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Height and Body Mass Index in Fragile X Syndrome: A Longitudinal Assessment

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Abstract

Objectives: Previously reported data regarding growth parameters in individuals with fragile X syndrome (FXS) are inconsistent. We conducted longitudinal analysis of height and body mass index (BMI) in large number of individuals with FXS.

Methods: Age- and sex-specific z-scores for height and BMI of 1,223 individuals with FXS were calculated based on published normative data. Mixed-effect linear regression models were fit separately for males and females, z-scores for height and weight were regressed against age and adjusted for intellectual disability (ID) and psychotropic medication use.

Results: Mean height z-score for both sexes decreased with age and was lower than normative data. Mean BMI z-score was greater than normative data in both sexes and this disparity increased with age. BMI z-score in females was greater for those with moderate or severe ID than those with no or mild ID. Individuals taking antipsychotics had higher BMI z-scores than those taking no or other medications; those taking anticonvulsants or stimulants had lower BMI z-scores.

Conclusions: Individuals with FXS are at elevated risk for overweight and obesity. The risk is higher in individuals taking antipsychotics and among females with severe ID. These findings warrant increased attention to obesity prevention for all individuals with FXS.

Introduction

Worldwide the prevalence of obesity between 1980 and 2013 has increased by 27.5% in adults and 47.1% in children[1]. Individuals with intellectual disability (ID) are considered a high-risk group for obesity, as studies have shown an increased obesity rates in children and adults with ID when compared to typically functioning controls[2,3,4,5]. Fragile X syndrome (FXS), caused by the silencing of Fragile X mental Retardation gene (*FMR1*) is the most common monogenic cause of inherited ID and autism spectrum disorder (ASD)[6]. Since the gene defect is located on chromosome X, the condition is typically more severe in males.

Recently concern have increased regarding obesity in childhood onset neurodevelopmental disordersand ASD. Because such neurodevelopmental disorders start early in life, an association with obesity starting in childhood could predispose them to long-term cardiovascular disease and reduce long term quantity of life[7]. It is most importantto understand the modifiable factors that might lead to obesity in children with neurodevelopmental disorders. For example, converging evidence suggest that the use of antipsychotic drugs can lead to obesity, lipid and blood glucose dysregulation and increased risk for premature cardiometabolic morbidity and mortality[8]. Thus, understanding if there is an association between obesity and FXS would be important for better management of this major neurodevelopmental disorder.

Several studies have examined obesity in FXS but have provided inconsistent results. A published survey of 885 families with FXS found that the prevalence of obesity in adults with FXS was similar to the prevalence in the general population; however, the obesity prevalence in boys with FXS was higher (31%) than in typically developing age matched controls (18%)[9]. A study conducted by the Fragile X Clinical and Research Consortium, which included 260 patients with FXS (198 males and 62 females), concluded that the weight of children and adolescents with FXS could be higher than in the general population[10], but this conclusion could have been influenced by an outlier subgroup of obese patients. A more recent study analyzed longitudinal data of 147 males and females with FXS followed during a 7-to-9-year period concluded that BMI progressively increases with age[11].

To better understand the association between FXS and obesity, we utilized a unique longitudinal data source. The Fragile X Online Registry with Accessible Research Database (FORWARD) is a longitudinal, multi-site collaborative database created through a cooperative agreement with the Centers for Disease Control (CDC). The FORWARD database is the largest such database in the US[12]. The FORWARD database includes data on cognitive functioning, problem behavior and current treatments as well as anthropometric measures. We analyzed FORWARD data to establish the prevalence of obesity in FXS in relation to normative data. We assessed group differences related to age, gender, severity of ID, and treatment with psychotropic medications.

Methods

Design of the FORWARD study

The FORWARD data collected from 33 participating clinical sites was obtained from 2012 to 2018. All participants have a full mutation confirmed by genetic testing. Individuals with FXS may enter the study at any point in the lifespan, and an attempt is made to evaluate each participant annually. At baseline, data are collected on a set of three forms designed by the project, Registration, Clinician Report, Parent Report, and three standardized assessment measures, the Aberrant Behavior Checklist (ABC), the Social Responsiveness Scale (SRS) and the Social Communication Questionnaire (SCQ). De-identified data were entered by site-based staff into a central REDCap database maintained at Columbia University. At annual follow-ups, data were collected on the Clinician, Parent Report and ABC forms. Given the clinic-based nature of the cohort, it is not possible to follow all FORWARD participants longitudinally. The anthropometric, medication and cognitive assessment data are contained in the clinician form and demographic information in the Registration form. All FORWARD subjects are consented for participation at the clinic of recruitment, and the study protocol has been approved by the IRB at each clinic site. The FORWARD study has been described in detail previously[12].

Study Sample and Statistical Analysis:

Height and weight data collected in 2,492 FORWARD baseline and follow-up evaluations were performed on 1,306 individuals with a confirmed full mutation This collected data was based on measurements by the clinic health professionals during the in person visits at the participating clinics.728 (55.7%) of the individuals had only a baseline evaluation, 265 (20.3%) had a total of two evaluations, 153 (11.7%) had three evaluations, 64 (4.9%) had four evaluations, 59 (4.5%) had five evaluations, 35 (2.7%) had 6 evaluations, and 2 (0.2%) had seven evaluations. 183 evaluations (6%) were excluded from the analyses due to inconsistencies in change over time or improbable age-specific values that could not be resolved. Specifically, observations were removed for subjects in whom height measurements decreased by ≥3cm at any time; height measurements that increased by ≥3 cm per month; height measurements that increased by more than 20cm after age 20; BMI z-scores that changed by ≥2 SD from one observation to the next; and BMI values ≥50. The final sample size for analysis was 1,223. Sensitivity analyses including the excluded observations yielded results consistent with those reported below.

To compare BMI and height in the study sample with corresponding parameters in the general population (normative data) z-scores for height and BMI were calculated using WHO formulations and data for participants aged 0-2 years[13] and CDC formulations and data for participants older than 2 years[14]. Mixed-effect linear regression models of BMI and height z-scores were developed; the initial models were fit with age as a continuous predictor, and indicators for use of eight classes of medications were included as covariates: alpha-agonists, antipsychotics, anxiolytics, mood stabilizers, non-SSRI anti-depressants, SSRIs, anticonvulsants, stimulants. An age-sex interaction was included in the models so that sex-specific estimates of the relationship of age and BMI could be generated. These models featured random intercepts for subject and an AR(1) correlation structure for

repeated observations within subject. Contrasts were derived from the model parameters to estimate mean z-scores by age group (0-5, 6-10, 11-18, 19+), and to determine whether these means were significantly different from the published normative data. To assess the influence of disease severity, separate models were also fit including ID (dichotomized as mild disability or less vs moderate or greater disability) as a predictor. Contrasts were derived from this model to estimate mean z-scores for participants of different ID levels. Some younger participants were reported to be developmentally delayed but did not have an assessment of ID severity. These participants were excluded from these analyses. The initial analyses included all evaluations in which height and weight data was obtained, including those from participants with only one evaluation. Separate analyses were also conducted in which only those with longitudinal data (2 or more evaluations) were included. All analyses were performed using SAS version 9.4. Significance level was set at 5%.

Results:

As shown in Table 1, the sample of 1,223 consisted of 954 males and 269 females who were on average ~12 years of age at the time of registration in FORWARD; 23.1% were 0-5 years of age, 31.3% were 6-10, 27.6% were 11-18 and 18.1% were 19 or older. The sample was predominantly white, non-Hispanic (75.7%), 7.3% Black non-Hispanic, 12.8% Hispanic and 2.9% Asian. For 513 individuals who had 2 or more assessments, the mean number of months between first and last assessment was 38.1 months.

Model-based estimates of height and BMI z-scores by age, adjusted for the effects of medications and ID are shown in Table 2. Among 2-year-old males, the mean BMI z-score of individuals with FXS was 0.54 SD greater than normative data ($p<.0001$) and increased steadily with age to .77 SD greater than the normative reference at age 20 ($p<.0001$). Similarly, among females, BMI z-score was 0.38 SD greater than normative data among females ($p=0.0135$) at age 2 and increased to .83 SD greater at age 20. The trend of increase in BMI z-score with age for both males and females is shown graphically in Figure 1a. While the slope of increase for females is somewhat steeper than for males, this difference is not statistically significant ($p=0.1284$).

Among 2-year-old males, the mean height z-score of individuals with FXS was 0.11 SD greater than in normative data, a non-significant difference ($p<0.2956$) and decreased steadily with age to −0.36 SD slightly greater than the normative data at age 20 ($p<.0001$). Similarly, among females, height z-score at age 2 was −0.01 SD less than the normative data among females, a non-significant difference ($p=.9761$) and decreased to −0.38 SD less than the normative data at age 20 ($p<0.0076$). The trend of decrease in height z-score with age for both males and females is shown graphically in Figure 1b. The difference in decline of height z-score with age between the sexes is not statistically significant ($p=0.4661$). Figure 2 shows distributions of FXS individuals BMI-Z scores (A) and height Z scores (B) at different ages.

In summary, among individuals with FXS, BMI is significantly greater compared to the normative reference at all ages and among both males and females, and this disparity

increases with age. Height decreases with age and is significantly lower than in the normative reference by adulthood.

There was no significant difference between males and females in BMI z-scores (p=0.1797) or height z-scores (p = 0.3159), controlling for age, and the gender-by-age interaction was also not significant (BMI p= 0.1284, height p =0.4661), indicating no significant sex difference in the association between age and BMI or height z-scores.

In terms of medications, as shown in Table 3 those using antipsychotics had higher BMI z-scores (p <.0001) while people taking anticonvulsants or stimulants had lower BMI z-scores (p=0.0266; p<.0001, respectively) than those not taking medications, adjusting for age and the effects of other medications. No medication was found to have significant influence on height z-scores.

The results shown in Table 4 indicate that ID severity was significantly associated with BMI z-score only among females (female p = 0.001, male p = 0.125). Females with moderate ID or greater, had higher mean BMI z-scores compared with those with mild ID or less, adjusted for medications and age (score difference=0.5021; p=0001). ID severity had no significant relationship with height z-score for either males (p = 0.3262) or females (p= 0.9205).

To determine that the significant effects reported above hold up when the analysis is limited to individuals with longitudinal data, the models were repeated, limited with participants with two or more annual visits (n=513). Demographic characteristics of those in this subset are similar to those shown in Table 1.

Among individuals with more than one visit, as with the analyses of the entire cohort, age was significantly associated with BMI z-score (p=0.0053) and older individuals had higher average BMI z-scores than younger patients in each age group (Table 5). Similarly, as in the full sample, height z-score decreased significantly with age (p<.0001).

The BMI z score slope among those with multiple visits was similar to that of the entire study cohort, with a progressive increase in BMI z-score discrepancies with increasing age. (longitudinal sample: b=0.018, p<.0001; full sample: b=0.013, p=.0053).

Discussion

This is the largest study of height and BMI in patients with FXS reported to-date (see Table 6). Unlike most previous studies, we report data in all age groups and assess the association of BMI and height z-scores to the ID severity and the use of psychotropic medications. Unlike some of the previous studies that showed increased BMI only in children or adolescents with FXS, our study found significantly elevated BMI z-scores into adulthood and increasing BMI with age compared to the normative population. These findings should motivate increased attention in FXS clinics to weight control and surveillance for potential obesity associated disorders.

BMI z-scores were significantly higher among individuals who used anti-psychotic medications. These findings are in concordance with previous studies that showed increased weight gain in young individuals with mental disorders, who were treated with antipsychotic medications[15]. It has also been shown that weight loss programs are less efficient for individuals on antipsychotic medications[16]. This medication-associated weight gain may involve interference of the medication with neurohormone receptor signaling, mitochondrial function or the constitution of the patients' microbiome[17] These findings suggest that weight awareness and weight control programs should be initiated for patients with FXS at the onset of antipsychotic medication therapy. While BMI z-scores were elevated among those with antipsychotic medications and severe ID, the increase in BMI z-score with age and the disparity in BMI z-score at all ages with respect to the general population remain statistically significant even after adjusting for the effects of medication and ID.

When evaluating obesity in FXS, it is important to consider the presence of a distinct group of FXS individuals with severe obesity, food seeking behavior and hypogonadism, who resemble patients with Prader-Willi syndrome referred to as Prader-Willi phenotype in Fragile X[18,19,20,21]. Individuals with apparent characteristics of this phenotype could not be identified based on our sample data. While the results of the analyses limited to those with longitudinal data were consistent with those that include participants with only one visit, it is important to note that participants may be recruited into FORWARD at any age, and that the span of longitudinal data for most individuals is only 2-3 years. If age at entry into FORWARD is associated with disease severity or medication use, this creates a potential for bias. However, our models incorporated adjustment for the effects of psychotropic medication and severity of ID. Moreover, our results show that BMI is significantly greater at *each age* than it is in the general population; this finding is not subject to bias with respect to age of study entry.

Only FXS females showed an association between the degree of ID and BMI z-scores (Table 4). A possible explanation of this finding may be related to a narrower range of ID in males that would decrease the statistical power to detect differences between the ID severity groups.

Metformin, a drug used to treat type 2 diabetes, was recently found to decrease obesity, improve language capability, and reduce aberrant behavior in patients with FXS'[22,23]. Expanded clinical trials with metformin are ongoing'[22,23]. Metformin is also effective in treating antipsychotic induced weight gain and may be considered even in FXS individuals without obesity. In addition to elevated obesity in the FORWARD sample, we found a significant reduction in mean height z-score with increasing age. In both males and females, at age 15, mean adult height became significantly lower among those with FXS than in the general population and further decreased by adulthood. Greater height of younger FXS individuals is consistent with results of previous studies in which height was measured over time[10,24]. However, we believe our study is the first to report that mean height in FXS individuals at an older age is substantially lower than in the general population.

In conclusion, 1) BMI z-scores in FXS were higher than in the published normative data at all ages; 2) this disparity increased with age among both sexes and 3) height z-scores

in FXS decrease with age and by adulthood are well below the mean height of the general population. These findings call for increased attention to weight control programs in FXS clinics. This is especially relevant for patients with more severe ID and those with prescribed antipsychotic medications.

Study limitations

FXS individuals with severe manifestations may be underrepresented in this study because of the difficulties and, possibly, the reluctance of their caregivers to travel to the clinic for a research visit. Female FXS patients with mild or absent symptoms are also likely underrepresented. Finally, individuals from some minority groups may be underrepresented in the clinic population due to underdiagnosis and limitations in access.

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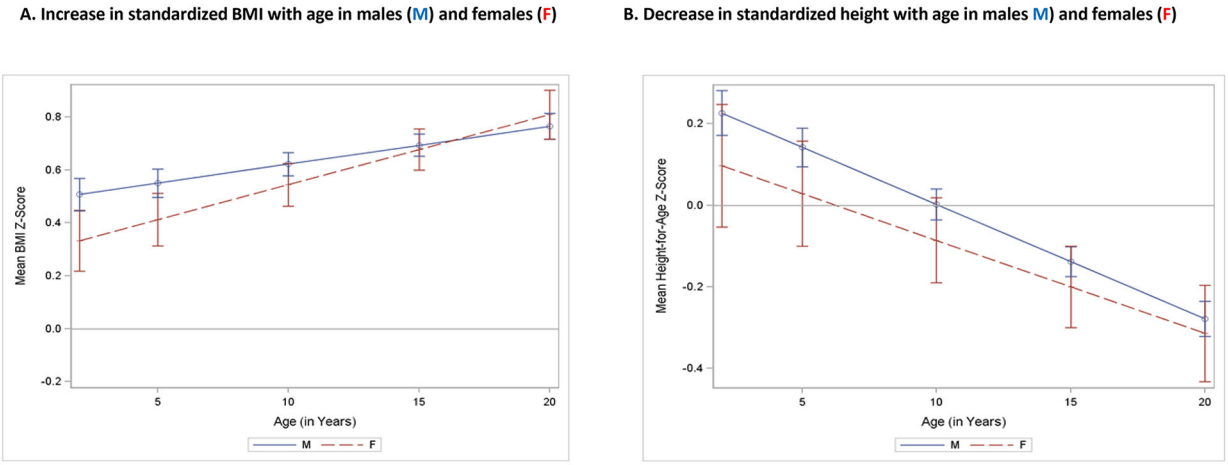

Figure 1.
BMI-z scores and Height z scores for age

BMI Z scores increase with increasing age, while height Z scores decrease with increasing age.

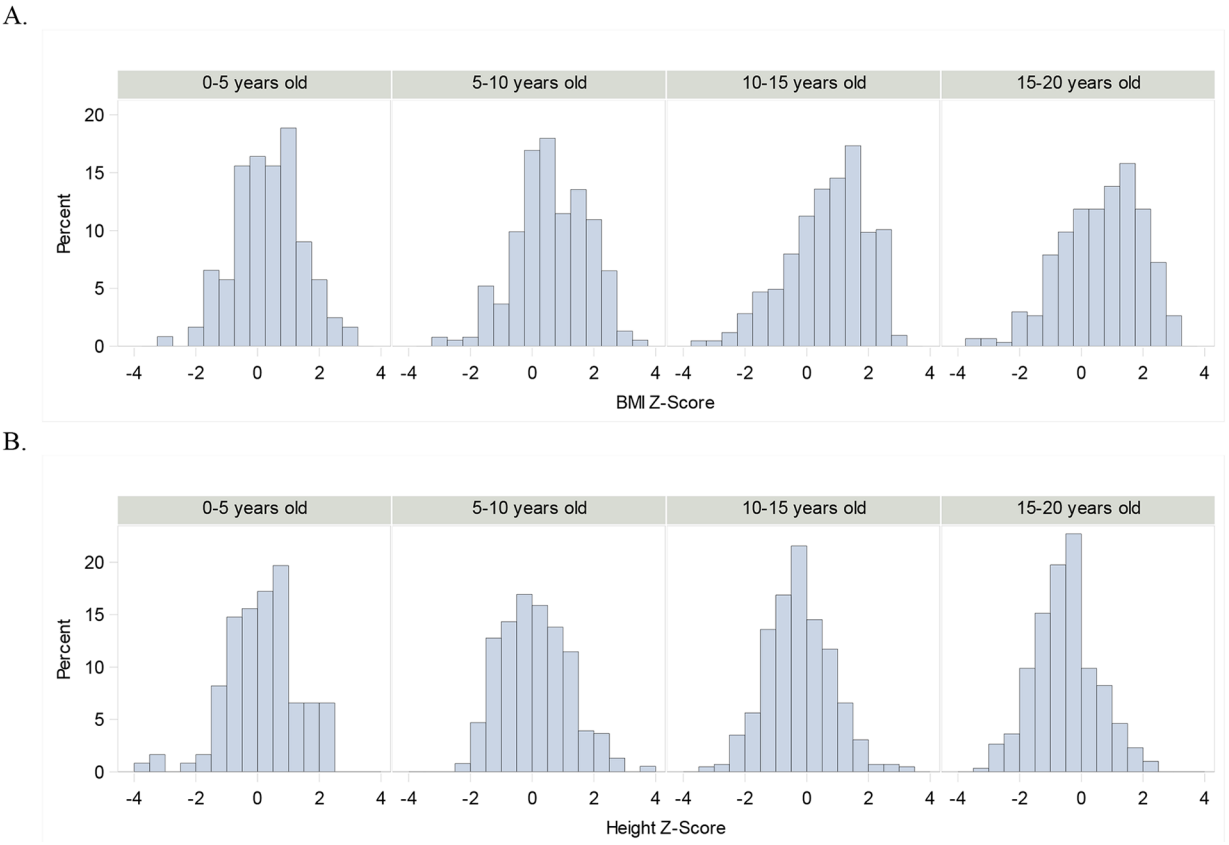

Figure 2.
Distributions of FXS individuals BMI-z scores (A) and height z scores (B) at different ages.

Table 1.

Individuals with fragile X syndrome included in the study

	Total Sample (n=1223)		Males (n=954)		Females (n=269)	
Variable	**n**	**%**	**n**	**%**	**n**	**%**
Race/ethnicity						
White non-Hispanic	926	75.7%	733	76.8%	193	71.7%
Black non-Hisp	89	7.3%	69	7.2%	20	7.4%
Asian	36	2.9%	28	2.9%	8	3.0%
Hispanic	156	12.8%	110	11.5%	46	17.1%
Other	16	1.3%	14	1.5%	2	0.7%
Age at Baseline [Mean (SD)]	1223	12.3 (9.3)	954	12.2 (9.0)	269	12.5 (10.3)
Age at Baseline -- categorized						
0-5	282	23.1%	217	22.7%	65	24.2%
6-10	383	31.3%	298	31.2%	85	31.6%
11-18	337	27.6%	264	27.7%	73	27.1%
19+	221	18.1%	175	18.3%	46	17.1%
Number of Follow up (FU) Assessments						
1	710	58.1%	549	57.6%	161	59.9%
2	247	20.2%	197	20.7%	50	18.6%
3+	266	21.7%	208	21.7%	58	21.5%
Time Followed in months (Only those with >1 FU Assessments) [Mean (SD)]	513	38.1 (20.4)	405	38.4 (20.6)	108	36.9 (19.7)
Height, cm [Mean (SD)]	1223	140.2 (27.0)	954	141.0 (28.1)	269	137.2 (22.5)

Table 2.

BMI and Height Z-Scores Relative to the General Population among Males and Females with FXS

	BMI Z-Score					Height Z-Score				
Sex and Age	**Estimate**	**SE**	**DF**	**t Value**	**Pr > |t|**	**Estimate**	**SE**	**DF**	**t Value**	**Pr > |t|**
Males										
2 y.o	0.5419	0.1147	1011	4.73	<.0001	0.1115	0.1066	1011	1.05	**0.2956**
5 y.o.	0.5793	0.1088	1011	5.32	<.0001	0.0322	0.1012	1011	0.32	**0.7504**
10 y.o.	0.6416	0.1016	1011	6.31	<.0001	−0.1000	0.0947	1011	−1.06	**0.2912**
15 y.o.	0.7039	0.0982	1011	7.17	<.0001	−0.2322	0.0915	1011	−2.54	**0.0113**
20 y.o.	0.7662	0.0991	1011	7.73	<.0001	−0.3643	0.0920	1011	−3.96	**<.0001**
Females										
2 y.o	0.3772	0.1524	1011	2.47	0.0135	−0.0052	0.1732	1011	−0.03	**0.9761**
5 y.o.	0.4531	0.1399	1011	3.24	0.0012	−0.0678	0.1543	1011	−0.44	**0.6614**
10 y.o.	0.5797	0.1254	1011	4.62	<.0001	−0.1722	0.1334	1011	−1.29	**0.1973**
15 y.o.	0.7062	0.1211	1011	5.83	<.0001	−0.2765	0.1288	1011	−2.15	**0.0320**
20 y.o.	**0.8328**	**0.1281**	**1011**	**6.50**	**<.0001**	**−0.3808**	**0.1425**	**1011**	**−2.67**	**0.0076**

Table 3.

Effects of Medications on BMI

Effect	DF	Den DF	F Value	Pr > F
Age,mos	1	1012	17.86	<.0001
AlphaAgonists	1	1012	1.46	0.2270
Antipsychotics	1	1012	17.24	<.0001
Anxiolytic	1	1012	0.02	0.9019
Mood Stabilizers	1	1012	2.90	0.0887
Non-SSRI AntiDepressants	1	1012	0.00	0.9495
SSRIs	1	1012	0.87	0.3512
Seizure Medications	1	1012	4.93	0.0266
Stimulants	1	1012	23.10	<.0001

Those using Antipsychotics had *higher* BMI Z-scores (Diff = 0.1977, p <.0001) while people taking Seizure medications (Diff = −0.2087, p = 0.0266) or Stimulants had *lower* BMI Z-scores (Diff = −0.2168, p<.0001) than those not taking medications, adjusting for age and the effects of other medications

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Table 4.

BMI-Z score is greater among those with intellectual disability (ID) among females, but not among males

Females	BMI z-score Estimate (age 10)	Standard Error	DF	t Value	Pr > |t|
Moderate, Severe or Profound ID ***Versus*** No ID/Borderline ID/Developmental Delay	0.4075	0.1484	193	2.75	.0066
Males					
Moderate, Severe or Profound ID *Versus* No ID/Borderline ID/Developmental Delay	0.078	0.0552	757	1.40	.1605

Table 5.

Individuals with two or more visits included in the longitudinal analyses

	Total Sample (n=513)		Males (n=405)		Females (n=108)		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	**Prob**
Race/ethnicity based on f1q8x and f1q6	.		.		.		0.3640
White non-Hispanic	412	80.3%	332	82.0%	80	74.1%	
Black non-Hisp	34	6.6%	26	6.4%	8	7.4%	
Asian	14	2.7%	9	2.2%	5	4.6%	
Hispanic	50	9.7%	36	8.9%	14	13.0%	
Other	3	0.6%	2	0.5%	1	0.9%	
Age at the time of registration, based on f1q4 [Mean (SD)]	513	11.8 (8.4)	405	11.9 (8.4)	108	11.6 (8.3)	0.8074
Age at Registration--categorized	.		.		.		0.6705
0-5	101	19.7%	79	19.5%	22	20.4%	
6-10	184	35.9%	148	36.5%	36	33.3%	
11-18	145	28.3%	110	27.2%	35	32.4%	
19+	83	16.2%	68	16.8%	15	13.9%	

Table 6.

Previous studies of obesity among individuals with fragile X and the *FORWARD* study

Reference number	Source of FXS Participants	Age Range	Number of Patients	Males	Females	Related Variables	Type of Study
6	National Fragile X Foundation, FRAXA Research Foundation, Conquer Fragile X Foundation	all ages	963	839	236	gender, age, overall health, learning, food habits	cross sectional
7	FXCRC	all ages	260	198	62	age, gender	cross sectional
8	University of Wisconsin study	>19	134			age, gender, ASD	longitudinal−9 years
Current study	***FORWARD*** Database, version 4	all ages	1223	954	269	age, gender, cognition psychoactive medications	Longitudinal, median follow up =38.9 months

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