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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 Luminex 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 testspecific and global cognition 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 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. 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.

Many parasite infections have been linked to cognitive decline. Among them is human toxocariasis, an infection with Toxocara spp larvae which are common ascarid roundworms found in mammals. 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. An infection could also occur from humans ingesting contaminated, undercooked meat. In the USA, about 14% of people are seropositive for toxocariasis, and the prevalence varies across ethnicity and regions.

Studies have shown that toxocariasis is associated with worse cognitive functioning in animals. 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. A few studies have examined the relationship between Toxocara spp seropositivity and cognitive functioning in children. To our knowledge, there is only one relevant study exclusively targeting older adults. However, the authors of that study failed to account for important confounders such as body mass index (BMI) and depressive symptoms 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) 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 19151 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.

Of the 19151 individuals, we excluded individuals aged <60 (n=15679) 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. 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. 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.

1. The CERAD-WL evaluated participants’ verbal learning abilities both immediately (immediate memory) and later (delayed memory). 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.
2. Participants’ language proficiency and executive function were assessed by the AFT. 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.

3. The DSST measured the participants’ working memory, sustained attention and processing speed. 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 2min to match the symbols to the appropriate symbols. The total number of accurate matches served as the basis for the score. The DSST had a possible score range of 0–133. 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), 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, 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. 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 \( \chi^2 \) 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.4.2.3.

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 111896309 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 recall, CERALD 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 recall, CERALD W-L delayed recall, AFT and DSST was 0.05, 0.05, 0.18 and 0.18, respectively. Similar pattern was seen...
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 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) | 0.897 |
| Age (years), mean (SD) | 69.6 (6.8) | 69.6 (6.8) | 69.6 (6.8) | 0.358 |
| Sex, % | | | | |
| 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/m²), % | | | | 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 | 36.2 | 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.
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 signification 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 five to seven years, no statistically significant association was found between *Toxocara* seropositivity and cognitive function. 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. 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.

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. 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 2015–2016) in a nationally representative sample from the NHANES 2015–16 cycle data to confirm earlier findings.

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

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>Negative mean (SD)</th>
<th>Positive mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD W-L immediate recall</td>
<td>0.20 (0.94)</td>
<td>0.05 (1.05)</td>
</tr>
<tr>
<td>CERAD W-L delayed recall</td>
<td>0.16 (0.97)</td>
<td>0.05 (1.02)</td>
</tr>
<tr>
<td>Animal fluency test</td>
<td>0.27 (1.04)</td>
<td>0.18 (0.95)</td>
</tr>
<tr>
<td>Digit symbol substitution test</td>
<td>0.37 (0.97)</td>
<td>0.18 (0.97)</td>
</tr>
<tr>
<td>Global cognition</td>
<td>0.23 (0.81)</td>
<td>0.08 (0.84)</td>
</tr>
<tr>
<td>CERAD W-L, Consortium to Establish a Registry for Alzheimer’s Disease Word Learning subtest.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Cognitive test z score</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD W-L immediate recall</td>
<td>−0.15 (−0.28 to 0.02)</td>
<td>−0.12 (−0.26 to 0.01)</td>
</tr>
<tr>
<td>CERAD W-L delayed recall</td>
<td>−0.11 (−0.26 to 0.03)</td>
<td>−0.11 (−0.26 to 0.03)</td>
</tr>
<tr>
<td>Animal fluency test</td>
<td>−0.09 (−0.29 to 0.11)</td>
<td>−0.04 (−0.28 to 0.20)</td>
</tr>
<tr>
<td>Digit symbol substitution test</td>
<td>−0.20 (−0.33 to 0.06)</td>
<td>−0.12 (−0.22 to 0.01)</td>
</tr>
<tr>
<td>Global cognition</td>
<td>−0.15 (−0.27 to 0.04)</td>
<td>−0.11 (−0.22 to 0.01)</td>
</tr>
</tbody>
</table>

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 pathophysiological alterations in the brain. Further, *Toxocara* larvae can cross the blood–brain barrier and increase the barrier permeability during infection. 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. 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. 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. Further 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.

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**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.

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