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Association between *Toxoplasma gondii* and Blood Pressure and Hypertension in US Adults

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Abstract: An intraneuronal parasite infecting approximately one-third of the world's population, *Toxoplasma gondii* has been associated with markers of cardiovascular disease. In this study, we used data from the Center for Disease Control and Prevention's National Health and Nutrition Examination Survey to investigate associations between *T. gondii* and blood pressure and hypertension. Multiple regression modelling adjusted for a range of covariates showed that *T. gondii* was associated with lowered probability of elevated blood pressure, with lower probability of Stages 1 and 2 hypertension, and with lower systolic and diastolic blood pressure. These findings suggest that *T. gondii* might alter hemodynamic regulation, although the clinical relevance of these associations requires additional investigation.

Keywords: *Toxoplasma gondii*; blood pressure; hypertension; NHANES

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1. Introduction

Sociodemographic factors such as income and educational attainment are known to influence health outcomes [1] including hypertension [2]. Hypertension is a risk factor for cardiovascular, cerebrovascular, and renal disease [3], and it is highly prevalent across the world, affecting between one-quarter and one-third of the population in many regions [4] and making hypertension an important public health problem across much of the world. Numerous genetic [5] and environmental factors are associated with blood pressure [6,7] such as educational attainment and employment status [2]. Additional factors associated with blood pressure include airborne pollutants, ambient temperature, latitude, and response to increased noise production [6]. Additionally, sleep-gene interactions are also associated with blood pressure [5]. In addition to these factors, research has investigated associations between the infectious disease *T. gondii* and blood pressure [8,9].

T. gondii is a protozoal obligate intracellular parasite that infects approximately one-third of the world's population with large interregional differences in prevalence [10]. Members of the cat family are the definitive hosts for *T. gondii*, although many birds and mammals including humans can be intermediate hosts [11]. In immunocompetent humans, acute infection with *Toxoplasma gondii* is often mild or asymptomatic [12]; however, *T. gondii* can form metabolically active cysts in human tissues such as brain and muscle that can persist for the life of the host [13]. Although chronic infection with *T. gondii* had been considered benign [14], accumulating findings indicate that chronic infection with *T. gondii* can have deleterious effects, including associations with schizophrenia [15], obsessive compulsive disorder, cognitive deficits, and epilepsy [16]. *T. gondii* can affect dopamine metabolism [17].

Although *T. gondii* has also been associated with cardiovascular diseases [18], with markers of cardiovascular disease [8], and with reductions in overall noradrenergic activity in the brain that could be associated with blood pressure [19], relatively few studies have investigated associations between *T. gondii* and blood pressure. In one of the available studies based on 2009–2010 data from the US National Health and Nutrition Examination Surveys (NHANES), anti-*T. gondii* IgG antibodies were associated with an overall index of biomarkers for cardiovascular disease. In bivariate models in this study, *T. gondii* infection was associated with higher systolic blood pressure, a finding that was not present in the adjusted models, which showed no associations with either elevated systolic or diastolic blood pressure [8]. In a study conducted in northern Mexico, there were no associations between infection with *T. gondii* and hypertension during pregnancy [20]. In a study conducted in Brazil, there were no differences in systolic and diastolic blood pressures between pregnant women treated for acute toxoplasmosis with sulfadiazine, pyrimethamine, and folinic acid compared to healthy controls [21]. Other studies have found mixed results when examining a possible relationship between *T. gondii* and hypertension [9].

Because of associations between *T. gondii* and noradrenergic activity, dopamine and blood pressure, the widespread distribution of *T. gondii* in humans, and associations between hypertension and cardiovascular and cerebrovascular disease, we sought to further characterize associations between *T. gondii* and hypertension in a large sample while controlling for several other variables that could potentially affect associations between *T. gondii* and hypertension.

2. Results

The average age of the sample was 49.10 years. Fifty-one percent of the sample were women. Forty-seven percent were White, 20 percent were non-Hispanic Black, 14 percent were Mexican American, and 20 percent were Other. Twenty-five percent had attained a college degree or more. The average body-mass index was 29.15. The average systolic blood pressure in this sample was 123.05, and the average diastolic blood pressure was 69.00. *T. gondii* seropositivity was 17 percent (Table 1). Table 1 also shows additional medical and demographic information.

Table 1. Descriptive statistics of study variables.

	Mean or Proportion	SD	Minimum	Maximum
Blood pressure				
Hypertension				
Normal	0.46		0	1
Elevated	0.16		0	1
Stage 1 hypertension	0.19		0	1
Stage 2 hypertension	0.19		0	1
Systolic	123.05	18.08	65	235
Diastolic	69.99	12.29	9	132
T. gondii seropositive	0.17		0	1
Controls				
Age	49.10	17.68	20	80
Female	0.51		0	1
Race/ethnicity				
Non-Hispanic white	0.47		0	1
Non-Hispanic black	0.20		0	1
Mexican-American	0.14		0	1
Other	0.20		0	1

Table 1. *Cont.*

	Mean or Proportion	SD	Minimum	Maximum
Immigrant	0.26		0	1
Marital Status				
Married	0.51		0	1
Cohabiting	0.08		0	1
Divorced or separated	0.14		0	1
Widowed	0.08		0	1
Never married	0.19		0	1
College degree or more	0.25		0	1
Poverty-to-income ratio	2.51	1.65	0	5
Self-rated health	3.20	0.97	1	5
Body-mass index	29.15	6.91	13	82
Smoking Status				
Non-smoker	0.79		0	1
Some days	0.04		0	1
Everyday	0.17		0	1
Alcoholic drinks/week	3.33	7.96	0	164
Caffeine (grams)	0.15	0.18	0	1

Note: N = 12,010. Source: National Health and Nutrition Examination Study, 2009–2010, 2011–2012, and 2013–2014 cycles.

Results in Table 2 are presented as relative risk ratios (RRR). *T. gondii* seropositivity was associated with lower risk of having elevated blood pressure (RRR = 0.843, $p < 0.05$), Stage 1 hypertension (RRR = 0.789, $p < 0.01$), and Stage 2 hypertension (RRR = 0.759, $p < 0.001$) compared to *T. gondii* seronegativity in models adjusted for age, sex, race/ethnicity, immigrant status, educational attainment, poverty-to-income ratio, self-rated health, body-mass index, smoking, alcohol intake, and caffeine use (Table 2). *T. gondii* seropositivity was also associated with lower systolic blood pressure ($\beta = -1.345$, $p < 0.001$) and lower diastolic blood pressure ($\beta = -0.905$, $p < 0.01$) in adjusted linear regression models (Table 3).

Table 2. Toxoplasma gondii seropositivity and hypertension: relative risk ratios from multinomial logistic regression.

	Normal [a]		
	Elevated	**Stage 1**	**Stage 2**
T. gondii seropositive	0.843 *	0.789 **	0.759 ***
Age	1.034 ***	1.040 ***	1.077 ***
Female	0.523 ***	0.506 ***	0.571 ***
Race/ethnicity			
Non-Hispanic white	1.000	1.000	1.000
Non-Hispanic black	1.346 ***	1.588 ***	2.266 ***
Mexican-American	0.969	0.847	1.117
Other	1.191	1.291 **	1.350 **
Immigrant	0.997	0.956	1.039
Marital status			
Married	1.000	1.000	1.000
Cohabiting	1.045	1.001	1.020
Divorced or separated	0.856	0.998	0.875
Widowed	1.251	1.045	1.213
Never married	1.084	0.985	1.110

Table 2. *Cont.*

	Normal [a]		
	Elevated	**Stage 1**	**Stage 2**
College degree or more	0.839 *	0.813 **	0.744 ***
Poverty-to-income ratio	1.025	1.003	0.981
Self-rated health	0.921 **	0.936 *	0.869 ***
Body-mass index	1.040 ***	1.054 ***	1.050 ***
Smoking status			
Non-smoker	1.000	1.000	1.000
Some days	1.033	0.884	1.015
Everyday	0.962	1.010	1.097
Alcoholic drinks/week	1.017 ***	1.015 ***	1.025 ***
Caffeine (grams)	1.060	0.979	0.701 *

Note: [a] Risk ratios in each column are relative to normal blood pressure. N = 12,010. * $p < 0.05$,.** $p < 0.01$, *** $p < 0.001$. Source: National Health and Nutrition Examination Study, including 2009–2010, 2011–2012, and 2013–2014 cycles.

Table 3. Toxoplasma gondii seropositivity and systolic and diastolic blood pressure: Unstandardized coefficients from linear regression.

	Systolic	**Diastolic**
T. gondii seropositive	−1.345 ***	−0.905 **
Age	0.463 ***	−0.037 ***
Female	−3.706 ***	−2.627 ***
Race/ethnicity		
Non-Hispanic white	0.000	0.000
Non-Hispanic black	4.510 ***	1.639 ***
Mexican-American	1.075 *	−0.716
Other	1.461 **	0.850 *
Immigrant	−0.329	1.102 **
Marital status		
Married	0.000	0.000
Cohabiting	0.805	−1.268 **
Divorced or separated	−0.660	1.052 **
Widowed	3.015 ***	−3.441 ***
Never married	1.601 ***	−1.990 ***
College degree or more	−2.252 ***	0.315
Poverty-to-income ratio	−0.329 **	0.114
Self-rated health	−0.644 ***	−0.094
Body-mass index	0.203 ***	0.227 ***
Smoking status		
Non-smoker	0.000	0.000
Some days	0.114	0.198
Everyday	0.125	−0.048
Alcoholic drinks/week	0.137 ***	0.082 ***
Caffeine (grams)	−2.879 ***	2.312 ***

Note: N = 12,010. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Source: National Health and Nutrition Examination study, including 2009–2010, 2011–2012, and 2013–2014 cycles.

In general, age, sex, educational attainment, and PIR did not modify the associations between *T. gondii* seropositivity and hypertension (Table 4). However, of the 12 interaction models, two were statistically significant. Figure 1 shows how age moderates the relationship between *T. gondii* seropositivity and hypertension. The interaction is evidenced by the increasing difference in the probability of having normal blood pressure between *T. gondii* seropositive and seronegative groups at older ages, with those being seropositive having a higher likelihood of having normal blood pressure. This pattern was significantly

different from those with Stage 1 hypertension, which indicated the opposite pattern. Those who were seronegative were more likely to have Stage 1 hypertension than seropositive individuals, and this pattern became more pronounced with increasing age.

Table 4. *Toxoplasma gondii* seropositivity interactions and hypertension: relative risk ratios from multinomial logistic regression.

	Normal [a]		
	Elevated	**Stage 1**	**Stage 2**
T. gondii seropositive	1.101	1.435	0.844
Age	1.035 ***	1.041 ***	1.078 ***
Interaction	0.995	0.989 *	0.997
T. gondii seropositive	0.919	0.730 **	0.719 **
Female	0.545 ***	0.491 ***	0.563 ***
Interaction	0.794	1.199	1.128
T. gondii seropositive	0.777 **	0.791 **	0.722 ***
College degree	0.791 **	0.817 **	0.714 ***
Interaction	1.525 *	0.966	1.328
T. gondii seropositive	0.877	0.925	0.879
Poverty-to-income	1.025	1.014	0.988
Interaction	0.983	0.933	0.938

Note: [a] Risk ratios in each column are relative to normal blood pressure. Each set of three rows represent different models, each adjusted for age, sex, race/ethnicity, marital status, immigrant status, education, poverty-to-income ratio, self-rated health, body-mass index, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Source: National Health and Nutrition Examination Study, including 2009–2010, 2011–2012, and 2013–2014 cycles.

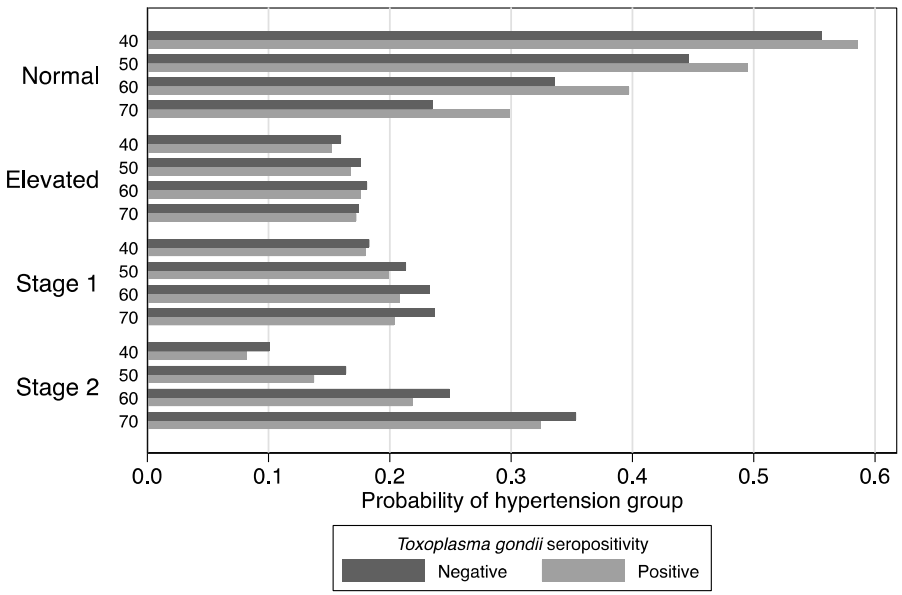

Figure 1. Interaction of *T. gondii* seropositivity and age on blood pressure status: Adjusted predictions from multinomial logistic regression. Note: Model adjusted for age, sex, race-ethnicity, immigrant status, marital status, poverty-to-income, self-rated health, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. Source: *National Health and Nutrition Examination Study*, including 2009–2010, 2011–2012, and 2013–2014 cycles.

Figure 2 shows how obtaining a college degree moderates the relationship between *T. gondii* and hypertension.

There appears to be no relationship between seropositivity status for those that have a college degree (i.e., both seropositive and seronegative individuals are about equally likely to have normal blood pressure), but there is a relationship for those without a college degree, where those who are seropositive are more likely to have normal blood pressure. In comparison to the Normal group, the Elevated group had a statistically different pattern, where being seropositive increased the likelihood of being in the Elevated group for those with a college degree but deceased the likelihood of being in the Elevated group for those without a college degree.

While sex and educational attainment did not affect the association between *T. gondii* and either systolic or diastolic blood pressure, both age and the poverty-to-income ratio moderated the association between *T. gondii* and diastolic blood pressure (Table 5). Figure 3 shows that age moderates the relationship between the relationship between *T. gondii* and diastolic blood pressure. Forty-year-old participants had an expected value of diastolic blood pressure of just over 70 mm Hg. There was only a slight decrease in diastolic blood pressure at older ages among those who were seronegative, but the drop in diastolic blood pressure was much more pronounced for those who are seropositive. Figure 4 shows how poverty-to-income moderates the relationship between *T. gondii* and diastolic blood pressure. At low levels of poverty-to-income, there was little difference in diastolic blood-pressure regardless of seropositivity. However, the diastolic blood pressure of those who were seronegative systematically increased with the poverty-to-income ratio while it systematically decreased those who are seropositive.

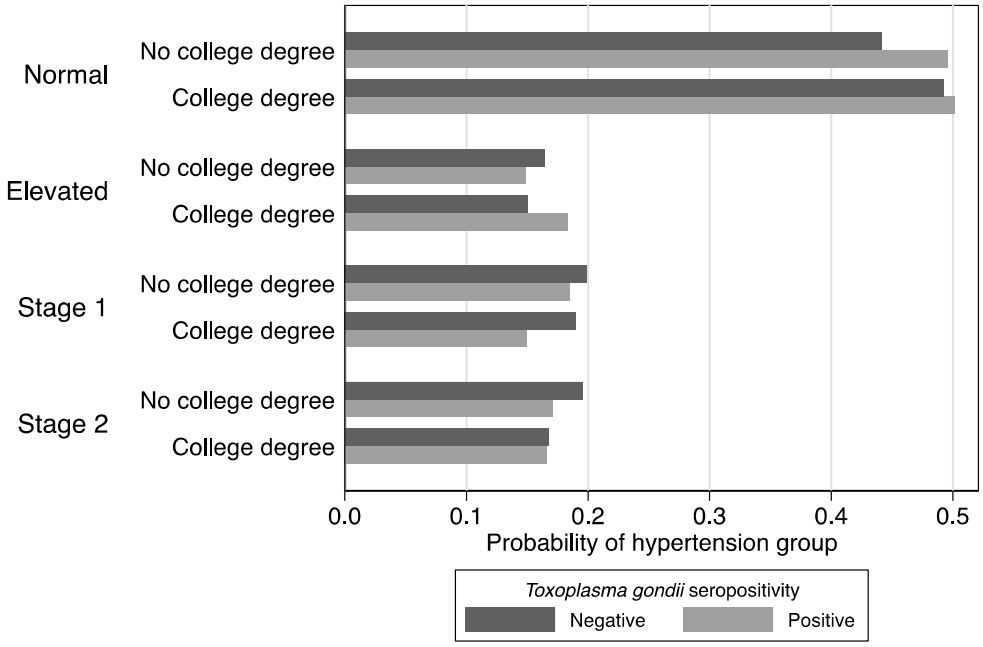

Figure 2. Interaction of *T. gondii* seropositivity and education on blood pressure status: Adjusted predictions from multinomial logistic regression. Note: Model adjusted for age, sex, race-ethnicity, immigrant status, marital status, poverty-to-income, self-rated health, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. Source: *National Health and Nutrition Examination Study*, including 2009–2010, 2011–2012, and 2013–2014 cycles.

Table 5. *Toxoplasma gondii* seropositivity interactions and blood pressure: unstandardized coefficients from linear regression.

	Systolic	**Diastolic**
T. gondii seropositive	−1.942	2.379 *
Age	0.460 ***	−0.023 **
Interaction	0.011	−0.060 ***
T. gondii seropositive	−1.762 **	−0.459
Female	−3.715 ***	−2.603 ***
Interaction	0.894	−0.972
T. gondii seropositive	−1.583 ***	−0.946 **
College degree	−2.443 ***	0.324
Interaction	1.286	0.198
T. gondii seropositive	−0.527	0.515
Poverty-to-income	−0.361 ***	0.310 ***
Interaction	−0.362	−0.629 ***

Note: Each set of three rows represent different models, each adjusted for age, sex, race/ethnicity, marital status, immigrant status, education, poverty-to-income ratio, self-rated health, body-mass index, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Source: National Health and Nutrition Examination Study, including 2009–2010, 2011–2012, and 2013–2014 cycles.

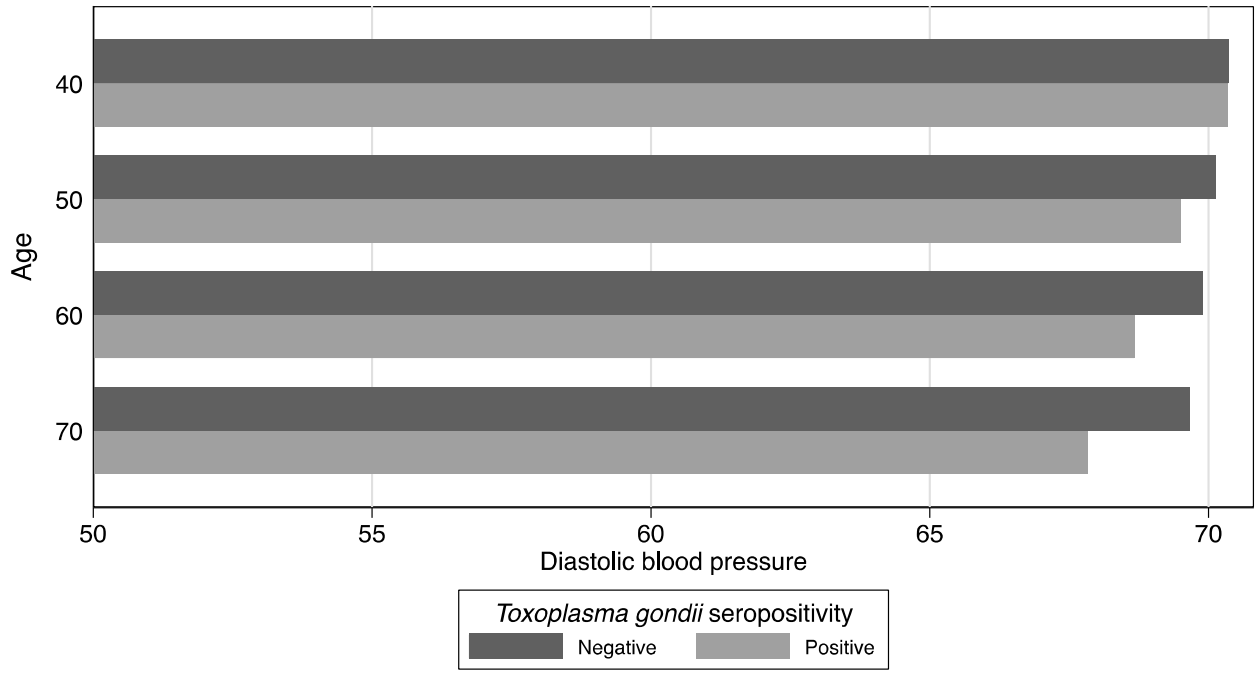

Figure 3. Interaction of *T. gondii* seropositivity and age on blood pressure status: adjusted predictions from linear regression. Note: The minimum value on horizontal axis is the 5th percentile of diastolic blood pressure. Model adjusted for sex, race-ethnicity, immigrant status, marital status, educational attainment, poverty-to-income, self-rated health, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. Source: *National Health and Nutrition Examination Study*, including 2009–2010, 2011–2012, and 2013–2014 cycles.

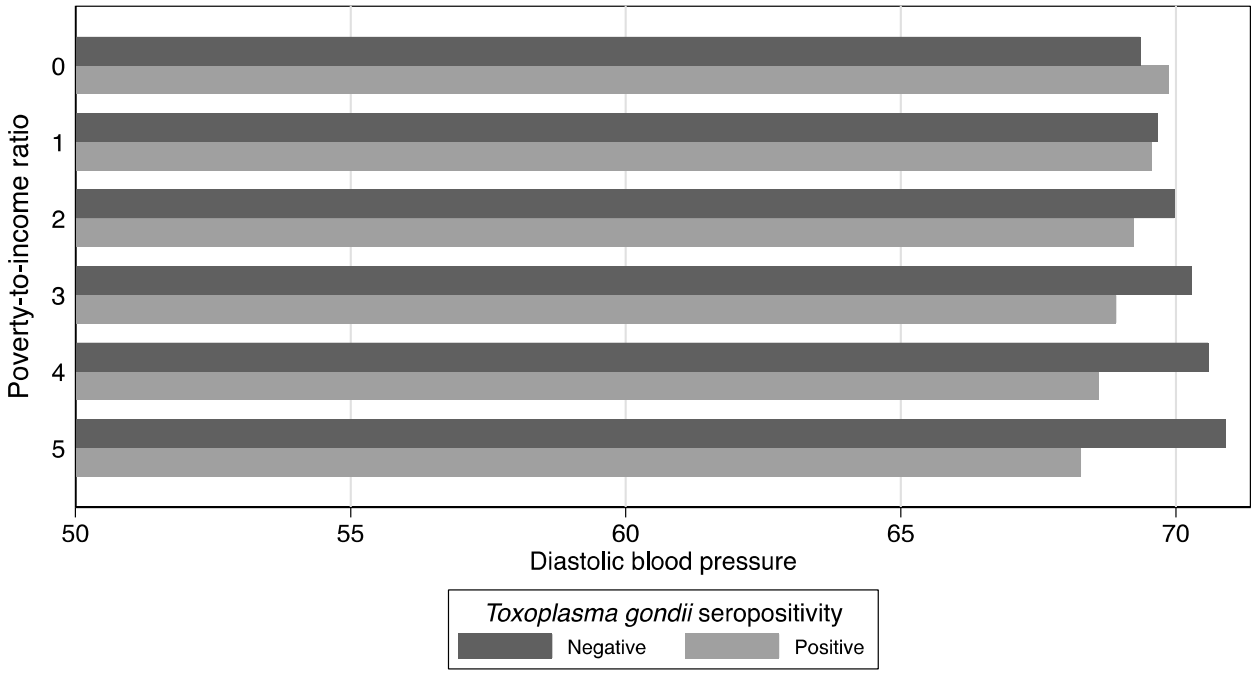

Figure 4. Interaction of *T. gondii* seropositivity and poverty-to-income on blood pressure status: adjusted predictions from linear regression. Note: The minimum value on horizontal axis is the 5th percentile of diastolic blood pressure. [a] Model adjusted for age, sex, race-ethnicity, immigrant status, marital status, educational attainment, self-rated health, smoking status, alcohol consumption, and caffeine consumption. N = 12,010. Source: *National Health and Nutrition Examination Study*, including 2009–2010, 2011–2012, and 2013–2014 cycles.

3. Discussion

T. gondii appears to affect human health in a variety of areas, including neurological, psychiatric, and cognitive function [9]. While many of these associations are potentially adverse, in the large, community-based US sample we used for this study, the primary findings were that *T. gondii* seropositivity seemed to be associated with lower likelihood of elevated blood pressure or hypertension. In particular, *T. gondii* seropositivity was associated with a higher likelihood of normal blood pressure (i.e., lower probability of elevated blood pressure and lowered probability of Stages 1 and 2 hypertension) and with lower systolic and diastolic blood pressure in statistical models adjusted for an array of variables that could potentially confound associations between *T. gondii* and hypertension and blood pressure. In addition, age and educational attainment moderated the association between *T. gondii* and hypertension, although the interactions with age and educational attainment could have been false positives in that only two of the 12 interaction models showed statistically significant effects. Age and the poverty-to-income ratio moderated associations between *T. gondii* and diastolic blood pressure. While *T. gondii* seropositivity was associated with lower probability of having elevated blood pressure or hypertension and with lower systolic and diastolic blood pressures, the results from the interaction models show that that age, educational attainment, and the poverty-to-income ratio can moderate these overall associations.

These findings differ somewhat from a previous study that used the 2009–2010 cycle of the NHANES dataset to investigate associations between *T. gondii* and blood pressure [8]. In contrast to our findings, Babekir et al. [8] in their adjusted models found no association between *T. gondii* and blood pressure. Several possibilities might account for these differences. While we too used data the NHANES dataset in our analyses, we included two additional data cycles (2011–2012 and 2013–2014) and examined whether *T. gondii*

seropositivity was related to the probability of being in Elevated, Stage 1, and Stage 2 hypertension groups.

While we did not design our study to identify mechanisms by which *T. gondii* could affect blood pressure, several findings about the immunological and physiological effects of *T. gondii* suggest possible hypotheses about the relationship between *T. gondii* and blood pressure regulation. However, without additional research, these hypotheses are tentative and offered merely as plausible mechanisms by which *T. gondii* could affect blood pressure. *T. gondii* elicits IFN-γ-mediated nitric oxide production [22,23]. Elevated nitric oxide can reduce arterial stiffness after maximal exercise, and inhibition of nitric oxide synthase may contribute to increased blood pressure after submaximal exercise [24]. Accordingly, increased nitric oxide production from *T. gondii* could result in lower blood pressure and reduced risk of hypertension. *T. gondii* has also been associated with reduced brain noradrenergic activity in animals by lowering gene expression of dopamine beta hydroxylase in males [19]. As norepinephrine is associated with blood pressure [25], lowered concentrations of norepinephrine could result in decreased blood pressure.

While we used a sample size of 12,010 and adjusted for several covariates that could affect associations between *T. gondii* and blood pressure and hypertension, several limitations of this study require consideration. Because of the study's cross-sectional design, we were unable to determine causal associations between *T. gondii* and elevated blood pressure and hypertension, although we think it more plausible that *T. gondii* causes lower systolic and diastolic blood pressure and a higher chance of being in the normal blood-pressure group than lower blood pressures increasing the risk of acquiring infection with *T. gondii*. We were also unable to identify when and how infection with *T. gondii* occurred. It is possible that initial infection at different stages of development could affect blood pressure or that the effect could strengthen over time since the initial infection. Further, it is likely that at least some of the participants had lower blood pressure before they were infected with *T. gondii*, but because we are unable to determine when the initial infection with *T. gondii* occurred, we do not know whether *T. gondii* would have resulted in additional changes in blood pressure. While we included several covariates in all statistical models, we might not have included other relevant variables, resulting in the possibility of residual confounding.

In conclusion, in this community-based sample of US adults, we found that *T. gondii* seropositivity was associated with lowered probability of elevated blood pressure, with lowered probability of Stages 1 and 2 hypertension and with lower systolic and diastolic blood pressure. Age and educational attainment might moderate the association between *T. gondii* and hypertension, and age and poverty-to-income ratio might moderate associations between *T. gondii* and diastolic blood pressure. In that our results differ somewhat from some previous findings, additional research investigating associations between *T. gondii* and hypertension is clearly needed to further characterize associations between *T. gondii* and blood pressure and hypertension.

4. Materials and Methods

4.1. Study Sample

The data we used in this study come from the US Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES). For this study, we combined data from the NHANES 2009–2010, 2011–2012, and 2013–2014 cycles, which are the most recent NHANES datasets containing the necessary data to investigate associations between *T. gondii* and hypertension. We included participants who had data for IgG *T. gondii* serostatus and systolic and diastolic blood pressure, as well as data for the preidentified covariates. The final analytic sample size was 12,010. To determine *T. gondii* serostatus, the NHANES used sera from participants with surplus sera leftover after sera for standard laboratory work was used (https://wwwn.cdc.gov/Nchs/Nhanes/2011--2012/SSTOCA_G.htm (accessed on 2 November 2021)). The NHANES uses complex sampling that is combined with appropriate weighting to represent the US population. However,

because the *T. gondii* serostatus data are from leftover serum samples, we did not weight the samples, which resulted in a convenience but non-representative sample.

4.2. Measures

4.2.1. Assessment of *T. gondii*

We used *T. gondii* serostatus variables provided by the NHANES, which were based on mean fluorescence intensity to detect and quantify IgG antibodies against *T. gondii* and evaluated against cutoff levels (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSTOXO_H.htm#SSTOXG (accessed on 2 November 2021)).

4.2.2. Assessment of Blood Pressure

After sitting for five minutes, NHANES staff obtained three consecutive blood pressure readings for participants. The systolic and diastolic blood pressures were the mean of the three respective readings. We used these means to categorize participants as Normal (less than 120/80 mm Hg), Elevated (systolic blood pressure between 120–129 and diastolic blood pressure less than 80), Stage 1 Hypertension (systolic blood pressure between 130–139 or diastolic blood pressure between 80–89), or Stage 2 Hypertension (systolic blood pressure at least 140 or diastolic blood pressure at least 90 mm Hg), according to the cutoffs for hypertension published by the American College of Cardiologists (https://www.acc.org/latest-in-cardiology/articles/2017/11/08/11/47/mon-5pm-bp-guideline-aha-2017 (accessed on 2 November 2021)).

4.3. Covariates

We included preselected covariates in all statistical models to adjust for possible confounding: age in years (respondents older than 80 were coded as 80 by NHANES to protect respondents from deductive disclosure), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), immigration status, marital status (married, cohabiting, divorced or separated, widowed, never married), educational attainment (attained a college degree or more), poverty-to-income ratio (total family income/US poverty threshold), self-rated health, body-mass index (weight in kilograms/height in meters squared), smoking status (no-smoker, smoking some days, smoking everyday), the number of alcoholic drinks per week, and caffeine intake. We included both educational attainment and the poverty-to-income ratio because these two variables together capture socioeconomic status [26].

4.4. Statistical Analysis

We calculated means and standard deviations or frequencies and standard deviations for systolic blood pressure, diastolic blood pressure, and the preselected covariates. The focal independent variable was presence or absence of *T. gondii* seropositivity defined according to NHANES cut-off values. We estimated separate models for hypertension (Normal, Elevated, Stage 1, and Stage 2), systolic blood pressure, and diastolic blood pressure. Hypertension was modeled using multinomial logistic regression, with Normal as the comparison category of the dependent variable. Systolic and diastolic blood pressures were modelled using linear regression. In separate analyses, we estimated interactions of *T. gondii* with age, educational attainment, and poverty-to-income ratio to examine whether these covariates might moderate the association of *T. gondii* and blood pressure.

We used Stata 17.0 (StataCorp, Stata Statistical Software, release 16, College Station, TX, USA) for all analyses.

Author Contributions: Conceptualization, D.W.H., L.D.E. and S.D.G.; methodology, L.D.E., D.W.H. and S.D.G.; software, L.D.E.; validation, L.D.E., D.W.H., S.D.G. and B.L.B.; formal analysis, L.D.E.; Investigation, L.D.E., P.B., D.S.W., S.D.G. and D.W.H.; resources, L.D.E.; data curation, L.D.E. and D.W.H.; formal analysis, L.D.E.; writing—original draft preparation, D.W.H., P.B., D.S.W. and L.D.E., writing—review and editing, L.D.E., P.B., D.S.W., S.D.G., B.L.B. and D.W.H.; visualization, L.D.E.; writing—review and editing, S.D.G., P.B., D.S.W., D.W.H., L.D.E. and B.L.B.; supervision, D.W.H. and

L.D.E.; project administration, D.W.H. and L.D.E.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The National Center for Health Statistics in the USA provided ethics board approval for the National Health and Nutrition Examination Survey conducted by the Centers for Disease Control. The study was conducted in accordance with the Declaration of Helsinki. Protocol approvals for each data set can be found at: https://www.cdc.gov/nchs/nhanes/irba98.htm (accessed on 22 April 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data, which is publicly available, can be found at https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2009, https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2011, https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013 (accessed on 16 November 2021).

Conflicts of Interest: The authors declare no conflict of interest.

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