Sex Differences in Age Trajectories of Physiological Dysregulation: Inflammation, Metabolic Syndrome, and Allostatic Load

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Extended Abstract

That women live longer than men is a well-known demographic fact. Why women live longer than men is much less well understood. The male survival disadvantages at all ages have been observed across human populations and species, which has generated much of the interest in the sources of the sex differences in longevity. In addition, there appear age patterns of sex mortality differentials which are not explained at this time. That is, the sex gap in mortality is more pronounced in young adulthood (Weden and Brown 2009) and decreases in postmenopausal ages due to a faster mortality rate acceleration for women after middle age that coincide with female fecundity decline (Horiuchi 1997). Studies of cause-specific mortality have further documented that cardiovascular diseases account for the majority of the sex gap in mortality and the decline of this gap at old ages (Horiuchi 1997; Waldron 1976).

The sex differences in age- and cause-specific mortality give rise to the hypothesis that male survival disadvantage has a biological base which cannot be directly tested using mortality data alone. To further understand age variations in sex differentials in mortality, it is essential to compare age trajectories of physiological functions between males and females that may be linked to sex-specific mortality patterns (Horiuchi 1997; Manton et al. 1995). Understanding the roles of biological and social risk factors underlying sex differences in mortality requires explicit measures of biological robustness. At present they are conspicuously absent from the majority of population studies on this topic. Biomedical research shows that two major biological functions – immune and metabolic functions – exhibit marked sexual dimorphism (IOM 2001) and have profound impacts on cardiovascular disease (Finch 2007). This body of research, however, relies on animal or small clinical samples that are of limited age ranges and/or single sex. Recent estimates from population-based surveys suggest important sex differentials in several

biomarkers for cardiovascular disease and stress for older adults (Goldman et al. 2004). But there is a paucity of knowledge from large nationally representative samples of the basic distributions and patterns of variations in inflammation and metabolic disorders by both sex and age. It is unclear whether genetic, hormonal, and social behavioral influences contribute to greater male or female preponderance in these physiological risk factors and how they vary with age.

This study fills these gaps by establishing sex differences in age trajectories of inflammation and metabolic disorders at the population level through a precise characterization of the variations of the sex differences across the life course. It has been shown that the cumulative burden of physiological dysregulation indicated by the allostatic load (AL) increases with age (Crimmins et al. 2003) and strongly predicts mortality in late life (Seeman et al. 2001). We extend the analysis to include the AL to further examine sex differences in general vulnerability across multiple systems for all adult ages. Using nationally representative data on about 38,000 individuals 17 and older for whom clinical examination and laboratory tests are available from the National Health and Nutrition Examination Survey (NHANES) III (1988 – 1994) and IV (1999 – 2006), we examined sex differences and age variations in these differences in 14 markers of physiological functions essential to cardiovascular health and vitality. These include three markers of *inflammation*: serum C-reactive protein (CRP), plasma fibrinogen, and urinary albumin; eight markers of *metabolic functions*: systolic blood pressure, diastolic blood pressure, triglycerides, HDL cholesterol, fasting glucose, Body Mass Index, waist circumference, and glycosylated hemoglobin (Hb_{A1c}); and three other markers: *serum homocysteine, lung function* – peak flow, and *urinary function* – creatinine clearance. We assessed both individual markers and summary indices of *inflammation burden, metabolic syndrome* (MetS), and the *allostatic load* (AL) based on clinical definitions of high risk for these markers. We conducted

both descriptive and multivariate regression including linear, logistic, Poisson, and negative binomial regression analyses to assess the associations of sex, age, and the sex by age interaction with biological variables.

We found substantial sex differences in all individual markers and summary measures. And we found nonlinear and mostly quadratic age patterns of change in these biological variables, indicating increasing risks that level off at older ages (with the exception of HDL cholesterol and homocysteine). It is also interesting that sex differences differ in direction and magnitude depending on ages. That is, there are significant sex by age interaction effects for all variables examined. The patterns of these differences vary by biological functions. Overall, women have a 76% higher inflammation burden than men on average, but the sex gap decreases greatly in postmenopausal ages. It is notable that women show higher mean levels but slower rates of increase with age. The likelihood of experiencing the MetS is three times higher for men than women on average. But the sex gap in MetS converges and crosses over at age 75 due to a larger decrease in men than women. The results on the AL show an 8% higher AL for women than men on average and the AL increases with age more for women than men, leading to a larger female excess in postmenopusal ages that persists after adjustment of other covariates. This finding, together with that of the MetS, indicate the loss of female advantages in various biological functions at older ages that are highly consistent with the reduction of sex difference in all-cause and CVD mortality with age. Reduction of the female excess in inflammation with age, on the other hand, may be one key factor that contributes to a persistent female advantage in survival into the old age.

We found that differential exposures and vulnerabilities to social status and behaviors partially account for the sex differences in age patterns of various biological functions. We found that obesity elevates inflammation burden index more in women than men but this effect decreases in older ages. Cigarette smoking is another important inflammatory stimulus whose effect is larger in men than women. These findings in part explain the sex difference in inflammation that narrows with age. In addition, smoking increases the odds of MetS more in women than men, which in part explains the reversal in sex gap of MetS after middle age. A considerable amount of sex and age variation in most physiological parameters is unexplained by the inclusion of a host of other covariates available in the NHANES data, however. This provides a most compelling reason for more in-depth examination of the biological base for sex difference as well as additional social processes such as stressful life events, social support, and other coping resources.

This study provides population based evidence for the potential physiological pathways through which age changes in sex mortality gaps occur. It suggests that sex differences and their age variations in multiple biological systems including immune and metabolic systems likely play important roles. We discuss sex-specific biological mechanisms underlying these differences especially reproductive physiology in relation to vascular inflammatory processes, fat and energy metabolism, and rate of biological aging. We also discuss the complexity of the measurement of phenotypic frailty and limitations of cross-sectional designs and invite more in-depth investigations in future longitudinal research using a broader spectrum of markers including physiological stress markers.

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