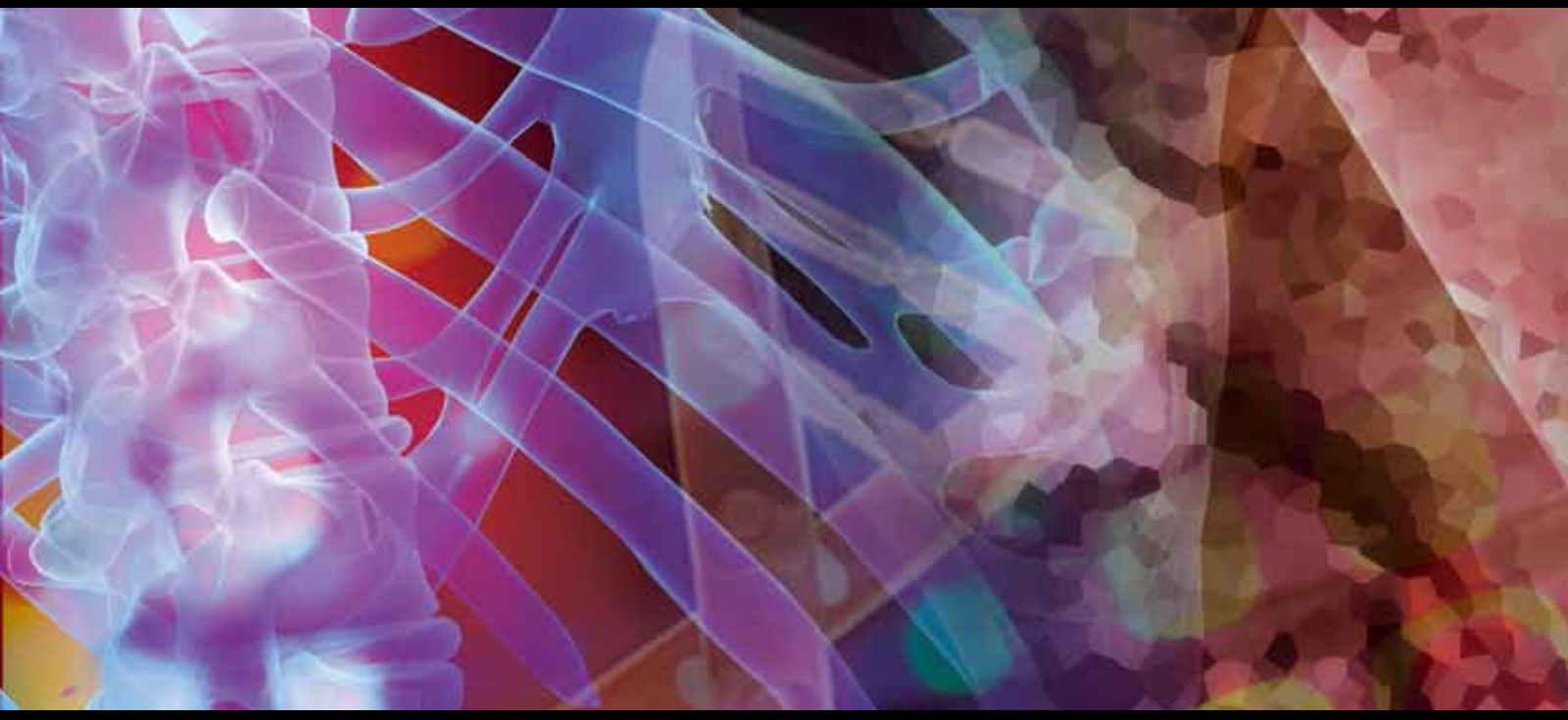
Current Gerontology and Geriatrics Research

Centenarian Studies: Important Contributors to Our Understanding of the Aging Process and Longevity

Guest Editors: Donald Craig Willcox, Bradley J. Willcox, and Leonard W. Poon



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Editorial Board

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Editorial

Centenarian Studies: Important Contributors to Our Understanding of the Aging Process and Longevity

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In the course of the next 10 years, say the watchers of consumer trends, a new generation—Generation C—will emerge. Born after 1990, they are referred to as "digital natives," now beginning to attend university and enter the workforce, they are expected to transform the world as we know it [1]. The "C" stands for "connected," "communicating," "content-centric," "creative," and "change"; however, it may just as well stand for "centenarian" as for the first time in history many of this birth cohort will live 100 years or more. The fact is that people are living longer and generally healthier lives than ever before. Mortality, and by some measures incident morbidity and disability, is being delayed considerably in today's elderly [2]. As a result, centenarians, once considered rare, are now becoming commonplace. Indeed, they are the fastest growing demographic group of the world's population, their numbers having roughly doubled every decade since 1950, and they are globally projected to more than quintuple between 2005 and 2030 [3].

According to some estimates [3], the odds of living to one hundred have risen from approximately 1 in 20 million to 1 in 50 for women in some low-mortality nations. If progress in reducing mortality continues at the same pace as it has over the past two centuries, which is still being debated [2, 4, 5], many, if not most, children born today in low-mortality countries can expect to become centenarians [6]. The US Social Security Administration [7] forecasts the number of centenarians in the US to surpass one million before the end of this century. Generation C will indeed be in full bloom.

This unprecedented phenomenon is largely the result of significant public health advancements that markedly reduced early life mortality, principally due to interventions that reduced infectious diseases in the first decades of the 20th century [4]. Lasting effects of such interventions from less lifetime inflammation, and other ancillary benefits, may have contributed [8]. More recently we have seen marked reductions in morbidity and mortality at older ages [9]. Less well understood, these late life health improvements coincide with the aging of younger cohorts who practiced healthier behaviors and had access to better medical care [10]. The culmination of these advances has resulted in the most rapid health improvement in the history of humanity. Centenarians, once rare, are now living testaments to these remarkable health advancements [11].

Despite the mounting weight of scientific evidence for the impending appearance of a new generation of oldest old and, moreover, one that might rival Generation X, Y or the baby boomers in social significance, the global implications of this phenomenon have yet to be fully appreciated. Nor have funding agencies in most nations, until recently, realized the value of investing research resources on the study of the oldest old [12]. In fact, the older population (including "young-old" aged 65–75 years) was formerly systematically excluded from clinical trials [13]. Indeed, many of the rare

and valuable prospective cohort studies on older adults that exist today were not begun as studies of aging. Instead, younger cohorts were followed for decades for other phenotypes, such as cardiovascular diseases, when prescient researchers and funding bodies began to add aging-related variables, phenotypes, and outcomes. Two such examples are the Honolulu Heart Program [14] and the Framingham Heart Study [15], each with over four decades of extensive followup and several ancillary studies of aging.

Since centenarian studies, like most centenarians themselves, have been a phenomenon of only the past several decades, there has been no large repository of prior biological, psychosocial, demographic, genetic, or clinical data from which to inform researchers, policy makers, or clinicians. Fortunately, this situation has begun to change in recent years, and centenarian studies, once in their infancy, are now themselves beginning to mature. Indeed, the world's longest continuously running centenarian study, the Okinawa Centenarian Study, began in 1975 and is now entering its fourth decade. The longest running centenarian study in the USA, the Georgia Centenarian Study [16], recently celebrated its 20th anniversary by hosting a conference with different centenarian research teams from around the world [17]. Representatives from the Ashkenazi Jewish, Chinese, Danish, French, Georgia, Hawaii, Korean, New England, Okinawa, and Tokyo centenarian studies, as well as the NIA Longevity Consortium, gathered to share information at this conference, many of whom also made contributions to the current special issue. Other major studies have been ongoing for a considerable period of time in Italy, Sweden, Germany, and other areas of the world.

There is no doubt that centenarian studies are quickly maturing with over a dozen major studies now operational worldwide for a decade (or more) [18] and several more either recently begun or in the planning stages. Therefore, it is timely that the manuscripts in this special issue exemplify the progress being made in this field.

Past work from centenarian studies has illuminated the field of aging with important discoveries. A brief and necessarily imperfect survey of some such highlights includes the key area of genetics of aging and longevity, where the first so-called "longevity-associated genes" emerged in the 1980s from the study of HLA polymorphisms in Okinawans [19]. Several years later, in the mid-1990s, APOE emerged [20] and was later widely replicated (for review see [21, 22]). Subsequently, there appeared genome-wide association studies (GWAS) as we ushered in the 2000s. As yet, there has been little replication of early GWAS findings [23, 24]. This may be due, in part, to statistical limitations of GWAS studies that require substantially larger sample sizes of the very old for adequate power. This has led to ever larger consortia for meta-analyses and related studies [25–27].

More recent advances in genotyping methodology have allowed for sophisticated, rapid, and inexpensive SNP genotyping, targeted DNA sequencing, and large-scale "deep" sequencing, particularly around "hot" genomic areas. Such developments are helping facilitate rapid discovery as well as rapid replication studies. For example, the original discovery that the evolutionarily conserved FOXO3A gene is important to healthy aging and longevity in humans was found in long-lived Japanese-Americans in Hawaii [28] and within a year was replicated in German and French [29], and Italian [30] centenarian populations as well as three other independent cohorts of oldest old [31]. Multiple other replications followed within 2 years [22]. Other promising gene variants, such as those within the CETP gene, may be population specific since to date robust findings have only appeared in Ashkenazi Jews [32] and Japanese-Americans [33] and they involved completely different gene variants that were either very rare or did not exist in the other population—but have broadly similar biological effects. There will likely be other such discoveries inspired by evolutionarily conserved biological pathways from model organisms of aging [34]. "Epigenetics," various "omics," and "mimetics," much of it inspired by model organism research, is also rapidly coming to studies of aging humans, and centenarian studies will be at the forefront of this new research tide [35].

A small sample of other important findings includes the discovery that centenarian families also seem to be longer-lived and healthier than the rest of us [36]. Centenarians appear to have brothers and sisters, as well as children, who tend to live longer with lower risk for age-associated disease [37, 38]. Population-based studies have revealed that centenarians are overwhelmingly female except in rare areas of the world [39]. Yet despite their superiority in numbers, phenotypic characterization has revealed that the few males who do live to 100 tend to have higher levels of functioning when compared to their female counterparts. Exploring the centenarian phenotype has been of great interest, and understanding aging-related phenotypes has taken on new importance for the gerontological research agenda [40–42]. Multiple studies (we introduce a few examples and concentrate on review papers) of centenarians have helped quantify and characterize the phenotype of exceptional survivors in terms of aging biomarkers, biochemistry, nutritional status and anthropometry [43–47], inflammation [48–50], cardiovascular risk profiles [51], physical and cognitive functioning [52–57], morbidity profiles [58], personality traits [59], among other aging-related phenotypes [42, 60]. Psychosocial studies have shown that adaptation to the challenges of aging is also a key protective factor for healthy aging and longevity (see a review of key findings in this special issue, by L. W. Poon et al., (2010). This is a mere sprinkling of findings from the numerous manuscripts now available from centenarian studies. This important body of work has helped shape the gerontological research knowledge base and has set a wider agenda for aging research.

The current special issue helps build on this knowledge base and begins with two important manuscripts that have focused upon the demographic characteristics of this new emerging generation of centenarians. The first manuscript, by R. D. Young et al. (2010) begins by challenging commonly held ideas (both by the lay public and by researchers) regarding exceptional longevity and builds preliminary typologies of extreme longevity myths based upon both field experience investigating claims to extraordinary longevity and data analysis of American Social Security Death Index files of supercentenarians (aged 110 and over). The conclusions are

sobering. Despite extraordinary claims to exceptional longevity regularly surfacing in the media and even in respected scientific journals, the majority of age claims over the age of 110 years, and nearly all over the age of 115 years, have turned out to be false. Acceptance of such extraordinary ages without adequate skepticism and evaluation (age validation) undermines responsible scientific research, journalism, and public knowledge in this field. The second manuscript in the issue, by J. Robine et al. (2010), aims to specify the level of mortality selection among centenarians from 5 low-mortality countries (Denmark, France, Japan, Switzerland and Sweden) all part of the 5-Country Oldest Old Project (5-COOP). Three levels of mortality selection were discovered: a milder level in Japan, a stronger level in Denmark and Sweden, and an intermediate level in France and Switzerland. These diverging trends offer an opportunity to study the existence of a trade-off between the levels of mortality selection and the functional heath status of the oldest old in low-mortality countries.

The next two manuscripts in the special issue deal with predictors and dynamic determinants of healthy aging and longevity. J. Arnold et al. (2010) employed morbidity profiles (originally developed by [58]) for their population-based sample from the Georgia Centenarian Study, to determine proportions of centenarians reaching 100 years as survivors (43%), delayers (36%), or escapers (32%) of chronic, age-associated diseases. Diseases fell into two morbidity clusters, one that involves diseases such as CVD, cancer, anemia, and osteoporosis and another associated with dementia. Major barriers to reaching centenarian status in a "healthy state" come from several incident chronic age-related diseases—increasing cancer risk from their sixties, cardiovascular risk from their seventies, and dementia risk from their eighties. Interestingly, 43% of centenarians in this population-based study managed to *escape* a clinical diagnosis of dementia, and, in concert with other studies of the oldest old, few had suffered from cancer. Consistent with their model of developmental adaptation, distal life events contributed to predicting survivorship outcome. Morbidity classification and health status appeared as critical adaptation variables in very late life. A. I. Yashin et al. (2010) in their manuscript on dynamic determinants of longevity, utilize data from the Framingham Study to assess longitudinal changes in physiological indices such as BMI, diastolic blood pressure, pulse pressure, pulse rate, blood glucose, hematocrit, and serum cholesterol. Their primary aim was to investigate the possibility that dynamic properties of age trajectories of these physiological indices could be important contributors to morbidity and mortality. The authors showed that indeed the *rate* of change in physiological state between forty and sixty years served as a good predictor of morbidity and mortality risk later in life and that the rates of decline after reaching the maximum, the actual maximal value itself, and the age at which maximal values were reached were important predictors of morbidity and mortality risk.

The next two manuscripts of the special issue focus upon assessment of physical capabilities of middle-aged adults, older adults, and the exceptionally old (centenarians). C. D. Ceria-Ulep et al. (2010) investigate the reliability and correlations with age of the balance components of the EPESE and NHANES tests and the Good Balance Platform System (GBPS) in a normal population of adults. It was found that the EPESE and NHANES batteries of tests were not sufficiently challenging to allow successful discrimination among subjects in good health, even older subjects. The GBPS allowed objective quantitative measurements but had low reliability coefficients except for the most difficult testing conditions. Both height and body fat were associated with GBPS scores necessitating adjusting for these variables if using balance as a predictor of future health, particularly in a population witnessing ever-increasing obesity. Assessing physical performance in middle-aged and older adults may be challenging but the broad variation in physical abilities (from independence to bed-bound immobility) found in centenarians makes it extremely difficult to evaluate function using a single instrument. A. E. Cress et al. (2010) utilize data from a population-based sample of 244 centenarians and 80 octogenarians to provide norms on the Short Physical Performance Battery and extend the range of this scale using performance on additional tasks and item response theory (IRT) models, reporting information on concurrent and predictive validity of this approach. Using the original SPPB scoring criteria, 73% of centenarian men and 86% of centenarian women were identified as severely impaired by the scale's original classification scheme. Results suggest that conventional norms for older adults need substantial revision for exceptionally old persons, such as near centenarians and centenarians, and that item response theory methods can be helpful to address floor and ceiling effects found with any single measure.

The next three manuscripts in the special issue deal with biological phenotypes of centenarians. What do centenarians look like underneath the skin? A. von Gunten et al. (2010), in a review article, explore brain aging in the oldest old revealing that pathological substrates of cognitive deterioration, such as the patterns of lesion distribution and neuronal loss, seem to be different in the oldest old compared to those observed in the younger old. In contrast to younger ages where dementia is mainly related to severe neurofibrillary tangle (NFT) formation within adjacent components of the medial and inferior aspects of the temporal cortex, the oldest old tend to display a preferential involvement of the anterior part of the CA1 field of the hippocampus, whereas the inferior temporal and frontal association areas are relatively spared. The authors suggest that microvascular parameters such as mean capillary diameters may be key factors to consider for the prediction of cognitive decline in the oldest old.

In the next manuscript, M. Suzuki et al. (2010) investigated blood lipid peroxidation and the role of tocopherols in oxidative stress and longevity among Okinawan centenarians. Oxidative stress, inflammation, and aging are intimately linked biological processes that are partly mediated by nutritional status. Finding micronutrients or other natural compounds that might protect against age-related diseases or might slow aging itself is of great interest. Suzuki and colleagues' finding of low plasma levels of lipid peroxides in centenarians compared to younger controls argues for protection against oxidative stress in the centenarian population

and is consistent with predictions of the Free Radical Theory of Aging. However, the study did not strongly support a role for vitamin E in this phenomenon. One intracellular tocopherol subtype (beta) was found to be significantly higher in centenarians and may deserve further study. In the next manuscript, C. S. Kwak et al. (2010) do interesting detective work to unravel the mystery of vitamin B12 status in Korean centenarians. They ask how it is possible for Korean centenarians, who ate minimal animal products over the course of their lives, to do relatively well in terms of avoiding vitamin B12 deficiency, a common problem for older people everywhere. The researchers discovered that the traditional plant-based Korean diet consumed by the centenarians was actually providing them with a considerable amount of this important nutrient and, upon screening, found fermented soybean foods such as kimchee and seaweeds to be potent sources of vitamin B12.

Finally, the last two manuscripts in this special issue focus upon the much neglected role of psychosocial factors in reaching centenarian status. Y. Zeng et al. (2010), using a unique data set from the Chinese Longitudinal Healthy Longevity Survey and the largest sample to date of centenarians, show that Chinese centenarians, as reflected in survey response items emphasizing coping and adjustment (such as personal tenacity, optimism, coping with negative moods, secure relationships, and self-control), are significantly more resilient than younger elders in their 90s, 80s or 70s. Their results argue for policies and programs that might promote this characteristic. The last manuscript in the special issue, by L. W. Poon et al. (2010), ties the issue together by examining the contributions of psychosocial dynamics to health and quality of life and arguing for the importance of an integrated biopsychosocial approach to the study of longevity and centenarians. The authors highlight recent data to demonstrate the impact of four pertinent psychosocial domains for future longevity research: (1) demographics, life events, and personal history; (2) personality; (3) cognition; (4) socioeconomic resources and support systems. L. W. Poon et al. (2010) recommend that the above items supplement the 2001 *NIA Panel on the Characterization of Participants in Studies of Exceptional Survival in Humans* [41] that was originally developed to provide guidelines on measures that are important for studies of exceptional survival.

This fine collection of manuscripts will no doubt add important insights to the growing knowledge base in the field of gerontology. As more and more of the global population joins *Generation "C"*, understanding what happens on the right tail of the survival curve will be critical for improving the quality of life of these special elders and, indeed, should help all of our elderly population. Centenarian studies have and will continue to be important contributors to the research agenda in aging and will no doubt yield more key discoveries in the quest for healthier and longer lives for us all.

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References

[1] AME Info, The Rise of Generation C, http://www.ameinfo.com/241120.html.

[2] J. W. Vaupel, "Biodemography of human ageing," *Nature*, vol. 464, no. 7288, pp. 536–542, 2010.

[3] U.S. National Institute on Aging, "Why population aging matters," Tech. Rep. NIH Publication no. 07-6134, U.S. Department of Health and Human Services PHS, National Institutes of Health, 2007.

[4] S. J. Olshansky, D. J. Passaro, R. C. Hershow et al., "A potential decline in life expectancy in the United States in the 21st century," *The New England Journal of Medicine*, vol. 352, no. 11, pp. 1138–1145, 2005.

[5] E. M. Crimmins and H. Beltrán-Sánchez, "Mortality and morbidity trends: is there compression of morbidity?" *Journals of Gerontology—Series B*, vol. 66, no. 1, pp. 75–86, 2011.

[6] J. W. Vaupel, "Setting the stage: a generation of centenarians?" *The Washington Quarterly*, vol. 23, pp. 197–200, 2000.

[7] Social Security Administration, Office of the Chief Actuary, Population Projections under Alternative II of the 2010 Trustees Report, 2010.

[8] C. E. Finch and E. M. Crimmins, "Inflammatory exposure and historical changes in human life-spans," *Science*, vol. 305, no. 5691, pp. 1736–1739, 2004.

[9] K. G. Manton, X. Gu, and G. R. Lowrimore, "Cohort changes in active life expectancy in the U.S. elderly population: experience from the 1982–2004 National Long-Term Care Survey," *Journals of Gerontology—Series B*, vol. 63, no. 5, pp. S269–S281, 2008.

[10] J. F. Fries, "Measuring and monitoring success in compressing morbidity," *Annals of Internal Medicine*, vol. 139, no. 5, part 2, pp. 455–459, 2003.

[11] B. J. Willcox, D. C. Willcox, and L. Ferrucci, "Secrets of healthy aging and longevity from exceptional survivors around the globe: lessons from octogenarians to supercentenarians," *Journals of Gerontology—Series A*, vol. 63, no. 11, pp. 1181–1185, 2008.

[12] R. Suzman and M. W. Riley, "Introducing the oldest old," *Milbank Memorial Fund Quarterly, Health and Society*, vol. 63, no. 2, pp. 177–186, 1985.

[13] W. B. Applegate and J. D. Curb, "Designing and executing randomized clinical trials involving elderly persons," *Journal of the American Geriatrics Society*, vol. 38, no. 8, pp. 943–950, 1990.

[14] J. D. Curb, D. M. Reed, F. D. DeWolfe Miller, and K. Yano, "Health status and lifestyle in elderly Japanese men with a long life expectancy," *Journals of Gerontology—Series B*, vol. 45, no. 5, pp. S206–S211, 1990.

[15] A. I. Yashin, I. V. Akushevich, K. G. Arbeev, L. Akushevich, S. V. Ukraintseva, and A. Kulminski, "Insights on aging and exceptional longevity from longitudinal data: novel findings from the Framingham heart study," *Age*, vol. 28, no. 4, pp. 363–374, 2006.

[16] L. W. Poon, S. M. Jazwinski, R. C. Green et al., "Methodological considerations in studying centenarians: lessons learned from the Georgia Centenarian Studies," in *Annual Review of Gerontology and Geriatrics: Biopsychosocial Approaches To Longevity*, L. W. Poon and T. T. Perls, Eds., pp. 231–264, Springer, New York, NY, USA, 2007.

[17] L. W. Poon and T. T. Perls, Eds., *Annual Review of Gerontology and Geriatrics: Vol. 27. Biopsychosocial Approaches to Longevity*, Springer, New York, NY, USA, 2007.

[18] B. J. Willcox, "Centenarians as models for aging research," *Age*, vol. 28, pp. 309–311, 2006.

[19] H. Takata, M. Suzuki, T. Ishii, S. Sekiguchi, and H. Iri, "Influence of major histocompatibility complex region genes on human longevity among Okinawan-Japanese centenarians and nonagenarians," *The Lancet*, vol. 2, no. 8563, pp. 824–826, 1987.

[20] F. Schächter, L. Faure-Delanef, F. Guenot et al., "Genetic associations with human longevity at the APOE and ACE loci," *Nature Genetics*, vol. 6, no. 1, pp. 29–32, 1994.

[21] D. C. Willcox, B. J. Willcox, W. C. Hsueh, and M. Suzuki, "Genetic determinants of exceptional human longevity: insights from the Okinawa Centenarian Study," *Age*, vol. 28, no. 4, pp. 313–332, 2006.

[22] W. H. Chung, R. L. Dao, L. K. Chen, and S. I. Hung, "The role of genetic variants in human longevity," *Ageing Research Reviews*, vol. 9, supplement 1, pp. S67–S78, 2010.

[23] A. A. Puca, M. J. Daly, S. J. Brewster et al., "A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 18, pp. 10505–10508, 2001.

[24] K. L. Lunetta, R. B. D'Agostino, D. Karasik et al., "Genetic correlates of longevity and selected age-related phenotypes: a genome-wide association study in the Framingham Study," *BMC Medical Genetics*, vol. 8, no. 1, supplement, S13, 2007.

[25] C. Franceschi, V. Bezrukov, H. Blanché et al., "Genetics of healthy aging in Europe: The EU-integrated project GEHA (GEnetics of Healthy Aging)," *Annals of the New York Academy of Sciences*, vol. 1100, pp. 21–45, 2007.

[26] A. Kahn and Longevity Consortium, "The Longevity Consortium: Harnessing diverse approaches to understand the genetic basis of human longevity and healthy aging. An introduction to a series of articles," *Ageing Research Reviews*, vol. 10, no. 2, pp. 179–180, 2011.

[27] A. B. Newman, S. Walter, K. L. Lunetta et al., "A Meta-analysis of Four Genome-Wide Association Studies of Survival to Age 90 Years or Older: The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium ," *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, vol. 65, no. 5, pp. 478–487, 2010.

[28] B. J. Willcox, T. A. Donlon, Q. He et al., "FOXO3A genotype is strongly associated with human longevity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 37, pp. 13987–13992, 2008.

[29] F. Flachsbart, A. Caliebe, R. Kleindorp, A. Sung et al., "Association of *FOXO3A* variation with human longevity confirmed in German centenarians," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 8, pp. 2700–2705, 2009.

[30] C. V. Anselmi, A. Malovini, R. Roncarati et al., "Association of the *FOXO3A* locus with extreme longevity in a Southern Italian centenarian study," *Rejuvenation Research*, vol. 12, no. 2, pp. 95–104, 2009.

[31] L. Pawlikowska, D. Hu, S. Huntsman et al., "Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity," *Aging Cell*, vol. 8, no. 4, pp. 460–472, 2009.

[32] N. Barzilai, G. Atzmon, C. Schechter et al., "Unique Lipoprotein Phenotype and Genotype Associated with Exceptional Longevity," *Journal of the American Medical Association*, vol. 290, no. 15, pp. 2030–2040, 2003.

[33] T. A. Koropatnick, J. Kimbell, R. Chen et al., "A prospective study of high-density lipoprotein cholesterol, cholesteryl ester transfer protein gene variants, and healthy aging in very old Japanese-American men," *Journals of Gerontology—Series A*, vol. 63, no. 11, pp. 1235–1240, 2008.

[34] C. J. Kenyon, "The genetics of ageing," *Nature*, vol. 464, no. 7288, pp. 504–512, 2010.

[35] E. Cevenini, E. Bellavista, P. Tieri et al., "Systems biology and longevity: an emerging approach to identify innovative anti-aging targets and strategies," *Current Pharmaceutical Design*, vol. 16, no. 7, pp. 802–813, 2010.

[36] A. B. Newman, N. W. Glynn, C. A. Taylor et al., "Health and function of participants in the Long Life Family Study: a comparison with other cohorts," *Aging*, vol. 3, pp. 63–76, 2011.

[37] B. J. Willcox, D. C. Willcox, Q. He, J. D. Curb, and M. Suzuki, "Siblings of Okinawan centenarians share lifelong mortality advantages," *Journals of Gerontology—Series A*, vol. 61, no. 4, pp. 345–354, 2006.

[38] E. R. Adams, V. G. Nolan, S. L. Andersen, T. T. Perls, and D. F. Terry, "Centenarian offspring: start healthier and stay healthier," *Journal of the American Geriatrics Society*, vol. 56, no. 11, pp. 2089–2092, 2008.

[39] M. Poulain, G. M. Pes, C. Grasland et al., "Identification of a geographic area characterized by extreme longevity in the Sardinia island: the AKEA study," *Experimental Gerontology*, vol. 39, no. 9, pp. 1423–1429, 2004.

[40] U.S. National Institute on Aging, " Report of the National Institute on Aging Advisory Panel on Exceptional Longevity (APEL)," Tech. Rep. NIH Publication no. 01-4951, U.S. Department of Health and Human Services PHS, National Institutes of Health, 2001.

[41] U.S. National Institute on Aging. National Institutes of Health, "NIA Panel on the Characterization of Participants in the Studies of Exceptional Survival in Humans," 2002, http://www.nia.nih.gov/ResearchInformation/ConferencesAndMeetings/NIAPanel.htm.

[42] E. C. Hadley and W. K. Rossi, "Exceptional survival in human populations: National Institute on Aging perspectives and programs," *Mechanisms of Ageing and Development*, vol. 126, no. 2, pp. 231–234, 2005.

[43] G. Ravaglia, P. Morini, P. Forti et al., "Anthropometric characteristics of healthy Italian nonagenarians and centenarians," *British Journal of Nutrition*, vol. 77, no. 1, pp. 9–17, 1997.

[44] Y. C. Chan, M. Suzuki, and S. Yamamoto, "Dietary, anthropometric, hematological and biochemical assessment of the nutritional status of centenarians and elderly people in Okinawa, Japan," *Journal of the American College of Nutrition*, vol. 16, no. 3, pp. 229–235, 1997.

[45] Y. Arai, M. Takayama, Y. Gondo et al., "Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age," *Journals of Gerontology—Series A*, vol. 63, no. 11, pp. 1209–1218, 2008.

[46] D. C. Willcox, B. J. Willcox, N. C. Wang, Q. He, M. Rosenbaum, and M. Suzuki, "Life at the extreme limit: phenotypic characteristics of supercentenarians in Okinawa," *Journals of Gerontology—Series A*, vol. 63, no. 11, pp. 1201–1208, 2008.

[47] D. B. Hausman, J. G. Fischer, and M. A. Johnson, "Nutrition in centenarians," *Maturitas*, vol. 68, no. 3, pp. 203–209, 2011.

[48] C. Franceschi, M. Bonafè, S. Valensin et al., "Inflamm-aging. An evolutionary perspective on immunosenescence," *Annals of the New York Academy of Sciences*, vol. 908, pp. 244–254, 2000.

[49] C. Franceschi and M. Bonafè, "Centenarians as a model for healthy aging," *Biochemical Society Transactions*, vol. 31, no. 2, pp. 457–461, 2003.

[50] S. Vasto, G. Candore, C. R. Balistreri et al., "Inflammatory networks in ageing, age-related diseases and longevity,"

Mechanisms of Ageing and Development, vol. 128, no. 1, pp. 83–91, 2007.

[51] A. Galioto, L. J. Dominguez, A. Pineo et al., "Cardiovascular risk factors in centenarians," *Experimental Gerontology*, vol. 43, no. 2, pp. 106–113, 2008.

[52] K. Andersen-Ranberg, M. Schroll, B. Jeune et al., "Healthy centenarians do not exist, but autonomous centenarians do: a population-based study of morbidity among danish centenarians," *Journal of the American Geriatrics Society*, vol. 49, no. 7, pp. 900–908, 2001.

[53] J. F. Calvert Jr., J. Hollander-Rodriguez, J. Kaye, and M. Leahy, "Dementia-free survival among centenarians: an evidence-based review," *Journals of Gerontology—Series A*, vol. 61, no. 9, pp. 951–956, 2006.

[54] Y. Gondo, N. Hirose, Y. Arai et al., "Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity," *Journals of Gerontology—Series A*, vol. 61, no. 3, pp. 305–310, 2006.

[55] D. C. Willcox, B. J. Willcox, S. Shimajiri, S. Kurechi, and M. Suzuki, "Aging gracefully: a retrospective analysis of functional status in Okinawan centenarians," *American Journal of Geriatric Psychiatry*, vol. 15, no. 3, pp. 252–256, 2007.

[56] D. F. Terry, P. Sebastiani, S. L. Andersen, and T. T. Perls, "Disentangling the roles of disability and morbidity in survival to exceptional old age," *Archives of Internal Medicine*, vol. 168, no. 3, pp. 277–283, 2008.

[57] A. Davey, M. F. Elias, I. C. Siegler et al., "Cognitive function, physical performance, health, and disease: norms from the Georgia Centenarian Study," *Experimental Aging Research*, vol. 36, no. 4, pp. 394–425, 2010.

[58] J. Evert, E. Lawler, H. Bogan, and T. Perls, "Morbidity profiles of centenarians: survivors, delayers, and escapers," *Journals of Gerontology—Series A*, vol. 58, no. 3, pp. 232–237, 2003.

[59] P. Martin, M. V. Long, and L. W. Poon, "Age changes and differences in personality traits and states of the old and very old," *Journals of Gerontology—Series B*, vol. 57, no. 2, pp. P144–P152, 2002.

[60] L. W. Poon, G. M. Clayton, P. Martin et al., "The Georgia Centenarian Study," in *The Georgia Centenarian Study: A Special Issue of the International Journal of Aging and Human Development*, L. W. Poon, Ed., Baywood, New York, NY, USA, 1992.

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Research Article

Typologies of Extreme Longevity Myths

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Purpose. Political, national, religious, and other motivations have led the media and even scientists to errantly accept extreme longevity claims prima facie. We describe various causes of false claims of extraordinary longevity. *Design and Methods*. American Social Security Death Index files for the period 1980–2009 were queried for individuals with birth and death dates yielding ages 110+ years of age. Frequency was compared to a list of age-validated supercentenarians maintained by the Gerontology Research Group who died during the same time period. Age claims of 110+ years and the age validation experiences of the authors facilitated a list of typologies of false age claims. *Results*. Invalid age claim rates increase with age from 65% at age 110-111 to 98% by age 115 to 100% for 120+ years. Eleven typologies of false claims were: Religious Authority Myth, Village Elder Myth, Fountain of Youth Myth (substance), Shangri-La Myth (geographic), Nationalist Pride, Spiritual Practice, Familial Longevity, Individual and/or Family Notoriety, Military Service, Administrative Entry Error, and Pension-Social Entitlement Fraud. *Conclusions*. Understanding various causes of false extreme age claims is important for placing current, past, and future extreme longevity claims in context and for providing a necessary level of skepticism.

1. Introduction

People have long been fascinated with claims to extreme longevity. Ancient Roman historians attempted to tally reports of extreme age in local villages. Medieval European alchemists kept tabs on reports of centenarians, possibly to find a "cure" for old age (the Fountain of Youth). Inexplicably, various historians and even "scientists" such as Roger Bacon accepted outlandish and wild reports of extreme age prima facie, without a critical examination or inquiry into whether the ages reported were true. It was not until the 18th century, with the advent of demographers such as Georges Buffon (1707–1788) that a limit to the human life span was proposed, with Buffon stating that "the man who does not die of incidental diseases reaches everywhere the age of ninety or one hundred years" [1].

The first reasonable attempts at age validation were performed by demographers such as Adolphe Quetelet, who conducted a systematic investigation of purported centenarian ages appearing in the first Belgian census of 1846 [2]. In the 1870s, Sir William Thoms (who coined the term "folklore" in 1846 and subsequently investigated folk tales of extreme old age) suggested the need to question extreme ages claimed in folk tales. Thoms investigated extreme age reports provided by village elders in the context of old age data provided by life insurance companies [3]. In his time, no age greater than 103 years old (Jacob Luning in 1870) had been verified using insurance company records, far younger than the claimed ages that were well beyond 110 years. Despite this important lesson of considering context, 140 years later many people in the media and elsewhere are willing to accept a claim of 130 years despite the fact that the maximum proven age having been reached by a human is 122 years [4].

To provide a current context to unsubstantiated age claims, we provide here some statistics concerning supercentenarian (a person age 110 years or older) prevalence. Kestenbaum and Ferguson at the U.S. Social Security Administration reported Medicare data indicating that, in 2000,

there were 32,920 centenarians and out of these, 105 or 0.3% were 110 years old and older [5]. Of 2,700 people who reportedly reached the age of 110+ years between 1980 and 1999, according to the SSA, only 355 (13%) could be confirmed. The US census listed 1,388 supercentenarians in 2000 (about 1 per 200,000) [6]. However, according to author R.D Young, per the surveillance efforts of the International Database on Longevity (IDL, http://www.supercentenarians.org/) and Gerontology Research Group (GRG, http://www.grg.org/), the number of living supercentenarians at present in the USA is approximately 60 to 70 (or approximately one living supercentenarian per five million people in developed countries and far fewer in less developed countries) and 250 to 300 world wide.

Academics and lay people interested in age validation generally fall into two camps: the skeptics and the optimists. The initial skeptics were actuaries, who found that humans did not live beyond 113 years or so. Thomas Emley Young of the Institute of Actuaries, London, for example, attempted the first validated list of centenarians in the 1890s, finding no one older than 106 [7]. An initial acceptance of the claim of Pierre Joubert to be 113, by the Tache investigation in Canada in 1878, was later overturned [8]. Interestingly, Alexander Graham Bell purportedly attempted such a list in1918 [9].

Optimists, on the other hand, have tended to accept extreme age claims, prima facie, and provided rationalizations as to why these people were "healthy" and lived longer than the rest. For example, scientists such as Elie Metchnikoff, the inventor of the term "gerontology" circa 1903, tended to believe extreme age claims of 140 and above [10, 11]. Jean Finot, a transhumanist, believed, at the turn of the twentieth century, that the growing number of centenarians at the time and the improvement in average life expectancy portended the likelihood of human life spans of 150 plus years [12]. 1973 articles in *Scientific American* [13] and the *National Geographic* [14] reported people over the age of 120 years in the Russian Caucusus, and in Vilcabamba, Ecuador. But later its author, Alexander Leaf, became wary of these claims due to inconsistencies in the stories, and he engaged Richard Mazess and Sylvia Forman to further investigate the Vilcabamba claims, which were eventually found to be false [15]. Optimists paved the way for amazing unquestioned claims in the United States as well. Sylvester Magee was said to be aged "130" [16] and an "ex-slave" and Charlie Smith, who also claimed to be an "ex-slave", was said to be age "137" when he died in 1979. Smith was later noted to be 100 years old at death based upon the 1900 census and was not, in fact, an ex-slave, having been born more than 15 years after the Emancipation Proclamation [17].

In 1955, given continued unbelievable extreme age claims, Norris and Ross McWhirter, the editors of the Guinness Book of World Records, noted the need to validate with sufficient records the "world's oldest person." In 1986, Norris stated: "No single subject is more obscured by vanity, deceit, falsehood and deliberate fraud than the extremes of human longevity" [18].

A resurgence of longevity myths in the 1970s, particularly in the Caucasus region of Soviet Russia, the Hunza Valley in Pakistan, and the Vilcabamba valley in Ecuador was finally debunked by objective scientific investigation in the early 1980s [15, 19, 20]. Even the skeptical Guinness Book of World Records was not infallible, however. For example, Shigechiyo Izumi of Japan was accepted as aged 113 years in 1978 and was thought to be the oldest verified person ever at age 120 years in 1986. However, in 1987 he was determined by Japanese researchers to more likely be only 105 years old at the time of his death [21]. Unfortunately in 2009, as discussed below, the fantastic age claim of Sakhan Dosova of Kazakhstan, age "130 years" (1879–2009), was supported in an issue of *Scientific American* [22] despite the lack of early-life documentation. Also in 2009, there was the claim of Tuti Yusupova of Uzbekistan who was claimed to have been born on July 1, 1880 and therefore was alleged to be "129" in 2009. The BBC news reported the event of her birthday as if it were valid, noting a "birth certificate." However, even the report's own video clip shows that the document was a late-life one issued in 1997, not proof of birth issued in 1880, or anywhere close to it [23]. Surprisingly, these and other similar reports provide little in the way of skepticism even when the individuals were not claimed as the oldest ever, seven or eight years earlier, when they would have broken the accepted record of 122 years, 164 days set by Jeanne Calment of France (February 21, 1875–August 4, 1997) [4]. Many claims, such as the one appearing in *Scientific American*, are characterized by geographically specific absences of records from the late 1800s and early 1900s from regions such as Armenia where most records were destroyed by the war. In the case of China, ages are traditionally recorded in 12-year increments or animal cycles according to the Chinese zodiac, and therefore animal signs rather than birth years are often more culturally salient among the oldest old. Additionally, in China one can encounter the tradition of ages beginning at the number one, rather than zero, which can lead to an additional year, as in the case of a former first lady of China, Madame Chiang Kai-shek, who died at age of 105, not 106 [24].

Despite this history of the overwhelming improbability of various extreme age claims, the Western media continue to report such claims, particularly from exotic regions, as if they might be true. Meanwhile, as discussed below, well-documented and validated cases generally do not exceed 115 years of age. The record for Germany is just 112 [25]; for Sweden, 113 [26]; for Italy [26] and Spain [27], 114. Since 1837, with the advent of compulsory birth registration, no one in the UK has been proven to survive beyond the age of 115 years [26]. Where birth registrations are available in the mid to late 19th century, valid claims of ages beyond 122 do not exist. As a result, in our experience, claims to age 130 exist only where records do not.

The problem, however, extends beyond the media. In 2007, Professor Orhan Kural, of Turkey, supported the dubious claim of Seher Bulut, age "122" [28, 29], despite no proof of birth and a generation gap suggesting that this woman gave birth at an age reasonably beyond menopause. Government officials have been willing to provide a benefit of the doubt in some cases, perhaps because of political pressure or community notoriety rather than any sincere desire to seek the truth. Even in the USA, the claim of William Coates

to be "114" was incorrectly accepted by Dr. Irving Smith of the Evelyn Cole Senior Center, Maryland, in 2004. Census research subsequently showed that Mr. Coates was only 92, not 114 as claimed [30, 31].

More scientifically rigorous treatment of the subject came about in the late 1980s and early 1990s; a group of demographers and gerontologists came together in a series of workshops to formulate criteria for effectively validating or invalidating extreme age claims. These efforts led to the International Database on Longevity (IDL, http://www.demogr.mpg.de/en/research/695.htm and http://www.supercentenarians.org/), an ongoing list of validated supercentenarians that is well described in a recent monograph produced by the Max Planck Institute for Demographic Research [32]. A number of monographs have been written by these experts on the subjects of age validation and invalidation [2, 32–34]. Another group, based in Southern California, named the Gerontology Research Group (GRG, http://grg.org/) and led by L. Stephen Coles, was formed to facilitate, particularly via the internet, a group of academic and lay investigators interacting with one another in the maintenance of a validated claims list that was begun in 1999. This effort eventually branched into an actual records database of supercentenarian cases. Finally, the ongoing efforts of the Guinness Book of Records also facilitate the adjudication of world record age claims, providing a "final appeals" process whereby any claim from around the world may be submitted. This was the case in 2005, when the claim of Maria Capovilla of Ecuador, said to be 116, was submitted [35]. The documents were deemed sufficient by Guinness research, and subsequent follow-up research by other groups, such as the International Database on Longevity, tended to agree with this conclusion. Of note, Ms. Capovilla lived in a big city near sea level (Guayaquil) and her age did nothing to bolster the Vilcabamba myth that people living high in the Andean mountains, far from big cities, had an extreme survival advantage.

A number of ongoing studies of human exceptional longevity, for example, the Georgia Centenarian Study [36, 37], the Ashkenazi Jewish Centenarian Study [38], the Okinawa Centenarian Study [39, 40], the Long Life Family Study [41], and the New England Centenarian Study [42, 43] have relied upon the age validation criteria formulated by the IDL in making sure that the claimed ages of their subjects are real. The results of all these efforts are in remarkable agreement that verified age claims above 115 are extremely rare.

The New England Centenarian Study (NECS) has, over the past five years, made a concerted effort to specifically enroll supercentenarians (age 110+ years). Because supercentenarians are so rare at approximately one per five million people in the United States, the NECS recruits and enrolls these subjects from throughout North America. The study has, to date, the largest such sample in the world with over 100 subjects attaining ages of 110–119 years [44]. The NECS recruitment and enrollment experience, along with Robert Young's broader experience, since 2000, of monitoring and validating or disproving supercentenarian claims for Guinness World Records [45] and since 1999 for the GRG, has led to our ability to observe and categorize some of the different reasons and causes of inaccurate claims of extraordinary ages. It is important for researchers studying supercentenarians to be aware of signs that the age being claimed may be false. Identifying typologies of invalid age claims that we and others [1, 46, 47] have encountered provides a contextual background to the striking age claims often reported in today's media, while knowledge of the demographics of supercentenarians helps us to place extreme age claims of 110+ years in proper context. Thus, our purpose here is to classify the various causes or reasons for false age claims, while providing a backdrop that places these claims in proper demographic context. A more general knowledge of the typical circumstances or motivating factors that underlie age misreporting may be helpful in decreasing irresponsible coverage and inclusion of such claims in government records and scientific research.

2. Methods

To obtain an estimate of how the rate of invalid age claims in an American sample changes with age, one of the authors, RY, queried Social Security Death Index (SSDI) data which cover about 95% of the deaths in the USA in a given year to determine the number of people with birth and death years that yielded ages greater than or equal to 110 years (e.g., someone listed as born in 1870 and dying in 1981 would have been 110 or 111; someone born in 1870 and dying in 1982 would have been 111 or 112). A list was then generated for possible deceased supercentenarians from 1980 to 2009 according to age (column 1 of Table 1). A range including two possible ages is listed for each row because the months and days of birth and of death were not included in the age calculation from the SSDI data (to do so would have made the review of the SSDI data too arduous and our priority in looking for SSDI-generated cases of supercentenarians was sensitivity, not specificity). Without the day and month data, the person's age of death could have been, for example, 110 or 111 years. This is why the age of 109 years is also included in the table, even though 109 years would not qualify the person as a supercentenarian. This list was then compared to the results of the ongoing validation effort conducted by Robert Young and colleagues associated with the Gerontology Research Group (GRG) for supercentenarians in the USA who died during the same time period (column 2). The GRG had access to name, exact dates of birth and death, and in most cases vital information about the potential supercentenarian's parents and siblings for all of the SSDI-generated cases. Other purported supercentenarians were located by the GRG via surveillance of the lay press and regular searches of the internet as well as referrals to the GRG by friends or family of the individual. A comparison of the two columns then yielded a valid claims rate. For example, the SSDI listed 24 persons born in 1870 and dying in 1980, for a total of 24 potential 110-year olds. Of these, four were listed as verified (about 17%).

In the course of validating cases for the NECS, GRG, and Guinness World Records, Robert Young has used the set of rules described below and summarized in Table 1.

Table 1: Social Security Death Index-generated frequencies of alleged supercentenarians whose deaths were reported between 1980 and 2009 and validation rate.

Age range	Total claims	Number validated	Validation rate (%)
109-110	1106	183	16.6%
110-111	610	219	35.9%
111-112	372	109	29.3%
112-113	257	63	24.5%
113-114	190	27	14.2%
114-115	222	16	7.2%
115-116	53	3	5.7%
116-117	39	0	0.0%
117-118	39	1	2.6%
118-119	32	1	3.1%
119-120	25	0	0.0%
120-121	7	0	0.0%
121-122	18	0	0.0%
122-123	9	0	0.0%
123-124	13	0	0.0%
124-125	8	0	0.0%
125-126	7	0	0.0%
126-127	6	0	0.0%
127-128	6	0	0.0%
128-129	3	0	0.0%
129-130	7	0	0.0%
Totals	3029	622	20.5%
Excluding 109-110:	1923	439	22.83%

Social Security Death Index-generated frequencies of alleged supercentenarians whose deaths were reported between 1980 and 2009. The number of these purported supercentenarians was compared with an age-validated list of supercentenarians, also who died during the same time period, generated by the Gerontology Research Group, to obtain the validation rate. The rate for the age 109-110 range was lower than might otherwise be expected because persons who died at age 109 (e.g., born in April 1870 and died in January, 1980) were counted as "not validated."

Generally, the rate of validation for potential oldest subjects in the NECS is high because these individuals are usually around ages of 107–110 years old, nearly all of them come from the USA and Canada (as noted in the results, higher ages and claims from less developed countries have lower validation rates), and their reason for cooperating with the NECS in the age validation process is to volunteer for study on the genetics of exceptional longevity. Cases adjudicated for Guinness tend to have much higher invalid rates (and therefore there is an ascertainment bias) because the claimed ages are much higher (approaching or surpassing the oldest age record). The validity rates for the GRG tend to be somewhere in between the NECS and Guinness because ages for the GRG list begin at 110 years, but the list also includes claims from all over the world with some coming from less developed countries or regions. Still, the vast majority of GRG cases come from the United States, Western Europe, Japan, Australia, and Canada. The ascertainment bias that is likely associated with the GRG effort enhances the sensitivity of the above validation effort for the oldest ages and strengthens the case that nearly all the claimed ages, particularly those in the United States, come to the GRG's attention and are therefore not missed.

Authors B. D. and M. P. also have a vast experience in assessing the validity of cases. It is out of the collective experience of the authors, as well as from a literature and media review, that a list of typologies for invalid cases was constructed.

The ability to validate an age claim is dependent upon the various resources available for that claim, and these in turn can vary according to the administrative, cultural, or religious settings. These data can increase the probability of either a true positive or a true negative age claim. Ideally, the person's original birth record or a certified copy of the record, registered at, or shortly after, the person's actual birth should be available. Importantly, one must be certain that the record relates to the person under scrutiny, namely, on the basis of first and last name, place of birth, and the parents' names, which are the elements that are normally available on the birth record. In the cases of the most extreme old, by virtue of their rarity and likelihood of being false, the birth record alone should not be sufficient because of the possibility, for example, of homonyms or namesakes (a person named after another person).

Consistency between birth, death, and marriage records according to name, surname, and parent and spouse names incrementally increases the probability that the alleged age is true. The ideal validation procedure must thus include a "family reconstitution," that is, an identification of the timing and composition of the births of the entire sibship in relation to the parents and their birth data to insure that there is no possibility of mistaking identity and to be sure that the birthdates make sense in relation to one another [33]. The use of family pedigree reconstitution and a check of other vital records, such as court documents, may be employed if the age claim is extreme (such as that of Jeanne Calment) [4].

A chapter by Michel Poulain appearing in a recent monograph on supercentenarians [34] provides a detailed discussion of the necessary steps for validating extreme age claims. As discussed in this contribution, all necessary investigations have to be consistent in order to prove validity of age. If one important piece of information is missing, the age cannot be validated with "no doubt at all." Nevertheless the lack of an important piece of information (e.g., no birth record) does not necessarily invalidate the claim, but rather precipitates the need for additional data to support the age validation. A proxy or substitute record, such as the 1900 census for someone born in 1897, listing them as age 3 for example, may be counted as a sufficient replacement for proof of birth. Internationally, the proxy-birth rule is limited to documents issued within 20 years of the birth event [4]. On the other hand, a single piece of information (such as the age of the oldest child) may make the claimed age highly improbable. For example, when Antisa Khvichava recently celebrated her "130th" birthday [48], the age of her oldest son (70) placed the claim squarely in the "probable age

exaggeration" category: her age report is likely off by 20–40 years. If one element is wrong, the entire validation process will be considered as highly improbable, and it is definitively easier to prove that this person is not a centenarian than the opposite. In fact, the validation will never be final, while the invalidation is generally final when clear grounds for invalidation are found.

The principles of age validation that we rely upon are summarized below.

Basic Principles for Age Validation.

(i) Ideally, age should be calculated from linking a birth registration with a death registration or with a living person.

(ii) In the absence of a birth registration, date of birth should be obtained from a document dating back as far as possible, and specifically be dated close to the person's alleged birth (e.g., a local census record).

(iii) The identification of the person must be unequivocal, thus necessitating matches with the names of parents and siblings or spouses and children, and place of birth.

(iv) Family reconstitution.

(v) Independent corroboration is required when name identification is not sufficient, in the form of other records recording age which do not rely on the same base source.

(vi) Life events-marriage, birth of children, schooling-must be consistent with the alleged date of birth.

(vii) The requirements of age validation should be proportionate to the exceptionality of the age claim. For example, claiming to be age 120 will require many different and consistent forms of proof (as was done with Jeanne Calment), while claiming to be 110 years old requires only the three basic proofs: proof of birth, survival to age 110 (identification), and proof that the person in the birth record is the person in the ID record. It has been suggested that for ages 105–109, proof of birth and death should be sufficient.

3. Results

In the comparison of supercentenarian cases generated by the Social Security Death Index to a validated list generated by the GRG, one observes that the rate of validation declines with age, from about 35% at age 110-111 to just 2% by age 115 and 0% for 120+ years (Table 1).

We provide below a list of eleven categories of how false claims emerge. Some categories are more historical while others are common causes of currently professed claims that are either proven false or do not have enough substantiating evidence to be believable. These categories are Religious, Patriarchal Myth, the Village Elder Myth, Fountain of Youth Myth (substance), Shangri-La Myth (geographic), Nationalist Pride, Spiritual Practice, Familial Longevity, Individual and/or Family Notoriety, Military Service, Administrative Error, and Pension Fraud. Each of these is elaborated upon below.

3.1. Religious, Patriarchal, Genealogical Myth. In tribal and village kinship networks, the eldest members can not only be a repository of wisdom and tribal knowledge, they can also be patriarchal or matriarchal figures and a living symbol of the family tree that holds together the past and present members of the family. Since very old age conferred status, some extreme ages were attributed to historically important individuals. Thus, in the Bible, Abraham is said to have lived "175" years. Some scholars believe that Aaron's age of "123" was meant to show that the priesthood was older than the law, represented by Moses (who lived to "120") [49].

Moses's successor, Joshua, was said to have died at a younger age of 110 perhaps because he was of a lesser status than Moses, but still important and therefore older than the "average" age of 70–80 years stated in Psalm 90:10. With the more recent King David portion of the Bible, incredible ages give way to ordinary ages of death: 70 for David, or 58 for Rehoboam, for example.

In some cases, ages were exaggerated to extend a pseudo-genealogy further back into the past. For example, in ancient Sumeria, claimed ages corresponded to calendar cycles and special dates [50]. A later and reduced form of the cyclical-calendar genealogy myth was used in Japan, which inflated ages of emperors in an attempt to date Japanese history back to 660 BC [51]. This type of myth may no longer be a problem for current claims under investigation, but it is important when claims of ancient kings to be 117 or older are made. For example, Emperor Yao of China is said to have ruled for 100 years from age 17 to 117 (circa 2333 to 2234 BC) [52].

3.2. Village Elder Longevity Myth. The "village elder" myth can be considered as a localized version of the patriarchal myth; only it involves common people, not elite members of society. It is generally assumed that persons today cannot attain the ages of the ancients, but still one's "village elder" should be honored. The village elder myth originally centered around a tribal chieftain, but in places where local power was decentralized, elderly men and women began to lose such positions of power. Instead, the "village elder" became a source of pride, oral history, and a person to commemorate. The ages claimed tend to be limited by the masses' ability to believe them. Most claims of this type have been to ages less than 200 years old, with ages of 120 to 160 years seemingly representing the cusp of believability for the uneducated. The purported ages are commonly rounded off to the nearest five or ten years (called "age heaping") (i.e., 125 or 130, not 123 or 129). These myths continue today in places such as Bangladesh, Nigeria, Indonesia, and Pakistan.

A typical example of a "village elder" longevity myth is that of Moloko Temo of South Africa (Figure 1) [53]. Her identity card was issued in 1988, purporting that she was born on July 4, 1874. She died on June 3, 2009 supposedly at the age of "134 years." There are no other documents substantiating her age. Most importantly, no one came forward with her age claim in 1988 when

Figure 1: Moloko Temo of South Africa at what was announced as her 134th birthday. Photo with permission from the Department of Health and Social Development, Limpopo Provincial Government, South Africa.

she would have become the oldest person in the world. The age of her children (some in their 70s) suggests that this woman was closer to 104 than 134. Interestingly, in interviews Temo discounted that she is the world's oldest person: "I think that there are others older somewhere" [54]. In other words, the motivation for her age might not be about national or international fame but rather local respect and a cultural reverence for extreme old age as exemplified by the local saying, "May you grow as old as the mountain, Khulu" (source: http://www.iol.co.za/news/south-africa/may-you-grow-as-old-as-the-mountains-khulu-1.217466#).

It should be noted that the "village elder" myth is now often co-opted into a "nationalist" myth of longevity. The difference, however, is motivation; the original motivation for the village elder myth is local pride and joy; however the claim can then be discovered by the national press, and it becomes a source of national pride.

Another example is Ruby Muhammad, a woman who, as the "mother of the Nation of Islam" is said to be 113, but is more likely 103, according to the 1910 U.S. census photo with permission from the Department of Health and Social Development, Limpopo Provincial Government, South Africa. No birth certificate exists [55]. Her position is one of "matriarchal" status, a position of honor, and few details of her early life exist. Moreover, she was said to be illiterate before 1946, and misreported age is highly correlated with illiteracy.

3.3. Fountain of Youth Myth. Unlike the previously mentioned myths, which are rooted in patriarchal, ancient, and communal beliefs, the Fountain of Youth myth is anchored in the individual. The idea that people could change their environment (such as in alchemists' attempts to turn lead into gold), while not often supported by facts, became popular during the 1400s and 1500s. Consequently, Spanish conquistadors, already searching for fabulous cities of gold (the "Seven Cities of Cibola"), added the idea of finding the "Fountain of Youth." Ponce de Leon explored Florida in 1513, seeking the fountain in vain.

The Fountain of Youth myth is connected to longevity in the idea of exampleism (or the "testimonial fallacy"). People need an example of success to believe that a special kind of water (e.g., "glacial milk" from the Andes), drug, or potion carries beneficial (magical) properties, bestowing extraordinary longevity on those who use it. To satiate this need, today's charlatans often provide made-up testimonials or anecdotes as "examples" of success (testimonial fallacy). The many websites and advertisements professing the age-reversing effects of growth hormone and other substances alleged to extend human longevity are a particularly egregious example due to the high frequency of adverse effects from these drugs and evidence that growth hormone actually shortens life span in adults [56, 57]. As an example, Dr. Norman Walker promoted "raw juicing," and ages attributed to him were often 118, 119, 120, or even 130. Yet recent investigations found that he was only 99 years old [58].

3.4. Shangri-La Longevity Myth. An extension and adaptation of the Fountain of Youth myth is the idea that a particular place, rather than a substance, possesses what is needed to attain extreme age. Shangri-La was a fictional paradise in the 1933 novel *Lost Horizon*. Author James Hilton describes a place where the residents are happy, isolated, and live many years beyond the normal lifespan. This myth was particularly popular in the 19th century during the "Age of Empire" when people went in search of exotic and mystical lands (an adventure for wealthy Europeans, called the "Grand Tour"). Once again, we see wealth and personal vanity as motivating factors in longevity myths.

This myth differs from the Fountain of Youth myth in that it focuses on an entire village or mountain region, where the water, air, and so forth, are said to be qualitatively different than elsewhere. Modern examples of this myth include the Caucasus mountain region, the mountainous Vilcabamba region in Ecuador, and the Hunza Valley in Pakistan. In this type of myths, many people are claimed to achieve extreme old age. Thus, the Caucasus did not merely claim to have 168-year olds, but to have hundreds of people older than 120 years [59, 60]. In some cases, apparent age heaping showed how unreliable the claims were. Claimants were also disproportionately male, further incriminating the claim because the vast majority of centenarians are female.

The Vilcabamba Claim. This "Valley of Longevity" was promoted in the 1970s. Out of a total population of 819, the town boasted seven men and two women older than 100 years old. One man, Miguel Carpio, said that he was 123 years old. Another, Jose David, claimed to be 142 years old. Gabriel Erazo claimed to be 132 years old. Victor Maza claimed to be 120. The source of longevity was variously described as a pristine environment ("mountain water"), healthy habits such as constant movement, and isolation from the mainstream world. However, an investigation in 1979 by Dr. Richard Mazess of the University of Wisconsin, Madison and Dr. Sylvia Forman of the University of California, Berkeley found that there was not a single centenarian living in Vilcabamba [15]. The oldest person in the village was found

Figure 2: A village in Guangxi county, China (Permission, China-Span.com).

to be 96. The average age of those claiming to be over 100 years was actually 86 years. Far from being a Shangri-La of very old people, the researchers concluded that: "Individual longevity in Vilcabamba is little, if any, different from that found throughout the rest of the world."

Note that in the case of Vilcabama, there is overlap with other categories of age misreporting. Vilcabamba means "Sacred Valley" in the Inca language, thus invoking an association with religious and mythical beliefs. Also, nearly all the extreme age claimants were male, suggesting an overlap with the patriarchal and village elder myths. Usually, about eighty-five percent of centenarians [61] and ninety percent of supercentenarians are women [46].

The Current Guangxi, China Claim. This Southern region of China, which borders Vietnam, claims a "longevity cluster" with 74 centenarians, including a 113-year old, in a population of 250,000 (thus, more than twice the prevalence of centenarians in industrialized countries). Perhaps due to skeptical pressure, ages above 113 are not used here; instead the claim is focused on prevalence of centenarians, rather than maximum ages. Hotels and other entrepreneurs call the region a spa vacation destination, where, according to an October 11, 2008 Wall Street Journal article by Stan Sesser, "simply breathing the air, drinking the local water and eating meals there" is claimed to lead to better health and longevity (Figure 2) [62].

3.5. Nationalist Longevity Myth. An extension of the Shangri-La myth is the "Nationalist" longevity myth. The idea of the Nationalist longevity myth was rooted in the rise of Nationalism in the 19th and 20th centuries. As people's ideas became focused on their "one nation" versus another (with their nation being the "right" one, "powerful" one, "God-blessed" one, etc.), extreme age claims became a source of pride.

The Soviets used the longevity claims of the Caucasus to help promote the asserted superiority of the Communist way of life and their nation [60]. These claims seemed to spark a longevity contest between the USSR and USA. The USSR proclaimed that Shirali Mislimov of Azerbaijan was 168 years old when he died on September 2, 1973 (note

Figure 3: 1956 USSR stamp depicting 148 years old Mahmud Eyvazov, the oldest person in the Soviet Union and living in Azerbaijan. The fact that a stamp was produced commemorating this man indicates the role of national pride in claims such as these (Permission, Azerbaijan International).

that no Western journalist was permitted to interview "old Shirali") [63]. Mahud Eyvazov was commemorated in a 1956 USSR stamp, for his 148th birthday and his being the oldest person in the Soviet Union (Figure 3) [63].

While the Soviet and American longevity race has lost its steam with the end of the cold war, extreme longevity claims from the former USSR still regularly appear in the press. Most recently, for example, Kazakhstan officials and the family of Sakhan Dosova claimed that she was the oldest person in the world at age 130 years old (Figure 4) (http://www.cbsnews.com/8031-504763_162-20010012-10391704.html) [22]. Perhaps this was a case of one-upsmanship since the claim appeared shortly after the Uzbekistan claim that Tuti Yusupova was 128. Most noteworthy about the Dosova claim is the fact that 8 years passed since she would have surpassed the long-held, accepted record of 122 years, and yet we only hear of the claim in 2009. Not surprisingly, there is no birth certificate supporting the claim; only a passport, a later-life census record, and an identification card, all of which could have been based upon one or the other. There are several other reasons why this claim is entirely unacceptable, including (1) the region from which the claim originates is well known for invalid claims with its poor recordkeeping, low rates of literacy, and a tradition of age inflation; (2) the claimed age is far beyond the accepted record holder and 16 years beyond the current oldest person in the world; (3) the ages of her children indicate that this claim is exaggerated, otherwise she would have given birth in her 60s [64].

Extreme age claims from Cuba, often in the 120–126 age range, have continued this tradition. Cuba even has a "120 club" [65], of which Fidel Castro is a member, as they wish him "120" years of health. The most recent

Figure 4: Sakhan Dosova's family and Kazakhstan officials claimed, as of April 1, 2009 that she was 130 years old. She died a month later. Photo permission from Radio Free Europe/Radio Liberty.

heralded claim is a person they claim is the oldest person in the world, Candelaria "Candulia" Rodríguez, age 125 years [65]. The club relies upon a church register, indicating a birthdate of February 2, 1885, as proof. For such an extreme and potentially sensational claim though, multiple forms of corroborating proof are necessary (see text box above, providing principles of age validation) [66].

3.6. Spiritual Practice. This myth asserts that certain philosophies or religious practices allow a person to live to extreme old age. These types of myths are most common in the Far East. For example, some Daoists have claimed to live to over 200 years. In China, Li-Ching-Yuen was noted to be 256 years old when he died in 1933 [67]. Not only was his age claim fantastical, and the number chosen as a multiple of eight (considered good luck in China), but the rationale was that he lived so long due to his following a certain practice or way of life. This type of myth is also found in Buddhism. For example, Nyala Rinpoche claimed to be 142 in 1978 and to have attained a state where he no longer consisted of flesh but was "pure light" [68].

Hindu yogis often also claim extreme age, such as the Swami Bua, variously said to be "118" (http://www.yogasutranyc.com/pdf/2007-Bua-Flier.pdf) or even "120," or Swami Kalyan Dev, who was noted to be "130 years old" (http://www.mangalyoga.com/team.htm). In a case such as this, followers can hope to live as long as the "Master" if they follow his guidance and direction. In the case of the spiritual practice myth, extreme age is associated with the supernatural and is often achieved through some activity. This is different than the concept of "religious blessing" common to monotheistic religions, whereby longevity is attained by finding grace or favor from God or gods, for example, the Religious Authority myth. Claims of this nature continue today.

3.7. Myths of Family Longevity. A relative living to an extreme age can be a source of significant pride for a family, and this is one of the most commonly encountered causes of inaccurate claims that we encounter. Many families relay stories of family members from many generations ago who lived to very old age. Often these ages are inflated, and there is no documented evidence for the claim. The farther back in time one goes, the easier it is to insert such a family member into the family tree. Sometimes one myth is used to prop up another. For example, Mattie Owens was claimed to be 119 years old in 2003 [69], and her son was said to be 87. An investigation by R.D. Young determined that Mattie was in fact 105 years old, and her son was just 80 years old [70]. These myths are quite common, even in the developed world. Macy Bare of North Carolina, said to be 115, turned out to be 107 [70]. In 2004, unequivocal census research revealed that William Coates of Maryland was 92, not 114 [30, 71].

The myth of persistent and extreme familial longevity is one of the more common typologies of age misreporting that we encounter, including countries such as the USA Though in the USA, it is relatively easy to find records, for example, from the U.S. census, to disprove claims, we encountered the claim of a Dominican Republic woman living in the U.S. who was supposedly 104 years old according to her immigration papers but her family indicated that she was "really 109" and that her mother lived to be 119, and her grandmother, to be 124 [72]. In reality, we do not even have sufficient proof that Ana Henriquez is 104, since the document was issued in 1963. Note that the age claims go higher the further back in the past the family tree goes. While many families insist a relative lived to "113" or even older, few families ever bother to investigate, and when they do, they are often disappointed.

3.8. Claims of Being the Oldest Person in the World: Individual and Family Notoriety. Some individuals, either purposefully or by mistake, claim that they are the oldest person in the world to bring notoriety to themselves and/or their family. They might do so completely convinced of their age, though they are mistaken because they have either been told by others what their (revised) age is, or because of cognitive frailty, they have forgotten about an intentional or erroneous change in their birth date from a long time ago. For example, Mariam Amash was surrounded by her family during all the media attention paid to her while recently claiming to be 120 years old (Figure 5). In a February, 2008 Daily Mail article, Moshe Hazut, a local official in the Northern Israeli town where Ms. Amash lived, stated that a birth certificate did not exist: "The woman was born during the Ottoman period, a time when the population registry was very inaccurate" [73]. Also, the age of her youngest son, Mohamed, 54 years old, would indicate that she gave birth at the age of 66, which particularly before the advent of modern fertility treatments, would be unheard of.

3.9. Military Age Misreporting. Motivations regarding military status can lead to age misreporting. In some cases, this is to make a child old enough to serve, in others to avoid war service. Various people in the 1940s and 1950s

Figure 5: Mariam Amash's family states that "She rises every morning around five for prayers.... She then goes for a walk and then spends most of her day with the family. She recognizes all of us." Such high function amongst people who validly claim ages even 10 years younger has never been observed by the New England Supercentenarian Study, which has enrolled 115 people aged 110 years or older as of December, 2010 (permission: The Daily Mail).

falsely claimed to be Confederate veterans, (and thus born in the mid-1800s) invoking a myth of Southern longevity. Arguing for the "Lost Cause," it was even stated that "if we cannot beat 'em, we can outlive 'em". Not one of the claimed Confederate ages turned out to be correct, and most were not even veterans [74]. For example, John Salling claimed to be 112 (http://generaljohnsalling.com/), but was 101. Walter Williams, the "last Confederate veteran" was not 117, but 105 years old (and not a veteran, either). Williams' motivation for age inflation could be partly monetary. He apparently inflated his age only in 1934, when a Confederate pension was offered during the Depression in Texas. At the time, Confederate promoters also claimed him as a heritage symbol [74].

Also of note, the last Union veteran, Albert Woolson, claimed to be 109 years old but research has shown that he was just 106 according to the census [74]. The oldest Union veteran, James Hard, claimed to be 111 years old in 1953 but investigation showed him to be 109 [74]. Fictionalized accounts of extreme age and war service continue to the present day. Merlyn Krueger recently claimed to be born in 1895 as well as a World War I veteran, but research by R.D. Young has shown him to be born in 1917. In some cases, the age is off by just a few years: Frank Buckles, the last surviving U.S. veteran of WWI, claimed to be "21" in 1917 so he could join the army, but he was just 16 years old then (and thus aged 110, but "115" according to his recruitment papers) [75].

In addition to the late-life military age myths, some men overstated their age earlier in an effort to avoid military service: claiming to be too old to be in the draft. If a man was 40 but claimed to be 50 in World War II, he could avoid military service, but would have to maintain the claim afterwards. This was common in Eastern Europe during World War II, when the draft age was often as high as 45. The claim that Pawel Parniak was 116 when he died in 2006 was just such an example. Research by R.D. Young showed that his mother was born in 1875 (just a 14-year generation gap) and that Mr. Parniak attempted to avoid recruitment in World War II (he was drafted anyway, despite being "49" on paper in 1939). It is far more likely that Mr. Parniak was closer to 111, having added about five years to his age in an attempt to avoid military service (it should be noted that he was also a World War I veteran), and his mother more likely gave birth to him at age 19 than 14.

3.10. Administrative Registration Errors. Administrative errors are an important source of inaccurate age claims, especially in more developed countries. For example, Damiana Sette in Sardinia was falsely noted to have died at the age of 110 years. In fact, she died at 107 years. The error was made several decades earlier in the transcription of administrative data. Damiana's data was replaced by those of her older sister who died at the age of 2 years, a few months before Damiana was born [34]. In Belgium, according to Michel Poulain's experience, the proportion of false claims due to administrative errors increases with age starting at 1% at age 100, 5% at 105, 50% at 110, and 100% at age 115. The reasons for such false cases include persons who emigrated abroad without reporting their birth date and accidentally unreported deaths (as opposed to purposefully unreported deaths, as in category 11, below) that result in administrative survivors.

Errors in the recorded birth date (generally a foreign-born person with inappropriate documentation for date of birth) are an important cause. For example, Kamato Hongo of Japan was under the impression that she was 116 years old in 2003, thus making her the oldest person in the world at the time. However, Michel Poulain's research showed that a likely administrative error in her date of birth casts doubt upon the claim [34]. Eva Jourdan of France was noted to be "112," but subsequent investigation discovered that she died at 102 and someone had copied "1890" as "1880" on a document (personal communication with INSERM, France). This suggests that original documentation is more reliable than copies of documentation. Whenever original documents can be secured, they are preferable to copies.

3.11. Unreported Deaths (Pension or Social Entitlement Fraud). Pension fraud claims have proven to be a major contributor to extreme age claims. In some cases, relatives with a similar name have continued to fraudulently collect a pension. For example, Pearl Hackney claimed to be 117 years old but was later noted to be 93. In this case, she assumed the identity of an aunt with the same name (this claim was investigated by the GRG, Jeff Knight). Others likely claimed an older age during middle age for the likely purpose of prematurely collecting social security. Eddlee Bankhead of Pennsylvania changed his age from 57 to 73 when he applied for social security in 1956, adding 16 years to his age. He died at the claimed age of "116", but census research showed that he was actually born in 1899 (per investigation by R.D Young).

In Japan, families have been caught collecting pensions for relatives that disappeared 40+ years ago (but were still listed as living, on paper, aged 110+) or even keeping the

dead body of a relative in a room. One man, supposed to be 107, had been dead for more than a decade as the family collected money and gifts [76]. In 2010, a similar scandal erupted as Japanese officials launched an investigation into at least 200 suspected cases of fraudulent pension claims involving people claimed to be very old but who likely died many years ago, including a person who would have been 125 years old if still living [77]. "111"-year-old Sogen Kato, turned out to have been dead since 1978, since the age of 79 [76]. A similar form of pension fraud recently took place in Greece, where 300 of 500 supposed living centenarians were found to have died in the previous seven years [78]. This is a reminder that the three minimum requirements for age validation of supercentenarians include proof of survival to an age of 110+ years; proof of birth alone is not sufficient.

4. Discussion

Extraordinary claims of extreme longevity regularly surface in the media without circumspection. These claims are often times not benign, however, given underlying motivations. In our experience, the vast majority of claims over the age of 110 and nearly all of those over 115 years are false, and therefore such claims must be regarded with great care and scrutiny.

The reporting of invalid ages as real can also cast a sensationalist shadow on the academic and responsible research of true supercentenarians. Extreme age claims do not deserve the benefit of the doubt, and without substantiating proof, like the Loch Ness monster and Bigfoot, they should be regarded as false.

Improvement in the quality of basic demographic data and the care with which it is managed may yield more reliable information as time moves forward, which will greatly enhance the ability to prove and disprove extreme age claims. But given human nature, however, and a number of the modern and historic sources of age misreporting that we list above, age validation will continue to need to be an integral part of valid exceptional longevity research. Even areas thought to have complete birth registration have seen problems with immigrant cases, unreported deaths, pension fraud, and the like. The older the alleged age of a longevity claim, the more in-depth must be the validation procedure.

Furthermore, as long as outrageous claims continue to be reported in the press without even a note of skepticism, they lend support to futurists and quacks who make claims that the average person today has the opportunity to achieve these purported ages. It is our hope that a more general knowledge of the typical circumstances under which age misreporting occurs may be helpful in decreasing irresponsible coverage of such claims and underscores the importance of skepticism and taking the substantial effort to proving or disproving a claim of extreme longevity.

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References

[1] B. Jeune, "In search of the first centenarians," in *Exceptional Longevity, From Prehistory to the Present*, B. Jeune and J. Vaupel, Eds., Odense University Press, Odense, Denmark, 1995.

[2] M. Poulain, D. Chambre, and M. Foulon, "Centenarian Validation in Belgium," in *Validation of Exceptional Longevity: Odense Monographs on Population Aging No. 6*, B. Jeune and J. W. Vaupel, Eds., Odense University Press, Odense, Denmark, 1999.

[3] W. Thoms, *The Longevity of Man: Its Facts and Its Fictions. With a prefatory letter to Prof. Owen, C.B., F.R.S. on the limits and frequency of exceptional cases*, F. Norgate, London, UK, 1879.

[4] J. M. Robine and M. Allard, "The oldest human," *Science*, vol. 279, no. 5358, pp. 1834–1835, 1998.

[5] B Kestenbaum and R. B. Ferguson, "Number of Centenarians in the United States Jan. 1, 1990, Jan. 1, 2000 and Jan. 1, 2010 Based on Improved Medicare Data," Society of Actuaries, Orlando, Fla, USA, 2005, http://www.soa.org/library/journals/north-american-actuarial-journal/2006/july/naaj0603-2.pdf.

[6] E. Hustead, "Ending the mortality table," in *Proceedings of the Living to 100 and Beyond Symposium*, 2005.

[7] H. Charbonneau, "Pierre Joubert a-t-il vécu 113 ans?" *Mémoires de la Société Généalogique Canadienne-Française*, vol. 41, pp. 45–48, 1990.

[8] T. E. Young, *On Centenarians; and the Duration of the Human Race: A Fresh and Authentic Enquiry, with Historical Notes, Criticisms, and Speculations*, Charles and Edwin Layton, London, UK, 1899.

[9] A. G. Bell, "Who shall inherit long life? On the existence of a natural process at work among human beings tending to improve the vigor and vitality of succeeding generations," *National Geographic*, pp. 504–514, 1919.

[10] Anonymous, "The prolongation of life. Elie Metchnikoff decalres human existence may be indefinitely extended—there are realms of life in which death is not natural," New York Times, January 1908, http://query.nytimes.com/mem/archive-free/pdf?res=F40C11FB3C5A17738DDDA10994D9405B888CF1D3.

[11] A. L. Benson, "Learning the length of life– Many new facts brought to light -curious investigations recently made by various experts indicate future progress in pursuit of longevity," May 1909 http://query.nytimes.com/mem/archive-free/pdf?res=9B01E5D91539E733A25755C1A9639C946897D6CF.

[12] I. Stambler, "Life extension—a conservative enterprise? Some fin-de-siecle and early twentieth century precursors of transhumanism," *Journal of Evolution and Technology*, vol. 21, pp. 13–26, 2010.

[13] A. Leaf, "Getting Old," *Scientific American*, pp. 29–36, 1973.

[14] A. Leaf, "Every day is a gift when you are over 100," *National Geographic*, vol. 99, 1973.

[15] R. B. Mazess and S. H. Forman, "Longevity and age exaggeration in Vilcabamba, Ecuador," *Journals of Gerontology*, vol. 34, no. 1, pp. 94–98, 1979.

[16] obituary, "America's oldest citizen dies in Mississippi at 130," JET Nov 4, 1971 Nov 4:10.

[17] L. Thompson, "132 years old? Not likely, the experts say," Washington Post, July 1986.

[18] N. McWhirter and R. McWhirter, Eds., *The Guinness Book of Records*, Random House Publishing Group, London, UK, 1986.

[19] E. B. Palmore, "Longevity in Abkhazia: a reevaluation," *Gerontologist*, vol. 24, no. 1, pp. 95–96, 1984.
[20] A. Leaf, "Long-lived populations: extreme old age," *Journal of the American Geriatrics Society*, vol. 30, no. 8, pp. 485–487, 1982.
[21] Y. Saito, "Supercentenarians in Japan," in *Supercentenarians*, H. Maier et al., Ed., Demographic Research Monographs, pp. 75–99, Springer, Berlin, Germany, 2010.
[22] A. Hadhazey, "Can someone live to be a supercentenarian? A woman in central Asia claims to have just celebrated her 130th birthday, a new record for keeping the grim reaper at bay," Scientific American, 2009, http://www.sciam.com/article.cfm?id=can-someone-live-to-be-a-supercentenarian.
[23] December 2010, http://news.bbc.co.uk/2/hi/asia-pacific/7857591.stm.
[24] S. Faison, "Madame Chiang Kai-shek, a Power in Husband's China and Abroad, Dies at 105," December 2010, http://www.nytimes.com/2003/10/24/international/asia/24CHIANG.html?ei=5007&en=f8b504bbb50d937b&ex=1382414400&partner=USERLAND&pagewanted=all&position=.
[25] December 2010, http://www.grg.org/Adams/L/Germany.HTM
[26] Decemebr 2010, http://www.grg.org/Adams/BB200.HTM.
[27] R. Gomez-Redondo and J. J. Garcia-Gonzalez, "Emergence and verification of supercentenarians in spain," in *Supercentenarians*, Springer, Heidelberg, Germany, 2010.
[28] Anonymous, "Gerontology: Secret of Long Life," Time Magazine, July 1967, http://www.time.com/time/magazine/article/0,9171,899657-1,00.html.
[29] Anonymous, "Turkish granny set to enter record book," zeenewscom, May 2006, http://www.zeeenews.com/news292131html.
[30] Times Wire Reports, "Census Shows 'Oldest Man' Wasn't 114, but 92," Los Angeles Times, March 2004, http://articles.latimes.com/2004/mar/03/nation/na-briefs3.4.
[31] December 2010, http://www.msnbc.msn.com/id/4428272/ns/us_news-weird_news/.
[32] A. Cournil, J.-M. Robine, H Maier, J Gampe, and J. W. Vaupel, "The international database on longevity: structure and contents," in *Supercentenarians*, H. Maier, J. Gampe, B. Jeune, J.-M. Robine, and J. W. Vaupel, Eds., pp. 31–40, Springer, Berlin, Germany, 2010.
[33] B. Desjardins, *Validation of Extreme Longevity Cases in the Past: The French-Canadian Experience*, Odense University Press, Odense, Denmark, 1999.
[34] M. Poulain, "On the age validation of supercentenarians," in *Supercentenarians*, H. Maier, J. Gampe, B. Jeune, J.-M. Robine, and J. W. Vaupel, Eds., pp. 3–30, Springer, Berlin, Germany, 2010.
[35] Anonymous, "World's oldest woman dies at 116," BBC News, August 2006, http://news.bbc.co.uk/2/hi/americas/5293436.stm.
[36] L. Poon, *The Georgian Centenarian Study*, Baywood, Amityville, NY, USA, 1992.
[37] P. Martin, M. Kliegel, C. Rott, L. W. Poon, and M. A. Johnson, "Age differences and changes of coping behavior in three age groups: findings from the Georgia Centenarian Study," *International Journal of Aging and Human Development*, vol. 66, no. 2, pp. 97–114, 2008.
[38] N. Barzilai, G. Atzmon, C. Schechter et al., "Unique lipoprotein phenotype and genotype associated with exceptional longevity," *Journal of the American Medical Association*, vol. 290, no. 15, pp. 2030–2040, 2003.
[39] D. C. Willcox, B. J. Willcox, Q. He, N. C. Wang, and M. Suzuki, "They really are that old: a validation study of centenarian prevalence in Okinawa," *Journals of Gerontology A*, vol. 63, no. 4, pp. 338–349, 2008.
[40] D. C. Willcox, B. J. Willcox, N. C. Wang, Q. He, M. Rosenbaum, and M. Suzuki, "Life at the extreme limit: phenotypic characteristics of supercentenarians in Okinawa," *Journals of Gerontology A*, vol. 63, no. 11, pp. 1201–1208, 2008.
[41] P. Sebastiani, E. C. Hadley, M. Province et al., "A family longevity selection score: ranking sibships by their longevity, size, and availability for study," *American Journal of Epidemiology*, vol. 170, no. 12, pp. 1555–1562, 2009.
[42] T. T. Perls, K. Bochen, M. Freeman, L. Alpert, and M. H. Silver, "Validity of reported age and centenarian prevalence in New England," *Age and Ageing*, vol. 28, no. 2, pp. 193–197, 1999.
[43] E. A. Schoenhofen, D. F. Wyszynski, S. Andersen et al., "Characteristics of 32 supercentenarians," *Journal of the American Geriatrics Society*, vol. 54, no. 8, pp. 1237–1240, 2006.
[44] December 2010, http://www.bumc.bu.edu/supercentenarian/.
[45] C. Glenday, Ed., *Guinness Book of World Records*, Bantam Books, New York, NY, USA, 2010.
[46] I. Rosenwaike and L. F. Stone, "Verification of the ages of supercentenarians in the United States: results of a matching study," *Demography*, vol. 40, no. 4, pp. 727–739, 2003.
[47] J. W. Vaupel and B. Jeune, "The emergence and proliferation of centenarians," in *Exceptional Longevity: From Prehistory to the Present*, B. Jeune and J. W. Vaupel, Eds., Odense University Press, Odense, Denmrak, 1995.
[48] L. Frayer, "Georgian woman's claim to be 130 is hard to prove," AOL News, July 2010, http://www.aolnews.com/2010/07/10/experts-cast-doubt-on-130-year-old-womans-age/.
[49] *Britannica Encyclopedia of World Religions*, Encyclopedia Britannica Inc., Chicago, Ill, USA, 2006.
[50] W. G. Plaut and D. E. Stein, *The Torah: A Modern Commentary*, URJ Press, New York, NY, USA, 2005.
[51] D. J. Lu, *Japan: A Documentary History: Volume I, The Dawn of History to the Late Tokugawa Period*, M.E. Sharpe, London, UK, 1997.
[52] December 2010, http://threekingdoms.com/history.htm#2_3_1.
[53] Telegraph.co.uk, "World's oldest woman dies. A woman who claimed to be the oldest in the world has died, apparently aged 134," June 2009, http://www.telegraph.co.uk/news/worldnews/africaandindianocean/southafrica/5451473/Worlds-oldest-woman-dies.html.
[54] December 2010, http://www.iol.co.za/news/south-africa/is-moloko-the-world-s-oldest-person-1.249646.
[55] http://gerontology.wikia.com/wiki/Ruby-mohammad.
[56] S. J. Olshansky and T. T. Perls, "New developments in the illegal provision of growth hormone for "anti-aging" and bodybuilding," *Journal of the American Medical Association*, vol. 299, no. 23, pp. 2792–2794, 2008.
[57] T. H. Perls, N. R. Reisman, and S. J. Olshansky, "Provision or distribution of growth hormone for "Antiaging": clinical and legal issues," *Journal of the American Medical Association*, vol. 294, no. 16, pp. 2086–2090, 2005.
[58] K. Friesen, "Norman Walker Really died at age 99," My genealogy search on Dr. Norman Wardhaugh Walker, http://chetday.com/normanwalker.htm.
[59] Anonymous, "Medicine: No Methuselahs," Time Magazine, August 1974, http://www.time.com/time/magazine/article/0,9171,908667,00.html.
[60] L. K. Garson, "The centenarian question: old-age mortality in the Soviet Union, 1897 to 1970," *Population Studies*, vol. 45, no. 2, pp. 265–278, 1991.

[61] T Perls and R. Fretts, "Why women live longer than men," *Scientific American*, vol. 9, pp. 100–103, 1998.
[62] S. Sesser, "Live long and prosper. China's longevity villages want tourists to come and breathe the air," Wall Street Journal, October 2008, http://online.wsj.com/article/SB122367266613424083.html.
[63] C. Gasimov, U. Hashimova, A. Abbasov, and A. Ismayilova, "Centenarians in Azerbaijan. Heredity as stored environment," *Azerbaijan International*, vol. 2.3, pp. 32–34, 1994.
[64] W. Stewart, "Is this woman really as old as the light bulb? 'Oldest person in the world' set to celebrate her 130th birthday," Daily Mail, July 2009, http://www.dailymail.co.uk/news/worldnews/article-1164503/Is-woman-really-old-LIGHT-BULB-Oldest-person-world-set-celebrate-130th-birthdayhtml#ixzz0LBewOGHI&D.
[65] G. Molina, "The fountain of 120 years," Digital Gramma Internacional, June 2010, http://www.granma.cu/ingles/cuba-i/10junio-23fuente.html.
[66] B. Desjardins, "Validation of Extreme Longevity in the Past: The French Canadian Experience," in *Validation of Exceptional Longevity*, Odense UP, Odense, Denmark, 1999.
[67] Anonymous, "China: Tortoise-Pigeon-Dog," Time Magazine, May 1933, http://www.time.com/time/magazine/article/0,9171,745510,00.html.
[68] N. Norbu, *The Crystal and the Way of Light: Sutra, Tantra and Dzogchen*, Snow Lion, 2000.
[69] S. Cassese, "Mattie Owens, Possibly the world's oldest person at 119," February 2003, http://articles.sfgate.com/2003-02-15/bay-area/17475983_1_guinness-world-records-mrs-owens-oldest-person.
[70] R. Young, "Age 115 in the United States: fact or fiction?" in *Supercentenarians*, H. Maier, J. Gampe, B. Jeune, and J.-M. Robine, Eds., pp. 270–272, Springer, Berlin, Germany, 2010.
[71] H. R. Harris, "To Maryland Man's Mourners, He Will Always be 114," Washtington Post, March 2004, B-2.
[72] K. Taylor, "Faith sustains Lynner at 104," The Item July 2010, http://www.itemlire.com/articles/2010/07/26/news/news01.txt
[73] Mail Online, "Israeli woman claims to be the world's oldest person," Daily Mail February 2008, http://www.dailymail.co.uk/news/article-515351/Israeli-woman-claims-worlds-oldest-person.html.
[74] W. Marvel, "The great imposters," Blue and Gray Magazine, February 1991, http://www.bluegraymagazine.com/Articleindex/index.php?page=Volume8.
[75] http://en.wikipedia.org/wiki/Frank-Buckles.
[76] BBC News, "A Japanese man said to be Itami city's oldest male has been found dead at his home up to a decade after his death," March 2005, http://news.bbc.co.uk/2/hi/asia-pacific/4333379.stm.
[77] Irish Examiner Staff, "'Missing' centenarians spark fraud probe," Irish Examiner, August 13, 2010, http://www.examiner.ie/world/missing-centenarians-spark-fraud-probe-127693.html.
[78] H. Smith, "Greek government to kill off payouts to dead claimants," The Guardian, August 26, 2010, http://www.guardian.co.uk/world/2010/aug/26/greece-pensions-dead-claimants.

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Research Article

Centenarians Today: New Insights on Selection from the 5-COOP Study

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The number of oldest old grew tremendously over the past few decades. However, recent studies have disclosed that the pace of increase strongly varies among countries. The present study aims to specify the level of mortality selection among the nonagenarians and centenarians living currently in five low mortality countries, Denmark, France, Japan, Switzerland, and Sweden, part of the 5-Country Oldest Old Project (5-COOP). All data come from the Human Mortality Database, except for the number of centenarians living in Japan. We disclosed three levels of mortality selection, a milder level in Japan, a stronger level in Denmark and Sweden and an intermediary level in France and Switzerland. These divergences offer an opportunity to study the existence of a trade-off between the level of mortality selection and the functional health status of the oldest old survivors which will be seized by the 5-COOP project.

1. Introduction

The number of very old people greatly increased during the past few decades, for instance, the number of centenarians (100+) increased from 154 people in Japan in 1963 when the first *centenarian list* (*Zenkoku koureisha meibo*) was released by the Ministry of Health and Welfare [1] to 40,399 people in 2009 [2]. In France, this number also increased from a few hundred in 1950 to 14,944 by 2010 [3]. The first study assessing the emergence of the centenarians at the global level, in the mid 1990s, concluded that their number doubled every 10 years since the 1960s in the low mortality countries [4]. However, recent studies disclosed that the pace of increase in the number of oldest old strongly varies among the developed countries which are no longer in a phase of convergence regarding their mortality conditions [5]. Indeed during the 10-year period, from 1996 to 2006, the number of centenarians was multiplied by 4 in Japan while it was only multiplied by 2 in Europe [6]. Among the 27 European countries studied, this increase varied from a factor higher than 2 in some countries such as Austria, Italy, Germany, and Spain to a factor lower than 1.5 in Nordic or Eastern European countries such as Norway, Iceland, Latvia, Lithuania or Bulgaria.

During the same time various reports from Japan suggested that the functional health status of the centenarian people strongly decreased, especially their mobility with a higher proportion of people bedridden or confined to their house, as their number increased [5, 7, 8], while Danish studies suggested a *statu quo* (cognitive scores), or even an improvement for females (self reported ADLs), in the functional health status of the centenarians living in

Denmark [9, 10]. In absence of reports examining the change over time in the functional health status of the centenarians in other countries, these Japanese and Danish studies suggest the possible existence of a trade-off between the proportion of people reaching the age of 100 and the functional health status of the survivors. Indeed the number of centenarians was only multiplied by 1.6 in Denmark between 1996 and 2006 (1.3 for males and 1.7 for females) versus 4.2 in Japan (3.0 for males and 4.5 for females) [6].

The trade-off between two characteristics, such as fertility and longevity, is not an uncommon phenomenon in biological science. Similar kinds of trade-offs seem to also exist in the social sciences, such as that between the quantity and the quality of goods. In population health science, this has translated into the ongoing debate about the quantity and quality of years lived and led to the development of summary measures of population health, such as health expectancies, in order to assess whether an increase in life expectancy (quantity of life) is accompanied by an equivalent increase in the quality of the years lived [11]. The existing theories, "compression of morbidity" [12], "pandemic of disability" [13, 14], and "dynamic equilibrium" [15], illustrate all possible combinations between the changes in the quantity and quality of years lived. They do not provide a theory on the relationship between the level of mortality selection (how easy or difficult it is to survive to a given age) and the functional health status of the survivors (i.e., the people reaching this given age). It is generally thought that it is the frail who succumb first, leaving alive the more robust. It has also been suggested that this selection may be strong enough at the highest ages to virtually stop mortality rates from rising, and even to result in a decline [16–18]. Kannisto has suggested that this selection process may impair the health of some survivors leaving them frailer. Thus when the selection process is stronger, causing extra deaths, the health of many survivors is impaired [19]. Under these conditions it seems difficult to predict the impact of the level of mortality selection on the health status of survivors. A stronger selection may only keep alive the most robust individuals but the selective process itself may have impaired them, while a milder selection may keep alive less robust persons, but without having resulted in a deterioration of their health.

The current divergence in the fall of mortality above age 80 observed among the low mortality countries, and therefore in the level of selection of the survivors at age 100, offers an opportunity to study the existence of such a trade-off between the level of mortality selection and the functional health status of the oldest old survivors. This opportunity has been seized by the 5-COOP project (5-Country Oldest Old Project) which aims to accurately compare the health status of centenarians living in Denmark, France, Japan, Sweden, and Switzerland. Although the 5-COOP project will focus on the cohorts of people born in 1911 (and later) who will reach their 100th birthday from 2011 onwards, this paper details the differences in mortality selection among the five countries using the mortality history of the 1905 and 1910 cohorts.

The results are presented in three sections. After Section 3.1 quickly reviews the centenarian figures, Section 3.2 describes the mortality experiences of the male and female 1905 birth cohorts, from age 50 in 1955 to age 100 in 2005, as well as the mortality experiences of the 1910 birth cohorts, from age 50 in 1960 to age 95 in 2005. Section 3.3 presents the results in terms of selection from the 80th to the 100th birthdates before the significance of the observed differences in mortality selection is discussed.

This paper does not provide direct information on the health status of the people currently reaching their 95th or 100th year in the 5 countries of the study but merely describes their mortality experience from ages 50 to ages 95 and 100, respectively.

2. Data

All data come from the Human Mortality Database—HMD (http://www.mortality.org/), except for the number of centenarians in Japan, and were downloaded in Spring 2009 for the number of centenarians and in Spring 2010 for the death rates. The numbers of centenarians used in Section 3.1 are estimated by January first of each year (HMD, period data, population size), except in Japan where a list of living centenarians provided annually by the Ministry of Health and Welfare has been used. The Japanese counts are by September 30th. The death rates used in Sections 3.2 and 3.3 are cohort data coming without exception from the HMD (HMD, cohort data, death rates). The centenarian terminology is vague. Therefore, it is specified in the paper when the number of centenarians (100) corresponds to the people in the single age 100 and when the number of centenarians (100+) corresponds to the people aged of 100 years and over.

3. Results

3.1. The Centenarian Figures in the Five Countries. Since 1946, the number of centenarians increased tremendously in the five countries under study. However a quick look at the graphs listed in Supplementary Material (Figure A1) discloses significant differences in this increase. If it looks exponential in France, it seems to be much more rapid in Japan and conversely almost linear in Denmark. Table 1 summarizes this information over the last decade preceding 2006. Beyond the size effect, the Japanese population, being about twofold the size of the French population, and the latter being about ten times the size of the Swiss population, it is clear that the pace of increase of the number of centenarians is not similar in the five countries. It is much more rapid in Japan and, comparatively, quite slow in Denmark and Sweden, especially for males (Table 1).

The 10-year increase factor, 1996–2006 for both sexes, varies from 4.2 in Japan to 1.6 in Denmark (2.0 in France, 1.9 in Switzerland and 1.7 in Sweden). The centenarian population is predominantly a female population with a sex-ratio close to six women for every man. Among the five countries, it is at a maximum in France with a ratio of 7.1 in 2006 and minimum in Switzerland with a ratio of 5.3.

Table 1: Number of centenarians (100+) in 2006 and 10-year increase by sex: Denmark, France, Japan, Sweden, and Switzerland.

	Number of centenarians (100 and over)			10-Year increase	
Country	Males	Females	Sex-ratio	Males	Females
Japan	3906	23236	5.9	3.0	4.5
France	1532	10941	7.1	2.3	2.0
Switzerland	155	821	5.3	1.9	1.9
Sweden	194	1115	5.7	1.4	1.7
Denmark	99	581	5.9	1.3	1.7

These differences in the pace of increase in the number of centenarians may be caused by two main factors, that is, a differential in population growth and/or a differential in mortality selection. The differential in population growth, and especially the differential in birth cohort growth, clearly contributed to the differences in the 10-year increase factor between Japan and the four European countries. Indeed, in the last quarter of the 19th century, the birth cohort size significantly increased in Japan, moving from 869,126 new born in 1875 to 1,420,534 new born in 1900. Although quite important, such a growth cannot explain, by far, the observed differences in the increase in the number of centenarians. The following sections explore the second mechanism, that is, the differential in mortality selection and its impact on the number of centenarians, beginning at age 50.

3.2. The Mortality Experiences of the 1905 and 1910 Birth Cohorts. The two cohorts, born in 1905 and 1910, have been selected both for several practical and analytical purposes: (i) availability of population and mortality data in the five countries studied until ages 95 and 100, which are the ages of interest in the 5-COOP project, (ii) proximity to the cohorts which will be involved in 5-COOP, born in 1911 and later, and (iii) correspondence with the study of the Danish nonagenarian and centenarian cohorts [9, 10, 20–22].

The mortality experiences of the Japanese cohorts born 1905 and 1910 display a lower age mortality trajectory above the age of 85 years compared to the four European countries in the study. In detail (see Figures 1(a) and 1(b)), the Japanese female cohort born in 1905 experienced a higher level of mortality than the European cohorts of our study from age 50, reached in 1955, to age 66, reached in 1971. Then, the morality rates of the various countries overlap until age 90, reached in 1995. From this age to the age of 100 years the Japanese cohort experienced the lowest level of mortality. The Japanese cohort still experienced several times the highest mortality level between ages 66 and 75, and yet several times the lowest mortality level between age 75 and 90. The last time this Japanese cohort experienced the highest mortality level was in 1980, at the age of 75 years, and the first time it experienced the lowest mortality level was in 1985 at the age of 80 years. Compared to this main difference, differences among European cohorts seem to be quite small, though the French cohort seems to have experienced an intermediary situation with a much larger overlap with the other European cohorts.

The second Japanese female cohort born in 1910 experienced a higher level of mortality than the European cohorts of our study from age 50, reached in 1960, to age 59, reached in 1969, with the exception of age 56. Then again the mortality rates of the various cohorts overlap until age 85, reached in 1995. From this year, where the cohort has reached its 85th birthday, this second Japanese cohort also experienced the lowest level of mortality. The 1910 Japanese cohort still experienced several times the highest mortality level between ages 59 and 64, and yet several times the lowest mortality level before age 85. The last time this Japanese cohort experienced the highest mortality level was in 1974, at age 64, and the first time it experienced the lowest mortality level was in 1984, at age 74.

Except in 1960 at the age of 55 years, the Japanese male cohort born in 1905 never experienced a higher level of mortality than the European cohorts of our study. The French male cohort experienced the highest mortality level from age 50 to age 70, reached in 1975, age 55 excepted. Conversely, from age 69 (in 1974) to age 100, the Japanese cohort experienced the lowest level of mortality, if we make exceptions for a few ages, that is, ages 75, 76, 82, 85–87, 89, 97–100. Although overlapping for a few years with other trajectories, the Japanese mortality trajectory with age, above the age of 70 years, is clearly lower than the European trajectories. On the other hand, the Swedish male cohort experienced the lowest mortality level from age 50 to age 68 (in 1973), with the exception of age 51, but experienced some of the highest mortality levels at age 95 and above (ages 95, 96 and 98) from the year 2000 and on.

The Japanese male cohort born in 1910 also never experienced a higher level of mortality than the European countries of our study. The French male cohort experienced the highest mortality level from age 50 to age 65, reached in 1975. Before age 65, reached in 1975, the Swedish cohort experienced the lowest level of mortality. At age 65 and above the Japanese cohort experienced the lowest level of mortality, if we exclude ages 82 and 84, ages at which the French cohort experienced the lowest mortality levels. Thus, the Japanese mortality trajectory with age is clearly lower than the European trajectories above age 65. The Swedish male cohort born in 1910 also experienced the lowest mortality level before age 65 and some of the highest above age 90 (ages 91, 93 and 94).

Beyond the most spectacular differences (i.e., the female Japanese cohorts experiencing the highest mortality levels before the 1970s and the lowest after the mid 1990s, or the male Swedish cohorts experiencing the lowest mortality levels before the mid 1970s and some of highest levels

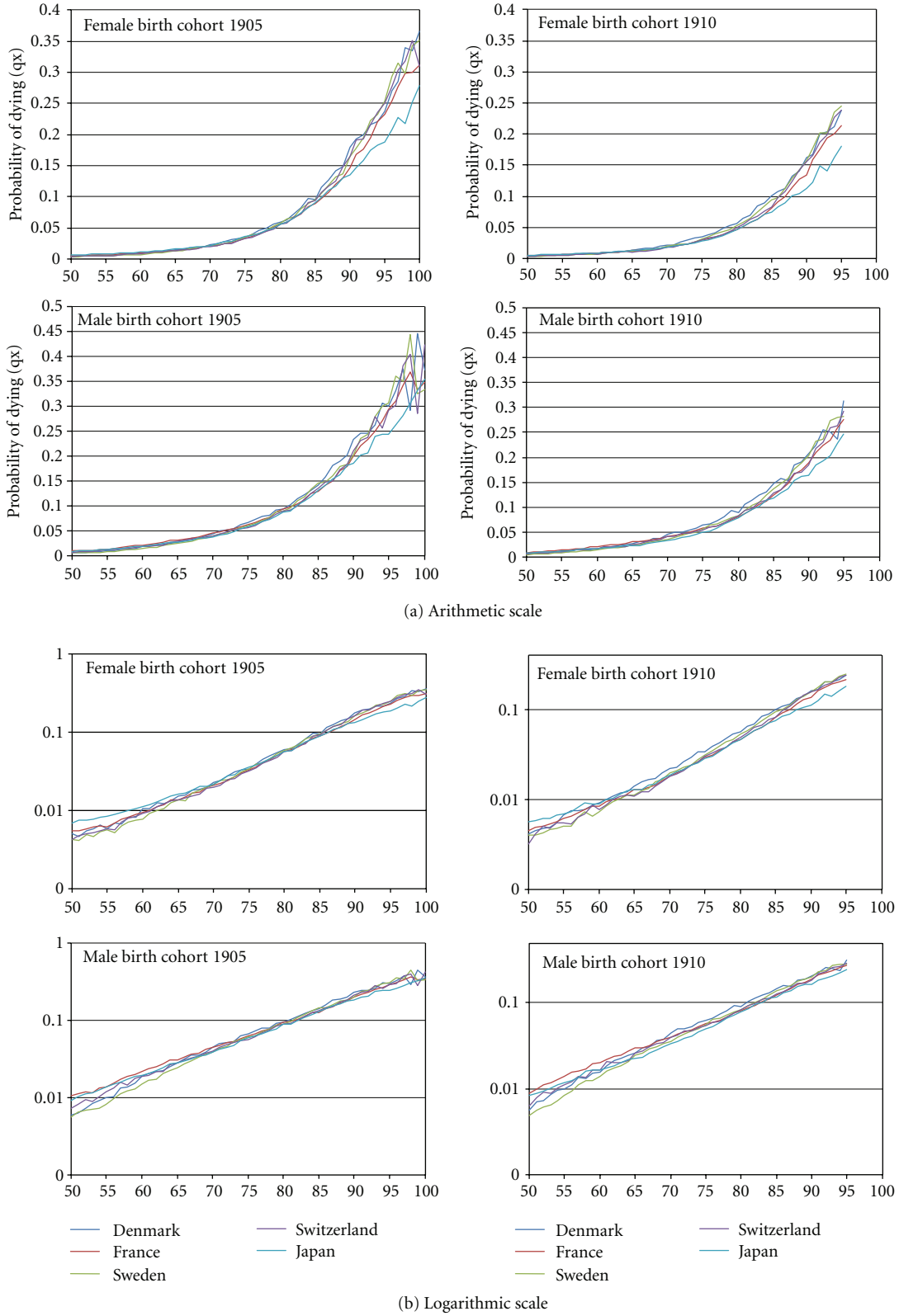

Figure 1: Mortality trajectory with age, from age 50, in the cohorts born in 1905 and 1910: Denmark, France, Japan, Sweden, and Switzerland.

since the year 2000), and some similarities between genders within the same country, the mortality experiences are clearly country and gender specific. The Danish cohorts often, but not always, experienced the highest morality levels since the 1970s for females and since the mid 1970s for males. The Swiss female cohorts regularly experienced the lowest mortality in the 1970s and 1980s while the 1910 Swiss male cohorts never experienced the highest or the lowest mortality levels. Contrary to the male cohorts, the French female cohorts never experienced the highest mortality levels. On the contrary they experienced some of the lowest levels at the beginning of the 1990s. These country-specific mortality experiences led to different levels of selection for the cohort members who reached their 95th birthday (birth cohort 1910) or 100th birthday (birth cohort 1905) during the calendar year 2005 and which are detailed in the following section.

The countries experiencing the lowest and the highest mortality levels by single age, for each gender and each cohort, through the age mortality trajectory above the age of 50 years, are reported in Supplementary Material (Table A1). The diagonal arrangement of the lowest and highest mortality levels in this Table suggests a strong period effect, the reasons for which will be debated in the discussion.

3.3. Selection from Age 80 to Age 100. The mortality selection process which occurred in the five countries above the age of 80 years is represented on Figure 2.

For the female cohorts born in 1905 and for 100,000 survivors at age 80, it led to very similar numbers of individuals surviving to age 100 in Denmark, Sweden, and Switzerland (1,957, 2,014 and 2,022 people, resp.), a noticeably higher number in France (2,928) and a strikingly higher number in Japan (4,780). This offers three levels of mortality selection: stronger (Denmark, Sweden, and Switzerland), milder (Japan) and intermediate (France).

For the male cohorts born in 1905, the mortality selection from age 80 led to low numbers of individuals surviving to 100 in Denmark and Sweden (532 and 570, resp.), noticeably higher numbers in Switzerland and France (776 and 856, resp.) and a strikingly higher number in Japan (1,376). This offers again three levels of mortality selection: stronger (Denmark and Sweden), milder (Japan) and intermediate (France and Switzerland).

For the female cohorts born in 1910 (for 100,000 survivors at age 80), the mortality selection led to similar numbers of individuals surviving to age 95 in Denmark and Sweden (12,709 and 12,923, resp.), noticeably higher numbers in Switzerland (14,241) and France (16,668) and a strikingly higher number in Japan (21,974). This offers three or four levels of mortality selection: stronger (Denmark and Sweden), milder (Japan) and intermediate (France), with Switzerland between France, on the one hand, and Denmark and Sweden, on the other hand.

For the male cohorts born in 1910, the mortality selection from age 80 led also to similar numbers of individuals surviving at age 95 in Denmark and Sweden (5,760 and 5,893, resp.), noticeably higher numbers in Switzerland (6,995) and France (7,593) and a strikingly higher number in Japan (9,622), offering three or four levels of mortality selection: stronger (Denmark and Sweden), milder (Japan) and intermediate (France) with Switzerland between France and both Denmark and Sweden.

4. Discussion

During the decade, 1996–2006, the number of centenarians in Japan increased two to three times faster compared with Denmark and Sweden, and two times faster when compared to Switzerland and France. The strong increase in the size of the Japanese birth cohorts at the end of the 19th century explained only a small part of the gaps. The main factor which explains the observed differences in the pace of increase in the numbers of oldest old in the five countries studied is the differential in mortality selection at older ages. Indeed, compared to Danish women, it has been 2.4 times easier for Japanese women born in 1905, and still alive at age 80 in 1985 to become a centenarian in 2005 (2.6 times easier for the male cohort) and 1.7 times easier for Japanese men and women born in 1910 and still alive at age 80 in 1990 to reach the age of 95 years in 2005 (see Table 2).

We studied the mortality experience of the various birth cohorts beginning at age 50. This does not mean that the mortality experience before age 50 does not matter in determining the number of people surviving to age 100 [23, 24], but in this study we were more interested in the mortality selection among adult people than in knowing how many persons in a certain birth cohort became centenarians. We are especially interested in the mortality selection among the oldest old. This is the reason why the last section focused on age 80 and above only. In a study of the demography of centenarians in England and Wales, it has been demonstrated that improved survival from age 80 to age 100 explained at least two times more the increase in the total numbers of centenarians (100+) than improved survival from birth to age 80 for the cohorts born between 1851 and 1896 [23].

The 1905 birth cohorts reached 50 years of age in 1955, ten years after World War II. The 20th century was not a tranquil century. The cohort born in 1905 and 1910 faced wars in Asia and in Europe and severe economic crises in their youth. The involvement of these cohorts in World War I and II varied strongly according to country, year of birth, and gender. Switzerland, for instance, escaped much of the devastation of the wars while France and Japan suffered both loss of manpower and destruction of property. Also, infant mortality was high in both 1905 and 1910 and stood at different levels in the five countries. However, recent studies demonstrated the preponderance of period factors to explain changes in mortality level, especially among the oldest old, even if early life and middle life factors also contribute to old age survival and mortality [25]. Nevertheless, ignoring mortality before age 50 is a limitation of this study.

Although the mortality experiences starting at age 50 were specific for each cohort, our study disclosed strong period effects punctuating these experiences. For instance, among cohorts born in 1905 and 1910, Japanese females experienced the highest level of mortality before 1970 and the lowest after 1995. Similarly, the French male cohorts

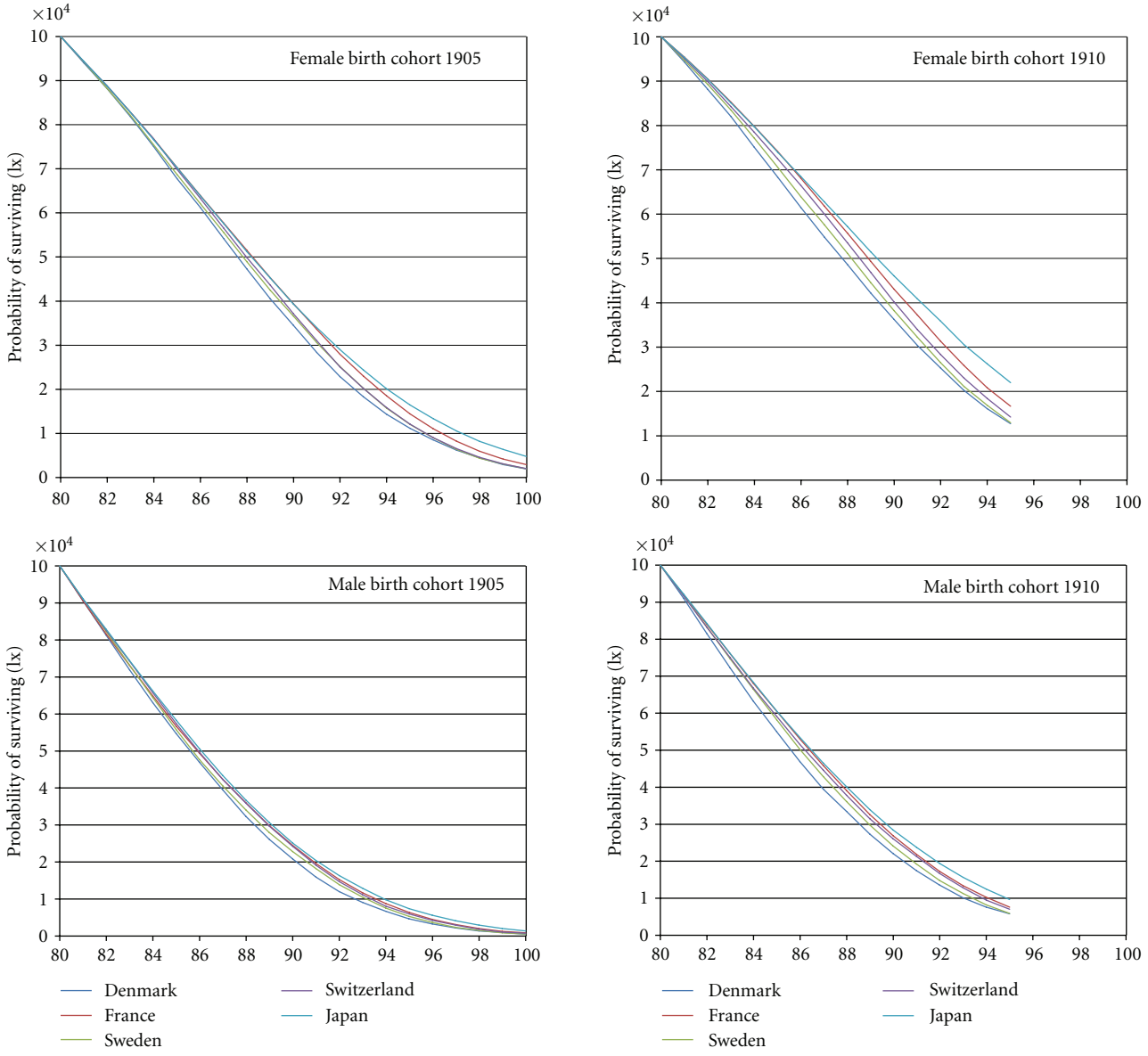

Figure 2: Survival curves from age 80, for the cohorts born in 1905 and 1910: Denmark, France, Japan, Sweden, and Switzerland.

Table 2: Chance to survive from 80 to 95 and 100 for cohorts born in 1905 and 1910: Denmark, France, Japan, Sweden, and Switzerland.

	Denmark (= 1)	France	Sweden	Switzerland	Japan
Cohorts born in 1905: Chance to survive from 80 to 100					
Females	1	1.5	1	1	2.4
Males	1	1.6	1.1	1.5	2.6
Cohorts born in 1910: Chance to survive from 80 to 95					
Females	1	1.3	1	1.1	1.7
Males	1	1.3	1	1.2	1.7

experienced the highest mortality level before 1975 and the Swedish male cohorts the lowest. These same Swedish cohorts experienced some of the highest mortality levels after 2000. In all these cases, the calendar year appears more important than the year of birth. This helps us to generalize the mortality experience of the oldest old of the five countries.

In summary, our study disclosed three levels of mortality selection among the centenarians currently living in the five countries.

(i) *A milder level of selection in Japan*. Indicated by the fact that Japanese women who became centenarians in 2005 had a 2.4 times higher chance to survive from age 80 to 100 than their Danish counterparts (2.6 times higher chance for the male cohort). The better mortality conditions observed in Japan are a recent phenomenon. Indeed before 1970 Japanese women experienced the highest level of mortality and crossed over the mortality trajectories of the other countries in the 1970s and 1980s.

(ii) *A stronger level of selection in Denmark and Sweden*. Denmark and Sweden, almost experienced the opposite mortality changes than Japan. Thus the worse mortality conditions mainly observed today in Denmark, and secondarily in Sweden, are also recent phenomena. In particular, before 1975, Swedish cohorts experienced the lowest level of mortality.

(iii) *An intermediary level of selection in France and Switzerland*. Indicated by the fact that the French (males and females) and Swiss males who became centenarians in 2005 had about a 1.5 times higher chance to survive from age 80 to 100 compared to their Danish counterparts—French men experienced similar mortality changes to those experienced by Japanese females. Indeed, before 1975, French males experienced the highest mortality level while they are second to Japan for the most recent years. On their side, the Swiss cohorts underwent specific changes over the same period of time. In particular the Swiss female cohorts regularly experienced the lowest mortality in the 1970s and 1980s.

These various epidemiologic histories have determined the current levels of mortality selection met by the centenarians living today in Denmark, France, Japan, Switzerland and Sweden. Three levels have been identified, milder, stronger and intermediary. However, due to the lack of studies or the lack of comparative studies, it is impossible to assess whether these different levels of selection have had an impact on the health status of the survivors. On one side reports have suggested a worsening in the functional health status of centenarians living in Japan over time [7, 8]. On another side reports have suggested a *status quo* (cognitive scores) and even an improvement for women (self reported ADLs), in the functional health status of centenarians living in Denmark [9, 10]. Although there are no similar reports on the health status of centenarians in Sweden, the Swedish Panel Study of the Living Conditions of the Oldest Old (SWEOLD) suggests some deterioration in the health status of the oldest old in the recent years [26, 27]. In France as well as in Switzerland, there is very little available information on the health status of the oldest old. The Danish 1905 cohort study is clearly in favor of the mainstream hypothesis that it is the frail who succumb first, strongly limiting the increase of the prevalence of geriatric conditions, such as ADL disability or dementia, with age [22].

It is worth reminding that some conditions have an effect on both disability and mortality, such as obesity and cardiovascular diseases, some on disability only, such as arthritis, macular degeneration or mild dementia, and some mainly on mortality, such as cancer [28, 29]. In addition to these various health outcomes specific for each disease, the possible role of the balance between life-saving medical interventions, rehabilitation of disabling conditions, and prevention of both disabling and lethal conditions must be mentioned. If a country mostly invests in life-saving interventions, disregarding the disabling conditions, the increased survival will be likely accompanied by an increase in the prevalence of disability. Different health policies, especially focusing on health behaviors such as alcohol and tobacco consumption, can entail survivorships with different functional health status. The characteristics of the daily care, formal and informal, provided to the oldest old, should also be at play. Can differences in survival between Europe and Japan or within European countries be explained by such factors?

It is in this context that the 5-Country Oldest Old Project (5-COOP) aims to provide prevalence estimates for a series of bio-markers, functional limitations, and geriatric conditions, including dementia and cognitive disorders, at ages 95 and 100, taking into account all available social and physical environmental factors, that is, "what they get", in six different cultural settings: Denmark, France (South), Japan (Tokyo and Okinawa), Switzerland and Sweden. These countries have been selected for their low mortality level, the quality of their population and mortality data [4, 6, 30–44], the possibility to draw representative samples of nonagenarians and centenarians, and the existence of research teams working on oldest-old issues [7–10, 20–22, 45–53].

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References

[1] Ministry of Health and Welfare, "*Zenkoku koureisha meibo* (A list of centenarians in Japan)," 1963–2009.

[2] J.-M. Robine and Y. Saito, "The demography of the oldest old in Japan," in *Frontiers of Japanese Demography*, Springer, Demographic Research Monographs, New York, NY, USA, In press.

[3] Insee. Bilan démographique 2009, Estimations de population (résultats provisoires arrêtés fin 2009). Insee Première, 1276, 1–4, January 2010, http://www.insee.fr/.

[4] J. W. Vaupel and B. Jeune, "The emergence and proliferation of centenarians," in *Exceptional Longevity: From Prehistory to the Present*, B. Jeune and J. W. Vaupel, Eds., vol. 2 of *Monographs on Population Aging*, Odense University Press, Odense, Denmark, 1995.

[5] J.-M. Robine, Y. Saito, and C. Jagger, "The relationship between longevity and healthy life expectancy," *Quality in Ageing*, vol. 10, no. 2, pp. 5–14, 2009.

[6] J. Robine and Y. Saito, "The number of centenarians in Europe," in *European Papers on the New Welfare, The Counter-Ageing Society: Steps Towards the European Welfare*, vol. 13, pp. 47–62, 2009.

[7] M. Suzuki, M. Akisaka, I. Ashitomi, K. Higa, and H. Nozaki, "Chronological study concerning ADL among Okinawan centenarians," *Nippon Ronen Igakkai Zasshi*, vol. 32, pp. 416–423, 1995.

[8] Y. Gondo, "Japanese centenarian studies," in *The Georgia Centenarian Study 20th Anniversary Conference*, Atlanta, Ga, USA, 2008.

[9] H. Engberg, K. Christensen, K. Andersen-Ranberg, and B. Jeune, "Cohort changes in cognitive function among Danish centenarians: a comparative study of 2 birth cohorts born in 1895 and 1905," *Dementia and Geriatric Cognitive Disorders*, vol. 26, no. 2, pp. 153–160, 2008.

[10] H. Engberg, K. Christensen, K. Andersen-Ranberg, J. W. Vaupel, and B. Jeune, "Improving activities of daily living in Danish centenarians - but only in women: a comparative study of two birth cohorts born in 1895 and 1905," *Journals of Gerontology A*, vol. 63, no. 11, pp. 1186–1192, 2008.

[11] J.-M. Robine, C. Jagger, C. D. Mathers, E. M. Crimmins, and R. M. Suzman, Eds., *Determining Health Expectancies*, John Wiley & Sons, Chichester, UK, 2003.

[12] J. F. Fries, "Aging, natural death, and the compression of morbidity," *New England Journal of Medicine*, vol. 303, no. 3, pp. 130–135, 1980.

[13] E. M. Gruenberg, "The failures of success," *Milbank Memorial Fund Quarterly, Health and Society*, vol. 55, no. 1, pp. 3–24, 1977.

[14] M. Kramer, "The rising pandemic of mental disorders and associated chronic diseases and disabilities," *Acta Psychiatrica Scandinavica*, vol. 62, no. 285, pp. 382–397, 1980.

[15] K. G. Manton, "Changing concepts of morbidity and mortality in the elderly population," *Milbank Memorial Fund Quarterly, Health and Society*, vol. 60, no. 2, pp. 183–244, 1982.

[16] V. Kannisto, "On the survival of centenarians and the span of life," *Population Studies*, vol. 42, pp. 389–406, 1988.

[17] J. W. Vaupel, K. G. Manton, and E. Stallard, "The impact of heterogeneity in individual frailty on the dynamics of mortality," *Demography*, vol. 16, no. 3, pp. 439–454, 1979.

[18] J. W. Vaupel, J. R. Carey, K. Christensen et al., "Biodemographic trajectories of longevity," *Science*, vol. 280, no. 5365, pp. 855–860, 1998.

[19] V. Kannisto, "Frailty and survival," *Genus*, vol. 47, no. 3-4, pp. 101–118, 1991.

[20] K. Andersen-Ranberg, M. Schroll, and B. Jeune, "Healthy centenarians do not exist, but autonomous centenarians do: a population-based study of morbidity among danish centenarians," *Journal of the American Geriatrics Society*, vol. 49, no. 7, pp. 900–908, 2001.

[21] H. Nybo, D. Gaist, B. Jeune, M. McGue, J. W. Vaupel, and K. Christensen, "Functional status and self-rated health in 2,262 nonagenarians: the Danish 1905 cohort survey," *Journal of the American Geriatrics Society*, vol. 49, no. 5, pp. 601–609, 2001.

[22] K. Christensen, M. McGue, I. Petersen, B. Jeune, and J. W. Vaupel, "Exceptional longevity does not result in excessive levels of disability," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 36, pp. 13274–13279, 2008.

[23] R. Thatcher, "The demography of centenarians in England and Wales," *Population*, vol. 13, no. 1, pp. 139–156, 2001.

[24] A. R. Thatcher, "Trends in numbers and mortality at high ages in England and Wales," *Population Studies*, vol. 46, no. 3, pp. 411–426, 1992.

[25] J. W. Vaupel, J. R. Carey, and K. Christensen, "It's never too late," *Science*, vol. 301, no. 5640, pp. 1679–1681, 2003.

[26] M. G. Parker, K. Ahacic, and M. Thorslund, "Health changes among Swedish oldest old: prevalence rates from 1992 and 2002 show increasing health problems," *Journals of Gerontology A*, vol. 60, no. 10, pp. 1351–1355, 2005.

[27] M. G. Parker and M. Thorslund, "Health trends in the elderly population: getting better and getting worse," *Gerontologist*, vol. 47, no. 2, pp. 150–158, 2007.

[28] W. J. Nusselder, J. van der Velden, M. E. Lenior, J. L. A. van Sonsbeek, and G. A. M. van den Bos, "The effect of elimination of selected chronic diseases on disability-free life expectancy: compression or expansion of morbidity? Preliminary results," in *Advances in Health Expectancies*, C. D. Mathers, J. McCallum, and J.-M. Robine, Eds., pp. 355–366, Australian Institute of Health and Welfare, Canberra, Australia, 1994.

[29] W. J. Nusselder, C. W. N. Looman, J. P. Mackenbach et al., "The contribution of specific diseases to educational disparities in disability-free life expectancy," *American Journal of Public Health*, vol. 95, no. 11, pp. 2035–2041, 2005.

[30] V. Kannisto, *Development of Oldest-Old Mortality, 1950–1990: Evidence from 28 Developed Countries*, vol. 1 of *Monographs on Population Aging*, Odense University Press, Odense, Denmark, 1994.

[31] B. Jeune, "In search of the first centenarians," in *Exceptional Longevity: From Prehistory to the Present*, B. Jeune and J. W. Vaupel, Eds., vol. 2 of *Monographs on Population Aging*, Odense University Press, Odense, Denmark, 1995.

[32] J.-M. Robine and G. Caselli, "An unprecedented increase in the number of centenarians," *Genus LXI*, vol. 1, pp. 57–82, 2005, Special issue: Increasing longevity: causes, trends, and prospects, Edited by S. Horiuchi and J.-M. Robine.

[33] J. R. Wilmoth and H. Lundstrom, "Extreme longevity in five countries: presentation of trends with special attention to issues of data quality," *European Journal of Population*, vol. 12, no. 1, pp. 63–93, 1996.

[34] A. Skytthe and B. Jeune, "Danish centenarians after 1800," in *Exceptional Longevity: From Prehistory to the Present*, B. Jeune and J. W. Vaupel, Eds., vol. 2 of *Monographs on Population Aging*, Odense University Press, Odense, Denmark, 1995.

[35] B. Jeune and A. Skytthe, "Centenarians in Denmark in the past and the present," *Population*, vol. 13, no. 1, pp. 75–94, 2001.

[36] F. Meslé and J. Vallin, *Comment améliorer la précision des tables de mortalité aux grands âges: le cas de la France?* INED, Paris, France, 2000, Communication présentée au Colloque de l'AIDELF "Vivre plus longtemps, avoir moins d'enfants, quelles implications ?", Byblos, Liban.

[37] F. Meslé, J. Vallin, and J.-M. Robine, "Vivre plus de 110 ans en France," *Gérontologie et Société*, vol. 94, pp. 101–120, 2000.

[38] J. Vallin and F. Meslé, "Vivre au-delà de 100 ans," *Population et Société*, vol. 365, pp. 1–4, 2001.

[39] J. M. Robine and F. Paccaud, "Nonagenarians and centenarians in Switzerland, 1860–2001: a demographic analysis," *Journal of Epidemiology and Community Health*, vol. 59, no. 1, pp. 31–37, 2005.

[40] L. Seematter-Bagnoud, F. Paccaud, and J.-M. Robine, *Le Futur de la Longévité en Suisse*, OFS, Neuchâtel, Switzerland, 2009.

[41] J.-M. Robine and Y. Saito, "Survival beyond age 100: the case of Japan," *Population and Development Review*, vol. 29, supplement, pp. 208–228, 2003.

[42] J. M. Robine, Y. Saito, and C. Jagger, "The emergence of extremely old people: the case of Japan," *Experimental Gerontology*, vol. 38, no. 7, pp. 735–739, 2003.

[43] D. C. Willcox, B. J. Willcox, Q. He, N. C. Wang, and M. Suzuki, "They really are that old: a validation study of centenarian prevalence in Okinawa," *Journals of Gerontology A*, vol. 63, no. 4, pp. 338–349, 2008.

[44] J. R. Wilmoth, L. J. Deegan, H. Lundstrom, and S. Horiuchi, "Increase of maximum life-span in Sweden, 1861–1999," *Science*, vol. 289, no. 5488, pp. 2366–2368, 2000.

[45] M. Allard and J.-M. Robine, *Les Centenaires Français. Etude de la Fondation IPSEN, 1990–2000*, Serdi, Paris, France, 2000.

[46] M. Allard, J. Vallin, J.-M. Andrieux, and J.-M. Robine, "In search of the secret of centenarians. A demographic and medical survey about centenarians in France," in *Health and Mortality Among Elderly Populations*, G. Caselli and A. D. Lopez, Eds., Clarendon Press, Oxford, UK, 1996.

[47] K. Andersen-Ranberg, K. Christensen, B. Jeune, A. Skytthe, L. Vasegaard, and J. W. Vaupel, "Declining physical abilities with age: a cross-sectional study of older twins and centenarians in Denmark," *Age and Ageing*, vol. 28, no. 4, pp. 373–377, 1999.

[48] K. Andersen-Ranberg, L. Vasegaard, and B. Jeune, "Dementia is not inevitable: a population-based study of Danish centenarians," *Journals of Gerontology B*, vol. 56, no. 3, pp. P152–P159, 2001.

[49] H. Nybo, H. C. Petersen, D. Gaist et al., "Predictors of mortality in 2,249 nonagenarians–the Danish 1905-cohort survey," *Journal of the American Geriatrics Society*, vol. 51, no. 10, pp. 1365–1373, 2003.

[50] M. Suzuki, B. J. Willcox, and D. C. Willcox, "Successful aging: secrets of Okinawan longevity," *Geriatrics & Gerontology International*, vol. 4, pp. S180–S181, 2004.

[51] D. C. Willcox, B. J. Willcox, S. Shimajiri, S. Kurechi, and M. Suzuki, "Aging gracefully: a retrospective analysis of functional status in okinawan centenarians," *American Journal of Geriatric Psychiatry*, vol. 15, no. 3, pp. 252–256, 2007.

[52] P. Schön and M. G. Parker, "Sex differences in health in 1992 and 2002 among very old Swedes," *Journal of Population Ageing*, vol. 1, no. 2–4, pp. 107–123, 2008.

[53] P. Schön, M. G. Parker, I. Kareholt, and M. Thorslund, "Gender differences in associations between health indicators and ADL in 1992 and 2002," *Aging Clinical and Experimental Research*. In press.

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Research Article

Predicting Successful Aging in a Population-Based Sample of Georgia Centenarians

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Used a population-based sample (Georgia Centenarian Study, GCS), to determine proportions of centenarians reaching 100 years as (1) survivors (43%) of chronic diseases first experienced between 0–80 years of age, (2) delayers (36%) with chronic diseases first experienced between 80–98 years of age, or (3) escapers (17%) with chronic diseases only at 98 years of age or older. Diseases fall into two morbidity profiles of 11 chronic diseases; one including cardiovascular disease, cancer, anemia, and osteoporosis, and another including dementia. Centenarians at risk for cancer in their lifetime tended to be escapers (73%), while those at risk for cardiovascular disease tended to be survivors (24%), delayers (39%), or escapers (32%). Approximately half (43%) of the centenarians did not experience dementia. Psychiatric disorders were positively associated with dementia, but prevalence of depression, anxiety, and psychoses did not differ significantly between centenarians and an octogenarian control group. However, centenarians were higher on the Geriatric Depression Scale (GDS) than octogenarians. Consistent with our model of developmental adaptation in aging, distal life events contribute to predicting survivorship outcome in which health status as survivor, delayer, or escaper appears as adaptation variables late in life.

1. Introduction

With the expected lifespan of humans increasing at a rate of 2.5 years per decade [1], it will not be uncommon for individuals born in developed countries in this decade to live into the next century (Figure 1(a)) [2]. This observation poses a substantial challenge to health care and other entitlement systems because chronic diseases, which are the cause of 60 percent of deaths worldwide, often dictate the conditions of our later lives. Here we develop a means to predict the health-related survivorship outcomes of centenarians entering the next century.

The GCS obtained a population-based sample of 244 centenarians and near-centenarians (98 years old or older) and 80 octogenarians [3] through voter registration roles, and sampling from a complete list of nursing homes (NH) and personal care homes (PCH) in a 44-county area of northeast Georgia [3]. The GCS sample was drawn from

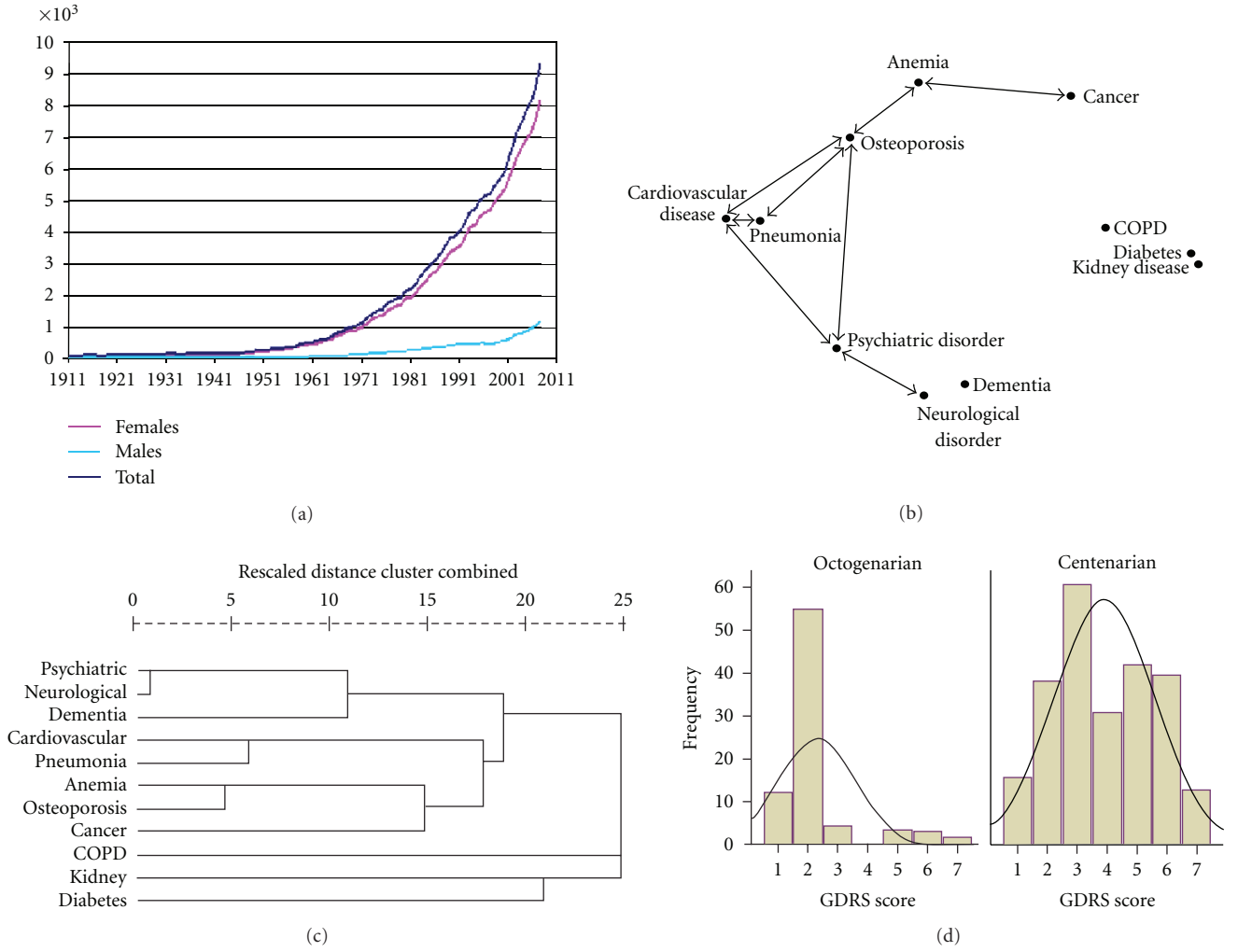

Figure 1: (a) Exponential growth of Centenarians in England over the last century [2]. (b) Network of morbidity in centenarians in the GCS [3] using lifetime prevalence of 11 most common chronic diseases in the GCS. All pairwise associations that were not significant by an exact test were set to zero, and the remaining significant (with $\alpha = 0.05$) pairwise correlations (r_{xy}) between chronic diseases x and y were all positive. These significant pairwise positive associations were graphically rendered using the distance 1-r_{xy} and multi-dimensional scaling [9] to compute coordinates for the chronic diseases. The coordinates were then graphed as a network [10]. COPD denotes chronic pulmonary obstruction disease. Chronic and acute pneumonia were not distinguished in the medical questionnaire. (c) Average linkage [11] was used to compute a dendrogram independently relating the 11 chronic diseases based on their pairwise correlations r_{xy}. (d) The distribution of GDRS scores [12] in centenarians is compared with the distribution of GDRS scores in 80 octogenarians as a control group. A GDRS score of 4–7 is indicative of dementia, a score of 3, of mild cognitive impairment, and a score of 1-2, as unaffected.

counties in 4 strata, which were compared for sample characteristics with the 2000 US Census in Table 1. There is a reasonable agreement between the 2000 Census and the sample in the GCS with a slight under-representation of African-Americans. Sampling weights were developed to match sample characteristics with the 2000 Census profile (see Supplement). Statistical analyses below were performed with and without these weights with no change in conclusions. To address appropriately our own successful aging, we first need to answer the following questions: at 100 years of age, (i) will we be cognitively intact? (ii) what will be our emotional state? (iii) how likely is it that we will be coping with a chronic disease [4]? (iv) what chronic diseases will we need to cope with? (v) when will we experience a chronic disease?

2. Materials and Methods

The recruitment rate (i.e., the percentage of those participating out of those contacted) was 67.2% for centenarians and 46.0%, for octogenarians. Data on GCS participants were collected under Institutional Review Board approval and Human Subjects consent and are deposited in the Georgia Centenarian Database [5]. In contrast to Phase 1 and Phase 2 of the GCS, centenarians in Phase 3 here spanned a wide range of functional capacity from being bedbound in a nursing home to living independently in the community [3]. Demographic and medical histories of GCS participants were collected onto computer generated questionnaires and completed in 4, ~2 hour interviews with GCS participants. Sources for answers on the health

Table 1: Demographics of 2000 Census in Georgia and GCS study participants. In (b) and (c) entries for Participants and 2000 Census are for centenarians and near-centenarians.

(a) Age Distribution, 2000 Census versus GCS Participants

	Participants		2000 Census	
Age	Number	Percent	Number	Percent
98	61	25%	362	30%
99	48	20	275	23
100–104	126	52	526	42
105+	9	4	81	6
TOTAL	244	100%	1244	100%

(b) Gender Distribution, 2000 Census versus Participants

	Participants		2000 Census	
Gender	Number	Percent	Number	Percent
Male	37	15%	237	19%
Female	207	85	1007	81
TOTAL	244	100%	1244	100%

(c) Race Distribution, 2000 Census versus Participants

	Participants		2000 Census	
Race	Number	Percent	Number	Percent
Black	52	21%	397	32%
Non-Black	192	79	847	68
TOTAL	244	100%	1244	100%

questionnaire were participants, their legal proxy, care professionals in NHs or PCHs, and medical charts at NHs or PCHs. The health questionnaire included medical history, current problems (such as, bedbound status, assistive devices, and restricted activity days), medications/oxygen, physical examination (including vital signs, skin fold/Arm Circumference and hand grip, hearing, vision, fine motor testing, lower leg extension, foot sensory, weight/height, and shoulder flexion and vision test), EPESE and PPME tests of functional capacity (including standing balance, 8-foot walk, chair stands, step-up, and Bed Mobility), gross physical abnormalities, global assessment of physical health, and GDS [6]. International Disease Classification 9 (ICD-9) provided a framework for constructing the health questionnaire. More details on data collected have been previously given [3]. The instruments available at http://qa.genetics.uga.edu/ were then scanned into a Teleform database [5], checked, corrected, and verified and saved as individual pdf images for loading into the Georgia Centenarian Database [5]. A serious issue in centenarian studies is age validation [7]. The GCS employed internationally-established criteria in age verification [8]. The principal guideline is that chronological age must be validated by convergent multiple and creditable sources and public records, such as birth and marriage certificates of the individuals as well as their offspring and relatives to create a consistent chronology. Driver's licenses, Social Security documents, census records, as well as death records of offspring are used.

To validate medical histories on centenarians, nonfasting blood samples were drawn by a skilled phlebotomist as previously described [3]. From these blood samples, glycated hemoglobin (HbA1c) and hemoglobin levels were assessed by a clinical diagnostic laboratory (LabCorp, Inc., Burlington, NC) and used for diagnosis of diabetes and anemia, respectively. Dementia status was also cross-validated by a combined neuropathological and clinical consensus report on 66 centenarians, who consented to neuropsychology followup and brain donation postmortem [3]. Results are to be reported elsewhere.

A multinomial logistic response model was fitted to the study data [13] with SPSS Software at (http://www.spss.com/). The response was whether or not a centenarian is a survivor (S), delayer (D), escaper (E), or other (O) with probability π_{ij}, where i indexes all levels of the independent variables, sex, race, institutional status, education, body mass index, use of tobacco (i.e., the ith subpopulation), and the 11 indicators of chronic diseases found in Figure 1(b) and j = S, D, E, or O. Using a "[" for closed and ")" for open as a standard mathematical notation, a survivor of chronic diseases is a centenarian who first experiences chronic diseases in earlier years from [0,80). A delayer is a centenarian who only first experiences chronic diseases late in life from [80,98), and an escaper is a centenarian who only encounters chronic diseases at the very end of life at 98 or older. These definitions of survivor, delayer, and escaper differ slightly from those in [4] by using a cutoff of 98 (instead of 100) for the escaper category and by using a different list of chronic diseases in Figure 1(b). For the multinomial response model here, we use all 11 chronic diseases in Figure 1(b) to define survivor, delayer, or escaper. More restrictive definitions for particular disease classes are also examined in the Results and Discussion (see Table 3).

The log-likelihood is product-multinomial and proportional to

$$l(B) = \sum_{i}^{m}\sum_{j}^{J} n_{ij} \ln\left(\pi_{ij}\right). \tag{1}$$

The cell probabilities π_{ij} are determined by the independent variables and given by

$$\pi_{ij} = \frac{\exp\left(x_i'\beta_j\right)}{1 + \sum_{k=1}^{J-1} \exp\left(x_i'\beta_k\right)}, \tag{2}$$

where x_i' is the vector of observations on the ith subpopulation and β_j is the vector of regression coefficients for the jth response. The reference response is J. The Other (O) category arose when there were missing data, and the reference response was survivor (S). The model was fitted by the method of maximum likelihood [13].

3. Results and Discussion

Will we be cognitively intact? The prevalence of cognitively intact centenarians is still being debated. There is broad variation (27%–100%) in the literature [3] about the

Table 2: The lifetime prevalences of psychiatric disorders other than dementia in centenarians versus octogenarian control group in GCS [3] do not differ.

Disease*	Octogenarians (%)	Centenarians (%)	Total #
Dementia	13 (14%)*	136 (57%)*	321
Depression	14 (17.5%)	36 (14.8%)	324
Anxiety	5 (6.3%)	17 (7.0%)	324
Psychosis	1 (1.3%)	6 (2.5%)	324
Total	33	185	324

*The row categories are not mutually exclusive, but dementia tends to be positively associated with psychiatric disorders (Figure 1(b)). The association of Dementia with age (Control versus Centenarian) is significant with $P < .00001$ by Fisher's Exact test [14] for a 2×2 table, but the associations of Depression, Anxiety, and Psychosis individually with age (Control versus Centenarian) are not significant with $P > .05$. If we combine mental health across Depression, Anxiety, and Psychosis and test for association with age (Control versus Centenarian) by Fisher's Exact test [14] for a 2×2 table, the association of the aggregate variable indicating Depression, Anxiety, or Psychosis with age is not significant. The percents reported in this table are among 80 octogenarians or 244 centenarians.

prevalence of dementia in centenarians partially due to differences in assessment methods and partially due to age, gender, race, educational attainment ratios, and sampling techniques (e.g., convenience samples versus population-based samples). Sampling methods can be vital to the results when one considers that the functional capacity of centenarians varies dramatically from one extreme of a Nobel Laureate [15], Dr. Rita Levi-Montalcini, who serves currently in the Italian Senate, to someone needing the support of a nursing home. A Global Deterioration Scale (GDRS) battery [12] was administered to GCS participants. Dementia is scored when an individual receives a score of 4–7 on the GDRS. As shown in Figure 1(d), approximately half of centenarians (57%) scored as having dementia, while the majority of octogenarians were cognitively intact.

What will be our emotional state once we reach 100? Based on a health history questionnaire, centenarians do not appear to experience more depression, anxiety, or psychoses relative to octogenarian controls (Table 2). This is surprising because the prevalence of dementia, which is associated with psychiatric and neurological diseases (Figure 1(b)), is significantly higher in centenarians versus octogenarians (Figure 1(d)). To validate concurrently these findings, centenarians and the control group were compared on the Geriatric Depression Scale (GDS) [6] short form (Figure 2(f)). The short form GDS has a range from 1 to 15, with 6–10 suggestive of depression and 11–15 almost always indicative of depression. In Figure 2(f), there is a significant difference by a t-test ($t = 3.68$, df $= 296$, $P < .001$) in the mean GDS between centenarians and octogenarians. What this means is that while there is no evidence for a difference in lifetime prevalences of psychiatric disorders (other than dementia) in Table 2, there is a subclinical difference in level of depression.

How likely is it that we will be coping with a chronic disease? There are three mutually exclusive avenues to 100 in this study [4]. We can be survivors of chronic diseases in earlier years from 0–80. Alternatively, we can be delayers and only first experience chronic disease late in life from 80–98, or we can be escapers and only encounter chronic disease at the very end of life at 98 or older. The avenue by which we achieve 100 years of age depends on the chronic disease encountered (Table 3c). There are significantly different outcomes with respect to cardiovascular disease and cancer when it comes to how we reach 100. For example, cardiovascular disease (i.e., congestive heart failure, myocardial infarction, high blood pressure, peripheral vascular disease, stroke, transient ischemic attack (TIA), or any other heart problems) has a more even distribution across the three avenues, while centenarians with cancer are mostly escapers (73%). Both categories, cardiovascular disease and cancer, aggregate across 8 or more distinct forms of cardiovascular disease or cancer.

We compared the avenues to 100 in the New England Centenarian Study (NECS) and GCS. These two studies differ in population, sampling methods, and chronic disease categories. Despite these differences, the NECS [4] percentage of survivors, delayers, and escapers is 38, 42, and 19%, respectively in Table 3a, which is similar (not significantly different by an exact test [14] in Table 3a) to the corresponding percentages in the GCS of 43, 36, and 17%, respectively. Matching to the NECS chronic disease, selection did not change this outcome (Table 3b). When all chronic diseases in Figure 1(b) are considered, the fraction

Table 3: Avenues by which we reach 100. Centenarians who first experience chronic disease before 80 are termed survivors. Centenarians who first experience chronic disease in the interval 80–98 years of age are termed delayers. Centenarians who experience chronic disease only at 98 or older are termed escapers. (a) Fraction of survivors, delayers, and escapers in the GCS [3] and NECS [4] studies. (b) Fraction of survivors, delayers, and escapers in the GCS and NECS studies when matched on the chronic diseases of NECS. (c) Fraction of survivors, delayers, and escapers by disease.

(a) Avenue to 100 in GCS ($N = 244$) and NECS studies ($N = 424$)

Avenue	Survivor (%)	Delayer (%)	Escaper (%)
GCS	43	36	17
NECS	38	42	19

Outcomes (columns) are not significantly different by exact test ($P = .27$) [14].

(b) Avenue to 100 in GCS and NECS studies when matched on chronic diseases

Avenue	Survivor (%)	Delayer (%)	Escaper (%)
GCS	35	35	24
NECS	38	42	19

Outcomes (columns) are not significantly different by exact test ($P = .14$) [14].

(c) Avenue to 100 in GCS dependent on disease category

Avenue	Survivor (%)	Delayer (%)	Escaper (%)
Cardiovascular disease	24	39	32
Cancer	11	14	73

Outcomes (columns) are significantly different ($P < .0001$) between disease categories by an exact test [14].

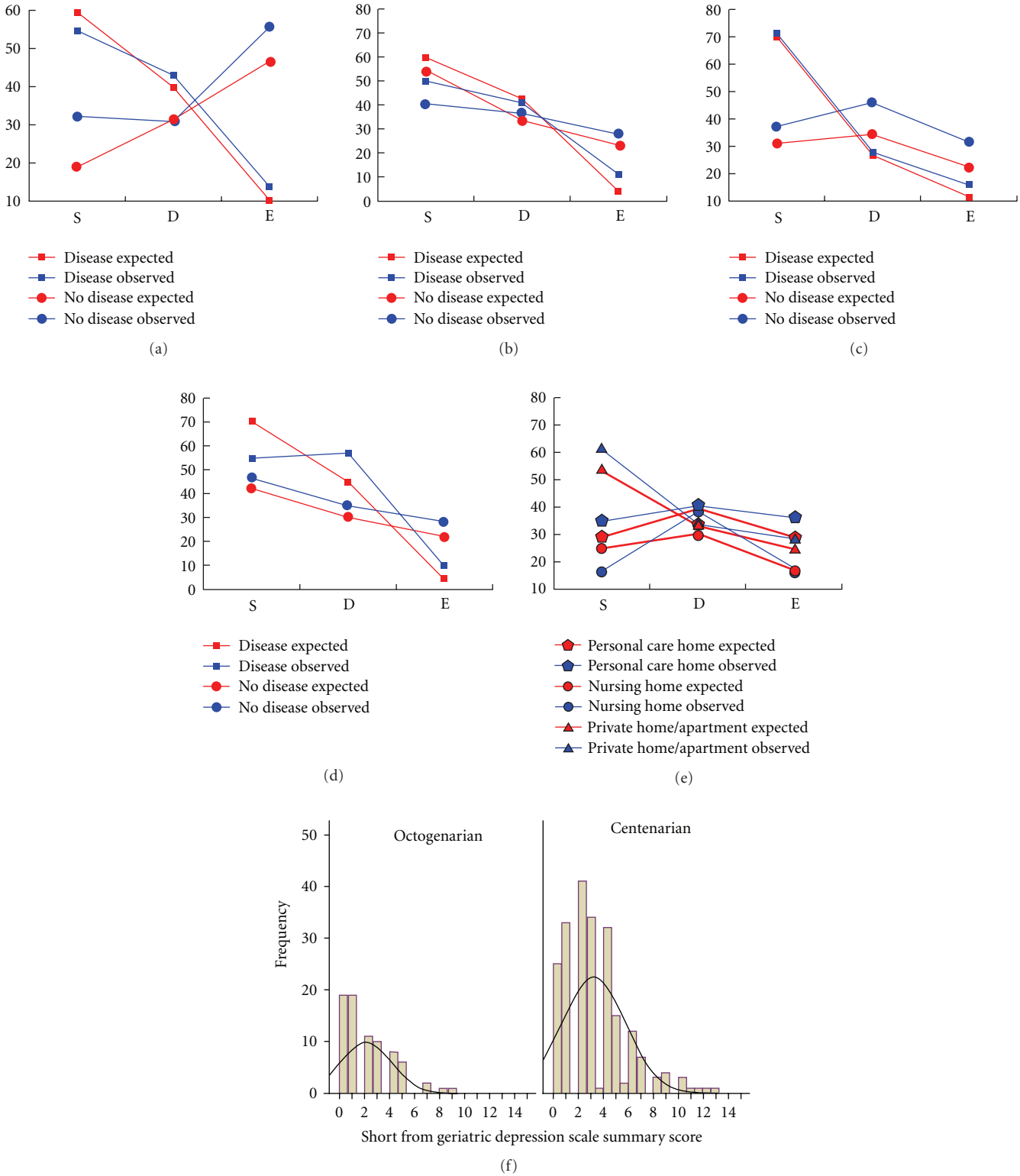

FIGURE 2: The factors of cardiovascular disease (a), cancer (b), pneumonia (c), psychiatric disorders (d), and living arrangement (e) determine the fraction of survivors, delayers, and escapers [4] among centenarians. The observed (in blue) and expected proportions (in red) track each other in that the logistic multinomial model well predicts the outcome of a being a survivor (S), delayer (D), or escaper (E) [4]. In panels (a)–(e), a square indicates the presence of a disease and a circle, the absence of a disease. (f). Centenarians were higher (with mean of 3.21 and standard deviation of 2.56) on the Geriatric Depression Scale (GDS) [6] than the control group of octogenarians (with mean of 2.13 and standard deviation of 2.62). The proportion (15.5%) of centenarians with GDS from 6–15 is significantly different from that proportion (4.6%) in octogenarians ($Z = 3.13, P < .001$).

Table 4: Age at onset of chronic disease and lifetime prevalence in control group of 80 octogenarians versus 244 centenarians. To correct for right censoring due to GCS study termination a stepwise Cox Regression [17] from survival analysis was performed to estimate average age at onset in centenarians. The average age at onset from the Cox regression [17] was computed at the mean of the covariates.

(a)

Disease	Average Age at Onset	n	Average Age at Onset from Cox regression	n
Cancer*	78±3	22	60±0.5	238
Cardiovascular	83±1	181	77±0.3	226

*Many cancers are absent, and skin cancers were excluded because of their later onset. The n above differs from the totals in (**b**) due to missing data.

(b)

Disease	No cancer	Cancer	Total
Octogenarians	58	22 (28%)	80
Centenarians	171	73 (30%)	244
Total	229	95 (29%)	324

A Fisher's exact test [14] is not significant at $\alpha = 0.05$, nor is a z-test, significant, with $z = 0.90$ on the proportions, 0.28 and 0.30.

(c)

Disease	No Cardiovascular	Cardiovascular	Total
Octogenarians	19	61 (76%)	80
Centenarians	48	196 (80%)	244
Total	67	257 (79%)	324

A Fisher's exact test [14] is not significant at $\alpha = 0.05$, nor is a z-test, significant, with $z = 1.80$ on the proportions, 0.76 and 0.80.

of escapers is relatively small among centenarians (17–24% in Table 3). This percentage is also very similar to a Danish nearly complete longitudinal, 1905 birth cohort study of successful aging in 40,000 Danes with 19% escapers [16].

Based on these survivorship outcomes and their apparent stability across three studies, we can make predictions about the cohort beginning in the year 2060. To do so we add one more category, the attritor, who never survives to be a centenarian. For the original cohort yielding the GCS centenarians, only about 0.0002 became centenarians now, and 0.9998 are attritors. For the cohort originating in 2060 [1], we would expect that ~0.5 will live to be centenarians, that is will not be attritors. Our prediction on the challenge to entitlement systems in the next century is that the percentages of escapers, delayers, survivors, and attritors will be 8.5%, 18%, 21.5%, and 50%, where for example $8.5\% = 100 \times (0.5) \times (0.17)$. Other factors affecting this prediction are now discussed.

Both genetic and environmental factors influence successful aging [18–21], particularly the successful outcome of no chronic diseases until very late in life. Other factors that might influence the three avenues to 100 include a participant's sex, race, institutional status (i.e., living in the community, PCH, or NH), education, chronic diseases experienced, body mass index, and smoking. A multinomial response model was fitted [13] stepwise to data on GCS centenarians in which the response was a centenarian classified as survivor, delayer, escaper, or other (missing data for 8 centenarians), and the independent variables were sex, race, institutional status, education, tobacco use, body mass index, and 11 chronic diseases in Figure 1(b) including dementia. The results in Table 4 and Figures 2(a)–2(e) display the significant factors (by likelihood ratio test with significance level of 0.05) to be lifetime prevalence of psychiatric disorder(s), cardiovascular disease, cancer and past prevalence of pneumonia as well as institutional status (i.e., living in the community, PCH, or NH). Goodness of fit for this multinomial response model is adequate (Pearson $\chi^2 = 59.5$ with df = 78). The Cox and Snell pseudo-R^2 was computed [13] as ~0.39. The influence of these five factors on the probability of being a survivor, delayer, or escaper is shown in Figures 2(a)–2(e) as well as the graphical fit of the model to the data. Being at risk for cardiovascular disease, cancer, and psychiatric disorders decreases the chance of becoming a delayer or escaper (Figures 2(a), 2(b), and 2(d)). Institutional status drops out as significant if the response categories of survivor and other are collapsed together.

Distal variables, such as level of education, mother's education, childhood health, and number of major life events (marriage, divorce, loss of spouse, etc.) for each centenarian can have an impact on current health [22]. Only for a subset of GCS participants (97) were all of these distal variables available. The number of major life events was significant ($P < .014$) in a stepwise fitting procedure to predict a centenarian's outcome as survivor, delayer, or escaper (see Materials and Methods). Goodness of fit remained adequate with the addition of this distal variable (Pearson $\chi^2 = 75.9$ with df = 90). The Cox and Snell pseudo-R^2 increased to 0.51 with this one additional independent variable, indicating distal variables do help to predict survival outcome.

What chronic diseases will we need to cope with? Individuals in the GCS were characterized by their history of chronic diseases based on medical histories and an extensive battery of psychosocial tests. The positive associations (edges) between the 11 most frequent chronic diseases (nodes) of centenarians are graphically rendered by multidimensional scaling and network software [9, 10] (Figure 1(b)). There appear to be two clusters of chronic diseases: one resembles a multicausal cluster having such common causes/determinants as smoking, imbalanced nutrition, sedentary lifestyle, and includes cardiovascular disease, pneumonia, osteoporosis, anemia, and cancer; and a second cluster including dementia, psychiatric disorders, and neurological disorders. Those diseases that are connected are significantly associated by an exact test [14] ($\alpha = 0.05$) of diseases X and Y, in which centenarians are classified by disease status for diseases X and Y in a 2×2 table. The two clusters were independently generated by clustering using average linkage [11] (Figure 1(c)).

The fact that dementia does not correlate with cardiovascular disease may at first sight seem surprising. This is, however, not the first time this observation has been made. In the Nun study [23], dementia did not necessarily correlate

Table 5: Lifetime Prevalence of chronic diseases among centenarians in the GCS.

	Prevalence		Prevalence	
Chronic Disease	Male (%)	Female (%)	Pooled over sexes (%)	Number of centenarians
cardiovascular	27 (73)	169 (82)	196 (80)	244
dementia	15 (41)	121 (60)*	136 (57)	240$
pneumonia	15 (41)	90 (43)	105 (43)	244
cancer	14 (38)	59 (29)	73 (30)	244
osteoporosis	1 (3)	58 (28)***	59 (24)	244
psychiatric	2 (5)	45 (22)*	47 (19)	244
anemia	5 (14)	37 (18)	42 (17)	244
diabetes	3 (8)	18 (9)	21 (9)	244
kidney	7 (19)	11 (5)**	18 (7)	244
neurological	4 (11)	11 (5)	15 (6)	244
COPD	2 (5)	2 (1)	4 (2)	244

*$P < .05$ by Fisher's Exact Test of disease associated with sex [19]; **$P < .01$ by Fisher's Exact Test of disease associated with sex [19];***$P < .001$ by Fisher's Exact test of disease associated with sex [19].
$Four centenarians had missing data.

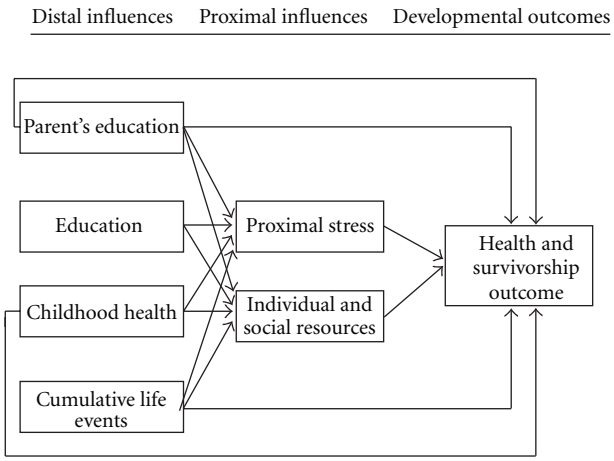

Figure 3: Developmental Adaptation: The influence of distal variables (e.g., cumulative life events, parents' education, education, and childhood health) on adaptational outcomes in very late life.

with neuropathology. There are in fact at least two forms of dementia, Alzheimer's disease and vascular dementia [24] with the latter being much less prevalent and correlated with vascular disease. In centenarians, only 12% of the cases of dementia were reported as vascular dementia [25]. The low prevalence of vascular dementia could be one explanation for the lack of correlation with dementia as scored by the GDRS in Figure 1(d), which does not distinguish the two forms of dementia. As discussed in the next section, cancer and cardiovascular disease have an earlier presentation than dementia. It is possible that other factors, such as coping mechanisms with stress and lifestyle (Figure 3), can also intervene to affect dementia status at 80 years of age and beyond and weaken the association further.

In some cases, the chronic condition reported in medical histories could be independently validated. For example, diabetes can be independently validated by glycated Hemoglobin (HbA1C) levels (a cutoff >7% is indicative of diabetes), and a declaration of diabetes by HbA1c levels is highly associated with reports from medical histories by Fisher's Exact test in both centenarians and octogenarians ($P < .005$). As a second example hemoglobin (Hb) levels (in grams/deciliter or g/dL) were determined on centenarians and octogenarians. When GCS participants are classified as anemic using a cutoff of 12 g/dL in females and 13 g/dL in males, an exact test of association between these two classifications of GCS participants for anemia is $P = .05$. There is underreporting of anemia from medical histories relative to anemia defined from participant Hb levels.

A summary of the prevalent chronic diseases among centenarians is summarized in Table 5. Cardiovascular disease and dementia are the most prevalent chronic diseases among centenarians. For some conditions, such as osteoporosis, dementia, and psychiatric disorders, the prevalence differs significantly between the sexes.

When will we experience a chronic disease? For centenarians, the development of chronic diseases varies by type. It is clear from Figure 1(d) that the prevalence of dementia rises sharply between the ninth and eleventh decade of life. A similar question is addressed about age of onset for cancers and cardiovascular disease among centenarians in Table 4b. Cancers (with the exception of skin cancers) tend to have early onset in the eighth decade (seventies) of life, and as a consequence we saw no difference in their frequency between octogenarians and centenarians (Table 4b). In contrast, cardiovascular disease has a later onset in the ninth decade of life in GCS (Table 4a). This presents a puzzle for why there is no difference in proportions between centenarians and octogenarians in cardiovascular disease (Table 4b). To correct for right censoring and to address this puzzle, we performed a separate Cox-regression analysis [17] on age at onset for cancer and cardiovascular disease as a function of the covariates used in the multinomial response modeling with race being a significant factor in a stepwise Cox-regression analysis of cancer age at onset. The effect of the Cox regression was to shift the estimated means of cancer and cardiovascular disease earlier to 60 and 77 years

of age, respectively. The earlier mean onset corrected for right censoring then explains why in Table 4b there is no difference in lifetime prevalence of cardiovascular disease between octogenarians and centenarians. In that GCS is a cross-sectional study, there is a need to validate this temporal pattern of barriers to successful aging being cancer and then cardiovascular disease in cohort studies [16, 18].

In summary, our data show that there are 11 chronic diseases that centenarians are likely to experience late in life. These diseases fall into two morbidity clusters, one involving such diseases as cardiovascular disease, cancer, anemia, and osteoporosis, and another cluster associated with dementia. These chronic diseases pose three major barriers to successful aging. In their sixties centenarians are at risk for cancer. In their seventies they are at risk for cardiovascular disease. In their eighties and beyond they are at risk for dementia. Approximately half (43%) of the centenarians did not experience dementia. Approximately 17% of the GCS centenarians escaped chronic disease till near the end of their life, while 36% delayed the onset into the 80's and 90's and 43% survived chronic diseases acquired earlier in life (<80 years of age). These proportions of escapers, delayers, and survivors serve as predictions for the 2060 cohort with median life expectancy of 100 in this population. The caveats on such a prediction include no cohort effects (i.e., war, disease, major health advance, or changes in the predictors in Figure 2) beyond those leading to the increase in life expectancy of 2.5 years per decade. With the exception of dementia, mental health status did not differ between centenarians and octogenarians, although levels of depressive symptomatology appeared to be higher on the GDS scale in centenarians than octogenarians. Consistent with our model of developmental adaptation [22] (Figure 3), distal life events contribute to predicting survivorship outcome. The morbidity classification put forth by the NECS [4] and current health status are critical adaptation variables in very late life.

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Authors Contributions

J. Arnold contributed to study design, analysis and interpretation, wrote the paper, and contributed to overall design of the study. S. M. Jazwinski contributed to study design, framed some of the questions addressed in this paper, advised on data collection, analysis, and interpretation. W. L. Rodgers developed and supervised the study sampling design. J. Dai developed software for study design and data analysis. A. Davey, I. C. Siegler, and L. W. Poon developed measures from the demographic and medical histories. A. K. and L. Nahapetyan carried out data analysis. M. A. Johnson and D.Hausman collected blood chemistry data in particular and supervised questionnaire collection in general. R.Hensley, P. Martin, and M. MacDonald formulated a study and collected data on distal variables, such as education, affecting health of centenarians. L. W. Poon led the design of the study, supervised the study, supervised data collection, advised on data analysis and interpretation, and supervised the design and analysis of cognitive measures employed.

References

[1] J. Oeppen and J. W. Vaupel, "Demography—broken limits to life expectancy," *Science*, vol. 296, no. 5570, pp. 1029–1031, 2002.

[2] 2008, http://www.statistics.gov.uk/cci/nugget.asp?id=1875.

[3] L. W. Poon and T. T. Perls, *Biopsychosocial Approaches to Longevity*, Springer, New York, NY, USA, 2008.

[4] J. Evert, E. Lawler, H. Bogan, and T. Perls, "Morbidity profiles of centenarians: survivors, delayers, and escapers," *Journals of Gerontology. Series A*, vol. 58, no. 3, pp. 232–237, 2003.

[5] J. Dai, A. Davey, I. C. Siegler, J. Arnold, and L. W. Poon, "GCSDB: an integrated database system for the Georgia Centenarian Study," *Bioinformation*, vol. 1, pp. 214–219, 2006.

[6] J. A. Yesavage, T. L. Brink, and T. L. Rose, "Development and validation of a geriatric depression screening scale: a preliminary report," *Journal of Psychiatric Research*, vol. 17, no. 1, pp. 37–49, 1982.

[7] B. Jeune and J. W. Vaupel, *Validation of Exceptional Longevity*, Odense University Press, Odense, Denmark, 1999.

[8] H. Maier, J. Gampe, and J.-M. Robine, *Supercentenarians*, Springer, New, York, NY, USA, 2010.

[9] J. B. Kruskal and M. Wish, *Multidimensional Scaling*, Sage Publications, Beverly Hills, Calif, USA, 1978.

[10] V. Pajek, V. Batagelj, and A. Mrvar, *Graph Drawing Software*, Springer, New York, NY, USA, 2003.

[11] J. A. Hartigan, *Clustering Algorithms*, John Wiley & Sons, New York, NY, USA, 1975.

[12] B. Reisberg, S. H. Ferris, M. J. De Leon, and T. Crook, "The global deterioration scale for assessment of primary degenerative dementia," *American Journal of Psychiatry*, vol. 139, no. 9, pp. 1136–1139, 1982.

[13] A. Agresti, *Categorical Data Analysis*, Wiley-Interscience, New York, NY, USA, 2002.

[14] C. R. Mehta and N. R. Patel, "Fexact—a fortran subroutine for fisher exact test on unordered RxC contingency-tables," *ACM Transactions on Mathematical Software*, vol. 12, no. 2, pp. 154–161, 1986.

[15] A. Abbott, "One hundred years of Rita," *Nature*, vol. 458, no. 7238, pp. 564–567, 2009.

[16] H. Engberg, A. Oksuzyan, B. Jeune, J. W. Vaupel, and K. Christensen, "Centenarians—a useful model for healthy aging? A 29-year follow-up of hospitalizations among 40000 Danes born in 1905," *Aging Cell*, vol. 8, no. 3, pp. 270–276, 2009.

[17] D. R. Cox and D. Oakes, *Analysis of Survival Data*, Chapman and Hall, London, UK, 1984.
[18] B. J. Willcox, D. C. Willcox, and L. Ferrucci, "Secrets of healthy aging and longevity from exceptional survivors around the globe: lessons from octogenarians to supercentenarians," *Journals of Gerontology. Series A*, vol. 63, no. 11, pp. 1181–1185, 2008.
[19] L. Fontana, L. Partridge, and V. D. Longo, "Extending healthy life span-from yeast to humans," *Science*, vol. 328, no. 5976, pp. 321–326, 2010.
[20] J. Vijg and J. Campisi, "Puzzles, promises and a cure for ageing," *Nature*, vol. 454, no. 7208, pp. 1065–1071, 2008.
[21] S. M. Jazwinski, S. Kim, J. Dai, et al., "HRAS1 and LASS1 with APOE are associated with human longevity and healthy aging," submitted to *Aging Cell*.
[22] P. Martin and M. Martin, "Proximal and distal influences on development: the model of developmental adaptation," *Developmental Review*, vol. 22, no. 1, pp. 78–96, 2002.
[23] D. A. Snowdon, "Aging and Alzheimer's disease: lessons from the Nun Study," *Gerontologist*, vol. 37, no. 2, pp. 150–156, 1997.
[24] B. L. Plassman, K. M. Langa, G. G. Fisher et al., "Prevalence of dementia in the United States: the aging, demographics, and memory study," *Neuroepidemiology*, vol. 29, no. 1-2, pp. 125–132, 2007.
[25] G. Ravaglia, P. Forti, D. De Ronchi et al., "Prevalence and severity of dementia among northern Italian centenarians," *Neurology*, vol. 53, no. 2, pp. 416–418, 1999.

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Research Article

Dynamic Determinants of Longevity and Exceptional Health

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It is well known from epidemiology that values of indices describing physiological state in a given age may influence human morbidity and mortality risks. Studies of connection between aging and life span suggest a possibility that dynamic properties of age trajectories of the physiological indices could also be important contributors to morbidity and mortality risks. In this paper we use data on longitudinal changes in body mass index, diastolic blood pressure, pulse pressure, pulse rate, blood glucose, hematocrit, and serum cholesterol in the Framingham Heart Study participants, to investigate this possibility in depth. We found that some of the variables describing individual dynamics of the age-associated changes in physiological indices influence human longevity and exceptional health more substantially than the variables describing physiological state. These newly identified variables are promising targets for prevention aiming to postpone onsets of common elderly diseases and increase longevity.

1. Introduction

Individual age trajectories of physiological indices result from complicated interplay among genetic and environmental (including behavioral) factors taking place during the aging process and so, they may differ substantially among individuals in cohort. Despite this fact the average age trajectories for the same index follow remarkable regularities. Figure 1 shows the average age trajectories of selected physiological indices evaluated from the data on the original cohort of the Framingham Heart Study (FHS).

One can see from this figure that some indices tend to change monotonically with age: the level of blood glucose (BG) increases almost monotonically; the pulse pressure (PP) increases from age 40 till age 85, then levels off and shows a tendency to decline only at later ages. The age trajectories of other indices are nonmonotonic: they tend to increase first and then decline. Physiological average body mass index (BMI) increases up to about age 70 and then declines, diastolic blood pressure (DBP) increases till age 55–60 and then declines, serum cholesterol (SCH) increases till age 50 in males, and till age 70 in females and then declines, pulse rate (PR) increases till age 55 in males and till age 45 in females and then declines, hematocrit (HC) declines after age 70 in both sexes. With small variations, these general patterns are similar in males and females.

The effects of these indices on mortality risk were studied in [1–3]. It was found that these effects are gender and age specific. The fact that the age dependence affects the shape of mortality risk function provided important insights into the mechanisms by which aging process affects the decline in stress resistance in individuals [4–6]. It was also found that dynamic properties of individual age trajectories of physiological indices may differ dramatically from one individual to the next.

Researchers continue the debates about determinants of the aging rate and about possible contribution of this rate to life span and healthy life span [7–17]. Since the rate of aging literally means the rate of changing with age, it would be reasonable to assume that individual differences in the aging rate are to be manifested in variability of dynamic properties of individual age trajectories of physiological indices. And if

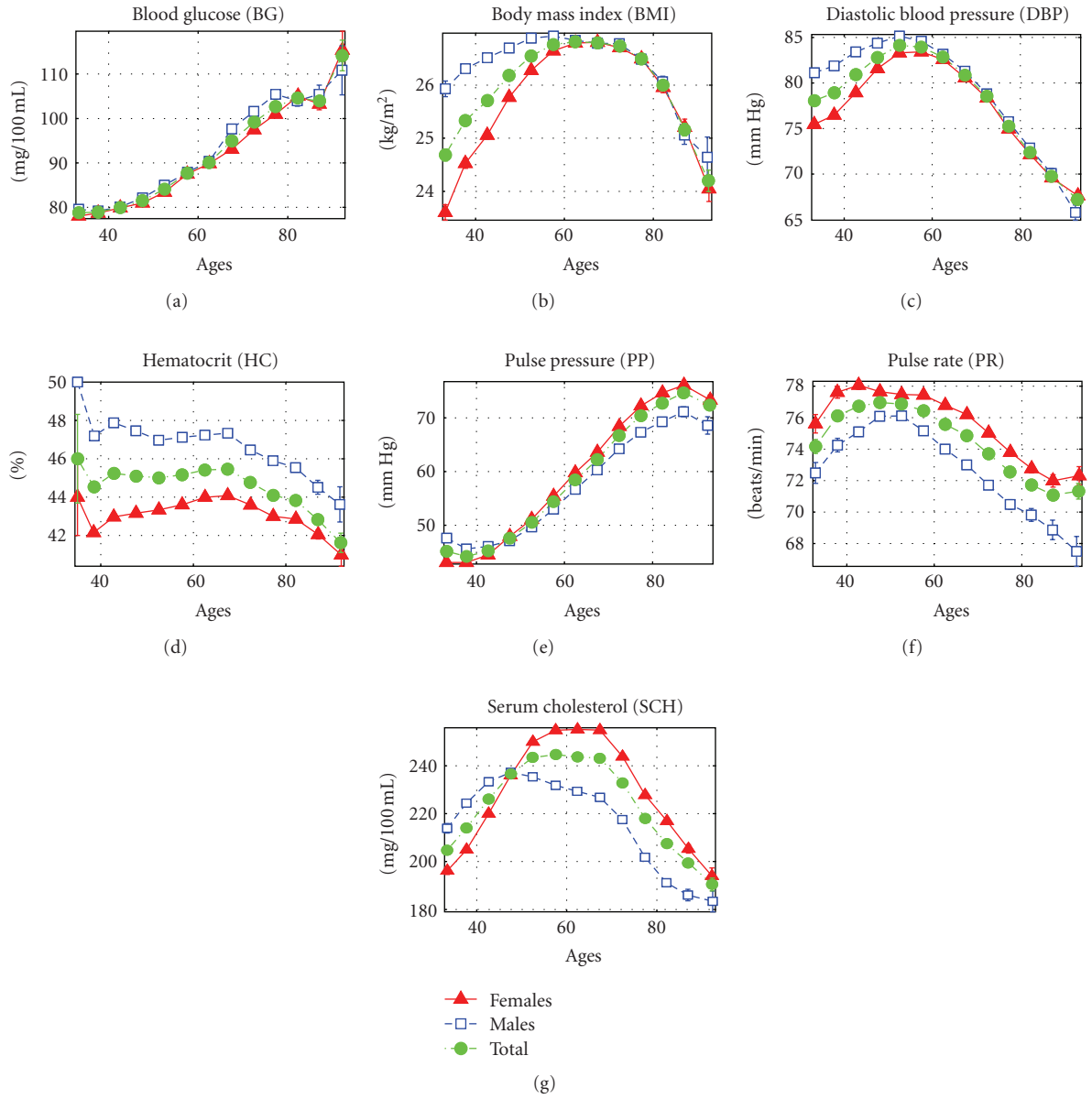

Figure 1: Mean values (± s.e.) of physiological indices in participants of the original cohort of the Framingham Heart Study (pooled data of available measurements from exams 1–25).

individual aging rate affects life span and healthy life span then one can expect that dynamic characteristics of such trajectories will affect morbidity and mortality risks.

A number of studies available in the literature support the view about the importance of using dynamic properties of individual age associated changes in physiological indices as the characteristics of aging process that predict morbidity and mortality risks, in addition to the use of the age-specific baseline measurements [18–24].

In this paper we investigate the effects of selected parameters describing the dynamic properties of the age trajectories of seven physiological indices on consequent morbidity and mortality risks in participants of the FHS original cohort.

2. Data and Method

2.1. The Framingham Heart Study (FHS). The FHS Original cohort was launched in 1948 (Exam 1), with 5,209 respondents (55% females) aged 28–62 years residing in Framingham, Massachusetts, who had not yet developed overt symptoms of cardiovascular disease, and continued to the present with biennial examinations (29 exams to date, data from exams 1–25 were used in this study) that include detailed medical history, physical exams, and laboratory tests.

2.2. Phenotypic Traits. Phenotypic traits collected in the FHS cohorts over 60 years and relevant to our analyses

include life span, ages at onset of diseases (with the emphasis on cardiovascular diseases (CVD), cancer, and diabetes mellitus), as well as indices characterizing physiological state. The occurrence of diseases (CVD and cancer) and death has been followed through continuous surveillance of hospital admissions, death registries, clinical exams, and other sources, so that all the respective events are included in the study. We used data on onset of CVD, cancer (calculated from the followup data) and diabetes (defined as the age at the first exam when an individual has a value of BG exceeding 140 mg/dl and/or takes insulin and/or oral hypoglycemic agent) to define the age at onset of "unhealthy life" as the minimum of ages at onset of these three diseases. If an individual did not contract any of these diseases during the observation period than the individual was considered censored at the age of the last followup or death. Individuals who had any of the diseases before the first FHS exam were excluded from the analyses of "unhealthy life." Data on physiological indices include random blood glucose (BG, exams 1–4, 6, 8–10, 13–23), body mass index (BMI, exams 1–25), diastolic blood pressure (DBP, exams 1–25), hematocrit (HC, exams 4–21), pulse pressure (PP, exams 1–25), pulse rate (PR, exams 1, 4–25), and serum cholesterol (SCH, exams 1–11, 13–15, 20, 22–25).

2.3. Definitions of "Dynamic" Risk Factors. We investigated dynamic properties of individual age trajectories of seven physiological indices mentioned above to select factors (referred to as "dynamic" risk factors) capable of affecting mortality risk and risk of onset of "unhealthy life." BG was excluded from the list of indices for analyses of onset of "unhealthy life" because in the FHS data the onset of diabetes is specifically defined from the values of BG.

First, we evaluated the effect of the rate of changes in physiological indices at ages 40–60 on mortality risk and risk of onset of "unhealthy life" at ages 60+. For this purpose, we approximated the individual trajectories of those physiological indices that have a nearly linear dynamics (both for females and males) at ages 40–60 (BG, BMI, HC, and PP) by a linear function of the form $y(x) = a_{40\text{–}60} + b_{40\text{–}60}(x - 40)$, where x is age and y is the value of a physiological index at age x. Individuals having less than 5 observations of respective index at ages 40–60 were excluded from the analyses. As a result, we have estimates of three risk factors for each individual and each index: an initial value of an index at age 40 (i.e., $a_{40\text{–}60}$, referred to as "$Intercept_{40\text{–}60}$" in Tables 1 and 2 and the text below), the rate of change in the physiological index at ages 40–60 ($b_{40\text{–}60}$, "$Slope_{40\text{–}60}$"), and the mean of absolute values of residuals, that is, deviations of observed values of an index from those approximated by a linear function at ages 40–60 ("$Variability_{40\text{–}60}$"). The joint effect of these risk factors on mortality and incidence of "unhealthy life" was estimated (separately for each physiological index) by the Cox proportional hazards model with delayed entry (the left truncation time was defined as the maximum of the age at the first FHS exam and 60). Respectively, individuals with ages at death (onset of "unhealthy life")/censoring below 60 were excluded from the analyses. Note that although the use of linear functions for describing individual aging-related changes is a rough approximation of monotonic changes, it captures important dynamic risk factor—the average rate of change of individual index at the age interval between 40 and 60 years.

Second, we evaluated the effect of dynamic characteristics of physiological indices with nonmonotonic age trajectories on mortality risk and risk of onset of "unhealthy life." For this purpose, we approximated the age trajectories of such indices (BMI, DBP, HC, PR, and SCH) by two linear functions. The first one approximates the increase in the trajectory at the initial interval $[x_L, x_{\max}]$: $y(x) = a_L + b_L(x - x_L)$, where x is age and y is the value of a physiological index at age x. The second one approximates the subsequent decline in the trajectory at the interval $[x_{\max}, x_R]$ after reaching the maximum value $y_{\max} = a_L + b_L(x_{\max} - x_L)$ at age $x_{\max}$: $y(x) = a_R + b_R(x - x_{\max})$. The intervals $[x_L, x_R]$ for the fit were defined empirically for each index and sex as follows: [35, 55] for PR (females); [40, 60] for PR (males) and SCH (males); [45, 65] for BMI (males) and DBP (females and males); [50, 70] for SCH (females); [55, 75] for BMI (females) and HC (females and males). Note that the following restrictions on parameters were used in the estimation procedures: $b_L > 0$, $b_R < 0$, and $a_R = a_L + b_L(x_{\max} - x_L)$ to ensure the appropriate shape of the fit. Individuals having less than 6 observations of respective index at ages $[x_L - 5, x_R + 5]$ and those having estimates of b_L, b_R at the boundary of allowable values (i.e., nearly zero) were excluded from the analyses. As a result, we have estimates of six risk factors for each individual and each index: an initial value of an index at age x_L (i.e., a_L, referred to as "$Intercept_{2L}$" in Tables 3 and 4 and the text below), the rate of increase in the physiological index at ages $[x_L, x_{\max}]$ (b_L, "*Left Slope*"), the maximal value of the index approximated by two linear functions describing increase and decline in respective individual indices ($y_{\max}$, "*Max Index*"), age at reaching the maximal value of the index ($x_{\max}$, "*Age Max*"), the rate of decline in the index at ages $[x_{\max}, x_R]$ (b_R, "*Right Slope*," see also Figure 2 for illustration), and the mean of absolute values of residuals, that is, deviations of observed values of an index from those approximated by two linear functions at ages $[x_L, x_R]$ ("$Variability_{2L}$"). The joint effect of these risk factors on mortality and incidence of "unhealthy life" was estimated (separately for each physiological index) by the Cox proportional hazards model with delayed entry (the left truncation time was defined as the maximum of the age at the first FHS exam and x_R). Respectively, individuals with ages at death (onset of "unhealthy life")/censoring below x_R were excluded from the analyses. If x_R is different for females and males for some index, then the maximum of the two values was used in the (sex-adjusted) model applied to that index. Note that all these calculations were performed for individual age trajectories of respective indices. As a result, each individual is now characterized by a vector of dynamic parameters.

We also evaluated the empirical (Kaplan-Meier) estimates of survival functions (and probabilities of staying free of the diseases defining the onset of "unhealthy life")

for individuals with different values of the dynamic risk factors based on the indices with nonmonotonic trajectories (separately for females and males). For each physiological index and each dynamic risk factor ("*Age Max,*" "*Max Index,*" "$Intercept_{2L}$," "*Left Slope,*" "*Right Slope,*" and "$Variability_{2L}$"), we calculated the values of the risk factor in all eligible individuals from the sample using the procedure described above. Then we evaluated the medians of such empirical distributions of risk factors, separately for females and males. These median values were used to define the sex-specific strata for estimation of survival curves. We assigned individuals of respective sex into one of two strata depending on whether the value of the risk factor for this individual is below (this stratum is denoted as "lower half" in Figures 3–6) or above (denoted as "upper half" in Figures 3–6) the (sex-specific) median value. In case of an odd number of individuals, the individual with the value of the risk factor equal to the median was assigned to the upper stratum. Then we calculated the Kaplan-Meier estimates of survival curves (conditional at the sex- and index-specific ages x_R) for individuals in these two strata. Note that individuals with ages at death (onset of "unhealthy life")/censoring below x_R were excluded from the analyses, as described above. Respective graphs are shown in Figures 3–6. For example, the median value of the right slopes calculated for BMI in females equals −0.103. Hence, individuals from the stratum denoted as "lower half" in the upper left graph of Figure 3 are females with values of the right slope of BMI smaller than −0.103. Individuals belonging to the stratum named "upper half" in the upper left graph of Figure 3 are females with values of the right slope of BMI larger than −0.103. The conditional survival curves for the two strata presented in this figure deal with individuals survived until age 75 years, which is the value of x_R for BMI in females, as described above.

2.4. Statistical Analyses. Statistical analyses and graphic output were performed with SAS/STAT (SAS Institute Inc.) and MATLAB (MathWorks Inc.) software packages. P values for the regression parameters in the tables were calculated using the Wald chi-square statistic with respect to a chi-square distribution with one degree of freedom using SAS/STAT PROC PHREG. The log-rank test was used to test the null hypotheses about the equality of the empirical survival curves in the strata. Respective P values are shown in Figures 3–6 (SAS/STAT PROC LIFETEST was used for these purposes).

3. Results

3.1. Effect of Individual Dynamics of Physiological Indices at Ages 40–60 on Mortality Risk and Risk of Onset of "Unhealthy Life" at Ages 60+. As described in Section 2, we evaluated the effect of individual dynamics of physiological indices at ages 40–60 on mortality risk and risk of onset of "unhealthy life" at ages 60+ for those indices that have a nearly linear pattern of change at the age interval 40–60 for both females and males. Table 1 shows the estimates of the joint effect

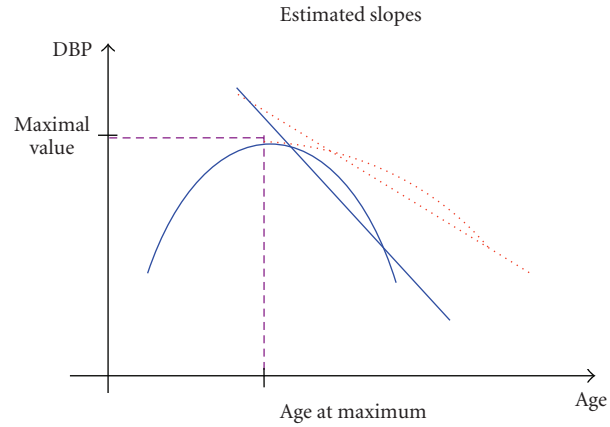

Figure 2: Dynamic characteristics of a hypothetical non-monotonically changing physiological index (denoted here "DBP") considered as potential risk factors: 1) Maximum value; 2) Age at which the maximum has been reached; 3) Average rate of decline after reaching the maximum. The figure illustrates evaluation of average rates of decline in two individuals having the same pattern of increase until reaching the maximum and different patterns of decline after reaching the maximum: a) the solid line for a rapidly declining index and its approximation by a straight line; b) the dotted line for a slowly declining index and its linear approximation. The slopes of respective straight lines are considered as risk factors for mortality and onset of "unhealthy life."

of these risk factors on mortality as evaluated by the Cox proportional hazards model. One can see from this table that the variability around the average linear trajectory ("$Variability_{40–60}$") and the average rate of change between ages 40 and 60 ("$Slope_{40–60}$") are significant risk factors for mortality for all indices. The significance is highest ($P < .0001$) for the slopes of HC and PP. The initial value of an index at age 40 ("$Intercept_{40–60}$") is also a highly significant ($P < .0001$) risk factor for mortality for HC and PP (i.e., higher values of respective index at age 40 correspond to higher risk of death compared to smaller values of this index), being nonsignificant for BG.

The effect of these dynamic characteristics on incidence of "unhealthy life" is similar (see Table 2). However, the variability is significant only for PP. Note that the effect of variable "*Sex*" on both mortality and risk of onset of "unhealthy life" is significant and that the risk for males is higher than those for females.

3.2. Effect of Dynamic Characteristics of Physiological Indices with Nonmonotonic Age Trajectories on Mortality Risk and Risk of Onset of "Unhealthy Life". For indices with nonmonotonic age trajectories, we evaluated the maximum value of respective index, age at which this maximum is reached, the intercept, and the left and right slopes of the linear functions approximating the increase and decline of respective indices as described in Section 2. Tables 3 and 4 show the estimates of the joint effect of these risk factors on mortality and incidence of "unhealthy life" as evaluated by the Cox proportional hazards model. One can see from

Table 1: Effect of "dynamic" risk factors calculated from individual trajectories of physiological indices at ages 40–60 on mortality risk at ages 60+ in the Framingham Heart Study (original cohort) estimated by the Cox proportional hazards model.

Physiological Index	Risk Factor (RF)	Mean RF (St. Dev.)	Cox Regression Model	
			Parameter (S.E.)	Hazard Ratio (95% C.I.)
BG ($N = 2224$, $N_e = 1447$, $N_c = 777$)	$\text{Intercept}_{40\text{–}60}$	77.468 (20.370)	0.003 (0.002)	1.056 (0.978, 1.140)
	$\text{Slope}_{40\text{–}60}$	0.553 (1.932)	0.059^{*} (0.029)	1.088 (1.002, 1.182)
	$\text{Variability}_{40\text{–}60}$	8.518 (6.798)	$0.017^{\#}$ (0.005)	1.086 (1.033, 1.141)
	Sex		$0.581^{\dagger}$ (0.053)	1.789 (1.611, 1.985)
BMI ($N = 3150$, $N_e = 2217$, $N_c = 933$)	$\text{Intercept}_{40\text{–}60}$	25.867 (4.215)	$0.016^{\#}$ (0.006)	1.086 (1.020, 1.157)
	$\text{Slope}_{40\text{–}60}$	0.050 (0.171)	-0.305^{*} (0.141)	0.945 (0.897, 0.995)
	$\text{Variability}_{40\text{–}60}$	0.697 (0.392)	$0.176^{\#}$ (0.060)	1.074 (1.024, 1.126)
	Sex		$0.564^{\dagger}$ (0.045)	1.757 (1.610, 1.918)
HC ($N = 2167$, $N_e = 1323$, $N_c = 844$)	$\text{Intercept}_{40\text{–}60}$	45.341 (4.664)	$0.086^{\dagger}$ (0.011)	1.622 (1.430, 1.839)
	$\text{Slope}_{40\text{–}60}$	−0.026 (0.272)	$0.932^{\dagger}$ (0.172)	1.311 (1.189, 1.446)
	$\text{Variability}_{40\text{–}60}$	1.548 (0.633)	0.089^{*} (0.044)	1.073 (1.002, 1.148)
	Sex		$0.255^{\S}$ (0.071)	1.291 (1.123, 1.484)
PP ($N = 3153$, $N_e = 2219$, $N_c = 934$)	$\text{Intercept}_{40\text{–}60}$	44.112 (13.095)	$0.024^{\dagger}$ (0.002)	1.349 (1.273, 1.428)
	$\text{Slope}_{40\text{–}60}$	0.506 (0.846)	$0.338^{\dagger}$ (0.035)	1.360 (1.277, 1.448)
	$\text{Variability}_{40\text{–}60}$	4.815 (2.032)	$0.036^{\#}$ (0.012)	1.090 (1.033, 1.150)
	Sex		$0.611^{\dagger}$ (0.044)	1.842 (1.691, 2.007)

Notes. $^{*}.01 \le P < .05$, $^{\#}.001 \le P < .01$, $^{\S}.0001 \le P < .001$, $^{\dagger}P < .0001$, for other estimates: $P \ge .05$; *Sex*: 1—male, 0—female; the other *Risk Factors* are continuous and calculated as described in Section 2; N denotes the total number of individuals; N_e is the total number of events (deaths); N_c is the total number of censored individuals; *Hazard Ratios* for continuous risk factors are for an increase from the first quartile to the third quartile of respective empirical distributions.

Table 2: Effect of "dynamic" risk factors calculated from individual trajectories of physiological indices at ages 40–60 on risk of onset of "unhealthy life" at ages 60+ in the Framingham Heart Study (original cohort) estimated by the Cox proportional hazards model.

Physiological Index	Risk Factor (RF)	Mean RF (St. Dev.)	Cox Regression Model	
			Parameter (S.E.)	Hazard Ratio (95% C.I.)
BMI ($N = 2458$, $N_e = 1824$, $N_c = 634$)	$\text{Intercept}_{40\text{–}60}$	25.587 (3.954)	$0.036^{\dagger}$ (0.007)	1.198 (1.119, 1.283)
	$\text{Slope}_{40\text{–}60}$	0.057 (0.162)	$0.609^{\S}$ (0.159)	1.116 (1.055, 1.180)
	$\text{Variability}_{40\text{–}60}$	0.679 (0.381)	0.013 (0.070)	1.005 (0.953, 1.060)
	Sex		$0.511^{\dagger}$ (0.049)	1.668 (1.513, 1.837)
HC ($N = 1659$, $N_e = 1192$, $N_c = 467$)	$\text{Intercept}_{40\text{–}60}$	45.044 (4.641)	$0.078^{\dagger}$ (0.012)	1.556 (1.365, 1.774)
	$\text{Slope}_{40\text{–}60}$	−0.021 (0.269)	$1.140^{\dagger}$ (0.182)	1.384 (1.250, 1.533)
	$\text{Variability}_{40\text{–}60}$	1.547 (0.635)	0.082 (0.046)	1.069 (0.993, 1.150)
	Sex		$0.287^{\dagger}$ (0.073)	1.332 (1.155, 1.536)
PP ($N = 2460$, $N_e = 1825$, $N_c = 635$)	$\text{Intercept}_{40\text{–}60}$	43.612 (12.635)	$0.018^{\dagger}$ (0.003)	1.249 (1.170, 1.334)
	$\text{Slope}_{40\text{–}60}$	0.480 (0.814)	$0.319^{\dagger}$ (0.040)	1.325 (1.237, 1.420)
	$\text{Variability}_{40\text{–}60}$	4.667 (1.944)	$0.046^{\S}$ (0.014)	1.111 (1.046, 1.181)
	Sex		$0.577^{\dagger}$ (0.048)	1.781 (1.622, 1.957)

Notes. $^{*}.01 \le P < .05$, $^{\#}.001 \le P < .01$, $^{\S}.0001 \le P < .001$, $^{\dagger}P < .0001$, for other estimates: $P \ge .05$; *Sex*: 1—male, 0—female; the other *Risk Factors* are continuous and calculated as described in Section 2; N denotes the total number of individuals; N_e is the total number of events (onset of "unhealthy life"); N_c is the total number of censored individuals; *Hazard Ratios* for continuous risk factors are for an increase from the first quartile to the third quartile of respective empirical distributions.

Table 3 that the effect of the rate of decline in the index after reaching the maximum ("*Right Slope*") on mortality risk is significant for all indices (the highest significance, $P < .0001$, is observed for BMI and DBP). In this case, the faster decline in the index after reaching the maximum corresponds to a significant increase in mortality risk (note that the values of "*Right Slope*" are negative by definition, see Section 2). On the contrary, the rate of increase in the index before reaching the maximum ("*Left Slope*") and the initial value from which the increase has started ("$Intercept_{2L}$") are not significant risk factors for mortality for any index. The estimated maximal value of the index reached is also a

Table 3: Effect of "dynamic" risk factors calculated from individual trajectories of physiological indices with nonmonotonic patterns on mortality risk in the Framingham Heart Study (original cohort) estimated by the Cox proportional hazards model.

Physiological Index	Risk Factor (RF)	Mean RF (St. Dev.)	Cox Regression Model	
			Parameter (S.E.)	Hazard Ratio (95% C.I.)
BMI ($N = 2686$, $N_e = 1824$, $N_c = 862$)	Age Max	62.063 (8.762)	−0.001 (0.004)	0.983 (0.887, 1.089)
	Max Index	27.869 (4.392)	−0.001 (0.012)	0.997 (0.884, 1.124)
	Intercept_{2L}	26.171 (4.187)	0.007 (0.012)	1.034 (0.925, 1.156)
	Left Slope	0.220 (0.505)	−0.017 (0.049)	0.996 (0.975, 1.018)
	Right Slope	−0.224 (0.576)	$-0.177^{\dagger}$ (0.025)	0.959 (0.948, 0.970)
	Variability_{2L}	0.729 (0.371)	$0.356^{\dagger}$ (0.073)	1.153 (1.088, 1.221)
	Sex		$0.561^{\dagger}$ (0.064)	1.753 (1.545, 1.989)
DBP ($N = 3133$, $N_e = 2242$, $N_c = 891$)	Age Max	55.165 (6.973)	-0.008^{*} (0.004)	0.903 (0.822, 0.992)
	Max Index	86.804 (10.465)	$0.016^{\dagger}$ (0.003)	1.245 (1.141, 1.358)
	Intercept_{2L}	80.471 (12.962)	0.001 (0.003)	1.008 (0.942, 1.079)
	Left Slope	0.842 (1.439)	0.006 (0.021)	1.006 (0.966, 1.047)
	Right Slope	−0.988 (1.976)	$-0.055^{\dagger}$ (0.010)	0.939 (0.918, 0.961)
	Variability_{2L}	3.984 (1.383)	$0.096^{\dagger}$ (0.016)	1.172 (1.114, 1.233)
	Sex		$0.514^{\dagger}$ (0.043)	1.671 (1.536, 1.818)
HC ($N = 2471$, $N_e = 1650$, $N_c = 821$)	Age Max	66.061 (7.020)	-0.009^{*} (0.004)	0.882 (0.795, 0.978)
	Max Index	46.567 (3.265)	0.024^{*} (0.012)	1.108 (1.003, 1.224)
	Intercept_{2L}	43.756 (4.848)	0.007 (0.008)	1.031 (0.960, 1.108)
	Left Slope	0.390 (0.733)	−0.011 (0.054)	0.996 (0.956, 1.037)
	Right Slope	−0.856 (3.533)	-0.018^{*} (0.007)	0.988 (0.979, 0.997)
	Variability_{2L}	1.472 (0.551)	0.099^{*} (0.045)	1.066 (1.006, 1.129)
	Sex		$0.398^{\dagger}$ (0.060)	1.488 (1.323, 1.675)
PR ($N = 1847$, $N_e = 1097$, $N_c = 750$)	Age Max	47.279 (7.676)	-0.012^{*} (0.005)	0.851 (0.742, 0.977)
	Max Index	81.206 (10.689)	$0.016^{\dagger}$ (0.004)	1.247 (1.126, 1.381)
	Intercept_{2L}	71.554 (15.226)	−0.002 (0.003)	0.979 (0.904, 1.059)
	Left Slope	1.535 (3.445)	0.007 (0.013)	1.011 (0.972, 1.052)
	Right Slope	−0.898 (1.980)	$-0.070^{\S}$ (0.021)	0.927 (0.886, 0.970)
	Variability_{2L}	5.057 (1.978)	0.028 (0.017)	1.070 (0.988, 1.159)
	Sex		$0.727^{\dagger}$ (0.070)	2.069 (1.804, 2.374)
SCH ($N = 2297$, $N_e = 1711$, $N_c = 586$)	Age Max	55.574 (8.298)	0.002 (0.005)	1.023 (0.923, 1.134)
	Max Index	261.965 (42.429)	0.001 (0.001)	1.059 (0.958, 1.170)
	Intercept_{2L}	225.428 (61.457)	−0.0003 (0.001)	0.981 (0.903, 1.066)
	Left Slope	5.517 (8.442)	−0.005 (0.005)	0.975 (0.921, 1.032)
	Right Slope	−4.121 (8.689)	-0.007^{*} (0.003)	0.969 (0.946, 0.993)
	Variability_{2L}	13.484 (6.237)	$0.014^{\#}$ (0.004)	1.101 (1.039, 1.166)
	Sex		$0.566^{\dagger}$ (0.073)	1.761 (1.526, 2.031)

Notes. $^{*}.01 \le P < .05$, $^{\#}.001 \le P < .01$, $^{\S}.0001 \le P < .001$, $^{\dagger}P < .0001$, for other estimates: $P \ge .05$; *Sex*: 1—male, 0—female; the other *Risk Factors* are continuous and calculated as described in Section 2; N denotes the total number of individuals; N_e is the total number of events (deaths); N_c is the total number of censored individuals; *Hazard Ratios* for continuous risk factors are for an increase from the first quartile to the third quartile of respective empirical distributions.

significant risk factor for mortality in case of DBP, PR (both have $P < .0001$), and HC ($P < .05$). This means that the larger (sex-adjusted) maximal values of respective indices (reached at "*Age Max*") correspond to a significant increase in mortality risk. The age at reaching the maximum is itself a significant risk factor for mortality for these indices. The negative values of respective estimates indicate that the later an individual reaches the maximum, the smaller mortality risk is. The variability in all indices except PR significantly affects mortality risks (the larger variability corresponds to higher mortality risks).

The effect of these dynamic characteristics on risk of onset of "unhealthy life" is less pronounced than that on mortality risks. Table 4 shows that the rate of decline after

Table 4: Effect of "dynamic" risk factors calculated from individual trajectories of physiological indices with nonmonotonic patterns on risk of onset of "unhealthy life" in the Framingham Heart Study (original cohort) estimated by the Cox proportional hazards model.

Physiological Index	Risk Factor (RF)	Mean RF (St. Dev.)	iCox Regression Model	
			Parameter (S.E.)	Hazard Ratio (95% C.I.)
BMI ($N = 1380$, $N_e = 782$, $N_c = 598$)	Age Max	63.199 (8.535)	0.012 (0.006)	1.189 (0.997, 1.417)
	Max Index	27.383 (4.016)	−0.011 (0.024)	0.947 (0.757, 1.186)
	Intercept_{2L}	25.696 (3.875)	0.037 (0.025)	1.184 (0.954, 1.469)
	Left Slope	0.194 (0.350)	0.340* (0.155)	1.073 (1.007, 1.143)
	Right Slope	−0.235 (0.801)	−0.041 (0.044)	0.991 (0.972, 1.011)
	Variability_{2L}	0.703 (0.359)	−0.007 (0.121)	0.997 (0.910, 1.092)
	Sex		0.497† (0.102)	1.644 (1.346, 2.009)
DBP ($N = 2139$, $N_e = 1512$, $N_c = 627$)	Age Max	55.325 (7.112)	−0.006 (0.004)	0.926 (0.827, 1.037)
	Max Index	85.806 (9.966)	0.017† (0.004)	1.239 (1.129, 1.360)
	Intercept_{2L}	79.309 (12.066)	0.001 (0.003)	1.013 (0.940, 1.093)
	Left Slope	0.912 (1.808)	0.009 (0.017)	1.008 (0.978, 1.040)
	Right Slope	−0.980 (2.390)	−0.014 (0.009)	0.986 (0.968, 1.004)
	Variability_{2L}	3.850 (1.311)	0.039 (0.020)	1.064 (0.999, 1.133)
	Sex		0.488† (0.053)	1.629 (1.470, 1.806)
HC ($N = 1254$, $N_e = 705$, $N_c = 549$)	Age Max	66.094 (7.125)	−0.011 (0.006)	0.863 (0.732, 1.017)
	Max Index	46.088 (3.141)	0.028 (0.018)	1.129 (0.967, 1.319)
	Intercept_{2L}	43.417 (3.810)	−0.002 (0.016)	0.990 (0.868, 1.130)
	Left Slope	0.372 (0.713)	−0.041 (0.078)	0.985 (0.933, 1.041)
	Right Slope	−0.775 (2.966)	0.0002 (0.013)	1.000 (0.985, 1.016)
	Variability_{2L}	1.442 (0.534)	0.033 (0.074)	1.021 (0.930, 1.122)
	Sex		0.363† (0.091)	1.438 (1.203, 1.718)
PR ($N = 1401$, $N_e = 1013$, $N_c = 388$)	Age Max	47.167 (7.589)	0.004 (0.005)	1.057 (0.921, 1.213)
	Max Index	80.449 (10.535)	0.009* (0.004)	1.129 (1.011, 1.262)
	Intercept_{2L}	71.162 (13.289)	−0.001 (0.004)	0.987 (0.893, 1.091)
	Left Slope	1.443 (3.034)	0.007 (0.013)	1.010 (0.973, 1.049)
	Right Slope	−0.850 (1.650)	0.013 (0.023)	1.014 (0.968, 1.062)
	Variability_{2L}	4.954 (1.936)	−0.002 (0.018)	0.994 (0.913, 1.082)
	Sex		0.569† (0.070)	1.766 (1.539, 2.025)
SCH ($N = 1361$, $N_e = 913$, $N_c = 448$)	Age Max	56.821 (8.200)	0.005 (0.006)	1.063 (0.908, 1.245)
	Max Index	261.843 (42.286)	0.002 (0.001)	1.120 (0.978, 1.282)
	Intercept_{2L}	225.919 (62.186)	−0.001 (0.001)	0.943 (0.854, 1.040)
	Left Slope	5.147 (8.013)	0.002 (0.007)	1.012 (0.936, 1.095)
	Right Slope	−4.329 (9.443)	−0.004 (0.004)	0.984 (0.952, 1.017)
	Variability_{2L}	13.452 (6.246)	0.010 (0.006)	1.070 (0.986, 1.161)
	Sex		0.595† (0.097)	1.813 (1.499, 2.192)

Notes. *$0.01 \le P < .05$, #$.001 \le P < .01$, §$.0001 \le P < .001$, †$P < .0001$, for other estimates: $P \ge .05$; *Sex:* 1—male, 0—female; the other *Risk Factors* are continuous and calculated as described in Section 2; N denotes the total number of individuals; N_e is the total number of events (onset of "unhealthy life"); N_c is the total number of censored individuals; *Hazard Ratios* for continuous risk factors are for an increase from the first quartile to the third quartile of respective empirical distributions.

reaching the maximum ("*Right Slope*"), age at reaching the maximum ("*Age Max*"), and the variability become nonsignificant for all indices. The maximal value reached is significant only for DBP ($P < .0001$) and PR ($P < .05$). The rate of increase of BMI before reaching the maximum becomes significant ($P < .05$), with the faster rate of increase corresponding to a higher risk of onset of "unhealthy life." Note again that the effect of variable "*Sex*" on both mortality and risk of onset of "unhealthy life" is significant and that the risk for males is higher than that for females.

3.3. Effect of Dichotomized Dynamic Characteristics of Physiological Indices with Nonmonotonic Age Trajectories. We also evaluated the Kaplan-Meier estimates of survival functions for individuals with different values of the dynamic risk

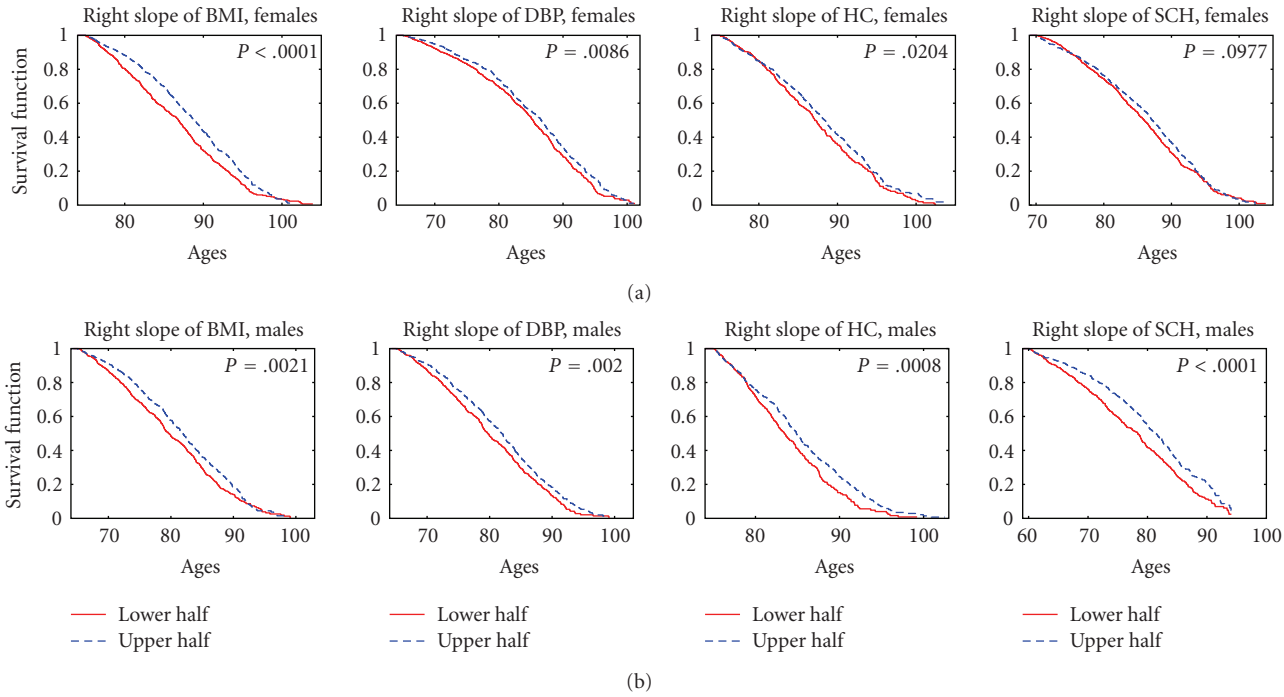

Figure 3: : Kaplan-Meier estimates of survival functions for females (a) and males (b) having the average rate of decline of different physiological indices after reaching the maximum ("right slope," see Section 2) from the lower and upper halves of empirical distributions of this risk factor for respective indices; P denotes P value for the null hypotheses about the equality of the survival curves in the strata evaluated by the log-rank test.

factors based on the indices with nonmonotonic trajectories dividing the entire sex-specific samples into strata representing individuals with the values of the index in the lower and upper halves of the empirical distribution of respective index (see Section 2).

Figure 3 shows the estimates of survival functions for females and males having the average rate of decline of different physiological indices after reaching the maximum ("*Right Slope*") from the lower and upper halves of empirical distributions of this risk factor for respective indices. One can see from this figure that the lower absolute values of the slope (i.e., the lower rates of the postmaximum decline) in individuals from the upper half of the distribution are associated with better survival for all indices except SCH for females (nonsignificant results for PR for both sexes are not shown). The highest significance ($P < .0001$) is observed for BMI in females and SCH in males.

Figure 4 illustrates similar estimates in case of "variability" of different physiological indices (the mean of absolute values of residuals, that is, deviations of observed values of an index from those approximated by two linear functions at respective age intervals, see Section 2). The higher "variability" of trajectories of BMI, DBP, and SCH at respective age intervals in individuals from the upper half of the distribution result in worse survival for both females and males (nonsignificant results for HC and PR are not shown). The highest significance ($P < .0001$) is observed for DBP in both females and males.

Later ages at reaching the maximal value of DBP and PR in females from the upper half of the distribution are associated with better survival (Figure 5), however this was not observed for males. The higher estimated maximal values of these indices in individuals from the upper half of the distribution correspond to worse survival for both females and males. All other indices did not produce any significant results and are not shown in Figure 5.

Similar calculations for probabilities of staying free of the diseases defining the onset of "unhealthy life" revealed a more mosaic picture. The most consistent results were observed for DBP (Figure 6).

The higher initial values of DBP at age 45 and the higher estimated values of DBP reached in individuals from the upper halves of respective distributions are associated with worse chances of staying free of the "unhealthy life," for both sexes. The lower rates of the postmaximum decline of DBP in females, but not males, from the upper half of the distribution correspond to better chances of staying free of the "unhealthy life" (Figure 6). In addition, earlier ages at reaching the maximum of SCH for females ($P = .008$), the smaller estimated maximal values of BMI ($P = .005$) and HC ($P = .02$) for females, and PR ($P = .001$) and SCH ($P = .017$) for males, and a smaller initial value of BMI at age 55 ($P = .001$) for females and a smaller initial value of SCH at age 40 ($P = .0004$) for males, were related to better chances of staying free of the "unhealthy life."

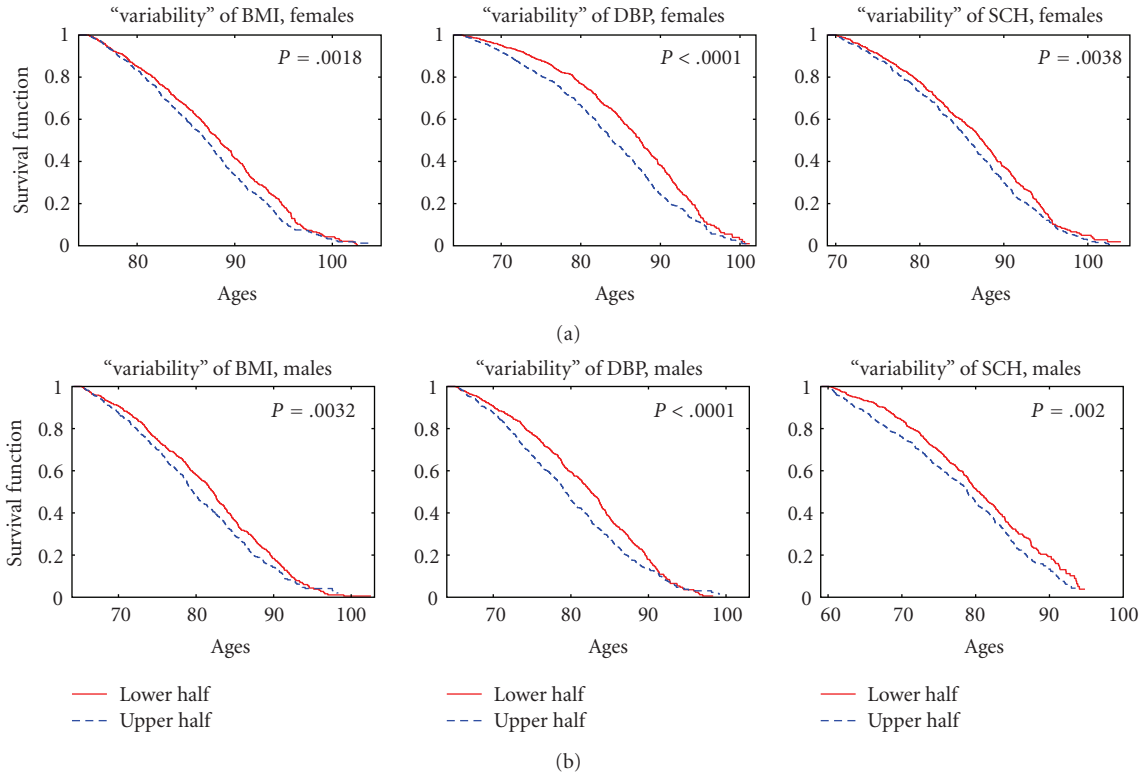

Figure 4: Kaplan-Meier estimates of survival functions for females (a) and males (b) having "variability" of different physiological indices (the mean of absolute values of residuals, i.e., deviations of observed values of an index from those approximated by two linear functions at respective age intervals, see Section 2) from the lower and upper halves of empirical distributions of this risk factor for respective indices; P denotes P value for the null hypotheses about the equality of the survival curves in the strata evaluated by the log-rank test.

3.4. Sensitivity Analyses. We should note that the question about the effect of the quality of estimates is important given that at most 11 observations for the monotone indices or 15 observations for non-monotone indices were used (note that for non-monotone indices data from 30-year intervals $[\mathbf{x_L} - \mathbf{5}, x_R + \mathbf{5}]$, where $x_R - \mathbf{x_L} = 20$, were used for calculating dynamic risk factors). These observations were used to estimate two parameters (those of the linear regression) for monotone indices and four parameters (age at reaching the maximal value of the index, intercept, and two slopes) for non-monotone indices. To partly reduce the effect of a poor fit due to a small number of longitudinal observations, we removed those individuals having less than 5 (less than 6 for non-monotone indices) observations from analyses. Clearly, the results could change had we used different numbers for the minimal allowable numbers of observations. To test how sensitive our results are to such changes, we performed sensitivity analyses with different minimal allowable numbers of observations: 4, 6, and 7 for monotone indices, and 5, 7, and 8 for non-monotone ones. The results showed that the effect of dynamic risk factors calculated from individual trajectories of monotone indices at ages 40–60 on mortality risk and risk of onset of "unhealthy life" at ages 60+ is stable across different studies. All risk factors for which the estimates of the regression parameters were significant ($P < .01$) in the original study, exhibited similar significant effects on mortality risk or risk of onset of "unhealthy life" in the other studies. Despite some variability in the values of the estimates across the studies, the "direction" of the effect (i.e., the sign of the estimate) was the same in all such cases. In the sensitivity analysis with the largest cutoff value, the P values were somewhat larger in some cases which may be explained by a smaller sample size compared to the original study. The effects of dynamic risk factors calculated from individual trajectories of physiological indices with nonmonotonic patterns on mortality risk and risk of onset of "unhealthy life" showed similar stability across the studies as the monotone indices. In all cases (except for the right slope of PR which appeared either marginally significant or nonsignificant in the other studies), risk factors for which the estimates of the regression parameters were significant ($P < .01$) in the original study exhibited similar significant effects on mortality risk or risk of onset of "unhealthy life" in other studies. The same observation regarding the sensitivity analysis based on the largest cutoff value was true for non-monotone risk factors too.

4. Discussion

An increase in mortality rate with age is traditionally associated with progressing aging. This influence is mediated by the aging-associated changes in thousands of biological and

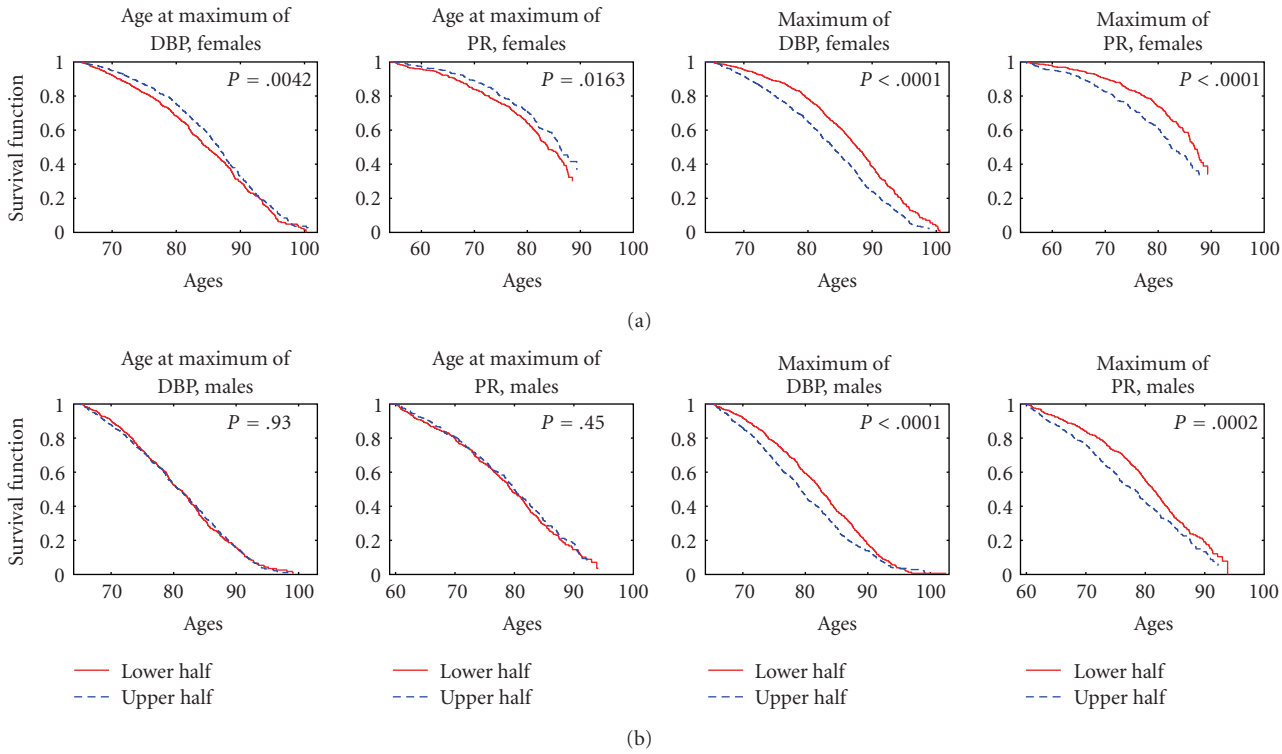

FIGURE 5: Kaplan-Meier estimates of survival functions for females (a) and males (b) having ages at reaching the maximum and the estimated maximal value (see Section 2) of different physiological indices from the lower and upper halves of empirical distributions of these risk factors for respective indices; P denotes P value for the null hypotheses about the equality of the survival curves in the strata evaluated by the log-rank test.

physiological variables, some of which have been measured in aging studies. The fact that the age trajectories of some of such variables differ among individuals with short and long life spans and healthy life spans indicates that dynamic properties of respective indices affect the life history traits. Our analyses of the FHS data clearly demonstrate that the values of physiological indices at age 40 are significant contributors to both life span and healthy life span (as show the estimates of $Intercept_{40\text{–}60}$ in Tables 1 and 2), suggesting that normalizing these variables around the age 40 is important for preventing age-associated morbidity and mortality later in life. Two dynamic parameters, $Slope_{40\text{–}60}$ and $Variability_{40\text{–}60}$, also have significant effect on mortality risk (the former being more important predictor in case of healthy life span). These data suggest that keeping physiological indices stable over the years of life could be as important as their normalizing around the age 40. Thus, a slower change in an index with age is likely to indicate the slower aging and the lower morbidity and mortality risks.

Table 3 shows that dynamic properties of the indices that change nonmonotonically with age significantly contribute to mortality risks and further demonstrates the importance of maintaining stability of physiological state in aging humans: the lower rate of decline in an index after reaching the age at maximum means the more beneficial effect on all-cause mortality.

The fact that the effect of the studied dynamic characteristics on risks of "unhealthy life" onset (Table 4) is less pronounced than that on all-cause mortality risk may indicate that the dynamic characteristics reflect basic aging-related processes in body that result in increasing nonspecific vulnerability to death with age rather than in increasing vulnerability to a particular pathology.

The review of the literature (below) supports our findings with respect to importance of taking into account longitudinal changes in physiological indices when evaluating/predicting morbidity and mortality risks. One should note, however, that the impact and comparative contributions of dynamic parameters (left and right slopes, variability, intercept) on mortality risks were evaluated in our study for the first time. In our two recent publications we demonstrated that individuals who have different rates of aging related changes in BG levels also differ in longevity [2, 3].

The effects of aging associated changes in serum cholesterol on coronary and all-cause mortality were evaluated in Finnish Cohorts of the Seven Countries study [22]. Men with greatest declines in the cholesterol levels had increased cardiovascular and all-cause mortality compared with men with least change in the levels. In the Paris Prospective Study [23], it was shown that not only a low baseline total cholesterol level but also its decline over time was associated with a higher cancer mortality.

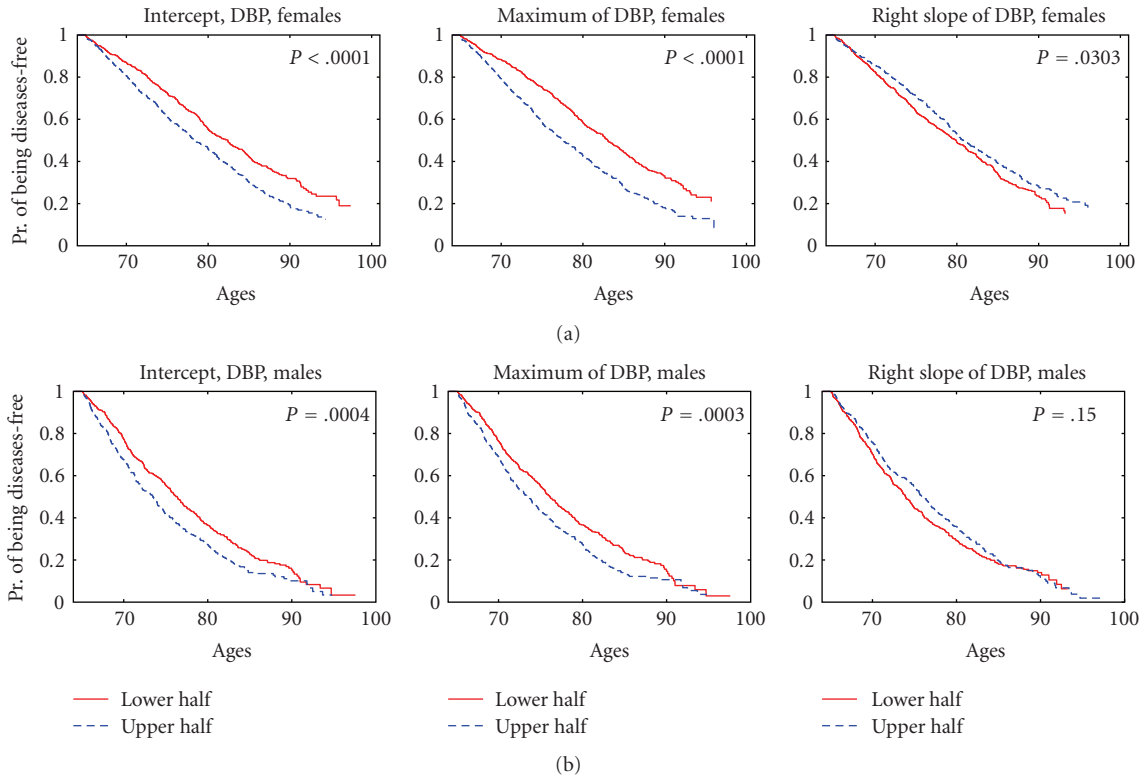

FIGURE 6: Kaplan-Meier estimates of probabilities of staying free of the diseases defining the onset of "unhealthy life" for females (a) and males (b) having initial values of diastolic blood pressure (DBP) at age 65, the estimated maximal values of DBP, and the average rates of decline of DBP after reaching the maximum ("intercept," "maximum," and "right slope," respectively, see Section 2) from the lower and upper halves of empirical distributions of these risk factors; P denotes P value for the null hypotheses about the equality of the survival curves in the strata evaluated by the log-rank test.

Similar to SCH, high blood pressure (BP) is a major risk factor for CVD. A study of two independent French male cohorts suggested that longitudinal changes in systolic and diastolic BP may be more accurate determinants of cardiovascular risks than baseline BP measures. In both cohorts, the group with a long-term increase in systolic and a decrease in diastolic BP (i.e., with increase in pulse pressure) had the highest relative risk of mortality from CVD compared to the group with no changes in either systolic or diastolic BP, independently of absolute values of BP or other risk factors [25]. Since this study included only males, it is important to note that changes in pulse pressure may in principle have different effects on mortality risks in males and females [26, 27].

The heart rate (HR) is one more index characterizing functioning of cardiovascular system. Prognostic importance of its baseline values as well as variability during 24-hour HR monitoring in patients with heart disease and in general population is recognized [28–30]. Contrarily, the prognostic role of the long-term and age-related dynamics of HR is not sufficiently investigated and respective studies are limited. A recent study of the effects of HR at baseline, final HR, and HR change during followup, on survival of patients attending the Glasgow Blood Pressure Clinic revealed that the highest risk of all-cause mortality was in patients who had increased their HR by ≥ 5 bpm at the end of followup, as compared with those who had a consistently high (high-high) or low (low-low) HR. Authors concluded that change in HR during the followup is a better predictor of mortality risk in hypertensive patients than baseline or final HR [31].

The body mass index (BMI) is, probably, the most intensively studied index in connection with health and survival. Over recent decades, many studies addressed the effect of BMI dynamics on morbidity and mortality, especially the effect of losing body weight in overweight/obese individuals on risk factors for CVD and diabetes. It was shown that overweight adults who lost weight over 9 years had more favorable (lower) total and LDL cholesterol levels compared to normal-weight control, but less favorable BG levels [32]. In other studies weight loss was associated with *excess* mortality when compared with weight stability, even when controlled for confounding due to diseases known to cause both weight loss and increased mortality [33, 34].

It was also shown that the weight stability was associated with a lower mortality risk as compared with weight change (gain or loss) [35, 36]. Nilsson et al. [37], showed that in men with decreasing BMI during 16 years of followup the noncancer mortality was higher compared to BMI-stable men. Authors hypothesized that involuntary weight loss in

otherwise healthy people could be a sign of premature aging, which in turn caused a nonspecific increase in mortality risk. In other studies, baseline weight and weight change had independent effects on total mortality, with both the associations exhibiting a U-shaped relation [38, 39].

Note that the seven physiological indices used in this paper do not exhaust the list of all possible physiological risk factors for mortality and morbidity. Therefore, the dynamic characteristics calculated from these seven indices cannot explain the entire variability in human life span and healthy life span. Other indices and risk factors can be explored on their association with mortality/morbidity risk if measurements of such indices are available in a longitudinal study for a substantially long-time period. See for example [40] where midlife risk factors were investigated for a cohort of Japanese American men with 40 years follow up.

5. Conclusion

In sum, our results indicate that the dynamic characteristics of age-related changes in physiological variables are important predictors of morbidity and mortality risks in the aging individuals. Previously published epidemiological findings are generally in concert with our results, which clearly indicates the need for further detailed studies of the dynamic parameters of aging related changes in human body with further application of these principles to the prevention strategies. We showed that the rate of changes in physiological state at the age interval between 40 and 60 years may serve as a good predictor of morbidity and mortality risks later in life. For nonmonotonically changing indices, the rates of decline after reaching the maximum, the maximal values, and the age at the maximum are important predictors of morbidity and mortality risks.

Senescence is likely to be the key player in physiological and biological changes observed in aging humans. The dynamic properties of these changes contain important information about the individual aging processes. This information, however, can be masked by the effects of compensatory adaptation and remodeling developing in response to the primary aging process. Studying mechanisms of such adaptation and its connection to morbidity and mortality risks is important for better understanding factors and mechanisms affecting long and healthy life.

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References

[1] A. I. Yashin, I. V. Akushevich, K. G. Arbeev, L. Akushevich, S. V. Ukraintseva, and A. Kulminski, "Insights on aging and exceptional longevity from longitudinal data: novel findings from the Framingham heart study," *Age*, vol. 28, no. 4, pp. 363–374, 2006.

[2] A. I. Yashin, S. V. Ukraintseva, K. G. Arbeev, I. Akushevich, L. S. Arbeeva, and A. M. Kulminski, "Maintaining physiological state for exceptional survival: what is the normal level of blood glucose and does it change with age?" *Mechanisms of Ageing and Development*, vol. 130, no. 9, pp. 611–618, 2009.

[3] A. I. Yashin, K. G. Arbeev, I. Akushevich et al., "Exceptional survivors have lower age trajectories of blood glucose: lessons from longitudinal data," *Biogerontology*, vol. 11, no. 3, pp. 257–265, 2010.

[4] A. I. Yashin, K. G. Arbeev, I. Akushevich, A. Kulminski, L. Akushevich, and S. V. Ukraintseva, "Stochastic model for analysis of longitudinal data on aging and mortality," *Mathematical Biosciences*, vol. 208, no. 2, pp. 538–551, 2007.

[5] A. I. Yashin, K. G. Arbeev, I. Akushevich, A. Kulminski, L. Akushevich, and S. V. Ukraintseva, "Model of hidden heterogeneity in longitudinal data," *Theoretical Population Biology*, vol. 73, no. 1, pp. 1–10, 2008.

[6] S. V. Ukraintseva and A. I. Yashin, "Individual aging and cancer risk: how are they related?" *Demographic Research*, vol. 9, pp. 163–195, 2003.

[7] S. Doubal and P. Klemera, "Influence of aging rate change on mortality curves," *Mechanisms of Ageing and Development*, vol. 54, no. 1, pp. 75–85, 1990.

[8] A. Ruiz-Torres, A. Gimeno, and F. J. Munoz, "Estimation of the aging rates of populations through the prevalence of age-related diseases," *Archives of Gerontology and Geriatrics*, vol. 19, no. 3, pp. 235–242, 1994.

[9] S. V. Ukraintseva and A. I. Yashin, "How individual age-associated changes may influence human morbidity and mortality patterns," *Mechanisms of Ageing and Development*, vol. 122, no. 13, pp. 1447–1460, 2001.

[10] K. G. Arbeev, S. V. Ukraintseva, L. S. Arbeeva, and A. I. Yashin, "Mathematical models for human cancer incidence rates," *Demographic Research*, vol. 12, pp. 237–272, 2005.

[11] S. N. Austad, "Diverse aging rates in metazoans: targets for functional genomics," *Mechanisms of Ageing and Development*, vol. 126, no. 1, pp. 43–49, 2005.

[12] M. De Martinis, C. Franceschi, D. Monti, and L. Ginaldi, "Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity," *FEBS Letters*, vol. 579, no. 10, pp. 2035–2039, 2005.

[13] D. H. Nussey, L. E. B. Kruuk, A. Morris, and T. H. Clutton-Brock, "Environmental conditions in early life influence ageing rates in a wild population of red deer," *Current Biology*, vol. 17, no. 23, pp. R1000–R1001, 2007.

[14] E. Nakamura and K. Miyao, "A method for identifying biomarkers of aging and constructing an index of biological age in humans," *Journals of Gerontology. Series A*, vol. 62, no. 10, pp. 1096–1105, 2007.

[15] E. Nakamura and K. Miyao, "Sex differences in human biological aging," *Journals of Gerontology. Series A*, vol. 63, no. 9, pp. 936–944, 2008.

[16] R. J. Colman, R. M. Anderson, S. C. Johnson et al., "Caloric restriction delays disease onset and mortality in rhesus monkeys," *Science*, vol. 325, no. 5937, pp. 201–204, 2009.

[17] S. Vasto, G. Scapagnini, M. Bulati et al., "Biomarkes of aging," *Frontiers in Bioscience (Scholar Edition)*, vol. 2, no. 2, pp. 392–402, 2010.

[18] T. Rantanen, S. Volpato, L. Ferrucci, E. Heikkinen, L. P. Fried, and J. M. Guralnik, "Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism," *Journal of the American Geriatrics Society*, vol. 51, no. 5, pp. 636–641, 2003.

[19] G. Ryan, M. W. Knuiman, M. L. Divitini, A. James, A. W. Musk, and H. C. Bartholomew, "Decline in lung function and mortality: the Busselton health study," *Journal of Epidemiology and Community Health*, vol. 53, no. 4, pp. 230–234, 1999.

[20] K. Sircar, E. Hnizdo, E. Petsonk, and M. Attfield, "Decline in lung function and mortality: implications for medical monitoring," *Occupational and Environmental Medicine*, vol. 64, no. 7, pp. 461–466, 2007.

[21] H. A. M. Kerstjens, B. Rijcken, J. P. Scheuten, and D. S. Postma, "Decline of FEV1 by age and smoking status: facts, figures, and fallacies," *Thorax*, vol. 52, no. 9, pp. 820–827, 1997.

[22] J. Pekkanen, A. Nissinen, E. Vartiainen, J. T. Salonen, S. Punsar, and M. J. Karvonen, "Changes in serum cholesterol level and mortality: a 30-year follow-up. The Finnish cohorts of the seven countries study," *American Journal of Epidemiology*, vol. 139, no. 2, pp. 155–165, 1994.

[23] M. Zureik, D. Courbon, and P. Ducimetière, "Decline in serum total cholesterol and the risk of death from cancer," *Epidemiology*, vol. 8, no. 2, pp. 137–143, 1997.

[24] R. Andres, D. C. Muller, and J. D. Sorkin, "Long-term effects of change in body weight on all-cause mortality: a review," *Annals of Internal Medicine*, vol. 119, no. 7, pp. 737–743, 1993.

[25] A. Benetos, M. Zureik, J. Morcet et al., "A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men," *Journal of the American College of Cardiology*, vol. 35, no. 3, pp. 673–680, 2000.

[26] L. T. Cooper, J. P. Cooke, and V. J. Dzau, "The vasculopathy of aging," *Journals of Gerontology*, vol. 49, no. 5, pp. B191–B196, 1994.

[27] P. M. Hall, "Hypertension in women," *Cardiology*, vol. 77, supplement 2, pp. 25–30, 1990.

[28] R. E. Kleiger, J. P. Miller, and J. T. Bigger Jr., "Decreased heart rate variability and its association with increased mortality after acute myocardial infarction," *American Journal of Cardiology*, vol. 59, no. 4, pp. 256–262, 1987.

[29] J. T. Bigger Jr., J. L. Fleiss, R. C. Steinman, L. M. Rolnitzky, R. E. Kleiger, and J. N. Rottman, "Frequency domain measures of heart period variability and mortality after myocardial infarction," *Circulation*, vol. 85, no. 1, pp. 164–171, 1992.

[30] H. V. Huikuri, T. H. Mäkikallio, K. E. J. Airaksinen et al., "Power-law relationship of heart rate variability as a predictor of mortality in the elderly," *Circulation*, vol. 97, no. 20, pp. 2031–2036, 1998.

[31] L. Paul, C. E. Hastie, W. L. S. Li et al., "Resting heart rate pattern during follow-up and mortality in hypertensive patients," *Hypertension*, vol. 55, no. 2, pp. 567–574, 2010.

[32] K. P. Truesdale, J. Stevens, and J. Cai, "The effect of weight history on glucose and lipids: the atherosclerosis risk in communities study," *American Journal of Epidemiology*, vol. 161, no. 12, pp. 1133–1143, 2005.

[33] T. I. A. Sørensen, "Weight loss causes increased mortality: pros," *Obesity Reviews*, vol. 4, no. 1, pp. 3–7, 2003.

[34] J. N. Ostergaard, M. Gronbaek, P. Schnohr, T. I. A. Sorensen, and B. L. Heitmann, "Combined effects of weight loss and physical activity on all-cause mortality of overweight men and women," *International Journal of Obesity*, vol. 34, no. 4, pp. 760–769, 2010.

[35] G. W. Somes, S. B. Kritchevsky, R. I. Shorr, M. Pahor, and W. B. Applegate, "Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program," *American Journal of Epidemiology*, vol. 156, no. 2, pp. 132–138, 2002.

[36] I.-M. Lee and R. S. Paffenbarger Jr., "Change in body weight and longevity," *JAMA*, vol. 268, no. 15, pp. 2045–2049, 1992.

[37] P. M. Nilsson, J.-Å. Nilsson, B. Hedblad, G. Berglund, and F. Lindgärde, "The enigma of increased non-cancer mortality after weight loss in healthy men who are overweight or obese," *Journal of Internal Medicine*, vol. 252, no. 1, pp. 70–78, 2002.

[38] K. L. Mikkelsen, B. L. Heitmann, N. Keiding, and T. I. A. Sørensen, "Independent effects of stable and changing body weight on total mortality," *Epidemiology*, vol. 10, no. 6, pp. 671–678, 1999.

[39] A. M. Kulminski, K. G. Arbeev, I. V. Kulminskaya et al., "Body mass index and nine-year mortality in disabled and nondisabled older U.S. individuals," *Journal of the American Geriatrics Society*, vol. 56, no. 1, pp. 105–110, 2008.

[40] B. J. Willcox, Q. He, R. Chen et al., "Midlife risk factors and healthy survival in men," *JAMA*, vol. 296, no. 19, pp. 2343–2350, 2006.

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Research Article

Physical Aspects of Healthy Aging: Assessments of Three Measures of Balance for Studies in Middle-Aged and Older Adults

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Objectives. To investigate the reliability and correlations with age of the balance components of the EPESE, NHANES, and the Good Balance Platform System (GBPS) in a normal population of adults. *Design*. Cross-sectional. *Setting*. Urban Medical Center in the Pacific. *Participants*. A random sample of 203 healthy offspring of Honolulu Heart Program participants, ages 38–71. *Measurements*. Subjects were examined twice at visits one week apart using the balance components of the EPESE, NHANES, and the good balance system tests. *Results*. The EPESE and NHANES batteries of tests were not sufficiently challenging to allow successful discrimination among subjects in good health, even older subjects. The GBPS allowed objective quantitative measurements, but the test-retest correlations generally were not high. The GBPS variables correlated with age only when subjects stood on a foam pad; they also were correlated with anthropometric variables. *Conclusion*. Both EPESE and NHANES balance tests were too easy for healthy subjects. The GBPS had generally low reliability coefficients except for the most difficult testing condition (foam pad, eyes closed). Both height and body fat were associated with GBPS scores, necessitating adjusting for these variables if using balance as a predictor of future health.

1. Introduction

Assessment of balance is important, especially in the elderly, since balance affects the ability of the individual to be mobile and functionally independent [1]. The term "balance" encompasses several different types of control mechanisms for stability including vestibular function [2], visual cues [3], the proprioceptive system [3, 4], and muscle control [4].

Balance has been measured in different ways including the use of force platforms [5] with both eyes either open or closed [6, 7], using the Berg Balance Scale [8], the Romberg stand, semi-tandem, full tandem, and side-by-side/parallel leg stands [9, 10]. Balance performance has been assessed dually with cognitive tasks [7, 11], with postural disturbance [12], and after a stroke rehabilitation [13]. A complicating factor is that some tests of balance might require simple muscular strength in addition to balance ability [14].

The quantification of balance, including the examination of sway [15–17], has been extensively studied among normal and subjects with some balance abnormality [18, 19] and

on various age groups [20]. Psychometric properties have been established for various balance measures utilizing older adults including but are not limited to Berg Balance Scale and Multidirectional Reach Test [21]; side-step test [22]; Fullerton Advanced Balance Scale [23]; Late-Life Function and Disability Instrument [24]; Dynamic Gait Index [25], and Activities-specific Balance Confidence Scale and the Survey of Activities and Fear of Falling in the Elderly [26]. These studies have helped define and improve the geriatric definition and utility of balance but have not addressed its potential utility as a predictor of future functional capacity in healthy adults. The purpose of the present study was to test the reliability of specific measures of balance to be included in an enhanced battery of measures of functional ability that would allow better discrimination among a random sample of individuals. Like grip strength [27], balance might be a predictor of future health. For research purposes, it is important to appraise methods of measuring balance to obtain a set of informative tools. This is rather different from using physical performance to detect current disease, since we hope to distinguish among people at the upper end of performance; at present, tools to assess balance are geared towards those with balance weakness or deficit.

The focus of this paper is to evaluate three measures of balance: the balance components of the EPESE [28] and NHANES [29] tests and the Good Balance Platform System [30]. The authors consulted with an internationally recognized panel of experts who recommended these commonly used measures possessing elements that test a broad range of functional levels. See Curb et al. [31] for further details. The reliability, correlations of these different tests with age, and correlations between the tests will be presented. To the best of our knowledge, this is the first published report of a reliability study comparing these three methods of measuring balance. Establishing the reliability and validity of balance measures is important to assess their suitability for use in clinical practice and research.

2. Methods

2.1. Study Design. The sample consisted of noninstitutionalized individuals, Japanese Americans who were drawn from lists of offspring of the Honolulu Heart Program participants, an epidemiological long-term cohort of 8,006 Japanese-American men in Hawaii [32]. These participants were randomly selected into two age groups: 35–55 and 56–71 years old. The two age groups provided a range in age and diversity in functional ability. Although the study required two examinations, two hundred ten agreed to participate for a recruitment rate of 50%. There were 105 per group stratified equally by sex. However, only 203 participants completed the two examinations—three did not return, two cancelled, and two did not have blood drawn. The two examinations were approximately a week apart. The first examination included a questionnaire on demographics, family and medical history, lifestyle, anthropometry (hip, seated mid-calf and waist circumference, maximum sagittal width, subscapular, and triceps skinfold), physical activity and function measures, and other physical measures such as heart rate, blood pressure, blood sample, and cognitive assessment. The second visit included all the measures except for the questionnaire, anthropometric measures, and blood draw. The first and second examination, took 2.5 to 3 hours and 1.5 to 2 hours, respectively. See Curb et al. [31] for further details on examinations and measures. Approval to conduct the study was given by the institutional review committee of Kuakini Medical Center where the study was performed, and informed consent was obtained from all participants.

2.2. Measurement of Variables

2.2.1. Established Populations for Epidemiologic Studies of the Elderly (EPESE) Battery of Tests. The EPESE battery includes semi-tandem, side-by-side, and fulltandem stands. This graded series of tests measures static balance while standing still for 10 and 30 seconds. For the semi-tandem test, the participant is instructed to stand with the side of the heel of one foot touching the big toe of the other foot for 10 seconds. Participants who cannot perform this proceed to the side-by-side stand. With the side-by-side stand, the participant is instructed to stand with his/her feet together, side-by-side for 10 seconds. If the semi-tandem stand test is passed, the participant proceeds to the fulltandem stand, with the heel of one foot in front of and touching the toes of the other foot for 30 seconds.

2.2.2. NHANES Balance Test. The Romberg Test of Standing Balance on Firm and Compliant Support Surfaces from the ongoing National Health and Nutrition Examination Surveys (NHANESs) of the National Center of Health Statistics required the participant to stand under four different conditions, on a hard stationary surface with eyes open/closed for 15 seconds and on a foam pad with eyes open/closed for 30 seconds each. The EPESE and NHANES measures were scored as qualitative pass/fail assessments of balance.

2.2.3. Good Balance Platform System. For the third set of tests, we incorporated the Romberg Test's four conditions into the *Good Balance Platform System* (GBPS) from Finland. The *GBPS* converts shifts in weight to digital data to obtain a quantitative assessment of maintenance of balance. The components of the system include a force platform and a handrail that wraps around the front and sides for safety. The *GBPS* records several functions of the amount and speed of the subject's mediolateral (ML) and anterior-posterior (AP) sway over a specified duration of time (our exams used 15 and 30 seconds). Table 1 describes the balance platform variables associated with the displacements.

Subjects stood for 30 seconds per test using the same four conditions as the NHANES test (hard surface with eyes open, then closed, followed by a foam surface with eyes open, then closed) and with the same safety precautions. For the first two conditions, the participants stood in the center of the triangular platform with their bare feet about a foot apart, with their hands together in front, right hand cupping the left, and the arms kept straight. For the last two conditions on a foam pad, the participant was instructed to stand with

Table 1: Balance platform main variables (×4 tests).

Variable name	Description
Mediolateral (ML) sway	Distance which contains 90% of lateral displacement of center of forces
Anterior-posterior (AP) sway	Distance which contains 90% of anterior-posterior displacement of center of forces
Length of side of square	Length of the smallest square containing 90% of path of center of forces
Mean X speed	Average speed of lateral movement of center of forces
Mean Y speed	Average speed of anteroposterior movement of center of forces
Velocity moment	Average horizontal area covered by movement of center of forces per second
Correlation	Correlation between lateral and antero-posterior movement of center of forces
Direction of main axis	Angle of direction of average movement of center of forces Right = 0 degrees Forward = 90 degrees Left = 180 degrees Backward = 270 degrees
Mean X value	Average value of center point on lateral axis (left is negative)
Mean Y value	Center point on anterior-posterior axis—leaning to the front/back

arms folded across the waist, holding the elbows with the hand (NHANES arm position). The use of the foam pad was adapted from the NHANES measures and was not part of the normal protocol recommended for the balance platform. Apparently, this is the first report of the use of the foam pad in combination with a computer-linked balance platform.

2.3. Analysis. For tests which were graded as pass/fail, such as the NHANES battery of tests, Fisher's exact test was used to test for association between repeated tests. Pearson product-moment correlations were used to estimate test-retest correlations; these estimate the intraclass correlation coefficients (the usual estimate of the reliability coefficients) but allow for a shift in means across visits in case there was some degree of learning experience. The effect of gender and physical characteristics on quantitative outcome variables was appraised using multiple linear regression models.

3. Results

A total of 203 subjects completed both visits, 87 aged 38–55 and 116 aged 56–71. There were 97 females and 106 males. The sample did not include the extreme elderly as the mean age was only 58. Generally, the participants were in reasonably good health, with no reported history of heart attack, stroke, or cancer. However, 46% were on medication for hypertension, 11% were being treated for diabetes, and 43% and 14% met body max index (BMI) WHO [33] criteria for overweight and obese, respectively. Refer to Tables 2 and 3 for further details.

Tests for which all participants pass (or all fail) do not have defined reliability coefficients because there is no variability across subjects (the calculation of the correlation coefficient would have division by zero). For the EPESE battery of tests of balance, all participants could perform the semi-tandem stand at both visits, while only 6.4% and 2.5% could not perform the fulltandem stand at visits 1, and 2, respectively. Since all of the participants could perform the semi-tandem stand, they did not have to do the easier side-by-side stand.

Table 2: Age, gender, medical history and body max index (BMI) ($N = 203$).

Age group (years)	% of sample
38–44	5.91
45–54	33.50
55–64	33.50
65–71	27.09
Gender	
Female	47.57
Male	52.43
Medical history	
Cancer	0.00
Heart attack/myocardial infarction (MI)	0.00
Stroke	0.00
On diabetes medication	11.33
On hypertension medication	46.00
*BMI categories	
<18.5 (underweight)	1.97
18.5–24.99 (normal range)	40.39
25.00–29.99 (preobese)	43.35
≥30 (obese)	14.29

* Note: According to World Health Organization (WHO) [33].

The NHANES set had four tests of balance, standing on a flat surface with eyes either open or closed, and standing on a foam pad with eyes either open or closed. For the standard, eyes open condition, all participants passed the test while for the standard, eyes closed condition, only one participant could not pass it at one exam only. For the foam pad, eyes open test, less than one percent could not pass the test, and only one person failed both exams. The foam pad, eyes closed test was somewhat more informative, with 9% and 6% of the

Table 3: Sample: Age and Anthropometric Measures ($N = 203$).

Variable	Mean	Minimum	Maximum	Standard deviation
Age	57.95	38.00	71.00	8.35
BMI	26.08	17.26	48.96	4.70
Height (cm)	161.48	137.90	182.00	8.72
Weight (kg)	68.32	38.00	119.60	14.63
Hip (cm)	97.09	74.00	142.00	8.48
Waist (cm)	89.21	62.00	140.00	11.94
Mid-calf circumference (cm)	36.64	28.70	52.00	3.57
Triceps skinfold (cm)	18.47	4.30	60.70	9.29
Subscapular skinfold (cm)	22.58	7.00	51.00	8.27
Maximum sagittal width (cm)	21.04	14.50	30.80	2.94

participants at visits 1 and 2, respectively, unable to perform it. However, its reliability correlation was only 0.26 (which was still significantly greater than zero, $P < .001$ by Fisher's exact test). Since the majority of the participants passed the EPESE and NHANES tests with the exception of the single leg stand, we did not do any further analysis such as adjusting for height and weight. Table 4 is a summary of the NHANES and EPESE balance tests.

Estimated reliability coefficients for the numerous *Good Balance Platform System* variables ranged from 0.22 to 0.73. While some variables such as "correlation" and "main axis" had low-reliability coefficients under all four testing conditions, the variables "mean X -speed," "mean Y-speed," and "velocity moment" had reasonably high-reliability coefficients under the most difficult testing condition (foam pad, eyes closed). To improve the reliability coefficient of these variables, we examined scatterplots and evaluated the following:

(1) deletion of outliers (for two participants, their values for some variables at the second exam were wildly discrepant with their first exam values);

(2) transformation by taking the logarithm;

(3) deletion of outliers and log transformation.

Table 5 summarizes the reliability coefficients in the original scale and after taking logs (some variables had a constant added to them to make the lowest value equal to 1 before log transformation). The reliability coefficients of five out of ten variables increased meaningfully after transformation, while the reliability of a few decreased by log transformation. Remarkably, removing two extreme outliers resulted in less improvement than simple log transformation (results not shown). Figures 1(a) and 1(b) display plots of the variable "velocity moment" (foam pad, eyes closed) before and after log transformation.

Apart from "mean Y-speed" (average speed moving front-to-back), Good Balance Platform System variables were correlated with age only when subjects stood on a foam pad (see values in parenthesis in Table 5). Under easier conditions (i.e., standard, eyes open and closed), the balance variables had low correlations with age, in keeping with their low reliability coefficients.

Further analysis in evaluating means and standard deviations showed that as test condition difficulty increased, so too did the variables' means and standard deviations, with foam, eyes closed having the most substantial impact. For example, for "mean Y-speed," the means (and standard deviations) are 6.2 (2.0), 8.9 (3.0), 12.6 (3.6), and 26.0 (8.3) for the four conditions, standard eyes open and closed, foam pad eyes open and closed, respectively. The increase in the standard deviation suggests that the effect of increasing the difficulty is not the same for everyone. When the values are log transformed, the standard deviations are nearly constant and range from about 0.3 to 0.35; this constancy of variance of log-transformed values improves their statistical properties if used as dependent variables.

The four variables with the highest reliability coefficients, "velocity moment," "mean X-speed," "mean Y-speed," and "length of side of square" were regressed on age and gender using the easiest and most difficult conditions, standard, eyes open and foam pad, eyes closed. The effect of age increased with difficulty of test condition. Women had better (lower) average balance scores than men, the advantage being greater under the more difficult testing condition.

We investigated the relationships between the four most reliably measured *GBPS* variables and (1) measures of body fat (waist circumference, sagittal diameter, mid-calf, triceps, and subscapular skinfold thicknesses), (2) distance walked in six minutes, and (3) failure to pass the *NHANES* full tandem stand on a foam surface, eyes closed. To improve the reliability of the variables, the averages of exam 1 and exam 2 *GBPS* variables, the distance walked in six minutes, and the total number of "failures" of the *NHANES* test were used. We included the 6-minute walk in the analysis because of its high reliability (.90) in this and Harada et al.'s [34] study, and its relationship to balance [34]. All variables were adjusted for age and gender.

(1) All five measurements of body fat were negatively correlated with all *GBPS* variables, with correlations being significant for three to four *GBPS* variables per body fat variable. These correlations could be substantial; for instance, the correlation between subscapular skinfold thickness and log "mean Y speed" was $r = -0.37$ ($P < .0001$). This means fatter people had better balance or less movement on the platform. (2) The distance walked in six-minutes was positively correlated with log "mean Y speed" ($P = .023$) and log "mean X speed" ($P = .006$) and of borderline significance with log "velocity moment" ($P = .06$); that is, greater movement on the balance platform was correlated with faster walking. The correlation between the six-minute walk score and balance platform values diminished after adjusting for height, with only log of "mean X speed" remaining significant. The difference between genders in means of six minute walk scores and balance platform scores also disappeared after adjusting for height. (3) The total number of failures for the *NHANES* full tandem stand on a foam surface, eyes closed test was highly significantly correlated

Table 4: NHANES and EPESE balance test results at visit 1 and visit 2.

Movement	Pass visit 1 Pass visit 2	Pass visit 1 Fail visit 2	Fail visit 1 Pass visit 2	Fail visit 1 Fail visit 2
NHANES				
Standard, eyes open	203	0	0	0
Standard, eyes close	202	1	0	0
Foam pad, eyes open*	201	0	1	1
Foam pad, Eyes close**	176	8	14	5
EPESE				
Semi-tandem	203	0	0	0
Full tandem	187	11	3	2

Test for association between visit 1 and visit 2 results: $^{*}P < .01$; $^{**}P < .001$.

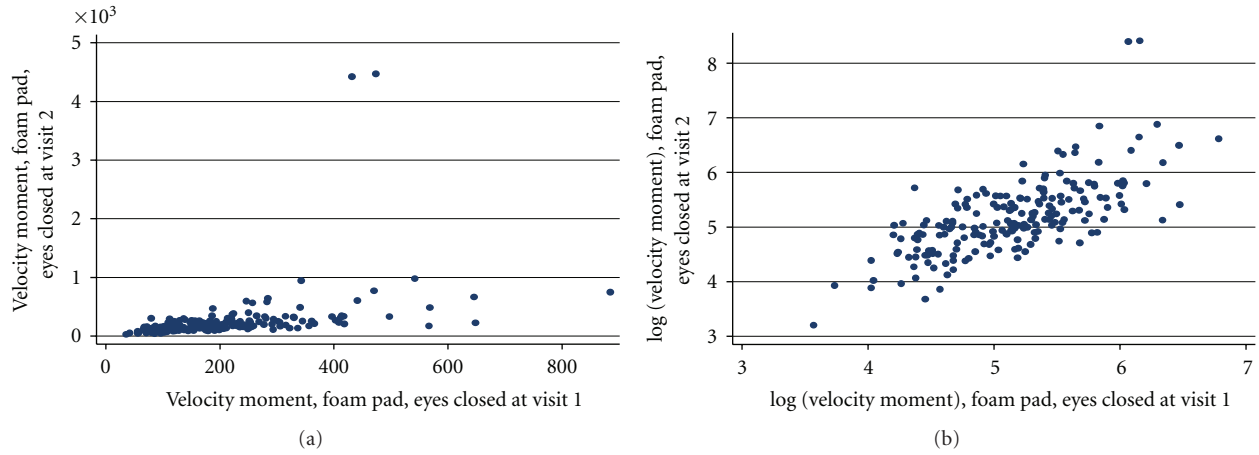

Figure 1: Velocity moment, foam eyes closed, before (a) and after (b) log transformation.

with all four *GBPS* variables, even though a single *NHANES* test had low reliability; using the average of the values over two exams improved the results. The correlations were 0.37, 0.23, 0.26, and 0.39 for log "velocity moment," log "mean X speed," log "mean Y speed," and log "length of square," respectively. The correlations between the sum of failures for NHANES foam pad, eyes closed with the balance platform scores remained high after adjusting for age, gender, height, and body mass index (BMI).

4. Discussion

The purpose of this study was to obtain tests of balance with good reliability to distinguish among people with at least normal functional abilities. None of the various measurements of balance had outstanding reliability coefficients in our sample of healthy men and women. The least discriminatory test was the EPESE battery of tests, since nearly all participants could perform the tests successfully, and those who failed to pass one test usually could succeed during the other examination. However, in another study [35] of adults aged 55–70 years old, semi-tandem and tandem stands had good reliability. For the NHANES set, most of the participants could pass all tests except for the foam pad, eyes closed testing condition, which averaged 8% failure but had a low-reliability coefficient. Thus, these tests do not appear to have been sufficiently challenging for subjects in good health, even among our older subjects, to allow discrimination between levels of function.

The *Good Balance Platform System* seemed promising since it allowed a quantitative score rather than a qualitative pass/fail result. Even so, the reliability coefficients were disappointing when subjects stood on a hard surface, whether or not their eyes were closed. Only one variable ("mean Y speed") had a reliability coefficient as high as 0.7. Standing on a foam pad increased the difficulty, particularly when the subjects had their eyes closed, which increased the test-retest correlation coefficients for half of the variables. Log transformation of the scores reduced heteroscedasticity and skewness and increased the reliability coefficients of several balance variables, but only three of the reliability coefficients were greater than 0.7 even for the foam pad, eyes closed test, the most difficult condition.

Women generally had better balance scores on the balance platform than men, which is consistent with Røgind et al.'s [36] findings but contrary to the findings of Wolfson et al. [37]. We found that this difference disappeared after adjusting for height. For four balance platform variables with the highest reliability coefficients, increased movement on the balance platform was associated with good performance

Table 5: Balance platform—test-retest reliability $N = 203$.

Variable name	Standard, eyes open	Standard, eyes closed	Foam, eyes open	Foam, eyes closed
ML sway	0.36‡	0.38‡	0.29‡	0.34‡
	(0.08)	(0.04)	(0.28†)	(0.32†)
Log ML sway	0.38‡	0.46‡	0.32‡	0.56‡
AP sway	0.29‡	0.39‡	0.36‡	0.36‡
	(0.12)	(0.09)	(0.14)	(0.36†)
Log AP sway	0.33‡	0.46‡	0.37‡	0.55‡
Length of side of square	0.29‡	0.29‡	0.43‡	0.43‡
	(0.12)	(0.12)	(0.21**)	(0.21**)
Log length of side of square	0.33‡	0.47‡	0.45‡	0.61‡
Mean X speed	0.42‡	0.36‡	0.62‡	0.64
	(0.07)	(0.02)	(0.32†)	(0.24†)
Log mean X speed	0.46‡	0.53‡	0.65‡	0.71‡
Mean Y speed	0.70‡	0.68‡	0.73‡	0.72‡
	(0.34†)	(0.26†)	(0.37†)	(0.29†)
Log mean Y speed	0.69‡	0.69‡	0.72‡	0.76‡
Velocity moment	0.37‡	0.46‡	0.49‡	0.40‡
	(0.15*)	(0.07)	(0.34†)	(0.31†)
Log velocity moment	0.42‡	0.59‡	0.55‡	0.70‡
Correlation	0.15*	0.24†	0.21**	0.04
	(0.07)	(0.002)	(−0.07)	(−0.0006)
Log correlation	0.18*	0.23†	0.21**	0.03
Main axis	−0.10	0.16*	0.13	0.09
	(−0.07)	(0.03)	(0.01)	(−0.04)
Log main axis	0.02	0.16	0.13	0.06
Mean X value	0.48‡	0.34‡	0.31‡	0.31‡
	(0.04)	(0.02)	(0.005)	(−0.10)
Log mean X value	0.35‡	0.26†	0.20**	0.24†
Mean Y value	0.28‡	0.34‡	0.22†	0.25†
	(−0.06)	(−0.05)	(0.17*)	(0.21**)
Log mean Y value	0.23**	0.21**	0.23**	0.27‡

* $P < .05$; ** $P < .01$; † $P < .001$; ‡ $P < .0001$.
The values in parenthesis are the age correlation for visit 1.

with the six-minute walk. These associations also diminished after adjusting for subject's height, with only one variable remaining significantly correlated. In contrast, the correlations between the sum of failures for NHANES foam pad, eyes closed with balance platform scores remained high after adjusting for age, gender, height, and BMI. Surprisingly, individuals with increased waist and mid-calf circumference and skinfold measurement had better balance, contrary to other findings [38, 39]. It should be pointed out that 14% of the subjects in the present study were obese. The correlations of balance scores with body fat means that investigators might misinterpret the health implications of GBPS balance score: we found that diastolic blood pressure had significant negative correlations with several GBPS variables, but that these correlations disappeared after adjusting for BMI (results not shown).

As test condition difficulty increased across the four conditions, so too did the mean and standard deviations, with foam pad, eyes closed being impacted the most. The increase in standard deviation apparently means that the effect of increasing test difficulty is not the same for all subjects. Four variables ("velocity moment," "mean X-speed," "mean Y-speed," and "length of side of square") with the highest test-retest reliability coefficients were regressed on age and gender using the easiest and most difficult conditions—standard, eyes open and foam, eyes closed. We found that the effect of age increased with difficulty of test condition and that women had better (lower) balance scores than men, the advantage being greater under the more difficult testing condition. Our results are consistent with other studies that reported low-reliability coefficients for computerized balance platforms unless subjects faced additional challenges [7, 40, 41]. Some of these challenges required specialized equipment [41]. We found that the simple addition of a foam pad and log transformation frequently increased the reliability coefficient substantially.

Since difficulty in maintaining balance varied across the testing conditions, taking the difference between the easiest and most difficult conditions might have generated meaningful balance variables. The difference in scores generally

increased with age, reflecting the greater difficulty the elderly experienced with the foam pad. However, the difference in scores generally had rather low reliability coefficients, with the best (for difference in log "mean Y speed") being only 0.66. Remarkably, the *GBPS* variable "correlation" had a test-retest correlation for the difference in scores of 0.65 although the reliability coefficients for each separate measurement was low. The meaning of a severely worsened balance score caused by using a more difficult testing condition is still largely unexplored at this time, but a difference in scores might be a useful complement to the more usual measurements.

Investigators might want to consider measuring participants' balance variables more than once to increase the reliability of the value. The reliability coefficient of values which are the means of m independent measurements per subject can be expressed as $\rho_m = (1+ [1-\rho]/\mathrm{m})^{-1}$, where ρ is the reliability coefficient of a single measurement. If the reliability coefficient of a measurement were, say 0.70, then using the average of two independent measurements per subject would increase the reliability coefficient to 0.82. While it probably would be best to have balance measurements measured at least a few days apart to insure that they are independent, one might improve the reliability of the variables a fair amount simply by having subjects repeat the balance platform test a second and third time during the same examination.

A limitation to this study needs to be considered. Data reported in this study may not be applicable to other ethnic groups since the subjects were of unmixed Japanese descent living in Hawaii.

5. Conclusions

The EPESE and NHANES tests, which are scored as pass/fail, were too easy for healthy subjects and did not allow differentiating among people. The Good Balance Platform System (GBPS) variables, which are quantitative, had rather low-reliability coefficients except under the most difficult testing condition (standing on foam pad with eyes closed) and generally were not correlated with age except when subjects stood on a foam pad; five out of ten of the variables had their reliability coefficients improved appreciably by using a log transformation of the scores. Taking the average of multiple balance platform measurements would improve the reliability even more. The GBPS variables were positively correlated with height and negatively correlated with measures of body fatness; for research on the value of balance as a predictor of future health, adjustment for height and body fat or relative weight should be made.

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References

[1] P. K. Yim-Chiplis and L. A. Talbot, "Defining and measuring balance in adults," *Biological Research for Nursing*, vol. 1, no. 4, pp. 321–331, 2000.

[2] L. M. Nashner, F. O. Black, and C. Wall, "Adaptation to altered support and visual conditions during stance: patients with vestibular deficits," *Journal of Neuroscience*, vol. 2, no. 5, pp. 536–544, 1982.

[3] A. Shumway-Cook and F. B. Horak, "Assessing the influence of sensory interaction on balance. Suggestion from the field," *Physical Therapy*, vol. 66, no. 10, pp. 1548–1550, 1986.

[4] L. M. Nashner, "Adaptation of human movement to altered environments," *Trends in Neurosciences*, vol. 5, pp. 358–361, 1982.

[5] K. Dodd, K. Hill, R. Haas, C. Luke, and S. Millard, "Retest reliability of dynamic balance during standing in older people after surgical treatment of hip fracture," *Physiotherapy Research International*, vol. 8, no. 2, pp. 93–100, 2003.

[6] B. M. Haas and A. M. Burden, "Validity of weight distribution and sway measurements of the balance performance monitor," *Physiotherapy Research International*, vol. 5, no. 1, pp. 19–32, 2000.

[7] J. E. Condron and K. D. Hill, "Reliability and validity of a dual-task force platform assessment of balance performance: effect of age, balance impairment, and cognitive task," *Journal of the American Geriatrics Society*, vol. 50, no. 1, pp. 157–162, 2002.

[8] K. Berg, S. Wood-Dauphinee, J. I. Williams, and D. Gayton, "Measuring balance in the elderly: preliminary development of an instrument," *Physiotherapy Canada*, vol. 41, no. 6, pp. 304–311, 1989.

[9] Y. Hong, J. X. Li, and P. D. Robinson, "Balance control, flexibility, and cardiorespiratory fitness among older Tai Chi practitioners," *British Journal of Sports Medicine*, vol. 34, no. 1, pp. 29–34, 2000.

[10] J. E. Rossiter-Fornoff, S. L. Wolf, L. I. Wolfson et al., "A cross-sectional validation study of the FICSIT common data base static balance measures," *Journals of Gerontology A*, vol. 50, no. 6, pp. M291–M297, 1995.

[11] A. Shumway-Cook, M. Woollacott, K. A. Kerns, and M. Baldwin, "The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls," *Journals of Gerontology A*, vol. 52, no. 4, pp. M232–M240, 1997.

[12] T. M. Owings, M. J. Pavol, K. T. Foley, and M. D. Grabiner, "Measures of postural stability are not predictors of recovery from large postural disturbances in healthy older adults," *Journal of the American Geriatrics Society*, vol. 48, no. 1, pp. 42–50, 2000.

[13] T. J. Stevenson, "Detecting change in patients with stroke using the Berg Balance Scale," *Australian Journal of Physiotherapy*, vol. 47, no. 1, pp. 29–38, 2001.

[14] H. Corriveau, R. Hébert, M. Raîche, M. F. Dubois, and F. Prince, "Postural stability in the elderly: empirical confirmation of a theoretical model," *Archives of Gerontology and Geriatrics*, vol. 39, no. 2, pp. 163–177, 2004.

[15] C. J. Morales and E. D. Kolaczyk, "Wavelet-based multifractal analysis of human balance," *Annals of Biomedical Engineering*, vol. 30, no. 4, pp. 588–597, 2002.

[16] J. A. Raymakers, M. M. Samson, and H. J. J. Verhaar, "The assessment of body sway and the choice of the stability parameter(s)," *Gait and Posture*, vol. 21, no. 1, pp. 48–58, 2005.

[17] B. Y. Jeong, "Contour representation of sway area in posturography and its application," *Archives of Physical Medicine and Rehabilitation*, vol. 75, no. 9, pp. 951–956, 1994.

[18] N. Nies and P. L. Sinnott, "Variations in balance and body sway in middle-aged adults. Subjects with healthy backs compared with subjects with low-back dysfunction," *Spine*, vol. 16, no. 3, pp. 325–330, 1991.

[19] P. B. Thapa, P. Gideon, R. L. Fought, M. Kormicki, and W. A. Ray, "Comparison of clinical and biomechanical measures of balance and mobility in elderly nursing home residents," *Journal of the American Geriatrics Society*, vol. 42, no. 5, pp. 493–500, 1994.

[20] N. R. Colledge, P. Cantley, I. Peaston, H. Brash, S. Lewis, and J. A. Wilson, "Ageing and balance: the measurement of spontaneous sway by posturography," *Gerontology*, vol. 40, no. 5, pp. 273–278, 1994.

[21] M. A. Holbein-Jenny, B. Billek-Sawhney, E. Beckman, and T. Smith, "Balance in personal care home residents: a comparison of the Berg Balance Scale, the Multi-Directional Reach Test, and the Activities-Specific Balance Confidence Scale," *Journal of Geriatric Physical Therapy*, vol. 28, no. 2, pp. 48–53, 2005.

[22] H. Fujisawa and R. Takeda, "A new clinical test of dynamic standing balance in the frontal plane: the side-step test," *Clinical Rehabilitation*, vol. 20, no. 4, pp. 340–346, 2006.

[23] D. J. Rose, N. Lucchese, and L. D. Wiersma, "Development of a multidimensional balance scale for use with functionally independent older adults," *Archives of Physical Medicine and Rehabilitation*, vol. 87, no. 11, pp. 1478–1485, 2006.

[24] I. Melzer, I. Kurz, O. Sarid, and A. M. Jette, "Relationship between self-reported function and disability and balance performance measures in the elderly," *Journal of Rehabilitation Research and Development*, vol. 44, no. 5, pp. 685–692, 2007.

[25] J. Jonsdottir and D. Cattaneo, "Reliability and validity of the dynamic gait index in persons with chronic stroke," *Archives of Physical Medicine and Rehabilitation*, vol. 88, no. 11, pp. 1410–1415, 2007.

[26] K. M. C. Talley, J. F. Wyman, and C. R. Gross, "Psychometric properties of the activities-specific balance confidence scale and the survey of activities and fear of falling in older women," *Journal of the American Geriatrics Society*, vol. 56, no. 2, pp. 328–333, 2008.

[27] T. Rantanen, K. Masaki, D. Foley, G. Izmirlian, L. White, and J. M. Guralnik, "Grip strength changes over 27 yr in Japanese-American men," *Journal of Applied Physiology*, vol. 85, no. 6, pp. 2047–2053, 1998.

[28] J. M. Guralnik, E. M. Simonsick, L. Ferrucci et al., "A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission," *Journals of Gerontology*, vol. 49, no. 2, pp. M85–M94, 1994.

[29] National Health and Nutrition Examination Survey (NHANES), "Balance Procedures Manual," May 2001.

[30] Metitur Oy Company, "Good Balance User's Manual Version 2.54a," September 2001.

[31] J. D. Curb, C. D. Ceria-Ulep, B. L. Rodriguez et al., "Performance-based measures of physical function for high-function populations," *Journal of the American Geriatrics Society*, vol. 54, no. 5, pp. 737–742, 2006.

[32] R. M. Worth and A. Kagan, "Ascertainment of men of Japanese ancestry in Hawaii through World War II Selective Service registration," *Journal of Chronic Diseases*, vol. 23, no. 5-6, pp. 389–397, 1970.

[33] World Health Organization (WHO), "Global database on body mass index," December 2010, http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.

[34] N. D. Harada, V. Chiu, and A. L. Stewart, "Mobility-related function in older adults: assessment with a 6-minute walk test," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 7, pp. 837–841, 1999.

[35] C. Ritchie, S. G. Trost, W. Brown, and C. Armit, "Reliability and validity of physical fitness field tests for adults aged 55 to 70 years," *Journal of Science and Medicine in Sport*, vol. 8, no. 1, pp. 61–70, 2005.

[36] H. Røgind, J. J. Lykkegaard, H. Bliddal, and B. Danneskiold-Samsøe, "Postural sway in normal subjects aged 20–70 years," *Clinical Physiology and Functional Imaging*, vol. 23, no. 3, pp. 171–176, 2003.

[37] L. Wolfson, R. Whipple, C. A. Derby, P. Amerman, and L. Nashner, "Gender differences in the balance of healthy elderly as demonstrated by dynamic posturography," *Journals of Gerontology*, vol. 49, no. 4, pp. M160–M167, 1994.

[38] K. M. Winters and C. M. Snow, "Body composition predicts bone mineral density and balance in premenopausal women," *Journal of Women's Health*, vol. 9, no. 8, pp. 865–872, 2000.

[39] D. T. Villareal, M. Banks, C. Siener, D. R. Sinacore, and S. Klein, "Physical frailty and body composition in obese elderly men and women," *Obesity Research*, vol. 12, no. 6, pp. 913–920, 2004.

[40] R. A. L. Liston and B. J. Brouwer, "Reliability and validity of measures obtained from stroke patients using the balance master," *Archives of Physical Medicine and Rehabilitation*, vol. 77, no. 5, pp. 425–430, 1996.

[41] B. Brouwer, E. G. Culham, R. A. L. Liston, and T. Grant, "Normal variability of postural measures:implications for the reliability of relative balance performance outcomes," *Scandinavian Journal of Rehabilitation Medicine*, vol. 30, no. 3, pp. 131–137, 1998.

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Research Article

Assessing Physical Performance in Centenarians: Norms and an Extended Scale from the Georgia Centenarian Study

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Centenarians display a broad variation in physical abilities, from independence to bed-bound immobility. This range of abilities makes it difficult to evaluate functioning using a single instrument. Using data from a population-based sample of 244 centenarians (M_{Age} = 100.57 years, 84.8% women, 62.7% institutionalized, and 21.3% African American) and 80 octogenarians (M_{Age} = 84.32 years, 66.3% women, 16.3% institutionalized, and 17.5% African American) we (1) provide norms on the Short Physical Performance Battery and (2) extend the range of this scale using performance on additional tasks and item response theory (IRT) models, reporting information on concurrent and predictive validity of this approach. Using the original SPPB scoring criteria, 73.0% of centenarian men and 86.0% of centenarian women are identified as severely impaired by the scale's original classification scheme. Results suggest that conventional norms for older adults need substantial revision for centenarian populations and that item response theory methods can be helpful to address floor and ceiling effects found with any single measure.

1. Introduction

The oldest old display a broad range and variability of physical and cognitive abilities [1–6]. The large range of performance presents a significant measurement problem to researchers. For example, about one-third of centenarians perform well cognitively, at the range of those who are in their 60s and 80s; on the other hand, about 50% of centenarians have some form of dementia, and about one-third have moderate to severe dementia [7]. Similar measurement issues are present for physical functions. Handgrip strength in the oldest varies from <5 kg to >30 kg [5, 8]. Some centenarians live independently and perform all physical and instrumental activities of daily living while others are immobile and bed bound [5, 8]. Few norms exist for physical performance among centenarians and a central problem is that current functional performance batteries display both floor and ceiling effects.

The purpose of this paper is to (1) present normative data for centenarians on the Short Physical Performance Battery and (2) provide evidence for the validity of an extended SPPB scaling that addresses issues of floor and ceiling effects by combining data from instruments with different levels of scaling into one continuous scale developed using item response theory (IRT). For those expected to perform well, we chose to use the Short Physical Performance Battery (SPPB) [9, 10]. It has been used in several large epidemiological studies and has been shown to have predictive validity for those with moderate to high levels of mobility disability and morbidity. For those physically

weak and nonambulatory participants, we chose to use items on the Physical Performance Mobility Exam (PPME) not included on the SPPB[11].

2. Methods

2.1. Participants. Participants were 244 centenarians and near centenarians (aged 98 and older) and 80 octogenarians recruited from 44 counties in northeast Georgia, with full details described elsewhere [2]. Because the study was population based, there were no exclusions although, to be included, all centenarians were required to provide blood samples. Overall, the recruitment rate (of those contacted participating) was 67.2% for centenarians and 46.0% for octogenarians. Further, our sample represents an estimated 19.6% of the entire population of centenarians in this geographic area. The GCS employed internationally established criteria in age verification [12] using convergent multiple and creditable sources and public records, such as birth and marriage certificates of the individuals as well as their offspring and relatives to create a consistent chronology. Driver's licenses, Social Security documents, census records, as well as death records of offspring are used.

2.2. Materials and Procedure. A complete list of measures included in the GCS appears elsewhere [13].

2.2.1. Short Physical Performance Battery (SPPB). Is a valid measure of lower extremity mobility, predictive of mortality and institutionalization in community-dwelling older adults with a broad range of abilities [9]. The SPPB consists of (1) three standing balance measures (tandem, semi-tandem, and side-by-side stands), (2) five continuous chair stands, and (3) a 2.44-meter walk. The scaling was developed by dividing the performance times on the original population Established Populations Epidemiological Studies in the Elderly (EPESE) into quartiles from 1 (the lowest) through 4 (the highest, with 0 assigned to nonperformers. The three balance tests are considered a hierarchy of difficulty when assigning a single score of zero to four for standing balance. Individuals unable to complete tasks are given the score of zero on that task. Completed tasks were assigned scores from one to four based on time, where the shortest time received the score of four. The scores were summed to get a total score ranging from zero to 12. Poor performance is a risk factor for mortality in data gathered from epidemiological studies on community-dwelling populations in their eighth and ninth decade [10].

2.2.2. Physical Performance Mobility Exam (PPME). It was developed and validated on hospitalized patients and includes lower functioning tasks in addition to those on the SPPB described above [11]. The additional tasks include (1) bed mobility to assess the ability to move from lying to sitting positions, (2) transferring from sitting on the edge of a bed to sitting in a chair, and (3) stepping up one step with or without the use of a bed handrail. This measure used a 3-level scoring system where 0 was assigned to nonperformers, and 1 was assigned to those completing without assistance in $\geq$10 seconds (bed mobility), with assistance (transfer), with use of handrail (step-up). 2 was assigned to those completing in <10 sec (bed mobility), without assistance (transfer), or without use of handrail (step-up).

2.2.3. GCS Composite Scale (GCS). It was developed using item response theory (IRT) methodology based on scores on the SPPB scores (using GCS cut-off values for timed tasks) along with PPME and grip strength. Participants' latent ability was estimated as a z-score from the difficulty of each test item and participants' responses to them. These scores were then rescaled in 11 even division points (2–12), with 1 assigned to nonperformers. (Figure S1 shows the information provided by each task as a function of latent ability. Table S1 shows time cut-offs to provide quartiles in the EPESE and the GCS data sets.)

2.2.4. Direct Assessment of Functional Status (DAFS). It is a clinician-rated scale based on performance on time orientation, communication, transportation, preparing for grocery shopping, financial skills, grocery shopping, dressing and grooming, and eating [14]. Transportation, preparing for grocery shopping, and grocery shopping tasks of the DAFS were omitted due to increased physical demands and low likelihood that centenarians were currently engaged in these activities. Each activity of daily living (ADL) tasks on the DAFS was scored on a dichotomous scale based on the participant's successful completion of the functional task. The BADL score was calculated by summing the grooming, dressing, and eating scales (possible range = 0–23 points and higher scores represent higher functional status); the IADL score was calculated by summing the time orientation, communication, and financial skills scales (possible range = 0–58 points and higher scores represent higher functional status). The DAFS has been validated with community-dwelling samples [15] and older adults with dementia [14].

2.2.5. Grip Strength. It was assessed using the Jamar (Detecto, Jackson, MI) hand grip dynamometer. After adjusting the handle to the second metatarsal, while sitting in a chair with the arm allowed to hang down at the side, maximal grip strength was tested three consecutive times on both the right and left hands. Peak force to the nearest tenth kilogram (0.1 kg) was calculated for each hand. Analyses use the average peak value across both hands (average values correlated $r > .97$ with values obtained from each hand.)

2.2.6. Knee Extensor Strength. It was tested using a manual muscle manometer (Nichols, LaFayette IN). Positioned in a straight backed chair with the lower leg hanging freely where the foot did not touch the floor and arms were folded across the chest to avoid use of the upper body, the participant was asked to straighten the leg as forcefully as possible while administrator maintained stability. Peak force to the nearest tenth kilogram (0.1 kg) was calculated for each leg. Analyses use the average peak value across both legs (average values correlated $r > .98$ with values obtained from each leg).

Table 1: Sample characteristics by age group.

	Octogenarians					Centenarians					
Characteristic	*N*	*M*/%	SD	Min	Max	*N*	*M*/%	SD	Min	Max	*P*-value
Age (years)[a]	80	84.32	2.78	80.53	90.06	244	100.58	2.04	98.10	108.55	.001
Female[b]	80	66.3				244	84.8				.001
Black[b]	244	17.5				80	21.3				.525
Institutionalized[b]	244	16.3				80	62.7				.001
SPPB[c]	80	5.63	3.22	0	12	244	1.46	2.19	0	9	.001
PPME[c]	80	4.48	2.01	0	6	244	2.31	2.11	0	6	.001
GCS[c]	80	9.08	3.15	2	12	244	5.18	3.08	1	12	.001
DAFS BADL[a]	77	21.23	5.25	0	23	231	16.29	8.26	0	23	.001
DAFS IADL[c]	78	47.67	17.12	0	58	235	25.74	18.28	0	58	.001
Leg strength (kg)[a]	80	11.06	7.87	0	40.05	241	5.05	5.83	0	35	.001
Grip strength (kg)[a]	80	21.49	12.22	0	63.50	243	10.32	10.54	0	60	.001

[a] *t*-test with unequal variances.
[b] Fisher's exact test.
[c] *t*-test with equal variances.

2.3. Test Administration. Based on results from pilot testing with 10 centenarians (not included in this sample), administration of SPPB and PPME was originally tailored to reduce participant burden using a decision rule based on participant ambulatory ability. If participants could stand, only items of the SPPB and the step-up of the PPME were administered. Otherwise, if they are unable to stand, only the bed mobility and transfer tasks were administered. During testing of the current sample, it was determined that these tasks were not strictly hierarchical for this population. As a result, the protocol was changed so that all tasks were offered to all participants. In most cases for participants who were administered only one scale or the other, it was possible to recreate ability on the nonadministered test by working with data from participants administered both scales as well as detailed administration notes provided by interviewers. (Procedures for completing these partial datasets is described fully under "Missing Values" in the Supplementary Material of this paper; see Supplementary Material available online at doi: 10.1155/2010/310610.) Conclusions were not altered by whether partial cases were included or excluded.

2.4. Statistical Analysis. SPSS (Version 17.0, Chicago, IL), Stata 11.1 (StataCorp, College Station, TX), and MULTILOG (Scientific Software International, Lincolnwood, IL) were used for all analyses. Descriptive statistics were used to determine means and standard deviations. *T*-tests were used to compare mean differences between age groups. Pearson's *r* was used for zero-order correlations, followed by comparisons of Fisher's z-transformed values across age groups [14] and for dependent correlation coefficients [14, 16]. Item response theory was used to develop the GCS Composite Score. Significance level was set at $P < .05$.

3. Results

3.1. Comparison of Physical Performance Data across Age Groups. Table 1 presents descriptive statistics for octogenarians and centenarians. As can be seen, octogenarians have significantly higher ($P < .001$) physical performance than centenarians on leg strength, grip strength, the SPPB, the PPME, and the IRT-derived physical performance measure. Consistent with the population-based nature of this study, a higher proportion of the centenarian sample was female and institutionalized compared with the octogenarian sample, but there were no differences in race.

3.2. Norms from the Georgia Centenarian Study. Figure 1 compares the proportion of the Georgia Centenarian Study sample in each of the four scoring categories reported in [5, 9]. For comparative purposes, we present our results alongside those derived from the EPESE sample for men and women aged 70 to 79 [9]. As can be seen, a large proportion of centenarians (73.0% and 86.0% of men and women, resp.) fall into the severely disabled categories whereas none could be classified as having no disability (0% for both men and women). Comparable values for octogenarians indicated that 22.2% and 30.2% of men and women, respectively, were in the most disabled category whereas 14.8% and 9.4% of men and women, respectively, were classified as having no disability. (Supplemental Table S2 provides norms by gender and age group on each performance scale. Table S3 presents the age group proportions of the sample performing at floor and ceiling for the three scales. Table S4 describes characteristics of the sample performing at the floor on each scale.)

3.3. Evidence for Concurrent Validity of the GCS Scale. Table 2 presents zero-order correlations among physical performance measures for octogenarians (above diagonal) and centenarians (below diagonal). For octogenarians, the GCS scale generally shows similar magnitude correlations with each of the other measures. GCS Composite scores correlate more highly with DAFS BADL scores than do SPPB scores but there are no other differences. In contrast with centenarians, GCS Composite scores correlate more highly

Table 2: Intercorrelations among performance measures and criterion variables for Centenarians (below diagonal) and Octogenarians (above diagonal).

	SPPB	PPME	GCS	DAFS BADL	DAFS IADL	Leg strength	Grip strength
SPPB	1.000	0.807	0.862	**0.503**	0.582	0.467	0.410
PPME	0.724	1.000	0.952	0.583	0.633	0.445	0.469
GCS	0.783	0.891	1.000	**0.630**	0.641	0.485	0.448
DAFS BADL	***0.406***	*0.487*	**0.585**	1.000	0.839	0.432	0.496
DAFS IADL	**0.533**	0.531	**0.610**	0.747	1.000	0.508	0.532
Leg strength	**0.510**	0.518	**0.581**	0.449	0.501	1.000	0.181
Grip strength	**0.461**	0.508	**0.613**	0.431	0.475	0.406	1.000

Note. Entries which share an attribute (**bold**, underline, *italics*) are significantly different within age group, $P < .05$.

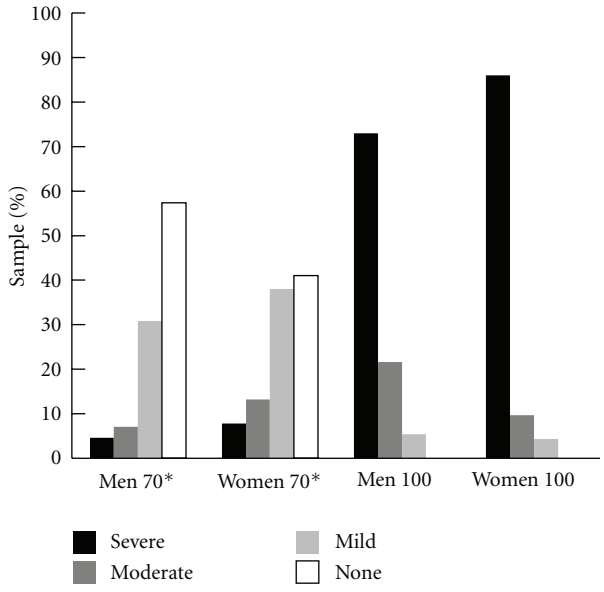

Figure 1: Comparison of SPPB performance categories between GCS Centenarians and EPESE 70–79 Cohort.

Table 3: Distance from mortality (months) by physical performance categories.

	% of column total			
Category	0–6	7–12	13–24	25+
		SPPB		
0–3	100.0	87.5	87.0	75.9
4–6	0.0	7.5	10.9	17.2
7–9	0.0	5.0	2.2	6.9
10–12 (not observed)	0.0	0.0	0.0	0.0
		PPME		
0	57.1	27.5	45.7	28.4
1-2	16.7	32.5	21.7	12.9
3-4	16.7	20.0	15.2	27.6
5-6	9.5	20.0	17.4	31.0
		GCS		
1–4	57.1	50.0	58.7	36.2
5-6	26.2	25.0	13.0	12.1
7–9	16.7	25.0	19.6	31.9
10–12	0.0	0.0	8.7	19.8

than SPPB and PPME with DAFS BADL and IADL scores, leg extensor strength, and grip strength. The PPME is more highly correlated with DAFS BADL scores than the SPPB, but there are no other differences between the SPPB and PPME for this age group. (Figure S2 shows a scatterplot of GCS Composite scores against SPPB and PPME scores.)

3.4. Evidence for Predictive Validity of the GCS Scale. Predictive validity is a very important criterion for any measure of physical performance in centenarians. The distribution of time to mortality by SPPB, PPME, and GCS Composite scores are shown in Table 3 with mortality within 0–6, 7–12, 13–24, or 25+ months from interview. Both the SPPB and PPME show some irregularity in proportionality of higher performers dying earlier and low performers still alive. In sharp contrast, the GCS Composite scale shows a regular progression of mortality where no high performers died within 6 months and a more systematic stepwise proportionality of those who died at successively longer times following assessment.

4. Discussion

Because of the vast range of functioning observed, centenarians present unique challenges to evaluation and assessment, particularly in the context of a population-based research. We set out to provide norms for physical performance in centenarians using established scales and to demonstrate the concurrent and predictive validity of an extended scale developed through IRT using the SPPB, PPME, and grip strength.

With regard to normative functioning, severe impairment is the modal category when the SPPB instrument was used as the criterion, and no centenarians performed at the highest levels on that scale. Centenarians score significantly lower on every indicator of physical performance than octogenarians. At the same time, however, use of a measure

intended for more severely impaired populations did not solve the problem. Rather, many centenarians performed at the ceiling on the PPME. Thus, of necessity, a scale that combines the information provided at each end of the continuum is essential. By combining the tasks from two psychometrically sound instruments (SPPB and PPME) and adding a measure of grip strength in order to provide information about those with the very lowest physical performance, we were able to capture a larger range of abilities, particularly among those in the lowest functioning range. Although many approaches to scaling could have been used, we adopted IRT methodology because its origins in scaling measures across disparate ability levels when underlying true values are unknown.

In terms of concurrent validity, our GCS Composite scale performed favorably compared with either the SPPB or PPME measures, correlating more highly with observed performance on BADLs and IADLs among centenarians, as well as grip strength and leg extensor strength. Equally importantly, it performed as well as these scales among octogenarians, suggesting that our methodology was sufficient to capture the wide differences in physical performance between these age groups.

Finally, the GCS Composite scale also had favorable properties in terms of predictive validity, with higher scores associated with progressively longer time to mortality. The patterning in the other scaling methods lacks the systematic pattern of longevity.

A primary limitation of this study was the missing data which resulted from the initial attempts to limit participant burden. This was addressed through statistical and field note procedures to recover a full complement of data. Likewise, it would have been desirable to have test-retest data on our instrument, but this was not generally possible due to the taxing nature of providing physical population in a study which was already divided into 5 2-hour sessions. The strengths of this study are that data from this population sampling of the oldest provides information on the order and patterning of the most commonly measured tasks. It also provides a single performance scale with negligible floor or ceiling effects. Given the incredibly rapid growth among the centenarian population, having high quality normative data available to researchers and clinicians is of the utmost importance.

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References

[1] B. Hagberg, B. B. Alfredson, L. W. Poon, and A. Homma, "Cognitive functioning in centenarians: a coordinated analysis of results from three countries," *Journals of Gerontology—Series B*, vol. 56, no. 3, pp. P141–P151, 2001.

[2] L. W. Poon, S. M. Jazwinski, R. C. Green, J. L. Woodard, P. Martin, and W. L. Rodgers, "Methodological considerations in studying centenarians: lessons learned from the georgia centenarian studies," in *Annual Review of Gerontology and Geriatrics*, L. W. Poon and T. T. Perls, Eds., pp. 231–264, Springer, New York, NY, USA, 2007.

[3] Y. Gondo, N. Hirose, Y. Arai et al., "Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity," *Journals of Gerontology—Series A*, vol. 61, no. 3, pp. 305–310, 2006.

[4] J. D. Curb, C. D. Ceria-Ulep, B. L. Rodriguez et al., "Performance-based measures of physical function for high-function populations," *Journal of the American Geriatrics Society*, vol. 54, no. 5, pp. 737–742, 2006.

[5] A. Davey, M. Elias, I. C. Siegler, et al., "Cognitive, physical performance, health, and disease: norms from the Georgia centenarian study," *Experimental Aging Research*. In press.

[6] J. Arnold, J. Dai, L. Nahepetyan, et al., "Predicting successful aging in a population-based sample of Georgia centenarians," *Current Gerontology and Geriatrics Research*. In press.

[7] L. W. Poon and T. T. Perls, Eds., *Annual Review of Gerontology and Geriatrics: Biopsychosocial Approaches to Longevity*, Springer, New York, NY, USA, 2007.

[8] B. Jeune, A. Skytthe, A. Cournil et al., "Handgrip strength among nonagenarians and centenarians in three European regions," *Journals of Gerontology—Series A*, vol. 61, no. 7, pp. 707–712, 2006.

[9] J. M. Guralnik, E. M. Simonsick, L. Ferrucci et al., "A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission," *Journals of Gerontology*, vol. 49, no. 2, pp. M85–M94, 1994.

[10] J. M. Guralnik, L. Ferrucci, E. M. Simonsick, M. E. Salive, and R. B. Wallace, "Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability," *The New England Journal of Medicine*, vol. 332, no. 9, pp. 556–561, 1995.

[11] C. H. Winograd, C. M. Lemsky, M. C. Nevitt et al., "Development of a physical performance and mobility examination," *Journal of the American Geriatrics Society*, vol. 42, no. 7, pp. 743–749, 1994.

[12] B. Jeune and J. W. Vaupel, Eds., *Validation of Exceptional Longevity: Odense Monographs on Population Aging*, University Press of Southern Denmark, Funen, Denmark, 1999.

[13] J. Dai, A. Davey, I. C. Siegler, J. Arnold, and L. W. Poon, "GCSDB: an integrated database system for the Georgia centenarian study," *Bioinformation*, vol. 1, no. 6, pp. 214–219, 2006.

[14] D. A. Loewenstein, E. Amigo, R. Duara et al., "A new scale for the assessment of functional status in Alzheimer's disease and related disorders," *Journals of Gerontology*, vol. 44, no. 4, pp. P114–P121, 1989.

[15] M. Mitchell and L. S. Miller, "Prediction of functional status in older adults: the ecological validity of four Delis-Kaplan Executive Function System tests," *Journal of Clinical and Experimental Neuropsychology*, vol. 30, no. 6, pp. 683–690, 2008.

[16] X.-L. Meng, R. Rosenthal, and D. B. Rubin, "Comparing correlated correlation coefficients," *Psychological Bulletin*, vol. 111, no. 1, pp. 172–175, 1992.

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Review Article

Brain Aging in the Oldest-Old

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Nonagenarians and centenarians represent a quickly growing age group worldwide. In parallel, the prevalence of dementia increases substantially, but how to define dementia in this oldest-old age segment remains unclear. Although the idea that the risk of Alzheimer's disease (AD) decreases after age 90 has now been questioned, the oldest-old still represent a population relatively resistant to degenerative brain processes. Brain aging is characterised by the formation of neurofibrillary tangles (NFTs) and senile plaques (SPs) as well as neuronal and synaptic loss in both cognitively intact individuals and patients with AD. In nondemented cases NFTs are usually restricted to the hippocampal formation, whereas the progressive involvement of the association areas in the temporal neocortex parallels the development of overt clinical signs of dementia. In contrast, there is little correlation between the quantitative distribution of SP and AD severity. The pattern of lesion distribution and neuronal loss changes in extreme aging relative to the younger-old. In contrast to younger cases where dementia is mainly related to severe NFT formation within adjacent components of the medial and inferior aspects of the temporal cortex, oldest-old individuals display a preferential involvement of the anterior part of the CA1 field of the hippocampus whereas the inferior temporal and frontal association areas are relatively spared. This pattern suggests that both the extent of NFT development in the hippocampus as well as a displacement of subregional NFT distribution within the Cornu ammonis (CA) fields may be key determinants of dementia in the very old. Cortical association areas are relatively preserved. The progression of NFT formation across increasing cognitive impairment was significantly slower in nonagenarians and centenarians compared to younger cases in the CA1 field and entorhinal cortex. The total amount of amyloid and the neuronal loss in these regions were also significantly lower than those reported in younger AD cases. Overall, there is evidence that pathological substrates of cognitive deterioration in the oldest-old are different from those observed in the younger-old. Microvascular parameters such as mean capillary diameters may be key factors to consider for the prediction of cognitive decline in the oldest-old. Neuropathological particularities of the oldest-old may be related to "longevity-enabling" genes although little or nothing is known in this promising field of future research.

1. Introduction

The rapid growth of the world population's oldest-old age segment has prompted awareness of age-related diseases including dementia as well as considerable interest in the study of the aging human brain. By 2020, people older than 60 years will account for more than 20% of the total population with those individuals reaching very old ages corresponding to the fastest growing age group worldwide. Rare at the beginning of the 20th century in Switzerland with about 650 people aged 90 or more, a steady increase occurred with a total of 2000 oldest-old persons by 1945. Near exponential growth of this oldest-old group occurred after 1945 with the total number of oldest-old citizens amounting to 47000 by 2001, that is, a multiplication of 25 in 56 years [1]. The number of centenarians was multiplied by 66 since 1950. The Swiss Federal Office for Statistics predicts between 90000 and 100000 persons over 90 years by 2040 and between 110000 and 146000 by 2060 with life expectancy in women possibly reaching 90 years. Similarly, the number of centenarians increases steadily in France, the USA, New Zealand, Japan (for review see [2–4]), and also in the African American community notwithstanding a lower life expectancy at birth [5].

Our ancestral fascination for extreme aging and the steady increase of the number of centenarians worldwide prodded the research community to look into psychobiological particularities of the "longevity outliers". The known socio demographic predictors of mortality such as smoking and obesity are less important in this age group [6–11]. Centenarians may be less prone to oxidative stress and have better nutritional status, immunologic profile, endocrinologic and metabolic characteristics than younger elderly cohorts [12, 13]. The oldest-old may have on average a better health with a rapid terminal decline relative to those who die earlier [14]. They report greater satisfaction with life and social and family relations and display lower scores for anxiety and depression and better coping abilities compared to younger-old individuals [15]. In the oldest-old, good health is associated with greater intellectual activity, while greater social activity was predicted by extraversion and, interestingly, negative life events [16]. Thus, centenarians may form a select cohort with relatively slow rates of aging and increased resistance to biological and psychological stress.

2. Dementia in the Oldest-Old

Life expectancy with or without incapacity has increased markedly: some subjects may remain independent for long periods into older age while others require help and care over extended periods of their lives. In Switzerland, the proportion of persons living in nursing homes increases from only 5% for those below 80 years to 40% for those between 90 and 94 years of age. Dementia clearly contributes to this reality. However, it remains unclear how to define dementia in the frail oldest-old and what it means to be a dementia-free centenarian despite the claim of some researches that up to a quarter of all centenarians may be cognitively intact [17, 18]. Thus, it does not come as a surprise that trustworthy prevalence and incidence data are still scarce in the oldest-old age group. In a community sample of 250000 people, 17 centenarians were traced down and 15 could be examined of whom all had cognitive impairment with a CDR ranging from 1 to 3 [19]. The authors' most conservative estimation of dementia in those 100 years old or more amounted to 88%. Very old age has long been thought to be associated with the highest prevalence of dementia [19–21]. More recent epidemiological and clinical studies in larger cohorts of very old individuals showed prevalence rates which varied widely. This variability suggests, on the one hand, that substantial methodological difficulties remain and, on the other hand, that dementia is not inevitable in very old individuals (for review see [2, 17]) and may even decrease after age 90 [22–24]. However, the pendulum is currently swinging back and preliminary results now indicate that dementia and AD continue to rise also at very high ages with both incidence and prevalence of dementia being highest in the oldest-old [25, 26]. Although further studies with better operational criteria for dementia in the oldest-old are still needed to settle these controversies, epidemiological and clinical studies nevertheless indicate that the oldest-old are likely to be biologically different from the younger-old. The lack of an association between Alzheimer's disease (AD) and ApoE4—a known risk factor for late-onset AD in younger cohorts—in centenarians adds further evidence to this hypothesis [27–30]. The study of oldest-old individuals may permit to define the spectrum and extent of changes in brain morphology that occur with normal brain aging and assess correlations between the neuropathological definition of normal brain aging and the clinical development of dementia [31–33].

3. AD-Related Lesion Distribution Patterns in the Normal Elderly

Brain aging is characterized by the formation of neurofibrillary tangles (NFTs) and senile plaques (SPs) as well as neuronal and synaptic loss in both cognitively intact individuals and patients with AD. The first cited diagnostic criteria for AD were intended to aid in the development of uniform procedures by proposing minimally required SP densities as a function of age [34, 35]. These recommendations were not broadly accepted and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) proposed another set of standardized neuropathological criteria [36]. These semiquantitative criteria were determined as a function of the development of neuritic plaques in three age groups (less than 50, 50 to 75, and over 75). The diagnosis was based on a combination of clinical information and an "age-related plaque score" that reflected the maximal cortical involvement. This combination yielded a tripartite level of diagnostic certainty (i.e., definite, probable, or possible AD). However, the lesion load in the hippocampal formation was not entered into the diagnostic algorithm despite its involvement in the pathogenesis of AD. At that, CERAD criteria have been inspired somewhat unilaterally by the amyloid cascade hypothesis and do not consider NFT densities in the neocortex, even though the latter correlate better with the severity of dementia. In other words, severe SP formation may take place in the neocortex in the presence of only very mild cognitive impairment (for review see [37, 38]). Furthermore, the central pathological hallmark of AD, that is, NFT, is found in subjects with no significant cognitive impairment. Indeed, there is a significant overlap in NFT and neuritic plaques burden between cognitively impaired and cognitively intact individuals [39]. Thus, in 97 nondemented people with a mean age of 84 years, about 40% met at least some level of and 20% strict criteria for neuropathological criteria for AD [40]. Clearly, the clinical significance of NFT is not unequivocal and other pathological predictors are likely to exist of which reduced neuron number appears to be a candidate. Indeed, stereological analyses have revealed age-related decreases in total neuron number of 30% and 50% in the dentate hilus of the hippocampus and subiculum, respectively, between ages 13 and 85. Conversely, no neuronal loss was found in CA1-3 fields and entorhinal cortex during normal aging in contrast to AD [41–43]. In normal aging, there is no additional depletion, as in AD, of neuronal cell bodies in the dentate hilus and subiculum, or a massive

reduction in the numbers of pyramidal neurons in the CA1 field and layers II and V of the entorhinal cortex [41–45].

4. Clinicopathological Correlations in Typical Alzheimer's Disease

While the definite diagnosis of AD is based on neuropathological criteria, the clinical diagnosis of probable and possible AD in clinical settings is usually made according to the NINCDS-ADRDA criteria [46]. Typical AD is characterized by an insidious onset and a progressively worsening course of episodic memory. The most common initial presentation of AD is that of a progressive amnestic syndrome [47]. Executive, linguistic, visuospatial, and other cognitive deficits are subsequently grafted upon the primary progressive memory impairment with functional deficits and increasing dependency paralleling the course of the cognitive decline. Prospective studies of large cohorts of patients with typical AD have shown a prototypical and predictable clinical course [48] although important atypical variations often occur (for a review [49]).

In terms of clinicopathological correlations, several lines of evidence indicate that the primary progressive amnestic syndrome so characteristic of the initial stages of typical AD is the consequence of the neuropathological changes in the medial temporal structures, in particular the entorhinal cortex and the hippocampus. Although there is still ongoing controversy as to the exact roles of these structures in cognition, they are likely to be important in encoding new information [50–52]. The initial stages of AD are characterized by NFT spread from the entorhinal cortex to the hippocampus, corresponding to Braak and Braak stages 1 and 2, which precedes the progressive invasion of the allocortex and isocortex [53]. The NFT distribution is not only area-specific but also cell-specific. In the hippocampus, particularly in the CA1 and CA2 regions, pyramidal cells are selectively damaged whereas glutamatergic cells degenerate in the entorhinal cortex presumably interrupting complex neuronal circuits in the medial temporal lobe that are indispensable for encoding new information [54–57]. Besides episodic memory deficits, early impairment of olfactory perception has been described and kindled hope that this observation might allow early and easy detection of AD [58–61]. Besides the early damage of the limbic system, previous clinicopathological studies also revealed strong relationships between the patterns of NFT distribution and cognitive deficits in typical AD cases. For instance, constructional apraxia correlated with NFT densities in Brodmann areas 7 and 18 [62], and other specific correlations were found for associative visual agnosia [63], naming and identification of famous faces [64], and spatial disorientation [65]. In contrast to NFT, SP correlate less well with clinical features and their presence may be associated with no or only minimal intellectual changes in the elderly (for a review see [50–52]).

5. AD-Related Lesion Distribution Patterns in the Oldest-Old

Most of the above studies have not included very old subjects. The question, thus, arises whether or not the pattern of lesion distribution and neuronal loss changes in extreme aging.

5.1. Oldest-Old versus Younger-Old with or without Dementia (cf. also Table 1 for a Schematic Representation). A recent study using the CERAD criteria for neuropathological diagnosis found a progressive increase of moderate to severe AD-type pathology with age in subjects between 69 and 103 years in those without dementia [66]. In the demented, dementia status is mainly related to severe NFT formation within adjacent components of the medial and inferior aspects of the temporal cortex in younger cases whereas oldest-old individuals with dementia display a preferential involvement of the anterior part of the CA1 field of the hippocampus with relative sparing of the inferior temporal and frontal association areas [44, 67]. The progression of NFT formation across the different CDR groups was significantly slower in nonagenarians and centenarians (from 1 to 17% in the entorhinal cortex and 1.7 to 37% in the CA1 field) compared to recent observations in a series of younger cases (from 4 to 79% in the entorhinal cortex and 3 to 80% in the CA1 field) [68]. The degree of interindividual variability for NFT numbers was, however, quite similar between younger and elderly cohorts [68]. The Oregon brain aging study on neuropathologic aging and cognitive function in healthy oldest-old individuals confirmed this pattern of NFT distribution in the CA1 field [32]. In agreement with previous observations in centenarian brains [44], even cases with moderate dementia display only mild NFT formation in the entorhinal cortex with more than 80% of preserved neurons. This contrasts with the results of several previous studies in younger samples which demonstrated that the entorhinal cortex is more severely affected and involved earlier in the degenerative process than hippocampal regions [38, 69–71].

The magnitude of neuronal loss in the entorhinal cortex and CA1 field in older subjects was significantly lower than that reported in younger AD cases [45, 58, 68, 72, 73]. Moreover, the extensive neuronal loss in the hippocampal formation reported in younger AD series [74] appears to be confined to layer II of the entorhinal cortex in nonagenarians and centenarians [44]. In this latter group, the number of layer II entorhinal cortex neurons is thought to decrease by 60% in patients with CDR 0.5 and by 90% in severe AD cases [45]. In the CA1 field, a depletion of 38% to 69% was reported [45, 58, 68, 72, 73]. These data imply that, like AD pathologic changes, neuronal loss is less prominent in the oldest-old even in the presence of AD [44]. In conjunction with the observations of only mild synaptic loss and cerebral amyloid angiopathy in centenarians [75] these findings give additional support to the notion that the occurrence and progression of AD-related pathologic changes are not a sine qua non concomitant of increasing age [32, 44, 76, 77].

Strong relationships between NFT counts and neuron loss in the hippocampal formation and neocortex have been

Table 1: Alzheimer's disease pathology in the cognitively impaired young-old versus oldest-old.

	Cognitively impaired young-old subjects	Cognitively impaired oldest-old subjects
Senile plaques	Higher amyloid load but lower correlation with neurone loss and cognitive status	Lower amyloid load but better correlation with neurone loss and cognitive status
Neurofibrillary tangles	Early and significant CA2-3 involvement	Invasion of anterior CA1 field
	Early and significant EC involvement	Mild invasion of EC
	Significant inferior temporal and frontal associative cortex involvement with increasing dementia	Relative sparing of inferior temporal and frontal associative cortex
	Less parietal and cingulate cortex involvement	More parietal and cingulate cortex involvement
	With advancing dementia, quick invasion of CA1 andspread to adjacent associative cortex	With advancing dementia, lower invasion of CA1 and less spread to associative cortex
	Higher strength of association with dementia	Lower strength of association with dementia
	High interindividual variability	
Neurones	Loss of pyramidal neurones in CA1 and EC	Less neurone loss in CA1 Possibly, relative sparing of EC neurones
	More NFT-related neurone loss	Less NFT-related neurone loss

NFT: neurofibrillary tangles; CA: Cornu Ammonis; EC: entorhinal cortex.

reported and suggest that neuronal loss is NFT-dependent [45]. However, our data reveal a dissociation between the patterns of progression of NFT and neuronal loss in the entorhinal cortex and CA1 field [78]. Non-NFT related mechanisms of neurodegeneration may therefore determine neuronal depletion in the oldest-old age group [44]. These mechanisms remain largely speculative, but recent contributions postulate that apoptosis, oxidative stress and excitotoxic mechanisms play a key role in inducing neuronal death that would predate NFT formation in some regions (for review see [73]).

Unlike younger cohorts where SP formation does not correlate with neuronal depletion and cognitive status [79–81], both earlier and more recent studies suggest that SP densities in the neocortex are related to the degree of neuronal loss and severe AD in the oldest-old [32, 44]. However, older cases also display significantly lower total amyloid volume in the areas studied compared to that reported in younger series (20 mm^3 versus 100–800 mm^3) [82].

5.2. Demented Oldest-Old versus Nondemented Oldest-Old (cf. also Table 2 for a Schematic Representation). As mentioned above, the association between AD-type pathology and dementia, in a cohort of 456 subjects between 69 and 103 years was stronger in the younger old persons than in the older old ones [66]. Oldest-old individuals with dementia display a preferential involvement of the anterior part of the CA1 field of the hippocampus with relative sparing of the inferior temporal and frontal association areas [44, 67]. Thus, NFT development in the hippocampus may be the key determinant of dementia in the very old. In line with this view, higher NFT densities were found in the CA1 field of one demented centenarian as compared to eleven cognitively intact centenarians [83]. NFT densities in the anterior CA1 but not in the posterior CA1 field and entorhinal cortex, were significantly different between demented and nondemented very old patients [31, 44, 77]. However, other studies find evidence for more extensive brain involvement in the oldest-old with dementia. In a such study of 19 centenarians including four AD cases, substantial NFT involvement was present not only in the hippocampus but also the entorhinal cortex [84].

5.3. Clinicopathological Correlations in the Oldest-Old

5.3.1. AD-Pathology. Several cases with minimal AD pathology and preserved cognitive functions [31, 33, 67], so called "supernormal centenarians", represent a rare phenotype relatively protected from AD pathology and bear witness to successful aging near the upper limit of the human life span. Recent studies attempted to define the cognitive impact of NFT, SP, and neuronal loss in this age group. As mentioned, the strength of the association between overall AD pathology and dementia declined with age [66]. However, not only the global lesion load, but also the lesion distribution may play a role. Thus, AD-related pathology including the assessment of total NFT, neuron numbers, and amyloid volume in entorhinal cortex, CA fields, and dentate gyrus was performed in 12 individuals over 90 years with variable degrees of cognitive decline [85]. Total neuron numbers and volumes of reference were fairly consistent among cases. In fact, the estimates of these variables fall well within the range of previous stereologic assessments in these regions from cognitively intact elderly individuals [45, 58, 68, 72, 74, 82, 86]. As mentioned, even cases with moderate dementia display only mild NFT formation and neuron loss in the entorhinal cortex while the entorhinal cortex is more severely affected and involved earlier in the degenerative process than other hippocampal regions in younger samples [38, 69–71]. Strikingly, correlations between AD pathological hallmarks in the hippocampal formation and clinical status after 90

Table 2: Alzheimer's disease pathology in the oldest-old with versus without cognitive impairment.

	Cognitively intact oldest-old subjects	Cognitively impaired oldest-old subjects
Senile plaques	Similar lesion load	Similar lesion load
	Overall, poor correlation with clinical status	
Neurofibrillary tangles	No or little invasion of anterior CA1 field	Invasion of anterior CA1 field
	Similar density in posterior CA1field	Similar density in posterior CA1 field
	Similar, mild invasion of EC	Similar, mild invasion of EC (controversial)
	Possibly less neuritic dystrophy	Possibly more neuritic dystrophy
	Overall, poor correlation with clinical status	
Neurones	Similar neurone counts	Similar neurone counts
	Overall, poor correlation with clinical status	

CA: Cornu Ammonis; EC: entorhinal cortex.

years were poor [85]. Only a modest percentage of the CDR variability was explained by NFT counts in CA2-3 (18%) and the dentate gyrus (17%). Neither neuron numbers nor total amyloid volumes were significantly related to the CDR score. In spite of the clear neuronal loss observed in cases with moderate to severe dementia, total neuron numbers in the entire sample did not significantly predict cognitive status. Overall, sparing of the entorhinal cortex and CA1 field in the oldest-old relative to younger cohorts suggests that independent morphometric variables may decisively contribute to the cognitive decline in this age group.

Indeed, neuritic dystrophy [87] may be a further contributor. Neuropil threads are thought to account for 85-90% of cortical tau pathology in normal brain ageing [88] and, thus, they may contribute to cognitive deterioration. However, neuropil thread formation in the hippocampus did not appear to be an independent marker of dementia severity as their length was strongly correlated with NFT numbers at least in the early stages of the degenerative process in the oldest-old [89]. Progression of hippocampal and entorhinal tau burden was associated with dementia status, but this effect disappeared when adjusted for Braak and Braak stages [90].

5.4. Other Pathological Changes. Synaptic loss may be an important factor [87]. Recently, significant hypertrophy of the cell bodies, nuclei, and nucleoli in the CA1 neurons was found in elderly nuns with normal cognition but substantial AD-type lesions suggesting that neuronal hypertrophy may constitute an early cellular response to AD or reflect compensatory mechanisms [91]. Structural parameters of the cerebral vasculature such as perivascular collagen deposits, atrophy of endothelium, basement membrane thickening and pericyte degeneration as well as qualitative changes in microvascular structure (such as glomerular loops and twisted capillaries) as described both in the aging brain and in AD offer themselves as still further contributors to cognitive decline (for review see [87, 92–95]). Quantitative analyses of structural parameters such as capillary density, diameters, or length led to controversial data [96–103]. The development of modern design-based stereological techniques allowed for a more accurate assessment of age-related changes in the capillary network [104, 105] and open up this field of study to nonagenarians and centenarians. In 19 very old individuals with various degrees of cognitive impairment, both mean diameters and total capillary numbers, but not total capillary length and capillary morphological parameters, were strongly related to total neuron numbers in the CA1 field and entorhinal cortex [106]. These results suggest a relationship between microvascular changes and AD-related neuronal depletion. Disruption of the balance between energy requirements and cerebral blood supply rendering the brain more vulnerable to oxidative stress damage and ultimately neuronal death may explain this link [93, 107–109]. Mean capillary diameters in the CA1 field and entorhinal cortex explained respectively 19% and 31.1% of the CDR scores, an association that persisted after adjustment for total neuron numbers, NFT numbers, or amyloid volume [106]. Instead of the recruitment of additional capillaries, increased cognitive load may induce differential distribution of flow [110], heterogeneity in blood flow velocity [111], and changes in capillary diameter [112].

In the longitudinal Oregon Brain Aging study, NFT and SP densities in neocortical areas were significantly related to cognitive scores [32]. Overt clinical signs of AD in oldest-old individuals appears to require a progressive damage of areas 7, 22, 23 and 24 suggesting a displacement of NFT, such that parietal and cingulate cortex are more affected than is usually the case in AD, whereas superior frontal and inferior temporal association areas are relatively preserved [44, 71].

6. Conclusions

The controversy over the continuity versus discontinuity between normal brain aging and dementia goes on. The hypothesis that AD is an ageing-related condition is supported by the nearly ubiquitous presence of AD pathologic changes in the course of brain aging and the exponential increase of AD prevalence after 65 years of age. However, contrasting with this view of the aging process, the study of oldest-old individuals indicates that the occurrence of AD pathology is not a mandatory phenomenon of increasing chronologic age. In particular, the neuropathology of advanced aging strongly suggests that very old individuals

with AD display a striking resistance to the neurodegenerative process with only mild neuronal loss in the hippocampal formation. Our hospital-based findings support a dissociation between the clinical expression and traditionally assessed AD pathology. These findings are consistent with the recent neuropathological observations of the New England Centenarian Study [8, 113] and show the limits of the lesional model for explaining the expression of dementia symptoms in this particular age group. Furthermore, they offer a new perspective in the field of clinicopathological correlations by revealing the cognitive impact of decreased capillary diameter, a structural but not lesional parameter of the aging brain. Similarly, we are not to forget changes at the cellular level reflecting both early cell stress to AD or compensatory mechanisms [91]. A further conclusion stemming from the observation of a looser association between AD-pathology and dementia in the oldest-old suggests the necessity to adapt current neuropathological criteria for the diagnosis of AD in this age group [114].

The biological background of the increased resistance to AD lesion development after 90 years is still poorly understood. Oldest-old people may show genetic variations that influence basic mechanisms of brain aging resulting in a decreased susceptibility to age-associated diseases [115]. In particular, the oldest-old may lack "disease genes" that predispose to fatal age-related diseases [116], or, alternatively, have so called "longevity-enabling" genes that confer protection against age-related illnesses and constitute future therapeutic targets to delay late-onset dementia [117, 118]. The sparing of CA1 field and entorhinal cortex in the oldest-old may be related to a genetically determined resistance of these neuronal subpopulations in very old people. Two candidate genes predisposing to longevity related to lipoprotein synthesis have been identified and suggest that protection against cardiovascular diseases may be primordial to achieve extreme old age [119–121]. Although the relationship between these vascular "longevity-enabling" genes and AD-related pathology is not clear, the link between preserved cognition and brain capillary diameter points to the need for exploring the genetic determinants of the microvascular system in very old individuals as well as possible links with compensatory mechanisms at the cellular level [91]. The development of structural investigation methods at the microscopic level in combination with differential gene expression studies may provide the future basis for a better understanding of longevity.

References

[1] J.-M. Robine and F. Paccaud, "Nonagenarians and centenarians in Switzerland, 1860–2001: a demographic analysis," *Journal of Epidemiology and Community Health*, vol. 59, no. 1, pp. 31–37, 2005.

[2] J. Ankri and M. Poupard, "Prevalence and incidence of dementia among the very old. Review of the literature," *Revue d'Epidemiologie et de Sante Publique*, vol. 51, no. 3, pp. 349–360, 2003.

[3] J.-M. Robine, Y. Saito, and C. Jagger, "The emergence of extremely old people: the case of Japan," *Experimental Gerontology*, vol. 38, no. 7, pp. 735–739, 2003.

[4] T. J. Wilkinson and R. Sainsbury, "The association between mortality, morbidity and age in New Zealand's oldest old," *International Journal of Aging and Human Development*, vol. 46, no. 4, pp. 333–343, 1998.

[5] T. P. Miles and M. A. Bernard, "Morbidity, disability, and health status of black American elderly: a new look at the oldest-old," *Journal of the American Geriatrics Society*, vol. 40, no. 10, pp. 1047–1054, 1992.

[6] P. Gueresi, L. Troiano, N. Minicuci et al., "The MALVA (MAntova LongeVA) study: an investigation on people 98 years of age and over in a province of Northern Italy," *Experimental Gerontology*, vol. 38, no. 10, pp. 1189–1197, 2003.

[7] H. Nybo, H. C. Petersen, D. Gaist et al., "Predictors of mortality in 2,249 nonagenarians—the Danish 1905-Cohort Survey," *Journal of the American Geriatrics Society*, vol. 51, no. 10, pp. 1365–1373, 2003.

[8] M. H. Silver, K. Newell, C. Brady, E. T. Hedley-White, and T. T. Perls, "Distinguishing between neurodegenerative disease and disease-free aging: correlating neuropsychological evaluations and neuropathological studies in centenarians," *Psychosomatic Medicine*, vol. 64, no. 3, pp. 493–501, 2002.

[9] M. L. Stek, J. Gussekloo, A. T. F. Beekman, W. Van Tilburg, and R. G. J. Westendorp, "Prevalence, correlates and recognition of depression in the oldest old: the Leiden 85-plus study," *Journal of Affective Disorders*, vol. 78, no. 3, pp. 193–200, 2004.

[10] P. von Heideken Wågert, B. Rönnmark, E. Rosendahl et al., "Morale in the oldest old: the Umeå 85+ study," *Age and Ageing*, vol. 34, no. 3, pp. 249–255, 2005.

[11] E. Von Strauss, L. Fratiglioni, M. Viitanen, Y. Forsell, and B. Winblad, "Morbidity and comorbidity in relation to functional status: a community-based study of the oldest old (90+ years)," *Journal of the American Geriatrics Society*, vol. 48, no. 11, pp. 1462–1469, 2000.

[12] H. R. Andersen, B. Jeune, H. Nybo, J. B. Nielsen, K. Andersen-Ranberg, and P. Grandjean, "Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians," *Age and Ageing*, vol. 27, no. 5, pp. 643–648, 1998.

[13] F. Moroni, M. L. Di Paolo, A. Rigo et al., "Interrelationship among neutrophil efficiency, inflammation, antioxidant activity and zinc pool in very old age," *Biogerontology*, vol. 6, no. 4, pp. 271–281, 2005.

[14] R. Hitt, Y. Young-Xu, M. Silver, and T. Perls, "Centenarians: the older you get, the healthier you have been," *Lancet*, vol. 354, no. 9179, p. 652, 1999.

[15] M. D. Buono, O. Urciuoli, and D. De Leo, "Quality of life and longevity: a study of centenarians," *Age and Ageing*, vol. 27, no. 2, pp. 207–216, 1998.

[16] P. K. Hillerås, A. F. Jorm, A. Herlitz, and B. Winblad, "Activity patterns in very old people: a survey of cognitively intact subjects aged 90 years or older," *Age and Ageing*, vol. 28, no. 2, pp. 147–152, 1999.

[17] M. Kliegel, C. Moor, and C. Rott, "Cognitive status and development in the oldest old: a longitudinal analysis from the Heidelberg Centenarian Study," *Archives of Gerontology and Geriatrics*, vol. 39, no. 2, pp. 143–156, 2004.

[18] T. Perls, "Dementia-free centenarians," *Experimental Gerontology*, vol. 39, no. 11-12, pp. 1587–1593, 2004.

[19] B. A. Blansjaar, R. Thomassen, and H. W. van Schaick, "Prevalence of dementia in centenarians," *International Journal of Geriatric Psychiatry*, vol. 15, no. 3, pp. 219–225, 2000.

[20] E. L. Schneider, "Aging in the third millennium," *Science*, vol. 283, no. 5403, pp. 796–797, 1999.

[21] R. Thomassen, H. W. van Schaick, and B. A. Blansjaar, "Prevalence of dementia over age 100," *Neurology*, vol. 50, no. 1, pp. 283–286, 1998.

[22] M. M. Fichter, I. Meller, H. Schroppel, and R. Steinkirchner, "Dementia and cognitive impairment in the oldest old in the community. Prevalence and comorbidity," *British Journal of Psychiatry*, vol. 166, pp. 621–629, 1995.

[23] D. B. Hoiuieson, A. Dame, R. Camicioli, G. Sexton, H. Payami, and J. A. Kaye, "Cognitive markers preceding Alzheimer's dementia in the healthy oldest old," *Journal of the American Geriatrics Society*, vol. 45, no. 5, pp. 584–589, 1997.

[24] N. T. Lautenschlager, L. A. Cupples, V. S. Rao et al., "Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old?" *Neurology*, vol. 46, no. 3, pp. 641–650, 1996.

[25] U. Lucca, M. Garri, A. Nobili, et al., "Risk of dementia continues to rise in the oldest old: the Monzino 80-plus study," *Alzheimer's & Dementia*, vol. 5, no. 4, supplement, p. 381, 2009.

[26] M. M. Corrada, R. Brookmeyer, D. Berlau, A. Paganini-Hill, and C. H. Kawas, "Prevalence of dementia after age 90: results from the 90+ study," *Neurology*, vol. 71, no. 5, pp. 337–343, 2008.

[27] K. Hestad, B. Kveberg, and K. Engedal, "Low blood pressure is a better predictor of cognitive deficits than the apolipoprotein e4 allele in the oldest old," *Acta Neurologica Scandinavica*, vol. 111, no. 5, pp. 323–328, 2005.

[28] K. Juva, A. Verkkoniemi, P. Viramo et al., "APOE $\varepsilon 4$ does not predict mortality, cognitive decline, or dementia in the oldest old," *Neurology*, vol. 54, no. 2, pp. 412–415, 2000.

[29] A. Salo, R. Ylikoski, A. Verkkoniemi et al., "Does apolipoprotein E influence learning and memory in the nondemented oldest old?" *International Psychogeriatrics*, vol. 13, no. 4, pp. 451–459, 2001.

[30] D. C. Spencer, T. Zitzelberger, D. Spielman, and J. Kaye, "MRS in relation to hippocampal volume in the oldest old," *Neurology*, vol. 60, no. 7, pp. 1194–1196, 2003.

[31] P. Giannakopoulos, P. R. Hof, M. Surini, J. P. Michel, and C. Bouras, "Quantitative immunohistochemical analysis of the distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of nonagenarians and centenarians," *Acta Neuropathologica*, vol. 85, no. 6, pp. 602–610, 1993.

[32] M. S. Green, J. A. Kaye, and M. J. Ball, "The Oregon Brain Aging Study: neuropathology accompanying healthy aging in the oldest old," *Neurology*, vol. 54, no. 1, pp. 105–113, 2000.

[33] T. Mizutani and H. Shimada, "Neuropathological background of twenty-seven centenarian brains," *Journal of the Neurological Sciences*, vol. 108, no. 2, pp. 168–177, 1992.

[34] M. Ball, H. Braak, P. Coleman et al., "Consensus recommendations for the postmortem diagnosis of Alzheimer's disease," *Neurobiology of Aging*, vol. 18, no. 4, supplement 1, pp. S1–S2, 1997.

[35] Z. S. Khachaturian, "Diagnosis of Alzheimer's disease," *Archives of Neurology*, vol. 42, no. 11, pp. 1097–1105, 1985.

[36] S. S. Mirra, A. Heyman, D. McKeel et al., "The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease," *Neurology*, vol. 41, no. 4, pp. 479–486, 1991.

[37] P. Giannakopoulos, P. R. Hof, J.-P. Michel, J. Guimon, and C. Bouras, "Cerebral cortex pathology in aging and Alzheimer's disease: a quantitative survey of large hospital-based geriatric and psychiatric cohorts," *Brain Research Reviews*, vol. 25, no. 2, pp. 217–245, 1997.

[38] J. H. Morrison and P. R. Hof, "Life and death of neurons in the aging brain," *Science*, vol. 278, no. 5337, pp. 412–419, 1997.

[39] P. G. Ince, "Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales," *Lancet*, vol. 357, no. 9251, pp. 169–175, 2001.

[40] J. L. Price, D. W. McKeel Jr., V. D. Buckles et al., "Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease," *Neurobiology of Aging*, vol. 30, no. 7, pp. 1026–1036, 2009.

[41] J. L. Price, P. B. Davis, J. C. Morris, and D. L. White, "The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease," *Neurobiology of Aging*, vol. 12, no. 4, pp. 295–312, 1991.

[42] M. J. West, "Regionally specific loss of neurons in the aging human hippocampus," *Neurobiology of Aging*, vol. 14, no. 4, pp. 287–293, 1993.

[43] M. J. West, P. D. Coleman, D. G. Flood, and J. C. Troncoso, "Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease," *Lancet*, vol. 344, no. 8925, pp. 769–772, 1994.

[44] P. Giannakopoulos, P. R. Hof, E. Kövari, P. G. Vallet, F. R. Herrmann, and C. Bouras, "Distinct patterns of neuronal loss and Alzheimer's disease lesion distribution in elderly individuals older than 90 years," *Journal of Neuropathology and Experimental Neurology*, vol. 55, no. 12, pp. 1210–1220, 1996.

[45] T. Gómez-Isla, J. L. Price, D. W. McKeel Jr., J. C. Morris, J. H. Growdon, and B. T. Hyman, "Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease," *Journal of Neuroscience*, vol. 16, no. 14, pp. 4491–4500, 1996.

[46] G. McKhann, D. Drachman, and M. Folstein, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[47] R. C. Petersen, "Clinical subtypes of Alzheimer's disease," *Dementia and Geriatric Cognitive Disorders*, vol. 9, supplement 3, pp. 16–24, 1998.

[48] B. Reisberg, S. H. Ferris, M. J. de Leon, and T. Crook, "The global deterioration scale for assessment of primary degenerative dementia," *American Journal of Psychiatry*, vol. 139, no. 9, pp. 1136–1139, 1982.

[49] A. von Gunten, C. Bouras, E. Kövari, P. Giannakopoulos, and P. R. Hof, "Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease," *Brain Research Reviews*, vol. 51, no. 2, pp. 176–211, 2006.

[50] J. C. Morris, M. Storandt, D. W. McKeel Jr. et al., "Cerebral amyloid deposition and diffuse plaques in "normal" aging: evidence for presymptomatic and very mild Alzheimer's disease," *Neurology*, vol. 46, no. 3, pp. 707–719, 1996.

[51] D. W. Dickson, H. A. Crystal, L. A. Mattiace et al., "Identification of normal and pathological aging in prospectively studied nondemented elderly humans," *Neurobiology of Aging*, vol. 13, no. 1, pp. 179–189, 1992.

[52] P. Delaere, C. Duyckaerts, C. Masters, K. Beyreuther, F. Piette, and J.-J. Hauw, "Large amounts of neocortical βA4 deposits without neuritic plaques nor tangles in a psychometrically assessed, non-demented person," *Neuroscience Letters*, vol. 116, no. 1-2, pp. 87–93, 1990.

[53] H. Braak and E. Braak, "Neuropathological stageing of Alzheimer-related changes," *Acta Neuropathologica*, vol. 82, no. 4, pp. 239–259, 1991.

[54] D. L. Price, "Aging of the brain and dementia of the Alzheimer type," in *Principles of Neural Science*, E. R. Kandel, J. H. Schwartz, and T. M. Jessell, Eds., pp. 1149–1168, McGraw-Hill, New York, NY, USA, 4th edition, 2000.

[55] L. R. Squire, "Mechanisms of memory," *Science*, vol. 232, no. 4758, pp. 1612–1619, 1986.

[56] L. R. Squire, "Memory systems of the brain: a brief history and current perspective," *Neurobiology of Learning and Memory*, vol. 82, no. 3, pp. 171–177, 2004.

[57] L. R. Squire, C. E. L. Stark, and R. E. Clark, "The medial temporal lobe," *Annual Review of Neuroscience*, vol. 27, pp. 279–306, 2004.

[58] J. L. Price, A. I. Ko, M. J. Wade, S. K. Tsou, D. W. McKeel, and J. C. Morris, "Neuron number in the entorhinal cortex and CA1 in preclinical alzheimer disease," *Archives of Neurology*, vol. 58, no. 9, pp. 1395–1402, 2001.

[59] L. M. Levy, R. I. Henkin, A. Hutter, C. S. Lin, D. Martins, and D. Schellinger, "Functional MRI of human olfaction," *Journal of Computer Assisted Tomography*, vol. 21, no. 6, pp. 849–856, 1997.

[60] R. I. Mesholam, P. J. Moberg, R. N. Mahr, and R. L. Doty, "Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Ahlzheimer's and Parkinson's diseases," *Archives of Neurology*, vol. 55, no. 1, pp. 84–90, 1998.

[61] D. P. Devanand, K. S. Michaels-Marston, X. Liu et al., "Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up," *American Journal of Psychiatry*, vol. 157, no. 9, pp. 1399–1405, 2000.

[62] K. A. Nielson, B. J. Cummings, and C. W. Cotman, "Constructional apraxia in Alzheimer's disease correlates with neuritic neuropathology in occipital cortex," *Brain Research*, vol. 741, no. 1-2, pp. 284–293, 1996.

[63] P. Giannakopoulos, G. Gold, M. Duc, J.-P. Michel, P. R. Hof, and C. Bouras, "Neuroanatomic correlates of visual agnosia in Alzheimer's disease: a clinicopathologic study," *Neurology*, vol. 52, no. 1, pp. 71–77, 1999.

[64] P. Giannakopoulos, G. Gold, M. Duc, J.-P. Michel, P.-R. Hof, and C. Bouras, "Impaired processing of famous faces in Alzheimer's disease is related to neurofibrillary tangle densities in the prefrontal and anterior cingulate cortex," *Dementia and Geriatric Cognitive Disorders*, vol. 11, no. 6, pp. 336–341, 2000.

[65] P. Giannakopoulos, G. Gold, M. Duc, J.-P. Michel, P. R. Hof, and C. Bouras, "Neural substrates of spatial and temporal disorientation in Alzheimer's disease," *Acta Neuropathologica*, vol. 100, no. 2, pp. 189–195, 2000.

[66] G. M. Savva, S. B. Wharton, P. G. Ince, G. Forster, F. E. Matthews, and C. Brayne, "Age, neuropathology, and dementia," *New England Journal of Medicine*, vol. 360, no. 22, pp. 2302–2309, 2009.

[67] P. Delaere, Y. He, G. Fayet, C. Duyckaerts, and J.-J. Hau, "βA4 deposits are constant in the brain of the oldest old: an immunocytochemical study of 20 French centenarians," *Neurobiology of Aging*, vol. 14, no. 2, pp. 191–194, 1993.

[68] P. R. Hof, T. Bussière, G. Gold et al., "Stereologic evidence for persistence of viable neurons in layer II of the entorhinal cortex and the CA1 field in Alzheimer disease," *Journal of Neuropathology and Experimental Neurology*, vol. 62, no. 1, pp. 55–67, 2003.

[69] C. Bouras, P. R. Hof, and J. H. Morrison, "Neurofibrillary tangle densities in the hippocampal formation in a non-demented population define subgroups of patients with differential early pathologic changes," *Neuroscience Letters*, vol. 153, no. 2, pp. 131–135, 1993.

[70] C. Bouras, P. R. Hof, P. Giannakopoulos, J.-P. Michel, and J. H. Morrison, "Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of elderly patients: a quantitative evaluation of a one-year autopsy population from a geriatric hospital," *Cerebral Cortex*, vol. 4, no. 2, pp. 138–150, 1994.

[71] P. R. Hof, L. M. Bierer, D. P. Perl et al., "Evidence for early vulnerability of the medial and inferior aspects of the temporal lobe in an 82-year-old patient with preclinical signs of dementia: regional and laminar distribution of neurofibrillary tangles and senile plaques," *Archives of Neurology*, vol. 49, no. 9, pp. 946–953, 1992.

[72] J. H. Kordower, Y. Chu, G. T. Stebbins et al., "Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment," *Annals of Neurology*, vol. 49, no. 2, pp. 202–213, 2001.

[73] J. J. Kril, S. Patel, A. J. Harding, and G. M. Halliday, "Neuron loss from the hippocampus of Alzheimer's disease exceeds extracellular neurofibrillary tangle formation," *Acta Neuropathologica*, vol. 103, no. 4, pp. 370–376, 2002.

[74] G. Šimić, I. Kostović, B. Winblad, and N. Bogdanović, "Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease," *Journal of Comparative Neurology*, vol. 379, no. 4, pp. 482–494, 1997.

[75] Y. Itoh, M. Yamada, N. Suematsu, M. Matsushita, and E. Otomo, "An immunohistochemical study of centenarian brains: a comparison," *Journal of the Neurological Sciences*, vol. 157, no. 1, pp. 73–81, 1998.

[76] P. Giannakopoulos, P. R. Hof, A.-S. Giannakopoulos et al., "Dementia in the oldest-old: quantitative analysis of 12 cases from a psychiatric hospital," *Dementia*, vol. 5, no. 6, pp. 348–356, 1994.

[77] P. Giannakopoulos, P. R. Hof, A.-S. Giannakopoulos, F. R. Herrmann, J. P. Michel -, and C. Bouras, "Regional distribution of neurofibrillary tangles and senile plaques in the cerebral cortex of very old patients," *Archives of Neurology*, vol. 52, no. 12, pp. 1150–1159, 1995.

[78] A. von Gunten, E. Kövari, T. Bussière et al., "Cognitive impact of neuronal pathology in the entorhinal cortex and CA1 field in Alzheimer's disease," *Neurobiology of Aging*, vol. 27, no. 2, pp. 270–277, 2006.

[79] P. V. Arriagada, K. Marzloff, and B. T. Hyman, "Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease," *Neurology*, vol. 42, no. 9, pp. 1681–1688, 1992.

[80] P. V. Arriagada, J. H. Growdon, E. T. Hedley-Whyte, and B. T. Hyman, "Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease," *Neurology*, vol. 42, no. 3, pp. 631–639, 1992.

[81] P. Giannakopoulos, F. R. Herrmann, T. Bussière et al., "Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease," *Neurology*, vol. 60, no. 9, pp. 1495–1500, 2003.

[82] T. Bussière, P. D. Friend, N. Sadeghi et al., "Stereologic assessment of the total cortical volume occupied by amyloid deposits and its relationship with cognitive status in aging and Alzheimer's disease," *Neuroscience*, vol. 112, no. 1, pp. 75–91, 2002.

[83] J.-J. Hauw, P. Vignolo, and C. Duyckaerts, "Etude neuropathologique de 12 centenaires: la fréquence de la démence sénile de type Alzheimer n'est pas particulièrement élevée danc ce groupe de personne très âgées," *Revue Neurologique*, vol. 142, no. 2, pp. 107–115, 1986.

[84] F. García-Sierra, J. J. Hauw, C. Duyckaerts, C. M. Wischik, J. Luna-Muñoz, and R. Mena, "The extent of neurofibrillary pathology in perforant pathway neurons is the key determinant of dementia in the very old," *Acta Neuropathologica*, vol. 100, no. 1, pp. 29–35, 2000.

[85] A. von Gunten, E. Kövari, C.-B. Rivara, C. Bouras, P. R. Hof, and P. Giannakopoulos, "Stereologic analysis of hippocampal Alzheimer's disease pathology in the oldest-old: evidence for sparing of the entorhinal cortex and CA1 field," *Experimental Neurology*, vol. 193, no. 1, pp. 198–206, 2005.

[86] A. J. Harding, G. M. Halliday, and J. J. Kril, "Variation in hippocampal neuron number with age and brain volume," *Cerebral Cortex*, vol. 8, no. 8, pp. 710–718, 1998.

[87] D. W. Dickson, H. A. Crystal, C. Bevona, W. Honer, I. Vincent, and P. Davies, "Correlations of synaptic and pathological markers with cognition of the elderly," *Neurobiology of Aging*, vol. 16, no. 3, pp. 285–298, 1995.

[88] T. W. Mitchell, J. Nissanov, L.-Y. Han et al., "Novel method to quantify neuropil threads in brains from elders with or without cognitive impairment," *Journal of Histochemistry and Cytochemistry*, vol. 48, no. 12, pp. 1627–1637, 2000.

[89] P. Giannakopoulos, A. von Gunten, E. Kövari et al., "Stereological analysis of neuropil threads in the hippocampal formation: relationships with Alzheimer's disease neuronal pathology and cognition," *Neuropathology and Applied Neurobiology*, vol. 33, no. 3, pp. 334–343, 2007.

[90] G. Lace, G. M. Savva, G. Forster et al., "Hippocampal tau pathology is related to neuroanatomical connections: an ageing population-based study," *Brain*, vol. 132, no. 5, pp. 1324–1334, 2009.

[91] D. Iacono, W. R. Markesbery, M. Gross et al., "The Nun Study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life," *Neurology*, vol. 73, no. 9, pp. 665–673, 2009.

[92] T. L. Bailey, C. B. Rivara, A. B. Rocher, and P. R. Hof, "The nature and effects of cortical microvascular pathology in aging and Alzheimer's disease," *Neurological Research*, vol. 26, no. 5, pp. 573–578, 2004.

[93] L. Buee, P. R. Hof, C. Bouras et al., "Pathological alterations of the cerebral microvasculature in Alzheimer's disease and related dementing disorders," *Acta Neuropathologica*, vol. 87, no. 5, pp. 469–480, 1994.

[94] E. Farkas and P. G. M. Luiten, "Cerebral microvascular pathology in aging and Alzheimer's disease," *Progress in Neurobiology*, vol. 64, no. 6, pp. 575–611, 2001.

[95] G. Gold, P. Giannakopoulos, and C. Bouras, "Reevaluating the role of vascular changes in the differential diagnosis of Alzheimer's disease and vascular dementia," *European Neurology*, vol. 40, no. 3, pp. 121–129, 1998.

[96] W. Meier-Ruge, J. Ulrich, and S. Abdel-Al, "Stereologic findings in normal brain aging and Alzheimer's disease," in *Senile Dementia: Outlook for the Future*, J. Werthemimer and M. Marios, Eds., pp. 125–135, Alan R. Liss, New York, NY, USA, 1984.

[97] W. B. Abernethy, M. A. Bell, M. Morris, and D. M. Moody, "Microvascular density of the human paraventricular nucleus decreases with aging but not hypertension," *Experimental Neurology*, vol. 121, no. 2, pp. 270–274, 1993.

[98] F. Amenta, D. Cavallotti, M. Del Valle et al., "Age-related changes in brain microanatomy: sensitivity to treatment with the dihydropyridine calcium channel blocker darodipine (PY 108-068)," *Brain Research Bulletin*, vol. 36, no. 5, pp. 453–460, 1995.

[99] F. Amenta, F. Ferrante, M. Mancini, M. Sabbatini, J. Vega, and D. Zaccheo, "Effect of long term treatment with the dihydropyridine-type calcium channel blocker darodipine (PY 108-068) on the cerebral capillary network in aged rats," *Mechanisms of Ageing and Development*, vol. 78, no. 1, pp. 27–37, 1995.

[100] D. M. A. Mann, N. R. Eaves, B. Marcyniuk, and P. O. Yates, "Quantitative changes in cerebral cortical microvasculature in ageing and dementia," *Neurobiology of Aging*, vol. 7, no. 5, pp. 321–330, 1986.

[101] W. E. Sonntag, C. D. Lynch, P. T. Cooney, and P. M. Hutchins, "Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1," *Endocrinology*, vol. 138, no. 8, pp. 3515–3520, 1997.

[102] M. A. Bell and M. J. Ball, "Morphometric comparison of hippocampal microvasculature in ageing and demented people: diameters and densities," *Acta Neuropathologica*, vol. 53, no. 4, pp. 299–318, 1981.

[103] O. Hunziker, S. Abdel'Al, and U. Schulz, "The aging human cerebral cortex: a serological characterization of changes in the capillary net," *Journals of Gerontology*, vol. 34, no. 3, pp. 345–350, 1979.

[104] G. D. Lee, J. H. Aruna, P. M. Barrett, D.-L. Lei, D. K. Ingram, and P. R. Mouton, "Stereological analysis of microvascular parameters in a double transgenic model of Alzheimer's disease," *Brain Research Bulletin*, vol. 65, no. 4, pp. 317–322, 2005.

[105] A. Løkkegaard, J. R. Nyengaard, and M. J. West, "Stereological estimates of number and length of capillaries in subdivisions of the human hippocampal region," *Hippocampus*, vol. 11, no. 6, pp. 726–740, 2001.

[106] C. Bouras, E. Kövari, F. R. Herrmann et al., "Stereologic analysis of microvascular morphology in the elderly: Alzheimer disease pathology and cognitive status," *Journal of Neuropathology and Experimental Neurology*, vol. 65, no. 3, pp. 235–244, 2006.

[107] J. C. de la Torre and T. Mussivand, "Can disturbed brain microcirculation cause Alzheimer's disease?" *Neurological Research*, vol. 15, no. 3, pp. 146–153, 1993.

[108] T. Kimura, T. Hashimura, and T. Miyakawa, "Observations of microvessels in the brain with Alzheimer's disease by the scanning electron microscopy," *Japanese Journal of Psychiatry and Neurology*, vol. 45, no. 3, pp. 671–676, 1991.

[109] G. I. De Jong, E. Farkas, C. M. Stienstra et al., "Cerebral hypoperfusion yields capillary damage in the hippocampal CA1 area that correlates with spatial memory impairment," *Neuroscience*, vol. 91, no. 1, pp. 203–210, 1999.

[110] W. Kuschinsky and O. B. Paulson, "Capillary circulation in the brain," *Cerebrovascular and Brain Metabolism Reviews*, vol. 4, no. 3, pp. 261–286, 1992.

[111] A. G. Hudetz, G. Fehér, and J. P. Kampine, "Heterogeneous autoregulation of cerebrocortical capillary flow: evidence for functional thoroughfare channels?" *Microvascular Research*, vol. 51, no. 1, pp. 131–136, 1996.

[112] T. Bär, "The vascular system of the cerebral cortex," *Advances in Anatomy, Embryology, and Cell Biology*, vol. 59, pp. 1–62, 1980.

[113] T. Perls, "Centenarians who avoid dementia," *Trends in Neurosciences*, vol. 27, no. 10, pp. 633–636, 2004.

[114] J. J. Kril, "Alzheimer disease neuropathology in the oldest old," *Nature Reviews. Neurology*, vol. 5, no. 8, pp. 411–412, 2009.

[115] R. G. Cutler, "Evolution of human longevity and the genetic complexity governing aging rate," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 72, no. 11, pp. 4664–4668, 1975.

[116] F. Schächter, "Causes, effects, and constraints in the genetics of human longevity," *American Journal of Human Genetics*, vol. 62, no. 5, pp. 1008–1014, 1998.

[117] J. A. Kaye, "Oldest-old healthy brain function: the genomic potentials," *Archives of Neurology*, vol. 54, no. 10, pp. 1217–1221, 1997.

[118] T. Perls, L. M. Kunkel, and A. A. Puca, "The genetics of exceptional human longevity," *Journal of the American Geriatrics Society*, vol. 50, no. 2, pp. 359–368, 2002.

[119] A. A. Puca, M. J. Daly, S. J. Brewster et al., "A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 18, pp. 10505–10508, 2001.

[120] B. J. Geesaman, E. Benson, S. J. Brewster et al., "Haplotype-based identification of a microsomal transfer protein marker associated with the human lifespan," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 2, pp. 14115–14120, 2003.

[121] N. Barzilai, G. Atzmon, C. Schechter et al., "Unique lipoprotein phenotype and genotype associated with exceptional longevity," *Journal of the American Medical Association*, vol. 290, no. 15, pp. 2030–2040, 2003.

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Research Article

Oxidative Stress and Longevity in Okinawa: An Investigation of Blood Lipid Peroxidation and Tocopherol in Okinawan Centenarians

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Background. The Free Radical Theory of Aging mechanistically links oxidative stress to aging. Okinawa has among the world's longest-lived populations but oxidative stress in this population has not been well characterized. *Methods*. We compared plasma lipid peroxide (LPO) and vitamin E—plasma and intracellular tocopherol levels (total α, β, and γ), in centenarians with younger controls. *Results*. Both LPO and vitamin E tocopherols were lower in centenarians, with the exception of intracellular β-tocopherol, which was significantly higher in centenarians versus younger controls. There were no significant differences between age groups for tocopherol: cholesterol and tocopherol: LPO ratios. Correlations were found between α-Tocopherol and LPO in septuagenarians but not in centenarians. *Conclusions*. The low plasma level of LPO in Okinawan centenarians, compared to younger controls, argues for protection against oxidative stress in the centenarian population and is consistent with the predictions of the Free Radical Theory of Aging. However, the present work does not strongly support a role for vitamin E in this phenomenon. The role of intracellular β-tocopherol deserves additional study. More research is needed on the contribution of oxidative stress and antioxidants to human longevity.

1. Introduction

Human longevity is a complex phenotype that is determined by environment, genetics, and chance [1]. Understanding the mechanisms by which aging leads to longevity, particularly healthy longevity would be of enormous benefit to our aging population. Unfortunately, most research on human aging has focused on phenomenological description of age-related diseases, and much less is known about the mechanisms of aging itself [2]. Among the most promising theories about how and why we age is the Free Radical Theory, initially proposed by Denham Harman in 1956 [3].

Harman proposed that oxygen radicals produced during aerobic respiration induce oxidative damage in DNA, cells, tissues, and organisms that lead to aging and death. Studies in Harman [3] hypothesized, based on observations of enzymatic redox chemistry, that oxygen radical generation occurs *in vivo* and that mechanisms exist to protect against such damage. Mitochondria were later found to be a principal source of these oxygen radicals [4]. The enzyme superoxide dismutase (SOD) provided early evidence for endogenous antioxidant defenses against such radical damage [5]. Exogenous antioxidant defenders have also been discovered in food sources, among the most studied being vitamin E [6, 7].

Vitamin E consists of a group of eight related fat soluble tocopherols and tocotrienols, which have significant antioxidant properties [6]. The highest bioavailability, absorption, and metabolization occur with α-tocopherol [7].

Some research supports α-tocopherol as the most important lipid soluble antioxidant since it protects cell membranes from chain reactions caused by radical-induced lipid peroxidation through quenching free radical intermediates [7]. While the antioxidant role of other forms of vitamin E is less clear, γ-tocopherol is a nucleophile that can quench electrophilic mutagens, β-tocopherol has similar properties, and tocotrienols can protect neurons from oxidative stress [8–10].

Based on this background, we and others have investigated LPO, SOD, and vitamin E as potential factors in human aging and longevity. Plasma LPO has been found to increase with age into the septuagenarian years [11] but little is known about population levels in exceptionally aged individuals, such as centenarians. Studies in Mezzetti et al. [12] found that lower plasma lipid peroxide and higher plasma vitamin E predicted lower risk of cardiovascular events (an important cause of premature mortality) in healthy Italian octogenarians over a 4-year period. Studies in Suzuki et al. [13] found that plasma LPO was lower in Okinawan centenarians than septuagenarians, consistent with their demographic selection against mortality. This is consistent with the hypothesis that protection against oxidative stress might be a survival factor in older Okinawans and possibly a marker of "slower" aging.

In order to assess potential connections between LPO and common endogenous or exogenous antioxidants, Suzuki et al. [14] studied whether Okinawan centenarians also displayed high levels of plasma or intracellular SOD. Contrary to expectations, SOD levels were lower in centenarians than in younger controls. This might be, in part, a reaction to low levels of oxidative stress in centenarians but it does not offer support for SOD as a major protector against oxidative stress in this population.

Conversely, vitamin E intake is known to be high in the traditional Okinawan diet due to abundant consumption of foods such as soy beans (tofu and soy bean oils), sweet potatoes, papaya (and its leaves), and green leafy vegetables (e.g., swiss chard, spinach, mustard greens, and numerous other local varieties) [15, 16]. This is reflected in relatively high plasma α-tocopherol in older Okinawans, who are more likely to consume a traditional diet [13]. A recent comparative study found that mean α-tocopherol levels were similar between Okinawan elderly and healthy elderly from the USA (Oregon) with and without adjustments for total cholesterol or triglycerides [16]. This was despite the fact that few Okinawans consumed vitamin supplements while more than a third of US elders did. α-tocopherol is typically the most abundant tocopherol in human serum since it is preferentially conserved by the liver. For example, one study of middle-aged Japanese women found that α-tocopherol formed 88% of serum tocopherol, while the reminder consisted of 8.5% γ-tocopherol, 1.8% δ-tocopherol, and 1.7% β-tocopherol [17].

Foods also vary markedly in their tocopherol content. For example, soy oil is mainly γ-tocopherol (>60%) whereas sunflower oil is mainly α-tocopherol (>90%) [17]. Few foods have a significant quantity of β-tocopherol [18] but some traditional Okinawan foods, including brown seaweed and hot red peppers, are rich in β-tocopherol; soy oil (in tofu, other soy foods and cooking oil), while not as β-tocopherol-rich, is consumed in quite high quantity, particularly in the traditional Okinawan diet, which is more likely to be consumed by centenarians [19].

As an important fat soluble antioxidant, Vitamin E and/or its various tocopherols could theoretically explain the low LPO in Okinawan centenarians. However, Suzuki et al. [13, 14, 20] showed in prior work that vitamin E, like SOD, was significantly lower in the plasma of centenarians than of younger controls, even after adjustment for lipids and other factors. Nevertheless, vitamin E subtypes (tocopherol subtypes) and/or intracellular tocopherol levels were not studied. Since the major exposure to oxidative stress in humans originates from mitochondria and this stress occurs mainly intracellularly, it is possible that intracellular concentrations of vitamin E (or its subtypes) may be more important than plasma vitamin E.

Therefore, we studied Okinawan centenarians and younger control populations with the following primary aims: (1) to quantify blood levels of lipid peroxide (LPO), a common proxy measure of oxidative stress; (2) to quantify blood and intracellular levels of vitamin E (measured in red blood cells), a common antioxidant; (3) to assess potential correlations between LPO and vitamin E levels.

2. Materials and Methods

This study was conducted under ongoing Institutional Review Board approval from Okinawa International University, and informed consent was received from all study participants. A total of 139 centenarians (30 males, 109 females, mean age = 100.3 years), residing in Okinawa, were previously studied and had banked blood samples [20]. Additional younger controls were recruited for comparison purposes in the current study. A physical examination was performed at the participants' place of residence. Examination included hematological and biochemical analysis of blood, activity of daily living survey, and anthropometric measurements. For the control group, 79 healthy community-dwelling people (34 males, 45 females, aged 20–80, mean age 62.5 years) were recruited and subjected to identical examinations under similar conditions. These controls consisted of younger (twenties, thirties) and older (sixties, seventies, eighties) participants. Total numbers of cases and controls varied according to the particular assay performed.

Blood samples were taken in EDTA tubes and stored on ice. Samples were then transported to the University of the Ryukyus Hospital, where they were separated into plasma and blood cell components by centrifugation. Ultracentrifugation was used to evaluate plasma total cholesterol and cholesterol subfractions. LPO was measured using the thiobarbituric acid (TBA) reaction for fatty acid oxidation

otherwise known as the "TBA method" [21, 22]. For tocopherol studies, samples were frozen on dry ice and sent to Eizai Research Institute, where tocopherol concentrations were measured by high performance liquid chromatography (HPLC) [23]. Cases and controls were compared using Student's t-test.

3. Results

Table 1 demonstrates that plasma LPO levels of centenarians were 1.49 ± 0.51 nmol/ml in males ($n = 30$), 1.72 ± 1.28 nmol/ml for females ($n = 109$), and 1.67 ± 1.16 nmol/ml overall ($n = 139$). Centenarians had significantly lower LPO levels than control subjects in their twenties ($n = 8$; 3.30 ± 1.25; $P < .001$), thirties ($n = 16$; 3.51 ± 1.08; $P < .001$), seventies ($n = 29$; 3.40 ± 0.79; $P < .001$), and eighties ($n = 8$; 2.91 ± 0.34; $P < .001$).

Table 2 displays average (mean) plasma tocopherol levels (total and by subtype) across age strata. Total plasma tocopherol (T-Toc) in centenarians was 8.89 ± 2.31 μg/ml for males ($n = 19$) and 11.05 ± 3.41 μg/ml for females ($n = 91$), and 10.58 ± 3.32 for both groups combined ($n = 110$). Centenarian plasma T-tocopherol (males and females combined) was significantly lower than that of every younger age group ($P < .001$). This trend generally held true for both genders as well, with T-tocopherol increasing with age in both genders until the age of 70s and then dropping thereafter.

We also compared the levels of plasma tocopherol subtypes (α-, β-, γ-tocopherol) in centenarians to younger controls. Plasma α-tocopherol in centenarian males (7.79 ± 2.10 μg/ml, $n = 19$), females (9.82 ± 3.35, $n = 72$), and combined total (9.37 ± 3.32 μg/ml, $n = 91$) showed similar trends as T-Toc, with combined plasma α-tocopherol level in centenarians significantly lower than in younger age groups across all age strata (significance levels ranged from $P < .05$ to $P < .001$). Comparisons of centenarians across age strata within gender groups were significant between septuagenarians in females and between all age groups in males. This was partly limited by small numbers. For both genders α-tocopherol tended to increase with age and peak at septuagenarian years, then dropped rapidly thereafter.

Total plasma β-tocopherol levels in centenarian males (0.18 ± 0.07 μg/ml, $n = 18$), females (0.20 ± 0.21 μg/ml, $n = 69$), and gender combined total (0.20 ± 0.19 μg/ml, $n = 87$) were significantly lower than in septuagenarians but not in other age groups (male $P < .05$; female $P < .01$). Similar relations were seen as with α-tocopherol where peak values appeared in the septuagenarian years and dropped rapidly thereafter.

Plasma γ-tocopherol levels for centenarian males (0.93 ± 0.42 μg/ml, $n = 18$), centenarian females (1.03 ± 0.59 μg/ml, $n = 72$), and both genders combined (1.01 ± 0.52 μg/ml, $n = 90$) were significantly lower than septuagenarians with regard to the combined ($P < .05$) and female ($P < .05$) centenarian groups. Levels tended to peak in the septuagenarian years for the combined group and were less reliable in individual groups, possibly due to small numbers.

Gender-related differences appeared with significantly higher T-tocopherol ($P < .05$) and α-tocopherol ($P < .01$) found in female centenarians compared to male centenarians.

Table 3 demonstrates comparisons between intracellular tocopherol levels (total and by subtype) between centenarians and controls in various age strata. Intracellular T-tocopherol in centenarian red blood cells in males (1.80 ± 1.00 μg/ml, $n = 19$), females (2.30 ± 1.22 μg/ml, $n = 77$), and both sexes combined (2.19 ± 1.19 μg/ml, $n = 96$) was significantly lower than in all other age groups for combined genders versus all individual age strata ($P < .001$). This relation held when separated by gender for most individual age groups.

Intracellular concentration of individual tocopherol subtypes (α-Toco, β-Toco, γ-Toco) was also compared between age groups by gender. In centenarians, α-tocopherol levels in males (1.51 ± 0.84 μg/ml, $n = 19$), females (2.00 ± 1.13 μg/ml, $n = 77$), and both sexes combined (1.89 ± 1.09 μg/ml, $n = 96$) were significantly lower than in all younger age groups when both sexes combined were compared to younger age groups; significance levels ranged from $P < .05$ (octogenarians) to $P < .001$ (septuagenarians). Peak values tended to be reached in octogenarian years in females with no clear pattern in males until a sharp decline in centenarians of both genders.

Intracellular concentration of β-Toco in male centenarians (0.08 ± 0.04 μg/ml, $n = 10$), female centenarians (0.10 ± 0.08 μg/ml, $n = 37$), and both sexes combined (0.09 ± 0.07 μg/ml, $n = 47$) was the highest of all age groups. However, only the difference between centenarians and controls in their seventies was significant ($P < .05$ males; $P < .01$ females; $P < .01$ combined). This was likely due to the small numbers of study participants in individual age groups other than the septuagenarian age group, since concentrations did not appear to be different across age strata until centenarian years.

Intracellular concentration of γ-tocopherol in centenarian males (0.25 ± 0.16 μg/ml, $n = 18$), females (0.23 ± 0.19 μg/ml, $n = 74$), and both sexes combined (0.24 ± 0.18 μg/ml; $n = 92$) appeared lower than all other age groups. However, it reached significance versus only two groups—septuagenarian females ($P < .05$) and septuagenarian sexes combined ($P < .05$). Lack of significant difference between centenarians and other groups may have been influenced by small numbers of participants in comparison groups.

Table 4 demonstrates T-tocopherol, α-tocopherol, and γ-tocopherol in centenarians versus a younger control group (septuagenarians) separated by gender and adjusted for plasma total cholesterol (Tc) and HDL cholesterol (HDL-C) by dividing tocopherol levels by cholesterol levels. This comparison was important since differences in tocopherol between age groups might be an artifact of differences in plasma lipid levels that occur commonly with age. Older populations (age 70 years or more) tend to have lower cholesterol levels, which may partly reflect malnutrition [24]. As a fat soluble vitamin, most tocopherol is carried in lipid subfractions and therefore might appear artificially low if not adjusted by plasma lipid levels. Despite adjustment, there

Table 1: Plasma lipid peroxide in young, middle-aged, and older age groups (mean and SD), nmol/ml. LPO levels were measured using the TBA method [21, 22].

	20s	30s	70s	80s	100s
Male	3.34 ± 1.79	4.06 ± 1.24	3.15 ± 0.70	2.92 ± 0.32	1.49 ± 0.51
(*n*)	(4)	(8)***	(11)***	(5)***	(30)
Female	3.18 ± 0.64	2.95 ± 0.53	3.56 ± 0.81	2.90 ± 0.46	1.72 ± 1.28
(*n*)	(4)*	(8)**	(18)***	(3)	(109)
Total	3.30 ± 1.25	3.51 ± 1.08	3.40 ± 0.79	2.91 ± 0.34	1.67 ± 1.16
(*n*)	(8)***	(16)***	(29)***	(8)***	(139)

Significant difference between centenarians and particular age group: $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.

Table 2: Mean plasma tocopherol (total and subtype) by age group (μg/ml).

	Age	20s	30s	70s	80s	100s
α Toc	Male	11.81 ± 3.03	12.35 ± 3.60	13.15 ± 7.82	9.44 ± 1.07	7.79 ± 2.10
	(*n*)	(4)**	(8)**	(17)*	(5)*	(19)
	Female	9.58 ± 2.62	11.07 ± 3.91	16.31±11.64	13.58 ± 3.63	9.82 ± 3.35
	(*n*)	(4)	(8)	(30)**	(3)	(72)
	Total	10.69 ± 2.88	11.71 ± 3.69	15.14 ± 11.41	11.28 ± 3.20	9.37 ± 3.32
	(*n*)	(8)**	(16)**	(47)***	(8)*	(91)
β Toc	Male	0.25 ± 0.04	0.22 ± 0.05	0.23 ± 0.08	0.20 ± 0.05	0.18 ± 0.07
	(*n*)	(4)	(8)	(17)*	(5)	(18)
	Female	0.22 ± 0.04	0.21 ± 0.04	0.31 ± 0.18	0.28 ± 0.13	0.20 ± 0.21
	(*n*)	(4)	(8)	(30)**	(3)	(69)
	Total	0.23 ± 0.04	0.21 ± 0.04	0.28 ± 0.16	0.23 ± 0.09	0.20 ± 0.19
	(*n*)	(8)	(16)	(47)**	(8)	(87)
γ Toc	Male	1.37 ± 0.58	1.17 ± 0.40	1.00 ± 0.51	1.18 ± 0.33	0.93 ± 0.42
	(*n*)	(4)	(8)	(17)	(5)	(18)
	Female	0.98 ± 0.22	1.04 ± 0.50	1.62 ± 1.76	1.16 ± 0.17	1.03 ± 0.59
	(*n*)	(4)	(8)	(30)*	(3)	(72)
	Total	1.17 ± 0.46	1.11 ± 0.44	1.39 ± 1.45	1.17 ± 0.49	1.01 ± 0.52
	(*n*)	(8)	(16)	(47)*	(8)	(90)
Total Toc	Male	13.42 ± 3.60	13.74 ± 3.70	14.38 ± 8.28	10.82 ± 1.37	8.89 ± 2.31
	(*n*)	(4)**	(8)***	(17)*	(5)*	(19)
	Female	10.78 ± 2.80	12.33 ± 3.87	18.24 ± 12.69	15.01 ± 3.62	11.05 ± 3.41
	(*n*)	(4)***	(8)	(30)***	(3)***	(91)
	Total	12.10 ± 3.31	13.03 ± 3.73	16.81 ± 11.32	12.68 ± 3.27	10.58 ± 3.32
	(*n*)	(8)***	(16)***	(47)***	(8)***	(110)

Toc: Tocopherol.
Significant difference between centenarians and particular age group: $^{*}P < .05$; $^{**}P < 0.01$; $^{***}P < .001$.
Significant difference between male and female centenarians: $P < .01$ in α Toc; $P < .05$ in total Toc.

were no significant differences between centenarians and septuagenarians across age strata.

Tables 5 and 6 show tocopherol: LPO ratios in plasma (Table 5) and intracellular (Table 6) compartments across age strata, separated by gender. No significant differences were found for either gender between the centenarians and controls in their seventies.

Table 7 shows correlation indices between plasma tocopherol/tocopherol subfractions and LPO as well as between intracellular tocopherol and LPO in two age groups: centenarians and septuagenarians. In centenarians, no significant correlations were found between plasma tocopherol nor tocopherol subfractions and LPO. However, in septuagenarians there were some correlations between tocopherol levels and LPO: (1) a weakly positive correlation was found between plasma T-tocopherol and LPO ($r = .34$; $P < .01$), and between α-tocopherol and LPO ($r = .33$; $P < .01$); (2) a weakly negative correlation was found between intracellular T-tocopherol and LPO ($r = -.32$; $P < .05$) and between intracellular α-tocopherol and LPO ($r = -.29$; $P < .05$).

4. Discussion

In 1956 Harman proposed the Free Radical Theory of aging [3]. He hypothesized that aging is partly due to cumulative oxidative damage, and over the last four decades many studies have supported this view. For example, the literature shows that a progressive accumulation of oxidation-derived damage to cellular machinery is linked to senescence [2, 25].

Table 3: Mean intracellular (red blood cell) tocopherol levels by age strata (total and subtype) (μg/ml).

		20s	30s	70s	80s	100s
α Toc	Male	2.47 ± 0.49	2.43 ± 0.35	2.48 ± 0.25	2.46 ± 0.28	1.51 ± 0.84
	(n)	(4)**	(8)**	(17)***	(5)*	(19)
	Female	2.53 ± 0.35	2.79 ± 0.82	2.61 ± 0.76	2.91 ± 0.87	2.00 ± 1.13
	(n)	(4)	(8)	(30)***	(3)	(77)
	Total	2.50 ± 0.40	2.61 ± 0.64	2.56 ± 0.62	2.66 ± 0.61	1.89 ± 1.09
	(n)	(8)**	(16)**	(47)***	(8)*	(96)
β Toc	Male	0.05 ± 0.00	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.08 ± 0.04
	(n)	(4)	(8)	(17)*	(5)	(10)
	Female	0.04 ± 0.00	0.04 ± 0.01	0.05 ± 0.02	0.06 ± 0.02	0.10 ± 0.08
	(n)	(4)	(8)	(30)**	(3)	(37)
	Total	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.05 ± 0.01	0.09 ± 0.07
	(n)	(8)	(16)	(47)**	(8)	(47)
γ Toc	Male	0.35 ± 0.06	0.31 ± 0.12	0.27 ± 0.09	0.39 ± 0.10	0.25 ± 0.16
	(n)	(4)	(8)	(17)	(5)	(18)
	Female	0.35 ± 0.08	0.32 ± 0.11	0.33 ± 0.17	0.31 ± 0.16	0.23 ± 0.19
	(n)	(4)	(8)	(30)*	(3)	(74)
	Total	0.35 ± 0.07	0.32 ± 0.11	0.31 ± 0.15	0.35 ± 0.13	0.24 ± 0.18
	(n)	(8)	(16)	(47)*	(8)	(92)
Total Toc	Male	2.87 ± 0.50	2.76 ± 0.41	2.79 ± 0.30	2.89 ± 0.37	1.80 ± 1.00
	(n)	(4)***	(8)***	(17)***	(5)*	(19)
	Female	2.92 ± 0.39	3.15 ± 0.75	2.98 ± 0.82	3.24 ± 0.76	2.30 ± 1.22
	(n)	(4)***	(8)	(30)***	(3)***	(77)
	Total	2.90 ± 0.42	2.95 ± 0.62	2.91 ± 0.67	3.05 ± 0.57	2.19 ± 1.19
	(n)	(8)***	(16)***	(47)***	(8)***	(96)

Toc: Tocopherol.
Significant difference centenarians and individual age groups: *$P < .05$; **$P < 0.01$; ***$P < .001$.

Lipids, the major component of cell membranes, which are in close proximity to mitochondria, the key source of endogenous free radicals, are prime targets for this damage [26]. As humans age this damage can be observed as a progressive increase in blood lipid peroxidation byproducts [26]. Therefore, lipid peroxidation may be a key player for initiating and/or mediating aspects of the aging process. Some work suggests that persons who live to exceptional ages, such as centenarians, might do so by aging more slowly [27]. If this is the case, then protection against lipid peroxidation may be a biological advantage that accounts, in part, for slower aging.

The present work finds some support for this view. We confirmed that plasma LPO level increases with age in Okinawans, a very long-lived population, and drops off significantly by centenarian years. This is consistent with a survivor effect where those with high blood LPO levels are selected out (by death) leaving a population enriched with low blood LPO. Some protective endogenous and/or exogenous antioxidant defenses may be responsible for this effect. However, there is no clear indication from the present study that tocopherol and its subtypes (both plasma and intracellular) are leading biological factors in such a system, since blood tocopherol was lower in centenarians than in younger controls, with the possible exception of intracellular β-tocopherol.

The fact that centenarians had higher intracellular β-tocopherol is interesting. While plasma β-tocopherol did not appear protective, some studies suggest that intracellular concentration of antioxidants might be more relevant than plasma levels since the source of most free radicals is intracellular mitochondria, and much damage occurs intracellularly—to DNA, cell membranes, and other cellular components. In addition, some data suggest that β-tocopherol might be a more effective antioxidant than α-tocopherol. For example, β-tocopherol is less likely to act as a free radical itself after quenching oxygen radicals than α-tocopherol [9]. This increased stability could, theoretically, result in better overall protection against oxidative stress. Researchers in [28] found that increased β-tocopherol was associated with decreased risk for metabolic syndrome, a life shortening prediabetic condition that increases oxidative stress. Researchers in [29] found that replacement of α-tocopherol by β-tocopherol enhances resistance to oxidative stress in a cell culture study.

Since tocopherols are lipid soluble, it is also possible that very old persons, who generally have low blood lipids, display artificially low blood tocopherol levels since it is mainly lipid bound. For example, our past data show that Okinawan centenarians have significantly lower total cholesterol and cholesterol subfractions (e.g., LDL, HDL) than elderly controls in their seventies [30]. Therefore, in older persons, tocopherol: lipid ratios might better reflect physiologic levels than blood tocopherol levels, whether in plasma or intracellular compartments. Nevertheless, correcting for different lipid levels across age strata was unrevealing.

Table 4: Plasma and intracellular tocopherols adjusted by lipid subfraction.

		Septuagenarians (aged 70s)			Centenarians (aged 100s)		
		Male (n)	Female (n)	Total (n)	Male (n)	Female (n)	Total (n)
Plasma	T-Toc/Tc	0.08 ± 0.267 (17)	0.08 ± 0.259 (30)	0.08 ± 0.283 (47)	0.075 ± 0.018 (16)	0.072 ± 0.023 (68)	0.072 ± 0.021 (84)
	α-Toc/Tc	0.07 ± 0.252 (17)	0.08 ± 0.238 (30)	0.07 ± 0.285 (47)	0.06 ± 0.017 (15)	0.07 ± 0.018 (50)	0.07 ± 0.017 (65)
Intracellular	T-Toc/Tc	0.016 ± 0.010 (17)	0.013 ± 0.017 (30)	0.015 ± 0.017 (47)	0.015 ± 0.007 (16)	0.016 ± 0.010 (55)	0.016 ± 0.009 (71)
	α-Toc/Tc	0.014 ± 0.008 (17)	0.012 ± 0.016 (30)	0.013 ± 0.016 (47)	0.013 ± 0.006 (16)	0.014 ± 0.009 (55)	0.013 ± 0.009 (71)
	γ-Toc/Tc	0.005 ± 0.016 (17)	0.007 ± 0.036 (30)	0.007 ± 0.036 (47)	0.007 ± 0.003 (15)	0.007 ± 0.004 (50)	0.007 ± 0.004 (65)
	β-Toc/Tc	0.002 ± 0.003 (17)	0.002 ± 0.003 (30)	0.002 ± 0.004 (47)	0.002 ± 0.001 (16)	0.002 ± 0.002 (54)	0.002 ± 0.002 (70)
Plasma	T-Toc/HDL-C	0.27 ± 0.55 (17)	0.37 ± 0.98 (30)	0.33 ± 0.81 (47)	0.28 ± 0.13 (16)	0.27 ± 0.10 (69)	0.27 ± 0.11 (85)
	α-Toc/HDL-C	0.25 ± 0.52 (17)	0.33 ± 0.90 (30)	0.30 ± 0.82 (47)	0.25 ± 0.12 (15)	0.25 ± 0.09 (50)	0.25 ± 0.09 (65)
	γ-Toc/HDL-C	0.019 ± 0.03 (17)	0.033 ± 0.14 (30)	0.027 ± 0.10 (47)	0.03 ± 0.02 (15)	0.03 ± 0.02 (50)	0.03 ± 0.02 (65)
Intracellular	T-Toc/HDL-C	0.052 ± 0.020 (17)	0.060 ± 0.063 (30)	0.057 ± 0.047 (47)	0.059 ± 0.037 (16)	0.056 ± 0.031 (55)	0.058 ± 0.032 (71)
	α-Toc/HDL-C	0.047 ± 0.017 (17)	0.053 ± 0.058 (30)	0.050 ± 0.044 (47)	0.049 ± 0.032 (16)	0.049 ± 0.029 (55)	0.049 ± 0.030 (71)
	γ-Toc/HDL-C	0.005 ± 0.006 (17)	0.007 ± 0.013 (30)	0.006 ± 0.010 (47)	0.008 ± 0.006 (16)	0.007 ± 0.005 (54)	0.007 ± 0.006 (70)

Tc: Total cholesterol; HDL-C: high density lipoprotein cholesterol; Toc: Tocopherol. Note: no significant differences between groups.

Table 5: Average plasma tocopherol fractions/LPO across age strata.

Plasma Toc		20s	30s	70s	80s	100s
Total Toc/LPO	Male (n)	4.02 ± 2.01 (4)	3.38 ± 2.98 (8)	4.57 ± 11.83 (11)	3.71 ± 4.28 (5)	6.43 ± 3.61 (16)
	Female (n)	3.39 ± 4.38 (4)	4.18 ± 7.30 (8)	5.12 ± 15.67 (18)	5.18 ± 7.87 (3)	9.43 ± 14.22 (83)
	Total (n)	3.67 ± 2.65 (8)	3.71 ± 3.45 (16)	4.94 ± 14.33 (29)	4.36 ± 9.62 (8)	8.95 ± 13.13 (99)
α Toc/LPO	Male (n)	3.54 ± 1.69 (4)	3.04 ± 2.90 (8)	4.17 ± 11.17 (11)	3.23 ± 3.34 (5)	5.75 ± 3.29 (15)
	Female (n)	3.01 ± 4.09 (4)	3.75 ± 7.38 (8)	4.58 ± 14.37 (18)	4.68 ± 7.89 (3)	9.07 ± 13.86 (67)
	Total (n)	3.24 ± 2.30 (8)	3.34 ± 3.42 (16)	4.45 ± 13.18 (29)	3.88 ± 9.41 (8)	8.47 ± 12.70 (82)
β Toc/LPO	Male (n)	0.07 ± 0.02 (4)	0.05 ± 0.04 (8)	0.07 ± 0.11 (11)	0.07 ± 0.16 (5)	0.12 ± 0.07 (15)
	Female (n)	0.07 ± 0.06 (4)	0.07 ± 0.08 (8)	0.09 ± 0.22 (18)	0.10 ± 0.28 (3)	0.19 ± 0.24 (64)
	Total (n)	0.07 ± 0.03 (8)	0.06 ± 0.04 (16)	0.08 ± 0.20 (29)	0.08 ± 0.26 (8)	0.17 ± 0.26 (79)
γ Toc/LPO	Male (n)	0.41 ± 0.32 (4)	0.29 ± 0.32 (8)	0.32 ± 0.73 (11)	0.40 ± 1.03 (5)	0.63 ± 0.47 (15)
	Female (n)	0.31 ± 0.34 (4)	0.35 ± 0.94 8	0.46 ± 2.17 (18)	0.40 ± 1.54 (3)	1.06 ± 1.59 (67)
	Total (n)	0.36 ± 0.37 (8)	0.32 ± 0.41 (16)	0.41 ± 1.84 (29)	0.40 ± 1.44 (8)	0.98 ± 1.46 (82)

Toc: Tocopherol; LPO: lipid peroxidase. Note: no significant differences between groups.

Table 6: Intracellular tocopherol: lipid peroxide ratios across age strata.

Intracellular Toc		20s	30s	70s	80s	100s
Total Toc/LPO	Male	0.86±0.28	0.68±0.33	0.89±0.43	0.99 ± 1.16	1.21 ± 1.12
	(*n*)	(4)	(8)	(11)	(5)	(16)
	Female	0.92 ± 0.61	1.07 ± 1.42	0.84±1.00	1.12 ± 1.65	1.67 ± 1.69
	(*n*)	(4)	(8)	(18)	(3)	(71)
	Total	0.88 ± 0.34	0.84 ± 0.57	0.86 ± 0.85	1.05 ± 1.68	1.58 ± 1.60
	(*n*)	(8)	(16)	(29)	(8)	(87)
α Toc/LPO	Male	0.74 ± 0.27	0.60 ± 0.28	0.79 ± 0.36	0.84 ± 0.88	1.02 ± 0.92
	(*n*)	(4)	(8)	(11)	(5)	(16)
	Female	0.80 ± 0.55	0.95 ± 1.55	0.73 ± 0.94	1.00 ± 1.89	1.40 ± 1.44
	(*n*)	(4)	(8)	(18)	(3)	(71)
	Total	0.76 ± 0.32	0.74 ± 0.59	0.75 ± 0.78	0.91 ± 1.79	1.33 ± 1.36
	(*n*)	(8)	(16)	(29)	(8)	(87)
β Toc/LPO	Male	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.03	0.06 ± 0.03
	(*n*)	(4)	(8)	(11)	(5)	(8)
	Female	0.01 ± 0.00	0.01 ± 0.02	0.01 ± 0.02	0.02 ± 0.04	0.12 ± 0.24
	(*n*)	(4)	(8)	(18)	(3)	(34)
	Total	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.03	0.02 ± 0.03	0.11 ± 0.22
	(*n*)	(8)	(16)	(29)	(8)	(42)
γ Toc/LPO	Male	0.10 ± 0.03	0.08 ± 0.10	0.09 ± 0.13	0.13 ± 0.31	0.18 ± 0.20
	(*n*)	(4)	(8)	(11)	(5)	(15)
	Female	0.11 ± 0.13	0.11 ± 0.21	0.09 ± 0.21	0.11 ± 0.35	0.22 ± 0.21
	(*n*)	(4)	(8)	(18)	(3)	(68)
	Total	0.11 ± 0.06	0.09 ± 0.10	0.09 ± 0.19	0.12 ± 0.38	0.21 ± 0.21
	(*n*)	(8)	(16)	(29)	(8)	(83)

Toc: Tocopherol; LPO: lipid peroxidase. Note: no significant differences between groups.

Table 7: Correlation coefficient between tocopherol and plasma lipid peroxide.

	Plasma tocopherol				RBC tocopherol			
	T-Toc	α-Toc	β-Toc	γ-Toc	T-Toc	α-Toc	β-Toc	γ-Toc
Centenarians ($n = 139$)	0.01	0.11	−0.03	−0.04	0.01	0.02	0.04	−0.06
Septuagenarians ($n = 61$)	0.34**	0.33**	−0.02	0.21	−0.32*	−0.29*	−0.16	−0.11

* $P < .05$, ** $P < .01$.

We did not find any significant differences between age groups for tocopherol: cholesterol and tocopherol: LPO ratios in centenarians versus younger controls.

Interestingly, a weakly negative correlation was found between intracellular tocopherol (T-tocopherol and α-tocopherol) and LPO in septuagenarians. Since mitochondria produce most of the oxidative stress in cells, higher intracellular levels of tocopherol should result in lower LPO levels and theoretically, less damage. However, this finding was only significant in septuagenarians and not in centenarians, and if this truly represents a protective factor for survival it is unclear why centenarians would not also exhibit this finding. More study of this issue is warranted.

Overall, the literature on oxidative stress as a longevity factor in humans is sparse. Some data from studies of Italian centenarians are in agreement with our LPO findings in Okinawan centenarians. For example, a study of 15 centenarians (3 males; 12 females) recruited from central Italy compared with equal numbers of controls (young, middle aged and elderly) showed that blood LPO levels, evaluated as MDA content, were lower in centenarians than in elderly control subjects (60–79 years of age) [31]. A larger study by the same research group also showed that LPO increased with age until centenarian years where a significant decrement occurred [32]. Centenarian LPO levels were lower than elderly controls (60–79 years) in that study as well but higher than young controls (aged 21–40 years). This suggests that centenarians might have mechanisms to keep oxidative stress at levels equivalent to persons who are decades younger, and this could help explain their exceptional longevity. Susceptibility to peroxidation of the erythrocyte membranes (when challenged) was also lower in centenarians than in older controls [32]. Vitamin E was not measured in these studies but another potential mechanism was identified. Centenarians were found to have increased levels of omega-3 polyunsaturated fatty acids (PUFAs) and reduced content of omega-6 PUFAs relative to younger controls. Long-chain omega-3 PUFAs decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species by acting directly to inhibit arachidonic acid metabolism and acting indirectly to modify inflammatory gene expression [33].

While there were tentative links established in the current study between oxidative stress and vitamin E in the Okinawans, we were not able to strongly link vitamin E-derived tocopherols to reduced oxidative stress across all measures. LPO was higher in those aged in their 20s, 30s, and 70s and dropped off in the 80s and 100s. Most measures of vitamin E in this study also increased with age until the 70s and then dropped off. Similar trends have been seen in studies of younger, middle-aged, and older persons, although few studies included exceptionally old persons [8, 34–36]. The literature is mixed with regard to gender differences, with reports of higher plasma α-tocopherol in males [37] or females [38]. The current study found that females tended to have significantly higher tocopherol (total and α) levels than males.

The lack of robust support in the current study and the literature in general for a powerful effect of vitamin E against LPO does not mean that vitamin E is unimportant to healthy aging. It is possible that measuring oxidative stress through TBA may not be the optimal method to assess vitamin E's antioxidant effects. Nevertheless, a clinical trial of vitamin E supplementation of up to 2,000 iu/day for 8 weeks was also not supportive of *in vivo* antioxidative effects. This study showed no change on three different indices of lipid peroxide (urinary 4-hydroxynonenal and 2 different isoprostanes) [39].

Interestingly, studies that focused on other measures of systemic defenses against oxidative stress *have* shown that centenarians exhibited higher red blood cell glutathione reductase and catalase activities, which could result in lower oxidative stress [40]. Studies of Danish centenarians also found that glutathione reductase activity was higher in centenarian erythrocytes than in younger controls. This was also linked to healthy aging where centenarians with the highest cognitive and physical function tended to have the greatest enzyme activity [41]. These might be fertile areas to search for relations with vitamin E.

Genes that influence oxidative stress might also be fertile areas for investigation, although genetic alterations of model organisms, including yeast, rodents, worms, and drosophila, have yielded conflicting data. In the fruit fly (*Drosophila melanogaster*), overexpression of antioxidative enzymes through knockout models or other means can dramatically increase lifespan. Conversely, the absence of CuZn superoxide dismutase, a major antioxidant, increases sensitivity to oxidative damage and reduces lifespan by approximately 80% but genetic rescue of half the enzyme restores lifespan [42, 43]. However, such dramatic effects are not seen in rodent models where mice with genetic alterations in antioxidant defenses typically show little alteration in lifespan, but do show alterations in healthspan [44]. For example, ApoE null mice have lower serum apolipoprotein E and develop significant early atherosclerosis [45] but overexpression of catalase, an important antioxidative defense, appears to confer protection against early atherosclerosis [46].

Interestingly, the two human genes that appear to have the strongest links to healthy aging and longevity, ApoE and FOXO3A [47–49] are both linked to oxidative stress. APOE genotype influences oxidative stress and inflammation in cell lines, rodents, and humans [50], and FOXO3A protects cells from oxidative stress [51]

It is also possible that vitamin-E derived tocopherols may act through mechanisms that are not clearly linked to oxidative stress, such as second messenger molecular signaling [52] and/or other cardioprotective mechanisms [53], or membrane fluidity [54]. In addition, high vitamin E consumption may merely reflect an overall dietary pattern that results in healthier aging. For example, work on Italian centenarians shows that they possess relatively high plasma vitamin E [55]. Moreover, the traditional healthy Okinawan diet, which is associated with a high prevalence of centenarians, has 16.6 mg a day of vitamin E, which is a remarkable 190% of the Japan RDA. This is markedly higher than the Japanese traditional diet with 6.3 mg a day and 72% of the RDA for Japan (RDAJ = males: 10 mg/d; females: 8 mg/d) [15]. A study of Polish centenarians also showed that centenarians had high vitamin E levels compared with healthy, young female adults [40]. However, there has been no *causative* link to longevity.

Along the same line of thinking, many epidemiologic studies show a protective *association* for vitamin E with age-related chronic diseases but support from interventional clinical trials has been lacking [56]. For example, in a longitudinal study of healthy oldest-old (ages 80-plus), low plasma concentration of vitamin E and high concentration of lipid peroxide at baseline predicted risk of cardiovascular events over a 4-year follow-up [12]. While adjustment for vitamin C, β-carotene, and serum lipids did not affect the relation, the possibility still exists that other factors correlated with vitamin E could have been responsible for the association. In fact, a cross-sectional epidemiologic study of over 700 men and women, aged 25–74, showed that plasma LPO was positively correlated with a great many cardiovascular risk factors, including triglycerides, cholesterol subtypes, BMI, fibrinogen, and WBC count, and was negatively correlated with vitamin C [11]. It is difficult to control for all such associations in epidemiologic work, and the possibility that vitamin E is simply correlated with another more active molecule(s) cannot be completely ruled out. Indeed, when clinical trials have been conducted with vitamin E on incidence and progression of age-related chronic diseases the bulk of the evidence is not supportive of an important protective effect [56].

It is likely that several mechanisms account for low LPO at exceptional ages. Exceptional longevity has been linked to lower caloric intake, more efficient metabolism, increased insulin sensitivity, among other factors that might lead to lower oxidative stress [1, 14]. We have also found genetic factors that may be important, such as variants in HLA genes that may lead to less inflammation [57] and genetic variants in the FOXO3A gene with potentially pleiotropic mechanisms for reducing oxidative stress [48].

Finally, if there is truly less ongoing oxidative damage in centenarians then the etiology is probably complex and involves interplay of genetic and environmental factors that operate over a lifetime. A combination of scientific approaches will be needed to tease out the important mechanisms.

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References

[1] B. J. Willcox, D. C. Willcox, and L. Ferrucci, "Secrets of healthy aging and longevity from exceptional survivors around the globe: lessons from octogenarians to supercentenarians," *Journals of Gerontology: Series A Biological Sciences and Medical Sciences*, vol. 63, no. 11, pp. 1181–1185, 2008.

[2] K. B. Beckman and B. N. Ames, "The free radical theory of aging matures," *Physiological Reviews*, vol. 78, no. 2, pp. 547–581, 1998.

[3] D. Harman, "Aging: a theory based on free radical and radiation chemistry," *Journal of Gerontology*, vol. 11, no. 3, pp. 298–300, 1956.

[4] E. D. Wills, "Mechanisms of lipid peroxide formation in animal tissues," *Biochemical Journal*, vol. 99, no. 3, pp. 667–676, 1966.

[5] J. M. McCord and I. Fridovich, "Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein)," *Journal of Biological Chemistry*, vol. 244, no. 22, pp. 6049–6055, 1969.

[6] D. J. Mustacich, R. S. Bruno, and M. G. Traber, "Vitamin E," *Vitamins and Hormones*, vol. 76, pp. 1–21, 2007.

[7] M. G. Traber, "Vitamin E regulatory mechanisms," *Annual Review of Nutrition*, vol. 27, pp. 347–362, 2007.

[8] W. A. Behrens and R. Madere, "Alpha- and gamma tocopherol concentrations in human serum," *Journal of the American College of Nutrition*, vol. 5, no. 1, pp. 91–96, 1986.

[9] S. Kaiser, P. Di Mascio, M. E. Murphy, and H. Sies, "Physical and chemical scavenging of singlet molecular oxygen by tocopherols," *Archives of Biochemistry and Biophysics*, vol. 277, no. 1, pp. 101–108, 1990.

[10] F. Galli and A. Azzi, "Present trends in vitamin E research," *BioFactors*, vol. 36, no. 1, pp. 33–42, 2010.

[11] A. G. Rumley, M. Woodward, A. Rumley, J. Rumley, and G. D. O. Lowe, "Plasma lipid peroxides: relationships to cardiovascular risk factors and prevalent cardiovascular disease," *QJM*, vol. 97, no. 12, pp. 809–816, 2004.

[12] A. Mezzetti, G. Zuliani, F. Romano et al., "Vitamin E and lipid peroxide plasma levels predict the risk of cardiovascular events in a group of healthy very old people," *Journal of the American Geriatrics Society*, vol. 49, no. 5, pp. 533–537, 2001.

[13] M Suzuki, M Adachi, and M. Akisaka, "Plasma lipid peroxide: decreasing effects after tocopherol administration," in *Proceedings of the International Symposium on Vitamin E*, p. 141, 1991.

[14] M. Suzuki, B. J. Willcox, and D. C. Willcox, "Implications from and for food cultures for cardiovascular disease: longevity," *Asia Pacific Journal of Clinical Nutrition*, vol. 10, no. 2, pp. 165–171, 2001.

[15] B. J. Willcox, D. C. Willcox, H. Todoriki et al., "Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span," *Annals of the New York Academy of Sciences*, vol. 1114, pp. 434–455, 2007.

[16] H. H. Dodge, Y. Katsumata, H. Todoriki et al., "Comparisons of plasma/serum micronutrients between Okinawan and Oregonian elders: a pilot study," *Journals of Gerontology: Series A Biological Sciences and Medical Sciences*, vol. 65A, no. 10, pp. 1060–1067, 2010.

[17] K. Warner and T. L. Mounts, "Analysis of tocopherols and phytosterols in vegetable oils by HPLC with evaporative light-scattering detection," *Journal of the American Oil Chemists' Society*, vol. 67, no. 11, pp. 827–831, 1990.

[18] USDA National Nutrient Database for Standard Reference, Release 23, "Composition of Foods Raw, Processed, Prepared," U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Nutrient Data Laboratory. 2010.

[19] D. C. Willcox, B. J. Willcox, H. Todoriki, and M. Suzuki, "The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load," *Journal of the American College of Nutrition*, vol. 28, no. 4, pp. 500S–516S, 2009.

[20] M. Suzuki, T. Akamatsu, Y. Hata, S. Ishi, and S. Inayama, "Medical and physiological analysis of centenarians—level of serum lipid peroxide, plasma amino acids, vitamin E," *Journal of the Japanese Society of Internal Medicine*, vol. 72, p. 224, 1983 (Japanese).

[21] T. Ono and K. Eto, "Clinical application of lipid peroxide measurement—thiobarbituric acid (TBA) values of the blood and other body fluids," *Rinsho Byori*, vol. 15, no. 9, pp. 601–603, 1967.

[22] T. Hendriks and R. F. T. A. Assman, "On the fluorometric assay of circulating lipoperoxides," *Clinica Chimica Acta*, vol. 174, no. 3, pp. 263–270, 1988.

[23] G. T. Vatassery, A. M. Krezowski, and J. H. Eckfeldt, "Vitamin E concentrations in human blood plasma and platelets," *American Journal of Clinical Nutrition*, vol. 37, no. 6, pp. 1020–1024, 1983.

[24] I. J. Schatz, K. Masaki, K. Yano, R. Chen, B. L. Rodriguez, and J. D. Curb, "Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study," *Lancet*, vol. 358, no. 9279, pp. 351–355, 2001.

[25] B. F. Oliveira, J. A. Nogueira-Machado, and M. M. Chaves, "The role of oxidative stress in the aging process," *The Scientific World Journal*, vol. 10, pp. 1121–1128, 2010.

[26] D. Pratico, "Lipid peroxidation and the aging process," *Science of Aging Knowledge Environment*, no. 50, p. re5, 2002.

[27] T. Perls and D. Terry, "Genetics of exceptional longevity," *Experimental Gerontology*, vol. 38, no. 7, pp. 725–730, 2003.

[28] F. Nayeem, M. Nagamani, K. E. Anderson, Y. Huang, J. J. Grady, and L. J. W. Lu, "Dietary β-tocopherol and linoleic acid, serum insulin, and waist circumference predict circulating sex hormone-binding globulin in premenopausal women," *Journal of Nutrition*, vol. 139, no. 6, pp. 1135–1142, 2009.

[29] A. Sirikhachornkit, J. W. Shin, I. Baroli, and K. K. Niyogi, "Replacement of α-tocopherol by β-tocopherol enhances resistance to photooxidative stress in a xanthophyll-deficient strain of chlamydomonas reinhardtii," *Eukaryotic Cell*, vol. 8, no. 11, pp. 1648–1657, 2009.

[30] M. Suzuki, H. Sakugawa, K. Furumi, T. Akamatsu, and K. Suzuki, "The medical and sociological survey of centenarians

in Okinawa," *Japanese Journal of Geriatrics*, vol. 15, p. 31, 1978 (Japanese).

[31] R. A. Rabini, A. Vignini, D. Martarelli et al., "Evidence for reduction of pro-atherosclerotic properties in platelets from healthy centenarians," *Experimental Gerontology*, vol. 38, no. 4, pp. 367–371, 2003.

[32] R. A. Rabini, N. Moretti, R. Staffolani et al., "Reduced susceptibility to peroxidation of erythrocyte plasma membranes from centenarians," *Experimental Gerontology*, vol. 37, no. 5, pp. 657–663, 2002.

[33] P. C. Calder, "n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases," *American Journal of Clinical Nutrition*, vol. 83, no. 6, pp. 1505S–1519S, 2006.

[34] I. Elmadfa, N. Both-Bedenbender, B. Sierakowski, and E. Steinhagen-Thiessen, "Significance of vitamin E in aging," *Zeitschrift fur Gerontologie*, vol. 19, no. 3, pp. 206–214, 1986.

[35] J. Hallfrisch, D. C. Muller, and V. N. Singh, "Vitamin A and E intakes and plasma concentrations of retinol, β- carotene, and α-tocopherol in men and women of the Baltimore longitudinal study of aging," *American Journal of Clinical Nutrition*, vol. 60, no. 2, pp. 176–182, 1994.

[36] E. S. Ford and A. Sowell, "Serum α-tocopherol status in the United States population: findings from the Third National Health and Nutrition Examination Survey," *American Journal of Epidemiology*, vol. 150, no. 3, pp. 290–300, 1999.

[37] E. S. Ford, R. L. Schleicher, A. H. Mokdad, U. A. Ajani, and S. Liu, "Distribution of serum concentrations of α-tocopherol and γ-tocopherol in the US population," *American Journal of Clinical Nutrition*, vol. 84, no. 2, pp. 375–383, 2006.

[38] S. Vogel, J. H. Contois, K. L. Tucker, P. W. F. Wilson, E. J. Schaefer, and C. J. Lammi-Keefe, "Plasma retinol and plasma and lipoprotein tocopherol and carotenoid concentrations in healthy elderly participants of the Framingham Heart Study," *American Journal of Clinical Nutrition*, vol. 66, no. 4, pp. 950–958, 1997.

[39] E. A. Meagher, O. P. Barry, J. A. Lawson, J. Rokach, and G. A. FitzGerald, "Effects of vitamin E on lipid peroxidation in healthy persons," *Journal of the American Medical Association*, vol. 285, no. 9, pp. 1178–1182, 2001.

[40] B. Kłapcińska, J. Derejczyk, K. Wieczorowska-Tobis, A. Sobczak, E. Sadowska-Krepa, and A. Danch, "Antioxidant defense in centenarians (a preliminary study)," *Acta Biochimica Polonica*, vol. 47, no. 2, pp. 281–292, 2000.

[41] H. R. Andersen, B. Jeune, H. Nybo, J. B. Nielsen, K. Andersen-Ranberg, and P. Grandjean, "Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians," *Age and Ageing*, vol. 27, no. 5, pp. 643–648, 1998.

[42] I. Reveillaud, J. Phillips, B. Duyf, A. Hilliker, A. Kongpachith, and J. E. Fleming, "Phenotypic rescue by a bovine transgene in a Cu/Zn superoxide dismutase- null mutant of Drosophila melanogaster," *Molecular and Cellular Biology*, vol. 14, no. 2, pp. 1302–1307, 1994.

[43] J. P. Phillips, S. D. Campbell, D. Michaud, M. Charbonneau, and A. J. Hilliker, "Null mutation of copper/zinc superoxide dismutase in Drosophila confers hypersensitivity to paraquat and reduced longevity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 86, no. 8, pp. 2761–2765, 1989.

[44] A. B. Salmon, A. Richardson, and V. I. Pérez, "Update on the oxidative stress theory of aging: does oxidative stress play a role in aging or healthy aging?" *Free Radical Biology and Medicine*, vol. 48, no. 5, pp. 642–655, 2010.

[45] M. Ohashi, M. S. Runge, F. M. Faraci, and D. D. Heistad, "MnSOD deficiency increases endothelial dysfunction in ApoE-deficient mice," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 10, pp. 2331–2336, 2006.

[46] H. Yang, L. J. Roberts, M. J. Shi et al., "Retardation of atherosclerosis by overexpression of catalase or both Cu/Zn-superoxide dismutase and catalase in mice lacking apolipoprotein E," *Circulation Research*, vol. 95, no. 11, pp. 1075–1081, 2004.

[47] D. C. Willcox, B. J. Willcox, W. C. Hsueh, and M. Suzuki, "Genetic determinants of exceptional human longevity: insights from the Okinawa Centenarian Study," *Age*, vol. 28, no. 4, pp. 313–332, 2006.

[48] B. J. Willcox, T. A. Donlon, Q. He et al., "FOXO3A genotype is strongly associated with human longevity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 37, pp. 13987–13992, 2008.

[49] W.-H. Chung, R.-L. Dao, L.-K. Chen, and S.-I. Hung, "The role of genetic variants in human longevity," *Ageing Research Reviews*, vol. 9, supplement 1, pp. S67–S78, 2010.

[50] L. Jofre-Monseny, A. M. Minihane, and G. Rimbach, "Impact of apoE genotype on oxidative stress, inflammation and disease risk," *Molecular Nutrition and Food Research*, vol. 52, no. 1, pp. 131–145, 2008.

[51] G. J. P. L. Kops, T. B. Dansen, P. E. Polderman et al., "Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress," *Nature*, vol. 419, no. 6904, pp. 316–321, 2002.

[52] A. Azzi, R. Gysin, P. Kempná et al., "The role of α-tocopherol in preventing disease: from epidemiology to molecular events," *Molecular Aspects of Medicine*, vol. 24, no. 6, pp. 325–336, 2003.

[53] N. G. Stephens, A. Parsons, P. M. Schofield et al., "Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS)," *Lancet*, vol. 347, no. 9004, pp. 781–786, 1996.

[54] M. G. Traber, "Regulation of xenobiotic metabolism, the only signaling function of α-tocopherol?" *Molecular Nutrition and Food Research*, vol. 54, no. 5, pp. 661–668, 2010.

[55] P. Mecocci, M. C. Polidori, L. Troiano et al., "Plasma antioxidants and longevity: a study on healthy centenarians," *Free Radical Biology and Medicine*, vol. 28, no. 8, pp. 1243–1248, 2000.

[56] B. J. Willcox, J. D. Curb, and B. L. Rodriguez, "Antioxidants in cardiovascular health and disease: key lessons from epidemiologic studies," *American Journal of Cardiology*, vol. 101, no. 10, pp. S75–S86, 2008.

[57] H. Takata, T. Ishii, M. Suzuki, S. Sekiguchi, and H. Iri, "Influence of major histocompatibility complex region genes on human longevity among Okinawan-Japanese centenarians and nonagenarians," *Lancet*, vol. 2, no. 8563, pp. 824–826, 1987.

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Review Article

Discovery of Novel Sources of Vitamin B_{12} in Traditional Korean Foods from Nutritional Surveys of Centenarians

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Human longevity can be explained by a variety of factors, among them, nutritional factor would play an important role. In our study of Korean centenarians for their longevity, the apparent nutritional imbalance in the traditional semi-vegetarian diet raised a special attention, especially on vitamin B_{12} status, supplied by animal foods. Interestingly, we found that the prevalence of vitamin B_{12} deficient Korean centenarians was not higher compared with those from Western nations with animal-oriented traditional foods. We assumed that there might be some unveiled sources for vitamin B_{12} in the Korean traditional foods. Screening of vitamin B_{12} contents has revealed that some traditional soybean-fermented foods, such as *Doenjang* and *Chunggukjang*, and seaweeds contain considerable amounts of vitamin B_{12}. Taken together, it can be summarized that the traditional foods, especially of fermentation, might be evaluated for compensation of the nutritional imbalance in the vegetable-oriented dietary pattern by supplying vitamin B_{12}, resulting in maintenance of health status.

1. Introduction

It is well known that older adults comprise the fastest growing portion of the world population and that the oldest old (including centenarians) are one of the fastest growing subgroups. The oldest population varies greatly depending upon nation, region, and biodemographic trends. At the end of the 20th century, it was reported that the centenarian population numbered approximately 1 per 100,000 persons, with higher numbers (10 per 100,000) in developed countries, and still higher numbers in the regions with very low mortality levels, such as Okinawa prefecture, in southern Japan (about 34 per 100,000) while about 4.7per 100,000 existed in Korea during this period [1].

Korean centenarian numbers were first reported to be 2,220 (172 males and 2,048 females) in the year 2000, based on the birth record data from Statistics Korea, and the ratio of centenarians to the elderly of 65 and older was reported to be 6.6% [2]. However, we have found that one third of birth records of older people may be mistaken due to problems within the civil registration system and therefore we produced a more conservative estimate of 1,481 Korean centenarians in the year 2000 [3]. Since that time, the National Bureau of Statistics of Korea has not officially reported the number of centenarians. The actual number of Korean centenarians is still waiting to be confirmed after individual age verification can take place.

When the gender difference in number of centenarians is taken into consideration, female centenarians are found to far outnumber male centenarians all over the world, except for some limited areas such as Sardinia, Western China, or the Middle East, the latter two of which are likely unreliable due to a lack of documentation and/or lack of a long-standing civil registration system [4]. However, the ratio of female centenarians to male centenarians in Korea was reported to be the highest among nations at 11.5 females

for every male in 2000 [2]. The exact reasons for these gender differences have yet to be elucidated; however, they are likely due to a combination of social, biological, and demographical factors. Moreover, our observations indicate that the gender gap seems to be closing in the recent years. Korean life expectancy has improved considerably during the post war period and reached 76.5 years for men and 83.3 years for women, with the older population (aging 65 and older) reaching 10.7% in 2009 [5].

In order to study human longevity and its related factors in a scientific manner, the analysis of the relative influence (and interaction) of a variety of variables may be necessary. For integration of these variables, we propose a new model for human longevity, which might be named "Park's Temple Model for Human Longevity" (Figure 1). The premise of this model is based on the concept that human longevity could be compared to building up a temple, consisting of 3 essential components as bottom, pillars, and roof top. For building up a temple, all the components should be strengthened and balanced for safety and stability. The bottom components of the temple are basically fixative or not readily changeable variables, such as genetics, gender, personality, ecology, social structures, or cultures. The pillar components of the temple, related with personal life styles or health behaviors, might be readily modifiable variables and include such factors as exercise, nutrition, social relationships, and social participation. The roof top components of the temple are socially or politically determined variables such as the adequacy of the social safety net, social support, and health care system. These three different layers of the components interact and compensate one another to determine longevity. In line with this conceptual framework, the Korean centenarian study has been carried out in a comprehensive manner with participation from multidisciplinary groups [6–9].

In this paper, we would like to focus on one of the pillars of our longevity model, that is, the nutritional characteristics of Korean centenarians. Vitamin B_{12} deficiency is a common nutritional deficiency among the elderly, particularly among the oldest old. Many of the oldest old suffer from atrophic gastritis, a thinning of the stomach lining that reduces the amount of B_{12} absorbed by the small intestine which may be related to Helicobacter pylori infection, pernicious anemia, and/or long-term ingestion of antacids or other medications. Surgery, digestive, and/or other medical conditions can also interfere with the absorption of this important micronutrient. Clinical manifestations are often subtle although they can be severe, particularly from a hematological or neuropsychiatric standpoint.

One of the mysteries of Korean longevity has come from medical and nutritional assessment of centenarians that has indicated that many are relatively healthy, despite the lifelong traditional grain and vegetable-oriented dietary pattern. These findings are contradictory to the modern nutritional concept of nutritional balance for maintenance of health, since it is a challenge for most vegetarian (or semivegetarian) diets to supply adequate levels of several key nutrients, in particular vitamin B_{12}. How Korean centenarians were able to avoid this serious age-related nutritional deficiency in spite of their low intake of animal products will be the focus of the this investigation.

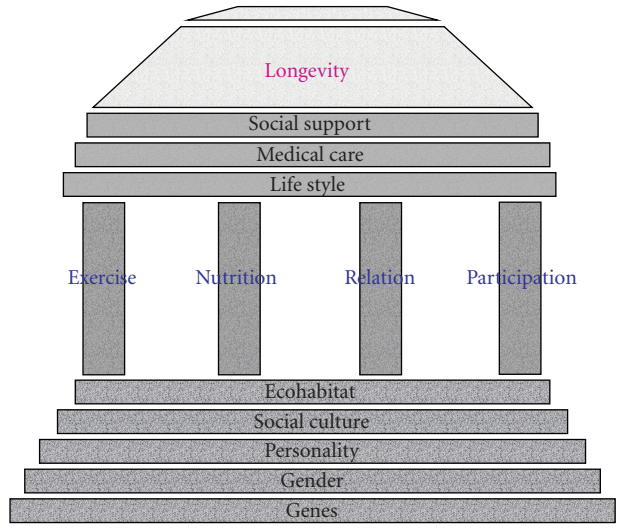

Figure 1: Park's Temple Model of Human Longevity.

2. Participants in Korean Centenarian Study

In our centenarian studies, age verification was prioritized. Since the civil registration system was not complete until the middle of 20th century in Korea, the age verification of the centenarians was processed by three different criteria including governmental registry, sibling age(s), and information from neighbors and acquaintances. Subjects who participated in our numerous centenarian studies [6–9] were randomly selected nationwide based on birth records, but those living in facilities like nursing homes or hospitals were excluded, because of the restriction in age verification due to lack of neighborhood information and family records. However, in Korea, there are generally fewer older people living in long-term care facilities compared to most developed nations and only 3.3% of people aging 65 or older are living in nursing homes or hospitals at present [10]. Unfortunately we do not have data on the exact numbers of centenarians in long-term care facilities, and it is well known that centenarians living in the community are generally higher functioning than those in long-term care facilities, therefore, we are likely dealing with a higher functioning sample population in our studies.

The basic characteristics of subjects who participated in three centenarian studies are shown in Table 1. To our knowledge, the three cohorts were partially overlapping, though this is likely to be limited.

The age range of centenarians was 100–108 years, and approximately 50% of male and 90% of female subjects were not educated at all, so that more than 80% were illiterate. Most of the centenarians were living with their family at home, and less than 10% of female centenarians were living alone.

Table 1: Characteristics of Korean centenarian subjects.

	Lee et al. [6]	Kwon et al. [7]	Kwak et al. [9]
n(M/F)†	54 (6/48)	117 (13/104)	70 (0/70)
Age (years)	102.1 ± 1.7 (100–108)	102.2 ± 1.9 (100–108)	102.2 ± 1.9 (100–108)
Education (%)			
None	50.0/89.6†		/90.5†
Elementary	50.0/10.4		/9.5
Illiteracy (%)		86.3	
Smoking, currently (%)	19.6	40.0/17.4†	/25.7
Living arrangement (%)			
Alone	0.0/6.3†		/9.2
With family	100/93.7		/90.8
Only with spouse	16.7/0.0		/0.0
Weight (kg)			
M		52.3 ± 3.9	
F		34.4 ± 7.6	
BMI			
M		22.2 ± 0.6	
F		17.6 ± 3.6	

† Male/female.

The average body weight and BMI were 52.3 kg and 22.2 kg/m^2 in males and 34.4 kg and 17.6 kg/m^2 in females, respectively [7].

3. Health Status and Blood Data of Korean Centenarians

Published data from three Korean centenarian surveys [6, 7, 9] on basic hematologic status and serum albumin, globulin, lipid, folate, vitamin B_{12} and homocysteine concentrations (nonfasting), were summarized in Table 2. Their results were similar to each other. The majority of these centenarian subjects were in relatively good health according to physical examinations and laboratory analyses. Ninety-five percent of the centenarian subjects had good appetites [6]. Kwak et al. [9] reported that average serum albumin concentration of Korean female centenarians was 3.75 g/dL, the prevalence of low serum albumin concentration (<3.5 g/dL) was 19.4%, and the average hemoglobin concentration and the anemic prevalence (<12.0 g/dL) were 11.3 g/dL and 56.7%, respectively, which were similar to the 12.1 g/dL and 50.2% found in Georgia centenarians [11].

Although Lee's study [6] has a limitation of small size regarding the number of male centenarians (only 6 subjects) and therefore caution should be exercised in making gender comparisons, it is nevertheless interesting to note that the RBC count and hematocrit level were significantly higher in male centenarians, and triglyceride and LDL-cholesterol levels were higher in females. Lee et al. [6] reported that none of the male centenarians were anemic, while 47.4% of female centenarians were mildly anemic (hemoglobin <11.2 g/dL), probably because of the higher consumption of protein and iron by male centenarians than female centenarians. Recently, Kwak et al. [9] reported that 56.7% of 62 Korean female centenarians were anemic (hemoglobin <12 g/dL). The Korean National Health and Nutritional Survey in 2005 (KNHNS) reported that the prevalence of anemia in older people aging 70 or more living in rural areas was 12.7% in males (hemoglobin <13 g/dL) and 14.5% in females (hemoglobin < 12.0 g/dL) [12].

Some notable regional differences in health status were observed [8]. Only 4% of mountain-dwelling centenarians had serum albumin levels lower than 3.3 g/dL in contrast to 26% of seaside-dwelling centenarians. There was also a higher incidence of centenarians with anemia among seaside dwelling centenarians. These data may be showing a better health status for centenarians living in the mountains, which could be due to a higher level of physical activity and better supply of nutrients in quality and balance compared to seaside dwelling centenarians [8]. The higher HDL-cholesterol levels for males could be due to the differences in the levels of exercise and intakes of energy and protein. This supposition is supported by the abnormally low serum HDL-cholesterol levels in four-fifths of seaside dwelling centenarians compared to those who reside in mountainous areas.

4. Vitamin B_{12}, Folate, and Homocysteine Status of Korean Centenarians

Risk factors for vitamin B_{12} deficiency include low animal protein intake, malabsorption associated with atrophic gastritis (which increases with age), or *Helicobacter pylori* infection, pancreatic or intestinal pathology, and gastric acid-reducing medications [13–16]. Poor vitamin B_{12} status has been associated with neurological problems [13, 17], hematological disorders [13, 18], and other health-related conditions, including poor cognition and Alzheimer's disease

Table 2: Blood biochemical variables including vitamin B_{12} level of Korean centenarians.¶

	Lee et al. [6]		Kwon et al. [7]		Kwak et al. [9]†
	Male ($n = 6$)	Female ($n = 37$)	Male ($n = 13$)	Female ($n = 104$)	Female ($n = 62$)
RBC ($\times 100^3/\mu$L)	4.0 ± 0.3*	3.6 ± 0.4			3.62 ± 0.66
WBC($\times 10^3/\mu$L)	4.7 ± 1.7	4.5 ± 1.2			4.77 ± 1.71
Hemoglobin (g/dL)	12.8 ± 0.9	11.4 ± 1.3			11.3 ± 2.0
Anemic (Hb < 11.2)	0.0%	47.4%			
Anemic (Hb < 12)					56.7%
Hematocrit (%)	38.0 ± 2.7*	34.9 ± 3.7			34.7 ± 5.9
Albumin (g/dL)	3.7 ± 0.5	3.7 ± 0.4	3.7 ± 0.5	3.8 ± 0.4	3.75 ± 0.39
Low (<3.5)					19.4%
Globulin (g/dL)	3.3 ± 0.4	3.2 ± 0.5			3.16 ± 0.47
Triglyceride (mg/dL)	69.7 ± 20.6*	104.1 ± 59.3			103.4 ± 55.4
Total cholesterol (mg/dL)	155.2 ± 22.4	168.2 ± 36.9			168.7 ± 37.1
LDL cholesterol (mg/dL)	97.7 ± 9.8*	112.6 ± 32.7			110.8 ± 32.9
HDL cholesterol (mg/dL)	46.8 ± 16.9	42.5 ± 9.3			42.1 ± 9.4
Vitamin B_{12} (pg/mL)	393.2 ± 45.5	405.5 ± 26.4			441.5 ± 243.1
Deficient (<200)	0.0%	15.8%			11.3%
Marginal (≥200,<340)					33.9%
Adequate (≥340)					54.8%
Folate (ng/mL)	4.67 ± 4.24	5.67 ± 4.01			5.79 ± 3.80
Deficient (<3)	33.3%	28.9%			33.8%
Homocysteine (μmol/L)	—	—	24.9 ± 9.3	21.1 ± 7.3	22.3 ± 7.6
Hyper (>17)			—	—	73.0%

Values are represented as mean ± SD.
¶All the parameters were analyzed in serum from notfasting blood samples.
†Data except vitamin B_{12} have not been published.
*Significantly different between males and females at $P < .05$.

[19–21], depression [22], hearing loss [23], cancer [24], and poor bone health [25, 26]. More vegetarians or older people suffer from vitamin B_{12} deficiency compared to omnivores or younger adults [27]. Since natural sources of vitamin B_{12} in human diets are restricted for those who consume a diet low in foods of animal origin, vegetarians or semi-vegetarians are susceptible to cobalamin deficiency [28]. Moreover, the age-related increase of atrophic gastritis reduces production of gastric acid and digestive enzymes, required for cleavage of protein-bound vitamin B_{12} from the natural form of vitamin B_{12} in foods, which might aggravate vitamin B_{12} deficiency in the older people.

It is known that the prevalence of atrophic gastritis and *Helicobacter pylori* is very high in Korean adults. Yim et al. [29] reported that the seropositivity of *H. pylori* in asymptomatic health checkup adults nationwide in 2005 decreased to 59.6% from 66.9% in 1998. Other studies have also reported that 65.3% [30] and 56.2% [31] of adults who visited hospitals were *H. pylori* positive.

Moreover, the prevalence of atrophic gastritis in antrum and body was reported to be 42.5% and 20.1%, respectively [30]. Therefore, it would be quite natural to assume that vitamin B_{12} status among Korean older people with lifelong habits of vegetable-oriented diets would be much worse when compared to that of older people in most Western societies where people tend to consume a diet much higher in foods of animal origin.

Serum vitamin B_{12} and folate were measured by dual radioimmunoassay using $^{57}Co/^{125}I$ as a tracer, the most common method, with COBRA γ-counter (Packard, UAS) by the lab at Eone Reference Laboratory [9] or Samsung Medical Center [6] in Korean centenarian studies.

As shown in Table 2, average serum vitamin B_{12} concentration was 393.2 pg/mL and 405.5 pg/mL in male and female centenarians, respectively, in Lee's study [6], and 441.5 pg/mL in female centenarians in Kwak's study [9]. The prevalence of female centenarians with low serum vitamin B_{12} (<200 pg/mL) was 15.8% in Lee's study and 11.3% in Kwak's study, similar to the 11.6% found in American centenarians from Georgia [11].

It has been previously pointed out by numerous researchers that the standard cutoff points for serum vitamin B_{12} level (150 pmol/L, 200 pg/mL) are probably too low and may underestimate the frequency of true vitamin B_{12} deficiency in the population [32–34]; therefore, higher cutoff points (221–258 pmol/L, 300–350 pg/mL) have been used for assessment of vitamin B_{12} deficiency in some surveys [11, 14, 32, 35]. Lindenbaum et al. [32] reported that 5.3% of the elderly group aging 67–96 years who participated in the Framingham study had serum vitamin B_{12} levels lower

than 200 pg/mL, whereas 40.5% of the same elderly group and 12% of free-living elderly population had serum vitamin B_{12} levels lower than 350 pg/mL. It was reported that 33% of Italian centenarians had serum vitamin B_{12} levels lower than 300 pg/mL [35], and 39.1% of Georgia centenarians had serum vitamin B_{12} level lower than 340 pg/mL [11]. When assessed with a cutoff value of 340 pg/mL, the prevalence of vitamin B_{12} insufficiency in Korean female centenarians was 45.2% [9], similar to American centenarians from Georgia [11] and Italian centenarians [35]. These data strongly suggest that despite the traditional vegetable-heavy diet of older Koreans, there may still be good sources of vitamin B_{12} present within the diet.

Metabolisms of vitamin B_{12}, folate, and homocysteine are associated with and play very important roles in preventing many disorders of neurological and cognitive impairments as well as hematological dysfunctions in older people [36–38].

Dodge et al. [39] compared blood micronutrients among the oldest old (85 and over) in Okinawa and Oregon and reported that serum folate and vitamin B_{12} levels were negatively associated with serum homocysteine levels for the Okinawa cohort, who also had a very low usage of vitamin supplements in contrast to the Oregon cohort (who had a relatively high usage of vitamin supplements) and who showed no relationship among folate, vitamin B_{12}, and homocysteine levels.

We have also analyzed associations among serum data for women aging 85 and over in a past study on elderly Koreans living in rural areas [9]. More specific data on multivitamin supplements were not collected, because few subjects of the cohort were taking vitamin supplements or functional foods, which are not commonly consumed among older people living in rural areas in Korea. We found that serum homocysteine concentration was not significantly correlated with age, serum folate, or vitamin B_{12}; however, serum vitamin B_{12} was found to be positively associated with serum folate ($r = 0.2266$, $P < .05$) as well as WBC levels ($r = 0.2623$, $P < .05$), and serum folate was also positively correlated with RBC levels ($r = 0.2685$, $P < .05$) in this elderly cohort. Serum homocysteine levels were measured with automated chemiluminescence immune assay (CLIA) system in our study as was the case for the Dodge et al. study [39].

In Kwak's study [9], the average folate concentration in serum from non-fasting blood of Korean female centenarians was 5.79 ng/mL (13.1 nmol/L), and therefore within normal range, and the prevalence of folate deficiency (<3 ng/mL) was 33.8% [9]. Serum folate levels of Korean female centenarians were found to be much lower when compared with the 29.2 nmol/L levels of the American centenarians from Georgia [11], but similar to the 11.5 nmol/L levels found in Italian centenarians without cognitive impairment [35]. It was speculated that the reason for the lower serum folate levels in Korean centenarians when compared to those of Georgian centenarians might be related to a lower folate intake due to very low availability of folate-fortified foods in Korea in contrast to possible higher supplementation in the American oldest old.

The average serum homocysteine concentration of male centenarians was 24.9 μmol/L and that of female centenarians was 21.2 μmol/L in Kwon's study [7] and 22.3 μmol/L in Kwak's study [9], showing no gender differences. These values were higher than the 14.5 μmol/L of Georgian centenarians [11] but similar to that of cognitively intact Italian centenarians (22.0 μmol/L) [35]. The prevalence of hyperhomocysteinemia (>17 μmol/L) in Korean female centenarians was 73.0% [9], which was also similar to 77% of Italian centenarians with normal cognition [35], and 46.6% of Georgian centenarians were assessed to have hyperhomocysteinemia by lower criteria (>13.9 μmol/L) [11]. To again exercise due caution in interpreting these results, it must be mentioned that different assay methods were used for measuring homocysteine (CLIA in Korean study, GC mass spectrometry in the Georgian study, and HPLC in the Italian study), so there may be some limitations when making these comparisons.

5. Food Intake, Variety, and Dietary Balance of Korean Centenarians

The Korean centenarian study [9] calculated the intake of dairy products, meat and eggs, fish and shellfish, cereals, potatoes and starch, sweets, legumes and tofu, vegetables and seaweeds, fruits, and soybean-fermented foods, as well as total food intake from a one-day dietary record (Table 3).

The average total food intake of these female centenarians was 787.1 g/day. Meals were comprised primarily of plant foods (87.1% of total) such as cereals, legumes and their products, vegetables, and fruits. The average intake of cereals was 219.0 g/day, mostly derived from rice, a staple food for Koreans. The subjects consumed 29.7 g/day of legumes, nuts, and tofu, a representative soybean product consumed in Korea. They consumed 222.7 g/day of vegetables and seaweeds including 65.7 g/day of *Kimchi*, the most popular vegetable-fermented food in Korea, and a large portion of vegetable intake was derived from various blanched vegetables (*Namul* in Korean language). They also consumed 24.4 g/day of soybean-fermented foods, such *Doenjang (miso equivalent), Chungkookjang (natto equivalent), Gochujang (hot pepper paste), and Ganjang (soy bean sauce)*. Fruit intake was very low at 37.6 g/day, compared to vegetable intake. The subjects consumed 101.6 g/day of animal foods (12.9% of total), including 43.8 g of meat, poultry, and eggs, 37.6 g of fish and shellfish, and 18.1 g of dairy products.

In addition, the dietary balance and variety of Korean centenarians' diet was evaluated using the dietary diversity score (DDS), the numbers of five food groups consumed in a day, and the dietary variety score (DVS), the number of different kinds of foods consumed in an entire day in two studies [6, 9]. The five groups and minimum amounts according to the DDS are (1) cereal and potatoes (≥60 g), (2) meat, fish, eggs, and their products (≥30 g), (3) milk and its products (≥60 mL/15 g in solid), (4) vegetables/vegetable juices (≥30 g/60 mL), and (5) fruits/fruit juices (≥30 g/60 mL) [40].

Table 3: Daily food intake and dietary balance and variety in Korean centenarians.

	Lee et al. [6]	Kwak et al. [9]
Food intake (g)		787.1 ± 361.6 (100.0%)†
Plant (g)		685.4 ± 318.8 (87.1%)†
Animal (g)		101.6 ± 106.3 (12.9%)†
Cereals (g)		219.0 ± 80.0
Potatoes and starch (g)		14.3 ± 39.7
Sweets (g)		23.5 ± 29.5
Legumes, nuts & tofu (g)		29.7 ± 88.8
Vegetables & seaweeds (g) (Kimchi) (g)		222.7 ± 172.4 (65.7 ± 80.8)
Fruits (g)		80.8 ± 139.5
Soybean-fermented foods (g)		24.4 ± 30.0
Meat, poultry & eggs (g)		43.8 ± 51.1
Fish & shellfish (g)		37.6 ± 52.6
Dairy product (g)		18.1 ± 64.1
DDS	3.33 ± 0.62 (M) 3.50 ± 0.68 (F)	3.36 ± 0.73 (F) (91.9%)‡
DVS	17.83 ± 3.66 (M) 18.60 ± 5.69 (F)	17.1 ± 6.2 (F) (48.7%)‡

Values are expressed as means ± SD.
†% to total food intake.
‡% of subjects consuming well-balanced diet with higher score than 3.0, 18.0 in DDS or DVS.
DDS: dietary diversity score (0–5 points); DVS: dietary variety score.

Table 4: Daily energy and nutrient intake of Korean centenarians.

	Lee et al. [6]		Kwak et al. [9]
	Male ($n = 6$)	Female ($n = 48$)	Female ($n = 70$)
Energy (kcal)	1.718 ± 327**	1.247 ± 363	1.186 ± 418
Protein (g)	69.2 ± 25.6**	40.8 ± 18.4	47.3 ± 21.7 (15.5%)†
Fat (g)	27.0 ± 8.7	19.3 ± 12.3	19.8 ± 12.4 (13.9%)†
Carbohydrate (g)	295.3 ± 67.9*	225.9 ± 65.1	215.6 ± 72.1 (70.6%)†
Fiber (g)	6.8 ± 4.45	5.0 ± 3.2	4.5 ± 2.9
Cholesterol (mg)	269.0 ± 259.4	115.8 ± 161.2	123.7 ± 159.3
Calcium (mg)	564.1 ± 237.9*	352.7 ± 202.8	351.7 ± 193.6
Iron (mg)	12.9 ± 4.1	8.90 ± 5.02	10.2 ± 5.9
Zinc (mg)	9.21 ± 3.76**	5.86 ± 2.31	5.8 ± 2.8
Vitamin A (RE)	878.9 ± 600.7	586.1 ± 438.7	497.2 ± 424.8
Vitamin B_1 (mg)	1.0 ± 0.2	0.7 ± 0.4	0.6 ± 0.3
Vitamin B_2 (*mg*)	0.9 ± 0.3	0.7 ± 0.4	—
Vitamin B_6 (mg)	2.0 ± 0.5**	1.3 ± 0.6	1.3 ± 0.6
Vitamin B_{12} (μg)	—	—	3.7 ± 5.7
Niacin (mg)	15.8 ± 5.8***	8.9 ± 4.4	8.5 ± 4.2
Vitamin C (mg)	72.8 ± 59.5	55.9 ± 39.0	47.6 ± 32.4
Vitamin E (mg)	10.7 ± 6.7*	5.8 ± 4.3	5.4 ± 4.3
Folate (μg)	—	—	150.6 ± 92.3

Values are represented as mean ± SD.
Significantly different between males and females at $^*P < .05$, $^{**}P < .01$, or $^{***}P < .001$.
†% to total calorie intake.

Looking at the results of Lee et al. [6], the average DDS was 3.33 in 6 male centenarians and 3.50 in 48 female centenarians, and the average DVS was 17.83 and 18.60, respectively (Table 3). Here, both DDS and DVS tended to be higher in female centenarians when compared to male centenarians, though not significantly so. Kwak et al. [9] reported that the average DDS and DVS of 74 female centenarians were 3.36 and 17.1, respectively. When assessed by the criteria for a well-balanced diet, which specify DDS > 3.0 and DVS > 18.0 [40, 41], 91.9% of these subjects scored above 3.0 in the DDS and 48.7% of subjects scored above 18.0 in the DVS (Table 3).

6. Energy and Nutrient Intake

Results of daily energy and nutrient intake of Korean centenarians [6, 9] are summarized in Table 4. Lee et al. [6] reported that the average energy intake was significantly higher in male centenarians when compared to female centenarians (1718 kcal/day versus 1247 kcal/day). Male centenarians consumed 85.9% of the estimated energy requirement (EER) for men aging 75 and over, 2000 kcal/day, and female centenarians consumed 77.9% of EER for women aging 75 and over, 1600 kcal/day [42]. EER for Korean men and women aging 75 and over was estimated on the reference body weight of 59.2 kg in men and 50.2 kg in women [42]. On comparing the average body weight of Korean centenarians, 52.3 kg in males and 34.4 kg in females [7], with the reference body weight of older people aging 75 and over, the body weight of female centenarians was much lower. The observed percentage of EER for energy intake in both Korean male and female centenarians was much higher when compared to the 60% found in a study of Okinawan centenarians [43].

Related with that higher energy intake, male centenarians consumed more protein and carbohydrate than female centenarians; however, fat intake in males and females was not different. Male centenarians consumed more calcium, zinc, vitamin B6, niacin, and vitamin E than female centenarians.

Recently, Kwak et al. [9] reported that female centenarians consumed 1,186 kcal/day (74.1% of EER for the female elderly aging 75 and over) and 15.5% of total energy intake from protein, 13.9% from fat, and 70.6% from carbohydrate. They consumed 105.1% of the recommended intake (RI) of protein for the female elderly aging 75 and over, 45 g/day [42]. These female centenarians consumed 4.5 g dietary fiber, 123.7 mg cholesterol, 351.7 mg calcium (43.9% RI), 10.2 mg iron (113.3% RI), and 5.8 mg zinc daily (82.9% RI). In terms of vitamins, these subjects consumed 497.2 μg RE of vitamin A (82.9% RI), 0.6 mg of vitamin B_1 (54.5% RI),

1.3 mg of vitamin B_6 (92.9% RI), 3.7 μg of vitamin B_{12} (154.1% RI), 8.5 mg of niacin (60.7% RI), 47.6 mg of vitamin C (47.6% RI), 5.4 mg of vitamin E (54.0% AI, adequate intake), and 150.6 μg of folate (37.6% RI). The average intake of fiber, calcium, niacin, and vitamins B_1, C, and E was below 75% of the RI or AI for the respective nutrient. However, their nutrient intake levels might be underestimated, because the dietary reference intakes for the elderly aging 75 and over (not for centenarians) were used.

7. Analysis of Vitamin B_{12} Content in Korean Traditional Foods

Vitamin B_{12} is known to be synthesized only in certain bacteria [44]. The vitamin B_{12} synthesized by bacteria is concentrated mainly in the bodies of higher predatory organisms in the natural food chain system. Animal foods (i.e., meat, milk, egg, fish, and shellfish) have been considered to be the major dietary sources of vitamin B_{12}.

Surprisingly, the results of preliminary studies of centenarian diets showed that vitamin B_{12} status of Korean centenarians, who have consumed vegetable-based diets throughout their lives, was higher than our expectations. Therefore, we traced the unknown natural sources of vitamin B_{12} in traditional Korean foods [45]. Recently, for the first time, we reported the significantly high level of vitamin B_{12} content in some Korean traditional foods, soybean-fermented foods such as *Doenjang, Chungkookjang*, *Kochujang,* and *Ganjang* and vegetable-fermented foods such as Kimchi, and some favorite seaweed foods, that were not listed previously in Food Composition Tables [45]. The method for vitamin B_{12} assay in foods was the following: food samples were freeze-dried and then powdered. Total B_{12} was extracted by boiling at acidic pH range and assayed by the microbiological method with *L. delbrueckii* ATCC 7830 according to the method described by Watanabe et al. [46]. Since *L. delbrueckii* ATCC 7830 can utilize deoxyribosides and deoxyribonucleotides (known as an alkali-resistant factor) as well as B_{12}, the amount of true B_{12} was calculated by subtracting the values of the alkali-resistant factor from the values of total B_{12}.

The key results were summarized in Table 5. It was interesting that vitamin B_{12} was not detected in steamed-soybeans and tofu; however, it was detected in fermented-soybean products. Moreover, traditional home-made soybean-fermented foods such as *Doenjang, Chungkookjang,* and *Gochujang* were found to contain higher vitamin B_{12} than commercial factory-made products. Traditional home-made *Doenjang* is a "slow food" taking at least 10 months for preparation and fermented by multiple microorganisms found in nature. However, the commercial product made in the factory takes only 3-4 months and is fermented by inoculated microorganisms under strict conditions. Due to the needs of space, time, and labor and the smell during the preparations and storage of *Doenjang*, the commercial *Doenjang* is increasingly popular, particularly to the younger generations living in urban areas. However, most Korean people living in rural areas still make it by themselves at home and consume it all year round. We observed that all the Korean centenarian subjects who participated in our studies were consuming the traditional home-made fermented foods.

Table 5: Vitamin B_{12} content in Korean fermented foods and some popular foods.[†]

Food	Vitamin B_{12} content[(1)]	
	(μg/100 g dry wt)	(μg/100 g wet wt)
Soybean, steamed	0.00	
Tofu	0.00	
Doenjang		
Traditional, home-made ($n = 30$)	0.30 ~ 9.82[(2)]	0.14 ~ 4.41[(3)]
Commercial, factory-made ($n = 4$)	0.07 ~ 0.49	0.04 ~ 0.25
Chungkookjang		
Traditional, home-made ($n = 5$)	0.05 ~ 1.40	0.03 ~ 0.60
Commercial, factory-made ($n = 3$)	0.08 ~ 0.31	0.04 ~ 0.15
Gochujang		
Traditional, homemade ($n = 10$)	0.02 ~ 0.43	0.01 ~ 0.28
Commercial, factory-made ($n = 3$)	0.00 ~ 0.14	0.00 ~ 0.01
Ganjang (Soy sauce)		(μg/100 mL)
Korean-style, homemade ($n = 29$)		0.02 ~ 6.76
Japanese-style, commercial ($n = 4$)		0.00
Fish sauce		(μg/100 mL)
Shrimp, salt-fermented ($n = 2$)		0.78 ~ 0.91
Anchovy, salt-fermented ($n = 2$)		1.52 ~ 1.77
Kimchi		
Korean Cabbage Kimchi ($n = 3$)	0.18 ~ 0.24	0.18 ~ 0.22
Seaweeds		
Laver, dried, seasoned & toasted ($n = 3$)	55.3 ~ 71.3	
Sea lettuce, raw ($n = 1$)	84.7	9.41
Sea tangle, dried ($n = 1$)	0.36	
Sea mustard, dried ($n = 1$)	1.90	
Anchovy,		
dried, medium size ($n = 1$)	17.12	

[†] Summary of key results from a report by Kwak et al. [45] and new data.
(1) Vitamin B_{12} = total vitamin B_{12} − alkali resistant factor.
(2) Range of vitamin B_{12} contents in more than two different products.
(3) Calculated from average vitamin B_{12} content measured in dried sample and drying yield.

Table 6: Daily mean intake and dietary source of vitamin B_{12} of female Korean centenarians.

	Kwak et al. (2010) [9] Female ($n = 70$)
Meat, eggs, fish & shell (μg)	3.04 ± 5.69 (67.2%)†
Dairy products (μg)	0.05 ± 0.19 (3.7%)
Animal (μg)	3.09 ± 5.68 (70.9%)
Kimchi (μg)	0.02 ± 0.02 (4.5%)
Soybean-fermented foods (μg)	0.08 ± 0.16 (13.9%)
Seaweeds (μg)	0.53 ± 1.37 (10.2%)
Others (μg)	0.01 ± 0.01 (0.5%)
Plant (μg)	0.64 ± 1.36 (29.1%)
Total B_{12} intake (μg)	3.73 ± 5.79 (100.0%)

Values are represented as mean ± SD.
†Mean of percent to total vitamin B_{12} intake.

Table 7: Distribution of daily vitamin B_{12} intake from total and animal foods.

	From total food(1) n (%)	From animal food(2) n (%)
B_{12} intake (μg/day)		
Deficient <1.0	24 (34.3)	30 (42.9)
≥1.0 and <2.0	10 (14.3)	15 (21.4)
Adequate ≥2.0(3)	36 (51.4)	25 (35.7)
	70 (100.0)	70 (100.0)

(1) Reference Kwak et al. [9].
(2) Newly analyzed.
(3) EAR of vitamin B_{12} for Korean older people aged 75 years and more.

Most of Koreans consume *Kimchi*, a vegetable-fermented food, at almost every meal. There are a multitude of varieties of *Kimchi* in Korea, but *Cabbage Kimchi* is the most popular. It is made of salted Chinese cabbage, red pepper, garlic, fermented fish sauce or/and fermented small fish, green onion, ginger, starch, and some other optional vegetables and generally fermented for a few days, but sometimes for a few months in low temperature. It has been reported that the vitamin B_{12} content of *Kimchi* would be derived from the fermented fish sauce, one of the ingredients of *Kimchi* [45], rather than newly produced during the fermentation process.

Some kinds of edible seaweeds are traditionally consumed with flavoring by Koreans in fresh or dried and in raw or cooked forms. In particular, Koreans enjoy dried and toasted laver with salt and sesame oil or perilla oil.

8. Vitamin B_{12} Intake and Dietary Sources for Korean Centenarians

Generally, Korean centenarians do not consume supplements, and there are few vitamin B_{12}-fortified foods in Korea. Only 3 out of 70 participants (4.3%) in a recent study [9] were found to be taking vitamin supplements.

We have updated the Korean vitamin B_{12} composition database [45] and have calculated daily dietary vitamin B_{12}, intake of the female centenarian subjects using that updated database [9]. Total daily vitamin B_{12} intake and its dietary sources among the Korean traditional foods are identified and shown in Table 6. On average, these female centenarians consumed 3.73 μg/day of vitamin B_{12} with 70.9% and 29.1% of total vitamin B_{12} intake derived from animal foods and plant foods, respectively.

Korean centenarians were obtaining approximately 30% of their dietary vitamin B_{12} from foods of plant origin. In addition, although average daily vitamin B_{12} intake (3.73 μg/day) of Korean centenarians was similar or less than that of female subjects aged 85 and older in Austria (3.9 μg/day) or UK (4.3 μg/day) [47], the prevalence of vitamin B_{12} deficiency in our cohort was not found to be higher when compared to cohorts in Western nations [9]. The primary food source of vitamin B_{12} was clearly meat, eggs, and fish, which provided two thirds of total vitamin B_{12} intake, and the next most popular food source was soybean-fermented foods, providing 13.9% of intake, followed by seaweeds, at 10.2%, and Kimchi and dairy products at 4.5% and 3.7%, respectively.

Korean centenarians have consumed soybean-fermented foods such as *Doenjang*, *Chungkukjang,* and *Gochujang* and fermented vegetables such as Kimchi daily as well as seaweeds very frequently, throughout their lives. Since these are consumed widely on a year-round basis, these foods represent very important sources of vitamin B_{12} for older Koreans.

Some edible algae, including laver, have already been reported to contain large amounts of vitamin B_{12} [45, 48], though there are debates regarding the bioavailability of vitamin B_{12} in seaweeds [49–51]. However, the high consumption of dried seaweeds such as laver by Koreans would, nonetheless, still be partly responsible for the normal status of the vitamin B_{12} [52, 53].

The estimated average requirement (EAR) of vitamin B_{12} for elderly Koreans aging 75 and older is 2.0 μg/day [42]. In order to find out how much foods of plant origin contributed to adequacy of vitamin B_{12} intake for Korean centenarians, we compared the adequacy of vitamin B_{12} intake from total foods to that from the animal foods. As shown in Table 7, the result from total food consumption showed that 51.4% of subjects consumed an adequate amount of vitamin B_{12} (above the EAR of 2.0 μg/day) and 34.3% of subjects consumed a very low level of vitamin B_{12} (under 50% of the EAR), while the result from the analysis of animal foods showed that only 35.7% of subjects consumed an adequate amount of vitamin B_{12} while 42.9% of subjects consumed an inadequate amount of vitamin B_{12}. These results imply that the consumption of Korean foods from plant sources, such as fermented foods and seaweeds, improved the nutritional status of vitamin B_{12} for these centenarians by increasing the percentage of the adequate vitamin B_{12} intake group by 15.7% and decreasing of the numbers of very low vitamin B_{12} intake group by 8.6%.

9. Summary and Conclusions

It is well known that most older Koreans traditionally consumed a diet low in animal foods and low in fat, dominated by cereals and vegetables. Centenarians in Korea seem to have been keeping to this traditional dietary pattern with one recent study revealing that female Korean centenarians were consuming 87.1% of the foods in their diet from plant sources [9].

Since major conventional food sources of vitamin B_{12} are well known to be of animal origins, we expected a higher prevalence of vitamin B_{12} deficiency in Korean centenarians compared to that found in centenarians in Europe or North America where consumption on animal products is much higher. However, the prevalence of Korean centenarians with a low serum vitamin B_{12} (<200 pg/mL) level was found to be only 11.3% and those with a marginal level of serum vitamin B_{12} (200–340 pg/mL) numbered only 33.9%. When assessed with a cutoff value of 340 pg/mL, the prevalence of vitamin B_{12} insufficiency in Korean female centeanrians was 45.2% [9], similar to American centeanrians from Georgia [11] and Italian centenarians [35].

When dealing with the mystery of why a much greater percentage of Korean centenarians did not suffer from vitamin B_{12} deficiency, we found that commonly consumed traditional Korean soybean-fermented foods (such as *Doenjang, Chungkukjang, and Ganjang*), vegetable-fermented foods with fermented fish sauce (such as *Kimchi*), and seaweeds (such as laver) contained higher than expected levels of vitamin B_{12}. Surprisingly, almost a third of vitamin B_{12} intake in the centenarian diet was coming from the consumption of these traditional foods.

These intriguing results from Korean centenarian studies suggest the value of a comprehensive, scientific approach in examining the traditional food culture and its potential contribution to maintaining an adequate nutritional status among the oldest old, as well as its potential contribution to healthy aging and longevity.

As nutritional deficiency is an important contributor to the disease process and a particularly salient problem for the oldest old, new and economically viable solutions that focus upon improving nutritional status should be explored that are applicable (and potentially available) in cultural context. An excellent example is that of the complementary role that traditional foods have been playing in maintaining nutritional balance among centenarians in Korea.

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References

[1] S. C. Park, "Korean centenarians-overall," in *Korean Centenarians*, S. C. Park, Ed., pp. 1–9, Seoul National University Press, Seoul, Republic of Korea, 2002.

[2] Y. H. Choi, C. H. Kim, and S. C. Park, "Health of Korean centenarians—medical and genetic characteristics," in *Korean Centenarians*, S. C. Park, Ed., pp. 187–211, Seoul National University Press, Seoul, Republic of Korea, 2002.

[3] S. J. Choi, "Social and psychological characteristics of Korean centenarians," in *Korean Centenarians*, S. C. Park, Ed., pp. 27–65, Seoul National University Press, Seoul, Republic of Korea, 2002.

[4] WHO (World Health Organization), "Health systems improving performance," The World Health Report, 2000.

[5] Statistics Korea, *Social Indicator in Korea*, National Statistical Office. Kangmoon Publishing, Dajeon, Republic of Korea, 2010.

[6] M. S. Lee, E. J. Yeo, and C. S. Kwak, "Gender differences in health and nutritional status of Korean centenarians," *Korean Journal of Gerontology*, vol. 13, no. 3, pp. 65–75, 2005.

[7] I. S. Kwon, C. H. Kim, H. S. Ko, S. I. Cho, Y. H. Choi, and S. C. Park, "Risk factors of cardiovascular disease in Korean exceptional longevity," *Journal of Korean Geriatrics Society*, vol. 9, no. 4, pp. 251–265, 2005.

[8] S. C. Park, M. S. Lee, I. S. Kwon, S. C. Kwak, and E. J. Yeo, " Environment and gender influences on the nutritional and health status of Korean centenarians," *Asian J Gerontology and Geriatrics*, vol. 3, no. 2, pp. 75–83, 2008.

[9] C. S. Kwak, M. S. Lee, H. J. Lee, J. Y. Whang, and S. C. Park, "Dietary source of vitamin B_{12} intake and vitamin B_{12} status in female elderly Koreans aged 85 and older living in rural area," *Nutrition Research and Practice*, vol. 4, no. 3, pp. 229–234, 2010.

[10] KMHW (Korea Ministry of Health and Welfare), "Report on the welfare facilities for the elderly," 2010, http://www.mw.go.kr/front/index.jsp.

[11] M. A. Johnson, D. B. Hausman, A. Davey, L. W. Poon, R. H. Allen, and S. P. Stabler, "Vitamin B_{12} deficiency in African American and white octogenarians and centenarians in Georgia," *Journal of Nutrition, Health and Aging*, vol. 14, no. 5, pp. 339–345, 2010.

[12] KMHW(Korea Ministry of Health and Welfare), "The third Korea National Health and Nutrition examination survey (KNHNES III), 2005-Health examination," 2006, http://www.mohw.go.kr/.

[13] H. W. Baik and R. M. Russell, "Vitamin B_{12} deficiency in the elderly," *Annual Review of Nutrition*, vol. 19, pp. 357–377, 1999.

[14] M. A. Johnson, N. A. Hawthorne, W. R. Brackett et al., "Hyperhomocysteinemia and vitamin B_{12} deficiency in elderly using Title IIIc nutrition services," *American Journal of Clinical Nutrition*, vol. 77, no. 1, pp. 211–220, 2003.

[15] A. Garcia, A. Paris-Pombo, L. Evans, A. Day, and M. Freedman, "Is low-dose oral cobalamin enough to normalize cobalamin function in older people?" *Journal of the American Geriatrics Society*, vol. 50, no. 8, pp. 1401–1404, 2002.

[16] S. Rajan, J. I. Wallace, S. A. A. Beresford, K. I. Brodkin, R. A. Allen, and S. P. Stabler, "Screening for cobalamin deficiency in geriatric outpatients: prevalence and influence of synthetic cobalamin intake," *Journal of the American Geriatrics Society*, vol. 50, no. 4, pp. 624–630, 2002.

[17] A. Miller, M. Korem, R. Almog, and Y. Galboiz, "Vitamin B_{12}, demyelination, remyelination and repair in multiple sclerosis," *Journal of the Neurological Sciences*, vol. 233, no. 1-2, pp. 93–97, 2005.

[18] V. Herbert, "Vitamin B_{12}: plant sources, requirements, and assay," *American Journal of Clinical Nutrition*, vol. 48, no. 3, pp. 852–858, 1988.

[19] W. Reynish, S. Andrieu, F. Nourhashemi, and B. Vellas, "Nutritional factors and Alzheimer's disease," *Journals of Gerontology Biological Sciences and Medical Sciences*, vol. 56, no. 11, pp. M675–M680, 2001.

[20] M. Lewis, L. S. Miller, M. A. Johnson, E. B. Dolce, R. H. Allen, and S. P. Stabler, "Elevated methylmalonic acid is related to cognitive imparement in older adults enrolled in an elderly nutrition program," *Journal of Nutrition for the Elderly*, vol. 24, no. 3, pp. 47–65, 2005.

[21] H. Hin, R. Clarke, P. Sherliker et al., "Clinical relevance of low serum vitamin B_{12} concentrations in older people: the Banbury B_{12} study," *Age and Ageing*, vol. 35, no. 4, pp. 416–422, 2006.

[22] B. W. J. H. Penninx, J. M. Guralnik, L. Ferrucci, L. P. Fried, R. H. Allen, and S. P. Stabler, "Vitamin B_{12} deficiency and depression in physically disabled older women: epidemiologic evidence from the women's health and aging study," *American Journal of Psychiatry*, vol. 157, no. 5, pp. 715–721, 2000.

[23] D. K. Houston, M. A. Johnson, R. J. Nozza et al., "Age-related hearing loss, vitamin B_{12}, and folate in elderly women," *American Journal of Clinical Nutrition*, vol. 69, no. 3, pp. 564–571, 1999.

[24] B. N. Ames and P. Wakimoto, "Are vitamin and mineral deficiencies a major cancer risk?" *Nature Reviews Cancer*, vol. 2, no. 9, pp. 694–704, 2002.

[25] M. S. Morris, P. F. Jacques, and J. Selhub, "Relation between homocysteine and B-vitamin status indicators and bone mineral density in older Americans," *Bone*, vol. 37, no. 2, pp. 234–242, 2005.

[26] R. A. M. Dhonukshe-Rutten, S. M. F. Pluijm, L. C. P. G. M. De Groot, P. Lips, J. H. Smit, and W. A. Van Staveren, "Homocysteine and vitamin B_{12} status relate to bone turnover markers, broadband ultrasound attenuation, and fractures in healthy elderly people," *Journal of Bone and Mineral Research*, vol. 20, no. 6, pp. 921–929, 2005.

[27] S. P. Stabler and R. H. Allen, "Vitamin B_{12} deficiency as a worldwide problem," *Annual Review of Nutrition*, vol. 24, pp. 299–326, 2004.

[28] V. Herbert, "Staging vitamin B_{12} status in vegetarians," *American Journal of Clinical Nutrition*, vol. 59, supplement, pp. 1213S–1222S, 1994.

[29] J. Y. Yim, N. Kim, S. H. Choi et al., "Seroprevalence of Helicobacter pylori in South Korea," *Helicobacter*, vol. 12, no. 4, pp. 333–340, 2007.

[30] N. Kim, Y. S. Park, S. I. Cho et al., "Prevalence and risk factors of atrophic gastritis and intestinal metaplasia in a korean population without significant gastroduodenal disease," *Helicobacter*, vol. 13, no. 4, pp. 245–255, 2008.

[31] E. J. Hong, D. I. Park, H. J. Sohn et al., "Correlations between the prevalence of chronic neoplasia and *Helicobacter pylori* infection," *Korean Journal of Medicine*, vol. 74, no. 6, pp. 605–610, 2008.

[32] J. Lindenbaum, I. H. Rosenberg, P. W. F. Wilson et al., "Prevalence of cobalamin deficiency in the Framingham elderly population," *American Journal of Clinical Nutrition*, vol. 60, no. 1, pp. 2–11, 1994.

[33] R. Carmel, "Cobalamin, the stomach, and aging," *American Journal of Clinical Nutrition*, vol. 66, no. 4, pp. 750–759, 1997.

[34] R. H. Allen, J. Lindenbaum, and S. P. Stabler, "High prevalence of cobalamin deficiency in the elderly," *Transactions of the American Clinical and Climatological Association*, vol. 107, pp. 37–47, 1995.

[35] G. Ravaglia, P. Forti, F. Maioli et al., "Elevated plasma homocysteine levels in centenarians are not associated with cognitive impairment," *Mechanisms of Ageing and Development*, vol. 121, no. 1–3, pp. 251–261, 2001.

[36] D. M. Kado, A. S. Karlamangla, M. H. Huang et al., "Homocysteine versus the vitamins folate, B_6, and B_{12} as predictors of cognitive function and decline in older high-functioning adults: MacArthur studies of successful aging," *American Journal of Medicine*, vol. 118, no. 2, pp. 161–167, 2005.

[37] R. Clarke, A. D. Smith, K. A. Jobst, H. Refsum, L. Sutton, and P. M. Ueland, "Folate, vitamin B, and serum total homocysteine levels in confirmed Alzheimer disease," *Archives of Neurology*, vol. 55, no. 11, pp. 1449–1455, 1998.

[38] B. Hultberg, E. Jensen, O. Dehlin, B. O. Hagberg, G. Samuelsson, and T. Svensson, "Concentrations of plasma methylmalonic acid in 80-year-olds show only weak relation to psychological performance," *Clinical Chemistry and Laboratory Medicine*, vol. 37, no. 10, pp. 963–967, 1999.

[39] H. H. Dodge, Y. Katsumata, H. Todoriki et al., "Comparisons of plasma/serum micronutrients between Okinawan and oregonian elders: a pilot study," *Journals of Gerontology Biological Sciences and Medical Sciences*, vol. 65 A, no. 10, pp. 1060–1067, 2010.

[40] R. D. Lee and D. C. Nieman, *Nutrtional Assessment*, McGraw-Hill, Singapore, 2nd edition, 1998.

[41] A. K. Kant, G. Block, A. Schatzkin, R. G. Ziegler, and M. Nestle, "Dietary diversity in the US population," *Journal of the American Dietetic Association*, vol. 91, no. 12, pp. 1526–1531, 1991.

[42] Korean Nutrition Society, *Dietary Reference Intakes for Koreans*, Kookjin Publishing, Seoul, Republic of Korea, 2005.

[43] S. Takeda, H. Noji, N. Hirose et al., "Nutritional intake by the oldest elderly Japanese Tokyo centenarian study," *Japanese Journal of Geriatrics*, vol. 35, no. 7, pp. 548–558, 1998.

[44] Z. Scheider and A. Stroiński, "Biosynthesis of vitamin B_{12}," in *Comprehensive B_{12}*, pp. 93–110, Walter de Gruyter, Berlin, Germany, 1987.

[45] C. S. Kwak, J. Y. Hwang, F. Watanabe, and S. C. Park, "Vitamin B_{12} content in some Korean fermented foods and edible seaweeds," *Korean Journal of Nutrition*, vol. 41, pp. 439–447, 2008.

[46] F. Watanabe, H. Katsura, S. Takenaka et al., "Pseudovitamin B_{12} is the predominant cobamide of an algal health food, spirulina tablets," *Journal of Agricultural and Food Chemistry*, vol. 47, no. 11, pp. 4736–4741, 1999.

[47] E. Fabian and I. Elmadfa, "Nutritional situation of the elderly in the European union: data of the European Nutrition and Health Report (2004)," *Annals of Nutrition and Metabolism*, vol. 52, supplement 1, pp. 57–61, 2008.

[48] F. Watanabe, S. Takenaka, H. Kittaka-Katsura, S. Ebara, and E. Miyamoto, "Characterization and bioavailability of vitamin B-compounds from edible algae," *Journal of Nutritional Science and Vitaminology*, vol. 48, no. 5, pp. 325–331, 2002.

[49] P. C. Dagnelie, W. A. Van Staveren, and H. Van den Berg, "Vitamin B_{12} from algae appears not to be bioavailable," *American Journal of Clinical Nutrition*, vol. 53, no. 3, pp. 695–697, 1991.

[50] H. Van den Berg, P. C. Dagnelie, and W. A. Van Staveren, "Vitamin B_{12} and seaweed," *Lancet*, vol. 1, no. 8579, pp. 242–243, 1988.

[51] F. Watanabe, "Vitamin B_{12} sources and bioavailability," *Experimental Biology and Medicine*, vol. 232, no. 10, pp. 1266–1274, 2007.

[52] K. Yamada, Y. Yamada, M. Fukuda, and S. Yamada, "Bioavailability of dried asakusanori (*Porphyra tenera*) as a source of cobalamin (vitamin B)," *International Journal for Vitamin and Nutrition Research*, vol. 69, no. 6, pp. 412–418, 1999.

[53] S. Takenaka, S. Sugiyama, S. Ebara et al., "Feeding dried purple laver (*nori*) to vitamin B-deficient rats significantly improves vitamin B_{12} status," *British Journal of Nutrition*, vol. 85, no. 6, pp. 699–703, 2001.

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Research Article

Resilience Significantly Contributes to Exceptional Longevity

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Objective. We aim to investigate whether centenarians are significantly more resilient than younger elders and whether resilience significantly contributes to exceptional longevity. *Data*. We use a unique dataset from the Chinese Longitudinal Healthy Longevity Survey with the largest sample to date of centenarians, nonagenarians, octogenarians, and a compatible group of young old aged 65–79. *Methods and Results*. Logistic regressions based on the cross-sectional sample show that after controlling for various confounders, including physical health and cognitive status, centenarians are significantly more resilient than any other old-age group. Logistic regression analyses based on the longitudinal data show that nonagenarians aged 94–98 with better resilience have a 43.1% higher likelihood of becoming a centenarian compared to nonagenarians with lower resilience. *Conclusions*. Resilience significantly contributes to longevity at all ages, and it becomes even more profound at very advanced ages. These findings indicate that policies and programs to promote resilience would have long-term and positive effects on the well-being and longevity for senior citizens and their families.

1. Introduction

Extant literature has highlighted the particular relevance of centenarians for healthy longevity research, given that they have outlived most of their cohort peers by several decades, and they represent a highly selected group. For example, according to recent life-table data, the probability of surviving from age 50 to age 100 is about 0.38% and 1.05% for Chinese men and women, respectively, which is slightly less than one-fifth of that in the U.S. As shown by Flachsbart [1], only about 4.8% of 90-year-olds and 16.0% of 95-year-olds in Germany are likely to reach the age of 100. A study by Yi and Vaupel [2] showed that about 3.4% of 90-year-olds and 14.9% of 95-year-olds in China are likely to survive to the age of 100. These figures indicate that centenarians are highly selected long-lived individuals, even among those who have reached 90–95 years old. A focus on extreme cases is often a good way to gain research leverage at reasonable expense; thus, investigating centenarians (some of whom are healthy and demonstrate successful aging) and comparing them with other younger age groups is an efficient way to learn what factors may contribute to healthy longevity.

Resilience, a psychological construct, has been defined differently in extant literatures. In this paper, we adopt the simplified and straightforward definition specified by Lamond et al. [3]; namely, resilience connotes the ability to adapt positively to adversity. Previous studies have demonstrated that resilience is generally positively correlated with cognitive function, physical health and self-reported health among the elderly [4–6], as well as with self-rated successful aging [3] in developed countries. Poon [7] discovered that the common characteristics of the Georgia centenarians sample are optimism and flexibility, which are documented to be associated with resilience [8]. Based on a Swedish sample, Nygren [9] found that mean resilience scores are higher in their oldest old sample (over age 85) compared to the scores of the younger adults. Selim [10] discovered that U.S. centenarian veterans are psychologically resilient despite their poor physical health. Jopp and Rott [11] also demonstrated that psychological resilience is well preserved

Table 1: Sample distributions of the elderly respondents in the CLHLS 2008-2009 wave.

Age group	Urban			Rural			Rural-urban combined		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
65–69	277	295	572	462	372	834	739	667	1,406
70–79	605	560	1,165	913	801	1,714	1,518	1,361	2,879
80–89	825	829	1,654	1,323	1,295	2,618	2,148	2,124	4,272
90–99	817	1,075	1,892	1,080	1,624	2,704	1,897	2,699	4,596
100+	319	974	1,293	369	1,751	2,120	688	2,725	3,413
Total	2,843	3,733	6,576	4,147	5,843	9,990	6,990	9,576	16,566

at the very end of the life span based on the Heidelberg Centenarian Study.

However, there are three major limitations in the previous research on centenarians and resilience. First, most of the prior studies were based on small samples with limited numbers of centenarians and nonagenarians, which restricted estimation efficiency [11, 12]. After a careful literature search, we have discovered that among all published studies concerning the characteristics and effects of resilience among centenarians with a comparison to other age groups, the largest sample was 272 Japanese centenarians by Yukie et al. [13].

Second, though some studies compared resilience between centenarians and young-old groups [7, 8, 10, 11], no prior research (to our knowledge) has explored whether resilience contributes to exceptional longevity at very advanced ages 95+.

Third, almost all previously published studies in this field dealt with developed countries; we found very few studies on centenarians and resilience from developing countries [2, 14, 15]. Shen and Zeng [15] reported on the positive association between resilience and survival among the Chinese elderly aged 65+, but they did not investigate whether the association still held at extremely advanced ages, for example, age 95 and older. As Ju and Jones [16] noted, in high-mortality populations, the oldest old are those highly selected individuals who have survived dangers when being born, risks in infancy and childhood, and hunger, sickness, and accidents at middle- and young-old ages. As evidence of the high-mortality selection in China, there were about five centenarians per million in China in the 1990s, compared with 50 per million in Western Europe [17]. Another important factor is that facilities to assist oldest old persons in their daily life are less likely to be available in developing countries than in industrial countries. This may force the oldest old in developing countries to perform daily activities by themselves, and the frequent exercise may enable them to maintain their physical capacities for a longer time than their counterparts in developed countries. These factors may help to explain why the elderly in Indonesia, Malaysia, the Philippines, Singapore, and Thailand have, in some comparative studies, found to be more active than the elderly in developed countries [16, 18]. Similarly, the functional capacity of centenarians in the three cities of Beijing, Hangzhou, and Chengdu in China has also been reported to be significantly better than that of Danish centenarians [19]. Thus, research on centenarians from developing countries including China, where the oldest old individuals are highly selected from poor early-life conditions and severe adversities, may be useful for identifying what factors may affect exceptional longevity.

Based on the cross-sectional data from 2008-09 wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) consisting of 16,566 elderly aged 65+ with 3,413 centenarians and 4,596 nonagenarians, as well as the follow-up data from the exceptionally long-lived individuals in the CLHLS 2002, 2005, and 2008-2009 waves, we test the following hypotheses.

H_1 after controlling for various potential confounders including physical health and cognitive status, centenarians are significantly more resilient than the younger elderly.

H_2 better resilience significantly contributes to exceptional longevity at very advanced ages.

2. Data, Measurements, and Methods

2.1. Data Source. The datasets used in this paper are from the CLHLS, which has been conducted in 1998, 2000, 2002, 2005, and 2008-2009 in a randomly selected half of the counties/cities in 22 Chinese provinces, covering 85% of the total population in China [20]. The 1998 baseline and the 2000 followup surveys interviewed the oldest old aged 80 and above only; since the 2002 wave, younger-old respondents aged 65–79 were also included in the sample. Careful and systematic evaluations (such as reliability coefficients and factor analysis, etc.) have shown that the data quality of the CLHLS surveys is reasonably good [21].

Cross-sectional data from the newest CLHLS wave conducted in 2008-2009, with a total sample size of 16,566 elderly aged 65 and above including 3,413 centenarians and 4,596 nonagenarians, is used to test hypothesis H_1. Table 1 presents the sample distribution of the CLHLS 2008-2009 wave by urban-rural residence, age groups, and gender.

Comparative analysis on the resilience scores between centenarians and the other age groups may only reveal the "de facto" differences in resilience scores between the centenarians and the younger elders. Such cross-sectional analysis may not be suitable to examine the impact of resilience on attaining exceptional longevity as proposed by hypothesis H_2. Thus, we conduct another set of multivariate

analyses based on the follow-up data including those aged 94–97 in the 2002 survey and those aged 97-98 in the 2005 survey (we include the nonagenarians who were interviewed in the 2002 and 2005 waves rather than the 1998 baseline and 2000 wave of CLHLS, because two of the seven resilience questions were not asked in the 1998 baseline and the 2000 wave). The rationale for these analyses is that we wish to investigate whether resilience significantly contributes to surviving to 100 years old before or in the 2008-2009 interview among the nonagenarians who are the potential candidates and need to survive for at least two more years to reach age 100. The eligible sample consists of 585 men (38.3%) and 943 women (61.7%), all of whom were either interviewed at age 94–97 in 2002 or interviewed at age 97-98 in 2005. Among them, 1,049 (68.7%) died at ages <100 (failed to become a centenarian) and 479 (31.3%) survived to age ≥100 before or in the 2008-2009 survey (successful in becoming a centenarian).

2.2. Measurements

2.2.1. Variables of Interest

Resilience. As the datasets used in this paper are derived from the CLHLS which is a typical demographic study on determinants of healthy longevity rather than a detailed psychological investigation, we use a simplified resilience score (abbreviated as SRS hereafter) emphasizing coping and adjustment among the elderly. Our SRS is theoretically guided by the general framework of, but different from, the Connor-Davidson Resilience Scale (CD-RISC) [22]. The SRS is based on the available data collected through seven questions related to resilience in the CLHLS (See Table 2). In general, the seven items reflect personal tenacity, optimism, coping with negative mood, secure relationship, and self-control, which are deemed as important factors of resilience [22]. These items have their own counterparts in CD-RISC which deliver similar meanings. For example, item 1 of SRS corresponds to the item "Think of self as strong person" in CD-RISC; item 2 corresponds to the item "See the humorous side of things"; items 3 and 4 correspond to the item "Can handle unpleasant feelings". In fact, some previous studies have also proposed resilience scales with very limited number of items focusing on one or two specific aspects of resilience. For example, Smith [23] proposed a Brief Resilience Scale (BRS), which included 6 items and focused on the ability to bounce back or recover from stress. Sinclair and Wallston [24] constructed a Brief Resilient Coping Scale (BRCS) with 4 items, emphasizing on the resilient coping process.

Items 1, 2, 3, 4, and 7 of SRS in the CLHLS carry a five-point (0, 1, 2, 3, and 4) range of the responses (see Table 2). We dichotomize the scores of items 5 and 6, because the rather detailed multiple choices of the answers for these two items only allow us to do so. With such scores which contain the maximum information, we can obtain from the survey the total SRS ranges from 0 to 22, with higher scores reflecting greater resilience.

The internal consistency of SRS measured by Cronbach's alpha coefficient is 0.69, indicating its reliability is reasonably adequate [25]. Principle component analysis generates three factors with eigenvalues >1, explaining 78.5% of the total variance. These basic indicators of the psychometric properties show that the SRS based on the CLHLS data are reasonably acceptable.

Table 2: Measures of resilience: questions of the seven items asked in the CLHLS interviews.

Items	Item statements questions	Scores based on answers
Item 1	Do you feel the older you get, the more useless you are?	0. always; 1. often; 2. sometimes; 3. seldom; 4. never
Item 2	Do you always look on the bright side of things?	4. always; 3. often; 2. sometimes; 1.seldom; 0. never
Item 3	Do you often feel fearful or anxious?	0. always; 1. often; 2. sometimes; 3. seldom; 4. never
Item 4	Do you often feel lonely and isolated?	0. always; 1. often; 2. sometimes; 3. seldom; 4. never
Item 5	To whom do you usually talk most frequently in daily life?	1. Family members/friends/neighbors/social workers/caregivers; 0. Nobody.
Item 6	Who do you ask first for help when you have problems/difficulties?	1. Family members/friends/neighbors/social workers/caregivers; 0. Nobody.
Item 7	Can you make your own decisions concerning your personal affairs?	4. always; 3. often; 2. sometimes; 1.seldom; 0. never

If the respondents are able to answer the questions 5 and 6 regarding social support, they do so; otherwise, proxy responses are allowed because spouses and close relatives typically know respondents' sources of social support (proxy responses are widely used in interviews with elderly [26]. The proportions of proxy answers for question 5 and 6 in the CLHLS are 27.17% and 26.97%, respectively. We also conducted regression analyses excluding the cases with proxy responses, and found very similar results between excluding and including the proxy responses). Questions concerning resilience items 1–4 and item 7 (see Table 2) relate to the self-feelings of the elderly and may not be judged accurately by others; thus, they are required to be answered by the elderly respondent him/herself in the survey. As a result, 17.1% of the respondents are unable to answer these questions due to poor cognitive ability. Simply, excluding these cases with the missing values might lead to sampling bias. Thus, we conduct multiple imputations for the missing values of these five resilience items based on the respondents' age, gender, race, education, physical health measured by Activities of Daily Living (ADL), and cognitive status measured by Mini Mental State Examination (MMSE) [27].

2.2.2. Potential Confounding Factors

Age Group. We categorize the continuous age variable into 4 groups: ages 65–79 (reference), ages 80–89, ages 90–99, and ages ≥100.

Demographic and Socioeconomic Characteristics. We include gender (male or female), race (Han ethnicity or minority), residential place (urban or rural), marital status (currently married or unmarried including widowed, divorced, and never married), education (literate or illiterate), and pension status (with or without pension) as demographic and socioeconomic controls. Each control variable is measured as a dummy variable.

Health Status. Health status is measured by ADL and MMSE, which are based on international standards and adapted to the Chinese culture and social context with carefully conducted pilot study tests. More specifically, ADL is based on Katz's ADL index, representing the physical health of the elderly [28]. If a person needs help to perform any of the six daily tasks of bathing, dressing, indoor transferring, going to the toilet and cleaning oneself afterwards, eating, and continence, he/she is considered to be ADL dependent; otherwise, he/she is regarded as ADL independent. MMSE has been widely used for assessing cognitive mental status both in clinical practice and in research [29, 30]. The MMSE questionnaire includes 24 items with a total possible score of 30. We define those who have a score of less than 24 as cognitively impaired [30].

Resilience might have an indirect impact on survival through health status of the elderly. Thus, we control for health status in the models so that we can examine whether resilience has a direct impact on survival among the elderly. A similar design has been used in previous studies. For example, to examine the effect of religious attendance on mortality, Hill et al. [31] first ran the regression without controlling for health status and then included ADL, cognitive function, and other health measures in the model to see whether the effect of religious attendance on survival persisted and whether part of the effect of religious attendance was mediated through health status.

2.3. Methods. In the empirical analyses, the original SRS variable (ranging from score 0 to 22) is dichotomized into two categories according to the mean of resilience scores: higher resilience (with a resilience score $\geq$16) and lower resilience (with a resilience score <16). We apply logistic regression based on the cross-sectional data from the CLHLS 2008-2009 wave to test hypothesis H_1 concerning whether centenarians are more resilient than any other age group. The independent variables of main interest are three age group dummy variables: centenarians, nonagenarians, and octogenarians, with age group 65–79 as the reference category. Potentially confounding variables including demographic and socioeconomic characteristics and health status are outlined above.

To test hypothesis H_2"Better resilience significantly contributes to exceptional longevity at very advanced ages," we apply the multivariate logistic regression model based on the longitudinal data. The dependent variable of the logistic regression is whether the nonagenarian aged 94–97 in 2002 or aged 97–98 in 2005 survived to age $\geq$100 or died at age <100 before the CLHLS 2008-2009 survey.

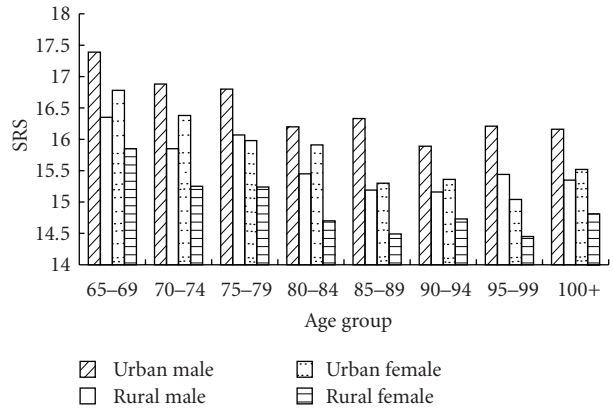

Figure 1: Average SRS by age groups, gender, and urban-rural residence.

The key independent variable is whether the elderly enjoy higher resilience (with an SRS $\geq$16) or lower resilience (with an SRS <16). We control for age, gender, race, residence, marital status, and pension status as well as physical health and cognitive status measured by ADL and MMSE. We also adjust for the year of the interview and for dummy variables indicating province.

3. Results

3.1. Descriptive Analysis. As shown by the descriptive statistics based on the cross-sectional data presented in Table 3, the mean SRS are the highest for the young-old aged 65–79 without controlling for other covariates, while there are very little differences among the octogenarians, nonagenarians, and centenarians. Men have better SRS than women. A much larger proportion of the older men are literate and enjoy pension compared to the older women, due to the social background of gender inequality in China in the past. Additionally, men are more advantaged in ADL and MMSE than women in each of the age groups.

Figure 1 depicts the weighted average SRS by 5-year age groups, gender, and urban-rural residence. Elderly men are always more resilient than their female counterparts in each of the age groups depicted in the figure. In general, the average SRS in urban and rural among the young old aged 65–69 is the highest and then decline as age increases. However, the SRS remains relatively stable after age 85. The Chinese elderly residing in urban area have higher resilience scores than their rural counterparts (see Figure 1).

3.2. Centenarians Are Significantly More Resilient than Any Other Elderly Adults, After Controlling for Various Confounders Including Health. Table 3 and Figure 1 have shown that the average SRS of centenarians is lower than that of the younger respondents aged below 85 (except the average SRS of the female rural centenarians which is slightly higher than that of female rural elderly aged 80–84). Table 4 presents estimates of the odds ratios regarding the associations of age-group dummy variables with better resilience among

Table 3: Descriptive statistics of the variables investigated in this study.

	Ages 100+		Ages 90–99		Ages 80–89		Ages 65–79	
	Men	Women	Men	Women	Men	Women	Men	Women
Mean SRS	15.8	15.0	15.6	14.9	15.8	14.9	16.6	15.7
Mean age	101.9	102.4	93.1	93.6	84.6	84.8	71.9	72.0
% Han ethnicity	93.6	93.4	94.6	93.2	94.6	94.1	94.0	94.1
% urban residence	45.4	35.0	43.0	39.7	38.3	39.0	39.2	42.2
% currently married	11.3	1.1	24.8	5.0	47.7	18.5	77.0	52.2
% literate	43.2	6.6	54.0	12.6	60.6	16.6	78.5	39.5
% having pension	23.6	2.7	27.9	7.3	27.3	9.2	33.2	21.5
% ADL independent	52.0	46.9	76.2	70.2	89.2	87.2	96.5	96.0
% normal cognition	33.3	16.6	49.3	32.4	72.2	57.2	92.1	85.9
Subsample size	666	2,677	1,883	2,677	2,139	2,110	2,253	2,023

Note: the mean SRS among the elderly aged 65–79, 80–89, and 90–99, presented in this table and in Figures 1(a) and 1(b) are weighted averages, using the 2000 census rural-urban-sex-age distributions and the corresponding CLHLS 2008-2009 sample distributions to compute the weights. The mean resilience scores of the centenarians are unweighted as the CLHLS study tried to interview all of the centenarians in the sampled areas.

the elderly population. The results of model 1 indicate that without adjusting for any confounders, the likelihoods of enjoying better resilience for the octogenarians, nonagenarians, and centenarians are 40.3%, 55.7%, and 69.7% ($P < .01$) lower than that for the young old aged 65–79. After adding demographic and socioeconomic characteristics into model 2, the odds ratios for the octogenarians, nonagenarians, and centenarians (as compared to the young old aged 65–79) increase substantially, but are still significantly less than 1.0, indicating that the age difference is largely reduced with the addition of these controls. Model 3 further adjusts for physical health and cognitive mental status measured by ADL and MMSE; once these health variables are controlled for, centenarians are in fact, significantly more resilient than the young old by a margin of 26.1% ($P < .01$), nonagenarians also marginally enjoy better resilience than the young old by a margin of 10.9% ($P < .1$), while there is no significant difference in resilience between octogenarians and the young old (we also ran ordinary least square regressions using the original SRS scores (ranging from 0 to 22) as the continuous dependent variable, and the results (data not shown due to space limitations) support the same conclusion as the logistic regressions do shown in Table 4). These results show that centenarians are a highly selected and special subpopulation with the best resilience after controlling for various confounders including health.

We further estimate the odds ratios separately for men and women in Model 4 and Model 5. We find that after adjusting for all potential confounders including ADL and MMSE, male and female centenarians are significantly more resilient than the young old, and the difference is substantially larger among men than among women.

The age pattern of resilience presented in Table 4 is, in general, similar to the findings from the study by Nygren and colleagues [9] on a Swedish oldest old sample aged 85 and older and the research by Lamond and colleagues [3] on the American elderly aged 65 and older, though both of these two studies did not provide explicit estimates for centenarians. We discover that centenarians' average SRS without adjusting for confounders is lower than that of the young-old due to their poorer objective health. After the health status variables are controlled for, the centenarians are much more resilient than the young old.

Regarding the confounding variables, we find that after adjusting for various other confounders, men are significantly more resilient than women; the elderly residing in urban areas, having at least one year of schooling, and enjoying pension benefits have significantly better resilience. Marriage has a very strong positive impact on resilience. Better physical health and cognitive status significantly improve resilience (see Table 4).

3.3. Better Resilience Significantly Contributes to Exceptional Longevity at Very Advanced Ages. As shown in Table 5, the likelihood of surviving to age 100 for the elderly aged 94–97 in 2002 or aged 97-98 in 2005 with higher resilience score was 74.6% ($P < .01$) higher than the likelihood of their counterparts with lower resilience scores in Model 1 with no controls. After the demographic and socioeconomic characteristics are adjusted for in Model 2, the odds ratio for high resilience slightly increase to 1.877, which indicates that the nonagenarians aged 94–97 with a higher resilience score have a 87.7% ($P < .01$) higher chance of becoming a centenarian as compared to their peers with similar demographic and socioeconomic characteristics but a lower resilience score. After further adjusting for health outcomes, the odds ratio substantially reduces from 1.877 to 1.431, but remains highly significant ($P < .01$). This indicates that resilience has a direct effect on achieving exceptional longevity, while part of its total effect operates indirectly through the pathway of health. We also further estimate the odds ratios separately for men and women in Models 4 and 5, controlling for demographic and socioeconomic characteristics and health outcomes. It turns out that the male and female nonagenarians with higher resilience scores have about 51.5% ($P < .1$) and 40.4% ($P < .05$) higher chances to become a centenarian, respectively.

Table 4: Estimates of odds ratios of higher simplified resilience scores (SRS) based on logistic regression.

Dependent variable: higher resilience score	Model 1 Total sample	Model 2 Total sample	Model 3 Total sample	Model 4 Men	Model 5 Women
Age group					
Age 80–89 (ages 65–79)	0.597*** [0.027]	0.740*** [0.036]	0.941 [0.047]	0.837** [0.059]	1.047 [0.076]
Age 90–99 (ages 65–79)	0.443*** [0.020]	0.633*** [0.032]	1.109* [0.062]	0.932 [0.076]	1.276*** [0.099]
Age 100+ (ages 65–79)	0.303*** [0.015]	0.526*** [0.030]	1.261*** [0.083]	1.412*** [0.162]	1.294*** [0.110]
Demographic characteristics					
Male (Female)		1.341*** [0.053]	1.248*** [0.051]		
Han (Minority)		0.957 [0.073]	0.985 [0.077]	1.15 [0.139]	0.894 [0.091]
Urban (Rural)		1.142*** [0.044]	1.176*** [0.046]	1.241*** [0.078]	1.118** [0.057]
Married (Notmarried including widowed, divorced, and single)		1.523*** [0.066]	1.451*** [0.065]	1.480*** [0.088]	1.400*** [0.096]
Literate (Illiterate)		1.322*** [0.055]	1.206*** [0.052]	1.215*** [0.071]	1.215*** [0.079]
With pension (No pension)		1.529*** [0.080]	1.464*** [0.080]	1.649*** [0.120]	1.255*** [0.110]
Healthstatus					
ADL independent (Impaired)			2.145*** [0.106]	2.309*** [0.192]	2.100*** [0.131]
Normal cognition (Impaired)			2.584*** [0.108]	2.344*** [0.153]	2.792*** [0.153]
Whether the province dummy is controlled for	Yes	Yes	Yes	Yes	Yes
Observations	16,428	16,428	16,428	6,941	9,487

Notes: (1) the categories in the parenthesis are reference groups. (2) Standard errors are indicated in the brackets ([ ]). (3) $^{*}P < .1$; $^{**}P < .05$; $^{***}P < .01$.

To our knowledge, there are no published studies which have investigated the association of resilience with surviving to age 100+ among nonagenarians. However, the findings of our present study can be explained by the general literature on resilience as the ability to adapt positively to adversity among old adults [3]. When individuals reach very advanced ages, accumulated negative conditions such as health deterioration and bereavement of loved family members represent serious challenges. Thus, nonagenarians who are more resilient may have stronger capacities and potentials for dealing successfully with these serious challenges, constraints, and adversities [11] to subsequently survive to age 100+.

4. Discussions and Conclusion

Based on a cross-sectional dataset with the largest sample size to date of centenarians, nonagenarians, and octogenarians plus a compatible group of young-old aged 65–79, the descriptive statistics show that the average resilience score among centenarians is lower than that of the other elderly age groups. However, our multivariate logistic analyses based on the same dataset have confirmed the hypothesis that after controlling for various potential confounders including physical health and cognitive status, centenarians are significantly more resilient than any other age group of the elders.

We also investigate the role resilience played in contributing to exceptional longevity based on the follow-up (up to 2008-2009) data from nonagenarians aged 94–97 in 2002 or aged 97-98 in 2005. The results confirm that better resilience contributes significantly to the likelihood of becoming a centenarian (i.e., exceptional longevity) among the nonagenarians.

A previous study based on CLHLS longitudinal data showed that on average, better resilience reduced mortality risk by about 15.5% among all elderly adults aged 65+, adjusted for various confounding factors including physical and mental health [15]. Our present multivariate analysis focuses on centenarians and nonagenarians. We have shown

Table 5: Odds ratios of the impact of the resilience on nonagenarians' likelihood to become a centenarian based on multivariate logistic regressions.

Dependent variable: whether survive to age ≥100	Model 1 Total sample	Model 2 Total sample	Model 3 Total sample	Model 4 Men	Model 5 Women
Higher resilience (Lower)	1.746*** [0.210]	1.877*** [0.234]	1.431*** [0.190]	1.515* [0.374]	1.404** [0.230]
Demographic characteristic					
Age—continuous variable		1.492*** [0.097]	1.517*** [0.100]	1.877*** [0.223]	1.405*** [0.116]
Male (Female)		0.703** [0.108]	0.603*** [0.096]		
Han (Minority)		0.670* [0.161]	0.634* [0.156]	0.515 [0.213]	0.664 [0.211]
Urban (Rural)		0.826 [0.108]	0.869 [0.118]	0.675* [0.159]	1.023 [0.176]
Married (Notmarried including widowed, divorced, and single)		1.637** [0.354]	1.588** [0.353]	1.34 [0.355]	3.144** [1.569]
Literate (Illiterate)		1.028 [0.164]	0.949 [0.156]	0.989 [0.222]	0.873 [0.226]
With pension (No pension)		0.964 [0.118]	0.941 [0.118]	0.941 [0.153]	1.005 [0.267]
Healthstatus					
ADL independent (Impaired)			1.983*** [0.278]	1.316 [0.338]	2.443*** [0.424]
Normal cognition (impaired)			1.819*** [0.252]	2.961*** [0.744]	1.418** [0.246]
Whether the province dummy is controlled for	Yes	Yes	Yes	Yes	Yes
Whether the year dummy is controlled for	Yes	Yes	Yes	Yes	Yes
Observation	1,528	1,528	1,528	585	943

Notes: the same as in Table 4.

that the positive effect of the resilience on enhancing the likelihood of surviving to the age of 100 among nonagenarians aged 94–98 is 43.1% ($P < .01$) for both genders combined (51.5% ($P < .1$) for men and 40.4% ($P < .05$) for women). It seems that the positive effects of the resilience on survival at very advanced ages may be more profound.

Why is resilience positively associated with survival at very advanced ages in China? One possible explanation is that resilience is correlated with improved physical and psychological health, and better health increases the probability of survival. As shown in our logistic regression analyses, the effect of resilience on the likelihood of becoming a centenarian shrinks substantially after variables of initial health status are included in the model. Prior investigations also lend support to this explanation. For instance, Wagnild [5] and Lamond [3] indicated that resilience was positively associated with physical and cognitive function. Ong [32] demonstrated that resilient individuals were more likely to hold positive emotions, which promoted both resistance to and recovery from stress and thus contributed to better health and longevity.

While the study presented in this paper is unique in terms of its largest sample size of centenarians and nonagenarians and interesting findings about the remarkable and significant effect of resilience on exceptional longevity at very advanced ages in a developing country, it should be interpreted with caution due to its inherent limitations. First, because the CLHLS is a demographic survey focusing on the determinants of healthy longevity such as demographic characteristics, socioeconomic status, life style, and health status of the elderly, we cannot assess as many resilience indicators as with other specific psychological surveys. Future research that collects more sophisticated psychological data could deepen our understanding of the impacts of resilience on healthy longevity in China. Second, we only examine the impact of resilience on exceptional longevity at advanced ages, rather than the mechanisms of how resilience works. Perhaps resilience strengthens the positive function of the immune system and certain gene(s) or ameliorates the negative impacts of some other gene(s). More detailed phenotypic and genotypic data and advanced interdisciplinary research across social and biomedical sciences are called for to explore the mechanisms.

In conclusion, the present study provides strong evidence to support the hypotheses that after adjusting for various confounders including current health, centenarians are significantly more resilient than any other age group of the elderly population and that better resilience contributes significantly to exceptional longevity even at very advanced ages. These findings are not only scientifically meaningful

but also have policy relevance, indicating that policies and programs aiming at the promotion of resilience among old citizens ought to be put on the agenda. We may learn from the successful practices in other countries, such as resilience-promotion interventions conducted in Norway, which involve promoting expression of feeling and encouraging participants' attempts to make meaningful connections between their past, present, and future lives [33]. Such efforts would have long-term and positive effects on the well-being and healthy longevity for elderly citizens and their families.

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References

[1] F. Flachsbart, A. Caliebe, R. Kleindorp et al., "Association of FOX03A variation with human longevity confirmed in German centenarians," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 8, pp. 2700–2705, 2009.

[2] Z. Yi and J. W. Vaupel, "Functional capacity and self-evaluation of health and life of oldest old in China," *Journal of Social Issues*, vol. 58, no. 4, pp. 733–748, 2003.

[3] A. J. Lamond, C. A. Depp, M. Allison et al., "Measurement and predictors of resilience among community-dwelling older women," *Journal of Psychiatric Research*, vol. 43, no. 2, pp. 148–154, 2009.

[4] S. E. Hardy, J. Concato, and T. M. Gill, "Stressful life events among community-living older persons.," *Journal of General Internal Medicine*, vol. 17, no. 11, pp. 832–838, 2002.

[5] G. Wagnild, "Resilience and successful aging: comparison among low and high income older adults," *Journal of Gerontology Nursing*, vol. 29, pp. 42–49, 3003.

[6] M. L. Caltabiano and N. J. Caltabiano, "Resilience and health outcomes in the elderly," in *Proceedings of the 39th Annual Conference of the Australian Association of Gerontology*, 2006.

[7] L. W. Poon, G. M. Clayton, P. Martin et al., "The Georgia centenarian study," *International Journal of Aging and Human Development*, vol. 34, no. 1, pp. 1–17, 1992.

[8] L. Riolli, V. Savicki, and A. Cepani, "Resilience in the face of catastrophe: optimism, personality, and coping in the Kosovo crisis," *Journal of Applied Social Psychology*, vol. 32, no. 8, pp. 1604–1627, 2006.

[9] B. Nygren, L. Aléx, E. Jonsén, Y. Gustafson, A. Norberg, and B. Lundman, "Resilience, sense of coherence, purpose in life and self-transcendence in relation to perceived physical and mental health among the oldest old," *Aging and Mental Health*, vol. 9, no. 4, pp. 354–362, 2005.

[10] A. J. Selim, G. Fincke, D. R. Berlowitz et al., "Comprehensive health status assessment of centenarians: results from the 1999 large health survey of veteran enrollees," *Journals of Gerontology A*, vol. 60, no. 4, pp. 515–519, 2005.

[11] D. Jopp and C. Rott, "Adaptation in very old age: exploring the role of resources, beliefs, and attitudes for centenarians' happiness," *Psychology and Aging*, vol. 21, no. 2, pp. 266–280, 2006.

[12] M. A. Pascucci and G. L. Loving, "Ingredients of an old and healthy life. A centenarian perspective," *Journal of Holistic Nursing*, vol. 15, no. 2, pp. 199–213, 1997.

[13] M. Yukie, Y. Gondo, I. Hiroki et al., "The influence of personality traits on longevity and centenarians' ADL," *The Gerontologist*, vol. 42, no. 1, p. 104, 2002.

[14] O. Baiyewu and R. O. Jegede, "Life satisfaction in elderly Nigerians: reliability and factor composition of the life satisfaction index Z," *Age and Ageing*, vol. 21, no. 4, pp. 256–261, 1992.

[15] K. Shen and Y. Zeng, "The association between resilience and survival among Chinese elderly," in *The Handbook of Resilience in Aging: The Key to Successful Aging*, B. Resnick, K. Roberto, and L. Gwyther, Eds., Springer, New York, NY, USA, 4th edition, 2010.

[16] C. A. Ju and G. Jones, *Aging in ASEAN: Its Socio-Economic Consequences*, Institute of Southeast Asian Studies, Singapore, 1989.

[17] B. Jeune, "In search of the first centenarians," in *Exceptional Longevity: From Prehistory to the Present*, B. Jeune and J. Vaupel, Eds., pp. 11–24, Odense University Press, Odense, Denmark, 1995.

[18] V. L. Lamb, "Active life expectancy of the elderly in selected Asian countries," NUPRI Research Paper Series no. 69, Population Research Institute at Nihon University, Tokyo, Japan, 1999.

[19] Z. L. Wang, Y. Zeng, B. Jeune et al., "A demographic and health profile of centenarians in China," in *Longevity: To the Limits and Beyond*, J. M. Robine et al., Ed., pp. 92–104, Springer, New York, NY, USA, 1997.

[20] Y. Zeng and D. Gu, "Reliability of age reporting among the Chinese oldest-old in the CLHLS datasets," in *Healthy Longevity in China: Demographic, Socioeconomic, and Psychological Dimension*, Y. Zeng, D. L. Poston Jr., D. A. Vlosky et al., Eds., pp. 61–78, Springer, Dordrecht, The Netherlands, 2008.

[21] D. Gu, "General data assessment of the Chinese longitudinal healthy longevity survey in 2002," in *Healthy longevity in China: Demographic, Socioeconomic, and Psychological Dimensions*, Y. Zeng, D. L. Poston Jr., D. A. Vlosky et al., Eds., pp. 39–59, Springer, Dordrecht, The Netherlands, 2008.

[22] K. M. Connor and J. R. T. Davidson, "Development of a new resilience scale: the connor-davidson resilience scale (CD-RISC)," *Depression and Anxiety*, vol. 18, no. 2, pp. 76–82, 2003.

[23] B. W. Smith, J. Dalen, K. Wiggins, E. Tooley, P. Christopher, and J. Bernard, "The brief resilience scale: assessing the ability to bounce back," *International Journal of Behavioral Medicine*, vol. 15, no. 3, pp. 194–200, 2008.

[24] V. G. Sinclair and K. A. Wallston, "The development and psychometric evaluation of the Brief Resilient Coping Scale," *Assessment*, vol. 11, no. 1, pp. 94–101, 2004.

[25] P. Bech, U. F. Malt, S. J. Dencker et al., "Scales for assessment of diagnosis and severity of mental disorders," *Acta Psychiatrica Scandinavica*, vol. 87, supplement 372, pp. 35–40, 1993.

[26] J. Magaziner, S. S. Bassett, J. R. Hebel, and A. Gruber-Baldini, "Use of proxies to measure health and functional status in epidemiologic studies of community-dwelling women aged 65 years and older," *American Journal of Epidemiology*, vol. 12, no. 3, pp. 283–292, 1996.

[27] P. Royston, "Multiple imputation of missing values: update," *Stata Journal*, vol. 5, no. 2, pp. 1–14, 2005.

[28] S. Katz, A. B. Ford, R. W. Moskowitz et al., "Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function," *Journal of the American Medical Association*, vol. 185, no. 12, pp. 914–919, 1963.

[29] R. M. Crum, J. C. Anthony, S. S. Bassett, and M. F. Folstein, "Population-based norms for the mini-mental state examination by age and educational level," *Journal of the American Medical Association*, vol. 269, no. 18, pp. 2386–2391, 1996.

[30] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[31] T. D. Hill, J. L. Angel, C. G. Ellison, and R. J. Angel, "Religious attendance and mortality: an 8-year follow-up of older Mexican Americans," *The Journals of Gerontology B*, vol. 60, no. 2, pp. S102–109, 2005.

[32] A. D. Ong, C. S. Bergeman, T. L. Bisconti, and K. A. Wallace, "Psychological resilience, positive emotions, and successful adaptation to stress in later life," *Journal of Personality and Social Psychology*, vol. 91, no. 4, pp. 730–749, 2006.

[33] T. Waaktaar, H. J. Christie, A. I. H. Borge, and S. Torgersen, "How can young people's resilience be enhanced? experiences from a clinical intervention project," *Clinical Child Psychology and Psychiatry*, vol. 9, no. 2, pp. 167–183, 2004.

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Research Article

Understanding Centenarians' Psychosocial Dynamics and Their Contributions to Health and Quality of Life

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While it is understood that longevity and health are influenced by complex interactions among biological, psychological, and sociological factors, there is a general lack of understanding on how psychosocial factors impact longevity, health, and quality of life among the oldest old. One of the reasons for this paradox is that the amount of funded research on aging in the US is significantly larger in the biomedical compared to psychosocial domains. The goals of this paper are to highlight recent data to demonstrate the impact of four pertinent psychosocial domains on health and quality of life of the oldest old and supplement recommendations of the 2001 NIA Panel on Longevity for future research. The four domains highlighted in this paper are (1) demographics, life events, and personal history, (2) personality, (3) cognition, and (4) socioeconomic resources and support systems.

1. Introduction

A recent review of centenarian research [1] shows a *biopsychosocial* approach that takes into account biological, psychological, and sociological mechanisms and their interactions may be most efficient to understand the multidimensional aspects of extreme longevity. A cursory search through PUBMED [2] on the number of publications in the last five years (2004–2009) in the study of longevity shows that biopsychosocial studies are rare. In fact, in the last five years, no study was noted by PUBMED on either extreme longevity or longevity using biopsychosocial approaches. When specific key words were employed in the search within the biomedical and psychosocial domains and longevity between 2004 and 2009, the ratio of biomedical to psychosocial studies ranged from a low of about 3 : 1 to a high of about 7 : 1. This contradictory situation might reflect the disproportional amount of funding on biomedical compared to psychosocial aspects of aging as evidenced by funding at the US National Institute on Aging [3] and perhaps a general lack of understanding by the research community of the impact and measurement of psychosocial factors among the oldest old.

In 2001, the NIA convened a panel of clinical, demographic, epidemiologic, and genetics research experts—*NIA Panel on the characterization of participants in studies of exceptional survival in humans*—to provide guidelines on measures that are pertinent in longevity studies and could provide precise information on the "survival" phenotype [4]. The goal of the panel was to develop a set of standard measures that could be used in all studies of exceptional survival. Recommendations were made on the measurement

of age, sociodemographic characteristics, health, functional status, psychological and social characteristics, group survival characteristics, data reporting, and availability. Since 2001, a significant amount of information on psychosocial parameters has been discovered to impact longevity and health. One of the goals of this paper is to supplement the 2001 recommendations from the psychosocial domains with recent empirical findings.

It is generally accepted that as a person ages, his or her experiences acquired over the life time, ways in dealing with the environment, economic and social resources, and relationships and support systems could profoundly impact longevity and quality of life [1]. Several significant issues for researchers are (1) how to measure these constructs in an experimental design, (2) which reliable and valid measures should be employed to adequately measure these constructs, (3) how much do these psychosocial factors singly and in combination impact longevity and quality of life, and (4) how do these factors interact with other variables?

The above research questions are important and worthy for future research agendas. We hope to inform our peers on how to better understand psychosocial processes and to incorporate pertinent psychosocial predictors to enrich future longevity research. This will be accomplished by sharing a summary of how these issues are addressed in the literature in combination with recent empirical data that demonstrate their impact on health and longevity.

The goal of this paper is threefold. One, we seek to define and increase our understanding on the measurement of two commonly-used psychosocial *outcome* measures in longevity research: self-rated health and quality of life. Two, we seek to outline the impact of four generally acknowledged psychosocial *predictors* of longevity and health. These are (1) demographics, life events, and personal history, (2) personality, (3) cognition, and (4) socio-economic resources and support systems. We use a similar format in each section starting with "*What do we know?*" which is used to provide a brief introduction of the concept, followed by "*Empirical Data*" which provides published or new data from the Georgia Centenarian Study [5], a multidisciplinary population-based study of centenarians, ending with "*Impact*" which attempts to delineate the relationship of the psychosocial construct to health and well being among the oldest old. Finally, based on recent psychosocial data, we seek to update and supplement the recommendations of the 2001 NIA Panel on Longevity.

2. Psychosocial Outcome Measures

2.1. Subjective Health. Health can be measured objectively through an inventory of past and present health history, diseases, medications, hospital and physician visits, blood chemistry, and an array of biomedical markers [6]. Interestingly and surprisingly, the best predictor of overall health is the individual's perception and self-rated health [7]. The following sections outline what we know about self-related health among the oldest old and recent empirical data on the relationship between self-rated health and other subjective and objective health outcomes (e.g., functional health), other self-reported measures of health (e.g., number of hospitalizations, number of lifetime diseases, number of health problems), and biomarkers (e.g., hemoglobin and albumin) from the Georgia Centenarian Study [5].

What Do We Know? A substantial amount of centenarian literature has focused on health outcomes at the limit of longevity [8–10]. The evidence is contradictory with some studies reporting high levels of frailty and morbidity among centenarians [8] whereas others reporting centenarians as being in relatively good health conditions [9, 11, 12]. In spite of the contradictory findings, there is a growing consensus that centenarians' health is a critical antecedent of well-being and quality of life in extreme old age [6, 13]. A number of studies have investigated associations involving general aspects of centenarian health such as global self-rated health [14, 15], functional health [16, 17], or the number of acute or chronic health conditions [8, 18, 19].

Of these multiple indicators of centenarian health, self-rated health might be useful to capture the multidimensionality of compounding health concerns in very old age [7, 20]. Self-rated health reflects a holistic picture of one's health and arguably may be the most meaningful dimension of health from the individual's perspective [7]. Self-rated health is a widely used health measure among oldest old adults due to its significant correlation with functioning and mortality [15, 21–23].

Empirical Data. As noted in the introduction, the empirical data sections in this paper are designed to discuss published or new data from the Georgia Centenarian Study. Methodological details of the study can be found in Poon, Clayton, Martin, Johnson et al. [24] and Poon, Jazwinski, Green et al. [5]. Discussion of data in this paper will focus on Phase 3 of the study (2001–2009). Phase 3 is a multidisciplinary, population-based study of 287 centenarians and near centenarians (98 yrs and older), 88 octogenarians, and 400 younger controls from 44 counties in northern Georgia. Phase 3 of the study examined genetics, neuropathology, nutrition, blood chemistry, health, diseases, medications, neuropsychology, cognition, personality, coping, distal and proximal influences, adaptation, and resources. For the present paper, we seek to focus on the two outcome variables of subjective health and quality of life as well as the four sets of predictors: life events, personality, cognition, and resources. As would be expected, the majority of the centenarian participants (85.9%) were women and White (77.4%). In terms of marital status, the majority (85.9%) was widowed, 5.6% were married, and 3.5% were divorced. A sizeable group (73.4%) had no more than a high school education whereas 15.6% had a college degree. Almost half of the centenarians resided in their private home or apartment (44.1%) whereas 19.2% resided in assisted living facilities and 36.7% in nursing facilities. Most centenarians (71.8%) reported that their health was either good or excellent. The average MMSE score of participants was 16.83. This score

Table 1: Predictors of centenarians' self-rated health.

Predictor variables	B	SE	β
Past diseases	−0.02	0.06	−0.03
Current diseases	−0.00	0.07	−0.01
No. of health problems	−0.04	0.02	−0.14†
No. of hospitalization	−0.00	0.03	−0.00
Physical ADL	0.08	0.02	0.27**
Albumin	0.49	0.17	0.22**
Hemoglobin	−0.05	0.04	−0.09
F		4.21***	
R^2		0.17	

†$P < .10$. **$P < .01$. ***$P < .001$.

suggests that about half of our centenarians showed at least severe levels of cognitive impairment.

Fries et al. [25] found that all measures of physical decline increased rapidly with each year of age among the very oldest-old; hence, it should be noted that the older the elder, the lower the level of self-rated health status. Contrary to this finding, however, Liu and Zhang [23] found that the centenarians were more likely to report positively their health status but nonagenarians and octogenarians were less likely to report better health status. Empirical data from the Georgia Centenarian Study [5] seem to replicate the findings from Liu and Zhang [23]. Almost 20% of our centenarians (19.4%) rated their health as excellent, and over half of them (52.7%) rated their overall health as good. There were no significant differences in the ratings of self-reported health between centenarians and their younger counterparts ($\chi^2 = 2.86$, $df = 3$, $P = .41$). This is also consistent with Idler [26], who suggested that older subjects reported disproportionately positive health assessments, and "processes of aging, selective survivorship, and cohort differences all appear to play a role in creating this pattern (p. S289)."

Consistent with the biopsychological approach, self-rated health showed a significant association ($P < .05$) with functional health ($r = .32$) and levels of albumin ($r = .24$) and a significant negative association with self-reported health problems ($r = -.19$). Specifically, the more health problems (e.g., chest discomfort, numbness, arthritis, and dizziness), the more dependent of physical activities in daily living (e.g., eating, dressing, walking, and bathing), and the lower the levels of albumin, which in turn lower centenarians' self-rated health.

Impact. Based on the above correlation results, we employed a regression model to verify the importance of health measures on self-rated health among centenarians. Significant predictors of self-rated health were number of health problems ($\beta = -.14$, $t = -1.67$), physical ADL ($\beta = .27$, $t = 3.38$), and levels of albumin ($\beta = .22$, $t = 2.78$) after controlling for all other variables in the model. As Table 1 shows, the model explained 17% of the variance in the centenarians' self-reported health.

2.2. Quality of Life, Happiness, and Well-Being. Another important outcome measure in longevity research as well as public policy is quality of life. "Adding life to years" is as important as "adding years to life" when evaluating interventions or treatment regiments among older adults. The World Health Organization [27] established a well-known definition of quality of life as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (p. 28). Contemporary social and behavioral gerontologists have traditionally conceptualized quality of life as the final criteria by which perceived resources (e.g., health, social support, socioeconomic status, cognitive functioning) influence well-being among centenarians [28–30] whereas clinical geriatric investigators have generally operationalized quality of life as contributing health-related indicators (e.g., biomarkers, type of acute illness or chronic disease, performance of activities of daily living, family health history) of disability and mortality in longevity [12, 19, 31, 32]. Nonetheless, there is consensus that quality of life reflects health related as well as nonhealth associated indicators [33]. A biopsychosocial approach may provide an effective alternative in differentiating quality of life among persons of exceptional old age.

What Do We Know? Although quality of life, happiness, and well-being denote similar constructs, psychologists have attempted to differentiate these constructs in subtle ways. Ryff [34] noted that perceptions surrounding quality of life, happiness, and well-being are in the eye of the beholder. Researchers often have the task of deciding whether to assess objective components (e.g., physical biomarkers or activities of daily living performance) or subjective characteristics (e.g., self-reported ratings) of well-being [33].

Happiness is often used as an outcome variable and is broadly defined as an individual's state of being [35]. Happiness is theorized to be a positive affective condition which arises from the comparison of former life accomplishments and achievements to current life situations and circumstances (e.g., health status, social support, economic status [35]). Diener and Biswas-Diener [36] have referred to this mechanism as psychological wealth. In other words, happiness is indicative of the degree to which persons feel they have effectively used resources in the past, yet remain optimistic and feel they still have enough to flourish in the present or future. Diener and Biswas-Diener [36] integrated this perspective into a common formula

$$\text{Happiness} = \frac{\text{What we have (attainments of life)}}{\text{What we want (current aspirations)}}. \quad (1)$$

From an evolutionary psychology perspective, happiness signifies the achievement of successful adaptation and expert survivorship in aging [37]. Happiness is achieved when appropriate steps are taken to attain acceptance and fulfillment with one's past (i.e., congruence) as well as to effectively use resources to solve everyday problems which threaten health, well-being, and survival [37]. Perhaps, happiness is most optimal among persons who have survived beyond advanced old age.

Older adults reaching advanced old age often experience physical inactivity, poor nutritional health, anxiety, and greater feelings of fatigue [38]. In turn, our work has focused on examining how perceived contentment with the past and psychosocial resources may bolster or diminish perceived well-being or happiness. We reported health impairment as a key indicator and mediating variable of congruence (e.g., perceived degree of contentment with the past) across a sample of old and very old adults [26]. In particular, social support and socioeconomic status (SES) had indirect associations on congruence and happiness through health impairment. Furthermore, we reported that social support, SES, health impairment, and congruence (e.g., degree of contentment with the past) explained 40% of the variance in happiness.

Empirical Data. In an investigation involving 158 centenarians, we were interested in understanding how perceived degree of available psychosocial resources would mediate the relationship between congruence and happiness [39]. Based on our previous work, it was hypothesized that perceived health status would emerge as a key indicator and mediating variable of happiness. However, there was no significant evidence of mediation. Instead, congruence emerged as a key predictor of how centenarians perceive resources and determinant of feeling happy. Greater satisfaction with the past had a significant direct association with perceived economic security, perceived health status, and current happiness. Forty-four percent of the variance in perceived health was explained by congruence, economic security, and social provisions. In addition, 25% of the variance in happiness was explained by congruence, perceived economic security, social provisions, and perceived health status.

Impact. Table 2 provides a summary of our most recent findings from the Georgia Centenarian Study using positive and negative effect as key mediating influences between health and psychosocial indicators and happiness among centenarians. Results confirm that positive emotionality is associated with greater feelings of happiness whereas negative effect diminishes happiness. Fatigue appears to be a salient predictor of positive and negative effect. Fatigue had a significant negative direct effect on positive emotionality but a significant positive direct effect on negative effect.

3. Psychosocial Predictors

As noted earlier, there is no argument that an individual's personal history, known as distal influences, and their current conditions, known as proximal influences, could combine to impact longevity and quality of life [1, 40]. The critical questions are which distal and proximal influences are most influential in determining longevity and quality of life and how do we investigate their direct and indirect impacts [40]. In this section, we review four selected psychosocial areas that have been found to influence longevity and quality life.

3.1. Demographics, Life Events, and Personal History. Life events are important determinants of physical and mental health in older adults, especially stressful events [41, 42]. Life events are experiences that can have a positive/negative and proximal/distal influence on centenarians' health and quality of life. Studying the effect of life events on the oldest-old is important because they most likely have experienced a significant number of positive and negative events over their life time. Centenarians may have experienced events such as decline in health, loss of loved ones, institutionalization, and even deterioration of their financial resources. Therefore, the events that many centenarians have experienced and have been exposed to may have impacted their current physical and mental health status as well as influenced their survivorship and overall quality of life.

What Do We Know? Life events can play a role in human development as both distal and proximal influences [40]. The literature provides support that distal factors could clearly impact health and quality of life in old age. For example, one of the most crucial studies published on this topic involves the work of Blackwell et al. [43]. In their research, they examined whether childhood health had long-term and enduring consequences for chronic morbidity. Results indicated that poor childhood health increases morbidity in later life, and that this correlation was found for cancer, lung disease, cardiovascular conditions, and arthritis. Childhood health was a key factor in the risk for a heart attack in later life in a study conducted by O'Rand and Hamil-Luker [44]. These researchers investigated how cumulative adversity across the lifespan influenced risk trajectory for heart attack. Their results suggested that early disadvantage and childhood illness have immense enduring effects and do increase the risk for heart attack in later life. However, adult pathways influence these risk trajectories and mediate the effects of early disadvantage. Building on the work of O' Rand and Hamil-Luker [44] and others, McEniry et al. [45] studied the influence of early life exposure to poor nutrition and infectious diseases on the health of older Puerto Ricans. These researchers found a strong association between exposure and heart disease, and a weaker association between exposure and diabetes. They concluded that the timing of birth is associated with conditions occurring around the time of birth that can affect heart disease and diabetes in later life. Distal influences and their effect on cognition in later life was the focus of a study done by Fors et al. [46]. This investigation looked at the association between childhood living conditions, socioeconomic position in adulthood, and cognition in later life. Results showed that exposure to conflicts during childhood, having a father classified as manual worker, low education, and/or being classified as a manual worker in adulthood was associated with lower levels of cognition in old age. Besides childhood health and living conditions, life events are also of interest to gerontologists in terms of their influence in lifespan development.

Empirical Data. In the Georgia Centenarian Study, we assessed events that occurred over the life span such as

Table 2: Positive and negative effect and happiness.

Variable (Model 1)	Direct effect	SE	Indirect effect	Total effect	r
Positive effect					
Perceived health	.17	.27	.04	.21	.31
Functional health	−.12	.06	−.03	−.15	.13
Cognition	.13	.11	.03	.16	.22
Fatigue	−.41**	.04	−.10	−.51	−.45
Distal events	.12	.17	.03	.09	.14
Happiness					
Positive effect	.24*	.09	—	—	.04
Variable (Model 2)	Direct effect	SE	Indirect effect	Total effect	r
Negative effect					
Perceived health	−.17	.16	.06	−.11	−.20
Functional health	.26*	.08	−.09	.17	-.08
Cognition	−.26*	.15	−.09	.35	−.21
Fatigue	.26**	.03	−.08	.18	.27
Distal events	.10	.10	.03	−.07	−.10
Happiness					
Negative effect	−.33**	.12	—	—	−.09

Note. Indirect effects calculated by multiplying direct effects between psychosocial indicators and positive and negative effects with the direct effects between positive and negative affect and happiness. Total effects equal sum of direct and indirect effects. Dashed lines indicate no calculation of indirect or total effect. $^{*}P < .05$, $^{**}P < .01$.

marriage, birth of a child, death of spouse, child, and siblings, health events, historical events, retirement, personal injury, worsening relationship with child, and institutionalization. Investigating the proportion of some of these life events experienced by centenarians at any time of their lives, we found that 87.3% of centenarians had experienced the death of a spouse and 32.1% had experienced the death of children. Centenarians reported a high proportion of decline in activities (89.9%) and hospitalization (97.8%).

When comparing centenarians' mean scores on several different measures of life events to octogenarians we concluded that centenarians reported significantly lower mean scores on number of proximal and positive events compared to octogenarians. In contrast, centenarians reported a higher mean score on number of distal events (Table 3).

Several distal influences were found to impact the health of centenarians from the Georgia Centenarian Study [47]. The data show that the number of children significantly predicted centenarian's ability to engage in activities of daily living ($\beta = .14$, $P < .05$) and loneliness ($\beta = -.23$, $P < .05$). In essence, the more children, the higher the activities of daily living score and the lower the loneliness scores. Family history variables could account for 12% of variance in loneliness. Moreover, distal variables also influenced physical health in centenarians [47]. First, childhood health significantly predicted current health problems ($\beta = -.233$, $P < .05$). The poorer one's health in childhood, the larger the amount of current health problems reported. In this investigation, family history variables accounted for 13% of the variance in current physical health problems. Second, lifetime negative events significantly predicted current health problems ($\beta = .33$, $P < .01$). The more life-time negative events, the greater the amount of current health problems reported. In these findings, life events accounted for 10% of the variance in current physical health problems. These results confirm the importance of distal family history variables (influences) on present-day functioning of older adults.

Impact. Looking at the relationship between positive/negative life events and self-rated health, we conclude that cognitively intact centenarians that experienced a high number of negative events reported lower scores on self-rated health ($r = -.21$, $P < .05$). In contradiction, positive life events was positively associated with self-rated health ($r = .19$, $P < .05$). In addition, a high number of negative events was negatively associated with lower levels of congruence (i.e., contentment with past achievements) ($r = -.27$, $P < .01$) and life satisfaction ($r = -.21$, $P < .05$), suggesting that centenarians with a high number of negative events in life rated lower levels of contentment with past achievements and life satisfaction. In addition, individuals who experienced a high number of total events had lower levels of contentment with their past achievements ($r = -.19$, $P < .01$). Drawing on the material presented, distal variables do indeed influence functional, mental, and physical health in the oldest old. Not only does evidence exist for the number of children affecting both activities of daily living and loneliness in older adults [47], but childhood health influences current health problems in centenarians.

3.2. Personality. When facing life stress or life changes, centenarians (like other age groups) draw on a number of different resources. One important individual resource

Table 3: Age group comparisons on life events.

	Centenarians ($n = 137$)		Octogenarians ($n = 71$)		F
	Mean	SD	Mean	SD	
Number of proximal events	2.14	1.39	3.70	1.69	50.76***
Number of distal events	5.07	1.62	4.38	1.37	9.51**
Total number of life events	11.76	1.98	11.62	1.81	.25
Positive life events	4.28	1.44	5.27	1.21	24.25***
Negative life events	7.44	2.22	7.01	2.07	1.78

*$P < .10$, **$P < .05$, ***$P < .001$.

centenarians can draw on is their own personality. Although many aspects in very late life may change, centenarians can rely on a set of personality traits that help with everyday problems. A personality trait approach is typically used to describe personality profiles of centenarians.

What Do We Know? Several studies have assessed personality traits of centenarians [48]. A Swedish centenarian study [49], for example, suggested that centenarians could be described as dependable, reliable, mature, conscientious, and less frequently participating in social activities. Furthermore, centenarians on average were responsible, easygoing, capable, relaxed, efficient, and not prone to anxiety. Results from the first Georgia Centenarian Study [24] indicated that centenarians had higher scores in dominance, suspiciousness, and shrewdness whereas they were lower in imagination and tension when compared to two younger groups [50]. When retesting centenarians after approximately 20 months, we found that centenarians had decreased scores in sensitivity, but higher scores in radicalism [51]. Martin [50] suggested that the "robust personality" among these highly selected centenarians was a possible indicator of survivorship but also an important resource that may help centenarians adapt to everyday problems in very late life. Findings from the most recent Georgia Centenarian Study using the Big-5 framework confirmed a unique set of robust personality traits including low levels of neuroticism, but high levels of extraversion, conscientiousness, and agreeableness [38]. These results confirmed that centenarians showed several unique traits, but that a special combination of traits (i.e., low levels of neuroticism, high conscientiousness, and moderately high extraversion) were also notable in this group of exceptional survivors [38].

Low levels of neuroticism in female centenarians as measured by the NEO Big-5 were also reported by Silver et al. [52] and a recent Japanese centenarian study indicated that male and female centenarians scored higher in openness. Another Japanese centenarian study reported that centenarians had high scores in femininity and low scores in Type-A behavior [53].

In summary, personality traits are usually included in centenarian studies because of their possible contribution to longevity and adaptation. The most consistent personality trait found in almost every centenarian study focused on low levels in Neuroticism [48].

Empirical Data. Although there is quite a bit of research on personality traits, their relationship to health and quality of life outcome measures is still not thoroughly investigated for centenarians. Are centenarians with low scores in neuroticism also healthier? Does extraversion improve quality of life? Table 4 summarizes our most recent findings using the Big-5 framework (i.e., neuroticism, extraversion, openness, agreeableness, and conscientiousness) to predict two different quality of life outcomes: mental health and subjective health. All personality trait ratings of centenarians were provided by proxy informants.

The results of two separate multiple regression analyses indicate that three of the five personality dimensions were significantly associated with mental and physical health measures. Conscientiousness was a consistent predictor: centenarians who were rated as more conscientious were reported to be in better health, but had lower scores in mental health. In addition, neuroticism was negatively and openness positively related to mental health.

Impact. Whether centenarians achieve high levels of quality of life or not may depend on many psychosocial or biological factors. However, personality traits may directly indicate why life for some centenarians is still as enjoyable and autonomous as it has been in their earlier years. The "robustness" of centenarians, as indicated by low levels of neuroticism and relatively high levels of openness to experience and especially conscientiousness, helps us understand individual differences in late life adaptation.

3.3. Cognitive Functioning. The 2001 NIA Panel on Longevity acknowledged that cognitive functioning is an important predictor to be included in the study of human longevity. It is noted that cognition is multi-dimensional consisting of both global measures and specific cognitive and neuropsychological mechanisms. Key decisions that confront longevity researchers in the design of longevity studies are which cognitive measures should be included and how comprehensive the cognitive battery should be [54]. While there are different schools of thought in response to these questions, the general rule of thumb is the selection needs to be based on the specific aims and hypotheses of the research [55]. The goal of this section is to demonstrate that cognition is highly correlated with other psychosocial variables as well

Table 4: Personality predictors of centenarians' self-rated mental health and physical health.

	Mental health			Physical health		
	B	SE	β	B	SE	β
Functional capacity	.19	.06	.28**	.04	.01	.40***
Subjective health	2.12	.43	.33***	x	x	x
Mental health	x	x	x	.06	.01	.39***
Neuroticism	−.08	.02	−.34***	.00	.00	−.06
Extraversion	.02	.02	.08	.00	.00	−.08
Openness	.05	.02	.16∗	.00	.00	−.08
Agreeableness	.00	.02	.01	.00	.00	−.11
Conscientiousness	−.04	.02	−.19*	.01	.00	.20*
Model R^2			.48			.39

Models controlled for sex, ethnicity, cognitive status, residential type, and education.
*$P < .05$. **$P < .01$. ***$P < .001$. (two-tailed tests).

as indicators of mental and physical health in determining quality of life among the oldest old.

What Do We Know? Cognitive functioning is a predictor of critical outcomes in older age including institutionalization, everyday functioning, and longevity [56]. Several factors are related to the achievement and maintenance of cognitive functioning and vitality among centenarians including social support, physical health, nutrition, personality, and mental health (for discussion see Margrett et al. [57]. Cognitive abilities work in concert with such factors to shape older adults' quality of life. Unfortunately most empirical work examining cognition in older adulthood relies on participants who represent the young old (i.e., 65–75) or old old (i.e., 75–84), thereby truncating the ability to examine the full developmental course of cognitive aging. Thus, centenarian studies are critical to improving knowledge regarding cognition and the role it plays, together with other skills and resources, in promoting longevity and successful aging. There are several issues of theoretical and methodological importance that should be noted when examining cognitive functioning in late life. One issue is the impact of physical and sensory limitations on test results. As discussed by Holtsberg et al. [58] an increased prevalence of sensory and mobility limitations can result in automatic deductions from tests such as the MMSE which includes items relying on visual cues (e.g., read and follow directions, copy write a sentence). For majority populations, the general cut-off for the MMSE is 23, with scores lower than 23 indicating likely impairment. For samples varying in ethnicity, education, and degree of sensory impairment or disability, this cut-off has been questioned resulting in use of an adjusted or lower cut-off score (i.e., 17, 21) [59, 60]. Many cognitive tests lack normative data, particularly for the oldest old. This can make group comparisons difficult (e.g., cohort differences in education) [58] as well as hamper interpretation of individual performance. As a result, researchers should carefully consider appropriate cut-off scores for centenarians and the oldest old.

A second issue related to investigation of cognition in late life is assessment choice. Cognitive measures vary along three related dimensions: (a) focus on normative age-related cognitive change in the context of understanding impaired functioning associated with dementia; (b) level of specificity ranging from global assessments of status (e.g., MMSE) to specific tests of particular cognitive abilities (e.g., episodic memory); and (c) degree of emphasis on the application of cognitive abilities to everyday life which can indicate probable day-to-day functioning and impairment. Heterogeneity of cognitive outcomes increases with age and the prevalence of dementia is greater among the oldest old (37%–50%). The possible prevalence approaches 80% among centenarians [56, 61, 62]. Owing to participant fatigue and potentially diminished cognitive capacity, multiple sources (e.g., self-report, proxy-ratings, interviewer observations, performance-based tests) are often included in studies of the oldest old. Recent analyses of the Georgia Centenarian Study demonstrate how differences in data sources can lead to varying interpretations [63].

Empirical Data. The assessment strategy employed in the Georgia Centenarian Study reflects the multidimensionality of cognition. The major hypotheses focused on the prevalence of dementia in a population-based sample as well as the identification of cognitive mechanisms associated with everyday functioning abilities among the oldest old. As is typical in many gerontological studies, cognitive or mental status was initially assessed by the Mini-Mental Status Exam (MMSE) [64]. We further included a clinician assessment scale, the Global Deterioration Scale [65, 66], to complement the MMSE. However, other more comprehensive measures were utilized including indicators of: (a) global cognitive ability (Severe Impairment Battery, SIB) [67], (b) executive control (Behavioral Dyscontrol Scale, BDS) [68], (c) verbal fluency (Controlled Oral Word Association Test, COWAT) [69], (d) memory (Fuld Object-Memory Exam, FOME) [70], and (e) language abilities (Similarities subtest from the WAIS-III) [71].

In the following analyses of data from the Georgia Centenarian Study, we first address the range of cognitive functioning among centenarians and second we compare the utility of several indicators of cognitive functioning

in predicting centenarians' self-rated mental and physical health. Prior research suggests that cognitive abilities may become more similar, or dedifferentiated [72] resulting in high correlations between measures. This hypothesis has not been fully explored among the oldest old, although work is underway using the GCS data. In the present study, the selected cognitive measures were strongly correlated among centenarians overall (i.e., range = .44–.87). Thus, we conducted separate multiple regression analyses to examine the utility of each cognitive measure in predicting subjective mental and physical health.

To address the first question, we examined MMSE performance among octogenarians and centenarians. While 85% of octogenarians scored 23 or greater, centenarians demonstrated greater diversity in performance with 32% achieving the same score. The use of multiple cutoff scores illustrates the importance of considering appropriate cutoff scores when assessing the cognitive functioning of very old individuals; our data suggest that 68% of centenarians would likely be classified as impaired using a traditional cutoff score of 23 on the MMSE. However, given this group's sensory impairments, educational level, and ethnic diversity such a conclusion may not be warranted. To illustrate, we recently published normative data from the GCS on several measures, including the MMSE [73]. In this case, at the point of this oldest old age group, MMSE scores declined on a nearly yearly rate (i.e., 50th%ile at 98-99 yo = 21; 100-101 yo = 16; 102+ yo = 13). As we recently argued [57], the entire range of cognitive functioning must be considered in order to appreciate the full spectrum of cognitive health in later life.

Table 5 depicts results of the regression analyses examining individual cognitive predictors of centenarians' health. Perhaps not surprising given the age-related physical limitations faced by many centenarians, cognitive measures were better predictors of mental health as compared to physical health accounting for a greater proportion of the explained variance. The analyses examining physical health revealed that COWAT performance was a significant predictor, as well as a trend for the WAIS-III Similarities subtest. For mental health, the MMSE, COWAT, and WAIS-III Similarities subtest ($P < .10$) were each significant predictors within the separate models above and beyond the effects of sex, ethnicity, residential status, and education. This finding suggests that cognitive status, abstract reasoning, and capacity for quickly producing verbal responses are important contributors to mental health, perhaps in the context of interpersonal relations. These regression analyses indicate the differential utility of cognitive assessments.

Impact. Because there have been no normative data for centenarians, the relative utility of any particular cognitive instrument is difficult to place into context. We found that the MMSE is probably sufficient to ascertain an overall level of cognitive functioning, and the MMSE predicts most of the variance in basic and instrumental activities of daily living (BADL and IADL). More specific neuropsychological instruments are somewhat time consuming to administer, but they are equally as predictive (as a group) as the MMSE of BADL and IADL. However, they are able to yield more domain-specific information about an individual's cognitive functioning. The extant literature, as well as recent findings from the Georgia Centenarian Study, demonstrate that cognitive abilities work in conjunction with other psychosocial variables as well as indicators of physical health in determining quality of life among the oldest old. It is also clear that generalizations across age groups can be misleading as differences can be profound between individuals classified as the "oldest old," as seen in differences between octogenarians and centenarians in this sample. These findings can inform prevention and intervention efforts, which would benefit from: (1) a more multi-dimensional, holistic approach and (2) targeting potential mediating factors earlier in the life course.

3.4. Social and Economic Resource Adequacy. Our final psychosocial predictor of centenarian longevity is based on the construct of resource adequacy, which includes dimensions of both economic resources and social resources. For this study, using the Duke OARS [74] we obtained Georgia centenarians' perceptions of the adequacy of their economic (i.e., perceived economic status) and social resources. In addition, we used Cutrona and Russell's [75] Social Provisions Scale which included various aspects of the quality of social relationships.

What Do We Know? About a decade ago, gerontologists began to describe centenarians' social networks and interactions [76, 77] as well as their economic resources [78]. A few centenarian studies began to establish the association of these resources to life satisfaction [79] and mental health [77]. Poon and colleagues [24] found that there was a significant bivariate association between social resources and Georgia centenarians' longevity. Martin [50] applied the Georgia resource model of developmental adaptation to predict centenarians' mental health and functional health, testing whether adverse and more distal cumulative life events would have direct, as well as indirect effects mediated by proximal social support and economic resources. Martin [50] found that adverse cumulative life events reduced both social resources and perceived economic status; both types of resources were positively related to mental health. In addition, it is understood that a centenarian's residential setting (e.g., private home, skilled nursing facility, or nursing home) is associated with these measures of social resource adequacy [80] and that the amount and type of services obtained from paid or unpaid caregivers are related to their physical and mental health [81]. The research reported here builds upon these studies to assess the impact of social and economic resource adequacy on centenarians' self-reported mental health and physical health in the Georgia Centenarian Study.

Randall et al. [80] found evidence of age-related social resource decline; centenarians self-reported significantly lower levels of social resources and social provisions than

Table 5: Cognitive predictors of centenarians' self-rated mental and physical health.

Predictors	Mental health				Physical health			
	B	SE	β	R^2	B	SE	β	R^2
Mini-Mental Status Exam	.26	.09	.26*	.13*	.02	.02	.12	.02
Global Deterioration Scale	−.63	.40	−.16	.11	−.04	.07	−.06	.03
Severe Impairment Battery	.08	.06	.14	.10	-.01	.01	−.09	.03
Behavioral Dyscontrol Scale	.12	.11	.11	.09	.02	.02	.12	.07
COWAT	.35	.13	.27*	.15*	.06	.03	.25*	.08*
FOME retention	−.03	.18	−.02	.09	−.05	.03	−.15	.04
WAIS-III Similarities subtest	.11	.06	.22[t]	.12[t]	.02	.01	.21[†]	.05[†]

Models controlled for sex, ethnicity, residential status, and education.
[†]$P < .10$. *$P < .05$. (two-tailed tests).

octogenarians. MacDonald et al. [81] found that centenarians also used more types of caregiving services than octogenarians, but there were no significant age group differences with respect to total caregiving hours, income support, or medical care usage. However there was a significant positive relationship between caregiving hours received and the personality trait of competence, controlling for residential setting, and perceived health status. MacDonald and colleagues [63] also analyzed the influence of perceived economic status on alternative perceptions of centenarians' mental health by comparing multivariate single-regression models predicting self-, proxy, and interviewer reports. There was a significant positive relationship of perceived economic status to both self- and proxy mental health reports (controlling for nursing home residence, distal engaged lifestyle and cumulative distal events, ADL, subjective health, and mental status). Recently, Randall et al. [82] also reported positive relationships of both self-reported perceived economic status and social resources with the outcome, centenarians' mental health (interviewer report), that were obtained from structural equation models including distal manifest variables (childhood socio-economic status, and stressful life events experienced at various ages) as exogenous predictors and intervening proximal latent economic and social resource variables. A single item measure of self-rated physical health as a summary assessment of overall health status has been validated in the literature and found predictive of outcomes such as mortality, BMI, physical activity, and hospitalization among others [83–85]. DeSalvo and colleagues [83] compared the predictive accuracy of a single-item measure of general health with multi-item scales (e.g., mental component summary and physical component summary). The single item performed as well as the multi-item measures regarding validity and reliability, in addition to saving time and money over the use of longer instruments. Similarly, studies have assessed single-item self reports of mental health. However, when possible it has been suggested to use multiple items to assess the breadth associated with such a construct as mental health [86].

Empirical Data. The present study, using data from the Georgia Centenarian Study, investigated predictors of centenarians' self-reported mental health (a summed index of the twenty OARS Mental Health self-reported items) and we used the same model to predict centenarians' self-reported physical health. This allowed us to compare how these predictors differentially were associated with key health and quality of life outcomes.

First, for the self-rated mental health outcome, we specified a hierarchical regression model with three blocks of predictors. (a) Control variables: residential type, sex, cognitive status, ethnicity, and education; (b) health correlates: functional and physical health; and (c) resource adequacy measures: perceived economic status, social provisions (an instrumental assessment of social support), and social resources (a structural assessment of social support). We present results from the final model including statistics for the health and socio-economic resource adequacy predictors (Table 6).

In the final model, two of the variables included in the third block of socio-economic adequacy resource measures were significantly associated with the outcome, mental health, as this block also significantly contributed to the increase in variance explained ($F\ \Delta = 5.73$; $P = .001$). Perceived economic status and social resources significantly predicted mental health; only social provisions did not contribute to an increase in centenarians' mental health controlling for all other variables in the model. As Table 6 shows, the final model explained 56% of the variance in the centenarians' self-reported mental health. The addition of the socio-economic resource adequacy predictors in the final block increased the variance explained by over 17% relative to the model that excluded those predictors.

Next, we investigated the same model predicting self-rated health. One intriguing finding was noted in the final model that explained 37% of the variance: social provisions significantly predicted physical health controlling for all other predictors in the total model. Thus, it appears that for centenarians, the type of social support provided is significantly related to their self-rated health whereas their perception of economic sufficiency and their amount of network contact do not.

Impact. As Antonucci et al. [87] theorized, assessments of social, economic, and personal resources significantly contribute to self-rated mental and physical health in advanced

Table 6: Predictors of centenarians' self-rated mental and physical health.

Predictors	Mental health			Physical health		
	B	SE	β	B	SE	β
Functional health	.27	.07	.30***	.01	.02	.02
Physical health	2.01	.47	.35***	x	x	x
Mental health	x	x	x	.09	.02	.51***
Perceived economic status	.7	.23	.25**	.03	.05	.06
Social provisions	−.07	.15	−.03	.06	.03	.17*
Social resources	.61	.22	.21**	.03	.05	.05
Model R^2			.56			.37

Models controlled for sex, ethnicity, cognitive status, residential type, and education.
*$P < .05$. **$P < .01$. ***$P < .001$. (two-tailed tests).

old age beyond the contribution of various controls (e.g., sex, race, residential setting, cognitive status, and education) and functional health.

4. Conclusions and Recommendations

The goal of this paper is to highlight the importance of psychosocial factors on longevity research. We have shown that a selected number of psychosocial predictors and outcome variables could provide a comprehensive picture of health, functioning, and quality of life at extreme old age. Inclusion of these variables along with biomedical mechanisms could enrich our understanding on what, how, and why some individuals survive to a ripe old age with high quality of life while others could not.

There is much to be done to better understand psychosocial contributors to longevity and the psychosocial and biomedical mechanisms that combine and interact to increase longevity and quality of life. It is worthwhile to note that experiences from seasoned centenarian researchers [1] cautioned us to pay particular attention to measurement fatigue among centenarians, issues of reliability and validity of short forms of tests, suitable use of criterion or cut-off scores owing to compromise sensory and cognitive functions [58], as well as the validity of using proxy when direct measures are not available.

The final goal of this paper is to supplement the *2001 NIA Panel on the characterization of participants in studies of exceptional survival in humans* with recommendations based on empirical psychosocial data associated with health and quality of life among the oldest old.

(1) Self-reported or subjective health serves as a useful index of physical trajectories of current health status as well as an indicator of the presence or absence of resources that might influence functional decline. Self-rated health shows a significant association with functional health ($r = .32$) and levels of albumin ($r = .24$) and a significant negative association with self-reported health problems ($r = -.19$).

(2) Quality of life, happiness, and well-being are important public health and public policy outcomes in the evaluation of intervention and treatments at the end of life. Care must be exercised in measuring these variables as positive and negative emotions and effects are associated with fatigue, functional health, and cognition.

(3) Information of distal life events and recent proximal influences provides meaningful information about the aged individual. A high number of negative events correlate with lower scores on self-rated health ($r = -.21$, $P < .10$), while positive life events are positively associated with self-rated health ($r = .19$, $P < .10$). In addition, a high number of negative events are negatively associated with lower levels of congruence (contentment with past achievements), $r = -.27$, $P < .10$ and life satisfaction ($r = -.21$, $P < .10$), suggesting that centenarians with a high number of negative events in life report lower levels of contentment with past achievements and life satisfaction.

(4) As noted by the 2001 NIA Panel, we concur that an individual's personality, as measured by the Big-5 personality traits, could impact longevity and health. In addition, we have found that three of the five personality dimensions are significantly associated with mental and physical health measures. Conscientiousness is a consistent predictor. Centenarians who are rated as more conscientious are reported to be in better health, but had lower scores in mental health. In addition, neuroticism is negatively and openness positively related to mental health.

(5) While the 2001 NIA Panel endorsed the measure of cognition as important to longevity, institutionalization, mental and physical health, we caution the need to include sensory capacities, literacy, and the choice and criteria in the selection of the cognitive instrument that is suitable to the sampled individuals as well as everyday functions.

(6) Social and economic resources in conjunction with functional and physical health could account for 56% of self-rated mental health and 37% of self-rated physical health. Social and economic resource adequacy are recommended as pertinent variables for better understanding health and longevity with particular relevance for public policy.

Evaluating comprehensive quality of life domains among centenarians is important. After all, life would only be worth extending to a second century if it came with a minimum level of health, autonomy, and functioning. However, focusing exclusively on health aspects would disregard the importance of a number of psychosocial domains, including life events, personality, cognition, and social supports, that are also essential for a rewarding life at 100 and beyond. The relative impact and significance of these domains are, of course, dependent on the research question. We conclude that these psychosocial domains are as important and have the highest potential to interact with biological and medical aspects in unearthing the secrets to exceptional longevity.

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References

[1] L. W. Poon and T. T. Perls, "The trials and tribulations of studying the oldest old," in *Annual Review of Gerontology and Geriatrics: Biophsychosocial Approaches to Longevity*, L. W. Poon and T. Perls, Eds., pp. 1–7, Springer, New York, NY, USA, 2007.

[2] U.S. National Library of Medicine and National Institutes of Health. (n.d.), "PubMed.gov.," December 2010, http://www.ncbi.nlm.nih.gov/pubmed.

[3] U.S. National Institute on Aging, (n.d.), December 2010, http:www.nia.nih.gov/NR/rdonlyres/169BAC4D-FDF9-4FB4-8CB9-1D323F0F83F9/8872/CJ200901808PDF.pdf.

[4] U.S. National Institutes of Health: National Institute on Aging, December 2010, http://www.nia.nih.gov/Researchinformation/ConferencesAndMeetings/NIAPanel.htm.

[5] L. W. Poon, M. Jazwinski, R. C. Green, et al., "Methodological considerations in studying centenarians: lessons learned from the Georgia centenarian studies," *Annual Review of Gerontology and Geriatrics*, vol. 27, no. 1, pp. 231–264, 2007.

[6] M. G. Parker and M. Thorslund, "Health trends in the elderly population: getting better and getting worse," *Gerontologist*, vol. 47, no. 2, pp. 150–158, 2007.

[7] E. L. Idler, S. V. Hudson, and H. Leventhal, "The meanings of self-ratings of health: a qualitative and quantitative approach," *Research on Aging*, vol. 21, no. 3, pp. 458–476, 1999.

[8] K. Andersen-Ranberg, M. Schroll, and B. Jeune, "Healthy centenarians do not exist, but autonomous centenarians do: a population-based study of morbidity among danish centenarians," *Journal of the American Geriatrics Society*, vol. 49, no. 7, pp. 900–908, 2001.

[9] R. Hitt, Y. Young-Xu, M. Silver, and T. Perls, "Centenarians: the older you get, the healthier you have been," *Lancet*, vol. 354, no. 9179, p. 652, 1999.

[10] T. Perls and D. Terry, "Understanding the determinants of exceptional longevity," *Annals of Internal Medicine*, vol. 139, no. 5, pp. 445–449, 2003.

[11] M. Motta, E. Bennati, L. Ferlito, M. Malaguarnera, and L. Motta, "Successful aging in centenarians: myths and reality," *Archives of Gerontology and Geriatrics*, vol. 40, no. 3, pp. 241–251, 2005.

[12] T. Perls, I. V. Kohler, S. Andersen et al., "Survival of parents and siblings of supercentenarians," *Journals of Gerontology. Series A*, vol. 62, no. 9, pp. 1028–1034, 2007.

[13] M. D. Buono, O. Urciuoli, and D. De Leo, "Quality of life and longevity: a study of centenarians," *Age and Ageing*, vol. 27, no. 2, pp. 207–216, 1998.

[14] Y. Jang, L. W. Poon, and P. Martin, "Individual differences in the effects of disease and disability on depressive symptoms: the role of age and subjective health," *International Journal of Aging and Human Development*, vol. 59, no. 2, pp. 125–137, 2004.

[15] M. E. Quinn, M. A. Johnson, L. W. Poon, and P. Martin, "Psychosocial correlates of subjective health in sexagenarians, octogenarians, and centenarians," *Issues in Mental Health Nursing*, vol. 20, no. 2, pp. 151–171, 1999.

[16] Y. Gondo, N. Hirose, Y. Arai et al., "Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity," *Journals of Gerontology. Series A*, vol. 61, no. 3, pp. 305–310, 2006.

[17] M. Takayama, N. Hirose, Y. Arai et al., "Morbidity of Tokyo-area centenarians and its relationship to functional status," *Journals of Gerontology. Series A*, vol. 62, no. 7, pp. 774–782, 2007.

[18] K. Andersen-Ranberg, L. Vasegaard, and B. Jeune, "Dementia is not inevitable: a population-based study of Danish centenarians," *Journals of Gerontology. Series B*, vol. 56, no. 3, pp. P152–P159, 2001.

[19] J. Evert, E. Lawler, H. Bogan, and T. Perls, "Morbidity profiles of centenarians: survivors, delayers, and escapers," *Journals of Gerontology. Series A*, vol. 58, no. 3, pp. 232–237, 2003.

[20] J. T. Newsom, T. L. Mahan, K. S. Rook, and N. Krause, "Stable negative social exchanges and health," *Health Psychology*, vol. 27, no. 1, pp. 78–86, 2008.

[21] E. L. Idler and Y. Benyamini, "Self-rated health and mortality: a review of twenty-seven community studies," *Journal of Health and Social Behavior*, vol. 38, no. 1, pp. 21–37, 1997.

[22] Y. Lee, "The predictive value of self assessed general, physical, and mental health on functional decline and mortality in older adults," *Journal of Epidemiology and Community Health*, vol. 54, no. 2, pp. 123–129, 2000.

[23] G. Liu and Z. Zhang, "Sociodemographic differentials of the self-rated health of the oldest-old Chinese," *Population Research and Policy Review*, vol. 23, no. 2, pp. 117–133, 2004.

[24] L. W. Poon, G. M. Clayton, P. Martin, et al., "The Georgia centenarian study," in *The Georgia Centenarian Study: A Special Issue of the International Journal of Aging and Human Development*, L. W. Poon, Ed., vol. 34, pp. 1–18, Baywood Publishing, Amityville, NY, USA, 1992.

[25] B. E. Fries, J. N. Morris, K. A. Skarupski et al., "Accelerated dysfunction among the very oldest-old in nursing homes,"

Journals of Gerontology. Series A, vol. 55, no. 6, pp. M336–M341, 2000.

[26] E. L. Idler, "Age differences in self-assessments of health: age changes, cohort differences, or survivorship?" *Journals of Gerontology*, vol. 48, no. 6, pp. S289–S300, 1993.

[27] World Health Organization, "World Health Organization constitution," in *Basic documents*, World Health Organization, Geneva, Switzerland, 1948.

[28] A. J. Bishop, P. Martin, and L. Poon, "Happiness and congruence in older adulthood: a structural model of life satisfaction," *Aging and Mental Health*, vol. 10, no. 5, pp. 445–453, 2006.

[29] D. Jopp and C. Rott, "Adaptation in very old age: exploring the role of resources, beliefs, and attitudes for centenarians' happiness," *Psychology and Aging*, vol. 21, no. 2, pp. 266–280, 2006.

[30] D. Jopp, C. Rott, and F. Oswald, "Valuation of life in old and very old age: the role of sociodemographic, social, and health resources for positive adaptation," *Gerontologist*, vol. 48, no. 5, pp. 646–658, 2008.

[31] A. M. Bernstein, B. J. Willcox, H. Tamaki et al., "First autopsy study of an Okinawan centenarian: absence of many age-related diseases," *Journals of Gerontology. Series A*, vol. 59, no. 11, pp. 1195–1199, 2004.

[32] D. F. Terry, V. G. Nolan, S. L. Andersen, T. T. Perls, and R. Cawthon, "Association of longer telomeres with better health in centenarians," *Journals of Gerontology. Series A*, vol. 63, no. 8, pp. 809–812, 2008.

[33] M. J. Power, "Quality of life," in *Positive Psychological Assessment: A Handbook of Models and Measure*, S. J. Lopez and C. R. Snyder, Eds., pp. 427–439, American Psychological Association, Washington, DC, USA, 2003.

[34] C. Ryff, "Happiness is everything, or is it? Explorations on the meaning of psychological well-being," *Journal of Personality and Social Psychology*, vol. 57, pp. 1069–1081, 1989.

[35] D. M. Haybron, "Philosophy and the science of subjective well-being," in *Science of Subjective Well-Being*, M. Eid and R. J. Larsen, Eds., pp. 17–43, Guilford Press, New York, NY, USA, 2008.

[36] E. Diener and R. Biswas-Diener, *Happiness: Unlocking the Mysteries of Psychological Wealth*, Blackwell, Malden, Mass, USA, 2008.

[37] S. Hill and D. M. Buss, "Evolution and subjective well-being," in *Science of Subjective Well-Being*, M. Eid and R. J. Larsen, Eds., pp. 62–79, Guilford Press, New York, NY, USA, 2008.

[38] P. Martin, A. Bishop, L. Poon, and M. A. Johnson, "Influence of personality and health behaviors on fatigue in late and very late life," *Journals of Gerontology. Series B*, vol. 61, no. 3, pp. P161–P166, 2006.

[39] A. J. Bishop, P. Martin, M. MacDonald, and L. Poon, "Predicting happiness among centenarians," *Gerontology*, vol. 56, no. 1, pp. 88–92, 2010.

[40] P. Martin and M. Martin, "Proximal and distal influences on development: the model of developmental adaptation," *Developmental Review*, vol. 22, no. 1, pp. 78–96, 2002.

[41] C. I. Cohen, J. Teresi, and D. Holmes, "Social networks, stress, and physical health: a longitudinal study of an inner-city elderly population," *Journals of Gerontology*, vol. 40, no. 4, pp. 478–486, 1985.

[42] D. B. Preston and P. K. Mansfield, "An exploration of stressful life events, illness, and coping among the rural elderly," *Gerontologist*, vol. 24, no. 5, pp. 490–494, 1984.

[43] D. L. Blackwell, M. D. Hayward, and E. M. Crimmins, "Does childhood health affect chronic morbidity in later life?" *Social Science and Medicine*, vol. 52, no. 8, pp. 1269–1284, 2001.

[44] A. M. O'Rand and J. Hamil-Luker, "Processes of cumulative adversity: childhood disadvantage and increased risk of heart attack across the life course," *Journals of Gerontology. Series B*, vol. 60, no. 2, pp. 117–124, 2005.

[45] M. McEniry, A. Palloni, A. L. Dávila, and A. G. Gurucharri, "Early life exposure to poor nutrition and infectious diseases and its effects on the health of older Puerto Rican adults," *Journals of Gerontology. Series B*, vol. 63, no. 6, pp. S337–S348, 2008.

[46] S. Fors, C. Lennartsson, and O. Lundberg, "Childhood living conditions, socioeconomic position in adulthood, and cognition in later life: exploring the associations," *The Journals of Gerontology. Series B*, vol. 64, no. 6, pp. 750–757, 2009.

[47] B. Hensley, P. Martin, M. MacDonald, and L. Poon, "Family history and adaptation among centenarians and octogenarians," *Gerontology*, vol. 56, no. 1, pp. 83–87, 2010.

[48] P. Martin, "Personality and coping among centenarians," in *Annual Review of Gerontology and Geriatrics: Biophsychosocial Approaches to Longevity*, L. W. Poon and T. Perls, Eds., pp. 129–149, Springer, New York, NY, UK, 2007.

[49] E. Samuelsson, "A population study of urinary incontinence and nocturia among women aged 20–59 years. Prevalence, well-being and wish for treatment," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 76, no. 1, pp. 74–80, 1997.

[50] P. Martin, "Individual and social resources predicting well-being and functioning in later years: conceptual models, research, and practice," *Ageing International*, vol. 27, no. 2, pp. 3–29, 2002.

[51] P. Martin, M. V. Long, and L. W. Poon, "Age changes and differences in personality traits and states of the old and very old," *Journals of Gerontology. Series B*, vol. 57, no. 2, pp. P144–P152, 2002.

[52] M. H. Silver, E. Jilinskaia, and T. T. Perls, "Cognitive functional status of age-confirmed centenarians in a population-based study," *Journals of Gerontology. Series B*, vol. 56, no. 3, pp. P134–P140, 2001.

[53] Y. Shimonaka, K. Nakazato, and A. Homma, "Personality, longevity, and successful aging among Tokyo metropolitan centenarians," *International Journal of Aging and Human Development*, vol. 42, no. 3, pp. 173–187, 1996.

[54] L. W. Poon, "Assessing neuropsychological changes in pharmacological trials," *Clinical Neuropharmacology*, vol. 16, no. 1, pp. S31–S38, 1993.

[55] L. W. Poon, T. Crook, B. J. Gurland, et al., *Handbook for Clinical Memory Assessment*, American Psychological Association, Washington, DC, USA, 1986.

[56] Y. Gondo and L. W. Poon, "Cognitive function of centenarians and its influence on longevity," in *Annual Review of Gerontology and Geriatrics: Biopsychosocial Approaches to Longevity*, L. W. Poon and T. Perls, Eds., pp. 129–149, Springer, New York, NY, USA, 2007.

[57] J. A. Margrett, B. T. Mast, M. C. Isales, and L. W. Poon, "Cognitive functioning and vitality among the oldest old: implications for well-being," in *Understanding Well-Being in the Oldest Old*, L. W. Poon and J. Cohen-Mansfield, Eds., Cambridge University Press, Cambridge, Mass, USA, in press.

[58] P. A. Holtsberg, L. W. Poon, C. A. Noble, and P. Martin, "Mini-Mental State Exam status of community-dwelling cognitively intact centenarians," *International Psychogeriatrics*, vol. 7, no. 3, pp. 417–427, 1995.

[59] G. V. Ostir, M. A. Raji, K. J. Ottenbacher, K. S. Markides, and J. S. Goodwin, "Cognitive function and incidence of stroke in older Mexican Americans," *Journals of Gerontology. Series A*, vol. 58, no. 6, pp. 531–535, 2003.

[60] T. N. Tombaugh and N. J. McIntyre, "The Mini-Mental State Examination: a comprehensive review," *Journal of the American Geriatrics Society*, vol. 40, no. 9, pp. 922–935, 1992.

[61] Alzheimer's Association, "Alzheimer's Disease facts and figures," April 2007.

[62] B. L. Plassman, K. M. Langa, G. G. Fisher et al., "Prevalence of dementia in the United States: the aging, demographics, and memory study," *Neuroepidemiology*, vol. 29, no. 1-2, pp. 125–132, 2007.

[63] M. MacDonald, P. Martin, J. Margrett, and L. W. Poon, "Correspondence of perceptions about centenarians' mental health," *Aging and Mental Health*, vol. 13, no. 6, pp. 827–837, 2009.

[64] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini mental state": a practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[65] B. Reisberg, S. H. Ferris, M. J. De Leon, and T. Crook, "The global deterioration scale for assessment of primary degenerative dementia," *American Journal of Psychiatry*, vol. 139, no. 9, pp. 1136–1139, 1982.

[66] B. Reisberg, S. H. Ferris, M. J. De Leon, and T. Crook, "Global Deterioration Scale (GDS)," *Psychopharmacology Bulletin*, vol. 24, no. 4, pp. 661–663, 1988.

[67] J. Saxton, K. L. McGonigle-Gibson, A. A. Swihart, V. J. Miller, and F. Boller, "Assessment of the severely impaired patient: description and validation of a new neuropsychological test battery," *Psychological Assessment*, vol. 2, no. 3, pp. 298–303, 1990.

[68] J. Grigsby, K. Kaye, and L. J. Robbins, "Reliabilities, norms and factor structure of the Behavioral Dyscontrol Scale," *Perceptual and Motor Skills*, vol. 74, no. 3, pp. 883–892, 1992.

[69] A. L. Benton and K. des Hamsher, *Multilingual Aphasia Examination*, AJA Associates, Iowa City, Iowa, USA, 1983.

[70] P. A. Fuld, *The Fuld Object Memory Test*, Stoelting Instrument, Chicago, Ill, USA, 1981.

[71] D. Wechsler, *WAIS-III/WMS-III Technical Manual*, Psychological Corporation, San Antonio, Tex, USA, 1997.

[72] C. M. de Frias, M. Lövdén, U. Lindenberger, and L.-G. Nilsson, "Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data," *Intelligence*, vol. 35, no. 4, pp. 381–392, 2007.

[73] L. S. Miller, M. Mitchell, J. Woodard, A. Davey, P. Martin, and L. Poon, "Cognitive performance in the oldest old: norms from the Georgia Centenarian Study," *Aging, Neuropsychology and Cognition*, vol. 17, no. 5, pp. 575–590, 2010.

[74] G. G. Fillenbaum, *Multidimensional Functional Assessment of Older Adults: The Duke Older Americans Resources and Services Procedures*, Lawrence Erlbaum Associates, Hillsdale, NJ, USA, 1988.

[75] C. E. Cutrona and D. Russell, "The provisions of social relationships and adaptation to stress," in *Advances in Personal Relationships*, W. H. Jones and D. Perlman, Eds., vol. 1, pp. 37–67, JAI Press, Greenwich, Conn, USA, 1987.

[76] S. Homma, N. Hirose, T. Inagaki, M. Suzuki, and Y. Wakida, "Lifestyle, familial history and social background of Japanese centenarians," in *Japanese Centenarians*, H. Tauch, T. Sato, and T. Watanabe, Eds., pp. 20–35, Institute for Medical Science of Aging, Aichi, Japan, 1999.

[77] P. Martin, L. W. Poon, E. Kim, and M. A. Johnson, "Social and psychological resources in the oldest old," *Experimental Aging Research*, vol. 22, no. 2, pp. 121–139, 1996.

[78] M. A. Goetting, P. Martin, L. W. Poon, and M. A. Johnson, "The economic well-being of community-dwelling centenarians," *Journal of Aging Studies*, vol. 10, no. 1, pp. 43–55, 1996.

[79] M. D. Buono, O. Urciuoli, and D. De Leo, "Quality of life and longevity: a study of centenarians," *Age and Ageing*, vol. 27, no. 2, pp. 207–216, 1998.

[80] G. K. Randall, P. Martin, M. McDonald, and L. W. Poon, "Social resources and longevity: findings from the Georgia centenarian study," *Gerontology*, vol. 56, no. 1, pp. 106–111, 2010.

[81] M. MacDonald, A. Aneja, P. Martin, J. Margrett, and L. W. Poon, "Distal and proximal resource influences on economic dependency among the oldest old," *Gerontology*, vol. 56, no. 1, pp. 100–105, 2010.

[82] G. K. Randall, P. Martin, M. MacDonald, J. Margrett, and L. W. Poon, "Convoys in very late life," in *Proceedings of the Annual Meeting of the Gerontological Society of America*, 2009.

[83] K. B. DeSalvo, W. P. Fisher, K. Tran, N. Bloser, W. Merrill, and J. Peabody, "Assessing measurement properties of two single-item general health measures," *Quality of Life Research*, vol. 15, no. 2, pp. 191–201, 2006.

[84] M. Jylhä, S. Volpato, and J. M. Guralnik, "Self-rated health showed a graded association with frequently used biomarkers in a large population sample," *Journal of Clinical Epidemiology*, vol. 59, no. 5, pp. 465–471, 2006.

[85] J. E. Rohrer, D. C. Herman, S. P. Merry, J. M. Naessens, and M. S. Houston, "Validity of overall self-rated health as an outcome measure in small samples: a pilot study involving a case series," *Journal of Evaluation in Clinical Practice*, vol. 15, no. 2, pp. 366–369, 2009.

[86] J. A. Fleishman and S. H. Zuvekas, "Global self-rated mental health: associations with other mental health measures and with role functioning," *Medical Care*, vol. 45, no. 7, pp. 602–609, 2007.

[87] T. C. Antonucci, K. S. Birditt, and H. Akiyama, "Convoys of social relations: an interdisciplinary approach," in *Handbook of Theories of Aging*, V. L. Bengston, D. Gans, N. M. Putney, and M. Silverstein, Eds., pp. 247–260, Springer, New York, NY, USA, 2nd edition, 2009.