Determinants of Aging and Health Across the Life Span:
Potential New Insights from Longitudinal Studies

Report of the July 2003 meeting of the
NIA Longitudinal Data on Aging Working Group

Understanding aging requires knowledge of the sequences of events and progressive processes in individuals that affect how they change with age. Longitudinal studies of individuals can provide many insights that cross-sectional comparisons of individuals of differing ages cannot, and resolve uncertainties in the interpretation of cross-sectional data.

Considerable longitudinal data in humans have yielded important findings. Nonetheless, there are opportunities to apply longitudinal studies more extensively to a much wider range of aging questions and issues than has occurred thus far. To explore opportunities for this research, the National Institute on Aging has constituted a Longitudinal Data on Aging (LDA) Working Group, consisting of epidemiologic, clinical, and basic researchers with experience and interests in this area.

Longitudinal studies represented at the first meeting of the LDA Working Group included:

- Aerobics Center Longitudinal Study (ACLS)
- Age, Gene/Environment Susceptibility (AGES) Study
- Baltimore Longitudinal Study on Aging (BLSA)
- Bogalusa Heart Study
- Cardiovascular Health Study (CHS)
- Chicago Health and Aging Project (CHAP)
- Coronary Artery Disease Risk Development in Young Adults (CARDIA) Study
- Danish 1905 Cohort Survey
- Framingham Study
- Health, Aging, and Body Composition (Health ABC) Study
- Longitudinal Study of Aging Danish Twins
- MacArthur Study of Successful Aging
- Reykjavik Study
- Rancho Bernardo Study
- Rochester Epidemiology Project
- Study of Women Across the Nation (SWAN)
- Tremin Trust Study

Presenters and discussants at this meeting were:

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Elizabeth Barrett-Connor
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Steve Blair
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Researchers from additional studies will be invited to participate in the LDA Working Group and its activities.

At its initial meeting, the group addressed certain areas in which longitudinal information could contribute much more than it has to date:

- *"Life course" pathways influencing health in mid-life and old age:* causal sequences of changes beginning in early or mid-life, and factors regulating their progression

- Differences in risk factors for age-related conditions at *different ages*, at *different stages of disease progression*, and in the *presence or absence of coexisting conditions.*

- Extent, causes and implications of *variability among and within individuals in rates of change with age* in physiologic, pathologic, and functional characteristics.

- Determinants of *exceptionally healthy aging*: protective factors that prevent or slow common adverse age-related changes or events

- Health and physiologic effects in human aging of factors that influence aging in other species

The group also considered strategies and resource needs for research on these topics. A summary of research opportunities and issues discussed at the meeting is presented below:

"Life course" pathways influencing health in mid-life and old age.
Many age-related conditions develop over a sequence of stages that span large segments of the life span, often with secondary complications overlying the original etiologic mechanisms. In many cases, these sequences may be initiated or affected by conditions or changes occurring as early as gestation.

Existing data on the relationship of early-life factors to later age-related outcomes suggest such pathways. For example, associations have been found between low birth weight and risk for diabetes, coronary artery disease, and low bone mass (Yarbrough 2000, Gale 2001). The bone size and geometric properties developed as a young adult appear to influence hip fracture risk late in life (Duan 2003). In the Chicago Health and Aging Project, relationships between childhood environment and cognitive status in old age have been noted. Data from the CARDIA study indicate that higher blood pressure in young adults is associated with a higher rate of rise in blood pressure later. There is also evidence suggesting pathways from mid-life changes to outcomes that are prominent in advanced age. For example, early menopause is associated with elevated risk of cardiovascular disease later in life. In the Honolulu Heart Study, low grip strength in middle-aged men has been associated with subsequent mortality over the next thirty years.

These examples suggest the great potential for broader applications of longitudinal approaches to delineate sequences of events and potential chains of causality, beginning as early as gestation, and to distinguish them from other potential confounding early- and mid-life factors that are associated with, but not causally related to, future outcomes.

Longitudinal data can help to identify earlier and earlier stages and risk factors in the development of age-related diseases, including the role of early age-related changes. For example, longitudinal data has demonstrated the role of impaired glucose tolerance as a precursor of Type 2 diabetes. This strategy could be extended to identify antecedent risk factors for the development of impaired glucose tolerance, and so on. Such risk factors could exert their effects quite early in life (as early as gestation), and

could be maturation-associated changes, or other physiologic factors operating before maturity and/or in young adulthood.

Many factors that change between youth and middle age may be early steps, essential precursors, or predisposing factors, in pathologic processes that do not become symptomatic until old age. (These may include factors that do not change much at later ages.) Similarly, early life events may have consequences that do not become apparent until much more advanced age. A frequently cited example is the increased risk, in victims of the post-World War I epidemic of von Economo encephalitis, for Parkinson disease decades later (Casals 1998). It is has been suggested that encephalitic damage to the basal ganglia, though insufficient to produce Parkinsonian symptoms in the young, depleted the basal ganglia cell population and reduced its reserve capacity, so that, when "normal" age-related cell loss was superimposed on this deficit, Parkinson disease occurred in middle age or later. Analogous effects of childhood infections have been suggested for other neurologic diseases of adult life (Martyn 1997).

Infections in early life have also been suggested to elevate risk for late-life conditions with inflammatory components, such as cardiovascular disease and Alzheimer's disease, by triggering chronic inflammatory processes that persist through adult life and accelerate age-related changes, possibly through mechanisms such as accelerated telomere shortening secondary to sustained inflammatory stimulation of cell proliferation. Sensitive measures to detect functional, biochemical, or physiologic effects of early aging changes or exposures in young persons may thus be useful in longitudinal studies for exploring pathways leading to pathology in old age.

Tracing causal sequences across the life span. A particular challenge, given the length of the human life span, and the duration of follow-up of most longitudinal studies, is to establish the trajectories of changes, and the entire series of links between early origins and consequences that may occur several decades later. Both prospective studies and retrospective analyses of longitudinal data can contribute insights on this topic. Relationships found in these studies indicating such links may provide clues to the mechanisms responsible for the progression of changes.

These approaches can be applied to the effects of early-life physiologic conditions and events. For example, findings indicating a relationship of low birth weight to high cardiovascular disease risk is mostly confined to persons with relatively high rates of weight gain by middle age, suggests potential intermediary metabolic processes. Similarly, it is likely that low birth weight is not itself the initiating factor in the chain of events, but reflects earlier fetal environmental factors, including nutrition and hormonal exposures. Longitudinal data that allow examining the relationship of these factors with mid- and late-life outcomes could help to clarify the long-term chain of effects.

Analogous considerations apply to factors affecting the timing and consequences of mid-life phenomena such as menopause. For example, in regard to findings by the Tremin Trust study and others, that late menopause is associated with increased subsequent breast cancer risk, and early menopause with increased subsequent mortality and cardiovascular disease risk, longitudinal data on multiple organ systems spanning pre- and post-menopausal ages could help to clarify whether these relationships are consequences of differences in the timing of aging changes in the ovarian hormone axis, and/or whether they are related to underlying factors that regulate both the rates of aging of the ovarian hormone axis and rates of aging changes in other tissues. Similarly, in regard to factors influencing age of menopause, findings from the Study of Women Across the Nation indicating that women with late menopause tend to have longer cycle lengths over the majority of their reproductive life span suggest that examination of the relationships between factors regulating cycle length to age of menopause and subsequent age-related outcomes could help to identify pathways leading from early-life factors to later-life effects. Analogous approaches could be used to explore the roles of other relevant earlier life events and conditions that may be related to age of menopause (e.g., age of menarche, insulin resistance, and stress exposures).

Tracing pathways across the life course may also help to identify *trajectories of changes* in risk factors over the life span that are particularly favorable or adverse. The relationship of body weight to insulin resistance and health outcomes provides a possible example: Data in younger persons indicate that a higher weight gain can be associated with increased risk for subsequent insulin resistance years later. In turn, data from the Rancho Bernardo study indicate that in middle-aged and older persons, insulin resistance is a predictor of subsequent (mainly involuntary) weight *loss*, which in advanced old age is associated with elevated mortality risk. Thus, profiles of high early weight gain may predict substantial late-life weight loss and the adverse events associated with it. Analogous approaches may be useful in regard to a variety of endocrine and metabolic factors.

Differences in risk factors, and in their effects, at different ages, at different stages of disease progression, and in the presence or absence of comorbid conditions.
Many factors affecting age-related changes and conditions probably do not exert consistent effects over the whole life span, and may in some case have beneficial effects at one stage and adverse effects at another. The effect of a factor on development of age-related changes or conditions may be influenced by the following factors:

Relationships to development and aging. Physiologic, cellular, and other differences between immature, mature, and old individuals may cause risk factors to have very differing effects at these different life stages. This possibility is of considerable interest in regard to trophic factors such as growth hormone, IGF-1 and testosterone. The positive and negative effects such factors in early life, during periods of growth and

maturation, may differ markedly from their effects in old age, in the presence of age-related atrophic changes and other changes that may affect tissue responses. In studies that include ages by which substantial mortality has occurred, longitudinal data are crucial to resolve whether observed differences between age groups reflect aging changes in individuals' responses to risk factors or protective factors, or preferential survivorship of individuals who are resistant or sensitive to these factors.

Longitudinal data that includes effects of risk or protective factors in individuals spanning a sufficient age range and time interval can be used to explore whether particular *trajectories of change in factors with age* (e.g., consistently high, consistently low, consistently increasing, consistently decreasing, increasing then decreasing, decreasing then increasing) are associated with particularly favorable or adverse effects. Such trajectories of change may be better predictors of outcomes than simply the factors' level at one age or their average level over some age interval. This approach may provide insights into effects of many physiologic factors, such as hormones, that could be studied longitudinally. Such trajectories may also provide clues to the mechanisms responsible for the aging outcomes that they influence.

Relationships to progressive stages of conditions. Some factors may affect the rate of development of only one stage of a progressive condition, or may aggravate it one stage and inhibit it in another. This has been suggested, for example, in regard to estrogen's effects on risk for cardiovascular disease in women, on the basis that estrogen may inhibit atherogenesis in the interval immediately after menopause, but increase risk for thrombosis in older women after significant atherosclerosis has developed. There may be analogous relationships in many chronic age-related diseases. The distinction between *background* (predisposing) factors, *intervening* factors that influence progression, and *precipitating* factors for clinical outcomes can be useful. Retrospective longitudinal analyses of the strength of specific risk factors at differing intervals prior to outcomes offer one approach to making such distinctions. An 15-year analysis of data from the Baltimore Longitudinal Study of Aging using this approach found that for cardiovascular disease outcomes in persons age 75-80, HDL was a background (but not a precipitating factor), while white blood cell count was a precipitating (but not a background) factor.

Relationships to coexisting conditions. Particularly in old age, the coexistence of multiple pathologies can introduce new risk factors for other outcomes, or alter the effects of risk factors that are also present in healthy persons. Two or more coexisting risk factors or pathologies can have synergic effects on risk of other outcomes. This has been found for several important outcomes in old age such as falls and delirium. Synergic relationships to disability in old age have also been found for combinations of conditions, for example arthritis and visual impairments, and lung disease and cancer, noted in the Women's Health and Aging Study.

Interactions of risk factors or conditions may also increase risk for outcomes or pathologies that are rarely associated with any of them individually. (This may be often the case for outcomes which tend to occur only when two or more redundant physiologic systems fail.) Such interactions may be important in the etiology and pathophysiology of geriatric conditions such as frailty, which are more commonly found in the presence of multiple coexisting conditions, and which may be caused or aggravated by risk factors ensuing from interactions. For such conditions, longitudinal studies, by virtue of their ability to clarify the sequence in which multiple changes develop, are particularly valuable for distinguishing etiologic factors that contribute to their onset from pathophysiologic processes that contribute to bad outcomes after onset. More broadly, longitudinal studies offer opportunities for insights into the full impact over the life span of factors that influence risk for conditions whose interactions in old age in turn affect risk for other important outcomes, either through synergic interactions or the generation of novel risk factors.

Extent, causes and implications of *variability among and within individuals in rates of change with age* in physiologic, pathologic, and functional characteristics.
The rates of progression of change with age in physiologic and pathologic factors affect many health outcomes directly. Rates of changes in such factors, even if they have no direct health effects, may also serve as markers of rates of progression of aging processes that do have health effects. Individuals vary considerably among one another in their rates of many of age-related changes. Data from the Study of Osteoporotic Fractures for example, indicate that despite the well-recognized decline in bone mineral density in older women on average, a small percentage of older women maintain bone mineral density over a long period. Rates of change may also vary over time in an individual, as exemplified by post-menopausal acceleration in bone loss (Ensrud 1995). Information on the causes and implications of variation in rates of change may be particularly valuable for the development of new prevention strategies.

Determinants of rates of change of some risk factors have been identified. For example, findings from the Rancho Bernardo Study and others indicate that the degree of weight loss affects the rate of bone loss (Beck 2001, Knoke 2003). Population subgroups with various patterns of change in other factors have been characterized. For example, this approach has been used in the CARDIA Study, to identify subgroups of young persons with stable and with rising levels of different cardiovascular risk factors over a ten year period. In the MacArthur Study of Successful Aging, in relatively healthy older persons over age 70, there was substantial variation in rates of change in physical performance abilities over seven years, with approximately one-fourth of participants maintaining or improving abilities while the remainder declined. Analyses of possible determinants of the rates of change in these studies have implicated demographic and educational factors. However, information on the determinants of variability in many important aging changes is still very limited.

In addition, the predictive value of rates of change over one age range period in regard to future rates of change, and risk and timing of other age-related outcomes, are also mostly not well characterized, and could be addressed fruitfully in longitudinal studies. The Aerobics Center Longitudinal Study finding, in persons with low aerobic fitness, that subsequent mortality was lower in those whose fitness improved with age compared with those whose fitness remained low, indicates that such changes can predict future outcomes, but the basis for such effects requires broader examination.

For age-related changes in other factors, *restricted* variability among individuals in rates of change is also related to important issues. For some risk factors for age-related conditions, there is evidence that individuals tend to "track" (i.e., maintain their risk level relative to others in the population) as they age. This has been observed, for example, for cardiovascular risk factors in children and young adults in the Bogalusa Heart Study, and for bone mineral density in middle-aged and older women studied in the Rochester Epidemiology Project (Melton 2000).

Determining the extent of tracking is important both for predicting future outcomes and considering the causes of age-related changes. To the extent that knowing the level of a factor in a person of a given age allows accurate inferences about its level when he or she was younger or older, one can gain insights about its relationship to aging changes and outcomes that otherwise would not be possible without longer term studies.

In addition, the presence of tracking suggests at least two types of causal factors to be explored. It may be explained by sustained effects of environmental or genetic factors whose level varies among individuals. Alternatively, it could be related to earlier life events that precede the onset of tracking and have lasting subsequent effects. There is evidence from developmental biology for the existence of critical periods during which factors could have such effects but no influence before or thereafter. Longitudinal studies could address the range of processes, ages, and age-related outcomes to which this might apply in humans.

Determinants of exceptionally healthy aging: protective factors that prevent or slow common adverse age-related changes or events.

The concept of exceptionally healthy aging includes several phenotypes such as *exceptional health span* (i.e., survival time with absence of any of a defined set of pathologies); *exceptionally "good" values of factors influencing future health* (e.g., hormone levels, bone density, immune system function) compared to their usual values at a given age, and *exceptionally slow rates of adverse changes with age in such factors* (e.g., exceptionally slow bone loss or arterial intimal thickening). Longitudinal studies on aging are particularly valuable for identifying persons with one or more of these exceptionally "positive" traits, protective factors that predispose to them, and their relationship to subsequent health. This information could contribute to development of better interventions to extend health throughout old age. Knowledge from studies on

exceptionally healthy individuals, even though they are rare, may provide insights that are applicable to many persons, analogous to the gains that insights from rare severe forms of chronic diseases can contribute to understanding of their more common types.

It is possible to identify "elite'' individuals with one or more of exceptional health traits, to study their relationships to risk factors and protective factors, and to subsequent outcomes. For example, the prevalence of coronary artery calcification, a strong cardiovascular disease risk factor, increases sharply with age. A recent study found that, over age 70, less than ten percent of men are calcification-free. In a prospective study, older calcification-free men were found to have markedly lower subsequent incidence of coronary heart disease events, even compared to the men in the lowest quartile of detectable calcification levels. They were also found to have modestly more favorable levels of a broad variety of cardiovascular risk factors, including blood pressure, lipids, metabolic factors, and aerobic fitness, as well as prevalence of statin use, suggesting that cumulative or synergistic effects of small differences in several factors may contribute to exceptionally healthy phenotypes.

Other studies have examined contributory factors to exceptionally good physical performance abilities (strength, balance and walking) in old age, as well as the relationship of such abilities to future outcomes. In the MacArthur Study of Successful Aging, among persons age 70-79 at baseline who were followed for seven years, maintenance of high physical performance was associated with higher educational level and physical activity over the time period (with strenuous activity indicating a stronger effect than moderate). In the Health, Aging, and Body Composition Study (Health ABC), among persons age 70-79 at baseline who were followed for four years, twenty indicators of physiologic function, disease risk factors neuromuscular function, and other factors were examined for their ability to predict high physical performance at the end of the follow-up period. Low values of traditional disease risk factors such as body mass index, cholesterol, and blood pressure were not good predictors of subsequent high functional abilities, but speed-dependent measures of physical and executive function were. Exceptionally good physical performance abilities in nonagenarian participants in the Danish 1905 Cohort Survey were strong predictors of subsequent survival over a 15-month interval (Nybo 2003).

There are a wide variety of exceptional health phenotypes for which longitudinal approaches such as the above could provide information regarding contributory factors and effects on subsequent aging changes and outcomes. These approaches need not be confined to the older age range: Studies of the long term implications of exceptionally "good" values of specific physiologic factors (or combinations of them) in youth and middle age could also make valuable contributions (Martin 2002). These would have the benefit of being able to be conducted in populations with a low prevalence of chronic diseases and their potential confounding effects, but face the challenge of obtaining sufficiently long follow-up to determine whether or not exceptionally "good" values of

a putative early- or mid-life measure are indeed associated with favorable effects later. At all age ranges, the study of the causes and consequences of exceptionally healthy aging requires measurement tools with sufficient high-end sensitivity to avoid ceiling effects, so as to distinguish the truly exceptional (e.g., 97th percentile and above) from the merely above-average.

Health and physiologic effects in human aging of factors that influence aging in other species.

Aging studies in nonhuman species have identified a variety of factors that influence life span, and the rate of aging changes and development of age-related conditions (Jazwinski 2002). It is clearly of interest to consider the potential relationship of such factors to human age-related changes and conditions. Longitudinal studies in humans provide potential opportunities to study predictive factors and outcomes suggested by data from life span studies of laboratory animals, cross-species comparisons, and studies on the effects of mutations and other genetic variants in nonhuman species. In the future, animal models (including models of the effects of early life factors) could be used for relatively rapid identification of additional factors, and genetic variants affecting them, whose effects could be examined in humans.

Variation in effects of the growth hormone (GH), insulin, and/or IGF-1 axes on aging illustrate the potential contribution of longitudinal studies to clarify the role of factors that influence aging in other species. Life span in various invertebrates and rodents indicate that that lower levels of IGF-1 and/or lower levels of activity in endocrine, metabolic, and other cellular pathways stimulated by IGF-1 or related factors, may contribute to slower aging changes and longer life span. Factors related to lower GH or IGF -1 axis activity, such as smaller body size and increased resistance to oxidative stress, have also been found to be associated with some of these outcomes and suggested as the mediators of the endocrine effects on aging. Human observational studies have indicated both beneficial effects of lower levels of some of these factors on age-related outcomes (e.g., lower risk of certain cancers associated with lower levels of insulin and IGF-1) and adverse effects (potential muscle atrophy in older persons associated with low IGF-1). In contrast to many studies in other species on effects of such alterations over the life span, these studies have been confined to intervals spanning relatively small proportions of the human life span.

Longitudinal studies that individually or in combination cover the human life span could clarify positive and negative effects of these endocrine factors, by comparing age-related outcomes in persons with differing basal levels, differences in changes in their levels in response to stimuli; differences in tissue responsiveness to them; and differences in characteristics thought to be related to one or more of them, such as body size or susceptibility to oxidative stress. Such studies could determine their predictive value for age-related changes and conditions over the life course. (Studies of differences in age-related outcomes among persons with functionally differing polymorphisms in

homologs or orthologs of genes regulating these factors can be useful in such strategies.) An important contribution would be analyses to detect possible differences in effects of these factors at different stages of the life span (as discussed in a previous section) that might explain a mixture of adverse and beneficial effects.

Longitudinal studies could address many analogous issues regarding other factors affecting human aging, including ones related to putative mechanisms of aging, such as oxidative protein and DNA damage, proliferative senescence, mitochondrial dysfunction, cell loss, depletion of precursor cells, and others (Stump 2003). Analyses of these data could help to identify common mechanisms underlying a variety of aging changes, by studying correlations within individuals of the rates of groups of aging changes (or the levels of factors that predict these changes) using two approaches: *hypothesis-based analyses* of specified clusters that are thought to be regulated by a putative common aging mechanism, and *hypothesis-generating analyses* to identify clusters that may suggest a possible common cause. The latter approach has been used to study the correlation of several predictors of high physical performance in old age in the Health ABC study. In this case little clustering was found.

Longitudinal studies to explore implications for humans of findings in other species face challenges often not encountered in laboratory studies of these species: the great heterogeneity of individuals' environments and genotypes at given time and across time periods in which environment may change dramatically, and the long time scale of aging changes in the species of interest. Analytic techniques to adjust for confounding covariates can address many heterogeneity-related problems. Another approach is the comparison of data from different populations, including international comparisons including environmental exposures and genotypes that are rare in the United States.

Aging changes that are shared by a wide variety of populations with very disparate environments and genotypes may reflect common underlying aging factors, while those specific to one or a few populations may reflect specific responses to these underlying changes related to particular genotypes or environments. Regarding the relatively very long time scale of human aging changes: Although long-term studies covering a large share of the human life span are feasible and provide unique information, much information can be gained by combining data for several studies that in combination span all or most of the human life span. This is discussed more fully in the following section.

Research strategies and resource needs.
Research to address the topics discussed in the previous sections would be aided by a variety of organizational strategies, as well as intellectual, technological, informational resources. These include:

Effective use of existing data and specimens. Many longitudinal studies (many of which are ongoing) have collected data and specimens, often over long time periods, that could be used to address the questions discussed in the preceding sections, but which have not been analyzed for these purposes. These include studies on children and midlife changes, and on particular conditions, as well as studies explicitly on aging. Such analyses would be cost-effective compared to *de novo* data collection, and also could identify promising lines of research for future studies. To encourage such analyses, the following steps would be useful:

- *Enhance availability of information about relevant studies*, including basic information on aspects such as study duration, age ranges, variables measured, and contacts for additional information, through resources such as Internet databases. The NIA Data Base of Longitudinal Studies (www.nia.nih.gov/ResearchInformation/ScientificResources/LongitudinalStudies.htm) was established in July 2004.

- *Expand accessibility of data from these studies for secondary analyses,* through archives and other resources. Availability of such data would particularly facilitate development and testing of new data analytic methods.

Common definitions for risk factors and outcomes that could be shared by two or more studies spanning differing segments of the life span. As noted in previous sections, the long time scale of the human life span poses large challenges for longitudinal studies of aging across it. Though very long-term longitudinal studies will continue to be crucial resources, analyses of longitudinal data from two or more studies on differing life segments (e.g., childhood to young adulthood, and young adulthood to middle age) could clarify causal sequences extending over their combined age ranges. For example, an outcome in young adults that is linked to childhood risk factors in one study could itself be tested as risk factor for outcomes in middle age in another study. To some extent this is possible at present, but opportunities for such analyses may be greatly enhanced by *a priori* development of shared definitions and documentation to facilitate use of data from more than one study.

New measures of physiologic aging changes in humans. Testing of many hypotheses about the role of factors affecting aging is limited by the lack of techniques that allow them to be studied serially in humans. In other cases, such techniques may be available but have not yet been applied in longitudinal studies. Tests of *in vivo* physiologic functions, including responses to stressors or other stimuli, that could link cellular or biochemical processes to health outcomes, are particularly needed.

Particularly for early aging changes, many current techniques suitable for human studies may not be sufficiently sensitive. For some factors related to proposed aging mechanisms, such as cell death, oxidative damage, and mitochondrial dysfunction, current techniques suitable for longitudinal measures might be enhanced considerably.

As noted, there is a need for techniques with sufficient sensitivity to differences at the "high end" of function to allow identification of exceptionally healthy characteristics. Current advances in bioimaging and biosensor technology, as well as new psychometric tests and techniques for measuring physical performance, could be applied to all the above issues.

New data analysis and study design strategies. Efforts to determine long-term effects of risk factors and identify causal sequences over the life course face analytic challenges regarding long-term serial measurements of risk factors (including issues related to deaths and incomplete follow-up over the study interval), intra- and inter-individual variability in rates of change with age, event rates that change markedly over long time intervals, and changes in environmental factors over long intervals. There is a need for techniques that deal with these factors appropriately to allow correct inferences. New methods for analyzing effects of time-varying covariates, non-linear survival analysis methods, and other relevant techniques could be applied and developed further for this purpose.

Accurate characterization of rates of change poses particular challenges for study design as well as analysis, particularly regarding the frequency of measurements and sample sizes needed for accurate estimates of variability in rates of change. There is also a need to develop longitudinal study designs that optimize their ability to gain insights on long-term effects of interactions of genetic, physiologic, and environmental factors (Hadley 2000). Designs that can obtain information to enhance analyses of genetic factors (which are often aided by inclusion of families) while also providing the power of population cohort designs to study multiple risk factors may be particularly valuable. Long-term longitudinal studies also offer the potential to address some limitations for genetic analyses posed by cross-sectional studies, e.g., lack of genotype and phenotypic information on the parents of the very old. By following multiple generations over a long time period, it is possible to relate parental information collected when participants are middle-aged to their outcomes when they become old.

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