Delay discounting, genetic sensitivity, and leukocyte telomere length

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In a graying world, there is an increasing interest in correlates of aging, especially those found in early life. Leukocyte telomere length (LTL) is an emerging marker of aging at the cellular level, but little is known regarding its link with poor decision making that often entails being overly impatient. Here we investigate the relationship between LTL and the degree of impatience, which is measured in the laboratory using an incentivized delay discounting task. In a sample of 1,158 Han Chinese undergraduates, we observe that steeper delay discounting, indexing higher degree of impatience, is negatively associated with LTL. The relationship is robust after controlling for health-related variables, as well as risk attitude—another important determinant of decision making. LTL in females is more sensitive to impatience than in males. We then asked if genes possibly modulate the effect of impatient behavior on LTL. The oxytocin receptor gene (*OXTR*) polymorphism rs53576, which has figured prominently in investigations of social cognition and psychological resources, and the estrogen receptor β gene (*ESR2*) polymorphism rs2978381, one of two gonadal sex hormone genes, significantly mitigate the negative effect of impatience on cellular aging in females. The current results contribute to understanding the relationship between preferences in decision making, particularly impatience, and cellular aging, for the first time to our knowledge. Notably, oxytocin and estrogen receptor polymorphisms temper accelerated cellular aging in young females who tend to make impatient choices.

telomere length | delay discounting | risk attitude | oxytocin receptor | estrogen receptor

With an increasing percentage of the world's population "graying," the determinants of successful aging are of paramount importance in public health planning and policy across the globe (1). In the last decades, there has been a surge in the epidemiological research body suggesting that telomere length, indexing cellular aging, serves as an early predictor of onset of disease and earlier mortality (2–4). Telomeres are nucleoprotein structures capping the ends of chromosomes functioning to prevent their fusion and degradation (5). In humans, telomeres consist of TTAGGG repeats. Each division of a cell erodes telomere length, and when telomeres reach a critical short length, the cell enters senescence and no longer divides (6), although it may remain metabolically active and functioning. Critically short telomeres will trigger DNA damage responses that inhibit cell cycle progression. Intriguingly, the seeds of biological aging are widely thought to be planted early in life (7), even as far back as in the womb (8). Beyond the fetal period, other factors, such as the early family environment, lifestyle, and stress, also have considerable impact on cellular aging (2, 9–13).

In addition to these factors, we suggest that economic preferences characterized as overly impatient or impulsive may also correlate with cellular aging. Behavioral studies on decision making have examined the individual's preference in choosing between a more future-oriented alternative (e.g., healthy snacks) and a more tempting, but ultimately inferior, option (e.g., junk foods) (14). Although impatience can be a virtue when individuals are facing survival risks (15), the tendency to devalue future outcomes relative to the present outcomes, coined as delay discounting, has been negatively associated with a wide spectrum of life domains essential to successful aging. These include unhealthy behaviors such as substance abuse (16) and physical inactivity (17). Beyond these relationships, impatience is linked to cognitive and social incompetence, inability to cope with life frustration and stress (18), and risk of mental disorders (19, 20). These untoward effects associated with impatience suggest that steeper delay discounting may be negatively correlated with telomere length, a process potentially mediated by inflammatory response and oxidative stress (12, 13).

Drawing on these observations, in the current study, we sought to clarify the link between delay discounting and leukocyte telomere length (LTL), an emerging marker of aging at the cellular level. We examined a large group of 1,158 nominally healthy Singaporean university undergraduates, and probed the relationship between LTL with delay discounting measured by behavioral economic tasks (Fig. 1, *SI Materials and Methods*, and Table S1). In this study, subjects made a series of choices between receiving a $100 reward tomorrow and larger rewards in 30 d. By varying the monetary value of the delayed rewards, we could observe the minimum acceptable amount (MAA) for the subjects to be willing to delay the $100 reward for 30 d. Higher MAA indicates a higher degree of impatience in response to

Significance

This paper makes a singular contribution to understanding the association between biological aging indexed by leukocyte telomeres length (LTL) and delay discounting measured in an incentivized behavioral economic task. In a large group of young, healthy undergraduates, steeper delay discounting is significantly associated with shorter LTL, while controlling for risk attitude and health-related behaviors. Notably, we found that delay discounting and risk attitude—two fundamental determinants of economic preferences—are independently associated with LTL. Moreover, for the first time to our knowledge, the effects of well-studied oxytocin and estrogen receptor polymorphisms are shown to specifically moderate the impact of impatience on LTL. Our work suggests a path to integrate behavioral economic methodology to supposed biological mechanisms associated with health outcomes.

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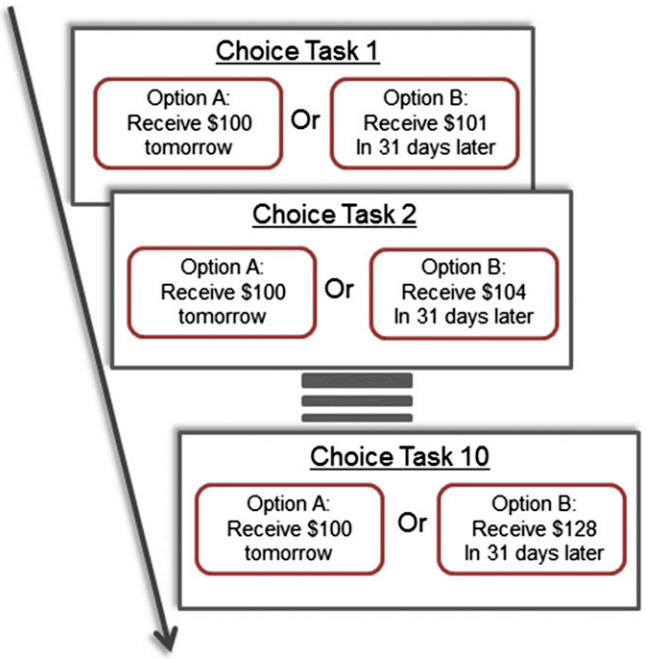

Fig. 1. Experimental tasks in measuring delay discounting. In the delay discounting task, subjects were asked to choose between receiving $100 tomorrow (option A) and a larger amount of money in 31 d later (option B). In a series of tasks, the amount in option B was increased from $101 to $128 in steps of $3. If the subject was willing to choose option B at a lower stake, for instance, $104, she would be willing to choose option B at a higher stake, for instance, $107. The task enables us to observe the MAA for the subjects to choose option B, the delayed reward.

proximate reward. We hypothesized that a higher degree of impatience would be associated with shorter LTL.

To better understand the role of impatience, we also investigated a delayed discounting task pertaining to tradeoffs in the distant future. Instead of choosing between two rewards in the near future (tomorrow versus in 31 d), subjects chose between receiving $100 in 351 d and receiving a larger amount in 381 d. Similarly, we elicited MAA for the subjects to be willing to delay the earlier reward in 351 d to a more distant future—381 d. Intriguingly, earlier neuroscience research suggested that making the tradeoff in the near future and distant future involves differential activation of separate neural systems (21). Delay discounting in the near future is driven by the limbic system, which is a neural network related to attention deficit hyperactivity disorder (22), drug dependence (23), and emotions regulation (24), whereas delay discounting in the distant future is mediated by the lateral prefrontal cortex, which is associated with deliberation and evaluating abstract rewards (25). Hence, we hypothesize that LTL is more likely to be negatively associated with MAA in the near future (MAAN)—evoking impulsive responses—but less likely to be associated with MAA in the distant future (MAAD)—involving deliberative responses.

The underlying mechanisms by which impatience is translated into telomere erosion are undoubtedly complex. Risk proneness (preference to choose riskier options) can often be a confounding factor toward understanding the role of impatience in the decision-making process. If individuals are averse to the risk inherent in delay, they may also prefer the immediate smaller rewards to the later larger reward. The degree of risk proneness is also reported to be negatively correlated with subjects' healthy behaviors (26). In this study, we elicited subjects' risk attitude by asking the subjects to decide how much to invest on an experimental stock (*SI Materials and Methods* and Table S2). Higher amount of investment in the stock indicates higher proneness to take risk. We also collected subjects' socioeconomic status (SES), approximated by family monthly income, as well as health-related variables such as body mass index (BMI) and healthy behaviors (see Tables S3 and S4 for the descriptions). Earlier studies also suggested that SES (27) and health-related behaviors (16, 17) could correlate with impatience as well as LTL (9, 10, 12). Hence, our design enables us to minimize the impact of confounds toward better understanding the relationship between delay discounting and LTL.

In addition to characterizing the behavioral processes underlying impatience and cellular aging, we investigate a number of important factors that may moderate this relationship. First, prior research suggests that early life adversity has a larger impact on females' cellular aging (28, 29). Moreover, young females tend to be more susceptible than males to stress, an effect partially explained by the inhibitory role of testosterone in males on hypothalamic pituitary axis (HPA) cortisol secretion (30, 31). Additionally, psychological stress is related to oxidative DNA damage [responsible for telomere shortening (32)] in females but not in males (33). Given these observations, we expect that females are more sensitive to impatience than males in telomere erosion.

Second, we also implement a neurogenetic strategy to further explore the biological pathways between impatience and LTL. The genetic markers we investigate in this study are known to affect inflammatory response and steroid hormone function, as well as physiological responses to psychological stress. We first genotype GST pi 1 (*GSTP1*) single-nucleotide polymorphism (SNP) rs1695, which is extensively linked to inflammatory response (34) and DNA damage (35). As earlier research suggests, inflammatory and oxidative agents play a critical part in telomere shortening, suggesting that such factors may mediate many of the adverse stressors that impinge LTL (36, 37). Additionally, we examine two well-studied estrogen receptor gene SNPs, *ESR1* rs3798577 and *ESR2* rs2978381, which are associated with endocrine abnormalities and cancer (38–42). Interestingly, telomerase is also modulated by steroid hormones such as estrogen (43, 44), potentially due to estrogens' antioxidant neuroprotective effects (45). Because its neuroprotective action is dependent on estrogen receptor activity (45), we conjecture that estrogen receptor genes may moderate the correlation between impatience and LTL. Last, we genotype the oxytocin receptor (*OXTR*) SNP rs53576 that is linked to a considerable range of cognitive and social cognitive processes (46–59). Prior evidence shows that individuals possessing the rs53576 G allele, relative to those with the A allele, are less affected by psychological stress, indicated by lower cortisol response (51) and greater psychological resources (52). Imaging studies of rs53576 (60) suggest underlying neural mechanisms of action for rs53576. We hypothesized that individuals with the G allele will be less susceptible to the deleterious effect of impatience in cellular aging.

Results

In our sample, the mean age of male university students is 1.5 y older than that of females [$M_{male} = 22$ vs. $M_{female} = 20.5$, $t(1,131) = 18.3$, $P < 0.001$], due to male subjects' 2-y compulsory military service. Females have longer LTL than males [$M_{male} = 1.01$ vs. $M_{female} = 1.06$, $t(1,026) = 3.44$, $P < 0.001$]. The age-adjusted regression confirms that females have significantly longer LTL than males ($\beta = 0.05$, $P < 0.01$). When controlling for sex, age is not significantly correlated with LTL, potentially due to the narrow age range in our sample ($M_{age} = 21.21$, SD = 1.54). These results are consistent with previous findings showing that, generally, males have shorter telomeres and higher erosion rates (61). In investigating the relationship between delay discounting and LTL, we consider sex and age as controls in the subsequent regression models.

Relationship Between Delay Discounting and LTL. The mean MAAN is $111.47 (SD = 10.42), indicating that the subjects need about $111.47 to be willing to delay a $100 reward for 30 d. There is no gender difference in MAAN [$M_{male} = 111.48$ vs. $M_{female} = 111.5$, $t(1,131) = -0.04$, $P > 0.9$]. MAAN is highly correlated with MAAD (Pearson's $\rho = 0.53$, $P < 0.001$). MAAD is significantly lower than MAAN [$M_{near} = 111.45$ vs. $M_{distant} = 108.63$, $t(1,136) = 9.4$, $P < 0.001$], suggesting that the subjects are more impatient

for the tradeoffs in the near future than the tradeoffs in the distant future. The discrepancy of impatience in the distant future and in the near future is often labeled as hyperbolic discounting (14).

We conduct linear regression analyses to test the association between MAAN (the focal independent variable) and LTL (the dependent variable) (see *SI Results* and Table S6 for full sets of model specifications and results). A significant correlation between MAAN and LTL is observed ($\beta = -0.00167$, $P < 0.05$). The sign of the coefficient is negative, indicating that higher MAAN, indicating steeper delay discounting, is associated with shorter LTL. As shown in Table 1, we further test the relationship by in turn adding two sets of control variables. In model 1, we add MAAD, sex, and age as control variables. In model 2, we add the second set of control variables consisting of risk proneness, SES, and health-related variables that are potentially confounding factors with respect to impatience and LTL. As can be seen, the association between MAAN and LTL is robust after controlling for other factors (model 1 and model 2). In contrast to MAAN, the regression models show no correlation between MAAD and LTL, consistent with our hypothesis that delay discounting in the near future, in comparison with the distant future, is related to telomere erosion.

As Table 1 model 2 shows, there is a significant correlation between LTL and risk proneness ($\beta = -0.0024$, $P < 0.05$), suggesting that the higher amount of investment, reflecting higher degree of risk proneness, is associated with shorter LTL. In the investment task, the expected rate of return on investment is 25%, i.e., it is profitable to invest money in the experimental stock. The mean investment amount in the experimental stock was \$13.27 (SD = 7.06), about half of the initial endowment \$27, which indicates that the subjects exhibit a considerable degree of risk aversion. Males, on average, invest significantly more than females [$M_{male} = \$13.96$ vs. $M_{female} = \$12.54$, $t(1,140) = 3.4$, $P < 0.001$], indicating that males are more risk-prone than females.

Among the set of control variables in model 2, low SES (family monthly income < \$2,300) and BMI are negatively correlated with LTL, which is consistent with earlier studies (10, 62). We do not find that other health-related variables we measure in this student population are significantly associated with LTL. Importantly, the relationship between MAAN and LTL is robust by controlling for these health-related variables.

The Role of Sex in Moderating the Relationship Between Delay Discounting and LTL. We hypothesized that impatience may have a sex-specific influence on LTL. We find a significant interaction effect between MAAN and sex on LTL after controlling for age [$\beta = -0.003$, $t(998) = -2.02$, $P < 0.05$]. Marked gender differences in risk and LTL shown above, as well as the differential effects of sex on stress (30, 31), led us to stratify our analyses by gender. Hence, we further analyze the data separately by sex (Table 1 model 3 for males and model 4 for females). We observe that the correlation between MAAN and LTL is significant in females ($\beta = -0.0039$, $P < 0.001$) but not in males ($\beta = -0.0015$, $P > 0.3$). We plot this relationship between LTL and MAAN in Fig. 2*A*. As can be seen from the estimated regression lines, females' LTL is more sensitive to the change in impatience than males'. By stratifying the sample by sex, other covariates are also gender sensitive. For instance, risk proneness is only negatively correlated with LTL in females but not in males (see Table 1 models 3 and 4, and Fig. 2*B*). SES and BMI are correlated with LTL in males but not in females.

Genetic Markers, Delay Discounting, and LTL. None of the genetic markers are correlated with MAAN (Pearson's correlation $P > 0.33$). Table 2 presents the estimated coefficients from the model testing the association between genetic marker and LTL (models 1 and 3), as well as the model testing the interaction effect between genetic marker and impatience on LTL (models 2 and 4) (see *SI Results* for detailed information and results for the full sample). As can be seen in Table 2 (models 1 and 3), none of the genetic markers are correlated with LTL, except *GSTP1* rs1695 (in males). The correlation between *GSTP1* and LTL is likely due to its role in modulating inflammatory response and detoxifying potentially mutagenic and toxic DNA-reactive electrophiles suggested by earlier research (34, 35).

As observed in Table 2 (models 2 and 4), *GSTP1* and *ESR1* rs3798577 do not moderate the relationship between MAAN and LTL. However, we found that the *ESR2* rs2978381 AA genotype buffers the relationship between MAAN and LTL in females (Table 2 model 4) but not in males (Table 2 model 2), as might be expected of a female gonadal hormone receptor. Fig. 2*C* illustrates the interaction effect of impatience and *ESR2* rs2978381 in females. Impatience significantly affects LTL only among females with the AG/GG genotype [$F(1,530) = 7.46$, $P < 0.01$]. There is no significant difference in LTL between patient and impatient females with the AA genotype [$F(1,530) = 0.074$, $P > 0.3$]. The findings lend some support to the notion that estrogen, perhaps due to its role as an antioxidant, can serve to protect women in response to the wear and tear evoked by chronic impatience.

As shown in Table 2, *OXTR* rs53576 GA/GG genotype, which is associated with greater psychological resources (52) in managing stress (51), buffers the impact of impatience on LTL in females ($\beta = 0.0054$, $P < 0.05$, model 4) but not in males ($P > 0.6$, model 2). We illustrate the interaction effect of impatience and *OXTR* rs53576 in females in Fig. 2*D*. Notably, impatience significantly affects LTL only among females with AA genotype

Table 1. Regression results of delay discounting on LTL

Variables	Model 1	Model 2	Model 3 (male)	Model 4 (female)
MAAN	−0.0019**	−0.0024**	−0.0015	−0.0039***
MAAD	0.0004	0.0008	0.0005	0.0011
Sex	0.0502***	0.0404**	—	—
Age	−0.0024	−0.0024	−0.0100	0.0028
Risk proneness		−0.0024**	−0.0005	−0.0034*
Low SES		−0.0726**	−0.1083***	−0.0597
BMI		−0.0095***	−0.0121***	−0.0066
Other variables on health	no	yes	yes	yes
Observations	1,000	748	344	404
R-squared	0.018	0.054	0.076	0.042

The dependent variable is LTL for all models. MAAN indexes delay discounting in the near future. We control for variables such as MAAD (indexing delay discounting in the distant future), sex, age, risk proneness, low SES (family monthly income <\$2,300), BMI, and other variables on health (physical activity, physical activity intensity, drug completion, frequency of flossing, eating healthy food, overeating, frequency of dentist visits, and smoking behavior); "yes" indicates that we included these health-related variables as controls in the model. The number of observations varies because of attrition of the participants in different waves of studies. Robust SEs corrected for heteroscedasticity were used and reported in *SI Results* and Table S6; *$P < 0.1$; **$P < 0.05$; ***$P < 0.01$ (two-tailed).

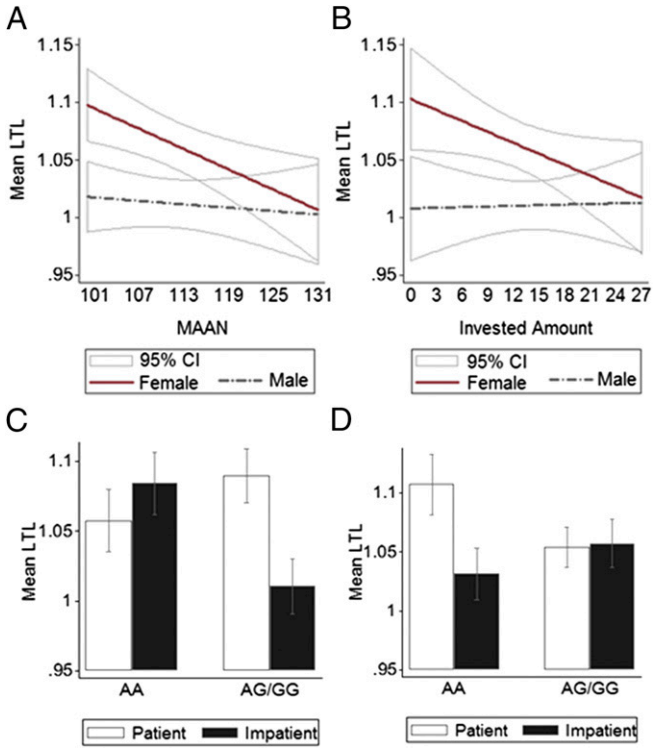

Fig. 2. (*A*) Estimated regression lines for impatience and LTL. From the estimated regression lines in the figure, females' LTL appears more sensitive to the change in impatience (indicated by MAAN) than males'. Along the regression lines, 95% confidence intervals are presented. (*B*) Estimated regression lines for risk proneness and LTL. From the estimated regression lines in the figure, females' LTL appears more sensitive to the change in risk proneness (indicated by larger amount of investment) than males'. Along the regression lines, 95% confidence intervals are presented. (*C*) Interaction between ESR2 and impatience. Subjects are categorized as "patient" if their MAA is smaller than $110 (the median); otherwise, they are "impatient." Impatience affects LTL only for females with the G genotype for ESR2 rs2978381. There is no significant difference in LTL between patient and impatient females if they lack the G allele. Error bars represent ±1 SE. (*D*) Interaction between OXTR and impatience. Subjects are categorized as "patient" if their MAA is smaller than $110; otherwise, they are "impatient." Impatience affects LTL only for females with the AA genotype for OXTR rs53576. There is no significant difference in LTL between patient and impatient females if they possessed the G allele. Error bars represent ±1 SE.

$[F(1, 531) = 5.45, P = 0.02]$. There is no significant difference in LTL between patient and impatient females if they are carriers of the GA/GG genotype $[F(1,531) = 0.01, P > 0.9]$. The results suggest that the G allele modulates the deleterious impact of impatience and that this allele plays the role of a protective buffer.

Discussion

Our results indicate that shorter LTL is associated with steeper delay discounting as measured in a behavioral economic task. The additional task measuring risk attitude allows us to disentangle the impact of delay discounting and risk attitude on LTL, and minimize the potential confound of these two variables. As we show, the correlation between delay discounting and LTL is robust to adjustments for sex, age, SES, risk proneness, and an array of lifestyle behaviors in this young sample. The results are consistent with prior findings that early life stress can already have a deleterious impact on telomere length at a young age (2, 9–13).

Notably, we found that gender moderates the relationship between impatience and cellular aging. When the sample in this study is stratified by sex, the association between delay discounting and LTL is observed in females but not in males. Our findings are in agreement with earlier evidence that females are more sensitive to social adversity and stress (28, 29, 63) with respect to cellular aging. Overall, shortened LTL mirrors the cell's mitotic history and replicative history of hematopoietic stem cells, and is further subjected to the effects of inflammation and oxidation (36, 37, 64). Interestingly, as prior reports show, there are gender-specific effects of oxidative stress and inflammation markers in response to psychological stress, lifestyle, and disease (33, 65, 66). Although estrogen was shown to have antioxidant neuroprotective effects in response to stress for females (45, 67), young women may be more sensitive to psychological stress (30). Higher susceptibility in response to psychological stress could potentially "trump" the positive impact of estrogen in modulating oxidative stress. Importantly, during the early years of development, psychological challenges appear to preferentially increase the risk for affective disorders in females, especially during their reproductive years, reflecting their greater vulnerability to psychological stress (30). Studies in rodents and humans point to an increased susceptibility to stress in females during the peripubertal and pubertal window of maturation, a period suggested to be critical for programming of long-term risk for stress-related affective disorders (68).

We also document that specific genetic polymorphisms moderate the impact of impatience on biological aging. The well-studied *OXTR* SNP rs53576 buffers the impact of impatience on LTL in the expected direction: Individuals with AG/GG genotype are less sensitive to the negative impact of impatience on LTL. This moderating effect is statistically significant in females but not in males, which is consistent with early studies showing that rs53576 has gender-specific effects on modulating stress (69) and anxiety-related temperament (70). We observe that *ESR2* rs2978381 AA genotype mitigates the impact of impatience on LTL for females but not for males. The effect we observe is only with *ESR2* consistent with a recent study showing a relationship between this receptor and anxiety (71). Altogether, our neurogenetic results indicate that oxytocin and estrogen receptors modulate the relationship between delay discounting and telomere length, an effect that is particularly pronounced in one gender.

Given the nature of the data in our study, we are unable to conclusively disentangle two potential underlying mechanisms, namely, impatience leads to shortened LTL or, alternatively, shortened telomeres lead to impatience (state-dependent model) as in Bateson et al. (72), who documented a similar phenomenon regarding the association between delay discounting and telomere length in European starlings (*Sturnus vulgaris*). Some results in our study are suggestive that impatience leads to shortened telomeres in contrast to the notion suggested by Bateson et al. (72) that shorter telomeres somehow lead to impatient behavior. For example, we would expect that if a state-dependent model is involved as Bateson et al. suggest (72), then shorter LTL would also be correlated with delay discounting in the distant future. However, if shorter telomeres are the consequence of impatient behavior as we suggest, only delay discounting in the near future should be significantly associated with the erosion of telomeres. We do not find any association between LTL and delay discounting in the distant future, implying that the correlation between impatience and LTL in our study is less aligned with the state-dependent decision-making model. The neurogenetic results are also consistent with our argument, because it is difficult to understand how a state-dependent decision-making model would predict the interaction effects of moderating variables such as *OXTR* or *ESR2* polymorphisms on LTL. Nevertheless, we emphasize that, regardless of the causal direction, the important notion is that the correlation between shorter telomeres and impulsive behavior is reproducible remarkably across boundaries of taxonomic species and even class. In addition to strengthening our findings, a similar observation in birds and humans further suggests that both findings may point to a shared evolutionary biological origin for an untoward relationship between impatient decision making and aging at the biological level.

An important limitation of our study pertains to its cross-sectional design, and therefore the results can only be interpreted as correlational. Whether or not shorter LTL is the consequence of

Table 2. Regression estimates of gene delay discounting interaction effect on LTL

	Male		Female	
Variables	Assoc. (model 1)	Interact. (model 2)	Assoc. (model 3)	Interact. (model 4)
MAAN	−0.0017	−0.0013	−0.0040***	−0.0051***
GSTP1	0.0786***	0.2094	0.0316	−0.3446
GSTP1 × MAAN		−0.0012		0.0034
MAAN	−0.0016	−0.0007	−0.0039***	−0.0039*
ESR1	0.0373	0.1798	0.0164	0.0213
ESR1 × MAAN		−0.0013		−0.0000
MAAN	−0.0015	−0.0022	−0.0039***	−0.0007
ESR2	0.0040	−0.1283	−0.0037	0.6461**
ESR2 × MAAN		0.0012		−0.0058**
MAAN	−0.0015	−0.0023	−0.0039***	−0.0073***
OXTR	−0.0067	−0.1551	−0.0327	−0.6489**
OXTR × MAAN		0.0013		0.0055**

The dependent variable is LTL for all models. The genetic markers we investigate are *GSTP1* rs1695, *ESR1* rs3798577, *ESR2* rs2978381, and *OXTR* rs53576. For all of the SNPs, we assumed a dominant model, and G-allele is the dominant allele. To test the association (Assoc.) between specific genes and LTL, and the interaction effect (Interact.) between genetic markers and impatience on LTL, we include all of the other control variables in the regression model, including MAAD, age, risk proneness, SES, and other health-related variables, but we omit these coefficients and R-squared in the table (see *SI Results* and Table S7 for fuller results). We add one genetic marker each time to the model. In models 1 and 3, we report the coefficients on MAAN and the genetic marker. In models 2 and 4, we report the coefficients on MAAN, the genetic marker, and the interaction between genetic marker and MAAN. Robust SEs corrected for heteroscedasticity were used (see *SI Results* and Table S7); $*P < 0.1$; $**P < 0.05$; $***P < 0.01$ (two-tailed).

impatience remains an open question. Future work can be carried out longitudinally to more tightly determine the factors that modulate telomere change over time. In addition, the absence of a physiological measure of stress in the current study prevents us from substantiating our conjecture that impatience leads to biological stress that in turn leads to shorter LTL. In the study, we attempted to explore whether *GSTP1* rs1695—a well-studied inflammatory marker—moderates the relationship between impatience and LTL. Although we did not find an interaction between *GSTP1* rs1695 and impatience on LTL, our finding of a main effect suggests that this inflammatory marker polymorphism may play an important role in telomere erosion. Future research can extend our investigation to consider direct measures of oxidative stress and inflammatory response or other genetic markers toward better understanding the relationship between impatience and cellular aging.

Notwithstanding these limitations, our research makes a number of salient contributions. First, our study links a fundamental determinant of decision making, delay discounting that is measured in an incentivized laboratory behavioral paradigm, to a molecular marker for cellular aging in humans. Hence, this study lays down a strategy toward integrating the crispness of behavioral economic tasks to biological mechanisms associated with health outcomes. We further show that the impact of impatience on LTL is gender-sensitive and impatient women are especially affected. Underlying biological pathways modulating the effect of impatience on LTL are revealed using a neurogenetic strategy. Specifically, a well-studied *OXTR* SNP rs53576 and an *ESR2* SNP rs2978381 interact with delay discounting to buffer the untoward effect of impatience on LTL in females. The results suggest that the trajectories by which impatience is translated into cellular aging depend on individual characteristics relating to gender and genotype, among others yet to be identified.

Materials and Methods

Participants. We recruited 1,158 (51.6% females; $M_{age} = 21.2$, SD = 1.5) Han Chinese undergraduate students at National University of Singapore to participate in an economic decision-making experiment. The study was approved by Institutional Review Board of National University of Singapore, and subjects gave written informed consent before participating. Subjects were reimbursed for participation in the project (Singapore $25 per hour on average).

The study consisted of three stages. In stage 1, we conducted an economic decision-making experiment measuring delay discounting and risk attitude. In stage 2 (a few days after stage 1), participants donated 10–20 mL of blood for extracting DNA information. In stage 3 (immediately after stage 2), participants received an email invitation for an online survey in which we administered questions on demographics (age, sex, and family monthly income), height, weight, and health-related variables (see *SI Materials and Methods*).

LTL Measurement and Genotyping. LTL was measured using techniques modified from Cawthon (73), which comprise distinct polymerase chain reactions (PCR) that are normalized to a single-copy gene, generating the relative telomere to single copy (T/S) gene ratio as a measure of relative LTL. Quantitative PCR were carried out on the CFX96 Real-Time PCR Detection System from Bio-Rad. The *GSTP1* rs1695, *ESR1* rs3798577, *ESR2* rs2978381, and *OXTR* rs53576 genotyping was carried out using a 5′-nuclease Taqman assay with primers and probes from Applied Biosystems (catalog number 4351379). PCRs were performed using Qiagen's HotStarTaq Plus DNA polymerase (catalog number 203601) on BioRad's CFX96 Real-Time PCR Detection System. Additional details are presented in *SI Materials and Methods* and Table S5.

Statistics. Most analyses were based on linear regression models. We reported both the coefficient from the regression and the significance level (two-tailed) of the coefficient. SEs corrected for heteroscedasticity were used and reported in *SI Results* and Tables S6 and S7. All of the statistics reported here are based on two-tailed tests. All analyses were conducted using Stata 12. See *SI Results* for detailed model specification and regression results.

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Supporting Information

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SI Materials and Methods

Overview of the Study Design. We recruited 1,158 (51.6% females; M_{age} = 21.2, SD = 1.5) Han Chinese undergraduate students at National University of Singapore. The study was approved by Institutional Review Board of National University of Singapore, and subjects gave written informed consent before participating. Subjects were anonymized by the assignation of a coded identification number, which was used for all work postrecruitment. Consent forms and the participant master list containing personally identifiable information were kept separately under lock and key by the principal investigator. The study consisted of three stages. In stage 1, we conducted economic decision-making experiments measuring delay discounting and risk proneness. All 1,158 subjects participated in an overall 2-h session with other unrelated experiments. The money earned in these other experiments was paid at the end of each session. At the time our subjects participated in this intertemporal choice task, they did not learn about the amount they might have earned in other tasks. In stage 2 (a few days after stage 1), participants donated 10–20 mL of blood for extracting DNA. In stage 3 (immediately after stage 2), participants received an email invitation for the online survey in which we administered questions on demographics (age, sex, and family monthly income), height, weight, and health-related variables.

Experimental Measurement of Impatience and Risk Proneness. Subjects' MAA was elicited from their choices in two menus related to the near and distant future. We used the multiple price list design, which is widely used in experimental economics (14). The task is based on the premise that if a subject prefers a smaller, earlier monetary reward, to a larger, later monetary reward, she/he is considered to be more impatient than someone who prefers a larger, later reward.

In the near future menu, subjects were asked to indicate their preferences with 10 choices between receiving \$100 (~US \$77 in 2010) on the next day and receiving \$101 (\$104/\$107/\$110/\$113/\$116/\$119/\$122/\$125/\$128) 31 d later (see Fig. 1*A* and Table S1). In another distant future menu of 10 choices, subjects chose between receiving \$100 351 d later and receiving a larger amount, from \$101 to \$128, 381 d later. One of his or her 20 choices was selected randomly for real payment, and one subject in each session was selected randomly to receive the payoff. Each session consisted of 50–100 subjects.

Because the payment on the next day (351 d later) was fixed at \$100 while the payment 31 d later (381 d later) was monotonically increasing in the menu, it can be surmised that, if they preferred \$110 31 d later rather than \$100 the next day, for instance, they should prefer \$112 31 d later rather than \$100 the next day. Hence, for both the near future and the distant future menu, we recorded the MAA for which the subjects were willing to postpone the reward for 30 d. If subjects prefer \$100 sooner to \$128 later, we coded their MAA as \$131. Higher discount rates were indexed by larger MAA. The money earned for this experiment was paid at the end of each session. The subject received a postdated check for his or her payment.

Instructions to Subjects in Discounting Task. Subjects were given the following instructions.

"This task involves your choosing between receiving a sum of money on a specific day and another sum of money on another specific day. There are 20 choices to make. The first 10 pairs of choices are about receiving \$100 tomorrow versus receiving a larger amount 31 d later; the next 10 pairs of choices are about receiving \$100 in 351 d versus receiving a larger amount of money in 381 d."

"For this task, we will pay one randomly selected participant in this room at the end of today's study. For this participant, we will choose randomly one out of the 20 choices and pay him/her accordingly. Specifically, we will give him/her a check with the specified date at the end of today's experiment. Under Singapore banking practices, a check can be cashed only on or within 6 mo of the date of the check."

"For each of the 20 rows in the table below (Table S1), please indicate your decision in the final column with a tick (√)."

Risk proneness was measured by an investment task. In the task, subjects are endowed with \$27. They have the option to invest any amount between \$0 and \$27 in steps of \$3 on an experimental stock constructed from a deck of 20 cards comprising 10 black cards and 10 red cards. For every dollar invested, they receive \$2.50 if they guess the color of a randomly drawn card correctly. Otherwise, they receive \$0 and lose their investment (see Table S2). The more subjects are willing to invest in the experimental stock, the more risk-prone they are. There are 10 options in the task, and we recorded which option the subjects chose. This investment task was first introduced by Gneezy and Potters (74). In the following are the instructions that were given to participants. Note that amounts in this section are in Singapore dollars (Singapore \$1 ≈ US \$0.77 in 2010).

Instructions to Subjects in Investment Task. Subjects were given the following instructions.

"In this task, you are endowed with \$27. You have the option to invest an amount on an experimental stock constructed from a deck of 20 cards comprising 10 black cards and 10 red cards. For every dollar invested, you receive \$2.5 if you guess the color of a randomly drawn card correctly. Otherwise, you receive \$0 and lose your investment. The following table displays your investment options, which consist of investing between \$0 and \$27 in steps of \$3 in this experimental stock and keeping the rest as cash. The last two columns indicate your total earnings given by cash + investment return for the cases of correct and incorrect guesses, respectively."

"For the following 10 investment options, listed in the table below (Table S2) in an ascending manner in terms of the amount of investment, please indicate the one option that you most prefer with a tick (√)."

Online Survey. An online survey was conducted on Qualtrics.com. Participants were asked to report their sex, age, family monthly income, height, weight, and health-related behaviors (see the actual questions below). The questions on health-related behavior followed the exact wording from Chabris et al. (75).

Questions on Health Related Behaviors. Subjects were asked the following questions.

i) How many hours per week are you physically active (for example, walking, working around the house, working out)?
ii) How many of those hours represent exercise primarily intended to improve or maintain your health or fitness? (1. Low. 2. Medium. 3.High)
iii) In a typical week, how often do you choose your food (the type and/or amount) with health and fitness concerns in mind? (1. Every meal. 2. Most meals. 3. Some meals. 4. Few meals. 5. No meals)

iv) How often do you visit your dentist for a check-up? (1. Two times a year. 2. Once per year. 3. Less than once a year. 4. Never)
v) When your doctor gives you a prescription to fill at the drugstore (excluding birth control), do you follow it exactly (for example, by going to the drugstore, picking up the medication, taking all of the medication on schedule, and finishing the entire prescription)? (1. Always. 2. Usually. 3. Sometimes. 4. Rarely)
vi) How often do you floss your teeth? (1. At least once per day. 2. Most days each week. 3. Once or twice each week. 4. Rarely or never)
vii) In a typical week, how often do you eat more than you think you should eat? (1. No meal. 2. Few meal. 3. Some meals. 4. Most meals. 5. Every meal)

Measurement of Relative Telomere Length. LTL was measured using techniques modified from Cawthon (73), which comprise distinct PCR reactions that are normalized to a single-copy gene, generating a T/S ratio as a measure of relative LTL. The qPCR assay for LTL shows reasonable correlation with results from the so-called gold-standard Southern blot analyses and has been widely adopted for high-throughput studies such as the current investigation. Forty randomly selected samples at 100-ng/μL concentrations were used to create a pooled DNA standard of 80 ng/μL, which was then serially diluted to produce standards of 40-ng/μL, 20-ng/μL, 10-ng/μL, 5-ng/μL, 2.5-ng/μL, and 1.25-ng/μL concentrations. Both standards and samples were assayed in triplicate for each DNA sample on opaque 96-well skirted hard-shell plate from Bio-Rad (catalog number HSP9655 or HSP9665). Quantitative PCR were carried out on the CFX96 Real-Time PCR Detection System from Bio-Rad.

The primer sequences used were 5′-ACACTAAGTTTGGGTTTGGGTTTGGGTTTGGGTTAGTGT-3′ for telg, 5′-TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCCTAACA-3′ for telc, 5′-CGGCGGCGGGCGGCGCGGGCTGGGCGGCTTCATCCACGTTCACCTTG-3′ for hbgu, and 5′-GCCCGGCCCGCCGCGCCCGTCCCGCCGGAGGAGAAGTCTGCCGTT-3′ for hbgd. Each reaction contained 5 μL of 2× QuantiFast SYBR Green PCR Master Mix (catalog number 204054; Qiagen), 0.9 μL each of 10 μM telg and telc primers, 0.5 μL each of 10 μM hbgu and hbgd primers, 20 ng of genomic DNA, 0.05 μL of 1 M DTT, and sterile water to a total volume of 10 μL.

Real-time quantitative polymerase chain reactions were performed using the following protocol: 15 min at 95 °C, two cycles of 15 s at 94 °C followed by 15 s at 52 °C, 32 cycles of 15 s at 94 °C, 10 s at 62 °C, 15 s at 74 °C with fluorescent signal acquisition, 10 s at 84 °C, and, finally, 15 s at 88 °C with signal acquisition. The amplification of the telomeres was read at the 74 °C fluorescence acquisition while the 88 °C signal acquisition read the amplification of the housekeeping beta-globin gene. PCR was performed on a CFX96 Real-Time PCR Detection System (Bio-Rad), and the cycle threshold values were calculated directly by the operating software. Means of the triplicate readings were used for determination of the starting quantity of telomeres and housekeeping genes, and the LTL is presented as the ratio of the telomeres to the housekeeping genes. A coefficient of variation (CV) cutoff of <10.0% was applied to filter the triplicate results by removing samples that gave inconsistent measurements even after repeated assays. These samples were then evaluated for quality on a second tier, using a <5.0% CV threshold for duplicate readings; 92 samples that failed both tiers of quality evaluation were dropped from analyses.

GSTP1 rs1695, ESR1 rs3798577, ESR2 rs2978381, and OXTR rs53576 Genotypes. The *GSTP1* rs1695, *ESR1* rs3798577, *ESR2* rs2978381, and *OXTR* rs53576 genotyping were carried out using a 5′-nuclease Taqman assay with primers and probes from Applied Biosystems (catalog number 4351379). PCRs were performed using Qiagen's HotStarTaq Plus DNA polymerase (catalog number 203601) on BioRad's CFX96 Real-Time PCR Detection System. The protocol used was as follows: 5 min at 95 °C, and 45 cycles of 15 s at 95 °C followed by 60 s at 60 °C with fluorescent signal acquisition.

SI Results

Descriptive Statistics. The summary statistics of LTL, delay discounting (in near future and distant future), risk proneness (indicated as amount of money invested), age, and family monthly income are presented in Table S3. The total number of subjects is not equal to the sum of male and female numbers, because nine subjects did not provide their gender information. The distribution of LTLs for the sample and the QQ plots by gender are given in Fig. S1. As can be seen, the distribution of female LTL is similar to male LTL. Females have, on average, longer LTL. The descriptive statistics for the health-related variables are provided in Table S4. These variables indicate that the participants in our study are relatively health. For instance, less than 3% of the subjects smoke, and the average BMI is low (M_{BMI} = 20.99, SD = 2.78). The distribution of genotypes for the *GSTP1* rs1695, *ESR1* rs3798577, *ESR2* rs2978381, and *OXTR* rs53576 is presented in Table S5.

Variables Used in the Regressions. Participants' BMI was calculated using the standard formula: BMI = weight (kg)/[height (m)]^2. As to SES, we first categorized the family monthly income by quartiles, representing income less than $2,300, $2,300 to ~$4,000, $4,000 to ~$6,700, and more than $6,700, respectively. In the regression analysis, we consider individuals whose family monthly income is <$2,300 as low SES. Hence SES is coded as "1" if family monthly income is <$2,300 and as "0" otherwise. Fifteen participants indicated more than 168 h of physical activity per week, which is logically impossible, and hence we excluded them in the regression analysis. Our main regression results were not affected by how we coded the income variable or whether we excluded the 15 participants with unrealistic physical activity hours.

In the analysis on genetic markers, we assumed dominant models. For the genetic markers we investigated, G allele is the minor allele. That is, we constructed the variable as "1" if the individual is AG or GG genotype; otherwise, we used "0." It is noteworthy that, for *OXTR* rs53576, we assumed a dominant model for G allele, which is consistent with some previous research from East Asia on rs53576 (50, 55). In East Asian populations, the AA homozygous are in much higher frequency than in Western populations (50), which sometimes leads to a so-called "allele flip-flop" phenomenon (76), and the protective allele is the G allele. An "allele flip" occurs when one investigation observes an allele to be protective and a second study finds the allele to be associated with enhanced disease risk. However, in the current study, we do not observe such an allele flip-flop. We constructed a dummy variable $OXTR = 1$ if the genotype wass AG or GG; otherwise, $OXTR = 0$.

Regression Model Specifications. We conducted linear regression analyses for investigating the relationship between delay discounting in the near future, indexed by MAAN and LTL. From model 1 to model 4 in Table S6, we gradually increased other control. In model 1, we simply regressed MAAN on LTL without any controls. In model 2, we added MAAD as a control. In model 3, we added sex and age as controls. In model 4—the full model—we added other controls: risk proneness, SES, BMI, and other health-related variables (physical activity, physical activity intensity, drug completion, frequency of flossing, eating healthy food, overeating, frequency of dentist visits, and smoking behavior). Formally, the regression model for model 4 is

$$\mathrm{LTL}_i = \beta_0 + \beta_1 MAAN_i + \beta_2 MAAD_i + \cdots + \beta_{14} Smoking_i + \varepsilon_i.$$

The subscript i indicates the observation for individual i. $\beta_0, \beta_1, \ldots, \beta_{14}$ represent the coefficients corresponding to each

independent variable. In total, we have 13 independent variables. Here β_0 is the constant. Table S6 presents coefficients from the full model. We interpret the negative coefficient for "smoker" in model 5 with caution. The coefficient indicates that being a nonsmoker leads to longer LTL in males. However, among 417 male subjects who provided their information on smoking status, only 13 (3%) subjects are smokers. Hence, the inference based on these 3% smokers is statistically inconclusive.

To examine the main effect of the gene marker on LTL, we regress the full model with all previous independent variables by adding the gene marker as an additional independent variable, the coefficients of which would indicate the direction of association between the gene marker and LTL. Specifically, we have the following model:

$$LTL_i = \beta_0 + \beta_1 MAAN_i + \beta_2 MAAD_i + \cdots + \beta_{14} Smoking_i + \beta_{15} Gene_i + \varepsilon_i.$$

The coefficient β_{15} denotes the impact of gene marker on LTL. We run this model specification for each gene marker separately (the *GSTP1* rs1695, *ESR1* rs3798577, *ESR2* rs2978381, and *OXTR* rs53576). In Table 2 models 1 and 3, we report the estimated coefficients for male and female samples, separately. We report the fuller results in Table S7 (models 1, 3, and 5 for full sample, males, and females, respectively).

To examine the gene × delay discounting interaction effect on LTL, we regress the full model (as in model 4 in Table 1) by adding the gene marker as well as the interaction between MAAN and the gene marker as additional independent variables. As a result, we have the following model:

$$LTL_i = \beta_0 + \beta_1 MAAN_i + \beta_2 MAAD_i + \cdots + \beta_{14} Smoking_i + \beta_{15} Gene_i + \beta_{16} Gene_i \times MAAN_i + \varepsilon_i.$$

The coefficient β_{16} denotes the gene × delay discounting interaction effect on LTL. Similarly, we run this model specification for each gene marker separately. In Table 2 models 2 and 4, we report the estimated coefficients for male and female samples, separately. We report the fuller results in Table S7 (models 2, 4, and 5 for full sample, males, and females, respectively).

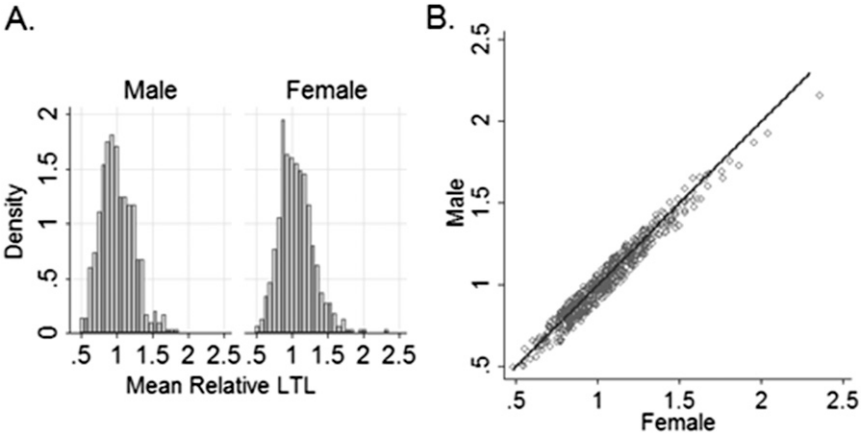

Fig. S1. Distribution of LTL (*A*) Distribution of LTL by sex. (*B*) QQ plot of LTL (male vs. female).

Table S1. Discounting Task

Tasks	Tomorrow	31 d later	Decision	Tasks	351 d later	381 d later	Decision
1	$100	$101	A □ B □	11	$100	$101	A □ B □
2	$100	$104	A □ B □	12	$100	$104	A □ B □
3	$100	$107	A □ B □	13	$100	$107	A □ B □
4	$100	$110	A □ B □	14	$100	$110	A □ B □
5	$100	$113	A □ B □	15	$100	$113	A □ B □
6	$100	$116	A □ B □	16	$100	$116	A □ B □
7	$100	$119	A □ B □	17	$100	$119	A □ B □
8	$100	$122	A □ B □	18	$100	$122	A □ B □
9	$100	$125	A □ B □	19	$100	$125	A □ B □
10	$100	$128	A □ B □	20	$100	$128	A □ B □

Table S2. Investment Task

	Investment, dollars		Total earnings, dollars	
Portfolio choices	Cash	Invest	Correct guess	Incorrect guess
1	27.00	0.00	27.00	27.00
2	24.00	3.00	31.50	24.00
3	21.00	6.00	36.00	21.00
4	18.00	9.00	40.50	18.00
5	15.00	12.00	45.00	15.00
6	12.00	15.00	49.50	12.00
7	9.00	18.00	54.00	9.00
8	6.00	21.00	58.50	6.00
9	3.00	24.00	63.00	3.00
10	0.00	27.00	67.50	0.00

Table S3. Descriptive statistics for relative LTL, MAAN, MAAD, risk proneness, age, and family monthly income

Variables	Number	Mean	SD	Min	Max
Relative LTL					
Male	493	1.01	0.23	0.51	1.84
Female	535	1.06	0.24	0.48	2.30
Total	1,028	1.04	0.24	0.48	2.30
MAAN					
Male	549	111.80	10.52	101	131
Female	584	111.76	9.71	101	131
Total	1,141	111.76	10.10	101	131
MAAD					
Male	549	108.90	10.19	101	131
Female	586	109.23	9.88	101	131
Total	1,144	109.11	10.05	101	131
Risk proneness					
Male	551	13.96	7.32	0	27
Female	591	12.54	6.74	0	27
Total	1,151	13.27	7.08	0	27
Age					
Male	549	21.97	1.39	18	30
Female	584	20.50	1.32	18	28
Total	1,133	21.21	1.54	18	30
Family monthly income					
Male	540	5,206.49	5,363.77	0	8,0000
Female	573	5,400.58	5,099.06	0	4,2000
Total	1113	5,306.41	5,227.71	0	8,0000

Table S4. Descriptive statistics for the health-related variables

Variables	Observations	Mean	SD	Min	Max
Physical activity					
Male	554	22.95	35.46	0	500
Female	591	23.02	31.75	0	200
Total	1,145	1.74	0.64	0	500
Physical intensity					
Male	554	1.87	0.64	1	3
Female	591	1.62	0.62	1	3
Total	1,145	1.74	0.64	1	3
Healthy food intake					
Male	417	3.19	0.96	1	5
Female	479	2.99	0.94	1	5
Total	896	3.08	0.95	1	5
Dental visit frequency					
Male	417	2.65	0.91	1	4
Female	479	2.60	0.90	1	4
Total	896	2.62	0.91	1	4
Drug completion					
Male	417	2.16	0.87	1	4
Female	479	2.19	0.89	1	4
Total	896	2.18	0.88	1	4
Flossing frequency					
Male	417	3.55	0.87	1	4
Female	479	3.41	0.92	1	4
Total	896	2.65	0.91	1	4
Overeating					
Male	417	2.61	0.84	1	5
Female	479	2.69	0.88	1	5
Total	896	2.65	0.86	1	5
Tobacco smoking					
Male	417	1.97	0.17	1	2
Female	479	1.97	0.16	1	2
Total	896	1.97	0.17	1	2
BMI					
Male	523	21.79	2.87	15.63	34.89
Female	559	20.24	2.46	15.06	31.25
Total	1,082	20.99	2.78	15.06	34.89

The variables are physical activity frequency, physical activity intensity, healthy food intake, dental visit frequency, drug completion when given prescription drugs, flossing frequency, overeating frequency, tobacco smoking behavior (1, smoker; 2, nonsmoker), and BMI.

Table S5. Distribution of genotypes

	Number, %											
	Male				Female				Full sample			
SNP	Homozy1	Heterozy	Homozy2	Total	Homozy1	Heterozy	Homozy2	Total	Homozy1	Heterozy	Homozy2	Total
OXTR rs53576 (A/G)	195 (39.6)	242 (49.1)	56 (11.4)	493	225 (42.0)	248 (46.4)	62 (11.6)	535	420 (40.9)	490 (47.7)	118 (11.5)	1,028
GSTP1 rs1695 (A/G)	321 (65.6)	152 (31.1)	16 (3.3)	489	358 (67.7)	156 (29.5)	15 (2.8)	529	679 (66.7)	308 (30.3)	31 (3.0)	1,018
ESR1 rs3798577 (A/G)	165 (33.6)	233 (47.5)	93 (18.9)	491	183 (34.3)	253 (47.4)	98 (18.4)	534	348 (34.0)	486 (47.4)	191 (18.6)	1,025
ESR2 rs2978381 (A/G)	228 (46.4)	215 (43.8)	48 (9.8)	491	245 (45.9)	240 (44.9)	49 (9.2)	534	482 (46.5)	458 (44.2)	97 (9.4)	1,025

Homozy1 and Homozy2 denote the homozygote genotypes in alphabetical order of the alleles, not in the order of allele frequencies. All SNP genotypes are in Hardy–Weinberg Equilibrium as tested by χ^2 tests. A/G denotes either the A or G allele of the SNP.

Table S6. Full regression results of delay discounting on LTL

Variables	Model 1	Model 2	Model 3	Model 4	Model 5 (male)	Model 6 (female)
MAAN	−0.0017**	−0.0019**	−0.0019**	−0.0024**	−0.0015	−0.0039***
	(0.0007)	(0.0009)	(0.0009)	(0.0010)	(0.0016)	(0.0014)
MAAD		0.0004	0.0004	0.0008	0.0005	0.0011
		(0.0009)	(0.0009)	(0.0010)	(0.0015)	(0.0014)
Sex			0.0502***	0.0404†	—	—
			(0.0164)	(0.0195)	—	—
Age			−0.0024	−0.0024	−0.0100	0.0028
			(0.0054)	(0.0063)	(0.0098)	(0.0084)
Risk proneness				−0.0024**	−0.0005	−0.0034*
				(0.0012)	(0.0016)	(0.0018)
Low SES				−0.0726**	−0.1083***	−0.0597
				(0.0294)	(0.0361)	(0.0463)
BMI				−0.0095***	−0.0121***	−0.0066
				(0.0030)	(0.0044)	(0.0043)
Physical activity				−0.0224	−0.0354*	−0.0097
				(0.0144)	(0.0208)	(0.0201)
Physical intensity				0.0002	0.0006	−0.0001
				(0.0003)	(0.0005)	(0.0004)
Drug completion				−0.0129	−0.0240*	−0.0035
				(0.0092)	(0.0141)	(0.0120)
Floss				0.0068	0.0172	−0.0061
				(0.0090)	(0.0133)	(0.0127)
Healthy food				0.0086	0.0123	0.0058
				(0.0088)	(0.0124)	(0.0124)
Overeat				0.0109	0.0205	0.0062
				(0.0116)	(0.0164)	(0.0161)
Dental				0.0005	−0.0098	0.0059
				(0.0103)	(0.0147)	(0.0157)
Smoker				−0.0336	−0.1722**	0.0856
				(0.0520)	(0.0743)	(0.0660)
Constant	1.2319***	1.2154***	1.1818***	1.5004***	1.9366***	1.3416***
	(0.0800)	(0.0876)	(0.1502)	(0.2190)	(0.3220)	(0.2874)
Observations	1,013	1,010	1,000	748	344	404
R-squared	0.005	0.006	0.018	0.054	0.076	0.042

In addition to Table 1, full results are presented here, including coefficients on health-related variables. Robust SEs corrected for heteroscedasticity were used and reported in parentheses; *$P < 0.1$; **$P < 0.05$; ***$P < 0.01$ (two-tailed).

Table S7. Regression estimates of gene delay discounting interaction effect on LTL

	Full		Male		Female	
Variables	Association (model 1)	Interaction (model 2)	Association (model 3)	Interaction (model 4)	Association (model 5)	Interaction (model 6)
GSTP1						
MAAN	−0.0025**	−0.0029**	−0.0017	−0.0013	−0.0040***	−0.0051***
	(0.0010)	(0.0012)	(0.0016)	(0.0018)	(0.0014)	(0.0016)
Risk proneness	−0.0027**	−0.0027**	−0.0008	−0.0009	−0.0033*	−0.0033*
	(0.0012)	(0.0012)	(0.0016)	(0.0016)	(0.0018)	(0.0018)
GSTP1	0.0525‡	−0.0655	0.0786***	0.2094	0.0316	−0.3446
	(0.0183)	(0.1933)	(0.0265)	(0.2762)	(0.0262)	(0.2724)
GSTP1 × MAAN		0.0011		−0.0012		0.0034
		(0.0017)		(0.0024)		(0.0024)
Observations	748	748	344	344	404	404
R-squared	0.060	0.060	0.101	0.101	0.045	0.049
ESR1						
MAAN	−0.0024**	−0.0017	−0.0016	−0.0007	−0.0039***	−0.0039*
	(0.0010)	(0.0014)	(0.0016)	(0.0021)	(0.0014)	(0.0020)
Risk proneness	−0.0027**	−0.0027**	−0.0004	−0.0005	−0.0034*	−0.0034*
	(0.0012)	(0.0012)	(0.0016)	(0.0016)	(0.0018)	(0.0018)
ESR1	0.0281	0.1686	0.0373	0.1798	0.0164	0.0213
	(0.0182)	(0.1876)	(0.0265)	(0.2764)	(0.0262)	(0.2619)
ESR1 × MAAN		−0.0013		−0.0013		−0.0000
		(0.0017)		(0.0025)		(0.0023)
Observations	746	746	343	343	402	402
R-squared	0.052	0.053	0.081	0.082	0.043	0.043
ESR2						
MAAN	−0.0024**	−0.0012	−0.0015	−0.0022	−0.0039***	−0.0007
	(0.0010)	(0.0013)	(0.0016)	(0.0018)	(0.0014)	(0.0019)
Risk proneness	−0.0027**	−0.0028**	−0.0005	−0.0005	−0.0034*	−0.0037**
	(0.0012)	(0.0012)	(0.0016)	(0.0016)	(0.0018)	(0.0018)
ESR2	−0.0020	0.2422	0.0040	−0.1283	−0.0037	0.6461**
	(0.0173)	(0.1863)	(0.0256)	(0.2782)	(0.0240)	(0.2558)
ESR2 × MAAN		−0.0022		0.0012		−0.0058**
		(0.0016)		(0.0025)		(0.0023)
Observations	748	748	344	344	403	403
R-squared	0.049	0.051	0.076	0.077	0.042	0.055
OXTR						
MAAN	−0.0024**	−0.0044***	−0.0015	−0.0023	−0.0039***	−0.0073***
	(0.0010)	(0.0015)	(0.0016)	(0.0020)	(0.0014)	(0.0022)
Risk proneness	−0.0027**	−0.0028**	−0.0005	−0.0005	−0.0036*	−0.0038**
	(0.0012)	(0.0012)	(0.0017)	(0.0017)	(0.0018)	(0.0018)
OXTR	−0.0166	−0.3794**	−0.0067	−0.1551	−0.0327	−0.6489**
	(0.0180)	(0.1919)	(0.0257)	(0.2770)	(0.0260)	(0.2667)
OXTR × MAAN		0.0032*		0.0013		0.0055**
		(0.0017)		(0.0025)		(0.0023)
Observations	748	748	344	344	404	404
R-squared	0.050	0.055	0.076	0.077	0.046	0.058

In models 1, 3, and 5, we mainly present coefficients for three variables: MAAN, risk proneness, and genetic markers. We included all of the other control variables in the regression model, including MAAD, age, family monthly income, and health-related variables, but we omitted the coefficients in the table. In models 2, 4, and 6, we mainly present coefficients on four variables: MAAN, risk proneness, genetic markers, and interaction term between NAAN and genetic markers. Robust SEs corrected for heteroscedasticity were used and reported in parentheses; *$P < 0.1$; **$P < 0.05$; ***$P < 0.01$ (two-tailed).