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Introduction

Background

- Fragile X syndrome (FXS) is the most common known genetic cause of inherited intellectual disability
- FXS is caused by a mutation of the FMR1 gene on the X chromosome involving too many CGG repeats
- FXS causes behavioral disorders, speech and language delays, and psychiatric co-morbidity beginning in early childhood

Purpose

- To describe the characteristics of children with FXS attending a national consortium of specialty clinics
- To focus on age and its relationship to features of development, school, use of psychopharmacological medications, and services
- To provide a preliminary snap-shot from cross-sectional data to establish important age-related hypotheses prior to future analyses of data being collected longitudinally

Why is this descriptive data important?

- There are very few studies of clinic populations with large enough numbers of children with FXS to obtain some precision about the characteristics
- In addition, this data is a comprehensive picture of children with FXS, combining both reports from parents about their children's experiences in the community and clinician reports on physical characteristics and co-morbidities of these children

Methods

Study design of the FXCRC On-Line Registry System

- This was a cross-sectional study funded by the Centers for Disease Control and Prevention (CDC) to determine the feasibility of collecting data on patients with FXS attending clinics around the country
- 9 clinics contributed data on 276 individuals
- Data collection closed as at October 1, 2011 (data on visits from 2005-2011)

Eligibility criteria

- All children had the full mutation of the FMR1 gene/FXS
- Subjects for this analysis were children aged from birth through 24 years of age (older individuals may be enrolled in the System but were not included in these analyses)
- Only patients attending clinics in the United States were included in the study

Data collection forms

- Parents provided Information about medication use, achievement of developmental milestones, services received, school setting, etc.
- Clinicians provided information about the clinic visit, including history of psychotropic medications, whether they had seizures, frequent ear infections, height, weight, etc.

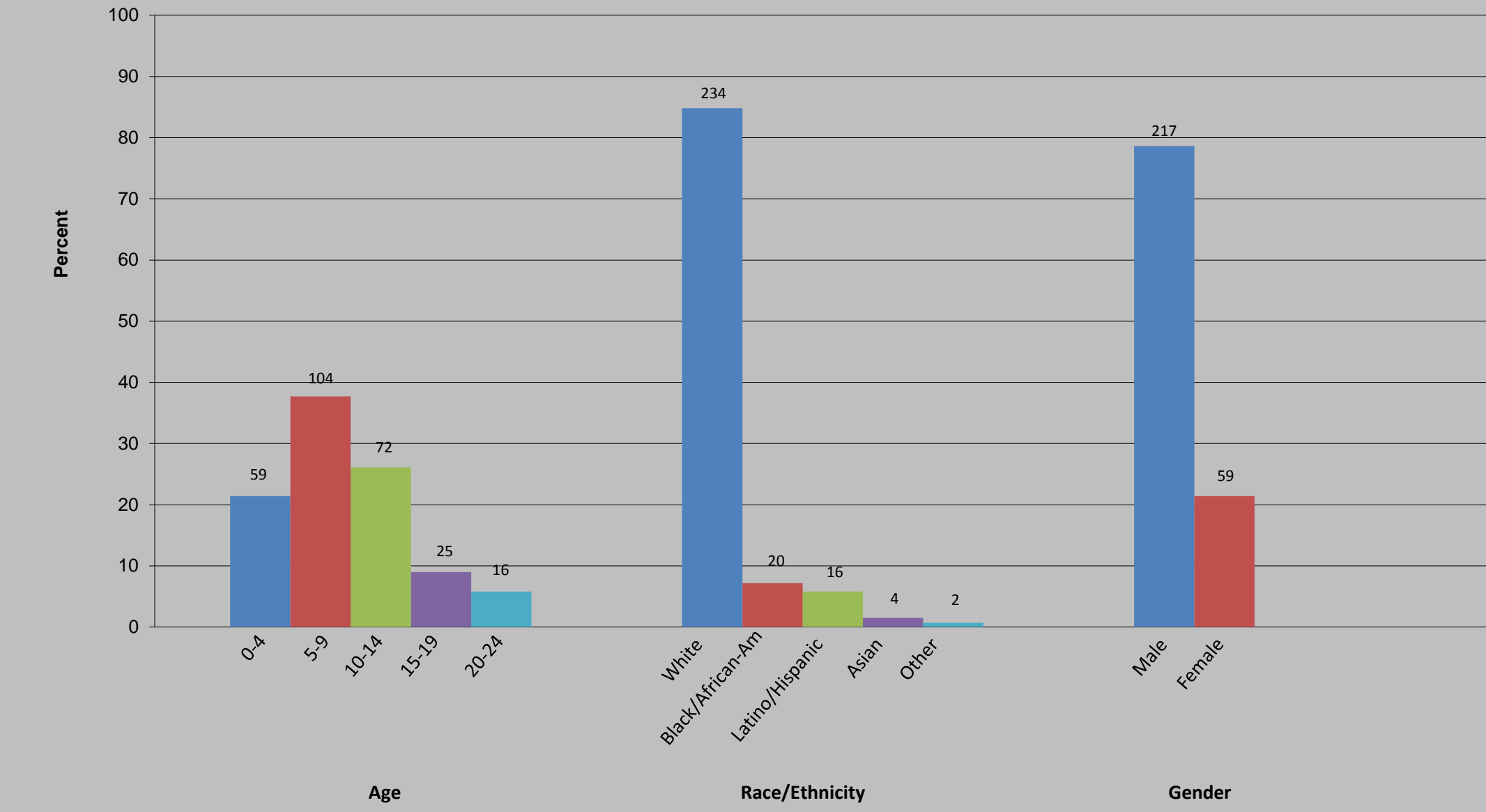
Analysis

- Frequency tabulations, means and medians, Spearman correlations, and chi-square tests were used for the analysis.

Results

The FXS clinic population was largely represented by school-age children (Figure 1). Most of the children were white, with the proportion from other race/ethnicities underrepresented as compared to a US population. The gender distribution was approximately a 4:1 ratio of males to females. We expect a higher ratio of males to females in FXS given that it is an X-linked condition.

Figure 1. Demographics of FXS population attending clinics



Birth weight and gestational age of children with FXS (Table 1) were not different from typically developing children. The proportion of births that was characterized as low birth weight (5%) was similar to estimates based on comparable births in the US (5.2%)*. The proportion that was preterm was slightly more than that of comparable data (10.9%)*, but was likely due to point preference for even numbers (36 vs 37), as the mean gestational age was 39 weeks.

* National Vital Statistics Reports, Births: Final data for 2009; non-hispanic white singleton births

Table 1. Birth weight and gestational age*

	Mean (std)
Birth weight (of the child) in grams	3443 (603)
Weeks of gestation (of the child)	38.9 (2.4)
	N (%)
Low birth weight (<2500 grams)	11 (5.0)
Preterm (<37 weeks)	31 (14.4)

* Singletons only; parent recall

We observed that the average age of diagnosis continues to be at approximately 3 years of age, lagging behind when intervention efforts are being started (2 years of age) (Table 2). There is a wide variation in both of these measures, and in the lag between the two.

Table 2. Average age at diagnosis and intervention

In Months...	Mean (std) age; Median (range)
What was age at FXS diagnosis?	38.1 (30.5); 30 (0 - 168)
What age started in intervention?	22.6 (13.3); 20 (0 - 72)
Time lag between early intervention and diagnosis	15.0 (27.9); 9 (48 before - 138 after)

Gross motor skills were not severely affected in this population (see Table 3), with 2/3 of children being able to walk by 18 months (the average was the milestone age). However, expressive language skills and being toilet trained were markedly delayed.

Table 3. Age when achieving developmental milestones

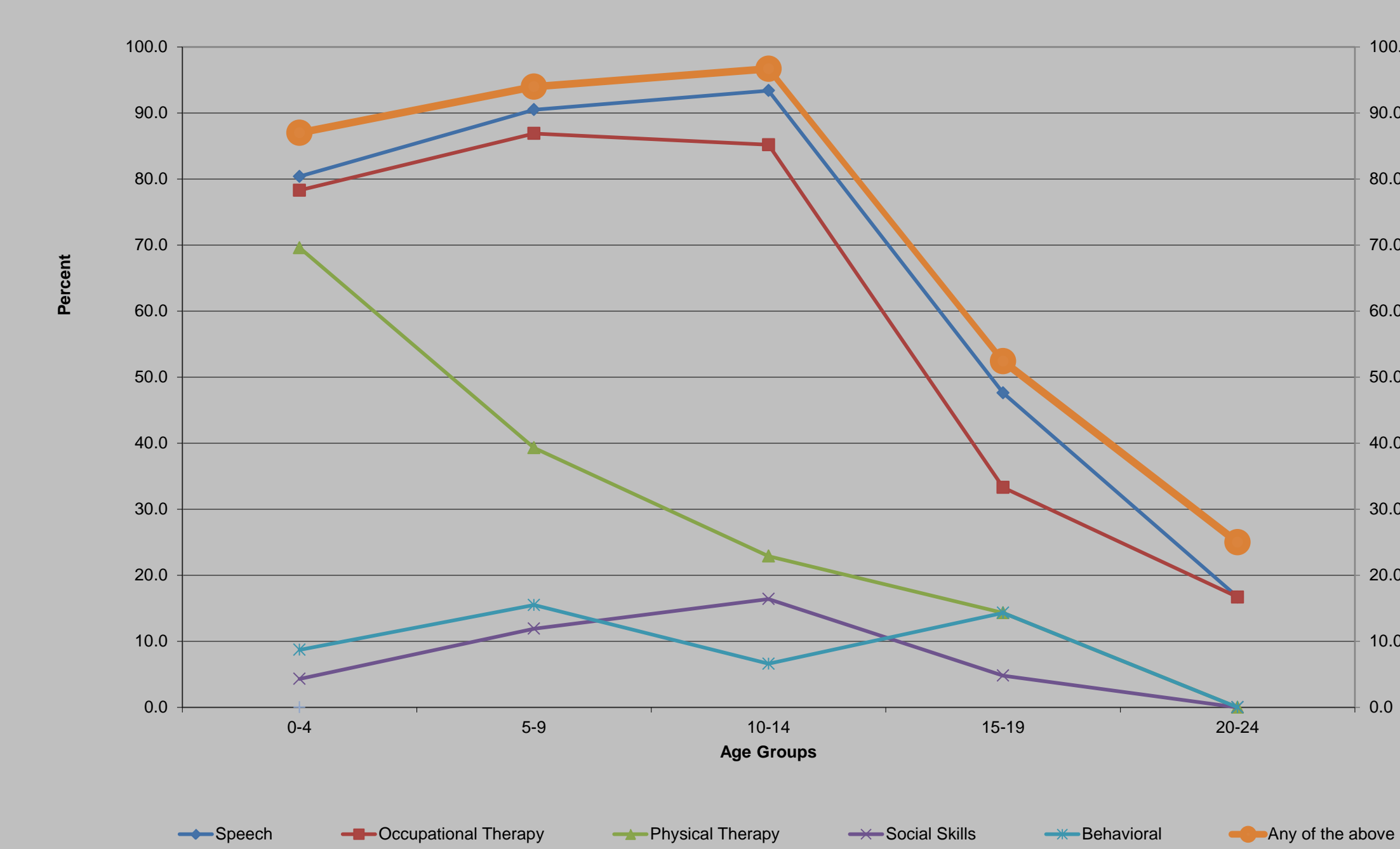
Age in months when child:	Mean (std)	Proportion achieved (by typical milestone age*)
Began to walk	17.5 (5.0)	67.7% (by 18 months)
Spoke first words	25.5 (14.0)	37.7% (by 18 months)
Was toilet trained	56.7 (25.6)	40.1% (by 60 months)

* CDC: Important milestones, checklists by age

Results (cont.)

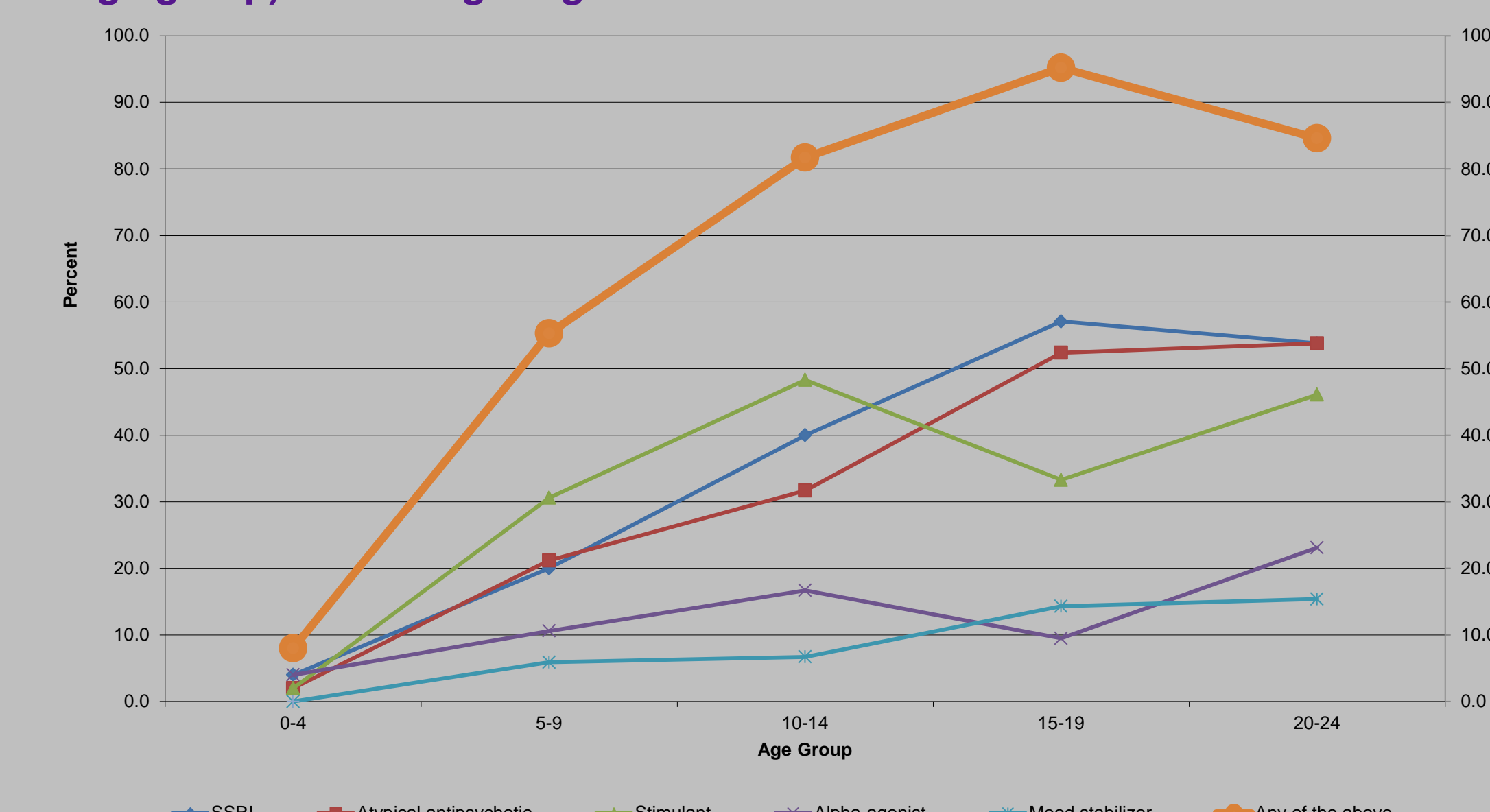
Although less than 20% of children use either Behavioral or Social Skills services across all age groups, some of the largely used services differed across age groups (Figure 2). Both Speech and Occupational Therapy were used highly in the younger ages, but both, along with Physical Therapy were decreased in use as children got older.

Figure 2. Current use of services by age group (% of age group) attending Fragile X Clinics



Overall, there was a greatly increased use of medications with age group, with at least 50% of children aged 5 or older using some psychopharmacology (Figure 3). Stimulants, SSRIs, and atypical antipsychotics were used most, with mood stabilizers and alpha-agonists used much less frequently.

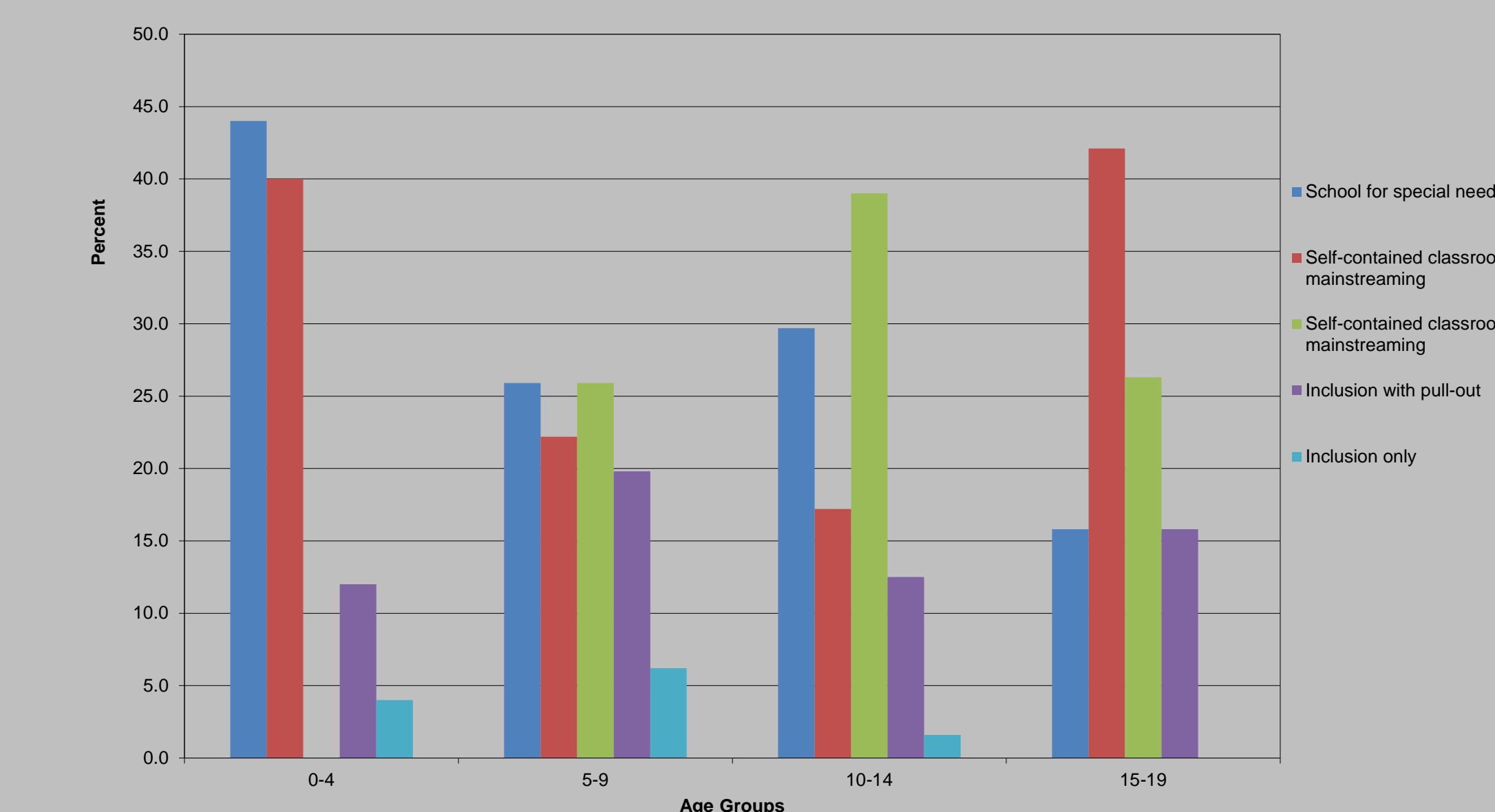
Figure 3. Current use of psychopharmacological medications by age group (% of age group) attending Fragile X Clinics



While there was a strong negative correlation (Spearman $r = -0.17$, $p < 0.01$) between use of medications and use of services (both measured as a count of the number of each item), this relationship was not found within age groups. Analyzing use as a dichotomous variable (yes/no) stratified by age also supported this conclusion. This suggests that rather than medications being used at the expense of services and vice versa, use is a function of age. With age there is an increasing tendency to rely on medications more than other therapeutic interventions for management.

Figure 4 displays the types of school settings in which different age groups spend most of their learning time. The most restrictive settings are shown from left to right and in the legend from top to bottom. About half of the children spend their learning time in the most restrictive settings (schools/classrooms without typically developing children).

Figure 4. Current school setting/classroom where patient spends most of learning time by age group (% of age group) attending Fragile X Clinics



Methodological Issues

- These cross-sectional data represent a subject's clinic visit. This may or may not be a subject's first visit, and thus is not equivalent to baseline attendance at a clinic.
- There may be missing data for a given question depending on the efforts of the family and clinic to obtain completeness. Although we cannot assure randomness in the distribution of the missing data, it is believed that missingness is due to the general burden of data collection on families and clinics.
- There was a limited precision in the measurement of some characteristics which was evidenced by the variance estimates.
- The data from parent report may be subject to recall inaccuracy due to historical recall of many years if the child is at the higher end of the study age range.

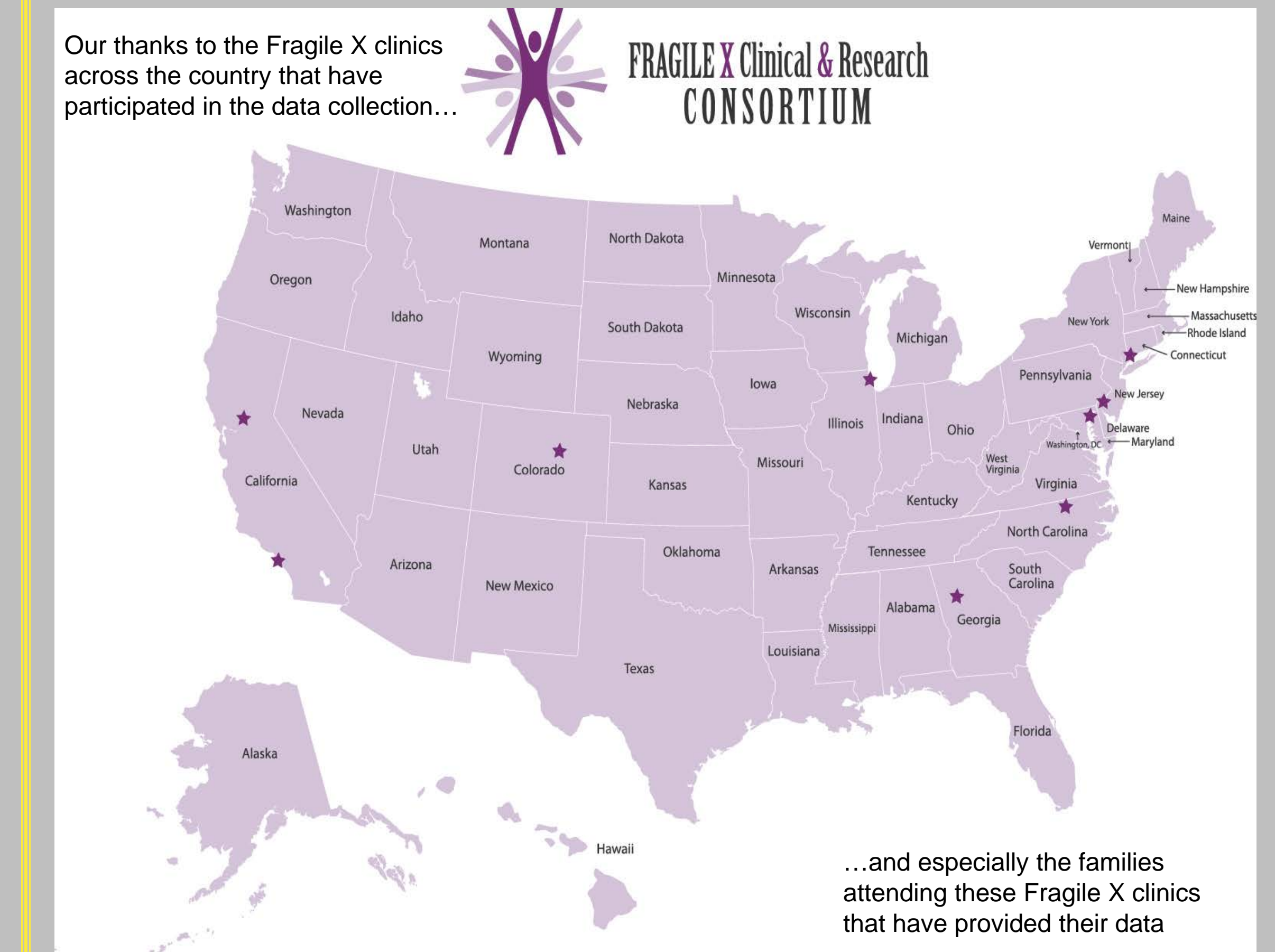
Conclusions

- Similar to results by Bailey et al (2009), we observed that the age at diagnosis was at preschool age. This has implications for the success of interventions which are expected to bring benefit the earlier that they are applied. Many of the children were receiving interventions a year before diagnosis, but without the diagnostic knowledge to assist their care plan.
- Children with FXS lag behind typically developing children in terms of their achievement of developmental milestones. Information about this developmental trajectory may be important in informing parents about the expectations for their children with FXS.
- Data suggest a strong preference overall to use services more frequently in the earlier ages and medications more frequently as children get older. Further analysis suggests that services are not utilized at the expense of medications and vice-versa.

Acknowledgments

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Our thanks to the Fragile X clinics across the country that have participated in the data collection...



...and especially the families attending these Fragile X clinics that have provided their data