Harmonized Cognitive Assessment Protocol (HCAP) U24 International Network Annual Meeting

Bethesda, Maryland

Meeting Summary

October 12–13, 2023

January 19, 2024

This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the University of Michigan (U24 AG065182). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of the University of Michigan or the National Institute on Aging. Contributions to and review of earlier versions of this meeting summary by the following individuals are gratefully acknowledged: Sparsha Muralidhara, Rose Maria Li, Carlos Mendes de Leon, Beatrice Baaba Tawiah, Jinkook Lee, Alden Gross, Andrew Steptoe, Minki Chatterji, Cherie Dewar, Dana Carluccio, Kenneth Langa.

Acronyms & Abbreviations

10/66	Dementia Research Group
A-Beta40	Beta-amyloid 40
A-Beta42	Beta-amyloid 42
AD	Alzheimer's disease
AD/ADRD	Alzheimer's disease and Alzheimer's disease-related dementias
ADAMS	Aging, Demographics, and Memory Study
AI	Artificial intelligence
AL-SEHA	A Longitudinal Study of Egypt Healthy Aging Initiative
AWI-Gen	Africa Wits-INDEPTH Partnership for Genomic Research
BASIC-Cog	Brain Attack Surveillance in Corpus Christi-Cognitive Aging Study
BSR	Division of Behavioral and Social Research
CADAS	Caribbean American Dementia and Aging Study
CDR	Clinical dementia rating
CHARLS	China Health and Retirement Longitudinal Study
Chile-Cog	Chile Cognitive Aging Study
CSF	Cerebrospinal fluid
CSID	Community Screening Interview for Dementia
CVFS-SCAN	Chitwan Valley Family Study-Study of Cognition and Aging in Nepal
Co-I	Co-investigator
Co-PI	Co-principal investigator
DNA	Deoxyribonucleic acid
EF	Executive function
ELSA	English Longitudinal Study of Ageing
ELSI	Brazilian Longitudinal Study of Aging
EOL	End-of-life
Gateway	Gateway to Global Aging Data
GFAP	Glial fibrillary acidic protein
GMS	Geriatric Mental State
GSA	Gerontological Society of America
HAALSI	Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa
HCAP	Harmonized Cognitive Assessment Protocol

HRS	Health and Retirement Study
INDEPTH	International Network for the Demographic Evaluation of Populations and their Health
IQCODE	Informant Questionnaire on Cognitive Decline
KLPS	Kenya Life Panel Survey
LASI-DAD	Longitudinal Aging Study in India – Diagnostic Assessment of Dementia
LMIC	Low- and middle-income countries
LOSHAK	Longitudinal Study of Health and Ageing in Kenya
LSAHA	Lebanon Study on Aging and HeAlth
MARS	Malaysia Ageing and Retirement Survey
MCI	Mild cognitive impairment
Mex-Cog	Mexican Cognitive Aging Ancillary Study
MHAS	Mexican Health and Aging Study
MLSFH	Malawi Longitudinal Study of Families and Health
MMSE	Mini-Mental State Exam
MPI	Multiple principal investigator
NHDSS	Navrongo Health and Demographic Surveillance System (Ghana)
NICOLA	Northern Ireland Cohort for the Longitudinal Study of Ageing
NfL	Neurofilament light
NIA	National Institute on Aging
PAA	Population Association of America
p-tau	Phosphorylated tau^{181}
PI	Principal investigator
SHARE	Survey of Health, Aging and Retirement in Europe
SPACE	Supportive environments for Physical and social Activity, healthy ageing, and CognitivE health
SPS	Social Protection Survey (Core Chilean)
SPS	Social Protection Systems (European Union)
T-tau	Total tau
TILDA	The Irish LongituDinal Study on Ageing

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Meeting Summary

Introduction

Ken Langa, David Weir

The Harmonized Cognitive Assessment Protocol (HCAP) U24 International Network met in Bethesda, Maryland October 12–13, 2023, to discuss study progress, pertinent field concerns, and next steps for harmonizing global systems for aging-related cognitive research. HCAP U24 Network members presented updates on Biomarker Core, Gateway to Global Aging Data (Gateway), and planned and ongoing HCAP studies (established and pilot). Issues of interest and suggested topics for future meetings were also discussed. The meeting agenda and list of in-person and remote participants are in Appendices A and B, respectively.

Ken Langa and David Weir, co-principal investigators (co-PI) of the HCAP U24 Network, welcomed attendees and provided a brief overview of the meeting agenda. Langa reviewed the progress across ongoing HCAP studies (Table 1) and highlighted two grant applications that propose to field HCAP studies in Egypt and Malaysia. Pilot studies have been funded in Brazil, Ghana, and Egypt, and one pilot study has been submitted for Malawi. Additional applications propose studies in Scotland, Philippines, Guatemala, Côte d'Ivoire, and Vietnam.

Minki Chatterji, a program officer at National Institute on Aging (NIA), and Jonathan W. King, a project scientist at NIA, presented NIA's upcoming research priorities and resources.

Table 1. HCAP International Network Study Status

Country	Study	Wave	Applied	Funded	Begun	Completed	Data Released
USA	HRS	1	✓	✓	✓	✓	✓
		2	✓	✓	✓		
Mexico	MHAS	1	✓	✓	✓	✓	✓
		2	✓	✓	✓	✓	✓
England	ELSA	1	✓	✓	✓	✓	✓
		2	✓	✓	✓		
S. Africa	HAALSI	1	✓	✓	✓	✓	✓
		2	✓	✓			
China	CHARLS	1	✓	✓	✓	✓	✓
India	LASI	1	✓	✓	✓	✓	✓
		2	✓	✓	✓		
Chile	ESPS	1	✓	✓	✓	✓	✓
S. Korea	KLOSA	1	✓	✓	✓	✓	✓
EU	SHARE	1	✓	✓	✓	✓	
		2					
Ireland	TILDA	1	✓	✓	✓		
		2					
N. Ireland	NICOLA	1	✓	✓	✓		
		2					
Caribbean	CADAS	1	✓	✓	✓		
Lebanon	LSAHA	1	✓	✓	✓		
Kenya	KLPS	1	✓	✓	✓		
	LOSHAK	1	✓	✓	✓		
Nepal	CVFS-SCAN	1	✓	✓			
Egypt	AL-SEHA	1	✓				
Malaysia	MARS	1	✓				

Anticipating a tighter NIA budget in FY2024, Chatterji noted that investment in the HCAP U24 Network to facilitate harmonization of data for cross-national analyses remains a priority.[1] Other NIA Division of Behavioral and Social Research (BSR) funding priorities are small grants for innovations in health longevity research, the study of the exposome relevant to Alzheimer's Disease (AD) and AD-related dementias (AD/ADRD), and the expansion of research capacity in low and middle-income countries (LMIC). Chatterji highlighted NIA/BSR resources[2] to expand HCAP research worldwide and identified upcoming opportunities to continue growing the HCAP network. Publications that used HCAP data document the prevalence of dementia in cross-national contexts and highlight factors that impact later life cognitive performance (e.g., sleep, wealth shocks, policy environments, and cultural context).[3]

HCAP U24 Network Updates

David Weir

Weir provided historical context behind the HCAP and the Health and Retirement Study (HRS) family of studies. The initial set of all HCAP studies was embedded in established HRS-harmonized longitudinal studies of aging. The core studies provide rich demographic and epidemiological data to be used with HCAP. It is important to maintain harmonization in the parent studies, which is facilitated through the NIA-funded HRS Around-the-World (HRS ATW) U24 Network[4] that is headed by Weir as its principal investigator (PI) and supported by Rose Li & Associates. Lindsay Kobayashi will be proposed to replace Weir as co-PI (or multiple principal investigator [MPI] working with Langa) in the HCAP U24 Network renewal (2024[5]). Both HCAP and HRS ATW can support pilot work, and there will be opportunities for some joint meetings.

Tremendous productivity and accomplishments across the network have been made with data collection, publications, and plans for new studies. The HCAP Network supported 12 pilot studies, including those in Kenya, Egypt, Ghana, and Brazil. Over 90 peer-reviewed published articles used HCAP study data, such as papers about the development of a cultural neuropsychological approach to harmonization and psychometric analyses to establish the cross-national comparability of HCAP measures. Additional HCAP plans include:

- Sub-Saharan Africa studies
- A 2024 meeting in Kenya organized by the Kenya Life Panel Survey (KLPS)
- A 2024 Advanced Psychometric Methods for Cognitive Aging Research Conference on cross-national comparisons in cognitive aging
- Pilot studies

[1] See RFA-AG-24-032: Enhancing Use of harmonized Cognitive Assessment Protocol Data with due date October 2, 2023.

[2] These include the National Academies' Committee on Population materials from the NIA-sponsored workshop on Population Aging and Social Research in Low- and Middle-Income Countries; NIA/BSR Global Aging Webpages, and summary statistics based on HCAP data from China, India, and Mexico produced by the US Census Bureau.

[3] See https://hcap.isr.umich.edu/publications/

[4] The HRS ATW U24 Network is funded by the National Institute on Aging (NIA), "Harmonization of Cross-National Studies of Aging to HRS" (U24 AG 037866).

[5] Langa, Weir, Richard Jones, Jennifer Manly, Lindsay Ryan, Jessica Faul, Amanda Sonnega to continue as Core leaders. Emily Briceño and Arce Rentería are proposed as collaborators on the Protocol and Administration Core.

- Virtual "hot topic" meetings
- Investigator exchanges
- Monthly research-in-progress seminars.

Updates from Latin American HCAP Studies

Mexican Health and Aging Study

Silvia Mejia-Arango

The Mexican Health and Aging Study (MHAS) team completed Wave 2 of the Mexican Cognitive Aging Ancillary Study (Mex-Cog) in July and August 2021. The Mex-Cog 2021 sample was comprised of a follow-up of Mex-Cog 2016 (N=1,495 of 2,042, or 73.2 percent) and a new sample (N=2,203) for a total sample size of 3,698. Participants who completed both waves in 2016 and 2021 were statistically more likely to be female, from urban localities, and younger (66.1 years, on average) than participants in either wave dataset. Wave 2 data show significantly higher rates of mild cognitive impairment (MCI) and dementia than the team observed in Wave 1 (Table 2).

Table 2. Mex-Cog Cognitive Status Classification: Weighted Rates

Cognitive Status	Mex-Cog 2016 N = 2,042	Mex-Cog 2021 N = 3,536
Normal	1,637 (82.5%)	1,899 (61.6%)
MCI	269 (11.7%)	1,145 (29.6%)
Dementia	136 (5.9%)	492 (8.7%)

Mejia-Arango noted that the team is currently processing additional genetic data and updating their 2021 predictive algorithm of dementia classification to account for these dramatic increases in age-related cognitive decline.[6]

King asked about COVID-19 serology data for the 2021 Mex-Cog and Weir said that MHAS conducted some analysis of its interaction with dementia. Rebeca Wong noted that the Mex-Cog data from Wave 2 are publicly available and that the 2016 classification variables will be released in November 2023.

Chile Cognitive Aging Study

David Bravo

Due to the COVID-19 pandemic, the Chile Cognitive Aging Study (Chile-Cog) team will develop its validation study between November 2023 and May 2024, per availability of the University of Chile Hospital Memory Center. The team will also administer HCAP surveys in person through winter 2023, conducting neural assessments with participants through May 2024. The Chile-Cog team is currently focused on: (1) preparing cohort publications for Chile-Cog and the Core Chilean Social Protection Survey (SPS), (2) conducting comparative analyses with Mex-Cog, and

[6] In the chat, Mejia-Arango clarified that the definition of cognitive impairment with the algorithm is based on two or more impaired cognitive domains. It is very different from the MMSE.

(3) collaborating with Gateway to harmonize and geocode SPS and Chile-Cog data (from earlier rounds of SPS, SPS 60+, and Chile-Cog) by November 15. After completing the 2023 round of SPS in March 2024, Bravo's team aims to apply for a second wave of Chile-Cog and link SPS and Chile-Cog samples with death records.

Caribbean American Dementia and Aging Study

William Dow

Building on work done by the 10/66 Dementia Research Group (10/99) at King's College London, the Caribbean American Dementia and Aging Study (CADAS) team aims to compare social determinants of health for AD/ADRD for US Caribbean-Americans with novel, nationally representative samples from the Dominican Republic, Puerto Rico, and Cuba.[7] The CADAS team is collecting data through 2025 using most 10/66 survey items and some additional cognitive tests to better harmonize data with HCAP protocols. Validation testing of the team's updated 10/66 dementia prediction algorithm demonstrated greater prediction performance on data from the Aging, Demographics, and Memory Study (ADAMS) than from previous algorithms based on the Telephone Interview for Cognitive Status. CADAS plans to collaborate with Jinkook Lee at the University of Southern California to validate an online consensus dementia diagnosis protocol used by Longitudinal Aging Study in India harmonized Diagnostic Assessment of Dementia (LASI-DAD) and Health and Aging in Africa: A Longitudinal Study of an International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) Community in South Africa (HAALSI).

Discussion[8]

Weir noted that HCAP development drew largely from 10/66 and the Community Screening Interview for Dementia to simplify later harmonization efforts. Lisa Berkman commended the CADAS team's approach to identifying country-level differences in dementia classification, noting that her own study found higher impacts on diagnoses from the professional background of diagnosticians (e.g., geriatricians, neurologists, and neuropsychologists). King acknowledged some key differences between 10/66 and the HCAP instrumentation, such as 10/66's exclusion of individuals with depression and HCAP's use of two logical memory tests compared to 10/66's single test. Dow clarified that 10/66 adjusted for respondents with depression but did not fully exclude them from the algorithm.

Updates on Latin American Pilot Studies

Harmonization of 10/66 Dementia Research Group, Mexican Health and Aging Study, and Brazilian Longitudinal Study of Aging

Jorge Llibre-Guerra

PIs from 10/66, MHAS, and Brazilian Longitudinal Study of Aging (ELSI) are collaborating to validate and identify genetic and socioenvironmental AD risk profiles in under-researched Latino populations. Previous work by 10/66 found significant, poorly understood disparities

[7] Parallel work happening in Cuba is funded by Davos Alzheimer's Collaborative.

[8] In the chat, Nina Silverberg noted that autopsies might be worth considering to better understand risk factors and frequency for other types of dementia.

between Latino subgroups, further driving the cross-team's effort to harmonize 10/66 data with MHAS and ELSI through a common cognitive impairment and dementia algorithm. Llibre-Guerra and his colleagues completed the first of the following three harmonization phases: (1) develop pre-statistical harmonization, (2) co-calibrate cognition factors based on 10/66 data, and (3) score assessments for ELSI and MHAS using a mapped 10/66 diagnostic algorithm. Despite some challenges in harmonizing 10/66 data with ELSI, the team still identified broad anchor items and found a promising 80% overlap between items in 10/66 and MHAS. Llibre-Guerra invited feedback from meeting participants on whether to use a pooled or parallel modeling strategy, and he asked for potential classification alternatives to use instead of the 10/66 diagnosis algorithm.

Discussion

Weir said that the 10/66 instrument used the Geriatric Mental State (GMS) while the HCAP did not, suggesting that harmonization efforts should examine how different tests account for differential diagnoses for dementia. Llibre-Guerra noted that the GMS was excluded in some preliminary analyses of ADAMS data due to its exclusion of several respondents from the algorithm, but more work is needed to characterize GMS sensitivity. Dow clarified that removing GMS from predictive algorithms retains 95% prediction accuracy for dementia, but he was unsure about its accuracy for MCI. Substituting the EURO-D depression screen for the GMS had similar 10/66 algorithm results (Stewart, Guerchet, Prince 2016).

Informant Measures in Health and Retirement Study, China Health and Retirement Longitudinal Study, and Mexican Health and Aging Study

Yuan Zhang, Phillip Cantu

Zhang and Cantu shared preliminary data from their pilot project to characterize cross-national differences in informant interviews. The team is developing a manuscript that will compare informant-based measures of cognitive function between study informants in the United States and Mexico; this information was presented at the 2022 HCAP Network meeting and to the Gerontological Society of America (GSA) and the Alzheimer's Association International Conference.

A second project explored the interactions between respondents' sex and informants' reports about cognitive change in the HRS-HCAP and Mex-Cog. Preliminary results, which were used for Cantu's K01 submission, indicate no significant difference in informant ratings of dementia based on the Community Screening Interview for Dementia (CSID), but they do indicate notable differences in measures based on a modified Mini-Mental State Exam (MMSE) and harmonized global cognitive function. Informants' characteristics differ depending on respondents' sex and the study, which reflects gender role differences in national contexts. In general, results showed that women had higher rates of cognitive impairment, informants were more likely to report symptoms of cognitive decline in the HRS than in the MHAS, and informants were more likely to report memory issues and difficulty with chores for women. Informants for Mex-Cog respondents were, on average, younger and less educated than HRS-HCAP informants. Nearly 80 percent of Mex-Cog informants and 50 percent of HRS-HCAP informants lived with their respondents, suggesting that Mex-Cog informants were more likely to be children rather than

spouses of the respondent compared to informants in HRS-HCAP. HRS-HCAP informants were nearly three times more likely than Mex-Cog informants to report difficulty handling money in female respondents; this difficulty is a symptom frequently used in predictive algorithms to determine dementia status.

The team's preliminary analyses of the 2016 and 2021 Mex-Cog waves reported a temporal component to informant assessments that may have driven cognition variance between the waves. Zhang reviewed informant characteristics and cognitive performance decline in each wave.[9]

Discussion

Langa underscored the importance of using informant data to assess whether a respondent has met the threshold of disability for dementia, and he noted that the LASI-DAD team's excellent work looking at differences in reporting by geography (e.g., urban/rural). Jennifer Manly expressed surprise at the lack of correlation between the Mexico-adapted MMSE and CSID, but she noted that this issue has been observed when using MMSE for longitudinal analysis; other instruments (e.g., global cognitive function) for comparison with CSID might be more insightful. Weir supported implementing additional instrument comparisons, highlighting the contradiction between dramatic increases in MCI/dementia cases in Mejia-Arango's presentation and longitudinal MMSE score improvement in Zhang and Cantu's pilot data. Cantu noted that further testing would examine if these discrepancies could be explained by test-retest effects that differ for informants and respondents. In response to a question, Zhang clarified that informant reports had not been categorized by whether the same informant had answered both waves, but the team could investigate this good suggestion in the future.

Education, Social Protection, and Cognition in Chile and Mexico

Rebeca Wong, Irma Elo

Data from the 2016 Mex-Cog (N=1,674) and the 2019 Chile-Cog (N=1,946) were used in a pilot study that compared socioeconomic covariates of cognition in older adults. The study implemented imputed data for Mex-Cog and submitted an abstract for the 2024 Population Association of America meeting. Wong noted that the two HCAP studies were already highly similar (e.g., they use the same instruments in Spanish, survey protocols, training materials/personnel, and scoring codes), and very little further harmonization was required for the core survey variables. On average, Mex-Cog respondents showed lower scores for adapted MMSE instruments than Chile-Cog, with Mex-Cog respondents more likely to have less education and be from poorer childhood socioeconomic backgrounds than Chilean counterparts. Regression analyses revealed that gender, nationality, and schooling were also predictive of adapted MMSE scores in both Mex-Cog and Chile-Cog respondents. Current findings from the pilot study ultimately suggest more rapid age-related performance declines in Mex-Cog respondents, who express greater negative effects for unobserved factors. However, Wong also emphasized the importance of intergroup similarities, such as the higher impact of

[9] In the chat, Mejia-Arango reported 16.4 percent deceased between 2016 and 2021 in Mex-Cog. There was substantial excess mortality from COVID. The two-wave sample includes only survivors.

schooling for women than men, in predicting total cognition score in both countries. Future work will incorporate imputed data for Chile-Cog, explore the underlying mechanisms driving the observed effects of schooling and gender alongside comparative analysis of other explanatory variables (especially social safety nets), and investigate alternative cognitive function measures.

Discussion

To measure education quality, Wong identified the need for additional contextual variables to account for variation in education between cohorts within a country, given the changing quality of education over time.[10] Jere Behrman reported that he and his collaborators have submitted an HCAP pilot study proposal that aims to compare education quality across several HCAP studies within the Gateway, with data ideally available by 2024.

Updates from Recent HCAP Field Studies

Longitudinal Aging Study in India Harmonized Diagnostic Assessment of Dementia

Jinkook Lee

The LASI-DAD team expanded the participant sample from 18 states and union territories in Wave 1 (2017–2020) to 4,500 older adults (> 60 years) from 22 states and union territories in Wave 2 (2022–2024). Wave 2 expanded study protocols to include fully implemented collection of neuroimaging, language assessments, audiometric assessment, health assessment (anthropometry, functional status, mental health, and venous blood collection and assay), and environmental exposome observation (ambient air pollution, indoor air pollution, physical environment [photos, GPS coordinates, walkability index]). Instruments have been validated in 12 local languages.

Wave 2 completed all validation studies for the following plasma-based neurobiological biomarkers: beta-amyloid 42 (A-Beta42), beta-amyloid 40 (A-Beta40), total tau (t-tau), phosphorylated tau^{181} (p-tau), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL). Wave 1's online clinical consensus diagnostic tools have been updated to use both in-person and telemedicine approaches to better capture clinical dementia ratings (CDRs), which include an artificial intelligence (AI) adjudicator.

Lee noted Wave 2's protocol changed to use new or expanded cognitive tests (e.g., literacy tests, executive function, judgement, and problem solving) and informant report items for caregiver burden, end-of-life interviews, and food consumption. The team completed whole genome sequencing for Wave 1 and plans to complete DNA methylation analyses for both Waves 1 and 2. More than 2,500 interviews were completed as of October 2, 2023 (about an 84 percent response rate) for Wave 2's Phases 1 and 2 data collection, and Phase 3's data collection (including neuroimaging) will launch in October 2023. An additional 2,000 respondents are being recruited to bring innovations to LASI-DAD as an "Innovation Panel."

[10] In the chat, Mejia-Arango noted that literacy and numeracy would be indicators for quality of education.

Discussion

Lee noted that blood sample collection challenges have been addressed through labor-intensive monitoring of both collection logistics and sample analyses. These efforts are well worth it to build science forward. Weir noted that the HCAP Network's biomarker component focuses on blood sample collection challenges[11].

English Longitudinal Study of Ageing

Andrew Steptoe

The English Longitudinal Study of Ageing (ELSA), started in 2018, will conclude its Wave 10 data collection and its second HCAP study by October 30, expecting to reach a target sample of 2,000 participants. Steptoe noted that securing follow-up respondents from the first ELSA-HCAP was a significant challenge, with 19 percent of the HCAP-1 respondents refusing to participate. However, the team successfully surpassed their goals for recruiting participants from ethnic minority groups with 282 of the required 300 participants. The study team distributed informant (friends and family of responder) interviews to 1,901 HCAP participants and it is calculating final response rates.

Discussion

Weir suggested that the high number of follow-up candidates' refusals may point to the need for more focused outreach and messaging on the importance of the follow-up study. Lindsay Ryan shared that HRS accounted for follow-up participants engagement by adjusting survey language to appear more novel to respondents.

Irish Longitudinal Study on Ageing

Christine McGarrigle

The Irish Longitudinal Study on Ageing (TILDA) team is completing Wave 6's data collection with a replenishment cohort. Eligible respondents (N=3,708) were randomly assigned to receive either the HCAP (N=1,800) or TILDA (N=1,908) Health Assessment. Seventy-one percent of available participants completed the replenishment HCAP interview and 75 percent of informants completed the friends and family interviews. Respondents refusing to nominate an informant was the main reason (204 of 219) for refused informant interviews.

Ninety-six percent of respondents voluntarily consented to provide a blood sample for genetic research on aging; the blood samples and extracted DNA can be shared with international research groups. Additionally,

- 89 percent of respondents consented to microbiome collection
- 79 percent of respondents provided HCAP blood samples, and
- 59 percent of respondents provided stool microbiome samples for future analysis.

The primary reasons for non-collection of blood were poor peripheral/venous access, absence of consent, contraindications (e.g., high/low blood pressure), and recent blood withdrawal.

[11] Those interested to sign on to biomarker network activities should feel free to contact Jessica Faul (contact PI) or David Braudt (NIA Program Officer) for more information.

McGarrigle said that selection effects (education, cognitive impairment) were associated with willingness to participate in HCAP and TILDA Core.

Northern Ireland Cohort for the Longitudinal Study of Ageing
Bernadette McGuinness
The Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) team completed the first and second phases of recruitment and 1,002 respondent interviews. Working with respondents in residential care will be tabled for NICOLA Wave 3 due to low recruitment for proxy interviews. Respondent refusals (30.4 percent of 2,068 attempted) were more frequently female, less educated, and slightly older than respondents who agreed to interview, and 10.5 percent of respondents refused to nominate a candidate for informant interviews. Informants were generally spouses or partners.

To investigate the influences of environmental exposomes, NICOLA is conducting the Supportive Environments for Physical and Social Activity, Healthy Ageing, and Cognitive Health (SPACE), funded by the Economic and Social Research Council. Four hundred HCAP participants have agreed to participate in SPACE, and the team is currently assessing the resultant data.

The team has completed interviews for its non-dementia diagnosis control group and is currently interviewing respondents with dementia diagnoses for a separate HCAP clinical validation study that is funded by the National Science Foundation. NICOLA plans to develop an HCAP algorithm based on current data, conduct joint study collaborations in conflict areas (e.g., Lebanon), and apply for NIA grants for NICOLA Wave 3 and HCAP 2.

Health and Retirement Study

Lindsay Ryan
The HRS team is following up with a subset of 2022 HRS core study respondents to complete Wave 2 of the HRS-HCAP. Roughly 2,700 interviews were conducted as of October 2023, and the goal of 3,000 interviews, with priority sampling of proxy reports and demographic minorities, should be completed in November 2023. Wave 2's sampled respondents were 71.9 percent White and 41 percent male. Preliminary analysis of Wave 2 MMSE scores show similar statistical distribution to Wave 1.

Langa and Weir briefly addressed a data version error identified in HRS-HCAP's Wave 1 which will be corrected and posted to the HRS website by late October. While the team expects no changes to overall dementia prevalence estimates, some factor scores and subgroup odds ratios may see adjustment.

Protocol amendments from Wave 1 to Wave 2 are dropping olfactory tests and switching to a paper Story Recall test. Respondents and interviewers will be able to wear clear masks, with interviewers documenting any potential impacts on test administration.

HRS plans to develop an informant tracker to determine if they change between HRS waves when respondents complete follow-up interviews.

Discussion

Langa clarified that the olfaction test was dropped due to insufficient evidence of its impact in previous literature, but it may be reimplemented to capture possible effects of long-term COVID-19. HCAP and Jayant Pinto (University of Chicago) are conducting an exploratory analysis of HCAP Wave 1 olfactory data in collaboration with the National Social Life, Health, and Aging Project.

Survey of Health, Aging and Retirement in Europe

Salima Douhou, Marcela Otero

The Survey of Health, Aging and Retirement in Europe (SHARE) team collected HCAP interview data following Wave 9 of the core study. Using respondents from Germany, Italy, Denmark, the Czech Republic, and France, the study team conducted interviews from May to November 2022. Douhou noted that, like HRS, SHARE interviewers tracked mask usage in respondent interviews. Response rates ranged from 78 percent in France and 99.4 percent in Italy, and they were expectedly lower in respondents with some degree of cognitive decline. Respondents' willingness to nominate an informant varied by country, potentially suggesting cultural differences that need further characterization. The SHARE team used both centralized scoring from trained (masters-level) student assistants and in-field scoring from external interviewers to establish measures of interrater reliability. The study team is developing a classification algorithm to account for demographically adjusted norms in future waves of cognition data.

Discussion

Douhou expressed interest in Manly's suggestion to use AI-based scoring tools to supplement more objective task scoring. Alden Gross noted that LASI-DAD's online diagnosis consensus tools use AI to substitute the score for a third clinician diagnosis of dementia. Manly emphasized consistency in scoring is key to detecting impairment. Weir suggested that a pilot study look at inconsistencies in logical memory and Story Recall scoring between interviewers and central scoring.

China Health and Retirement Longitudinal Study

Yaohui Zhao

Following the 2018 China Health and Retirement Longitudinal Study (CHARLS)-HCAP study (N=9,164 administered both HCAP tests and informant surveys), the CHARLS team is surveying a subset of HCAP respondents and informants from a current wave of the core study to inform changes during the 6-year interval between HCAP surveys. This mini-HCAP survey, conducted 2021–2023, focused mainly on a revised version of the MMSE and supplemental informant interviews. Zhao noted key takeaways from HCAP data so far, focusing primarily on issues with (1) translating HCAP tests to LMIC contexts, (2) accounting for lower literacy or illiteracy, and (3) changing cognitive performance due to visual ability.[12]

[12] In the chat, Josh Ehrlich reported that a study of LASI tests of visual acuity using differential item functioning (DIF) testing did not find visual function to be associated with salient bias in cognitive test performance. As the LASI-DAD team starts to look at the high-quality hearing data being collected and delve into asking similar questions. Ehrlich and Nichols are working on a paper concerning vision DIF findings for presentation at GSA.

Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa
Lisa Berkman
After completing HCAP Wave 2 in 2023 (N=683), the HAALSI team will commence Wave 3 in late 2024 or early 2025. Wave 2 collected data for biomarkers, neurological and clinical exams, informant interviews, and a cognitive battery, all of which were adjusted since Wave 1 to better capture participant data. Wave 1 HAALSI-HCAP data are publicly available and Wave 2 data should be released by the end of October 2023. Using a web-based dementia diagnosis consensus system and multiple dementia prediction algorithms, the study team found an 18 percent prevalence of dementia in the HAALSI cohort, with steep age-associated increases in dementia rate. The MRI sub-study captured HAALSI respondents' neurophysiology that aligned with the HCAP diagnosis quite well. Several studies using HAALSI-HCAP data are in progress to analyze potential factors in predicting dementia risk, including structural brain markers, sensory impairment, vascular disease, COVID-19 serology status, and various social exposomes. The team aims to launch a nationally representative sample study and to expand performance validation efforts for urban regions within the HAALSI study within the next three years.

Discussion
Manly noted that the high HAALSI prevalence rates of dementia align with previously observed rates in older South African populations. Darina Bassil clarified that adjudicators used CDR classifications or categorical classifiers (e.g., dementia/MCI/normal). Berkman noted that HIV-positive respondents demonstrated higher cognitive function and physical health features than non-HIV respondents.

Kenya Life Panel Survey
Ted Miguel
The KLPS team has gathered longitudinal data on a cohort of 6,500 Kenyan individuals for 25 years and it recently launched Wave 5 to specifically assess aging-related measures, such as cognition. Miguel highlighted salient elements of KLPS-5's (2023–2027) studies of aging, including its (1) clinical trial linking increased child health with boosts to human capital, (2) survey data broadly relevant across research disciplines, (3) longitudinal data collection, (4) low survey attrition rates, and (5) intergenerational data. The KLPS team will harmonize measurements with the Longitudinal Study of Health and Ageing in Kenya (LOSHAK) team. Over 4,800 KLPS-5 surveys have been collected as of October 2023, with a survey tracking rate for each round between 84 to 87 percent. Visit 1 focuses on cognitive measures and exposome measures for 1) occupational complexity and work-related stress, 2) social interactions and support, and 3) air pollution exposure. KLPS-5 Visit 2 will focus on health measures, biomarkers (including deep brain stimulation), migration, and sociodemographic and intergenerational child data collection. KLPS-5 Visit 3 will feature socioeconomic and living standards measures, economic preferences, and social attitudes. Future work will continue planning and conducting pilots for Wave 5.

Longitudinal Study of Health and Ageing in Kenya

Josh Ehrlich

The LOSHAK team is harmonizing a suite of aging measures with KLPS to generate robust data analyses from the KLPS randomized clinical trial and LOSHAK population-based survey. LOSHAK will focus largely on cognitive health, psychosocial measures, sensory health and disability, economics/retirement/cash transfers, caregiver stress and wellbeing, molecular biomarkers, physiologic measures, and environmental exposomes. For its pilot study, the LOSHAK team sampled 205 individuals for validation testing from a well-defined cohort of 14,000 individuals (ages 45+ years) who participate in a regularly updated Kenyan health and demographic surveillance system. The pilot study's in-home interviews were conducted by trained nurses and clinical officers. Psychometric analyses led by Gross have similar respondent scores to KLPS data in various cognitive measures. After completing the pilot work, the LOSHAK team aims to collaborate with the Kenyan Ministry of Health and the Kenya National Bureau of Statistics to establish a nationally representative, HRS-harmonized cohort study on aging in Kenya. In February 2024, the team will apply for an NIH grant to undertake Wave 1 of the full LOSHAK, which would begin by summer 2026. If funded, this LOSHAK aging study would be second one in Africa after HAALSI's South African study.

Biomarker Core Update

Alzheimer's Disease Biomarker Activities in the National Institute on Aging Biomarker Network

Jessica Faul

The NIA Biomarker Network is conducting an HRS pilot study to test promising biomarkers of neurodegeneration in 2016 HRS-HCAP venous blood samples. The pilot's priorities are to identify highly reliable and replicable measures in blood (plasma/serum) and to validate correlations with AD/ADRD neuropathology from cerebrospinal fluid or autopsy measures. In consultation with NIA intramural dementia experts, the team utilized a Simoa Human Neurology 4-Plex E (N4PE) assay to capture A-beta42, A-beta40, NfL, and GFAP biomarker data. An additional assay tested for pTau-181. The assays (N=2,392 HRS-HCAP participants) revealed modest correlations between cognitive performance and biomarkers, most prevalently with NfL, p-Tau-181, and GFAP. Faul noted differences in biomarker correlation between racial and ethnic groups—within a combined racial and ethnic composition, only NfL found significant associations with cognitive task scores that remained after adjusting for respondent *APOE* gene status. When predicting dementia classification, NfL and GFAP biomarkers moderately correlated with dementia diagnosis, while other biomarkers showed inconclusive results. In the pooled racial and ethnic model, only GFAP showed high correlation with dementia diagnosis. Another 202 respondents converted to dementia between 2016 to 2020 in the longitudinal analysis of dementia/death status and blood-based biomarkers. NfL's presence was, once again, highly predictive of a dementia diagnosis or death within two and four years of the 2016 HCAP survey. Faul acknowledged that dementia has a complex phenotype, meaning the relationship between dementia and biomarker data may be more nuanced than current biomarker panels can illustrate. A blood-based biomarker test for AD pathology is now commercially available.

Supplemental NIA funding will be requested for a pilot study that will test different ultrasensitive A-beta 42/40 ratio assessment[13] to compare the types of specimens (serum/plasma) currently collected and add new assay methodologies (e.g., immunoassay, mass spectrometry-based methods, Roche standard chemistry kit).

Comparison of Neurodegenerative Assays in Health and Retirement Study and Longitudinal Aging Study in India Harmonized Diagnostic Assessment of Dementia

Bharat Thyagarajan

Thyagarajan reported pilot study results from two research institutions, the University of Minnesota Advanced Research and Diagnostics Laboratory and the All-India Institute of Medical Sciences in Delhi, that concurrently analyzed 84 identical samples using the same HD-X instrument. Both labs were blinded to the results. Eileen Crimmins and Jung Ki Kim (University of Southern California) analyzed the data, which revealed a high degree of correlation and minimal differences across different reagent lots. Preliminary results indicate a reasonable correlation of P-tau-181 measured from HRS serum and LASI-DAD plasma. These promising results suggest that biomarker studies can be successfully harmonized across the two HCAP studies.

Gateway Update on Harmonized Cognitive Assessment Protocol-Related Data and Activities

Alden Gross, Jinkook Lee

Gateway continues to support HCAP studies by assisting with data production, dementia measurements, survey protocol considerations, and dissemination activities. Gateway recently completed imputations for Chile-Cog, as it has for LASI-DAD, ELSA-HCAP, Mex-Cog, and HRS-HCAP. The Gateway team published a paper in *The Lancet* on harmonization of later-life cognitive function across national context (Gross, et al., 2023).

The Gateway team developed and implemented CDR websites for HCAP studies (e.g., LASI-DAD, CADAS, and HRS-HCAP) to further consensus of dementia diagnostics. Gross noted that information provided to adjudicators should be carefully considered when comparing cross-national prevalences based on these adjudications because the level of detail provided between studies often varies. For example, the CDR website for LASI-DAD provides basic cognitive information on respondents to mimic the clinical experience in India, while the CDR website for HAALSI provides more detailed HCAP cognitive measures. Gateway will further assist with dementia diagnostic harmonization by creating comparison tables of existing study-specific dementia prediction algorithms for HRS, LASI-DAD, and Mex-Cog.

Gateway is documenting, and, if possible, standardizing interviewer protocols and collecting data on informant relationships to respondents because these factors may externally influence how respondent data are understood.

[13] Measuring A-beta42/40 provides greater assessment accuracy than measuring A-beta 42 alone because it controls for the natural variance of beta-amyloid production between patients.

Gateway has sponsored the following dissemination activities: (1) an HCAP data user workshop in May 2023 that was useful for mid-career investigators, (2) an HCAP "hackathon" research challenge in August 2023 that stimulated the analysis of HCAP and core cognition data; another hackathon is planned for 2025;[14] and (3) a special issue of the *American Journal of Epidemiology*, projected for January 2025, that will focus on cross-national comparisons in aging.[15]

Discussion

Feeney and Gross discussed the interpretation of "doesn't do" responses about specific tasks, which could support examination of change in behavior over time or simply reflect socialized or cultural behavior. Langa noted that discrepancies between HCAP survey instruments might need better operationalization. Douhou suggested that Gross' recommendation to probe respondents for more thorough responses might be more useful in HCAP where harmonization is a key interest, instead of in core studies. After Langa highlighted potential issues with probing participants with low academic success or exposure, Gross clarified that any probing for answers should be sufficiently intentional and respectful.[16]

Updates from Planned Studies

Seven countries presented their plans to integrate HCAP into their core studies.

Malawi

Hans-Peter Kohler, Iliana Kohler

In response to the accelerated aging observed in Malawi's older population, the Malawi Longitudinal Study of Families and Health (MLSFH) team is integrating HCAP to measure variations in biological aging and to focus health interventions across lifespans. The team aims to understand accelerated aging and AD/ADRD through biosocial life course dynamics tracked through cohort studies of key epigenetic markers. A planned study will collect two rounds of HCAP-harmonized survey data and health indicators (e.g., dried blood spots for DNA methylation profiling and DNA whole-genome sequencing) in 2024 and 2027 from roughly 3,500 mature adults (aged 45+ years). The team plans to pilot-study an MLSFH HCAP instrument in 2024 (target N=450) to integrate into the MLSFH socioeconomic and cognition survey by early 2025. Phone surveys will be conducted between rounds and contextual data (e.g., village characteristics, access to healthcare and water) will be collected. All data will be linked to the parent MLSFH 1998–2022.

[14] The August 2023 HCAP Hackathon welcomed 24 participants selected from 48 applications, who formed seven teams, in response to two challenges: Disparities in late-life cognition across race/ethnicity, gender, urbanicity, and underlying pathways, and cross-national comparisons of late-life cognition, dementia risk, and risk factors. Participants came from within the United States, as well as from China, S. Korea, and Europe. Some of the coaches came from SHARE countries as the latter are interested in hosting a hackathon in 2024 related to end-of-life topics.

[15] Call for papers to be announced May 6, 2024 with submissions due August 1, 2024.

[16] Jon King referenced a kick off meeting of the awardees associated with RFA-AG-23-001, Understanding the Role of Bilingualism in Cognitive Reserve/Resilience in Aging and AD/ADRD, where it was noted that prodding respondents to perform better did not necessarily have the desired effect. Gross highlighted the importance of reminding respondents to work through questions as quickly as they can.

Egypt

Mohamed Salama

The Longitudinal Study of Egypt Healthy Aging Initiative (AL-SEHA) team has screened and validated HCAP in Arabic for use in a subsequent Egyptian national population-based prevalence survey. The team, in collaboration with the Lebanon Study on Aging and HeAlth (LSAHA), used in-person and telephone interviews to collect respondent and informant data from 197 participants. The team provided comprehensive 3-day training to all field teams; standardized procedures to promote uniformity in test administration and data collection; performed data monitoring; maintained continual communication with the field; diagnosed cognitive impairments with psychiatrists' and neurologists' clinical assessments and a panel of expert clinicians; selected cognitive tests; and performed data cleaning. Cognitive diagnoses of the survey's respondents were 55 percent normal, 25 percent with MCI, 15 percent with early dementia, and 5 percent with severe dementia. While current descriptive statistics of the data show promising diversity in educational and age distribution, the team is preparing further statistical modeling to ensure the validity of the Arabic HCAP instrument. Remaining steps include factor analysis, model evaluation, and the establishment of norms and standards for the assessment protocol to assist in interpreting individual performance.

Ghana

Irma Elo

Sourcing pilot data from the Navrongo Health and Demographic Surveillance System (NHDSS) dataset, Elo and colleagues are currently recruiting about 500 participants for a pilot study of HCAP implementation in Ghana. Ghana, a LMIC in West Africa, is experiencing a rapid increase in individuals ages 60 years and above. The pilot study's long questionnaire and short questionnaire can be linked to NHDSS data elements (e.g., sociodemographics, mortality, and migration from 2007–-2023). Elo noted that participants between ages 45–64 could be sourced from the Navrongo subset of the Africa Wits-INDEPTH Partnership for Genomic Studies (AWI-Gen), further linking pilot data with previous waves of AWI-Gen and increasing the power of the pilot study validation.

Brazil

Cleusa Ferri

ELSI's team is recruiting participants for its third wave. Ferri noted that studies that used clinical diagnoses reported more dementia cases than studies that used predictive algorithms, illustrating a need for more standardized instrumentation. The ELSI-HCAP pilot test will assess 180 respondents (60+ years old and not drawn from the ELSI-Brazil study participants) to (1) adapt HCAP instruments for use in Brazil, (2) validate the cognitive battery with a similar participant sample to ELSI's population, and (3) evaluate the burden of interview on participants. While the cognitive battery will be similar to the HRS-HCAP, the final version of the protocol is still being finalized. The resulting pilot data will be harmonized with other partner studies and compared cross-nationally to support efforts to integrate HCAP into the original ELSI sample.

Malaysia

Norma Binti Mansor

As the first comprehensive longitudinal data collection effort on AD/ADRD in Malaysia, the Malaysia Ageing and Retirement Survey (MARS) team aims to field an integrated MARS-HCAP in 2025 to both enrich existing MARS data on AD/ADRD and to share MARS data with the international research community. The study team will adapt HCAP cognitive batteries to a Malaysian context for dementia assessment in its mature adult population (aged 55+ years). MARS is aiming to include about 1,200 respondents and their respective informants. The study will specifically examine salient health domains for Malaysia, such as the interaction effects between AD/ADRD and noncommunicable diseases.

Lebanon

Carlos Mendes de Leon

As of October 2023, the LSAHA team has collected data from 3,000 Lebanese older adults (aged 60+ years) using a comprehensive survey, cognitive battery, and blood sample collection. The study team aims to build LSAHA on the existing 10/66 study protocol from King's College London and to add further tests to harmonize the assessment with HCAP; however, Mendes de Leon also noted that the study should capture risk factors unique to Lebanese context, such as exposure to political instability and the status of care arrangements for older adults in the country. Future developments will implement informant questionnaires alongside the eventual development of a predictive algorithm for dementia classification.

Nepal

Carlos Mendes de Leon

The Chitwan Valley Family Study-Study of Cognition and Aging in Nepal (CVFS-SCAN) team aims to integrate the HCAP cognitive battery into their testing protocol on a study population of roughly 4,000 Nepalese older adults (aged 50+ years), with a follow-up interview two years later. General objectives are to develop a new, longitudinal study of ADRD and other aging-related changes in health among older Nepalese adults and to build capacity for the conduct of systematic population research in ADRD. The cognitive battery currently uses LASI-DAD's protocol as a baseline, and additional tests will be validated to cover all cognitive domains of interest. The team recently finished its focus group review of the Nepali HCAP translation, and it is working to train local staff on effective implementation of the battery in interviews.

Hot Topic: Evaluation of Literacy Across the HCAP Network

Miguel Arce Rentería and Emily Briceño

The influence of education, and quality of education, on neuropsychological test performance is well established, making associated factors important to capture when conducting cognitive battery tests. Testing respondents with little to no literacy or schooling therefore raises a challenge in ensuring neuropsychological test validity, especially given the prevalence of such individuals in LMICs. Rentería and colleagues found that illiteracy independent of education predicted lower baseline cognition and increased risk of dementia in subjects; literacy may need to be expanded as a health factor to fully characterize its impacts on cognitive health at

varying levels of aptitude. Briceño identified three main challenges for the HCAP network:

- How to measure literacy and illiteracy cross-nationally in a comparable manner
- How to measure cognition in analogous ways across literate, low-literacy, and illiterate populations, and
- Whether HCAP adaptations for illiteracy change the cognitive construct being measured.

When asked why literacy test instruments need cross-national harmonization, Briceño responded that conceptual harmonization of illiteracy can be helpful, to understand the extent to which low literacy in one context represents a risk factor in another context. King recommended a previous suggestion to operationalize numerical and alphabetical text as an important first step in adapting tests for illiterate respondents. Manly clarified that even though other dimensions of literacy might not be as dependent on reading, keeping reading level tests would preserve literacy information that would not decline with cognitive performance.

Creating a version of the HCAP survey free of literacy tasks would lose valuable data. Looking at literacy using education data from parent studies raised the issue of how education quality may have changed throughout a respondent's lifetime. Bassil emphasized the importance of capturing detailed information on literacy rather than simple polar items, noting the success of HAALSI's approach to comparing literacy task performance with respondent education level and validating tasks through consultation with local teachers and students.[17] Weir subsequently proposed developing a standardized protocol for HCAP studies to administer literacy testing. Additional discussion underscored the benefits of nonverbal performance tasks, or use of shapes (circles and squares in Trails; symbols cancellation) that avoids letters and numbers (e.g., Army Beta); survey protocols do not need to be fully identical, adapting tests for country-specific considerations might be more productive. It is notable that many who are illiterate are cognitively healthy; examining earlier test results for these individuals could be informative. There might be more evidence of practice effects for low-literacy individuals, especially for cohorts who are relatively new to testing.[18]

Hot Topic: Measuring Executive Function Across the HCAP Network

Jennifer Manly, Lindsay Kobayashi

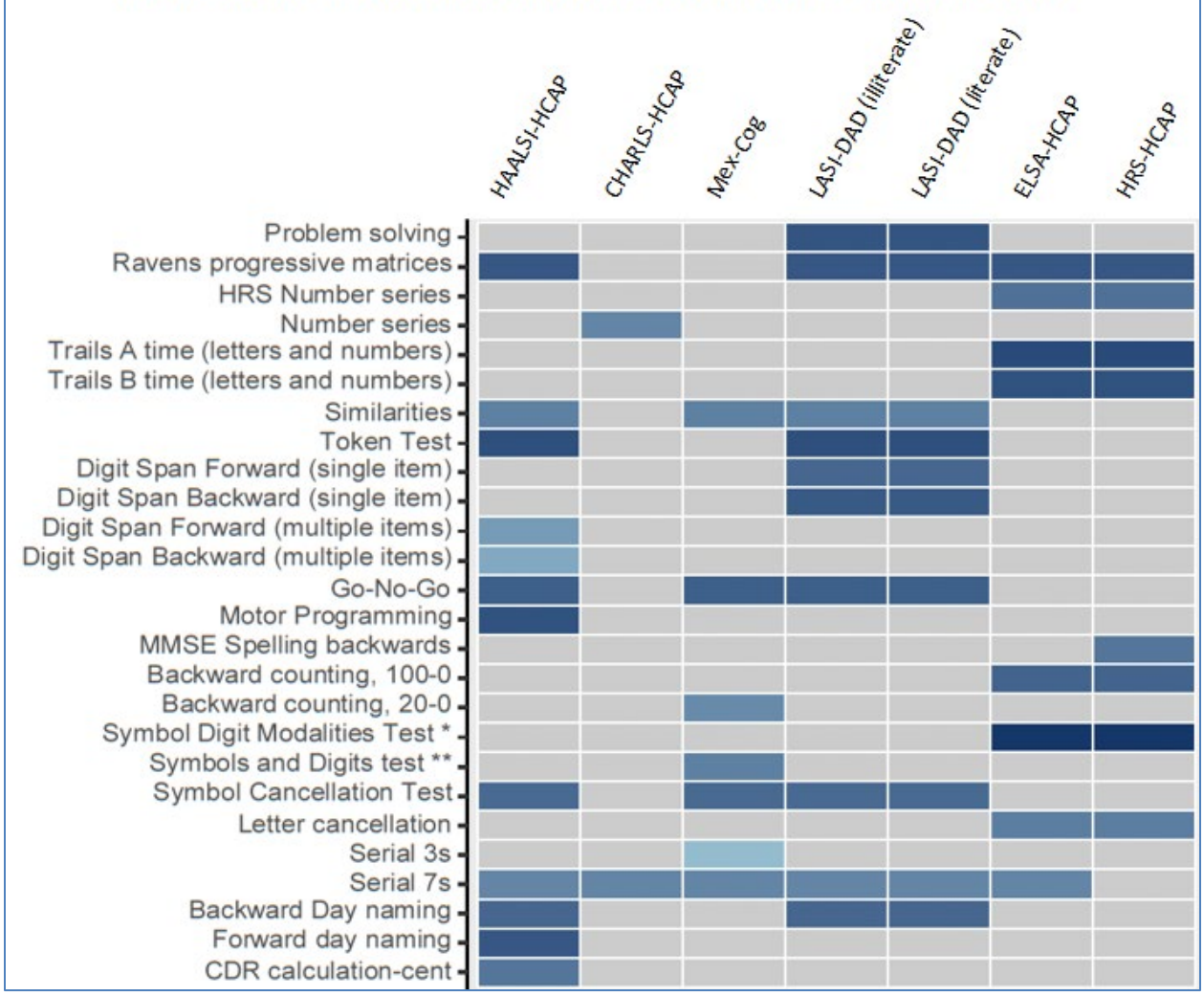
Executive function (EF) covers a broad range of cognitive abilities (e.g., planning, strategic thinking, initiation, sequencing, organization, self-monitoring, updating, persistence, judgement, decision-making, abstraction) that generally revolve around "control and coordination of cognitive operations"; Salthouse, 2005 found that most of the assumed EF variables load onto fluid intelligence and psychomotor speed factors. Test items that try to capture EF tend to probe one of three core subdomains: (1) the ability to set-shift (cognitive flexibility); (2) the ability to update working memory; or (3) the ability to inhibit responses.

[17] In the chat, Bassil noted that HAALSI-HCAP administers a vision and hearing test. Even when taking into consideration the high prevalence of visual impairment, there are still strong levels of discordance between the objective tests and self-reported education. They also show each letter or word on the tablet in a VERY large font, one letter/number at a time. Wong subsequently asked whether cognitive tests should be adjusted or skipped based on results of vision/hearing tests.

[18] See also Salthouse, 2013 on effects of first occasion test experience on longitudinal cognitive change.

However, the definition of EF remains nebulous enough that current tests may not accurately capture its function. Although HCAP studies employ a broad range of EF tests, these tests also rely on literacy and cultural knowledge that warrants later adaptation to specific country protocols (Table 3).

Table 3. HCAP Executive Functioning Test Items Across Six HCAP Studies



Note: The strength of the blue shading indicates the strength of association (the factor loading) between the test item and the latent trait for the domain it represents. Cells in gray indicate that an item was not administered.

Kobayashi highlighted the challenge of adapting EF measures for HCAP while deciding whether to prioritize cognitive function assessments or dementia diagnosis. Several studies have adapted various EF measures that may be promising anchors, but this adaptation would require further validation across HCAP studies. Kobayashi emphasized that the HCAP network would prioritize providing guidance and support for measuring cognitive domains like EF, with a specific goal to implement common protocol guidance for all HCAP studies. Meeting participants supported using cultural context-specific measures of EF and harmonizing data later, especially because HCAP studies in Latin America and South Africa prioritize different

components of EF tasks than other regions prioritize. Part of these cultural considerations include adapting EF tasks to low-literacy and illiterate populations; child studies of EF could inform adaptations, given that children also express low levels of literacy.

Several meeting participants also suggested that EF tasks in HCAP should capture a broad range of cognitive abilities. Gross and Bassil listed the token task, single digit mentality test, Raven's Progressive Matrices test, Go/No-Go task, and additional visuospatial tasks as measures previously shown to be effective, with Gross noting that instrumentation should be standardized between studies. King noted that although several of these EF tasks are well-established and facilitate data linkage, HCAP studies might benefit from implementing newer tasks more sensitive to nuances in EF. He also added that the UK Biobank has a speed of processing measure that captures simple reaction time administered to a range of ability levels. Rentería also supported EF task expansion but emphasized that the metrics for task effectiveness need to be better defined and ideally set in relation to the goals of the HCAP network.

Weir and Manly reiterated the goal of including EF in HCAP cognitive batteries, asking what EF tasks are critical for daily use in cultural contexts and how these tasks could inform more specific dementia diagnoses. Subject matter experts with specific cultural familiarity could potentially inform this discussion, such as local neuropsychologists consulting for each HCAP study. Network studies could use upcoming waves as an opportunity to pilot test the EF tasks discussed before deciding on a single method.

Pilot Study Updates

Effect of Informant Cognition and Relationship Quality on Ratings

Joanne Feeney

Using data from ELSA (N=1,050), TILDA (est. N=952), and HRS-HCAP (N=3,183) studies, an ongoing pilot project aims to (1) investigate how type and quality of informant relationships to the respondent affect reports of cognitive change, (2) measure the impact of informant cognitive function on reporting by spouse/partner informants, and (3) evaluate how accounting for such informant data might improve instruments and protocols for future HCAP work. The pilot study commenced in September 2023 and is projected to finish by May 2024. HRS and ELSA show similar proportions of child-parent and spouse/partner informants in their samples for the pilot; while TILDA data are still being collected, to date TILDA shows a higher prevalence of child rather than spouse/partner as informant.

Children were more likely than spouses to report cognitive decline in respondents, though this difference was negligible after adjusting for respondent age. Among spousal informants, decreases in closeness were predictive of increased data missingness on the Informant Questionnaire on Cognitive Decline (IQCODE) but did not correlate with increased scoring of cognitive decline. Higher spousal relationship quality, however, predicted significant reductions in reporting several IQCODE items. The pilot study team will focus future work on characterizing parent-child informant relationships and expanding analyses of spousal cognition in both the

ELSA and HRS datasets, ultimately repeating the analyses with TILDA in early 2024 when data become available.

Discussion

Weir noted that because informants are not experimentally assigned, differences in study protocols may influence the distribution of informant types (e.g., children, spouses); in particular, because TILDA uses spouses as informants, they cannot be re-used, potentially skewing informants toward other types. Feeney clarified that all three studies assessed in the pilot evaluated parallel measures of relationship quality in spouse/partner informants, but the number of responses from TILDA would likely be low since respondents' spouses were often in the study themselves.

Harmonizing TILDA, NICOLA, ELSA, and HRS

Andrew Steptoe on behalf of Shabina Hayat and Sarah Assaad

Steptoe presented updates on a pilot grant examining the implementation of the HRS protocol across ELSA, HRS, TILDA, and NICOLA HCAP studies. A literature review to inform qualitative questionnaires is currently underway, to be followed by interviews of stakeholders from each study team. Current data from the literature review has identified several opportunities for harmonization, including recruitment methods for respondents, treatment of interviewers, tools and technology, fieldwork management, costs, and quality assurance. The literature review additionally identified gaps in coverage of data collection and analysis. Hayat and Assaad welcomed advice on other potential resources to include in their literature review. By February 2024, the study team will compare quantitative data on HCAP data collection with operational factors across the four studies, concluding with potential ELSA focus group sessions to inform how to best adapt HCAP for English and Irish contexts.

Discussion

Douhou suggested that the team contact Germany's GESIS institute for insights on how to harmonize data within multicultural communities like those in the UK and United States.

Weighting to Account for Selective Attrition in TILDA-HCAP

Christine McGarrigle

The TILDA team has begun scoping work for a pilot study developing population weights to account for potential selection bias in TILDA-HCAP as a longitudinal cohort study of aging. The study is set for launch in December 2023. McGarrigle's team will calculate the inverse probability censored meant to mimic the cohort population lost to attrition. By linking attrition data with external bias parameters (e.g., death certificates, medication use data), the team will also develop inverse probability selection weighting to understand death-related study attrition. Early scoping work revealed that deceased study attritors expressed lower MMSE scores than living attritors and respondents who remained in the study. Of attritors from the TILDA study, 21 percent had died specifically from dementia, illustrating the loss of data on severe cognitive decline due to death-related attrition. Lower MMSE scores were also observed in respondents who participated in proxy or end of life (EOL) interviews—McGarrigle noted that

data from some respondents with significant cognitive decline were excluded because the TILDA HCAP protocol could not conduct proxy reports, which future weighting should account for.

Discussion

Weir noted the importance of this pilot study to compensate for a loss in representativeness when core studies lose respondents due to cognitive difficulty. Bravo also compared the pilot study to Chile-Cog's efforts to link respondents to population death certificates and suggested future collaboration, which McGarrigle welcomed.

Activity Measures in Informant Interviews

Céline De Looze, Christine McGarrigle

A separate pilot study by the TILDA team examines how changes in informant activity measures reduce risk stratification for dementia classification, and how imputing cognitive function as a proxy measure for informant activity might reduce data missingness. Using subsamples from the HRS (N=3,032), ELSA (N=958), and TILDA (N=426 to date) HCAP studies, the team will develop factor scores for cognitive function to assess emergent clustering patterns with informant activity measures. In a sample k-means clustering model of HRS data, De Looze found respondents could be classified generally as active-social, sedentary-social, or sedentary-nonsocial. Preliminary regression modeling revealed higher education, MMSE scores, and cognitive function in the TILDA population than in ELSA or HRS; this pattern was also reflected in the informant activity measures. Pooling data from the three cohorts found that both the informant measures and the HRS k-means clusters were significantly associated with composite cognitive battery scores. De Looze noted that more work would be needed to account for less clear sensitivity analyses of these measures in TILDA cognitive data compared to HRS and ELSA. Future development will also focus on imputation for missing cognitive data and informant scores, weighted analyses, and other research questions.

Group Discussion and Next Steps

Harmonization among HCAP Studies

With the shifting focus towards LMICs, King noted that HCAP batteries should standardize sensory impairment testing. A NICOLA sub-study currently implements visual acuity tests for respondents through a smartphone app, which the team hopes to use to collect three visual and hearing tests in the future. King also suggested that HCAP studies agree on a strategy for recording interviews to inform data quality checks and scoring. Douhou noted that studies like SHARE lacked legal permissions to record and attempts to standardize such recordings would need to consider legal parameters as well as the comfort of the respondent and interviewer. Douhou raised concerns that increased training could result in interviewer burden and issues with harmonization; however, Gross clarified that such issues would likely be negligible when considering much larger data variance between study cohorts.

Given the number of potential items for harmonization, de Leon suggested the HCAP network communicate what resources it could provide to study teams as well as what resources teams

would need to independently secure. NIA staff clarified that statistical harmonization is better approached through a centralized effort, such as Gateway, than by independent teams.[19]

Topics for Future Discussion

Langa summarized suggestions for topics of interest for future calls, including:

- executive function as a critical domain for assessing dementia
- measures of processing speed
- literacy, including measures of quality of education
- informant effects on respondent reports
- sensory impairments, especially in LMICs and how to accommodate for changes in sensory perception over the lifespan that might impact cognitive test performance
- attrition effects on survey data quality

Meeting participants added other topics, including:

- Super agers (ages 80+) and factors that generally contribute to positive brain health
- Harmonization of biomarker analyses cross-nationally, including accounting for the increasing number of individuals receiving amyloid monoclonal antibody treatments[20]
- Further discussion of relevant data to collect in the HCAP survey (e.g., when an HCAP has no parent survey; various aspects of interview quality, such as a narrative account from interviewers) and recommended intervals between HCAP waves[21]
- How to use results from vision and hearing assessments
- Potential testing effects from core study-embedded HCAP respondents who may receive more exposure to the HCAP cognitive battery

Other suggested action items include:

- Document instrumentation for interviewer reports throughout testing to better inform respondent answers
- Document how cognitive testers are certified/trained
- Collect more systematic feedback about the interviewer experience with the project

[19] The HCAP Network has a statistical harmonization core led by Rich Jones; Jones, Weir, Langa, and Kobayashi can provide additional support and refer study PIs to relevant SMEs. See Briceño, et al. 2022 and Briceño, et al. 2021 for pre-statistical considerations for harmonization of cognitive instruments. In the chat, Briceno noted that "Wechsler tests would be a good reference for the types of details that are helpful for documentation of the details of administration and scoring procedures. For example, the WMS-IV manual has a detailed appendix with the specific criteria used for scoring responses for the Logical Memory story, and the administration instructions are very specific." She also indicated that copyright issues are a big issue in sharing the administration/scoring details publicly, which is why the details are often unpublished. Rentería added that some of the most comprehensive documentation are readily online through the MHAS/Mex-Cog website mhasweb.org.

[20] LASI-DAD and HRS have previously collaborated on biomarker calibration studies, and Faul noted that the Biomarker core pilot testing is examining the utility of NfL as the most promising candidate for harmonization. Following a question on whether measuring any other biomarkers was necessary given NfL's clear efficacy, responses from Faul, Weir, and Manly indicated that other biomarkers (i.e., t-tau, A-Beta42, GFAP) have historically demonstrated efficacy to justify continuing current 4-Plex A assays.

[21] Recognizing that large surveys would likely need to weight frequency of waves against full utilization of the representative power of the sample size; intervals could be variable according to respondent age at baseline.

beyond the current perfunctory post-interview questions; more systematic responses can help with training the next group and interviewer retention
- Document elements of field data collection (e.g., where examinations took place) using the Mex-Cog check-off chart as a reference
- Encourage exchanges of fieldworkers across HCAP-integrated studies[22]
- Connect the NICOLA team with a SHARE collaborator to examine measures of cognitive resilience and "super-agers" within HCAP
- Circulate the CHARLS recommendations on interviewer training and coding for missing data prepared by Gross and Kobayashi

NIA Closing Remarks

Following Chatterji's remarks that the balance between harmonization and context-specific accuracy is a longer-term issue that solutions may only be able to approximate, Kobayashi suggested that achieving both goals may be a matter of understanding the methodology used for statistical harmonization and implementing intentional anchor items. The incorporation of HCAP into several longitudinal studies also poses new methodological opportunities for data linking, but unique challenges for harmonization as well.

[22] HRS regularly opens up its interviewer training for observation by other studies.

Appendix A: Meeting Agenda

5th Annual Meeting of the Harmonized Cognitive Assessment Protocol (HCAP) International Network

October 12–13, 2023
Embassy Suites by Hilton Washington DC Chevy Chase Pavilion
4300 Military Road, NW ● Washington, DC 20015

MEETING AGENDA

*Virtual Presenter

Thursday, October 12

9:30 AM **Morning Refreshments, Tenleytown Ballroom**

10:00 **Welcome and Introductions**
Ken Langa, David Weir

NIA Welcome
Minki Chatterji, Jonathan King

10:15 **HCAP U24 Network Updates (Including Plans for Renewal Grant Submission)**
David Weir, Ken Langa, Lindsay Kobayashi

10:30 **Updates from Latin American HCAP Studies** (10 minutes each)
- MEX-COG | Silvia Mejia-Arango*
- CHILE-COG | David Bravo
- CADAS | William Dow*

11:00 **Updates on Pilot Studies in Latin America** (15 minutes each)
- Harmonization of 10/66, MHAS, ELSI | Jorge Llibre-Guerra*
- Informant Measures in HRS, CHARLS, Mex-Cog | Yuan Zhang*, Phillip Cantu*
- Education, Social Protection and Cognition in Chile and Mexico | Irma Elo*, Rebeca Wong*

12:00 PM **LUNCH | Onsite**

1:00 **Updates from HCAP Studies Recently in the Field** (10 minutes each)

- LASI | Jinkook Lee*
- ELSA | Andrew Steptoe*
- TILDA and NICOLA | Christine McGarrigle, Bernadette McGuinness
- HRS | *Lindsay Ryan
- SHARE | Salima Douhou
- CHARLS | Yaohui Zhao*
- HAALSI | Lisa Berkman
- Kenya (KLPS) | Ted Miguel*
- Kenya (LOSHAK) | Josh Ehrlich*

3:00 **Biomarker Core Update**

Jessica Faul and Bharat Thyagarajan*

- AD Biomarker Activities in the NIA Biomarker Network

3:30 **BREAK**

3:45 **Gateway Update on HCAP-Related Data and Activities**

Alden Gross, Jinkook Lee*

4:15 **Updates from Planned Studies** (10 minutes each)

- Malawi | Hans-Peter Kohler*, Iliana Kohler*
- Egypt | Mohamed Salama*
- Ghana | Irma Elo*
- Brazil | Cleusa Ferri*
- Malaysia | Norma Binti Mansor*
- Lebanon and Nepal | Carlos Mendes de Leon

5:15 **ADJOURN**

6:00 **GROUP DINNER | Maggiano's Little Italy**
5333 Wisconsin Ave. NW., Washington, DC
(4-minute walk from the hotel)

Friday, October 13

8:30 AM **Morning Refreshments, Tenleytown Ballroom**

9:00 **Hot Topics: Evaluation of Literacy Across the HCAP Network**

Emily Briceño, Miguel Arce Rentería

Discussion questions:

- *How do HCAP network studies measure literacy, and how is information about literacy used procedurally in HCAP assessments (e.g., skip patterns, test item substitutions, etc.)?*
- *Which items/tests in the HCAP battery work well for illiterate and low literacy participants, and which items do not work well?*
- *What are some of the unique needs of illiterate and low literacy populations in engaging in the HCAP informant interviews, and how have HCAP teams addressed these needs?*

9:30 **Updates on Pilot Studies** (15 minutes each)

- Effect of Informant Cognition and Relationship Quality on Ratings | Joanne Feeney
- Harmonizing TILDA, NICOLA, ELSA, HRS | Andrew Steptoe*
- Weighting to Account for Selective Attrition in TILDA-HCAP | Christine McGarrigle
- Activity Measures in Informant Interviews | Céline De Looze*, Christine McGarrigle

10:45 **Hot Topics: Measuring Executive Function Across the HCAP Network**
Jennifer Manly, Lindsay Kobayashi

Discussion questions:

- *What aspects of EF are important for measuring AD/ADRD in each HCAP study context?*
- *What EF test items are being adapted/developed and are working well in the experience of HCAP teams working in low-to-middle income and/or low literacy settings? What items are not working?*
- *What items could be suitable anchors to recommend for inclusion in all HCAP studies?*
    - *Anchors must be as free as possible of literacy/numeracy, language, or cultural assumptions.*

11:15 **Group Discussion and Next Steps**

- Preparing for HCAP Wave 2 data; what are key issues to address?
- Current concerns and roadblocks?
- Plans for joint analyses and publications?
- Solicitation of ideas for small-group follow-up sessions.
- Future priorities and directions from NIA's perspective (Minki Chatterji, Jon King)

12:30 PM **ADJOURN**

Appendix B: Meeting Attendees

***In-person Participants**

U.S. Health and Retirement Study (HRS) and HCAP Network Team

***David Weir**, Co-PI and Sampling Core Leader, HCAP Network; Co-Investigator (Co-I), HRS-HCAP; PI, Irish HCAP R01, Director, HRS; University of Michigan

***Ken Langa**, Co-PI and Diagnosis and Validation Core Leader, HCAP Network; PI, HRS-HCAP; Co-I, HRS; Brain Attack Surveillance in Corpus Christi-Cognitive Aging Study **(**BASIC-Cog), University of Michigan

***Jessica Faul**, HCAP Network Biomarker Core Leader; Co-I, HRS-HCAP; Co-I, HRS; University of Michigan

Steve Heeringa, Co-I, HRS-HCAP, BASIC-Cog; University of Michigan *(Day 1 Only)*

***Richard Jones**, HCAP Network Statistical Harmonization Core Leader; Co-I, HRS-HCAP; Co-I, HRS; Brown University

***Lindsay Kobayashi,** Assistant Professor, University of Michigan, HRS

***Sarah Kwiatek,** Project Manager**,** University of Michigan, HRS

***Jennifer Manly**, Co-I, HRS-HCAP; Co-I, HRS; Columbia University

Ryan McCammon, HRS-HCAP Collaborator; University of Michigan

Lindsay Ryan, HCAP Network Protocol Content and Administration Core Leader; co-I, HRS-HCAP; University of Michigan

Bharat Thyagarajan, HRS co-I, and Professor, University of Minnesota *(Day 1 Only)*

Brain Attack Surveillance in Corpus Christi (BASIC-Cog)

Emily Briceño, Co-I, University of Michigan and HCAP Pilot grantee

Caribbean American Dementia and Aging Study (CADAS)

William Dow, PI, University of California, Berkeley

Jorge Llibre-Guerra, Team Member; Washington University in St. Louis

Chile Cognitive Aging Study (Chile-Cog)

Jere Behrman, Co-PI, University of Pennsylvania *(Day 1 Only)*

***David Bravo**, Co-PI, Catholic University of Chile

Irma Elo, Co-PI, University of Pennsylvania

Catalina Bravo, Team Member, Pontifical Catholic University of Chile *(Day 1 Only)*

China Health and Retirement Longitudinal Study (CHARLS)

Yaohui Zhao, PI, Peking University

English Longitudinal Study of Ageing (ELSA)

Andrew Steptoe, PI, University College London

Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI)

***Lisa Berkman**, PI, Harvard University *(Day 1 In-Person, Day 2 Virtual)*
Darina Bassil, Co-I, Harvard University
Julia Rohr, Project Director, Harvard Center for Population & Development Studies *(Day 1 Only)*

Kenya Life Panel Surveys (KLPS-5A)

Edward (Ted) Miguel, PI, University of California, Berkeley *(Day 1 Only)*
Madeline Duhon, Postdoctoral Scholar, University of California, Berkeley
Michael Walker, Economist, University of California, Berkeley

The Irish LongituDinal Study on Ageing (TILDA)

Céline De Looze, Research Fellow, Trinity College Dublin
***Joanne Feeney**, Senior Researcher, Trinity College Dublin
***Christine McGarrigle**, Senior Research Fellow Epidemiology, Trinity College Dublin
Ann Monaghan, Project Manager, Trinity College Dublin *(Day 1 Only)*
Sinead McLoughlin, Senior Data Manager, Trinity College Dublin

Lebanon Study on Aging and HeAlth (LSAHA)

***Carlos Mendes de Leon**, PI, Nepal Study on Dementia and Aging (NSDA), Georgetown University
Monique Chaaya, Co-PI, American University of Beirut
Martine El Bejjani, PI, American University of Beirut
Lara Chehabeddine, Team Member, American University of Beirut *(Day 1 Only)*

Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD)

Jinkook Lee, PI, University of Southern California
***Alden Gross**, Co-I, LASI-DAD, and MPI, Gateway to Global Aging Data; John Hopkins Bloomberg School of Public Health
Erik Meijer, Senior Economist, Center for Economic and Social Research (CESR), University of Southern California
Emma Nichols, Research Scientist, CESR, University of Southern California
Pranali Khobragade, Survey Director, University of Southern California

Longitudinal Study of Health and Ageing in Kenya (LOSHAK)

Joshua Ehrlich, Co-PI, and co-I, LASI-DAD; University of Michigan *(Day 1 Only)*
Niranjani Nagarajan, Team Member, University of Michigan *(Day 1 Only)*

Mexican Health and Aging Study – Cognitive Aging Ancillary Study (Mex-Cog)

Rebeca Wong, PI, Mex-Cog; University of Texas Medical Branch
Miguel Arce Rentería, Mexican Health and Aging Study (MHAS), Mex-Cog, HCAP Network Pilot Awardee; Columbia University
Phillip Cantu, Team Member, University of Texas Medical Branch
Silvia Mejia-Arango, Team Member, The University of Texas Rio Grande Valley

Joseph Saenz, Team Member, Mex-Cog; University of Southern California *(Day 1 Only)*

Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA)
***Bernadette McGuinness**, co-PI, Queen's University Belfast
Charlotte Neville, Scientific Officer, Queen's University Belfast
Leeanne O'Hara, Research Fellow, Queen's University Belfast

Survey of Health, Aging and Retirement in Europe (SHARE)
***Salima Douhou**, Coordinator, Max Planck Institute
Marcela Otero, Research Scientist, Munich Center for the Economics of Aging
David Richter, Director SHARE Infrastructure *(Day 1 Only)*
Beatrice Baaba Tawiah, Researcher, Munich Research Institute for the Economics of Aging and SHARE Analysis

Other Interested Study Contributors
Isaac Acosta, Study PI, 10/66, MHAS harmonization advisors (Mexico)
Halimah Awang, PI, Malaysia Ageing and Retirement Survey (MARS) *(Day 1 Only)*
Yamunah Devi Apalasamy, Team Member, MARS *(Day 1 Only)*
David Bell, PI, Healthy Aging in Scotland (HAGIS) *(Day 1 Only)*
Fernando Bertolotto, PI, Study of Health and Aging in Uruguay (ELSE Uy) *(Day 1 Only)*
Ian Deary, Co-investigator, HAGIS *(Day 1 Only)*
Elaine Douglas, Co-Researcher, HAGIS
Cleusa Ferri, Researcher, ELSI-Brazil, Universidad Federal de Sao Paulo
Elizabeth Frankenberg, Co-PI, Study of the Tsunami Aftermath and Recovery (STAR)
Hans-Peter Kohler, PI, Malawi Longitudinal Study of Families and Health (MLSFH) *(Day 1 Only)*
Ying Liu, Research Scientist, Gateway to Global Aging Data, University of Southern California (*Day 2 only*)
Juan Llibre-Rodriguez, Study PI, 10/66, MHAS harmonization advisors (Cuba/USA) *(Day 1 Only)*
Sneha Mani, Team Member, Gateway to Global Aging Data and Chile-Cog (SPS), Johns Hopkins University
Norma Binti Mansor, PI, MARS *(Day 1 Only)*
Sara A. Moustafa, Co-I, A Longitudinal Study of Egyptian Healthy Aging (AL-SEHA) *(Day 1 Only)*
Mohamed Salama, PI, AL-SEHA, The American University in Cairo *(Day 1 Only)*
Duncan Thomas, co-PI, STAR, Duke University
Jenny Wilkens, Senior Programmer, Gateway to Global Aging Data, University of Southern California
Yuan Zhang, Assistant Professor, Columbia University, HCAP pilot grantee

National Institute on Aging (NIA)
Richard Hodes, Director *(Day 1 Only)*
***Amy Kelley**, Deputy Director *(In-person morning of Day 1 only)*
Lis Nielsen, Director, Division of Behavioral and Social Research (BSR)
***Minki Chatterji**, Program Officer, Population and Social Processes Branch, BSR

***Jonathan King**, HRS Project Scientist; Program Director, BSR

Dallas Anderson, Director, Epidemiology of Dementia Program, DN *(Day 1 Only)*
David Braudt, NIA, Program Official, BSR
Shanna Briel, Social Science Analyst, BSR
Elena Fazio, Program Official, BSR
Kimberly Firth, Supervisory Health Scientist Administrator, Scientific Review Branch, Division of Extramural Activities (DEA)
Maryam Ghaleh, Program Official, DN *(Day 1 Only)*
Amelia Karraker, Program Official, BSR *(Day 2 Only)*
Theresa Kim, Program Officer, PSP, BSR *(Day 1 Only)*
Charlie Le, Social Science Analyst, BSR
Marilyn Miller, Program Director, DN *(Day 1 Only)*
Carmen Moten, Health Scientist Administrator, Scientific Review Branch, DEA *(Day 1 Only)*
Dana Plude, Deputy Director, BSR
Nina Silverberg, Director, Alzheimer's Disease Centers Program, DN *(Day 1 Only)*
Luke Stoeckel, Program Official, BSR

Rose Li and Associates, Inc. (RLA)
***Rose Li**, Senior Project Director
***Sofia Jones**, Meeting Manager
***Rebecca Lazeration**, Lead Meeting Tech
***Sparsha Muralidhara**, Science Writer