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Childhood Maltreatment and Biological Aging in Middle Adulthood: The Role of Psychiatric Symptoms

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ABSTRACT

BACKGROUND: Childhood maltreatment and psychiatric morbidity have each been associated with accelerated biological aging primarily through cross-sectional studies. Using data from a prospective longitudinal study of individuals with histories of childhood maltreatment and control participants followed into midlife, we tested 2 hypotheses examining whether 1) psychiatric symptoms mediate the relationship between childhood maltreatment and biological aging and 2) psychiatric symptoms of anxiety, depression, or posttraumatic stress disorder (PTSD) act in conjunction with childhood maltreatment to exacerbate the association of child maltreatment to aging.

METHODS: Children (ages 0–11 years) with documented histories of maltreatment and demographically matched control children were followed into adulthood (N = 607) and interviewed over several waves of the study. Depression, anxiety, and PTSD symptoms were assessed at mean ages of 29 (interview 1) and 40 (interview 2) years. Biological age was measured from blood chemistries collected later (mean age = 41 years) using the Klemera-Doubal method. Hypotheses were tested using linear regressions and path analyses.

RESULTS: Adults with documented histories of childhood maltreatment showed more symptoms of depression, PTSD, and anxiety at both interviews and more advanced biological aging, compared with control participants. PTSD symptoms at both interviews and depression and anxiety symptoms only at interview 2 predicted accelerated biological aging. There was no evidence of mediation; however, anxiety and depression moderated the relationship between childhood maltreatment and biological aging.

CONCLUSIONS: These new findings reveal the shorter- and longer-term longitudinal impact of PTSD on biological aging and the amplifying effect of anxiety and depression on the relationship between child maltreatment and biological aging.

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Childhood maltreatment is a major public health concern in the United States and the world (1), with long-term consequences that include psychiatric disorders (2–5) and effects on physical health, social relationships, and economic productivity (1,6–10). Increasing evidence also suggests that childhood maltreatment may lead to an overall acceleration of the biological aging process. Biological aging is the progressive loss of system integrity that occurs with the passage of time, mediating aging-related risk for disease and disability. Although there is currently no gold-standard measure of biological aging (11), several methods have accumulated evidence as being valid and reliable. The current state-of-the-art measurements include multivariate algorithms that combine information from clinical or genomic measurements to track changes that occur in peoples' bodies as they age (12).

Recent studies have reported evidence of accelerated aging in children and adults with histories of exposure to childhood adversities, including maltreatment (13–17). Mid- and later-life retrospective reports of childhood adversity have been associated with older biological age and faster pace of aging as measured by epigenetic clocks (18–21). In longitudinal studies, children in the E-Risk and Dunedin birth cohorts who were exposed to more adversity exhibited a faster pace of aging and older biological age in midlife (14,15,20).

Psychological and behavioral factors are important drivers of aging-related health outcomes (22,23). In epidemiological studies, people with psychiatric disorders experienced an excess burden of multiple different aging-related diseases and premature mortality compared with those without psychiatric disorders (24–28). Adults with psychiatric disorders, including depression, anxiety, and posttraumatic stress disorder (PTSD), also tend to exhibit molecular signs of accelerated biological aging (16,17,29–37).

Together, these studies suggest that both childhood maltreatment and later psychiatric disorders each contribute to accelerated biological aging. In parallel, there are mechanistic connections between the biology of stress and the biology of aging, including mitochondrial dysfunction, systemic

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inflammation, epigenetic alterations, and DNA damage (38–40). These connections suggest potential mechanisms that may explain the associations between childhood maltreatment, psychiatric disorders, and accelerated biological aging. A small number of studies have sought to connect exposure to early adversity with mental health problems and subsequent acceleration of biological aging. In analyses of the HRS (Health and Retirement Study), NESDA (Netherlands Study of Depression and Anxiety), and DNHS (Detroit Neighborhood Health Study) cohorts, mental health problems partially mediated associations between retrospective reports of childhood adversity and later accelerated biological aging (17,36,41). One study found that retrospective reports of maltreatment were associated with epigenetic age acceleration in individuals with major depressive disorder (42). Using data from the DNHS, the researchers found few direct effects of childhood adversity on biological age, and direct effects of biological age on depression and tests for mediation were not significant (41).

Another possibility is that the combination of child maltreatment and psychiatric symptoms exacerbates the aging process. To our knowledge, no previous study has examined potential interaction effects. However, it is possible that there is a synergistic effect wherein individuals with histories of childhood maltreatment and high levels of psychiatric symptoms show faster biological aging. Psychiatric symptoms themselves may reflect vulnerability earlier on that would impact the body's ability to deal with stressors.

Thus, there are several possible pathways from childhood maltreatment to biological aging. Childhood maltreatment and psychiatric disorders could be independent influences on biological aging, they could combine in a chain-of-risk pathway (maltreatment → psychiatric disorder → accelerated biological aging), or they could combine synergistically with the psychiatric symptoms moderating the relationship between child maltreatment and biological aging. However, few studies have used prospective designs that can more closely establish the temporal ordering of childhood maltreatment, psychiatric disorders, and biological aging, and most studies have relied on retrospective reports of childhood maltreatment. As a result, there is ambiguity in the existing evidence base about whether biological aging is a direct consequence of childhood maltreatment or whether psychiatric disorders that may be consequences of childhood maltreatment drive accelerated biological aging or moderate the relationship.

The Current Study

We capitalized on existing data from a unique prospective study in which children with documented histories of childhood maltreatment and a demographically matched control group of nonmaltreated children were followed and assessed in adulthood. Psychiatric evaluations were conducted when participants were young adults (mean age = 29 years) and again in midlife (mean age = 40 years). Blood samples and clinical assessments were collected later (mean age = 41 years). We measured biological aging from clinical parameters using the method proposed by Klemera and Doubal (43) and Levine (44). We previously reported that in this cohort, individuals with histories of childhood maltreatment exhibited accelerated biological aging compared with control participants (45).

Here, we examined the role of 3 psychiatric disorders (depression, anxiety, and PTSD) as potential mediators or moderators of the relationship between childhood maltreatment and accelerated biological aging using a longitudinal design and documented cases of childhood maltreatment. We considered the roles of psychiatric symptoms assessed in young adulthood (interview 1) and again in middle adulthood (interview 2). Information from interview 1 was based on lifetime symptoms through (mean) age 29 (young adulthood) and may be expected to have an enduring stressful impact leading to accelerated biological aging. The assessment at the second interview (mean age = 40 years) was based on past week or current symptoms of anxiety, depression, and PTSD, and thus, these symptoms represent a shorter time between the assessment and interview 3, when the participants had a mean age of 41, making analyses of symptoms from interview 2 more similar to existing studies based on cross-sectional designs. The causal direction is somewhat ambiguous for the associations of interview 2 psychiatric symptoms and biological aging assessment at interview 3 because the psychiatric symptoms were assessed such a short time before the biological aging assessment. However, including both short- and long-term longitudinal assessments of the roles of these psychiatric symptoms allowed us to evaluate the ways in which study design may affect findings. Given the lack of longitudinal evidence from prior studies, we tested both sets of predictions in individuals with documented histories of childhood maltreatment.

Our analysis proceeded in 3 steps. First, we tested long-term and short-term longitudinal associations between the psychiatric disorders (PTSD, anxiety, and depression symptoms) and biological aging. Second, we conducted mediation analyses to determine whether psychiatric symptoms mediate the relationship between childhood maltreatment and biological aging. Finally, we tested whether childhood maltreatment and psychiatric disorders combine synergistically to accelerate biological aging.

METHODS AND MATERIALS

Design and Participants

The data used here are from a prospective cohort design study in which children who had experienced abuse and/or neglect were matched with children who had not experienced abuse or neglect and followed into adulthood. The description of the methods and sample selection used here draws heavily on previous descriptions from earlier work (46). The initial phase of the study was archival and defined the samples of children with a history of abuse and/or neglect and the matched comparison group (n = 1575) (46,47). The second phase involved locating and interviewing both groups during 1989 to 1995 (mean age = 29 years), approximately 22 years after the incidents of abuse and neglect (n = 1196). Further follow-up interviews with both groups were conducted from 2000 to 2002 (mean age = 40 years) and 2003 to 2005 (mean age = 41 years). The current study uses information collected during these 3 interviews.

The original sample of children with histories of abuse and/or neglect (n = 908) comprised court-substantiated cases of

childhood physical and sexual abuse and neglect processed from 1967 to 1971 in the county juvenile (family) or adult criminal courts of a Midwestern metropolitan area. Cases of abuse and neglect were restricted to children 11 years or younger at the time of the incident. This design characteristic was adopted to minimize ambiguity and maximize the likelihood that the temporal direction of consequences would be clear.

A critical element of the design involved the selection of a control group of children without documented histories of child abuse or neglect (n = 667) who were matched with the children with abuse/neglect histories on age, sex, race/ethnicity, and approximate family social class at the time that the abuse and neglect cases were processed. Matching for approximate family social class was important because it is theoretically plausible that any relationship between child abuse and neglect and subsequent outcomes may be confounded with or explained by social class differences (47–51). The matching procedure used here is based on the neighborhood schools that the children attended and hospitals of birth as a proxy for social class. Neighborhood and hospital controls are recommended for use when researchers want to match participants on variables related to outcomes and when random sampling is not possible (52). The comparison group establishes the base rates of pathology that we would expect to see in a sample of adults from comparable circumstances who did not come to the court's attention in childhood as victims of abuse or neglect.

Children who were under school age at the time of the abuse and/or neglect were matched with children of the same sex, race, date of birth (±1 week), and hospital of birth using county birth record information. For children of school age, records of more than 100 elementary schools for the same period were used to find matches with children of the same sex, race, date of birth (±6 months), and class in elementary school during the years from 1967 to 1971. Overall, matches were found for 74% of the children with an abuse/neglect history. Nonmatches occurred in the following situations: 1) where the maltreated child was born outside the county or state, 2) when date of birth information was missing, 3) because of a lack of adequate identifying information for the maltreated child, or 4) because the elementary school had closed and class registers were not available.

Because of the matching procedure, individuals in the study are assumed to differ only on the risk factor (i.e., having experienced childhood sexual or physical abuse or neglect). Because it is not possible to randomly assign people to groups, the assumption of equivalency for the groups is an approximation. The control group may also differ from the abused and neglected group on other variables associated with abuse or neglect.

Of the 1196 individuals interviewed during 1989 to 1995, 896 (75%) were interviewed again during 2000 to 2002 (interview 2), and 807 were interviewed during 2003 to 2005 (interview 3). Although there has been attrition due to death, refusals, and inability to locate participants, the demographic characteristics of the sample have remained essentially the same over time (Table 1). Bivariate analyses of characteristics of participants in the first and third interviews showed no significant differences in child maltreatment status, race, and age.

Table 1. Characteristics of the Sample Over Four Waves

Characteristics	Records	Interviews		
		1	2	3
Dates	1967–1971	1989–1995	2000–2002	2003–2005
n	1575	1196	896	807
Sex, % Female	50.7%	48.7%	51.0%	52.7%
White, %	66.2%	62.9%	62.2%	60.4%
Black, %	32.6%	34.9%	35.2%	37.3%
Abuse/Neglect, %	57.7%	56.5%	55.8%	56.8%
Age at Petition, Years, Mean (SD)	6.4 (3.3)	6.3 (3.3)	6.2 (3.3)	6.3 (3.3)
Age at Interview, Years, Mean (SD)	–	29.3 (3.8)	39.5 (3.5)	41.1 (3.5)

However, females were more likely to participate in the third interview than males (beta = 0.50, $p < .01$).

In the current article, we used data from all participants from interview 1 who self-identified as non-Hispanic White or non-Hispanic Black (n = 1124) and who agreed to provide blood samples during the third interview (n = 607). At interview 3, the overall sample was 54.8% female and 60.4% non-Hispanic White, and the mean age was 41 years. A comparison of the demographic characteristics of the interview 3 sample and the analytic sample used here revealed no significant differences in age (p = .52), sex (p = .53), race (p = .62), and maltreatment status (p = .46).

Procedures

Interviews took place in participants' homes or other convenient places. The interviewers were not informed of the purpose of the study, the participants' group membership, or that there was an abused and/or neglected group. A licensed registered nurse performed a medical status examination in the participant's home or other quiet location of the person's choosing (10). Participants were also not informed of the purpose of the study but were told that they had been selected to participate as part of a large group of individuals who grew up in that area during the late 1960s and early 1970s. Institutional review board approval was obtained for each wave of the study, and participants provided written informed consent. For individuals with limited reading ability, the consent form was presented and explained verbally. This study was approved by the Human Research Protection Program at the City University of New York (Protocol #: 2015-0133).

Measures and Variables

Childhood Maltreatment. Children with documented court cases of physical and sexual abuse and neglect (ages 0–11 years) were identified through a review of court records from the years 1967 to 1971. Physical abuse cases included injuries such as bruises, welts, burns, abrasions, lacerations, wounds, cuts, and bone and skull fractures. Sexual abuse cases included felony sexual assault, fondling or touching, sodomy, incest, and rape. Neglect cases reflected a judgment that the parents' deficiencies in childcare were beyond those found acceptable by community and professional standards at the time and represented extreme failure to provide adequate

food, clothing, shelter, and medical attention to children. For the purposes of this article, we used a dichotomous variable that represents whether the participant had experienced any form of documented childhood maltreatment (coded 1) or not (coded 0).

Psychiatric Symptoms. During the first interview at a mean age of 29 years, psychiatric disorders were assessed through the administration of the National Institute of Mental Health Diagnostic Interview Schedule, Version III, Revised (53), a standardized psychiatric assessment that yielded diagnoses consistent with the DSM-III-R (54). The Diagnostic Interview Schedule, Version III, Revised, has demonstrated adequate reliability (55,56). We reported DSM-III-R lifetime symptoms for PTSD (4), major depressive disorder (5), and generalized anxiety disorder.

During the second interview (mean age 39 years), depression symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (57), a 20-item self-report measure with high internal consistency in both general and psychiatric populations. Participants were asked to indicate how they felt during the past week on a 4-point scale ranging from rarely or none of the time (<1 day) to most or all of the time (5–7 days). Total scores ranged from 0 to 60 (mean = 13.82, SD = 10.94, α = 0.90). Anxiety symptoms were assessed with the Beck Anxiety Inventory (58), a 21-item self-report measure in which participants were asked to rate how much they had been bothered by specific symptoms over the past week on a 4-point scale from 0 (not at all) to 3 (severely). Total scores ranged from 0 to 63 (mean = 10.54, SD = 11.11, α = 0.93). High internal consistency, test-retest reliability, and good concurrent and discriminant validity have been reported for the Beck Anxiety Inventory (58,59). PTSD symptoms were assessed with a modified version of the Composite International Diagnostic Interview PTSD module (60), a structured diagnostic interview used to evaluate exposure to traumatic events and symptoms based on DSM-IV criteria for PTSD. The PTSD module of the Composite International Diagnostic Interview demonstrated acceptable internal consistency and good concurrent validity (61). The PTSD module of the Composite International Diagnostic Interview symptom count scores (present or not present) ranged from 0 to 17 (mean = 6.39, SD = 4.70).

Biological Aging. While there is no single gold-standard measure of biological aging (11), algorithms that combine information from clinical parameters measuring organ system integrity are among the most predictive of morbidity and mortality, have validation evidence in young and midlife as well as in older adults, and indicate more advanced aging in adults with a history of childhood adversity (14,62–65). We measured biological aging from clinical parameters using the method proposed by Klemera and Doubal (43) and the approach originally described by Levine (44). Klemera-Doubal method (KDM) biological age can be interpreted as the age at which a participant's physiology would be approximately normal in a reference population. We followed our established method from prior work to derive the KDM biological age by modeling associations of biomarkers with chronological age in the U.S. National Health and Nutrition Examination Survey and then applying parameters derived from these models in this dataset to compute participants' biological age values (66,67). Biomarkers, measured from serum blood tests and complete blood counts, included albumin, creatinine, C-reactive protein, white blood cell count, lymphocyte percentage, mean cell volume, red cell distribution width, alkaline phosphatase, and glycated hemoglobin. In previous work with this sample, participants with documented histories of childhood maltreatment had an older KDM biological age than individuals without such a history (45).

Control Variables. Sex, age, and race were included as control variables. Sex was coded as male (0) or female (1). To determine race and ethnicity, participants were shown a card with the names of racial and ethnic groups and asked to indicate which race or ethnic group best described them. For the current analysis, race was coded as non-Hispanic White (n = 368) and non-Hispanic Black (n = 239); we excluded the small number of individuals who identified as Hispanic, Native American, Pacific Islander, or other. Age was measured in years.

Statistical Analysis

Descriptive statistics for the maltreated and control groups were calculated and compared using t tests for continuous variables and Pearson's χ^2 for categorical variables. We conducted a series of path analyses to test for mediation, with childhood maltreatment as the independent variable, psychiatric symptoms as hypothesized mediators, and biological age in middle adulthood as the outcome. Each hypothesized mediator was fitted separately in individual models estimated for interviews 1 and 2 predicting biological age at interview 3.

For mediation analyses, we followed the recommendations of Rucker *et al.* (68) that focus on testing the mediation effects themselves rather than finding the difference in direct effects using a stepwise procedure. Accordingly, indirect effects were tested using bootstrapping using 1000 resamples and were assessed based on 95% bias-corrected confidence intervals. The indirect effect is considered significant when the 95% bias-corrected confidence interval does not contain 0. There was <1% missing data for all variables included in the analysis, and we handled the small amount of missing data through full-information maximum likelihood, a recommended approach for including all available data and minimizing loss of statistical power (69). Fit indices were examined to determine goodness of fit (for χ^2, $p > .05$; comparative fit index > 0.95; Tucker-Lewis index > 0.95; root-mean-square error of approximation ≤ 0.05; standardized-root-mean-square residual ≤ 0.05). Standardized coefficients (β) are reported for conditional models. All analyses were conducted in R version 4.2.1 using the R package *lavaan* version 0.6-13 (70).

To determine whether psychiatric symptoms moderated the relationship between childhood maltreatment and biological age, we conducted 3 linear regression analyses that each included an interaction term representing the product of maltreatment and anxiety, depression, or PTSD.

RESULTS

Table 2 shows that individuals with documented histories of childhood maltreatment did not differ from matched control

Table 2. Descriptive Characteristics of Individuals With Documented Histories of Childhood Maltreatment and Matched Control Individuals

Variable	Overall, *n* = 1124	Control, *n* = 497	Maltreated, *n* = 627	Statistics
Demographic Characteristics				
Female	549 (48.8%)	232 (46.7%)	317 (50.6%)	$\chi^2 = 1.52$, $p = .218$
White, Non-Hispanic	735 (65.4%)	319 (64.2%)	416 (66.3%)	$\chi^2 = 0.48$, $p = .488$
Age at Interview 1, Years	29.3 (3.8)	29.4 (3.9)	29.1 (3.8)	$t = 1.46$, $p = .143$
Age at Interview 2, Years	39.5 (3.5)	39.6 (3.5)	39.5 (3.6)	$t = 0.79$, $p = .433$
Age at Interview 3, Years	41.1 (3.5)	40.9 (3.7)	41.2 (3.4)	$t = 0.81$, $p = .418$
Interview 1 (Mean Age = 29.3 Years)				
Psychiatric Symptoms (DSM-III-R)				
Major Depressive Disorder	3.4 (2.7)	3.1 (2.7)	3.6 (2.7)	$t = 2.86$, $p = .004$
Posttraumatic Stress Disorder	5.2 (5.7)	4.1 (5.1)	6.1 (6.0)	$t = 5.90$, $p < .001$
Generalized Anxiety Disorder	4.1 (5.1)	3.7 (4.6)	4.4 (5.6)	$t = 2.56$, $p = .011$
Interview 2 (Mean Age = 40.0 Years)	*n* = 833	*n* = 376	*n* = 457	
Psychiatric Symptoms				
Major Depressive Disorder	13.8 (10.9)	10.6 (10.0)	14.8 (11.6)	$t = 5.48$, $p < .001$
Posttraumatic Stress Disorder	6.4 (4.7)	5.8 (4.5)	7.0 (4.8)	$t = 3.74$, $p < .001$
Generalized Anxiety Disorder	10.5 (11.1)	7.8 (8.7)	10.6 (11.3)	$t = 3.96$, $p < .001$
Interview 3 (Mean Age = 41)	*n* = 607	*n* = 250	*n* = 357	
KDM Biological Age	39.8 (8.7)	38.7 (8.4)	40.6 (8.9)	$t = 2.46$, $p = .014$
KDM Biological Age Acceleration	−1.3 (7.9)	−2.2 (7.4)	−0.6 (8.2)	$t = 2.37$, $p = .018$

Values are presented as mean (SD) or *n* (%).

Interview 1 symptoms represent lifetime DSM-III-R symptoms based on responses to the National Institute of Mental Health Diagnostic Interview Schedule-III-R. For interview 2, depression symptoms are based on scores from the Center for Epidemiological Studies Depression Scale, anxiety symptoms from the Beck Anxiety Inventory, and posttraumatic stress disorder symptoms from the Composite International Diagnostic Interview.

KDM biological age = age at which the average physiology in NHANES III matches the physiology of the participant. KDM biological age acceleration = the difference between algorithm-predicted values and the true chronological age.

KDM, Klemera-Doubal method.

participants on demographic characteristics of sex, race, and age. However, compared with control participants, maltreated participants reported significantly more symptoms of depression, PTSD, and anxiety at interview 1 and at interview 2 ten years later. Finally, compared with control participants, maltreated individuals had significantly accelerated KDM biological age.

Psychiatric Symptoms Predicted Biological Aging

Table 3 shows that lifetime PTSD symptoms at interview 1 in young adulthood and at interview 2 in middle adulthood predicted accelerated KDM biological age later in midlife. In addition, depression and anxiety symptoms at interview 2 predicted accelerated KDM biological age at interview 3.

Do Depression, Anxiety, or PTSD Symptoms in Young or Middle Adulthood Mediate the Relationship Between Childhood Maltreatment and Biological Aging?

The results of path analyses (Table 4) show significant bivariate relationships; however, the results do not support the hypothesis that psychiatric symptoms mediate the relationship between childhood maltreatment and biological aging.

Do Depression, Anxiety, or PTSD Symptoms Moderate the Relationship Between Childhood Maltreatment and Biological Aging?

Table 5 shows the results of regression analyses testing the hypothesis that psychiatric symptoms moderated the relationship between childhood maltreatment and biological aging. For interview 1 (see Figure 1), the relationship between anxiety symptoms and biological aging levels varied depending on childhood maltreatment status (β = 0.04; SE = 0.02; 95% CI 0.01–0.07); for adults who did not experience

Table 3. Results of Linear Regressions Showing the Extent to Which Psychiatric Symptoms in Young Adulthood (Interview 1) and Middle Adulthood (Interview 2) Predict KDM Biological Age Acceleration (Interview 3)

	β (SE)	*p*	*b*
At Interview 1			
Depression	−0.001 (0.02)	.98	−0.002
Anxiety	−0.005 (0.01)	.56	−0.04
PTSD	0.01 (0.007)	.04[a]	0.11
At Interview 2			
Depression	0.01 (0.004)	.02[a]	0.14
Anxiety	0.009 (0.004)	.03[a]	0.07
PTSD	0.02 (0.01)	.05[a]	0.07

β refers to standardized coefficient, and *b* refers to unstandardized coefficients. Interview 1 symptoms are lifetime DSM-III-R symptoms based on responses to the National Institute of Mental Health Diagnostic Interview Schedule-III-R. For interview 2, depression symptoms are based on scores from the Center for Epidemiological Studies Depression Scale, anxiety symptoms from the Beck Anxiety Inventory, and PTSD symptoms from the Composite International Diagnostic Interview. All analyses controlled for age, sex, and race.

KDM, Klemera-Doubal method; PTSD, posttraumatic stress disorder.

[a]$p \leq .05$.

Table 4. Results of Path Analyses Testing Whether Psychiatric Symptoms Mediate the Relationship Between Childhood Maltreatment and KDM Biological Age Acceleration

	β	SE	95% BCCI	*p*
Interview 1				
Total Effects	0.10	0.04	0.02, 0.18	.01
Direct: Maltreatment → KDM Biological Age Acceleration	0.10	0.04	0.02, 0.18	.01
Maltreatment → Depression	0.09	0.03	0.03, 0.14	.004
Depression → KDM Biological Age Acceleration	−0.01	0.04	−0.09, 0.07	.78
Maltreatment → Depression → KDM Biological Age Acceleration	0.00	0.00	−0.01, 0.01	.78
Direct: Maltreatment → KDM Biological Age Acceleration	0.11	0.04	0.02, 0.19	.01
Maltreatment → Anxiety	0.07	0.03	0.02, 0.13	.01
Anxiety → KDM Biological Age Acceleration	−0.03	0.04	−0.11, 0.04	.39
Maltreatment → Anxiety → KDM Biological Age Acceleration	0.00	0.00	−0.01, 0.01	.41
Direct: Maltreatment → KDM Biological Age Acceleration	0.09	0.04	0.01, 0.17	.04
Maltreatment → PTSD	0.17	0.03	0.11, 0.23	<.001
PTSD → KDM Biological Age Acceleration	0.06	0.04	−0.02, 0.15	.11
Maltreatment → PTSD → KDM Biological Age Acceleration	0.01	0.01	0.00, 0.03	.13
Interview 2				
Total Effects	0.11	0.04	0.03, 0.19	.01
Direct: Maltreatment → KDM Biological Age Acceleration	0.09	0.04	0.01, 0.17	.03
Maltreatment → Depression	0.18	0.03	0.12, 0.25	<.001
Depression → KDM Biological Age Acceleration	0.08	0.04	0.01, 0.17	.04
Maltreatment → Depression → KDM Biological Age Acceleration	0.02	0.01	0.00, 0.03	.06
Direct: Maltreatment → KDM Biological Age Acceleration	0.09	0.04	0.01, 0.18	.02
Maltreatment → Anxiety	0.13	0.03	0.07, 0.2	<.001
Anxiety → KDM Biological Age Acceleration	0.08	0.04	0.00, 0.16	.046
Maltreatment → Anxiety → KDM Biological Age Acceleration	0.01	0.01	0.00, 0.02	.08
Direct: Maltreatment → KDM Biological Age Acceleration	0.09	0.04	0.01, 0.18	.02
Maltreatment → PTSD	0.13	0.03	0.06, 0.20	<.001
PTSD → KDM Biological Age Acceleration	0.07	0.04	−0.01, 0.16	.09
Maltreatment → PTSD → KDM Biological Age Acceleration	0.01	0.01	0.00, 0.02	.12

Interview 1 symptoms are lifetime DSM-III-R symptoms based on responses to the National Institute of Mental Health Diagnostic Interview Schedule-III-R. For interview 2, depression symptoms are based on scores from the Center for Epidemiologic Studies Depression Scale, anxiety symptoms from the Beck Anxiety Inventory, and PTSD symptoms from the Composite International Diagnostic Interview. All analyses controlled for age, sex, and race.

BCCI, bootstrap-corrected confidence interval; KDM, Klemera-Doubal method; PTSD, posttraumatic stress disorder.

childhood maltreatment, higher levels of anxiety at interview 1 predicted lower levels of biological aging (β = −0.03; SE = 0.01; 95% CI = −0.06 to −0.01). The relationship was not significant for adults with a history of childhood maltreatment (β = 0.005; SE = 0.01; 95% CI = −0.01 to 0.02).

For anxiety and depression assessed at interview 2, the results provide support for the moderation hypothesis. Figures 2 (anxiety) and 3 (depression) show that at the lowest levels of anxiety and depression, there were no differences between the maltreated and control groups in biological aging. However, for adults with histories of childhood maltreatment, higher levels of anxiety or depression assessed at interview 2 were associated with accelerated biological aging, whereas the relationship was not significant for adults who were not maltreated. PTSD symptoms assessed at interviews 1 and 2 did not moderate the relationship between childhood maltreatment and biological aging.

DISCUSSION

Previous studies have linked childhood adversity and adult psychiatric disorders to accelerated biological aging (71). In this new study, we used data from a unique longitudinal study of children with court-documented maltreatment histories and demographically matched control participants who were followed into middle adulthood to investigate the role of psychiatric symptoms to better understand the relationship between child maltreatment and biological aging. Although we cannot infer causality, the prospective design of this study allowed us to ensure the correct temporal sequencing of these relationships.

First, we confirmed expectations that individuals with documented histories of childhood maltreatment would have significantly more symptoms of these psychiatric disorders (depression, anxiety, and PTSD) in both young and middle adulthood than demographically matched control participants.

Table 5. Results of Ordinary Least Squares Regressions Testing Whether Psychiatric Symptoms in Young Adulthood (Interview 1) and Middle Adulthood (Interview 2) Moderate the Relationship Between Childhood Maltreatment and KDM Biological Age Acceleration (Interview 3)

	At Interview 1			At Interview 2		
	β (SE)	*p*	*b*	β (SE)	*p*	*b*
Anxiety						
Child maltreatment	0.21 (0.08)	.01	1.67	0.20 (0.09)	.03	1.53
Anxiety	−0.01 (0.01)	.39	−0.05	0.01 (0.004)	.05	0.06
R^2	0.04	<.001		0.05	<.001	
Child maltreatment	0.04 (0.11)	.69	0.34	0.01 (0.12)	.96	0.05
Anxiety	−0.03 (0.01)	.01	−0.26	−0.01 (0.01)	.47	−0.04
Anxiety × maltreatment	0.04 (0.02)	.02[a]	0.31	0.02 (0.01)	.02[a]	0.15
R^2	0.05	<.001		0.06	<.001	
Depression						
Child maltreatment	0.21 (0.08)	.01	1.63	0.19 (0.08)	.03	1.47
Depression	−0.004 (0.02)	.78	−0.03	0.01 (0.004)	.04	0.06
R^2	0.04	<.001		0.05	<.001	
Child maltreatment	0.12 (0.14)	.39	0.95	−0.05 (0.13)	.74	−0.36
Depression	−0.02 (0.02)	.45	−0.15	−0.003 (0.01)	.59	−0.03
Depression × maltreatment	0.02 (0.03)	.45	0.19	0.02 (0.01)	.02[a]	0.14
R^2	0.04	.004		0.06	<.001	
PTSD						
Child maltreatment	0.17 (0.09)	.05	1.32	0.19 (0.09)	.03	1.51
PTSD	0.01 (0.01)	.12	0.09	0.02 (0.01)	.09	0.12
R^2	0.05	<.001		0.05	<.001	
Child maltreatment	0.08 (0.11)	.45	0.69	0.13 (0.15)	.41	0.99
PTSD	0.001 (0.01)	.91	0.01	0.01 (0.02)	.51	0.07
PTSD × maltreatment	0.02 (0.02)	.31	0.12	0.01 (0.02)	.59	0.08
R^2	0.05	.04		0.05	<.001	

β refers to standardized coefficients, and *b* refers to unstandardized coefficients. Interview 1 symptoms are lifetime DSM-III-R symptoms based on responses to the National Institute of Mental Health Diagnostic Interview Schedule-III-R. For interview 2, depression symptoms are based on scores from the Center for Epidemiologic Studies Depression Scale, anxiety symptoms are from the Beck Anxiety Inventory, and PTSD symptoms are from the Composite International Diagnostic Interview. All analyses controlled for age, sex, and race.

KDM, Klemera-Doubal Method; PTSD, posttraumatic stress disorder.

[a]These values indicate significant interactions.

In addition, adults with histories of childhood maltreatment had more advanced biological age in middle adulthood than control participants.

Second, PTSD symptoms at both time points (interviews 1 and 2) predicted accelerated biological age. In contrast, lifetime measures of anxiety and depression in young adulthood (interview 1) did not predict biological age, although there were significant short-term associations between anxiety and depression symptoms assessed at interview 2 and biological age (i.e., symptoms of anxiety and depression assessed closer to the time when biomarkers were assessed). These findings are consistent with the existing cross-sectional literature showing associations of depression (16,17,24,33,34) and anxiety (30) with biological age and suggest that methodological differences in study designs (short-term vs. longer-term longitudinal) may be important to consider when interpreting these relationships.

Third, while there were significant bivariate relationships between child maltreatment, psychiatric symptoms, and biological age, we did not find evidence that psychiatric symptoms mediated the relationship between childhood maltreatment and biological age. However, it is possible that evidence of accelerated biological age may have been evident earlier in the lives of the individuals in the current study. In 2 recent studies of young children who had substantiated cases of child maltreatment prior to study entry (72,73), there was evidence of accelerated aging in relation to anxiety, depression, and PTSD. As pointed out by Zannas (74), existing research has "assumed unidirectional causality that stress and mental suffering drive accelerated aging" (page E1). Our use of 2 distinct reporting periods for the mental health assessments provides an opportunity to compare the long-term impact of mental health problems on biological aging as well as to report separate results based on a design closer to the most commonly cross-sectional design represented in this literature. However, long-term longitudinal studies with childhood assessments of stress that also measure the onset of psychiatric symptoms and biological age markers are needed that will permit examinations of bidirectional causality.

Fourth, we found that psychiatric symptoms of anxiety and depression moderated the relationship between childhood maltreatment and biological age, exacerbating the aging

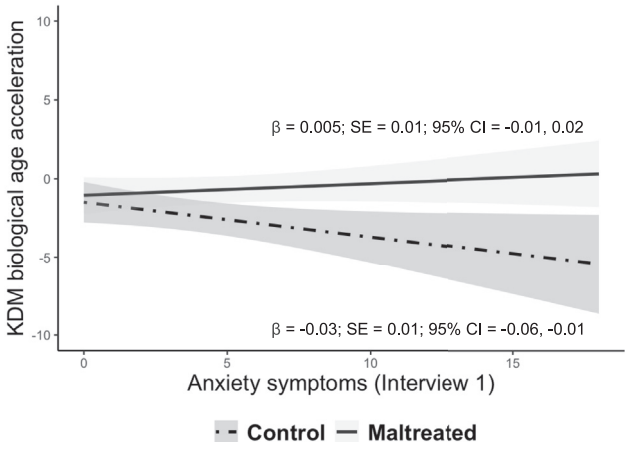

Figure 1. Interaction plot showing that the relationship between anxiety symptoms at interview 1 and biological aging varied depending on childhood maltreatment status (β = 0.04; SE = 0.02; 95% CI = 0.01–0.07). For adults who did not experience childhood maltreatment, higher anxiety symptoms predicted slower biological aging (β = −0.03; SE = 0.01; 95% CI = −0.06 to −0.01), whereas the relationship was not significant for adults with a history of childhood maltreatment (β = 0.005; SE = 0.01; 95% CI = −0.01 to 0.02). KDM, Klemera-Doubal method.

process for maltreated individuals. The fact that the moderation effect was based on short-term assessment of anxiety and depression (closer to the time of the assessment of biomarkers) raises questions about these relationships. Is this finding the result of intervening events from young to middle adulthood that may have reversed or partly reversed the aging trajectory, or does this finding reflect a substantive and

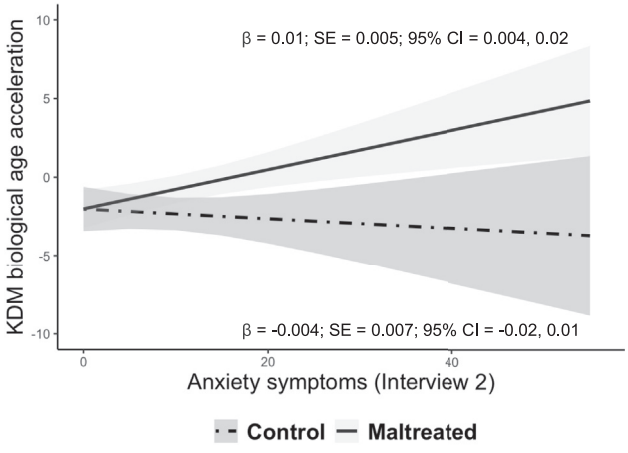

Figure 2. Interaction plot showing that the relationship between anxiety symptoms at interview 2 and biological aging varied depending on childhood maltreatment status (β = 0.02; SE = 0.01; 95% CI = 0.003–0.04). For adults who did not experience childhood maltreatment, the relationship between anxiety symptoms and biological aging was not significant (β = −0.004; SE = 0.007; 95% CI = −0.02 to 0.01), whereas for adults with a history of childhood maltreatment, higher levels of anxiety symptoms predicted accelerated biological aging (β = 0.01; SE = 0.005; 95% CI = 0.004 to 0.02). KDM, Klemera-Doubal method.

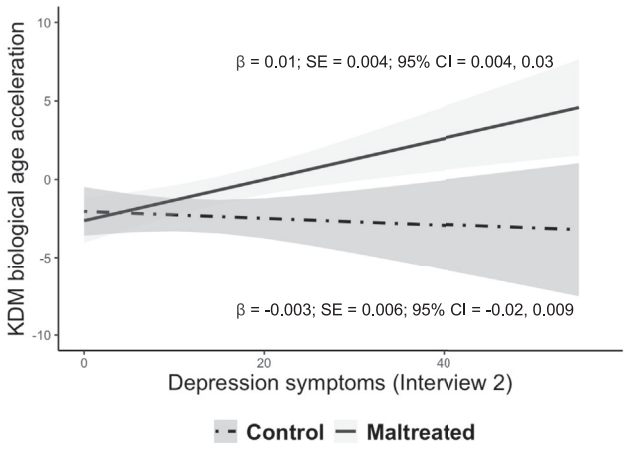

Figure 3. Interaction plot showing that the relationship between depression symptoms at interview 2 and biological aging varied depending on childhood maltreatment status (β = 0.02; SE = 0.01; 95% CI = 0.002–0.03). For adults who did not experience childhood maltreatment, the relationship between depression symptoms and biological aging was not significant (β = −0.003; SE = 0.006; 95% CI = −0.02 to 0.009), whereas for adults with a history of childhood maltreatment, higher levels of depression symptoms predicted accelerated biological aging (β = 0.01; SE = 0.004; 95% CI = 0.004 to 0.03). KDM, Klemera-Doubal method.

apparently more acute and short-term effect on the biomarkers that were collected?

Finally, one unexpected finding warrants comment. We found that higher levels of anxiety in young adulthood predicted slower biological aging for the control participants (nonmaltreated individuals). One possible explanation for this is that the nonmaltreated children and adolescents with high levels of anxiety might have had better health care, medication for their anxiety, and greater social support, and these may have led to their managing their anxiety with more positive coping strategies. We conducted post hoc analyses to explore this possibility and found that significantly more control individuals (48%) were "high anxiety" at interview 1 than those who were "high anxiety" at interview 2 (36%). Thus, there were fewer control participants who reported "high anxiety" at interview 2 than at interview 1, which provides some support for this potential explanation of unexpected findings. Growing up in the late 1960s and early 1970s, the maltreated children in this study were not likely to have received extensive health care or therapy to deal with their anxiety and had less social support (75). Without efforts to address their anxiety, maltreated children continued to report higher levels of anxiety into adulthood.

Limitations

Despite the numerous strengths of this work, some limitations need to be noted. Because these cases were identified through the courts, the findings are not generalizable to unreported or unsubstantiated cases of maltreatment. This sample is predominantly from the lower end of the socioeconomic spectrum, and therefore these findings cannot be generalized to cases of abuse and neglect that may occur in middle- or upper-class families. These characteristics may raise concerns

about applying these findings to the current society. However, the maltreatment cases studied here are similar to current cases being processed by the child protection system and the courts. One important difference is that these children were not provided with extensive services or treatment options as are available today, although it is important to note that there are still not enough services for abused and neglected children. Finally, although it is beyond the scope of the current article, the question of whether substance use mediates associations between mental health problems and biological aging warrants attention.

Conclusions

These new findings reveal both the long-term and short-term longitudinal impact of PTSD on biological aging and the amplifying effect of anxiety and depression on the relationship between child maltreatment and biological aging. Identifying and understanding the role of critical moderators has the potential to help direct limited resources toward those who are most likely to benefit from them and may have implications for the development of personalized clinical care for people with histories of childhood maltreatment. The current findings contribute to a better understanding of these complex associations and the role of psychiatric symptoms, and ultimately, they may translate into interventions that may mitigate negative outcomes associated with child maltreatment over the life course.

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The data reported in the current article are not publicly available because they contain sensitive information that could compromise research participant privacy and confidentiality. We cannot provide individual-level data from this project because our confidentiality agreement with the participants in this study precludes it.

DWB is a Fellow of the Canadian Institute for Advanced Research Child Brain Development Network. He is listed as an inventor of DunedinPACE, a Duke University and University of Otago invention licensed to TruDiagnostic. He is consulting Chief Scientific Officer and Scientific Advisory Board Chair of BellSant and Scientific Advisory Board member of the Hooke Clinic. All other authors report no biomedical financial interests or potential conflicts of interest.

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