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# Psychiatric and Cognitive Features in Italian Women With the *FMR1* Premutation: A Comprehensive Assessment Using SCID-5 and Standardized Cognitive Measures

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## ABSTRACT

Women with the *FMR1* premutation (PM) are at increased risk for fragile X-associated conditions (FXPAC), including cognitive and psychiatric features collectively termed fragile X-associated neuropsychiatric disorders (FXAND). This study is the first to systematically investigate cognitive and psychiatric features in Italian female premutation carriers (PCs). One hundred Italian women with the PM were stratified into four age-groups ( $\leq 40$ , 41–50, 51–64, and  $\geq 65$  years). Cognitive performance was assessed using Raven's Standard Progressive Matrices (RSPM) and the Telephone Montreal Cognitive Assessment (T-MoCA). Psychological symptoms were measured with standardized self-report questionnaires, and psychiatric diagnoses were determined through the Structured Clinical Interview for DSM-5 (SCID-5) disorders. Cognitive scores were generally within the normal range; however, participants aged  $\geq 65$  years performed significantly worse on both RSPM and T-MoCA. SCID-5 interviews showed that 51% met criteria for at least one current psychiatric disorder, most commonly generalized anxiety (37%) and major depression (18%). Early-life neurodevelopmental difficulties were frequently reported. Self-report measures often underestimated clinical severity relative to interview findings. These findings underline significant psychiatric vulnerability in female PCs and emphasize the need for prevention and timely intervention, including routine psychiatric assessment in clinical care.

## 1 | Introduction

The premutation (PM) of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene is defined by an expansion of 55–200 CGG trinucleotide repeats in the 5' untranslated region, resulting in elevated levels of *FMR1* mRNA (Tassone et al. 2023). The *FMR1* gene is best known for its association with fragile X syndrome (FXS), the most common inherited cause of intellectual disability (ID) and autism spectrum disorder (ASD). Mothers of

children with FXS frequently carry the PM and are often identified through cascade genetic testing, making adult women a large and clinically relevant but historically understudied PM population (Tassone et al. 2023).

The prevalence of the PM in women is relatively high, with estimates from Western populations suggesting that approximately 1 in 150–200 females carry the PM (Tassanakijpanich et al. 2021). Despite this frequency, PM carriers (PCs) were

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long considered asymptomatic, as general intellectual functioning typically falls within the normal range. Over the past decade, however, accumulating evidence has demonstrated that the PM is associated with a constellation of medical, cognitive, and psychiatric vulnerabilities, collectively referred to as fragile X premutation-associated conditions (FXPAC) (Johnson et al. 2020).

In adult women, FXPAC manifestations are heterogeneous and span endocrine, immune, cognitive, and psychiatric domains. During reproductive and mid-adulthood, female PCs show increased rates of endocrine and immune dysregulation, including hypothyroidism, fibromyalgia, chronic fatigue, and fragile X-associated primary ovarian insufficiency (FXPOI), which is defined by ovarian dysfunction before the age of 40 and affects approximately 20%–25% of women with the PM (Coffey et al. 2008; Espinel et al. 2016). These conditions frequently co-occur with psychiatric symptoms and may complicate clinical recognition and management.

Neuropsychiatric and neurological manifestations in PCs are increasingly conceptualized under the umbrella of fragile X-associated neuropsychiatric disorders (FXAND), which include anxiety, depression, sleep disturbances, psychosis, migraines, neuropathy, memory complaints, and autonomic symptoms (Hagerman and Hagerman 2020; Tassone et al. 2023). FXAND is estimated to affect up to 50% of adult PCs, with women exhibiting particularly high rates of anxiety and mood disorders (Moser et al. 2021; Klusek et al. 2025). Cognitive vulnerabilities in female PCs most commonly involve executive functioning, working memory, and processing speed (Grigsby et al. 2014; Shelton et al. 2016). Longitudinal studies suggest that decline in these domains may precede overt neurodegenerative syndromes, indicating a slowly progressive process that begins earlier than clinically recognized (Wang et al. 2017; Schneider et al. 2020).

With advancing age, a subset of PCs develop fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disorder characterized by intention tremor, ataxia, parkinsonism, autonomic dysfunction, and progressive cognitive decline. Although FXTAS is more prevalent in men, affecting up to 50% of male carriers, women are increasingly recognized as vulnerable, albeit with lower penetrance and a broader, often subtler clinical presentation (Schneider et al. 2020). In women, FXTAS frequently presents with cognitive and psychiatric symptoms that may precede or occur in the absence of prominent motor signs, increasing the risk of misdiagnosis and delayed recognition.

Despite growing recognition of FXAND and related conditions, the clinical boundaries of FXAND remain debated. Different studies from Europe and North America have reported elevated rates of anxiety, depression, and related psychiatric symptoms in women with the PM compared with the general population (Roberts et al. 2009; Kenna et al. 2013; Cordeiro et al. 2015; Jiraanont et al. 2017; Allen et al. 2020; Flavell et al. 2023; Klusek et al. 2025), independent of the psychosocial burden associated with raising a child with FXS (Rodriguez-Revenga et al. 2008; Gossett et al. 2016). In contrast, large record-based studies, including recent analyses from Israel, have not identified an increased prevalence of formally coded psychiatric diagnoses among women with the PM (Klausner et al. 2025).

Consistent with the former line of evidence, an anonymous Italian survey of PCs found that, although few female PCs self-identified with a formal FXAND diagnosis, many reported clinically relevant levels of anxiety and mood disturbance, as well as subjective difficulties in memory and executive functioning (Montanaro et al. 2024). These findings suggested a substantial burden of under-recognized neuropsychiatric symptoms in Italian women with the PM. However, the reliance on self-report data and the absence of standardized diagnostic interviews in that study limited diagnostic specificity and precluded formal prevalence estimates. Methodological differences across studies, particularly the reliance of administrative datasets on routine diagnostic coding without systematic clinical assessment, may therefore contribute to inconsistent findings by under-ascertaining subclinical or undiagnosed conditions (Montanaro et al. 2024).

Importantly, relatively few studies have been conducted in European cohorts, and systematic investigations at the national level remain scarce. In particular, no comprehensive studies have examined adult women with the PM in Italy. Although the underlying genetic background of the PM is expected to be comparable across populations, national-level studies remain essential, as sociocultural factors, healthcare system organization, and diagnostic practices may influence symptom recognition, reporting, access to care, and ultimately the expression of cognitive and behavioral phenotypes. In Italy, where mental health services are delivered through a universal public healthcare system, little is known about how women with the PM experience neuropsychiatric symptoms, obtain diagnoses, and receive treatment. To date, no study has systematically evaluated cognitive and psychiatric functioning in Italian adult women with the PM using standardized diagnostic instruments. The present study addresses this gap through an exploratory, cross-sectional investigation of a nationwide cohort of adult Italian women carrying the PM. Building on our prior survey-based findings, the primary aims were to estimate the prevalence of psychiatric symptoms and to characterize cognitive functioning using standardized self-report measures and clinician-administered diagnostic interviews. Secondary aims included examining whether CGG repeat length, age, and educational level predicted clinical symptomatology. To enhance clinical relevance, we also documented comorbid medical conditions commonly associated with the PM (e.g., migraine, fibromyalgia) and explored participants' perceived treatment needs, experiences with the Italian National Health Service, and current therapeutic interventions, thereby addressing ethically and clinically relevant aspects of care in this population.

## 2 | Methods

### 2.1 | Participants

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Department of Education, Psychology, and Communication, University of Bari "Aldo Moro" (ET-23-15). Participants were recruited via flyers distributed by the Italian Fragile X Syndrome Association and through the social media platforms.

Inclusion criteria were:

1. Confirmation of PM carrier status through DNA genetic testing indicating the number of CGG repeat allele size;
2. Age 18 years or older;
3. Access to a stable internet connection, given that all study activities were conducted online to facilitate nationwide participation.

A total of 88 women responded to the first recruitment announcement. Among them, nine underwent genetic testing to confirm their CGG repeat numbers and were subsequently enrolled. Three middle-aged volunteers were excluded upon discovery that they had the full mutation, a discrepancy likely stemming from limited genetic counseling at the time of their initial diagnosis. Additionally, two participants withdrew shortly after enrolling, and an additional two were excluded due to the absence of confirmed PM status. Excluded individuals were offered an explanation regarding their exclusion from the study. Following this process, the comprised 81 women participants were included in the study. A second recruitment effort, conducted in collaboration with the Italian Fragile X Association, yielded an additional 19 woman participant carriers of a PM. Thus, the total number of participants was 100. Table 1 presents key sociodemographic and clinical characteristics of participants, collected at the time of recruitment. Data were obtained via a structured Google Form distributed by email, which included electronic informed consent (e-consent) and a battery of self-report questionnaires assessing psychological symptoms and the presence of self-reported clinical diagnoses. The mean age of participants was 50.0 years ( $SD=9.35$ ), with the youngest participant aged 29.4 years. Only 9 women were in the  $\geq 65$  age-group, and just 5 participants were over the age of 70. Nearly half of the participants (46%) had completed high school, and 74% reported having at least one child with FXS. The average number of CGG repeats was 89.2 ( $SD=22.61$ ). As part of the self-report questionnaire, participants were asked, “Do you present any FXPAC condition?” 63% percent responded “none,” while 26% participants reported a diagnosis of FXPOI, and five reported FXTAS. Only three participants identified themselves as having any FXAND condition at the time of enrolment. An additional three selected “other,” which included two cases of thyroid disorders and one of fibromyalgia, conditions that fall under the FXPAC umbrella, though these participants appeared unaware of the formal classification.

## 2.2 | Measures

### 2.2.1 | Online Self-Report Questionnaires

**2.2.1.1 | DSM-5 Self-Rated Level 1 Crosscutting Symptom Measure—Adult.** The crosscutting symptom measure (CCSM) is a 23-item self-report screening tool developed by the American Psychiatric Association to assess the presence and severity of mental health symptoms across 13 transdiagnostic domains, including depression, anxiety, mania, psychosis, sleep problems, substance use, and suicidal ideation, among others (American Psychiatric Association 2019). Each item is rated on a 5-point Likert scale (0=none to 4=severe) based

on symptoms experienced over the past 2 weeks. The measure is designed to provide a broad overview of current psychiatric symptomatology, identifying areas that may warrant further evaluation using more specific assessments. A score of 2 or higher on most domains, or a score of 1 or higher in high-risk areas such as suicidality, psychosis, or substance use, indicates the need for additional clinical inquiry. This tool is commonly used in both clinical and research settings for initial screening and to monitor changes in symptom patterns over time.

**2.2.1.2 | Behavior Rating Inventory of Executive Function—Adult Version.** The behavior rating inventory of executive function—adult version (BRIEF-A) is a standardized rating scale consisting of 75 items that are divided in nine theoretically and empirically derived clinical scales reflecting different aspects of executive functioning (EF): Inhibit (INH), Shift (SHFT), Emotional Control (EC), Self-Monitor (SMON), Initiate (INIT), Working Memory (WM), Plan/Organize (P/O), Task Monitor (TMON), and Organization of Materials (OMAT). These clinical scales contribute to two broader index scores: the Behavioral Regulation Index (BRI), which includes INH, SHFT, EC, and SMON; and the Metacognition Index (MI), which includes INIT, WM, P/O, TMON, and OMAT. Together, the BRI and MI yield a Global Executive Composite (GEC) score, representing overall executive functioning. The BRIEF-A self-report scale has high internal consistency (Cronbach’s  $\alpha$  ranging from 0.73 to 0.90), as well as excellent test–retest stability ( $r_s$  ranging from 0.82 to 0.93) (Gioia et al. 2000). BRIEF-A raw data were converted to standardized  $T$ -scores ( $M=50$ ,  $SD=10$ ) based on standardization data provided in the Professional Manual.  $T$ -scores  $\geq 65$  are considered “elevated” and reflective of subjective executive dysfunction.

**2.2.1.3 | Symptom Checklist-90-R.** The symptom checklist-90-R (SCL-90-R) is designed to assess a wide range of psychological symptoms in individuals aged 13 and older (Derogatis and Kathryn 2000). This 90-item self-report questionnaire evaluates nine primary symptom dimensions: Somatization, Obsessive–Compulsive (OC) symptoms, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. Each item is rated on a 5-point Likert scale, ranging from 0=Not at all to 4=Extremely, reflecting the severity of the symptom. Scores for each dimension are calculated as the mean of the items within that symptom construct. In addition to these scales, the instrument provides three global indices: the Global Severity Index (GSI), which reflects overall psychological distress; the Positive Symptom Total (PST), representing the number of symptoms reported (i.e., items rated above zero); and the Positive Symptom Distress Index (PSDI), which captures the average intensity of endorsed symptoms. For clinical interpretation, raw scores are converted to standardized  $T$ -scores, with a normal range defined as  $T$ -scores between 40 and 60.

**2.2.1.4 | Pediatric Quality of Life Inventory 4.0 Generic Core Scales—Adult Version.** The Pediatric Quality of Life Inventory (PedsQL) is a standardized instrument designed to measure health-related quality of life (QoL) in adults aged 18 years and older (Varni et al. 1999). Adapted from the pediatric version, it maintains conceptual equivalence while being developmentally appropriate for adult respondents. The

**TABLE 1** | Sociodemographic and clinical features at time of recruitment.

Variable	Level	Frequency (N= 81)	Percentage (%)		
Geographic area	Central Italy	47	47%		
	Northern Italy	29	29%		
	Southern Italy	24	24%		
Education	Primary school or less	1	1.2%		
	Middle school	6	6%		
	High school	46	46%		
	Bachelor's degree	14	14%		
	Master's degree	22	22%		
	Postgraduate program	9	9%		
	PhD or more	2	2%		
Marital status	Married	67	67%		
	Divorced	17	17%		
	Single	11	11%		
	In a relationship	5	5%		
Child status	Children with FXS	74	74%		
	Children without FXS	12	12%		
	No children	14	14%		
Income	≤15,000 euros	17	17%		
	15,001–28,000 euros	37	37%		
	28,001–50,000 euros	27	27%		
	≥ 50,000 euros	6	6%		
	Prefer not to answer	13	13%		
FXPAC diagnosis (self-report)	None	63	63%		
	FXPOI	26	26%		
	FXTAS	3	3%		
	FXAND	3	3%		
	FXPOI + FXTAS	2	2%		
	Other	3	3%		
Age range	≤40 (29.4–40.9)	12	19%		
	41–50.11 (41.1–50.9)	51	37%		
	51–64.11 (51.0–64.5)	28	35%		
	≥ 65 (66.2–81.0)	9	9%		
Descriptive	Mean	Med	SD	Min	Max
Age	50.0	48.3	9.35	29.4	81.0
CGG rep	89.2	84	22.61	57	199
Education years	15.1	13	3.21	8	22

Abbreviations: CGG, cytosine, guanine, guanine repeats; FXAND, fragile X-associated neuropsychiatric disorders; FXPAC diagnosis: Fragile X premutation-associated conditions diagnosed prior of the study; FXPOI, fragile X-associated primary ovarian insufficiency; FXTAS, fragile X-associated tremor/ataxia syndrome; Max, maximum; Med, median; Min, minimum; SD, standard deviation.

questionnaire consists of 23 items across four core dimensions: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and Work/School Functioning (5 items). Respondents rate how much of a problem each item has been over the past month on a 5-point Likert scale (0=Never a problem to 4=Almost always a problem), which are then reverse-scored and transformed to a 0–100 scale, with higher scores indicating better functioning or quality of life. The PedsQL has demonstrated strong psychometric properties, including high internal consistency and validity across diverse populations and health conditions.

**2.2.1.5 | Parenting Stress Index Short Form—Third Edition.** To further investigate the psychological well-being of mothers of children with FXS, this subgroup was administered the Parenting Stress Index Short Form (PSI-SF). This questionnaire is a widely used screening instrument designed for parents of children aged 1 month to 12 years (Abidin 1990; Guarino et al. 2008). It is particularly effective in assessing the intensity of parenting stress across three core domains: child-related characteristics, parent-related characteristics, and contextual or demographic stressors. The short form includes 36 items grouped into three subscales: Parental Distress (PD), Parent–Child Dysfunctional Interaction (PCDI), and Difficult Child (DC), along with a Total Stress (TS) score. Items are rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), with raw scores converted into standardized *T*-scores. Higher scores reflect greater levels of perceived parenting stress, and scores at or above the 90th percentile are considered clinically significant. The PSI-SF also includes a Defensive Responding (DR) index, calculated from a subset of items. A DR score of 24 or lower may indicate a tendency to minimize or distort responses, potentially due to social desirability or feelings of guilt. For children older than 12 years, the highest available age range was applied.

## 2.2.2 | Online Cognitive Screening

**2.2.2.1 | Raven's Standard Progressive Matrices.** Intelligence Quotient (IQ) was assessed using the Raven's Standard Progressive Matrices (RSPM), which consists of five sets (A–E), each containing 12 items, for a total of 60. Each item presents a geometric analogy problem with one missing piece in a matrix of shapes; participants are required to choose the correct completion from eight options. Set A begins with relatively simple items, with difficulty progressively increasing across subsequent sets. All sets and items were administered in a fixed order for all participants.

Raw scores were converted into percentile ranks to evaluate individual performance relative to normative data. Percentile scores were then classified into six categories following the Wechsler classification system: intellectually superior ( $\geq 95$ th percentile), above average (75th–94th percentile), average (25th–74th percentile), below average (6th–24th percentile), and intellectually impaired ( $\leq 5$ th percentile) (Raven 2008). The RSPM has consistently demonstrated high internal consistency, with Cronbach's alpha typically reported between 0.80 and 0.90 in adult samples (Raven 2008). Among available cognitive measures, we

selected the RSPM due to its ease of online administration and its independence from prior educational experience or culturally acquired knowledge, thereby ensuring comparability and interpretability across individuals. Finally, as normative data for the RSPM is available only up to age 60 and given the small number of participants exceeding this age in our sample, scores for older individuals were adjusted using the highest available age bracket provided by the test norms.

**2.2.2.2 | Telephone Montreal Cognitive Assessment.** The Telephone Montreal Cognitive Assessment (T-MoCA) is a cognitive screening tool designed as a telephone-administered analog of the standard Montreal Cognitive Assessment (MoCA-30) (Nasreddine et al. 2005). The MoCA-30 evaluates a broad range of cognitive domains, including memory, executive functioning, attention, concentration, language, abstract reasoning, visuospatial abilities, and orientation. A score of 26 or higher is generally considered within the normal range. It has strong internal consistency, with a Cronbach's  $\alpha$  of 0.83 (Nasreddine et al. 2005). Owing to its high sensitivity to mild cognitive changes, the MoCA-30 is widely utilized in both clinical and research contexts. It is also particularly useful in detecting cognitive impairments associated with Parkinsonism, making it relevant for use in the fragile X field where similar impairments can occur in FXTAS (Niu et al. 2014; Santos et al. 2023). The T-MoCA omits items requiring visual stimuli or drawing (see Table S1), allowing for effective remote administration. The T-MoCA has demonstrated acceptable internal consistency, with Cronbach's  $\alpha$  typically ranging from 0.70 to 0.80, depending on the population studied (Katz et al. 2021; Wang et al. 2023). The cut-off score for the T-MoCA is usually set at 18 points (Katz et al. 2021). For compatibility with in-person assessments, T-MoCA scores can be converted to MoCA-30 equivalents using the equipercentile method developed by Katz et al. (2021), who also provide normative data for this conversion. In our analyses, we utilized both the T-MoCA scores and the converted MoCA-30 (hereinafter referred to as MoCA).

## 2.2.3 | Online Clinical Assessment

**2.2.3.1 | Structured Clinical Interview for DSM-5 Disorders.** The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured diagnostic interview designed to systematically assess and diagnose mental disorders according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (First et al. 2015). It is considered a gold standard tool for clinical diagnosis and research purposes due to its reliability, comprehensiveness, and alignment with DSM-5 diagnostic criteria. The administration of the SCID-5 typically requires between 45 and 90 min, depending on the complexity of the individual's clinical presentation. The interview includes modules for the assessment of a broad range of psychiatric conditions, such as psychotic spectrum disorders, mood disorders (including major depressive disorder and bipolar disorder), substance use disorders, anxiety disorders, obsessive–compulsive and related disorders, post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), adjustment disorders, and other specified or unspecified mental disorders. In this study, the SCID-5 was administered to all participants

by the same CBT therapist, who had specific training and clinical experience in conducting structured diagnostic interviews. To ensure consistency and diagnostic reliability across cases, particularly in situations where symptom presentation was ambiguous or comorbidities were suspected, the therapist was used to consult with an external senior clinician. This external consultant, not involved in the study, was a licensed CBT therapist with extensive expertise in adult psychiatric assessment and SCID-5 administration. Such consultations were used as a quality assurance measure to support diagnostic accuracy, reduce subjectivity, and promote methodological rigor in the evaluation process. Each SCID-5 administration was conducted during one single session and was followed by psychoeducational feedback, ensuring both diagnostic clarity and therapeutic engagement within the same structured session (see Section 2.3).

**2.2.3.2 | Clinical History, Health Problems and Treatment Needs.** After the psychodiagnostic evaluation, participants were asked a series of open-ended questions to explore their clinical history, current health conditions, treatment needs, and perspectives related to the PM. The following questions were administered:

1. How did you receive the diagnosis of the PM?
2. Did you have any problems during childhood?
3. Do you have any FXPAC? Are you currently experiencing any other medical problems?
4. Are you currently receiving any medical or psychotherapeutic treatment?
5. In your opinion, what actions should the State or public health authorities take to support individuals with the PM?
6. Would you support the implementation of preneonatal screening for FXS?

These qualitative responses were collected to gain a deeper understanding of participants' medical context, perceived needs, and attitudes toward public health initiatives related to fragile X-associated conditions.

## 2.3 | Procedure

Following enrolment in the study, participants received a secure Google Forms link containing the e-consent, socio-demographic questions, and a battery of standardized self-report questionnaires (listed in Section 2.2.1). Completion of this form was mandatory to proceed to the next phases of the protocol. In the second phase, participants underwent the first structured online assessment: a cognitive screening conducted via Zoom by one of two trained psychologists. This was followed by a psychodiagnostic interview through the SCID-5 and a psychoeducational session, both conducted in the same Zoom meeting and led by a licensed CBT therapist with expertise in the field of FXS and PM. To preserve objectivity and foster therapeutic engagement, the therapist remained blind to the participant's self-report questionnaires and cognitive test results until after the clinical interview. The participant's

clinical report was then reviewed collaboratively during the session. This specific session, termed the Psychoeducational Assessment (PA), constituted the central element of a broader, tailored protocol known as FRAX-TA (Fragile X Therapeutic Assessment), specifically designed for women with the PM. The PA integrated principles of therapeutic assessment with a Single-Session Cognitive Behavioral Therapy (SS-CBT) intervention and aimed to collect structured data, while offering therapeutic support and psychoeducation about FXPAC (Montanaro et al. Forthcoming under review).

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## 3 | Data Analysis

All statistical analyses were performed using JAMOVI software (version 2.3.26.0). Descriptive statistics were used to summarize sample characteristics across age-groups. Prior to conducting the main analyses, Chi-square tests ( $\chi^2$ ) and nonparametric one-way ANOVAs (Kruskal–Wallis tests) were used to assess group comparability on key demographic and clinical variables, including age, CGG repeat size, education, marital status, maternal status, and income.

Given the small sample sizes across age categories, group differences in self-report measures were analyzed using the Kruskal–Wallis test. Where appropriate, significant omnibus results were followed by pairwise comparisons using the Dwass–Steel–Critchlow–Fligner procedure. Effect sizes were estimated using epsilon squared ( $\epsilon^2$ ), with thresholds of  $\epsilon^2 \leq 0.06$  indicating a small effect, 0.06–0.14 a medium effect, and  $\epsilon^2 \geq 0.14$  a large effect. Pearson's correlation coefficients were computed to explore associations between CGG repeat size, years of education, and psychological outcomes.  $\chi^2$  tests were also used to evaluate differences across diagnostic groups. A significance threshold of  $p < 0.05$  was applied to all inferential analyses. To account for multiple comparisons, correction for multiple testing was applied within families of conceptually related outcome measures. Specifically, Bonferroni correction was used when multiple variables within the same domain (e.g., executive functioning, psychological symptoms, quality of life) were examined simultaneously, consistent with recommendations to control for multiple comparisons within families of conceptually related hypotheses rather than across unrelated tests (Bender and Lange 2001). Given the exploratory nature of the study and the relatively small sample sizes, results that did not survive domain-specific correction are reported as exploratory and interpreted with caution.

For the analysis of open-ended responses, a thematic coding approach was employed. Responses were open-coded to identify recurring themes, and a representative keyword was assigned to each theme. The frequency of each theme was then calculated to capture the relative distribution of participant perspectives and preferences.

## 4 | Results

Descriptive statistics for RSPM, T-MoCA, BRIEF-A, SCL-90, and PedsQL measures are reported in Table S1. Prior to conducting the main analyses,  $\chi^2$  tests and nonparametric

**TABLE 2** | Kruskal–Wallis results summary.

Measure	$\chi^2$	df	<i>p</i>	Bonferroni-adjusted $\alpha$	Survives correction	$\varepsilon^2$	Significant pairwise comparisons
RSPM PC	17.01	3	<0.001	0.05	Yes	0.17	41–50 vs. $\geq 65$ ( $p=0.003$ )
T-MoCA	10.51	3	0.015	0.05	Yes	0.11	41–50 vs. $\geq 65$ ( $p=0.012$ ); 51–64 vs. $\geq 65$ ( $p=0.033$ )
BRIEF-A TMON	9.19	3	0.027	0.017 <sup>a</sup>	No	0.09	51–64 vs. $\geq 65$ ( $p=0.023$ )
SCL-90-R somatization	9.50	3	0.023	0.006 <sup>b</sup>	No	0.10	51–64 vs. $\geq 65$ ( $p=0.021$ )
PedsQL activity	11.82	3	0.008	0.0125 <sup>c</sup>	Yes	0.12	41–50 vs. $\geq 65$ ( $p=0.008$ )

Note:  $\varepsilon^2$  = effect size. Bonferroni correction was applied within families of conceptually related measures.

Abbreviations: PC, percentile; RSPM, Raven's Standard Progressive Matrices; TMON, task monitoring.

<sup>a</sup>BRIEF-A correction based on three executive indices ( $\alpha=0.05/3$ ).

<sup>b</sup>SCL-90-R correction based on nine symptom dimensions ( $\alpha=0.05/9$ ).

<sup>c</sup>PedsQL correction based on four subscales ( $\alpha=0.05/4$ ). Pairwise comparisons were conducted using the Dwass–Steel–Critchlow–Fligner procedure.

one-way ANOVAs confirmed that the age-groups did not differ significantly on key sociodemographic or clinical variables, including CGG repeat size, years of education, marital status, maternal status, and income (all  $p > 0.05$ ). Kruskal–Wallis tests revealed age-related differences across several domains (see Tables 2 and S2). When needed, correction for multiple comparisons was applied within families of conceptually related measures.

#### 4.1 | Cognitive Functioning

Within the cognitive domain, which included a single outcome per instrument, statistically robust age-related group effects were confirmed for both RSPM percentile scores ( $\chi^2=17.01$ ,  $p < 0.001$ ,  $\varepsilon^2=0.17$ ) and T-MoCA scores ( $\chi^2=10.51$ ,  $p=0.015$ ,  $\varepsilon^2=0.11$ ), indicating poorer cognitive performance in the  $\geq 65$  group. Post hoc analyses showed that the oldest group scored significantly lower than younger age-groups on both measures.

#### 4.2 | Self-Report Psychological Measures

A nominal age-related effect was observed for the BRIEF-A Task Monitoring subscale; however, this association did not survive domain-specific correction for multiple comparisons. Similarly, for the SCL-90-R, the only nominal age-group difference emerged for Somatization, which did not withstand correction and should therefore be interpreted cautiously. For quality of life, Bonferroni correction was applied across the four PedsQL subscales. After correction, only the Activity subscale showed a significant age-related group effect ( $\chi^2=11.82$ ,  $p=0.008$ ,  $\varepsilon^2=0.12$ ), with the  $\geq 65$  group reporting greater impairment than younger groups. Other PedsQL subscales, including Work/Study, showed nominal effects that did not survive correction.

#### 4.3 | DSM-5 CCSM

CCSM results are presented separately, as this instrument provides symptom-level prevalence estimates based on

categorical severity thresholds rather than continuous scores suitable for inferential group comparisons. Overall, most participants scored in the nonclinical range across DSM-5 symptom domains; however, a substantial proportion reported symptoms at levels warranting further clinical consideration. Specifically, scores of 3 or 4 were considered clinically significant, while scores of 2 reflected symptoms that may require additional clinical attention. The most frequently reported clinical symptoms (scores 3–4) were anxiety (22%), memory problems (16%), somatic symptoms (16%), sleep disturbances (16%), mania (17%), depression (15%), and anger (12%). When including individuals who scored 2, these proportions increased substantially: anxiety affected 44% of participants (22% clinical; 22% additional attention), depression 41% (15% clinical; 26% additional attention), memory problems 39% (16% clinical; 23% additional attention), and sleep disturbances 34% (16% clinical; 18% additional attention). Anger affected 34% in total, with 12% in the clinical range and 22% requiring further attention. Other domains such as substance use (12% clinical; 19% moderate) and somatic symptoms (16% clinical; 19% moderate) also showed proportions of individuals possibly needing support.

Chi-square analyses indicated nominal age-group differences in memory problems ( $\chi^2=25.0$ ,  $p=0.012$ ) and repetitive behaviors ( $\chi^2=18.2$ ,  $p=0.004$ ), both more frequently endorsed in the  $\geq 65$  group. However, these associations did not survive correction for multiple comparisons across CCSM domains and should therefore be interpreted as exploratory (see Table 3).

#### 4.4 | Structured Clinical Interview for DSM-5 Disorders

##### 4.4.1 | Current Disorders

Of the 100 participants, 99 completed the SCID-5 interview. One participant was noncompliant during the assessment, and her data were excluded from the analysis. Overall, most participants did not meet diagnostic criteria for current psychiatric disorders, with the majority scoring 0 across domains. However, subclinical traits (score = 1) and full diagnoses (score = 2) were observed across a range of disorders. The most prevalent current

**TABLE 3** | DSM-5 symptoms by severity and age-group differences.

CCSM domain	% Score = 2 (moderate)	% Score = 3–4 (clinical)	Total % (≥ 2)	Nominal age-group differences (uncorrected)
Anxiety	22	22	44	No
Depression	26	15	41	No
Mania	22	17	39	No
Memory problems	23	16	39	Yes ( $\chi^2 = 25.0, p = 0.012$ )
Somatic Symptoms	19	16	35	No
Sleep disturbances	18	16	34	No
Anger	22	12	34	No
Substance use	19	12	31	No
Dissociation	10	6	16	No
Personality functioning	10	6	16	No
Repetitive behaviors	23	3	26	Yes ( $\chi^2 = 18.2, p = 0.004$ )
Psychosis	9	5	14	No
Suicidal ideation	7	5	12	No

Note: Age-group differences were tested using  $\chi^2$  analyses. After Bonferroni correction for multiple comparisons across CCSM domains, no age-related differences remained statistically significant.

disorder was Generalized Anxiety Disorder (GAD), with 37.4% of participants meeting full diagnostic criteria (score = 2) and an additional 20.2% reporting subclinical traits. Similarly, Major Depressive Disorder (MDD) was diagnosed in 18.2%, and Panic Disorder in 18.2% of the sample, with additional proportions scoring 1 (12.1% and 14.1%, respectively). Other notable current disorders included Social Anxiety Disorder (SAD, 14.3% with score = 2; 27.6% with score = 1) and Current Depressive Episode (13.1% disorder; 14.1% trait). Less commonly endorsed current diagnoses included Agoraphobia (7.1% disorder), Bipolar Disorder II (2.0%), and Substance Use Disorders (Alcohol or Drugs: 1.0% each).

Overall, 51% of participants met criteria for at least one current SCID-5 diagnosis at the time of the interview. Chi-square analyses did not reveal age-group differences. Table S4 shows scores for all measures.

#### 4.4.2 | Lifetime Disorders

Lifetime psychiatric conditions were more frequently endorsed. Past GAD was reported by 41.4% of participants (score = 2) and 14.1% had subclinical symptoms (score = 1). Past Panic Disorder also showed high endorsement (29.3% disorder; 8.1% trait), along with SAD (23.2% disorder; 25.3% trait). Other notable past diagnoses included Past MDD (24.2% disorder; 11.1% trait), Past OCD (2.0% disorder; 28.3% trait), and Past Phobia (17.2% disorder; 5.1% trait). Eating disorders such as Past Anorexia (7.1%) and Past Bulimia (3.0%) were also reported, though less frequently.

Overall, 61% of participants met criteria for at least one lifetime SCID-5 diagnosis at the time of the interview. Chi-square

analyses did not depict age-group differences. See Table S4 for all measures.

## 4.5 | Correlation Between Measures

Pearson correlation analyses were conducted in the full sample to examine associations among demographic and cognitive variables. No significant correlations were observed between CGG repeat length and any cognitive or psychological measures (all  $p > 0.05$ ). Age was negatively correlated with years of education ( $r = -0.200, p = 0.046$ ) and RSPM percentile scores ( $r = -0.314, p = 0.001$ ), indicating lower educational attainment and reduced fluid reasoning with increasing age. Years of education were positively associated with RSPM percentile scores ( $r = 0.426, p < 0.001$ ) and T-MoCA scores ( $r = 0.216, p = 0.031$ ), suggesting a general association between educational attainment and cognitive performance. Additionally, to assess whether these associations might be influenced by caregiving-related factors, both correlational and age-group analyses were repeated after excluding mothers of children with FXS. Results from these sensitivity analyses showed a comparable pattern of associations; detailed results are reported in Tables S5–S7.

### 4.5.1 | Correlational Analysis of Parenting Stress, Executive Function, Psychological Symptoms and Quality of Life in Mothers of Children With FXS

To further investigate the psychological well-being of mothers of children with FXS ( $n = 74$ ), and to characterize the associations between caregiving-related stress and psychological functioning within this specific subgroup, Pearson correlation analyses were

conducted to examine relationships among parenting stress (PSI subscales), executive functioning (BRIEF-A domains), psychological symptomatology (SCL-90-R subscales), and quality of life (PedsQL).

Strong and consistent positive correlations emerged between PSI scores and BRIEF-A domains (all  $p < 0.005$ ), indicating that higher levels of parenting stress were associated with greater self-reported executive difficulties. For example, PSI Total Stress was significantly correlated with all BRIEF-A domains, including Inhibit ( $r = 0.418$ ), Shift ( $r = 0.474$ ), WM ( $r = 0.444$ ), and the GEC ( $r = 0.557$ ). See Table S8 for all measures.

PSI subscales were also significantly positively correlated with nearly all SCL-90-R dimensions (all  $p < 0.001$ ; see Table S9 for full results). Specifically, PSI Total showed correlations with the GSI ( $r = 0.526$ ), as well as with depression ( $r = 0.503$ ), anxiety ( $r = 0.444$ ), and somatization ( $r = 0.456$ ). Moderate associations were also found with OC symptoms ( $r = 0.500$ ), Hostility ( $r = 0.403$ ), and interpersonal sensitivity ( $r = 0.423$ ). In addition, PSI scores were correlated with the SCL-90-R PS ( $r = 0.555$ ) and PSDI ( $r = 0.398$ ), suggesting that elevated parenting stress is associated with both the breadth and perceived intensity of psychological symptoms.

Finally, inverse correlations were observed between parenting stress and QoL outcomes (see Table S10). The strongest association was found between PSI Total Stress and the PedsQL Total Index ( $r = -0.564$ ), followed by the Work/Study subscale ( $r = -0.456$ ) and the Emotional Functioning subscale ( $r = -0.560$ ). Notably, PedsQL Emotional Functioning was inversely correlated with multiple PSI domains, including PSI Total ( $r = -0.560$ ) and PSI-Difficult Child ( $r = -0.350$ ).

## 4.6 | Clinical History, Health Problems, and Treatment Needs

For the following open-ended questions, responses were coded for recurring themes and clustered into meaningful categories to capture shared challenges and priorities among participants.

### 4.6.1 | Childhood Issues

Retrospective self-reports of childhood experiences were used to characterize early developmental and emotional difficulties and should be interpreted with caution given the potential for recall bias. From the interviews, it emerged that a notable proportion of participants endorsed developmental and emotional difficulties during infancy. Specifically, learning disorders were relatively frequent with 17.3% reporting symptoms suggestive of dyslexia, 14.3% of dyscalculia, and 15.3% of other learning disabilities. Attention-related concerns were also common, with 23.5% reporting symptoms consistent with ADHD. Emotional and behavioral difficulties emerged as another key area: 16.3% of participants had experienced clinically relevant anxiety, while 11.2% reported significant shyness and 7.1% depressive symptoms during childhood. Additionally, 8.2% endorsed a history of language delay, and 9.2% reported motor coordination difficulties. These findings suggest that a non-negligible portion

of the sample experienced neurodevelopmental and emotional challenges early in life.

### 4.6.2 | FXPAC Conditions

In adulthood, different medical and psychological conditions were reported by participants. Based on open-ended responses, conditions were clustered thematically. Thyroid dysfunction, particularly autoimmune thyroiditis (e.g., Hashimoto's thyroiditis), emerged as one of the most reported conditions, endorsed by approximately 18% of participants. A cluster including chronic fatigue, fibromyalgia, and autoimmune disorders (e.g., lupus, rheumatoid arthritis) was reported by 10% of the participants. Additionally, neuropathic pain symptoms were mentioned by 8%, while gastrointestinal disturbances, including irritable bowel syndrome, were reported by 7%. Migraine or frequent headaches were endorsed by 6% of participants. Table 4 depict the new diagnostic classification after the psychodiagnostics interview.

### 4.6.3 | Medication and Psychotherapy

Participants were asked whether they had ever received psychopharmacological or psychotherapeutic treatment for psychological difficulties, either currently or in the past. At the time of the interview, 16 participants were undergoing pharmacological treatment, while an additional 28% reported having received such treatment in the past. In contrast, 20 participants were currently engaged in psychotherapy, and 50% of the entire sample reported having participated in psychotherapy at least once in the past.

### 4.6.4 | Public Health Support and Prenatal Screening

Participants expressed a range of public health needs to improve care and support for individuals with the PM. Specifically, 34% of respondents emphasized the need for greater access to accurate information about FXS and PM, as well as more specialized and knowledgeable healthcare professionals. Routine gynecological care was a priority for

**TABLE 4** | New diagnostic classification after clinical assessment.

Condition	Frequency
FXAND	32
FXAND/FXTAS	1
FXPOI	19
FXPOI/FXAND	19
FXPOI/FXAND/FXTAS	3
FXTAS	4
NONE	22

Abbreviations: FXAND, fragile X-associated neuropsychiatric disorders; FXPAC diagnosis, fragile X premutation-associated conditions diagnosed after the psychodiagnostics interview; FXPOI, fragile X-associated primary ovarian insufficiency; FXTAS, fragile X-associated tremor/ataxia syndrome.

60% of the sample, while 45 participants advocated for regular neurological and neuropsychological evaluations (e.g., every 2 years). Additionally, 35% of women indicated a need for free access to psychological therapy. Notably, a vast majority (94%) supported the implementation of prenatal screening for FXS, underscoring the broad consensus on the value of early detection and its role in enabling informed reproductive decision-making.

## 5 | Discussion

To the best of knowledge, this study provides the first comprehensive characterization of cognitive, psychological, and clinical features in Italian women with the PM. By integrating clinician-administered diagnostic interviews with standardized cognitive and self-report measures, this work extends the growing international FXAND literature and yields three main findings: (1) age-related cognitive vulnerability emerging primarily in later adulthood; (2) a high prevalence of anxiety and mood-related psychopathology identified through structured clinical assessment despite largely subclinical self-report scores; and (3) substantial under-recognition of premutation-associated conditions (FXPAC) within the Italian healthcare context. Together, these findings support evidence that women with the PM experience heightened vulnerability across multiple mental health domains and may benefit from tailored clinical monitoring and intervention (Flavell et al. 2023; Tassone et al. 2023).

From a neuropsychological perspective, the most salient cognitive finding was an age-related decline in performance that emerged predominantly in the oldest subgroup ( $\geq 65$  years). Older women showed significantly lower scores on both the RSPM and the T-MoCA, with mean performance falling within the clinical range, suggesting increased vulnerability in fluid reasoning and global cognitive functioning in later adulthood. This pattern is broadly consistent with prior studies reporting subtle but measurable cognitive differences in female PCs, particularly affecting nonverbal and executive domains, while verbal abilities tend to remain relatively preserved (Schneider et al. 2020; Grigsby et al. 2014). Importantly, the interpretation of age effects must be considered in light of cohort-related differences in educational attainment. In the present sample, older participants had also fewer years of formal education, and educational attainment was positively associated with cognitive performance, particularly on the RSPM. These findings align with the concept of cognitive reserve (Stern 2009) and suggest that education may partially buffer age-related cognitive vulnerability in PCs. In contrast, caregiving status did not account for cognitive differences: age-related patterns remained comparable after excluding mothers of children with FXS, indicating that the observed decline is unlikely to be driven solely by caregiving demands. No significant associations were observed between CGG repeat length and cognitive outcomes. Although this diverges from some reports linking CGG expansion within the PM range to subtle executive deficits (Tassone et al. 2023), the absence of activation ratio (AR) data in the present study may have limited the detection of gene-brain-behavior relationships. These findings should therefore be interpreted cautiously and warrant further investigation in studies integrating molecular markers.

Despite objective evidence of age-related cognitive differences, self-reported executive functioning (BRIEF-A) was largely within normative ranges, with only nominal age-related effects that did not survive correction for multiple comparisons. This discrepancy between objective cognitive performance and subjective executive complaints is noteworthy and suggests that self-report measures alone may underestimate functional difficulties in this population (Montanaro et al. 2025). In contrast, among mothers of children with FXS, perceived executive difficulties were robustly associated with parenting stress, indicating that chronic caregiving demands may amplify subjective cognitive complaints even in the absence of measurable cognitive impairment. Similar patterns have been reported in parents of children with neurodevelopmental disabilities, where sustained stress contributes to attentional fatigue and reduced perceived executive control (Lovell et al. 2014; Maltman et al. 2023).

Consistent with the BRIEF-A findings, self-reported psychological symptoms on the SCL-90-R were generally within the non-clinical range, although older women showed nominally higher scores in somatization and obsessive-compulsive symptoms. While these effects did not survive correction and should be interpreted with caution, they are consistent with prior reports suggesting that female PCs may experience subclinical but clinically meaningful emotional distress (Loesch et al. 2015; Gossett et al. 2016). For instance, elevated somatic symptom reporting in older women may reflect a combination of increased physical health burden, heightened attentional focus on bodily sensations, or early, nonspecific manifestations of FXTAS-related neuropathology (Polo-Morales et al. 2021), although these interpretations remain exploratory.

Further analyses in the subgroup of mothers of children with FXS revealed significant positive correlations between PSI and SCL-90-R. Notably, these correlations included not only traditional clinical domains such as anxiety and depression but also the PSDI, which reflects the average intensity of psychological symptoms. This finding could suggest that mothers reporting higher levels of parenting stress not only endorse a greater number of psychological symptoms but also perceive these symptoms as particularly distressing. Although the present study did not directly assess challenging behaviors in children, our findings are consistent with previous research indicating that maternal mental health is a significant predictor of parental stress and is frequently associated with increased behavioral difficulties in children with FXS (Roberts et al. 2016; Bangert et al. 2021).

Parenting stress emerged as a central factor shaping psychological well-being among mothers of children with FXS. PSI scores were clinically elevated across subdomains, particularly in younger mothers, and were strongly associated with executive difficulties, psychological distress, and reduced quality of life. These findings replicate and extend prior evidence of heightened stress among caregivers of individuals with FXS (Abbeduto et al. 2004; Bullard et al. 2021; Potter et al. 2022) and underscore the need for early identification and targeted support, particularly given the heightened stress reactivity reported in PCs (Tassone et al. 2023).

A key contribution of this study is the discrepancy observed between self-report screening instruments and

clinician-administered psychodiagnostic interviews. While SCL-90-R scores were, on average, within the nonclinical range, the DSM-5-TR-based CCSM revealed substantial symptom endorsement across multiple domains, particularly anxiety, depression, memory difficulties, sleep disturbances, and somatic complaints. This divergence suggests the presence of a broad neuropsychiatric vulnerability that may not be adequately captured by self-report measures alone. At the same time, reliance on the CCSM in isolation would also limit the ability to disentangle whether the reported symptoms primarily reflect psychopathology, emerging cognitive decline, or adaptive coping responses. In fact, although the CCSM has demonstrated good sensitivity for detecting anxiety, depressive, and substance-related symptoms (Mikhalyuk et al. 2024), it cannot substitute for structured diagnostic interviews in complex clinical populations such as female PCs, where distress, stigma, and potential cognitive changes may reduce insight and compromise self-report validity (Montanaro et al. 2025). Accordingly, the use of the SCID-5 was essential to achieve accurate diagnostic characterization in this cohort.

The SCID-5 diagnoses were consistent with the symptomatology captured by the CCSM, underscoring the critical role of using well-matched screening instruments, especially in research settings focused on assessing the frequency of psychological and behavioral issues. In accordance with previous studies (Lachiewicz et al. 2010; Grigsby et al. 2014; Klusek et al. 2018, 2025; Hocking et al. 2021; Maltman et al. 2021; Tassone et al. 2023), our findings showed that anxiety and depressive disorders were the most frequently diagnosed current psychiatric conditions among women with the PM. Over one-third of participants met criteria for current GAD, and lifetime prevalence exceeded 50%, which is substantially higher than estimates in the general Italian population (ISTAT 2017). SAD was also common, with both full-syndrome and trait-level presentations. Depressive disorders were frequent, although the prevalence of current MDD was lower than in other studies, such as Kenna et al. (2013) and Schneider et al. (2020), which found the disorder to be present in approximately half of their participants. A possible explanation for the lower prevalence observed in our study may be that we did not identify the significant impairment in personal, social, or occupational functioning among most participants, an essential criterion for a formal diagnosis. Additionally, in many cases, the reported symptomatology appeared more consistent with features of an adjustment disorder rather than a full-syndrome mood disorder (Geer 2023). This may suggest that, while emotional distress was present, in our sample it may have been context-dependent, potentially related to situational stressors rather than indicative of a chronic depressive condition. Such distinctions are clinically relevant, particularly when considering the differential diagnosis between MDD and Adjustment Disorder in populations exposed to sustained caregiving stress or life changes associated with the PM phenotype. It is important to note that this interpretation does not imply that the psychological difficulties observed are solely attributable to parenting stress. Rather, the combination of genetic vulnerability associated with the PM and the demands of raising a child with FXS may reduce resilience and increase susceptibility to adjustment-related disorders. While these presentations may not meet full criteria for MDD, they are by no

means less clinically significant and warrant appropriate recognition and support.

Alongside psychiatric and cognitive findings, this study highlights substantial under-recognition of FXPAC within the Italian healthcare context. Although Italy operates under a universal public healthcare system, results suggest that access to services does not necessarily ensure accurate recognition or coordinated management of PM-associated conditions. Many participants described fragmented care and limited communication among gynecological, neurological, and mental health services. Medical conditions commonly linked to the PM, including thyroid dysfunction, fibromyalgia, migraine, chronic fatigue, and neuropathic symptoms, were frequently identified during structured clinical interviews but were not spontaneously conceptualized as part of a broader PM-associated profile. Additional cases of FXPOI and FXTAS were identified during clinical assessment beyond those self-reported at enrollment, often in women who had not received comprehensive counseling regarding the spectrum of FXPAC. Together, these findings suggest that awareness of PM-associated conditions within the Italian National Health Service may remain variable and that greater integration among genetic counseling, primary care, neurology, gynecology, and mental health services may facilitate earlier recognition and more coordinated management of FXPAC.

Importantly, under-recognition was not limited to healthcare providers. A substantial proportion of participants were themselves unaware of the range of conditions encompassed within the FXPAC umbrella diagnosis. At enrollment, 63% reported no PM-associated condition, and only three women identified themselves as having FXAND. However, structured assessment revealed a markedly higher prevalence of psychiatric and medical manifestations consistent with FXAND, FXPOI, or FXTAS. This discrepancy, consistent with recent national survey data from Italian PCs (Montanaro et al. 2024) suggests that limited psychoeducation may contribute to normalization of symptoms, delayed help-seeking, or misattribution of PM-related difficulties to unrelated causes. These findings underscore the importance of providing clear and comprehensive information at the time of genetic diagnosis, along with periodic clinical reevaluation across the lifespan.

Taken together, these findings reinforce the multidimensional nature of FXAND in women and highlight the value of integrating self-report tools with clinician-administered assessment. In this regard, it is important to note that the diagnostic interview and discussion of sensitive personal information occurred within a single psychoeducational assessment session delivered under the FRAX-TA protocol. FRAX-TA integrates diagnostic evaluation with a brief SS-CBT-informed intervention (Montanaro et al. under review), which may have facilitated participants' willingness to self-disclose and enhanced the ecological validity of the clinical information collected.

Finally, the strong similarity between this Italian cohort and previously studied international samples supports the view that the psychiatric and cognitive manifestations of the PM are largely shaped by underlying genetic mechanisms (Tassone et al. 2023), while healthcare organization and sociocultural context may influence the timing of recognition, diagnostic labeling, and

access to care. In this perspective, the development of internationally consensus-based assessment protocols employing comparable diagnostic interviews and cognitive measures would be highly valuable. The use of standardized tools across countries would facilitate more precise cross-national comparisons, reduce methodological heterogeneity, and further clarify the relative contribution of biological and contextual factors in shaping the PM phenotype.

While these findings contribute to the emerging literature on cognitive, psychological, and neurodevelopmental difficulties among Italian women with the PM, several limitations should be acknowledged. First, the sample consisted exclusively of women who either self-referred or were recruited through the Italian Association of FXS, which may have resulted in a sample biased toward individuals with more pronounced symptoms or greater engagement with the condition. However, it is important to note that the participants were not limited to mothers of individuals with FXS and included women from all regions of Italy and from a range of socioeconomic backgrounds, enhancing the diversity and representativeness of the sample in terms of geography and social context. Second, although the use of a semi-structured clinical interview provided rich qualitative and diagnostic data, the cross-sectional design and absence of a control group limit the ability to draw causal inferences or directly compare outcomes with women without the PM or with different caregiving experiences. However, given the exploratory nature of the study, the primary objective was not to establish causality or make between-group comparisons, but rather to characterize the cognitive and psychological features potentially associated with the PM. Third, qualitative data derived from open-ended questions regarding infancy and early-life experiences should be interpreted with caution, as retrospective self-reports may be subject to recall bias. These data were therefore included for descriptive and contextual purposes and were not used to support inferential conclusions.

Further, our ability to detect potential correlations between CGG repeat length and psychological or cognitive features, as reported in previous studies, was limited as measures of the AR were not available.

Despite these limitations, this study offers important strengths. First, it is among the few investigations to focus specifically on Italian women with the PM, addressing a significant gap in the international FXAND literature. Second, the use of standardized, clinician-administered diagnostic measures, including semi-structured interviews and validated psychological scales, enabled a more reliable and comprehensive assessment across cognitive, emotional, and neurodevelopmental domains compared to studies relying solely on self-report. Finally, the integration of psychoeducational feedback within the FRAX-TA framework may have enhanced ecological validity and participant engagement.

## 6 | Conclusions

This study provides evidence of a high prevalence of cognitive and psychological difficulties among women with the PM, consistent with the FXAND profile. Findings indicate substantial

vulnerability across mental-health domains, most notably anxiety, depressive symptoms and attentional/executive difficulties, alongside frequent medical comorbidities. Together, these results corroborate and extend international evidence, underscoring the complexity of the female PM phenotype and its relevance across the lifespan. We also identified gaps in awareness among both participants and healthcare professionals, pointing to a need for targeted education and clearer communication about the broader manifestations of FXPAC. Clinically, our data support integrated, PM-focused care pathways, including routine psychiatric assessment, systematic screening for common medical comorbidities, and timely access to psychological support.

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### Author Contributions

Conceptualization: Federica Alice Maria Montanaro and Andrea Bosco. Formal analysis: Federica Alice Maria Montanaro, Giuseppina Spano, and Andrea Bosco. Investigation: Federica Alice Maria Montanaro and Giuseppina Spano. Methodology: Federica Alice Maria Montanaro, Randi J. Hagerman, Flora Tassone, and Giuseppina Spano. Project administration: Andrea Bosco, Flora Tassone, and Randi J. Hagerman. Validation: Federica Alice Maria Montanaro, Andrea Bosco, Randi J. Hagerman, Flora Tassone, and Giancarlo Logroscino. Writing – original draft: Federica Alice Maria Montanaro. Writing – review and editing: Federica Alice Maria Montanaro, Giuseppina Spano, Randi J. Hagerman, Flora Tassone, Andrea Bosco, and Giancarlo Logroscino. All authors have read and agreed to the published version of the manuscript. Authorship must be limited to those who have contributed substantially to the work reported.

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### Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Department of Education, Psychology, and Communication, University of Bari “Aldo Moro” (ET-23-15).

### Consent

All participants provided written informed electronic consent.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### References

Abbeduto, L., M. M. Seltzer, P. Shattuck, M. W. Krauss, G. Orsmond, and M. M. Murphy. 2004. “Psychological Well-Being and Coping in Mothers of Youths With Autism, Down Syndrome, or Fragile X Syndrome.” *American Journal of Mental Retardation* 109, no. 3: 237–254.

- Abidin, R. R. 1990. *Parenting Stress Index-Short Form*, 118. Pediatric Psychology Press.
- Allen, E. G., K. Charen, H. S. Hipp, et al. 2020. "Clustering of Comorbid Conditions Among Women Who Carry an FMR1 Premutation." *Genetics in Medicine* 22, no. 4: 758–766.
- American Psychiatric Association. 2019. "Online Assessment Measures [WWW Document], n.d." <https://www.psychiatry.org/psychiatrists/practice/dsm/educational-resources/assessment-measures>.
- Bangert, K., C. Moser, L. Friedman, and J. Klusek. 2021. "Family as a Context for Child Development: Mothers With the FMR1 Premutation and Their Children With Fragile X Syndrome." *Seminars in Speech and Language* 42, no. 4: 277–286.
- Bender, R., and S. Lange. 2001. "Adjusting for Multiple Testing – When and How?" *Journal of Clinical Epidemiology* 54, no. 4: 343–349. [https://doi.org/10.1016/s0895-4356\(00\)00314-0](https://doi.org/10.1016/s0895-4356(00)00314-0).
- Bullard, L., D. Harvey, and L. Abbeduto. 2021. "Maternal Mental Health and Parenting Stress and Their Relationships to Characteristics of the Child With Fragile X Syndrome." *Frontiers in Psychiatry* 12: 716585. <https://doi.org/10.3389/fpsy.2021.716585>.
- Coffey, S. M., K. Cook, N. Tartaglia, et al. 2008. "Expanded Clinical Phenotype of Women With the FMR1 Premutation." *American Journal of Medical Genetics Part A* 146A, no. 8: 1009–1016. <https://doi.org/10.1002/ajmg.a.32060>.
- Cordeiro, L., F. Abucayan, R. Hagerman, F. Tassone, and D. Hessl. 2015. "Anxiety Disorders in Fragile X Premutation Carriers: Preliminary Characterization of Proband and Non-Proband." *Intractable & Rare Diseases Research* 4: 123–130. <https://doi.org/10.5582/irdr.2015.01029>.
- Derogatis, L. R., and L. Kathryn. 2000. "The SCL-90-R and Brief Symptom Inventory (BSI) in Primary Care." In *Handbook of Psychological Assessment in Primary Care Settings*, 310–347. Routledge.
- Espinell, W., K. Charen, L. Huddleston, J. Visootsak, and S. Sherman. 2016. "Improving Health Education for Women Who Carry an FMR1 Premutation." *Journal of Genetic Counseling* 25, no. 2: 228–238.
- First, M. B., J. B. Williams, R. S. Karg, and R. L. Spitzer. 2015. *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. American Psychiatric Association.
- Flavell, J., C. Franklin, and P. J. Nestor. 2023. "A Systematic Review of Fragile X-Associated Neuropsychiatric Disorders." *Journal of Neuropsychiatry and Clinical Neurosciences* 35, no. 2: 110–120.
- Geer, K. 2023. "Adjustment Disorder: Diagnosis and Treatment in Primary Care." *Primary Care* 50, no. 1: 83–88. <https://doi.org/10.1016/j.pop.2022.10.006>.
- Gioia, G. A., P. K. Isquith, S. C. Guy, and L. Kenworthy. 2000. *BRIEF: Behavior Rating Inventory of Executive Function*. Psychological Assessment Resources.
- Gossett, A., S. Sansone, A. Schneider, et al. 2016. "Psychiatric Disorders Among Women With the Fragile X Premutation Without Children Affected by Fragile X Syndrome." *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* 171, no. 8: 1139–1147.
- Grigsby, J., K. Cornish, D. Hocking, et al. 2014. "The Cognitive Neuropsychological Phenotype of Carriers of the FMR1 Premutation." *Journal of Neurodevelopmental Disorders* 6, no. 1: 28. <https://doi.org/10.1186/1866-1955-6-28>.
- Guarino, A., P. di Blasio, M. D'Alessio, E. Camisasca, and G. Sserantoni. 2008. "Parenting Stress Index SF."
- Hagerman, R. J., and P. J. Hagerman. 2020. *Fragile X Syndrome and Premutation Disorders: New Developments and Treatments*. Mac Keith Press.
- Hocking, D. R., D. Z. Loesch, P. Stimpson, F. Tassone, A. Atkinson, and E. Storey. 2021. "Delineating the Relationships Between Motor, Cognitive-Executive and Psychiatric Symptoms in Female FMR1 Premutation Carriers." *Frontiers in Psychiatry* 12: 742929. <https://doi.org/10.3389/fpsy.2021.742929>.
- ISTAT. 2017. *La Salute Mentale Nelle Varie Fasi della vita*. Istituto Nazionale di Statistica. <https://www.istat.it/it/archivio/207102>.
- Jiraanont, P., S. R. Sweha, R. R. Alolaby, et al. 2017. "Clinical and Molecular Correlates in Fragile X Premutation Females." *eNeurologicalSci* 7: 49–56.
- Johnson, K., J. Herring, and J. Richstein. 2020. "Fragile X Premutation Associated Conditions (FXPAC)." *Frontiers in Pediatrics* 8: 266.
- Katz, M. J., C. Wang, C. O. Nester, et al. 2021. "T-MoCA: A Valid Phone Screen for Cognitive Impairment in Diverse Community Samples." *Alzheimer's & Dementia (Amsterdam, Netherlands)* 13, no. 1: e12144.
- Kenna, H. A., M. Tartter, S. S. Hall, et al. 2013. "High Rates of Comorbid Depressive and Anxiety Disorders Among Women With Premutation of the FMR1 Gene." *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* 162B, no. 8: 872–878.
- Klausner, L., S. Carmi, S. Ben-Shachar, N. Lev-El Halabi, L. Basel-Salmon, and D. Brabbing-Goldstein. 2025. "No Association Between FMR1 Premutation and Either ADHD or Anxiety in 53,707 Women Undergoing Genetic Testing for Family Planning Purposes." *Genetics in Medicine* 27, no. 7: 101428.
- Klusek, J., L. Jenner, A. L. Hogan, et al. 2025. "Depression Symptom Trajectories in Mothers With the FMR1 Premutation Vary by CGG Repeat Length: A Longitudinal Study of 73 Women Spanning 20–75 Years of Age." *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* 198, no. 7: 103–119. <https://doi.org/10.1002/ajmg.b.33033>.
- Klusek, J., A. Ruber, and J. E. Roberts. 2018. "Impaired Eye Contact in the FMR1 Premutation Is Not Associated With Social Anxiety or the Broad Autism Phenotype." *Clinical Neuropsychologist* 32, no. 7: 1337–1352. <https://doi.org/10.1080/13854046.2017.1384063>.
- Lachiewicz, A., D. Dawson, G. Spiridigliozzi, M. Cuccaro, M. Lachiewicz, and A. McConkie-Rosell. 2010. "Indicators of Anxiety and Depression in Women With the Fragile X Premutation: Assessment of a Clinical Sample." *Journal of Intellectual Disability Research* 54, no. 7: 597–610. <https://doi.org/10.1111/j.1365-2788.2010.01290.x>.
- Loesch, D. Z., M. Q. Bui, E. Hammersley, et al. 2015. "Psychological Status in Female Carriers of Premutation FMR1 Allele Showing a Complex Relationship With the Size of CGG Expansion." *Clinical Genetics* 87, no. 2: 173–178. <https://doi.org/10.1111/cge.12347>.
- Lovell, B., H. Elliot, C. C. Liu, and M. A. Wetherell. 2014. "Memory Failures for Everyday Tasks in Caregivers of Children With Autism." *Research in Developmental Disabilities* 35, no. 11: 3057–3061. <https://doi.org/10.1016/j.ridd.2014.07.019>.
- Maltman, N., L. S. DaWalt, J. Hong, et al. 2023. "FMR1 CGG Repeats and Stress Influence Self-Reported Cognitive Functioning in Mothers." *American Journal on Intellectual and Developmental Disabilities* 128, no. 1: 1–20.
- Maltman, N., J. Guilfoyle, K. Nayar, et al. 2021. "The Phenotypic Profile Associated With the FMR1 Premutation in Women: An Investigation of Clinical-Behavioral, Social-Cognitive, and Executive Abilities." *Frontiers in Psychiatry* 12: 718485.
- Mikhalyuk, I., L. A. R. Stein, M. Yang, B. Lamoureux, D. Achin, and J. J. van den Berg. 2024. "Validity of the Revised Diagnostic and Statistical Manual of Mental Disorders-5 Cross-Cutting Symptom Measure as Implemented in Community Mental Health Settings." *Journal of Affective Disorders* 344: 662–673.
- Montanaro, F. A. M., P. Alfieri, C. Caciolo, et al. 2024. "Fragile X Syndrome and FMR1 Premutation: Results From a Survey on Associated

- Conditions and Treatment Priorities in Italy.” *Orphanet Journal of Rare Diseases* 19, no. 1: 264. <https://doi.org/10.1186/s13023-024-03272-0>.
- Montanaro, F. A. M., G. Spano, R. J. Hagerman, G. Logroscino, and A. Bosco. “Forthcoming. Optimizing Single-Session CBT Delivery in an 8-Session Longitudinal Therapeutic Assessment (FRAX-TA) for Women With FMR1 Premutation.” *Frontiers in Molecular Neuroscience*.
- Montanaro, F. A. M., F. Tassone, A. Schneider, et al. 2025. “Correspondence on “No Association Between FMR1 Premutation and Either ADHD or Anxiety in 53,707 Women Undergoing Genetic Testing for Family Planning Purposes” by Klausner et al.” *Genetics in Medicine* 27: 101511.
- Moser, C., L. Schmitt, J. Schmidt, A. Fairchild, and J. Klusek. 2021. “Response Inhibition Deficits in Women With the FMR1 Premutation Are Associated With Age and Fall Risk.” *Brain and Cognition* 148: 105675.
- Nasreddine, Z. S., N. A. Phillips, V. Bedirian, et al. 2005. “The Montreal Cognitive Assessment (MoCA): A Brief Screening Tool for Mild Cognitive Impairment.” *Journal of the American Geriatrics Society* 53: 695–699.
- Niu, Y. Q., J. C. Yang, D. A. Hall, et al. 2014. “Parkinsonism in Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Revisited.” *Parkinsonism & Related Disorders* 20, no. 4: 456–459.
- Polo-Morales, A., Á. Alcocer-Salas, M. Rodríguez-Violante, D. Pinto-Solis, R. Solis-Vivanco, and A. Cervantes-Arriaga. 2021. “Association Between Somatization and Nonmotor Symptoms Severity in People With Parkinson Disease.” *Journal of Geriatric Psychiatry and Neurology* 34, no. 1: 60–65.
- Potter, S. N., D. J. Harvey, A. Sterling, and L. Abbeduto. 2022. “Mental Health Challenges, Parenting Stress, and Features of the Couple Relationship in Parents of Children With Fragile X Syndrome.” *Frontiers in Psychiatry* 13: 857633.
- Raven, J. C. 2008. *SPM – Matrici Progressive Standard di Raven: Manuale di Istruzioni*. 4<sup>a</sup> edizione ed. Giunti Psychometrics.x.
- Roberts, J. E., D. B. Bailey, J. Mankowski, et al. 2009. “Mood and Anxiety Disorders in Females With the FMR1 Premutation.” *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics* 150B: 130–139.
- Roberts, J. E., B. L. Tonnsen, L. M. McCary, A. L. Ford, R. N. Golden, and D. B. Bailey Jr. 2016. “Trajectory and Predictors of Depression and Anxiety Disorders in Mothers With the FMR1 Premutation.” *Biological Psychiatry* 79, no. 10: 850–857. <https://doi.org/10.1016/j.biopsych.2015.07.015>.
- Rodriguez-Revenge, L., I. Madrigal, M. Alegret, M. Santos, and M. Milà. 2008. “Evidence of Depressive Symptoms in Fragile-X Syndrome Premutated Females.” *Psychiatric Genetics* 18, no. 4: 153–155. <https://doi.org/10.1097/YPG.0b013e3282f97e0b>.
- Santos, E., C. Clark, H. M. B. Biag, et al. 2023. “Open-Label Sulforaphane Trial in FMR1 Premutation Carriers With Fragile-X-Associated Tremor and Ataxia Syndrome (FXTAS).” *Cells* 12, no. 24: 2773.
- Schneider, A., S. Summers, F. Tassone, et al. 2020. “Women With Fragile X-Associated Tremor/Ataxia Syndrome.” *Movement Disorders Clinical Practice* 7, no. 8: 910–919.
- Shelton, A. L., K. M. Cornish, C. M. Kraan, R. Lozano, M. Bui, and J. Fielding. 2016. “Executive Dysfunction in Female FMR1 Premutation Carriers.” *Cerebellum* 15, no. 5: 565–569. <https://doi.org/10.1007/s12311-016-0782-0>.
- Stern, Y. 2009. “Cognitive Reserve.” *Neuropsychologia* 47, no. 10: 2015–2028.
- Tassanakijpanich, N., R. J. Hagerman, and J. Worachotekamjorn. 2021. “Fragile X Premutation and Associated Health Conditions: A Review.” *Clinical Genetics* 99, no. 6: 751–760.
- Tassone, F., D. Protic, E. G. Allen, et al. 2023. “Insight and Recommendations for Fragile X-Premutation-Associated Conditions From the Fifth International Conference on FMR1 Premutation.” *Cells* 12, no. 18: 2330.
- Varni, J. W., M. Seid, and C. A. Rode. 1999. “The PedsQL: Measurement Model for the Pediatric Quality of Life Inventory.” *Medical Care* 37, no. 2: 126.
- Wang, J. Y., D. Hessl, R. J. Hagerman, et al. 2017. “Abnormal Trajectories in Cerebellum and Brainstem Volumes in Carriers of the Fragile X Premutation.” *Neurobiology of Aging* 55: 11–19.
- Wang, C., C. O. Nester, K. Chang, et al. 2023. “Tracking Cognition With the T-MoCA in a Racially/Ethnically Diverse Older Adult Cohort.” *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* 15, no. 1: e12410.

### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Descriptive measures. **Table S2:** Nonparametric one-way ANOVA. **Table S3:** Dwass–Steel–Critchlow–Fligner—pairwise comparisons. **Table S4:** Results of binomial tests for SCID-5 diagnoses. **Table S5:** Kruskal–Wallis analyses: Age-group differences in cognitive measures after excluding mothers of children with FXS. **Table S6:** Pairwise comparisons for cognitive measures (Dwass–Steel–Critchlow–Fligner test). **Table S7:** Pearson correlation matrix among cognitive and demographic variables in women without children with FXS. **Table S8:** Correlation matrix—BRIEF-A—PSI. **Table S9:** Correlation matrix SCL-90-R—PSI. **Table S10:** Correlation matrix PEDS-QL—PSI.