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The Joint Contribution of Childhood Exposure to Parental Smoking and Genetic Susceptibility to Smoking to Epigenetic Age Acceleration in Late Adulthood: The Health and Retirement Study

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Abstract: The impact of childhood exposure to parental smoking on epigenetic age acceleration (EAA) in later life has not been thoroughly investigated. This study investigates the relationship while considering genetic susceptibility to smoking. We analyzed data from 3102 participants in the Health and Retirement Study (HRS) who also participated in the 2016 Venous Blood Study and the 2015–2017 Life History Mail Survey. Self-reported measures included childhood parental smoking exposure and smoking status in late adulthood. We utilized five epigenetic clocks—HorvathAA, HannumAA, GrimAA, PhenoAA, and DunedinAA—and assessed genetic susceptibility with a polygenic risk score (PRS) for smoking initiation, categorized into tertiles. We regressed the clocks against chronological age to derive EAA residuals. Associations between childhood exposure and EAA were examined in the overall sample and by PRS tertiles, stratified by race. The model controlled for age, sex, education, smoking, alcohol consumption, body mass index, and CESD scores. Significant associations were found between childhood exposure to parental smoking and the EAA measured by GrimAA ($\beta = 0.98$; $p < 0.001$) and DunedinAA ($\beta = 0.01$; $p = 0.002$) among White participants, with stronger effects in those with a high PRS. Similar patterns were observed in Black participants, highlighting the importance of preventing secondhand smoke exposure in children.

Keywords: childhood; parental smoking; epigenetic age acceleration; polygenic risk score; older adults

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1. Introduction

DNA methylation (DNAm) changes capture interactions between environmental factors and the human genome and may serve as disease biomarkers and therapeutic targets. Meanwhile, DNAm alterations are influenced by genetic variations [1], reflecting the biological status of the human body. Epigenetic age, measured through DNAm patterns, has emerged as a powerful predictor of health outcomes and mortality risks, offering insights into biological aging that chronological age alone cannot provide [2–5]. Epigenetic clocks—tools that quantify methylation at specific genomic sites—have revolutionized our understanding of aging and its interplay with environmental and lifestyle factors [6–8].

Smoking is a well-known factor that significantly influences epigenetic age by inducing widespread DNAm changes [9–12]. These changes often result in "epigenetic age acceleration (EAA)", where an individual's biological age exceeds their chronological age [13]. This acceleration is linked to increased risks of various disease incidences and

mortalities [14–16], highlighting the profound impact of smoking on cellular health and the aging process.

Previous studies have demonstrated that early life is a critical time window, in which lifestyle exposures trigger dramatic DNAm changes that can persist until later life and exert health impacts [17–21]; many chronic diseases in later life originate from early life [18–21]. Research indicates that epigenetic profiles are especially susceptible to environmental influences during early development [22,23]. These findings underscore the critical role of early developmental periods in shaping long-term health trajectories. Despite these advances, a significant knowledge gap exists regarding how parental smoking during childhood influences epigenetic age in late adulthood.

Therefore, this study aims to address the above-mentioned gap by investigating whether childhood exposure to parental smoking leads to EAA in later life among a nationally representative sample of middle-aged and older US adults from the Health and Retirement Study. Many previous studies have demonstrated that the effect of lifestyle behaviors can be modified by genetic compositions [24–26]. Therefore, we also aimed to evaluate whether parental smoking-related EAA is heterogenous according to individual's genetic profiles. By elucidating the long-term epigenetic consequences of early-life smoke exposure, we aim to provide critical biological evidence that can inform public health strategies to protect children from the harmful effects of secondhand smoke.

2. Methods

2.1. Study Population

The Health and Retirement Study (HRS) is a series of panel surveys conducted among a nationally representative sample of middle-aged and older adults in the United States. Each survey included approximately 20,000 participants, with attrition being addressed by replacing lost participants in subsequent surveys. The HRS has collected a rich body of longitudinal data on health, social well-being, and retirement.

The current study was conducted among HRS participants who took part in both the 2015–2017 Life History Mail Survey (LHMS) and the 2016 Venous Blood Study (VBS). The 2016 VBS was the first HRS survey to collect venous blood samples. Participants in the 2016 survey were asked to consent to a venous blood draw, which was managed by Hooper Holmes Health & Wellness. Among the eligible participants in the 2016 wave, 65% consented and completed the blood draw, resulting in a total sample size of 9934. DNAm data were profiled for a random sample of approximately 4000 participants from the 2016 VBS. Of these, 3102 were also part of the 2015–2017 LHMS and were included in the current study.

2.2. Childhood Exposure to Parental Smoking and Childhood Smoking

Data on childhood exposure to parental smoking before the age of 16 were collected using the following question: "Did your parents or guardians smoke during your childhood?". Additionally, the participants' smoking status during childhood was assessed by the following question: "Did you regularly smoke cigarettes while you were in grade school or high school? By 'regularly' we mean at least one cigarette a day for most days of the week, for six months or more".

2.3. Epigenetic Clocks and EAA

In the HRS, a total of 13 epigenetic clocks, calculated using the DNAm data collected in 2016, are publicly available (https://hrsdata.isr.umich.edu/data-products/epigenetic-clocks (accessed on 1 October 2024)). This current study focused on the five most commonly used epigenetic clocks, including HorvathAA, HannumAA, GrimAA, PhenoAA, DunedinAA, and ZhangAA.

HorvathAA was developed using 391 CpGs to measure the age of human fibroblasts and other skin cells, demonstrating high correlations with chronological age and predicting lifespan and many age-related conditions [27]. HannumAA, based on DNAm from whole

blood samples, also shows a strong correlation with age [5]. GrimAA is composed of DNAm sites related to plasma proteins and cigarette smoking, exhibiting an excellent predictive ability for time until death, coronary heart disease, and cancer [28]. PhenoAA was developed to reflect phenotypic age, estimating an individual's mortality risk using nine markers of tissue and immune function [29]. DunedinAA is derived from DunedinPoAm38, a measure of the pace of aging based on a composite slope across 18 biomarkers, assessing aging rates in cardiovascular, metabolic, renal, hepatic, pulmonary, periodontal, and immune systems [30]. This measure estimates the pace of aging in years per chronological year [30]. ZhangAA is based on 10 CpGs that show strong associations with all-cause mortality, and therefore, this clock predicts the risk of death, particularly by cancer and cardiovascular disease [31]. The EAA was calculated as the residuals from regressing the five epigenetic clocks on chronological age in 2016.

2.4. Genetic Susceptibility to Cigarette Smoking

The HRS has calculated polygenic scores (PGSs) for a series of disease phenotypes and health behaviors, including smoking, using genome-wide genotypes and summary statistics from genome-wide associations studies (GWASs). Briefly, a PGS for a phenotype was calculated as the sum of the product between the risk allele dosage and the reported effect sizes of the risk alleles across the whole genome. To evaluate whether childhood exposure to parental smoking influences EAA based on individuals' genetic susceptibility to smoking, we selected the PGS for smoking initiation as a measure of this susceptibility. The PGS for smoking initiation was calculated as the sum of the products of the genetic variants and their corresponding effect sizes of the coded alleles, as reported in a GWAS involving more than 1.2 million individuals of European ancestry [32].

2.5. Covariables

Covariables were determined a priori, based on a literature review, and included demographics (age, sex, race, and education), adulthood lifestyle behaviors (smoking, drinking, body mass index [BMI]) and depressive symptoms), as well as childhood family events (parental divorce, parental death, separation from the mother, and separation from the father). All the covariables were based on self-reported data. Race was categorized as Black, White, and Other. Education was classified into three levels: did not complete high school, completed high school only, and completed college or more. Smoking status was categorized as never smoker, former smoker, and current smoker. Drinking status was assessed with three questions: "Do you ever drink any alcoholic beverages, such as beer, wine, or liquor?"; "In the last three months, on average, how many days per week have you had any alcohol to drink?"; and "In the last three months, on the days you drink, about how many drinks do you have?" [33]. Drinking amount was calculated as the product of drinking days per week and drinks per day. Based on the answers to the three questions, the participants were categorized as never drinkers, light-to-moderate drinkers, and heavy drinkers [34]. Depressive symptoms were measured using the 8-item Center for Epidemiologic Study of Depression (CES-D), with the total scores ranging from 0 to 8, where higher scores indicate more depressive symptoms.

2.6. Statistical Analyses

Participant characteristics were presented as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Continuous variables were checked for normality and transformed as necessary.

Associations between childhood exposure to parental smoking and the five EAA were evaluated using two multivariable linear regression models: a base model adjusting for age, sex, and race and a full model additionally adjusting for education, smoking, drinking, the BMI, the CESD score, parental divorce, parental death, and separation from the mother/father in the overall sample. The associations were then examined in the White and the Black participants separately, using the same two models without race.

To determine whether these associations differ by genetic susceptibility to smoking, we tested interactions between the childhood exposure to parental smoking and the PGS for smoking initiation, by adding an interaction term, exposure*PGS, along with individual variables of the term in the two models. For the purpose of illustration, the participants were categorized into PGS tertiles, and associations between childhood exposure to parental smoking and each EAA were presented by these tertiles in each race group.

All the analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided *p*-values were calculated, with a significance threshold set at $p < 0.05$.

3. Results

As shown in Table 1, the participants in the 2016 VBS had a mean age of 69.8 years, with 60% being females and 77.8% identifying as White. The average education level was 13 years. Approximately 10% were current smokers, 44.4% were former smokers, and 38.6% were never drinkers. More than 67% of the participants reported childhood exposure to parental smoking. Compared to those without such exposure, the participants with childhood exposure were more likely to be male and White, included a higher proportion of current and former smokers, and were more likely to consume alcohol. Additionally, the exposed participants had higher BMIs than the non-exposed participants.

Table 1. Characteristics of the study participants overall and by childhood parental smoking status.

Variables	Overall	Parents or Guardians Smoked During Childhood	
		Yes	No
Mean age (SD), years	69.8 (9.5)	69.7 (9.3)	69.9 (10.1)
Male, %	1242, 40.0%	847, 41.0%	373, 37.3%
Race, %			
Black	494, 16.0%	275, 13.3%	207, 20.8%
White	2407, 77.8%	1684, 81.7%	702, 70.4%
Smoking status			
Current	320, 10.4%	236, 11.5%	82, 8.2%
Former	1369, 44.4%	988, 48.2%	363, 36.5%
Never	1394, 45.2%	827, 40.3%	551, 55.3%
Drinking status			
Regular drinking	98, 8.0%	72, 8.6%	25, 6.7%
Occasional drinking	658, 53.5%	468, 55.8%	178, 48.0%
Never drinking	475, 38.6%	299, 35.6%	168, 45.3%
Mean years of education (SD)	13.0 (3.0)	13.1 (3.0)	13.0 (3.1)
Mean CESD (SD)	1.3 (1.9)	1.4 (1.9)	1.3 (1.9)
Mean BMI (SD), kg/m^2	28.9 (6.3)	29.1 (6.4)	28.6 (6.2)

Note. BMI = body mass index; CESD = Center for Epidemiologic Study of Depression; SD = standard deviation.

Childhood Exposure to Parental Smoking and EAA

After controlling for age, sex, and race, childhood exposure to parental smoking was significantly associated with the EAA measured by GrimAA ($\beta = 0.98$; $p < 0.001$) and DunedinAA ($\beta = 0.01$; $p = 0.002$). These associations remained significant for GrimAA ($\beta = 0.70$; $p = 0.03$) and nominally significant for DunedinAA ($\beta = 0.01$; $p = 0.06$), even after adjusting for adulthood lifestyle behaviors and other childhood adverse family events.

Among the White participants, when stratified by tertiles of genetic susceptibility to cigarette smoking, childhood exposure to parental smoking showed significantly stronger effects on GrimAA (p for interaction < 0.001) and DunedinAA (p for interaction < 0.001) among those in the highest tertile of the genetic risk (Table 2). After controlling for age and sex, childhood parental smoking increased GrimAA by 1.41 ($p < 0.001$), 0.84 ($p = 0.02$), and 0.74 ($p = 0.03$) years in the top, middle, and bottom tertiles of genetic risk, respectively. Similarly, the exposure was associated with an increase in DunedinAA of 0.02 ($p = 0.01$), 0.01 ($p = 0.06$), and 0.01 ($p = 0.41$) units across the tertiles of the genetic risk.

Table 2. Associations between exposure to parents or guardians smoking during childhood and epigenetic age acceleration in late adulthood among the White participants of the Health and Retirement Study overall and by the tertiles of the polygenic risk score for smoking.

Tertiles of Genetic Susceptibility to Smoking	Age and Sex Adjusted Model			Full Model		
	Beta (SE)	P	P_Interaction	Beta (SE)	P	P_Interaction
HannumAA	−0.23 (0.26)	0.39		−0.49 (0.43)	0.26	
Bottom	−0.43 (0.44)	0.33	**0.005**	−0.44 (0.71)	0.54	0.25
Middle	−0.53 (0.43)	0.22		−0.72 (0.64)	0.26	
Top	0.32 (0.50)	0.53		−0.30 (0.91)	0.75	
PhenoAA	−0.07 (0.34)	0.84		−0.49 (0.53)	0.35	
Bottom	0.25 (0.58)	0.67	**0.04**	0.41 (0.88)	0.64	0.57
Middle	−0.15 (0.58)	0.80		−0.03 (0.84)	0.97	
Top	−0.25 (0.63)	0.69		−1.88 (1.03)	0.07	
HorvathAA	−0.20 (0.22)	0.36		−0.10 (0.36)	0.79	
Bottom	−0.10 (0.37)	0.78	**0.02**	0.67 (0.66)	0.31	0.54
Middle	−0.59 (0.38)	0.12		−0.45 (0.55)	0.42	
Top	0.11 (0.41)	0.80		−0.44 (0.70)	0.53	
ZhangAA	0.01 (0.02)	0.59		−0.05 (0.03)	0.13	
Bottom	−0.00 (0.04)	0.90	**0.003**	−0.10 (0.06)	0.07	0.49
Middle	−0.01 (0.04)	0.71		−0.05 (0.05)	0.29	
Top	0.06 (0.04)	0.16		0.02 (0.06)	0.69	
GrimAA	0.98 (0.21)	**<0.001**		0.70 (0.32)	**0.03**	
Bottom	0.74 (0.35)	**0.03**	**<0.001**	0.91 (0.53)	0.09	**0.01**
Middle	0.84 (0.36)	**0.02**		0.56 (0.52)	0.28	
Top	1.41 (0.41)	**<0.001**		0.79 (0.60)	0.19	
DunedinAA	0.01 (0.00)	**0.002**		0.01 (0.01)	0.06	
Bottom	0.01 (0.01)	0.41	**<0.001**	0.02 (0.01)	0.20	0.10
Middle	0.01 (0.01)	0.06		0.01 (0.01)	0.19	
Top	0.02 (0.01)	**0.01**		0.01 (0.01)	0.30	

Note. Full model adjusted for the covariables measured during the 2016 visit survey, including age, sex, education, smoking, drinking, the CESD score, and the BMI. Bold values (p) denote statistical significance ($p < 0.05$).

As shown in Table 3, childhood exposure to parental smoking had stronger effects on GrimAA (β = 1.47; $p = 0.003$) and DunedinAA (β = 0.03; $p = 0.003$) in the Black participants. However, the effects did not differ by the tertiles of genetic susceptibility to cigarette smoking ($p \geq 0.56$). When adjusting for adulthood lifestyle behaviors, the associations became non-significant.

Table 3. Associations between exposure to parents or guardians smoking during childhood and epigenetic age acceleration in late adulthood among the Black participants of the Health and Retirement Study overall and by the tertiles of the polygenic risk score for smoking.

Tertiles of Genetic Susceptibility to Smoking	Age and Sex Adjusted Model			Full Model		
	Beta (SE)	P	P_Interaction	Beta (SE)	P	P_Interaction
HannumAA	0.27 (0.55)	0.63		−1.51 (1.10)	0.17	
Bottom	0.81 (0.93)	0.39	0.06	3.37 (2.02)	0.10	0.06
Middle	0.44 (0.90)	0.63		−2.11 (1.68)	0.22	
Top	−0.15 (1.06)	0.89		−4.84 (2.83)	0.10	
PhenoAA	0.71 (0.77)	0.36		1.17 (1.59)	0.46	
Bottom	0.98 (1.29)	0.45	0.65	2.72 (2.54)	0.29	0.90
Middle	1.31 (1.27)	0.30		−0.29 (2.63)	0.91	
Top	−0.63 (1.42)	0.66		−0.90 (4.26)	0.83	
HorvathAA	−0.35 (0.47)	0.46		−0.38 (0.94)	0.69	
Bottom	−0.47 (0.80)	0.56	0.53	3.70 (1.89)	0.06	0.23
Middle	0.09 (0.81)	0.91		−1.13 (1.26)	0.38	
Top	−0.57 (0.86)	0.51		−3.41 (2.09)	0.11	

Table 3. *Cont.*

Tertiles of Genetic Susceptibility to Smoking	Age and Sex Adjusted Model			Full Model		
	Beta (SE)	**P**	**P_Interaction**	**Beta (SE)**	**P**	**P_Interaction**
ZhangAA	0.05 (0.05)	0.33		−0.12 (0.09)	0.17	
Bottom	0.08 (0.08)	0.34	0.63	0.19 (0.17)	0.28	0.19
Middle	0.09 (0.08)	0.30		0.13 (0.19)	0.51	
Top	0.02 (0.08)	0.81		−0.36 (0.20)	0.08	
GrimAA	1.47 (0.48)	**0.003**		−0.51 (0.83)	0.54	
Bottom	2.55 (0.81)	**0.002**	0.56	−0.27 (1.31)	0.84	0.48
Middle	1.39 (0.86)	0.11		2.67 (1.54)	0.09	
Top	0.71 (0.87)	0.42		−2.94 (1.88)	0.13	
DunedinAA	0.03 (0.01)	**0.003**		0.02 (0.02)	0.34	
Bottom	0.04 (0.02)	**0.02**	0.93	0.00 (0.03)	0.94	0.74
Middle	0.05 (0.02)	**0.006**		0.10 (0.04)	**0.02**	
Top	0.00 (0.02)	0.83		−0.03 (0.04)	0.47	

Note. Full model adjusted for the covariables measured during the 2016 visit survey, including age, sex, education, smoking, drinking, the CESD score, and the BMI. Bold values (p) denote statistical significance ($p < 0.05$).

4. Discussion

In a nationally representative sample of middle-aged and older US adults, we found that childhood exposure to parental smoking was associated with EAA as measured by GrimAA and DunedinAA. These effects remained significant in the White participants even after adjusting for adult lifestyle behaviors, but not in the Black participants. Additionally, we demonstrated that the adverse effects of parental smoking on EAA were more pronounced among the individuals with a high genetic susceptibility to smoking. These findings underscore the importance of reducing childhood exposure to secondhand smoke, particularly for those with a genetic predisposition to smoking initiation.

Parental smoking exposure was associated with EAA as estimated by GrimAA and DunedinAA, but not with the other three EAA measures. This aligns with earlier research in the same population [35]; however, our study adds that parental smoking exposure was not linked to the other three EAA measures. The three EAA measures were developed using CpG sites related to chronological age or mortality, while GrimAA and DunedinAA involve CpG sites directly or indirectly related to smoking. Nevertheless, parental smoking exposure tended to show different effects on the three EAA measures by the levels of the PGS. Future studies examining the interaction of genes with parental smoking exposure may identify individual groups who are particularly vulnerable to smoking. Furthermore, we identified the race-specific effects of parental smoking exposure and the joint impact of exposure and genetic susceptibility on EAA. Both our study and previous research indicate that early-life smoking exposure affects EAA independently of the adult smoking status [35]. Collectively, these findings suggest that early life is a critical period during which smoking exposure may trigger lasting changes in the epigenome and accelerate aging.

We found that parental smoking exposure was more strongly associated with accelerated aging among the participants with a high genetic susceptibility compared to those with a low susceptibility. This finding may also have biological significance. It is likely that the PRS is enriched by genetic pathways related to accelerated aging, and early life exposure to smoking can trigger the pathways that lead to accelerated aging. This is the first study to demonstrate the varying effects of parental smoking exposure on EAA based on genetic susceptibility. Genetic susceptibility, estimated using polygenic risk scores, reflects the lifetime likelihood of smoking [36]. As shown in numerous studies, polygenic risk scores provide a more accurate estimate than the smoking behaviors assessed in limited surveys [25]. Preventing secondhand smoking in childhood, especially among those with a high genetic risk, may have a greater impact on aging. Given that genetic testing is non-invasive, affordable, and widely available, our findings are significant for precision health.

Our study has notable strengths. First, the participants were drawn from a nationally representative survey, enhancing the generalizability of our findings. Second, we assessed a comprehensive range of epigenetic clocks, allowing us to evaluate the impact of early-life smoking on EAA. Third, polygenic risk scores for cigarette smoking were available for all the participants, enabling us to explore the heterogeneous effects of parental smoking exposure on EAA based on these scores. Finally, our study design provides a clear temporal relationship. However, there are limitations. First, childhood exposure to parental smoking was self-reported, which may introduce an information bias. Nonetheless, such a bias is likely non-differential, potentially biasing estimates toward the null and reducing the statistical power to detect significant associations, thereby demonstrating the robustness of our findings. Second, the PGS was developed based on genome-wide association studies conducted predominantly among the participants of European ancestry. Its performance in Black participants was less optimal. Future studies with a better PGS for Black participants are needed.

In conclusion, we found that childhood exposure to parental smoking led to accelerated aging in later life, with more pronounced effects among the individuals with a high genetic susceptibility to cigarette smoking. These findings provide strong evidence for minimizing secondhand smoking exposure among children, particularly those with a genetic predisposition to smoking. Future genome-wide studies testing the interactions of genetic variants with childhood exposure to parental smoking may identify the genes contributing to accelerated aging among the participants. Our take-home message is that childhood is a critical period during which smoking exposure may trigger lasting changes in the epigenome and accelerate aging until late adulthood, particularly among those with a high genetic susceptibility to smoking.

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Institutional Review Board Statement: The current study was approved by Tulane University Institutional Review Boards (Approved #: 2020–2091).

Informed Consent Statement: Not applicable. The current study is a secondary analysis of the publicly available, de-identified data.

Data Availability Statement: The HRS is publicly available and can be obtained at https://hrs.isr.umich.edu/ (accessed on 1 October 2024). SAS codes for the current project are available upon request to the corresponding author, Changwei Li.

Conflicts of Interest: The authors declare no conflicts of interest.

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