J Autism Dev Disord (2012) 42:1836–1846
DOI 10.1007/s10803-011-1422-7

ORIGINAL PAPER

Daily Health Symptoms of Mothers of Adolescents and Adults with Fragile X Syndrome and Mothers of Adolescents and Adults with Autism Spectrum Disorder

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Published online: 14 December 2011

Abstract Health symptoms of mothers of adolescents and adults with fragile X syndrome (FXS; n = 112) were compared to a nationally-representative sample of mothers of similarly-aged children without disabilities (n = 230) as well as to a sample of mothers of adolescents and adults with autism spectrum disorders (ASD; n = 96). Health symptoms experienced in the previous 24 h were recorded during 8 consecutive days of a daily diary study. Both mothers of a son or daughter with FXS and mothers of a son or daughter with ASD had a higher proportion of days with headaches, backaches, muscle soreness, fatigue, and hot flashes than mothers of children without disabilities. Mothers of children with disabilities appear to be at particular risk for health problems, highlighting a need for comprehensive services for families across the lifespan.

Keywords Fragile X premutation · Autism spectrum disorders · Health symptoms

Introduction

In studies of parents of children with disabilities, the impact of caregiving stress on parental psychological well-being is well-established. Children with disabilities often display challenging behavior problems which can lead to high levels of stress and low levels of well-being for parents (Abbeduto et al. 2004; Blacher and McIntyre 2006; Eisenhower et al. 2005; Herring et al. 2006; Smith et al. 2010). Notably, many individuals with fragile X syndrome (FXS) as well as individuals with autism spectrum disorder (ASD) exhibit challenging behaviors not only during childhood, but also during adolescence and adulthood (Abbeduto et al. 2004), resulting in caregiving stress for parents which remains high across the life course.

Building on this literature regarding the impact of caregiving on *psychological* well-being, researchers have recently begun to explore connections between caregiving stress and indicators of *physiological* well-being in parents of children with disabilities. Seltzer et al. have found patterns of dysregulated cortisol, a stress hormone, in mothers of children with various disabilities (Seltzer et al. 2009), mothers of children with FXS (Hartley et al. 2011; Seltzer et al. 2011), and mothers of children with ASD (Seltzer et al. 2010). Dysregulated cortisol has been associated with a variety of health conditions including suppression of bone growth, immune difficulties, and poor cognitive performance (McEwen 1998; Segerstrom and Miller 2004). Given these associations, it is important to consider how having a child with a disability may contribute to the development and maintenance of health symptoms in parents. The present study examined daily health symptoms in mothers of adolescents and adults with FXS and compared them to a nationally-representative sample of mothers of similarly-aged children without disabilities as well as to a group of mothers of a son or daughter with ASD. Mothers of children with ASD are a strong comparison group for mothers of children with FXS given that although both groups have many of the same caregiving stressors (e.g., challenging child behaviors such as uncooperative behavior or self-injury), most mothers of children with FXS are carriers of the premutation of the fragile X mental retardation 1 (*FMR1*) gene, resulting in an added specific genetic vulnerability for these mothers that is not shared by mothers of children with ASD.

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Risks to Health in Mothers of Children with FXS

FXS is a neurodevelopmental disability caused by an expansion of greater than 200 CGG repeats of the *FMR1* gene on the X chromosome. Mothers of children with FXS frequently are carriers of the premutation of the *FMR1* gene (defined as 55–200 CGG repeats). Premutation carriers were originally considered to be unaffected, but in recent years consensus has been growing among researchers and practitioners that at least some premutation carriers display signs of impairment, with high levels of premutation-containing mRNA suspected to result in "toxicity" leading to disease (Berry-Kravis et al. 2004). As such, FXS is now considered to be part of a multigenerational collection of clinical conditions including the Fragile X Tremor Ataxia Syndrome (FXTAS) and Primary Ovarian Insufficiency (POI; Chonchaiya et al. 2009; Hagerman and Hagerman 2004; Wittenberger et al. 2007). These difficulties are not uncommon, with prevalence rates for female carriers over the age of 50 reported to be 18.6 and 16.5% for POI and FXTAS, respectively (Rodriguez-Revenga et al. 2009). There is also new evidence suggesting that carrier status may be associated with other types of physical health conditions. For instance, Coffey et al. (2008) found increased prevalence of thyroid disease, hypertension, seizures, peripheral neuropathy, and fibromyalgia in female carriers with FXTAS. In the same study, carriers without FXTAS reported higher rates of muscle pain and history of tremors than controls (Coffey et al. 2008). Similarly, Rodriguez-Revenga et al. (2009) reported high rates of thyroid disease and chronic muscle pain in female carriers.

In addition to risks for physical health conditions, premutation carriers may be at risk for mental health problems including anxiety, mood, and other psychiatric disorders (Bourgeois et al. 2009). For instance, in a large sample of children and adults with the premutation, female carriers were more likely to have been diagnosed with and/or treated for attention problems, anxiety, and depression compared to matched controls (Bailey et al. 2008). Carrier status also has been associated with higher levels of negative affect (Hunter et al. 2008a) and anxiety (Lachiewicz et al. 2010) in samples of adult carriers. Furthermore, studies from two separate labs have found premutation carriers to have higher lifetime prevalence rates of panic disorders compared to national norms using the DSM-IV-based Structured Clinical Interview for DSM-IV Disorders (SCID; First et al. 2002; Bourgeois et al. 2010; Roberts et al. 2009). As Hunter and colleagues documented in their review (Hunter et al. 2009), there are inconsistencies across studies regarding the presence of a neuropsychological phenotype among premutation carriers. Two recent studies provided evidence of cognitive impairments in older females (Goodrich-Hunsaker et al. 2011) and males (Cornish et al. 2011) with higher repeats, highlighting the need for further investigation in this area.

Differences Across Studies

Although past research has documented elevated levels of physical and mental health conditions in premutation carriers, not all studies have found significant differences between carriers and unaffected women after controlling for covariates (Hunter et al. 2009, 2010). Accordingly, questions remain regarding the prevalence of health problems in premutation carriers and how closely the etiology of these conditions is linked to carrier status. One possible explanation for these inconsistent findings is that some premutation-related health problems may produce sub-threshold symptomatology (i.e., a profile of problems that fails to meet clear diagnostic criteria for a particular disease). For instance, in a sample of daughters of men with FXTAS, premutation women had higher prevalence of symptoms including tremors, balance problems, memory problems, dizziness, menopausal symptoms, sleep problems, and anxiety (Chonchaiya et al. 2010) than non-carrier controls. The authors concluded that, even though symptoms may not be elevated consistently enough or sufficiently to meet diagnostic criteria, symptoms in premutation carriers still may be related to mRNA toxicity (Chonchaiya et al. 2010). Similarly, findings from a study of neuropsychological profiles of premutation carriers by Hunter et al. (2008b) suggest that females with the premutation may have greater severity of ADHD symptoms, but not necessarily a clinical level of ADHD. Although most past studies examined the current or lifetime prevalence of diagnosed illnesses or conditions, the present study addresses this hypothesis by examining the daily health symptomatology of premutation carriers over an eight-day period. By studying symptoms on a daily basis, it is possible to capture day-to-day and potentially sub-threshold health problems as well as reduce error associated with retrospective reporting.

Another possible explanation for the inconsistent findings in the literature on health in premutation carriers relates to the quality of comparison groups used in past research, as some studies have employed well-matched control groups whereas others have based comparisons on national norms. Studies using comparison groups consisting of other groups of parents of children with a disability often have failed to find differences between carriers and non-carriers in terms of psychological well-being. For instance, in a study comparing premutation-carrier mothers of children with FXS to mothers of children with mental retardation, there were no statistically-significant differences between the groups on any psychological domains from the Symptom Checklist-90 (SCL-90; Derogatis 1997; Rodriguez-Revenga et al. 2008). Relatedly, Franke et al. (1998) failed to find differences in

the prevalence of affective disorders between mothers with the premutation and mothers of children with autism, although mothers with the premutation did have higher rates of social phobia than mothers of children with autism. It may be that, in addition to biological causes of disease in premutation carriers, caregiving stress plays a contributing role in the development of health difficulties (Bourgeois et al. 2009; Hunter et al. 2009).

The Present Study

The present study examined the daily health symptoms of premutation-carrier mothers of adolescent and adult children with FXS. Health symptoms of premutation mothers were compared to a nationally representative sample of mothers of similarly-aged children without disabilities as well as to a sample of mothers of adolescents and adults with ASD. Mothers of children with ASD are an appropriate comparison group for mothers of children with FXS given that there are several similarities between the groups including frequent difficulties in gaining appropriate diagnoses and treatments and high levels of child behavioral problems (Seltzer et al. 2004). Specifically, we compared the three groups of mothers on daily symptoms that are clinically-relevant for premutation carriers including pain, dizziness, menstrual-related symptoms, and mood as well as symptoms not specifically related to carrier status (e.g., flu symptoms, allergies).

Based on the growing literature relating premutation carrier status to various health conditions including FXTAS and POI (Hagerman and Hagerman 2004), our first hypothesis was that mothers in the FXS group would experience more days with premutation carrier-related health symptoms than mothers in either comparison group. Our second hypothesis was that mothers of a son or daughter with ASD would also report more symptomatic days than mothers of children without disabilities, given that the chronic stress of raising a child with ASD has been shown to take a physiological toll on parents (Seltzer et al. 2010). We also hypothesized that both groups of caregiving mothers additionally would report more days with health symptoms not associated with the premutation than mothers of children without disabilities, given the high level of chronic stress experienced by mothers of individuals with FXS and by mothers of children with ASD. For our third hypothesis, consistent with past work on psychological distress in parents of children with disabilities (Abbeduto et al. 2004; Blacher and McIntyre 2006; Eisenhower et al. 2005), we expected mothers of adolescent and adult children with disabilities (both FXS and ASD) would report lower levels of daily positive affect and higher levels of daily negative affect compared to mothers of similarly-aged children without disabilities.

Methods

Participants

Participants were drawn from three linked longitudinal studies: (1) Families of Adolescents and Adults with FXS (FXS), (2) Adolescents and Adults with Autism (AAA) and (3) the National Survey of Midlife in the US (MIDUS). The FXS study is an ongoing longitudinal study of 147 mothers of adolescent and adult children with the full mutation of FXS conducted by Seltzer and colleagues (Hartley et al. 2011; Seltzer et al. in press; Smith et al. in press). Mothers in the FXS study were recruited through service agencies, clinics, research registries, and FXS foundations across the United States. Study participation required that mothers be the biological parent of a son or daughter with the *FMR1* full mutation, that the son or daughter be 12 years of age or older, and that the son or daughter live in the parental home or have at least weekly contact with the mother either in person or by phone. Documentation from a health care professional confirming that the son or daughter had the full mutation of the gene causing FXS was also required. If a mother had more than one child with FXS, the child that was living in the family home was selected as the target child. If there was more than one co-residing child, the mother was asked to report on the child that was the most severely affected in her opinion.

Since the present study was focused on mothers with the premutation, 7 mothers who either had the full mutation (>200 CGG repeats) or a normal *FMR1* gene (<55 CGG repeats) were excluded from the current analyses. Of the 140 mothers with the premutation, 126 participated in the Daily Diary component of the research (described below), which provided measures of daily symptoms. Of these 126 mothers, we excluded 14 who were not currently co-residing with their children, resulting in a sample of 112 for the present analysis. Our rationale for including only mothers who were co-residing with their child with FXS was to insure that there would be daily contact with the son or daughter, as the focus of the present study is on daily symptoms. The mothers in the present analysis ranged in CGG repeat length from 67 to 155, with an average of 96.25. The sons and daughters with FXS ranged in age from 12 to 44 ($M = 19.66$, SD = 6.49). There were no differences between families in the sample included in the present analysis and families in the larger sample on household income, maternal health, marital status, child gender, or child behavior problems. However, mothers in the present analysis were significantly younger than mothers in the full sample, $F(1, 145) = 5.24$, $p < .05$. Notably, 28 of the adolescents and adults with FXS also had a diagnosis of ASD. There were no significant differences in response rates for mothers with a dually-diagnosed child (FXS and

ASD) compared to mothers of a son or daughter with FXS alone. Dual-diagnosis was determined by a case review procedure reported in Smith et al. (in press).

A comparison group of mothers of a son or daughter with ASD were drawn from an ongoing, multi-wave, longitudinal study of 406 families of adolescents and adults with an ASD (the AAA study; Barker et al. 2010; Seltzer et al. 2010; Smith et al. 2010). At entry into the AAA study, families met three criteria: (a) the child was 10 years of age or older; (b) the child had received a diagnosis of ASD from a medical, psychological, or educational professional; and (c) scores on the research-administered Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994; Rutter et al. 2003) were consistent with the parental report of an ASD. An additional criterion for participation in the Daily Diary Study was that the son or daughter with ASD lived at home with the mother; 96 mothers of co-residing children participated in this component of the AAA study. As described in Smith et al. (2010), families who participated in the Daily Diary Study were not significantly different from eligible co-residing families who declined in terms of maternal factors (age, income, marital status, and health) or child variables (age, gender, and behavior problems). Adolescents and adults with ASD in the present analysis ranged in age from 17 to 53 ($M = 24.78$, SD = 7.28). Based on maternal report, none of the adolescents or adults with ASD had a diagnosis of FXS.

A second comparison group of 230 mothers of co-residing adolescent and adult children *without disabilities* was drawn from the National Study of Daily Experience (NSDE), one of the projects in the National Survey of Midlife in the United States (MIDUS). MIDUS is a nationally-representative study of English-speaking, non-institutionalized adults who were aged 25–74 in 1994 (MIDUS I; Brim et al. 2004; Gruenewald et al. 2008). Data used in the present study were collected from 2003 to 2005 as part of a second wave of data collection (MIDUS II). There were 1,265 individuals who participated in the second wave of the Daily Diary Study (NSDE II) during the MIDUS II data collection. For this comparison sample, we excluded 548 cases where the respondent was male (as the FXS and AAA studies consisted only of mothers) and 66 cases where the respondent was female and had a child with a developmental disability or mental health condition. Additionally, 421 female respondents in NSDE II were excluded because they did not have any children living in their home, resulting in a comparison group of 230 mothers of co-residing children without disabilities. For the current analysis, mothers ranged in age from 33 to 84 years of age.

The three groups of mothers were similar in terms of ethnicity and marital status (see Table 1). Mothers in the AAA sample were significantly older and had lower family incomes than mothers in either the FXS sample or the MIDUS sample. There was also a marginally significant difference between the groups in terms of educational attainment. Subsequently, maternal age, education level, and family income were controlled in all analyses.

Procedure

The Daily Diary Study protocol was developed for the NSDE II (as described above) and incorporated into the research designs of the FXS and AAA studies. For the Daily Diary Study, respondents were interviewed by telephone each evening for 8 consecutive days. The daily telephone interview, which lasted approximately 15–25 min, included questions about daily experiences in the previous 24 h. Questions focused on time use, daily stressors, positive events, mood, and physical symptoms. The current analysis focuses on the mood and physical symptoms data. Interviews for all three groups were conducted by the Survey Research Center at The Pennsylvania State University. This ensured that the procedures for interviewing mothers in the FXS, AAA, and MIDUS

Table 1 Sample demographics

	FXS (n = 112)	AAA (n = 96)	MIDUS (n = 230)	*F*	
% Married	81.3%	79.2%	74.8%	1.01	
% White	94.6%	91.7%	90.9%	.74	
Education	3.14 (.66)	3.13 (.76)	2.95 (.94)	2.62†	
Family income	6.98 (1.72)	6.10 (2.01)	6.41 (2.04)	5.58**	FXS > AAA FXS > MIDUS
Age	49.47 (6.96)	54.45 (9.05)	48.04 (9.60)	16.25***	AAA > FXS AAA > MIDUS

FXS is a sample of premutation carrier mothers of adolescent and adult children with FXS; AAA is a sample of mothers of adolescent and adult children with ASD; MIDUS is a nationally-representative sample of mothers of similarly-aged children without disabilities

† $p < .10$; * $p < .05$, ** $p < .01$; *** $p < .001$

studies were identical. Mothers in all groups were asked the same set of questions each day at the same time of day. Mothers of children with FXS and mothers of children with ASD were additionally asked whether the child manifested episodes of behavior problems during the day. University IRB approval was received prior to recruitment and data collection.

Measures

Health Symptoms

As part of the diary interview, daily health symptoms were measured each evening using an adapted version of Larsen and Kasimatis' (1991) symptoms checklist. For each health symptom, respondents indicated if they had experienced the symptom in the past 24 h (yes = 1). The following symptoms were selected for the present analysis based on published reports of health problems in premutation carriers, as reviewed above: headache, backache, muscle soreness, fatigue, joint pain, muscle weakness, dizziness, nausea, diarrhea, constipation, menstrual-related symptoms, and hot flashes or flushes. For each health symptom, the proportion of days in which the symptom was experienced during the 8-day study period was calculated. Additionally, composite scores were created to reflect the proportion of days the participant experienced any premutation carrier-related health symptoms (headache, backache, muscle soreness, fatigue, joint pain, muscle weakness, dizziness, nausea, diarrhea, constipation, menstrual-related symptoms, and hot flashes or flushes), any pain symptoms (backache, muscle soreness, fatigue, joint pain, and muscle weakness), and any gastrointestinal (GI) symptoms (nausea, diarrhea, and constipation). We also created a composite score of symptoms not empirically linked to premutation carrier status: cough, sore throat, fever, chills, other flu symptoms, allergies, poor appetite, chest pain, and shortness of breath.

Positive and Negative Affect

Daily positive and negative emotions were measured using a shortened version of the Positive and Negative Affect Schedule (PANAS; Watson et al. 1988). Each day, respondents indicated how frequently they felt each emotion over the past 24 h on a 5-point scale from "none of the time" to "all of the time." The positive affect scale was created from 5 items including feeling enthusiastic, attentive, proud, active, and confident; each item was summed, resulting in possible range of 6–25, with higher scores reflecting higher levels of positive affect. The negative affect scale was comprised of 5 items including feeling afraid, jittery, irritable, ashamed, and upset; items were summed to create a possible score of 6–25, with higher scores indicating greater negative affect. Cronbach's alphas for the positive affect scale, averaged across days, were .83 for the FXS sample, .86 for the AAA sample, and .87 for the MIDUS sample. Cronbach's alphas for the negative affect scale, averaged across days, were .74 for the FXS sample, .69 for the AAA sample, and .59 for the MIDUS sample.

Other Characteristics

Other characteristics of the mothers that were included in the analysis were mothers' level of education (coded as 1 = less than high school, 2 = high school graduate, 3 = some college, 4 = college graduate), family income (assessed on a scale of 1–8, with higher scores reflecting higher income), and age (in years). In addition, for the FXS and AAA Daily Diary Studies, mothers reported about episodes of behavior problems exhibited each day by the son or daughter with the disability using a modified version of the Scales of Independent Behavior-Revised (SIB-R; Bruininks et al. 1996). Mothers indicated if their child manifested episodes of the following behavior problems that day (each coded 1 if yes and 0 if no): uncooperative behavior, repetitive behavior, socially offensive behavior, withdrawn behavior, self-injurious behavior, hurtful to others, and hurtful to property. For each item, we calculated the proportion of days that the child exhibited episodes of the behavior problem; these scores were averaged to create a total behavior problems score. Mothers also reported the number of children in the family who had disabilities.

Results

We used analysis of covariance (ANCOVA) to describe the daily health symptoms and mood of premutation-carrier mothers of adolescents and adults with FXS in comparison to (a) mothers of individuals with ASD and (b) mothers of individuals without disabilities. Bonferroni post hoc multiple comparisons were used to determine the specific differences between the groups.

First, we investigated differences between the three groups in the proportion of days with each health symptom, controlling for maternal age, education, and family income. We hypothesized that mothers of adolescent and adult children with FXS would have a greater proportion of days with premutation carrier-related symptoms than mothers of adolescents and adults with ASD or mothers of similarly-aged children without disabilities. This hypothesis was only partially supported. Mothers of a son or daughter with FXS reported a higher proportion of days with headaches,

backaches, muscle soreness, fatigue, and hot flashes than mothers of children without disabilities, but they did not differ significantly from the comparison group with respect to joint pain, muscle weakness, nausea, diarrhea, constipation, or menstrual related symptoms (see Table 2). Of particular note, mothers of children with FXS experienced twice as many days with hot flashes as did mothers of children without disabilities. Mothers of adolescent and adult children with FXS also reported over three times as many days with dizziness as did mothers of similarly-aged children without disabilities.

However, counter to our first hypothesis, mothers of adolescents and adults with FXS did not exceed mothers of adolescents and adults with ASD on any premutation carrier-related health symptom, and in fact were significantly less likely to experience joint pain, muscle weakness, constipation, and menstrual-related symptoms than mothers in the ASD group. Furthermore, mothers of adolescents and adults with ASD had significantly elevated levels of all daily symptoms (with the exception of dizziness) as compared with mothers of children without disabilities, which was consistent with our second hypothesis.

Next, we compared the three groups on four composite measures of health symptoms: (a) proportion of days with any premutation carrier-related symptoms, (b) proportion of days with any pain symptoms, (c) proportion of days with any GI symptoms, and (d) proportion of days with any other symptoms. Both caregiving groups reported more days with any premutation carrier-related symptoms, pain symptoms, GI symptoms, and other symptoms compared to mothers of children without disabilities (see Table 3). Mothers of adolescents and adults with FXS and mothers of adolescents and adults with ASD did not differ significantly from each other on the composites of premutation carrier-related symptoms, pain symptoms, or other symptoms; however, mothers of adolescents and adults with ASD reported significantly more days with GI symptoms than mothers of adolescents and adults with FXS. Notably, both groups of caregiving mothers reported at least one premutation carrier-related health symptom on approximately three-fourths of days in the 8-day diary study, compared with about 50% of days for the mothers of children without disabilities, and they experienced pain symptoms on at least two-thirds of the days.

To examine our third hypothesis, we compared differences between the three groups in daily mood, specifically, negative and positive affect. We hypothesized that mothers in both caregiving groups would have higher average negative affect and lower average positive affect compared to mothers of children without disabilities. Our hypothesis was again partially supported. Findings indicated that mothers of adolescents and adults with ASD reported significantly higher levels of negative affect than mothers of adolescents and adults with FXS who, in turn, had higher

Table 2 Proportion of days with symptoms controlling for age, education, and family income

	FXS (n = 112) (%)	AAA (n = 96) (%)	MIDUS (n = 230) (%)	*F*	
Headache	26.9	26.7	13.6	18.94***	FXS > MIDUS AAA > MIDUS
Backache	21.9	25.7	13.0	7.97***	FXS > MIDUS AAA > MIDUS
Muscle soreness	26.6	36.2	16.6	16.23***	FXS > MIDUS AAA > MIDUS
Fatigue	41.8	49.2	24.9	22.00***	FXS > MIDUS AAA > MIDUS
Joint Pain	25.6	41.4	18.3	15.17***	AAA > FXS AAA > MIDUS
Muscle weakness	6.2	13.0	4.5	6.74**	AAA > FXS AAA > MIDUS
Dizziness	5.0	4.6	1.3	5.44**	FXS > MIDUS
Nausea	4.7	7.1	2.5	6.52**	AAA > MIDUS
Diarrhea	3.5	7.1	2.5	5.73**	AAA > MIDUS
Constipation	3.2	7.6	1.4	8.07***	AAA > FXS AAA > MIDUS
Menstrual related symptoms	4.0	9.5	3.4	5.40**	AAA > FXS AAA > MIDUS
Hot flashes or flushes	15.4	19.2	6.9	8.57***	FXS > MIDUS AAA > MIDUS

Adjusted means are reported. FXS is a sample of premutation carrier mothers of adolescent and adult children with FXS; AAA is a sample of mothers of adolescent and adult children with ASD; MIDUS is a nationally-representative sample of mothers of similarly-aged children without disabilities

† $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$

Table 3 Health composite scores controlling for age, education, and family income

	FXS (n = 112) (%)	AAA (n = 96) (%)	MIDUS (n = 230) (%)	*F*	
Any premutation carrier-related symptoms	75.1	80.4	54.0	31.25***	FXS > MIDUS AAA > MIDUS
Any pain symptoms	66.2	72.8	43.2	32.92***	FXS > MIDUS AAA > MIDUS
Any GI symptoms	11.2	19.3	6.2	16.26***	AAA > FXS > MIDUS
Any other symptoms	45.1	46.9	26.7	15.40***	FXS > MIDUS AAA > MIDUS

Adjusted means are reported. FXS is a sample of premutation carrier mothers of adolescent and adult children with FXS; AAA is a sample of mothers of adolescent and adult children with ASD; MIDUS is a nationally-representative sample of mothers of similarly-aged children without disabilities

† $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$

Table 4 Negative and positive affect controlling for age, education, and family income

	FXS (n = 112)	AAA (n = 96)	MIDUS (n = 230)	*F*	
Negative affect	6.47 (.11)	6.93 (.12)	5.66 (.08)	41.93***	AAA > FXS > MIDUS
Positive affect	17.01 (.37)	15.52 (.41)	17.38 (.26)	7.09**	AAA < FXS AAA < MIDUS

Adjusted means are reported. FXS is a sample of premutation carrier mothers of adolescent and adult children with FXS; AAA is a sample of mothers of adolescent and adult children with ASD; MIDUS is a nationally-representative sample of mothers of similarly-aged children without disabilities

† $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$

levels of negative affect than mothers of similarly-aged children without disabilities (see Table 4). In contrast, although mothers of a son or daughter with ASD reported a significantly lower level of positive affect than mothers of adolescent and adult children with FXS and mothers of children without disabilities, there were no significant differences between the FXS group and the comparison group of mothers of children without disabilities in positive affect.

Follow-Up Analyses

As a follow-up analysis, we examined whether controlling for the level of child behavior problems would reduce the differences between the FXS and ASD groups in health symptoms and positive and negative affect. Past research indicates elevated levels of behavior problems in both adolescents and adults with ASD and their peers with FXS, but the particular behavioral phenotype of the two groups may differ (Smith et al. in press), and those with FXS who also have an ASD diagnosis often have the most severe behavior problems. In the present study, there was a trend for individuals with FXS to exhibit fewer behavior problems than those with ASD (55.9% of days with at least one behavior problem versus 64.8% of days with at least one behavior problem, $F = 3.26$, $p = .07$). However, when we further divide the sample of adolescents and adults with FXS into those with an additional ASD diagnosis and those who did not have this diagnosis, the three-group comparison revealed that those dually-diagnosed with both FXS and ASD had more study days with at least one type of behavior problem ($F = 12.16$, $p < .001$). Individuals dually-diagnosed with FXS and ASD experienced behavior problems on 81.1% of study days compared to only 47.4% of days for individuals with FXS-only ($p < .000$). The FXS-ASD group also had more behavior problem days than individuals with ASD-only (81.1% of days vs. 64.8% of days), but this trend was not significant at the .05 level ($p = .07$). Individuals with ASD-only also had more behavior problem days (64.8% of days) than individuals with FXS-only ($p < .000$).

Based on these differences in behavior problems, we conducted separate ANCOVAS, first comparing the two groups of mothers (mothers of children with FXS (with and without ASD) and mothers of children with ASD-only), controlling for average daily behavior problems in the target child and the number of children with disabilities in their family, as well as maternal age, maternal education

level, and family income. When controlling for behavior problems and the number of children with disabilities in the family, the contrasts between the two groups of mothers were no longer statistically significant for the maternal symptoms of muscle weakness, constipation, or any GI symptoms. However, even after controlling for child behavior problems, mothers of adolescents and adults with ASD reported a significantly higher proportion of days with joint pain and menstrual symptoms, a lower level of positive affect, and a higher level of negative affect compared to mothers of a son or daughter with FXS (data available from first author).

We further compared the health symptoms of mothers of dually-diagnosed children (FXS and ASD) to mothers of children with FXS-only as a follow-up analysis within the FXS sample. Although mothers of children dually-diagnosed with both FXS and autism reported more days with symptoms than mothers of children with FXS-only, only one contrast (menstrual symptoms) was statistically significant at the .05 level (data available from first author).

Discussion

The present study has important implications for our understanding of physical and psychological health in mothers of children with neurodevelopmental disorders. Most notably, mothers of adolescent and adult children with such disorders in the present study experienced very high levels of daily health symptoms compared to mothers of children without disabilities. Caregiving mothers experienced at least one premutation carrier-related health symptom on approximately three quarters of the days in the 8 day study, suggesting that the majority of time, mothers of adolescent and adult children with disabilities are coping with their own health difficulties, even as they are providing care for their children. These findings clearly highlight the need for family-centered services and comprehensive supports for parents of adolescent and adult children with disabilities.

Based on prior studies documenting health problems in premutation carriers (Coffey et al. 2008; Rodriguez-Revenga et al. 2009), we had hypothesized that premutation-carrier mothers would experience more days with health symptoms than mothers of a son or daughter with ASD. Counter to our hypothesis, results revealed that, in general, premutation-carrier mothers had similar levels of daily symptoms as mothers of a son or daughter with ASD. Even more surprising, however, was that for some symptoms (i.e., muscle weakness, joint pain, and menstrual symptoms), mothers of adolescents and adults with ASD reported *more* days with symptoms than mothers of children with FXS. These findings seem to suggest that the caregiving stress may carry an equal, if not more powerful, weight in influencing day-to-day health symptoms than genetic vulnerability.

One likely explanation for these findings is that carrier status and caregiving stressors play different, and potentially interconnected, roles in the development of particular types of health problems. As an example, in the present study, premutation mothers reported symptoms of dizziness on significantly more days than mothers of children without disabilities. However, we did not find elevated dizziness in the ASD group, even though the FXS and ASD caregiving groups displayed similarly-elevated levels of many other symptoms including backaches and fatigue. This is congruent with Coffey et al.'s (2008) suggestion that while mRNA toxicity may directly influence certain neurodegenerative symptoms, alternative disease pathways may exist for other types of health problems. Thus, our findings are consistent with other studies indicating that symptoms such as dizziness may be related to carrier status (Chonchaiya et al. 2010). In contrast, caregiving stress may be driving the emergence of symptoms such as fatigue and muscle soreness, which is why these symptoms would be heightened in both groups of caregiving mothers.

Another possible explanation to consider regarding in the lack of elevated symptoms in the FXS group relative to the ASD group is that the present study focused on only one point in the life course: midlife. There is some evidence to suggest that genetic vulnerability, specifically carrier status, may play a greater role in health symptoms as women age. Work in the area of FXPOI has shown that premutation carriers may not display difficulties with ovarian function prior to age 30, but that problems may arise during the later reproductive years (Sullivan et al. 2005). Similarly, based on clinical reports, symptoms of FXTAS often are not evident for some carriers until they are in their 70s or 80s and the rate of symptom progression can be highly variable (Hagerman and Hagerman 2004). It may be that some mothers in our study will go on to develop additional premutation-specific symptoms as they age. Prospective longitudinal studies are needed to document how symptoms may develop and change over time for premutation carriers as well as how correlations of symptoms and various biological markers (e.g., CGG repeat length) may differ depending on the particular period in the life course.

It is also important to highlight the findings regarding daily positive and negative affect. As we hypothesized, mothers of adolescent and adult children with disabilities (FXS and ASD) reported higher levels of negative affect than mothers of similarly-aged children without disabilities. We also found that negative affect was particularly elevated in mothers of children with ASD. Consistent with prior studies (Smith et al. 2010), positive affect was lower

for mothers of children with ASD than mothers of children without disabilities. Interestingly, in contrast with our hypothesis, mothers of a son or daughter with FXS did not differ significantly in positive affect from mothers of children without disabilities. Additionally, even after controlling for child behavior problems, mothers in the FXS group had higher levels of positive affect than mothers in the ASD group. This finding underscores that positive and negative affect are not necessarily opposite emotions on a shared continuum and raises interesting questions regarding possible protective mechanisms for premutation-carrier mothers. Given that higher levels of positive affect have been repeatedly associated with better health in other populations (Cohen and Pressman 2006; Xu and Roberts 2010), a valuable area for future research would be to consider both what contributes to positive affect in premutation mothers and how positive affect may relate to their long-term health outcomes.

The present study was not without limitations. First, although mothers in the FXS group were drawn from across the United States and Canada, families in the current study likely are not representative of all families of children with FXS, as the majority of mothers in our study reported high levels of educational attainment. Second, mothers of children with ASD were significantly older than mothers of children with FXS and mothers of children without disabilities; as such, we controlled for age in all of our analyses. Third, given the AAA and MIDUS studies did not measure CGG repeat length, we cannot entirely rule out the possibility that some mothers in those samples may have been premutation carriers. However, given that the prevalence of the premutation is approximately 1 in 149 for females (Song et al. 2003) and that none of the children in either comparison groups were diagnosed with FXS, we feel this is a minimal risk. Fourth, the present study did not measure the phase of the menstrual cycle for mothers or their menopausal status, which could have influenced the level of symptoms. However, the start day of the study was randomized, so the distribution of menstrual days was likely equivalent across the groups. Fifth, our sample size was small for our follow-up analyses comparing mothers of children dually-diagnosed with FXS and ASD to mothers of children with FXS only, perhaps explaining the lack of statistically significant differences.

Next, although mothers of individuals with ASD are a well-suited comparison group for mothers of children with FXS given the similar types of caregiving stresses experienced by both groups of mothers (Seltzer et al. 2004), there are still weaknesses associated with this approach. Some parents of children with ASD evidence aspects of the broader autism phenotype (Piven et al. 1997), so it is possible that mothers of children with ASD may carry their own biological propensity for health problems. However, at this time the genetic underpinnings of ASD, as well as how genes may influence maternal coping and health, are not well understood. To account for this possible confound, future work should incorporate additional comparison groups of parents of children with disabilities such as Down syndrome, where the genetic condition is not inherited. Additionally, more characterization is needed of genetic and physiological factors in mothers of children with developmental disabilities as such factors may elucidate our understanding of the impact of caregiving stress on maternal health. Finally, to better control for caregiving stress, population-based studies are needed to determine the prevalence of health symptoms and conditions in premutation carriers both with and without children with FXS.

In conclusion, the present study documented elevated levels of daily health symptoms in premutation-carrier mothers of adolescents and adults with FXS and mothers of similarly-aged children with ASD. The study also found differences in daily mood between caregiving mothers and non-caregiving controls, with mothers of children with disabilities (both FXS and ASD) reporting higher levels of negative affect than mothers of children without disabilities. However, mothers of children with FXS reported similar levels of positive affect compared to mothers of children without disabilities, highlighting syndrome-specific differences in the daily experiences of caregiving mothers and underscoring a call for more investigation into the interplay of genetics and the environment in the development of health symptoms for caregiving parents. Most importantly, results from the current study indicate a significant need for interventions and services that support the health and well-being of parents of children with disabilities across the life course.

Acknowledgments This research was supported by grants from the National Institute on Aging to support longitudinal research on families of adolescents and adults with autism (R01 AG08768, M. Seltzer, PI) and to conduct a longitudinal follow-up of the MIDUS (Midlife in the US) investigation (P01 AG020166, C. Ryff, PI, and R01AG019239, D. Almeida, PI). The original MIDUS study was supported by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development. This study also was supported by a grant from the National Institute of Child Health and Human Development to the IDDRC at the University of North Carolina (P30 HD003100-S1) to support a Fragile X Research Center. The Fragile X Research Center has three additional sites (Research Triangle Institute International, the University of Wisconsin-Madison, and University of Kansas). The present analysis was based on data collected at the UW-Madison Waisman Center site (M.M. Seltzer, PI). We also received support from the Waisman Center (P30 HD03352, M.M. Seltzer, PI). We would like to thank the National Fragile X Foundation for providing informational materials to share with families in the FXS study. We additionally thank Don Bailey for his thoughtful comments on an earlier draft of this paper. Finally, we are extremely grateful to the families who participated in this study; without their generous support and commitment, our research would not be possible.

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