Diagnostic Assessment Of Dementia for LASI

POLYGENIC RISK SCORES FROM 2019 GENOME-WIDE GENOTYPE DATA (RELEASE 1)

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The Longitudinal Aging Study of India – Diagnostic Assessment of Dementia

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I. Summary and recommendations

This report describes the construction of polygenic risk scores (PRSs) for Alzheimer's Disease and general cognitive function for LASI-DAD respondents who provided whole blood DNA in 2018. These scores will help harmonize research across studies among LASI-DAD data users. PRSs for each phenotype are based on a single, replicated genome-wide association study (GWAS). These scores will be updated as sufficiently large GWAS are published for new phenotypes or as new meta-analyses for existing phenotypes emerge. This document describes the general method of PRS construction with details on each phenotype included as appendices.

a. Rationale

Health outcomes and traits are often highly polygenic, reflecting the aggregate effect of many different genes so the use of single genetic variants or candidate genes may not capture the dynamic nature of more complex phenotypes. A PRS aggregates individual loci across the genome and weights them by effect sizes derived from a GWAS as an estimate of the strength of their association to produce a single quantitative measure of genetic risk and to increase power in genetic analysis.

b. Project Overview

The Longitudinal Aging Study of India (LASI) is a groundbreaking nationally-representative, longitudinal survey to examine aging and retirement among India's population aged 45 years and up. It follows a nationally representative sample of over 72,000 Indians aged 45 years and older over time. LASI is modeled after the Health and Retirement Study (HRS) in the United States and is comparable to similar studies in Asia, including the China Health and Retirement Longitudinal Study (CHARLS), the Japanese Study of Aging and Retirement (JSTAR), and the Korean Longitudinal Study of Aging (KLoSA). In 2014, it launched the Diagnostic Assessment of Dementia for LASI (LASI–DAD) as an add-on study of late-life cognition and dementia, drawing a sub-sample of 4,096 LASI respondents aged 60 or older and administering in-depth cognitive tests and informant interviews. In 2018, 960 respondents from LASI-DAD who consented to the blood sample collection have been genotyped using the Illumina Infinium Global Screening Array.

c. LASI-DAD Study Design and Sample Selection

LASI is an ongoing cohort study of 72,000 community-residing older adults aged 45 and older and their spouses regardless of age, with an oversample of persons aged 65 and above.[1] The study design involves following all individuals who move into institutions, although that number is expected to be very small in India. Using the Census as the sampling frame, LASI is representative of both the nation as a whole and each state and union territory. Due to administrative and linguistic considerations, the fieldwork for the main LASI unfolded in three phases, and therefore the LASI-DAD fieldwork was also carried out in phases, recruiting most respondents about 6 – 7 months after the core LASI interview.

LASI-DAD is an in-depth study of late-life cognition and dementia. It draws a sub-sample of 4,000+ LASI respondents aged 60 and older and administers in-depth cognitive tests and informant interviews. The sample represents the population aged 60

and over (N=4,096), drawn from 18 states and union territories (see Figure 1 for the states and union territories where a sample was drawn and the local Co-I sites for fieldwork supervision). We drew the sample based on a two-stage stratified random sampling process: we first stratified the entire LASI sample based on risk of cognitive impairment and state of residence. Cognitive impairment risk was determined based on the performance on memory and non-memory tests, overall test performance, refusal or inability to participate in the cognitive testing, and proxy interview in the core LASI. We set the sample size for each state proportionally to that of the core LASI sample, which, in turn, is proportional to each state's population size, and randomly drew samples with an equal number of individuals at high and low risk of cognitive impairment. See Lee et al.[2] for further details of the sample.

LASI-DAD developed a project protocol to assess dementia and late-life cognition among community-residing older adults in India, that is harmonized with the Health and Retirement Study (HRS) and its sister studies. HRS developed the Harmonized Cognitive Assessment Protocol (HCAP) for the assessment of dementia and mild cognitive impairment (MCI) to be used in the U.S. and around the world to enable international research collaborations and provide valid cross-country comparisons. HCAP consists of cognitive tests and informant reports that include best-practice instruments for multiple cognitive domains. It was also designed for flexible statistical harmonization. Through multiple pretests, we carefully evaluated the HCAP in local Indian settings, making culturally appropriate modifications and adding cognitive tests that enable comparison with prior studies in India.

d. Administration Procedures

Our study protocol started with blood draws. Certified and trained phlebotomists from Metropolis laboratory, our industry partner for venous blood collection and assay, drew a total of 17 ml of venous blood sample in five tubes, four of which were processed within an hour, yielding whole blood (for Complete Blood Count and HbA1c assay), serum, plasma, and buffy coat. All specimens were shipped to the Metropolis laboratory in Delhi within approximately 24 hours via a cold chain (-20°C for plasma and 4°C for other specimens) where lab work was completed for 33 assays. Our genomics initiative partner, MedGenome, a global genomics company headquartered in California, but, importantly, with facilities spread across India, picked up the remaining tubes and shipped them directly to their laboratory based in Bangalore for DNA extraction.

II. LASI-DAD Genomic Data

The DNA samples were genotyped at MedGenome. A total of 1008 study subjects and controls were genotyped on the Illumina Infinium Global Screening Array-24 v2.0 BeadChip, which measures ~600,000 SNPs. All versions of the array are designed to Human Genome Build 37. The total 1008 scans derived from 993 unique subjects (including 960 LASI-DAD subjects and 33 1000G control subjects). Individuals with missing call rates > 2%, SNPs with call rates < 98%, HWE p-value < 0.0001, chromosomal anomalies, and kinship coefficient > 0.088 in the LASI-DAD were removed. Principal component (PC) analysis[3] was performed to identify population group outliers and to provide sample eigenvectors as covariates in the statistical model used for association testing to adjust for

possible population stratification. SNPs used for PC analysis were selected by linkage disequilibrium (LD) pruning from an initial pool consisting of all autosomal SNPs with a missing call rate < 5% and minor allele frequency (MAF) > 5%, and excluding any SNPs with a discordance between 1000G pedigree controls genotyped along with the study samples and those in the external 1000G (phase 3 version 5) data set. In addition, the 2q21 (LCT), HLA, 8p23, and 17q21.31 regions were excluded from the initial pool. The final sample set consisted of 932 unrelated study samples after quality control. For more information on the genotype data and quality control process see the LASI-DAD genotype data QC Report.

Imputation to the 1000G Genomes Project reference panel phase 3 version 5 (initial release on May 2013, haplotypes released Oct 2014) was performed by the University of Michigan using Minimac4 (http://genome.sph.umich.edu/wiki/Minimac4), with phasing performed using Eagle2.4. Overall, ~49 million SNPs were imputed from the original 533,348 SNPs that were genotyped and passed quality control. Masking of genotyped SNPs to assess the accuracy of imputation was performed to estimate the median concordance between actual and imputed genotypes (median concordance>0.91 for common variants), and additional quality control metrics indicate high quality imputation. Please refer to the LASI-DAD Imputation report using the 1000 Genomes Project Phase 3 reference panel for more details.

a. PRS Construction

To best capture the most significant SNPs from the published GWAS meta-analysis studies, we construct PRSs for genome-wide significant SNPs only ($P < 5 \times 10^{-8}$), noted as a "top SNPs" PRS. In addition, for some traits, we also generated PRSs for all independent SNPs with ($P < 1 \times 10^{-4}$) after clumping ($r^2 < 0.25$ within a 250 kb window) using the LD structure in South Asian ancestry from 1000 Genome Reference Panel, indicated as an "all SNPs" PRS. In either case, only SNPs with high imputation quality ($R^2 > 0.8$) in LASI-DAD were included.

Weighted sums were chosen to calculate the PRSs. Weights were defined by the odds ratio or beta estimate from the GWAS meta-analysis files corresponding to the phenotype of interest. If the beta value from the GWAS meta-analysis was negative (or the odds ratio (OR) < 1), the beta/OR measures were converted to positive values (OR >1) and the reference allele flipped to represent phenotype-increasing PRSs. PRSs are calculated using the following formula:

$$PRS_i = \Sigma W_j G_{ij} / 2J$$

where i is individual i (i=1 to N), j is SNP j (j=1 to J), W_j is the meta-analysis effect size for SNP j, G_{ij} is the genotype, or the number of reference alleles (zero, one, or two), for individual i at SNP j, and J is the total number of SNPs. The "all SNPs" PRSs were constructed using PRScie-2[4] and the "top SNPs" PRSs" were constructed in PLINK[5].

b. Sources for SNP weights

To incorporate externally valid SNP weights from replicated GWAS, we performed a search of the most recent literature to identify large GWAS meta-analysis studies related to the selected phenotype. SNP weights were downloaded from consortium webpages, requested from consortium authors, or obtained from published supplemental material. All base SNP files from GWAS meta-analyses were converted to NCBI build 37 annotation for compatibility with LASI-DAD SNP data.

c. Notes about the use of PRSs

PRSs are released for current LASI-DAD samples (N=932). However, it should be noted that the majority of GWAS used to inform the SNP weights come from GWAS on European ancestry groups and, as a result, PRSs for LASI-DAD samples from South Asian ancestry may not have the same predictive capacity[6,7].

Standardized versions of ancestry specific PCs 1-10 are included in the LASI-DAD PRS data release. **To protect identifiable information, PCs 1-5 and PCs 6-10 were scrambled**. To control for confounding from population stratification, or to account for any ancestry differences in genetic structures within populations that could bias estimates, ***we highly recommend that users perform analyses adjusted for PCs 1-10***. The PCs control for any genetic aspects of common ancestry that could be spuriously correlated with the PRS and the outcome of interest[3].

d. PRSs for Alzheimer's disease (AD)

The three "top SNP" PRSs for Alzheimer's disease (AD) were created using results from three large-scale GWAS meta-analyses: 1) a 2013 GWAS conducted by the International Genomics of Alzheimer's Project (IGAP)[8]; 2) a 2019 GWAS meta-analysis using samples from the International Genomics of Alzheimer's Project (IGAP)[9]; 3) a 2019 GWAS meta-analysis using cohorts from the Alzheimer's disease working group of Psychiatric Genomics Consortium (PGC-ALZ), the International Genomics of Alzheimer's Project (IGAP), the Alzheimer's Disease Sequencing Project (ADSP), and UKBiobank[10].

Please note that all three GWAS are conducted using individuals of European ancestry. *See Section C: "Notes about the use of PRSs" for more information on the use of PRSs in other ancestry groups.*

Three PRSs were constructed using all the identified genome-wide significant AD risk SNPs from each AD GWAS separately. Note that there is overlap in some of the SNPs that comprise these three scores. Since key SNPs in the *APOE* gene have a strong association with AD, we excluded variants in the *APOE* region from the three PRSs, but also released rs7412 and rs429358 (the two SNPs that define the *APOE* ε2, ε3, and ε4 alleles) as independent units. The effect size of each SNP was calculated as the $\ln(OR)$ reported in the corresponding GWAS. The predictive performance of the three "top SNPs" PRSs on memory scores in LASI-DAD have been reported in Smith et al[7].

1) A GWAS meta-analysis[8] of AD was conducted across 20 independent studies using data from four international consortia: Alzheimer's Disease Genetic Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the European Alzheimer's Disease Initiative (EADI), and the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) Consortium. The stage 1 meta-analysis included 54,162 participants (N_{cases} =17,008 and $N_{controls}$ =37,154) of European decent with a total of 7,055,881 SNPs imputed to 1000 Genomes (2010 release). The stage 2 replication sample included 19,884 participants of European ancestry (N_{cases} =8,572 and $N_{controls}$ =11,312) with a total of 11,632

genotyped SNPs. In addition to the *APOE* locus (encoding apolipoprotein E), the two-stage combined discovery and replication GWAS identified 19 SNPs with genome-wide significant associations with AD. Please refer to Table S1 in Smith et al.[7] for the list of 19 SNPs. Adjustment covariates within each contributing cohort included age, sex, and genetic principal components.

The released PRSs in LASI-DAD contains all 19 SNPs. The descriptive statistics and the distribution of the PRS are presented in Table 1 and Figure 1.The posted PRS have been standardized to a standard normal curve (mean=0, standard deviation = 1).

2) Another GWAS meta-analysis[9] was conducted by the same group in (1) by using a larger Stage 1 discovery sample of 63,926 participants from 46 datasets (N_{cases} = 21,982, $N_{controls}$= 41,944) of non-Hispanic Whites (NHW) with a total of 36,648,992 SNPs imputed to 1000 Genomes (phase 1 integrated release 3, March 2012). After quality control, 9,456,058 common variants and 2,024,574 rare variants were selected for analysis. Stage 1 meta-analysis was first followed by Stage 2, using the I-select chip previously developed in Lambert et al.[7] and finally Stage 3A (n = 11,666) or Stage 3B (n = 30,511) (for variants in regions not well captured in the I-select chip). The final sample was 35,274 clinical and autopsy-documented Alzheimer's disease cases and 59,163 controls. Meta-analysis of Stages 1 and 2 produced 24 genome-wide-significant associations with AD. Please refer to Table S1 in Smith et al.[7] for the list of 24 SNPs.

   The released PRS in LASI-DAD contains 20 SNPs that overlap between the LASI-DAD genetic data and the genome-wide significant SNPs from the GWAS meta-analysis. The descriptive statistics and the distribution of the PRS are presented in Table 1 and Figure 1.The posted PRS have been standardized to a standard normal curve (mean=0, standard deviation = 1).

3) A large genome-wide association study of clinically diagnosed AD and AD-by-proxy was performed using a total sample of 455,258 participants (N_{cases} =71,880, $N_{controls}$ =383,378)[10]. Phase 1 involved a genome-wide meta-analysis for clinically diagnosed AD case-control status using cohorts collected by 3 independent consortia (Alzheimer's disease working group of the Psychiatric Genomics Consortium (PGC-ALZ), the International Genomics of Alzheimer's Project (IGAP), and the Alzheimer's Disease Sequencing Project (ADSP)), totaling 79,145 of European ancestry and 9,862,738 genetic variants passing quality control. In phase 2 they performed a GWAS of AD-by-proxy using 376,113 individuals of European ancestry from UKB. They defined proxy cases as individuals with one or two parents with AD (giving higher weight to cases with two parents). The proxy controls include individuals whose parents had no AD (giving higher weights to individuals with older parents as younger parents may still have a chance to develop AD). Given the high genetic overlap, in phase 3 they conducted a meta-analysis of the clinical AD GWASs and the AD-by-proxy GWAS. The meta-analysis in phase 3 identified 28 genome-wide significant loci associated with AD. Please refer to Table S1 in Smith et al.[7] for the list of 28 SNPs.

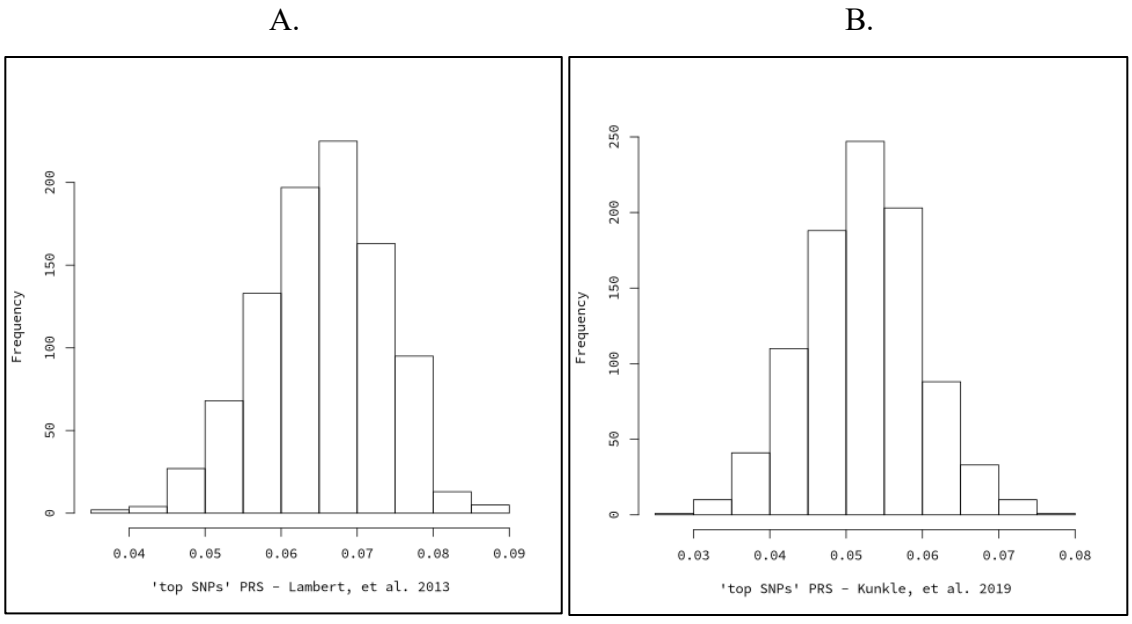
The released PRSs in LASI-DAD contain 19 SNPs that overlap between the LASI-DAD genetic data and the genome-wide significant SNPs from the GWAS meta-analysis. The descriptive statistics and the distribution of the PRS are presented in Table 1 and Figure 1. The posted PRS have been standardized to a standard normal curve (mean=0, standard deviation = 1).

Table 1. Descriptive statistics of polygenic risk scores (PRSs) for Alzheimer's disease

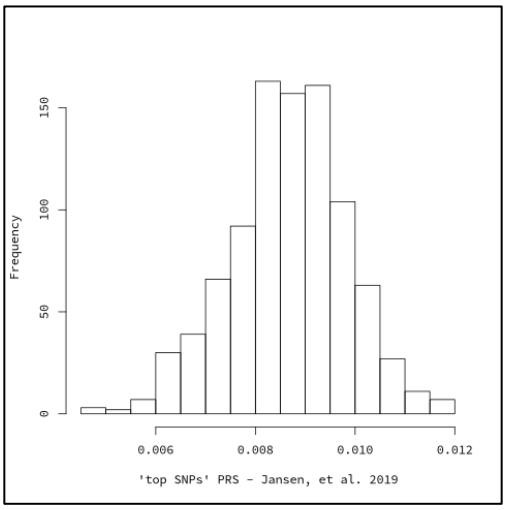
	Unstandardized PRS (original scale)					Standardized PRS				
Study	Min	Max	Median	Mean	SD	Min	Max	Median	Mean	SD
Lambert, et al. 2013[8]	0.0375	0.0889	0.0659	0.0654	0.0082	-3.4038	2.8821	0.0593	0.0000	1.0000
Kunkle, et al. 2019[9]	0.0297	0.0798	0.0523	0.0522	0.0075	-3.5223	2.7530	0.0170	0.0000	1.0000
Jansen, et al. 2019[10]	0.0046	0.0119	0.0087	0.0087	0.0012	-2.9886	3.6543	0.0065	0.0000	1.0000

The PRSs were constructed using the genome-wide significant SNPs reported from three independent genome-wide association studies (GWAS) of Alzheimer's disease (AD).

Figure 1. Histogram of the "top SNPs" polygenic risk scores (PRS) constructed using the genome-wide significant SNPs reported from genome-wide association studies (GWAS) of Alzheimer's disease (AD): (A) Lambert et al[8]; (B) Kunkle et al[9]; (C) Jansen et al[10].



C.



e. PRSs for General Cognitive Function

The PRSs for general cognition were created using results from a 2018 GWAS[11] conducted using genetic data from the CHARGE and COGENT consortia, and UK Biobank (total N = 300,486; ages 16–102). A total of 300,486 participants undertook multiple, diverse cognitive tests from which a general cognitive function phenotype was created within each cohort by principal component analysis. In some instances, a single test that captures multiple cognitive functions was used as a proxy for general cognitive ability (e.g. the Moray House Test of Verbal and Numerical Reasoning). A total of 178 genome-wide significant independent lead SNPs from 148 loci were identified for association with general cognitive function. Adjustments for age, sex and population stratification were include in study-specific GWAS association analyses. Cohort-specific covariates such as site or familial relationships were also included as required.

The summary results for all variants with z-score statistics were downloaded from the website "https://www.ccace.ed.ac.uk/node/335". The formula below was used to further obtain the beta estimates for all the variants. Here, "p" was the minor allele frequency (MAF) of the European samples from the 1000G reference panel (phase 3 version 5).

$$Beta = \frac{z}{\sqrt{2p(1-p)(n+z^2)}}$$

We constructed two versions of the PRSs for general cognitive function: "top SNPs" and "all SNPs" PRSs. The "top SNPs" PRS included 130 lead SNPs out of the 178 reported lead SNPs from the 148 loci that overlap between the LASI-DAD genetic data and the GWAS meta-analysis. The "all SNPs" PRS included all independent lead SNPs with ($p < 1 \times 10^{-4}$). Clumping was used to obtain SNPs in linkage disequilibrium with r^2<0.25 within a 250 kb window. The LD was hard to obtain in the MHC region on chromosome 6 (26-33MB) due to long-range LD structure, thus this region was omitted from "all SNPs" PRS. The final "all SNPs" PRS contains 1938 SNPs that overlap between the LASI-DAD genetic data and the GWAS meta-analysis. The descriptive statistics and the histogram of the PRSs are presented in Table 2 and Figure 2. The

posted PRSs have been standardized within the study sample (mean = 0, standard deviation = 1).

Please note the GWAS was conducted using individuals of European ancestry. See Section C: "Notes about the use of PRSs" for more information on the use of PRSs in other ancestry groups.

Table 2. Descriptive statistics of polygenic risk scores (PRSs) for general cognitive function

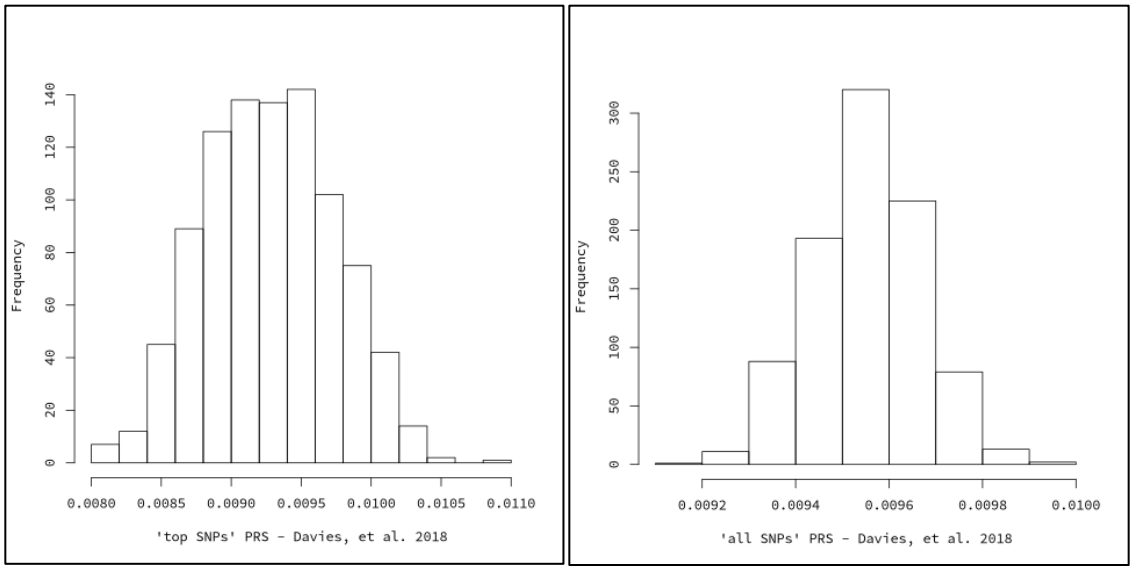
	Unstandardized PRS (original scale)					Standardized PRS				
	Min	Max	Median	Mean	SD	Min	Max	Median	Mean	SD
"top SNPs" PRS[a]	0.0081	0.0109	0.0093	0.0093	0.0005	-3.4305	3.6653	-0.0172	0.0000	1.0000
"all SNPs" PRS[b]	0.0092	0.0100	0.0096	0.0096	0.0001	-2.5715	3.4787	-0.0251	0.0000	1.0000

a. The "top SNPs" PRS was constructed using the genome-wide significant SNPs reported from the genome-wide association study (GWAS) of general cognitive function[11].

b. The "all SNPs" PRS was constructed using independent SNPs (p<10E-04) reported from the genome-wide association study (GWAS) of general cognitive function[11]. Independent SNPs were selected using a clumping approach (r^2<0.25, window size 250kb) with LD estimated in South Asian ancestry from 1000 Genomes Reference Panel.

Figure 2. Histogram of the polygenic risk scores (PRS) constructed using (A) genome-wide significant SNPs or (B) independent SNPs at p<10E-4 reported from the genome-wide association study (GWAS) of general cognitive function[11].

A. B.



III. Setup

By downloading this data set, you agree to use its contents only for research and statistical purposes, making no effort to identify the respondents. You also agree inform LASI-DAD of any papers, publications, or presentations based on the data set. Please send a copy of such publications in PDF format via e-mail to help@lasi-dad.org with "Attn: Papers and Publications" in the subject line. You may also include a bibliographical reference for your preference. As an alternative, you may transmit publications in paper format by postal mail:

Program on Global Aging, Health & Policy (CESR)
Suite 305, Verna and Peter
Dauterive Hall
635 Downey Way
University of Southern California
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IV. Other resources and citations

This document is intended to serve as a brief overview to provide guidelines for using the LASI-DAD Polygenic Risk Scores data product. If you have questions or concerns that are not adequately addressed here, or if you have any comments, please contact us. We will do our best to provide answers.

A. LASI-DAD Internet Site

LASI-DAD public release data and addition information about the study are available online. To access public data or to find out more about restricted data products and procedures, visit the lasi-dad.org..

B. Contact Information

If you need to contact us, you may do so by one of the methods listed below.

E-mail: help@lasi-dad.org

Postal Service:

Program on Global Aging, Health & Policy (CESR)
Suite 305, Verna and Peter
Dauterive Hall, 635 Downey Way,
University of Southern California,
Los Angeles, CA 90089, USA

C. Citing this Document

Please include the following citation in any research reports, papers, or publications based on these data along with the citation for the reference GWAS:

In text:

"The LASI-DAD (Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India) was sponsored by the National Institute on Aging (NIA R01AG051125, U01AG065958)."

In references:

"Smith JA, Zhao W, Yu M, Dey A.B., Kardia Lee J, SL. LASI-DAD Polygenic Risk Scores – Release 1. Department of Epidemiology, School of Public Health, University of Michigan; Department of Geriatric Medicine, All India Institute of Medical Sciences, New Delhi, India; Center for Economic and Social Research, University of Southern California; 2020."

V. Acknowledgements

We have modeled this report after the Health and Retirement Study (HRS) polygenic score report to ensure consistency in the presentation of information across studies (https://hrs.isr.umich.edu/data-products/genetic-data/products). We thank the investigators at the University of Michigan for providing a template for this report.

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