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A Review of Selected Longitudinal Studies on Aging: Past Findings and Future Directions

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Abstract

A review of the 51 longitudinal aging studies currently in the National Institute on Aging Database of Longitudinal Studies was conducted to identify major information gaps and areas for future research. Database information, which included posted study summaries, study details from principal investigators or directors of these projects, and more than 300 recent publications based on the studies, were reviewed to identify significant findings of each study. This review summarizes the main findings and identifies the need for future work within six broad study topics: cognitive function, socioeconomic status, health and physical performance, morbidity and mortality predictors, healthcare costs, and genetics. The percentages of these 51 studies addressing the four most common topics are as follows: cognitive function (44%), health and physical performance (51%), socioeconomic factors (55%), and predictors of morbidity/mortality (63%). Important areas not addressed to any major degree were healthcare costs and genetics. Only two studies reported findings on genetics or epigenetics of human aging, and only a single study reported on associations between aging and financial costs, especially healthcare costs, which have been postulated to be important determinants of care and life quality. The results of this review, together with the specific directions proposed by other investigators with longitudinal study expertise, will inform the strategic planning of future long-term studies of aging.

Keywords

elderly; review; longitudinal study; aging

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The south Florida community is a diverse and rapidly aging population that has not been intensively studied over time, but a broad academic and community collaboration to launch a pilot study of aging in this region has been organized. In preparation for this research, existing longitudinal studies on aging were reviewed, and a panel of experienced investigators of aging was engaged to determine what foci and aspects of human aging previous research programs have not yet investigated or reported to any major degree.

Studies reviewed were restricted to those listed in the Database of Longitudinal Studies (DLS), a component of the Resources Branch of the National Institute on Aging (NIA) Division of Aging Biology Program Initiatives.¹ According to the NIA, the DLS was created “to assist with the development of research initiatives for identifying the physiologic and other types of factors across the life span, affecting onset and progression of disease with advancing age, as well as elucidation of protective factors contributing to exceptionally healthy aging.” Still, it could be argued that the DLS is not a comprehensive list and that other studies, of significant value, have been omitted, although and as reported by the NIA, the DLS was created based on input from the Longitudinal Data on Aging Work Group. Thus, although the DLS is representative of aging research and not totally inclusive, total inclusion is unlikely because of the volume and variety of longitudinal studies worldwide. For example, some have examined life-span development (aging from adolescence into adulthood). Also, the time to complete these studies is usually long, so ongoing studies or studies in early stages when the DLS was completed may have been omitted.

An important focus of work in south Florida will be studying the last third of life. Most major health problems surface during this time, providing an opportunity to identify associations and timing of the emergence of various health problems in relationship to specific behavioral, environmental, and genetic analyses and measures that identify specific physiological and pathophysiological determinants of life trajectory. A focus on the latter part of life provides opportunities to understand financial and other effects of increasing medical encounters, risks, and costs, especially hospitalizations, on the life trajectory. Thus, future longitudinal analyses will identify the predictors of disease and of health that can then be assessed and ultimately manipulated for their determinant roles in reducing the functional decline and other burdens of aging persons.

METHODS

The DLS was examined with the goal of identifying major research themes (e.g., cognition). Although most of the studies in the DLS examined older adults ranging in age from 55 to 105, several studies (e.g., Age, Gene/Environment Susceptibility Study, Interdisciplinary Longitudinal Study of Adult Development, Normative Aging Study) did include adolescents and younger adults. The studies with younger participants were typically longer-duration projects (e.g., >20 years) and included an emphasis on developmental as well as age-related decline. Subject selection for the longitudinal studies, as reported or implied, was primarily based on the research questions. For example, studies aimed at understanding the effects of “late life” cardiovascular disease risk management on life expectancy might require a different subset of subjects than those individuals selected for the more-conventional longitudinal study describing factors that contribute to physiological and functional decline.

The review of longitudinal studies of aging (Table 1 identifies the studies and their designations) revealed four major categories (summarized in Table 2): cognitive function, socioeconomic status (SES), health and physical performance, and predictors of morbidity and mortality. Examples of measures from each of the categories are listed in Table 3. In addition, two of the authors independently reviewed a representative collection of more than 300 publications based on the 51 longitudinal studies with the intention of broadly

categorizing 300 studies into the four major categories. To be included, both authors had to agree on which category a particular study best represented. Ultimately, the studies reviewed provided evidence as to the importance of the categories created, in terms of the amount of attention given a category and the potential for affecting aging research. These findings were then presented to speakers in the Richard C. Reynolds Symposium (Longitudinal Studies on Aging: Lessons Learned and Future Directions held in January 2009, upon which this supplement is based) to validate or modify the list of categories. This became an exercise in strategic planning in which an evolving protocol for a longitudinal study of aging in south Florida emerged.

RESULTS AND DISCUSSION

Cognitive Function

Thirty-five of the 51 studies addressed various cognitive domains in relation to age and mortality, but several important unanswered questions remain that relate to the linkage between cognition and mortality.² First, substantial disagreement persists on whether loss in crystallized (fixed knowledge of facts) cognitive ability or intelligence is more or less predictive of mortality than fluid (problem-solving skills) cognitive ability or intelligence.²

The onset of even mild cognitive impairment can decrease quality of life and function,³ but virtually no information is available on how such mild changes could affect healthcare utilization and outcomes (e.g., hospitalizations) or alter roles (work, marriage). Such information is critical to designing and delivering specific support and guidance to forestall likely adverse effects.

Socioeconomic Status

SES factors and measures are routinely studied, but relatively little has been concluded in terms of which specific individual measures are linked to overall mortality, morbidity, and functional status. With the exception of the link between educational level and dementia observed in the Nun Study,⁴ few other components of SES have significant and consistent predictive values. Several studies have failed to show any link between age, sex, self-assessment of physical health, or living conditions and mood.^{5,6} The Women's Health and Aging Study reported a strong link between race and SES in the United States but found that neither race nor SES is associated with rate of functional decline in old age.⁷ One major study (Established Populations for Epidemiologic Studies of the Elderly) has identified SES linkages for mortality, although the nature of these associations differs for men and women.⁸ Although occupational prestige, income, and education all predicted mortality in men, only income predicted mortality in women. These factors were more predictive in regions with more-heterogeneous populations.

Although these studies also point to various SES disparities with regard to access to health care and health literacy and education, they do not reveal to what extent they could reflect mismatches between providers and clients in terms of communication and understanding of cultural beliefs.

Health Status and Physical Performance

Health-based assessments and physical performance measures have been central concerns in the analysis of 42 of 51 of the longitudinal studies examined. Although many of these physical performance measures are associated with declines in health status, no one measure has emerged as a preferred predictor. Thus, unlike physical disability, which has several powerful predictors, health status and mortality prediction rests on a multitude of physical performance measures. These studies have generated a short list of physical performance

measures, such as gait speed, grip strength, ability to rise from a chair, and balance. Body mass index (BMI) and gait speed are associated with heart disease, falls, functional impairment, hospitalizations, mortality, and cognitive decline.^{9,10} Therefore, the aforementioned studies and the suggestions of the expert faculty panel that participated in the symposium, make BMI and gait speed an important pair of physical performance measures for future studies. BMI and gait speed may emerge as an index, or part of an index, to predict health status and mortality, as well as the trajectory after hospitalization and major acute illnesses.

Predictors of Morbidity and Mortality

Although the data are limited, studies suggest that morbidity, by itself, is only a weak predictor of mortality. The longitudinal studies offer unique opportunities, through the timing of changes in various parameters in relation to health status and mortality, to address the question of why some persons cope with chronic disease and major acute challenges and others succumb rapidly. In this regard, insights are lacking into the linkages between morbidities and mortality and specific behavioral parameters (physical activity, weight changes, diet, coping style), environmental factors (e.g., transportation, hospitalization, access to postacute care coordination, medication reconciliation), and genetics (especially epigenetic changes). Research in these areas should seek specific modifiable factors that affect morbidity, mortality, and quality of life.

The experience with inflammatory markers as predictors of morbidity and mortality illustrate the challenges of this type of research well. Although one research group focused on C-reactive protein, as well as blood pressure and total cholesterol, to predict coronary artery disease (CAD),¹¹ another group has emphasized the value of erythrocyte sedimentation rate (ESR) in predicting CAD.¹² Subsequent studies have suggested that specific inflammatory factors (e.g., interleukin-6) associated with CAD could underlie some of the changes in ESR and CRP.¹³

Healthcare Costs

Today's national concerns are increasingly focused on healthcare costs, yet any meaningful investigation into the economic effect of these costs on aging persons through direct individual effects, as well as the indirect effects on limiting society's infrastructure (e.g., public transit, hospitals, emergency systems), are lacking, and although the importance of behavior changes to reduce morbidity and disability are touted, the cost outcomes of changing behaviors is not known. It can be assumed that, by identifying risk factors for disease and dependency, these factors can then be targeted and reduced or eliminated. To calculate the economic effect of reducing risk factors for disease and dependency, what specific benefits will cost and the effect on the healthcare system and other aspects of society must first be known. Of the 51 studies reviewed, only one (the National Long Term Care Study) addressed this important topic.¹⁴ That study reported that higher costs (and spending) are associated with a greater degree of health problems,¹⁴ but many questions remain with regard to the health and economic effect of specific conditions and encounters (e.g., hospitalization). Understanding the effect of different healthcare models on spending and health would ideally involve comparing distinct approaches (e.g., limited health-care spending vs ad libitum spending) using similar populations. Although this design is scientifically sound, most oversight committees would view it as unethical because of the concern that those receiving health care as needed would suffer less disease and disability. For example, a cumulative measure of health and well-being and aging status (a frailty index or index of cumulative deficits and health problems) has emerged that predicts mortality and rate of decline in later years.¹⁵ Such a measure could be used in a longitudinal study as a

surrogate measure of mortality and disability to ascertain the effect of different approaches to healthcare spending.

Genetics

Genetic studies on a larger scale than was imaginable 10 years ago are now ongoing in many centers. Although the NIA-reviewed studies did not focus on a genetic cause of aging, there are many investigations currently under way that may be able to validate their findings using retrospective analysis of blood and tissue samples collected in earlier studies of aging.

Large-scale gene-sequence analyses have only recently become feasible. No information is available in the DLS regarding epigenetics, an emerging frontier of science addressing the changes in the regulation of gene activity and expression that are not dependent on gene sequence, although studies examining such are currently under way. The challenge in earlier studies, and to a lesser degree in future work, is to identify specific genomic sequences that should be monitors for gene mutations and epigenetic modifications. Only two of the 51 longitudinal studies reported associations between health status and specific gene sequences, and none have addressed the question of age-related epigenetic modifications, specifically the critical parameters of telomere length, oxidative damage to deoxyribonucleic acid and ribonucleic acid, gene methylation, and histone acetylation changes.

Although only two of the 51 longitudinal studies included genetic analyses, such an approach appears to have clinical importance. The Nun Study identified the apolipo-protein E4 allele as a likely risk factor for development of dementia in older women.⁴ The AGES Study focused on polymorphisms for the genes for monocyte chemotactic protein-1 (MCP-1) and its receptor CCR2.¹⁶ It identified specific polymorphisms of the MCP-1 gene that are associated with the development of atherosclerosis and myocardial infarction.¹⁶

Given these encouraging early studies, the rapid growth of genomic and proteomic capabilities and informatics, and the opportunities for validation of new genetic associations through analyses of samples from prior longitudinal studies, future longitudinal studies must include collaborative arrangements not only for discovering important gene sequence polymorphisms, but also addressing the likelihood of substantial epigenetic changes that could provide early predictors of aging trajectories by virtue of their linkage with specific modifiable health behaviors and environmental factors.

FUTURE LONGITUDINAL STUDIES OF AGING

Review of the 51 longitudinal studies reveals a wide spectrum of quality- and length-of-life predictors and an ever-expanding and improved set of tests and management strategies that open the way to reducing the burden of chronic illness and related costs, particularly during the last third of life. Campaigns such as *Agita Mundo* out of São Paulo, Brazil,¹⁷ and *Exercise Is Medicine* by the American College of Sports Medicine¹⁸ teach us that strategies for health forecasting and modifying behaviors must be adjusted to the diverse segments of our population.

A critical gap in designing such modified approaches is lack of understanding of how specific SES and behavioral factors, such as education, culture, language, healthcare access and literacy, media and technology access, and coping styles, influence the use and utility of such proactive approaches. Biobehavioral research including epigenetics, related to initiation, personalization, and maintenance of behavior change, has not been an element of prior studies. Thus, future longitudinal studies must be designed to identify and characterize when and how specific SES, epigenetic, and behavioral factors influence usability and utility of education, technology, media, and other devices for engaging diverse populations in the

pursuit of healthier aging. This information is critical to modifying interventions that will have the reach, fidelity, and sustainability to be effective in our heterogeneous society. South Florida's diverse aging population opens the way to contributing to the longitudinal studies needed to develop effective approaches to healthier aging.

No efforts to improve aging on a large scale will be implemented if they do not improve life and reduce total costs. The expenses and revenues and savings related to behavior modification, including effects on healthcare utilization, worker longevity and productivity, and quality of life across SES segments of our heterogeneous aging population, must therefore be discovered in future longitudinal studies. If those who are denied or fail to seek interventions or lack "medical homes" end up with the largest (and costliest) health problems, then interventions that target early-life healthcare and primary care relationships would be warranted. Certain subgroups could be identified that have easy access to fee-for-service healthcare and as a result undergo more procedures and hospitalizations with resulting deconditioning and mismanagement during transitions and a paradoxical greater disability and dependence not seen in comparable populations without such open access to the fee-for-service care system. Such studies would argue strongly that, for many older adults, "less is more" in terms of the effect of procedures, hospitalizations, and other interventions on health, function, and the overall cost of care.

Assessing and managing cost-benefit balance as the nation and the world age become major challenges that future studies must begin to address. This could be addressed through the media and through communication and information technology. Because technology cost-effectiveness for communication, training, and monitoring is rapidly expanding, future longitudinal studies such as the South Florida Quality Aging Registry must seek to discover how such technology can improve the effectiveness of targeting and delivering interventions that promote healthier aging.

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Table 1

Abbreviation Key for 51 Longitudinal Studies Reviewed by the National Institute on Aging

Abbreviation	Full Name of Study
AGES	Age, Gene/Environment Susceptibility Study
AIM	Aging in Manitoba
Alameda	Alameda (CA) County Study
ALSA	Australian Longitudinal Study on Ageing
BLSA	Baltimore Longitudinal Study on Ageing
Bangor LSA	Bangor Longitudinal Study on Aging
BASE	Berlin Aging Study
Betula	Betula Project
BHS*	Bogalusa Heart Study
BOLSA	Bonn Longitudinal Study on Aging
CaMos	Canadian Multicentre Osteoporosis Study
CSHA	Canadian Study of Health and Aging
CHS	Cardiovascular Health Study
EXCELSA	Cross-European Longitudinal Study of Ageing
DLSNA I & II	Duke Longitudinal Study of Normal Aging (I & II)
ELSA	English Longitudinal Study of Aging
EPESE	Established Populations for Epidemiologic Studies of the Elderly
Fredericton	Fredericton 80+ Study
H70	Gothenburg Study
HRS	Health and Retirement Study
Health ABC	Health, Aging and Body Composition Study
HHP	Honolulu Heart Study
HAAS	Honolulu-Asia Aging Study
ILSE	Interdisciplinary Longitudinal Study of Adult Development
ILSA	Italian Longitudinal Study on Aging
LASA	Longitudinal Aging Study Amsterdam
LSAA	Longitudinal Study of Ageing in Africa
LSOA I & II	Longitudinal Study of Aging (I & II)
LUND	Lund 80+
MAAS	Maastricht Aging Study
McArthur	MacArthur Study of Successful Aging
MFUS	Manitoba Follow-up Study
MMAP	Melton Mowbray Ageing Project
NLTCS	National Long Term Care Survey
NPHS	National Population Health Survey
NMAPS	New Mexico Aging Process Study
NHEFS	NHANES I Epidemiologic Follow-up Study

Abbreviation	Full Name of Study
NAS	Normative Aging Study
NLSAA	Nottingham Longitudinal Study of Activity and Ageing
NUN	Nun Study
OLSA	Ontario Longitudinal Study of Aging
Bernardo	Rancho Bernardo Study
RHS	Retirement History Study
Rotterdam	Rotterdam Study
SLS	Seattle Longitudinal Study
SAP	Southampton Ageing Project
SHARE	Survey on Health, Ageing and Retirement in Europe
TamELSA	Tampere Longitudinal Study on Aging
NLS *	The National Longitudinal Survey Original Cohorts
SWAN	The Study of Women's Health Across the Nation
VLS	Victoria Longitudinal Study
WLS	Wisconsin Longitudinal Study
WHAS	Women's Health and Aging Study

* Used mostly participants younger than 55 and were excluded from this analysis.

Table 2

Comparison of Significant Findings from 51 Longitudinal Studies

Study	Cognitive	Socioeconomic	Health and Physical Performance	Predictors of Morbidity and Mortality
AGES	No	No	Yes	Yes
AIM	No	No	Yes	Yes
Alameda	No	Yes	Yes	Yes
ALSA	No	No	Yes	Yes
BLSA	Yes	No	Yes	Yes
Bangor LSA	No	Yes	Yes	No
BASE	No	Yes	No	Yes
Betula	Yes	Yes	Yes	No
BHS	Excluded	Excluded	Excluded	Excluded
BOLSA	No	Yes	No	Yes
CaMos	No	No	Yes	Yes
CSHA	Yes	No	Yes	Yes
CHS	Yes	No	Yes	Yes
EXCELSA	Yes	Yes	No	No
DLSNA I&II	No	Yes	Yes	No
ELSA	Yes	Yes	Yes	No
EPESE	Yes	Yes	Yes	Yes
Fredericton	No	Yes	No	Yes
H70	No	Yes	No	Yes
HRS	Yes	Yes	No	Yes
Health ABC	Yes	Yes	Yes	Yes
HHP	No	No	No	Yes
HAAS	Yes	No	Yes	No
ILSE	Yes	Yes	Yes	Yes
ILSA	No	Yes	Yes	Yes
LASA	Yes	Yes	Yes	Yes
LSAA	No	Yes	Yes	No
LSOA I & II	Yes	Yes	Yes	Yes
LUND	No	Yes	No	Yes
MAAS	Yes	Yes	Yes	No
McArthur	Yes	Yes	Yes	Yes
MFUS	No	No	No	Yes
MMAP	No	No	No	Yes
NLTCS	Yes	No	No	Yes
NPHS	No	Yes	No	No
NMAPS	No	No	No	Yes
NHEFS	Yes	No	Yes	Yes

Study	Cognitive	Socioeconomic	Health and Physical Performance	Predictors of Morbidity and Mortality
NAS	No	Yes	No	Yes
NLSAA	No	No	Yes	Yes
NUN	Yes	Yes	No	No
OLSA	No	Yes	No	No
Bernardo	Yes	No	No	Yes
RHS	No	Yes	No	No
Rotterdam	Yes	No	No	Yes
SLS	Yes	Yes	No	No
SAP	Yes	Yes	No	No
SHARE	Yes	Yes	No	No
TamELSA	No	No	No	Yes
NLS	Excluded	Excluded	Excluded	Excluded
SWAN	No	No	Yes	Yes
VLS	Yes	No	No	No
WLS	No	Yes	No	No
WHAS	Yes	Yes	Yes	Yes

See Table 1 for full names of studies.

Table 3

Examples of Measures Used in Previous and Ongoing Longitudinal Studies of Aging

Research Focus	Examples of Measures
Cognitive function measures	Mini-Mental State Evaluation, ³ Rey Auditory Learning Test, ⁴ Letter–Digit Substitution test, Benton’s Visual Retention Test, Wechsler’s Digit Symbol Substitution Test, Verbal Fluency Test
Socioeconomic status	Age, race, sex, marital status, education, income, housing characteristics, ethnicity, language, retirement status, prior occupation, religion, immigration/emigration status
Health status and physical functioning	Height, weight, physical activity level, Short Physical Performance Battery, activities of daily living, sleep pattern, medical history, electrocardiogram, self- reported health, hospitalizations, Center for Epidemiologic Studies Depression Scale
Predictors of morbidity and mortality	Family history, blood pressure, body composition, weight history, falls, alcohol consumption, cigarette smoking, blood glucose, cytokines and inflammatory markers, reactive oxygen species, and vitamin D