

Interdisciplinary and Multilevel Research on Determinants of Healthy Aging

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Editorial

Populations in many countries in the world are aging rapidly, with an extraordinary increase of the oldest-old. For example, there were about 18 million oldest-old (aged 80+) in China in 2010; this number will climb dramatically to about 114 million in 2050 [1]. This dramatic increase deserves serious attention because the oldest-old consume services and medical care at a much higher rate than the young-old [2]. The average annual rate of increase of China's oldest-old in 2000-2050 is estimated to be about 4.4%, which is twice that of industrialized countries [3]. Given that human lifespan is increasing and the number of elderly (especially oldest-old) is rapidly growing, is it possible to realize compression of morbidity [4], or at least dynamic equilibrium [5], rather than expansion of disability [6]? Why do some people survive to advanced ages with good health while others suffer severe disability and morbidity? So far, there are few answers to these critical questions, which determine quality of life not only for the elderly but also for all members of society. Thus, it is important to investigate the determinants of healthy aging through interdisciplinary and multilevel research.

Multilevel Factors Associated with Healthy Aging

Many studies suggest that healthy aging is closely related to individual lifestyles and behavioral factors [7-9]. Multilevel studies suggest that socioeconomic and physical environmental factors at the community level may also have fundamental effects on healthy aging. For instance, air pollution in industrialized areas leads to significantly higher morbidity and mortality rates [10]; the elderly, especially the oldest-old, are more sensitive to environmental quality [11]. Using longitudinal datasets at both individual and community (i.e., county/city) levels from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), multilevel analyses by Zeng et al. [12] show that, after adjusting for various confounding factors at the individual level, higher employment rate in the community reduces one's risk of activity of daily living (ADL) disability, cognitive impairment, high deficit index (DI), and mortality by 20-45% ($p < 0.001 \sim 0.05$); higher per capita GDP and lower illiteracy rate decrease one's risk of cognitive impairment by 30-40% ($p < 0.001 \sim 0.05$); air pollution increases risks of high deficit index, ADL disability, and cognitive impairment by 10-25% ($p < 0.001 \sim 0.05$); and too low or too high seasonal temperatures increase the risk of poor health outcomes and mortality by 30-50% ($p < 0.001 \sim 0.05$).

Studies on elderly twins show that about one fourth of the differences in individual lifespan are heritable [13] and that genetic effects become increasingly significant with advancing age. Compared to disease-focused genetic studies, healthy aging research demands much larger sample sizes because the very complex phenotype of elderly health encompasses absence or presence of multiple chronic diseases, environmental factors, candidate genes, and their interactions [14,15]. Including studies reviewed by Christensen et al. [16] and the studies published afterward, the literature has reported 44 candidate genes associated with aging and longevity. But to date, with the exception of APOE and FOXO3A, genetic associations have seldom been replicated in multiple studies to reach consensus. Clearly, small

sample size is a major reason for lack of international consensus in this field [17]. Larger sample sizes are needed, as concluded by Newman et al. [18] in their meta-analysis on genome wide association studies (GWAS) of longevity. These larger datasets also need multiple levels of data to adequately examine genetic, behavioral, and environmental determinants of healthy aging.

Interactions between Social, Behavioral and Genetic Factors

Research has shown that interactions between genetic and environmental factors play a crucial role in health [15,19,20]. Environmental factors may regulate gene expression via DNA methylation and histone modification, which then influence health and longevity [21]. Based on intensive literature reviews and discussions at several workshops, the Institute of Medicine (IOM) Committee concluded in their widely-cited report: "...to expand our knowledge of how to improve the health of individuals and populations, it becomes imperative to conduct research that explores the effects of interactions among social, behavioral and genetic factors on health" [15]. However, research on this crucially important topic is very underdeveloped. For example, among the 77 published studies on candidate genes of healthy aging to date, only 16 (20.8%) included discussions about interactions of the gene(s) with social and behavioral factors; no previous studies on such topics included social and physical environment conditions at community levels.

Conclusion Remarks: Greater Insights May be Gained by Triple Comparisons among Centenarians, Patients with Diseases or Disorders, and Normal People as Controls

Based on the evidence and analyses reviewed above, it is clear that there is an urgent public health need for interdisciplinary and multilevel research to investigate the effects of social, behavioral, environmental, and genetic factors and their interactions on healthy aging. Currently, researchers in the field of healthy aging studies use two comparative research models: they either compare genotypic and phenotypic data between elderly patients with a specific disease or disorder (extremely poor health) and healthy elderly people of similar ages and same gender as controls, or they compare genotypic and phenotypic data between a small sample of centenarians (exceptional longevity) and middle-aged controls. Although these dual comparisons are valid, greater insights

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Received May 31, 2012; Accepted June 02, 2012; Published June 04, 2012

Citation: Zeng Y (2012) Interdisciplinary and Multilevel Research on Determinants of Healthy Aging. J Gerontol Geriat Res 1:e113. doi:10.4172/2167-7182.1000e113

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may be gained by triple comparisons among centenarians who may likely carry positive genes and/or live with good behavior/environment, patients with diseases or disorders who may likely carry negative genes and/or live with poor behavior/environment, and healthy people as controls. Such triple comparisons may not only reconfirm and enhance the findings of dual comparisons between patients and controls or between centenarians and controls, but also provide new insights on the effects of disease-preventive genes, behavioral and environmental factors, and their interactions on healthy aging. Although databases for patients with various diseases and controls already exist widely, genotypic data from large samples of centenarians are not yet available worldwide. Clearly, the analysis of effects of genetic and behavioral/environmental factors and their interactions on disease prevention in general for the entire population, including the elderly, would be significantly enhanced if databases with large enough samples of centenarians containing genotypes and phenotypes become available internationally.

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