Expert Meeting on Using Longitudinal Studies of Younger Cohorts for Aging Research

The National Academies of Sciences, Engineering, and Medicine Committee on Population (CPOP)

June 25-26, 2018

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Introduction

On June 25-26, 2018, the National Academies of Sciences, Engineering, and Medicine's Committee on Population and the National Institute on Aging (NIA) of the National Institutes of Health convened an expert meeting in Washington, DC, to discuss ways to integrate longitudinal studies of younger cohorts into aging research. Kathleen Mullan Harris, PhD, from the University of North Carolina, Chapel Hill, opened the meeting by welcoming the attendees and explaining the purpose of the meeting. See the appendices for the agenda and participants list.

Dr. Harris noted that aging is a lifelong process, yet most aging studies begin when participants are in their 50s and 60s. To understand the mechanisms and processes underlying aging, the relationships between early-life factors and later-life outcomes must be investigated. The experts who attended this meeting approach aging research from different perspectives. Throughout the meeting, they described issues in the use of longitudinal studies of younger cohorts and highlighted opportunities to study aging from a full life-course perspective.

Overview

Michael Shanahan, University of Zurich

Life-course models—such as life-course epidemiology models of risk accumulation—can link early-life influences and later-life outcomes. Past research suggests that these models work best with rich longitudinal datasets, which implies the need for high-frequency data collection. However, frequent data collection raises costs and complicates logistics. In addition, repeating measures can drastically increase the number of factors that can explain an observed relationship and thus render specific hypotheses impossible to test with existing models and test cases.

Another tension emerges from the use of directed acyclic graphs (DAGs) to establish causality. DAGs should be drawn in advance of data collection waves to model risk pathways that enable precise testing of causal hypotheses. However, this means the data will be shaped by the *a priori* hypotheses used to design the DAG. This in turn introduces a conundrum: to draw a DAG that is sufficiently detailed to test a specific causal mechanism, researchers must already have sufficient knowledge of that mechanism to draw the appropriate DAG. Researchers should construct life-course models with the aim of validating the earliest possible etiological factors that act as predictors of pre-disease pathways.

Many levels of causal mechanism appear to be involved in aging pathways, including genetics and epigenetics, material and social environments such as socioeconomic status (SES) and culture, and high-level psychological factors such as uncertainty and group identity. Investigators must consider the self-selection and feedback relationships among these levels, which complicates the construction of DAGs. Furthermore, future research may require alternative measurement methods to the traditional paper-and-pencil method, which may not adequately capture many relevant pre-disease factors such as perceptual tendencies.

Discussion

Although DAGs have limitations (e.g., they place statistical constraints on data interpretation), some of them, such as the need for embedded assumptions, apply to all study designs and do not necessarily lessen the data's value. However, being aware of the assumptions, and incorporating them into explanations of the phenomena being observed, can both clarify the aging process and ensure the proper use of DAG data by other investigators. Integrating longitudinal data from multiple studies may help to account for the complexity of aging and of feedback interactions among environmental factors, epigenetics, stress, and behavior.

Feedback processes such as the accumulation of advantage and disadvantage are partially understood, but substantial work to clarify those relationships remains to be completed. At present, risk factors are better understood than protective factors, but improving explanations of both is a key aim of aging research that considers the entire life course.

Gestational, Infancy and Childhood Predictors of Aging Outcomes

Chris Kuzawa, Northwestern University

Research suggests that the earliest stages of life—gestation, infancy, and childhood—contain many predictors of long-term aging outcomes. Across the lifecycle, homeostatic systems adapt bodily functions to maintain internal stability despite changes in the external environment. However, environments experienced during critical or sensitive periods in very early life can lead to long-term health effects by durably modifying developmental processes (developmental plasticity). Early-life indicators that predict aging outcomes operating through these pathways can be broadly divided into *gestational* and *postnatal* factors.

Gestational factors include nutrition, stress, immune function, and toxicants such as pollutants. Altered gestational environments can cause enduring changes to bodily processes that, for example, may raise the child's future risk of developing a cardiometabolic disease (CMD). Although gestational nutrition is an important predictor of many aging-related outcomes, delivery of macronutrients (energy, carbohydrates, and protein) to the fetus is buffered by the homeostatic processes that regulate maternal metabolism, which minimize the effects of short-term nutritional stress, as well as of nutritional supplementation, experienced by the mother during pregnancy. The mother's history of pre-pregnancy nutrition, extending back to her own early developmental nutrition, may be a more important influence on fetal nutrition, particularly in low resource settings in which early life nutrition is suboptimal. This finding suggests the need to take a long-term perspective when studying the intergenerational role of nutrition in later health. In contrast to nutrition, even a short-term spike in maternal stress during pregnancy can elevate levels of cortisol passed to the fetus[1] and thus influence its long-

[1] Z.M. Thayer and C.W. Kuzawa. "Ethnic discrimination predicts poor self-rated health and cortisol in pregnancy: insights from New Zealand," *Soc. Sci. Med.* 128, 36–42 (2015).

term physiology. Maternal immune functions, especially non-specific defenses such as inflammation,[2] can also impair fetal development, resulting in long-term health effects.

Nutrition remains an important influence on development and future trajectories of aging in the postnatal environment. For example, breastfeeding has been shown to protect against obesity and diabetes later in life.[3] Postnatal indicators also include growth and pathogen factors. For example, rapid childhood weight gain, especially in infants born small, predicts elevated future CMD risk, while early childhood environments that are overly sterile can impair the development of immune system regulation, potentially leading to allergy, asthma, and elevated inflammation later in life.[4] From a complementary perspective, postnatal cues that signal a harsh or unpredictable environment, such as traumas or parental absences, are also linked to aging-related processes. Cues that signal harsh environments can incentivize short-term reward and influence risk-taking behaviors, modifying lifestyle, health behaviors, and reproductive strategies, all of which can affect chronic degenerative processes and mortality.[5]

These various early-life indicators could be integrated into existing older-cohort longitudinal aging studies because much of the data are available retrospectively.

Discussion

Different intervals of data collection can have important implications for linking early-life indicators with later health and aging outcomes. To determine which mechanisms are linked to which outcomes measurements, a researcher must capture the relevant predictors as well as the outcomes at the other end of the causal chain. For example, infant weight after 6 months has been shown to predict later adiposity more effectively than earlier measurements because infant weight tends to fluctuate during the first 6 months after birth.

Although the long-term effects of early environments were initially thought to reflect varying degrees of developmental impairment (e.g., to organ growth), there is evidence that some of these effects instead reflect changes in epigenetic settings as the fetus' body learns about the external environment by interpreting information gained from the mother's body and biology. Such interpretive shifts can re-frame existing data and help to inspire novel hypotheses.

[2] C.W. Kuzawa, et al. "Maternal pregnancy C-reactive protein predicts offspring birth size and body composition in metropolitan Cebu, Philippines," *J. Dev. Orig. Health Dis.* 7, 1 (2017).
[3] J. Yan et al., "The association between breastfeeding and childhood obesity: a meta-analysis," *BMC Public Health* 14, 1267 (2014).
[4] T.W. McDade et al., "Early origins of inflammation: Infectious exposures in infancy predict lower levels of C-reactive protein in adulthood," *Proc. R. Soc. B* 277(1684), 1129–1137 (2010).
[5] C.W. Kuzawa and J.M. Bragg, "Plasticity in human life history strategy: Implications for contemporary human variation and the evolution of genus *Homo,*" *Curr. Anthropol.* 53(6), s369–s382 (2012).

Attention to Life Stages

Sara McLanahan, Princeton University, Moderator

Measurement of Psychosocial Stress in Longitudinal Studies

Elissa Epel (by videoconference), University of California, San Francisco

Chronic psychosocial stress (i.e., toxic stress) can affect aging trajectories[6] through biological pathways or by inducing unhealthful behaviors. Thus, research that seeks to predict and explain aging processes should integrate measures of psychosocial stress, which occur at three levels: (1) objective stress factors such as SES and chronic stressors, (2) subjective perceptions of stress based on self-reports (often neglected), and (3) biological stress responses.

Stress perceptions and biological stress responses vary among individuals and can be conditioned by impaired homeostatic processes induced by trauma during early brain development. This impairment of biological function can intensify stress perception across the life course, which can in turn intensify physiological stress responses and interfere with normal homeostatic function. In addition, aging is linked with poor homeostatic capacity. To integrate measures of toxic stress into aging studies, researchers must collect baseline measurements at allostasis so that they can assess changes in stress response under varying stress conditions and across the life course.

However, measurement of stress is influenced by multiple variables. In general, researchers group measures by timescale, life period, and stressor attributes. For example, daily (chronic) and acute stressor timescales are associated with different aging outcomes and different biomarkers. Studies have identified a so-called "caregiver effect" that links chronic daily feelings of negative anticipation with shorter telomeres.[7] Identification of that kind of association may lead to new explanations of differential aging across individuals. To discover links between stress and aging, longitudinal studies should adopt a life-course approach and should integrate measurements of both stress exposure and response at the individual level.

Discussion

Although measurement of subjective experiences of stress can be a valuable indicator of aging processes, there are some inherent difficulties in obtaining reliable data. Self-reports can vary when respondents are asked about the same life event at different times. However, this subjective variability is less problematic when the subjective perception (or the evolution of a subjective perception) is itself the cause of a biological outcome.

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[6] L.M. Hanssen et al., "The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis," *Health Psychol. Res.* 5(1), 6378 (2017).
R. Coelho et al., "Childhood maltreatment and inflammatory markers: a systematic review," *Acta Psychiatr. Scand.* 129(3), 180–192 (2014).

[7] K.A. Leger et al., "Let it go: Lingering negative affect in response to daily stressors is associated with physical health years later," *Psychol. Sci.* (2018).

Evidence suggests that some psychological and biological effects of psychosocial stress may be reversible. For example, the presence of a strong role model is associated with improved psychological resilience following childhood trauma, and health behaviors[8] and meditation[9] have been linked to telomere lengthening. However, because stress factors such as low SES and abuse or neglect appear to have different effects, the different categories of stressor should be isolated to clearly distinguish their relationships to aging.

Empirical Research Using All Life Stages (Gestation, Birth, Childhood, Young Adulthood, Mid-Life) to Understand Aging Outcomes

Aryeh Stein, Emory University

Early-life studies can provide valuable empirical data to inform aging trajectories. From 1969 to 1977 the Institute of Nutrition of Central America and Panama (INCAP) conducted a nutrition study in four Guatemalan villages to test the impact of nutritional supplements on mental development. Researchers gave children up to the age of 7 and pregnant or breastfeeding mothers one of two supplements: Atole (a protein and energy beverage) or Fresco (a soft drink). Their aim was to investigate the impact of nutrition supplementation, especially of protein, on cognitive development. Researchers defined children exposed to supplements from conception (via their mothers' intake) to 2 years old—roughly corresponding to their first 1,000 days of life—as "fully exposed." Because the study lasted 9 years, researchers could perform double-difference estimations using four categories of data:

- Mean outcomes for *full* Atole exposure vs. Mean outcomes for *partial* Atole exposure
- Mean outcomes for *full* Fresco exposure vs. Mean outcomes for *partial* Fresco exposure

Data models that exploit double-difference relationships can inform development of causal explanations and can establish links between early-life environments and aging outcomes. For example, follow-up data collected from the Guatemalan cohorts revealed that early-life physical measures such as elevated rates of stunting were associated with a series of diminished cognitive outcomes in adulthood.[10] Researchers also linked different treatment groups to outcomes, such as wages, body mass index (BMI), diabetes, obesity, and CMD risk.

Ongoing findings from this cohort, which is now middle-aged, indicate that early-life nutrition can have lasting effects on aging trajectories. In general, investigators can apply analytical and statistical methods to early-life empirical data to inform aging research. With techniques such as adjusting data analysis methods to fit different definitions (e.g., defining Atole and Fresco exposure groups by "birth to 36 months" versus "minus 9 to 24 months") investigators can use early-life data to test a range of aging-related hypotheses and to discover new correlational and

[8] D. Ornish et al., "Increased telomerase activity and comprehensive lifestyle changes: a pilot study," *Lancet Oncol.* 9, 1048–1057 (2008).
[9] H. Lavretsky et al., "A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: Effects on mental health, cognition, and telomerase activity," *Int. J. Geriatric Psychiatry* 28(1), 57—65 (2014).
[10] J. Hoddinott et al., "Adult consequences of growth failure in early childhood," *Am. J. Clin. Nutr.* 98(5), 1170–1178 (2013).

causal relationships. One important and ongoing effort focuses on locating biomarkers in older cohorts that can convey information about early-life environments. Such markers would substantially enrich data for older cohorts that were not followed during early life.

Discussion

Studies such as the INCAP Nutrition Supplementation Trial provide valuable empirical data, but to inform understanding of aging trajectories, analyses of these data must try to account for the large number of possible confounding variables and the complexity of their interactions. Researchers controlled for many village features, but designing controls that are strict and comprehensive enough to bolster any specific interpretation of highly complex data is a major challenge. For example, establishing biological pathways that link nutrition supplementation in early life and later health outcomes must account for possible confounds at the level of lifestyle and behavior, including which factors influenced participation in the trials.

Intergenerational Transmission and Life Stage Timing

Vicki Freedman, University of Michigan, moderator

Inter- and Multi-Generational Processes in the Reproduction of Inequality and Health

Fabian Pfeffer, University of Michigan

In response to shifting demographics, investigators looking at inter- and multi-generational interactions that affect aging have begun to shift away from the classic "two-generation" framework. Nascent work seeks to account for the increasing amount of overlap between the lives of grandparents and their grandchildren (from 5 to 30 years over the past century). These trends create new opportunities for exposure[11] (e.g., changes in child-rearing practices) and exchange in terms of resources such as money and time among generations. Multigenerational correlations, including some independent grandparental influences, have been identified across biological and social indicators, including variables such as obesity, asthma, wealth, and education. This work is in its initial stages, but some researchers believe increased grandparent involvement in childrearing and sharing of resources across family networks may explain these effects. Further work seeks to extend the concept of family networks to include cousins, aunts and uncles, and step-grandparents, and to involve factors such as racial differences to broaden the investigation of resource distribution.

However, existing research has only provided descriptive accounts, and many challenges impede efforts to establish causal relationships. For example, insufficient parental generation (G2) controls may introduce bias, but G2 controls may introduce endogenous selection biases that confound causal explanations. Problems of longitudinal measurement, including the length of time required, the complexity of interacting variables, and the restrictions imposed by administrative datasets, can also hinder this research. Nonetheless, the possibility of linking to prior generations through historical records presents a valuable opportunity, as do prospects to

[11] V.L. Bengtson, "Beyond the nuclear family: the increasing importance of multigenerational bonds," *J. Marriage Fam.* 63(1), 1–16 (2001).

harmonize pre- and post-hoc longitudinal panel data and to measure transfer flows to capture "generation-jumping" transfers that skip G2.

Discussion

Further nuances that complicate efforts to propose causal explanations for multigenerational interactions include

- intergenerational migration and administrative data differences and restrictions between countries,
- complex interaction between social transmission processes and demographic factors, such as fertility patterns (e.g., generational overlap is determined by fertility timing, which itself may correlate across generations), and
- dominance of retrospectively collected data restricts the ability to establish population-level effects (that are the focus of prospective approaches to the multigenerational transmission of status and health).

When Do the Late-Life Disparities That We Observe in Aging Studies Emerge in Earlier Stages of the Life Course?

Rucker Johnson (by videoconference), University of California, Berkeley

Research has demonstrated persistent health disparities between whites and blacks in the United States, especially in prevalence of hypertension and cardiovascular disease. Recent work indicates that these disparities are linked to past governmental policies, including desegregation and the rollout of Medicaid and Head Start. Investigators have analyzed the relationships between racial disparities and government policy that emerge from this history by combining data from the Panel Study of Income Dynamics (PSID) with Medicaid and Head Start policy records. In 2015 researchers followed up with white and black children born between 1945 and 1975 and included in PSID so that links between childhood SES and access to Head Start and Medicaid (which became available in different areas from 1960 to the 1980s based on eligibility criteria for funding) could be analyzed alongside educational attainment and later-life health outcomes.

Difference-in-differences analyses revealed correlations between racial health disparities and racial differences in childhood conditions including parental income, access to Medicaid, and neighborhood poverty. Using data linkages, investigators could isolate geography, poverty, and disparities in access to Medicaid to find relationships between childhood access to health insurance and later-life outcomes such as educational attainment and SES. These analyses showed that early-life Medicaid access was linked to higher educational attainment, better adult health, and lower incidence of poverty. These results support the notion that multiple aspects of early environments interact to raise or lower risk factors for later-life outcomes. Health and education, for example, are linked by the fact that healthier children are more able to focus on educational attainment than those struggling with poor health. It is thus important to design future policy interventions that achieve "dynamic complementarity" by addressing racial disparities on several interacting levels all at once.

Discussion

This work was motivated by the theory that early childhood factors such as birth rate and nutrition are significantly affected by policy and that these early factors may link to later-life disparities. Current results do not demonstrate causation, but they are consistent with that theory. More work is needed to probe whether a causal account is the best explanation for these relationships, and one important step will be to collect higher resolution data on where respondents grew up. These data could help to root out confounds by differentiating family investments in child rearing from community-level policy structures to account for the links between early-life factors and later-life racial disparities.

In addition to underscoring the importance of dynamic complementarity in future policy interventions, analyses of Head Start data suggest that sustained investment in early childhood support is crucial to improving later-life outcomes. For example, beneficial outcomes of Head Start faded if exposure to the program in early years was cut short.

How Does the Role of Biology and Genetics Fit In? Can Biological and Genomic Measures Be Used to Study Aging in Young and Middle-Aged Adults?

Morgan Levine, Yale Medical School

Although most aging studies look at older cohorts, the aging process begins at conception. Genetic and other biomarkers may provide ways to predict aging trajectories during early life and even during gestation. The search for physiological and molecular markers of aging has led to development of tools for predicting aging trajectories. Chronological age is a weak measure because individuals age at different rates. Researchers developed a biomarker-based measure at the physiological level called "Phenotypic Age" to predict chronological age and to capture aging heterogeneity. Phenotypic Age predicts all-cause mortality, even for disease-free people with healthy BMI at baseline, which suggests that it captures preclinical markers of aging.

Researchers have also created epigenetic clocks to measure aging factors at the molecular level even before birth. These clocks—called the Horvath,[12] Hannum,[13] and Levine[14] clocks—measure DNA methylation at different CpG sites throughout the genome and are each linked to a variety of aging outcomes (investigators developed the Levine clock to predict Phenotypic Age). However, the three clocks together share only five CpG sites and seem to capture different phenomena. Work is ongoing to understand what each clock measures and to select one clock, or a combination of clocks, to use in measurement.

Overall, molecular and physiological measures of aging offer clear advantages for early-life aging research. However, several important tradeoffs exist between these two types of measures. Investigators can collect early-life molecular data, which can capture mechanistic information, but data collection is expensive and technologically challenging. Physiological

[12] S. Horvath, "DNA methylation age of human tissues and cell types," *Genome Biol.* 14, 3156 (2013).
[13] G. Hannum et al., "Genome-wide methylation profiles reveal quantitative views of human aging rates," *Molec. Cell* 49(2), 359–367 (2013).
[14] M. Levine et al., "An epigenetic biomarker of aging for lifespan and healthspan," *Aging* 10(4), 573–591 (2018).

measurements are less expensive and easier to collect, and are less complex, but they capture manifestations rather than mechanisms and cannot be collected as early as molecular measures.

Discussion

The concept of an individual being a single "age" is likely simplistic. Different aging-related processes will progress differently within each person's body, but the immediate goal is to develop biomarkers that can serve as proxies to measure more complex underlying processes.

Investigators do not understand why measurements of DNA methylation at certain CpG sites—even during gestation—work as markers of later aging. It is possible that the measured CpG sites tend to accumulate damage over the life course more than other sites, perhaps because they are "mutation hot spots" or are responding to stressors or stochastic events.

Discussion of Day 1 topics

Kathleen Mullan Harris, University of North Carolina, Chapel Hill; Terrie Moffitt, Duke University, moderators

To develop preventive interventions, researchers must include younger cohorts in aging research. Limiting study to older cohorts creates three problems: (1) reliable information about participants' earlier lives is difficult to obtain, (2) older-aged participants who live long enough to be selected for aging studies are an unrepresentative sample, and (3) participants are changed by enduring disease and treatment regimens, blurring causes with consequences. Aging is a multifactorial phenomenon, and longitudinal data are needed to test theories about pathways that extend across the life course to explain aging trajectories and outcomes.

One example of bringing younger cohorts into aging research is work that links the quality of one's social relationships during adolescence to better health outcomes later in life[15] (perhaps social embeddedness buffers the physiological consequences of stress). Another example is work that reveals racial and ethnic disparities in health outcomes at older ages, even when controlling for SES.[16] Several explanations of this effect have been proposed. First, it could be that minorities experience adversity in early life, which sets aging along a pathway that persists into later life regardless of later SES. Second, the extra effort required for minorities to achieve a higher SES may itself produce deleterious health outcomes ("John Henryism"). Third, minorities may find the culture of a higher SES to be unfamiliar, which may cause adverse health outcomes. One way to test these explanations is to look at the difference between "working up" and "marrying up" the SES ladder. This work could clarify whether it is the stress and exertion required to achieve mobility or the cultural shift of achieving mobility that is responsible for the observed health disparities.

[15] Y.C. Yang et al., "Social relationships and physiological determinants of longevity across the human life span," *PNAS* 113(3), 578–583 (2016).

[16] L. Gaydosh et al., "College completion predicts lower depression but higher metabolic syndrome among disadvantaged minorities in young adulthood," *PNAS* 115(1), 109–114 (2018).

Incorporating younger cohorts into aging research raises an important funding-related question: What is the appropriate "discount rate" to seek when investing in knowledge that will take many decades to produce? The longer it takes for an investment to pay off, the higher the payoff needs to be for the initial investment to be worthwhile. Although these calculations are often considered in terms of "dollar per life year," it is important to consider the return on investment derived from the long-term economic productivity of a society with more healthy people.

Recruitment and Presence of Population Subgroups over the Life Course: Maintaining Representativeness in Longitudinal Studies

Peter Lynn (by videoconference), Essex University

Participant retention is crucial to the collection of rich and representative longitudinal data. However, the need to collect data often and over an extended period introduces some difficulties. Participants who drop out cannot be replaced, repeated waves of data collection risk high dropout rates, and participants who change their contact information become more difficult to track. One effective way to minimize attrition is to build retention strategies into each study design. Choosing the starting age and the frequency of observation and adding incentives are a few ways to customize a study design to minimize attrition. Another approach is to ask which life stages are most crucial to the study and to concentrate data collection during those periods and to minimize collection at other times. Researchers can also identify which participant subsets are most likely to drop out and can implement targeted measures to reduce their attrition rates. However, because these measures are likely to affect participants differently, they should be carefully targeted.

Longitudinal studies always contain tradeoffs among cost, attrition, and data quality. Collecting more data raises costs and can raise attrition rates. However, the more participant information researchers collect at the outset of a study the easier it will be to track participants over time even if they move or drop out. Longitudinal studies tend to have high dropout rates during early data collection waves, and low dropout rates thereafter. This biases the sample and makes it important to use the data from early waves to inform attrition adjustment methods. (It is also important to use robust methods to estimate emigration and mortality among those who have dropped out to avoid skewing samples.) Securing linkages to administrative data sources early in a study can improve attrition adjustment methods and obviate the need to strongly skew priorities toward cost, attrition, or data quality.

Discussion

In general, response rates in survey research are decreasing, suggesting the need to invest more to collect rich data. However, budgets are also decreasing, which could be exaggerating the role of cost tradeoffs in longitudinal studies. Improving retention rates could make up some of the lost ground, and costs can be lowered when retention strategies are implemented early in a study and are well targeted. For example, creating different versions of initial letters, aimed at different participant subsets, is inexpensive and may improve both retention and response rates.

Some researchers are moving away from probability sampling and developing inferential methods for non-probability sampling. However, because there is no widespread agreement on which non-probability sampling methods work well (and in which circumstances), the best approach for now is to continue using probability sampling for longitudinal research. Another key issue is that effective statistical adjustments require researchers to choose appropriate auxiliary variables and to ensure that those variables are well measured. Otherwise, statistical adjustments will not achieve their purpose

Retrofitting Current Ongoing Aging Studies (e.g. parallel analyses of cohorts across life course, pooling data from younger cohort with aging cohorts; linking estimates of empirical relationships in theoretical pathways of influence)

Scott Hofer, University of Victoria, Canada

Testing hypotheses that link early- and mid-life factors with aging trajectories requires full life-course data. However, longitudinal data take a long time to collect. In addition, studies can vary widely in their measurement models, populations and samples, design factors, and statistical methods, making cross-study comparisons difficult and researchers skeptical of any single result. However, methods that compare data across different study designs do exist. Data pooling combines individual-level data into large datasets for comparison, and "lowest common denominator" harmonization combines the data that can be compared directly across studies and ignores everything else. These approaches are useful for harmonization, but they sacrifice data richness. Other approaches, known as integrative data analysis methods, aggregate longitudinal data from different studies (including dissimilar data) and analyze them in identical ways through meta-analyses. This method maintains the richness of longitudinal data and enables testing of hypotheses that none of the single studies could test.

One coalition of studies that uses integrative data analysis methods is the Integrative Analysis of Longitudinal Studies of Aging (IALSA) network, which includes more than 110 longitudinal studies on aging, health, and dementia. IALSA focuses on construct-level comparisons, searching for novel pathways that connect early- and mid-life factors with aging trajectories. Statistical methods process large datasets to test hypotheses that cut across cohorts and the lifespan. The general aim is to exploit the richness of diverse data to uncover fundamental relationships that emerge across contexts. For example, IALSA used cross-cohort analyses to investigate the pathways linking educational attainment, SES, and early-life cognition to adult cognition.[17] Results were consistent with theories of both educational selection and educational benefits. This integrative analysis approach allows researchers to retrofit current aging studies and to uncover directional patterns within rich and varied datasets.

[17] S.A.P. Clouston et al., "Educational inequalities in health behaviors at midlife: Is there a role for early-life cognition?" *J. Health Soc. Behav.* 56(3), 323–340 (2015).

Alternatively, longitudinal studies can be consciously designed to promote harmonization across cohorts (e.g., designing studies in parallel to secure cross-linkages). However, such approaches cannot be retrofitted to past or ongoing studies, which is crucial for existing longitudinal cohorts given the timespans needed to collect rich data.

Discussion

Combining data across longitudinal studies is a logistical challenge. Gathering members of each research team in a single location during data aggregation and analysis is crucial because in-depth knowledge of each dataset is needed to ensure valid comparisons. Although these data comparisons produce an essentially new data pool, drawing clear conclusions from disparate datasets (e.g., data collected using different selection criteria) remains a challenge.

Exploiting Other Data Sources, Linking Administrative Data, Collecting Life History Data

David Johnson, University of Michigan

Longitudinal survey data would be substantially enriched by creating extensive linkages to existing administrative data sources. Several efforts are under way (IPUMS-MLP, CLIP, AOS, and LIFE-M) to create a robust and integrated longitudinal infrastructure to which new and ongoing studies can link. Though it remains a distant goal, it should be possible to digitize and link all past census data and use Social Security Administration and Internal Revenue Service records to link children to social security numbers. This would enable further linkages to other administrative sources such as the National Death Index (NDI) and recent longitudinal datasets such as the American Community Survey. With that infrastructure in place, longitudinal survey questions covering topics such as health, occupation, education, and family structure could link to it and be extended automatically.

Research would benefit substantially from these efforts. Extensive administrative linkages would encourage cooperation and data sharing across agencies, allow for linking of non-federal surveys, improve the ability to evaluate under-reporting and measurement error, and develop a standard method of researcher access and disclosure. A crucial step is to secure funding to digitize past census data, which cannot be linked in its current form.

Once linkages are established, several challenges will remain. Researchers must determine when consent and permission are needed, establish data acquisition practices that match regulations, set standards for data dissemination and access, develop measures to protect data and minimize disclosure risks, and evaluate data quality and total survey error.

Discussion

Data security was raised as a potential issue. Once linked to the census, survey data are protected by Title 13 regulations. However, only those portions of a survey that are census-linked will be protected. Another challenge is that funds are still required to link to the NDI for cause of death data.

Open Discussion: Themes of the Meeting, Future Questions, and Directions for Ongoing and Future Studies

John Haaga, National Institute on Aging, kick off discussion

Most of the 2-day meeting focused on identifying aging mechanisms and integrating different life phases into longitudinal aging research. NIA must stay ahead of these research trends so that funding strategies continue to drive the understanding of aging. Several issues emerged from the discussion that relate to the tension between uncovering aging mechanisms and broadening longitudinal cohorts.

Balancing research needs to address specific questions and produce generalizable data

Existing datasets can become useful in unpredictable ways. Researchers and funders should be aware of those opportunities and capitalize on serendipity when possible. However, to ensure responsible allocation of funds, investigators must consciously design their studies to address a specific question. A clear scope for data collection will help researchers to interpret each dataset and to determine which data can be appropriated for other studies.

Valuing collaborative or team studies in aging research

Aging research that seeks mechanisms must focus on detailed levels of data. However, for larger cohort studies that seek longitudinal representation, collaboration and team science are often necessary. When investigators across a field know in advance that they will be able to profit from each other's data, they can coordinate their collection methods from the outset. In other cases, the value of custom-designing studies to address specific questions outweighs the data-sharing benefits of up-front coordination. As an alternative to coordination, NIA and other funding bodies should be cognizant of ways to facilitate network-based funding opportunities. NIA could hire a full-time person to manage data infrastructure and availability, and to leverage communications and sharing technologies. NIA could also make infrastructure investments to promote public data availability through the enclave, although several legal hurdles would need to be overcome.

Bridging research objectives with junior investigator career incentives

Junior investigators are driven by career incentives to pursue individual recognition, eschew repeated collaborations with the same partners, and avoid participating in consortia that will hold them at bottom rank. However, studies with large cohorts that require team studies and collaborations are increasingly necessary to grow knowledge of aging trajectories. Network-based funding strategies may provide a solution. They could recognize individual contributions to larger longitudinal projects, thus providing a combined incentive that bridges the gap between research objectives and career incentives. NIA also offers funding for ancillary studies to which junior investigators can apply.

Maximizing the research value of existing cohorts

One strategy is to create standardized "cohort profiles" such as those used by the *International Journal of Epidemiology.* Profiles could display cohort characteristics and associated policies, which could facilitate data sharing among investigators. Another strategy is to use existing

cohorts for new purposes. This strategy must be approached with serious caution, however, because an existing cohort member who has provided data across multiple collection waves is too valuable to risk losing. If investigators retire a cohort subset from an existing study and re-purpose that subset for a new regimen of data collection, then all the past data from that subset can be linked to the new data. However, shifting the purpose of a cohort may confound any later efforts to reconcile that subset with the original cohort and warrants caution.

Appendix A: Agenda

Monday, June 25, 2018

9:00 am	Introductions and goals for meeting *Kathleen Mullan Harris*, University of North Carolina, Chapel Hill *John Haaga*, Office of Behavioral and Social Research, National Institute on Aging
9:15 am	Overview *Michael Shanahan*, University of Zurich
10:00 am	What data from gestation, infancy, and childhood do aging researchers need in order to study how early life affects aging processes and outcomes? *Chris Kuzawa*, Northwestern University
10:45 am	BREAK

Attention to Life Stages
Sara McLanahan, Princeton University, moderator

11:00 am	Reversibility of early-life exposures *Elissa Epel (by videoconference)*, University of California, San Francisco
11:45 am	Empirical research using all life stages (gestation, birth, childhood, young adulthood, mid-life) to understand aging outcomes *Aryeh Stein*, Emory University
12:30 pm	LUNCH

Intergenerational Transmission and Life Stage Timing
Vicki Freedman, University of Michigan, moderator

1:30 pm	Inter- and multi-generational processes in the reproduction of inequality and health *Fabian Pfeffer*, University of Michigan
2:15 pm	When do the late-life disparities that we observe in aging studies emerge in earlier stages of the life course? *Rucker Johnson (by videoconference)*, University of California, Berkeley
3:00 pm	BREAK

3:15pm	How does the role of biology and genetics fit in? Can biological and genomic measures be used to study aging in young and middle-aged adults *Morgan Levine*, Yale Medical School
4:00 pm	Discussion of Day 1 topics *Kathleen Mullan Harris*, University of North Carolina, Chapel Hill moderator
5:00 pm	Adjournment

Tuesday, June 26, 2018

8:30 am	Approaches to maintain the representative recruitment and presence in longitudinal surveys of population subgroups over the life course; methods for estimating and adjusting for differential mortality and attrition *Peter Lynn (by videoconference)*, Essex University
9:15 am	Retrofitting current ongoing aging studies (e.g., parallel analyses of cohorts across life course, pooling data from younger cohort with aging cohorts; linking estimates of empirical relationships in theoretical pathways of influence) *Scott Hofer*, University of Victoria, Canada
10:00 am	BREAK
10:15 am	Exploiting other data sources, linking administrative data, collecting life history data *David Johnson*, University of Michigan
11:00 am	Open Discussion: Themes of the meeting, future questions, and directions for ongoing and future studies *John Haaga*, National Institute on Aging, kick off discussion
12:30 pm	Adjournment

Appendix B: Participants List

Invited Experts

Elissa Epel, University of California, San Francisco
Vicki Freedman, University of Michigan
Scott Hofer, University of Victoria, Canada
David Johnson, University of Michigan
Rucker Johnson, University of California, Berkeley
Chris Kuzawa, Northwestern University
Morgan Levine, Yale Medical School
Peter Lynn, Essex University
Sara McLanahan, Princeton University
Terrie Moffitt, Duke University
Kathleen Mullan Harris, University of North Carolina, Chapel Hill
Fabian Pfeffer, University of Michigan
Michael Shanahan, University of Zurich
Aryeh Stein, Emory University

National Institute on Aging

John Haaga
Amelia Karraker
Lisbeth Nielsen
Emerald Nguyen

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Juanita Chinn
Rebecca L. Clark
Stephen E. Gilman

National Academies of Sciences, Engineering, and Medicine

Jere Behrman
Mary Ghitelman
Brian Harris-Kojetin
Malay Majmundar