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An Overview of the Design, Implementation, and Analyses of Longitudinal Studies on Aging

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Abstract

Longitudinal studies have contributed substantially to understanding of aging and geriatric syndromes. These efforts have provided a base of knowledge of the critical factors to consider in designing and implementing new longitudinal studies in older adults. This review highlights some of the major considerations in planning and implementing this type of study. Longitudinal studies can assess change over time and specific disease endpoints. Such projects require multidisciplinary teams with expertise in the many health and contextual factors that must be considered. Recent advances in study design include the use of imaging and biomarkers to assess mechanisms and approaches that raise the ceiling on measurement and integrate assessment of exposures over time. Study implementation requires careful planning and monitoring to maintain fidelity to the scientific goals. Analysis of longitudinal data requires approaches that account for inevitable missing data. New studies should take advantage of the experience obtained from longitudinal studies on aging already conducted.

Keywords

longitudinal studies; observational studies; study design; data analysis

Longitudinal observational studies have played a major role in geriatric research and in defining the scope of many health concerns in older adults, their risk factors, and their natural history. Because all older adults have significant risk for death and disability, studies that include large samples of community-dwelling older adults have provided an important perspective on the scope of the problems facing an aging population. For example, early studies of disability from the Established Populations for the Epidemiologic Study of the Elderly1 and the National Long Term Care Survey2 have demonstrated the large burden of difficulty with functioning in daily life after age 65. More-focused efforts on identifying risk factors have shown that disability is multifactorial, and the more-common conditions that should be targeted to prevent disability have been identified. Furthermore, studies that assess risk broadly have illustrated the commonality of risk factors across geriatric syndromes.3 Focused studies on specific age-related health conditions such as osteoporosis,4 cardiovascular disease,5,6 stroke,7 and dementia8 have not only been able to assess specific biological pathways that lead to adverse outcomes, but have also assessed the role of other conditions in exacerbating these common problems. Other important contributions have

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focused on social, behavioral,9 and economic outcomes.10 Current and future studies on older populations will be designed to better address this complexity by developing life-course approaches that address early changes, precipitants, and earlier stages of disability.11,12

LONGITUDINAL STUDY DESIGN

The design of longitudinal studies on aging should focus on a set of primary questions and hypotheses while taking into account the important contributions of function, comorbid health conditions, and behavioral and environmental factors. By focusing on primary questions and hypotheses, other methodological concerns can be put into perspective, because it is far too costly and burdensome to measure all aspects of health to the same degree as is necessary to address the primary hypotheses. Design concerns can be classified into those addressing the target population, the exposures, the outcomes, and potential confounders. Cost and practicality may limit the degree of precision in measurement, driving questions back to the priorities determined by the primary questions. Thus, remaining focused on the primary study goals is critical for setting priorities.

To ensure the best design and ultimate productivity, the study's scientific and administrative leader should assemble a team of investigators and staff who have the skills to contribute to successful design and implementation. This includes content experts in relevant diseases, disability, and aging processes important to the scientific questions, as well as methodological experts in sampling, measurement, and biostatistics. The administrative team must have expertise in budget, environment, and human resource issues. Staff need not have prior medical training but should be detail oriented and dedicated to maintaining fidelity to protocol.

The design of a longitudinal study will vary depending on whether the primary goal is to study changes over time or discrete outcomes. Changes over time generally require frequent contacts. Some outcomes such as stroke or cancer can be assessed using record review, whereas dementia requires in-person examinations. Generalizability needs to be weighed against maintaining follow-up, and these are often competing goals. The requirement for an extensive evaluation and years of follow-up can reduce participation rates. Tiered designs can be used to collect screening data to assess representativeness, with more-intensive data collection from a smaller sample. The internal validity of within-person analysis strengthens longitudinal designs. The sample size needed should be based on power calculations for the primary outcomes of interest and thus vary with the outcome rate. Many health outcomes occur at rate of a few percentage points per year in this age group. Thus, sample sizes of several thousand are often needed to have enough events to study within a reasonable time frame.

The target population will vary with the questions being asked. A fundamental question is what age is most appropriate? Today, 65-year-old people are generally healthier than ever and have low rates of disability and most major health events. Several studies have moved to age 70 to better target the problems of aging.13,14 Conversely, interest in the origins of aging requires targeting earlier ages. For example, the Study of Women's Health Across the Nation targeted women in the perimenopausal period to understand the role of hormonal change in early age-related processes.15,16 Inclusion and exclusion criteria depend on the outcomes and the outcomes measurement criteria. For example, a study of mobility disability17 excluded individuals using a cane to walk 400 m at baseline, because inability to walk independently was to be the primary study outcome. Recruitment of individuals within the full spectrum of health, including the frailest,18 will increase generalizability, although having a large number of participants who have already experienced the outcome,

reducing power for incidence studies, may offset this strategy. Careful consideration of the level of cognitive function required for participation can dictate the exclusion criteria for dementia. Regardless of the current level of cognitive function, all longitudinal studies of older adults should identify a potential proxy respondent in case of future compromised cognition of the participant.19 Studies in the United States need to consider the diversity of the target population and whether to overrecruit subgroups to have adequate power within the groups. In most cases, additional resources are needed to reach minority populations.20

Ethical concerns in longitudinal studies of older adults warrant special attention. Methods must be in place to establish competency for informed consent21 and procedures put into place if proxy consent is needed at baseline (for studies of cognitively impaired individuals) or is anticipated for the future, which is the case for most long-term follow-up studies. Results from laboratory testing should be reviewed and reported to subjects if clinically significant findings are identified. Procedures should be designed for, and staff should be trained to attend to, patient safety in the use of any diagnostic or other testing equipment being employed in the study.

Longitudinal observational studies are often designed to assess multiple outcomes. Although it is important and efficient to assess more than a primary outcome, the choice of outcomes should be based on the primary hypothesis, and the study should be powered to address the most important questions. This will, in turn, dictate the sample size to be recruited, which is the major driving factor of the study's cost and feasibility. Nevertheless, there is a huge scientific advantage to assessing other outcomes, in that risk–benefit ratios can be evaluated. The relationship between multiple health events can be assessed together to determine relative importance and contributions to individual-and societal-level outcomes, such as disability and healthcare utilization. For example the Women's Health Initiative,22 by including the observational component, was able to assess breast cancer, fracture, cardiovascular events, and cognitive decline because of the sample size recruited.23 Together, the findings provide a rich picture of the role that these major conditions play in the functional health of older women.23–26 Linkage of cohort data to the National Death Index, Medicare Beneficiary files, the Minimal Data Set, and other public use files can greatly expand opportunities for outcomes assessment.27–32

Disability is an important outcome that has been assessed using a variety of methods, including self-report, professional assessments, and performance-based measures, such as gait speed and timed tests of specific tasks. Important observations regarding the natural history of exacerbations and remission in these outcomes has led to refinements in defining disability outcomes, such as requiring persistence over time,14 task modification,33,34 and direct assessment35 with performance measures. These methods continue to evolve, and there is no consensus on a single approach to define disability outcomes. Recent studies on healthy aging outcomes have shown that there is tremendous variation in functioning that is well above the level designated as disabled. To capture the full spectrum of function and to detect early decline, the study designers should consider using instruments designed to capture a full range of function, including normal, high, and exceptional levels.36

Exposures of interest should be considered together with the design of the outcomes. Major risk factors are usually identified from the literature or hypothesized from new information on etiology. Behavioral and biological factors should be considered. For example, studies of outcomes of vitamin D exposure should assess diet, sun exposure and season, and blood levels of vitamin D and diseases that can affect its metabolism.37 Medications can be part of the exposure assessment, in that many medications can alter the primary risk factor being assessed. Examples include vitamin supplements and vitamin levels, lipid levels in the era of statin use, and blood pressure in light of antihypertensive use. Although "baseline" exposure

assessments are usually conducted, increasing attention is being paid to including more of a life-course perspective and incorporating historical exposure information from self-report38 or from other sources, such as geocoding.39,40 Efforts to continue long-term follow-up of younger populations will provide the best estimates of life-course exposures in old age.41-43

Potential confounders that should be considered are so numerous that they can greatly expand the cost and burden of studies in older adults. It is important first to rank all measures according to their role as primary outcomes or exposures so that potential confounders do not overtake resources. Most studies of older adults include measures of common psychosocial factors that can influence function, such as depression, social support, and cognition. Education and smoking history are risk factors for almost every adverse health outcome and should always be included. Age itself is usually assessed according to self-report, but studies of longevity show the importance of more-careful assessment and validation of even this apparently simple confounder.44 Finally, medication, even if not related directly to the exposure or outcome, can be important to assess as a potential confounder, but collection of information on medications requires special expertise to code them in a way that is useful and accessible for analysis.45-47

Blood laboratory testing is often a major component of a longitudinal study. Most large cohort studies have invested in setting up banks of stored serum, plasma, cells, and deoxyribonucleic acid. Blood tests can be used to define clinical health status, as in determining fasting blood sugar to classify diabetes mellitus, but have been most valuable for allowing for later evaluation of important biomarkers and for genetic testing. As novel markers emerge, stored specimens can be analyzed in a cost-effective case–cohort design.

STUDY IMPLEMENTATION

Once a study is designed, numerous procedures must be put into place to ensure that the data are collected with fidelity to the scientific goals. These steps can take weeks to months or even longer. In multicenter observational cohort studies, it is typical to spend a year or more developing and beginning to implement the study design before actually launching the study. This planning phase should include finalizing the protocol and writing a manual of operations and procedures. All data collection forms should be pretested before the data entry systems are designed, and the system for entry should be in place before the study begins. Time is also needed to hire and train staff, to lay the groundwork for recruitment, and to be sure that the institutional review board has addressed and approved all human subject concerns.

Fielding a study that is to be conducted over the long term requires special attention to measurement. The scientific rationale of each measure, including its role as an outcome, mediator, or potential confounder, should be spelled out in the operations manual. Reproducibility, even if documented in the literature, should be tested in the specific cohort and setting, especially for longitudinal studies that include measurement of change over time. Measurement error can bias associations with change over time, and this analytical concern can be mitigated with adjustment for measurement error per se.48 All measures should be pretested individually and as a package to work out the study flow. Regular tracking of major measurements through study logs, with commentary and review of all procedures at regular staff meetings, is critical for the identification of potential problems and solutions. Manuals should be revised as needed and staff retrained and certified at least annually.

Data entry can go smoothly when forms are well designed, when staff members complete them without error, and when reports are set up and reviewed regularly for quality control. Keeping up with data entry and running quality checks daily will avoid future recalls and reduce edits. Backlogs of data entry make it more difficult to identify and correct errors in form completion. Real-time data entry and edits are more feasible with software programs that build in range checks and logic.

A successful longitudinal study is proactive in retaining participants. Numerous aspects of study operation lead to successful retention. Suggested methods include keeping to the requested study visit date and duration as agreed to during enrollment and respecting participants' time. An exit interview should be conducted with every participant to explain follow-up plans and expectations. Regular contacts for follow-up, newsletters, and birthday and holiday cards maintain the relationship between participants and staff. Finally, it is critical that alternative methods be provided to obtain follow-up, including telephone methods,49 home and nursing home visits, and proxy interviews.50 As older adults become more impaired, there is inevitable dropout from full participation. Alternative methods that include home visits, telephone interviews, and proxy interviews can lead to high levels of retention for major morbidity and mortality.50

DATA ANALYSIS

Once the data are in hand, numerous analytical concerns will arise. Missing data are "a given" in longitudinal studies of older adults because of unanticipated illness and death. Methods should be in place to ensure that this is kept to a minimum.51 Other analytical concerns in longitudinal studies include measurement error; protocol drift over time; migration in equipment specifications and software that affect estimates of change over time; determining changes that are nonlinear, with curvilinear or threshold effects; and substantial biological variability over time. These should be considered in the study design. Analysis of an outcome might be enhanced if time-dependent covariates can be considered. This level of detail of data also needs to be in place in the study design. The analysis should take into account the previously discussed matters of variability and fluctuations over time.

CONCLUSION

Given the many challenges of conducting longitudinal studies in older adults, it may seem impossible to do it well; such studies are challenging. Successful studies require leadership, teamwork, and excellent communication. Ultimately, prioritizing the primary focus of each study and applying the best science will optimize success. Lessons learned from previous and ongoing longitudinal studies outlined in this review should be helpful in the design of future longitudinal studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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