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Translating Research to Promote Healthy Aging: The Complimentary Role of Longitudinal Studies and Clinical Trials

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Abstract

An important challenge in epidemiology is the difficulty in inferring causality from observational studies. Even the best longitudinal studies have limitations in this regard, and when clinical trials are feasible they will provide more definite evidence of causality. However, even when clinical trials are feasible, we can learn a great deal about the disease process, assessment techniques, subject selection criteria, and the impact of potential interventions from longitudinal studies. This review covers the theoretical issues supporting the value and limitations of longitudinal studies, the practical utilization in clinical trials of different aspects of knowledge that can be gained from longitudinal studies, critical issues in the translation of longitudinal observational studies into clinical trials, and the value of observational studies in broadening the applicability of specific trials. Relevant issues are illustrated with examples of both unsuccessful and successful trials, with a major emphasis on clinical trials of physical activity in older persons.

Keywords

longitudinal studies; observational studies; clinical trials

Introduction

Improvements in the standard of living and the quality and availability of medical care have led to an historically unprecedented rise in life expectancy in the United States, from about 47 years of age in the year 1900 to age 78 in 2006. As a result, the percentage of older people in the United States is growing rapidly and by the year 2030 it is estimated that 20% of the U.S. population will be 65 year of age or older. The increase in the number of older adults is a concern given the likelihood that it will entail an increasing societal burden of age-related health problems, including chronic disease, physical and mental impairment, and disability. Therefore, a key goal of gerontological research is to identify and evaluate strategies by which older adults can maintain independence and forestall the onset of disability.

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The past quarter-century has seen an increasing emphasis on “evidence-based” medicine. This approach applies critical and systematic quantitative reasoning to issues surrounding disease prevention, diagnosis, and treatment. Of the quantitative tools employed, the randomized trial is accepted as providing the most valid evidence. Confidence in the randomized trial is based on the idea that randomization minimizes the likelihood that confounding variables can explain differences in outcomes between the groups being compared. Importantly, randomization controls confounding both from known and unknown or unmeasured factors. However, trials can be costly to implement and must be carefully designed to provide reliable results in an efficient manner. The intellectual “raw materials” for trial design include: 1) a hypothesis to be tested, 2) an estimate of the frequency of the study outcome, 3) an intervention to be tested (including dose and duration), and 4) a prediction regarding the strength of the intervention (see Figure 1). These “raw materials” typically come from observational studies, especially longitudinal studies, as well as basic and translational science that contribute to both the development and selection of promising trials. Longitudinal studies (defined here as observational studies of cohorts followed over time) help identify “good bets” for further evaluation by providing information on which factors may influence the frequency of the outcome. In disability research, for example, the emphasis is often on identifying modifiable behaviors that could be important in reducing the burden of disability. However, behaviors evaluated in longitudinal studies are self-selected, so it is difficult to fully account for other attributes that may be associated with the behavior of interest and which may predict the onset of disability. Nevertheless, not only will a longitudinal study of disability provide support for a given hypothesis, it will also provide an estimate of the rate on disability onset (providing guidance for the number of persons that will have to be enrolled for an adequately powered study), and the amount of the behavior (i.e., dose) that is associated with benefit (providing guidance for the design of the intervention).

The goal of this paper is to present the complementary strengths and limitations of longitudinal studies and randomized trials to increase the understanding of their relative roles in developing evidence-based approaches to the problem of disability prevention in older adults.

STRENGTHS AND LIMITATIONS OF LONGITUDINAL STUDIES

Studies of older adults document great heterogeneity in health and function. The fact that function declines at different rates is evidence that strategies to prevent functional decline can be identified. Early knowledge about risk factors for diseases and conditions in older people frequently comes from associations observed in cross-sectional studies, or from the initial, cross-sectional analyses of the baseline assessment of a cohort or patient group that will be followed up in the future. These studies can offer valuable insights into potential risk factors, but there are limitations in what we can learn from cross-sectional associations. This is especially true in the older population, where multiple conditions and risk factors frequently co-exist and there is potential circularity in the relationships. For example, sedentary lifestyle is strongly associated with disability, but in a cross-sectional design it is not possible to understand if the lack of physical activity causes the disability, if the disability leads to reduced physical activity or, more likely, both. Similarly, depression will have a strong cross-sectional association with disability, but from this association it is not possible to untangle whether depression causes disability or disability causes depression. Because of this potential circularity in cross-sectional relationships, we frequently turn to longitudinal observational studies to attempt to understand the temporal relationship between potential causes and outcomes.

Longitudinal epidemiological studies are extremely valuable tools in observational research and have many uses and strengths. Table 1 shows a simplified outline of the uses of longitudinal studies. At the most basic level, if we want to understand change over time in any of the characteristics or diseases of a population under study, we must obtain repeated measures of that characteristic or disease over time. A great deal of valuable information can be obtained from documenting the natural history of a condition. For example, innovative longitudinal studies of older people beginning at the time of hip fracture have revealed the very high rate of poor medical and functional outcomes subsequent to fracture, providing important information for clinicians and demonstrating potential targets for interventions.¹

The most classic use of longitudinal studies in chronic disease epidemiology is to identify risk factors for the onset of diseases and conditions. While a great many biological, social, and psychological factors can be studied prospectively with this design, the greatest contributions of these studies are when they give insight into risk factors that can be utilized as screening tests for clinical and public health practice and when they identify potentially modifiable risk factors. Many of these studies are performed on large, population-based cohorts but a great deal can also be learned from longitudinal studies that follow clinical populations, often recruited from health maintenance organizations or health care providers that service the majority of a people in a community. These latter study designs may provide more detailed clinical information, may be useful for evaluation of medications and may offer value in comparative effectiveness research. Clinical trials developed from large, population-based cohorts often focus on prevention, while the trials that grow out of the latter study designs may be more intensive interventions to treat specific diseases and conditions.

Finally, the third broad area mentioned in Table 1, in which longitudinal studies make important contributions, is when we use them to sort out mechanisms by which risk factors may cause the conditions they predict in these studies. A biologically plausible mediator of a relationship between a risk factor and an outcome can be assessed for its relationships with the risk factor and the outcome and the degree to which it attenuates their association, with a large reduction implying that the mediator under study is in fact on the pathway from the risk factor to the outcome. Furthermore, longitudinal studies provide the opportunity to study mechanisms associated with disease progression, which may be different from factors that predict disease onset.

The clarity of the design of longitudinal studies makes them very appealing, but it must be recognized that they also have limitations, particularly related to the issue of causality. An observational study can provide evidence for, but can never truly prove causality, and several design issues are relevant in this regard. In any observational study, those with a specific risk factor differ from those without the risk factor in many ways, some of which can have an effect on the observed relationship. Some of these potential confounders are measured in the study and can be adjusted for, but residual confounding by unmeasured factors is often present and difficult to assess. Furthermore, if a potential confounder is measured poorly, it may not be possible to fully account for the influence of the confounder using statistical tools. Longitudinal studies require follow-up assessments and there is always a loss of study participants over time. Often, those who have higher levels of the risk factor under study are more likely to be lost to follow-up. If the relationship between the risk factor and the outcome is particularly strong in those lost to follow-up, this can cause substantial bias in the findings.

In chronic diseases that develop gradually over time, the outcome under study can have a direct or indirect effect on the risk factor itself, a phenomenon referred to as “reverse causality.” In studying dementia onset it was found that low blood pressure in old age was

associated with higher rather than lower dementia risk, but low blood pressure in middle age was found to be strongly protective of dementia.² The explanation for this was that low blood pressure near the time of dementia onset in old age was probably caused by the dementia itself or diseases causing dementia while in middle age low blood pressure is protective against vascular disease that can cause dementia many years in the future. Another example of reverse causality, where poor health affects the risk factor, was the observation that in persons age 71 and older those with lower cholesterol were found to have poorer survival, opposite to what was expected.³ This was likely due to chronic disease and poor dietary intake affecting both cholesterol and mortality, and demonstrates that in the older population even a longitudinal study can give difficult-to-interpret results.

The information that comes from longitudinal studies may be highly relevant to interventions that prevent or reduce the risk of disease, but at times observational studies may offer limited guidance because they do not reflect the clinical or public health intervention under consideration. For example, there was a great deal of observational evidence indicating that women on long-term estrogen replacement therapy after menopause were at reduced risk of myocardial infarction, but the reverse was found in a randomized clinical trial, the Women's Health Initiative (WHI).⁴ Prentice et al compared the WHI clinical trial results to those generated from the WHI observational study. They found that in both studies there was an increase in risk of coronary and stroke deaths within two years of initiation of therapy, but a suggestion of a reduced risk of events in both studies after five years of initiation of therapy. Thus, the discrepancy between the WHI trial findings and epidemiologic findings might be explained by the fact that observational study participants are weighted towards long-term users, while the trial evaluates, by necessity, the effects of the initiation of therapy.⁴ In general, using observational data to assess the value of specific drugs can have special pitfalls. As for all risk factors in observational studies, medication use is not randomized in study participants and often the severity of disease plays an important role in the physician's selection of a drug. Thus, drugs selected for sicker people may be associated with poorer outcomes in longitudinal studies, a phenomenon termed "confounding by indication," and it may not be possible to fully adjust for the residual bias.

The potential impact of unmeasured confounding on outcomes of potential geriatric interest can be appreciated by looking at data from the placebo groups of randomized trials. Simpson et al undertook a meta-analysis of the relationship between the adherence to the placebo and total mortality in eight randomized clinical trials.⁵ They found that good adherence to the placebo was associated with a statistically significant 44% reduction in the odds of death. The basis for this reduction is not known, and there is currently no sure way to predict adherence. However, the study population enrolled in any longitudinal study will include some proportion of persons who would have been "adherers" had they be enrolled in a randomized trial, and to the extent that the behavior under study is correlated with "being an adherer" the benefits of the behavior as assessed in a longitudinal study may be overstated.

IMPORTANCE OF OBSERVATIONAL LONGITUDINAL STUDIES FOR CLINICAL TRIAL DESIGN: EXAMPLES FROM TRIALS DEVELOPED FOR THE AGING POPULATION

Although, as discussed above, observational studies are often limited in proving the value of a particular intervention, they may play a major role in the development of high-quality randomized clinical trials. For certain types of interventions, particularly drug therapy, animal experimentation may be the first step in recognizing a potential intervention. For other types of interventions, especially behavioral or social interventions or when an animal model of a condition does not exist, findings from observational studies may offer the first

step in identifying and refining a potential intervention. There are numerous instances in which longitudinal studies provided the incentive to follow up with clinical trials and offered valuable insights into the design of these trials. The following examples are from high impact trials in the older population.

Longitudinal studies may play a role in beginning the process of overturning long-standing clinical beliefs that have not been empirically tested. Observational studies showed an exponential increase in the prevalence of isolated systolic hypertension with increasing age.⁶ For many years it was thought that elevated isolated systolic blood pressure in older people was necessary in order to maintain good perfusion to the brain, and there was fear that lowering this pressure could lead to strokes. Longitudinal studies, however, demonstrated that high systolic blood pressure in the absence of elevated diastolic pressure was predictive of higher likelihood of stroke⁷ and led to important clinical trials testing the lowering of isolated systolic blood pressure. The Systolic Hypertension in the Elderly Program (SHEP) was a highly successful trial that demonstrated a 36% reduction in stroke and a 27% reduction in myocardial infarction and coronary death.⁸ SHEP has had a major influence on the approach to treatment of blood pressure in older people.

Medical complexity increases in the older population and longitudinal studies can provide insights into the information that should be collected on older people who participate in a clinical trial. This information includes variables that help to fully characterize the study participants. Some of these variables, based on observational data, may be used for statistical adjustment or even to evaluate results of the trial within strata defined by the variables. Observational studies may give insights into the multiple risk factors that play a role, and are targets for intervention, in conditions that have multiple causes in the older population. A good example of this is the pioneering work of Tinetti and colleagues in first using longitudinal epidemiologic research to identify many risk factors for falls in older adults.⁹ They then applied these observational findings to the development of a multifactorial intervention to reduce risk of falling, which demonstrated a 25% reduction in fall risk in a randomized clinical trial.¹⁰ In general, investigators should be parsimonious in collecting data in large, simple clinical trials, but observational studies with much more information available will provide very good insight into what specific data are important to collect.

Longitudinal observational studies may be important for setting the stage and preparing the scientific community for large, long-term clinical trials. Longitudinal observational research on prostate specific antigen (PSA) showed that it predicted the onset of prostate cancer¹¹ but demonstrated that there was often a long interval between PSA elevation and onset of cancer, and that difficulties with the specificity of the test made it hard to untangle risk of cancer and benign prostatic hypertrophy. The many observational studies led to widespread clinical use of PSA to screen older men, but the longitudinal data also showed that many older men with high PSA levels would die from other diseases before being affected by prostate cancer, or before small cancers had an adverse effect on them. It was clear from the longitudinal studies that large clinical trials were needed to prove the value of PSA testing in actually saving lives, not just in finding slow-growing cancers at earlier stages. Recent publication of two large, long-term clinical trials in the U.S. and Europe have shown somewhat contradictory results and still have not led to a final conclusion on the value of this testing.¹²⁻¹⁴

Longitudinal studies may offer important evidence that certain subsets of the population are affected differently by a risk factor, which would influence clinical trial design. In the U.S., anemia is present in about 10% of older persons overall, but the prevalence is three times higher in older African Americans.¹⁵ Longitudinal research has shown that older people

with anemia are at higher risk of mortality and aging-related outcomes such as functional decline,¹⁶ but studies of adverse outcomes stratified by race indicate that blacks don't have these outcomes until they reach lower levels of hemoglobin,^{17,18} indicating that there may be different causes of anemia affecting mortality differently by race or that there is a biological set point for hemoglobin according to race and that the standard definition of anemia may not be appropriate for blacks. Clinical trials to treat anemia and test whether this would reduce associated adverse outcomes would be relevant in all older persons, but the observational studies indicate that the target population in regard to hemoglobin level might be different in whites and blacks.

Two important aspects of observational studies that enhance the quality of clinical trials will be discussed in relation to the development of randomized controlled trials to evaluate whether physical activity prevents the onset of disability in older persons. First, longitudinal studies have demonstrated a reduced incidence of disability in those who are physically active and have put the magnitude of this effect into perspective. A recent comprehensive literature review by the Department of Health and Human Services Physical Activity Guidelines Advisory Committee found that active mid-life and older individuals have approximately a 30% lower risk of developing moderate or severe functional limitations or role limitations compared with inactive individuals.¹⁹ This risk estimate is an example of how initial estimates of effect size and subsequent calculations of sample size for a clinical trial can be obtained from observational studies. The report noted that these results were strongly consistent across studies, but that no large clinical trials had assessed the effect on disability onset of a physical activity intervention. Healthier people choose to exercise more and have lower rates of adverse outcomes, and the only definitive way to assess whether the exercise is causal or is a marker of better health status is through a randomized controlled trial. A second area where observational studies have provided important information for clinical trial development is the demonstration that objective physical performance testing can identify a subset of the older population that is not currently disabled but is at high risk for future disability onset.²⁰ In the Lifestyle Interventions and Independence for Elders (LIFE) Study,²¹ the Short Physical Performance Battery (SPPB, a battery testing balance, gait speed, and time to rise from a chair five times and scored on a scale of 0–12, with 12 being the highest level of performance) was administered during screening. Those with SPPB scores of 10–12, demonstrated in longitudinal studies to be associated with low rates of future disability, were excluded.

LIMITATIONS OF CLINICAL TRIALS

While it would be theoretically desirable to subject every hypothesis and recommendation to the rigor of a randomized trial, it is clearly impractical, and in some cases unethical, to do so. There is substantial evidence from longitudinal studies showing that smoking cigarettes is harmful. There cannot be a randomized trial to prove this, however, because it is unethical to expose a study subject to potential harm without a balancing benefit. Moreover, because of the strong evidence that smoking is dangerous, it is also unethical to randomize current smokers to either quit or not. One cannot ask or require a study subject to maintain a behavior that is believed to be harmful. Therefore, the evaluation of potentially harmful exposures can only be evaluated based on the observation of self-selected (e.g., smoking) or unintentional exposures (e.g., occupational exposure) and not random allocation. However, different types or intensities of interventions to stop a harmful behavior can be examined in clinical trials.

In many situations the use of clinical trials is constrained by cost, and the primary driver of cost is sample size. In a randomized trial there are two alternative explanations if the outcome between the two treatment groups is not statistically different: the treatment does

not have an effect, or sample size was too small to demonstrate the statistical significance of an effect. A key task in trial design is the identification of the smallest number of people to study that yields an acceptably high likelihood of finding a treatment effect of the intervention under study if that intervention truly has an effect of a specified size. This is the statistical power of the trial. The sample size should also be adequate to rule out chance as the explanation, should a clinically meaningful difference exist between the groups. For clinical outcomes, the main driver of the sample size is the frequency of the event under study. Even many common geriatric conditions occur at relatively low rates, so the necessary sample sizes to detect clinically important differences can be quite large. For example, as common as it is, the incidence of mild cognitive impairment/dementia (MCI/D) in older adults is about 2% per year. Based on this, the design team for the LIFE Trial estimated that approximately 1,800 people 70–89 years of age would have to be enrolled to have a 90 % chance (90% power) of detecting a 50% reduction in the incidence MCI/D in a four-year physical activity trial. This is a large hypothesized reduction, and the sample size rises quickly as the anticipated difference in MCI/D rates between the groups falls.

To be able to study relatively infrequent outcomes, one must study a large number of people, and/or conduct the study over a long period of time, and/or select only people at high risk, to increase the event rate. The Coronary Primary Prevention Trial (CPPT) employed all three strategies to prove that lowering cholesterol reduced the incidence of coronary heart disease.²² The CPPT validated claims regarding serum cholesterol's role in causing coronary disease that arose from both animal experiments and human longitudinal studies. The study enrolled 3,806 men with type II hyperlipidemia in a 10-year randomized placebo controlled trial of the cholesterol lowering agent, cholestyramine. Only men in the highest 5% of the cholesterol distribution were included. Although the trial was successful, its limitations were highlighted when the first questions following its completion concerned the degree to which the findings applied to women and lower risk populations.

Aside from selecting participants based on their risk of the outcome, enrollment criteria for trials are often structured to exclude people who may have difficulty complying with interventions, or who may be at high risk for dropping out. Consequently, many trials exclude people with low scores on cognitive screening tests or people with serious comorbidities. This is a major issue for geriatrics research, because an unintended side effect of exclusion criteria is to reduce the ability to generalize trial findings to typical geriatric populations.

The cost of randomized trials also limits the number of interventions that can be evaluated to address a particular question. Usually, trials can only evaluate a single “dose” or type of intervention, not a range of possible doses. In order to gain efficiencies, sometimes people will be randomized to two different interventions simultaneously—a 2×2 factorial design. However, these trials are rarely designed to examine synergies or antagonistic relationships between the two factors being evaluated because of sample size considerations.

Due to ethical and practical constraints, the direct application of results of randomized trials are often limited by the kinds of people studied, the duration of observation, and the variety of types and doses of treatments evaluated. These limitations can, at times, be addressed by longitudinal studies. The CPPT proved the concept that lipid lowering prevented coronary heart disease, and longitudinal studies provided the evidentiary basis to generalize this finding to people beyond type II hyperlipidemic men. Subsequent trials have proven the validity of this inference, as cholesterol reduction has been proven to be effective in both genders and across a wide range of disease risk. Figure 2 presents the conceptual relationship between trials and longitudinal studies depicting how evidence from trials can be extended by careful observational research.

CONCLUSION

This brief review has described the strengths and weaknesses of both longitudinal observational studies and randomized, controlled clinical trials. Neither approach stands on its own, and both are needed to maximize advances in the prevention and treatment of disease and disability in old age. The complementary roles of clinical trials and longitudinal studies are summarized in Figure 1. Longitudinal studies provide information used in the design of clinical trials, including natural history and frequency of the outcome and key risk determinants. Clinical trials then provide proof for the causal basis of the associations detected in longitudinal studies. Other analyses of clinical trial data provide information on subgroups in which the intervention might be more or less effective, and information regarding an individual's expectation of benefit from adopting the intervention under study. With the proof of efficacy from the trial in hand, longitudinal studies can be used to extend clinical trial findings beyond the groups initially evaluated. Finally, on-going longitudinal studies can be used to quantify changes in behavior and practices in populations as the final step in the translation between scientific hypothesis and the improved health and well being of the older population.

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Figure 1.
The complementary roles of longitudinal studies and randomized trials

Figure 2.
Longitudinal studies extend and generalize randomized controlled trial findings

Table 1**The Uses of Longitudinal Studies**

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- Characterizing the natural history of conditions and risk factors
 - Prospectively identifying risk factors and protective factors
 - Screening tests for clinical and public health practice
 - Potentially modifiable risk factors
 - Understanding mechanisms
 - Mediators of risk factor effects
 - Factors affecting disease progression
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