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## Infectious Burden and Cognitive Decline in the Northern Manhattan Study

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### Abstract

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**Objectives**—To determine whether infectious burden (IB) is associated with worse performance and decline on a battery of neuropsychological tests.

**Design**—Prospective cohort study (Northern Manhattan Study (NOMAS)).

**Setting**—Community.

**Participants**—A subsample of 588 stroke-free NOMAS participants with IB and cognitive data (mean age 71±8, 62% female, 14% white, 16% black, 70% Hispanic) and 419 with repeat cognitive testing.

**Measurements**—Samples used for IB data were collected at baseline. Two waves of neurocognitive assessments occurred during follow-up. Participants underwent a neuropsychological battery and had repeated testing (mean time span 6±2 years). Using factor analysis–derived domain-specific Z scores for language, memory, executive function, and processing speed, associations between a quantitative stroke risk-weighted IB index (IBI), based on five common infections (*Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, herpes simplex viruses 1 and 2), and cognitive performance and decline in each domain was examined.

**Results**—Adjusting for demographic characteristics, socioeconomic status, crystallized cognitive abilities, and vascular risk factors, the IBI was inversely associated with executive function at baseline (beta=−0.10, p=.01) but not with baseline language, memory, or processing speed performance in adjusted analyses. The IBI was associated with cognitive decline in the memory domain, adjusting for demographic and vascular risk factors (p=.02).

**Conclusion**—A quantitative measure of IB explained variability in baseline executive function performance and associated with decline in memory. Past exposure to common infections may contribute to vascular cognitive impairment and warrants further study.

## Keywords

infections; bacterial infections; viral infections; cognitive decline; epidemiology

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There is growing evidence that inflammation caused by infectious agents, viral and bacterial, may contribute to late-life cognitive decline. Infectious agents play a role in vascular dysfunction, which in turn contributes to a large portion of cognitive disorders. Infectious agents previously associated with cognitive impairment and dementia include herpes simplex virus type 1 (HSV-1), cytomegalovirus (CMV), *Chlamydia pneumoniae*, and *Helicobacter pylori* (1).

In the multiethnic stroke-free community-based Northern Manhattan Study (NOMAS), it was previously reported that a weighted infectious burden (IB) index (IBI) was associated with stroke risk(2) and carotid artery atherosclerosis(3). It was also recently reported that the IBI was associated with worse global cognitive performance as measured using the Mini-Mental State Examination (MMSE) and the modified Telephone Interview for Cognitive Status (TICS-m)(4). Although cross-sectional associations between the IBI and these screening measures of cognitive performance have been found in NOMAS, it is unknown whether specific domains of cognitive performance are preferentially affected. Our cognitive assessment battery, used here, provides a more-thorough assessment of cognitive

capabilities, needed to elucidate the relationship between IB and cognitive health and further clarify differential effects on cognition from vascular damage and neurodegenerative processes (e.g. amyloid deposition). As the population ages, the need to identify modifiable risk factors for cognitive impairment becomes imperative. Therefore, the goal of the current study was to examine the relationship between the IBI and four domains of cognitive performance and decline: language, memory, executive function, and processing speed.

## METHODS

### Study Population

NOMAS is a prospective community-based cohort study designed to determine stroke incidence and risk factors in a racially and ethnically diverse urban population. Northern Manhattan is a well-defined area of New York City made up of 63% Hispanic, 20% non-Hispanic black, and 15% non-Hispanic white residents. Study details were published previously(5). Briefly, eligible participants had never been diagnosed with a stroke, were aged 40 and older, and had resided in Northern Manhattan for 3 months or longer in a household with a telephone. Subjects were identified using random-digit dialing, and trained bilingual research assistants conducted interviews. Subjects were recruited from the telephone sample to have an in-person baseline interview and assessment from 1993 to 2001. The enrollment response rate was 75%, and the overall participation rate was 69%, resulting in a cohort size of 3,298. A substudy of 1,290 participants with magnetic resonance imaging (MRI) and neuropsychological assessments included participants aged 55 and older and had no contraindications to MRI who remained clinically stroke-free and were recruited sequentially during annual follow-up. The institutional review boards of Columbia University and the University of Miami approved the study, and all subjects provided written informed consent.

### Covariate Data Collection

Data were collected through interviews with trained bilingual research assistants in English or Spanish. Study physicians conducted physical and neurological examinations. Race and ethnicity were based upon self-identification through a series of questions modeled after the U.S. Census and conforming to standard definitions outlined by Directive 15(6). Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention regarding hypertension, diabetes mellitus, smoking, and cardiac conditions(7, 8). Smoking was categorized as current (within the past year), former, or never smoker of cigarettes, cigars, or pipes. Moderate alcohol use was defined as current drinking of between two drinks per day and one drink per month. Moderate to heavy physical activity level was defined as engaging in one or more of selected rigorous physical activities in a typical 14-day period, as described previously(9). Blood pressure was measured in the right brachial artery after a 10-minute rest in a seated position, measured twice (before and after each examination) and averaged. Hypertension was defined as a blood pressure of 140/90 mmHg or greater, participant self-report of hypertension, or antihypertensive medication use. Fasting blood specimens were analyzed to determine glucose and lipid profiles, as described previously(10). Diabetes mellitus was defined according to participant self-report of such a history, use of insulin or oral antidiabetic

medication, or fasting glucose of 126 mg/dL or greater. Hypercholesterolemia was defined as having a total cholesterol level greater than 200 mg/dL, cholesterol lowering medication use, or self-reported history of hypercholesterolemia.

Imaging was performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Hatch Research Center. The processing of MRI scans to extract white matter hyperintensity volumes (WMHVs) and cerebral, lateral ventricular, and intracranial volumes and to identify MRI-defined infarcts has been described previously(11).

### Infectious Burden Index

Infectious disease serology was measured for five pathogens in baseline blood samples using enzyme-linked immunosorbent assay (ELISA). Antibody titers were measured for *C. pneumoniae* (immunoglobulin (Ig)G and IgA; Sayvon Diagnostics, Ashdod, Israel), *H. pylori* IgG, CMV IgG (Wampole Laboratories, Princeton, NJ), and HSV 1 and HSV 2 IgG (Focus Diagnostics, Cypress, Crete). IgG and IgA titers were measured for *C. pneumoniae*, but based on previous results in this population and others, IgA titers were used (12, 13). All ELISA kits are commercially available, and positive serological results were identified according to manufacturer-recommended thresholds. Serological testing protocols were published previously(2). The Center for Laboratory Medicine at Columbia University conducted serological testing, and technologists were blinded to participant data.

A weighted IBI based on the relationship of individual serological tests to stroke risk was created, as previously described(2). Briefly, multivariable-adjusted Cox models were used to estimate the regression coefficients and 95% confidence intervals (CI) for the association between each serological result (positive vs negative) and risk of stroke in models including all other serologies. Parameter estimates from this model were used to derive a weighted index designated as the IB. Each parameter estimate represents the strength of the association between the individual positive serological result and incident stroke risk. The IBI represents the summation of individual parameter estimates for serological results for which an individual was positive. Parameter estimates for an individual's negative serological results are not counted in the index. Thus, the IBI was calculated using the following formula, given the presence (X=1) or absence (X=0) of the specific pathogen serology, with weighted beta-coefficients from the stroke outcomes model:  $IBI=0.26(X \text{ C. pneumoniae IgA})-0.086(X \text{ H. pylori IgG})+0.69(X \text{ CMV IgG})+0.22(X \text{ HSV-1 IgG})+0.18(X \text{ HSV-2 IgG})$ .

### Cognitive Assessments

On the day of MRI, trained research assistants administered a neuropsychological battery in a quiet room in English or Spanish. Domain-specific z-scores were calculated for the cognitive domains of memory, processing speed, language, and executive function. The domain scores were computed for each subject by taking an average of construct-relevant z-transformed neuropsychological test scores. Tests were selected for each domain based on an exploratory factor analysis and findings reported in previous studies(14, 15). Specifically, memory was assessed using three subscores on a 12-word five-trial list-learning task: list learning total score, delayed recall score, and delayed recognition score. Executive function

was assessed using two subscores: difference in time to complete the Color Trails test Form 1 and Form 2 and the sum of the Odd-Man-Out subtests 2 and 4. Processing speed was assessed using the Grooved Pegboard task with the nondominant hand, the Color Trails test Form 1, and the Visual-Motor Integration test(16). Language ability was assessed using three tests: modified Boston Naming (picture naming), Animal Naming (category fluency), and C, F, L in English speakers and F, A, S in Spanish speakers (phonemic fluency). Crystallized intelligence was estimated according to performance on the Peabody Picture Vocabulary Test, Third Edition, and performance on the reading subtest of either the Wide Range Achievement Test (English speakers) or the Word Accentuation Test intelligence (Spanish speakers)(17–19). Similarly, for changes in scores over time, composite scores for changes in the four domains were computed using regression-based reliable change indices of the corresponding individual test after adjustment for age, years of education, and the time interval between the two assessments(20).

### Statistical Analysis

The IBI was examined continuously per standard deviation as the independent variable of interest. The distribution of the IBI among categories of the covariates was examined. Then, a series of multivariable-adjusted linear regression models was constructed to examine the association between the IBI and the four distinct cognitive domains (executive function, memory, language, processing speed) at the first neuropsychological assessment and with the z-scores for the change in the domains from first assessment to follow-up assessment. Because domain z-scores were not strongly correlated, each domain was examined as a separate outcome. Model 1 included age at neuropsychological testing, sex, and the time from serological testing at baseline blood collection to the time of neuropsychological assessment. Model 2 additionally included education, race and ethnicity, medical insurance status (Medicaid or no insurance vs Medicare without Medicaid or private insurance), and crystallized intelligence. Model 3 added MRI variables to Model 2, including WMHVs, brain atrophy (total cerebral volume/total intracranial volume), lateral ventricular enlargement (lateral ventricular volume/total intracranial volume), and MRI-defined infarction. Model 4 did not include the MRI variables and instead added vascular risk factors to Model 2, including diabetes mellitus, hypertension, hypercholesterolemia, body mass index, moderate alcohol, moderate to heavy physical activity, and smoking. For analyses of the z-scores representing change in performance in each cognitive domain from first assessment to follow-up, Models 2 through 4 were ran again, but age and education were not added because they were included in the regression analyses used to create the z-scores(20). In sensitivity analyses, C-reactive protein (CRP) was added to Model 4 as a measure of systemic inflammation.

## RESULTS

Five hundred eighty-eight NOMAS participants had IBI and cognitive data. In the NOMAS cohort, IBI was not different between those with and without neuropsychological data, and in those with an initial assessment, the IBI was not different between those with and without follow-up cognitive data (not shown). Mean age at neuropsychological assessment was  $71 \pm 8$  (range 50–96). Of these participants, 38% were male, 14% white, 16% black, and 70%

Hispanic. Mean time from baseline to neuropsychological assessment was  $6.7 \pm 2.2$  years (range 2.2–14.0 years). Table 1 shows the mean  $\pm$  standard deviation of IBI across categories of the covariates (overall mean IBI  $0.99 \pm 0.34$ ).

Multivariable-adjusted associations between IBI and the four cognitive domain z-scores are shown in Table 2. The IBI was inversely associated with all four cognitive domains in Model 1, adjusting only for age, sex, and time from baseline to neuropsychological assessment, but in the fully adjusted model, the inverse association remained significant only for executive function (Table 2).

Of the above participants, 419 had two neuropsychological assessments, with a mean time between assessments of  $6 \pm 2$  years. Table 3 shows the association between IBI and age- and education-adjusted z-scores for changes in the four cognitive domains. IBI was associated with decline over time in memory performance in all three multivariable-adjusted models. There were inverse associations for the other three domains (executive function, language, processing speed) that did not reach significance. All results were unchanged when CRP was added to Model 4.

## DISCUSSION

An inverse association between IBI and two global measures of cognitive performance (MMSE, TICS-m) has previously been found (4). The current study suggests pathogen-related processes, such as chronic inflammation, may adversely affect cognitive health through variable effects on specific cognitive domains. Although the IBI explained significant variability in baseline executive function, analysis of the IBI in relation to change in cognition over time showed an association with decline in memory.

The previous NOMAS study did not show a significant association between the IBI and changes in the TICS-m over time, but this could have been due to a lack of sensitivity of this telephone measure, insufficient length of follow-up, or other causes(4). It is felt that this study's noncontextual verbal list-learning task is more sensitive than the memory item on the TICS-m. The finding that the IBI was significantly associated with executive function at the baseline assessment, with declines only in the memory domain, could indicate that common infections (and related inflammation) interacted with different processes (e.g., aging, vascular, neurodegenerative) that were static or progressive, depending on the individual. For example, the association with baseline executive function could mean that some people had insults before the first measurement that were not destined to progress, whereas the association with decline in memory could mean that others had progressive amyloid deposition. This is purely speculative, and although such inferences are tempting, adjusting for reasonably robust measures of vascular and neurodegenerative damage (cerebral and ventricular atrophy) did not alter the strength of the associations between the IBI and cognitive performance in this study. For example, adjusting for white matter lesion load did not alter the strength of the association between IBI and executive function, a domain that is known to be susceptible to such damage. Likewise, adjusting for cerebral and lateral ventricular volume did not alter the association with memory.

Two viruses included in the IBI, CMV and HSV1, have previously been independently associated with risk of dementia. HSV1 is associated with cognitive impairment and Alzheimer's disease(21–23), CMV deoxyribonucleic acid has been associated with vascular dementia(24), and CMV antibody levels have been associated with cognitive decline(25). Data from two studies suggest that the viral component of overall IB may be primarily responsible for the relationship with cognitive impairment(1). In an exploratory analysis in NOMAS on IBI and global measures of cognitive performance, the association with cognition remained essentially the same when IB was restricted to viral serologies(4), although bacterial infections have also been related to cognitive impairment. *C. pneumoniae* has been observed in brain areas with neuropathology indicative of Alzheimer's disease(26, 27), and *H. pylori* has been suggested as a risk factor for dementia(28, 29). One study examined the burden of infection with *C. pneumoniae* and/or *M. pneumoniae* and did not show an association of seropositivity with cognition, although in that study cognitive impairment and dementia were observed more commonly in those who were seropositive to HSV1, HSV2, and/or CMV. The current study expands on these findings and explores the hypothesis that several chronic infections may be etiologically relevant for cognitive impairment. If the overall burden of infection and any corresponding inflammation contribute to cognitive decline, and the relationship is not specific to any particular pathogen, then studies that focus only on individual infectious agents may not find significant associations.

In the current study, the association between the IBI and executive function persisted after accounting for brain changes that reflect vascular damage, including WMHV and MRI-defined infarction, and loss of cerebral volume and enlargement of the lateral ventricles that may be expected with age and neurodegenerative processes. These variables may be considered effect mediators on a potential causal pathway linking IB and cognitive performance. The association also persisted after controlling for behavioral and vascular risk factors that may be confounders or effect mediators, including diabetes mellitus, hypertension, hypercholesterolemia, obesity, alcohol intake, physical activity, and smoking, as well as CRP, a marker of systemic inflammation. The underlying mechanisms linking infectious exposures to cognition are not well understood. Vascular damage in the brain often contributes to cognitive impairment, and traditional vascular risk factors have been shown to be risk factors for cognitive impairment as well(30–32). Vascular damage may be partly due to bacterial and viral infections that can affect lipid metabolism, invade vessel walls, and lead to cytokine release. In NOMAS, the IBI was positively associated with two markers of atherosclerosis that are closely linked to lipids and inflammatory and immune processes: carotid plaque thickness and plaque irregularity(3).

The use of an extensive battery of neuropsychological tests, allowing for a more-accurate and -detailed assessment of cognitive performance than global measures, strengthened the current study. An additional strength is the population-based cohort of Hispanic, white, and black adults living in the same urban community, which includes underrepresented groups in studies of risk factors for cognitive impairment. Lastly, data were available on many established vascular risk factors and MRI measures, which are necessary to examine whether the associations persisted after accounting for a wide range of potential confounders and effect mediators. Most notably, CRP was controlled for in sensitivity analyses; few other



studies have adjusted for a systemic inflammatory marker. Nevertheless, there were limitations. Most importantly, for the analysis of IB in relation to initial cognitive performance, inferences about causality and temporality are limited, despite the fact that the IBI was assessed before neuropsychological testing. Second, the current study was conducted in a subcohort of the NOMAS sample with IBI and neuropsychological data. The subcohort with neuropsychological testing was selected for being alive and stroke free at enrollment and therefore may have been healthier than the overall population. Likewise, although the majority of participants returned for a second neuropsychological assessment, not everyone who received initial neuropsychological testing returned for follow-up. It is possible that individuals with greater decline were less likely to return for follow-up assessment, and it is possible that participants who were less healthy in other ways were less likely to have follow-up. It was not possible to exclude potential selection bias, although IBI was unrelated to availability of neuropsychological testing data and of follow-up cognitive data in those with an initial assessment.

In conclusion, this study adds to an existing body of literature showing that chronic infections are associated with worse cognitive performance in late life, and suggests that damage that affects cognitive flexibility and crystallized abilities may cause this cognitive impairment. Furthermore, chronic IB may be associated with decline in cognitive performance over time, particularly in relation to memory function. Bacterial and viral infections are potential modifiable risk factors for cognitive impairment and should be examined in future large prospective studies. Interventions with an antiinflammatory purpose, including treatment of infections as well as physical activity and dietary modifications, have the potential for preserving cognitive health.

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**Table 1**

Covariates in Relation to Infectious Burden Index (IBI)

Variable	n (%)	IBI, Mean±Standard Deviation <sup>b</sup>
Age at neuropsychiatric assessment <sup>a</sup>		
<60	16 (3)	0.74±0.50
60–65	139 (24)	1.01±0.32
>65	433 (74)	1.00±0.34
Sex <sup>a</sup>		
Male	225 (38)	0.95±0.38
Female	363 (62)	1.02±0.31
Education		
High school	248 (42)	0.86±0.40
<High school	340 (58)	1.09±0.25
Race and ethnicity <sup>a</sup>		
White	80 (14)	0.66±0.43
Black	94 (16)	0.99±0.38
Hispanic	414 (70)	1.06±0.27
Medicaid or uninsured		
Yes	308 (52)	1.07±0.26
No	280 (48)	0.91±0.39
Magnetic resonance imaging–defined infarction		
Yes	63 (11)	0.93±0.35
No	525 (89)	1.00±0.34
White matter hyperintensity volume		
> 0.35	294 (50)	0.99±0.34
0.35	294 (50)	1.00±0.34
Diabetes mellitus <sup>a</sup>		
Yes	104 (18)	1.06±0.27
No	484 (82)	0.98±0.35
Hypertension		
Yes	401 (68)	1.00±0.33
No	187 (32)	0.97±0.36
Hypercholesterolemia		
Yes	384 (65)	0.98±0.34
No	204 (35)	1.02±0.33
Body mass index <sup>a</sup>		

Variable	n (%)	IBI, Mean±Standard Deviation <sup>b</sup>
Normal	153 (26)	0.94±0.39
Overweight	268 (46)	0.99±0.33
Obese	165 (28)	1.04±0.30
Moderate alcohol use <sup>a</sup>		
Yes	233 (40)	0.95±0.37
No	355 (60)	1.02±0.32
Moderate to heavy physical activity		
Yes	53 (9)	0.90±0.42
No	533 (91)	1.00±0.33
Smoking		
Never	270 (46)	1.01±0.33
Former	226 (38)	0.97±0.35
Current	92 (16)	0.99±0.35

<sup>a</sup> p<.05 using t-tests or analysis of variance.

<sup>b</sup> Range=0–1.35

**Table 2**

Effect of Infectious Burden Index and Cognitive Domains in the Northern Manhattan Study (N=588)

Model	Executive Function	Language	Memory	Processing Speed
	Effect of IBI (per SD) on cognitive domain Z-score, P-value			
1 <sup>a</sup>	-0.31, <.001	-0.30, <.001	-0.22, <.001	-0.23, <.001
2 <sup>b</sup>	-0.10, .01	-0.03, .24	-0.03, .35	-0.04, .29
3 <sup>c</sup>	-0.10, .01	-0.04, .23	-0.03, .35	-0.04, .28
4 <sup>d</sup>	-0.10, .01	-0.03, .25	-0.03, .34	-0.04, .28

<sup>a</sup> Adjusted for age, sex, time from baseline to neuropsychiatric testing.

<sup>b</sup> Adjusted for variables in Model 1 + education, race and ethnicity, Medicaid, crystallized intelligence.

<sup>c</sup> Adjusted for variables in Model 2 + magnetic resonance imaging (MRI) variables (white matter volume, cerebral and lateral ventricular volumes, MRI-defined infarction).

<sup>d</sup> Adjusted for variables in Model 2 + vascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, body mass index, alcohol consumption, physical activity, smoking).

**Table 3**

Infectious Burden Index (IBI) and Cognitive Change in the Northern Manhattan Study (N=419)

Model	Executive Function	Language	Memory	Processing Speed
	Effect of IBI (per SD) on cognitive domain Z-score, P-value			
2 <sup>a</sup>	-0.08, .15	-0.07, .18	-0.12, .03	-0.06, .25
3 <sup>b</sup>	-0.08, .15	-0.07, .20	-0.12, .04	-0.06, .26
4 <sup>c</sup>	-0.07, .20	-0.07, .18	-0.13, .02	-0.07, .23

Change in domain z-scores with age and education included in the regression analyses used to create the z-scores.

<sup>a</sup> Adjusted for time from baseline to neuropsychiatric testing, sex, race and ethnicity, Medicaid, crystallized intelligence.

<sup>b</sup> Adjusted for variables in Model 2 + magnetic resonance imaging (MRI) variables (white matter volume, cerebral and lateral ventricular volumes, MRI-defined infarction).

<sup>c</sup> Adjusted for variables in Model 2 + vascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, body mass index, alcohol consumption, physical activity, smoking).