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Unconventional Views of Frailty

Guest Editorial

A Life Course Approach to Healthy Aging, Frailty, and Capability

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OVER the last 25 years, investment in aging research has been greater in the United States than the United Kingdom, particularly in population studies investigating healthy aging or frailty and their determinants, or cohort changes in health and functioning. It is still unclear, in the U.K. context, whether age-related declines in health and functioning of cohorts now in late middle age will differ from that of current older people, and whether socioeconomic and gender differences in aging and expectations of life at older ages are changing. In 2005, a House of Lords scientific report on aging (1) called for new research to address these questions with a focus on the underlying lifetime process of biological aging that could integrate the rather separate research on specific age-related diseases, and translate evidence into policy and practice.

Investment in U.K. aging research is beginning to change. Healthy aging has become a preoccupation of the British government. For example, the U.K. Treasury, as part of the 2007 Spending Review, highlighted aging as one of the Grand Challenges faced by the U.K.; it is concerned with the economic and social consequences of the rapid increase in the old age dependency ratio as the baby boom generation reaches retirement age (2). There are calls for a step change in multidisciplinary research to understand healthy aging and how to maintain a population that remains healthy and productive longer (3). Policymakers recognize that healthy, independent, and active aging not only enhances individual lives but also addresses the social and economic implications of an aging population, and relieves pressure on public spending (4). U.K. research councils are making available new funding streams for aging initiatives, often spanning several councils, to address these concerns. The New Dynamics of Ageing research program (5) and the recent call for Medical Research Council Centres for Lifelong Health and Wellbeing (6) epitomize the growing interest in multidisciplinarity, life course approaches to aging, and expectations for knowledge transfer and user engagement.

These calls for research highlight the consensus that the aging process operates from the beginning of life, driven by the rate of accumulation of molecular and cellular damage. Growing evidence from life course and historical cohort studies that adult function and age-related chronic diseases have their origins in early life experience and share common risk factors and causative mechanisms support this consensus (7,8). Modifiable factors such as nutrition and activity and chance events acting across the life course can alter exposure to sources of damage and the effectiveness of body systems for maintenance and repair (9). While genes have traditionally been seen as a nonmodifiable factor, there is growing evidence linking epigenetic DNA modification through environmental exposures to a wide range of aging phenotypes. This focus on early life and life course determinants of aging is stronger in the U.K. than the U.S. It partly arises from greater opportunities in the U.K. to capitalize on the maturing birth cohort studies and the historical cohort studies that have imaginatively linked development and early environment to later health outcomes (10,11).

Investigators of maturing birth cohort and aging cohort studies increasingly share a common interest in characterizing aging trajectories and the extent of variation between individuals and across gender or social groups. They are interested in how dynamic relationships between different aging trajectories unfold over time and the common mechanisms or sources of risk, and in relating aging trajectories and their determinants to disease incidence, quality of life, and survival. The advantage of birth cohort studies is that they permit exploration of how biological, psychological, and social risk factors or risk factor trajectories, acting independently, cumulatively, or interactively across the whole life course, influence aging trajectories. This growing focus on life course determinants of aging has implications for studies of capability, the mechanisms of biological aging, and the clinical syndrome of frailty.

Life Course Approach to Physical and Cognitive Capability

To address the growing interest in aging trajectories, epidemiological studies are increasingly focusing on

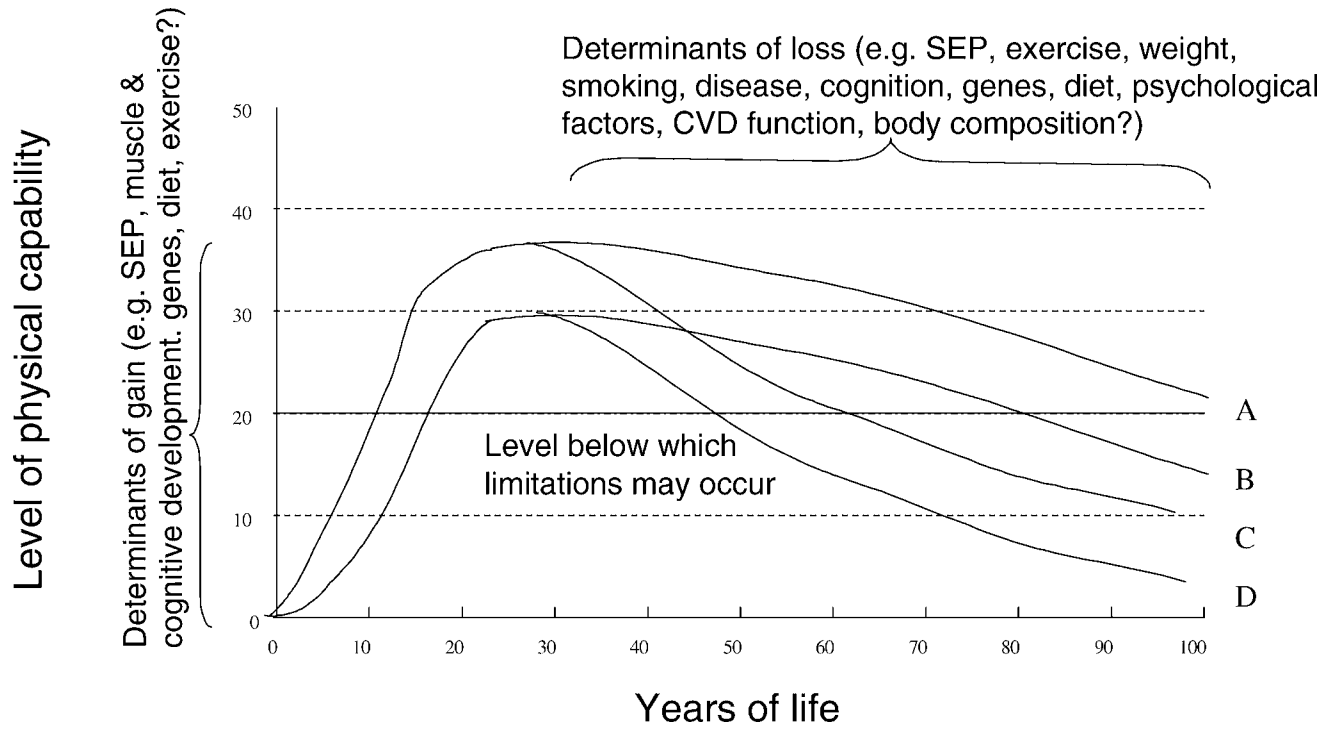

Figure 1. Physical capability across the life course.

age-related change in functional capability, using tests of physical performance (such as grip strength, chair rising, standing balance, and gait speed), cognitive performance (both crystallized and fluid intelligence), and sensory function (such as visual and auditory acuity). These tests are markers of biological aging (9), strongly associated with quality of life, ability to carry out everyday tasks, and subsequent frailty, disability, and death (12–20). They allow the full spectrum of function to be studied, from high-functioning individuals showing healthy aging to low-functioning or frail individuals.

A life course approach highlights the need to study long-term, ideally lifelong, changes in capability. The lifetime trajectory of physical and cognitive capability, and the physiological systems on which these capabilities depend, show rapid growth and development in the early years rising to a peak or plateau at maturity, and then a gradual decline with age (Figure 1), although growing evidence, mainly from cognitive aging studies, suggests that individual rates of decline can be discontinuous, particularly in the face of certain disease processes (21). The ''biological capital'' acquired during growth and the rate of decline determine how long aging individuals remain above a critical threshold of risk for adverse outcomes associated with loss of function. Thus, where an individual ends up in old age (at A, B, C, or D in Figure 1), and the potential for the compression of morbidity in a population, depend on both the peak attained and the rate of decline. Early life factors may influence both the development of biological ''capital,'' and, alongside adult factors, the timing and rate of decline. There is growing evidence from U.K. life course cohorts that the early social environment and developmental characteristics, such as early growth and cognitive ability, are associated with physical and cognitive capability in later life (10,22–27).

Evidence is accumulating that cognitive and physical capability and their rate of change with age may be associated, and various explanations have been advanced (28,29). While the associations or covariation may be an artefact of age heterogeneous study designs (30), the ''common cause hypothesis'' attributes them to underlying endocrine and other physiological systems that jointly regulate these functions, and change with age (31). The life course perspective extends this debate by considering developmental processes that may shape initial differences in these capabilities and their decline. There are also common lifetime social and lifestyle pathways that may lead to covariation in age-related decline in physical and cognitive capability. However, life course research is also needed to identify circumstances (such as disease processes or socioeconomic conditions) under which these capabilities differentiate, and whether risk factors for this differentiation, or patterning of differentiation itself, occur early in the life course.

Life Course Approach to the Aging Cell

Biological mechanisms of aging at the molecular, cellular, or physiological system level are of interest to life course researchers as potential markers of lifetime exposures and because there is growing evidence that they are influenced by early life factors. Long-term and eventually lifelong studies are required of the dynamic interplay between these mechanisms and markers of biological aging at the multisystem or organism level. Current evidence is

generally limited to associations in cross-sectional (32) or occasionally short-term longitudinal studies (33). For example, there has been a recent explosion of interest in telomere length as a biomarker for aging (34–38). White blood cell telomere length is highly heritable and variable between individuals and a single measure reflects initial length and rate of attrition. As with capability, one objective should be to understand the lifetime trajectory (39). From what is known so far about telomere attrition, rapid loss occurs until around age 5, followed by a period of stability until early adulthood, and then gradual decline thereafter (40,41). Thus white blood cell telomere aging occurs at a faster pace at the beginning rather than the end of life. Contemporary reflections that growth and aging are part of the same continuum (42) are a revival of ideas from over 50 years ago. Nathan Shock, the first scientific director of the National Institute on Aging, declared that ''in the broadest sense, problems of growth, development and maturation are as much a part of gerontology as are those of atrophy, degeneration and decline'' (43). From a life course aging perspective, we should know whether poor childhood social conditions or early growth patterns characterized by low birth weight followed by accelerated postnatal weight gain (both associated with reduced adult function and an increased risk of cardiovascular and other age-related chronic diseases) are associated with a greater rate of attrition in telomere length than better childhood conditions or more favorable patterns of weight gain (44).

Life Course Approach to Frailty

Despite multiple models, definitions, and criteria of the ''slippery concept'' of frailty (45,46), there is a growing consensus that it refers to a state of increased vulnerability to stressors due to age-related declines in physiologic reserve across neuromuscular, metabolic, and immune systems (47). Frailty research has focused on the oldest people, distinguishing those who have the clinical syndrome of frailty from those who do not, according to *a priori* criteria, and comparing characteristics between these groups at the individual or system level. The most common set of criteria used to identify the syndrome are weakness (lowest 20% grip strength, adjusted for gender and body mass index), weight loss (lost >10 pounds unintentionally in the last year), exhaustion (self-reported), slowness (slowest 20% on a 15-foot walk test, adjusted for gender and height), and decreased activity level (lowest 20% in kcals per week, adjusted for gender) (48).

The life course approach has various implications for current frailty research. First, if frailty is the eventual consequence of accelerated aging (trajectory B or D in Figure 1), then there would be benefit, from an etiological and policy perspective, from studying the long-term dynamic development of frailty and its lifetime determinants. Some components of frailty are already being studied from a life course perspective. Investigators from U.K. cohorts have shown that the origins of sarcopenia may lie in prenatal, prepubertal, and pubertal growth patterns (10,22–24); this research has yet to be applied to measures of walking time, but other markers of adult motor performance have been shown to be associated with patterns of prepubertal weight gain (25). These findings suggest that prenatal and postnatal development of muscle fibers and muscle growth during puberty may have critical, or at least sensitive (49), effects on musculoskeletal aging and risk of frailty. Other components of frailty, such as weight loss, exhaustion, and decreased activity levels could also be studied from a life course perspective, although they may have different meanings and determinants at different life stages. While short-term loss of weight and vitality and reduced activity in older people may herald the emergence of frailty, there may be earlier life characteristics associated with individual variability in these markers in later life, or with underlying mechanisms.

Second, rather than assuming the frailty syndrome is a useful entity, life course researchers prefer to study each component separately, and then to test whether these characteristics do cluster together at different life stages, and covary over time, and share common causes and effects. Among frailty researchers, there is also a growing consensus that empirical testing of the frailty syndrome is long overdue, and that research should aim to identify ''clusters of vulnerabilities, weaknesses, instabilities, and limitations with shared causes'' (45,47). A similar debate has recently been had about the usefulness of the metabolic syndrome (50).

Third, there has been extensive discussion in the frailty literature about the potential role of the nervous system in frailty and whether to include cognitive function as part of the syndrome. From a life course perspective, it makes sense to understand the dynamic relationship between cognitive and physical function over time, and reasons for covariation and differentiation. Motor performance involves planning and generating movement, and current research on the 1946 British birth cohort shows that it is more closely linked to changes in cognitive performance than isometric grip strength, which predominantly reflects motor unit and muscle function. Other evidence suggests that change in motor function is more strongly associated with subsequent mortality than change in muscle strength (12). Childhood cognitive and motor abilities are also related more strongly to midlife chair-rising and standing balance than to grip strength (24,25), and these associations were only partially explained by adult cognition. This suggests at least two not mutually exclusive pathways may be operating. Either variation in motor development reflects variation in structural and functional maturation of brain motor systems and these differences are sustained across life, or, because motor and cognitive function are highly integrated during development and aging, these early factors reflect complex cortical–subcortical neural circuits that underpin higher cognitive function in adult life, and hence impact on later physical performance.

Fourth, a life course perspective is just as concerned with resilience as it is with vulnerability associated with frailty. Resilience is the capacity for adaptation in the face of ever-changing environmental challenges. Biological aging, in effect, represents a reduced capacity to respond to these challenges due to loss of physiologic reserve; frailty is one end of this spectrum. Of interest from a population health and prevention perspective is to identify the characteristics

of those who maintain their level of capability and biological function at a higher level than would be expected from their lifetime risk exposure, or are able to recover after adverse health events. One methodological difficulty in identifying such individuals is being able to measure environmental challenges more precisely so that we can distinguish resilience on the basis of equivalent normal challenges of daily living. A life course approach would also take into account age at onset and chronicity as well as severity of these challenges. High-level acute challenges, for example injury or chemotherapy, are more easily distinguished.

Fifth, what about social and psychological resilience that maintains individual well-being, active engagement, and independence in the face of biological aging or physical frailty? Evidence suggests that subjective well-being is maintained or enhanced with age perhaps because older people have a greater investment in emotional regulation. More use should be made of person-centered as well as variable-centered analyses investigating lifetime patterns and trajectories of extrinsic and intrinsic factors associated with psychological and social resilience to the challenge of biological aging and frailty. For example, what are the pathways to resilience for those with high well-being or social participation despite a profile of accelerated biological aging? Are those who show resilience to adversity earlier in life also resilient to biological aging, or does early resilience come at a later cost? This is an area ripe for longitudinal research across life course cohorts.

Finally, from a policy perspective, evidence of the early life origins of the components of frailty suggests that the prevention of frailty in later life may need to start early. Certainly by midlife there is already considerable variation in capability (51), and predictors of decline can be identified (52–54). If we can identify from simple assessments those who may be vulnerable to accelerated aging, timely interventions may be able to modify such a trajectory and delay the emergence of frailty. At the population level, this will allow planners to more precisely understand the health and functional characteristics of the older population in order to plan public health interventions and predict future health status and resources utilization. At the clinical level, such early vulnerability markers may also help to identify those who respond less well to certain treatments, such as chemotherapy, allowing health professionals more opportunities to predict outcomes and tailor treatment regimes to individual needs.

Future Directions

We need to harness the power of the life course approach and study design with the biomedical and social research on frailty and biomarkers of aging, and undertake comparative studies using different cohorts. These are the fundamental questions. First, to identify what factors across the life course, from the molecular to the societal level, independently, cumulatively, or interactively influence whether people as they age maintain their physical and cognitive capability and stay intellectually and socially connected? Are these same factors involved in the natural history of components of frailty and the emergence of any frailty syndrome? This requires greater investment in multidisciplinary lifelong general population-based studies, as well as basic biological and disease-specific research. Second, how can we transfer this knowledge to people themselves and to the institutions that exist to improve human health? This bringing together of researchers and users of research is rapidly becoming an essential requirement for all U.K. research council aging research, yet the skills to achieve successful knowledge transfer, particularly for public health research, are still being defined. We would suggest that a life course approach has the potential to identify when and how to intervene at different life stages to maximize the chance of healthy aging for the population and for susceptible subgroups, and minimize variation by gender and socioeconomic group.

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