Genetics in Medicine Open (2023) 1, 100829

ELSEVIER

Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ARTICLE

Social and physical predictors of mental health impact in adult women who have an *FMR1* premutation

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ARTICLE INFO

Article history:
Received 6 June 2023
Received in revised form
13 August 2023
Accepted 15 August 2023
Available online 26 August 2023

Keywords:
Fragile X-associated primary ovarian insufficiency (FXPOI)
Fragile X-associated tremor/ataxia syndrome (FXTAS)
social anxiety
depression
premutation

ABSTRACT

Purpose: Clear understanding of mental health phenotypes and associated socioeconomic, physical health and well-being impacts in adult women with an *FMR1* premutation (PM) is needed for counseling and primary healthcare.

Methods: A questionnaire captured mental health conditions in women with a PM, using lifetime diagnosis and nested psychometric scales (Liebowitz Social Anxiety Scale; Depression and Anxiety Stress Scale). Socioeconomic, physical health and well-being data were entered into 2 multivariable logistic regression models (1 with depression status as the outcome variable and 1 with social anxiety as the outcome).

Results: 137 participants were included. Depression was found in ~30% and social anxiety in ~38%. With depression status the outcome variable, strongest associations were for low education, diagnosis of migraine, diagnosis of irritable bowel syndrome, and self-reported hearing loss symptoms. With social anxiety status as the outcome, strongest associations were with education, migraine, irritable bowel syndrome, relationship status, and subjective memory complaints.

Conclusion: Mental health impacts were found in more than 1 in 3 women. Poor mental health was significantly associated with socioeconomic and physical health factors. Findings may inform health care professionals about personalized treatment options for women with a PM.

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Introduction

Individuals who have a trinucleotide CGG expansion (55–200 repeats) of the *FMR1* gene are known to have a premutation (PM). Those with PMs may have children with fragile X syndrome (FXS) and may develop fragile X-associated tremor/ataxia syndrome (FXTAS), a late-onset neurodegenerative disorder with motor, cognitive and autonomic symptoms.[1] Females can develop fragile X-associated primary ovarian insufficiency (FXPOI), a condition characterized by reduced ovarian function and early menopause.[2]

Mental health concerns are reportedly common among adults who have PM alleles, particularly in females who represent ~1 in 300 individuals in the general population.[3] For example, studies suggest that when applying

The Article Publishing Charge (APC) for this article was paid by Claudine M. Kraan.

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doi: https://doi.org/10.1016/j.gimo.2023.100829

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structured clinical interview or self-report techniques, such as the Structured Clinical Interview for the DSM (SCID) and Symptom Checklist-90-Revised (SCL-90-R), which target DSM disorders, females with PM alleles show rates of depression at ~40%[4–6] and any anxiety condition at ~30%.[4–7] The most common anxiety conditions described have been social anxiety or social phobia, panic disorder, and agoraphobia without panic. These have been labeled as fragile X-associated neuropsychiatric disorders (FXAND) if they meet DSM-5 criteria for a disorder. Fragile X-associated neuropsychiatric conditions (FXPAC) is the umbrella term that includes FXAND and milder or sub-threshold symptoms.[8]

The reported proportions of female individuals who live with depression and/or anxiety disorders exceed those reported in Australian population level data sets. For instance, as stated in the 2020-2021 Australian Bureau of Statistics Australian National Study of Mental Health and Well-being, female prevalence of a 12-month anxiety disorder is 21.0% and 12-month affective disorder is 8.5%.[9] These data reflect the current percentage of people in Australia with a previous lifetime diagnosis who experienced symptoms of the disorder in the 12 months before the survey.[10]

A challenge for this field is to understand the full impacts associated with the PM in the general population. This is an issue of rising importance specifically for females, given expanded carrier screening programs in Australia (eg, Mackenzie's Mission).[11] Such programs are expected to identify large numbers of females with PMs who are not from FXS-affected families and will require accurate descriptions of PM phenotypes for counseling and for health education.

A large data-driven study has partially addressed the challenge of understanding the population-level impact of PM phenotypes. This study concurrently overcame the impact of knowledge of genetic status, parenting factors, and ascertainment bias via review of 20,000 electronic health records and found elevated rates of agoraphobia, social anxiety or social phobia, and panic disorder in adult females with PMs compared to those without a PM, with no elevation to major depression single episode.[12] However, because these data were based on ICD-9 and ICD-10 codes on a patient medical history health record, population-level research with psychometric methods is needed to confirm the findings and extend our understanding of symptomatology.[13]

A second unresolved challenge for the field of mental health in females with PMs is to understand if/how mental health is associated with physical health and well-being factors, particularly those that may exacerbate symptoms or share underlying mechanisms. A relevant example is the relationship between mental health and both FXPOI and the FXPOI spectrum of irregular menstrual cycles and menopausal symptoms (eg, hot flushes).[14,15] Further health risks that have been described in adult females with a PM that are potentially relevant are autoimmune disorders, thyroid dysfunction and migraine[16–18] (see Supplemental Table 1). The additional impacts of parenting/family stress and socioeconomic status on mental health cannot be understated.[19,20]

An emerging approach to better delineate the mental-physical correlates forming in females with PMs is to use logistic regression to understand the change in odds ratio (OR) or risk for one condition in the instance of another.[21,22] However, a majority of outcomes from studies using this approach have limited psychometric data (often relying solely on lifetime diagnosis) and have included a very broad age range (up to 93 years old) inclusive of patients who have probable to definite FXTAS (see Supplemental Table 1).

This study aimed to demonstrate a survey approach to quantify the mental health occurrences and associated socioeconomic, physical health, and well-being impacts in a female PM cohort, using nested psychometric scales. The survey was designed to be both brief and sensitive so that it can (in the future) be adapted for larger studies. The cohort selected was ascertained through family support networks and was aged ≤55 years old to reduce the likelihood of including participants who have FXTAS. Association between depression and social anxiety and an extensive range of socioeconomic, physical health and well-being outcomes were analyzed.

Materials and Methods

Study population and recruitment

The study cohort comprised adult females who have a PM, aged between 23 and 55 years. Participants were recruited during 2015 via an online advertisement with the heading "General health and well-being in women with an altered fragile X gene," in collaboration with the Fragile X Association of Australia. The questionnaire was English speaking. It was administered using Qualtrics software and was designed to be completed in 30 minutes; however, no time limits were imposed. All responses were anonymous, thought participants were provided the option to provide contact details for re-identification for future recruitment and/or contact to access additional data.

Survey details

The survey collected demographic, socioeconomic, health and well-being information. Lifetime diagnosis of a previous mental or physical health condition was queried in the following format: "Have you ever had one of the following diagnosed or treated by a doctor"? A list of common outcomes was provided with space to type in "other" for responses not listed. The study covered the following domains for lifetime diagnosis: (a) mental health, (b) cardiovascular, (c) thyroid, (d) autoimmune and inflammatory, (e) sleep, (f) muscles, skeleton and nerves, (g) functional somatic syndromes, migraine and headache, (h) audiological, and (i) women's health.

Additional items included current self-reported symptoms of the following: (a) audiological concerns (eg, tinnitus/sensation of fullness in the ears/nausea/headaches/hearing loss/vertigo/vomiting) and (b) subjective memory complaints (eg, have you noticed any difficulties with your memory? Have you been concerned about your memory? Have you mentioned any concerns about your memory to anyone?). The selected framework for querying subjective memory complaints reflected recognized aspects associated with risk of cognitive decline (ie, noticing/concern/seeking medical attention).[23]

Body mass index (BMI) was calculated as per the Australian Institute of Health and Welfare classification system for females (normal: 18.5–24.99; overweight: 25–29.9; obese: 30+). Alcohol use was measured using the CAGE questionnaire for detection of alcoholism. This covers aspects of cutting down drinking, getting annoyed at criticism of drinking, feelings of guilt, and having ever taken an early morning drink). Scores of 2 or higher on the CAGE have been found to have a 93% sensitivity/76% specificity for the identification of "excessive drinking" and a 91% sensitivity/77% specificity for the identification of alcoholism.[24] Exercise frequency was assessed via tick-box (ie, How often do you exercise? never/everyday/2–3 times a week/once/twice a week/once per fortnight/once per month/a few times a year).

For depression and social anxiety, both lifetime diagnosis and nested psychometric scales were used: Depression Anxiety Stress Scale (DASS) and Liebowitz social anxiety scale (LSAS). The depression axis of the DASS measures symptoms in the prior week and has good test-retest reliability (r = .71), excellent internal consistency (α = .97), as well as good convergent validity of r = .79 when correlated with the Beck depression inventory.[25,26] The LSAS is a self-report measure gauging respondents fear and avoidance of social situations over the past week. The LSAS total score has excellent internal consistency (α = .95), adequate convergent validity with a range of measures of social anxiety with correlations of r = .63 to .73 and good test-retest reliability (r = .83).[27] Both DASS Depression axis and LSAS total score have been shown to be sensitive to the PM phenotype.[28,29]

The study procedures were consistent with the Declaration of Helsinki and approved by a formal Ethics Committee.

Statistical analysis

Binary variables based on "tick-box" yes/no responses for lifetime diagnosis were created. A total of 9 items with multi-level responses were collapsed into binary variables: (a) "not partnered" and "partnered," (b) "high school or trade qualification" and "postsecondary qualification," (c) "not homeowner" and "homeowner," (d) "unable to save" and "able to save," (e) "FXPOI and/or early menopause" and "typical fertility/menopause," (f) "subjective memory complaints" and "no subjective memory complaints," (g) "overweight or obese BMI" and "normal BMI," (h) "low levels of exercise" and "good levels of exercise," and (i) "alcohol overuse" and "no alcohol overuse" (see Supplemental Table 2 for details).

For depression and social anxiety outcome variables, binary data were created using a two-step methodology. This required presence of both self-reported lifetime diagnosis (step 1) and current elevated symptoms (step 2). Symptoms for depression were measured using the DASS depression axis (ie, 10+ indicating mild to extremely severe symptoms). Those for social anxiety were quantified with the LSAS total score (ie, 30+ indicating mild to very severe symptoms) (step 2). Although type of lifetime anxiety diagnosis was not queried, the presence of elevated symptoms on the LSAS, which targets social anxiety, was taken to indicate a likely social anxiety condition.

Depression and social anxiety results were compared with population level data for 12-month mental conditions (ie, lifetime diagnosis and symptoms across previous 12 months) in affective and anxiety conditions from the 2020–2021 ABS Australian National Study of Mental Health and well-being, using one-sample test for proportion.[9] This study used the most recent ABS data set because it is a better estimate of current Australia-wide impact and was not largely different to pre-pandemic data from 2017-2018 (see Supplemental Table 3).

All other variables with occurrence >10% of the cohort were entered into 2 separate univariate logistic regression models, 1 with depression status as the outcome variable and 1 with social anxiety as the outcome. This cutoff for entry into logistic regression was based on the need for a sufficient sample size of predictors in the models. This has been performed by other similar studies.[21,22] Variables with P value < .1 in the univariate analysis were selected to be included in 2 further multivariable logistic regression models—1 for depression status and 1 for social anxiety. The final 2 multivariable models were chosen using stepwise logistic regression. 5% level of significance with 95% CI and P value < .05 was selected.

Results

A total of 147 adult females identifying as PM consented to complete the online survey. Ten were removed from the analysis: 2 because of self-reporting a CGG size ≥ 200 repeats, 5 were aged > 55 years old, 2 were found to have gray zone alleles (CGG 41-54) on their diagnostic report, and 1 did not provide enough data for analyses. This left a cohort of 137 for the statistical analysis (98 of whom opted for re-identification and provided contact details). Majority of responses obtained were from participants in Australia (n = 68) and the United States (n = 50). Participants from The United Kingdom, Canada, New Zealand, France, and Ireland were also represented (n = 19).

CGG size was accessed for 87 participants (~64% of cohort) to confirm PM status and explore relationships with expansion size. Data were accessed in 3 ways: (a) participants were asked to complete a field that detailed CGG size, location and timing of genetic testing at time of survey completion (67/87 or 77.0%), (b) formal reports were accessed via email correspondence with participants consented for re-identification in 2022 (15/87 or 17.2%), and (c) cross-checking against previous studies[29] with formal CGG testing (5/87 or 5.8%). If reports/direct assessment data and self-report data were available, direct data were used and discrepancy was checked. This occurred for 17 participants: (a) 14 or 82.4% of whom had a 0 to 5 repeat discrepancy, (b) 1 with a 15 repeat discrepancy if the most recent report used (2 sent in), (c) and 2 who self-reported ranges instead of a single result, who had 1 result closest to the lower range (1 with an 8 repeat difference and 1 different by 5 repeats).

The mean age for the cohort was 42.1 years of age (standard deviation (SD) = 8.5 years) and the mean CGG repeat size was 89.1 repeats (SD = 24.3). Summary statistics for demographic, socioeconomic, mental health, physical health, and well-being are presented in Table 1. For physical health and well-being data, we only report results with occurrence of >10%. Variables with occurrence <10% are presented in Supplemental Table 4.

Proportion of cohort with depression and social anxiety

The depression outcome variable (based on the two-step methodology) occurred in 29.9% (n = 41) and the social anxiety outcome (also two-step methodology) was found in 38.0% (n = 52). These proportions are increased when compared with 2020–2021 ABS population-level data for women with affective conditions (8.5%) ($P < .0001$) and anxiety conditions (21.0%) ($P < .0001$) (Figure 1A and B). A total of 32 participants (23.5%) met criteria for both depression and anxiety.

For depression based on lifetime diagnosis alone, the occurrence was 45.7% with comparable 49.3% for elevated symptoms as per the DASS depression axis score (Figure 1A). For anxiety based solely on lifetime diagnosis, the occurrence was 41.3%, whereas 71.7% of the tested cohort had elevated total scores recorded on the LSAS (Figure 1B). The breakdown of elevated scores by subcategory showed that 19.6% of the cohort had severe to extremely severe scores on the DASS depression axis and 18.8% had severe to very severe scores on the LSAS (see Figure 1C and D).

Age and CGG size were analyzed for association with the depression and social anxiety outcome variables. Age was not significantly linearly associated with depression (OR = 0.99; P = .67) or social anxiety (OR = 0.98; P = .31). Similarly, CGG size was not significantly linearly associated with depression (OR = 1.00; P = .88) or social anxiety (OR = 1.01; P = .52). Additional analysis was performed across previously defined low (CGG: 55-70), mid (CGG: 71-100) and high (CGG: 101-199) repeat categories[30] (Supplemental Table 5). For social anxiety, proportions were slightly reduced in the mid category (low: 47%, mid: 30%, and high: 46%), but this was not significant. The proportions for depression were comparable (low: 32%, mid: 28%, and high: 27%).

Table 1 Summary statistics

Variable	*N*	*n*	%
Demographic and socioeconomic			
Relationship status (not partnered)	136	24	17.7
Education (high school &/or trade qualification)	137	57	41.6
Governmental benefits or pension (currently receiving)	137	62	45.3
Living arrangement (not homeowner)	137	41	29.9
Family finance (unable to save)	119	41	34.5
Child(ren) diagnosed with FXS (1 or more)	133	85	63.9
Mode of inheritance (paternal)	108	59	54.6
Mental health			
Depression	137	41	29.9
Social anxiety	137	52	38.0
Depression and social anxiety	137	32	23.5
Physical health and well-being			
Overweight or obese BMI	126	74	58.7
Subjective memory complaints	136	71	52.2
Heavy menstruation &/or acne	136	54	39.7
Low levels of exercise	136	51	37.5
Migraine	137	51	37.2
FXPOI &/or early menopause	134	30	22.4
Ovarian cysts	136	29	21.3
Irritable bowel syndrome	133	26	19.6
Alcohol overuse	135	26	19.3
Endometriosis	136	20	14.7
Hearing loss symptoms	136	18	13.2
Flat feet	137	18	13.1
High cholesterol	130	16	12.3
Uterine fibroids	136	16	11.8

Note: Depression and anxiety proportions reflect those classified with two-step methodology (ie, lifetime diagnosis and symptoms scoring at mild or above level on the DASS and LSAS). Physical health and well-being shown if reported in >10% of cohort. Items with occurrence <10% shown in Supplementary Table S4. *N*, sample size; *n*, number of positive outcomes; %, percentage of positive outcome.

BMI, body mass index; FXPOI, fragile X-associated primary ovarian insufficiency; FXS, fragile X syndrome.

Logistic regression with depression as the outcome variable

Depression status associated with 4 socioeconomic variables: relationship status (not partnered), education level (high school and/or trade/technical qualification), living arrangement (not homeowner), and family finance (unable

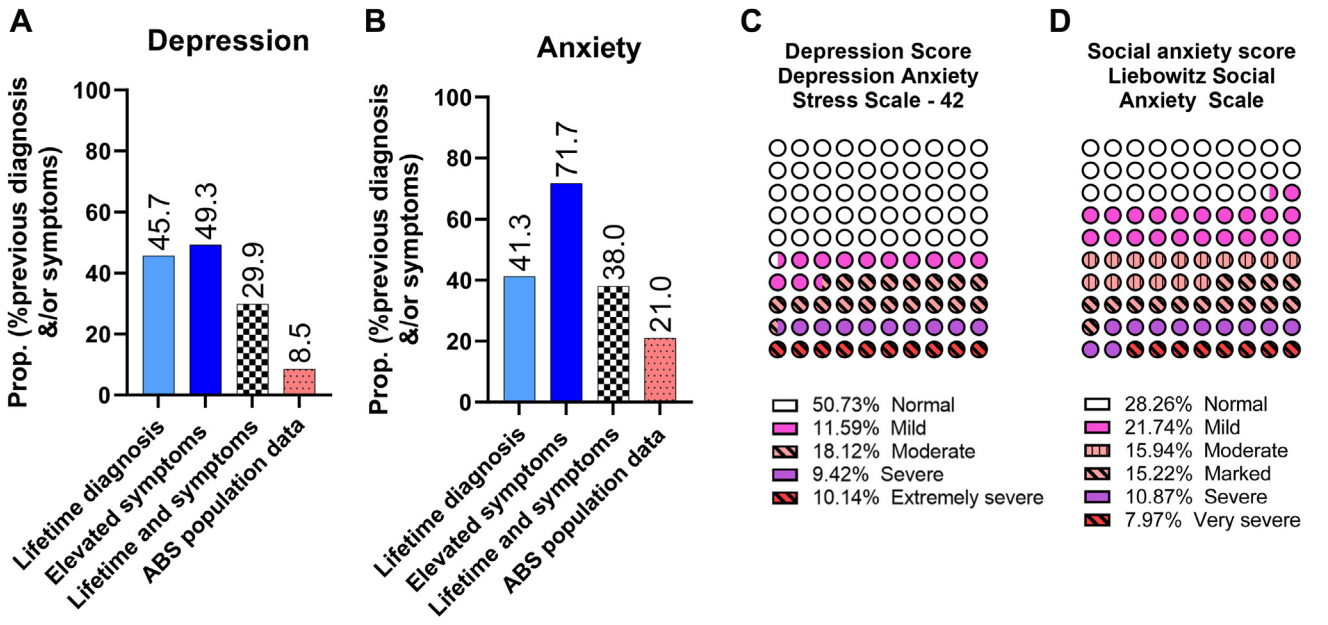

Figure 1 **Depression and social anxiety outcomes in the PM cohort (n = 137).** A and B. Proportion with the following: lifetime diagnosis (first column: light blue bar); current elevated symptoms on psychometric scale (ie, DASS depression axis score or LSAS Total Score) (second column: dark blue bar) and mental health impact outcome variable (based on two-step methodology) (third column: checked bar). Fourth column (pink dotted bar) demonstrates 2020-2021 ABS statistics for (A) affective conditions and (B) anxiety (C and D), which are based on presence of both diagnosis and symptoms in previous 12 months. DASS/LSAS proportions within each threshold (DASS: normal: 0-9; mild: 10-13; moderate: 14–20; severe: 21-27; extremely severe: 28+; LSAS: normal: 0-29; mild: 30-49; moderate: 50-64; marked: 65–79; severe: 80–94; very severe: >95). ABS, Australian Bureau of Statistics; DASS, Depression Anxiety Severity Scale; LSAS, Liebowitz social anxiety scale.

to save). Depression also associated with overweight or obese BMI, subjective memory complaints, heavy menstruation and/or acne, low levels of exercise, migraine, FXPOI and/or early menopause, irritable bowel syndrome (IBS), and hearing loss symptoms (all P values < .05) (Figure 2A, Supplemental Table 6). Education, migraine, IBS, and hearing loss symptoms remained significant in the multivariable logistic regression (Figure 2C, Supplemental Table 8).

Logistic regression with social anxiety as the outcome variable

Majority of the predictors that associated with depression were also associated with social anxiety in the univariate logistic regression (Figure 2B, Supplemental Table 7). However, living arrangement, BMI, and FXPOI and/or early menopause were not associated with social anxiety status (all P > .05). In the multivariable logistic regression, social anxiety was associated with relationship status, education, subjective memory complaints, migraine, and IBS (all P < .05) (Figure 2D, Supplemental Table 8).

Discussion

Depression and social anxiety conditions are associated with significant personal distress, impairment and disability.[31] Depression is a mood disorder that impacts activity (eg, fatigue or loss of energy), cognition (eg, concentration issues), and emotion (eg, depressed mood),[32] whereas social anxiety is a chronic disorder characterized by a fear of being negatively judged by others. Consistent with previous research into depression[5–7] and social anxiety,[4,12,28] the present study found ~30% penetrance for depression and ~38% for social anxiety. This suggests that mental health concerns are common in adults with a PM but not fully penetrant.

This study has distilled a wide range of social, physical and well-being variables into a digestible shortlist of key predictors of PM-related mental health impacts. The value of these data lies within its scope, which was inclusive of "cardiovascular health," "thyroid function," "autoimmune and inflammatory disorders," "sleep," "disorders of the muscles, skeleton, and nerves," "functional somatic syndromes, migraine, and headache," "audiological symptoms," "women's health," "parental factors," and key well-being markers, such as alcohol overuse, BMI, and exercise. Findings support previously reported associations between mental health impact and overweight or obese BMI, low levels of exercise, IBS, migraine, and, FXPOI and/or early menopause in women with a PM.[21,22] Additional (and previously unreported) female-specific mental-physical health associations were for subjective memory complaints, heavy menstruation and/or acne, and hearing loss symptoms.

Health care practitioners should be aware of the mental-physical health correlates described in this study and how and where they reflect what is seen outside the PM field,

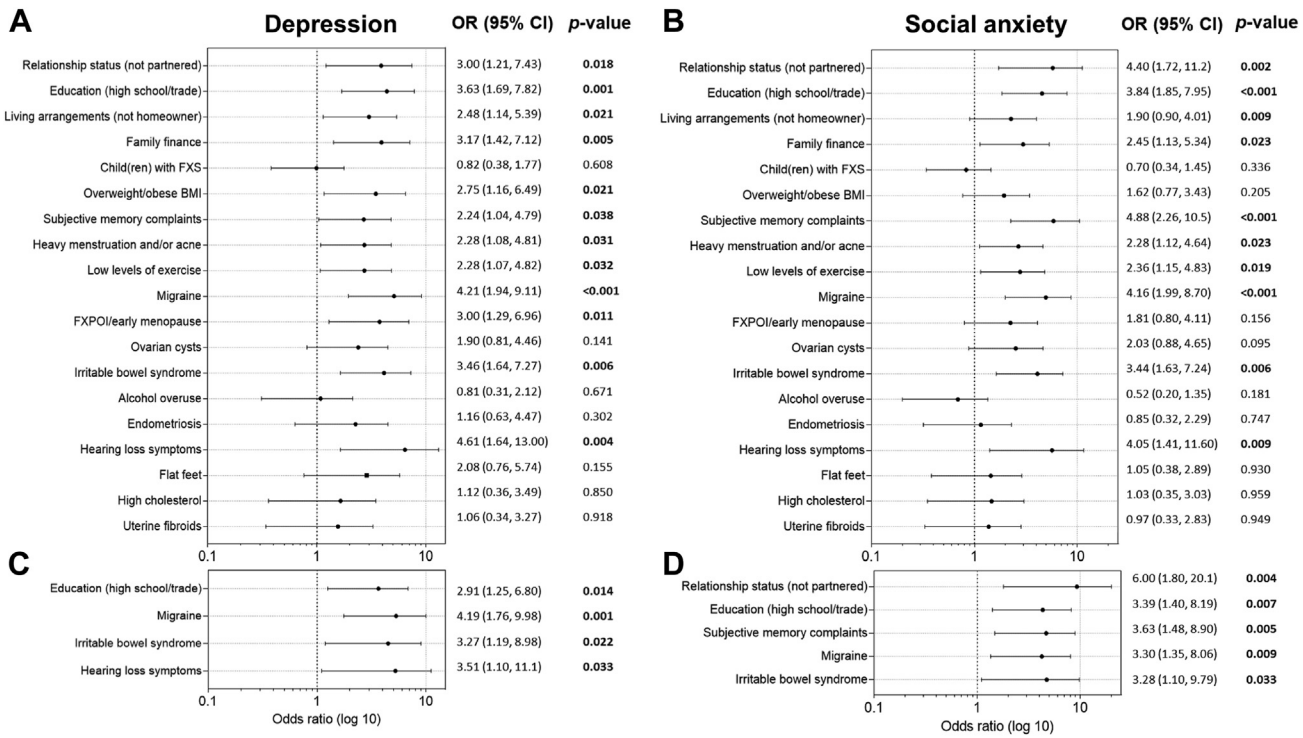

Figure 2 Univariate and multivariable models showing associations between predictors and mental health status. Mental health status outcome variable (based on two-step methodology that classified on basis of both lifetime and current elevated symptoms. A. Univariate analysis with depression status as the outcome variable (N = 119-137). B. Univariate analysis with social anxiety status as the outcome variable (N = 119-127). C. Multivariable analysis with depression status as the outcome variable (N = 133). D. Multivariable analysis with social anxiety status as the outcome variable (N = 131). Data specifics shown in Supplemental Tables 5–7. Black dots in (A) and (B): Odds Ratio (OR); Black dots in (C) and (D): adjusted OR (aOR). Error bars show 95% CI.

especially in women. Such knowledge will aid conversations about health monitoring. For instance, up to 50% of people with migraine are diagnosed with comorbid depression and anxiety;[33] perimenopause and the menopausal transition period, which have been associated with risk of onset or recurrence of psychiatric conditions;[34] IBS is a common health problem with a potential link to mental health via the gut microbiota and/or dysregulation of the hypothalamic-pituitary-adrenal axis;[35] and, subjective memory complaints are known to be associated with psychiatric symptoms in older individuals.[23]

In addition to the physical-mental correlates, the current findings suggest an equally important association between educational attainment and mental health impact. Education is associated with socioeconomic status, health behaviors and better health, and with longevity.[36–38] Interestingly, research has demonstrated associations in females with PMs between low attainment of education and the following: (a) poor motor and cognitive performance (non-FXTAS adults aged 26 to 85, majority >50 years),[39] (b) increased frequency of self-reported daily health symptoms (eg, headache, backache, and fatigue),[40] and (c) faster rate of decline in FXTAS symptoms.[38] The present data corroborate a role of education in the PM lived experience, particularly for mental health impact. Moreover, these data suggest that mental health is similarly associated with partner status, obtaining home ownership, and ability to save money.

A discrepancy between the proportion of adult females with PMs with lifetime diagnosis versus those fitting criteria for elevated symptoms was observed for anxiety but not depression. In fact, >70% of the cohort had an elevated score signaling social anxiety symptoms as mild or worse on the LSAS (score 30+), with ~19% in the severe to very severe range (score 80+). By contrast, only ~41% self-reported a lifetime diagnosis of an anxiety condition. For depression, symptoms (49%) and lifetime (~46%) proportions were largely comparable. The increased penetrance for symptoms of social anxiety is important. Even at a low threshold, people with social anxiety can experience impairment in social and occupational functioning.[41] The higher social anxiety symptoms may reflect poorer awareness of social anxiety by health care practitioners and persons with lived experience. Other potential explanations are long delays accessing help for social anxiety disorders that are common,[42] presence of different anxiety phenotypes that were not explored in the study (eg, panic disorder or agoraphobia),[6,12] and/or some effect of treatment on depression symptoms.

Regarding CGG-size, a slightly decreased proportion of participants with social anxiety was noted in the mid-range

bandwidth (CGG: 71–100; 30%) versus low and higher repeat ranges (CGG: 55–70 and 101–199; 45–47%). However, the sample sizes in the sub-categories were very small; therefore, this requires replication in a larger study. There were no linear associations between CGG size and mental health outcomes.

The approach taken in this study differs to that of previous studies of mental-physical associations in females with PMs. First, the current study has employed a two-step method for classifying the mental health conditions examined in the logistic regression models. For instance, a person was classified only if they had a lifetime diagnosis and current elevated symptoms. This approach reduced recall reliance for the type of diagnosed disorder by overlaying a targeted psychometric scale. Indeed, although step 1 could not differentiate type of anxiety disorder at lifetime diagnosis (eg, panic disorder, social anxiety disorder, and generalized anxiety disorder), this was minimally impacting as step 2 detected social anxiety symptoms. This approach was designed to be scalable yet without compromise to sensitivity to the type and severity of the condition. As the field moves to larger scale measurement to fully understand the impact of the PM on society, it will need approaches that balance brevity with phenotypic sensitivity. This approach also avoids people with a once-off lifetime diagnoses that may be environmentally related (eg, after diagnosis of child). However, it does have a limitation of potentially missing those who have not presented to services previously.

Second, actual biomedical diagnosis was collated, rather than clustering multiple similar health concerns into a category (eg, hypo and hyperthyroid disorders and distinct autoimmune conditions). This is different to the approach of other studies that have collapsed across categories.[16,17] This is a strength because it targets distinct biological pathways and/or conditions.

Third, this study has undertaken two-levels of analyses, which phased from univariable to multivariable logistic regression. The use of multivariable analysis enabled the study to demonstrate the mental-physical associations that remained significant while controlling for important socioeconomic predictors such as education and relationship status. This narrowed our short-list for depression, to migraine, IBS, and hearing loss symptoms. For anxiety, similar associations were found with migraine and IBS, in addition to subjective memory complaints. These are likely to be the strongest predictors of mental health impact in adult females with a PM. However, with a larger sample size further predictors from the univariate model (eg, overweight or obese BMI, heavy menstruation and/or acne, and low exercise), could potentially remain significant in the multivariable models, and this should be addressed in future studies.

This study has limited ability to probe associations with mental health impact for variables with occurrences in <10% of the cohort. Consequently, the study may miss important relationships between mental health outcomes and less common occurrences previously reported as potential PM phenotypes. These include fibromyalgia that was just under the cutoff at 9.8%, restless leg syndrome, which was 7.6% and attention deficit hyperactivity disorder found in 8.0%, to name a few (see Supplemental Table 4). An important variable that may have been missed in this study is chronic muscle pain because this was not directly queried by the survey.[16]

The lack of association with parental status and alcohol use disorder indicates additional layers of complexity for these data. For example, it is possible that the "no child(ren) with FXS" group requires further unpacking, particularly because it included parents of children with PM alleles and individuals with no children who may be experiencing FXPOI. Further unaccounted factors are child behavior, number of children, and age of children. Moreover, relationships between alcohol use and mental health in females may be affected by carer roles and the impact of managing FXPOI (eg, undergoing fertility treatments), which was not explored in this study.

Because of the use of self-reported CGG size, there is a possibility that people with other expansions such as gray zone or full mutation completed the survey. However, using this approach this study has replicated findings in previous studies with direct assessment[18] and those that include biospecimen collection.[21,22] The study also found very low discrepancy between self-reported CGG and CGG on ascertained diagnostic reports, which strengthens the validity of the data.

The next step is to expand this questionnaire and statistical approach to a non-biased group. Currently, it is unclear if these data can be generalized to the broader population, including females with PMs who are recruited via different techniques, especially those identified via population screening programs who may not have a family history of FXS-related disorders. Indeed, the present cohort has an average higher CGG (89 CGGs) than which has been observed in population-level adult carrier screening data (61 CGGs), newborn screening data (60 CGGs), and linkage data (67 CGGs).[3,12] Thus, the data may not reflect people outside this cohort. Another next step is to replicate the approach in females with a non-expanded CGG size matched for age and socio-demographic factors. Associations found to be unique or more strengthened in a PM cohort as opposed to controls could point to pathways to pursue for treatments.

In conclusion, more than 1 in 3 females in the cohort met our criteria for depression and/or social anxiety. Mental health impact was significantly associated with multiple variables that crossed socioeconomic, physical health and well-being categories. The most robust associations were for education, relationship status, lifetime diagnosis of migraine, lifetime diagnosis of IBS, self-reported hearing loss symptoms, and subjective memory complaints. Causation could not be addressed in this study—thus the direction of the relationships should be investigated with a longitudinal cohort study. Mental health challenges in the PM do not appear to be fully penetrant yet should be recognized in the clinical setting and treated carefully with awareness of

potential physical (eg, with migraine) and social (eg, educational attainment) associations. Future studies are warranted to adopt the proposed approach at a wider scale in screening populations to delineate the population-level impact.

Data Availability

Data and materials available upon request to the corresponding author.

Acknowledgments

We express our thanks to the Fragile X Association of Australia for their support in recruitment. We are indebted to all the families who participated in this research.

Funding

Funding support provided by an Australian Research Council Discovery grant to K.C. and J.N.T. (DP110103346), National Health and Medical Research Council (NHMRC) Early Career Fellowship to C.M.K. (GNT1120561), NHMRC Leadership Fellowship to J.N.T. (GNT2009771), the Murdoch Childrens Research Institute and Fragile X Alliance Inc.

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Ethics Declaration

Informed consent was obtained from all participants and all data were de-identified. The study procedures were consistent with the Declaration of Helsinki and approved by the Southern Health Ethics Committee (project 10147B).

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2023.100829) contains supplemental material, which is available to authorized users.

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