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

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Abstract

There is a paucity of knowledge from population data about sex differences and their age variation in physiological determinants of longevity. This study fills this gap using nationally representative samples of 38,000 individuals aged 17+ from the National Health and Nutrition Examination Survey (1988 – 2006). It examined sex differences in the age trajectories of 14 markers of physiological functions across multiple systems and three summary indices including inflammation burden, metabolic syndrome, and allostatic load. Statistical analyses show substantial sex differences, age variation, and sex by age interaction effects for all variables examined. Nonlinear and mostly quadratic age patterns of change in these biological variables indicate increasing risks that level off at older ages. Women exhibit more inflammation and allostatic load, but less metabolic disorders on average than men. The female excess in inflammation decreases in older ages. Female cardiovascular and metabolic advantages decrease and disadvantage in allostatic load increases after menopause. These patterns are highly consistent with the persistent sex difference in survival and the reduction of this difference in mortality with age. Differential exposures and vulnerabilities to social and health behaviors, especially obesity and cigarette smoking, partially account for the sex differences in age patterns of various biological functions.

Word Count: 200

That women live longer than men is a well-known demographic fact. Why women live longer than men is much less well understood. Despite much interest in the sources of the sex differences in health and longevity, a full understanding of the underlying mechanisms, particularly as they unfold with individual aging, is still lacking (1). The male survival disadvantages at all ages have been observed across human populations and even species in biodemography, population biology, and epidemiology (2-5). In addition to the overall difference in life expectancy, there appear age patterns of sex mortality differentials that remain poorly understood. Both historical and contemporary human mortality data suggest that the sex gap in mortality is more pronounced in young adulthood (6) and decreases in postmenopausal ages due to a faster mortality rate acceleration for women after middle age that coincides with female fecundity decline (7). Studies of cause-specific mortality have further documented that cardiovascular diseases (CVD) account for the majority of the sex gap in adult mortality and the decline of this gap at old ages (7-9). The sex differences in age- and cause-specific mortality suggests the hypothesis that the 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 (7, 10).

The synergies between immune functions and energy metabolism have profound impacts on CVD and other degenerative diseases and are fundamental to the biology of human longevity (11). Systemic inflammation and the metabolic syndrome (MetS) are important pathogenic mechanisms in a host of age-related conditions such as arterial disease, diabetes, and Alzhiemer's disease (11-14) and strongly predict mortality (15-17). In addition, the aging and frailty process is characterized by a progressive dysregulation of the homeostatic network and

accelerated decline in function across multiple physiological systems (18). The allostatic load (AL), a count of high risk biological parameters across systems, has been increasingly utilized as a generalized indicator of cumulative burden of physiological dysregulation (19) and has substantial explanatory power as a summary index of population frailty and predicts major health outcomes and mortality in the oldest ages (20, 21). Biomedical research documents marked sexual dimorphism across species in both immune and metabolic functions. Females in human and animals show elevated immune response and a higher incidence of autoimmune diseases (2, 22-24). Males and females also differ widely in anthropometric measures and various aspects of fat and glucose metabolism which are linked to reproductive functions (1, 25-28).

Although there are compelling theoretical explanations for the biological foundations of sex differences in immune, metabolic, and multiple physiological systems, extant empirical evidence in biomedical research mostly is based on animal or small regional clinical samples that are of single sex and/or limited age ranges. Age variations in sex differences in biological functions contribute to the complexity of explanations but have not been systematically examined or rigorously modeled in population based samples. Recently emerging population-based studies suggest substantial sex differentials in several biomarkers such as C-reactive protein (CRP) (29-32), fibrinogen (33), individual components of MetS (17, 34), glycated hemoglobin (HbA1C) (30, 34), and the AL (35). Because these studies vary widely in geographic location, sample size, demographic compositions (especially age), and statistical adjustment for covariates, it is difficult to assess the generalizability of the findings. Extant studies largely focused on individual biomarkers but not overall burden of physiological disorders. Patterns of sex differences in many of these biomeasures only pertain to older adult samples and have yet to be extended in analysis of adults of wider age ranges.

In all, there is a paucity of knowledge from large nationally representative community samples of the distributions and patterns of variations in major biological measures of inflammation, metabolic disorders, and cumulative physiological dysregulation among subgroups by sex and age within the same study population. It is unclear whether genetic and hormonal influences contribute to greater male or female preponderance in these physiological determinants of longevity and how they vary with age. In addition, few studies attempted at multivariate analysis of sex and age differences in multiple domains of biological functions with statistical adjustment for other demographic, social, behavioral, and morbidity risk factors. Recent studies increasingly point to the possibility, however, that social processes, such as socioeconomic status and social integration, strongly affect inflammatory markers (12, 32) and the AL (19, 35). It remains to be determined how changes in sex-specific exposures with age to social status, social relationships, socially learned lifestyles and behaviors may contribute to sex differences in age trajectories of biological factors.

This study fills these gaps through a precise characterization of the sex differences in inflammation, MetS, and AL across the adult life course in population data. We model both sex and age differences in these physiological variables to better understand the narrowing sex gap in mortality in post-reproductive life span. We test the hypothesis that women enjoy immunological and metabolic advantages until menopause but these advantages decrease in older ages. By examining the associations of social behavioral factors and biological parameters in the age and sex effects models, the study also sheds light on the interconnections between biological and social processes and how social conditions "get under the skin" to produce sex phenotypic differences throughout the life span.

MATERIALS AND METHODS

Study population

The data come from the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics between 1988 and 1994 (III) and 1999 – 2006 (IV) that used a multistage stratified sampling design and includes a representative cross-sectional sample of the noninstitutionalized U.S. population, with an oversample of older persons and minorities (36). This study includes about 38,000 individuals aged 17 and older for whom interview, clinical examination and laboratory tests are available. We examined 14 markers of physiological functions listed in Table 1 including three markers of inflammation, eight markers of metabolic functions, and three additional markers: serum homocysteine – an amino acid shown to be related to health and frailty (21); lung function – peak flow, and urinary function – creatinine clearance. The cutoff points for high risk levels are based on clinical practice for 11 markers and empirically defined for three (fibrinogen, peak flow, and creatinine clearance) as the top quartile at risk based on previous studies (21, 30). The assays used to measure CRP and fibrinogen differed at the two study periods (NHANES IV values are higher). The laboratory doing the assays for CRP performed an adjustment of NHANES IV values that produced highly comparable CRP values (30). We are not aware of a similar adjustment for fibrinogen, so we adopted wave-specific top quartile cutoff points. We found no difference in results using different cutoff points for CRP (3.0 mg/l and 4.0 mg/l) and the same cutoff point for fibrinogen (top quartile for NHANES III), which suggests low sensitivity of findings to the choice of cutoff points.

We constructed summary indices based on these high risk cutoff points. The burden of inflammation index is the sum of the positive indicators and ranges from 0 – 3. The MetS is

defined based on the NCEP/ATP III criteria (37) as positive for those having three or more of five metabolic disorders: abdominal obesity, high blood pressure (BP) (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg), hypertriglyceridemia, low HDL cholesterol, and high fasting glucose. The AL is a count of positive indicators of all markers. We present results using the 13-factor AL (without fibrinogen) to include all ages (additional analyses show no difference in results from those using the 14-factor AL). Sample characteristics (weighted) by age and sex are shown in Table 2. The inclusion of all individual biomarkers and other covariates largely decreases the sample sizes for the summary indices, but the combined NHANES samples provide sufficient numbers of observations for multivariate analyses.

Statistical analysis

We first conducted descriptive analyses to examine distributions of measured biological functions by sex using the *t* test and by sex and age using ANOVA and the χ^2 test. We then estimate multivariate regression models to assess the parametric relationships of sex and age with biological variables. We used log transformations of continuous outcomes to account for skewed sampling distributions. Results show improved model fit to data on all markers using the log transformation. We estimated ordinal logit and Poisson regressions for inflammation index, logistic regression models for MetS, and Poisson and negative binomial models for the AL. We used various codings of the age variable (continuous and categorical) and tested for its polynomial functional forms. We chose the best model specifications based on tests of statistical significance of coefficient estimates and model fit statistics using BIC. We further examined social, behavioral, and morbidity factors in relation to summary biological variables to understand how they may account for sex and age differences observed. All statistical analyses

were performed using Stata 10.0 and adjusted for the complex survey designs using sampling weights for descriptive analysis and the **svy** procedures for the regression analysis.

RESULTS

Individual biological parameters

Sex differences in individual markers are highly significant for all ages (Table 1) and within age groups. Figure 1 presents the observed data together with smoothed age curves from the best fitting models using polynomials of continuous age variable (e.g., age, age^2, age^3, etc.), sex, and their interactions. The regression coefficients for these effects (not shown) are all highly significant and do not differ significantly by wave.

Inflammation increases sharply with age, but the nonlinear age patterns are somewhat different for the three markers examined (Panel A). While levels of CRP decrease at older ages and those of albumin increase (less inflammation) after age 50, increases in levels of fibrinogen appear continuous. The sex differentials in inflammation converge or cross over with age. Women have higher levels of CRP and fibrinogen at most ages, but these excesses largely decrease or disappear at older ages. In contrast, women have higher levels of albumin (less inflammation) before age 40 but lower levels afterwards. Six out of eight metabolic factors show increases and then decreases with age (Panel B). Women show lower levels and hence advantages in all individual metabolic functions except BMI at most ages. These differences largely decrease at older ages. The other three markers of physiological functions all show large deterioration with age and persistent female disadvantages at all ages (Panel C). While the sex gap decreases at older ages for homocysteine and max flow, it increases for creatinine clearance.

Results are similar using logistic regressions of high risk biological variables and after adjusting for other covariates.

Summary indices of physiological dysregulation

Table 3 presents the model estimates for age, sex, and age by sex interaction effects from the ordinal logit regressions of the inflammation index, the logistic regressions of the MetS, and the negative binomial regressions of the AL. The regression coefficients of age and sex variables do not differ significantly between waves, so these models are based on the pooled samples adjusting for wave difference in the mean. There are significant quadratic age effects for all three indices suggesting increases in physiological disorders with age that decelerate at older ages. Model 1a shows that women have an about 76%-higher inflammation burden than men on average (P<0.001), but the sex gap decreases with age (P<0.001). Adjusting for other factors, obesity is associated with substantially more inflammation (Odds Ratio (OR) = 7.0, 95% Confidence Interval (CI): 3.2, 15.5, P<0.001), and the increase is much greater in women than man (P=0.003 for the sex by obesity interaction) and for younger than older ages (P=0.008 for the age by obesity interaction), as illustrated by the adjusted age curves in Figure 2A. In addition, cigarette smoking is also associated with an elevated inflammation burden (OR = 1.3, 95% CI: 0.5, 3.2) and this effect is significantly larger for men than women (P<0.001 for the sex by smoking interaction) such that the age curves of the inflammation index by sex converge much earlier and cross over among current smokers (Figure 2B). Model 1b shows that adjusting for other covariates slightly reduced the age, sex, and age by sex interaction effects in magnitude and/or significance level, but the overall results remain robust.

Model 2a shows that the odds of experiencing the MetS are more than three times higher for men than women on average ($P<0.001$), but this difference decreases with age ($P<0.001$). The results hold and become stronger in Model 2b with adjustment of covariates. Figure 3 further suggests that adjusting for other factors, the sex gap in the probability of MetS converges and reverses later in life at different ages depending on smoking status. Current smokers are more likely to exhibit the MetS on average (OR = 2.5, 95% CI: 1.4, 4.6, $P=0.003$), but the detrimental effect of smoking is more pronounced in women than men ($P<0.001$ for the sex by smoking interaction) and younger than older ages ($P=0.023$ for the age by smoking interaction) so that the female advantage in metabolic functions before menopause is much smaller for current smokers than non-smokers.

Model 3a shows that women appear to have an 8%-higher AL than men on average ($P<0.001$). The sex difference decreases somewhat after adjusting for other covariates (Model 3b). Although the sex by age interaction effect is not statistically significant in this model of continuous age effects, it is highly significant in the model using a dichotomous age variable (age < 60 vs. 60+), suggesting a widening sex gap in persons aged 60 and older ($P=0.008$). Figure 4 further compares the adjusted means by sex and age groups. It shows that the AL increases with age more for women than men, leading to a larger female excess in postmenopausal ages that persists after adjustment of other covariates ($P=0.025$).

DISCUSSION

This study provides population based evidence for important sex differences in physiological determinants of longevity including markers of immune and metabolic systems and cumulative burden of physiological dysregulation. The study found nonlinear and mostly

quadratic age patterns of change in these biological variables, indicating increasing risks that level off at older ages with a few exceptions. Sex differences vary in direction and magnitude depending on ages. That is, there are strong and significant sex by age interaction effects for all biomarkers and indices examined. Excluding persons with CRP levels>10 mg/l (indicating acute infections) and controlling for the effect of estrogen medications in women did not change the results. The patterns of these differences vary by biological functions and adjustment of social, behavioral, and morbidity risk factors.

Women show higher mean levels of inflammatory markers and the overall burden but slower rates of increase in inflammation with age. This suggests the complicated nature of the interaction of sex-specific reproductive anatomy and functions with vascular inflammatory processes. The female sex hormone estrogen has been hypothesized to have a protective anti-inflammatory effect that may improve host resistance to degenerative diseases (28). It has also been proposed that endogenous estrogens may reduce the risk of CVD in females by modulation of the fibrinolytic factors much more than by affecting the levels of inflammatory markers or coagulation factors (28). The female reproductive senescence due to the exhaustion of ovarian oocytes and ovarian steroid loss may interact with these processes and contribute to the age changes in inflammation. The higher inflammation but lower risk of CVD in women than men also seems to suggest the use of sex-specific high risk cutoff points for inflammatory markers in future research (29, 31).

There are large male excesses in a host of metabolic disorders and the overall MetS that disappear in late life. Recent research points to the importance of long-lasting effects of female sex hormone changes. Fluctuations in estrogens especially in 17β-estradiol (E2) during the menstrual cycle and pregnancy induce endocrine and vascular challenges in women that decrease

vascular resistance and arterial blood pressure, increase cardiac output by as much as 40%, and create optimal cardiovascular compliance comparable to the effects of exercise and even the circulatory efforts of athletes (28). The "jogging female heart" may thus protect women against CVD risks during reproductive years. Post-menopausal increase in these risks in women then follow their physiological changes with age as a result of reductions of estrogen and increased fat storage and deposition of fat in abdominal areas.

Women exhibit a higher cumulative burden of physiological dysregulation across multiple systems indicated by the AL than men. While such difference is small before menopause, it grows larger afterwards. The relationship between the AL and age can be used to characterize the rate of biological aging (20). A faster rate of increase in the AL with age in women compared with men indicates the lack of a female biological aging superiority. In fact, 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. 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. We examined additional

covariates, some of which are only available in the NHANES III, including health insurance, ties with friends and family relatives, religious attendance, membership in social organizations, physical activity, and diet and nutrition. Only religious attendance is significantly related to physiological functions adjusting for all other factors. In particular, lack of religious attendance is associated with more inflammation and MetS in men than women but more AL in women than men and these effects are restricted to ages 60+. A considerable amount of sex and age variation in most physiological parameters is unexplained by the inclusion of the above factors, however. This provides a most compelling reason for more in-depth examination of the biological base for sex difference as well as additional social psychological processes such as stressful life events, social support, and other coping resources.

This study is based on cross-sectional data as prospective data containing multiple biomeasures are rare. The age trajectories revealed here then represent the distributions by age of the surviving population from cohorts born earlier. The mortality risk and hence force of selection with respect to physiological status is greater with the increase of age. Therefore, the acceleration of physiological dysregulation with age is reduced by selective survival. This is particularly relevant in the case of male smokers who exhibited lower predicted probability of MetS than nonsmokers (Figure 3). Selective survival is not the only explanation, however, because the age patterns vary by physiological measures and adjustment of other risk factors. To the extent that selection decreases population heterogeneity later in life and slows down the age increase in frailty for all groups, one should observe 1) smaller gaps in men and women and 2) similar downward age patterns in both. The first is not observed in findings of the AL and the second is not observed in findings of MetS. Nonetheless, collection and analysis of longitudinal data on biomarkers should be a priority for future research because they would facilitate the test

of selection effect and produce estimates of within-cohort age trajectories that represent true developmental changes with age.

Limitations in the measurement of biological variables invite future investigations using a broader spectrum of markers. Although the NHANES is among the few national surveys that offer a wide range of indicators of biological functions, many other biomarkers are not currently included such as other proinflammatory cytokines (e.g., interleukin-6) and physiological stress responses in terms of stress hormones regulated by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. There may be sex differences in biobehavioral response to stress ("fight-or-flight" for males vs. "tend-and-befriend" for females) that have a neuroendocrine basis which may modulate risks for stress-related disorders and survival (39). Including measurement of these responses is essential to a more comprehensive characterization of sex difference in physiology in population.

This study presents some initial evidence of the potential physiological pathways through which age changes in sex mortality gaps occur. The full establishment of the links between physiological processes and sex difference in age-specific mortality at the individual level requires additional analysis of mortality follow-up data which we now are conducting.

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Table 1. Sample Size, High Risk Cutoff Point, and Weighted Descriptive Statistics of Biological Variables in NHANES (1988 - 2006)

Variable	High risk cutoff point	Men				Women				Difference
		N	Mean	Standard Deviation	% High Risk	N	Mean	Standard Deviation	% High Risk	*P* value[c]
Inflammation										
C-reactive protein (CRP)	>3.0 mg/dL	18,052	0.34	0.79	19.8	19,909	0.49	0.75	34.4	<0.001
Plasma fibrinogen	≥341/411 mg/dL[a]	7,289	340.4	85.0	21.5	7,751	355.5	85.9	29.1	<0.001
Urinary albumin	≤3.5 ug/mL	18,241	19.7	54.2	22.0	20,251	17.7	47.7	27.0	<0.001
Inflammation Index (age 40+)		6,952	0.67	0.78		7,239	0.99	0.85		<0.001
Metabolic factors										
Waist circumference	>102/88 cm[b]	18,139	98.2	15.0	36.6	19,942	92.2	16.0	55.3	<0.001
Systolic blood pressure	≥130 mm Hg	17,264	124.3	16.5	15.5	18,950	121.4	21.6	17.8	<0.001
Diastolic blood pressure	≥85 mm Hg	17,263	73.1	13.2	9.0	18,949	69.5	12.9	4.9	<0.001
Serum triglycerides	≥150 mg/dL	14,607	154.6	160.8	34.8	16,155	126.6	102.9	25.6	<0.001
HDL cholesterol	<40 mg/dL	18,026	46.9	13.3	30.2	19,845	57.3	16.1	10.7	<0.001
Fasting glucose	≥110 mg/dL	12,438	102.6	29.8	15.7	13,727	98.6	30.7	11.8	<0.001
Body Mass Index (BMI)	≥30 kg/m^2	18,883	27.6	5.6	26.9	20,935	27.8	7.0	31.3	<0.001
Glycated hemoglobin (HbA1c)	≥6.4%	18,258	5.5	0.9	6.6	20,204	5.40	0.90	5.8	0.031
Metabolic Syndrome (MetS)		9,317	0.19	0.40		10,163	0.14	0.35		<0.001
Other Physiological Functions										<0.001
Serum homocysteine	≥15 umol/L	13,099	9.4	4.2	5.0	14,882	8.0	4.1	3.8	<0.001
Peak flow (largest value)	<2113 mL	7,724	3,447.7	1,484.1	19.4	8,735	2,691.8	1,179.5	32.5	<0.001
Creatinine clearance	<66.7 mg/dL	18,484	152.6	85.6	16.0	20,401	111.2	75.8	33.8	<0.001
Allostatic Load (AL)		6,775	2.3	1.9		7,710	2.6	1.9		<0.001

[a]Top quartile high risk cutoff points for NHANES III and IV, respectively.
[b]Clinical high risk cutoff points for men and women, respectively - the clinical criteria for high risk are only sex-specific (39).
[c]Test for sex difference in the means (2-sided). Results for sex difference in the % high risk are similar.
Note: Fibrinogen was only measured for respondents aged 40 years and older. The glucose measures require fasting and have smaller samples. Homocysteine was assayed only in the second half of NHANES III (1991-1994). And peak flow was not available for NHANES IV.

Table 2. Characteristics (Weighted) of the Allostatic Load Sample[a] in NHANES (1988 - 2006)

Variable	Men			Women		
	All Ages[b] (N = 5347)	17 - 59 years (N = 3531)	60+ years (N = 1816)	All Ages[b] (N = 6253)	17 - 59 years (N = 4375)	60+ years (N = 1878)
Race (Non-black) %						
Non-Hispanic white	74.4 (43.6)	72.0 (44.9)	84.1 (36.6)	73.4 (44.2)	70.3 (45.7)	83.3 (37.3)
Non-Hispanic black	9.4 (29.3)	10.3 (30.4)	6.3 (24.4)	10.8 (31.1)	11.9 (32.4)	7.7 (26.6)
Mexican American	7.5 (26.3)	8.6 (28.0)	3.2 (17.6)	6.1 (23.8)	7.0 (25.6)	2.9 (16.8)
Other	8.6 (28.1)	9.2 (28.9)	6.4 (24.5)	9.6 (29.5)	10.8 (3.1)	6.1 (23.9)
Education %						
0 - 8 years	3.6 (18.5)	2.8 (16.4)	6.6 (24.8)	3.2 (17.6)	2.1 (14.3)	6.7 (25.0)
9 - 12 years	43.7 (49.6)	43.2 (49.5)	46.0 (49.9)	43.7 (49.6)	40.1 (49.0)	55.3 (49.7)
13 + years	52.3 (49.9)	54.1 (49.8)	47.4 (49.9)	53.1 (49.9)	57.8 (49.4)	38.0 (48.6)
Family Income (median in 1991$)	35961	37500	30283	30283	32500	22712
Marital Status %						
Married	70.1 (45.8)	67.4 (46.9)	81.0 (39.3)	62.9 (48.3)	66.3 (47.3)	52.1 (50.0)
Widowed	2.2 (14.7)	0.6 (7.5)	8.7 (28.2)	9.4 (29.2)	1.8 (13.1)	33.9 (47.4)
Divorced/Separated	9.3 (29.0)	9.6 (29.4)	8.1 (27.2)	13.9 (34.6)	15.0 (35.7)	10.3 (30.5)
Never Married	18.4 (38.7)	22.5 (41.8)	2.2 (14.8)	13.8 (34.5)	17.0 (37.6)	3.6 (18.6)
Cigarette smoking %						
Never	40.2 (49.0)	43.4 (49.6)	27.7 (44.8)	56.2 (49.6)	56.4 (49.6)	55.3 (49.7)
Former	30.2 (45.9)	23.3 (42.3)	57.4 (49.4)	21.4 (41.0)	18.1 (38.5)	32.1 (46.7)
Current	29.6 (45.6)	33.3 (47.2)	14.8 (35.5)	22.4 (41.7)	25.5 (43.6)	12.7 (33.3)
Alcohol use (mean days per month)	6.8 (9.2)	6.6 (8.7)	7.6 (10.9)	3.3 (6.6)	3.2 (6.1)	3.6 (7.9)
Number of chronic conditions[c]	0.8 (1.2)	0.7 (1.0)	1.6 (1.5)	1.0 (1.2)	0.7 (1.0)	1.8 (1.5)
Female hormone therapy %				25.3 (43.5)	18.2 (38.6)	48.3 (50.0)
Hypertension medication %	18.9 (39.1)	9.9 (29.8)	40.6 (49.1)	16.2 (36.8)	10.4 (30.6)	46.0 (50.0)
Cholesterol medication %	10.8 (31.0)	7.1 (25.6)	25.3 (43.5)	9.3 (29.0)	4.9 (21.7)	23.3 (42.2)

[a]Characteristics for the Inflammation Index and MetS samples are similar and not presented; only variables that are common across two waves are included (social integration, physical activity, diet and nutrition were included only in the analysis of NHANES III).

[b]Age ranges 20+ for NHANES III and 17+ for NHANES IV.

[c]Includes 14 self-reported chronic illnesses: angina, arthritis, asthma, bronchitis, diabetes, emphysema, heart attack, heart failure, cancer, stroke, hip fracture, osteoporosis, spine fracture, and wrist fracture.

Table 3. Estimates from Regressions of Summary Indices of Biological Dysregulation in NHANES (1988 - 2006)

	Inflammation Index (N = 6864)				MetS (N = 15143)				AL (N = 11600)			
	Model 1a		Model 1b		Model 2a		Model 2b		Model 3a		Model 3b	
Variables	Odds Ratio (95% CI)	*P* value[a]	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value
Age	2.56 (1.78, 3.68)	<0.001	2.34 (1.32, 4.16)	0.004	3.90 (3.15, 4.84)	<0.001	4.40 (3.33, 5.80)	<0.001	1.65 (1.56, 1.74)	<0.001	1.61 (1.50, 1.71)	<0.001
Age^2	0.93 (0.90, 0.96)	<0.001	0.94 (0.90, 0.98)	0.005	0.92 (0.90, 0.94)	<0.001	0.90 (0.88, 0.92)	<0.001	0.97 (0.96, 0.97)	<0.001	0.96 (0.96, 0.97)	<0.001
Sex (Male=1)	0.24 (0.15, 0.38)	<0.001	0.26 (0.12, 0.58)	0.001	4.38 (2.91, 6.59)	<0.001	9.37 (5.56, 15.80)	<0.001	0.92 (0.89, 0.95)	<0.001	0.96 (0.92, 0.99)	0.023
Sex × Age	1.13 (1.05, 1.22)	0.001	1.13 (1.01, 1.28)	0.041	0.82 (0.76, 0.88)	<0.001	0.77 (0.70, 0.84)	<0.001	0.95 (0.92, 0.99)	0.225	0.96 (0.92, 1.00)	0.156
NHANES (IV=1)	0.86 (0.79, 0.94)	0.001	0.71 (0.61, 0.84)	<0.001	1.02 (0.92, 1.13)	0.722	0.99 (0.85, 1.15)	0.891	0.87 (0.84, 0.90)	<0.001	0.88 (0.85, 0.92)	<0.001
Model Fit: BIC	33080.98		16069.39		16948.88		13150.63		56057.36		45065.12	

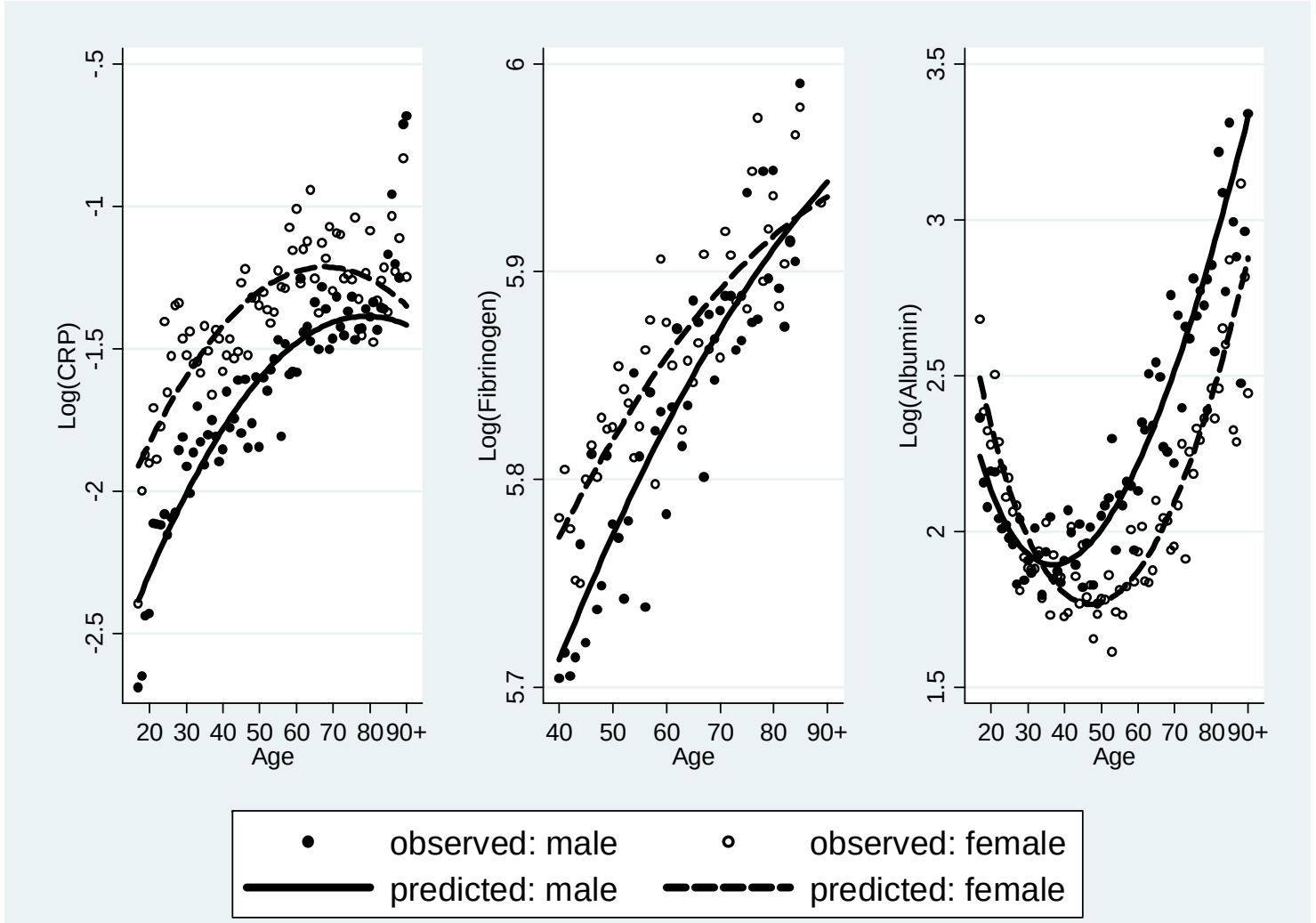
Abbreviations: CI, confidence interval.

[a]Two-sided test for all models.

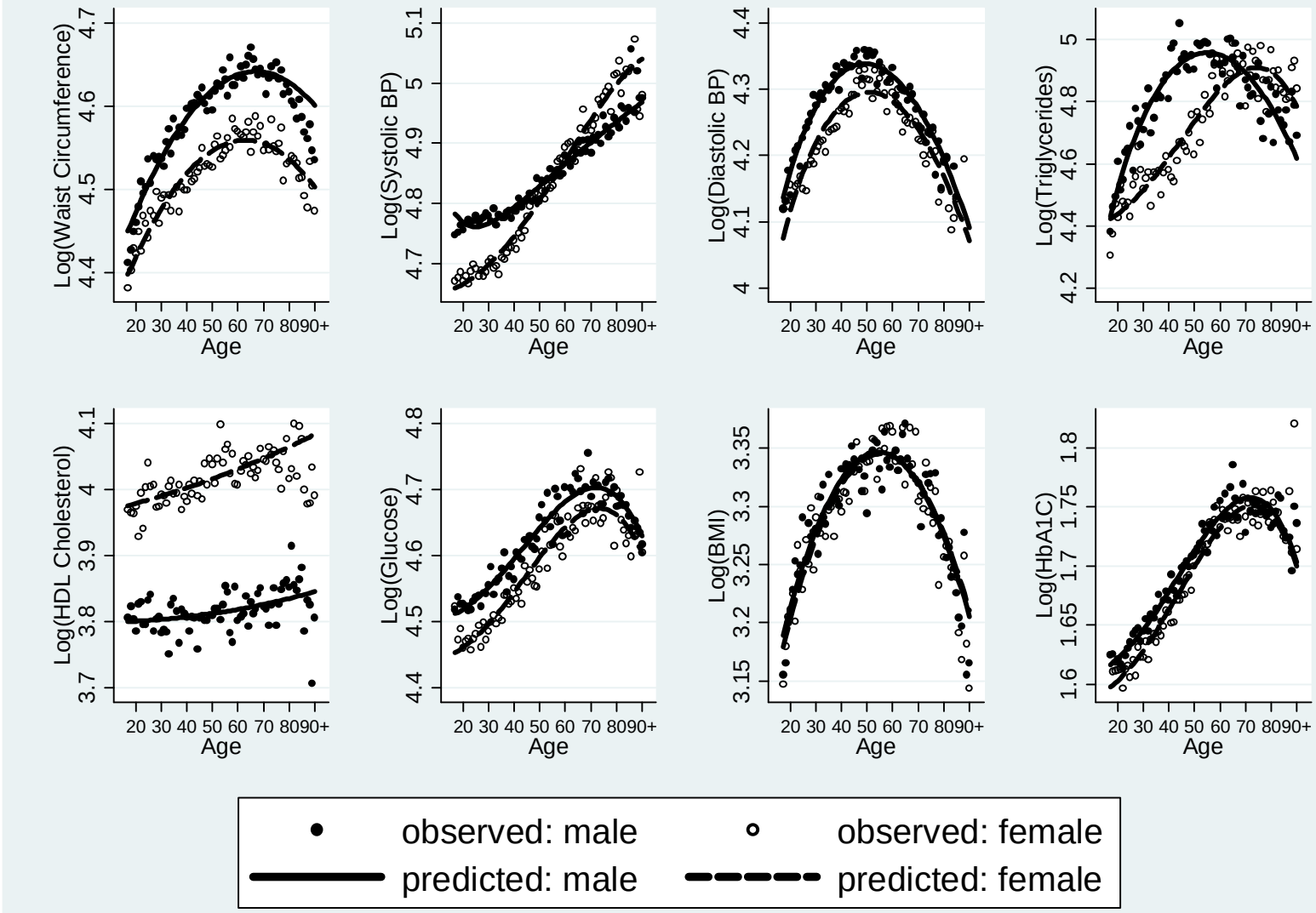
Note: Models 1b, 2b, and 3b all control for race, education, family income, marital status, cigarette smoking, alcohol use, and chronic conditions. Model 1b also controls for obesity, MetS, sex*smoking, age*smoking, sex*obesity, age*obesity. Model 2b also controls for CRP, albumin, hypertension medication, cholesterol medication, sex*smoking, age*smoking (obesity has an overwhelming influence on waist circumference and omitted from the controls; additional analysis that includes obesity as a control did not show significantly different results for age, sex, or other covariates). Model 3b also controls for hypertension medication and cholesterol medication. Female hormone use is included in sex-stratified analysis for women only. Interactions of covariates with sex and age were tested for all models but included only when statistically significant.

Figure 1. Sex Difference and Age Variation in Individual Biological Factors in NHANES (1988 - 2006)

A. Inflammatory Markers



B. Metabolic Factors



C. Other Physiological Functions

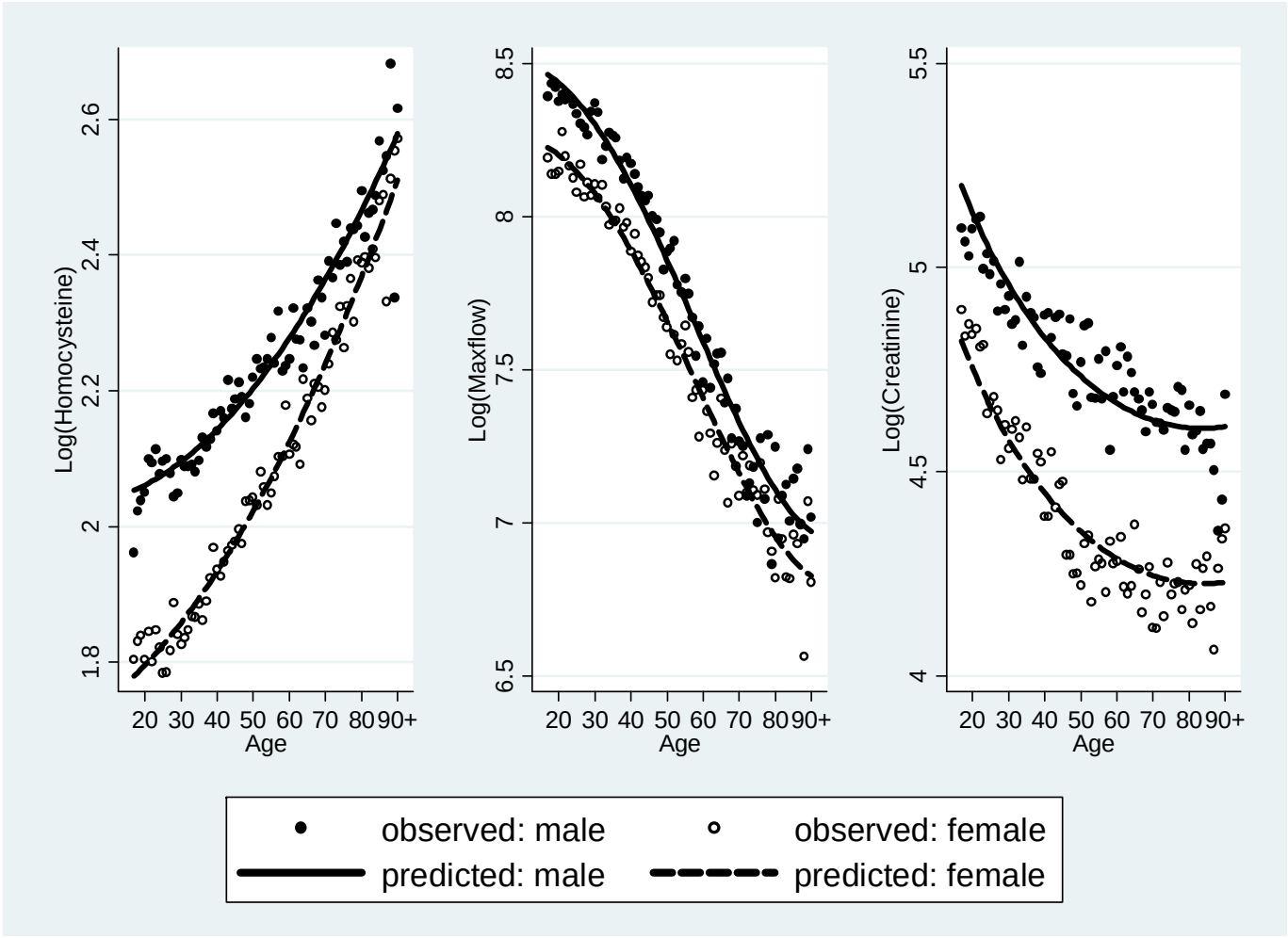
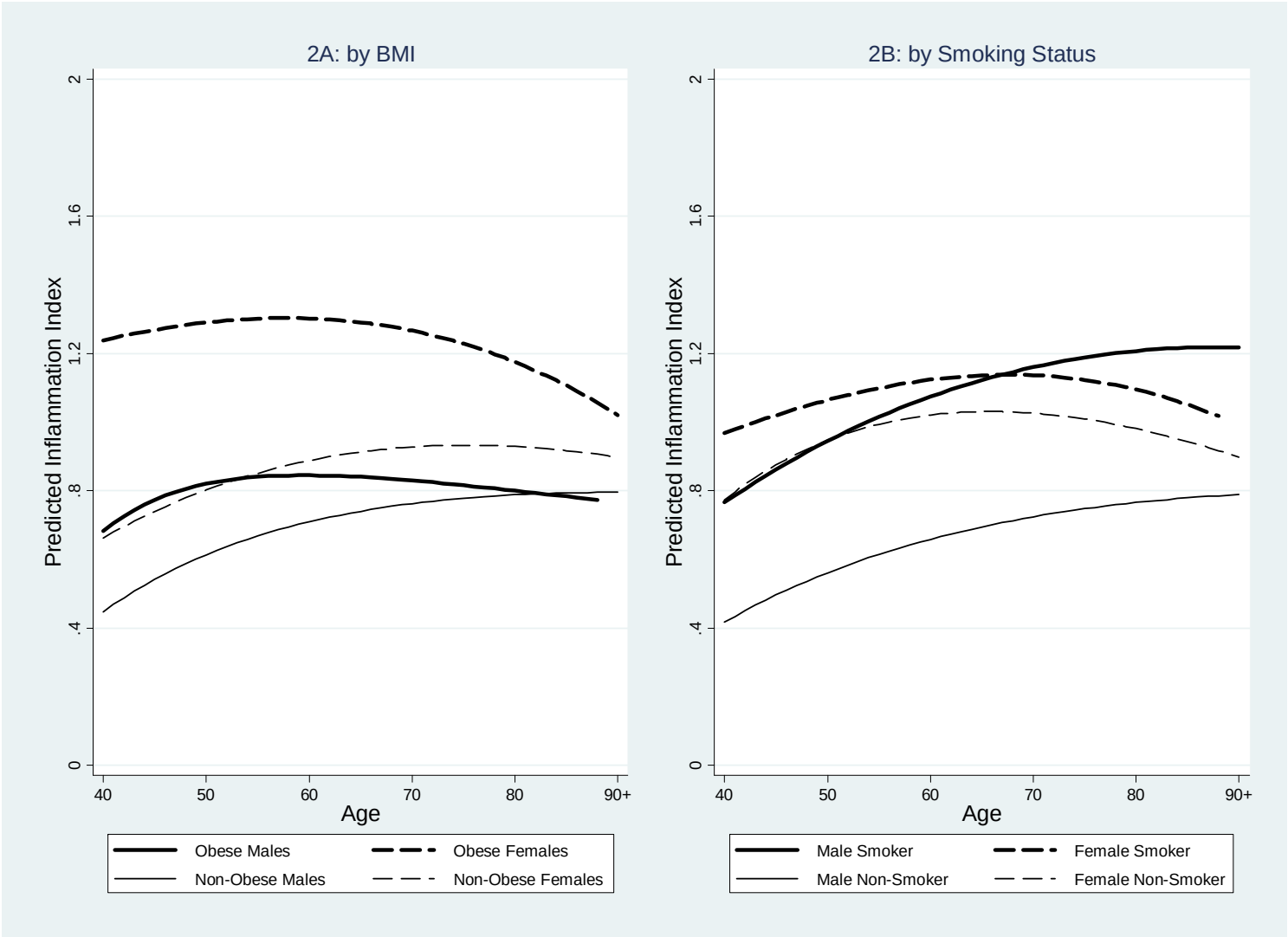
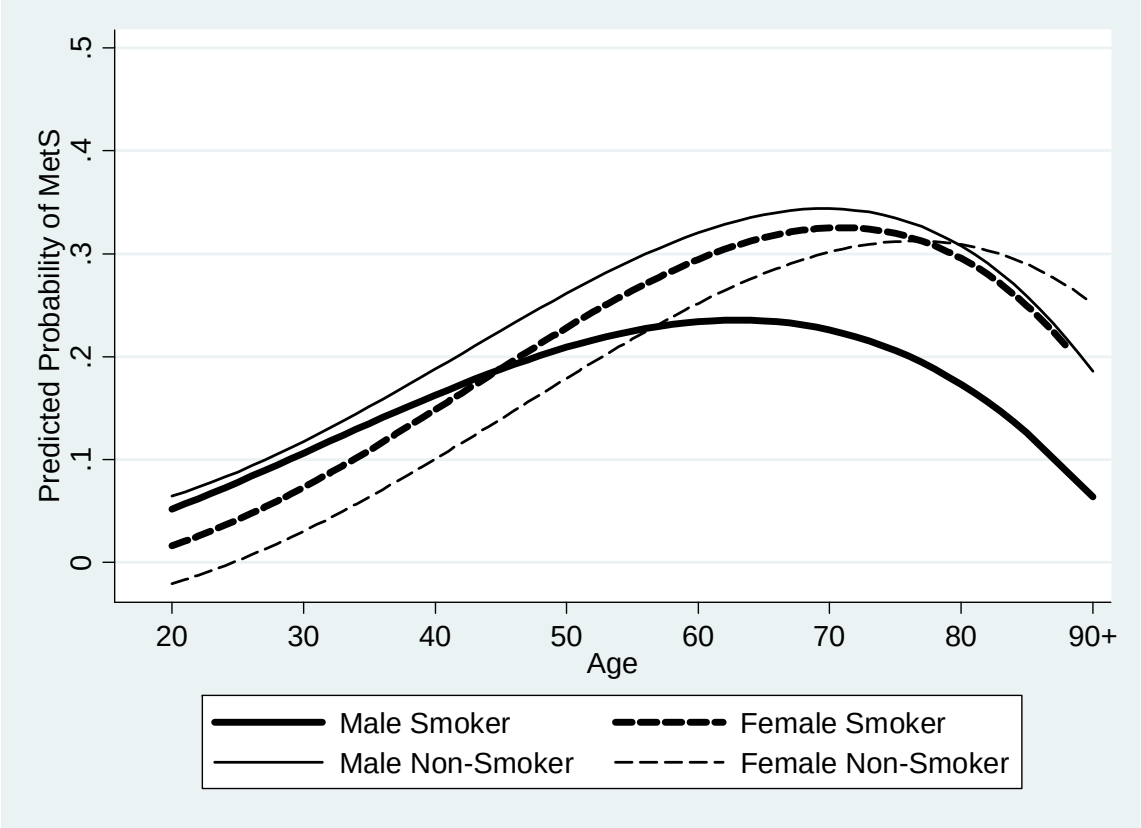


Figure 2. Sex Difference and Age Variation in Inflammation Index



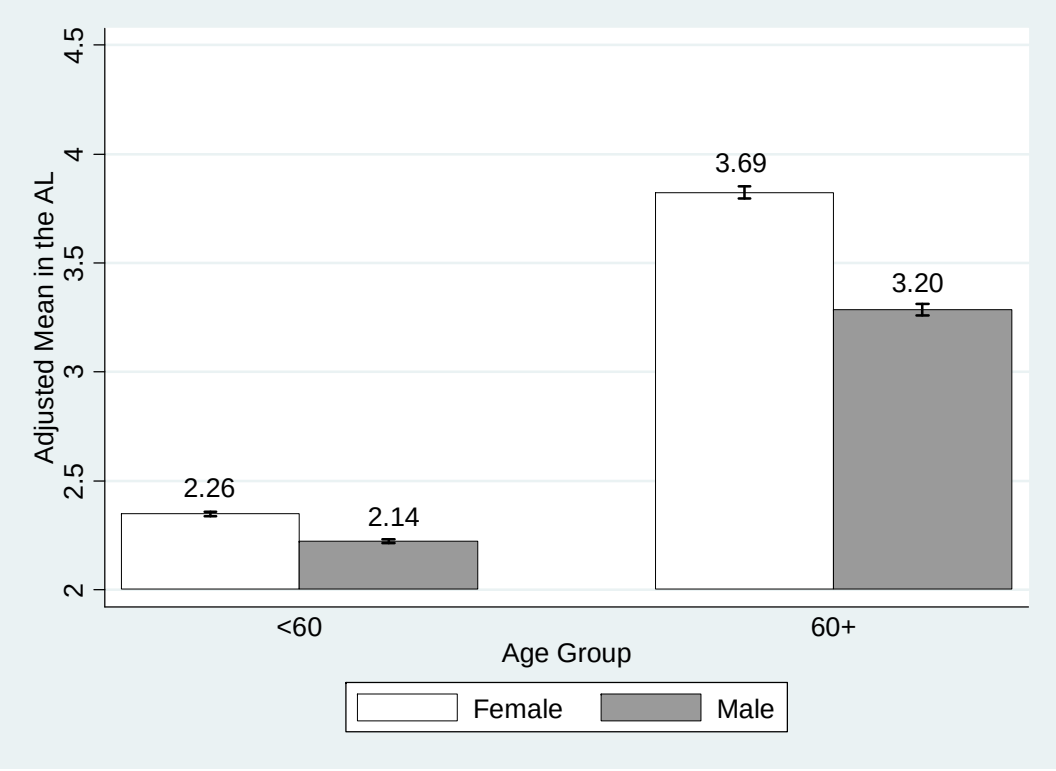
Note: Presented are predicted values from Model 1b that adjusts for all other covariates.

Figure 3. Sex Difference and Age Variation in Probability of MetS by Smoking Status



Note: Presented are predicted values from Model 2b that adjusts for all other covariates.

Figure 4. Sex Difference and Age Variation in Allostatic Load



Note: mean values adjust for all other covariates.