HARMONIZED DIAGNOSTIC ASSESSMENT OF DEMENTIA FOR THE LONGITUDINAL AGING STUDY IN INDIA

LASI-DAD Wave 1

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Background

The Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI-DAD) is the first nationally representative study of dementia in India.

The LASI-DAD aims to:

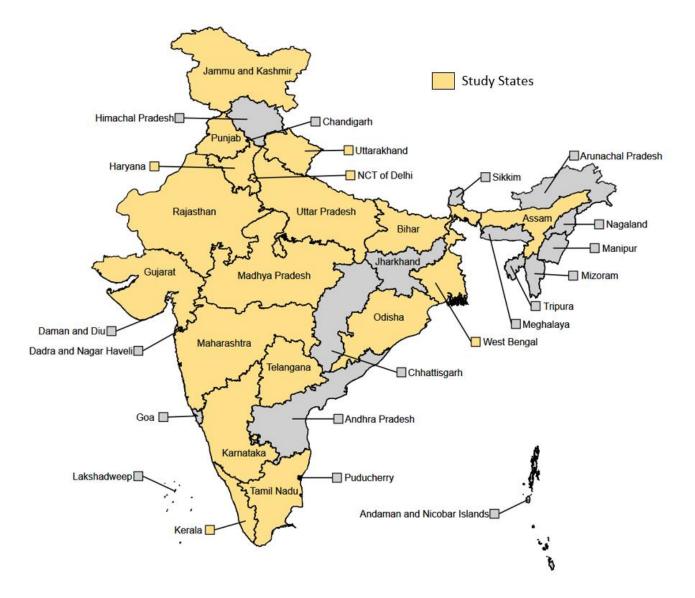
- Collect high-quality data on late-life cognition and dementia
- Obtain clinical consensus diagnosis
- Estimate the prevalence and incidence of dementia and mild cognitive impairment (MCI)
- Investigate the determinants of late-life cognition, dementia, and MCI
- Study the impact of dementia, cognitive impairment, and MCI on families and society
- Disseminate anonymized data to the larger research community

LASI-DAD administered a rich battery of neuropsychological tests to adults aged 60 or older and interviewed their closest family member or caregiver. It drew its sample from a largescale, nationally representative survey, the Longitudinal Aging Study in India (LASI). This has ensured the representation of the population at the national level and availability of rich background information. LASI is a nationally representative survey on the health, economic, and social well-being of the Indian population aged 45 and older. Its large sample of 73,000+ adults represents not only the country as a whole, but also each state.

The LASI-DAD study has adopted the Health and Retirement Study's (HRS) Harmonized Cognitive Assessment Protocol (HCAP) to enable cross-country analysis, as well as additional cognitive tests drawn from 10/66 and other studies in India.¹ LASI-DAD also collected rich data on risk factors through geriatric assessments (e.g. anthropometry, blood pressure measurements, hearing tests, and venous blood assays), as well as nutritional and environmental assessments (exposure to air pollution and neighborhood conditions). For a subsample, brain imaging data were collected using the Alzheimer's Disease Neuroimaging Initiative (ADNI)-3 protocol. Whole genome sequencing was also completed to better define the mutational spectrum underlying dementia risk.

Study Sample

The Harmonized LASI-DAD drew a sub-sample of LASI respondents aged 60 and older (N=4,096) in three phases from 2017 to 2020, on average seven months after the main LASI interview. In collaboration with the Regional Geriatric Centers, National Institute of Mental Health and Neurosciences, Bengaluru, and other medical schools, we interviewed respondents at their homes from both rural and urban areas in 18 states and union territories across the country, representing the country as a whole.



When selecting the study sample, we examined their cognitive test performance during the baseline LASI study and the proxy interviews for those who did not participate in the cognitive tests. Through these performance reviews, we identified those who were at high risk of cognitive impairment. We then oversampled those at high risk, while also recruiting those at low and very low risk.

Study Protocol

Respondent Interview

In order to measure the cognitive ability of the older Indian population, the project team carefully evaluated the HCAP protocol and modified it to suit the local context. For example, the Mini Mental State Exam (MMSE) developed by Folstein, Folstein, and McHugh (1975)² was replaced by the Hindi Version of the MMSE (HMSE) developed by Ganguli et al. (1995).³

We further considered other test batteries developed by the National Institute of Mental Health and Neurosciences, (NIMHANS) Bengaluru, India, and consulted with other experts in the field, including geriatricians, community medicine experts, psychiatrics, cognitive psychologists, and advisory board members. All tests were validated in India.

Wave 1 Cognitive Tests

Neurocognitive testing was conducted to measure different **domains of cognition** including:

- Memory
- Executive Functioning
- Processing Speed
- Language
- Constructional Praxis

The instrument was translated into **12** languages:

Hindi	Assamese			U	rdu			
Kanna	da Tamil			0	Dd	iya		
Malayalam			Punj	ak	oi	Tel	ugi	u
Gujara	ti	Marathi			В	eng	ali	

1. <mark>Hindi</mark> Mental State Exam	11. Logical Memory (Recognition)
2. HRS TICS	12. Retrieval Fluency
3. Word Recall (Learning)	13. Constructional Praxis (Recall)
4. Digit Span Forward & Backward	14. Backward Count*
5. Symbol Cancellation	15. Executive Function**
6. Word Recall (Delayed)	16. Judgement & Problem Solving**
7. Word List (Recognition)	17. Serial 7's
8. Logical Memory	18. CSI-D
9. Constructional Praxis	19. Raven's
10. Logical Memory (Delayed)	20. Go-No-Go Task

*Phase 1 only

**Phase 2 & 3 only

Red font indicates modification from the HCAP protocol.

Informant Report

The informant is someone who knows the respondent well, interacts with them frequently, and therefore knows their ability to complete daily functions and can report on them. Informants are most likely to be spouses, partners, children, or caregivers. Occasionally, they may be other relatives, friends, or neighbors.



DEMOGRAPHICS

Informant's demographic characteristics and relationship to the respondent.

JORM IQCODE

Asks about changes they observed about the respondent's cognitive abilities and memories compared to 10 years ago.

BLESSED SCALE PART 2

Asks questions about the respondent's ability to take care of himself/herself without assistance from anyone or with some level of assistance.

ACTIVITIES

Asks about activities the respondent is doing, the frequency with which they are doing these activities, and whether they are doing them alone or with someone else.

AFFECT SECTION

Asks about the feelings the respondent experienced during his/her day while doing various activities.

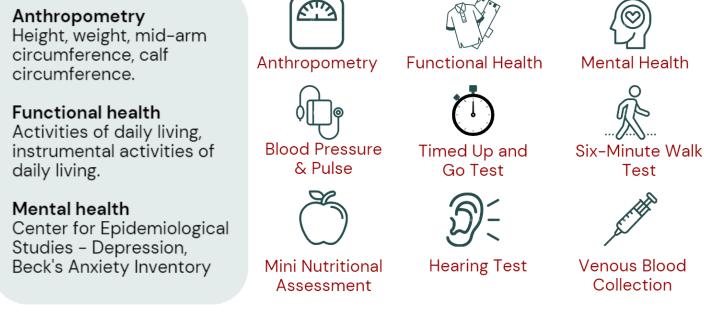
CSI-D

Asks about the level of decline the respondent experienced while doing various daily activities in the past few years.

BLESSED SCALE PART 1

Asks about the respondent's loss of ability

Geriatric Assessment



Metropolis, Inc. - Industry Partner

Pathology laboratory accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL) in India

Wide range of network laboratories at all study sites

Ensures processing of venous blood to serum and plasma within 2 hours of its receipt

Collects a total of **17 mL** of venous blood from respondents by trained phlebotomists

Venous Blood Assays were selected based on the following principles:

1. Potential **risk factors** for dementia

2. Assay **feasibility** in India

3. Harmonization with other studies within the Health and Retirement Study (HRS) family

Whole blood-based assays

Complete blood cell counts (CBC)

Glycosylated hemoglobin (HbA1c)

Serum based assays

Glucose	Pro-B-type natriuretic peptide (ProBNP)	Homocysteine	
Lipid panel		Vitamin B12	
Lipoprotein (a)	Metabolic panel, including renal and liver functions	Folic acid	
High-sensitivity C-		25-OH-Vitamin D	
reactive protein (hsCRP)	Cystatin C	Thyroid-stimulating hormone (TSH)	

Brain Imaging

Through the use of magnetic resonance imaging (MRI), we aim to better understand cognitive aging and impairment. We have obtained brain images from a subsample (N=137) of LASI-DAD respondents.

MRI Protocol

Each individual going through MRI testing received numerous structural and functional MRI scans, according to the Laboratory of Neuro Imaging (LONI) Alzheimer's Disease Neuroimaging Initiative (ADNI) 3 protocol.

Scan sequences such as T1, T2, DTI, and FLAIR allow us to better comprehend the presentation and physical development of MCI and dementia, while resting state fMRI can be used to help decipher functional differences that develop as these individuals begin to lose cognitive functionality.

Structural and functional images were collected and will be compared with other areas of our study, including:

- Genetics
- Cognitive and behavioral testing
- Blood-based biomarkers

Goals

- 1) Obtain a rich dataset that details the initiation and progression of mild cognitive impairment and dementia.
- Better correlate the presentation and progression of the disease with other areas of the project to give us a better understanding as to how structural and functional brain data align with behavioral and cognitive deficits.

Data Availability

Neuroimaging data are available through the Image and Data Archive (IDA) online database hosted by the Laboratory of Neuro Imaging (LONI) at the University of Southern California https://ida.loni.usc.edu/. All available MRI modalities are available from download in DICOM or NIFTI formats. Currently, the LASI-DAD neuroimaging data are hosted under a restricted-sharing policy: permission can be requested by submitting a data use application.

Genomics

Genomics has been one of the key initiatives of the LASI-DAD study. As the first step under this initiative, we conducted the **whole genome sequencing (WGS)** validation study on a small number of samples. This study demonstrated the feasibility of collecting blood samples in the field that could be shipped effectively to our industry partner and from which we could obtain high-quality genotyping measures. We then genotyped 960 geographically dispersed LASI-DAD respondents, using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip. It contains over 640,000 genetic markers including highly optimized multi-ethnic genome-wide content, curated clinical research variants, and QC markers.

Polygenic Risk Scores

Since health outcomes and traits are often highly polygenic, reflecting the aggregate effect of many different genes, the use of single variants or candidate genes may not capture the dynamic nature of more complex phenotypes. In light of this, polygenic risk scores (PRS) were constructed for Alzheimer's Disease and general cognitive functioning for consenting LASI-DAD respondents who provided whole blood DNA in 2018. These scores will help harmonize research across studies conducted by LASI-DAD data users.

Whole Genome Sequencing

Currently, we are in the process of preparing whole genome sequencing and population genetic analyses on 2,700 participants from 18 states and union territories of India.

Data Availability	Dataset	Decription	Report
The following datasets are available for download at	GWAS Data	Original genotype data from the GSA array, containing 1008 scans derived from 993 unique subjects (including 960 LASI-DAD subjects and 33 control subjects from the 1000 Genomes Project)	Quality Control Report for the 2019 Genome-Wide Genotype Data ⁴
NIAGADS:	1000 G Imputed Data	Genotype data imputed to the 1000G reference panel (phase 3 v5)	LASI-DAD Imputation Report for the 2019 Genome-Wide Genotype Data – 1000 Genomes Project Reference Panel ⁵
	TopMed Imputed Data	Genotype data imputed to the TOPMed reference panel (r2)	LASI-DAD Imputation Report for the 2019 Genome-Wide Genotype Data – Trans-Omics for Precision Medicine (TOPMED) Reference Panel ⁶

Findings to Date

Clinical Consensus Diagnosis

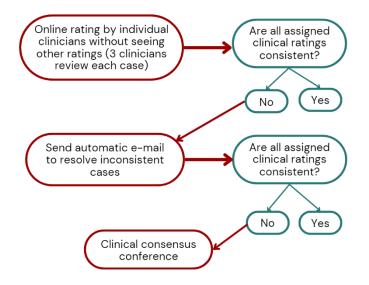
Lee et al. (2020) aimed to introduce a cost-effective expert clinical diagnosis of dementia into population-based research using an online platform and to demonstrate its validity against in-person clinical assessment and diagnosis.

The online platform provides standardized data necessary for clinicians to rate participants on the **Clinical Dementia Rating** (CDR®). Multiple clinicians independently rate each participant on each CDR domain using standardized data and expert clinical judgement.

Summary Score

The overall summary score is calculated by an algorithm. When there are discrepancies among clinician ratings, clinicians discuss the case through a virtual consensus and arrive at a consensus overall rating. For Wave 1 of LASI-DAD, clinical consensus ratings were obtained for cases in Phases 2 and 3 only. The **CDR**[®] is comprised of six cognitive and functional domains (Morris, 1993)⁷:

- Memory
- Orientation
- Judgement and Problem Solving
- Community Affairs
- Home and Hobbies
- Personal Care



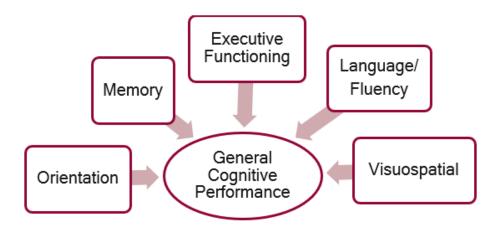
Main Findings

To compare the in-person and online consensus diagnosis, we calculated the k interrater agreement measure. A k value of 0.75 is generally considered excellent, and values between 0.40 and 0.75 are considered fair to good agreement.⁸ Overall, the online clinical consensus diagnosis based on standardized interview data provides consistent clinical diagnosis with in-person clinical assessment and consensus diagnosis (k coefficient = 0.76). A web-based clinical consensus platform built on the Harmonized LASI-DAD interview data is a cost-effective way to obtain reliable expert clinical judgements. A similar approach could be used for other epidemiological studies of dementia.

Measurement and Structure of Cognition

Cognitive tests administered in LASI-DAD can be empirically organized into domains in the same way as in the US and other Western samples. Gross et al. (2020) derived **summary factor scores** representing memory, executive function/attention/speed, language/fluency, visuospatial and orientation.

Furthermore, cognitive tests were invariant by language. That is, findings suggest that the translation of neuropsychological tests into 12 different languages was successful and did not significantly impact the psychometric properties of the tests.



Cross-country calibration



Data for **3,496 HRS HCAP** (≥65 years) and **3,152 LASI-DAD** (≥60 years) participants were **statistically harmonized** for episodic memory and language performance using confirmatory factor analysis (CFA) methods.

Vonk et al. (2022) successfully co-calibrated cognitive domains of memory and language ability between the US and India. This has huge implications for the direct comparisons of cognition and will facilitate cross-national research.

Future Direction



Ongoing analyses by Gross et al. show that we can derive a measure of dementia in India using widely recognized **DSM-5 criteria**.

The prevalence of major and mild neurocognitive disorder in India is **7.0%** and **14.6%** respectively. These dementia classifications follow expected demographic patterns and broadly concur with clinician-rated Clinical Dementia Ratings[®].

Hypertension and Cognitive Health

Farron et al. (2020) assessed the prevalence of diagnosed and undiagnosed hypertension and their relationship to cognitive function in older adults in India.

Cognitive Function

Cognitive function was assessed using a **summary cognitive score** composed of 18 cognition measures administered in LASI-DAD (range O-360), with a higher score indicating better cognitive function.

Hypertension Classification

Hypertension	Self-report of physician diagnosis or measured blood pressure (BP) of 140/90 mmHG or higher
Undiagnosed Hypertension	Hypertensive BP measurements, but no physician diagnosis
Controlled Hypertension	BP lower than 140/90 mmHg among those with a physician diagnosis
Total Hypertension	Includes both diagnosed and undiagnosed hypertension

Relationship between Cognition & Hypertension

Neither diagnosed nor undiagnosed hypertension was related to cognitive function in fully adjusted models.

Characteristics independently associated with worse cognitive test performance

older age	history of stroke			less educat	ion
female sex	v	vidowed	low c	onsumption	
underweight schedule caste or			north or ce regions	ntral	

Further research is needed to assess hypertension as a possible mediator between socioeconomic disadvantage and worse cognitive function.

Cognitive Function and Cardiometabolic-Inflammatory Risk Factors

Hu et al. (2020) investigated the association between cardiometabolic-inflammatory risk factors and cognition among respondents in India (using LASI-DAD) and in the United States (using HRS-HCAP). The distribution of both total cognition scores and of cardiometabolic risk factors differed significantly between India and the United States.

CARDIOVASCULAR RISK

Indicated by systolic and diastolic blood pressure, pulse rate, pro-B-type natriuretic peptide (proBNP), and homocysteine

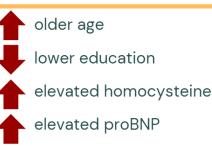
METABOLIC RISK

Measured by body mass index, glycosylated hemoglobin (HbA1c), highdensity lipoprotein cholesterol, and lipoprotein (a) (only in India)

INFLAMATORY RISK

Indicated by white blood cell count, C-reactive protein, albumin, and uric acid (only in India)

In both countries, **lower cognition** was associated with:



lower albumin levels

The associations between **HbA1c levels** and **cognitive measures** were statistically significant in both countries, but in the **opposite direction**



5 coefficient 5 in India

(p<0.001) for a one percentage increase in absolute HbA1c value

2.4 coefficient in USA

(p<0.001) for a one percentage increase in absolute HbA1c value

Relationship between select cardio-metabolic biomarkers and total cognitive scores

Biomarkers *	LASI-DAD	HRS-HCAP
Pro-BNP	Inverse	Inverse
Homocysteine	Inverse	Inverse
Body mass	Inverse	Inverse (only in
index (BMI)		BMI<18.5 kg/m ²)
HbA1c	Positive	Inverse
Albumin	Positive	Positive
Uric acid	Positive	Not measured

*All variables are statistically significant after adjusting for age, sex, and education

Cardiometabolicinflammatory biomarkers are associated with cognitive functional levels in each country, but the *relationships may vary across countries*.

Further research is needed to tease out this biological relationship.

Sex Differences in Cognitive Health

Angrisani et al. (2020) investigated sex differences in late-life cognitive function and early-life determinants among older Indian adults using the LASI-DAD study. Given the low levels of literacy and numeracy among older Indian adults, two composite cognitive scores were considered as outcome variables: Score I & Score II.

Score I

Score II

Sum of the scores on the cognitive tasks that <u>do not</u> require literacy or numeracy

Sum of the scores on the cognitive tasks that <u>do</u> require literacy or numeracy

Main Findings

Across most cognitive domains, **women perform significantly worse** than men: -0.4 standard deviations for score I and -0.8 standard deviations for score II.

Early-life SES, health, and education explain **90%** of the gap for score I and **55%** for score II. Results are similar across hospital-based and home testing.

Percent of the Female Gap Explained by Education 60% 40%

are the main determinant of the observed female gap in late-life cognition.

Sex differences in education

Percent of the Female Gap Explained by **Childhood Nutrition**

for Score II

30% for Score I for Score I

for Score I

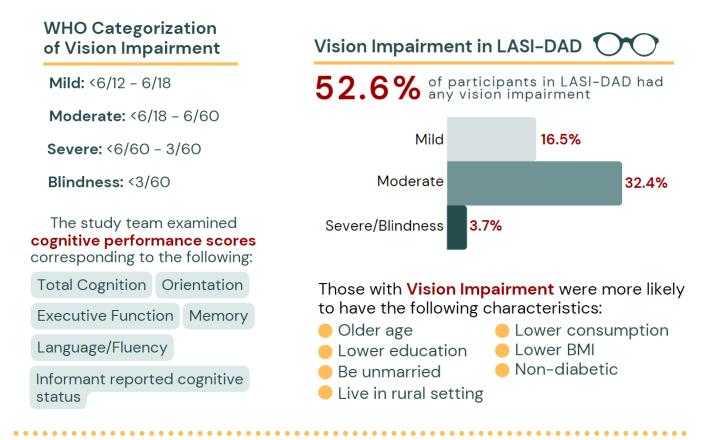
proxied by knee height, is the second largest contributor to the existing disparities in late-life cognitive performance.

Childhood nutrition, as

Findings suggest the disadvantage in cognitive performance of women can be largely attributed to early-life differences in nutrition, education, and other factors. These disparities highlight the need for public policy aiming at reducing gender disparities in early life.

Cognition and Visual Function

Ehrlich et al. (2021) examined the association of **vision impairment (VI)** with overall and domain specific cognitive function in LASI-DAD. Vision was measured in the LASI survey using a Tumbling E chart displayed on a laptop situated at 3 meters distance from the participant. Each eye was tested separately using the participant's habitual refractive correction (e.g., eyeglasses, contact lenses) for distance vision, if available. Categorization of VI was based on World Health Organization definitions using measured visual acuity in the better-seeing eye.



Main Findings

Vision impairment was independently associated with **lower cognitive scores** across all domains, even after adjustment for known dementia risk factors.

In fully adjusted models of total cognition (mean score: 130.7), mild, moderate, and severe VI/blindness were associated with a significant change of -3.5 (95%CI: -6.3, -0.6), -8.2 (95%CI -10.5, -5.6), and -16.8 (95%CI -22.3, -11.3) units, respectively.

This study illustrates that **vision impairment is cross-sectionally associated with lower cognitive performance**, largely in a dose-response pattern, across various cognitive domains in the Indian population. These findings are important for informing future longitudinal and interventional studies.

Genetic Risk Factors

The role of **genetic factors for Alzheimer's Disease** and cognitive aging was examined in India by Smith et al. (2020). More specifically, Smith et al. (2020) investigated the allelic distribution and cognitive associations of 56 known AD risk **single-nucleotide polymorphisms (SNPs)** identified from three European ancestry (EA) genome-wide association studies (EA-GWASs) in LASI-DAD. Single SNP and genetic risk score (GRS) associations with measures of episodic memory were assessed.

A total of 906 individuals had genotype data, covariate data (sex, age, and education), and at least one cognitive measurement.

Genotyping and Imputation

The Illumina Infinium Global Screening Array-24 (GSA) BeadChip, version 2.0 (Illumina) was used to genotype 960 LASI-DAD participants.

Genotypes were imputed to the 1000G Project worldwide reference panel (phase 3, version 5). Cognitive Measures

- •Total learning score (0-30 words)
- •Delayed word recall score (0-10 words)

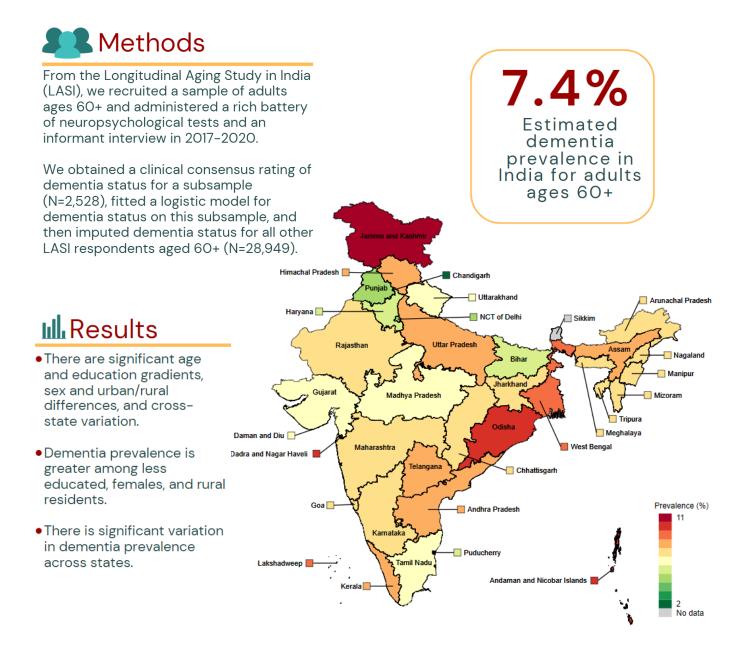
Main Findings

Although only a few SNPs were significantly associated with memory scores (P < .05), effect estimates from the EA-GWAS and LASI-DAD were moderately correlated (0.35-0.88) in the expected direction. GRSs were also associated with memory scores, although the percentage variation explained was small (0.1%-0.6%).

Discrepancies in allele frequencies and cognitive association results suggest that genetic factors found predominantly through EA-GWASs may play a limited role in South Asians. However, the extent of differences in the genetic architecture of AD and cognition in EA and South Asians remains uncertain. There is also a critical need to perform a more comprehensive assessment of the mutational spectrum of South Asia to identify novel genetic variants associated with AD and cognition in this population.

Prevalence of Dementia in India

Lee et al. (2023) estimated the **dementia prevalence** in India using the nationally representative Longitudinal Aging Study in India (LASI).



An estimated **8.8 million** Indians older than 60 years have dementia. The burden of dementia cases is unevenly distributed across states and sub populations and may therefore require different levels of local planning and support.

Real Time Insights – COVID-19 India

RTI COVID-19 India: Study Design

The Real Time Insights (RTI) COVID-India Study is the first and only nationally representative and publicly available dataset on the health and socioeconomic effects of COVID-19 in India. We have a unique opportunity to track the effects of the crisis on a vulnerable elderly population in one of the world's largest emerging economies. Such tracking is particularly important in India, where access to health care is limited and the economy is largely dependent on the informal sector, likely resulting in official reports underestimating the health and socioeconomic effects of the pandemic.

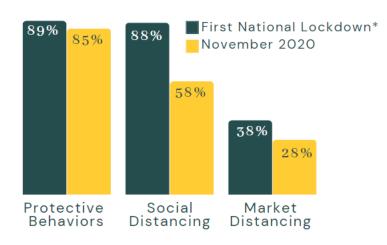
The questionnaire was designed to allow for the investigation of several research questions by including various modules while keeping the survey administration time about 15-20 minutes. Therefore, some modules may be asked every round, only one round, or rotated through multiple rounds. Economic and healthcare questions were asked at the household level, while other questions were asked at the individual level. As the pandemic progressed, questions were added to better capture the impact of the COVID-19 pandemic on Indian households.

The sample for the RTI-COVID India Phone Survey was developed through leveraging the LASI-DAD study. We invited LASI-DAD household members, aged 18 years and older, for a phone interview and followed them throughout the pandemic, starting in May 2020. With this survey, we aimed to measure individual respondent's perceptions, attitudes, and behavioral reactions related to the pandemic. We completed a total of 9 rounds of data collection.

Survey Wave	Start Date	End Date	Households Interviewed	Individuals Interviewed	DAD Respondents Interviewed
Wave 1	May 5, 2020	June 25, 2020	1521	2836	839
Wave 2	July 7, 2020	August 26, 2020	1224	2343	793
Wave 3	September 7, 2020	October 23, 2020	1257	2261	720
Wave 4	November 9, 2020	January 4, 2021	1260	2346	761
Wave 5	January 18, 2021	March 1, 2021	1264	2410	811
Wave 6	March 15, 2021	May 5, 2021	1231	2379	799
Wave 7	July 4, 2021	September 7, 2021	1215	2316	748
Wave 8	September 24, 2021	January 5, 2022	1171	2248	727
Wave 9	March 13, 2022	May 11, 2022	1043	1969	584

RTI COVID-19 India: Knowledge, Behaviors, and Symptoms

Schaner et al. (2022) assessed adherence to COVID-19 protective behaviors in India from May to December 2020. Findings suggest a decline in protective behaviors related to social distancing over the observation period. They argue that the changes in behavior could reflect 'COVID-19 fatigue', where adherence to social distancing becomes more difficult over time irrespective of the surrounding disease environment.



Projective Behaviors

Handwashing and wearing a face mask

Social Distancing

Did not visit other households or have visitors over to one's own household

Market Distancing

Did not gather with 10 or more people, have close contact with non-household members, travel for work, or go shopping

*The first national lockdown in India occurred in May 2020

Sources of Information (Jan - Feb 2021)Image: Sources of Information (Jan - Feb

Symptoms Knowledge (Nov - Dec 2020)

High awareness of **fever** and **cough** as symptoms of COVID-19 infection. Low awareness of **difficulty breathing** and l**oss of taste or smell** as symptoms of COVID-19 infection.

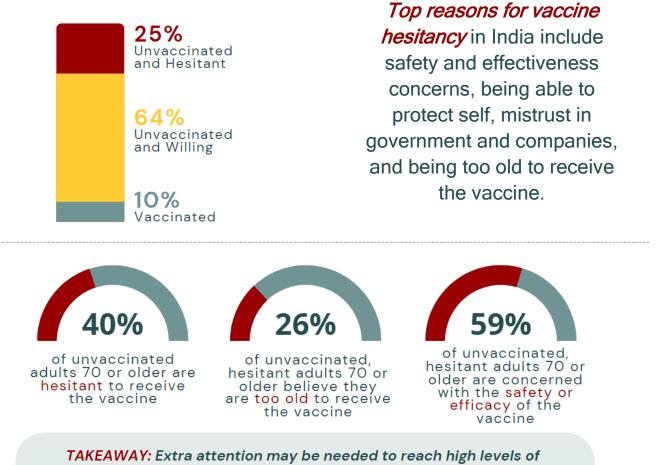


RTI COVID-19 India: Vaccine Hesitancy

After the initial rollout of the COVID-19 vaccine, data were collected in March-May 2021 (round 6) to assess whether respondents had received the vaccine, their willingness to receive the vaccine, and reasons why they may be hesitant to get vaccinated. The following data demonstrate the vaccine hesitancy seen throughout the study population during this time. Individuals are considered to be vaccine hesitant if they are unwilling or unsure about getting vaccinated.



Many are vaccine hesitant



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lasi-dad.org

vaccination among one of the highest at-risk groups - older generations.

LASI-DAD Partner Hospitals

Institution	Collaborator(s)
All India Institute of Medical Sciences, Bhubaneshwar	RR Mohanty
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Madras Medical College, Chennai	GS Shanthi
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LASI-DAD Publications

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