

Sex Differentials in Biological Risk Factors for Chronic Disease: Estimates from Population-Based Surveys

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ABSTRACT

Background: In light of substantial sex differences in health outcomes, researchers need to focus on disentangling the underlying biological and social determinants. The objective of this study is to determine whether two populations that differ in many cultural and social dimensions—Taiwan and the United States—also vary with regard to sex differentials in biological markers of chronic disease.

Methods: The analysis is based on three population-based surveys that include interviews, urine and blood specimens, and physical examinations: the Social Environment and Biomarkers of Aging Study (SEBAS) in Taiwan, the Wisconsin Longitudinal Survey (WLS), and the MacArthur studies of successful aging. The outcomes comprise six indicators of cardiovascular risk (total/high-density lipoprotein [HDL] cholesterol, HDL cholesterol, systolic and diastolic blood pressure, glycosylated hemoglobin, and waist/hip ratio) and four markers of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis functioning (epinephrine, norepinephrine, cortisol, and dehydroepiandrosterone sulfate [DHEA-S]).

Results: U.S. males have significantly higher risk than females for all indicators of cardiovascular risk except glycosylated hemoglobin ($p < 0.05$). Sex differences are less consistent and smaller in Taiwan. Indicators of SNS and HPA axis functioning reveal a significant female disadvantage in both countries.

Conclusions: The analysis identifies important sex differences between Taiwan and the United States in biomarkers of cardiovascular risk that are consistent with cause of death data and may emanate from cultural and social differences between the two societies. The similarity of sex differences in SNS and HPA axis functioning across studies may reflect either stable sex differences in biological aging of these axes or commonalities in the social construction of gender-based responses to life experiences.

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INTRODUCTION

IT IS A TRUTH UNIVERSALLY ACKNOWLEDGED that age and sex are related to health. Increasingly, researchers are working to unpack the meaning of these characteristics and to disentangle the biological and social determinants of the connection. A recent report issued by the Institute of Medicine (IOM) of the National Academy of Sciences underscores the need for additional research and documentation about the extent to which mechanisms and origins of sex differences in the prevalence and severity of disease are strictly biological and how differences in exposure interact with biology to affect health outcomes.¹ Inclusion of sex as a factor in research design and analysis is important not only for knowledge about the etiology of sex differences in health and illness but also for the implementation of more effective interventions. From a policy perspective, additional information on sex-based differences is a critical component in the development of strategies for improving women's health status and healthcare.²

This paper compares data on older men and women in Taiwan and the United States, opening a window onto potential gender-related differences in biological markers related to health and well-being. Traditionally, Taiwanese culture was (and in some respects continues to be) highly patriarchal, emphasizing sex, generation, and age as fundamental bases for stratification. Women have been disadvantaged economically (with respect, for example, to their share of familial inheritance), legally, and politically.³⁻⁵ In contrast, although gender equality is not fully realized in U.S. society, it is, nevertheless, a stated normative value.

The present study focuses on 10 biological markers for which we have comparable data for middle-aged and elderly persons in Taiwan and the United States. These biomarkers come from three community-based studies that are among the few population-based surveys that contain a broad range of physiological measurements on moderate or large-sized samples. We use these data to explore whether sex differences in the biomarkers are similar in these two societies that differ in many social and cultural dimensions, including gender roles.

The biological factors comprise 6 established markers of cardiovascular risk (total/high-density lipoprotein [HDL] cholesterol, HDL chole-

sterol, systolic and diastolic blood pressure, glycosylated hemoglobin, and waist/hip ratio) and 4 markers of sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal axis (HPA) activity (epinephrine, norepinephrine, cortisol, and dehydroepiandrosterone sulfate [DHEA-S]). These biomarkers are associated with longevity as well as numerous chronic diseases and conditions, including cardiovascular disease (CVD), diabetes, cognitive impairment, and depression. They also have been linked to a variety of experiences related to the social environment—a person's relative position in social hierarchies, characteristics of an individual's social networks, and exposure to stressful situations. Particularly high (or low) levels of these biomarkers have been hypothesized to reflect cumulative wear-and-tear and possible dysregulation of the biological systems with which they are associated.⁶⁻⁸

There is extensive research documenting differences between male and female distributions of these biomarkers.⁹⁻²³ However, the vast majority of this research was carried out in North America and western Europe, so we know little about whether nonwestern populations exhibit similar patterns. Cause-specific mortality data for the United States and Taiwan suggest that sex differences in these biomarkers are likely to differ between the two populations. Specifically, although Taiwan and the United States have similar life expectancies (about 77 years in the United States and 75 in Taiwan in 1999^{24,25}), death rates from causes associated with these biomarkers reveal distinct sex differentials between countries.

For example, death rates among older men and women from ischemic heart disease and diabetes (the two causes with comparable published estimates for Taiwan and the United States) indicate that the ratios of male/female death rates reported in Taiwan are generally lower than those in the United States (Table 1). These estimates reveal a greater female disadvantage in mortality from these causes (relative to males) in Taiwan than in the United States, a finding that is consistent with the relative social disadvantage of Taiwanese females.

MATERIALS AND METHODS

Data

The data analyzed in this paper come from three distinct sources: a recent (2000) national

TABLE 1. AGE-SPECIFIC DEATH RATES FROM ISCHEMIC HEART DISEASE AND DIABETES BY SEX, TAIWAN (1996–1999) AND THE UNITED STATES (1998)

Age group	Taiwan ^a			United States		
	Male	Female	Ratio (M/F)	Male	Female	Ratio (M/F)
Ischemic heart disease (ICD-9: 410–414)						
60–64	1.01	0.40	2.53	3.42	1.38	2.48
65–69	1.68	0.78	2.14	5.37	2.38	2.26
70–74	2.47	1.50	1.65	8.50	4.24	2.01
75–79	3.81	2.82	1.35	13.05	7.31	1.79
80+	7.25	6.83	1.06	29.71	24.67	1.20
Diabetes mellitus (ICD-9: 250)						
60–64	1.30	1.24	1.05	0.55	0.44	1.24
65–69	1.90	2.42	0.78	0.82	0.66	1.23
70–74	2.62	4.04	0.65	1.19	0.99	1.20
75–79	3.79	5.85	0.65	1.62	1.38	1.18
80+	5.23	7.95	0.66	2.66	2.40	1.11

^aTaiwan rates are: (Σ deaths 1996–1999)/(the midperiod population*4), where the midperiod population is (1996 population + 1999 population)/2.

Sources:

United States death data: www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/gmwk292.htm

United States population data. Population Estimates Program, Population Division, U.S. Census Bureau, Washington, DC.

Taiwan death data: Department of Health, Taiwan, ROC. 1996, 1997, 1998, and 1999 *Republic of China Health and Vital Statistics*, Vol 2: Vital Statistics, Table 13.

Taiwan population data: Department of Health, Taiwan, ROC. 1996, 1997, 1998, and 1999 *Republic of China Health and Vital Statistics*, Vol 2: Vital Statistics, Table 2.

survey in Taiwan, the Social Environment and Biomarkers of Aging Study (SEBAS), and two surveys in the United States, the MacArthur studies of successful aging and the Wisconsin Longitudinal Survey (WLS).^{26–28} All three sources sampled a relatively broad segment of the general population within their defined age intervals and collected extensive biomedical information along with interview data. All three surveys include sample sizes larger than those typically used in clinical studies; for example, two of the three surveys comprise more than 1000 participants. The surveys have been extensively analyzed by the authors and by other researchers and have been shown to contain high-quality information.^{26–28}

Data collection in each of the three studies entailed physical assessments, 12-hour (overnight) urine collections, and blood specimens that together yielded information on the 10 biomarkers considered in the present analysis. The urine specimens provided integrated estimates of cortisol, epinephrine, and norepinephrine; results for these measures were calibrated to creatinine levels in the urine to adjust for body size. Blood samples provided estimates of DHEA-S, HDL and total cholesterol, and glycosylated hemoglobin. The physical assessments included blood pressure

readings (based on an average of two [SEBAS] or three [WLS and MacArthur]) taken with a mercury sphygmomanometer, with the respondents in a seated position, and measurement of the waist and hips.

SEBAS

The Taiwan data are based on a follow-up of the Survey of Health and Living Status of the Near Elderly and Elderly. This longitudinal survey began in 1989 with a national sample (including the institutionalized population) of 4049 persons aged ≥ 60 (the “elderly” cohort) and was extended in 1996 to include a national sample of 2462 persons aged 50–66 in 1996 (the “near elderly” cohort).^{29,30}

In 2000, a national subsample of respondents from the 1989 and 1996 waves of the Survey of Health and Living Status was selected randomly to participate in SEBAS. Respondents were interviewed in their homes between July and December 2000. On a scheduled day several weeks after the interview, participants collected 12-hour overnight urine samples, fasted overnight, and were examined by physicians in nearby hospitals the following morning. Informed consent in writ-

ing was obtained for participation in the interview and, separately, for participation in the physical examination. Respondents age ≥ 71 (in 2000) were oversampled relative to those 54–70, and urban areas were oversampled relative to rural areas.

Among the 1713 respondents selected for this study, a total of 1497 provided interviews (a response rate of 92% among survivors), and 1023 participated in the physical examination (68% of those interviewed). Among participants in the examination, compliance was extremely high. All but 10 individuals followed the urine protocol and provided sufficient volumes of blood suitable for analysis. The sample of 1013 participants with biomarker information consists of 585 men and 428 women. This atypical excess of older men relative to older women results from the substantial influx of Nationalist soldiers from Mainland China in the late 1940s.

Because the vast majority of sampled persons in SEBAS responded to the preexamination interview, the potential effects of nonparticipation in the medical examination can be assessed readily by a comparison of the characteristics of nonparticipants and participants. These comparisons reveal that although respondents $>$ age 70 were less likely than younger persons to participate, sex and various measures of socioeconomic status were not significantly related to participation. Moreover, because of higher nonparticipation rates among both the healthiest and the least healthy individuals, persons who received the medical examination reported the same general health status, on average, as those who did not. These results suggest that in the presence of controls for age, estimates derived from the biomarkers are unlikely to be seriously biased.³¹

The MacArthur studies of successful aging

The MacArthur studies of successful aging are based on a longitudinal cohort of high-functioning men and women. Subjects were subsampled in 1988 from the East Boston, MA, Durham, NC, and New Haven, CT, sites of the Established Populations for the Epidemiologic Study of the Elderly (EPESE) based on a set of criteria designed to identify those in the top third of persons aged 70–79 with respect to physical and cognitive function. Data collection took place during 1988–1989. Among the 1313 subjects who met the screening criteria, 1189 (91%) agreed to participate, and

among these, 970 (82%) consented to provide blood samples and 1019 (86%) consented to provide urine samples. In addition to this sample of high-functioning individuals, data were also collected for two comparison groups of 70–79-year-olds; 80 medium-functioning and 82 low-functioning people. Additional details of the data collection are described by Berkman et al.²⁶ and Seeman et al.³²

The WLS

The WLS is a survey of 10,317 men and women randomly selected from persons who were graduates of Wisconsin high schools in 1957. Respondents were interviewed in 1957, 1975, and 1992–1993. In 1997, additional survey data along with biological measures were obtained from a subsample of 106 men and women, then aged 58–59. Although these participants were not selected randomly, members of the subsample are characterized by levels of income and other demographic characteristics similar to those in the overall sample. Additional information about this WLS sample is provided in Singer and Ryff³³ and the WLS website.³⁴

For this analysis, the samples for these three surveys are limited to participants with measures for all 10 biomarkers: 1013 in SEBAS, 95 in WLS, and 731, 54, and 41 for the high-functioning, medium-functioning, and low-functioning groups, respectively, in the MacArthur study.

Statistical methods

As described, the three surveys are not strictly comparable with regard to their sampling designs. The Taiwan survey is based on a national sample, but the MacArthur and WLS surveys have inclusion criteria that compromise their representativeness of the general U.S. population. Consequently, we do not use statistical tests to compare results across samples; rather, we offer a heuristic assessment of differences between the Taiwanese and the American cohorts. However, we use statistical tests to compare findings by sex within each dataset, as described in more detail below.

Because of the presence of outliers for some of the biomarkers, we summarize the distributions with robust measures. In particular, for each biomarker, we present three percentile measures in Table 2: the lower quartile (the 25th percentile), the median (the 50th percentile), and the upper

TABLE 2. MEDIAN, LOWER QUARTILE (Q1), AND UPPER QUARTILE (Q3) FOR 10 BIOMARKERS, TAIWAN AND THE UNITED STATES^{a,b,c}

Biomarker	SEBAS: near elderly						SEBAS: elderly					
	Males (n = 308)			Females (n = 265)			Males (n = 277)			Females (n = 163)		
	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Indicators of cardiovascular risk												
Total cholesterol/HDL cholesterol	4.5**	3.5	5.4	4.1	3.3	5.0	4.1	3.3	5.1	4.1	3.4	4.9
HDL cholesterol (mg/dl)	44.0**	37.0	52.5	51.0	41.0	61.0	47.0	38.0	55.0	49.0	43.0	60.0
Systolic blood pressure (mm Hg)	131.5*	120.0	145.0	136.0	121.0	148.0	140.0	128.0	155.0	142.0	130.0	155.0
Diastolic blood pressure (mm Hg)	82.0	75.0	91.0	81.0	75.0	90.0	80.0	73.0	89.0	80.0	73.0	89.0
Total glycosylated hemoglobin (% of Hb)	5.4	5.1	5.7	5.4	5.1	5.9	5.3**	5.1	5.6	5.5	5.2	6.2
Waist/hip ratio	0.91**	0.87	0.94	0.83	0.80	0.87	0.90*	0.87	0.94	0.88	0.83	0.93
Indicators of SNS and HPA axis functioning												
Epinephrine ($\mu\text{g/g}$ creatinine)	2.0	1.0	3.3	2.2	0.8	3.9	2.0	0.7	3.5	2.4	0.0	4.9
Norepinephrine ($\mu\text{g/g}$ creatinine)	18.4**	14.2	23.1	22.8	18.0	28.7	18.3**	13.6	25.5	24.5	16.5	32.2
Cortisol ($\mu\text{g/g}$ creatinine)	16.4**	11.0	24.0	21.8	14.5	33.7	18.1**	12.3	27.9	22.6	14.5	37.2
DHEA-S ($\mu\text{g/dl}$)	96.8**	60.0	140.9	53.9	31.6	85.0	74.0**	46.6	106.9	46.7	24.9	75.5
WLS males (n = 52)												
WLS females (n = 43)												
Indicators of cardiovascular risk												
Total cholesterol/HDL cholesterol	4.6**	4.0	5.6	3.9	3.5	4.8	3.9	3.5	4.8	3.9	3.5	4.8
HDL cholesterol (mg/dl)	45.0**	36.0	51.0	56.0	45.0	66.0	56.0	45.0	66.0	56.0	45.0	66.0
Systolic blood pressure (mm Hg)	139.0*	124.5	148.5	133.0	125.0	144.0	133.0	125.0	144.0	133.0	125.0	144.0
Diastolic blood pressure (mm Hg)	82.0**	75.0	87.5	74.0	69.0	80.0	74.0	69.0	80.0	74.0	69.0	80.0
Total glycosylated hemoglobin (% of Hb)	5.7	5.4	6.0	5.6	5.4	6.0	5.6	5.4	6.0	5.6	5.4	6.0
Waist/hip ratio	0.94**	0.91	0.97	0.81	0.74	0.86	0.81	0.74	0.86	0.81	0.74	0.86
Indicators of SNS and HPA axis functioning												
Epinephrine ($\mu\text{g/g}$ creatinine)	2.0	1.4	2.8	2.2	1.9	3.6	2.2	1.9	3.6	2.2	1.9	3.6
Norepinephrine ($\mu\text{g/g}$ creatinine)	26.5**	20.0	30.5	32.8	29.3	46.9	32.8	29.3	46.9	32.8	29.3	46.9
Cortisol ($\mu\text{g/g}$ creatinine)	28.9	19.8	41.5	35.3	22.7	49.5	35.3	22.7	49.5	35.3	22.7	49.5
DHEA-S ($\mu\text{g/dl}$)	94.0**	60.5	134.5	43.0	33.0	82.0	43.0	33.0	82.0	43.0	33.0	82.0

(continued)

TABLE 2. (CONT'D) MEDIAN, LOWER QUARTILE (Q1), AND UPPER QUARTILE (Q3) FOR 10 BIOMARKERS, TAIWAN AND THE UNITED STATES^{a,b,c}

Biomarker	MacArthur: high						MacArthur: medium					
	Males (n = 359)			Females (n = 372)			Males (n = 23)			Females (n = 31)		
	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Indicators of cardiovascular risk												
Total cholesterol/HDL cholesterol	5.0*	4.1	6.1	4.6	3.7	5.8	5.2	3.8	6.5	4.7	3.8	5.9
HDL cholesterol (mg/dl)	40.0*	33.0	49.0	49.0	40.0	61.0	38.0	34.0	56.0	45.0	36.0	62.0
Systolic blood pressure (mm Hg)	136.7	125.3	149.3	134.7	126.0	148.7	141.3	129.3	158.0	141.3	122.0	151.3
Diastolic blood pressure (mm Hg)	77.3	70.0	84.0	76.0	70.0	82.0	84.7	76.0	90.0	77.3	70.0	86.7
Total glycosylated hemoglobin (% of Hb)	6.5	5.8	7.2	6.4	5.9	7.1	6.1	5.7	7.1	6.6	6.1	7.7
Waist/hip ratio	0.93*	0.90	0.97	0.83	0.79	0.88	0.98*	0.93	0.99	0.82	0.79	0.90
Indicators of SNS and HPA axis functioning												
Epinephrine ($\mu\text{g/g}$ creatinine)	2.9*	2.2	4.0	4.0	2.9	5.5	3.3	2.5	4.5	4.0	2.4	5.1
Norepinephrine ($\mu\text{g/g}$ creatinine)	32.9*	25.0	43.3	38.9	29.8	50.0	30.1	24.0	41.0	35.0	23.1	52.5
Cortisol ($\mu\text{g/g}$ creatinine)	15.2*	9.6	23.3	17.9	12.8	27.4	11.4	8.6	19.8	14.2	11.0	21.4
DHEA-S ($\mu\text{g/dl}$)	69.0*	45.0	108.0	50.0	31.0	75.5	39.0	17.0	100.0	38.0	16.0	56.0
MacArthur: low												
Biomarker	Males (n = 21)			Females (n = 20)								
	Median	Q1	Q3	Median	Q1	Q3						
	Median	Q1	Q3	Median	Q1	Q3						
Indicators of cardiovascular risk												
Total cholesterol/HDL cholesterol	4.6	3.7	6.9	4.4	3.6	5.9						
HDL cholesterol (mg/dl)	37.0*	32.0	49.0	48.0	38.5	63.0						
Systolic blood pressure (mm Hg)	135.3	122.7	154.7	133.3	118.0	155.3						
Diastolic blood pressure (mm Hg)	86.0	70.0	90.0	77.7	67.7	83.3						
Total glycosylated hemoglobin (% of Hb)	7.5	6.3	9.4	6.8	6.4	7.1						
Waist/hip ratio	0.95*	0.88	0.97	0.88	0.83	0.91						
Indicators of SNS and HPA axis functioning												
Epinephrine ($\mu\text{g/g}$ creatinine)	3.4	2.6	3.9	3.8	3.0	6.7						
Norepinephrine ($\mu\text{g/g}$ creatinine)	32.1	22.7	42.7	39.1	28.8	60.5						
Cortisol ($\mu\text{g/g}$ creatinine)	11.18*	9.7	23.8	17.6	10.3	28.4						
DHEA-S ($\mu\text{g/dl}$)	50.0*	36.0	80.0	24.5	5.0	39.0						

^aThe age of survey respondents are as follows: SEBAS: 54–70 (near elderly sample) and 71–91 (elderly sample); WLS: 58–59; MacArthur: 70–79.

^bThe MacArthur studies consist of three samples: high-functioning, medium-functioning, and low-functioning individuals. See text for details.

^cStatistical tests of sex differences are based on the two-sample median test.

*Gender difference is significant at $p < 0.05$.

**Gender difference is significant at $p < 0.01$.

Median values are shown in boldface.

quartile (the 75th percentile). The difference between the third and the first measures, known as the interquartile range, encompasses the central half of values for a given biomarker and provides an alternative measure of spread to the standard deviation (SD) or variance. Unlike conventional measures, such as the mean and the variance, these percentiles are generally unaffected by the presence of outliers.

These summary values are used to assess differences in biomarkers between Taiwan and the United States and differences between men and women within each country. Because the two U.S. surveys differ in age coverage, separate values from SEBAS are calculated for the two cohorts. This age division permits a more direct comparison between the older SEBAS cohort (ages ≥ 71) and MacArthur respondents and between the younger SEBAS cohort (ages 54–70) and WLS respondents. It also eliminates the need to weight the SEBAS sample by age. (We investigated the effect of the inclusion of weights for urban vs. rural residence on the estimates, but the estimates barely changed.)

Separate biomarker values are presented by sex. To assess the statistical significance of sex differences within each dataset, a nonparametric test (the two-sample median test³⁵) was performed.

The biomarkers are classified into two categories: one that comprises the 6 risk factors for cardiovascular disease and a second composed of the 4 indicators of HPA axis and SNS activity. For 8 of the 10 measures, higher values generally indicate higher risk of disease, whereas for 2 of the measures (HDL cholesterol and DHEA-S), higher values designate lower risk.

In order to facilitate comparisons by sex across the various datasets, the percentile values in Table 2 are shown graphically in Figure 1, based on a simplified form of a boxplot.³⁶ In Figure 1, the length of the vertical bar denotes the interquartile range, the upper and lower horizontal bars denote the upper and lower quartiles, respectively, and the middle bar represents the median. Because of the small sample sizes and selective nature of the MacArthur medium-functioning and low-functioning samples, we place greater emphasis on the remaining datasets in the comparisons we discuss.

RESULTS

Despite variations in sampling frames across the surveys included in this analysis, the findings (Table 2 and Fig. 1) are generally consistent across

datasets. Sex differences for the 6 cardiovascular markers reveal a male disadvantage for 5 of the measures in the United States. Results for the sixth measure, glycosylated hemoglobin, show little if any sex difference. The sex differences in Taiwan are less consistent and considerably smaller. For 3 of the measures (total/HDL cholesterol, HDL cholesterol, and waist/hip ratio), Taiwanese males are at a significantly greater risk than females among the near elderly; among the elderly, however, only the sex difference for the waist/hip ratio is significant. Even for these measures, however, the male-female differential in Taiwan is typically smaller than that in the United States. This general finding is especially apparent for the waist/hip ratio (Fig. 1A). In contrast to Taiwan, the interquartile ranges for U.S. males in 3 of the 4 datasets do not even overlap those for U.S. females. For 2 of the measures (glycosylated hemoglobin and systolic blood pressure), Taiwanese females appear to be at a disadvantage relative to men.

Unlike the cardiovascular measures, the results for the 4 indicators of SNS and HPA axis functioning reveal a fairly consistent female disadvantage in both countries (although the sex differences for epinephrine are generally not significant in either). Results from the WLS are characterized by much larger sex differences in several of these measures than those from the MacArthur studies, but some of the differences for WLS are not significant because of the relatively small sample size. The magnitude of the sex differences for Taiwan generally falls between these two sets of U.S. values.

The results also indicate that the most salient differences between the two countries pertain to the waist/hip ratio, glycosylated hemoglobin, epinephrine, norepinephrine, and blood pressure. American men have higher waist/hip ratios than their Taiwanese counterparts, and American women have somewhat lower ratios than Taiwanese women, leading to a substantially greater sex difference in this measure in the United States. American men and women generally have higher values of glycosylated hemoglobin, epinephrine, and norepinephrine than their Taiwanese counterparts. Finally, Taiwanese women have modestly higher systolic and diastolic blood pressures than American women.

DISCUSSION

The distributions of biomarkers for cardiovascular risk and HPA/SNS activity in Taiwan and

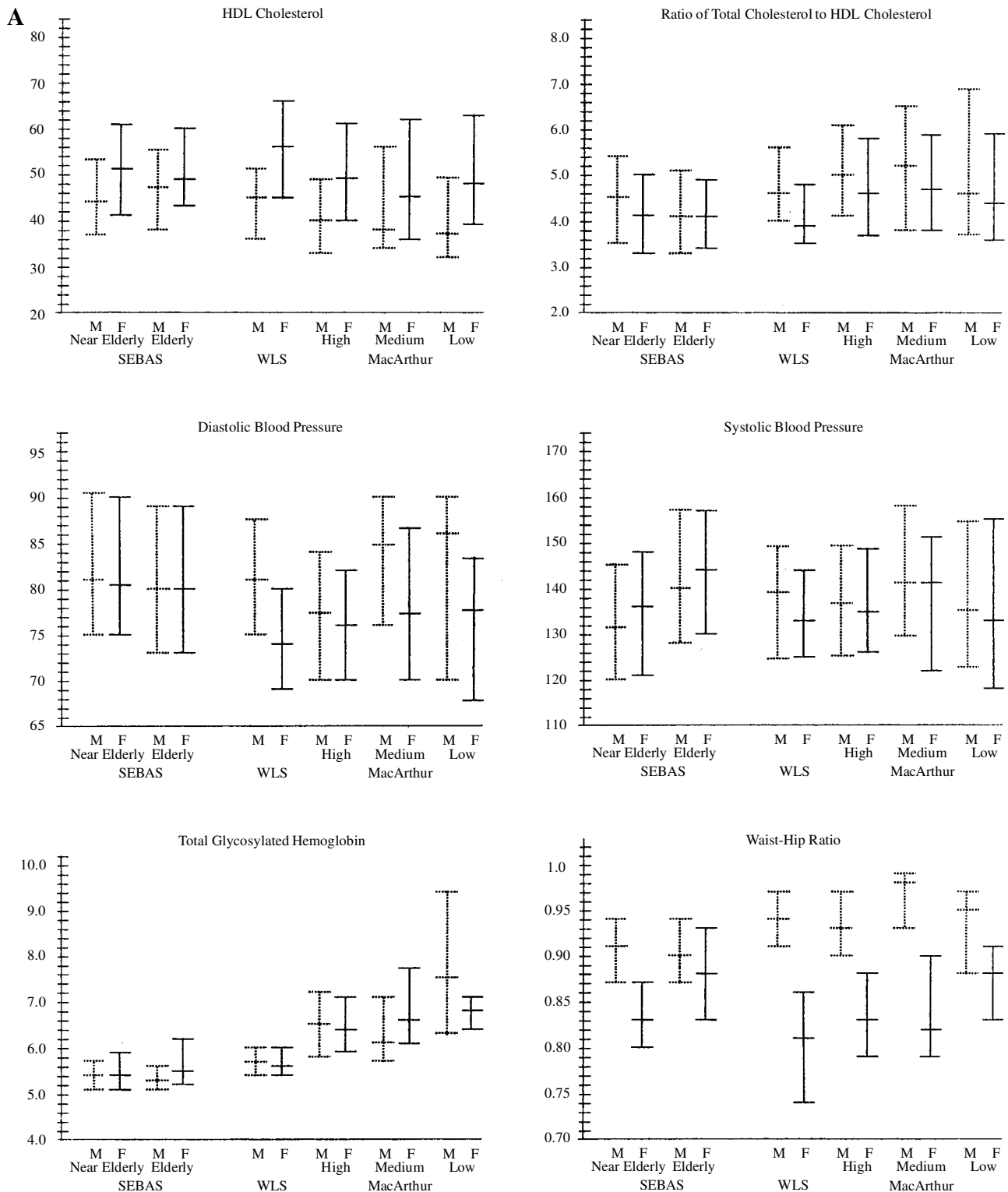


FIG. 1. (A) Gender differences in indicators of cardiovascular risk: Taiwan and the United States.

the United States reveal important sex differences between the two populations that are consistent with the cause of death data shown in Table 1. These sex differences are similar across datasets

despite variations in study designs. Most previous research on factors related to CVD in western countries show that men are at higher risk than women^{17,21} (and, at any given level of the

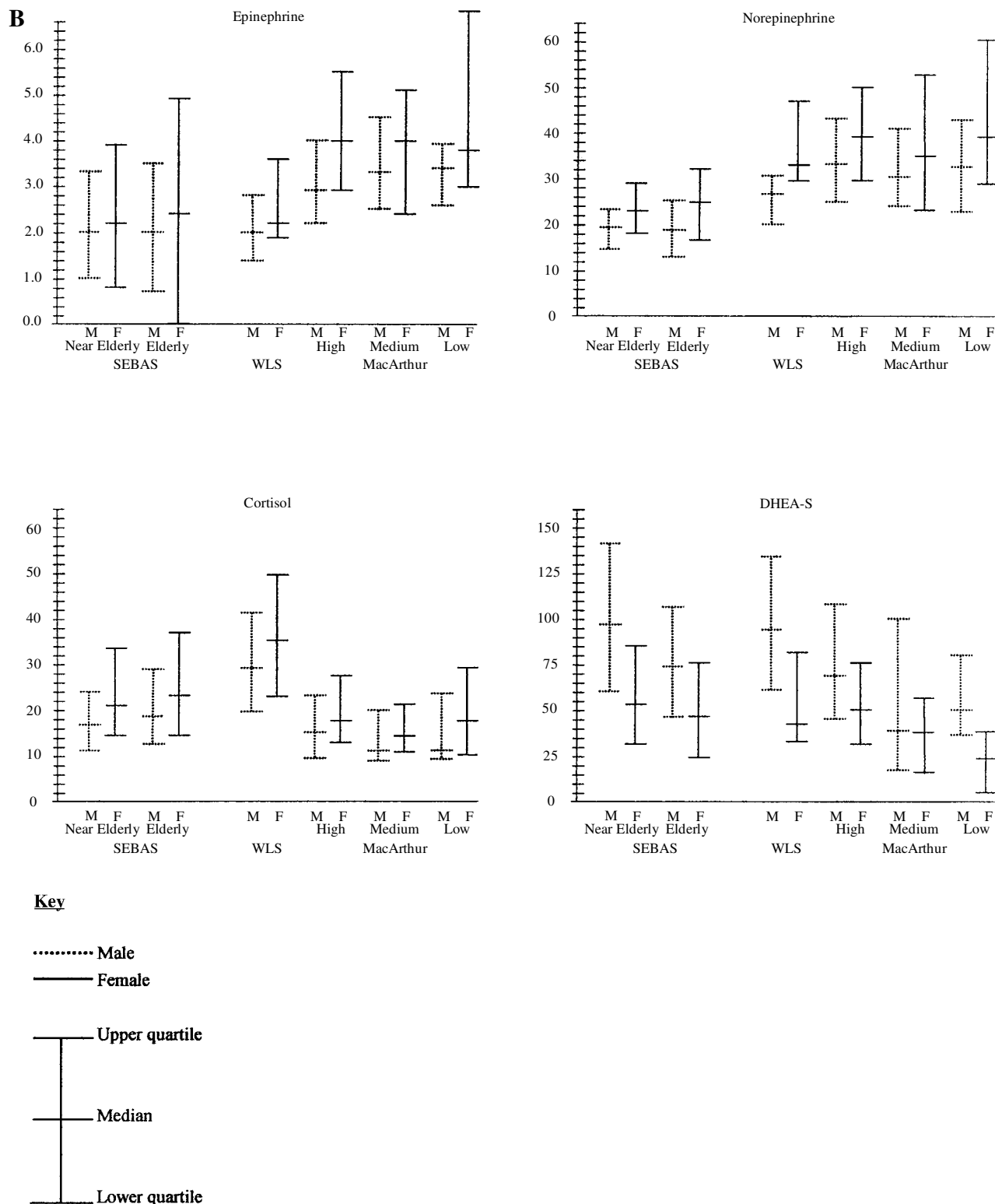


FIG. 1. (B) Gender differences in indicators of SNS and HPA axis functioning: Taiwan and the United States.

biomarker, women are at a reduced risk of adverse health outcomes^{18,19,22}). These data, however, reveal that this finding does not hold for Taiwan. Males are at a clear disadvantage with

regard to risk factors for CVD *vis-à-vis* females in the United States but not in Taiwan. The disparate findings for these two populations cast doubt on the notion of inherent fixed sex differences in

these biomarkers, suggesting instead that environmental factors, such as socioeconomic status, cultural practices, social roles, diet, and lifestyle, may either decrease levels of risk factors among Taiwanese males relative to their female counterparts (as compared with the United States) or increase the corresponding risk factors among Taiwanese females relative to their male counterparts. Nevertheless, we cannot rule out the possible role of genetic differences between these populations. One potentially informative area of future focus entails an assessment of differences in employment, occupational position, sense of control, and stress in the workplace between men and women in the two societies.

These patterns with respect to CVD are distinct from those related to SNS and HPA activity, which reveal a female disadvantage in both populations. The data on norepinephrine, epinephrine, and cortisol from each of the studies suggest that levels of SNS and HPA activity tend to be higher among women than men. The consistency of these findings across the studies suggests that this is not a culture-specific finding but rather may reflect either stable sex differences in biological aging of these axes or commonalities in the social construction of gender-based responses to life experiences. The pattern of greater female SNS and HPA activity observed in these surveys parallels evidence suggesting that women may be more reactive than men to interpersonal stress, particularly marital stress.^{37,38}

A neglected area of research is the identification of combinations of biomarkers that best predict patterns of comorbidity. In light of the fact that comorbidity is the norm rather than the exception among elderly populations in the United States,³⁹ the co-occurrence of elevated biomarkers is centrally important for understanding downstream comorbidity. For example, long-term activation of glucocorticoids, assessed here via urinary cortisol, has significant implications for the distribution of body fat,⁴⁰ suggesting the co-occurrence of elevated cortisol and waist/hip ratio. In WLS and the MacArthur aging study (data not shown), women tend to have co-occurring elevated-risk levels of pairwise combinations of cortisol, epinephrine, norepinephrine, and DHEA-S with greater frequency than men. In contrast, for the 6 cardiovascular biomarkers, men have a higher degree of co-occurrence than women. Preliminary tabulations for Taiwanese males and females suggest combinations of ele-

vated biomarkers that are similar to those in the United States. A more comprehensive analysis of sex differences in profiles of biomarkers is an important issue for future analysis with these data.

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