Demographic Research a free, expedited, online journal
of peer-reviewed research and commentary
in the population sciences published by the
Max Planck Institute for Demographic Research
Konrad-Zuse Str. 1, D-18057 Rostock · GERMANY
www.demographic-research.org

DEMOGRAPHIC RESEARCH

VOLUME 19, ARTICLE 43, PAGES 1575-1586
PUBLISHED 05 SEPTEMBER 2008
http://www.demographic-research.org/Volumes/Vol19/43/
DOI: 10.4054/DemRes.2008.19.43

Reflexion

Human biodemography: Some challenges and possibilities for aging research

Kaare Christensen

This publication is part of the proposed Special Collection "Reflections on the Future of Biodemography", edited by Erica Spotts.

Table of Contents

Demographic Research: Volume 19, Article 43
reflexion

Human biodemography: Some challenges and possibilities for aging research[1]

Kaare Christensen[2]

Abstract

This opinion report - in a series on the future of biodemography - focuses on promising areas that I think will be valuable to develop in the future in order to get a better understanding of the determinants of the health and well-being of elderly people. I discuss two major themes:

i) the benefits of strengthening the ties between biodemography and medical-clinical disciplines to better understand the link between functioning/diseases/vulnerability and mortality,
ii) the male-female health-survival paradox (i.e., males report better health than females, but encounter higher mortality at all ages), and how this paradox may shed light on fundamental aging processes.

[1] Opinion report solicited by Behavioral and Social Research (BSR) Program, National Institute on Aging in response to recommendation from National Advisory Council on Aging (NACA), BRS Report, May 2004.

[2] Professor of Epidemiology, Director of the Danish Aging Research Center and the Danish Twin Registry, University of Southern Denmark, 5000 Odense C, Denmark.

1. Introduction

The purpose of this opinion report on the future of biodemography is to outline what I consider to be promising areas of human biodemographic research that could lead to a better understanding of the determinants of the health and well-being of elderly people.

2. Strengthening the ties between biodemography and medical-clinical disciplines to better understand the link between functioning/diseases/vulnerability and mortality

While biodemography has been exceptionally successful in establishing strong ties to and collaboration with research areas as diverse as biology - especially evolutionary biology - genetics, epidemiology, and public health (Ewbank 2004; Carey and Vaupel 2005) links to the clinical sciences, in particular geriatrics, in the case of aging, and obstetrics, in the case of fertility, could be further developed. Specifically, biodemographic aging research traditionally uses mortality as outcome, but some studies also include the phenotypes that are most central to elderly people, namely physical and cognitive functioning. This is typically operationalized as ADL (activity of daily living) (Katz and Akpom 1976) and cognitive tests (such as MMSE - Mini-Mental-State-Examination) (Folstein, Folstein and McHugh 1975). These measures are known to be both valid and reliable and are by now well integrated in many biodemographic studies.

2.1 Including diseases in human biodemographic research

Diseases are occasionally included in biodemographic analyses, often in the form of cause-of-death or (number of) self-reported diseases. There is, however, considerable concern about the validity of disease assessment made this way, and collaboration with geriatrics is needed to improve this. Also conceptually, the terms "co-morbidity" and "multi-morbidity" (the latter used more in Europe) are often used interchangeably, but have different meanings. Multi-morbidity is the occurrence of several diseases in an individual, while co-morbidity denotes pre-existing diseases or conditions in reference to an index disease (e.g. diabetes (co-morbidity) will increase the mortality risk due to hip fracture (index disease)) (Yancik et al 2007).

The tradition of using number of diseases (often from a pre-existing list) as a measure of multi-morbidity has the advantage of being conceptually simple and easy to handle in statistical models, but it assumes that all the diseases on the list have the same impact and it ignores interaction and common etiologies. This is sometimes addressed by weighting and categorizations which on the other hand requires additional assumptions (Lash et al

2007). When diseases are included in the analyses it is furthermore important to be clear of the importance of the data source and its limitations (self-report, medical records, administrative data) and whether the co-morbidity/multi-morbidity is a confounder, a modifier (interactor), or an outcome in the analyses. Work is in progress to deal with these problems (Boyd et al 2007; Lash et al 2007), and the field of biodemography could clearly benefit from this development.

2.2 Including frailty/vulnerability in human biodemographic research

A concept in geriatrics receiving increasing attention is frailty - not the statistical model developed by Vaupel, Manton and Stallard (1979) - but a concept which is not equal to either ADL's or disease: a "clinical vulnerability" measure (Fried et al 2001). There is no definition of frailty that is generally agreed upon, but most definitions operationalize frailty through assessment of exhaustion, weakness, low and slow activity, and unintentional weight loss (Walston et al 2006; Strandberg and Pitkälä 2007). There is still some conceptual disagreement in frailty research: whether it is an intermediate factor between morbidity and disability, and whether it is a single syndrome or range of phenotypes related to clinical traits associated with aging (Walston et al 2006). However, when disabilities, diseases, and frailty are operationalized in field studies there is a substantial overlap, but also distinct features of the three measures of the health and functioning of the elderly. These three measures are also clearly related to "*allostatic load*" (Seeman et al 2001) - a concept developed initially as a measure of "accumulated damage", but now moving more towards a concept of physiological dysregulation.

A better understanding of these concepts and their operationalizations is needed and several initiatives funded by WHO and NIA already address this need (Gruenewald et al 2006). It will require a close collaboration with geriatricians and physiologists to integrate this new knowledge into the biodemographic framework. If better measures of the health resources, functioning, and vulnerability of the elderly can be developed, this will provide an important outcome to biodemography: not only will this hopefully lead to a better understanding of the mechanisms behind age-related loss of health and functioning, but it could also be a powerful tool in understanding mortality trajectories.

2.3 Other potentially productive research directions

A number of other promising research areas that could shed light on the link between disability/morbidity/frailty and mortality could be:

- Development of specific disability/frailty/morbidity measures, their evolutionary and theoretical background, their physiological plausibility, and their empirical as-

sociation with mortality. The latter should take into account the statistical challenges of the individual level versus the population level analyses mentioned below.
- Evolutionary perspectives. Is the "end-stage disability and frailty", which is the focus of most human research, relevant in an evolutionary perspective or should minor disabilities and frailty be considered? The justification is that in nature, and hence during evolution, such minor disabilities would be associated with very high mortality.
- Animal models of disabilities/frailty will be an important concept to develop. In particular, the use of animal models to study sex-differences in disability-mortality associations, as mentioned below.

3. The male-female health-survival paradox

In the April 8, 2006 issue of the British Medical Journal, an editorial announced: Life expectancy: Women now on top everywhere. During 2006, even in the poorest countries, women could expect to outlive men (Barford et al 2006). However, there is a remarkable discrepancy between the health and survival of men versus women: According to a recent report on health differences in 21 European countries, men rated their health better than women in all but one country, Finland, with significant differences in 13 countries (Olsen and Dahl 2007). An example: Grip strength is shown to predict disability, morbidity, and mortality in both sexes but still the mean grip strength of 80-year-old men corresponds to the mean grip strength of 45-year-old women (Frederiksen et al 2006). Generally men are stronger, report fewer diseases, and have fewer limitations in the activities of daily living at older ages. Nonetheless, female death rates are substantially lower than male rates for all age groups. That is, in terms of mortality, women are healthier than men.

Interpretation of this apparent contradiction is complicated by several factors, and a number of explanations have been proposed that are rooted in biological, social, and psychological interpretations. Among the explanations for these sex differences in health, the most commonly proposed are: biological risks, risks acquired through social roles and behaviors, illness behavior, health reporting behavior, physicians' diagnostic patterns, and differential health care access, treatment, and use (Waldron 1985, Verbrugge 1985, Preston 1976, Case and Paxson 2005).

3.1 Sex differences in morbidity

The issue of sex differences in morbidity is more complex than the pattern of sex differences in ADL and physical performance tests. The complexity is due to variations in definitions of diseases, diagnostic procedures and age-related changes in incidence rate for many diseases. For example, coronary heart disease (CHD) incidence starts rising about

10 years earlier in males than in females and is about twice as high in middle-aged men compared to women of the same age (Castelli 1988, Wingard et al 1983, Wingard et al 1989, Heart Statistics 2004), but the male excess of CHD incidence and mortality declines after sixty, and in the eighties the difference is small (Wingard et al 1989, Rich-Edwards et al 1995, Jousilahti et al 1999). Further, the severity of diseases may also interfere with female-male differences. Current literature reveals inconsistent patterns of disease severity among females and males. Thus, the excess of disease and disease severity in either males or females will depend on the illness under investigation and the procedures used to measure the severity. Studies generally show that women have a significantly higher mean number of reported symptoms for, and prevalence of, migraine and arthritis as well as other musculoskeletal and autoimmune diseases (all low mortality risk diseases), while males have an earlier and higher incidence of cardiovascular diseases (high mortality risk diseases) (Macintyre et al 1996).

3.2 Biological and behavioral explanations

Among the most prominent biological explanations are the hormonal, autoimmune and genetic explanations which suggest that biological factors unique for women can compensate for their lesser muscle strength and higher prevalence of disability compared to males. The observation that males have a rise in cardiovascular disease approximately 10 years before females combined with the known favorable effect of estrogen on serum lipids and its protective effect on brain cells and consequent prevention of degenerative processes (Austad 2006) has led to the hypothesis that estrogen is a central factor in the paradox.

The "immunocompetence" hypothesis states that increased male mortality throughout life may be caused in part by a greater susceptibility of males to infections (Owens 2002, Crimmins and Finch 2004, 2006) although today mortality due to infectious diseases is not a major cause of death in the Western world.

According to the X-chromosome hypothesis the lack of a second X chromosome in the male is associated with increased mortality. Studies of peripheral blood cells from elderly monozygotic female twins show a strong tendency for the same cell line to become predominant in two co-twins, which suggests that X-linked genetic factors influence human hematopoietic stem-cell kinetics and potentially organismal survival. The fact that females have two cell lines with different potentials could be one of the reasons why women live longer than men (Christensen et al 2000, Austad 2006).

The health-survival paradox is likely to be due to multiple causes including fundamental biological differences between the sexes such as genetic factors, immune system response, hormones and disease patterns. Behavioral differences such as risk taking or reluctance to seek and comply with medical treatment are also likely to play a role. An-

other consideration is that part of the difference could be due to bias in surveys if males are more reluctant than females to participate and/or accurately report in surveys if they have disabilities or diseases.

3.3 Potentially productive research directions

- Important research questions that need more attention to shed light on the male-female paradox of health and survival are:
- To what extent is the health-survival paradox due to the definition of health and how health is measured (disabilities vs. diseases, self-reported vs. measured vs. health care use)?
- To what extent is the health-survival paradox due to male reluctance to report diseases and to seek medical treatment?
- To what extent is the health-survival paradox due to different transition rates from an "unhealthy state" to either death or "a healthy state" for males and females? Do "unhealthy" men have higher mortality rates and is the sex difference in transition rates dependent on how "unhealthy" is defined?
- To what extent is the health-survival paradox due to fundamental biological processes which are constant across populations and can these processes be identified in animal models?

4. Methodology and design developments

In this last section I will touch upon a methodological challenge as well as an opportunity for a new research design option in aging research that takes advantage of changes in contemporary family structures.

4.1 Individual versus population differences

A striking disconnect between the trajectories of individuals and populations is seen among the oldest-old. When physical functioning is followed longitudinally in a cohort of the oldest-old, only a slight decline in the mean functioning of the entire cohort is observed. The functioning for those individuals who have survived to 100, however, has declined considerably from how they were functioning at age 92. The difference in individual-level versus cohort-level aging is due to selection, whereby the frailest individuals die first (Christensen et al. 2008). Furthermore, risk factors known to affect lifespan earlier in life seem to lose importance later in life. Better methods for getting insight into the underlying mechanisms taking the selection into account are warranted to address the question of risk factors at the highest ages. This will probably come from

the survival analysis field, but there is also a need for development of better approaches to the treatment of missing data in aging research. The longitudinal studies of aging in biodemography needed for causal inference are challenged by drop-outs due to death and "usual non-response" that is often associated with severe disease. Currently, the techniques used are (multiple) imputations, inverse probability weighting, GEE (Generalized Estimating Equations), EM Algorithms (Expectation-Maximization Algorithms), and multilevel models assuming that the missing values are "missing at random" (conditional on the last measurement)which in most cases is an assumption that is likely to be violated (Raudenbush and Chan 1993, Dufouil et al 2004, Taylor 2004). Furthermore, bio-demographic aging research meets special challenges because the number of drop-outs due to death considerably exceeds what is usually seen in other studies.

4.2 Aging studies of half-siblings and full siblings

Studies of half-siblings, full siblings, and adopted siblings have been widely used in reproductive research on adverse pregnancy outcome and early life health. In countries with population registers it is possible, on a nationwide level, to identify individuals who changed spouse or residence (or other environmental factors). This study design is particularly well suited for studying nature-nurture effects on reproductive outcomes and is named the "computerized square dance study design" (like a traditional square dance, modern life often involves more than one partner and one place) (Olsen, Schmidt and Christensen 1997).

In its simplest form, it tests whether genetic factors are important for adverse pregnancy outcomes: a risk reduction is expected after change of partner. In its more elaborate form, the design provides the opportunity to disentangle similarities due to common family environment from genetic effects (Basso, Olsen and Christensen 1999) although it will present analytical challenges such as different kin connections among half-sibs may have implications for childhood environment and that this may differ between paternal and maternal half-sibs.

Due to high divorce rates in many western countries from the 1960ies onwards the number of middle-aged individuals with siblings, half-sibs and foster sibs will increase dramatically in the coming years. The establishment of longitudinal aging studies of sib-ships will provide important leverage to the ongoing studies of aging in relatives such as twin and adoption studies. Sib-ships studies will increase the power to disentangle the effect of genes and environment in aging and especially to shed light on the effect of genes as well as early environment on the health and mortality trajectories at older ages.

5. Conclusion

Biodemography has the potential to synthesize the ever increasing amount of biological (in particular genetic) and medical data on large populations to help understand the determinants of health and well-being among elderly people. It is important that biodemography strengthens its ties with geriatrics and physiology to take advantage of the greater understanding of disability, frailty, and diseases and how they affect the well-being and survival of the elderly. The basis for the sex differences in health and survival is still poorly understood, and much is likely to be learned by biodemographic studies of why, around the globe, males have a shorter lifespan despite the fact that in nearly all countries they report a better health status than women.

6. Acknowledgments

This report was strengthened by input from Matt McGue, Anna Oksuzyan, and James W. Vaupel. I would also like to thank Erica Spotts for her editorial help.

References

Austad, S. N. (2006). Why women live longer than men: Sex differences in longevity. *Gend Med*, 3(2):79–92.

Barford, A., Dorling, D., Smith, G., and Shaw, M. (2006). Life expectancy: Women now on top everywhere. During 2006, even in the poorest countries, women can expect to outlive men. *British Medical Journal*, 332:808.

Basso, O., Olsen, J., and Christensen, K. (1999). A study of environmental, social and paternal factors in preterm delivery using sibs and half sibs. A population-based study in Denmark. *Journal of Epidemiology and Community Health*, 53:20–23.

Boyd, C. M., Weiss, C. O., Halter, J., Han, K. C., Ershler, W. B., and Fries, L. (2007). Comorbidity. Framework for evaluating disease severity measures in older adults with comorbidity. *Journal of Gerontology: Medical Sciences*, 62A(3):286–295.

Carey, J. R. and Vaupel, J. W. (2005). Biodemography. In *Handbook of Population*, pages 625–658. New York: Kluwer Academic/Plenum Publishers.

Case, A. and Paxson, C. (2005). Sex differences in morbidity and mortality. *Demography*, pages 189–214.

Castelli, W. P. (1988). Cardiovascular disease in women. *Am J Obstet Gynecol*, 158:1553–60, 1566–7.

Christensen, K., Kristiansen, M., Hagen-Larsen, H., Skytthe, A., Bathum, L., Jeune, B., Andersen-Ranberg, K., Vaupel, J. W., and Ørstavik, K. H. (2000). X-linked genetic factors regulate hematopoietic stem-cell kinetics in females. *Blood*, 95(7):2449–2451.

Christensen, K., McGue, M., Petersen, I., Jeune, B., and Vaupel, J. W. (2008). Exceptional longevity does not result in excessive levels of disability. *PNAS - Proceedings of the National Academy of Sciences*. (doi:10.1073/pnas.0804931105).

Crimmins, E. and E, F. C. (2004). Inflammatory exposure and historical changes in human life-spans. *Science*, 305(5691):1736–9.

Dufouil, C., Brayne, C., and Clayton, D. (2004). Analysis of longitudinal studies with death and drop-out: A case study. *Statistics in Medicine*, 23:2215–2226.

Ewbank, D. C. (2004). The APOE gene and differences in life expectancy in Europe. *Journal of Gerontology: Biological Sciences*, 59A(1):16–20.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state examination: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatrical Research*, 12:189–198.

Frederiksen, H., Hjelmborg, J., Mortensen, J., Mcgue, M., Vaupel, J. W., and Christensen, K. (2006). Age trajectories of grip strength: Cross-sectional and longitudinal data among 8,342 Danes aged 46 to 102. *Annals of Epidemiology*, 16(7):554–562.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., and McBurnie, M.A. for the Cardiovascular Health Study Collaborative Reseach Group (2001). Frailty in older adults: Evidence for a phenotype. *Journal of Gerontology: Medical Sciences*, 56A(3):M146–M156.

Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A., and Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *PNAS - Proceedings of the National Academy of Sciences of the USA*, 103(38):14158–14163.

Jousilahti, P., Vartiainen, E., Tuomilehto, J., and Puska, P. (1999). Sex, age, cardiovascular risk factors, and coronary heart disease: A prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*, 99(9):1165–1172.

Katz, S. and Akpom, C. A. (1976). Index of ADL. *Medical Care*, 14(5):116–118.

Lash, T. L., Mor, V., Wieland, D., Ferrucci, L., Satariano, W., and Silliman, R. A. (2007). Methodology, design and analytical techniques to address measurement of comorbid disease. *Journal of Gerontology: Medical Sciences*, 62A(3):281–285.

Macintyre, S., Hunt, K., and Sweeting, H. (1996). Sex differences in health: Are things really as simple as they seem? *Social Science & Medicine*, 42(4):617–624.

Olsen, J., Schmidt, M., and Christensen, K. (1997). Evaluation of nature-nurture impact on reproductive health using half-siblings. *Epidemiology*, 8:6–11.

Olsen, K. M. and Dahl, S. A. (2007). Health differences between European countries. *Soc Sci Med*, 64(8):1665–78.

Owens, I. P. F. (2002). Sex differences in mortality rate. *Science*, 297:2008–2009.

Preston, S. H. (1976). *Mortality pattern in national populations*. New York: Academic.

Raudenbush, S. W. and Chan, W. S. (1993). Application of a hierarchical linear model to the study of adolescent deviance in an overlapping cohort design. *J Consult Clin Psychol*, 61(6):941–951.

Rich-Edwards, J. W., Manson, J. E., Hennekens, C. H., and Buring, J. E. (1995). The primary prevention of coronary heart disease in women. *N Engl J Med*, 332(26):1758–1766.

Seeman, T. E., McEwen, B. S., Rowe, J. W., and Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *PNAS*

- *Proceedings of the National Academy of Sciences of the USA*, 98(8):4770–4775.

statistics/Hjertestatistik 2004, H. (2004). The Danish Heart Foundation and the Danish National. Institute of Public Health.

Strandberg, T. E. and Pitkälä, K. H. (2007). Frailty in elderly people. comment. *Lancet*, 369:1328–1329.

Taylor, A. (2004). The consequences of selective participation on behavioral genetic findings: Evidence from simulated and real data. *Twin Research*, 7(5):485–504.

Vaupel, J. W., Manton, K. G., and Stallard, E. (1979). The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography*, 16(3):439–454.

Verbrugge, L. M. (1985). Sex and health: An update on hypotheses and evidence. *J Health Soc Behav*, 26:156–82.

Waldron, I. (1985). What do we know about causes of sex differences in mortality? A review of the literature. *Popul Bull UN*, pages 59–76.

Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., Ershler, W. B., Harris, T., and Fried, L. P. (2006). Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology: Summary from the American Geriatrics Society/National Institute on aging research conference on frailty in older adults. *JAGS*, 54:991–1001.

Wingard, D. L., Cohn, B. A., Kaplan, G. A., Cirillo, P. M., and Cohen, R. D. (1989). Sex differentials in morbidity and mortality risk examined by age and cause in the same cohort. *Am J Epidemiol*, 130(3):601–610.

Wingard, D. L., Suarez, L., and Barrett-Connor, E. (1983). The sex differentials in mortality from all causes and ischemic heart disease. *Am. J. Epidemiol*, 117(2):165–172.

Yancik, R., Ershler, W., Satariano, W., Hazzard, W., Cohen, H. J., and Ferrucci, L. (2007). Report of the national institute on aging task force on comorbidity. *Journal of Gerontology: Medical Sciences, 2007*, 62A.