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The effect of college degree attainment on neurodegenerative symptoms in genetically at-risk women

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A B S T R A C T

Using longitudinal data, the present study examined the association between college degree attainment and the manifestation of neurodegenerative symptoms among women (n = 93) at elevated genetic risk. The neurodegenerative symptoms investigated in this study are due to FXTAS (Fragile X-associated Tremor/Ataxia Syndrome), a condition with onset after age 50. Those at risk for FXTAS have a mutation of a single gene found on the X chromosome. FXTAS is characterized by intention tremor, gait ataxia, executive function deficits, memory issues, and neuropathy. College degree attainment has been shown to provide neuroprotective effects in the general population, delaying the development of neurodegenerative conditions such as Alzheimer's disease. For this reason, college degree attainment is a potentially salient resource for those at risk of FXTAS. The results of the present research indicated significantly more severe FXTAS symptoms in women who did not attain a college degree as compared with those who were college graduates, although the two groups were similar in age, genetic risk, household income, health behaviors, and general health problems. Furthermore, symptoms in those who did not attain a college degree worsened over the 9-year study period at a significantly faster rate than the college graduates. The association between college degree attainment and FXTAS symptoms was significantly mediated by depression, which was lower among the graduates than those who did not attain a college degree. Thus, the present research is an example of how a sociodemographic factor can mitigate neurodegenerative conditions in genetically at-risk adults.

1. Introduction

Education has been characterized as a 'fundamental cause' of population-level disparities in health, disease, and longevity (Masters, Link, & Phelan, 2015; Rydland, Solheim, & Eikemo, 2020). In particular, research has shown that attaining a college degree confers substantial advantages for health (Johnson-Lawrence, Zajacova, & Sneed, 2017; Krueger, Tran, Hummer, & Chang, 2015). Notably, fewer than 40% of U. S. adults have attained a bachelor's degree (U.S. Census Bureau, 2022).

Although educational attainment is a well-established social determinant of health (Kawachi, Adler, & Dow, 2010; Zajacova & Lawrence, 2018), only a few studies have examined whether it can delay the manifestation of specific diseases for which individuals are at heightened genetic risk as distinct from general health (Cook & Fletcher, 2015; Liu et al., 2015). In this study, we examine the relationship between attaining a college degree and the symptoms characteristic of FXTAS (Fragile X-associated Tremor/Ataxia Syndrome), a neurodegenerative disease with onset generally after age 50 that is caused by a mutation of a single gene found on the X chromosome. Carriers of this mutation (referred to as *premutation carriers*) are relatively common in the population (1 in 151–209 females and 1 in 439–468 males) (Seltzer et al., 2012; Tassone et al., 2012). Premutation carrier women are at heightened risk of giving birth to a child with fragile X syndrome (FXS), the most common inherited cause of intellectual disability and autism (R. J. Hagerman et al., 2009; Mila, Alvarez-Mora, Madrigal, & Rodriguez-Revenga, 2018). Adult carriers are also at heightened risk of FXTAS (R. J. Hagerman & Hagerman, 2013; Wheeler et al., 2014), which is the focus of the present research. Specifically, using data drawn from a longitudinal study, we examine the association between college degree attainment and the manifestation of FXTAS-type symptoms among female premutation carriers, and the extent of change in symptoms over time. As such, the present research is an example of how a sociodemographic factor is associated with the health of genetically at-risk adults.

1.1. Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)

FXTAS is one of several syndromes caused by expansions in the number of repeats of the cytosine-guanine-guanine (CGG) sequence of nucleotides comprising the 5' untranslated region of the *FMR1* gene on the X chromosome. (The *FMR1* gene was formerly referred to as Fragile

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X **M**ental **R**etardation **1**, but was recently renamed as **F**ragile X **M**essenger **R**ibonucleoprotein **1**; National Library of Medicine, 2022). The *FMR1* gene and its protein products play an essential role in neurological development and functioning across the lifespan (Mila et al., 2018). In the population, the modal number of CGG repeats is 30. The most severe condition caused by expansions of *FMR1* CGG repeats is FXS, a neurodevelopmental disorder caused by an expansion of more than 200 CGG repeats that is associated with significant behavioral challenges, health impairments, and cognitive limitations.

While mothers of children with FXS may themselves have the full mutation, they are more likely to be *FMR1* premutation carriers (defined as 55–200 CGG repeats). Premutation carriers were previously thought to be unaffected except for their heightened risk of having a child with FXS. However, research over the last 20 years has revealed extensive clinical involvement for at least some premutation carriers (see Wheeler et al., 2014 and Wheeler, Raspa, Hagerman, Mailick, & Riley, 2017 for reviews), including mental health problems (Roberts et al., 2016), chronic pain (Rodriguez-Revenga et al., 2009), and reproductive difficulties (Allen et al., 2007).

Additionally, and of particular relevance for the present research, some premutation carriers are at risk for FXTAS, a neurodegenerative disorder characterized by intention tremor, gait ataxia, and white matter disease (Berry-Kravis et al., 2007). Executive function deficits, memory issues, neuropathy, and Parkinsonism are additional signs and symptoms that can contribute to the diagnosis (P. J. Hagerman & Hagerman, 2015; D. A. Hall et al., 2016). FXTAS is diagnosed in approximately 16% of premutation carrier women aged 50 years and older (Coffey et al., 2008; Rodriguez-Revenga et al., 2009) and is more frequent among those with >100 CGG repeats (Jacquemont et al., 2004). Most prior research on FXTAS has focused on men, for whom the disorder is more common and severe (Jacquemont et al., 2004). The lower prevalence and milder symptoms of FXTAS in female carriers are likely due to the protective effects of the unmutated *FMR1* gene on the second X chromosome (Berry-Kravis et al., 2007). Sub-clinical signs of FXTAS are evident in some premutation carriers who do not meet the full diagnostic criteria for the syndrome (Mailick et al., 2021; Storey et al., 2021). FXTAS symptoms become more severe with advancing age (Leehey et al., 2008; Mailick et al., 2021).

Studies have shown that the associations between *FMR1* CGG repeats and health can be moderated by risk factors, including stressful life events (Hong et al., 2021; Seltzer et al., 2012) and older age (Shickman et al., 2018), as well as by protective factors, such as emotional support (Hartley, DaWalt, Hong, Greenberg, & Mailick, 2019). As the symptoms of FXTAS are not evident until older-age, questions can be raised about the role that life experiences might play in their development. In this research, we evaluate whether education (particularly college degree attainment) is associated with a reduction of FXTAS-type symptoms in a cohort of midlife and older premutation carrier mothers of children with FXS. In addition, we probe potential pathways through which attaining a college degree might influence FXTAS-type symptoms by exploring the mediating effects of psychological symptoms and health behaviors.

1.2. Effects of education

Education, along with income and occupational status, is one of three key variables used to measure socioeconomic status (Simandan, 2018), and is regarded as a primary pathway to social success (Gugushvili, Zhao, & Bukodi, 2019). Of particular relevance to the present study, greater educational attainment has been linked to better health and longevity. In the general population, adults with higher levels of education have better self-rated health (Präg & Subramanian, 2017); fewer chronic conditions, including diabetes (Davies, Dickson, Davey Smith, van den Berg, & Windmeijer, 2018), cardiovascular disease (Kubota, Heiss, MacLehose, Roetker, & Folsom, 2017), and kidney disease (Choi et al., 2011); and have longer life expectancies (Hummer & Hernandez, 2013). Additionally, there appear to be unique benefits experienced by those who obtain a bachelor's degree as distinct from the equivalent years of education without a degree. Those who attain a college degree exhibit more positive health behaviors (Lawrence, 2017), experience fewer chronic conditions (Johnson-Lawrence et al., 2017), and have a lower risk of mortality (Krueger et al., 2015) compared to those without the credential. Completing a college degree fosters the values, skills, and habits that enable individuals to take self-directed action toward setting and achieving goals (Burks et al., 2015; Lawrence, 2017). Although these associations may be partially endogenous to earlier life circumstances such as childhood socioeconomic status, or intra-individual factors such as stress-reactivity (Boardman & Fletcher, 2015; Schafer, Wilkinson, & Ferraro, 2013), there is strong evidence that the health effects of college degree attainment persist even after adjusting for potential prior influences (Cook & Fletcher, 2015; Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, 2015; Zajacova & Lawrence, 2021).

Only a few studies have examined the association between educational attainment and FXTAS. Storey et al. (2021) assessed signs of neurological impairment in 57 female premutation carriers and found that those with higher levels of education exhibited better motor and cognitive functioning. Within a sample of 134 premutation carrier mothers of children with FXS (that partially overlapped with the present study's sample), Klusek, Hong, Sterling, Berry-Kravis, and Mailick (2020) found that educational attainment accounted for a significant portion of the variance in executive function deficits. Executive dysfunction is prevalent in the FXTAS phenotype (Grigsby et al., 2014) and may also be an early marker for those who do not yet meet the full diagnostic criteria for FXTAS (Brega et al., 2008). A few other studies have noted educational differences between premutation carriers with FXTAS compared to those without FXTAS. In a study by Brega et al. (2009), 71% of premutation carriers without FXTAS symptoms had 16 or more years of education but only 43% of premutation carriers with FXTAS symptoms had achieved a similar amount of schooling, a pattern also reported by Lozano et al. (2016) and Grigsby et al. (2016).

College degree attainment has been shown to provide neuroprotective effects in the general population (Bowles et al., 2019; Greenia, Yan, Paganini-Hill, Corrada, & Kawas, 2020), delaying the development of neurodegenerative symptoms (C. B. Hall et al., 2007; Paradise, Cooper, & Livingston, 2009). As such, it may be a particularly salient resource for *FMR1* premutation carriers, with its impact possibly increasing as carriers age and become at risk for FXTAS. Thus, there is a need to better understand whether and how education also may exert a protective effect among *FMR1* premutation carriers.

1.3. Pathways linking education to FXTAS

In population research, education has been shown to impact health through financial, social, psychological, and health behavioral mechanisms (Kawachi et al., 2010; Matthews, Gallo, & Taylor, 2010; Zajacova & Lawrence, 2018). In the present research, we focus on psychological and health behavioral pathways that potentially link college degree attainment and FXTAS-type symptoms based on past research and clinical observations regarding their specific association with FXTAS (R. J. Hagerman & Hagerman, 2016; Seritan, Bourgeois, et al., 2013).

Regarding psychological mechanisms, prior research has demonstrated robust associations between educational attainment and mental health in the general population (Erickson et al., 2016; Muñoz & Santos-Lozada, 2021). One explanation for this association is that a college education supports the development of coping resources to manage emotional reactions to stressful life circumstances. This explanation is of particular relevance to premutation carrier mothers of children with FXS who are exposed to high levels of parenting-related stress (Seltzer et al., 2012) and therefore are at higher risk of developing depressive symptoms (Roberts et al., 2009). The pathway between educational attainment and depressive symptoms may have further relevance for premutation carriers because of the known association between depression and neurodegenerative diseases (Barnes et al.,

2012). Additionally, in studies of *FMR1* premutation carriers, there is evidence that mental health difficulties *precede* the development of the motor symptoms of FXTAS (Seritan, Bourgeois, et al., 2013; Seritan, Ortigas, Seritan, A.Bourgeois, & J.Hagerman, 2013). Mental health may therefore be a potential pathway linking prior educational attainment and subsequent FXTAS-type symptoms.

Health behaviors are another plausible mechanism through which educational attainment may impact FXTAS-type symptoms. In general population studies, people with higher levels of education are less likely to smoke, drink excessive amounts of alcohol, and have poor diets, and are more likely to engage in physical activity, as compared to people with lower levels of education (Kershaw, Mezuk, Abdou, Rafferty, & Jackson, 2010; Lawrence, 2017). With respect to premutation carriers, several case reports and clinical guidelines have noted that both the onset and progression of FXTAS may be impacted by lifestyle factors and behaviors, such as alcohol consumption, smoking, substance use, and exercise (R. J. Hagerman & Hagerman, 2016; Muzar, Adams, Schneider, Hagerman, & Lozano, 2014, 2015; Sodhi & Hagerman, 2021; Song et al., 2016). As such, health behaviors may be another important factor mediating the relationship between educational attainment and FXTAS.

1.4. Research questions

The current study extends past research by examining to what extent college degree attainment is associated with FXTAS-type symptoms in a cohort of premutation carrier mothers of children with FXS, all of whom were in the age-range of risk for this syndrome. We investigated two primary and one exploratory research questions and related hypotheses.

1. To what extent is college degree attainment associated with FXTAS-type symptoms? Given the past research evidence of the neuro-protective benefits of education, we hypothesized that premutation carrier mothers who achieved a college degree would have lower levels of FXTAS-type symptoms than those who did not attain a college degree.
2. To what extent do changes in FXTAS-type symptoms over time differ between premutation carriers with and without a college degree? We hypothesized that FXTAS-type symptoms would increase over time, and that the rate of increase would be faster for those who have not attained a college degree.
3. In an exploratory analysis, we probed the mechanisms through which college degree attainment may be longitudinally associated with FXTAS-type symptoms. Building on past research on the *FMR1* premutation, we explored whether psychological factors (depressive symptoms and anxiety) and health behaviors (drinking and smoking) mediate the effects of college degree attainment on FXTAS-type symptoms.

2. Methods

2.1. Data source and sample

Participants in the current study included 93 premutation carrier mothers of individuals with FXS, drawn from a longitudinal study that currently encompasses five waves of data (Mailick, Hong, Greenberg, Smith, & Sherman, 2014). Initially, 135 premutation carrier mothers participated in the study. They were recruited through existing sources: service agencies, clinics, and national organizations and from university-based research registries. Hence, the sample did not meet racial and ethnic representativeness or diversity standards. Almost all of the recruited participants were White non-Hispanic (95.6%). Of the original participants, 93 continued to participate through the fifth wave of the study. The present analysis included data from the second through the fifth waves, spanning an average of nine years per participant (from 2010–2011 to 2019–2020). FXTAS-type symptoms were not measured at Time 1, but were measured at each study point starting at Time 2 and continuing through Time 5.

To be included in the present analysis, participants had to be the biological mother of an adolescent or adult (aged 12+ years) who had the full mutation of FXS. Mothers' premutation status was verified by medical records and/or molecular assays conducted by the Rush University Medical Center Molecular Diagnostics Laboratory under the direction of Elizabeth Berry-Kravis, MD, PhD. DNA was isolated from buccal samples using standard methods. *FMR1* genotyping to determine CGG repeat length was conducted with the Asuragen AmplideX® Kit (Chen et al., 2010; Grasso et al., 2014).

Institutional Review Boards at the University of Wisconsin-Madison and the Marshfield Clinic Research Institute approved the data collection protocol. Written informed consent was obtained from all mothers prior to data collection.

2.2. Measures

Mothers participated in telephone interviews and completed self-administered questionnaires at each time point. To measure college degree attainment, which was the key independent variable for the present analysis, participants were classified as having achieved at least a Bachelor's degree (coded 1) versus less than a Bachelor's degree (coded 0).

Although the present study did not include a clinical assessment of FXTAS, we evaluated symptoms associated with FXTAS via self-reported responses from the *Family Study Questionnaire* (Chonchaiya et al., 2010). The 14 items covered four domains (Tremor, Neuropathy, Memory, Balance), with questions such as "Do you have tremor (shakiness) of the hands?", "Any problems with burning or pain in the legs?", "Do you have problems with memory?" and "Have you had any problems with your balance?" Items were rated on a scale of 0–2 (0 = no problems, 1 = have problems but not clinically diagnosed or treated with medication for this symptom, and 2 = have clinically diagnosed problems or treated with medication for this symptom) and summed into a total score. Higher scores signify greater levels of FXTAS-type symptoms.

Depressive symptoms were measured using the 20-item *Center for Epidemiologic Studies Depression Scale* (CES-D; Radloff, 1977). Participants rated how many days over the past week they experienced depressive symptoms (e.g., depressed mood, feelings of loneliness, lack of positive affect) on a 4-point scale from 0 (never) to 3 (5–7 days). Total scores can range from 0 to 60 with higher scores indicating greater depressive symptoms. The mean score of the CES-D from Times 2, 3, and 4 was used in the analyses. The reliability coefficient (Cronbach alpha) for this sample ranged from 0.91 to 0.93 across the three time points. The frequency of anxiety symptoms was measured by the 9-item anxiety subscale of the *Profile of Mood States* (POMS; McNair, Lorr, & Droppleman, 1981). Symptoms such as feeling tense, shaky, uneasy, nervous as experienced over the previous week were rated on a 5-point scale from 0 (not at all) to 4 (extremely). Total scores can range from 0 to 36 with higher scores indicating higher levels of anxiety. Similar to the depressive symptoms measure, the mean score of anxiety symptoms from Times 2, 3, and 4, was used in the analyses. The reliability coefficient (Cronbach alpha) for this sample ranged from 0.88 to 0.91 across the three time points.

The amount of alcohol intake was measured by the number of drinks a week. The variable was created based on the number of days per week when the participant drank any alcohol, from 0.5 (<1/day) to 7 (every day) and multiplied by the number of drinks a day to create the *number of drinks per week* variable. This measure of drinking was collected at Times 2 and Time 4, and the mean of the two measures was used as the mediator. About one-fifth (20.4%) of the participants were non-drinkers and coded 0. Years of smoking was measured based on two questions: "At what age did you first start smoking at least one cigarette a day" and "How old were you the last time you smoked regularly (at least a few cigarettes every day)." The difference between the two ages was computed for the past smokers. For current smokers, the difference

between current age and age when first smoked was computed. Non-smokers (68.5%) were coded 0 years of smoking. The most recent measure of lifetime smoking (collected at Time 4) was used in this study.

Covariates included age, *FMR1* CGG repeat number, household income, and general health problems. Household income was covaried to estimate the college attainment effect, net of the financial advantage that a college degree might confer on graduates. It was measured on an ordinal scale, from 1 = $1 - $9999 to 14 = $160,000 or greater at each wave of data collection. The indicator of general health problems was the number of health conditions the participant experienced or had been treated for during the previous twelve months, drawn from a list of conditions included in the national MIDUS study (Midlife in the United States, 2022). The full list included 40 health conditions (e.g., asthma, high cholesterol, hypertension, obesity, diabetes, stroke, cancer, heart disease, colitis, etc.). Fourteen of the conditions have been linked in past research with FXTAS or other *FMR1* premutation symptoms (e.g., thyroid disease, autoimmune disorders, migraine headaches, swallowing difficulties, Parkinson's disease, neurological disorder, anxiety, depression) and these were not included in the indicator of health used as a covariate in this study. This covariate is referred to as *general health problems* to avoid confusion with FXTAS-type symptoms.

2.3. Analysis plan

All analyses were conducted using Stata version 17.0 (StataCorp, 2021). The level of significance was set at less than 0.05.

For the first research question, which asked to what extent is college degree attainment associated with FXTAS-type symptoms, analysis of covariance (ANCOVA) was used to test the difference in FXTAS-type symptoms between the two education groups at each time point (Times 2, 3, 4, and 5), controlling for age, CGG repeat number, household income, and general health problems.

For the second research question, which asked whether the degree of change in FXTAS-type symptoms over time differed for the two education groups, growth curve models were estimated. To evaluate the hypothesis that the rate of change over time would be greater for those who did not attain a college degree, we evaluated a quadratic cross-level interaction term (time X college degree attainment) in predicting change in FXTAS-type symptoms. We tested a quadratic interaction term to evaluate our hypothesis that FXTAS-type symptoms would accelerate more rapidly over time for those who did not attain a college degree than for college-degree graduates. Further, as there was unequal spacing between time points, for this analysis the time variable was defined as the average elapsed time in years from Time 2 which was set as baseline: Time 2 = 0, Time 3 = 1.4, Time 4 = 5.3, Time 5 = 8.4. In the growth curve models, general health problems and household income at each time point were included as time-varying covariates, while CGG repeat number and age of mothers at Time 2 were included as person-level covariates.

For the third research question, we first examined bivariate correlations between the independent variable (college degree attainment), the dependent variable (FXTAS-type symptoms), and the four potential mediators. Subsequently, guided by the bivariate correlations, we conducted mediation analyses via the *sem* command in Stata with the Full Information Maximum Likelihood (FIML) estimation method to estimate direct and indirect effects of educational attainment on FXTAS-type symptoms. For the indirect effects, the bias-corrected bootstrap 95% confidence intervals based on 2000 bootstrap samples were reported. Since FXTAS-type symptoms are known to be related to aging, this dependent variable was measured at the latest data point, i.e., Time 5. All mediators were measured before Time 5, and age of mothers, CGG repeat number, household income, and general health problems were controlled. For household income and general health problems, the averages of three measures obtained at Times 2, 3, and 4 were used as the covariates.

3. Results

3.1. Descriptive findings

Table 1 presents descriptive statistics for the full sample and comparisons of study variables between premutation carriers with and without a college degree. The average age of mothers at Time 5 was 60.8 years, ranging from age 47 to 79. About two-thirds (65%) were college graduates, a considerably higher percentage than in the overall U.S. population (U.S. Census Bureau, 2022). The average CGG repeat length of these premutation carriers was 95, ranging from 67 to 138; notably the CGG repeat length was not significantly different between premutation carriers with and without a college degree. Compared to premutation carriers in this study without a college degree, those with a college degree had significantly lower levels of depressive symptoms and anxiety, but were not significantly different with respect to the other study variables, including general health problems.

3.2. FXTAS-type symptoms associated with college degree attainment

Table 2 presents means of FXTAS-type symptoms by college degree attainment at each time point. Supporting the hypothesis for Research Question 1, the two groups significantly differed at each time point, with symptom scores consistently higher (signifying worse FXTAS-type symptoms) among premutation carriers without a college degree compared to those with a college degree ($p < 0.05$ for each comparison).

Next, for Research Question 2, the trajectory of change in FXTAS-type symptoms was estimated using growth curve modeling, with age, CGG repeats, household income, and general health problems controlled (see Table 3). Of control variables, household income was negatively associated with FXTAS-type symptoms at each time point, whereas general health problems was positively correlated with FXTAS-type symptoms. There was a significant cross-level interaction between college degree attainment and the quadratic term of the time variable. Decomposing this interaction term, the trajectory of FXTAS-type symptoms was significant for premutation carriers without a college degree (time-squared: b = 0.069, s.e. = 0.027, p = 0.011), whereas for the those with a college degree, the quadratic term of the time was not

Table 1
Comparison of demographic characteristics and study variables by college degree attainment.

	Total (N = 93)	without a college degree (n = 33, [35.5%])	with a college degree (n = 60, [64.5%])	t-score
Age at Time 5	60.8 (7.1) [47, 79]	60.3 (7.6) [47, 79]	61.1 (6.8) [47, 78]	0.53
CGG repeat length	95.0 (16.8) [67, 138]	94.1 (17.5) [69, 138]	95.5 (16.7) [67, 134]	0.40
Household income (Median)	$90,000	$86,000	$93,000	1.15
General health problems	2.2 (1.8) [0, 7]	2.7 (2.2) [0, 7]	2.0 (1.6) [0, 7]	−1.72
Number of drinks a week	2.4 (2.9) [0, 14]	2.1 (2.8) [0, 10]	2.5 (2.9) [0, 14]	0.77
Years of smoking	5.0 (9.9) [0, 45]	7.1 (12.0) [0, 45]	3.7 (8.3) [0, 33]	−1.58
Depressive symptoms	11.2 (9.1) [0, 39]	16.1 (11.3) [2, 39]	8.5 (6.3) [0, 23]	−4.20***
Anxiety	9.0 (5.7) [1, 29]	11.1 (7.0) [1, 29]	7.8 (4.5) [2, 23]	−2.78**

Note. Except for "household income," means are presented with standard deviation in parentheses and the range in brackets. For "household income" the sample medians are reported with the continuity corrected chi-squared statistics from a 2-sample test on the equality of median presented at the t-value column. **p < 0.01, ***p < 0.001.

Table 2
FXTAS-type symptom scores at each wave by college degree attainment.

	without a college degree	with a college degree	F-value
Time 2	3.19 (3.5) [0, 11]	1.45 (2.0) [0, 9]	4.72*
Time 3	3.83 (4.4) [0, 19]	1.63 (1.9) [0, 7]	7.81**
Time 4	3.91 (3.9) [0, 14]	2.07 (2.1) [0, 11]	5.07*
Time 5	6.47 (6.2) [0, 21]	2.59 (2.5) [0, 9]	12.2***

Note. Means are presented with standard deviation in parentheses and the range in brackets. F-values are from ANCOVA, controlling for age, CGG repeats, household income, and general health problems. *p < 0.05, **p < 0.01, ***p < 0.001.

Table 3
Estimates from the growth curve model predicting FXTAS symptoms over time.

Fixed part	Estimate (s.e.)
Control variables	
Age (at Time 2)	0.07 (0.04)
CGG repeats	0.02 (0.02)
Household income	−0.14 (0.05)**
General health problems	0.15 (0.07)*
Main effects	
College degree attainment (= 1)	−1.76 (0.66)**
Time (in years from Time 2)	−0.24 (0.17)
Time-squared	0.069 (0.027)*
Cross-level interactions	
Time x College degree	0.30 (0.19)
Time-squared x College degree	−0.061 (0.030)*
Constant	3.35 (0.61)***
Random part	
Var (Time)	0.000 (0.000)
Var (Time squared)	0.002 (0.002)
Var (intercept)	4.66 (1.28)
Log likelihood	−786.68

Note. Regression coefficients are presented with robust standard errors in parentheses. *p < 0.05, **p < 0.01, ***p < 0.001.

significant (b = 0.008, s.e. = 0.012, p = 0.468). Thus, the trajectory of change accelerated for premutation carriers who did not have a college degree, but not for the college graduates.

For descriptive purposes, these results are illustrated in Figs. 1 and 2. Fig. 1 depicts the estimated mean trajectories of FXTAS-type symptoms for the two groups. Fig. 2 depicts individual trajectories of each carrier's FXTAS-type symptoms over time for those with and without a college degree. These figures show that members of the two groups manifested different patterns of change, with higher levels of symptom severity and greater variation in symptoms among carriers without a college degree.

3.3. Mediation of educational attainment on FXTAS-type symptoms

Table 4 presents Pearson correlations among the study variables. As shown in Table 4, college degree attainment was associated with FXTAS-type symptoms. Neither drinking nor smoking were associated with college education or FXTAS-type symptoms. Given the lack of association of these two potential mediators with the independent and dependent variables, we did not conduct a mediation analysis for drinking and smoking.

In contrast, depressive symptoms and anxiety were significantly associated with both college degree attainment and FXTAS-type symptoms. Motivated by these associations, we conducted analyses to evaluate whether these mental health indicators revealed a path by which college degree attainment was associated with subsequent FXTAS-type symptoms. As depression and anxiety symptoms were significantly associated with each other (r = 0.81), the mediation models were estimated separately for these two indicators controlling for age, CGG repeats, household income, and general health problems. Among these covariates, household income was a significant predictor of depression, anxiety symptoms, and FXTAS-type symptoms. In contrast, general health problems was a correlate of FXTAS-type symptoms only.

College degree attainment had significant direct effects on FXTAS-type symptoms. Additionally, the indirect effect of college degree attainment via depressive symptoms was significant, indicating mediation. Fig. 3A shows how the effects of educational attainment on FXTAS-type symptoms were significantly mediated through depressive symptoms (indirect effect coefficient = −0.60, 95% CI [−1.53, −0.06], p <

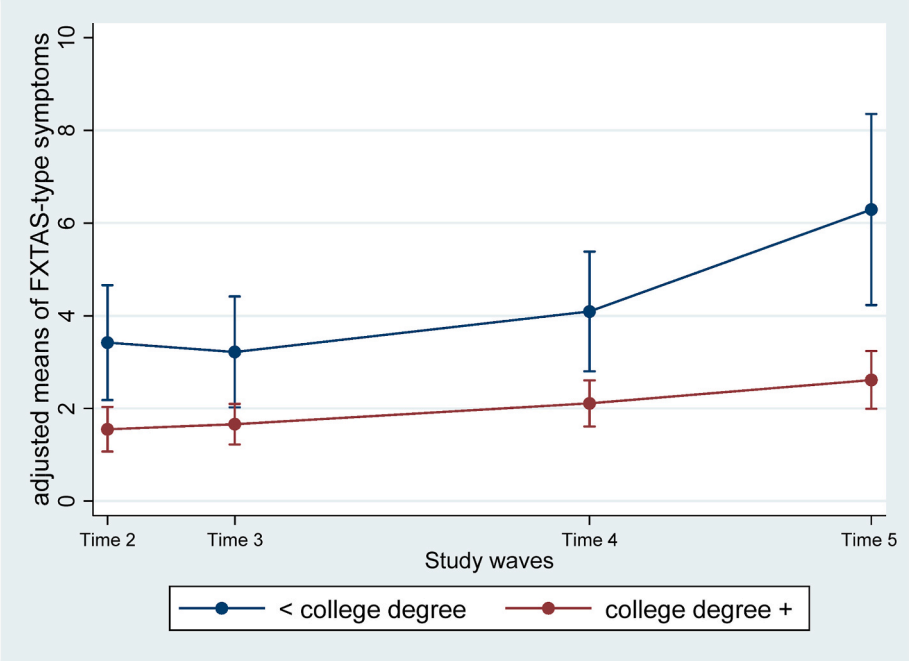

Fig. 1. Adjusted means of FXTAS-type symptoms by college degree attainment over time. The model adjusts for age, CGG repeats, household income, and general health problems.

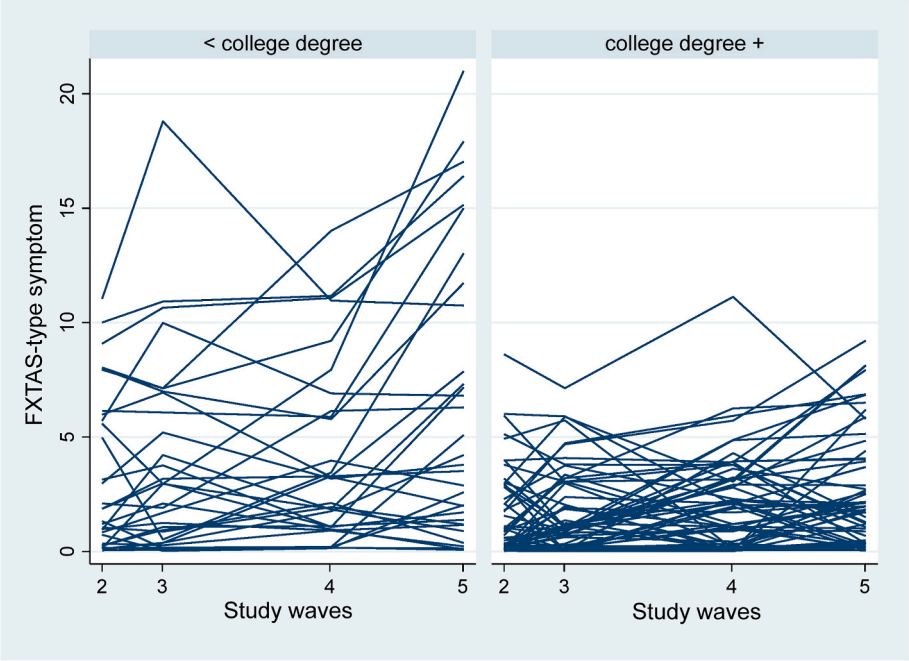

Fig. 2. Individual trajectories of FXTAS-type symptoms by college degree attainment.

Table 4
Correlations among study variables.

Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1) having a college degree	1.000									
(2) Maternal age	0.055	1.000								
(3) CGG repeats	0.042	−0.234*	1.000							
(4) Household income	0.166	0.095	0.028	1.000						
(5) General health problems	−0.178	0.104	0.017	0.005	1.000					
(6) Depressive symptoms	−0.403***	−0.172	−0.026	−0.411***	0.166	1.000				
(7) Anxiety	−0.280**	−0.146	−0.035	−0.308**	0.195	0.809***	1.000			
(8) Number of drinks a week	0.080	−0.067	−0.009	0.024	−0.113	−0.097	−0.078	1.000		
(9) Years of smoking	−0.165	0.057	0.030	−0.122	0.217*	0.156	0.199	−0.043	1.000	
(10) FXTAS-type symptoms	−0.391***	0.106	0.001	−0.290**	0.434***	0.400***	0.466***	0.084	0.184	1.000

Note. *p < 0.05, **p < 0.01, ***p < 0.001.

0.05). Compared to premutation carriers without a college degree, those who had a college degree had lower levels of depressive symptoms prior to Time 5 (b = −5.94, s.e. = 1.69, p < 0.001), which subsequently were associated with a lower level of FXTAS-type symptoms (b = 0.10, s.e. = 0.05, p < 0.05) at Time 5. About 22% of the total effect of college degree attainment was mediated by depressive symptoms. Although the indirect effect via anxiety showed a similar pattern of path coefficients, it did not reach statistical significance (indirect effect coefficient = −0.58, 95% CI [−1.48, 0.10], p < 0.10) (see Fig. 3B). Notably, about 20% of the total effect of college degree attainment was mediated by anxiety.

4. Discussion

Epidemiological research has documented that approximately one in 150–200 females is a carrier of the *FMR1* premutation (Seltzer, Baker, et al., 2012; Tassone et al., 2012), although all *FMR1*-related conditions including the premutation are significantly under-diagnosed (Movaghar et al., 2021). After age 50, women who carry the *FMR1* premutation are at risk for developing symptoms of FXTAS. Yet studies have suggested that only about 16% are clinically diagnosed with this condition. Most past studies identified carriers from specialized FXS clinics or via family cascade testing. For this reason, the prevalence and severity of FXTAS-type symptoms in premutation carriers in the general population has not been fully established. Thus, rates of FXTAS may be different than reported in the research literature. Studies are therefore needed to parse the factors that account for whether at-risk individuals actually develop FXTAS-type symptoms.

The women in this sample had the two primary risk factors for FXTAS – older age and higher CGG repeats within the premutation range. Specifically, they ranged in age from 47 to 79 years at the final point of data collection for this analysis, with an average age of 61. Their number of CGG repeats in the *FMR1* gene ranged from 67 to 138, with an average of 95 repeats.

The purpose of the present study was to track the development of FXTAS-type symptoms in premutation carriers, and to identify ways that the risk of such symptoms could be mitigated above and beyond older age and genetic vulnerability. The longitudinal research design used in the present study revealed a general pattern of increasing FXTAS-type symptoms over nearly a decade, with the rate of increase significantly greater among those who did not have a college degree. These patterns suggest that cognitive enrichment might be a resource that could be brought to bear on the risks faced by premutation carriers.

Notably, the study participants who had a college degree did not differ from those who did not attain a degree in age, CGG repeat length, household income, or general health problems. This pattern of similarity thus contributed to creation of a level playing field by which the effect of college degree attainment could be evaluated to determine its effect on FXTAS-type symptoms. Additionally, the two groups did not differ in

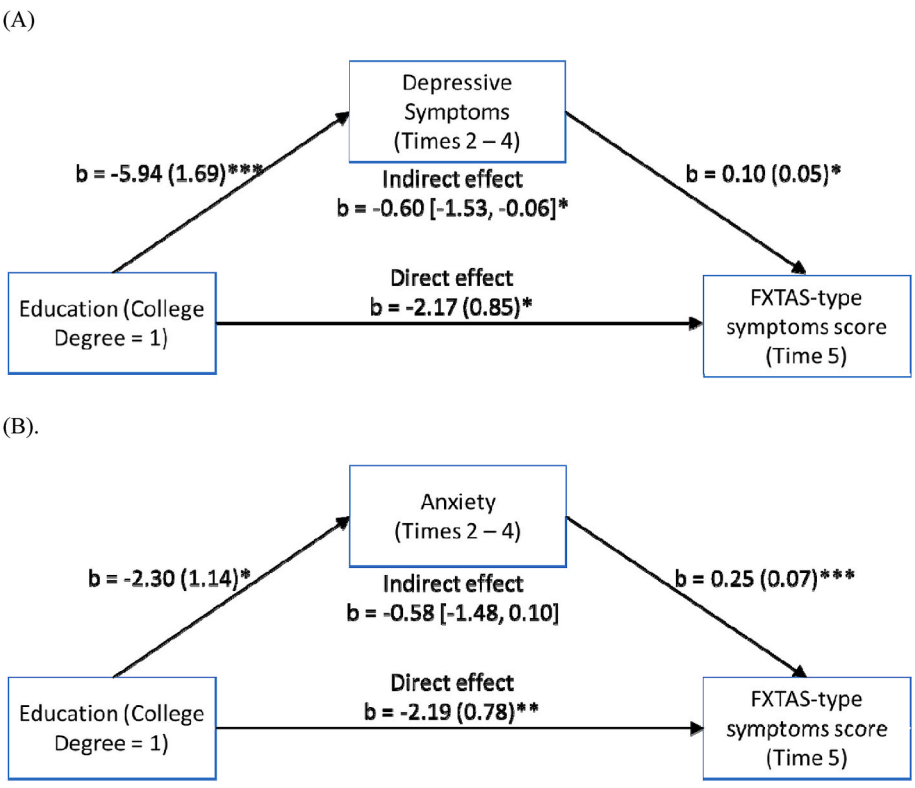

Fig. 3. Direct and indirect effects of college degree attainment on FXTAS-type symptoms. Models adjust for age, household income, CGG repeats, and general health problems. Panel (A): Mediation through depressive symptoms. Panel (B): Mediation through anxiety.
Notes. For each path, regression coefficients are presented with robust standard errors in parentheses. For the indirect effects, the coefficients are presented with bias-corrected bootstrap 95% confidence intervals based on 2000 bootstrap samples in brackets. *p < 0.05, **p < 0.01, ***p < 0.001.

their frequency of drinking alcohol or smoking cigarettes, and thus these two health behaviors do not appear to account for the differential outcomes of the two groups. However, the data suggest that those without a college degree were significantly more likely than those who completed college to experience depressive symptoms during the longitudinal study period. Importantly, some prior research on premutation carriers has suggested that depressive symptoms *precede* the development of the motor symptoms of FXTAS (Seritan, Bourgeois, et al., 2013; Seritan, Ortigas, et al., 2013). There are significant clinical implications of this pattern of longitudinal research results.

The present study built on prior research conducted on the general population regarding the association between educational attainment and neurological diseases and symptoms. These studies lend support to the theory of passive cognitive reserve, wherein individuals with higher educational attainment exhibit greater cognitive functioning throughout adulthood (Lenehan, Summers, Saunders, Summers, & Vickers, 2015; Wilson et al., 2009). Extant research has also identified associations between lower levels of educational attainment and worse neurological signs and symptoms, including vestibular dysfunction (Agrawal, Carey, Della Santina, Schubert, & Minor, 2009), slower gait speed (Steptoe & Wardle, 2017), and reduced verbal and working memory in older adults (Díaz-Venegas, Downer, Langa, & Wong, 2016).

However, it remains possible that other variables, such as early childhood advantage or IQ, might have influenced both greater educational attainment and lower risk of FXTAS-type symptoms, despite the specific genetic etiology of FXTAS. Explanations of why IQ would have an effect on health (e.g., Deary, Weiss, & Batty, 2010; Gottfredson, 2004) have focused on the *g* factor of intelligence, referring to the general mental ability that underlies performance on multiple cognitive tasks, and its correlation with health. Although this correlation is robust, not all diseases are equally associated with intelligence and studies have attempted to separate its effects on general health from specific diseases. Of particular relevance to the present study, a few studies have attempted to address this concern with respect to neurodegenerative diseases. For example, Cook and Fletcher (2015) evaluated the association between college degree attainment and later life cognitive decline in a population at genetically high risk for dementia. The study used a sibling fixed effects research design to control for unobserved variables that could be correlated with both educational attainment and later life cognition. They found that having a college degree reduced the association between having the *APOE4* variant and later life cognitive decline to non-significance, whereas there was a significant association for people without a college degree. They controlled for income, access to medical care, job characteristics, and other factors related to both education and cognitive decline. The present research, which lacks a measure of IQ, cannot directly evaluate its effect on FXTAS-type symptoms.

Separate from IQ, however, the beneficial influence of college degree attainment on FXTAS-type symptoms might be distinct from the effect of education on overall health. By incorporating a measure of general health problems in the study, we showed that the specific association between education and FXTAS-type symptoms remained significant, even when general health problems were controlled. FXTAS is caused by a mutation in a single gene (*FMR1*), with an identified and unique pattern of neuropathology and neuromotor dysfunction, and is not the result of poor health in general. As such, an alternative explanation for our findings is that college degree attainment confers a neuroprotective effect that is distinct from its effect on general health. This neuroprotective effect of education has also been observed for other neurodegenerative diseases such as Alzheimer's (Bowles et al., 2019) and Parkinson's (Kotagal et al., 2015) diseases.

There are significant racial and ethnic differences in access to higher education in the US. According to the U.S. Census Bureau (2022), among adults aged 25 and older in 2021, 61% of Asian Americans, 42% of non-Hispanic Whites, 28% of Blacks, and 21% of Hispanics had a bachelor's degree or higher. This racial and ethnic gradient has significant implications for the differential risk for FXTAS among *FMR1* premutation carriers, and points to one of the limitations of the present research, as the participants were largely White non-Hispanic. Future research on premutation carriers should strive for greater demographic

representativeness.

Additionally, the study did not include a clinical evaluation of FXTAS and instead relied on a self-report measure of symptoms. However, as FXTAS is significantly under-diagnosed, a screening measure such as the one used here may be particularly useful in research and clinical care. The present study did not evaluate all possible pathways by which attaining a college degree might have reduced the manifestation of FXTAS-type symptoms, and these pathways warrant continued research.

Juxtaposed against these limitations are notable strengths of the study. Importantly, the results reported here show the direct effects of college degree attainment on FXTAS-type symptoms beyond advantages conferred by household income and the risk factors of age, CGG repeats, and general health problems. Although household income was significantly associated with FXTAS-type symptoms, college degree attainment significantly and negatively predicted FXTAS-type symptoms beyond the benefits of socioeconomic resources, consistent with Lawrence (2017). Additionally, the longitudinal research design with multiple points of measurement over a nine-year period reveals how FXTAS-type symptoms can worsen over time in premutation carriers. The study also revealed that depression might be one pathway by which the lack of a college education leads to worse outcomes. Since depression was shown to be linked to worse outcomes, concrete preventive actions could be taken to support at-risk patients, as well as the development of cognitive enrichment programs, especially for carriers who did not attain a college degree.

In conclusion, the present study illustrates how cognitively enriching life experiences, such as attaining a college degree, can reduce the risk of neurocognitive and neuromotor symptoms for *FMR1* premutation carriers by way of improved mental health. These results underscore the potential public health benefits of population screening for the premutation. They also add to the broader literature on the health and cognitive benefits of a college education and show how cognitive enrichment can mitigate the effects of specific genetic risks across the life course.

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Ethical statement

Institutional Review Boards at the University of Wisconsin-Madison and the Marshfield Clinic Research Institute approved the data collection protocol. Written informed consent was obtained from all mothers prior to data collection.

CRediT authorship contribution statement

Jinkuk Hong: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Robert S. Dembo:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Leann Smith DaWalt:** Conceptualization, Project administration, Writing – review & editing, Resources, Project administration. **Murray Brilliant:** Writing – review & editing. **Elizabeth M. Berry-Kravis:** Writing – review & editing, Supervision. **Marsha Mailick:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft.

Declaration of competing interest

None.

Data availability

The dataset analyzed in this study is not publicly available per IRB. Due to the sensitive nature of the study, participants were assured raw data would not be shared.

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