HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2024 November 15.

Published in final edited form as:

J Neurol Sci. 2023 November 15; 454: 120856. doi:10.1016/j.jns.2023.120856.

Herpes simplex virus 2 serology is associated with thinner whole-brain cortex in community-dwelling older adults

Jackson A. Roberts[1], **Mitchell SV Elkind**[1,2], **Minghua Liu**[1], **Clinton B. Wright**[3], **Tatjana Rundek**[4], **Jose Gutierrez**[1]

[1]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032

[2]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032

[3]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

[4]Department of Neurology, Evelyn F. McKnight Brain Institute, Miller School of Medicine, Miami, FL

Abstract

Prior work in the Northern Manhattan Study (NOMAS) identified impaired cognition in cross-sectional analyses and more rapid memory decline in individuals with evidence of prior common infectious disease exposures. In this study, we sought to determine the cross-sectional relationship between prior exposure to cytomegalovirus, herpes simplex viruses 1 and 2, *Chlamydia pneumoniae*, and *Helicobacter pylori* and three magnetic resonance imaging (MRI) signatures (whole-brain cortical thickness, a previously validated AD signature, and hippocampal volume) in 455 NOMAS participants. We performed confounder-adjusted linear regression analyses between neuroimaging scores and both continuous serologies and categorical seropositivity of each pathogen, as well as a combined infectious burden index (IBI). We identified that increased serologic titers of herpes simplex virus 2 were associated with reduced whole-brain cortical thickness, and a combined score of HSV-2 and *C. pneumoniae* displayed an additive effect on reduced cortical thickness. Our findings suggest herpes simplex virus 2 seropositivity may contribute to accelerated brain aging, possibly resulting in an increased vulnerability to cognitive impairment and neurodegenerative disease in aging populations.

Corresponding author: Jose Gutierrez, MD, MPH., Florence Irving Associate Professor of Neurology, Columbia University Irving Medical Center, Address: 710 W 168th Street, 6th floor, Suite 639, New York, NY, 10032. jg3233@cumc.columbia.edu, Phone: (212) 305-1710, Fax: (212) 305-1658.

Disclosure Information: The authors report no personal or financial interests that may be considered as competing interests.

Keywords

Herpesviridae; dementia; Alzheimer's disease; infectious disease; magnetic resonance imaging

1. Introduction

The contribution of lifetime infectious disease exposures to risk of dementia has re-emerged as an area of research focus over the last several years. Indeed, identifying associations between infectious disease and dementia may serve as an important extension of the neuroinflammatory hypothesis of Alzheimer's disease (AD) that chronic central and peripheral inflammation are key drivers of disease pathophysiology [1].

Previously, work conducted among Northern Manhattan Study (NOMAS) participants identified that a composite serologic measure, or infectious burden index (IBI), of *Chlamydia pneumoniae (C. pneumoniae)*, *Helicobacter pylori (H. pylori)*, cytomegalovirus (CMV), herpes simplex virus 1 (HSV-1), and herpes simplex virus 2 (HSV-2) was associated with impaired cognition in cross-sectional analyses [2]. IBI was additionally found to be associated with memory decline in the NOMAS cohort [3]. Another research group similarly developed an infectious burden index composed of CMV, HSV-1, *Borrelia burgdorferi, C. pneumoniae, and H. pylori* that was found to be elevated in individuals with AD and additionally displayed a negative correlation with Mini-Mental State Examination (MMSE) scores [4]. Furthermore, two prior histopathologic studies investigated the presence of infectious pathogens in the AD brain and identified the presence of *C. pneumoniae* in AD brains at autopsy [5, 6]. HSV-1 has also been identified in the AD brain [7], and multiple studies have identified an increased risk for development of AD in those with evidence of prior HSV-1 infection [8, 9].

The relationship between accumulated infectious exposures and neuroimaging markers of accelerated brain aging remains to be explored. Existing evidence suggests certain infectious diseases may impact neuroimaging findings in both age-related changes and AD pathology. Few studies have examined the relationship between pathogens included in the IBI and neuroimaging outcomes; however, one study identified a more rapid rate of white matter volume loss and astrogliosis in those with a history of symptomatic herpesvirus infection but failed to identify an association with an AD-related neuroimaging signature [10]. Prior work has also identified decreased cortical thickness in individuals with CMV infection with schizophrenia [11] or concussion [12], but not healthy controls. Lastly, biopsy-confirmed *H. pylori* infection has also been associated with parieto-occipital cortical thinning in a homogenous cohort of adult men [13]. How specific viral serologies relate to these neuroimaging outcomes in an otherwise healthy, diverse community-dwelling population remains to be explored.

For that reason, we sought to determine the association between prior infectious disease exposures and MRI-derived signatures of cortical thickness, AD, and hippocampal volume in a subset of NOMAS participants without known cognitive impairment. We hypothesized that increased infectious disease titers would be associated with reductions in neuroimaging scores, primarily cortical thickness, and that herpesviruses HSV-1 and HSV-2 would display

the strongest association with neuroimaging outcomes given the strength of their association with dementia in prior work.

2. Methods

2.1 Participants

Participants included in this study were a subset of individuals in the Northern Manhattan Study (NOMAS), a longitudinal population-based epidemiologic study of urban-dwelling adults, as described previously [14]. NOMAS includes participants randomly selected from those living in northern Manhattan with access to a home telephone, age ≥ 40 years, and reported to be stroke-free at time of enrollment. Between 2003 and 2008, remaining participants who were ≥ 50 years and stroke-free were offered brain magnetic resonance imaging (MRI). From 2006 to 2008, additional household members of NOMAS participants were offered MRIQ. This resulted in a total sample of 1,290 participants with MRI data. Among them, 455 participants had serology data available for this analysis. As such, 455 participants were included in the final analysis.

At enrollment, demographic information such as age, gender, education, race, and ethnicity were collected. Past medical history was obtained by structured questionnaire. Laboratory testing was performed to evaluate glucose and lipid profiles, both at enrollment and time of MRI. Presence of hypertension, diabetes, and hyperlipidemia was determined via self-report and laboratory testing. In brief, hypertension was defined as two brachial blood pressure measurements with an average ≥ 140/90 mm Hg on separate occasions. Diabetes was defined as a fasting glucose ≥ 126 mg/dL. Hypercholesterolemia was defined as a total cholesterol ≥ 240 mg/dL. Presence of additional risk factors was determined during annual follow-up phone calls, which included medication changes, smoking patterns, and changes in the diabetes and dyslipidemia status. Apolipoprotein E (APOE) genotyping was performed for all participants as previously described [15].

2.2 Serologic Testing

Serologic testing for prior infectious disease exposures has been described previously [16]. In brief, enzyme-linked immunoassay (ELISA) was performed with baseline visit blood samples collected, on average 10 years prior to MRI. Antibody titers were obtained for 5 pathogens: *C. pneumoniae* IgA (Sayvon Diagnostics, Israel), *H. pylori* IgG and cytomegalovirus IgG (Wampole Laboratories, Princeton, NJ), and HSV-1 and HSV-2 IgG (Focus Diagnostics, Cypress). Testing was performed at the Columbia University Center for Laboratory Medicine with commercially available ELISA kits in accordance with prior studies [17, 18]. A comprehensive infectious burden index (IBI) was calculated as in prior NOMAS studies [16] using the beta coefficient generated from a model including the individual exposure agents. If multiple serologies were positive for an individual participant, beta coefficients were summed.

In accordance with our prior work [19], we analyzed antibody titers in both a continuous and binary manner. Binary outcomes (i.e., seropositive or seronegative) were determined utilizing a cutoff based upon manufacturer-recommended threshold values.

2.3 Brain Magnetic Resonance Imaging

Neuroimaging data were obtained using a 1.5 T MRI system (Philips Medical Systems, Best, Netherlands) at Columbia University Irving Medical Center. Region of interest (ROI) scores were constructed utilizing FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) methods on Volumes T1-weighted images (Echo time 2.09, repetition time 20, slice thickness 1.5mm, Acquisition Matrix 256\201).

2.4 Statistical Analysis

Participants with MRI data and serologic data were compared to those without serologies using chi-square and Student *t* tests. Three separate neuroimaging signatures were constructed as outcomes for analyses. Our primary outcome was a composite whole-brain cortical thickness signature derived by obtaining the mean thickness across 34 ROIs, as previously described [20]. As a secondary outcome, an AD thickness score, shown to discriminate AD and cognitively-normal individuals, was calculated from FreeSurfer variables for each participant in accordance with prior work [21, 22]. The score was composed of the average entorhinal cortex, inferior temporal, middle temporal, inferior parietal, fusiform, and precuneus region thicknesses. Lastly, as an additional secondary outcome, a hippocampal volume signature was obtained by deriving the mean hippocampal volume across hemispheres for each participant. We utilized 3 separate linear regression models to evaluate the association of infectious exposures with cortical thickness, AD thickness score and hippocampal volume. The independent variables were antibody titers for each exposure, as well as the summative IBI. Initial models (Model 1) included age at MRI, gender, race, ethnicity, and high school completion as covariates. Models were then progressively adjusted for possible confounding demographic and risk factor variables, as in prior work [19]. Variables included in additional models were as follows: (a) Model 2: adjusted for age at MRI, gender, ethnicity, high school education, hypertension, diabetes, hypercholesterolemia, and smoking at time of aging and (b) Model 3: adjusted for age at MRI, gender, ethnicity, high school education, and hypertension, diabetes, hypercholesterolemia, and smoking at the time of imaging, prior subclinical infarction, logarithmic white matter hyperintensities, total volume of small perivascular spaces, and total cranial volume.

Informed by the initial results, we performed *post hoc* analyses in which we determined the relationship between a combined score of *C. pneumoniae* and HSV-2, as well as an interaction term of the two pathogen serologies, and the neuroimaging signatures utilizing the same methodology as above. A combined score was derived by averaging the z-score of *C. pneumoniae* and HSV-2 titers for each participant. A categorical variable was also constructed using combinations of seropositivity for the two pathogens in four categories: 0=seronegative for both, 1 = seropositive for *C. pneumonia*, 2 = seropositive for HSV2, 3 = seropositive for both. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC). Additionally, we performed an additional analysis in which we included APOE ε4 carrier status as an interaction term in HSV-2 and *C. pneumoniae* continuous analyses in fully-adjusted models (Model 3).

3. Results

3.1 Demographic Characteristics

Of the 1290 participants with MRI data, 455 individuals with serologic testing were included in the final analysis. The demographic characteristics of participants included in this study are included in Table 1. Participants were on average 70 years old, 36% male, and 69% Hispanic; 42% completed high school. Compared to the 835 participants excluded from this study, those included were similar in age, gender, race and ethnicity, smoking status, and medical history of hypertension and hypercholesteremia. Excluded participants had higher rates of high school completion, diabetes mellitus, and history of a prior subclinical brain infarction ($p < 0.05$).

The frequency of seropositivity and mean values of antibody titers are presented in Table 2. The highest seropositivity was identified for HSV-1 (87%), while the lowest seropositivity was identified for *H. pylori* (55%). On average, serological testing preceded MRI by 7.10 years; there were no differences between seropositive and seronegative individuals in terms of time from testing to MRI for any of the 5 pathogens (Supplementary Table 1).

3.2 Associations Between Infectious Exposures and Whole-Brain Cortical Thickness

In models utilizing continuous measurements of antibody titers, HSV-2 IgG was inversely associated with reduced cortical thickness in initial (beta coefficient = −3.11; $p = 0.0460$) and confounder-adjusted (beta coefficient = −3.07; $p = 0.0475$) models (Table 3). *C. pneumoniae* IgA levels were inversely associated with reduced cortical thickness in initial models (beta coefficient = −4.25; $p = 0.0418$) but were not associated with cortical thickness in confounder-adjusted models ($p = 0.0875$). Continuous measurements of HSV-1 IgG, *H. pylori* IgG, and CMV IgG were not associated with cortical thickness in initial or confounder-adjusted models.

In confounder-adjusted models utilizing binary measurements (i.e., seropositivity vs. seronegativity), only HSV-2 IgG seropositivity was associated with decreased cortical thickness (beta coefficient: −17.2; $p = 0.0436$). All other associations between pathogen seropositivity and cortical thickness were not significant (Supplementary Table 2).

3.3 Associations Between Infectious Exposures and Alzheimer's Disease-Related Neuroimaging Signature

In models utilizing continuous measures of antibody titers, there were no significant associations between titers of any infectious disease exposure or the IBI and an AD neuroimaging signature in initial or confounder-adjusted models (Supplementary Table 3). Similarly, there were no significant associations between binary measurements (i.e., seropositivity vs. seronegativity) and the AD signature (Supplementary Table 4).

3.4 Associations Between Infectious Exposures and Hippocampal Volume

In models utilizing continuous measures of antibody titers, there were no significant associations between titers of any infectious disease or the IBI and hippocampal volume (Supplementary Table 5). In models utilizing binary measurements (i.e., seropositivity vs.

seronegativity), *H. pylori* IgG seropositivity was associated with an increased hippocampal volume (beta coefficient: 0.0222; $p = 0.0183$; Supplementary Table 6).

3.5 Association of Combined HSV-2 and C. pneumoniae with Neuroimaging Signatures

Given their significant associations with cortical thickness, we performed a *post hoc* analysis to explore the association between a combined seropositivity of HSV-2 and *C. pneumoniae* with neuroimaging signatures (Supplementary Table 7). The combined continuous measure derived from the average of *C. pneumoniae* and HSV-2 z-scores was associated with reduced cortical thickness in initial (beta coefficient: −13.0; $p = 0.0268$) and fully-adjusted (beta coefficient: −12.3; $p = 0.0340$) models. Using a combined seropositive score (as above), we found that being seropositive to both had the largest effect size (beta coefficient = −22.7), followed by being seropositive to HSV-2 only (beta coefficient = −10.8), and being seropositive to *C. pneumoniae* only (beta coefficient: −2.2, *p*-value for the trend 0.02), which suggested an additive dose-effect.

Across all models, combined seropositivity, combined z-score, and interaction of *C. pneumoniae* and HSV-2 were not significantly associated with the AD-related neuroimaging signature or hippocampal volume (data not shown). We performed additional analyses in which we included APOE ε4 carrier status as an interaction term in continuous HSV-2 and *C. pneumoniae* models. This interaction was not significant in fully-adjusted models for all neuroimaging models.

4. Discussion

The primary finding of this investigation was that HSV-2 exposure, as defined by positive serology, was consistently associated with decreased cortical thickness across multiple confounder-adjusted models, while no pathogen antibody titers were associated with an AD-related neuroimaging signature. In addition, exposure to HSV-2 combined with *C. pneumoniae* was associated with decreased cortical thickness, and seropositivity for both pathogens was associated with decreased cortical thickness. Taken together, these findings suggest a potential additive effect of the two pathogens on risk of cortical tissue loss, with HSV-2 most likely to be the greatest contributor. While we also identified *H. pylori* seropositivity was associated with an increased hippocampal volume, this finding was not expected and likely a spurious finding.

Previously, researchers with the Baltimore Longitudinal Study of Aging examined the relationship between symptomatic herpesvirus infections, either HSV-1 or HSV-2, and cognitive, laboratory, and neuroimaging endpoints [10]. They identified a faster rate of decline in attention, increased astrogliosis, and white matter volume loss in those with a symptomatic infection, while identifying no relationship of infection to an AD-related neuroimaging signature or volume-based total brain signatures. These findings and research design contrast to a certain extent with our study, in which we utilized separate serologic titers for HSV-1 and HSV-2 indicative of viral exposure, rather than a clinical diagnosis of symptomatic infection with either viral strain, and identified a significant relationship between HSV-2 and reduced total brain cortical thickness.

HSV-2, along with HSV-1, is a common infection in the general population and belongs to the family of herpesviruses that are capable of undergoing variable periods of latency and reactivation that can induce significant peripheral inflammation with impacts on multiple organ systems [23]. While HSV-1 is primarily transmitted by oral contact and reactivates most efficiently from trigeminal ganglia, HSV-2 spreads by sexual contact and reactivates from lumbosacral ganglia causing genital herpes [24]. Though HSV-1 seroprevalence in the United States as of 2010 was 54 percent, HSV-2 is less ubiquitous with a seroprevalence of 16 percent [25]. Of the two viruses, HSV-2 displays a stronger association with meningoencephalitis, with aseptic meningitis occurring in 36 percent of women and 13 percent of men with a primary genital infection [26], and recurrence of meningitis is common particularly for HSV-2 with rates of 20-40 percent [27]. These clinical features suggest that HSV-2 may have more profound impacts on the CNS than HSV-1, particularly in the setting of relapsing episodes, which offers one potential explanation for the observation that HSV-2 was associated with reduced cortical thickness, whereas HSV-1 was not. Though we were unable to assess the effects of active HSV-2 infection or latency in this study, these represent plausible mechanisms by which HSV-2 results in cortical atrophy and warrant further investigation.

There is some evidence for a link between exposure to herpesviruses and dementia that suggest a potentially causal role of these pathogens in a subset of patients with AD, though findings to date have primarily identified risk associated with HSV-1 rather than HSV-2 as identified in our study [8, 9]. Interestingly, those with symptomatic herpesvirus infections treated with antiviral therapy have been reported to demonstrate a reduced incidence of AD compared to untreated individuals, suggesting that disease activity may impact risk of developing dementia [8]. It remains unclear whether these effects are a result of peripheral inflammation, chronic central nervous system inflammation, or a combination of the two. It has been found that mild or asymptomatic cases of herpes simplex encephalitis can occur and be followed by periods of latency and reactivation triggering chronic brain inflammation and microglial activation paralleling that found in AD [28]. Interestingly, amyloid beta has been found to proliferate in response to herpesvirus exposure in cell culture models and triggers a protective antiviral response, which may be therapeutic in acute infections but becomes detrimental in the setting of chronic inflammation resulting from cycles of reactivation by these viruses [29]. In an additional synergistic mechanism, HSV-2 has also been linked to peripheral and intracranial atherosclerosis, furthering individuals' vascular risk profile known to be associated with cognitive impairment [19, 30].

C. pneumoniae is a common pathogen that has similarly been identified as a possible risk factor for late onset AD. Indeed, the predominately respiratory pathogen has been demonstrated to be present at a much higher rate in post-mortem brain tissue in AD patients compared to cognitively-normal individuals [5, 31]. The impact of *C. pneumoniae* on AD risk appears to be particularly pronounced in carriers of the APOE ε4 allele, as presence of the ε4 allele possibly enhances attachment of the pathogen to microglia and astroglia [32]. Furthermore, astrocytes infected with *C. pneumoniae* display an upregulation of pathways related to neuroinflammation and amyloid processing, resulting in greater amyloid beta deposition [33]. Mouse model research has demonstrated that *C. pneumoniae* infection of the olfactory bulb and trigeminal nerves occurs relatively quickly after upper respiratory

tract inoculation and results in dysregulation of multiple AD-related pathways, as well as inducing amyloid beta deposition in the olfactory bulb [34]. Similar to HSV-2, treatment of *C. pneumoniae* infections with antibiotics may reduce risk of AD development compared to those with untreated infections, as evidenced by a Taiwanese national cohort study [35].

Though HSV-2 exposure was associated with diminished whole-brain cortical thickness, it displayed no significant association with an AD-related neuroimaging signature. It is notable that the participants in this study were without known clinical dementia, and the AD-related neuroimaging signature utilized as an outcome was developed by comparing individuals with clinical AD to cognitively-normal controls [21]. However, while multiple studies suggest a regional pattern of cortical thinning in AD, particularly involving the temporal lobes, amygdala, and hippocampus, preceding onset of disease [36, 37], decreases in global cortical thickness demonstrate a substantial impact on cognition in later life [38]. Indeed, diminishing cortical thickness is thought to be a primary driver of declining brain volume and may represent pathologic cognitive aging [39, 40]. Therefore, these findings may provide evidence that HSV-2 exposure, and possibly *C. pneumoniae*, accelerates brain aging in a pathologic manner and may also increase risk for AD through reduction in viable cortical tissue. These effects may be mediated by increased systemic inflammation, as individuals with other pro-inflammatory conditions, including obesity and autoimmune disease, also display reduced cortical thickness in middle age and late adulthood that corresponds with impaired cognition [41-44]. The possible mediating influence of peripheral inflammation on this association remains to be explored.

This study is limited by its cross-sectional nature, which precludes analysis regarding rates of decline in neuroimaging endpoints with respect to the included infectious exposures. In addition, serologic titers in this study are markers of disease exposure, not disease activity, which does not account for periods of active infection or latency and reactivation in included individuals. We were also unable to assess the impacts of potential treatments received for infections. Additional limitations include the relatively small sample compared to the overall NOMAS cohort, as well as the time span between serologic sampling and MRI assessment that limits causal inference with respect to our findings. However, there are multiple strengths of this study. The study was conducted among a community-dwelling population without known neurocognitive disease with socioeconomic, racial, and ethnic diversity that is more reflective of the general population than prior work conducted in homogenous study populations. In addition, we controlled for multiple possible confounding comorbidities and sociodemographic variables that might impact the link between infectious disease exposure and neuroimaging alterations.

In sum, we provide evidence that exposure to HSV-2 is associated with decreased cortical thickness, but not with an AD-related neuroimaging signature or hippocampal volume, suggesting that exposure to this pathogen may accelerate brain aging in otherwise cognitively-normal individuals. Future work should be directed towards better understanding the mechanisms of this association by testing for peripheral markers of inflammation, investigating the impact of antiviral therapies on this relationship, and validating results in larger neuroimaging studies. In addition, further research should be conducted regarding the

central nervous system effects of HSV-2, which remains relatively understudied compared to HSV-1 in this domain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank the NOMAS participants for their invaluable contributions to this work.

Funding:

This work is supported by National Institutes of Health grants: R01 AG057709 (J.G.), R01 AG066162 (J.G.), R01 NS36286 (M.E.) The funders had no role in study design, collection, analysis, or interpretation of the data.

Data Availability:

NOMAS data is available for sharing by the investigators upon reasonable request.

References

1. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y). 2018;4:575–90. Epub 2018/11/09. doi: 10.1016/j.trci.2018.06.014. [PubMed: 30406177]
2. Katan M, Moon YP, Paik MC, Sacco RL, Wright CB, Elkind MS. Infectious burden and cognitive function: the Northern Manhattan Study. Neurology. 2013;80(13):1209–15. Epub 2013/03/27. doi: 10.1212/WNL.0b013e3182896e79. [PubMed: 23530151]
3. Wright CB, Gardener H, Dong C, Yoshita M, DeCarli C, Sacco RL, et al. Infectious Burden and Cognitive Decline in the Northern Manhattan Study. J Am Geriatr Soc. 2015;63(8):1540–5. Epub 2015/08/21. doi: 10.1111/jgs.13557. [PubMed: 26289683]
4. Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, et al. A study on the association between infectious burden and Alzheimer's disease. Eur J Neurol. 2015;22(12):1519–25. Epub 2014/06/10. doi: 10.1111/ene.12477. [PubMed: 24910016]
5. Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, et al. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol. 1998;187(1):23–42. Epub 1998/09/28. doi: 10.1007/s004300050071. [PubMed: 9749980]
6. Gerard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, et al. Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. FEMS Immunol Med Microbiol. 2006;48(3):355–66. Epub 2006/10/21. doi: 10.1111/j.1574-695X.2006.00154.x. [PubMed: 17052268]
7. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet. 1997;349(9047):241–4. Epub 1997/01/25. doi: 10.1016/S0140-6736(96)10149-5. [PubMed: 9014911]
8. Lopatko Lindman K, Hemmingsson ES, Weidung B, Brannstrom J, Josefsson M, Olsson J, et al. Herpesvirus infections, antiviral treatment, and the risk of dementia-a registry-based cohort study in Sweden. Alzheimers Dement (N Y). 2021;7(1):e12119. Epub 2021/02/23. doi: 10.1002/trc2.12119. [PubMed: 33614892]
9. Itzhaki RF. Overwhelming Evidence for a Major Role for Herpes Simplex Virus Type 1 (HSV1) in Alzheimer's Disease (AD); Underwhelming Evidence against. Vaccines (Basel). 2021;9(6). Epub 2021/07/03. doi: 10.3390/vaccines9060679.
10. Duggan MR, Peng Z, An Y, Kitner Triolo MH, Shafer AT, Davatzikos C, et al. Herpes Viruses in the Baltimore Longitudinal Study of Aging: Associations With Brain Volumes, Cognitive

Performance, and Plasma Biomarkers. Neurology. 2022;99(18):e2014–24. Epub 2022/08/20. doi: 10.1212/WNL.0000000000201036. [PubMed: 35985823]

11. Andreou D, Jorgensen KN, Nerland S, Yolken RH, Haukvik UK, Andreassen OA, et al. Cytomegalovirus Infection Associated with Smaller Total Cortical Surface Area in Schizophrenia Spectrum Disorders. Schizophr Bull. 2022;48(5):1164–73. Epub 2022/04/08. doi: 10.1093/schbul/sbac036. [PubMed: 35388401]
12. Savitz J, Goeckner BD, Ford BN, Teague TK, Zheng H, Harezlak J, et al. The effects of cytomegalovirus on brain structure following sport-related concussion. Brain. 2023. Epub 2023/04/19. doi: 10.1093/brain/awad126.
13. Park J, Kim TJ, Song JH, Jang H, Kim JS, Kang SH, et al. Helicobacter Pylori Infection Is Associated with Neurodegeneration in Cognitively Normal Men. J Alzheimers Dis. 2021;82(4):1591–9. Epub 2021/06/29. doi: 10.3233/JAD-210119. [PubMed: 34180413]
14. Sacco RL, Anand K, Lee HS, Boden-Albala B, Stabler S, Allen R, et al. Homocysteine and the risk of ischemic stroke in a triethnic cohort: the NOrthern MAnhattan Study. Stroke. 2004;35(10):2263–9. Epub 2004/09/04. doi: 10.1161/01.STR.0000142374.33919.92. [PubMed: 15345803]
15. Gutierrez J, Kulick E, Park Moon Y, Dong C, Cheung K, Ahmet B, et al. Brain Arterial Diameters and Cognitive Performance: The Northern Manhattan Study. J Int Neuropsychol Soc. 2018;24(4):335–46. Epub 2017/11/24. doi: 10.1017/S1355617717001175. [PubMed: 29166955]
16. Elkind MS, Ramakrishnan P, Moon YP, Boden-Albala B, Liu KM, Spitalnik SL, et al. Infectious burden and risk of stroke: the northern Manhattan study. Arch Neurol. 2010;67(1):33–8. Epub 2009/11/11. doi: 10.1001/archneurol.2009.271. [PubMed: 19901154]
17. Elkind MS, Tondella ML, Feikin DR, Fields BS, Homma S, Di Tullio MR. Seropositivity to Chlamydia pneumoniae is associated with risk of first ischemic stroke. Stroke. 2006;37(3):790–5. Epub 2006/01/21. doi: 10.1161/01.STR.0000202624.89869.e9. [PubMed: 16424371]
18. Elkind MS, Lin IF, Grayston JT, Sacco RL. Chlamydia pneumoniae and the risk of first ischemic stroke : The Northern Manhattan Stroke Study. Stroke. 2000;31(7):1521–5. Epub 2000/07/08. doi: 10.1161/01.str.31.7.1521. [PubMed: 10884447]
19. Mehta A, Khasiyev F, Wright CB, Rundek T, Sacco RL, Elkind MSV, et al. Intracranial Large Artery Stenosis and Past Infectious Exposures: Results From the NOMAS Cohort. Stroke. 2022;53(5):1589–96. Epub 2022/02/03. doi: 10.1161/STROKEAHA.121.036793. [PubMed: 35105181]
20. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968–80. Epub 2006/03/15. doi: 10.1016/j.neuroimage.2006.01.021. [PubMed: 16530430]
21. Schwarz CG, Gunter JL, Wiste HJ, Przybelski SA, Weigand SD, Ward CP, et al. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. Neuroimage Clin. 2016;11:802–12. Epub 2017/01/05. doi: 10.1016/j.nicl.2016.05.017. [PubMed: 28050342]
22. Caunca MR, Siedlecki K, Cheung YK, Alperin N, Lee SH, Elkind MSV, et al. Cholinergic White Matter Lesions, AD-Signature Cortical Thickness, and Change in Cognition: The Northern Manhattan Study. J Gerontol A Biol Sci Med Sci. 2020;75(8):1508–15. Epub 2020/01/17. doi: 10.1093/gerona/glz279. [PubMed: 31944231]
23. Grinde B. Herpesviruses: latency and reactivation - viral strategies and host response. J Oral Microbiol. 2013;5. Epub 2013/10/30. doi: 10.3402/jom.v5i0.22766.
24. Margolis TP, Imai Y, Yang L, Vallas V, Krause PR. Herpes simplex virus type 2 (HSV-2) establishes latent infection in a different population of ganglionic neurons than HSV-1: role of latency-associated transcripts. J Virol. 2007;81(4):1872–8. Epub 2006/12/08. doi: 10.1128/JVI.02110-06. [PubMed: 17151134]
25. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2--United States, 1999-2010. J Infect Dis. 2014;209(3):325–33. Epub 2013/10/19. doi: 10.1093/infdis/jit458. [PubMed: 24136792]

26. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983;98(6):958–72. Epub 1983/06/01. doi: 10.7326/0003-4819-98-6-958. [PubMed: 6344712]
27. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008;65(5):596–600. Epub 2008/05/14. doi: 10.1001/archneur.65.5.596. [PubMed: 18474734]
28. Marcocci ME, Napoletani G, Protto V, Kolesova O, Piacentini R, Li Puma DD, et al. Herpes Simplex Virus-1 in the Brain: The Dark Side of a Sneaky Infection. Trends Microbiol. 2020;28(10):808–20. Epub 2020/05/11. doi: 10.1016/j.tim.2020.03.003. [PubMed: 32386801]
29. Bourgade K, Le Page A, Bocti C, Witkowski JM, Dupuis G, Frost EH, et al. Protective Effect of Amyloid-beta Peptides Against Herpes Simplex Virus-1 Infection in a Neuronal Cell Culture Model. J Alzheimers Dis. 2016;50(4):1227–41. Epub 2016/02/03. doi: 10.3233/JAD-150652. [PubMed: 26836158]
30. Wu YP, Sun DD, Wang Y, Liu W, Yang J. Herpes Simplex Virus Type 1 and Type 2 Infection Increases Atherosclerosis Risk: Evidence Based on a Meta-Analysis. Biomed Res Int. 2016;2016:2630865. Epub 2016/05/20. doi: 10.1155/2016/2630865. [PubMed: 27195284]
31. Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. BMC Neurosci. 2010;11:121. Epub 2010/09/25. doi: 10.1186/1471-2202-11-121. [PubMed: 20863379]
32. Gerard HC, Fomicheva E, Whittum-Hudson JA, Hudson AP. Apolipoprotein E4 enhances attachment of Chlamydophila (Chlamydia) pneumoniae elementary bodies to host cells. Microb Pathog. 2008;44(4):279–85. Epub 2007/11/13. doi: 10.1016/j.micpath.2007.10.002. [PubMed: 17997273]
33. Al-Atrache Z, Lopez DB, Hingley ST, Appelt DM. Astrocytes infected with Chlamydia pneumoniae demonstrate altered expression and activity of secretases involved in the generation of beta-amyloid found in Alzheimer disease. BMC Neurosci. 2019;20(1):6. Epub 2019/02/23. doi: 10.1186/s12868-019-0489-5. [PubMed: 30786875]
34. Chacko A, Delbaz A, Walkden H, Basu S, Armitage CW, Eindorf T, et al. Chlamydia pneumoniae can infect the central nervous system via the olfactory and trigeminal nerves and contributes to Alzheimer's disease risk. Sci Rep. 2022;12(1):2759. Epub 2022/02/19. doi: 10.1038/s41598-022-06749-9. [PubMed: 35177758]
35. Ou H, Chien WC, Chung CH, Chang HA, Kao YC, Wu PC, et al. Association Between Antibiotic Treatment of Chlamydia pneumoniae and Reduced Risk of Alzheimer Dementia: A Nationwide Cohort Study in Taiwan. Front Aging Neurosci. 2021;13:701899. Epub 2021/09/08. doi: 10.3389/fnagi.2021.701899. [PubMed: 34489674]
36. Coupe P, Manjon JV, Lanuza E, Catheline G. Lifespan Changes of the Human Brain In Alzheimer's Disease. Sci Rep. 2019;9(1):3998. Epub 2019/03/10. doi: 10.1038/s41598-019-39809-8. [PubMed: 30850617]
37. Twamley EW, Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc. 2006;12(5):707–35. Epub 2006/09/12. doi: 10.1017/S1355617706060863. [PubMed: 16961952]
38. Sele S, Liem F, Merillat S, Jancke L. Age-related decline in the brain: a longitudinal study on inter-individual variability of cortical thickness, area, volume, and cognition. Neuroimage. 2021;240:118370. Epub 2021/07/11. doi: 10.1016/j.neuroimage.2021.118370. [PubMed: 34245866]
39. Fjell AM, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, et al. High consistency of regional cortical thinning in aging across multiple samples. Cereb Cortex. 2009;19(9):2001–12. Epub 2009/01/20. doi: 10.1093/cercor/bhn232. [PubMed: 19150922]
40. Storsve AB, Fjell AM, Tamnes CK, Westlye LT, Overbye K, Aasland HW, et al. Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change. J Neurosci. 2014;34(25):8488–98. Epub 2014/06/21. doi: 10.1523/JNEUROSCI.0391-14.2014. [PubMed: 24948804]
41. Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav Immun. 2015;48:195–204. Epub 2015/04/18. doi: 10.1016/j.bbi.2015.03.015. [PubMed: 25882911]

42. Cho J, Seo S, Kim WR, Kim C, Noh Y. Association Between Visceral Fat and Brain Cortical Thickness in the Elderly: A Neuroimaging Study. Front Aging Neurosci. 2021;13:694629. Epub 2021/07/13. doi: 10.3389/fnagi.2021.694629. [PubMed: 34248609]

43. Li S, Bai R, Yang Y, Zhao R, Upreti B, Wang X, et al. Abnormal cortical thickness and structural covariance networks in systemic lupus erythematosus patients without major neuropsychiatric manifestations. Arthritis Res Ther. 2022;24(1):259. Epub 2022/11/30. doi: 10.1186/s13075-022-02954-z. [PubMed: 36443835]

44. Fleischman DA, Arfanakis K, Kelly JF, Rajendran N, Buchman AS, Morris MC, et al. Regional brain cortical thinning and systemic inflammation in older persons without dementia. J Am Geriatr Soc. 2010;58(9):1823–5. Epub 2010/09/25. doi: 10.1111/j.1532-5415.2010.03049.x. [PubMed: 20863359]

HIGHLIGHTS

- We explore the association between infectious disease serologies and neuroimaging signatures
- Herpes simplex virus 2 was robustly associated with reduced whole-brain cortical thickness
- *C. pneumoniae* and HSV-2 display a potentially additive effect on reduced cortical thickness
- Exposure to HSV-2 may contribute to accelerated brain aging and dementia risk, possibly due to chronic latency and reactivation in the central nervous system

Table 1.

Demographic characteristics of participants

	Participants Included
N	455
Age, y (mean ± SD)	70 ± 7.7
Male gender, %	36
Race and ethnicity, %	
Non-Hispanic White	16
Non-Hispanic Black	15
Hispanic	69
Completed high school, %	42
Hypertension, %	80
Diabetes, %	22
Hypercholesterolemia, %	83
Current smoking, %	11
Brain infarction, %	14

Table 2.

Frequency of seropositivity and mean antibody titer values.

	Seropositivity, %; antibody titers (mean±SD)
Herpes simplex virus 1	87%, 3.9±1.7
Herpes simplex virus 2	63%, 3.3±2.7
Cytomegalovirus	84%, 2.6±1.3
Chlamydia pneumoniae	62%, 2.0±2.0
Helicobacter pylori	55%, 34±39

Table 3.

Associations between continuous antibody titers and whole-brain cortical thickness

	Model 1		Model 2		Model 3	
Pathogen	**Beta estimate**	**P-value**	**Beta estimate**	**P-value**	**Beta estimate**	**P-value**
HSV-1	−2.79	0.282	−2.63	0.309	−2.64	0.302
HSV-2	**−3.11**	**0.0460**	**−3.20**	**0.0397**	**−3.07**	**0.0475**
Cytomegalovirus	−2.84	0.378	−2.27	0.486	−1.38	0.672
C. pneumoniae	**−4.25**	**0.0418**	−4.02	0.0532	−3.55	0.0875
H. pylori	−0.0572	0.595	−0.0270	0.802	−0.0494	0.645
Infectious Burden Index	−9.82	0.462	−8.58	0.518	−6.13	0.644

Model 1: Adjusted for age at MRI, gender, ethnicity, and high school education

Model 2: Adjusted for age at MRI, gender, ethnicity, high school education, and hypertension, diabetes, hypercholesterolemia, and smoking at the time of imaging

Model 3: Adjusted for age at MRI, gender, race-ethnicity, high school education, and hypertension, diabetes, hypercholesterolemia, and smoking at the time of imaging, prior subclinical infarction, logarithmic white matter hyperintensity volume, total volume of small perivascular spaces, and total cranial volume