National Institutes of Health
National Institute on Aging

The Effect of Education on Recent Dementia Trends: A Look Forward

The Keck Center of the National Academies
Washington, DC
September 14, 2016

Meeting Summary

Revised April 10, 2017

This meeting summary was prepared by Rose Li and Associates, Inc., under contract to the National Institutes of Health (Contract no. HHSN271201400038C). The views expressed in this document reflect both individual and collective opinions of the meeting participants and not necessarily those of the National Academy of Sciences, National Institutes of Health, and/or the U.S. Department of Health and Human Services. Contributions to the preparation of earlier versions of this meeting summary by the following individuals is gratefully acknowledged: Neon Brooks, Eileen Crimmins, Carole Dufouil, Vicki Freedman, John Haaga, Mark Hayward, Jonathan King, Kenneth Langa, Rose Li, Jennifer Manly, David Miller, Christina Szalinski, Samuel Thomas, Nancy Tuvesson, and Jennifer Weuve.

Table of Contents

Acronym Definitions

ADAMS	Aging, Demographics and Memory Study
CDC	Centers for Disease Control and Prevention
CFAS	Cognitive Function and Aging Studies
DNA	deoxyribonucleic acid
FHS	Framingham Heart Study
GWAS	genome-wide association study
HCAP	Harmonized Cognitive Assessment Protocol; Healthy Cognitive Aging Project
HRS	Health and Retirement Study
ICD	International Classification of Diseases
IALSA	Integrative Analysis of Longitudinal Studies of Aging and Dementia
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
P3G	Public Population Project of Genomics
PET	positron emission tomography
PIK	protected identification key
RNA	ribonucleic acid
SNP	single-nucleotide polymorphism
WHICAP	Washington Heights Inwood and Columbia Aging Project

Meeting Summary

The National Institutes of Health (NIH) National Institute on Aging (NIA) commissioned the Committee on Population to convene an expert meeting on September 14, 2016, to provide advice on the most pressing issues related to dementia trends and education and to generate new ideas for research that will contribute to the welfare of the United States.

The meeting agenda included introductory remarks followed by invited presentations and discussions.

The following themes emerged from the presentations and discussion:

- Dementia is linked to early- and mid-life variables including socioeconomic status, physical activity, cognitive activity, stress, occupation, income, environmental exposures, and vascular health. Education can be a confounder for each of these variables.
- The incidence and prevalence of dementia appear to be declining in the general population, alongside a parallel increase in educational attainment. At the same time, there has been an increase in the prevalence of dementia among older adults who have completed high school or higher education.
- The content and quality of a year of educational attainment can vary widely between geographic areas and among racial and ethnic groups within the same locality and over time. This variation may lead to differences in the relationship between educational attainment and cognitive outcomes.
- Research on diverse cohorts is valuable for revealing trends and mechanisms of trends in dementia. Unique insights can be derived from studies of diverse populations.
- Historical events can be a source of natural experiments. Studying cohorts before and after changes in education policies can provide valuable information on education's effects on cognition.
- Historical context should be considered when evaluating cohorts. Wars, disease outbreaks, changes in social structure, improvements in social welfare and health care, and education reform can be significant early-life confounders of the relationship between education and later life cognitive functioning.
- Past early-life studies can be revisited to evaluate cognitive function in mid-life. Databases are now available to find mid-life data for participants in early-life studies and to track them passively through growing datasets.
- New –omics research provides the opportunity to study how genetics influences cognition and educational attainment, as well as how environmental factors shape gene expression and gene transcription that may also contribute to cognition and education.

This report summarizes the presentations and discussions that occurred during the seminar. Appendix 1 contains the meeting agenda, and Appendix 2 identifies the list of participants.

Introductory Remarks

Mark Hayward, University of Texas

The goal of this meeting was to inform the latest scientific and technical progress and challenges related to education and cognitive aging/dementia. There are 46 million dementia cases worldwide, and 131.5 million cases are projected for 2050. The estimated total worldwide cost of dementia was $818 billion in 2015.[1] The economic burden of dementia could grow three-fold in the next 35 years without effective interventions to prevent or delay onset. Education may improve cognitive outcomes, even later in life. Education in this context spans from early-life interactions with parents, formal schooling, occupational complexity, leisure time activities, and cognitive training. The research and discussion in this meeting highlight the progress being made to understand the link between education and dementia and inform next steps.

Invited Presentations

Overview of the Relationship Between Education and Dementia Trends in the United States

Kenneth Langa, University of Michigan

Dr. Langa explained that dementia is caused by Alzheimer's disease (60-70 percent), vascular disease (20-30 percent), or other causes (e.g., Parkinson's disease, reversible causes). However, mixed dementia—a combination of Alzheimer's disease and vascular pathology—is likely the most common cause.

There are several challenges to diagnosing dementia in clinics and in populations. First, cognitive decline often progresses slowly, and the threshold of disability can be hard to distinguish reliably. Second, there is not a one-to-one correspondence between brain pathology and cognition— a recent study suggested that common brain pathologies explain only about 40 percent of cognitive decline.[2] Third, several methodological factors complicate diagnosis: (1) disease trajectories may be very different in samples that do not represent the general population (e.g., the Alzheimer's Disease Neuroimaging Initiative), (2) there is selective attrition (i.e., frail people are more likely to leave studies), (3) proxies must be used when people can no longer answer surveys for themselves, (4) recruiting participants from nursing homes is difficult, and (5) there may be reverse causality from cognition to social interactions.

The theory of human brain development suggests that from birth through age 6 there is substantial growth in connections between neurons and neural connections that are not used and are subsequently pruned away. This sensitive period might be important for the development of cognitive reserve, the health of the neurons, and the number of connections among neurons. Although neurogenesis seems especially important for the school years, the process likely continues through the life course.

[1] Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Printa M. World Alzheimer's Report 2015. Alzheimer's Disease International. 2015 Aug.

[2] Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, Bennett DA. Much of late life cognitive decline is not due to common neurodegenerative pathologies. Ann Neurol. 2013; 74(3):478-89

The cranial nerves are the direct connection between the world and the brain. They carry signals of sight, smell, taste, and hearing, which then spread to other parts of the brain. Education is transported primarily through vision and hearing—this is the neurobiology of learning.

According to Hayward and colleagues, early-life factors such as parental education and income, individual endowments (e.g., genes), childhood physical and mental health, and childhood social context influence a person's educational attainment. Education influences adult health behaviors and life opportunities, including healthy lifestyles and access to health care, access to good jobs and networks/relationships, and sophisticated cognitive skills, all of which likely influence mortality. However, the complexities of these early-life factors can confound these adult mechanisms.[3] Identifying what is causal about education is challenging but important for identifying clinical and policy interventions.

The cognitive reserve hypothesis[4] suggests that people with high cognitive reserve, often correlated with many years of education, may be able to compensate for age-related brain pathology and therefore stave off cognitive decline until later in life, compared to someone with low cognitive reserve or few years of education. A person with high cognitive reserve may therefore face a lower lifetime risk of dementia and a longer cognitively healthy life expectancy.

Some recent studies in the United States and other countries suggest a decline in the incidence and prevalence of dementia in people from high-income countries. The Framingham Heart Study (FHS) showed that the incidence of dementia in people ages 60 and older declined significantly between 1977 and 2008—particularly in those with at least a high school diploma. In the Health and Retirement Study (HRS) sample, the average years of education increased by almost 1 year from 2000 to 2010. During the same timeframe, the prevalence of dementia in people ages 65 and older decreased from 11.6 percent to 9.2 percent; controlling for education accounts for about half of that decline.

Dr. Langa summarized his remarks by stating that dementia prevalence in the United States declined from 2000 to 2010, consistent with other high-income countries. Rising levels of education in more recently born cohorts, as well as better control of cardiovascular risk, may be contributing to a decline in age-specific risk for dementia. Finally, primary prevention of dementia through social and behavioral interventions appears possible and valuable.

Dr. Langa concluded by posing future research questions: (1) What are the "active ingredients" of early-life and later-life education on brain health, and how can they be delivered in low-, middle-, and high-income countries? (2) What are the brain health implications of recent differential life-expectancy gains for rich and poor? (3) What are the internet and smart phones doing to our brains? and (4) How will population levels of cardiovascular risk factors change in the coming decades?

[3] Hayward MD, Hummer RA, Sasson I. Trends and group differences in the association between educational attainment and U.S. adult mortality: Implications for understanding education's causal influence. Soc Sci Med. 2015 Feb;127:8-18.

[4] Stern, Y. What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society. 2002 Mar; 8(3):448-460.

Discussion

Age of Onset

Dementia is not a condition with an acute onset. The midpoint of a study interval is used as an estimate of age of onset, which allows for an estimation of the age of onset across a population. However, cognitive performance varies over time, and although providing robust evidence of prevalence, a cross-section of the population cannot be translated to individual incidence, because a year later the same person might perform better on a cognitive assessment. Observing individual change-points requires many more observations than can typically be obtained.

Studies often measure a lower-bound threshold of cognitive functioning. When more sensitive measures are applied early and often, a cognitive decline starting 10-12 years prior to diagnosis of the dementia might be revealed. Acquiring earlier measures and determining what is cognitive reserve versus change in cognition, then linking that forward to dementia, could inform understanding of the decline. However, more intensive modeling might not add to an epidemiological study.

Changes Over the Life Course

Most dementia data focus on early cohorts in the 1900s when the education experience was variable. The experience did not stabilize until education reforms occurred during the 1940s and 1950s. Many adverse events occurred during the early 1900s—a measure of height can serve as a measure of early adversities for early cohorts.[5]

In one of the last rounds of the Whitehall Study, researchers noted an increase in functioning of women, which seemed to be entirely due to their educational attainment before and after the war. Similarly, the UK Biobank studied people before and after a change in rules that added 1 additional year of schooling. Significant changes to outcomes resulted from that one rule change. These natural experiments are valuable but rare.

Hayward stated that the world into which a person is born differs from the one to which his or her adult body is exposed. The pace of social change and development in the world is rapid, and complexities from the life course make it difficult to measure early-life influences. Often increases in education are linked to rapid changes in adult exposures and achievement processes.

An International Perspective on Dementia Trends and Their Association with Educational Attainment

Carole Dufouil, INSERM France

Dr. Dufouil summarized five important studies of trends in dementia prevalence in Europe:

[5] Li L, Dangour AD and Power C. Early life influences on adult leg and trunk length in the 1958 British birth cohort. Am J Hum Biol. 2007 Nov-Dec;19(6):836-43.

Cognitive Function and Ageing Studies (CFAS) in the United Kingdom,[6] Stockholm,[7] SNAC-Nordanstig,[8] Zaragoza,[9] and GOT7075.[10] The CFAS study observed a reduction in dementia prevalence across the population across age cohorts, but reported no data on education changes. The SNAC-Nordanstig and Zaragoza studies observed declines across cohorts only in men. Adjusting for differences in education levels did not explain the dementia prevalence differences in men in the SNAC-Nordanstig study, and participants in both cohorts of the Zaragoza study had very low levels of education. The Stockholm and GOT7075 studies reported no changes in dementia prevalence between cohorts.

Dr. Dufouil also summarized three studies of dementia incidence: Rotterdam,[11] Bordeaux (3C and PAQUID),[12] and CFAS. The Rotterdam study observed a non-significant trend toward lower incidence across cohorts, along with a significant increase in educational attainment. Educational attainment was not accounted for in the analysis of dementia incidence. The Bordeaux study observed a decreased incidence in women. This effect was reduced, but still significant, when adjusting for education. The CFAS study found a decreased incidence in men between cohorts but did not take into account education changes.

In summary, there is evidence for decreased dementia incidence and prevalence over time, with some gender differences, but not in all cohorts. All studies except Zaragoza showed evidence for a rise in educational attainment, but this explained only partially, when taken into account, the trends in dementia prevalence and incidence. Education is related to dementia risk, and there are secular trends in educational attainment. A review of prevalence and incidence of dementia risk found that 58 percent of studies showed a predictive effect of education, particularly in developing countries.[13] However, there is no evidence for a link between improved educational attainment and dementia risk.

Dr. Dufouil highlighted issues in the way that dementia is diagnosed: researchers cannot make valid inferences if they cannot compare an outcome between people and across time. A good approach is to look at trends in cognitive trajectory that are independent of the issue of changes in diagnostic criteria. In addition, education variables do not capture all of the

[6] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. Lancet. 2013 Oct 26;382(9902):1405-12.

[7] Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology. 2013 May 14;80(20):1888-94.

[8] Wimo A, Sjölund BM, Sköldunger A, Qiu C, Klarin I, Nordberg G, et al. Cohort effects in the prevalence and survival of people with dementia in a rural area in northern Sweden. J Alzheimers Dis. 2015;50(2):387-96.

[9] de Pedro-Cuesta J, Virués-Ortega J, Vega S, Seijo-Martínez M, Saz P, Rodríguez F, et al. Prevalence of dementia and major dementia subtypes in Spanish populations: a reanalysis of dementia prevalence surveys, 1990-2008. BMC Neurol. 2009 Oct 19;9:55.

[10] Wiberg P, Waern M, Billstedt E, Ostling S, Skoog I. Secular trends in the prevalence of dementia and depression in Swedish septuagenarians 1976-2006. Psychol Med. 2013 Dec;43(12):2627-34.

[11] Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012 May 8;78(19):1456-63.

[12] Grasset L, Brayne C, Joly P, Jacqmin-Gadda H, Peres K, Foubert-Samier A, et al. Trends in dementia incidence: Evolution over a 10-year period in France. Alzheimers Dement. 2016 Mar;12(3):272-80.

[13] Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord. 2011 Oct-Dec;25(4):289-304.

beneficial effects of education, such as greater socioeconomic resources, personal skills, and health behaviors. Education's causal effect on dementia may be smaller than the partial correlation between education and dementia, and therefore it is essential to consider other ways to look at education, other variables, and health behavioral changes.

Discussion

Historical Considerations

The United States started and finished the expansion of secondary education earlier than most countries, which could be significant for epidemiology. In addition, these study participants were children during WWI and WWII. The effects of their wartime experiences may override those of any other experiences. The international results might look different if historical events and education changes are considered.

The portion of the population with less than a high school education was greater than one-third in earlier cohorts, but with a trend toward more education in later cohorts. That group with less than a high school education is becoming increasingly selected, and therefore it is not surprising that mortality has not changed in that portion. The upper group with the most education is growing, so the mortality advances in a growing group of people is a positive finding.

Prevalence Versus Incidence

Eileen Crimmins noted that almost all conditions of old age have increased in prevalence, in part because of a decline in mortality. No change in prevalence in a population that is experiencing a decline in mortality, and therefore living longer, may actually be a decline in incidence.

Disease Pathways and the Relationship Between Education and Dementia Trends

Sudha Seshadri, Boston University

The Framingham Heart Study is exploring whether trends in vascular and other disease pathways explain education trends. Among people enrolled, there is a 98 percent follow-up for mortality. Researchers initiated FHS in 1948-1950 to understand atherosclerosis. They invited two-thirds of all adults ages 30-59 in Framingham, Massachusetts, to participate. Researchers continue to follow participants beyond age 65. The original cohort is seen every 2 years, and four new cohorts have been added since 1972.

Researchers have looked at stroke since the beginning and dementia since 1995. All cohorts undergo ongoing surveillance. Since 1999, participants have undergone periodic magnetic resonance imaging (MRI) and cognitive assessments. The most recent exam included a functional MRI and positron emission tomography (PET) imaging of tau pathology. FHS has 200 donated brains and is following 800 registered brain donors. The FHS biorepository includes ~1.3 million biospecimens and a variety of biomarkers, including amyloid beta, clustrin, and tau. FHS also follows diet, toxins, occupation, socioeconomic status, depression, social network analysis, and biological pathways of its participants.

FHS has a multitude of genomic resources, including Marshfield genome scan, genome-wide genotyping, whole exome and whole genome sequencing, and MediSeq. The National Institute

of Diabetes and Digestive and Kidney Diseases (NIDDK) recently funded an FHS project to study brain RNA expression as well as proteomic screens, telomere length, exosomes, and microRNA.

FHS is following temporal trends in dementia with four epochs of 5 years starting in 1978. Participants are free of dementia at exam and followed beyond that. Participants flagged for dementia receive additional surveillance. Of the 5,000 people followed for dementia, 373 have been diagnosed with dementia. Researchers have observed a decrease in age-adjusted dementia incidence for the 373 participants, but only those with at least a high school education. This trend could be explained by education's positive influences on vascular health, lifestyle, or cognitive reserve. In addition, education could be a marker for early-life socioeconomic status, nutrition, environment (e.g., no lead), or genetics.

Vascular pathologies have been linked to Alzheimer's disease. In the FHS sample, people without a high school diploma showed smaller declines in systolic blood pressure and smaller increases in high-density lipoprotein (HDL) cholesterol. However, adjusting for midlife vascular risk factors did not change the FHS dementia trends. Although having a stroke is associated with increased dementia risk, that risk declines with each epoch.

Dr. Seshadri concluded by noting that the age-specific risk of dementia for FHS participants appears to have decreased over the past 30 years, but only for those with at least high school degree. This trend may be partially explained by slower improvement in vascular risk factors (VRF) in the less educated stratum.

The Role of Genetic Factors in the Relationship Between Education and Dementia Trends

Jessica Faul, University of Michigan

There are many risk factors for dementia: age, ethnicity, education, genetics, smoking, obesity, diabetes, cholesterol, hypertension, stress, and social and cognitive environment. The relative influence of these factors is changing over time. Dr. Faul is interested in examining how social and psychosocial factors modify the relationship between genomics and chronic disease.

ApoE ε4 was one of the first gene alleles to be associated with an increased risk of Alzheimer's disease, both for age of onset and rate of cognitive decline. ApoE ε4 is also a risk factor for non-pathological decline in verbal memory, abstract reasoning, and processing speed. Age-related memory decline in ApoE ε4 carriers diverge from non-carriers before age 60. ApoE ε4 predicts faster decline in people with higher education, but not consistently. ε4 allele carriers score lower in cognitive measures at every education level, but those with a higher education decline slower and those with a lower education decline faster.

Cognitive function is relatively heritable across the lifespan, but the genes influencing cognition are largely unknown. Dr. Faul and colleagues conducted a genome-wide association study (GWAS) analysis of 31 cohorts (approx. 54,000 people), looking at general cognitive function with 2.5 million SNPs. They found four hits: ApoE and its neighboring gene TOMM40; MIR2113, an uncharacterized microRNA previously associated with bipolar disorder and educational attainment; Akap6/NPAS3, a protein kinase/transcription factor previously associated with Alzheimer's disease and brain development; and HMGN1, a nucleosome binding protein important for regulating DNA methylation. DNA methylation is an important epigenetic

mechanism. They also studied how the effect of genes is influenced by age. The general trend was that for younger ages ApoE does not affect cognition as much as for older ages.

More recently, Dr. Faul and colleagues have used gene-based analysis techniques to determine how the genetic variations within specific genes work together to influence memory. They are looking beyond candidate genes and incorporating information from population-based studies. GWAS have revealed that complex health outcomes and behaviors, including cognition, are often highly polygenic. Use of a single genetic variant or candidate genes may not capture the dynamic nature of more complex phenotypes. In a project with Jennifer Smith, Dr. Faul looked at novel ways to include information from GWAS in tests that incorporate genetic and environment interactions.

Drs. Faul and Smith performed gene-based analyses to assess the impact of combined effects of genetic variation across an entire gene region and to examine both common and rare variations to determine relative contributions to trait variability. Their data showed that, for European Americans, a few gene regions were significantly associated with memory: ApoE was suggestively associated before age 80, and other genes after age 80. The results were not consistent for African Americans, probably because all of the genes identified from GWAS were in European Americans.

Beyond genomics, more work is needed on the roles of epigenomics (whether or not a gene is expressed) and transcriptomics (the level to which the gene is expressed) in cognition. Needed are more longitudinal studies that measure genomic and epigenomic variation. HRS is often used in genetic studies, and Dr. Faul is adding a repository of biomarker and epigenetic data, including a minority oversample to find key differences in epigenetics.

Future studies will seek to identify where important genetic variation exists and how to best represent that, as well as changes in the environment, in models. Social scientists can help to decide how to best measure the phenotype and how to account for survival and selectivity, which geneticists might not be considering. The research community should have realistic expectations of what can come of genetics—it is not a science of short-term gain—and to not lose sight of environment. Genes do not change, but epigenetics and other –omics do change in individuals and between cohorts.

Discussion

Genetic Data in Minorities

Dr. Seshadri explained that the rare variants selected for the exome chip were based on Europeans. With sequence data it might be possible to find different rare variants in the same genes for minority samples. Jennifer Weuve added that in her data ApoE ε4 is associated with mortality, and there is increased mortality for African Americans in general, which suggests that selective processes may operate more strongly in this group. Dr. Hayward noted that the survivors are often not very representative of the original birth cohort.

Next Steps in Genetic Studies

Currently, researchers are estimating regression coefficients using the top 70,000 hits from GWAS. The data can then be analyzed into pathways, such as inflammation pathways

implicated in Alzheimer's disease. This process returns researchers to questions related to potential exposures and points research in useful directions. However, it will be necessary to continue to identify individual genes implicated in Alzheimer's disease. It will allow researchers to do cell screens, or organ-on-a-chip screens, and identify what drugs can work against those 70,000 candidates. Ultimately genetics may not be the sole explanation for cognitive aging, but it will explain some of the heterogeneity of outcomes.

The Relationship Among Dementia Trends, Work Conditions, Leisure, and Socioeconomic Factors

Jennifer Weuve, Boston University

Understanding the interplay of occupation, leisure activity, and socioeconomic characteristics with education and dementia can help us determine whether and how to intervene. Working U.S. adults spend more than one-third of their weekday hours at work, which translates to a long exposure over a long period time. The following aspects of occupations could influence dementia risk: cognitive engagement, psychological stress, physical activity, chemical exposures, income, and the material resources available from that income.

A cognitively demanding and/or complex occupation is associated with better cognitive performance, lower risk of dementia, and probably slower cognitive decline. The context of the complexity is important. The complexity of working with people is associated with the most benefit. An occupation's demands and degree of control are also relevant: in theory, the worst, most stressful, and perhaps most health-hazardous job is one with high psychological demands but little sense of control. The most striking finding is that jobs with high degrees of control are associated with better cognitive performance, but overall, the data are sparse and results are mixed.

An older age at retirement is associated with lower risk of dementia. Cognitive performance is worse in retired persons than in same-age unretired persons; performance declines more quickly, as well. One caveat of many studies of occupational cognitive demands and control is that they assessed cognitive function in people who were still working. Nevertheless, those findings interpreted in the context of pre-/post-retirement study results lead to a possible conclusion that cognitive engagement at work has acute effects—lending credence to the possible benefit of postponing retirement. Several studies suggest that cognitive benefits of work extend beyond retirement, although it is not clear that they do. One study suggests that assumption of more physical and cognitive activity after retirement could fill the cognition-preserving role of occupation.

Several issues exist with these studies. Often the studies aimed to maximize the model prediction rather than generate an unbiased estimate of the occupational attribute, perhaps resulting in underestimation of the effects of occupational attributes and misinterpretation of the attenuated effects as evidence of mediation. In addition, no study accounted for potential selective attrition. Occupational attributes are known to be associated with survival, continuation, and participation. By not accounting for factors that predict survival and cognitive outcome, the studies may have underestimated the cognitive benefits of occupational attributes. Furthermore, reverse causation is a possibility in some of these studies. In HRS, poor

health led to exit from the labor force. There is little data examining the influence of unemployment and job security on late-life cognitive performance. Finally, education shapes occupation: More years of education corresponds to being employed at all, retiring at an older age, and holding a job with high cognitive demands.

Recently observed trends in occupations include an increase in jobs that are cognitively intense and psychologically stressful, a decrease in jobs with heavy physical demands and exposure to lead (a neurotoxicant), and an increase in retirement age.

Leisure activity includes both physical activity and cognitive engagement. More years of education leads to more leisure-time physical and cognitive activity. Jobs involving physical activity are disappearing, but the percentage of people engaged in leisure-time aerobic activity is increasing for all age groups. However, cardiorespiratory fitness among U.S. youth is on the decline. The data on leisure activities are confounded by education, illness, and innate intelligence. In her research, Dr. Weuve found that a confounding variable is unlikely to explain the totality of findings on cognitive activity.[14] She also found that reverse causation, whether incipient disease diminishes desire and ability to be cognitively active, could explain some of the observational findings.

Income is salubrious for cognitive health in older age. Income is an effect of, and independent of, occupation. More years of education correspond to higher income and to a lower risk of poverty, a trend that has become more exaggerated over the past four decades. Childhood household income might also have an effect on educational attainment. However, is it the income itself or what was purchased with that income that is important? Marden *et al.* recently showed that accounting for time-varying confounders in study of socioeconomic status over the life course results in an even larger effect on cognitive outcomes.[15]

Discussion

Assessing Career Progression

It is difficult to monitor long-term exposure to occupational conditions, that is, where a person starts in the workplace, the shape of his or her career mobility, whether he or she stays in the same job, or whether he or she experiences within-job changes. The resource O*NET tracks jobs but does not account for the fact that a job starting in 1958 could change drastically over 20 years. It is also difficult to characterize jobs.

Studies often look at the longest held job or the last job, but it is difficult to determine whether the last held job before retirement is a good proxy for what happened 20-30 years prior. People generally hold four to five jobs over their lives, and that number is likely getting larger.

Vicki Freedman mentioned that the Panel Study of Income Dynamics, a nationally representative cohort of families followed since 1968, has collected occupation data over the

[14] Sajeev G, Weuve J, Jackson JW, VanderWeele TJ, Bennett DA, Grodstein F, Blacker D. Late-life Cognitive Activity and Dementia: A Systematic Review and Bias Analysis. Epidemiology. 2016 Sep;27(5):732-42.

[15] Marden JR, Tchetgen Tchetgen EJ, Kawachi I, Glymour MM. (2017). "Contribution of Socioeconomic Status at Three Lifecourse Periods to Late Life Memory Function and Decline: Early and Late Predictors of Dementia Risk." *American Journal of Epidemiology* (in press).

participants' lifetimes, a few cognitive measures as early as 1972, and new cognitive measures in a 2016 supplement. It has also added stylized time-use questions and a dementia screen in 2017. This study could serve as another source to answer some of these questions.

New Types of Workers

Lisbeth Nielsen mentioned the substantial growth in contingent workers. Surveys might be able to identify features of contingent versus non-contingent workers who fulfill the same role, but the sources of those data are largely the workplaces themselves, which do not collect data on contingent workers. Contingent workers who are performing the same job, but at a distance, are missing elements that past people with the same job would have had. Being a contingent worker could also be related to uncertainty, which is related to stress.

Racial and Ethnic Disparities in Dementia Trends: The Role of Cognitive Reserve

Jennifer Manly, Columbia University

Dr. Manly summarized several studies that have shown evidence of ethic disparities in cognitive aging in Alzheimer's disease and dementia. The Washington Heights Inwood and Columbia Aging Project (WHICAP) enrolled functionally normal individuals at the onset of the study and followed them for 7 years on average. The researchers found higher incidence of Alzheimer's disease in African Americans and Hispanics above age 65. Adjusting for cardiovascular disease, years of education, and presence of the ApoE ε4 allele did not alter the magnitude or significance of inequalities. An HRS study of people ages 55 and older found higher prevalence of cognitive impairment among African American and Hispanics as compared to non-Hispanic Whites.[16] A Kaiser Permanente Northern California study monitored ICD-9 codes for dementia of health care system members ages 60 and older and found that African Americans are about 65 percent more likely to develop dementia than Asian Americans, who were the reference group because they were the group at lowest risk for incident AD. The large differences in dementia were at age of onset, and the cumulative lifetime risk for all groups was high.[17] Racial differences in baseline cognition complicate research on disparities in dementia, since groups whose average test scores are closer to a dementia threshold will reach that threshold at an earlier age, even if rates of decline are parallel across racial groups.

Several studies provide hints about the cause of racial and ethnic disparities. Dr. Maria Glymour used CDC data based on place of birth to look at mortality due to all-cause dementia and Alzheimer's disease and found that the concentration of the effect for blacks and whites was in stroke belt, even if individuals moved out of the stroke belt after childhood.[18] Looking at several socioeconomic and lifestyle factors, researchers from the Health ABC study found that socioeconomic and educational factors were differentially predictive of incident dementia

[16] Tang MX, Cross P, Andrews H, Jacobs DM, Small S, Bell K, Merchant C, Lantigua R, Costa R, Stern Y, Mayeux R. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. Neurology. 2001 Jan 9;56(1):49-56.

[17] Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Alzheimer's & Dementia. 2016 Mar 31;12(3):216-24.

[18] Mayeux R, Reitz C, Brickman AM, Haan MN, Manly JJ, Glymour MM, Weiss CC, Yaffe K, Middleton L, Hendrie HC, Warren LH. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment—Part 1. Alzheimer's & Dementia. 2011 Jan 31;7(1):15-34.

among African Americans and whites. It was only after socioeconomic factors were added, not ApoE ε4 or cardiovascular comorbidities, that the racial disparity in incident dementia was accounted for.[19]

Cognitive reserve offers a possible explanation for racial and ethnic disparities. Dr. Manly's colleague Yaakov Stern thinks of reserve in two ways: (1) active, which includes compensatory activities that could increase capacity to resist neuropathology, or (2) passive, which includes changes in brain structures that allow for continued efficient cognitive processing in the face of pathology. Years of education could provide reserve either by increasing brain size or neuronal number or density or by increasing cognitive reserve. Studies of cognitive reserve should include a measure of pathology, a proxy for cognitive reserve, and a measure for cognitive function. Most epidemiological studies do not include a measure for pathology.

Most research on education uses the variable "years of school"; however, this ignores variability in the quality and quantity of education. The length of a school year differs by state and race. For example, in the 1930s, a school year for African Americans in South Carolina was about half the days as compared to African American students in New York. In addition, the student-teacher ratio is often much higher for African Americans. These historical data have been leveraged into studies of cognitive function. In Alabama, where average income varies widely county by country, student-teacher ratio and length of school year, but not per-pupil expenditures, were associated with baseline cognitive function (but not change in cognition over time). An HRS study of racial disparities by U.S. region of primary school education found highest disparities between blacks and whites in the South.

Dr. Manly and colleagues are examining changes in the incidence rates of dementia in multi-ethnic cohorts of elderly from the WHICAP study. They found an overall decline in incidence of Alzheimer's disease among blacks, whites, and Hispanics. Vascular risk factors attenuated the decline in whites, and secular increases in years of school explained the decline in blacks. None of the variables explained the lower rates in Hispanics. The absolute racial and ethnic disparities in the incidence of Alzheimer's disease narrowed over time, which were accounted for by years of school and a proxy for school quality (reading level measure).

Dr. Manly concluded by saying that data indicate that studies should measure educational experience, not just years attended. In addition, the burden of neuropathology needs to be assessed in studies of cognitive reserve. For future studies of racial and ethnic disparities, incidence and trajectory data are critical. There is now the opportunity to begin more detailed follow-up studies of cognitive function of people in mid- and later-life who were studied when they were school-aged.

Discussion

Using Pathology To Measure Cognitive Reserve

Participants discussed the idea of using pathology to measure cognitive reserve. Dr. Haaga stated that amyloid proteins may accumulate in the brain with no change in function, or

[19] **Yaffe K**, Falvey C, Harris TB, Newman A, Satterfield S, Koster A, Ayonayon H, Simonsick E. Effect of socioeconomic disparities on incidence of dementia among biracial older adults: prospective study. BMJ. 2013; 347:f7051

proteins may not accumulate because a person has an effective clearance mechanism. Dr. Manly responded that reserve is a differential between the level of pathology that is present and the extent of cognitive decline, so a measure of pathology is necessary. Only proxies for cognitive reserve can be measured in a healthy brain in which there is no neuropathology.

Dr. Langa said it can be helpful to think of neuroprotection versus compensation in the reserve discussion. A person can have the pathology but clear it so well that it is not visible, which is similar to not creating amyloid, or neuroprotection. With compensation, if the pathology remains, a person can use a different brain region or network and not appear to have cognitive decline. Education may be useful for doing both of those things.

Dr. Nielsen inquired about which brain measure would be most useful in informing the relationship between education and dementia. Dr. Manly responded that her interest in racial and ethnic disparities would lead her to prioritize structural MRI measures of cerebrovascular disease, as these seem to be more predictive of incidence of Alzheimer's disease among African Americans than hippocampal volume or total brain volume measures. Different brain measures have different prediction of dementia across ethnic and racial groups.

Opportunities for Data Collection and Analysis of Dementia Trends and Education in Ongoing Studies

Scott Hofer, University of Victoria

Dr. Hofer explained that the Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) project, which began 4 years ago, now has 100 studies (50 with completed catalogs), and its database is searchable within each study to enable users to ask particular questions. The goal is to provide tools and opportunities for international multi-study harmonization and comparative analysis.

Many secular trends affect a variety of cognitive outcomes. Later born cohorts perform better cognitively, about three IQ points of improvement per decade. The potential causes are schooling, test sophistication, nutrition, stimulating environment, fertility patterns, and/or infectious disease. The importance of these factors for Dr. Hofer's research is in terms of aging and cross-sectional aging trends.

In one study, Hofer and colleagues evaluated the effects of educational attainment, socioeconomic status, and early-life cognition on adult cognition in three cohorts. This was a test of selection, that is, education is merely a credential into which people are selected if they have the requisite cognitive ability, versus a beneficial impact that conveys protective value. They saw evidence of selection: people with high childhood cognition would enter university, and those with very low childhood cognition would not. People in the middle range saw a cognitive benefit later in life from earning a 4-year degree. The data suggest that education has a casual benefit on level of cognitive performance later in life.

Education has an important impact on level of cognitive functioning, but rarely on rate of change. Researchers typically organize individuals based on time of dementia diagnosis, then look back at when that inflection point occurred with other cognitive measures. An idea is that education is predictive of change point onset; the change point happens later with more education. Education does delay onset of cognitive decline, although there is faster decline on

cognitive tests post-diagnosis. These findings provide evidence for the cognitive reserve hypothesis.

The effects of education include improved socioeconomic status throughout life, decreased exposure to severe stressors, lowered risk of chronic disease, and improved health behaviors. Dr. Hofer and colleagues examined what drives educational benefit for the health behaviors of smoking, drinking, and physical activity in three cohorts. The probabilities of smoking and physical activity in mid-life were dramatically reduced in those with a university degree compared to those without a university degree. Education alone predicts better health behaviors, but post-education effects are likely.

Dr. Hofer hopes that IALSA can provide the opportunity to conduct natural experiments with an international framework. First, to allow for natural experiments, it is important to understand the events, policy changes, and practices in different places at different times (e.g., education reforms occurred in the 1950s in European countries). However, those individuals are only ages 60-65, so identification of studies that consider earlier policy changes is necessary to answer questions about dementia now. Most current data on dementia trends and rates focus on early birth cohorts from the late 1800s to early 1900s, who experienced education quite differently from younger cohorts. A preliminary task is to harmonize education in earlier birth cohorts.

Another key challenge is that the studies in the IALSA database differ in important ways (populations and samples, design factors, selectivity/incomplete data, re-test effects, statistical models) that may limit harmonization and data pooling. Most of these studies differ in cognitive outcomes. In IALSA they have focused on a coordinated analysis approach that evaluates the same questions, with the same constructs, using the same modeling decisions.

The Maelstrom research website[20] was developed by the Public Population Project of Genomics (P3G) and BioShare to provide a harmonization platform and metadata catalog. IALSA partnered with them to generate an integrated data set to search on a variety of levels. Variables have been classified into 17 sections and subdomains. The search tool allows users to search on particular variables to identify the studies with exact measures. Maelstrom staff has developed tools to harmonize variables. Site development is ongoing, but 49 studies have been fully completed.

Opportunities for Data Collection and Analysis of Dementia Trends and Education in New Studies

David Weir, University of Michigan

Dr. Weir and colleagues recently launched a global study of dementia based on the international family of HRS studies and using a Harmonized Cognitive Assessment Protocol (HCAP; also sometimes referred to as the Healthy Cognitive Aging Project) that everyone can share. HRS itself conducts 20,000 interviews every other year and has been joined in this effort by other countries—forming the HRS family of international studies. The global network is now conducting 200,000 interviews in a cycle. The studies are intentionally designed to be harmonized on a wide range of measurement dimensions.

[20] https://www.maelstrom-research.org/

The longitudinal setting for the HRS global network is excellent for studying the epidemiology of dementia. It is rich in relevant covariate measurement, including retrospective variables such as education, occupation, and cardiovascular diseases. Most studies are rigorously representative of national populations ages 50 and older. Although useful, cognitive assessment is limited in main studies. The 2002 Aging, Demographics and Memory Study (ADAMS) set the precedent and has become a cohort of interest in its own right. It can be used to harmonize core study measurements to a more rigorous diagnosis and establish diagnosis in all of the core studies.

With additional funding to support research on Alzheimer's disease, Dr. Weir and colleagues initiated a two-staged approach to build a global population-based study of dementia. In stage one, the researchers implemented a new survey-based approach to assess dementia/mild cognitive impairment (MCI). In stage two, international sister studies will harmonize with HRS, through the HCAP. The U.S. study aims to enroll 3,000 participants over the age of 65. Studies in Mexico, India, Ireland, China, England and South Africa are in progress or planning stages.

The goal of HCAP is to produce comparable diagnostic classifications of dementia, MCI, and cognitive impairment without dementia in subsamples drawn from HRS family of studies to permit combined longitudinal epidemiological studies in these subsamples. Survey interviewers will administer the protocol in the home through 1 hour of cognitive testing and 20 minutes of informant reporting. They will then use appropriate weights to compare national population prevalence rates and make all data publicly available. Within and across these studies there is a great variation in educational experience. These samples will be followed going forward with comparable measurement, so that researchers can track trends in incidence by education, along with intermediate variables.

Dr. Weir sees several opportunities for future new research. Many small studies with high-intensity measurement require *ex-post* harmonization to allow for their combination. Also important are large studies with lower intensity measurements. It is only possible to study the impact of education and other early-life circumstances if there are data on early life, and contemporaneous observation is better than retrospective recall. Therefore, studies with early-life data that are old enough to be interesting for study of cognitive aging should also be considered for funding.

Project Talent is an example of a study with early-life data. Project Talent started in 1960 with 1,300 schools and 377,000 students. At that time, school quality was very diverse and information of student abilities was rich. The participants are now ages 70-74 and therefore about to enter the high-risk period for dementia. However, it is difficult to locate and recruit them back into a study. The Census Bureau Protected Identification Key (PIK) is a procedure to link individuals across censuses within the confines of secure government servers. Using PIK it is possible to link people to social security number, earning, employment, and disability history, and Medicare records. Although improving, Medicare records are not good sources of dementia data, because people who worry about developing dementia seek frequent checkups and people who have dementia and are not being treated. However, making inferences about education's impact on dementia from a sample of more than 100,000 Project Talent survivors does not require the same accuracy for diagnosis as a clinical study.

Summary and Next Steps

Mark Hayward, University of Texas

In his summary, Dr. Hayward said the meeting covered decades of history, explored research in a variety of populations including international and racially diverse cohorts, considered a wide range of early- and mid-life variables, and spanned biological contexts from genes to the brain. For the health of our global populations, and future generations, it is essential to move forward on these issues of education and dementia.

Dr. Hayward asked the meeting participants to recommend projects and ideas they believe would help move the agenda forward. The following are consensus recommendations:

- **Data that already exist could be leveraged.** Existing databases could provide information about early- and mid-life in cohorts with rich late-life data, or about mid- and late-life in cohorts that were studied in early life. Medicare records, electronic health records, the Census Bureau PIK, and state and regional educational archives are all databases that could be utilized.
- **New studies should consider harmonization.** New studies should include designs that can be translated to other studies so one can inform the other.
- **Diverse populations should be included in new studies.** Research on diverse cohorts is valuable for elucidating cognitive trends and their link to education. It is important to remember that some of the confounds that can occur across the life course will differ across racial and ethnic groups.
- **Validation studies would have value to the research community.** Studies that validate existing databases would be valuable for data analysis and interpreting results. Knowing the extent to which resources, such HRS and Medicare records, are representative of the population would be helpful to their users.
- **Biological repositories would have value for future –omics studies**. There was little consensus as to the best approach for –omics data today. Epigenomics and transcriptomics will likely be where early- and mid-life experiences have the greatest effects, but these fields are still in their infancy and tools still need to be developed. Genomics is now inexpensive, and the technology is good, but genes do not change much between cohorts, and key dementia genes have been identified. Biological repositories would allow future research to go back and do –omics studies as the technologies improve.

APPENDIX 1. Meeting Agenda

9:00 am	Welcome and meeting orientation, *Mark Hayward, University of Texas*
9:15 am	Overview of the relationship between education and dementia trends in the United States, *Kenneth Langa, University of Michigan*
10:00 am	An international perspective on dementia trends and their association with educational attainment, *Carole Dufouil, INSERM France*
10:45 am	Break
11:00 am	Disease pathways and the relationship between education and dementia trends, *Sudha Seshadri, Boston University*
11:45 am	The role of genetic factors in the relationship between education and dementia trends, *Jessica Faul, University of Michigan*
12:30 pm	Lunch
1:30 pm	The relationship among dementia trends, work conditions, leisure, and socioeconomic factors, *Jennifer Weuve, Boston University*
2:15 pm	Racial and ethnic disparities in dementia trends: the role of cognitive reserves, *Jennifer Manly, Columbia University*
3:00 pm	Break
3:15 pm	Opportunities for data collection and analysis of dementia trends and education in ongoing studies, *Scott Hofer, University of Victoria*
4:00 pm	Opportunities for data collection and analysis of dementia trends and education in new studies, *David Weir, University of Michigan*
4:45 pm	Summary and Next Steps, *Mark Hayward, University of Texas*
5:30 pm	Adjourn

APPENDIX 2. List of Participants

Invited Speakers
Eileen Crimmins, University of Southern California
Carole Dufouil, INSERM France
Jessica Faul, University of Michigan
Scott Hofer, University of Victoria
Kenneth Langa, University of Michigan
Jennifer Manly, Columbia University
Sudha Seshadri, Boston University
Jennifer Weuve, Boston University

Members of the Committee on Population
Vicki Freedman, University of Michigan
Mark Hayward, University of Texas
David Weir, University of Michigan

National Institute on Aging Staff
Dallas Anderson, Division of Neuroscience
Partha Bhattacharyya, Division of Behavioral and Social Research
Prisca Ndella Fall, Division of Behavioral and Social Research
John Haaga, Division of Behavioral and Social Research
Jonathan King, Division of Behavioral and Social Research
Lenore Launer, Laboratory of Epidemiology and Population Science
Laura Major, Division of Behavioral and Social Research
Evelyn Neil, Division of Behavioral and Social Research
Lisbeth Nielsen, Division of Behavioral and Social Research
Georgeanne Patmios, Division of Behavioral and Social Research

National Academies Staff
Peter Donaldson, Interim Board Director
Tina Latimer, Program Coordinator

Other Participants
Rose Li, Rose Li and Associates, Inc.
Christina Szalinski, Rose Li and Associates, Inc.