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Aging in fragile X premutation carriers

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Abstract

It is now recognized that *FMR1* premutation carriers (PC) are at risk to develop a range of neurological, psychiatric, and immune-mediated disorders during adulthood. There are conflicting findings regarding the incidence of hypertension, hypothyroidism, diabetes, and cancer in these patients that warrant further study. A retrospective controlled study was performed in a convenience sample of 248 controls (130 men, 118 women) and 397 FMR1 PC with and without fragile X-associated tremor ataxia syndrome (FXTAS) (176 men, 221 women); all participants were at least 45 years old (men: mean 62.4, SD 9.5; women: mean 62.8, SD 9.9; p = 0.63). Memory and cognitive assessments (Wechsler Adult Intelligence Scale (WAIS-III), Wechsler Memory Scale (WMS-III)) and molecular testing (CGG repeats and *FMR1*-mRNA levels) were performed. Additional data included body mass index (BMI), cholesterol levels, blood pressure, hemoglobin A1c (HbA1c) levels, and medical history. A higher percentage of PC subjects self-reported having a diagnosis of hypertension (50.0 vs. 35.0 %, p = 0.006) and thyroid problems (20.4 vs. 10.0 %, p = 0.012) than control subjects. When comparing controls versus PC with FXTAS, the association was higher for diabetes (p = 0.043); however, the effect was not

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Conflict of interest

Dr Hagerman has received funding from Novartis, Roche, Neuren, and Alcobra for treatment trials in fragile X syndrome. She has also consulted with Roche/Genentech, Zynerba, Alcobra and Novartis regarding treatment trials in fragile X syndrome. Dr. Hessl has received consultation funding from Novartis and Roche for fragile X syndrome treatment trials. All authors have no further financial disclosures to make and report no conflict of interests.

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significant after adjusting for demographic predictors. Blood pressure, blood glucose levels, HbA1c, and BMI values were not significantly different between the two groups. The PC with FXTAS group performed consistently lower in neuropsychological testing compared with the PC without FXTAS group, but the differences were very small for all but the WAIS full-scale IQ. Based on these findings, it appears that the risk for hypertension, thyroid problems, and diabetes may be more frequent in PC with FXTAS, which will require verification in future studies.

Keywords

FMR1; FXTAS; permutation; fragile X syndrome; ataxia; cognition

Introduction

Fragile X syndrome (FXS) is the main inherited cause of intellectual disability (ID) and the most common single gene mutation associated with autism spectrum disorders. It is caused by a trinucleotide CGG repeat expansion (>200 CGG repeats) in the 5′-UTR of the *FMR1* gene that results in the absence of the encoded protein, fragile X mental retardation protein (FMRP), a translational repressor, with a key role in synaptic plasticity. Worldwide, at least 1:200 women and approximately 1:500 men carry an *FMR1* premutation allele (55–200 CGG repeats) [1]. The gray zone mutation is defined by the presence of 45 to 54 CGG repeats.

Female premutation carriers (PC) were historically seen as clinically unaffected until the description of fragile X-associated primary ovarian insufficiency (FXPOI) in 1991, affecting 20% of female carriers under the age of 40. Fragile X-associated tremor/ataxia syndrome (FXTAS), identified in 2001, is a neurodegenerative condition with a clinical presentation of intention tremor, cerebellar gait ataxia, parkinsonism, neuropathy, autonomic dysfunction, and cognitive deficits. It is diagnosed in about 40 % of males and about 20 % of females with the premutation [2–4].

It is now widely recognized that PC are at risk to develop a range of mild cognitive and behavioral problems during childhood and neurological, psychiatric, and immune-mediated disorders during adulthood [3]. There are conflicting findings regarding the incidence of hypertension, hypothyroidism, diabetes, and cancer in these patients. The pathophysiology of complications is thought to be due to the toxic gain of function effect of increased *FMR1* mRNA leading to intranuclear inclusions [5–6].

Hypertension has been previously described in patients with FXTAS [7–9]. Coffey et al. noted a statistically significant increase in self-reported hypertension in female PC with FXTAS compared to controls (18.0 % controls vs. 61.1 % of PC with FXTAS, $p = 0.0020$) [9]. Hamlin et al. studied hypertension among adult male PC with and without FXTAS over the age of 40 and also noted a statistically significant increase in hypertension compared to controls (27.4 % controls vs. 14.5 % of PC without FXTAS vs. 67.0 % of PC with FXTAS) [9]. The increased incidence of hypertension among PC is suspected to be related to autonomic dysfunction caused by the intranuclear accumulation of *FMR1* mRNA in many peripheral tissues and neurons [10].

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Thyroid disease has inconsistently been associated with PC with and without FXTAS. Coffey et al. reported thyroid problems in 15.4 % of controls vs. 50.0 % of PC with FXTAS ($p = 0.0096$) [9]. Rodriguez-Revenga et al. described the clinical phenotypes associated with PC and found that 15.9 % of women suffered from thyroid disease with onset in adulthood [11]. Hundscheid et al. did not observe a difference in thyroid disease among PC compared to controls [12]. The conflicting results of these studies may be due to differences in age of inclusion ranging from 18 to 45 years, control group recruitment bias, and other limitations of performing surveys over the phone and chart review methodologies.

Hunsaker et al. demonstrated the accumulation of intranuclear inclusions in pancreatic tissue, among other organs, in humans with FXTAS and in a CGG knock-in mice, likely leading to pancreatic insufficiency [10]. The exact effect that these inclusions have on the pancreatic cells is unknown, but may result in the development of diabetes mellitus in PC. Anecdotally, it has been suggested that PC have a higher prevalence of diabetes type 1 and 2 than the general population.

There has also been a suggestion of a possible association between cancer and PC status. Initially, many hypothesized that due to the fragility of the X chromosome, patients with FXS may be more susceptible to cancer [13–15]. Numerous case reports have described cancers of the testes, brain, lungs, kidneys, and leukemias in patients with FXS [14–24]. Luca et al. hypothesized that FMRP may have a role in regulating mRNA metabolism of cancer genes and that increases of FMRP levels correlate with prognostic factors in aggressive breast cancer and metastatic lung cancer [25]. There are no dedicated studies examining the cancer risk among PC.

As previously mentioned, the presence of elevated *FMR1* mRNA levels observed in PC leads to a toxic RNA gain-of-function effect [1] that, along with FMRP deficits, may account for the pathophysiology of the premutation [26]. In addition, environmental factors and comorbid diseases can lead to more severe phenotypes or early presentation of symptoms [27, 28]. We have recently hypothesized that the presence of chronic diseases, such as hypertension, diabetes, or malnutrition, can accelerate or exacerbate the symptomatology of PC [29]. We aim to add to the literature and understanding of the increased prevalence of late onset medical problems in PC with and without FXTAS, as well as their association with other demographic variables.

Materials and methods

Data collection

This is a retrospective controlled study of patients seen at the University of California Davis (UCD), Medical Investigation of Neurodevelopmental Disorders (MIND) Institute. Participants were at least 45 years old with or without the premutation. All participants were clinically referred for an evaluation of premutation status or seen as part of a research protocol. Controls were those without the premutation and were recruited by identifying family members of research participants with fragile X syndrome or PC, volunteers at the MIND Institute, and emeritus faculty associated with UCD (mainly from California, but also from other states.). Clinical data were obtained by self-report of the participant's medical

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history, performing a physical exam, and a targeted *FMR1*-associated disorder neurological examination [30, 31]. The neuropsychological and neuropsychiatric assessments included standardized IQ tests with the Wechsler Adult Intelligence Scales (WAIS-III) and the Wechsler Memory Scale (WMS-III) [32]. WMS-III is a neuropsychological test designed to measure different memory functions in people 16 to 90 years of age. Body mass index (BMI = weight(kg)/height(m^2)) was used to assess obesity, with overweight defined as BMI between 25 and less than 30 and obese defined as BMI greater than or equal to 30 [33]. All procedures were approved by the UCD Institutional Review Board, and all participants and their families provided informed consent for collection and use of data.

Molecular status

Molecular measurement of the CGG trinucleotide expansion was used to separate controls from PC. Analysis of blood drawn from research subjects was completed using a combination of PCR and Southern Blot analysis and the Alpha Innotech FluorChem 8800 Image Detection System (Alpha Innotech Co., San Leandro, CA). The specific protocol has been previously outlined [34, 35]. Repeat sizes between 55 and 200 inclusive were considered PC. Repeat numbers under 45 were treated as controls. Subjects displaying mosaicism (into the full mutation range) were excluded. *FMR1* mRNA levels were determined as described previously [1].

Statistical analysis

Descriptive summaries were prepared (means and standard deviations, frequencies, and proportions) for the demographic variables, presence of comorbid conditions, and cognitive measures, by diagnostic category: controls, PC, and PC subgroups, divided into PC with FXTAS and PC without FXTAS. Proportions for categorical variables were compared across diagnostic groups (controls vs. PC; controls vs. PC with FXTAS vs. PC without FXTAS). Diagnostic group means were compared by *t* test or analysis of variance (ANOVA) for quantitative measurements. The relationship of diagnostic group to the odds of other conditions (hypertension, diabetes, thyroid problems) was assessed by logistic regression, adjusted for age, sex, education, and race/ethnicity. Similarly, the relationship of diagnostic group to the mean on cognitive measurements was assessed by linear regression, also adjusted for demographics. All two-group comparisons (controls vs. PC) were at level 0.05; three-group comparisons (controls vs. PC with FXTAS vs. PC without FXTAS) were adjusted for multiple testing by a Bonferroni correction. All analyses were in SAS version 9.3 (SAS Institute Inc., Cary NC).

Results

Participants included 248 controls and 397 PC, of whom 170 had FXTAS, 108 did not have FXTAS, and 119 had unknown FXTAS status (Fig. 1). Among those with known FXTAS status, 236 had information on at least one clinical diagnosis of interest and 218 had at least one cognitive measurement.

The mean age, 62 years, was similar for PC and controls, but PC with FXTAS averaged 8 years older than their PC without FXTAS counterparts (Table 1, $p < 0.001$). Controls were

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somewhat less likely to be female (48 vs. 56 %, $p = 0.045$), but PC with FXTAS were more likely to be male than female (2:1 ratio, exactly reversed in PC without FXTAS, $p < 0.001$). All participants in this study were well educated, with mean years of education corresponding to completion of a 4-year college degree. Controls were better educated than their premutation counterparts, but the difference was driven entirely by PC with FXTAS, with 1 year less formal education on average ($p = 0.002$). Participants, other than non-Hispanic whites, were better represented in controls than in PC (15 vs. 9 %, $p = 0.078$), but there was no difference between PC without FXTAS and PC with FXTAS.

Approximately half of PC had hypertension compared to a third of controls ($p = 0.006$, Table 1), with PC without FXTAS having more hypertension than controls (42 %) and PC with FXTAS having an even higher prevalence at 58 % ($p < 0.001$). Mean blood pressure (BD) readings for the groups were similar (135.8/79.3 in controls, 130.9/79.9 in PC without FXTAS, and 134.2/76.9 in PC with FXTAS, $p = 0.16$ for systolic BP, $p = 0.01$ for diastolic BP; Table 2). After adjusting for age, sex, education, and race/ethnicity, only the difference between PC with FXTAS and controls remained significant with an almost 2.3-fold greater odds of hypertension in this group (adjusted confidence interval 1.23, 4.54; Table 3).

Unadjusted prevalences suggested a higher prevalence of diabetes in the PC with FXTAS group (Table 1), but this finding was largely accounted for by differences in demographic predictors (Table 3) and may reflect the small number of participants with a diabetes diagnosis. When comparing PC with FXTAS versus controls and PC without FXTAS, the association was significant for type 2 diabetes mellitus ($p = 0.026$); however, the effect was not significant after adjusting for demographic predictors (data not shown). Mean glucose levels were higher in the PC with FXTAS than for controls and PC without FXTAS (102 vs. 98 and 89, respectively, $p = 0.089$, Table 2). HbA1c levels were also higher (6.0 vs. 5.8 and 5.6, respectively, $p = 0.013$), but mean BMIs were similar (29.7 vs. 29.1 and 28.8, $p = 0.499$).

Thyroid problems were reported by 20 % of PC, twice as many as in controls ($p = 0.012$), a rate consistently higher, at 21 %, among both participants with and without FXTAS ($p = 0.028$, Table 1). Adjusting for demographic differences reduced the disparity for PC without FXTAS compared to controls, but PC with FXTAS were still 3.3-fold more likely to report thyroid problems compared to controls (confidence interval 1.19, 8.91 Table 3.) There were no significant differences between PC with and without FXTAS in the rate of reporting thyroid problems. Other medical conditions were considered, including hyperthyroidism, thyroid cancer, prostate cancer, and other cancers; however, no statistically significant differences were found among the three groups. A pilot study presented at the second international meeting of the *FMR1* premutation showed that higher levels of *FMR1* mRNA were associated with higher odds of having hypertension (OR 1.36, 95 % confidence limits 1.03–1.80). However, in the current study which includes a bigger sample, the association of medical conditions and serum *FMR1* mRNA levels was not significant (data not shown).

PC had lower scores on all five measures of cognitive function included in this study with differences in group means on standardized tests (mean 100, standard deviation 15 in reference populations) ranging from 5 to 10 points (Table 1). The PC with FXTAS group performed consistently lower than did PC without FXTAS, but the differences were very

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small for all but the WAIS full-scale IQ. After adjusting for demographics, the WAIS full-scale IQ again showed the most striking differences, with the mean for PC with FXTAS almost 13 points lower than that for controls and 9 points lower than that for PC without FXTAS ($p < 0.01$, Table 4). PC with FXTAS had significantly lower adjusted mean scores than did controls on all WMS subscales. PC without FXTAS performed almost as poorly on the working memory subscale as did their PC with FXTAS counterparts, in both cases about 10 and 11 points lower than controls ($p < 0.01$, Table 4.). PC without FXTAS did not have significant differences in all the other cognitive measures (Table 4).

Discussion

The objective of this study was to describe the prevalence of medical problems and cognitive function in PC over the age of 45. PC with FXTAS in this study were older than controls and PC without FXTAS, which is expected, as FXTAS is rare among individuals under age 55 [3, 4]. PC without FXTAS were also more likely to be female, which can mostly be explained by the presence of two X chromosomes in females. The participants were highly educated, with most obtaining a 4-year degree. Small differences between groups in educational attainment likely do not have any clinical significance.

As in previous studies, we show that PC carry a substantial burden of morbidity beyond their elevated risk for FXTAS. The difference in risk was most pronounced for PC with FXTAS, who had 2.4-fold greater odds of reporting hypertension than controls. PC with and without FXTAS had very similar blood pressure readings to controls, likely owing to the effective use of antihypertensive medications.

In this study, both PC without FXTAS and with FXTAS endorsed a history of thyroid problems, with 2.7-fold and 3.3-fold greater risk of thyroid problems than the controls, respectively. Our results support the findings seen by previous research and may show an effect on thyroid tissues even in PC without FXTAS. However, more studies are necessary to determine if there is an association in larger cohorts.

Diabetes mellitus was relatively uncommon in this cohort; PC with FXTAS had a higher prevalence, but the rate did not differ significantly. Both mean blood glucose levels and HbA1c levels were significantly elevated for PC with FXTAS compared to the other two groups, and this may be related to the lack of exercise, sedentary lifestyle, and perhaps a higher rate of metabolic syndrome in those with FXTAS.

Other medical problems self-reported by participants included hyperthyroidism, thyroid cancer, prostate cancer, and other cancers. These numbers were small, and no statistically significant differences were found among the three groups. Larger cohorts will be required to determine whether there are true differences in these less common outcomes.

The cognitive performance was significantly worse for PC with FXTAS on four (WAIS: full-scale IQ, and WMS: auditory immediate index score, auditory delayed index score, and working memory index score) of the five performance measures (WMS: auditory delayed index scores were lower, but this was not statistically significant). The effect sizes were from 7.7 to 13.4 points lower on standardized scales with a mean = 100 (standard deviation 15) in

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the general population. The adjusted full IQ difference in particular was almost a full standard deviation lower, and the working memory index was about 0.75 standard deviations lower than the controls, after adjustment for age, education, and other demographics. These differences are clinically important and are consistent with findings reported by other authors [36]. Since PC with FXTAS had completed almost as much formal education (1 year less on average) than controls had, this reinforces the concept that FXTAS is a neurodegenerative disorder and causes cognitive decline later in life [37]. Further studies are necessary to describe the cognitive function on PC without FXTAS.

There are potential limitations to this study, starting with the retrospective study design. Not all PC had information indicating if they had or did not have FXTAS, and not all participants had neurocognitive testing. This reduced the sample sizes for some variables examined. The selection of participants was not population-based, but rather a convenience sample of people who were enrolled in studies at a large medical center clinic. They are not likely to represent the full range of people in this geographic area; participant education levels are higher, and the participant group is less racially and ethnically diverse than our catchment area. Some of the controls were obtained from a group of participants being referred for premutation evaluations that had normal *FMR1* repeat sizes and therefore may not represent a truly “normal” control. It is possible that the cohort of PC without FXTAS may be pre-symptomatic or are in the early stages of the disease and are therefore not diagnosed with FXTAS yet. Although used in previous studies, medical history information was self-reported and may lead to recall bias. Finally, the data was aggregated for male and female PC with and without FXTAS, which may influence the significance of the overall outcomes due to decreased penetrance of symptoms in females.

Our study points to important directions for future research. PC are at statistically higher risk for hypertension, and this risk increases with having a higher number of CGG repeats [38]. Hypertension is a treatable illness, and thus, PC would benefit from early detection and treatment. Second, the cognitive deficits observed were most pronounced and were potentially of high impact, in the PC with FXTAS group. Since all groups were highly educated and differed only slightly between PC and controls, this supports the concept of neurodegeneration in FXTAS and reflects the neurobiological damage of this disorder on cognition [3, 36]. More research needs to be done to assess the impact of PC status on other medical co-morbidities including diabetes mellitus, thyroid disorders, and cancers.

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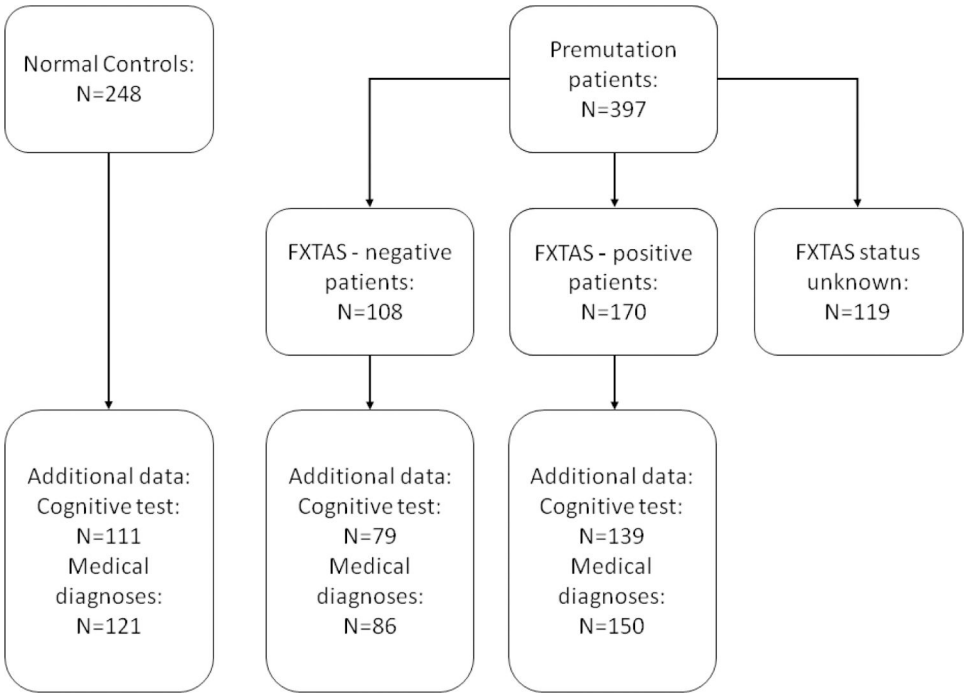

Figure 1.
CONSORT diagram showing number of study participants and available data.

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Table 1.

Characteristics of study participants and differences across diagnostic groups. Comparisons of categorical variables are by chi-square test; comparisons for control vs. premutation means are by *t* tests; comparisons of controls vs. PC without FXTAS (FXTAS(−)) vs. PC with FXTAS (FXTAS(+)) means are by analysis of variance.

					Premutation		
		Controls (N=248)	**Premutation (N=397)**	**P-value: 2-group diff.**	**FXTAS(−) (N=108)**	**FXTAS(+) (N=170)**	**P-value: 3-group diff.**
	mean	62.4	62.8		58	66.2	
Age	SD	9.5	9.9	P=0.627	8.3	8.2	**P<0.001**
	Male	130 (52.4%)	176 (44.3%)		37 (34.3%)	110 (64.7%)	
Gender	Fem	118 (47.6%)	221 (55.7%)	**P=0.045**	71 (65.7%)	60 (35.3%)	**P<0.001**
	mean	16.3	15.5		16.5	15.2	
	SD	3.1	3.3		2.9	3.2	
Education	N	112	275	**P=0.028**	91	151	**P=0.002**
	White	119 (85.0%)	281 (90.7%)		88 (91.7%)	148 (93.1%)	
	Others	21 (15.0%)	29 (9.3%)		8 (8.3%)	11 (6.9%)	
Race	N	140	310	P=0.078	96	159	P=0.055
	Yes	42 (35.0%)	133 (50.0%)		36 (42.4%)	87 (58.4%)	
	No	78 (65.0%)	133 (50.0%)		49 (57.6%)	62 (41.6%)	
Hypertension	N	120	266	**P=0.006**	85	149	**P<0.001**
	Yes	12 (9.9%)	36 (13.6%)		6 (7.1%)	26 (17.4%)	
	No	109 (90.1%)	229 (86.4%)		78(92.9%)	123 (82.6%)	
Diabetes	N	121	265	**P=0.311**	84	149	**P=0.043**
	Yes	12 (10.0%)	54 (20.4%)		18 (21.4%)	32 (21.5%)	
	No	108 (90.0%)	211 (79.6%)		66 (78.6%)	117 (78.5%)	
Thyroid problem	N	120	265	**P=0.012**	84	149	**P=0.028**
	mean	117.4	108.2		113.1	105.4	
	SD	14.9	14.2		13.7	12.9	
FSIQ (W Full scale)	N	110	234	**P<0.001**	78	128	**P<0.001**
	mean	113.6	106.3		108.5	105	
	SD	15.3	16.3		12.3	17.5	
WMS: auditory immediate index score	N	63	128	**P=0.003**	39	88	**P=0.005**
	mean	114.4	108.6		112.2	106.8	
	SD	15.9	16.4		11.9	17.8	
WMS: auditory delayed index score	N	63	127	**P=0.021**	39	87	**P=0.014**
	mean	111.4	106		109	104.5	
WMS: auditory recog delayed index score	SD	12.7	15.4	**P=0.012**	10.8	16.9	**P=0.015**

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					Premutation		
		Controls (N=248)	Premutation (N=397)	P-value: 2-group diff.	FXTAS(−) (N=108)	FXTAS(+) (N=170)	P-value: 3-group diff.
	N	63	125		38	86	
WMS: working memory index score	mean	111.5	101.6		103.2	100.7	
	SD	14.2	13.5		13.1	13.7	
	N	61	116	**P<0.001**	36	79	**P<0.001**

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Table 2.

Laboratory test results for study participants and differences across diagnostic groups. Comparisons of controls vs. PC without FXTAS (FXTAS(−)) vs. PC with FXTAS (FXTAS(+)) means are by analysis of variance.

		Controls	FXTAS(−)	FXTAS(+)	P-value
	mean	135.8	130.9	134.2	
	SD	17.3	16.7	17.8	
BP (systolic)	Total N	109	80	142	P=0.158
	mean	79.3	79.9	76.9	
	SD	8.3	9.8	7.8	
BP (diastolic)	Total N	109	80	142	P=0.019
	mean	98.3	88.6	101.9	
	SD	24.8	14.2	41.4	
Blood Glucose	Total N	72	41	96	P=0.089
	mean	5.8	5.6	6	
	SD	0.6	0.4	0.9	
Hemoglobin A1c	Total N	64	36	80	**P=0.013**
	mean	29.1	28.8	29.7	
	SD	5.9	5.7	4.9	
BMI (exclude BMI>50 or BMI <15)	Total N	94	75	132	P=0.499

Footnote: BMI; body mass index

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Table 3.

Association between diagnostic category (controls, PC without FXTAS (FXTAS(−)), and PC with FXTAS (FXTAS(+))) and odds of having additional medical conditions, adjusted for sex, age in years, years of formal education, and race/ethnicity.

	Odds Ratio (Confidence interval)		
Effect	**Hypertension**	**Diabetes**	**Thyroid problem**
* FXTAS(−) vs. Controls	1.83 (0.84, 3.99)	1.05 (0.28, 3.93)	2.66 (0.87, 8.17)
* FXTAS(+) vs. Controls	**2.36** (1.23, 4.54)	2.13 (0.80, 5.66)	**3.26** (1.19, 8.91)
* FXTAS(+) vs. FXTAS(−)	1.29 (0.61, 2.71)	2.03 (0.60, 6.89)	1.23 (0.48, 3.12)
Female vs. male	0.98 (0.61, 1.57)	0.72 (0.36, 1.46)	**3.76** (1.99, 7.11)
Age in years (age 60 as reference)	1.05 (1.02, 1.08)	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)
Education (12 years as reference)	1.00 (0.999, 1.001)	1.001 (1.00, 1.002)	1.00 (0.998, 1.001)
Other race vs. Non-Hispanic White	0.89 (0.40, 2.00)	**3.62** (1.42, 9.24)	0.62 (0.17, 2.22)

Bonferroni multiple comparison adjustments were used to calculate confidence intervals with overall 5% error rate.

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Table 4.

Difference in cognitive test performance, comparing three diagnostic groups, adjusted for sex, age in years, years of formal education, and race/ethnicity.

	Coefficient *: p-value <0.05 **: p-value <0.01				
Effect compared to mean for reference group	**FIQ**	**WMS: auditory immediate index score**	**WMS: auditory delayed index score**	**WMS: auditory recognition delayed index score**	**WMS: working memory index score**
Intercept	**119.11 ****	**110.75 ****	**111.91 ****	**110.35 ****	**113.49 ****
FXTAS(−)	**−4.33 ***	**−6.59 ***	-3.98	−3.26	**−10.29 ****
FXTAS(+)	**−13.38 ****	**−9.96 ****	**−8.73 ****	**−7.67 ****	**−10.73 ****
Female	−1.89	**8.00 ****	**7.66 ****	3.71	−0.78
Age in years	0.11	0.26	0.19	0.13	−0.30
Education	0.0003	−0.002	−0.0001	−0.001	0.001
Other race	**−8.44 ****	**−8.38 ***	**−8.49 ***	−5.41	−3.80
Least square mean differences					
Normal – FXTAS(−)	4.33	6.59	3.98	3.26	**10.29 ****
Normal – FXTAS(+)	**13.38 ****	**9.96 ****	**8.73 ****	**7.67 ****	**10.73 ****
FXTAS(−) - FXTAS(+)	**9.05 ****	3.37	4.75	4.41	0.44

Reference group: Controls, males, age=60, education=12 years, non-Hispanic white. Least squares means used Bonferroni correction for multiple comparisons.