CHILDHOOD ADVERSITY AS A RISK FACTOR FOR DEMENTIA: FAMILY DYSFUNCTION AND THE CHANGE IN PHOSPHORYLATED TAU AMONG MIDDLE-AGED BLACK AMERICAN WOMEN

by

YU-WEN LU

(Under the Direction of Leslie Gordon Simons)

ABSTRACT

While adverse childhood experience is a strong social determinant of health for multiple later life outcomes, its effect on the risk of dementia remains unclear. Using 20-year longitudinal data from middle-aged Black American women, we employed a path modeling approach to examine the direct effect of family childhood adversity on changes in phosphorylated tau 181 (p-tau 181) levels, a biomarker associated with Alzheimer's disease risk. Our results revealed that experiencing more familial trauma in childhood predicted higher p-tau 181 levels over time, suggesting an elevated risk of Alzheimer's disease. Additionally, childhood adversity was positively linked to a higher number of chronic illnesses in adulthood but did not mediate its effect on p-tau levels. These findings extend the sensitive period model in the life course perspective, demonstrating that childhood is a critical period shaping later-life cognitive health.

INDEX WORDS: Adverse childhood experience, Family dysfunction, Dementia, Phosphorylated tau, Chronic health conditions

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YU-WEN LU

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by

YU-WEN LU

Major Professor:	Leslie Gordon Simons
Committee:	Man-Kit Lei
	William Alex Pridemore

Electronic Version Approved:

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
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CHAPTER 1

INTRODUCTION

Alzheimer's disease and related dementias disproportionately affect older Black Americans. According to the National Institution of Health (2021), around 5.8 million older American adults are estimated to have dementia, with the prevalence among older Black Americans being approximately twice that of older White Americans (Alzheimer's Association 2021). This disparity is exacerbated by the higher prevalence of adverse childhood experiences, a risk factor for dementia (Huang et al. 2023; Schickedanz et al. 2022). Studies have shown that Black American children are exposed to a higher probability of childhood adversity, including emotional and physical abuse, and family conflict, and contribute to structural brain change related to cognitive-affective dysfunction compared with other racial groups (Dumornay et al. 2023). Another nationally representative study reveals that Black American males experienced more childhood adversity than their white counterparts, and these exposures impacted disadvantaged interpersonal relationships and stress levels in adulthood, eventually leading to racial health disparities (Umberson et al. 2014). However, the mechanisms linking childhood adversity to adulthood health conditions and dementia remain unclear, with a particular lack of evidence regarding Black American women.

Recent advancements in biomarker research have provided a new direction for investigating the relationships between childhood adversity and dementia. Blood-based biomarkers, particularly phosphorylated tau (p-Tau), have become promising indicators for early

detection and prediction of Alzheimer's disease progression (Karikari et al. 2020). Previous studies have shown that childhood adversity is effective in predicting the increase of various biomarkers related to dementia risk factors, including inflammatory cytokines and biological aging in middle-aged Black Americans (Simons et al. 2019; Simons et al. 2022).

This study investigates whether experiencing childhood adversity increases the risk of Alzheimer's disease in middle-aged Black American women with a life course perspective. Three mechanisms are explored: the cumulative disadvantage theory, the critical and sensitive period model, and the pathway model. The cumulative disadvantage framework suggests that stress caused by childhood adversities accumulates over time, impacting brain structure and physiological function, and potentially leading to subsequent cognitive decline. The critical and sensitive period model posits that early life is a critical period, vulnerability caused in childhood lasts through the lifetime, directly increasing the risk of dementia in late life. The pathway model assumes the effect of childhood adversity on dementia mediated by young adulthood health conditions. By incorporating these mechanisms, we aim to investigate not only the direct effects of childhood adversity on dementia risk but also the roles of other health risk factors throughout the lifespan.

CHAPTER 2

LITERATURE REVIEW

The Role of Adverse Childhood Experiences in Life Course Perspective

Childhood has been recognized as a critical life stage that significantly impacts long-term life chances, health outcomes, and mortality (Hayward and Gorman 2004; Monnat and Chandler 2015). Substantial evidence has demonstrated that adverse childhood experiences, childhood trauma, and early life disadvantages contribute to health disparities throughout the lifespan. Childhood adversity, covering negative events and environments experienced during childhood and adolescence, has become a research focus due to its profound effects on health and well-being.

McLaughlin and Sheridan (2016) proposed a dimensional model categorizing different types of childhood adversity. Segregating by levels of threat and deprivation, eight types of childhood adversity including neglect, institutionalization, poverty, community violence, domestic violence, and physical and sexual abuse are conceptualized. Different dimensions are connected to different impacts on children's development. For instance, psychological maltreatment and emotional neglect with high deprivation have shown a relationship with depression in adolescence (Hanson et al. 2015). Conversely, violence with high threat increases the risk of brain damage and externalizing psychopathology (McLaughlin et al. 2016). Childhood socioeconomic disadvantages, physical abuse, and emotional abuse also increase risky health behaviors such as smoking and drinking in middle age (Ferraro et al. 2016). Moreover, cohabiting with mentally ill or violent family members during childhood is associated with poorer self-reported health,

functional limitations, diabetes, and cardiovascular disease in adulthood (Monnat and Chandler 2015). Compared to previous childhood adversity research using the cumulative-risk approach, we considered the different dimensions of childhood adversity from McLaughlin and Sheridan (2016) and their impacts on adulthood health, focusing on the domestic violence and physical abuse to theorize the childhood family dysfunction to explore their relationships with physical health and brain damage.

Three main life course casual models differentiate the impacts of childhood adversity through adulthood to later life (Shonkoff et al 2009; Umberson et al. 2014; Wagner et al. 2022). The first mechanism is based on cumulative disadvantage theory, which posits that risk factors occurring in early life accumulate stress over time and end up causing disparities in later life (Ferraro et al. 2016; O'Rand and Hamil-Luker 2005). Stress studies have concentrated on the chain reaction of the stress system stimulated by adverse childhood experiences (Ehlert 2013). Stressors created by childhood adversity continue, repeat, and proliferate throughout the life span, increasing health risks in adulthood (Pearlin et al. 2005). The accumulation of allostatic load offers one explanation for this stress response mechanism (McEwen 2012). Adverse childhood experiences are biologically embedded "under the skin"; the physiological stress-response system's frequent activation eventually causes long-term dysregulation (McEwen 2012; McLaughlin and Sheridan 2016). The second mechanism is the critical and sensitive period models. During the sensitive childhood period of development, adverse experiences amplify lifelong reactions to stress and increase health risks (Shonkoff et al. 2009). Wagner and colleagues (2022) further distinguish this pathway into two models: the critical and sensitive period models. The critical period model suggests that childhood adversity contributes to both adult adversity and later-life health conditions, while the sensitive period model only shows the independent impact of childhood on

later-life outcomes. The third one is the pathway model, which emphasizes the childhood effect mediated by adulthood exposures (Wagner et al. 2022). Miller and colleagues (2011) extend the biological embedding model, indicating that childhood stressors cause hormonal dysregulation, amplify inflammation risk, and eventually lead to chronic diseases and health risks.

These different life course models demonstrate the complex effects of early life on adulthood and late-life health. For instance, evidence shows that childhood adversity independently predicts depression in young adults while also being mediated by adulthood stress and self-esteem (Turner and Butler 2003). Thus, adopting a life course perspective is essential for understanding how adverse childhood experiences contribute to poor health outcomes. In this study, we focus on the last two models to explore the unique role of childhood adversity in shaping late-life dementia risk.

Adverse Childhood Experiences and Chronic Disease Development

Growing evidence suggests that adverse childhood experiences contribute significantly to the development of chronic diseases in adulthood. Studies have consistently shown a strong association between adverse childhood experiences and cardiovascular disease. Individuals exposed to childhood adversity have a higher likelihood of reporting ischemic heart disease in adulthood (Dong et al. 2004). This effect is partially mediated by psychological risk factors related to childhood adversity. A nationally representative study further corroborates these findings, revealing a positive correlation between childhood adversity and chronic illnesses such as coronary heart disease and stroke (Gilbert et al. 2015).

One of the risk factors linking cardiovascular disease and childhood adversity is diabetes. Evidence shows a positive association between experiencing more childhood adversity events and

an increased risk of diabetes (Campbell et al. 2016). Having a parent with mental illness and experiencing domestic abuse in childhood are associated with a higher probability of having diabetes in adulthood (Campbell et al. 2018). Research shows that individuals with four or more categories of adverse childhood exposures have 3.9 times higher odds of developing chronic bronchitis or emphysema compared to those without such exposures (Felitti et al. 1998).

Although evidence has shown the linkage between childhood adversity and several chronic diseases, current research suggests that most Americans live with multiple co-occurring chronic conditions rather than a single condition, with the prevalence of these multiple conditions increasing substantially with age (Vogeli et al. 2007). A cross-sectional study conducted in Ireland found a positive association between reported adverse childhood experiences and multimorbidity status in older adults, which the status was measured by 20 chronic diseases, including asthma and rheumatoid arthritis (Sinnott et al. 2015).

Dementia including Alzheimer's disease and vascular dementia, often interact and coexist as multiple chronic health conditions (Craft 2009). Notably, more than 95% of Alzheimer's and related dementia patients have multiple chronic health conditions (Alzheimer's Association 2025). Both cardiovascular disease and diabetes have been linked to dementia through specific physiological mechanisms. In the case of cardiovascular disease, evidence supports that cerebrovascular conditions lead to chronic cerebral hypoperfusion, a potential mechanism for brain damage, cognitive decline, and dementia (Stefanidis et al. 2017). Similarly, diabetes contributes to dementia risk through multiple pathways. Hyperglycemia and vascular complications, primary characteristics of diabetes (Chau et al. 2020), have been shown to play significant roles in both Alzheimer's disease and vascular dementia (Ninomiya 2014). The toxicity of hyperglycemia can potentially impact brain function and induce microvascular changes, which are related to cognitive

decline and brain damage (Biessels et al. 2006). Type 2 diabetes-related vascular damage has been significantly observed in clinical syndromes of vascular dementia and Alzheimer's disease (Exalto et al. 2012). Individuals with cardiovascular multimorbidity have been found higher hazards for dementia (Grande et al. 2021). Moreover, patients with type 2 diabetes who present either cardiovascular comorbidities or non-cardiovascular comorbidities, such as chronic lung conditions and chronic kidney diseases, show a higher risk of dementia than those not present (Zheng et al. 2022). Alzheimer's disease, one of the most prevalent forms of dementia, is particularly associated with various comorbid conditions (Santiago and Potashkin 2021). These findings highlight the importance of understanding how multiple chronic conditions may contribute to dementia risk, and how early life experiences might shape these relationships.

The Path from Adverse Childhood Experiences to Alzheimer's Disease

Recent studies have focused on testing the independent impact of childhood adversity on the risk of dementia, but the effects and pathway are still unclear. One study shows that experiencing more than four types of childhood adverse events is associated with a higher probability of a positive dementia screen in a sample of American older adults (Schickedanz et al. 2022). A cross-country meta-analysis reveals that exposure to childhood maltreatment significantly increases the risk of dementia, however, inconsistent measurements of adverse childhood experiences and the limited number of studies make it difficult to assess the reliability of this association (Abouelmagd et al. 2024). In addition, most measurements of dementia rely on clinical screening tools, while earlier literature heavily depended on cognitive functioning tests and self-reported cognitive scales (Farias et al. 2008). One drawback of such indicators is that they

only capture incidents and prevalent cases or significant cognitive impairment, precluding the detection of the pre-symptomatic stage of structural brain changes (Ahmed et al. 2014).

In recent years, researchers have continuously developed biomarkers to more accurately detect Alzheimer's disease and neurodegeneration. Among these developments, blood-based biomarkers have become popular due to their accuracy and accessibility. Three main blood-based biomarkers – amyloid, phosphorylated tau (p-Tau), and neurofilament light chain (NfL) – have been generally implemented in clinical practice (Teunissen et al. 2022). Notably, blood phosphorylated tau 181 (p-Tau 181) has been proven to differentiate Alzheimer's disease and predict cognitive decline within one year (Karikari et al. 2020). These blood biomarkers have also been applied to examine associations with social determinants of health; for instance, chronic stress from discrimination has been found to be associated with increased serum P-tau 181 and NfL concentration in a longitudinal Black American sample (Simons et al. 2024). Incorporating these biomarkers to examine the pathway from childhood adversity to Alzheimer's disease will help to understand this complex relationship.

Intersectionality Among Black American Women

The intersectional burden of childhood adversity and Alzheimer's disease experienced by Black American women underscores the urgent need to consider the structural determinants contributing to their cognitive health disparities. Rich evidence reveals that individuals with lower socioeconomic status, females, and people of color significantly report more childhood adversity experiences than other demographic groups (Merrick et al. 2018). A large national study shows that black and Latinx teenagers experienced more severe, more childhood adversity, and poorer health conditions than their white counterparts (Liu et al. 2018). Studies across different countries

reveal the gender interaction with early life adversity on dementia and cognitive function, indicating a possibly higher vulnerability and sensitivity to women's cognitive health when experiencing childhood adversity (Nilaweera et al. 2022; Ritchie et al. 2010; Tani et al. 2020).

However, limited evidence has examined the existence of an interaction between gender and race. Umberson and colleagues (2014) found that black males and females were more vulnerable in adulthood social relationships if they experienced childhood adversity than their white counterparts, while childhood adversity did not explain the health disparity compared white and black females. Misiura and colleagues (2023) highlighted the gap in research on the interaction of race and biological sex in Alzheimer's disease, emphasizing the lack of representation in clinical trials, the impact of social stress and social determinants of health disparities, and the higher prevalence of risk factors such as vascular problems and inflammation among Black women.

Based on the above evidence, this study aims to provide an intersectional perspective exploring the association between childhood adversity and the risk of Alzheimer's disease among Black women. The hypotheses in this study provided:

H1: Black American women who experienced childhood adversity have a higher increase in concentration of p-tau levels in middle and older age than those who did not experience them.

H2: Black American women who experienced childhood adversity suffer more chronic health conditions in young adulthood than those who did not experience them.

H3: Black American women who have chronic health conditions in young adulthood have a higher increase in concentration of p-tau levels in middle and older age than those who did not experience them.

H4: The effect of childhood adversity is partially mediated by chronic health conditions in young adulthood, contributing to an increase in the concentration of p-tau levels in middle and older age.

CHAPTER 3

METHODS

Participants

This study uses Wave 1 (collected in 1997), Wave 2 (1999), Wave 3 (2002), Wave 4 (2005), Wave 5 (2007), and Wave 8 (2018) from the caregivers in the Family and Community Health Study (FACHS). The FACHS is one of the few longitudinal datasets that contain both biomarkers of dementia and sociological characteristics. They initially recruited 889 Black American families with one fifth-grade student, 467 in Iowa, and 422 in Georgia State. The family sampling lists come from the Iowa school officials and the Georgia community coordinators. Families were chosen using a stratified random sampling procedure and a 72% complete rate from the recruitment list. The 1990 Census data was used to ensure that families reside in neighborhoods representing a range of socioeconomic statuses, racial combinations, and other demographic characteristics by identifying block group areas (BGAs), a cluster of blocks within a census tract. Therefore, this sampling process can capture the variance and diversity of the Black American Families in the US.

The sample in this study is from the 889 participants in Wave 1 are the primary caregivers of the fifth-grade students, mainly their mothers (96.2%). 628 participants in Wave 5 and 480 participants in Wave 8 provided blood to access their DNA methylation evaluations, including the biomarkers detecting dementia and Alzheimer's disease. After being analyzed by the University of Minnesota Advanced Research and Diagnostics Laboratory (ARDL), 257 participants' serum

samples were successfully assayed for biomarkers and were included in the study. 45 male participants from the 257 participants in Wave 8 are excluded to focus our result and inference on the Black American women population. After employing the Listwise method to address four missing cases of childhood adversity, our final sample size is 208.

To assess sample representativeness, Table 1 compared demographic characteristics between our analysis sample and the Wave 1 female sample (n = 831), after excluding 58 male participants. Independent sample t-tests were conducted to compare age, years of education, marital status, and negative financial life events occurring within the previous year. Our analysis sample was on average 2 years younger, there were no significant differences in other demographic variables. The Institutional Review Board approved all of the protocols and study procedures at the University of Georgia.

Table 1. Demographic Characteristics of Analysis and Wave 1 Female Samples.

	Analysis Sample (N = 208)	Female Sample in Wave 1 (N = 831)		
	Mean (SD)	Mean (SD)	t-value	p-value
Age	35.526	37.493	3.792	.000
	(6.170)	(8.037)		
Years of Education	12.372	12.452	.496	.620
	(1.911)	(2.207)		
Married	.327	.342	.407	.684
	(.470)	(.475)		
Negative Financial Events	1.389	1.273	-.911	.363
	(1.667)	(1.556)		

Note: All variables are measured at Wave 1.

Measures

Independent variable: Family Childhood / Adolescent Adversity

Family childhood adversity was measured from four different retrospective questions from the FACHS across Wave 1 to Wave 4, and Wave 8. Participants reported familial adverse experiences occurring in their childhood or adolescence. In Waves 1 to 4, they were asked: "*While you were growing up, (1) did your parents or the people who raised you have serious marital problems? (2) did anyone in your home have a mental health problem? (3) was anyone in your family violent toward another family member?"* and in Wave 8: *"Prior to age 10, would you say people in my family (4) hit me so hard that it left me with bruises or marks?*". The responses were initially dichotomized (1 = Yes, 0 = No) for each question. We then recoded the Wave 1 to Wave 4 responses with if they reported in any Wave as 1 = Yes, 0 = No. We employed a sequential imputation approach across waves to address missing data: if Wave 1 data were missing, responses from Wave 2 were used, and this pattern continued through Wave 4. We then combined into four categories of family dysfunction: (1) family members had severe marital problems, (2) had mental health issues, (3) had violence toward other family members, and (4) did severe physical abuse on the participant. Finally, we calculated the mean score of these four categories, yielding a scale of family childhood adversity ranging from 0 to 1.

Dependent variable: Change Level of P-Tau181

A change in scores between Wave 5 and Wave 8 in the concentration of a serum tau phosphorylated at position 181 (p-tau181) biomarker is calculated to measure the risk of dementia. It is measured using the Simoa p-tau181 Advantage version 2.1 kit (item #103714) (Simons et al. 2024). Compared with the prestigious biomarkers of Alzheimer's disease, collecting p-tau181

based on the blood test is relatively safe, noninvasive, and affordable. A higher level of serum p-tau181 is associated with a higher risk of Alzheimer's disease and cognitive decline (Karikari et al. 2020). The concentration of p-tau181 is firstly log transferred to normalize, then a residual method is employed to capture the change of concentration and obtain the residual value from the regression of Wave 8 p-tau181 on Wave 5. The range of the concentration of p-tau 181 is 2.48 to 98.06 picograms per milliliter (pg/mL) on Wave 5 and 2.48 to 108.54 pg/mL on Wave 8.

Mediator: Multiple Chronic Health Conditions

Chronic diseases were measured in FACHS by self-reported medical diagnosis. Participants were asked: "*Has a doctor ever told you that you were suffering from…*" with 27 different chronic health problems, and responses were dichotomized (1 = Yes, 0 = No) in each illness. In this study, 13 of them were selected including (1) arthritis or rheumatism, (2) asthma, (3) emphysema or chronic bronchitis, (4) high blood pressure, (5) heart trouble, (6) circulation trouble in arms or legs, (7) diabetes, (8) ulcers of the digestive system, (9) other stomach or intestinal disorders or gall bladder problems, (10) kidney disease, (11) other urinary tract disorders (including prostate trouble), (12) cataracts, and (13) thyroid or other glandular disorders. These 13 items were summed together and created a multiple chronic health conditions index range from 0 to 13. The Cronbach's alpha is 0.70.

Covariates

The analysis adjusted for demographic characteristics including age, education level, and economic hardships. Age is measured from the survey year deducting the reported actual birth year. Previous research has identified age as a significant factor in Alzheimer's disease, with

prevalence increasing in late life (Savva et al. 2009). Marital status has also been associated with dementia risk, with married individuals showing a lower risk compared to other marital status groups (Sommerlad et al. 2017). Marital status is operationalized as a binary variable, where 1 indicates currently married, and 0 indicates not currently married, based on participants' self-reported relationship status. Economic hardship is assessed using a two-item summative scale of the inability to make ends meet during the past year, adapted from Conger and Elder (1994). Participants were first asked how much difficulty they had to pay bills, responses ranged from (1) a great deal of difficulty to (5) no difficulty at all, a five-point Likert scale. Another item asked them "*Generally, at the end of each month did you end up with...*" with a five-point Likert scale response from (1) more than enough money left over to (5) not enough to make ends meet before we reversed it to sum. The Cronbach's alpha of the scale is 0.74.

The study sample comprised 208 Black American female caregivers. The mean age of participants was 45.4 years in 2007. Approximately 31% of the sample reported being currently married. Average economic hardships are around 5.5, meaning that participants experience moderate difficulty in making ends meet on average. The average number of multiple chronic health conditions is 1.8, representing individuals in the sample generally suffering from around two chronic diseases. Individuals experienced approximately one out of four measured categories of family childhood adversity. On average, individuals' concentration of p-Tau decreases by 0.012 units, with a maximum increase of 2.1 units. All the covariates are drawn from Wave 5 data to ensure temporal causality.

Table 2. Descriptive statistics of variables.

Variable	*N*	Mean/%	Std. Dev.	Min	Max
Δ P-Tau 181	208	-.012	.70	-1.4	2.1
Wave 5 P-Tau 181	208	11.015	9.07	2.5	98.1
Wave 8 P-Tau 181	208	11.582	10.58	2.5	108.5
Childhood Adversity	208	.181	.24	.0	1.0
Chronic conditions index	208	1.803	2.05	.0	10.0
Age	208	45.365	6.30	25.0	70.0
Marital Status					
Not Married	144	69.23			
Married	64	30.77			
Economic hardships	208	5.538	2.36	2.0	10.0

Note: Covariates are measured at Wave 5.

Analytic Strategy and Interpretations

This study has two parts of analysis. In the first part, we employ ordinary least squares regression (OLS) models in STATA 14.0 (StataCorp 2015). We first examine the main effects of childhood adverse experiences on the change level of p-tau 181 (Δ p-tau 181) in the OLS regression and then add our covariates to control the confounding. To interpret the results from OLS regression, a positive and significant coefficient of childhood adversity on Δp-tau 181 represents a one-unit increase in experiencing childhood adversity associated with the coefficient-unit change in p-tau 181 levels, holding other variables constant. In the second part, we use *lavaan* (0.6-18 version) package in R version 4.3.1 to conduct the path model (Rosseel 2012), testing the direct and indirect effects of childhood adversity. To demonstrate the significance of the effects, we adopted 95% confidence intervals as the criterion. When the 95% confidence interval does not contain zero, we considered the effect to be statistically significant ($p < .05$).

CHAPTER 4

RESULT

Main Effects of Childhood Adversity

The results from the OLS regression models in Table 3 demonstrate that childhood adversity is significantly associated with an increased risk of Alzheimer's disease, as indicated by the change in p-tau levels. In Model 1, without any covariates, the effect of childhood adversity on the change in p-tau 181 is statistically significant ($\beta = 0.461$, $p < .05$). After accounting for covariate variables including age, marital status, and adulthood economic hardship in Model 2, the main effect of childhood adversity remains significant ($\beta = 0.434$, $p < .05$). We then test the potential mediator, the multiple chronic health condition index, in Model 3. The coefficient of chronic conditions is not significant, and the coefficient of childhood adversity remains significant ($\beta = 0.422$, $p < .05$). The results support our hypothesis one, suggest that Black women who reported higher experienced familial childhood adversity exhibit elevated changes in p-tau 181 levels across a decade, which is associated with increased risk of Alzheimer's disease from their adulthood through middle and late life.

Table 3. OLS Regression Models of Childhood Adversity for Δ P-tau 181.

	Model 1	**Model 2**	**Model 3**
	coef. (SE)	coef. (SE)	coef. (SE)
Childhood Adversity	.461*	.434*	.422*
	(.200)	(.201)	(.203)
Chronic Conditions			.011
			(.025)
Economic hardships		.008	.006
		(.021)	(.021)
Age		.012	.011
		(.008)	(.008)
Married		.142	.140
		(.105)	(.105)
Constant	-.096	-.714	-.671
	(.060)	(.382)	(.395)
R^2	.025	.044	.045
N	208	208	208

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Path Analysis of Direct and Indirect Effects

Table 4 and Table 5 present the results of testing the path from childhood adversity to the change of p-tau level via chronic health conditions. In Table 4, the total effect including direct and indirect effects is significant (β = .436, SE = .198, 95% CI [.048, .824]). After controlling all the covariates, the direct effect of childhood adversity on p-tau change is significant (β = .424, SE = .200, 95% CI [.032, .816]), representing 97.25% of the total effect. Namely, individuals who experience all four types of childhood adversities including family members with mental health issues, severe marital problems, violence in the family environment, and physical abuse, showed a .424 unit increase in p-tau levels over time.

However, our analysis revealed no significant indirect effect of childhood adversity on p-tau levels through multiple chronic conditions (β = .012, SE = .028, 95% CI [-.043, .067]). This indicates that chronic disease burden in early adulthood does not significantly mediate the relationship between childhood adversity and changes in p-tau levels. Additionally, as shown in Table 5, we did not find evidence that the level of multiple chronic conditions contributes to changes in p-tau levels. This result rejects our hypotheses 3 and 4, that Black American women having more severe chronic health conditions do not have a higher risk of Alzheimer's disease in later life, and chronic health conditions also do not mediate the effect of childhood adversity on Alzheimer's disease.

Table 4. Direct and Indirect Effects of Childhood Adversity on Alzheimer's Disease Risk.

Type of Effect	β	SE	95% CI	% of Total Effect
Direct Effect (Childhood Adversity → Δ pTau181)	.424	.200	[.032, .816]	97.25%
Indirect Effect (via Multiple Chronic Conditions)	.012	.028	[-.043, .067]	2.75%
Total Effect	.436	.198	[.048, .824]	100.00%

Note: Age, marital status, and adulthood economic hardships are controlled.

Despite the lack of mediation, we observed an independent effect of childhood adversity on multiple chronic conditions. As presented in Table 5, childhood adversity significantly predicted multiple chronic conditions (β = 1.096, SE = .551, 95% CI [.016, 2.176]), suggesting that individuals who experienced all four types of childhood adversity had approximately 1.1 additional chronic conditions on average. This result supports our hypothesis 2, which black American women who experienced higher childhood adversity suffer more chronic health conditions in adulthood. These findings align with the critical period model assumption, which

proposes that childhood disadvantage has persistent effects across the lifespan, independently influencing both young adulthood health outcomes and dementia risk in late adulthood.

Table 5. Individual Path Coefficients

Path	β	SE	95% CI
Childhood Adversity→ Multiple Chronic Conditions	1.096	.551	[.016, 2.176]
Childhood Adversity → Δ pTau181	.424	.200	[.032, .816]
Multiple Chronic Conditions → Δ pTau181	.011	.025	[-.038, .060]

CHAPTER 5

DISCUSSION

This study examines the life course pathway from childhood adversity, chronic health conditions in young adulthood, and Alzheimer's disease risk among middle-aged Black Americans. Our findings provide evidence that individuals who experienced childhood family dysfunction directly impacted chronic health conditions and the increase of Alzheimer's disease risk. This pattern emphasizes the importance of childhood as a critical developmental period with lasting consequences for health trajectories in different stages. It aligns with the critical and sensitive period models of the life course perspective (Wagner et al. 2022). A possible biological mechanism explaining these findings is that adverse experiences occurring during specific stages in brain development may permanently alter the reaction of neural pathways, potentially creating a vulnerability that accelerates the progression of brain damage later in life (Gabard-Durnam and McLaughlin 2019). The interruption of brain development threatens and weakens children's adaptive system, a mechanism that reflects reduced resilience, potentially amplifying the negative effects of adversity throughout the later life course (Masten and Obradovic 2006).

This study contributes to the growing body of research on Black Americans' cognitive health disparities and identifies its key social determinants. By examining the specific effect of family dysfunction on the risk of Alzheimer's disease that Black American women have disproportionately experienced, this study provides insight into addressing the intersectional challenges that Black Americans experience. Our findings emphasize the importance of the family

role and the intervention to support family functionality. Policy interventions, including community and educational institution caring and consulting systems, can be a possible direction to reduce children's exposure to family violence.

Several limitations should be addressed in this research. First, sample size and demographic composition limit the generalizability of our findings. After decades of data collection and the difficulty of assessing blood samples, participant attrition was inevitable. Additionally, our sample consists of Black American female caregivers, which may restrict the generalizability of findings to other racial groups, Black American men, and Black women without motherhood. However, this focus on Black American women is also a strength of our study, as it addresses a significant gap in the literature and provides valuable and intersectional insights into a population historically underrepresented in cognitive function and dementia research. A potential limitation of internal validity relates to the measurement of childhood family dysfunction across multiple waves. Participants recalled their early life experiences across decades, which may introduce recall bias and affect the consistency of responses. However, multiple time points checking also equips the ability to reduce the recall bias. Furthermore, the lack of significant relationships between multiple chronic health conditions and dementia risks suggests that our aggregated chronic health measure may not successfully capture the specific impact of certain chronic illnesses on dementia that previous studies have identified. This finding could also be explained by the complex interplay and confounding effects among different diseases, making it difficult to isolate clear associations.

The absence of association between chronic health conditions and dementia reveals another important area for further exploration: resilience against dementia onset probability. Previous research establishing linkages between chronic illness and dementia has primarily relied on

diagnosed cases of dementia. leaving the exploration between chronic illness and dementia risk incomplete. That is, there is a resilience gap, in which people with similar physical and sociological conditions present different levels of the actual incidence. Our utilization of biomarkers provides a key pathway to explore this mismatch between risk factors and actual disease incidence, providing a possible protective mechanism perspective for further study in this population.

While the majority of existing literature emphasizes the biological mechanisms linking adverse experiences to brain damage, our study aims to bring back attention to the sociological pathways between early nurturing environments and health outcomes. The consistent and robust effect of childhood adversity observed in our findings demonstrates that adulthood health disparities substantially stem from early parenting environments, highlighting another important dimension of resilience. Specifically, family dysfunction contributes to the increased risks for both physical and cognitive health problems, while conversely, positive family functionality may serve as a protective buffer against dementia risk during the aging process among individuals. Future research should delve deeper into the potential mediation connecting childhood adversity and young adulthood factors to Alzheimer's disease risk, contributing to revealing the differential impact and pathway of life course adversity impact on dementia. Future studies should also explore potential protective factors that might buffer the impact of adversity on dementia. Evolving studies have started investigating how social support, family support, and health promotion behaviors might protect and prevent various aspects of dementia risk differently (Daly 2024; Pakstis et al. 2018). In addition, examining more innovative measures of cumulative adversity across several life stages will enrich our understanding of life course theory. For instance, researchers have operationalized cumulative socioeconomic disadvantages and found their association with dementia biomarkers (Lei et al., 2024). To extend our findings to a broader population, our future

studies will also consider the effect of racial discrimination. Simons and colleagues (2024) have found that higher exposure to racial discrimination in middle-aged Black Americans leads to an increase in p-tau biomarker levels. Therefore, examining how racial discrimination interacts with the biological stress reaction process and psychological factors can contribute to generalizing the pathway between childhood adversity and dementia risk. In conclusion, this research significantly advances our understanding of the social determinants of Alzheimer's disease and related dementias, providing valuable insights for developing effective and contextual intervention policies and knowledge to promote healthy cognitive aging in historically underrepresented and vulnerable populations.

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APPENDIX A. CORRELATION FOR STUDY VARIABLES

	1.		2.		3.		4.		5.		6.		7.	8.
1. Δ P-Tau 181	1													
2. Wave 5 P-Tau 181	.041		1											
3. Wave 8 P-Tau 181	.979	*	.246	*	1									
4. Childhood Adversity	.159	*	-.029		.148	*	1							
5. Chronic conditions	.083		.076		.097		.119		1					
6. Economic hardships	-.005		-.119		-.029		-.096		.151	*	1			
7. Age	.105		.135		.130		.020		.300	*	-.054		1	
8. Married	.104		-.008		.099		.103		.024		-.108		-.022	1

APPENDIX B. MEASURE ITEMS FOR FAMILY CHILDHOOD ADVERSITY

1. Wave 1 to Wave 4:

(1) Marital problem:

Question: While you were growing up, did your parents or the people who raised you have serious marital problems?

Response Categories: (1) Yes (2) No (3) Never married

(2) Mental problem:

Question: While you were growing up, did anyone in your home have a mental health problem?

Response Categories: (1) Yes (2) No (3) Never lived together

(3) Violence:

Question: While you were growing up, was anyone in your family violent toward another family member?

Response Categories: (1) Yes (2) No (3) Never lived together

2. Wave 8:

(1) Physical Abuse:

Question: Prior to age 10, would you say...People in my family hit me so hard that it left me with bruises or marks.

Response Categories: (1) Yes (2) No (3) Don’t know (4) Refused

APPENDIX C. MEASURE ITEMS FOR CONTROL VARIABLES

1. Marital Status:

   Question: What best describes your current relationship status? Would you say you are...

   Response Categories: (1) married (2) living with someone in a steady, marriage-like relationship (3) in a steady, romantic relationship with one person, but not currently living with a romantic partner (4) dating, but do not have a steady, romantic relationship with one person (5) not dating or seeing anyone right now

2. Economic Hardships:

   Question 1: During the past 12 months, how much difficulty have you had paying your bills? Would you say...

   Response Categories: (1) A great deal of difficulty (2) Quite a bit of difficulty (3) Some difficulty (4) A little difficulty (5) No difficulty at all

   Question 2: Think again over the past 12 months. Generally, at the end of each month did you end up with...

   Response Categories: (1) More than enough money left over (2) Some money left over (3) Just enough to make ends meet (4) Almost enough to make ends meet (5) Not enough to make ends meet