical computing. Vienna, Austria; 2013. Available: <http://www.R-project.org/>
- 32 Worley G, Green JA, Frothingham TE, et al. Toxocara canis infection: clinical and epidemiological associations with seropositivity in kindergarten children. *J Infect Dis* 1984;149:591–7.
- 33 Erickson LD, Gale SD, Berrett A, et al. Association between toxocariasis and cognitive function in young to middle-aged adults. *Folia Parasitol (Praha)* 2015;62:2015.048.
- 34 Liao C-W, Fan C-K, Kao T-C, et al. Brain injury-associated biomarkers of TGF-beta1, S100B, GFAP, NF-L, ttg, abetapp, and tau were concomitantly enhanced and the ups was impaired during acute brain injury caused by toxocara canis in mice. *BMC Infect Dis* 2008;8:1–15.
- 35 Liao CW, Cho WL, Kao TC, et al. Blood-Brain barrier impairment with enhanced sp, NK-1R, GFAP and claudin-5 expressions in experimental cerebral toxocariasis. *Parasite Immunol* 2008;30:525–34.
- 36 Waindok P, Strube C. Neuroinvasion of toxocara canis- and T. cati-larvae mediates dynamic changes in brain cytokine and chemokine profile. *J Neuroinflammation* 2019;16:147.
- 37 Lu H, Cole SR, Howe CJ, et al. Toward a clearer definition of selection bias when estimating causal effects. *Epidemiology* 2022;33:699–706.