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Cynthia Elizabeth Perry
Brigham Young University

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Cynthia Elizabeth Perry

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Dawson Hedges, Chair
Wendy Birmingham
Julianne Holt-Lunstad

Department of Psychology

Brigham Young University

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ABSTRACT

Association Between Polymorphisms Associated with Major Depression, Cognitive Function, and Stress Regulation and Telomere Length in Older Community-Dwelling Adults and in Older Competitive Athletes

Cynthia Elizabeth Perry
Department of Psychology, BYU
Master of Science

Introduction: Many factors detrimental to healthy aging have been proposed including depression, stress, cognitive decline, and telomere shortening. Of specific interest are the genetic factors that may contribute to these factors and subsequently lead to accelerated telomere shortening and aging, namely the Bcl1, 5-HT, DRD2, and ApoE polymorphisms. We sought to: 1) further clarify the role of depression, stress tolerance, and cognitive decline in aging by examining the effect of associated polymorphisms (Bcl1, 5-HT, DRD2, and ApoE) on telomere length in two samples of older adults and 2) determine the difference in absolute telomere length between the two groups.

Method: We examined two samples of older adults: participants in a competitive, athletic event (N=220; mean age=66.8 years) and a sample of community-dwelling older adults (N=208; mean age=69.1 years). Participants completed a questionnaire with demographic information and provided a saliva sample. The Bcl1, 5-HT, DRD2, and ApoE polymorphisms were determined using PCR and Taqman assays. Telomere length was determined using qPCR analysis.

Results: The community-dwelling group had significantly shorter telomere lengths than the athletic group ($t=-4.82$, $p< .0001$). Additionally, for males in the athletic group, the L/S genotype of the 5-HT polymorphism was associated with longer telomere length. In males in the community-dwelling group, the GC genotype of the Bcl1 polymorphism was associated with shorter telomere length. In females in the athletic group, the GC and GG genotypes of the Bcl1 polymorphism were associated with shorter telomere length with the opposite being true for females in the community-dwelling group: the GC genotype of the Bcl1 polymorphism predicted longer telomere length. Exercising nearly everyday and the length of exercise were associated with telomere length in both groups.

Conclusion: Our results indicate that competitive athletic activity in older age is associated with increased telomere length, longer periods of exercise at one time may contribute to longer telomere length, and the Bcl1 and 5-HT polymorphisms are associated with telomere length in older adults.

Keywords: telomeres, healthy aging, Bcl1 polymorphism, 5-HT polymorphism, exercise.

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Introduction

The older adult population in the United States is growing and is projected to more than double by 2050, from 40.2 million in 2010 to 88.5 million in 2050 (U.S. Census Bureau, 2008). Due to the projected large expansion of the older adult population in the next few decades, determining factors contributing to healthy aging is of paramount importance (Administration on Aging, 2010). Many factors detrimental to healthy aging have been proposed and elucidated, including depression, stress, and cognitive decline. Specifically, Strawbridge, Cohen, Shema, and Kaplan (1996) report that absence of depression is one of three key factors contributing to healthy aging based on a longitudinal study spanning six years. Secondly, chronic cortisol activation as well as activation of the HPA axis can lead to cognitive decline. Most cortisol elevation is due to stress (Depp, Vahia, & Jeste, 2010). Finally, cognitive decline is at the essence of aging and is intuitively included as a factor in aging. In fact, cognitive functioning is included as an essential part of many definitions of aging (McLaughlin et al., 2012).

In addition to depression, stress, and cognitive decline, telomere shortening may be a key factor in healthy aging. Telomeres are deoxyribonucleic acid (DNA) caps on chromosomes, and telomere shortening during cell replication is normal and helps regulate the process of cell aging as well as senescence. However, accelerated telomere shortening is associated with disease. For example, mutations in telomere maintenance genes are associated with rare genetic diseases (called "telomere syndromes"), which have symptoms of premature aging, thus helping to establish a causal link between telomere biology and aging (Shalev et al., 2013). In addition, the rate of telomere shortening has been shown to be an indicator of biological aging, in that those with shorter telomere length and a higher rate of telomere shortening tend to age at a faster rate (Boccardi & Paolisso, 2014). Also, shorter telomere length has been associated with higher rates

of age-related diseases such as Alzheimer's disease (Hochstrasser et al., 2012), cancer (H. Ma et al., 2011), cardiovascular disease (Starr et al., 2007), dementia with Lewy-bodies (Kume et al., 2012), diabetes (Zhou et al., 2013) and increased overall disease burden (Sanders et al., 2012).

Of particular interest are the associations of depression and cognitive decline with telomere length shortening, both of which are implicated in accelerated aging. Depression is associated with high rates of comorbid medical diseases that are more prevalent in older adults, such as cardiovascular disease, stroke, and dementia, indicating an association of depression with aging. Specifically, six studies have found significant telomere shortening in depressed participants, with more severely depressed or chronically depressed participants showing greater telomere length shortening (Shalev et al., 2013). Along with depression, several studies have shown associations between telomere length and measures of cognitive functioning (Flostein et al., 1975; Robbins et al., 1994; Devore et al., 2011; Harris et al., 2012; S. L. Ma et al., 2013; Valdes et al., 2010), findings that, together with the shortened telomere lengths associated with diseases such as Alzheimer's disease and dementia with Lewy-bodies, further expand the putative connection between cognitive functioning and telomere length.

Along with the diseases associated with telomere length, stress also affects telomere length. Chronic stress both in childhood and adulthood has been shown to be associated with shortened telomere length (Shalev et al., 2013). For example, one study found significantly shorter telomeres in women in high-stress situations (shorter by about 550 basepairs, or about 15 percent of telomere length) than those in low-stress situations (Epel et al., 2004). In addition, higher levels of cortisol in response to a laboratory stressor have been associated with shorter telomere length (Shalev et al., 2013). Along with stress, dysregulation of the physiological mechanism that handles stress – the hypothalamic-pituitary-adrenal (HPA) axis - leads to

increased oxidative damage and immune response, with subsequent decrease in telomere length (Wolkowitz, 2010). Thus, the processing of stress and its dysregulation may be major contributors to accelerated telomere shortening.

Given the connections between telomere shortening and depression, cognitive decline, and stress regulation, of specific interest are the genetic factors that may contribute to the propensity to develop these conditions, and subsequently lead to accelerated telomere shortening and aging. One important factor is one genetic polymorphism affecting HPA regulation – the Bcl1 variant of the glucocorticoid receptor gene. Carriers of the minor allele of the Bcl1 polymorphism have been shown to have decreased cortisol levels in response to psychosocial stress, resulting in dysregulation of the HPA axis (DeRijk & Kloet, 2005; Kumsta et al., 2007). Further, variants of both the serotonin reuptake receptor (5-HT) and the dopamine 2 receptor (DRD2) genes have been associated with depression. The Apolipoprotein E (ApoE) polymorphism has been implicated in cognitive decline and in the development of Alzheimer's disease (Dorey, Chang, Liu, Yang & Zhang, 2014). Despite these associations, few to no studies to date have directly measured the relationship between telomere length and the polymorphisms of Bcl1, 5-HT and DRD2. Only the relationship between ApoE and telomere length has been measured by a few studies, albeit with mixed results (Jacobs et al., 2013; Wikgren et al., 2012; Valdes et al., 2010) that are likely due to differences between samples.

In the present study, we sought to: 1) further clarify the role of depression and stress tolerance in aging by examining the effect of the previously mentioned polymorphisms (Bcl1, 5-HT, DRD2, and ApoE) on telomere length in two samples of older adults, 2) determine the difference in absolute telomere length between the two groups and 3) clarify the role of exercise and exercise duration on telomere length in older adults between the two groups. The first group

consists of older adult participants in a competitive athletic event. This is a particularly unique group of older adults in that it includes active older adults who participate in various athletic activities such as indoor sports (basketball, volleyball, etc.), track and field events, and outdoor sports (softball, cycling, pickleball, etc.) at the annual World Senior Games. The World Senior Games has been described as one of the premiere senior athletic events in the world. The participants in this group are not just active older adults but competitive athletic older adults as well. Some previous research has been performed on similar groups of competitive older adults, which suggests physical benefits of competitive sports for older adults as well as other benefits such as self-actualization, feelings of accomplishment, and social interaction and belongingness (Heo, Culp, Yamada & Won, 2012; DeVan & Seals, 2012). Social interaction and belongingness are associated with reduced risk of depression in older adults (Schwarzbach, Luppa, Forstmeier, König, & Riedel-Heller, 2014). This research suggest that participation in such competitive athletic events for older adults is associated with successful and healthy aging.

In this study, of particular interest is healthy, successful aging and factors that contribute to it. As mentioned previously, many factors have been elucidated that are detrimental to healthy aging. However, the definition of "healthy aging" varies widely across studies, and there is no universally accepted definition of healthy aging. Rowe and Kahn's idea of "successful aging" has been the most used definition, however (McLaughlin et al., 2012). Rowe and Kahn's definition of successful aging includes the following: being "free of disease, risk factors for disease, and disability; [having] high physical and cognitive functioning; and [being] socially and productively engaged" (McLaughlin et al., 2012, p. 783). However, many find this definition overly restrictive and limits those that could be considered aging "successfully"; in some estimates, up to only ten percent of the older adult population is considered to be aging

successfully. Despite its restrictive nature, participation in the World Senior Games would require meeting at least some, if not all, of the aspects included in Rowe and Kahn's definition. For example, for older adults to participate on a basketball team at the World Senior Games, they would at least need to be "free of disease and disability" to a degree to allow for them to be able to run up and down the court. It is unlikely that they would be free of all risk factors for diseases, however. Also, their mere participation in such an event points to "high physical functioning" as well as being "socially and productively engaged." Thus, while no universally accepted definition exists for healthy aging, our use of participation in the World Senior Games as a definition of healthy aging seems to fit well into the most widely used definition and provides substantial evidence of healthy aging for this sample.

In addition, we selected participation in the World Senior Games as evidence of healthy aging in order to study factors that contribute to healthy aging. Thus, we hope to examine selection criteria that allow for participation in the World Senior Games (and by extension, healthy, successful aging), particularly biological factors connected to psychological functioning.

The second group of participants includes a group of community-dwelling older adults. These participants are similar and different in many respects compared to the participants from the World Senior Games; however, they did not self-select to participate in competitive athletic events as older adults, which participation is the main consideration in the present study.

Because longer telomere length is associated with longevity and better aging, we hypothesize first, that absolute telomere length between the two groups will be significantly different and longer in the group of older adults participating in the World Senior Games. Additionally, given the interaction between telomere length and genes, as well as the association between specific genes and psychological functioning, we hypothesize that the specific alleles of

the polymorphisms associated with depression, cognitive function, and stress tolerance will be associated with shorter telomere lengths in both groups.

Methods

Participants

To obtain the sample of athletic older adults, during a general health assessment provided to participants at the World Senior Games in 2008, members of the research group invited older-adult athletes to participate in this study. Study participants completed a questionnaire prior to providing a salivary sample for genetic analysis, which included demographic data such as age, gender and level of education.

Our definition of healthy, high-functioning older adults for this study was formal participation in the World Senior Games, as noted above. We assumed that older adults participating in a formal athletic event would have to surpass a certain minimal level of good health to participate. All subjects actively participated in athletic events in either 2008. To avoid population stratification, we limited our analysis to the 220 responding subjects who identified themselves as White. Age of the participants ranged from 50 to 92 years with a mean of 66.8 years (see Table 1). Thirty-seven percent of participants were female, and more than 94 percent of the sample reported their health as good or excellent as compared to the health of others their age.

The participants in the second sample were community-dwelling older adults. To obtain this sample, we identified areas in one US county zoned specifically for older adults. We sent letters in 2010 to all residents in these areas requesting their participation. Again, to avoid population stratification, we limited our analysis to the 208 subjects responding subjects who identified themselves as White. There was not a sufficient number of ethnic minorities in either

sample to include other ethnic groups in the analyses. The subjects completed a questionnaire nearly identical to the one completed by the subjects in the competitive athletic event. In this sample, age ranged from 54 to 96 years with a mean age of 69.1 years, and 52 percent of the subjects were female (see Table 1). Approximately 88 percent of the sample said their health was good or excellent compared to others their age. Appropriate Institutional Review Boards approved this study.

Procedure

After the subjects signed informed-consent documents and completed the questionnaire, we collected saliva from the participants using DNA Genotek – OG – 250 kits (DNA Genotek, Ontario, Canada) and isolated DNA according to protocols provided by the manufacturer. For the Bcl1, DRD2, and 5-HT polymorphisms, we amplified the isolated DNA using standard polymerase chain reactions (PCR). We obtained appropriate primers for each DNA segment to be amplified and added them to the PCR reaction along with Taq polymerase and nuclease-free water (Bachmann et al., 2005; Grandy, Zhang, & Civelli, 1993; Stein, Seedat, & Gelernter, 2006). DNA from each participant was added to the PCR reactions, and the PCR cycling conditions were run according to the appropriate protocols (Bachmann et al., 2005; Grandy, Zhang, & Civelli, 1993; Stein, Seedat, & Gelernter, 2006). The amplified DNA was digested using the appropriate restriction enzyme (Bcl1 for Bcl1, TaqI for DRD2, and MspI for 5-HT) for the specified length of time (Bachmann et al, 2005. Grandy, et al., 2005, Stein, Seedat, & Gelernter, 2006). For Bcl1 and DRD2, the digested DNA samples were electrophoresed on a 1.5 percent agarose gel in order to separate the cut restricted DNA bands. For 5-HT, SDS-polyacrylamide gel electrophoresis was used to separate the restriction cut digested DNA bands

due to the close similarity in sizes of the bands (Stein, Seedat, & Gelernter, 2006). An ethinium bromide stain and UV visualizer were used to visualize the gels.

Genotyping used for the ApoE SNPs was accomplished using Taqman assays (rs429358 and rs7412 define the APOE E2/E3/E4 isoforms). DNA for these assays was isolated using QIAamp DNA Mini Kit (Qiagen, Germantown, USA) due to increased need for DNA purity.

Telomere length was determined using qPCR analysis (using Lightcycler 480) according to the protocol by O'Callaghan et al. (2008) with a few exceptions. The positive control used was a sample of DNA from a participant and was used as a positive control for calibration from plate to plate and no normalization plate was used. Additionally, in order to reduce variation, both telomere and single copy gene samples were run on the same plate. QiaAMP DNA Mini Kits (Qiagen, Germantown, USA) were used to isolate the sample DNA. If the triplicate runs for any sample had a standard deviation greater than one, the sample was run again. Additionally, if on the second run of the sample, the standard deviation for the single copy gene analysis of the sample was within a standard deviation of one while the telomere analysis was not, we included the sample in the final data analysis. We reasoned that the pipetting accuracy of the procedure was validated by the low standard deviation of the single copy gene and the variance in the telomere analysis of the sample was due to the age of the cells being assayed.

Results

We examined the descriptive characteristics of each group, including range of telomere lengths and variables shown to affect telomere length such as exercise, age, and current stress levels for each group (Tables 1 and 2).

For the first hypothesis, we compared the two groups on mean absolute telomere lengths using a t-test. The community-dwelling group had significantly shorter telomere lengths than the athletic group ($t=-4.82$, $p< .0001$, CI 95% [-82.2, -34.5]).

For the second hypothesis concerning the association between genetic variants and telomere length, we used linear regressions with each gene separately predicting telomere length in each group, controlling for potential confounding variables including age, gender and amount of exercise, all of which have been associated with telomere length (Guan et al., 2007; Cherkas et al., 2008). We performed the analyses separately because of the potential effect participation in the World Senior Games may have on telomere length. We also performed the regressions for each group with males and females separated due to potential gender differences. In the athletic group and community-dwelling groups as a whole, we did not find an association between polymorphisms and telomere length. However, when we performed the regressions with males and females separated, we found associations between polymorphisms and telomere length. Specifically, in males in the athletic group, the L/S genotype of the 5-HT polymorphism was associated with longer telomere length. In males in the community-dwelling group, the GC genotype of the Bcl1 polymorphism was associated with shorter telomere length. In females in the athletic group, the GC and GG genotypes of the Bcl1 polymorphism were associated with shorter telomere length. However, the opposite was true for females in the community-dwelling group: the GC and GG genotypes of the Bcl1 polymorphism predicted longer telomere length. Only six participants had the GG genotype in the community-dwelling females, however, which may make this finding spurious. Additionally, exercising nearly everyday and the length of exercise were associated with telomere length in both the community-dwelling and athletic groups. Specifically, in males in the community-dwelling group, longer exercise duration was

associated with decreased telomere length. However, in females in the athletic group, longer exercise duration and exercising nearly everyday predicted increased telomere length (see Tables 3-5).

Discussion

We tested two groups older adults - one athletes competing in the World Senior Games and the other a group of community-dwelling older adults - for average telomere length and genetic polymorphisms known to affect conditions influencing aging, specifically depression, stress, and cognitive decline. The group of older adult athletes had significantly longer telomere lengths than the community-dwelling older adults. Both groups were similar in sample size, age, amount of education, annual income, smoking frequency, alcohol use, marital status, PCL-C and UCLA Loneliness Scale total scores. While frequency of exercise each week was similar for each group, the amount (length) of exercise were very different, with the athletic group exercising for longer. This result is not necessarily surprising given previous literature suggesting exercise influences telomere length. However, little literature to date has examined the association between exercise and telomere length in older adults. If exercise truly does protect in some way against telomere shortening, then longer telomeres would be expected in those who exercise regularly into old age. Some studies have examined differences in telomere length between endurance athletes and moderate exercisers (see Mathur et al., 2013; Osthus et al., 2012; LaRocca, Seals & Pierce, 2010) with two studies examining telomere length in older adults but with very small sample sizes. To our knowledge, this is the first study examining telomere length in older adults in a White population with two distinct levels of exercise with a larger sample size (208 to 220 participants). Another study by Gardner et al. (2013) performed a meta-analysis of older adults' telomere lengths associated with measures of fitness such as

walking speed, balance or grip strength. Participation in the World Senior Games can also be considered a measure of fitness, as mentioned previously and may be a more exhaustive measure. Thus, overall, our results seem to indicate that competitive athletic activity in older age is associated with increased telomere length.

Additionally, our results suggest that the duration of exercise at one time and the frequency of exercise are also associated with telomere length in both older adults with and without competitive athletic activity, differently for each gender. For females in the athletic group, longer exercise duration at one time and increased frequency of exercise periods were associated with increased telomere length. The finding that increased frequency of exercise periods are associated with longer telomere length is not necessarily surprising given the amount of research linking exercise to maintaining telomeres. In fact, Kim, Ko, Lee, Lim, & Bang (2012) found habitual exercise (three times a week for 60 minutes) in postmenopausal women was associated with longer telomere length. However, the finding that longer periods of exercise at one time is associated with longer telomere length for females is a novel finding to the best of our knowledge. This may be due to many factors. One such factor may be that more "intense" sports (such as badminton, basketball, etc.) were recently associated with longer telomere lengths (Saβenroth, et al., 2015). These sports may provide a relatively longer period of exercise which may relate to our finding. However, Saβenroth et al. (2015) did not report the length of exercise periods for their participants, making this possibility difficult to assess.

Interestingly, longer exercise duration was associated with shorter telomere length for men in the community-dwelling group. While many studies have found a positive association between exercise and telomere length, some have found an inverted U relationship between activity and telomere length. Specifically, participants with moderate activity during midlife had

longer telomere lengths than those with high activity and low activity levels (Ludlow, Ludlow, & Roth, 2013). A similar situation may be happening in our study: for those males who are not competitive older adult athletes, longer duration of exercise may actually be detrimental to telomere length.

In regards to our second hypothesis that polymorphisms associated with depression, stress, and cognitive decline (5-HT, DRD2, Bcl1, and ApoE polymorphisms) would be associated with shorter telomere lengths in both groups, we found associations between the 5-HT polymorphism and Bcl1 polymorphism when analyzing the groups with genders separated. In the males of the athletic group, the L/S genotype of the 5-HT polymorphism was associated with longer telomere length. Li et al. (2014) found the S/S genotype of the 5-HT polymorphism to be associated with shorter telomere length in young adult females. No other study has examined this association in older adults to our knowledge. The association between this polymorphism and telomere length may be due to the impact of psychological stress on telomere length. The S/S genotype has been associated with hypervigilance, increasing the amount and/or frequency of psychological stress in an individual (Li et al., 2014). Thus, only having one of the S allele may decrease this type of psychological stress and reduce its negative impact on telomere length.

In addition, we found associations between the Bcl1 polymorphism and telomere length in both the athletic and community-dwelling groups. For males, the GC genotype was associated with shorter telomere length for those in the community-dwelling group. For females, the GC and GG genotypes were associated with longer telomere length in the community-dwelling group and shorter telomere length for the athletic group. To our knowledge, no other studies have examined the possible relationship between the Bcl1 polymorphism and telomere length. As mentioned previously, the Bcl1 variant of the glucocorticoid receptor gene is associated with

HPA axis regulation which regulates the body's physiological response to stress. Carriers of the G allele of the polymorphism have a dysregulation of the HPA axis in response to stress which may increase the negative impact stress has on telomere length. More research is needed to determine if this is an effect only seen later in life as well as the mechanism by which this effect may come about. It seems likely from our results, however, that the level of exercise and gender of the participant may be moderating factors in how the Bcl1 polymorphism interacts with telomere length.

Our study has several strengths and additional weaknesses. One strength is that of having a group of older adults with a high level of physical activity overall. Also, the two groups were similar on many measures, as mentioned previously. Some weaknesses to the study include that we only measured telomere length using one method qPCR rather than with two methods (including Southern blot with qPCR). This was due to the expense and intensive labor needed to perform Southern blots along with qPCR. Additionally, a recent trend in genetic research is toward the use of genome-wide association studies (GWAS) rather than candidate gene studies (candidate gene studies being the study format we used). While some GWAS have been performed to find specific polymorphisms associated with telomere length, most have yet to be replicated in determining which polymorphisms contribute to telomere length. In addition, while there is concern about the reliability of candidate gene studies, some candidate genes have been shown to be replicated reliably as relating to various disorders, in particular 5-HT and anxiety, ApoE and Alzheimer's disease and cognitive decline, and DRD2 and stress predicting alcohol abuse (Duncan, Pollastri, & Smoller, 2014), suggesting our use of these genetic variants was appropriate even without GWAS confirmation. Another limitation is that the group of participants from the World Senior Games was self-selected. Given the self-selection of the

participants in the World Senior Games, other factors may be contributing to their selection that are not being measured in the study, such as motivation, for example. Lastly, the participants in the study are all older adults and have some restrictive characteristics such as being all of the same ethnicity, all non-smokers, and all with minimal alcohol use. Thus, the ability to generalize findings to other populations (of other ethnic backgrounds, for example) is limited.

In sum, we found a significant difference in telomere lengths between a group of competitive, athletic older adults and a group of relatively healthy older adults with longer lengths in the former group. Additionally, we found an association between length of exercise and frequency of exercise and longer telomere lengths in both groups. We found associations between polymorphisms of 5-HT and Bcl1 and telomere length in both group. Our results indicate that competitive athletic activity in older age is associated with increased telomere length, longer periods of exercise at one time may contribute to longer telomere length, and the Bcl1 and 5-HT polymorphisms are associated with telomere length in older adults.

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Appendix

Table 1.

Demographic Characteristics of the Athletic and Community-Dwelling Groups.

Characteristics	Athletic Group	Community-Dwelling Group
Sample Size	220	208
Mean age (years), SD	66.8, 7.4	69.1, 8.6
Women (percent)	36.8	52.4
Ethnic Background (Caucasian)	100	100
College education, percent	68.6	62.0
Income over $60,000/year, percent	48.6	58.7
Exercise several times a week, percent	40.9	38.5
Length of exercise per day in minutes, mean, SD	99.6, 63.6	36.3, 15.2
Never smoked, percent	73.2	81.3
No alcohol use in past 30 days, percent	42.3	90.4
Currently married, percent	89.1	87.0

Table 2.

Genetic and Questionnaire Characteristics of the Athletic Group and Community-Dwelling Group.

Characteristics	Athletic Group	Community-Dwelling Group
Sample Size	220	208
5-HT genotypes (percent)		
SS	32.7	33.6
LS	44.5	44.7
LL	20.9	20.7
No data	1.8	0.9
DRD2 genotypes (percent)		
A1A1	4.5	2.9
A1A2	27.2	29.8
A2A2	68.2	65.9
No data	0.0	1.4
Bcl1 genotypes (percent)		
GG	18.6	13.5
GC	52.3	48.6
CC	28.6	37.5
No data	0.5	0.4
ApoE genotypes (percent)		
E1/E2	0.5	0.0
E2/E2	0.0	0.0
E3/E2	10.0	6.3
E3/E3	42.7	46.6
E4/E2	3.2	1.4
E4/E3	14.5	25.5
E4/E4	0.9	1.9
No data	28.2	18.3
Telomere length (kb/diploid genome), mean, SD, [range]	242.6, 128.2, [22.3, 741.8]	184.2, 122.4, [19.4, 598.9]
CES-D total score, mean, SD	5.3, 7.7	8.3, 11.2
PCL-C total score, mean, SD	21.3, 5.4	22.9, 6.4
UCLA Loneliness Scale total score,	31.7, 10.9	33.7, 9.0

mean, SD

Table 3.

Regressions with Each Polymorphism Predicting Telomere Length for Athletic and Community-Dwelling Groups.

	Athletic Group		Community-Dwelling Group	
5-HT	b	SE	b	SE
L/S	29.56	(21.76)	-13.58	(31.60)
L/L	24.01	(26.20)	14.91	(37.59)
Age	-2.59*	(1.29)	1.66	(1.57)
Female	-9.15	(20.14)	16.49	(27.21)
Frequency of exercise				
Nearly 1x/day	21.42	(28.64)	15.88	(47.24)
Several times/week	31.15	(27.24)	30.64	(43.62)
1x/week	-11.10	(42.67)	-25.18	(101.54)
<1x/week	110.53	(97.92)	-30.05	(61.55)
Exercise (in mins.)	.00	(.15)	-1.12	(.93)
R^2	.04		.06	
N	199		103	
DRD2				
A1/A2	16.91	(50.36)	1.85	(96.11)
A2/A2	47.29	(48.35)	-4.07	(95.22)
Age	-2.47*	(1.28)	1.39	(1.52)
Female	-12.97	(19.85)	7.29	(27.36)
Frequency of exercise				
Nearly 1x/day	18.56	(27.90)	2.70	(45.71)
Several times/week	21.07	(26.39)	30.86	(42.93)
1x/week	-8.02	(41.91)	-33.30	(101.84)
<1x/week	123.90	(97.08)	-22.66	(60.62)
Exercise (in mins.)	.04	(.15)	-.99	(149.74)
R^2	.04		.04	
N	203		102	
Bcl1				
GC	-37.64	(21.87)	35.81	(28.88)
GG	-22.78	(28.07)	55.73	(44.49)
Age	-2.52*	(1.28)	1.77	(1.57)
Female	-9.41	(19.86)	16.14	(26.94)
Frequency of exercise				
Nearly 1x/day	20.10	(27.90)	3.27	(46.60)
Several times/week	26.50	(26.33)	15.39	(44.68)
1x/week	-7.15	(42.01)	-37.95	(100.76)
<1x/week	123.39	(96.96)	-24.66	(60.61)
Exercise (in mins.)	.03	(.15)	-1.07	(.91)
R^2	.05		.07	

N	202		103	
ApoE				
E3/E2	32.56	(134.39)	9.69	(54.33)
E4/E3	9.62	(131.85)	50.57	(57.30)
E4/E2	36.04	(139.18)	138.27	(107.40)
E4/E3	24.10	(133.47)		
E4/E4	-12.39	(160.89)		
Age	-3.08*	(1.55)	1.46	(1.52)
Female	9.94	(23.23)	2.04	(27.35)
Frequency of Exercise				
Nearly 1x/day	36.86	(32.56)	33.76	(44.36)
Several times/week	44.14	(30.24)	29.08	(44.01)
1x/week	-10.68	(51.96)	-27.52	(95.86)
<1x/week	120.42	(134.54)	-56.65	(58.15)
Exercise (in mins.)	.12	(.19)	-1.70	(.92)
R^2	.06		.15	
N	145		83	

Abbreviations: SE = Standard error. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 4.

Regressions with Each Polymorphism Predicting Telomere Length for Athletic and Community-Dwelling Groups for Males Only.

	Athletic Group		Community-Dwelling Group	
5-HT	b	SE	b	SE
L/S	60.53*	(28.53)	17.57	(38.51)
L/L	38.83	(32.74)	8.28	(40.43)
Age	-4.11*	(1.74)	-.25	(1.93)
Frequency of exercise				
Nearly 1x/day	8.62	(39.91)	11.95	(67.12)
Several times/week	22.14	(37.20)	52.52	(66.12)
1x/week	-24.64	(51.65)	N/A	N/A
<1x/week	N/A	N/A	-39.66	(80.51)
Exercise (in mins.)	-.14	(.18)	-2.58*	(1.03)
R^2	.10		.21	
N	123		47	
DRD2				
A1/A2	-12.07	(65.14)	-67.93	(106.32)
A2/A2	30.28	(63.67)	-122.25	(108.48)
Age	-4.02*	(1.73)	.56	(1.79)
Frequency of exercise				
Nearly 1x/day	1.74	(38.19)	-8.94	(62.82)
Several times/week	7.32	(35.67)	32.24	(63.18)
1x/week	-16.44	(50.55)	N/A	N/A
<1x/week	N/A	N/A	-34.66	(77.38)
Exercise (in mins.)	-.08	(.18)	-1.65	(170.43)
R^2	.08		.26	
N	127		48	
Bcl1				
GC	-24.17	(27.21)	-75.73*	(33.67)
GG	.71	(37.9)	-63.27	(47.42)
Age	-3.95*	(1.75)	.06	(1.79)
Frequency of exercise				
Nearly 1x/day	-5.47	(39.41)	16.56	(62.35)
Several times/week	5.81	(35.99)	81.56	(63.20)
1x/week	-26.70	(52.38)	N/A	N/A
<1x/week	N/A	N/A	-49.51	(75.66)
Exercise (in mins.)	-.11	(.18)	-2.58**	(.96)
R^2	.06		.29	
N	126		48	
ApoE				
E3/E2	-11.79	(134.28)	N/A	N/A

E3/E3	15.99	(128.95)	75.81	(73.42)
E4/E2	-17.46	(140.45)	N/A	N/A
E4/E3	28.04	(131.87)	152.16	(81.07)
E4/E4	5.27	(157.81)	N/A	N/A
Age	-4.50*	(2.05)	.48	(1.76)
Frequency of Exercise				
Nearly 1x/day	-10.10	(45.44)	41.92	(58.19)
Several times/week	9.37	(40.55)	99.44	(62.84)
1x/week	-28.95	(63.04)	N/A	N/A
<1x/week	N/A	N/A	-38.92	(75.55)
Exercise (in mins.)	.00	(.21)	-3.43**	(1.00)
R^2	.08		.44	
N	91		36	

Abbreviations: SE = Standard error. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 5.

Regressions with Each Polymorphism Predicting Telomere Length for Athletic and Community-Dwelling Groups for Females Only.

	Athletic Group		Community-Dwelling Group	
5-HT	b	SE	b	SE
L/S	-23.10	(33.66)	-17.45	(49.90)
L/L	-10.60	(43.61)	45.53	(69.76)
Age	.23	(1.94)	1.79	(2.55)
Frequency of exercise				
Nearly 1x/day	68.84	(41.80)	39.24	(69.92)
Several times/week	44.59	(40.22)	6.95	(60.49)
1x/week	-9.41	(81.99)	-12.82	(121.07)
<1x/week	158.80	(100.13)	-34.21	(96.17)
Exercise (in mins.)	.46	(.28)	.42	(1.59)
R^2	.09		.06	
N	76		56	
DRD2				
A1/A2	37.89	(83.74)	73.86	(157.10)
A2/A2	33.81	(78.37)	136.03	(153.65)
Age	.24	(1.94)	1.77	(2.39)
Frequency of exercise				
Nearly 1x/day	64.38	(42.16)	7.63	(67.52)
Several times/week	48.28	(40.20)	11.86	(58.94)
1x/week	-10.43	(82.04)	19.03	(122.02)
<1x/week	149.66	(99.66)	-28.59	(92.51)
Exercise (in mins.)	.44	(.28)	.74	(1.51)
R^2	.08		.06	
N	76		54	
Bcl1				
GC	-90.34*	(37.78)	113.29*	(42.81)
GG	-87.47*	(44.15)	148.94*	(70.40)
Age	.11	(1.88)	2.72	(2.36)
Frequency of exercise				
Nearly 1x/day	80.47*	(40.39)	-7.91	(65.21)
Several times/week	66.42	(40.39)	-30.47	(58.50)
1x/week	24.34	(80.65)	-43.31	(112.72)
<1x/week	193.37*	(96.73)	-33.51	(87.83)
Exercise (in mins.)	.56*	(.28)	.40	(1.47)
R^2	.16		.19	
N	76		55	
ApoE				
E3/E3	-63.15	(50.75)	33.68	(82.56)

E4/E2	73.12	(95.50)	N/A	N/A
E4/E3	-49.06	(63.84)	81.77	(91.81)
E4/E4	N/A	N/A	189.85	(140.40)
Age	-.22	(2.45)	1.63	(2.54)
Frequency of Exercise				
Nearly 1x/day	106.10*	(49.95)	59.17	(66.69)
Several times/week	81.82	(48.46)	-3.92	(60.07)
1x/week	-65.95	(107.17)	-6.34	(116.29)
<1x/week	161.64	(141.80)	-59.00	(86.51)
Exercise (in mins.)	.72	(.41)	.77	(1.69)
R^2	.22		.13	
N	54		37	

Abbreviations: SE = Standard error. * $p < .05$, ** $p < .01$, *** $p < .001$.