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Cognitive Function and Cardio-Metabolic-Inflammatory Risk Factors among Older Indians and Americans

Short Running Title: Cognition and Cardio-Metabolic Risk Factors

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ABSTRACT

OBJECTIVES: To investigate how cardio-metabolic-inflammatory risk factors are related to cognition among older adults in India and the United States.

DESIGN: The Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) and the Harmonized Cognitive Assessment Protocol of the Health and Retirement Study (HRS-HCAP) in the United States conducted an in-depth assessment of cognition, using protocols designed for international comparison.

SETTING: Cognitive tests were conducted in hospital or household settings in India and in household settings in the United States.

PARTICIPANTS: Respondents aged 60 and older from LASI-DAD (N=1,865) and respondents aged 65 and older from HRS-HCAP (N=2,111) who provided venous blood specimen.

MEASUREMENTS: We used total composite scores from the common cognitive tests administered. Cardiovascular risk was indicated by systolic and diastolic blood pressure, pulse rate, pro-B-type-natriuretic-peptide (proBNP), and homocysteine. Metabolic risk was measured by body mass index, glycosylated hemoglobin (HbA1c), HDL-cholesterol, and lipoprotein (a) (only in India). Inflammatory risk was indicted by white blood cell count, C-reactive protein, albumin, and uric acid (only in India).

RESULTS: The distribution of both total cognition scores and of cardio-metabolic risk factors differed significantly between India and the United States. In both countries, lower cognition was associated with older age, lower education, elevated homocysteine, elevated proBNP, and lower

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albumin levels. The associations between HbA1c levels and cognitive measures were statistically significant in both countries, but in the opposite direction, with a coefficient of 1.5 ($p<0.001$) in India and -2.4 ($p<0.001$) in the United States for one percentage increase in absolute HbA1c value.

CONCLUSION: Cardio-metabolic-inflammatory biomarkers are associated with cognitive functional levels in each country, but the relationships may vary across countries.

Key words: dementia risk factors, Harmonized Cognitive Assessment Protocol, Longitudinal Aging Study in India, Health and Retirement Study, international comparisons

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INTRODUCTION

Dementia has become an important public health and socioeconomic challenge in India as well as in the United States.[1,2] Because of population aging, the prevalence of dementia will continue to increase in both countries, leading to higher medical and personal care expenses, decreased functioning and quality of life for affected individuals, and stress and loss of productivity for family caregivers. With ongoing population aging, it is estimated that the number of worldwide dementia cases will triple by 2050.[3]

Cardio-metabolic diseases may increase the risk for cognitive decline and dementia through multiple causal pathways, including direct effects on neurons, hypoperfusion due to reduced cerebral blood flow, and promotion of amyloid cascade.[4] Cardiovascular disease may also alter epithelium cells, which dislocate blood brain barrier, resulting in disturbance in amyloid clearance. India has been undergoing a significant change in disease burden with swift increase in cardiovascular and metabolic diseases. Data from the Global Burden of Diseases, Injuries, and Risk Factors Study indicated that cardiovascular diseases accounted for 28.1% of the total deaths in India in 2016, compared with 15.2% in 1990.[5] However, this epidemiological transition is occurring decades later than that in the United States. Indians appear to have a unique “South Asian phenotype” with high propensity for metabolic syndrome, insulin resistance, greater degree of central obesity as well as a high prevalence of hypertension at relatively young ages.[6] In addition, there appears to be suboptimal management of cardio-

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metabolic diseases in India with only 10.7% of rural hypertension patients and 20.2% of urban patients having their blood pressure under control.[7,8]

This study provides an analysis of how risk factors – biological and sociodemographic – relate to cognitive functioning in a representative sample of Indians over the age of 60 and compares the results to those in a representative sample of Americans aged 65 and above. This comparison offers a unique opportunity to compare and contrast how cardio-metabolic risk factors are related to cognitive functioning in these two populations. One has virtually complete literacy and the other has a large non-literate component. The marked difference in educational levels between older Indians and older Americans leads to significant differences in late life cognition. In addition, the American older population has had extensive medical care throughout much of its life; while care for most Indians remains classified as fairly rudimentary.

METHODS

Study Populations

The study population in India is participants of the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) Study. The details of study design and methodology have been described in this special issue.[9] LASI-DAD, a subsample from the population-representative Longitudinal Aging Study in India (LASI), was established to provide a more accurate prevalence estimate of dementia at the national level and study key risk factors associated with cognitive decline and dementia in India. It recruited 3,224 LASI participants

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aged 60 years and above with oversampling of those at high risk of cognitive impairment. To facilitate cross-country comparisons, LASI-DAD adopted the protocol from the Health and Retirement Study Harmonized Cognitive Assessment Protocol Project (HRS-HCAP) to assess cognitive function and modified where necessary, considering India's higher illiteracy and innumeracy as well as cultural context.

The details about HRS-HCAP have been published previously.[10] Briefly, the HRS is an ongoing nationally-representative panel study of about 20,000 adults aged 51 or older in the United States. HRS-HCAP is a sub-study within HRS designed to better measure and identify cognitive impairment and dementia in a representative population-based sample of U.S. adults aged 65 and above. It interviewed the target HRS respondents as well as informants nominated by respondents when self-response was not possible. The HRS-HCAP cognitive test battery was designed to measure a range of key cognitive domains affected by cognitive aging and to allow harmonization and comparisons to other studies in the United States and around the world.

For this analysis, we included 1,865 individuals from LASI-DAD and 2,111 individuals from HRS-HCAP. Among 3,224 initial LASI-DAD respondents, 2,254 respondents provided venous blood specimen (VBS) samples. We lost 139 respondents who were missing in various VBS assays including pro-B-type-natriuretic-peptide (proBNP), C-reactive protein (CRP), albumin, homocysteine, HDL cholesterol, glycosylated hemoglobin (HbA1c), and white blood cell count (WBC). In addition, we lost 250 respondents due to missing body mass index (BMI),

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pulse rate, systolic and diastolic blood pressure. The details of venous blood collection and assay protocol are described in Dey et al.[11] available on the project website (www.lasi-dad.org).

A total of 3,347 HCAP participants attempted the cognitive testing. Of these, 3,210 had complete data on all the tests used here, and another 124 had nearly complete data for which imputation was done for missing tests using the performance on all other tests. We excluded 13 for incomplete data on cognition and about 340 because they did not have complete data on blood tests from the 2016 whole blood draw. In addition, we dropped about 900 because they did not have data from the HRS 2014 or HRS 2016 home visit which was used for data on blood pressure, pulse, and BMI. For a total of 229 persons in the remaining sample of 2,111 we imputed a missing value of HbA1c based on their fasting plasma glucose using the relationship between the two observed in the cases with both measures.

Comparing respondents who had missing information with those who had complete data, we found that, in India, missingness was associated with being 75 years or older, having no education, and living in a rural area; in the United States, being missing was associated with being 75 years or over and being female. In each country, these predictors explained only 1% of the variance in missingness.

Measures

Cognitive function measure

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For cross-country comparisons, we used a harmonized total cognitive score, which provides a comprehensive assessment of various cognitive domains. The total cognitive score is a summary score based on the following tests: 10-word learning, including immediate and delayed recall and recognition[12]; logical memory (i.e., Brave Man story only), including immediate and delayed recall and recognition[13]; Mini Mental State Exam (MMSE)[14] or a validated Hindi version of MMSE (HMSE) summary score[15]; verbal fluency score,[16] which was the number of named animals within 60 seconds; the community screening instrument for dementia (CSID) score[17]; and Raven's test,[18] a count of the number of correct answers to a series of images that required the respondent to select the missing piece. The range of total cognitive scores was from 0 to 175 (see Table 2 for the range and mean for each component test).

We imputed information for missing values in the cognitive tests. The implemented method used for the Indian data was inspired by the imputations of cognition variables used in the HRS.[19] In a nutshell, this imputation method replaces missing values with random draws from a conditional distribution such that the estimated joint distribution from the completed (imputed) data is an unbiased estimator of the true joint distribution of these variables. The conditional distribution for each test score is obtained by regressing the to-be-imputed test score on other, previously imputed test scores, as well as demographic, health, and socioeconomic variables. Further details of imputation strategy are described in another paper in this issue.[20] Imputation has not yet been done on the available HRS-HCAP data; for this analysis, we imputed data for the 124 cases using a conventional nearest neighbor approach.

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Cardio-metabolic-inflammatory biomarkers

Both LASI-DAD and HRS-HCAP conducted face-to-face computer-assisted personal interviews (CAPI) on respondents and their informants, measured anthropometric and physical parameters, and collected venous blood for laboratory tests, including those related to cardio-metabolic-inflammatory diseases.

Cardiovascular system: Biomarkers included high blood pressure defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, pulse rate, proBNP, and homocysteine. At-risk proBNP was defined as a level of ≥ 900 pg/mL for 50-74 year-olds, and ≥ 1,800 pg/mL for ≥ 75 years-old. These cut-off points are usually used to diagnose congestive heart failure (CHF).[21,22]

Metabolic system: Biomarkers included BMI based on measured height and weight (self-reported if measured height and weight are not available), glycosylated hemoglobin (HbA1c), HDL-cholesterol, and lipoprotein (a) (which was not available in HRS). In HRS-HCAP, we have imputed HbA1c for those who have glucose in the VBS data but no value for HbA1c. Imputation was done separately for fasting and non-fasting samples. Because LASI-DAD had a significant percentage of non-fasting participants at the time of blood collection, we did not include glucose, LDL-cholesterol, and triglycerides in this analysis.

Inflammatory system: Biomarkers included white blood cell count (WBC), C-reactive protein (CRP), albumin (a negative acute-phase reactant), and uric acid.

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Covariates

Demographic characteristics included age and sex. Education was included as a categorical variable with three categories for the United States (0-11, 12, 13+ years) and four categories for India (0, 1-11, 12, 13+ years). The extra category for India is because a large proportion of older population has no formal education while this is not true in the United States. Household wealth was also included as a categorical variable based on quintile distribution.

Statistical Approach

We use multivariate ordinary least squares regression analysis with the cognitive measure as the outcome variable. There are three equations for each country. The first includes cardio-metabolic-inflammatory biomarkers only, the second adds age and sex, and the third adds education and household wealth. Comparison of these equations allows us to assess how the biomarkers are associated with cognitive function, independent of sociodemographic characteristics. In addition, we can assess how much of the variability in the outcomes is explained by these variables when we compare the R^2 of the three equations.

We examined the intercorrelations among all the biomarkers and found high correlation coefficients only between systolic and diastolic blood pressure values. As a result, we defined high blood pressure as either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, and included this dichotomous variable in the models. To assess possible non-linear

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relationships, we categorized four variables in the regression analysis: age (60-64, 65-69, 70-74, and 75 years and above); BMI (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, and ≥ 30 kg/m^2); and education and household wealth as described above. Other cardio-metabolic-inflammatory biomarkers were included as continuous variables in the models. Log transformations were done for WBC, CRP, and proBNP due to significant right-skewed distributions. To explore potential effects from residual confounding, we have also conducted a sensitivity analysis among HRS participants to include race/ethnicity as a covariate.

RESULTS

The characteristics of the samples are summarized in Table 1. The two populations differed markedly in age and education. The Americans were much older, with no members of the cohort less than 65 years, while about 28% of the Indians were of this age, and many more Americans were 75 or older, about 41% in the United States and 23% in India (Table 1). Almost half (46%) of the Indian sample had no formal schooling, while 84% of the American cohort had at least a high school education as did only 8% of the Indian cohort. The percent of the sample with high-risk levels of most of the cardiovascular and metabolic risk factors was higher in India than in the United States. The notable exception was BMI: less than one third of Indians and more than three-fourths of Americans were overweight. The prevalence of elevated measured blood pressure was significantly higher in India than in the United States: both systolic and diastolic blood pressures were more likely to be elevated in India. Although more Indians had

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HbA1c equal to or higher than 6.5%, the distribution of HbA1c values was fairly similar in the two countries. The prevalence for high homocysteine levels was three times higher in India than in the United States and adverse levels of HDL (low levels) were much higher in India than in the United States. As indicated above, we used age-specific cut-off points for CHF to define high proBNP, which are ≥ 900 pg/mL for those between ages 60 and 74, and ≥ 1,800 pg/mL for those ≥ 75 years-old. The prevalence of high-risk proBNP levels was quite similar between India and the United States. Prevalence of elevated levels of CRP, an indicator of overall systemic inflammation, was fairly similar in two countries.

Figure 1 shows distribution of total cognitive scores for the two countries. It is clear that the scores are much higher in the United States than in India. Because educational attainment differs so much in the two populations and has been shown to be so highly related to cognitive functioning, we also examine mean total cognitive scores by education levels in the two countries (Figure 2). The data confirmed that cognitive functioning score increased with more education. However, even though the whole sample of Indians had significantly lower total cognitive scores than Americans, at the same education level these differences were relatively small between the two countries. This pattern of similar education-specific cognitive performance was observed in all individual components of the total cognitive score (Table 2). For example, the mean MMSE score was 27.0 for Indians with 12 years of education and 26.9 for Americans at same education level. For those with 13 years of education and above, the mean MMSE score was identical at 28.1 for both countries. Because HRS-HCAP had very few

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respondents without any formal education, we were not able to do cross-country comparison of cognitive performance among illiterate individuals.

Multivariate regression analysis indicates that the cardiovascular biomarkers most consistently associated with cognitive function in both countries were homocysteine and proBNP. The associations were negative for both measures. They were also fairly similar in coefficient size with proBNP of -3.3 in India and -2.8 in the United States; and for homocysteine, the coefficients were -0.1 and -0.6, respectively (Table 3, Model 1). The associations between HbA1c and the cognitive measure were also significant, but in the opposite direction between India and the United States, with a regression coefficient of 1.5 in India and -2.4 in the United States for one percentage increase in absolute HbA1c value. This pattern did not change after including quadratic and cubic terms of HbA1c in the regression equation or categorizing HbA1c values into < 5.7%, 5.7-6.4%, and ≥ 6.5%. BMI was associated with cognitive function in India, with people with higher BMI performing better, including those in the range of obesity. On the other hand, low BMI (< 18.5 kg/m^2) was not significantly associated with poor cognitive functioning but obesity (BMI ≥ 30.0 kg/m^2) was related to better cognitive functioning among Americans. Among inflammatory markers, albumin was consistently and positively associated with cognitive function in both countries.

Older age and lower educational attainment were independently associated with lower total cognitive scores in both Indians and Americans (Table 3, Models 2 and 3). Compared to those with less than 12 years of education, the mean total cognitive scores were 19.3 points lower

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among Indians who were illiterate, 4.5 points higher among Indians who completed high school, and 13.2 points higher among those who had at least some college. Among Americans, the difference in total cognitive scores among those with higher education levels were 13.0 and 20.1 points, respectively. Compared to males, female scored lower in India but higher in the United States, although this sex-difference in India was not statistically significant after controlling for education and wealth.

After sociodemographic variables were added to the models, the associations of total cognitive scores with proBNP, homocysteine, BMI, and HbA1c remained statistically significant (Table 3, Model 3), although the strength of associations decreased. For example, the coefficients for higher proBNP decreased from -3.3 to -1.4 in India and from -2.8 to -1.4 in the United States.

R-square values from the analysis indicate that a greater proportion of the variance in total cognitive scores was explained in India than in the United States (0.41 versus 0.32). R-squares for cardio-metabolic-inflammatory biomarkers alone were 0.18 in India and 0.10 in the United States. Addition of education levels and household wealth significantly improved our ability to predict cognitive function in both countries.

To assess the effects of other potential confounding variables, we conducted a sensitivity analysis among HRS participants to include race/ethnicity, an important correlate of cognitive functioning in the United States. Adding race/ethnicity only increases the variance explained by

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1%. It reduces the magnitude of effects for glycosylated hemoglobin and albumin, so that they are no longer significantly associated with cognitive functioning.

DISCUSSION

In this analysis of the associations between cognitive function and cardio-metabolic-inflammatory risk factors, our data showed that several cardio-metabolic-inflammatory risk factors were independently associated with cognitive functional levels. Cognitive functioning was lower among those with high homocysteine and proBNP levels, and among those with low albumin levels in both countries. The association between HbA1c and cognitive measure was consistently significant, but in the opposite direction between the two countries, negative in the United States and positive in India. The link between weight and cognition seems strong in India, with a clear pattern of higher weight and better cognition; while in the United States only those with obesity have better cognition than those in the normal range.

Studies of older adults in many countries have shown that lower educational levels predict worse global cognitive functioning.[23-26] Education attainment is a well-established indicator of cognitive reserve capacity in older people and may have a direct effect on cognition through more developed and effective use of brain networks or cognitive paradigms.[27] Our analysis extends previous findings by demonstrating that, across two countries with very different distributions of education attainment, the difference in cognitive functioning is relatively small when we compare individuals with similar education levels. This observation

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appears true for both overall cognitive functioning as well as many of the individual domains (Table 2 and Figure 2).

In addition to the direct effect of education on cognition, years of formal education may also be a surrogate for other factors that might influence cognition, including development and management of cardiovascular and metabolic diseases. The proposed causal pathways through which cardio-metabolic diseases lead to cognitive decline and dementia include direct damage of neurons, cerebral blood hypoperfusion, and promotion of amyloid cascade.[4] Our finding of an inverse association between cognitive function and homocysteine and proBNP levels is consistent with previous research. In a prospective cohort of individuals 75 years and above, Blasko et al. reported that increased homocysteine levels were independently associated with decline of cognitive performance in normal older subjects and patients with Alzheimer's disease.[28] It has been postulated that homocysteine plays a role in promoting oxidative stress, inflammation, thrombosis, endothelial dysfunction, and cell proliferation.[29] Earlier studies in developed countries also showed that both cross-sectionally measured proBNP levels and increase in proBNP levels are related to subsequent risk of cognitive decline and dementia, mostly because of the association between proBNP levels and macro- and micro-ischemic changes of brain.[30-32] Our study confirmed the same relationship between adverse cardiovascular biomarkers and cognitive decline in India. The inverse association with homocysteine might be particularly relevant, because two-thirds (67.1%) of the Indian study population had at-risk homocysteine levels (Table 1).

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HbA1c level is a measure of average glucose metabolism during the previous 3 months, and has been used clinically to diagnose diabetes mellitus and monitor glucose control. A recent meta-analysis indicates that poorer glycemic control is related to cognitive dysfunction.[33] However, we found that, unlike Americans, Indians with higher HbA1c levels actually had higher total cognitive scores. This may reflect different stages of epidemiological transition for these two countries. With more recent economic development, Indians with higher socioeconomic status are more likely to adopt a western diet and have decreased level of physical activities, leading to a higher prevalence of non-communicable diseases. Previous analysis has shown that obesity and hypertension are more common among LASI participants who have higher education level, while these medical conditions are less common among Chinese older adults with better education.[34] Therefore, the positive association between HbA1c levels and cognitive function in India highlights the complexity of how cardio-metabolic-inflammatory risk factors may influence cognitive decline in countries that are undergoing rapid economic and societal transitions.

This study has some important strengths. LASI-DAD and HRS-HCAP are nationally representative samples of older adults in the two countries. Both studies generated high quality cognitive functioning and biomarker data. More importantly, cognitive assessment protocols were harmonized conceptually to allow more accurate cross-country comparisons. Several limitations should also be noted. First, even though LASI-DAD and HRS-HCAP are designed as longitudinal studies, our current analysis is cross-sectional. It does not allow us to examine the

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temporal relationship between cognitive function and cardio-metabolic-inflammatory risk factors. It is possible that the association works in both directions, as severe cognitive decline may affect management of cardio-metabolic diseases, causing more pathophysiological dysfunction. Second, only 32% of LASI-DAD respondents provided fasting blood specimens – limiting our ability to examine biomarkers that typically require fasting specimens (e.g., LDL cholesterol) or to formally define metabolic syndrome. Third, some of the cardio-metabolic-inflammatory biomarkers may be indicators for more than one system. For example, homocysteine is associated with cardiovascular disease, but its level also goes up in the setting of folate or vitamin B12 deficiency. Lastly, even though we adjusted for categories of age, sex, education and wealth, residual confounding remains a possibility.

Despite these limitations, this cross-country study sheds a new insight to the relationships between cognition and cardio-metabolic-inflammatory risk factors in two countries, India and the United States. Lower cognitive function is associated with older age, lower educational attainment, elevated homocysteine, elevated proBNP, lower albumin levels, and lower body mass index in both countries. The associations between HbA1c and cognitive measure are consistently significant, but in opposite direction between India and the United States. Longitudinal data from the future waves of LASI-DAD and HRS-HCAP will enable us to further investigate how changes in biomarkers are related to changes in cognitive function. These longitudinal analyses could provide more insight on biological pathways for cognitive decline and to explore potential interventions aimed at reducing cognitive decline and dementia.

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References

1. Alzheimer's & Related Disorders Society of India (ARDSI). The dementia India report: prevalence, impact, costs, and services for dementia. In: Shaji KS, Jotheeswaran AT, Girish N, Bharath S, Dias A, Pattabiraman M, Varghese M, eds. New Delhi: ARDSI, 2010.
2. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80:1778-1783.
3. Prince MJ, Wimo A, Ali G, Wu Y, Prina M. World Alzheimer Report 2015: The Global Impact of Dementia. London: Alzheimer's Disease International; 2015. Available at: https://www.alz.co.uk/research/world-report-2015. Accessed January 9, 2020.

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4. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst) 2017;7:69-87.
5. India State-Level Disease Burden Initiative CVD Collaborators. Nations within a nation: Variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study. Lancet 2017;390:2437-2460.
6. Jadhav UM. Cardio-metabolic disease in India-the up-coming tsunami. Ann Transl Med 2018;6:295.
7. Anchala R, Kannuri NK, Pant H et al. Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertens 2014;32:1170–1177.
8. Prenissl J, Manne-Goehler J, Jaacks LM et al. Hypertension screening, awareness, treatment, and control in India: A nationally representative cross-sectional study among individuals aged 15 to 49 years. PLoS Med. 2019 May 3;16(5):e1002801. doi: 10.1371/journal.pmed.1002801.
9. Lee J, Khobragade PY, Banerjee J et al. Design and methodology of the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD). J Am Geriatr Soc, forthcoming.

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Author Manuscript

10. Langa KM, Ryan LH, McCammon RJ et al. The Health and Retirement Study Harmonized Cognitive Assessment Protocol Project: Study Design and Methods. Neuroepidemiology 2020;54:64-74.
11. Dey AB, Banerjee J, Khobragade P et al. Diagnostic Assessment of Dementia for LASI Documentation – 2019 Wave 1, Early Release Version A, Venous Blood Collection and Assay Protocol, All India Institute of Medical Sciences and University of Southern California, 2019.
12. Morris JC, Heyman A, Mohs RC et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. Neurology 1989;39:1159–1165.
13. Wechsler D. Wechsler Memory Scale—Fourth Edition (WMS–IV) technical and interpretive manual: Pearson, 2009.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
15. Ganguli M, Ratcliff G, Chandra V et al.. A Hindi version of the MMSE: the development of a cognitive screening instrument for a largely illiterate rural elderly population in India. Int J Geriatr Psychiatry 1995;10:367-377.
16. Morris JC, Heyman A, Mohs RC et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. Neurology 1989;39:1159–1165.

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17. Hall K, Hendrie HC, Brittain HM et al. The development of a dementia screening interview in two distinct languages. Int J Methods Psychiatr Res 1993;3:1–28.
18. Raven J. The Raven's progressive matrices: change and stability over culture and time. Cogn Psychol 2000;41:1–48.
19. Fisher GG, Hassan H, Faul JD, Rodgers WL, & Weir DR. Health and Retirement Study: Imputation of Cognitive Functioning Measures: 1992 – 2014 (Final Release Version): Data Description. Ann Arbor, MI: University of Michigan, Survey Research Center, 2017.
20. Gross A, Khobragade PY, Meijer E, Saxton JA. Measurement and structure of cognition in the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD). Under review of a supplemental issue of J Am Geriatr Soc.
21. Hildebrandt P, Collinson PO, Doughty RN et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. Eur Heart J 2010;31:1881-1889.
22. Quest Diagnostics. NT-proBNP: Reference Ranges. 2019. Available at: https://testdirectory.questdiagnostics.com/test/test-detail/11188/?cc=MASTER. Accessed January 9, 2020.
23. Evans DA, Beckett LA, Albert MS et al. Level of education and change in cognitive function in a community population of older persons. Ann Epidemiol 1993;3:71-77.
24. Lei X, Hu Y, McArdle JJ, Smith JP, Zhao Y. Gender differences in cognition among older adults in China. J Hum Resour 2012;47:951-971.

This article is protected by copyright. All rights reserved.

Author Manuscript

25. Wilson RS, Hebert LE, Scherr PA, Barnes LL, Mendes de Leon CF, Evans DA. Educational attainment and cognitive decline in old age. Neurology 2009;72:460-465.
26. Zahodne LB, Glymour MM, Sparks C et al. Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. J Int Neuropsychol Soc 2011;17:1039-1046.
27. Crimmins EM. Physiological differences across ageing populations reflecting early life and later life nutritional status and later life risk for chronic disease. J Popul Ageing 2015;8:51-69.
28. Blasko I, Jellinger K, Kemmler G et al. Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine. Neurobiol Aging 2008;29:1-11.
29. Ansari R, Mahta A, Mallack E, Luo J. Hyperhomocysteinemia and neurologic disorders: a Review. J Clin Neurol 2014;10:281–288.
30. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the Atherosclerosis Risk in Communities study. Stroke 2013;44:961-967.
31. Ostovaneh MR, Moazzami K, Yoneyama K et al. Change in NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) Level and Risk of Dementia in Multi-Ethnic Study of Atherosclerosis (MESA). Hypertension 2020;75:316-323.

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32. Zonneveld HI, Ikram MA, Hofman A et al. N-terminal pro-B-type natriuretic peptide and subclinical brain damage in the general population. Radiology 2017;283(1):205-214.
33. Mansur RB, Lee Y, Zhou AJ et al. Determinants of cognitive function in individuals with type 2 diabetes mellitus: A meta-analysis. Ann Clin Psychiatry 2018;30:38-50.
34. Hu P, Wang S, Lee J. Socioeconomic gradients of cardiovascular risk factors in China and India: results from the China health and retirement longitudinal study and longitudinal aging study in India. Int J Public Health. 2017;62:763-773.

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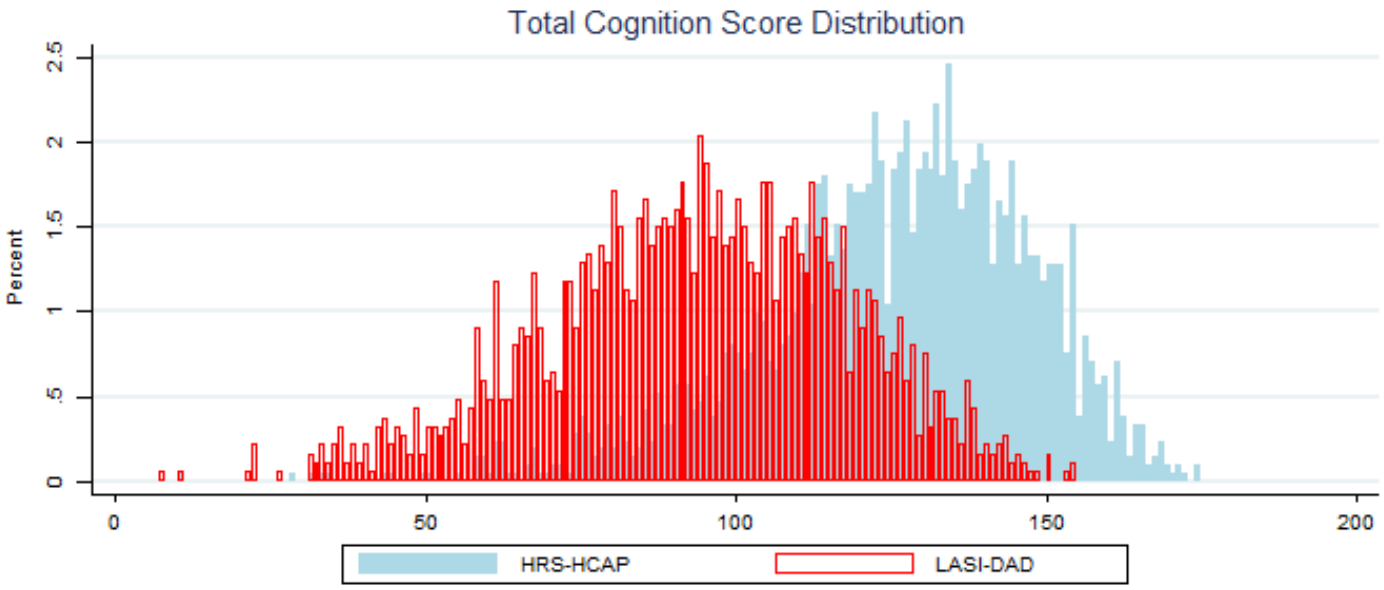

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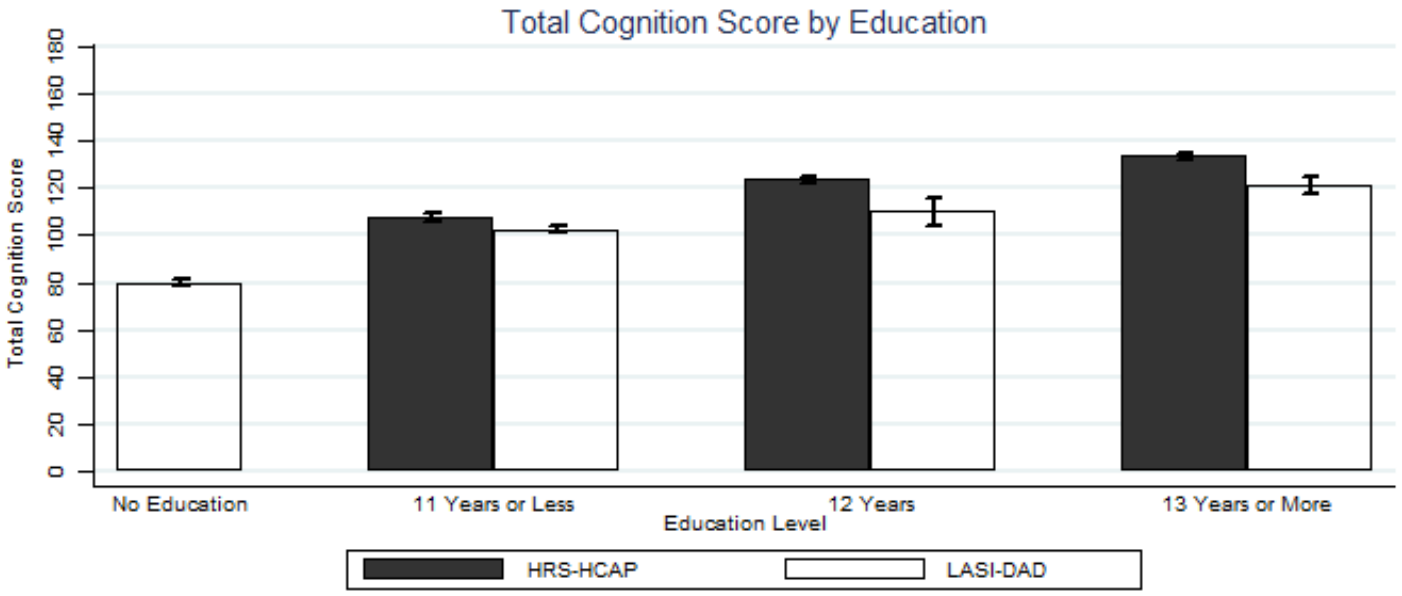

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Table 1. Comparison of select sample characteristics between LASI-DAD (N=1,865) and HRS-HCAP (N=2,111)

Variables	LASI-DAD	HRS-HCAP
Age (years)		
60-64	27.9%	--
65-69	29.8%	33.9%
70-74	18.9%	25.6%
75 +	23.3%	40.6%
Gender (% female)	52.9%	54.9%
Education		
% 0 year (LASI-DAD)	46.0%	
% 11 years or less[a]	46.1%	16.2%
% 12 years	3.0%	33.5%
% 13+ years	4.9%	50.3%
Cardiovascular characteristics		
% systolic blood pressure ≥ 140 mmHg	38.5%	26.2%
% diastolic blood pressure ≥ 90 mmHg	22.5%	9.8%
% systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg	42.5%	28.0%
% pulse > 100 beats per minute	6.5%	1.2%
% homocysteine > 15 umol/liter	67.1%	22.3%
% at risk pro-B-type-natriuretic peptide (proBNP)†	4.5%	5.1%
Metabolic characteristics		
% body mass index ≥ 25 kg/m^2	29.9%	77.9%
% glycosylated hemoglobin ≥ 6.5%	26.8%	15.6%
% HDL-cholesterol < 40 mg/dL	39.7%	16.0%
% lipoprotein (a) > 30 mg/dL	41.3%	--
Inflammation characteristics		
% C-reactive protein > 3 mg/L	36.8%	35.7%
% white blood cell count > 11,000/mm^3	5.7%	2.8%
% albumin < 3.5 g/dL	3.2%	6.1%
% uric acid > 7 mg/dL	7.1%	--

LASI-DAD=the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia Study, HRS-HCAP=the Health and Retirement Study Harmonized Cognitive Assessment Protocol Project

[a]HRS-HCAP includes the sample that never attended school in this category (N=12)

†proBNP ≥ 900 pg/mL for 60-74 years-old, and ≥ 1,800 pg/mL for ≥ 75 years-old

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Table 2. Comparison of scores of individual cognitive domains by education levels between the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia Study (LASI-DAD) and the Health and Retirement Study Harmonized Cognitive Assessment Protocol (HRS-HCAP)

	Range	LASI-DAD					HRS-HCAP			
Years of education		**0**	**1-11**	**12**	**13+**	**ALL**	**0-11**	**12**	**13+**	**ALL**
10 word list immediate recall	0-30	10.0	13.7	14.3	15.9	11.9	14.8	17.7	19.2	18.0
10 word list delayed recall	0-10	2.6	4.0	3.8	5.0	3.3	4.0	5.2	5.9	5.4
10 word list recognition	0-20	15.0	17.4	17.5	18.3	15.2	17.6	18.7	19.1	18.7
Logical memory recognition score	0-15	6.9	8.3	8.8	10.5	7.7	8.8	10.4	11.2	10.6
Brave Man immediate recall score	0-12	4.8	6.3	6.7	7.5	5.6	5.9	7.2	7.8	7.3
Brave Man delayed recall score	0-12	1.8	4.1	5.1	5.4	3.0	3.6	5.1	6.1	5.3
MMSE summary score	0-30	20.7	25.8	27.0	28.1	23.3	24.3	26.9	28.1	27.1
Verbal fluency score	0-43*	10.6	12.9	13.7	15.9	11.9	12.6	16.2	19.2	17.1
CSID score	0-4	3.3	3.6	3.8	3.8	3.5	3.6	3.7	3.8	3.8
Raven's test	0-17	6.6	8.8	10.1	11.4	7.8	9.8	12.6	14.2	13.0
Total cognition score	0-175	82.3	104.9	110.7	121.8	94.2	104.9	123.8	134.5	126.1

LASI-DAD=the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia Study, HRS-HCAP=the Health and Retirement Study Harmonized Cognitive Assessment Protocol Project; MMSE=Mini-mental state examination; CSID= community screening instrument for dementia

*The upper limit is set at maximum number of correct answers provided by respondents.

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Table 3. Comparison of the relationship between biological and sociodemographic characteristics and total cognitive function scores between LASI-DAD (N=1,865) and HRS-HCAP (N=2,111)

	LASI-DAD						HRS-HCAP					
	Model 1 (Biomarkers)		Model 2 (Biomarkers + age + sex)		Model 3 (Biomarkers + age + sex + education, wealth)		Model 1 (Biomarkers)		Model 2 (Biomarkers + age + sex)		Model 3 (Biomarkers + age + sex + education, wealth)	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Cardiovascular characteristics												
Hypertension (systolic blood pressure≥140 mmHg or diastolic blood pressure≥90 mmHg)	-0.1 (1.0)	0.905	0.1 (1.0)	0.926	0.2 (0.9)	0.842	-4.7 (1.0)	<.0001	-3.5 (1.0)	0.0005	-2.1 (0.9)	0.0201
Pulse	-0.2 (0.0)	<0.001	-0.2 (0.0)	<0.001	-0.1 (0.0)	0.007	-0.0 (0.0)	0.4446	-0.1 (0.0)	0.1521	-0.0 (0.0)	0.8939
Homocysteine	-0.1 (0.0)	0.048	-0.1 (0.0)	0.012	-0.1 (0.0)	0.019	-0.6 (0.1)	<.0001	-0.5 (0.1)	<.0001	-0.3 (0.1)	0.0012
proBNP (log)	-3.3 (0.5)	<0.001	-1.9 (0.5)	<0.001	-1.4 (0.4)	0.002	-2.8 (0.4)	<.0001	-1.6 (0.4)	<.0001	-1.4 (0.4)	0.0001
Metabolic characteristics												
Body mass index (reference: 18.5-24.9 kg/m^2)												
<18.5 kg/m^2	-9.3 (1.4)	<0.001	-9.5 (1.4)	<0.001	-6.7 (1.2)	<0.001	-8.0 (5.6)	0.1525	-8.7 (5.4)	0.1059	-7.0 (4.9)	0.1477
25.0-29.9 kg/m^2	5.6 (1.3)	<0.001	6.1 (1.3)	<0.001	2.9 (1.2)	0.013	-0.3 (1.3)	0.8061	-0.4 (1.3)	0.7297	-0.1 (1.1)	0.9498
≥30.0 kg/m^2	8.4 (2.0)	<0.001	9.1 (1.9)	<0.001	4.9 (1.7)	0.004	4.0 (1.4)	0.0031	2.8 (1.3)	0.0326	2.8 (1.2)	0.0198
Glycosylated hemoglobin	1.5 (0.3)	<0.001	1.3 (0.3)	<0.001	0.6 (0.3)	0.033	-2.4 (0.5)	<.0001	-2.4 (0.5)	<.0001	-1.0 (0.5)	0.0318
HDL-cholesterol	-0.1 (0.1)	0.068	-0.1 (0.1)	0.282	-0.1 (0.0)	0.139	0.1 (0.0)	0.0233	0.0 (0.0)	0.4689	-0.0 (0.0)	0.0649
Lipoprotein (a)	-0.0 (0.0)	0.669	-0.0 (0.0)	0.707	0.0 (0.0)	0.842	--	--	--	--	--	--
Inflammation characteristics												
C-reactive protein (log)	-0.4 (0.4)	0.336	-0.4 (0.4)	0.379	0.0 (0.4)	0.921	0.8 (0.5)	0.1059	0.4 (0.5)	0.4562	0.4 (0.4)	0.3657
White blood cell count (log)	-0.9 (1.8)	0.628	-1.0 (1.8)	0.563	-0.1 (1.6)	0.977	0.4 (1.7)	0.8285	0.5 (1.6)	0.7512	0.9 (1.5)	0.5584
Albumin	9.6 (1.7)	<0.001	7.4 (1.7)	<0.001	4.4 (1.5)	0.003	5.7 (1.6)	0.0004	4.9 (1.6)	0.0020	2.9 (1.4)	0.0429
Uric acid	2.1 (0.4)	<0.001	1.6 (0.4)	<0.001	0.8 (0.4)	0.028	--	--	--	--	--	--
Age (reference: 65-69 year- old)												
60-64 year-old			3.3 (1.3)	0.011	2.3 (1.1)	0.041			--	--	--	--
70-74 year-old			-4.4 (1.4)	0.002	-4.6 (1.3)	<0.001			-3.3 (1.3)	0.0109	-3.2 (1.2)	0.0060
≥ 75 year-old			-10.4 (1.4)	<0.001	-11.4 (1.3)	<0.001			-11.7 (1.1)	<.0001	-11.2 (1.0)	<.0001
Sex (reference: male)												
Female			-6.4 (1.1)	<0.001	0.1 (1.0)	0.926			3.9 (1.0)	<.0001	6.5 (0.9)	<.0001
Education (reference: 1-11 years for LASI-DAD and 0-11 years for HRS-HCAP)												
0 year (LASI)					-19.3 (1.0)	<0.001					--	--
12 years					4.5 (2.7)	0.093					13.0 (1.2)	<.0001
13+ years					13.2 (2.0)	<0.001					20.1 (1.2)	<.0001
Household Wealth (reference: 3rd Quintile)												

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1st Quintile					-0.4 (1.4)	0.771					-6.4 (1.3)	<.0001
2nd Quintile					-2.5 (1.4)	0.075					-1.5 (1.3)	0.2514
4th Quintile					2.1 (1.3)	0.108					1.4 (1.3)	0.2804
5th Quintile					1.9 (1.4)	0.170					4.5 (1.3)	0.0005
R-square	0.18		0.23		0.41		0.10		0.16		0.32	

LASI-DAD=the Longitudinal Aging Study in India – Diagnostic Assessment of Dementia Study, HRS-HCAP= is the Health and Retirement Study Harmonized Cognitive Assessment Protocol Project, proBNP=pro-B-type-natriuretic peptide

Data are presented as coefficients (standard errors)

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