Is 60 the New 50?
Examining Changes in the Pace of Biological Aging

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Abstract

Historical increases in life expectancy have been taken to signify that the rate of aging may be slowing among the population (2, 3). However, mortality may not always serve as a reliable proxy for how fast an individual or population is aging on a biological level. Using nationally representative data, the goal of this paper is to examine how biological aging changed between 1988 and 2010 for U.S. males and females, while also estimating the contribution of changes in smoking, obesity, and medication use. Our analytic sample included 21,575 subjects ages 20-79 from the third and fourth waves of the National Health and Examination Survey—NHANES III (1988-1994), NHANES IV (2007-2010). Results from Ordinary Least Squares (OLS) regression models, stratified by sex and 20-year age categories, suggests that the pace of aging may have slowed for the population, however, the degree of change has not been consistent across age and sex groups. Overall, older adults experienced greater decreases in biological age than did young adults, and even at younger ages, there were difference between the sexes—with young males exhibiting larger decreases in biological age over the 20 year period compared to young females. Finally, we found that differences between the age and sex groups were partially explained by age and sex-specific changes in behaviors, such as smoking and obesity, as well as medication

Introduction

Life expectancy has been rapidly increasing over the past sixty years (1). Because mortality schedules are often used to estimate the rate of aging, researchers have taken this to signify that the pace of aging may be slowing (2, 3). However, mortality may not always serve as a reliable proxy for how fast an individual or population is aging on a biological level. For instance, medical interventions and treatments that are enacted after a diagnosis has occurred have the potential to extend lifespan while not affecting the pace of aging-related physiological decline (4). In such instances, the extra years of life gained may not be coupled with an extension of healthy lifespan or a compression of morbidity and therefore, are probably not reflective of a deceleration of the aging process (5). As a result, it may be more beneficial to try to estimate biological aging directly, in order to determine whether the pace of aging has slowed in a given population.

Biological age measures were developed to quantify the degree of aging an individual has undergone on a physiological level (6, 7), and as a result, may enable us to more accurately estimate changes in the pace of aging for different historical periods. Measures of biological age combine information from multiple physiological systems to estimate where an individual is on the aging trajectory (8, 9). For instance, an individual with a biological age of fifty is estimated to have a physiological status which characterizes someone who is fifty years old chronologically. Furthermore, if the given individual is forty years old chronologically and fifty years old biologically, it may suggest that he/she is aging at an accelerated rate. As a result, biological age measures have been found to be reliable predictors of both morbidity and mortality and are thought to provide more precise estimates of an individual's true remaining life expectancy (9, 10).

The pace of biological aging is believed to be strongly influenced by environmental factors, genetic characteristics, and some level of stochasticity (11, 12). While for the most part, the genetic makeup of a population does not change much from year to year (13) and therefore would not lead to differences in the pace of aging over a short period of time, environments and behaviors do change more rapidly, and as a result may lead to changes in how quickly populations age. For instance, there have been a number of recent changes in the prevalence of smoking and obesity that could have altered the pace of aging over the past few decades. Smoking prevalence has decreased dramatically since the 1980s, which has the potential to cause the pace of aging to decelerate (14). On the other hand, during this time obesity rates have more than doubled, which may counteract the declines in smoking, causing an acceleration of the aging process (15).

Nevertheless, there is evidence that the changes in smoking and obesity prevalence have not been equivalent across different subpopulations—for instance for men and women. In the mid to late twentieth century, smoking contributed to significantly more excess deaths for men than for women (16). However, the prevalence of smoking among the sexes has started to equalize and as a result, the degree of deceleration in the pace of aging that can be attributed to smoking cessation should be greater for males. This is one explanation for the decrease in the longevity gender gap since the 1980s, with males gaining more additional years of life than females (17). Additionally, mean Body Mass Index (BMI) has increased faster for females than for males. BMI was higher for males during the latter half of the 20^{th} century; however, it is estimated that between 1994 and1999, the average BMI of females surpassed that of males (18).

Finally, the use of pharmaceutical drugs to control blood pressure and cholesterol has also increased substantially over the past few decades, potentially attenuating some of the age-

related declines in physiological functioning related to cardiovascular and metabolic health. For instance, over the decade between 1988-1991 and 1999-2000 treatment and overall control of hypertension increased by approximately 6.0-6.4% among US adults (19). Additionally, statin use to control high cholesterol increased by almost ten-fold, from about 2% to 25%, among US adults ages 45 and over. Nevertheless, the use of such drugs has been more common among men than women (20). While the number of Americans on hypertensive medication grew between 1988-1991 and 1999-200, most of this was due to increases among males (19). Furthermore, among adults ages 65-74 in 2005-2008 approximately half of men, but only one-third of women reported taking a statin drug in the past month.

Using nationally representative data, the goal of this paper is to examine how biological aging changed between 1988 and 2010 for U.S. males and females, while also estimating the contribution of changes in smoking, obesity, and medication use.

Materials and Method

Study Population

Our analytic sample included 21,575 subjects ages 20-79 from the third and fourth waves of the National Health and Examination Survey—NHANES III (1988-1994), NHANES IV (2007-2010). Data for NHANES were collected from at-home interviews as well as examinations which took place at a Mobile Examination Center (MEC). Complete biomarker data were available for approximately 70% of the age-eligible sample. Excluded subjects were older, more likely to be black, and had lower levels of education.

Biological Age Measure

Our biological age estimation was calculated using information on eight factors—glycosylated hemoglobin, total cholesterol, systolic blood pressure, ratio of forced expiratory volume at 1 second (FEV1) to forced vital capacity, serum creatinine, serum alkaline phosphatase, serum albumin, and C-reactive protein (CRP). These biomarkers were included in our model given that they had been used in prior estimations of Biological Age, and had been found to significantly correlate with chronological age at $r > 0.10$ (9). Collectively, these biomarkers indicate metabolic, cardiovascular, inflammatory, kidney, liver, and lung functioning.

Biological age was estimated using the algorithm proposed by Klemera and Doubal (8). Estimates from this method have been found to predict mortality more accurately than chronological age or biological age estimated using other methods (cite). The calculation produces estimates that are linearly related to chronological age, with a slope of 1, intercept of 0, and residual deviation. As a result, for the population, mean biological age should equal mean chronological age. The equation used to calculate biological age (Eq. 1) combines information on the participants' measured biomarker values (x_j), as well as the slope (k_j), intercept (q_j), and root mean squared error (s_j) from the equation of chorological age regressed on each biomarker. Additionally, the equation also incorporates information on the variance ($s_{BA}^2$of the random variable, R_{BA}, which represents the difference between participants' biological and chronological ages. Its calculation takes into account the variability in the first half of the equation, the mean variance of the biomarkers that is explained by chronological age, the range of chronological age, and the number of biomarkers included in the analysis..

$$(1) \qquad BA = \frac{\sum_{j=1}^{m}(x_j - q_j)\frac{k_j}{s_j^2} + \frac{CA}{s_{BA}^2}}{\sum_{j=1}^{m}\left(\frac{k_j}{s_j}\right)^2 + \frac{1}{s_{BA}^2}}$$

Behavioral Characteristics

Smoking status was estimated using information from two self-reported questions—"Have you smoked at least 100 cigarettes during your lifetime?", and "Do you currently smoke cigarettes". Based on their answers to these two questions, participants were classified as current smokers if they answered yes to both questions; former smokers if they reported smoking at least 100 cigarettes during their lifetime, but did not currently smoke; and never smokers if they answered no to both question. Body mass index (BMI), calculated as measured weight (kg) divided by measured height (meters) squared. Participants with a BMI between 25 and 29.9 were classified as overweight, while those with a BMI of 30 or above were classified as obese.

Medications

Medication use was determined using self-reports. NHANES participants were asked whether or not they were currently taking prescribed medication for 1) high blood pressure and 2) high cholesterol. Using their answers to these two questions, we recalculated biological age using imputed measures for systolic blood pressure and total cholesterol if participants reported that they took either statins or hypertensive medications. If they answered "yes" that they were currently taking prescribed medication for high blood pressure, their biological age was recalculated substituting 140 for their systolic blood pressure, assuming the level they had when measured was ≤140. If participants answered "yes" that they were currently taking prescribed medication for high cholesterol, their biological age was recalculated substituting 200 for their total cholesterol, assuming the level they had when measured was ≤200. Those reporting that

they took both medications had their biological age recalculated using imputed levels for both systolic blood pressure and total cholesterol.

Sociodemographic Characteristics

Race, education, sex, and chronological age were self-reported. Subjects were categorized into four race ethnicity groups—Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other. Years of schooling, reflecting the highest grade attended, was used to create four education groups—those with less than 12 years of schooling, those with exactly 12 years of schooling, those with 13-15 years of school, and those with 16 or more years of schooling. A dummy variable for sex was created with males coded as 0 and females coded as 1. Finally, subjects were categorized into three twenty year age categories based on whether they were young (20-39), middle-aged (40-59), or old (60-79).

Statistical Analysis

All analyses were run controlling for covariates such as chronological age, race/ethnicity, and education. Ordinary Least Squares (OLS) regression, stratified by 20-years age categories, was used to measure the association between biological age and the interaction between time period (1988-1994 and 2007-2010) and sex, to determine 1) what the pace of aging was for young, middle aged, and older males and females during the two time periods, 2) whether the pace of aging changed over time, and 3) whether changes were similar for both sexes (Eq. 2). Next, interactions with obesity and smoking were sequentially added into sex and age-stratified OLS models of the association between biological age and period to examine whether changes in the levels and effects of smoking and obesity could partially account for changes in the pace of biological aging (Eq. 3, 4). Finally, Eq. 2 was rerun using the biological age measure with

imputed levels for participants on hypertensive and cholesterol-lowering medications, to determine how much improvement in biological aging could be attributed to increased pharmaceutical use, and whether it benefited males more than females.

(2) $BiologicalAge = \alpha + \beta_1 Female + \beta_2 Period + \beta_3 Female * Period + \beta_4 Age + \beta_5 Black + \beta_6 Hispanic + \beta_7 Other + \beta_8 Edu1 + \beta_9 Edu2 + \beta_{10} Edu3$

(3) $BiologicalAge = \alpha + \beta_1 CurrentSmoking + \beta_2 Period + \beta_3 CurrentSmoking * Period + \beta_4 FormerSmoking + \beta_5 FormerSmoking * Period + \beta_6 Age + \beta_7 + \beta_8 Hispanic + \beta_9 Other + \beta_{10} Edu1 + \beta_{11} Edu2 + \beta_{12} Edu3$

(4) $BiologicalAge = \alpha + \beta_1 Overweight + \beta_2 Period + \beta_3 Overweight * Period + \beta_4 Obese + \beta_5 Obese * Period + \beta_6 Age + \beta_7 + \beta_8 Hispanic + \beta_9 Other + \beta_{10} Edu1 + \beta_{11} Edu2 + \beta_{12} Edu3$

Results

Sample Description

As shown in Table 1, both chronological and biological age had means of 43.9 years; however, as expected the standard deviation was slightly larger for biological age (17.0) compared to chronological age (15.5). Overall, the sample is mostly made up of whites (74.3%), with only about 10% Non-Hispanic black, 11% Hispanic, and 4.4% other. Approximately 21% of the sample never completed high school, 30% had a high school degree or GED, 25% had some college education, and another 25% completed at least four years of college. Just over half of participants are female (50.6%). Overall, the majority of subjects had a BMI less than 25 (39%), while 33.4% were overweight, and 27.4% were obese. Just over half the sample had a history of smoking, with 25.1% reporting they were former smokers, and 26.4% reporting that

they were current smokers. Approximately 15.8% of participants reported being on hypertensive medications and 7.5% reported being on cholesterol-lowering medications. Finally, 59.5% of participants took part in NHANES between 1988 and 1994, while the other 40.5% took part in NHNAES between 2007 and 2010.

Period Differences in Biological Age

Biological age decreased for all age and sex groups over the twenty year time period (Figure 1). Additionally, during both periods, sex differences in biological age were larger at younger ages. Among participants ages 20-39, males had biological ages of 31.8 years and 30.5 years for period 1 and period 2, respectively, which were significantly higher than the biological ages of women during period 1 (28.3 years) and period 2 (27.7 years). Nevertheless, although both males and females, ages 20-39, had significant decreases in biological age between the two periods, the decrease for males was significantly larger ($p=.003$), contributing to a reduction in the gender gap over time.

For middle-aged subjects, males and females had similar decreases in biological age between period 1 and period 2, with females continuing to have biological ages that were about 1.5 years lower than males at both time points. In 1988-1994 the mean biological age was 50.7 years for middle aged males and 48.5 years for middle-aged females, while in 2007-2010 the mean biological age declined to 48.1 years for middle aged males and 46.2 years for middle-aged females.

No sex differences in biological age were found for subjects age 60-79 at either time period. However, both males and females had similar reductions in biological age of about four years. For males, mean biological age was 70.3 years at period 1 and 66.0 years at period 2, while for females, mean biological age was 69.0 years at period 1 and 65.4 years at period 2.

Smoking, Obesity, and Biological Aging

Based on predicted probabilities, controlling for age, race/ethnicity, and education, the prevalence of current smoking and obesity were estimated for each age by sex category (Figure 2). Among both males and females, obesity was significantly higher for all age groups in period 2 compared to period 1. From 1988-1992 until 2007-2010 obesity prevalence increased for males from 14.8% to 30.9%, for those ages 20-39; 26.0% to 35.5% for those age 40-59; and 22.8% to 40.4% for those ages 60-79. For females, prevalence to obesity increased from 20.1% to 33.3% for 20-39 year olds; 29.7%-36.8% for 40-59 year olds; and 26.7%-42.6% for 60-79 year olds.

Among males, the proportion of current smokers significantly decreased for all age groups, with the largest decreases taking place among middle-aged men. In 1988-1992 current smokers made up 35.9%, 32.9%, and 17.2% of the male population ages 20-39, 40-59, and 60-79, respectively. However, by 2007-2010, current smokers accounted for 34%, 25.8%, and 14.6% of males ages 20-39, 40-59, and 60-79, respectively. Among females, the prevalence of current smoking decreased for those ages 20-39 (from 30.4% to 25.7%) and for those ages 60-79 (from 14.4%-11.4%), between the two time periods. However, there was no change in current smoking for females age 40-59, for which the prevalence of smoking was 22.5% for both time periods.

The association between biological age and smoking and BMI after adjusting for covariates such as sex, chronological age, race/ethnicity, and education are shown in Figure 3. Both smoking and BMI were associated with significant increases in biological age. Furthermore, when considering them simultaneously results suggest that they have an additive effect on the pace of aging. Compared to never smokers with a normal BMI, never smokers who

were overweight were 1.2years older biologically, while never smokers who were obese were 2.4 years older biologically. Similarly, former smokers who were normal weight were about half a year older biologically, while current smokers who had normal BMIs were 1.15 years older biologically. Finally, compared to normal weight participants who had never smoked, overweight former smokers were 1.6 years older biologically, overweight current smokers were 2.4 years older biologically, obese former smokers were 2.8 years older biologically, and obese current smokers were over 3.7 years older biologically.

The Contributions of BMI and Smoking to Decreases in Biological Age over Time

When examining the association between changes in BMI and smoking prevalence and changes in biological age (Figure 4), we found that for younger adults reductions in the prevalence of smoking did not contribute to the decreases in biological between period 1 and period 2; however, increases in BMI during this time counteracted the decrease in biological age. Overall males and females ages 20-39 were 1.28 and 0.64 years younger biologically in period 2 compared to period 1, respectively. However, when controlling for differences in the levels and effects of BMI between the two periods, young males and females were 1.80 and 1.15 years younger biologically in period 2 compared to period 1, respectively—suggesting that if the distribution of BMI had not changed, males ages 20-39 would have had an additional 40.6% decrease in biological age, while females ages 20-39 would have had an additional 79.7% decrease in biological age.

Similarly, middle-aged females (40-59 years) did not benefit from reductions in smoking, but were hurt by increases in BMI. Overall, their biological age was 2.36 years lower in period 2 than in period 1. However, if BMI had remained constant across the two periods, the group

would have had an extra 10% reduction in biological age. Conversely, middle aged males benefited from reductions in smoking and were hurt by increases in BMI. Overall, middle-aged males had reductions in biological age of about 2.65 years between the two periods. However, controlling for smoking suggests that approximately 10% of their reductions in biological age could be accounted for by decreases in smoking prevalence and its effects. However, increases in BMI appeared to counteracted decreases in smoking. Controlling for BMI in the model suggests that if BMI levels had not changed between the two periods males ages 40-59 would have had an additional 7% reduction in biological age..

Finally, decreases in smoking also appeared to have a large influence on changes in biological age for older males. Our results showed that the decreasing prevalence and effects of smoking accounted for 8% of the reductions in biological age of males ages 60-79. On the other hand, changes in BMI among males age 60-79 had no significant association with changes in biological age. Nevertheless, for older women, decreases in smoking did not account for the decreases in biological age, while increases in obesity lessened the declines in biological age by about 7%.

Medication Use and Changes in Biological Age

Biological age was re-estimated for participants self-reporting that they took medications for either hypertension or hypercholesterolemia, by setting total cholesterol and systolic blood pressure values just above the cut-offs used for prescribing such treatments. Using OLS regression, controlling for age race/ethnicity, and education we compared the sex-specific differences in biological age between the two periods using our original biological age estimate and the estimate incorporating medication usage (Figure 5). Overall, it appears increased

medication use accounted for some of the decreases in biological age at every age for both sexes. However, medications seemed to have the largest influence on older adults, especially older males. While drugs to combat hypertension and hypercholesterolemia were only associated with 0.12 and 0.14 years of the reduction in biological age for males and females ages 20-39, respectively, among those age 40-59 they were associated with a 0.57 year reduction in biological age of males and a 0.52 year reduction in the biological age of females, and among those ages 60-79, medication use was associated with a 1.33 year reduction in the biological age of males, and a 0.99 year reduction in the biological age of females.

Discussion

Over the past twenty years, the pace of aging appears to have slowed for males and females across the age range. However, the degree of change has not been the same for men and women or by age. Our results showed that young males experienced a greater decrease in biological age than did young females. This may explain why early adult mortality has decreased more for males than females, contributing to a narrowing of the gender mortality gap. Additionally, decreases in biological age were also larger for older adults than for younger adults.

The differences in the association between biological age and changes in both behaviors and medication use may partially explain why older adults had more dramatic decreases in biological aging between 1988-1994 and 2007-2010 compared to younger adults. For instance, our results suggest that decreases in smoking may have disproportionately benefited participants who were older, especially older men. Decreases in smoking prevalence were most pronounced for middle-aged and older men, accounting for a significant proportion of their improvement in

biological age. Conversely, the biological ages of younger adults, especially females, were the most affected by increases in BMI. According to our results, if the distribution of BMI had not shifted up over time, younger males would have had an additional 40% decrease in biological age, while younger females may have had decreases in biological age that were 80% larger than what they actually experienced.

Another explanation for the differences in change over the two periods between younger and older adults is medication use. Similar to what has been reported previously (21, 22), we showed that the proportion of persons, especially middle aged and older adults taking cholesterol and blood pressure lowering medications has increased significantly over the past few decades. Given that medications are typically administered at secondary or tertiary prevention stages, younger individuals will not experience as much benefit (23). This was evidenced when we compared biological ages before and after adjusting for medication usage. While adjusting for medication use lessened the differences in biological age between the two periods only slightly among the 20-39 year old population, differences shrunk much more for middle-aged and older adults—with the largest decrease occurring among males ages 60-79.

Finally, another reason biological age may have slowed more for older adults could be due to the fact that the variance in biological age increases with chronological age. Given that the negative effects of environment and genes accumulate over the lifetime (24), biological age may not differentiate individuals to the same degree at younger ages. For example, in a heterogeneous population, it may be harder to detect differences in the pace of aging earlier in life; however, as age, and damage increase over the life course, the physiological profile of frail individuals (those with accelerated aging) and robust individuals (those with decelerated aging) may increasingly

diverge. Finally, at younger ages, when negative effects have not yet manifested, only so much improvement can occur.

There are limitations in the present study that should be acknowledged. First, due to missing biomarker data, our analytic sample included approximately 70% of NHANES participants ages 20-79, and those excluded from our analysis were older, more likely to be race/ethnic minorities, and had fewer years of schooling. Although this could affect our estimates, there doesn't appear to be a difference in the patterns of missing data between the two periods, and therefore, this should not bias our conclusions regarding changes in biological age over time. Finally, because NHANES only collects cross-sectional data, we are unable to compare changes across individuals or attenuate for mortality selection. Nevertheless, our study is strengthened by its use of a large nationally-representative data that includes multiple biomarker, sociodemographic, and behavioral measures.

In conclusion, we showed that the pace of aging has slowed over the past twenty years and that the largest improvements have been for males and older adults. We also showed that changes in smoking, obesity, and medication use may explain part of the decrease and why improvements have not been as dramatic for females and young adults. In moving forward, it may be useful to examine how cumulative disadvantage linked to socioeconomic factors and psychosocial stressors have influenced changes in biological aging over time. Overall, research examining how changing environments impact aging and health is important given that our ability to extend healthy lifespan is influenced by our understanding of the factors that regulate the pace of aging.

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Table 1: Sample Characteristics (N=21,575)

Characteristic	Statistic
Chronological Age, mean (s.d.)	43.91 (15.5)
Biological Age mean (s.d.)	43.91 (17.0)
Female (%)	50.6
Race/Ethnicity (%)	
Non-Hispanic White	74.3
Non-Hispanic Black	10.1
Hispanic	11.2
Other	4.4
Education (%)	
<12 Years	21.0
High School Degree/GED	29.9
Some College	24.7
College Degree	24.5
BMI (%)	
Overweight	33.4
Obese	27.4
Smoking (%)	
Former	25.1
Current	26.4
Taking Anti-Hypertensive Medication	15.8
Taking Cholesterol-lowering Medication	7.5
Period (%)	
1 (1988-1994)	59.5
2 (2007-2010)	40.5

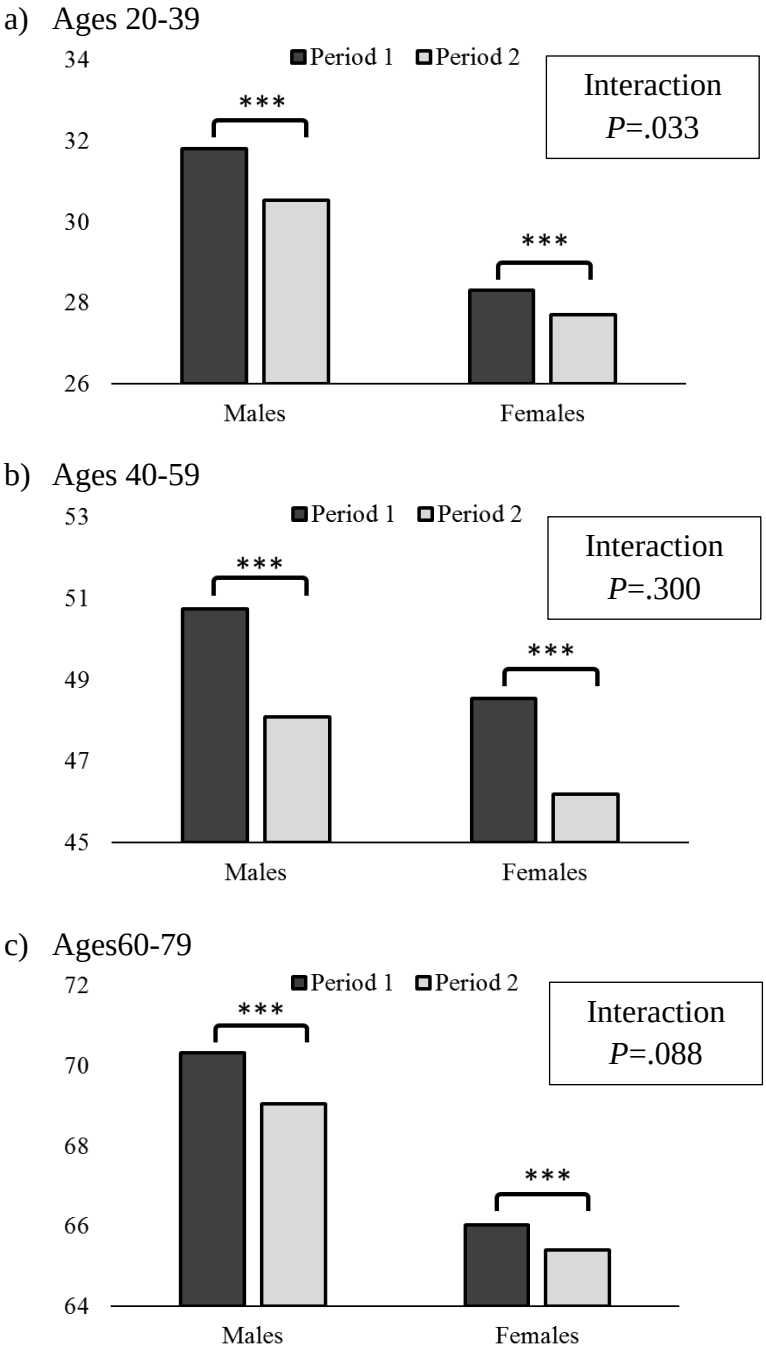
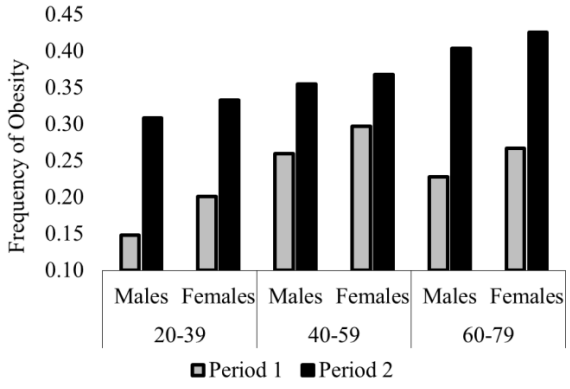


Figure 1: Changes in biological age between period 1 (1988-1994) and period 2 (2007-2010) by sex and age.

Although there were decreases in biological age for all sex by age groups (P<.001), sex difference were more pronounced at younger ages (fig. 1a). Furthermore, for adults ages 20-39 the decreases for males were significantly greater than the decreases for females (*P*=.033). Finally, for adults ages 40-59 and 60-79 (fig. 1b, 1c), there were no significant sex differences in the decrease between period 1 and period 2.

a)



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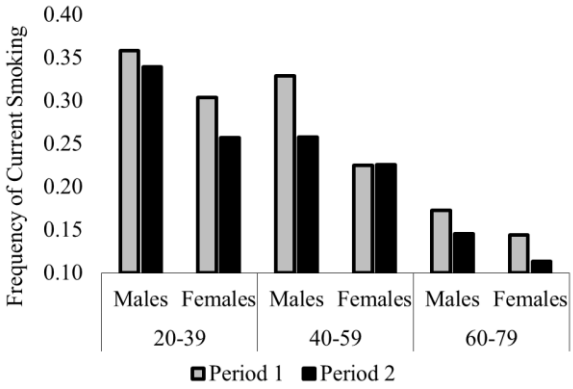

Figure 2: Changes in the frequency of smoking and obesity between period 1 (1988-1994) and period 2 (2007-2010)

The prevalence of obesity significantly increased for males and females of all ages (fig. 1a,). Conversely, the prevalence of current smoking was significantly reduced for males of all ages, as well as younger and older females.

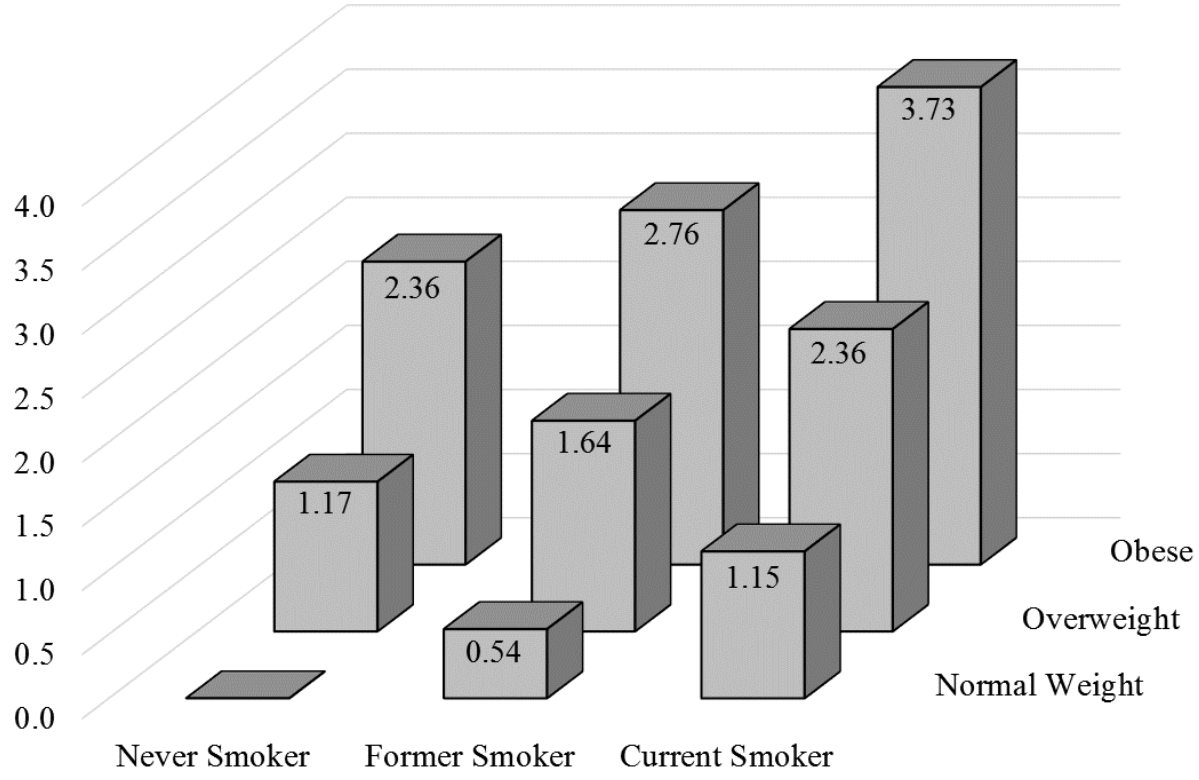

Figure 3: Additions to biological age related to smoking and obesity
Biological age was increased for current and former smokers, as well as participants who were overweight or obese. Furthermore, there appeared to be an additive effect between smoking and BMI. On average, subjects who were current smokers and obese had the highest biological age, which was almost 4.5 years more than the biological age of normal weight individuals who had never smoked.

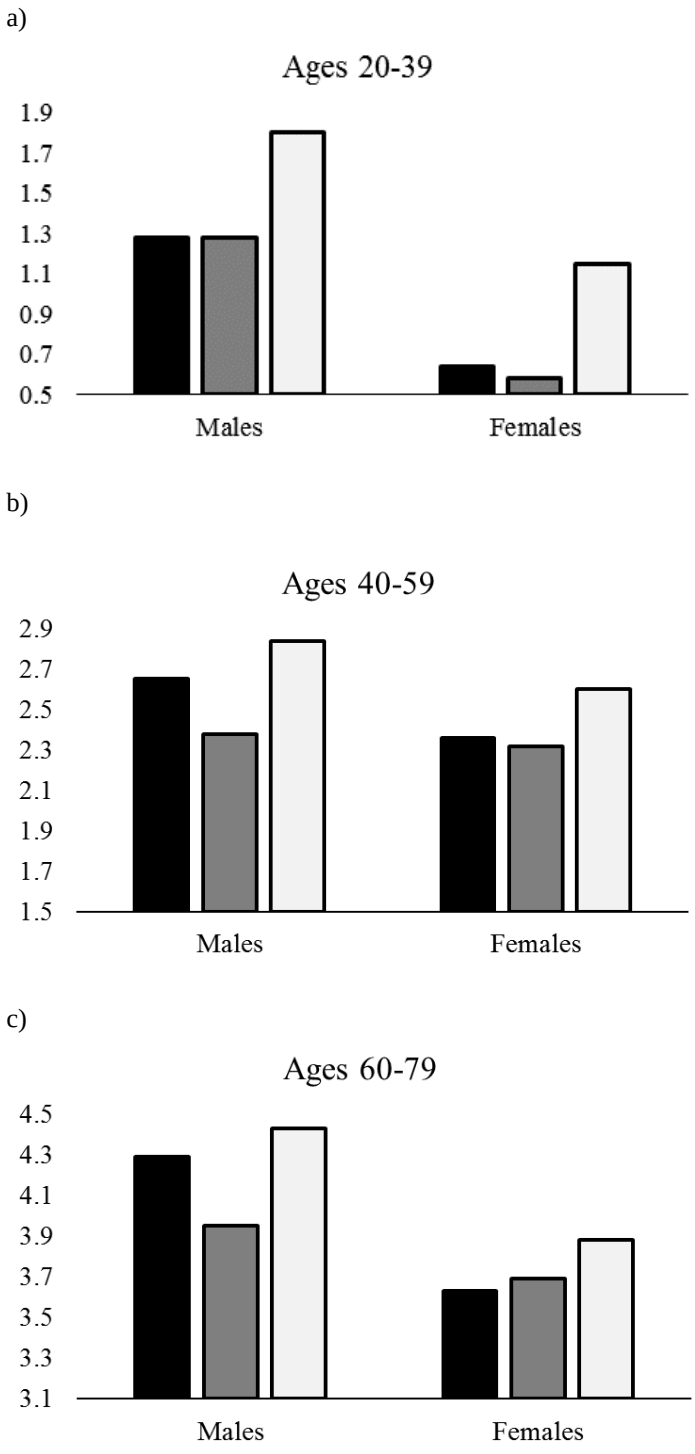

Figure 4: The Contributions of BMI and Smoking to Decreases in Biological Age between Period 1 (1988-1994) and Period 2 (2007-2010)

Changes in smoking prevalence did not appear to influence the decreases in biological age of females, as well as younger males (4a). However, declines in smoking was associated with approximately 10% of the decreases in biological age among 40-59 year old (4b) and 8% of the decreases in biological age among 60-79 year old males (4c). On the other hand, obesity was found to counteract the decreases in biological age for younger males and females (4a), as well as middle-aged females (4b). When controlling for differences in the distribution of BMI between period 1 and period 2, males ages 20-39 had an additional 41% decrease in biological age, while females ages 20-39 and 40-59 had an additional 80% and 10% decrease in biological age, respectively.

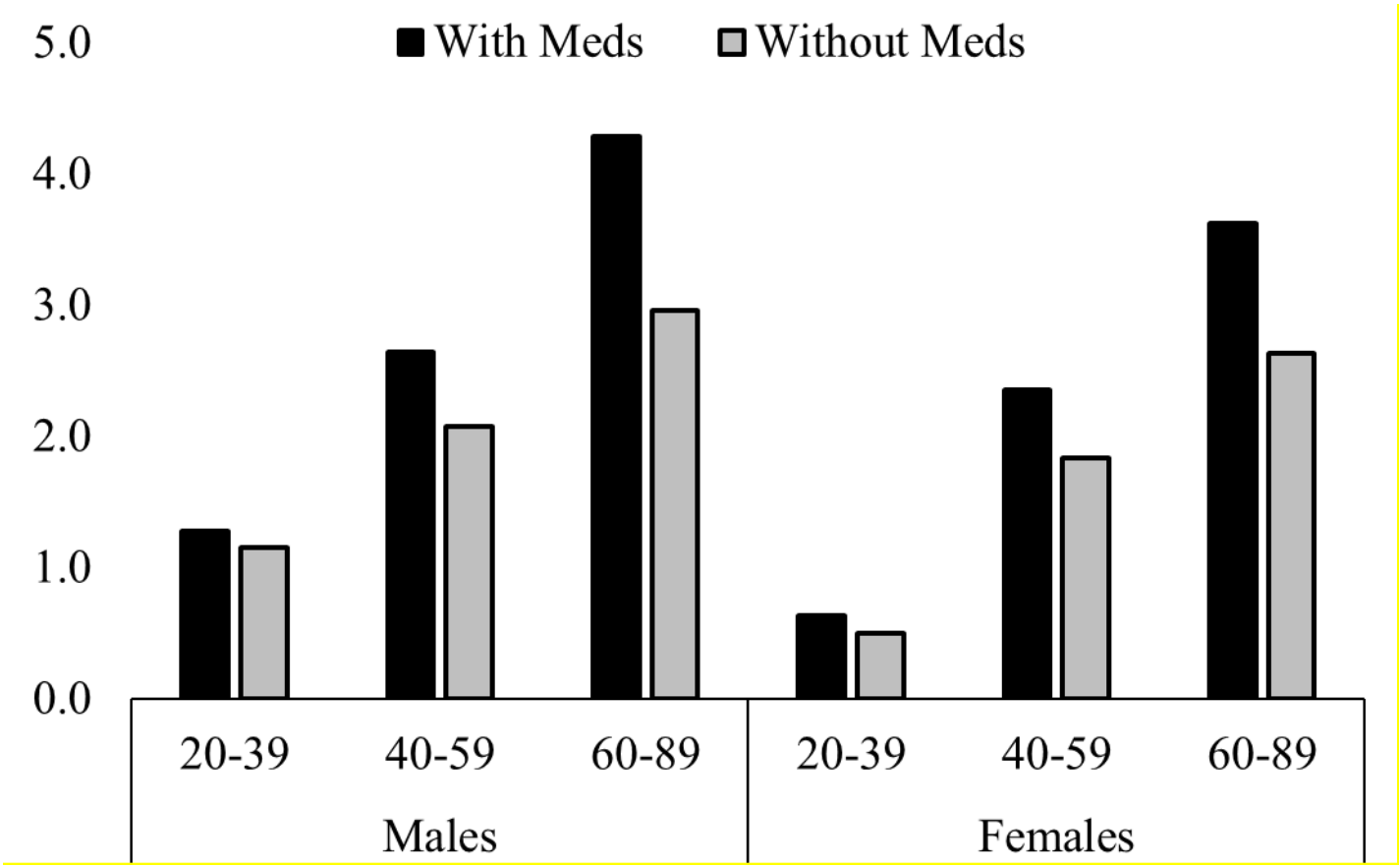

Figure 5: Medication Use and Decreases in Biological Age

Period differences in biological age estimated with and without adjustments for medication use did not vary significantly for males and females ages 20-39. However, among middle-aged and older adults differences in biological age were significantly higher before adjusting for medication use; thus, suggesting that the increased prevalence of persons on hypertension and/or hypercholesterolemia medication in 2007-2010 relative to 1988-1992 contributed to a proportion of the decreases in biological age for males and females ages 40-59, and 60-79. Finally, this was most apparent for the oldest age group, particularly males.