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Adolescent Empathy and Epigenetic Aging in Adulthood: Substance Use as a Mediator

Marlon Goering¹, Amanda Moore¹, Malcolm Barker-Kamps¹, Amit Patki², Hemant K. Tiwari², Sylvie Mrug¹

¹Department of Psychology, University of Alabama at Birmingham; 1720 2nd Ave South, Birmingham, Alabama, USA

²Department of Biostatistics, University of Alabama at Birmingham; 1720 2nd Ave South, Birmingham, Alabama, USA

Abstract

Prosocial behavior during adolescence has been associated with better physical health, including slower epigenetic aging. However, little is known about the specific role of empathy in epigenetic aging and the mechanisms explaining this relationship. One such mechanism may be substance use, which is predicted by low empathy and contributes to accelerated epigenetic aging. Thus, the present study examined whether empathy during early adolescence predicts epigenetic aging in young adulthood and whether substance use in late adolescence and young adulthood mediates this effect. Participants included 343 individuals (58% female, 81% Black, 19% White) who were interviewed at mean ages 13, 17, and 27 years. Participants self-reported their empathy at Time 1 and their alcohol, tobacco, and cannabis use at Times 2 and 3. At Time 3, epigenetic aging was assessed from salivary DNA using the GrimAge, DunedinPACE, and PhenoAge clock. A regression analysis demonstrated that higher empathy in early adolescence uniquely predicted lower epigenetic aging on the GrimAge clock in young adulthood even after adjusting for environmental and socio-demographic risk factors. Mediation models revealed that the link between empathy and lower epigenetic aging on all three clocks was mediated by lower tobacco use. These results suggest that higher empathy during early adolescence may contribute to better health throughout the lifespan due to lower tobacco use and slower epigenetic aging.

Keywords

Empathy; Substance Use; Epigenetic Aging; Longitudinal

Empathy, defined as the ability to understand and share the feelings of others, is associated with positive developmental outcomes throughout adolescence, including lower engagement in antisocial behaviors (Goering & Mrug, 2021) and more supportive social relationships (Boele et al., 2019). However, some studies suggest that empathy can also be costly to an individual's well-being by inducing emotional and cognitive stress (Cameron et al., 2019;

Hofmeyer et al., 2020). Little is known about how individual differences in empathy during adolescence predict subsequent physical health and chronic disease risk, which can be estimated with DNA methylation-based indices of epigenetic aging as a biomarker of health status before the onset of chronic disease (Perna et al., 2016). Accelerated epigenetic aging, which refers to higher biological age than chronological age, has been linked with chronic disease risk across the lifespan (Hillary et al., 2020). If empathy is related to later epigenetic aging, it would also be helpful to understand the mechanisms that explain this relationship. One such mechanism may involve health-risk behaviors especially substance use, which has been linked with low empathy during adolescence (Winters et al., 2020) as well as accelerated epigenetic aging (Carter et al., 2022). Thus, the present study examined whether empathy during early adolescence predicts epigenetic aging in adulthood and whether this relationship is mediated by substance use.

Empathy and Epigenetic Aging

Empathy is a prosocial skill that describes the ability to both understand and vicariously share the feelings of others (Singer, 2006). Like other prosocial skills such as compassion and sympathy, empathy involves a concern for others and can thus generate prosocial behavior (Knafo & Israel, 2012). In the present study, empathy is operationalized as a form of social emotional competence that involves adolescents' understanding and caring about the feelings of both peers and adults, which can initiate supportive emotional and behavioral responses. Previous research has shown that prosocial emotions and behavior not only benefit others but also increase individual well-being and physical health (Brown & Brown, 2015; Konrath et al., 2012). For example, being prosocial and empathic can provide internal emotional rewards described as a "warm glow" (Ferguson et al., 2021), leading to positive emotions in the form of a greater sense of self-satisfaction (McKinnon, 2005), which in turn may lead to better health outcomes (Steptoe et al., 2009).

Early adolescence is a particularly sensitive period for empathy development due to the rapid maturation of brain areas involved in empathy (Blakemore, 2008; Crone & Dahl, 2012). Moreover, developing empathy is critical for adolescents' ability to navigate the increasingly complex social environment and develop healthy and supportive peer relationships (Portt et al., 2020). Previous studies have shown that adolescents with higher empathy receive greater support from peers (Boele et al., 2019), which in turn alleviates stress and predicts better physical health (Auerbach et al., 2011; Hale et al., 2005). Conversely, lower empathy has been linked with social difficulties during early adolescence and poorer health in late adolescence (Meehan et al., 2019). Thus, developing high levels of empathy during early adolescence may be particularly critical for subsequent health outcomes.

One aspect that distinguishes empathy from other prosocial emotions is that empathic sharing of others' negative feelings can make individuals more prone to experiencing situational distress (Carrera et al., 2013). Indeed, empathizing with another person's suffering has been associated with distress fatigue (Hofmeyer et al., 2020). Heightened levels of psychosocial stress have in turn been linked with physical health problems

(Benham, 2006). Given the multifaceted role of empathy for social-emotional experiences, it is important to better understand its association with physical health outcomes.

Social-emotional experiences may affect subsequent health outcomes through various mechanisms, including DNA methylation, an epigenetic process that can modify gene expression in response to various environmental influences (Cunliffe, 2016; Hao et al., 2018). Building on associations between DNA methylation and various aspects of health and aging, epigenetic aging clocks estimate biological age and disease risk from DNA methylation across sets of CpG loci (Lin et al., 2016). Among the various epigenetic clocks that have been developed, this study utilizes three epigenetic clocks from the second and third generations (i.e., GrimAge, DunedinPACE, and PhenoAge). These clocks were developed based on clinical indicators of health and provide estimates of biological aging as well as chronic disease and mortality risk (Belsky et al., 2020; Levine et al., 2018; Lu et al., 2019).

Only a few studies have examined links between prosocial skills and biological markers of health and epigenetic aging. These studies linked higher compassion with lower inflammation during adolescence (Pace et al., 2013) and slower epigenetic aging during young adulthood (Dobewall et al., 2023). Additionally, prosocial behavior in the form of volunteering has been linked with slower epigenetic aging in older adults (Nakamura et al., 2023). However, it is unclear if empathy has a similar association with slower epigenetic aging. Empathy may generate more supportive social relationships (Boele et al., 2019), which contribute to less social stress and more positive emotions (Auerbach et al., 2011), which in turn predict slower epigenetic aging (Beydoun et al., 2019; Cunliffe et al., 2016). However, empathy may also increase susceptibility to emotional distress (Carrera et al., 2013), which in turn may accelerate epigenetic aging (Palma-Gudiel et al., 2020). The only study examining empathy in relation to epigenetic aging found a link between empathy and slower epigenetic aging among mothers with neglectful parenting, but not in control mothers (Herrero-Roldan et al., 2021). However, no studies have examined associations between empathy during the critical period of early adolescence and subsequent epigenetic aging in adulthood, as well as mechanisms that may explain the links between empathy and epigenetic aging.

Substance Use as a Mechanism

One potential mechanism underlying the link between empathy during adolescence and later epigenetic aging is engagement in health-risk behaviors, specifically substance use. Lower empathy has consistently been linked with greater substance use during adolescence (Winters et al., 2020) and substance use disorders in adulthood (Massey et al., 2018). Lower empathy in adolescence has been related to greater use of multiple substances, including alcohol (Schmits & Glowacz, 2019), tobacco (Romero et al., 2017), and cannabis (Nguyen et al., 2011). Additionally, brain-imaging studies showed that adolescents at higher risk for alcohol dependence had lower activation of brain regions involved in empathy and perspective taking (Hill et al., 2007). As empathy involves the cognitive process of taking different perspectives (Singer, 2006), youth with higher empathy may be better equipped to consider the long-term consequences of their behavioral choices (Steinberg & Cauffman,

1996) and may therefore refrain from health-compromising and illegal behaviors such as substance use during adolescence (Keeler & Kaiser, 2010). Similarly, adolescents with higher empathy show greater recognition of the negative social consequences of substance use, which impedes subsequent substance use (Winters et al., 2023). In turn, substance use during late adolescence and young adulthood is associated with poorer health outcomes in the long term (Patrick et al., 2020), and alcohol, tobacco as well as cannabis use have been linked with accelerated epigenetic aging (Allen et al., 2022; Gao et al., 2016; Kresovich et al., 2021). Thus, prospective links between empathy during adolescence and epigenetic aging during adulthood may be mediated by substance use including alcohol, tobacco, and cannabis use.

Potential Environmental and Sociodemographic Confounders

When examining links between empathy and epigenetic aging it is important to adjust for potential environmental confounders and sociodemographic variables that may affect both empathy during adolescence and subsequent epigenetic aging. For example, empathy development during adolescence is predicted by warm and supportive parenting (Goering & Mrug, 2023), which in turn has been linked with better health outcomes in young adulthood (Beach et al., 2015). Additionally, environmental stress such as violence exposure has been linked with both lower empathy (Goering et al., 2024) and accelerated epigenetic aging (Jovanovic et al., 2017). Previous research has also shown that empathy during early adolescence and epigenetic aging during adulthood differ across sociodemographic characteristics. For example, adolescent empathy increases with age and females show higher empathy during early adolescence as compared to males (Van der Graaff et al., 2014). Additionally, epigenetic aging is lower in female adults as compared to males (Kankaanpää et al., 2022). Being from a racial/ethnic minority background and from a lower-income family has also been linked with accelerated epigenetic aging during adulthood (Fiorito et al., 2017). Thus, it is important to adjust for environmental factors such as parental nurturance and violence exposure, as well as sociodemographic characteristics such as biological sex, age, race, and family income when examining links between empathy and epigenetic aging.

Current Study

Given the limited knowledge regarding links between adolescent empathy and subsequent health outcomes, the present study examined whether empathy during early adolescence predicts epigenetic aging in young adulthood. A second aim of the study was to better understand the mechanisms that may explain the prospective link between adolescent empathy and later epigenetic aging. Based on previous research documenting associations between lower empathy and greater substance use, as well as between substance use and accelerated epigenetic aging, this study examined alcohol, tobacco, and cannabis use averaged across late adolescence and young adulthood as mediators of links between empathy and epigenetic aging. It was hypothesized that higher empathy during early adolescence will predict slower epigenetic aging in young adulthood. It was also hypothesized that this relationship would be mediated by lower use of alcohol, tobacco, and cannabis across late adolescence and young adulthood.

Methods

Participants and Procedures

Participants consisted of 343 individuals (58% female, 42% male, 81% Black, 19% Non-Hispanic White) who were interviewed during early adolescence (Mean age = 13), late adolescence (Mean age = 17), and young adulthood (Mean age = 27) as part of the Birmingham Youth Violence Study (BYVS). The sample was recruited from 5th-grade classrooms across 17 public schools in Birmingham (Alabama), a medium-sized city in the Southeastern United States (N=704) and followed over time. This study uses data from Wave 2 (Time 1), Wave 3 (Time 2), and Wave 4 (Time 3) collected between 2005 and 2022 and only included participants with epigenetic data at Wave 4 (N = 343).

After providing written consent, participants were interviewed privately by trained interviewers using computer-assisted interview procedures. Sensitive questions were completed by participants privately using Audio-Computer-Assisted-Self-Interview (ACASI). At Time 3, a saliva sample was collected with Oragene DNA OG-500 kits. About 30 minutes before collecting the sample, participants rinsed their mouth with water and did not eat or drink until sample collection. All study procedures were approved by the Institutional Review Board and participants were financially compensated for their time at each wave.

Measures

Empathy in Early Adolescence—At Time 1, adolescents self-reported on their empathy using the nine-item social-emotional competence - empathy subscale from the student version of the Social Skills Rating System (Gresham & Elliott, 1990). The scale includes items that address understanding feelings of others (e.g., “How often do you try to understand how your friends feel when they are angry, upset, or sad?”) and items that address sympathetic emotional responses (e.g., “How often do you feel sorry for others when bad things happen to them?”). The participants responded to each item on a three-point scale (0 – ‘Never’, 1 – ‘Sometimes’, 2 – ‘Very often’). Responses to the individual items were averaged with higher scores indicating higher levels of empathy (Cronbach’s $\alpha = .73$).

Alcohol Use in Late Adolescence and Young Adulthood—At Times 2 and 3, participants reported on their alcohol use by indicating whether they drank any alcohol in the last 12 months, and if yes, how often. The seven-point response scale for the frequency of alcohol use ranged from ‘1 – A few times’ to ‘7 – Every day’. At both time points, participants who reported any alcohol use were also asked how many drinks they usually had in a day when they drank alcohol in the last 12 months. Responses to this quantity question ranged from ‘1 – 1 drink a day’ to ‘9 – More than 8 drinks a day’. To index the total amount of alcohol used during the last 12 months, a quantity index was computed at each time point by multiplying the frequency and quantity items. If participants reported that they did not use any alcohol within the last 12 months, a score of zero was assigned. The quantity-frequency index scores from Times 2 and 3 were then averaged to obtain an estimate of cumulative alcohol use across late adolescence and young adulthood ($r = .29, p <$

.001). If a score was missing at one time point, only the score from the other time point was used.

Tobacco Use in Late Adolescence and Young Adulthood—At Times 2 and 3, participants reported whether they smoked cigarettes during the last 12 months. If endorsed, they rated their frequency of smoking on a seven-point scale from ‘1 – A few times’ to ‘7 – Every day’ and the number of cigarettes usually smoked per day on a five-point scale from ‘1 – less than 1 cigarette per day’ to ‘5 – More than 20 cigarettes per day’. As with alcohol use, a quantity-frequency index was computed by multiplying the responses for the two questions at each time point. If participants endorsed no cigarette smoking during the last 12 months, a score of zero was assigned. The quantity-frequency indices from Times 2 and 3 were then averaged for a cumulative tobacco use score ($r = .46, p < .001$). If a score was missing at one time point, only the score from the other time point was used.

Cannabis Use in Late Adolescence and Young Adulthood—At both Time 2 and Time 3, participants reported whether they used any cannabis in the past 12 months, and if yes, how often on a seven-point scale ranging from ‘1 – A few times’ to ‘7 – Every day’. No use was coded zero. As for alcohol and tobacco use, the cannabis use scores from Times 2 and 3 were averaged for a cumulative use index ($r = .26, p < .001$). If a score was missing at one time point, only the score from the other time point was used.

Epigenetic Aging in Young Adulthood—GrimAge, DunedinPACE, and PhenoAge scores of epigenetic aging were estimated from the DNA that was extracted from participants’ saliva samples using the PureGene extraction method. After extracting DNA, methylation analyses were conducted using the Illumina Infinium MethylationEPIC BeadChip. The DNA methylation was quantified using beta-values, which were computed as the proportion of methylated fluorescent intensity and overall intensity (Bibikova et al., 2006). The GrimAge scores were computed from 1030 CpG sites using a DNA methylation (DNAm) age calculator (<https://dnamage.genetics.ucla.edu/>) so that a single overall score of epigenetic age was estimated for each participant. The DunedinPACE scores were computed from the DNA methylation pattern across 173 CpG sites utilizing elastic net regression and were scaled to a mean of one so that scores indicate the increase in biological aging for each one-year increase in chronological age (Belsky et al., 2022). Finally, PhenoAge scores were computed from the DNA methylation pattern across 513 CpG sites using a linear function (Enmix) in the R package minfi, which was based on published intercepts and linear regression coefficients. The GrimAge, DunedinPACE, and PhenoAge scores were regressed on chronological age and the resulting residuals were used as indicators of accelerated epigenetic aging with higher positive values indicating more accelerated epigenetic aging on each clock.

Covariates

Parental Nurturance. At Time 1, participants reported on their parents’ warm and supportive parenting using the five-item Parental Nurturance scale (Barnes & Windle, 1987). The individual items addressed physical warmth (e.g., “How often do your parents give you a hug or kiss?”) and emotional support (e.g., “How often do your parents give you praise or

encouragement?”). The five items were coded on a three-point scale from ‘0 – almost never’ to ‘2 – almost always’ and averaged (Cronbach’s $\alpha = .66$).

Exposure to Violence.: At Time 1, youth also reported whether they witnessed or experienced violence at home, at school, and in their neighborhood for three types of witnessing and three types of direct victimization. The resulting 18 dichotomous items were summed (Cronbach’s $\alpha = .66$). More details on this measure can be found in a previous study (Mrug et al., 2008).

Sociodemographics.: Participants’ ages were computed from their date of birth and the date of the interview at each time point. At Time 1, participants’ caregivers reported on their gross annual family income on a 13-point scale of income intervals ranging from ‘1 – Less than \$5,000’ to ‘13 – More than \$90,000’. At the initial assessment, youth reported their biological sex and caregivers reported the participants’ race. Biological sex was coded as ‘1 = Female’ and ‘0 = Male’ and race was coded as ‘1 = Black’ and ‘0 = White’.

Saliva Cell Types.: Since saliva samples show inter-individual variability in leucocyte counts which can affect DNA methylation (Middleton et al., 2022), counts of CD4T, CD8T, B-cells, Monocytes, and Granular cells were assessed using the deconvolution method (Houseman et al., 2012).

Data Analysis

Since the analyses only included individuals with available epigenetic data at Time 3, an attrition analysis was performed to examine if cases retained at Time 3 differ from those lost to attrition on any baseline variables. Additionally, for the 343 cases included in the analyses, we examined the amount of missing data and whether missingness was related to the study variables. Then, descriptive statistics and distributions (i.e., skewness and kurtosis) were examined for all continuous variables. A final preliminary analysis examined bivariate correlations among all variables.

The main analyses were conducted in Mplus version 8.1. First, a multivariate regression model examined the unique effects of empathy at Time 1 on GrimAge, DunedinPACE, and PhenoAge acceleration at Time 3 when controlling for parental nurturance, violence exposure, and sociodemographic variables at Time 1 (i.e., family income, age, biological sex, and race). Next, three mediation path models were estimated with alcohol use, tobacco use, and cannabis use mediating the links between empathy and GrimAge (Model 1), DunedinPACE (Model 2), and PhenoAge (Model 3). Specifically, the models included paths from empathy at Time 1 to each of the three substances at Times 2/3 and paths from empathy at Time 1 and the three substances at Times 2/3 to epigenetic aging at Time 3. Alcohol, tobacco, and cannabis use at Times 2/3 were allowed to covary. All paths were adjusted for Time 1 parental nurturance, violence exposure, family income, biological sex, race, and age at Time 2. Due to non-normal distributions of the substance use variables (skewness > 2), the mediation model used maximum likelihood estimation with robust standard errors (MLR). The indirect effects of empathy at Time 1 on each epigenetic age acceleration at Time 3 through alcohol use, tobacco use, and cannabis use at Time 2/3 were

tested with bias-corrected bootstrapping (5,000 samples). Missing data were handled with Full Information Maximum Likelihood, which minimizes bias under Missing at Random and preserves the full sample size ($N=343$) (Cham et al., 2017).

The main analyses did not adjust for salivary cell types because low leucocyte counts have also been associated with chronic disease risk (Heiss & Brenner, 2017) and may therefore overlap with accelerated epigenetic aging as a biomarker of health (Qi & Teschendorff, 2022). However, a sensitivity analysis was conducted to examine the robustness of the results if cell type counts (i.e., counts of CD8T, CD4T, B-cells, Monocytes, and Granular cells) were included as additional covariates when predicting epigenetic aging in the main models. A second sensitivity analysis was conducted in which the mediation models were examined including substance use during late adolescence (Time 2) instead of combining substance use measures from Time 2 and Time 3.

Transparency and Openness

We report how the sample size is determined with all data exclusions. All measures and coding of variables are described. The data and analysis code are available and can be accessed in the Open Science Framework (OSF) repository (<https://osf.io/w3sv2>; Goering et al., 2024). Data analyses were conducted in SPSS and Mplus version 8.1. This study was not preregistered.

Results

Preliminary Analyses

Results from the attrition analysis showed that participants included in the analytic sample ($N=343$) were more likely to be female (58% vs. 37%; $\chi^2_{(1)} = 30.84$, $p < .001$) and had higher empathy scores at Wave 1 (1.65 vs. 1.60, $t_{(702)} = 2.27$, $p = .023$, Cohen's $d = 0.15$) but did not differ in race, family income, parental nurturance, or violence exposure from the rest of the initial sample. Within the analytic sample, 27% of participants had missing data on one or more variables for a total of 5.6% of missing data points. Compared to those with complete data, participants with any missing data were more likely to be White (29% vs. 16%, $\chi^2_{(1)} = 7.49$, $p = .006$), had a lower family income at Time 1 (5.53 vs. 6.89, $t_{(290)} = 2.14$, $p = .033$), used more tobacco at Times 2/3 (5.44 vs. 3.33, $t_{(340)} = -2.06$, $p = .042$, Cohen's $d = 0.27$), and had higher PhenoAge acceleration at Time 3 (1.12 vs -0.38 , $t_{(341)} = 2.47$, $p = .014$, Cohen's $d = 0.30$). Participants with complete data did not differ from participants with missing data on any other variables included in the analysis.

Descriptive statistics and information on skewness and kurtosis on all variables are reported in Table 1. The three substance use variables showed the highest skewness and kurtosis, which were addressed by using the robust MLR estimator in the mediation analysis. Bivariate correlations (see Table 2) showed that higher empathy at Time 1 was associated with lower GrimAge acceleration at Time 3 but not associated with DunedinPACE or PhenoAge acceleration. Additionally, higher empathy was associated with lower tobacco use at Time 2/3, but only marginally related to lower cannabis use and unrelated to alcohol use at Time 2/3. Alcohol, tobacco, and cannabis were positively intercorrelated and both

tobacco and cannabis use were associated with accelerated GrimAge. However, neither tobacco nor cannabis use were associated with DunedinPACE or PhenoAge acceleration. Alcohol use was only marginally associated with accelerated GrimAge, not associated with PhenoAge, and contrary to expectations associated with slower DunedinPACE. Higher parental nurturance was associated with higher empathy and lower tobacco use, whereas higher violence exposure was linked with lower empathy, higher cannabis use, and accelerated DunedinPACE. Higher family income was associated with higher empathy and alcohol use but lower tobacco use and slower epigenetic aging on GrimAge and DunedinPACE.

Main Analysis

The results from the multivariate regression model are shown in Table 3. After adjusting for parental nurturance, violence exposure, and sociodemographic variables, higher empathy uniquely predicted lower GrimAge acceleration but not DunedinPACE or PhenoAge acceleration. Violence exposure and parental nurturance did not predict epigenetic aging on any clock. Higher family income at Time 1 predicted slower epigenetic aging on GrimAge and DunedinPACE. Being female predicted lower GrimAge acceleration but higher DunedinPACE and PhenoAge acceleration. Black individuals had higher GrimAge acceleration and DunedinPACE compared to Whites.

The results from the first mediation path model predicting GrimAge acceleration are shown in Figure 1. The model was just-identified and thus had perfect fit. Higher empathy at Time 1 uniquely predicted lower tobacco use at Time 2/3 but not alcohol or cannabis use. Both higher tobacco and cannabis use uniquely predicted accelerated GrimAge at Time 3, whereas alcohol use did not predict GrimAge acceleration at Time 3. After adjusting for the mediators, empathy at Time 1 had no unique direct effect on GrimAge. Results from the bootstrapping analysis revealed a significant indirect effect of higher empathy at Time 1 on lower GrimAge at Time 3 through lower tobacco use at Time 2/3 ($\beta = -0.060$; $CI_{95\%} = [-0.122, -0.015]$). However, the effect of empathy on GrimAge acceleration was not mediated by alcohol use ($\beta = -0.001$; $CI_{95\%} = [-0.017, 0.005]$) or cannabis use ($\beta = -0.015$; $CI_{95\%} = [-0.049, 0.016]$).

The results from the second mediation path model predicting DunedinPACE are shown in Figure 2. As in the previous model, higher empathy uniquely predicted lower tobacco use at Time 2/3 but not alcohol or cannabis use. Moreover, higher tobacco use predicted accelerated DunedinPACE, whereas cannabis use did not predict DunedinPACE. The results also showed an unexpected effect of higher alcohol use on slower DunedinPACE. After adjusting for mediators, the results showed an unexpected direct effect of higher empathy on accelerated DunedinPACE at Time 3. Similar to the previous model, the bootstrapping analysis revealed a significant indirect effect of higher empathy at Time 1 on lower DunedinPACE at Time 3 through lower tobacco use at Time 2/3 ($\beta = -0.037$; $CI_{95\%} = [-0.085, -0.009]$) but not through alcohol ($\beta = -0.007$; $CI_{95\%} = [-0.035, 0.005]$) or cannabis use ($\beta = 0.000$; $CI_{95\%} = [-0.011, 0.013]$).

The results from the third mediation path model predicting PhenoAge acceleration are shown in Figure 3. As in the previous models, higher empathy predicted lower tobacco

use but did not predict alcohol or cannabis use. Additionally, higher tobacco use predicted less accelerated PhenoAge, whereas alcohol and cannabis use did not predict PhenoAge acceleration at Time 3. Finally, empathy had no direct effect on PhenoAge acceleration in the mediation model. Consistent with the previous models, the bootstrapping results showed an indirect effect of higher empathy at Time 1 on lower PhenoAge acceleration at Time 3 through lower tobacco use at Time 2/3 ($\beta = -0.021$; $CI_{95\%} = [-0.058, -0.003]$) but not through alcohol ($\beta = -0.002$; $CI_{95\%} = [-0.021, 0.003]$) or cannabis use ($\beta = -0.001$; $CI_{95\%} = [-0.014, 0.005]$).

Sensitivity Analyses

Results from the first sensitivity analysis, which included cell type counts as additional covariates when predicting epigenetic aging almost entirely replicated the original analysis. As in the original analyses, higher empathy uniquely predicted lower GrimAge acceleration ($\beta = -0.18$, $p = .004$) but not DunedinPACE or PhenoAge acceleration. As in the original analysis, the mediation models showed that lower tobacco use mediated links between higher empathy and slower epigenetic aging on the GrimAge ($\beta = -0.055$; $CI_{95\%} = [-0.116, -0.011]$), DunedinPACE ($\beta = -0.028$; $CI_{95\%} = [-0.068, -0.005]$), and PhenoAge clocks ($\beta = -0.015$; $CI_{95\%} = [-0.049, -0.001]$). Also consistent with the original analyses, links between empathy and epigenetic aging were not mediated by alcohol or cannabis use. As in the original analysis, higher cannabis use predicted accelerated GrimAge ($\beta = 0.27$, $p < .001$) but not DunedinPACE or PhenoAge acceleration, whereas higher alcohol use predicted lower DunedinPACE ($\beta = -0.10$, $p = .021$) and did not predict GrimAge or PhenoAge. Contrary to the original analyses, empathy had no direct effect on DunedinPACE when adjusting for cell-type counts as additional covariates ($\beta = 0.04$, $p = .313$).

The second sensitivity analysis examined alcohol, tobacco, and cannabis use at Time 2 as mediators rather than combining the substance use measures from the Time 2 and Time 3 assessments. The results replicated the original analysis by showing a unique effect of higher empathy at Time 1 on lower tobacco use at Time 2 ($\beta = -0.26$, $p < .001$) as well as a unique effect of higher tobacco use at Time 2 on accelerated GrimAge at Time 3 ($\beta = 0.28$, $p < .001$). Consistent with the original analysis, lower tobacco use at Time 2 mediated links between higher empathy at Time 1 and slower epigenetic aging on the GrimAge clock at Time 3 ($\beta = -0.075$; $CI_{95\%} = [-0.152, -0.021]$). Contrary to the original analysis, empathy had no significant indirect effects on DunedinPACE and PhenoAge acceleration through tobacco use when only measured at Time 2. In line with the original results, empathy at Time 1 did not predict alcohol or cannabis use at Time 2 but higher cannabis use at Time 2 predicted accelerated GrimAge at Time 3 ($\beta = 0.23$, $p < .001$). Contrary to expectations, higher alcohol use at Time 2 predicted slower epigenetic aging at Time 3 for both GrimAge ($\beta = -0.12$, $p = .043$) and DunedinPACE ($\beta = -0.18$, $p = .005$).

Discussion

Substantial research suggests that prosociality has benefits for individual health and well-being including slower epigenetic aging (Dobewall et al., 2023). However, little has been known about the role of empathy during adolescence in subsequent epigenetic aging and the

potential underlying mechanisms of this relationship. This longitudinal study examined if empathy during early adolescence predicts lower epigenetic aging in young adulthood over and above sociodemographic and environmental factors. Additionally, this study examined substance use in the form of alcohol, tobacco, and cannabis use across late adolescence and young adulthood as mediators of the links between empathy and epigenetic aging. The results showed that higher empathy during adolescence uniquely predicted slower epigenetic aging in young adulthood on the GrimAge clock even after adjusting for demographic variables and socioenvironmental factors such as family income, parental nurturance, and violence exposure. Results from the mediation analyses revealed that the effect of higher empathy on slower epigenetic aging was mediated by lower tobacco use across all three epigenetic clocks included in this study. However, neither alcohol nor cannabis use mediated the links between empathy and epigenetic aging. Together, the present findings support the hypothesis that developing high levels of empathy during early adolescence is protective against subsequent accelerated epigenetic aging and that lower engagement in health risk behaviors, specifically tobacco use, accounts for this effect.

Empathy, Substance Use, and Epigenetic Aging

The present findings provide new insights into the role of empathy in individual health by showing that higher empathy during early adolescence predicts slower GrimAge in young adulthood beyond demographic and socioenvironmental risk factors. By focusing on empathy during adolescence, these findings complement and extend previous research linking compassion with lower epigenetic aging in young adulthood (Dobewell et al., 2023). Since the GrimAge epigenetic clock is a reliable marker of health status and chronic disease risk (Lu et al., 2019; McCrory et al., 2021), the present findings suggest that higher empathy during early adolescence may presage better health during adulthood. Thus, despite some research indicating that empathy can make individuals more prone to stress (Hofmeyer et al., 2020), developing higher empathy during early adolescence may ultimately have more benefits than costs for subsequent health outcomes. These findings add to the growing evidence indicating that being prosocial is associated with improved health, well-being, and increased longevity (O'Reilly et al., 2008; Poulin & Holman, 2013). It is not clear why links between empathy and slower epigenetic aging did not replicate for the DunedinPACE and PhenoAge clock. A possible explanation may be that GrimAge outperformed other epigenetic clocks including PhenoAge as a predictor of chronic disease risk and health status (McCrory et al., 2021). Moreover, prior research found GrimAge to be more consistently related to lifestyle related factors as compared to other epigenetic clocks (Zhao et al., 2019).

To better understand the underlying mechanisms of links between empathy and epigenetic aging, this study examined substance use, specifically alcohol, tobacco, and cannabis use as potential mediators. Partly consistent with the hypotheses, the results showed that the effect of empathy in early adolescence on epigenetic aging in adulthood is mediated by tobacco use combined across late adolescence and young adulthood. Specifically, the mediation models demonstrated that youth with higher empathy during early adolescence engaged in less tobacco use during late adolescence and young adulthood, which in turn predicted less accelerated epigenetic aging. The indirect effect of empathy on lower epigenetic aging through lower tobacco use replicated across the GrimAge, DunedinPACE, and the PhenoAge

clock. These results are consistent with previous studies linking adolescent empathy with lower tobacco use (Romero et al., 2017) and establishing tobacco use as a strong predictor of accelerated epigenetic aging (Gao et al., 2016). One explanation for the links between empathy and lower tobacco use may be that youth with higher empathy are more capable of perspective-taking (Singer, 2006). Better perspective-taking may not only be useful in social situations (e.g., refusing offers to smoke) but can also make youth more considerate of long-term consequences (Steinberg & Cauffman, 1996) and thus reduce the risk of maladaptive health behaviors such as tobacco use (Keeler & Kaiser, 2010).

In contrast to the hypotheses, neither alcohol nor cannabis use mediated links between empathy and epigenetic aging. This was partially due to empathy uniquely predicting only lower tobacco use but not cannabis or alcohol use in the adjusted models. The unadjusted correlations, however, showed a marginal association between empathy and lower cannabis use, which is consistent with previous evidence of links between empathy and lower cannabis use (Nguyen et al., 2011). However, after adjusting for sociodemographic and environmental factors, empathy was not a unique predictor of cannabis use in this study. Further, the present results did not show any links between empathy and alcohol use, which contrasts with previous research (Schmits & Glowacz, 2019). There are several possible explanations for why empathy uniquely predicted tobacco usage but not the other substances. One explanation may be that youth have a greater awareness of the negative health consequences of tobacco use compared to alcohol and cannabis use. Indeed, previous research has shown that young adults perceive tobacco use as more harmful than alcohol and cannabis use (Thornton et al., 2013). Thus, if empathy predicts lower substance use because of better perspective taking and consideration of long-term consequences, it may be most strongly linked with lower tobacco use due to the greater awareness of its harmful effects. A second explanation may be that smoking tobacco not only affects the individual's own health but can also have negative health effects on others due to second-hand smoke exposure (Flouris et al., 2010). Youth with higher empathy may be more considerate of the detrimental effects of second-hand smoke exposure on others and thus refrain from smoking. Moreover, causing second-hand smoke exposure is socially stigmatized in the US (Stuber et al., 2008), and higher empathy make adolescents more aware and sensitive to the social unacceptability of smoking. Recent findings also show that adults in the US perceive second-hand smoke exposure to tobacco as more harmful compared to cannabis (Chambers et al., 2023), which may explain why empathy is more strongly linked with lower tobacco use than cannabis use.

Ultimately, the present findings suggest that tobacco and cannabis use uniquely predict accelerated epigenetic aging in young adulthood with the effect of cannabis use being limited to the GrimAge clock. Multiple studies have found similar effects of tobacco and cannabis use on epigenetic aging (Allen et al., 2022; Gao et al., 2016), suggesting that both tobacco and cannabis use increase the risk of chronic disease throughout the lifespan. Alcohol use had no unique effect on GrimAge and PhenoAge and paradoxically predicted lower DunedinPACE, which contrasts with prior research suggesting links between alcohol use and accelerated epigenetic aging (Kresovich et al., 2021). However, the unadjusted correlations showed a marginal association of alcohol use and accelerated GrimAge. The mediation models showed no direct effects of empathy on accelerated GrimAge or

PhenoAge and contrary to expectations showed a direct link between higher empathy during adolescence and accelerated DunedinPACE in adulthood. However, since there was no bivariate association between adolescent empathy and DunedinPACE, this likely results from suppressor effects by related predictors and does not carry any substantive meaning (Paulhus et al., 2004). Moreover, this unexpected effect of empathy on accelerated DunedinPACE dissipated when adjusting for leucocyte type cells (i.e., CD4T, CD8T, B-cells, monocytes, granular cells) in a sensitivity analysis. All other main and indirect effects replicated when adjusting for leucocyte type cells, which adds to the robustness of the results. When assessing substance use only during late adolescence in a sensitivity analysis, the mediating role of lower tobacco use in links between higher empathy and slower epigenetic aging replicated for the GrimAge clock adding to the robustness of these results. In summary, the present findings suggest that lower tobacco use presents a key mechanism explaining links between higher empathy during adolescence and slower epigenetic aging in adulthood.

Implications

The findings of this study have theoretical implications for future research as well as practical implications for intervention programs. The present findings add a new perspective to the ongoing discussion of whether showing empathy towards others is beneficial or costly to one's own well-being. Several studies found that empathy can be costly to oneself by generating cognitive and emotional stress (Hofmeyer et al., 2020; Cameron et al., 2019). By demonstrating that empathy predicts slower epigenetic aging over more than a decade, the present findings suggest that empathy is not harmful to physical health and instead may promote better health outcomes. These results may inspire future research to focus on disentangling the specific costs and benefits of empathy for individual well-being. Additionally, the present findings highlight the important role of tobacco use as a mechanism underlying links between empathy and epigenetic aging. These results may inform future studies to continue examining mechanisms underlying empathy effects on health, such as other health behaviors.

The present findings also have practical implications for intervention and prevention programs. By showing that the benefits of empathy go beyond the societal level and include better individual health, the present findings may provide additional motivation for families, schools, and communities to promote empathy development in youth. Educational settings can play a pivotal role in implementing social-emotional learning programs designed to foster empathy development (Malti et al., 2016) and thus contribute to better epigenetic health and longevity. Finally, the present findings could inform early smoking prevention programs to incorporate empathy-building modules, which may help adolescents resist social pressures to use substances, consider long-term consequences, and make informed decisions regarding tobacco use, which then contribute to better health in the long term.

Limitations

Several limitations need to be considered when interpreting the results from the present study. An important limitation is that empathy was measured only via self-reports during early adolescence and may therefore have been affected by social desirability bias. Future

studies would benefit from more sophisticated assessments of empathy or multi-informant measurement. Another limitation may be that the empathy scale includes individual items that also construe sympathy and compassion (e.g., “feeling sorry for others when bad things happen to them”) and may therefore not fully differentiate empathy from other prosocial emotions. The substance use measures were also based on self-report and may therefore have been affected by social desirability bias. Furthermore, the measures of the covariates parental nurturance and violence exposure were limited by relatively low internal consistencies. Another limitation is that epigenetic aging was only assessed during adulthood, which did not allow adjusting for previous levels of epigenetic aging during early and late adolescence. While this prevented the statistical testing of whether empathy precedes epigenetic aging, it is conceptually unlikely that epigenetic aging would influence empathy development during adolescence. Nevertheless, causal inferences about the effects of empathy and substance use on epigenetic aging cannot be made from these results. Future studies should therefore replicate the results of the present study in independent samples to strengthen inferences that the observed effects are not due to chance associations. Ultimately, establishing that higher empathy and lower substance use temporally precede slower epigenetic aging remains an important area of study to address by future research. A third limitation is the focus on substance use as a single mechanism of links between empathy and epigenetic aging. Future studies should consider alternative mechanisms such as social support, stress, and other health-risk behaviors.

Conclusion

While previous research has established a connection between prosociality and better health outcomes including slower epigenetic aging, this study specifically examined the role of empathy during adolescence in subsequent epigenetic aging as well as the underlying mechanisms focusing on substance use. The present findings suggest that youth with higher empathy during early adolescence experience slower epigenetic aging on the GrimAge clock during young adulthood, which is associated with better health outcomes. Additionally, this study identified lower tobacco use as a key mechanism underlying links between adolescent empathy and slower epigenetic aging, whereas alcohol and cannabis use did not mediate these links. Together, these results underscore the importance of cultivating high levels of empathy during early adolescence in reducing subsequent tobacco use and promoting health and longevity across the lifespan.

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Public Significance Statement:

This study suggests that adolescents with higher empathy have better health status in the form of slower cellular aging in young adulthood. Tobacco use presents a mechanism for this relationship as adolescents with higher empathy used less tobacco from late adolescence to adulthood, which then contributed to better health and less cellular aging in adulthood.

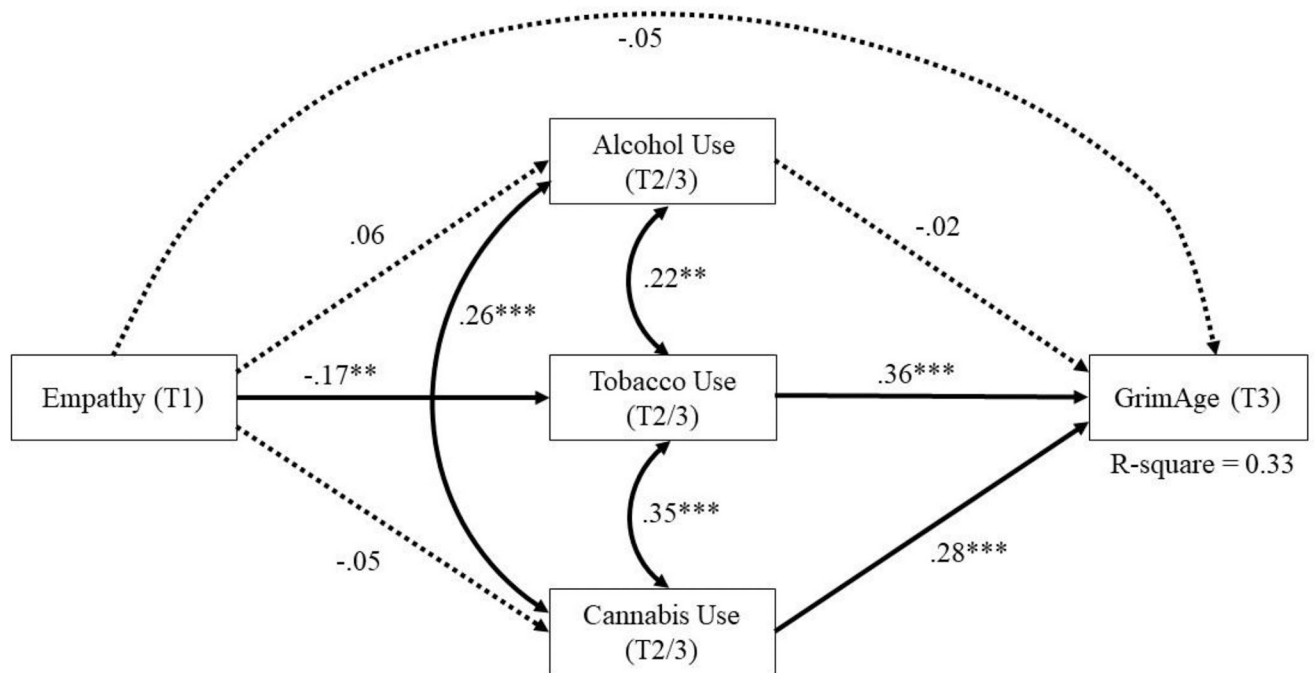


Figure 1. Mediation Model Predicting GrimAge Acceleration

Note: Standardized path coefficients are shown. T1 – Time 1, T2 – Time 2, T3 – Time 3. GrimAge was adjusted for chronological age at Time 3. All paths were adjusted for parental nurturance at T1, violence exposure at T1, family income at T1, age at T2, biological sex, and race. Dotted lines were not statistically significant at $p < .05$.

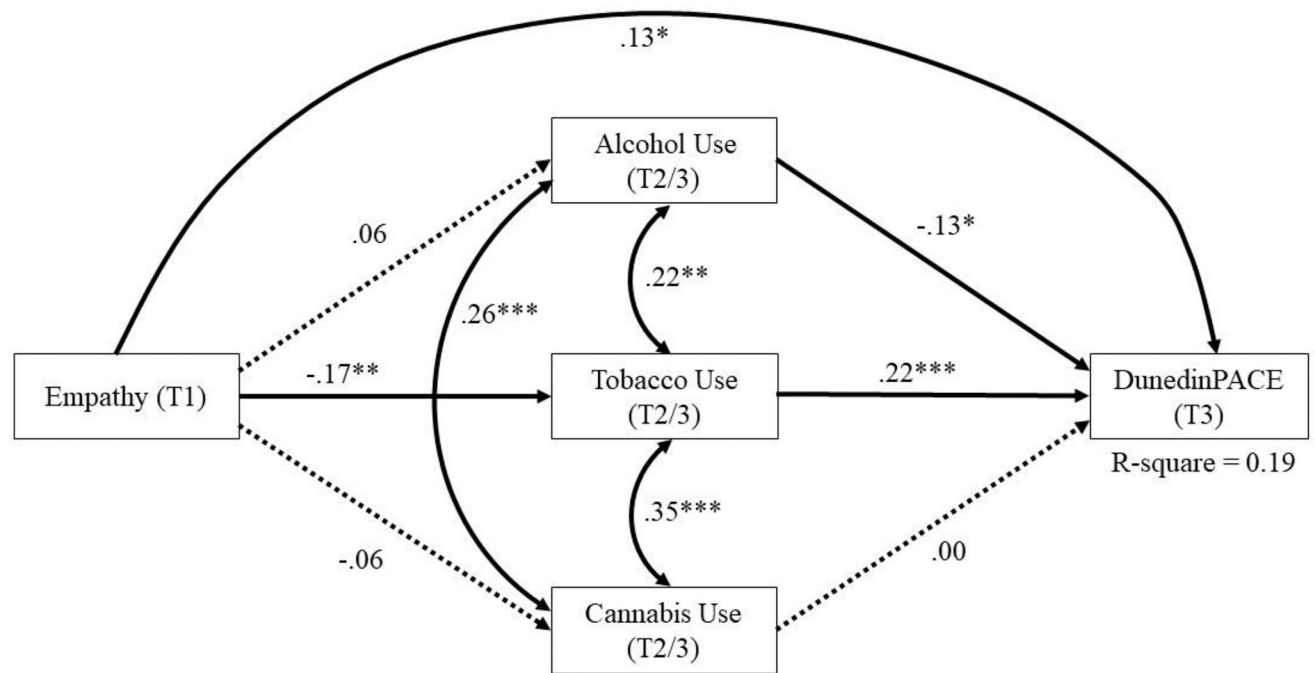


Figure 2. Mediation Model Predicting Accelerated DunedinPACE

Note: Standardized path coefficients are shown. T1 – Time 1, T2 – Time 2, T3 – Time 3. DunedinPACE was adjusted for chronological age at Time 3. All paths were adjusted for parental nurturance at T1, violence exposure at T1, family income at T1, age at T2, biological sex, and race. Dotted lines were not statistically significant at $p < .05$.

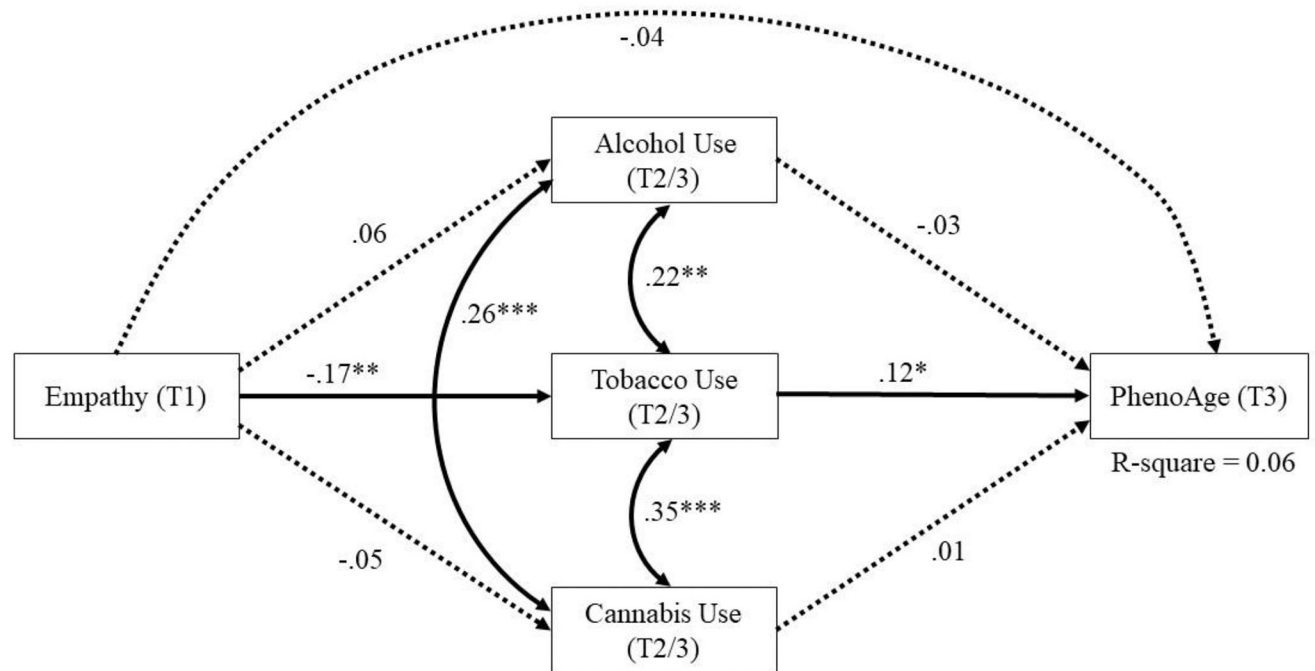


Figure 3. Mediation Model Predicting PhenoAge Acceleration

Note: Standardized path coefficients are shown. T1 – Time 1, T2 – Time 2, T3 – Time 3.

PhenoAge was adjusted for chronological age at Time 3. All paths were adjusted for parental nurturance at T1, violence exposure at T1, family income at T1, age at T2, biological sex, and race. Dotted lines were not statistically significant at $p < .05$.

Table 1
Descriptive Statistics and Information on Normality for the Variables Included in the Analyses

	M (SD) / %	Min, Max	Skewness, Kurtosis
Empathy (T1)	1.61 (0.30)	0.44, 2.00	-1.06, 1.49
Alcohol Use (T2/3)	5.46 (6.79)	0.00, 40.00	2.19, 5.63
Tobacco Use (T2/3)	3.33 (5.94)	0.00, 31.50	2.02, 3.81
Cannabis Use (T2/3)	1.46 (1.96)	0.00, 7.00	1.33, 0.81
GrimAge (T3)	-0.14 (3.68)	-7.68, 9.14	0.42, -0.50
DunedinPACE (T3)	0.00 (0.15)	-0.42, 0.49	0.18, 0.21
PhenoAge (T3)	0.03 (5.09)	-17.78, 14.63	0.01, 0.15
Parental Nurture (T1)	1.45 (0.40)	0.00, 2.00	-0.83, 0.54
Violence Exposure (T1)	2.42 (2.00)	0.00, 12.00	1.28, 2.18
Family Income (T1)	6.89 (3.87)	1.00, 13.00	-0.03, -1.34
Age (T2)	17.57 (1.03)	16.00, 22.00	1.82, 4.54
Female	58%	-	-
Black	81%	-	-

Note: T1 – Time 1, T2 – Time 2, T3 – Time 3. GrimAge, DunedinPACE, and PhenoAge were adjusted for age at Time 3.

Table 2

Bivariate Correlations among the Main Variables and Covariates

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Empathy (T1)	1.00											
2. Alcohol Use (T2/3)	.04	1.00										
3. Tobacco Use (T2/3)	-.23**	.23**	1.00									
4. Cannabis Use (T2/3)	-.11 ⁺	.28**	.36**	1.00								
5. GrimAge (T3)	-.16**	.10 ⁺	.44**	.42**	1.00							
6. DunedinPACE (T3)	.04	-.17**	.10	.01	.46**	1.00						
7. PhenoAge (T3)	-.03	-.04	.07	.00	.20**	.30**	1.00					
8. Parental Nurture (T1)	.41**	-.01	-.17**	-.08	-.02	-.03	.01	1.00				
9. Violence Exposure (T1)	-.14*	.04	.03	.12*	.10	.16**	-.08	-.28**	1.00			
10. Family Income (T1)	.17**	.13*	-.19**	-.02	-.18**	-.21**	.03	.18**	-.25**	1.00		
11. Age (T2)	-.14*	.03	.10	.08	-.01	-.04	-.13*	-.13*	.04	-.20**	1.00	
12. Female	.07	-.24**	-.20**	-.21**	-.12*	.24**	.14**	.01	-.07	-.13*	.01	1.00
13. Black	-.17**	-.16**	-.08	.12*	.19***	.26**	-.03	-.12*	.21**	-.31**	.20**	.16**

Note: T1 – Time 1, T2 – Time 2, T3 – Time 3. GrimAge, DunedinPACE, and PhenoAge were adjusted for age at Time 3.

⁺ $p < .06$,* $p < .05$,** $p < .01$

Regression Model Predicting Accelerated Epigenetic Aging from Empathy and Covariates

Table 3

Variable	GrimAge β	DunedinPACE β	PhenoAge β
Empathy (T1)	-0.15*	0.07	-0.07
Parental Nurture (T1)	0.07	-0.01	-0.01
Violence Exposure (T1)	0.02	0.11	-0.08
Family Income (T1)	-0.16**	-0.12*	0.02
Age (T1)	-0.15*	-0.11	-0.11
Female	-0.17**	0.19**	0.14**
Black	0.18**	0.21**	-0.02

Note. All coefficients are standardized. T1 – Time 1, T2 – Time 2, T3 – Time 3. GrimAge, DunedinPACE, and PhenoAge were adjusted for age at Time 3.

*
 $p < .05$,
**
 $p < .01$.