

RESEARCH ARTICLE

Autism Heterogeneity in a Densely Sampled U.S. Population: Results From the First 1,000 Participants in the RI-CART Study

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The objective of this study was to establish a large, densely sampled, U.S. population-based cohort of people with autism spectrum disorder (ASD). The Rhode Island Consortium for Autism Research and Treatment (RI-CART) represents a unique public-private-academic collaboration involving all major points of service for families in Rhode Island affected by ASD. Diagnosis was based on direct behavioral observation via the Autism Diagnostic Observation Schedule, Second Edition. For the first 1,000 participants, ages ranged from 21 months to 64 years. Using Geographic Information System and published prevalence rates, the overall cohort is estimated to represent between 20% and 49% of pediatric age persons in Rhode Island with ASD, with demographics representative of U.S. Census. We observed a high rate of co-occurring medical and psychiatric conditions in affected individuals. Among the most prominent findings of immediate clinical importance, we found that females received a first diagnosis of ASD at a later age than males, potentially due to more advanced language abilities in females with ASD. In summary, this is the first analysis of a large, population-based U.S. cohort with ASD. Given the depth of sampling, the RI-CART study reflects an important new resource for studying ASD in a representative U.S. population. Psychiatric and medical comorbidities in ASD constitute a substantial burden and warrant adequate attention as part of overall treatment. Our study also suggests that new strategies for earlier diagnosis of ASD in females may be warranted. *Autism Res* 2020, 13: 474–488. © 2020 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: The Rhode Island Consortium for Autism Research and Treatment (RI-CART) represents a unique public-private-academic collaboration involving all major points of service for families in Rhode Island affected by autism spectrum disorder (ASD). In this article, we provide results from the first 1,000 participants, estimated to represent >20% of affected families in the state. Importantly, we find a later age at first diagnosis of ASD in females, which potentially calls attention to the need for improved early diagnosis in girls. Also, we report a high rate of co-occurring medical and psychiatric conditions in affected individuals.

Keywords: autism spectrum disorder; comorbidity; female autism; population study; registry

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by social impairment and restricted, repetitive behavior (RRB) [American Psychiatric Association, 2013; Lord, Cook, Leventhal, & Amaral, 2000; Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018]. Despite the clear delineation of these core diagnostic features, ASD often manifests in a manner that can affect nearly all medical and functional domains, including emotional, behavioral, developmental, neurological, medical, and physical domains [Bishop-Fitzpatrick et al., 2018; Joshi et al., 2014; Lord et al., 2000; Lord et al., 2018; Maski, Jeste, & Spence, 2011; McElhanon, McCracken, Karpen, & Sharp, 2014]. While diagnostic classifications can be made with a high level of reliability, the significant heterogeneity of ASD manifestations across multiple levels of analysis (e.g., genetic, neural, behavioral, cognitive) has created a notable degree of variability in well-designed research studies [Fein & Helt, 2017; Gillberg & Fernell, 2014; Rutter, 2014].

One of the possible contributors to ASD heterogeneity in research may relate to the availability of optimal methodologies for sample ascertainment [Joshi et al., 2014]. ASD research is often conducted using modestly sized sample numbers derived from the clinic or, alternatively, using large sample numbers derived from epidemiological studies. While epidemiological studies are well powered with reduced sampling bias, participants are often not directly evaluated, and characterization of the presentation is subsequently dependent on medical or educational records. Diagnoses and symptoms are therefore often based on insurance billing codes. The insurance billing code-based method limits opportunities for detailed characterization of participants and, additionally, is associated with bias, billing errors, and inter-provider diagnostic variability [Farmer, 2007; Tyrer & Heyman, 2016]. On the other hand, clinic-based studies obtain a wealth of detailed information and well-characterized presentations, yet they may have limited sample size, be underpowered, and lack applicability to the whole ASD population [Georgiades, Szatmari, & Boyle, 2013; Lenroot & Yeung, 2013].

It is recognized that heterogeneity in clinical presentation is influenced by genetic variability, comorbidity, and sex [Beggiato et al., 2017; Bishop et al., 2017; Havdahl et al., 2016; Masi, DeMayo, Glozier, & Guastella, 2017], and small studies will sample unevenly across these dimensions, limiting both the reproducibility and generalizability of findings. In addition, the importance of demographic factors such as socioeconomic status (SES) is particularly important to address, given the strong link between demographic factors (e.g., SES, minority status) and presentation and outcomes in ASD [Dickerson et al., 2017; Zamora, Williams,

Higareda, Wheeler, & Levitt, 2016]. Namely, disadvantaged individuals are underrepresented in ASD research and, more generally, in all clinical research. A combination methodology that can appropriately characterize the participant presentation within a large, well-represented, population-based sample may yield a more optimal ASD research sample, although practical issues such as feasibility and funding are ongoing barriers [Fein & Helt, 2017].

Given these challenges associated with ASD research, the Rhode Island Consortium for Autism Research and Treatment (RI-CART) was developed. RI-CART represents a relatively unique public-private-academic collaboration in the state of Rhode Island and includes every major point of care and service to families affected by ASD in the state [Gerber, Morrow, Sheinkopf, & Anders, 2013]. The goal of RI-CART was to create a major statewide population-based research registry for individuals with ASD and their families that also involves standardized, research level, in-person autism assessments. Here we describe the results from the first 1,000 participants enrolled in the RI-CART registry, with a particular focus on (a) the ability to obtain a large, well-characterized, population-based ASD sample that can generalize to the U.S. population; (b) the overall presentation of these participants, particularly in females with autism; and (c) the manifestation of neuropsychiatric and medical comorbidities affecting participants.

Methods

Participants and Enrollment Procedure

Study procedures were approved by the institutional review boards (IRBs) at all relevant institutions, with Lifespan Health System representing the lead IRB. Written informed consent was obtained from all participants. Participants were recruited through a broad effort across the state of Rhode Island that included outreach to providers and advocacy organizations, including encounters in treatment settings and community events, and deliberate inclusion of community members in the research team. Recruitment strategies included distribution of information by way of fliers and word-of-mouth to all relevant points of care and service for families in Rhode Island. Participating sites are listed in the Acknowledgments section. Monthly meetings were held with representatives from participating service programs across the state. RI-CART staff also held annual outreach events for families and providers, as well as attended events of participating service programs.

Participants were eligible to participate in the registry study if (a) the participant had previously been diagnosed as having ASD and/or (b) there was concern on the part of the participant, a family member, or a community clinician about a possible diagnosis of ASD or a related neurodevelopmental

disorder. Enrollment for the analyses presented here was from March 2013 through January 2016. Most recruitment efforts focused on Rhode Island (all cities and towns), with additional participants enrolled from areas of Connecticut and Massachusetts that border Rhode Island, that is, regions in the catchment area for Rhode Island-based hospitals and clinics. Assessments, typically conducted in a single visit, included a demographics questionnaire; an individual and family medical, neuropsychiatric, and developmental history; the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [Sparrow, Balla, & Cicchetti, 2005]; the Social Responsiveness Scale, Second Edition (SRS-2) [Constantino & Gruber, 2012]; and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [Lord et al., 2012], which was administered by a research-reliable ADOS-2 assessor.

Measures

Demographics and medical history forms. Parents, caregivers, and/or participants completed a custom-designed individual and family medical history. Medications were divided into classes according to those assumed by the Physicians' Desk Reference and are not necessarily representative of the prescribed indication [PDR Staff, 2016].

Adaptive behavior and verbal status. The VABS-II [Sparrow et al., 2005] was completed by a parent or caregiver. This measure provides an overall adaptive behavior composite (ABC) score and standard scores in the domains of communication, daily living skills, and social skills. Categorization of a participant as verbal was based on the parent response at the time of evaluation by RI-CART staff to the question: "Is your child verbal?"

Autism classification and symptoms. The ADOS-2 [Lord et al., 2012] was administered as a semi-structured interview and observation of ASD symptoms. Assessor reliability was established using standard methods; all ADOS-2 administrations were conducted by assessors who were trained to research reliability. The SRS-2 [Constantino & Gruber, 2012] was administered as an additional quantitative measure of individual differences in behaviors associated with ASD. The SRS-2 was completed by a parent or caregiver using one of three versions (i.e., preschool, school-age, or adult forms). Where appropriate, some adults completed the self-report version of this measure, either instead of or in addition to the caregiver report. Information concerning whether a participant had received a previous community-based diagnosis of ASD was also collected and, if so, age at time of diagnosis was recorded. The absence of a community ASD diagnosis could reflect that the community-based healthcare provider did not consider an ASD diagnosis, did not believe an ASD diagnosis was warranted, or was unsure about an ASD diagnosis; or that a formal ASD assessment was not conducted prior to study

enrollment. Information concerning the reason for lack of evidence of a community ASD diagnosis was not recorded.

GIS and estimation of depth of population sampling.

In order to describe the geographic representativeness of the sample, place-of-residence for participants was mapped using ArcGIS software, Version Release 10.3.1 [ESRI ArcGIS Desktop, 2014]. The resulting descriptive maps focus on all U.S. Census tracts in Rhode Island and on selected regions from neighboring towns in Southeast Massachusetts. In order to estimate the percentage of total people with ASD ascertained, this analysis was restricted to participants between the ages of 3 and 21 years old and to Rhode Island Census tracts—the region of focus for recruitment efforts. For the current study, analyses were restricted to participants falling in the 3- to 21-year-old age range, because diagnoses are not generally made before an age of 3 years and because of challenges in enrollment of adults [Haas et al., 2016]. We calculated four estimates of the predicted number of people in Rhode Island in this age range with ASD based on the range of prevalence statistics from recent studies (i.e., 1.0%, 1.5%, 2.0%, and 2.5%). A base rate of 1.0% of the population is consistent with ascertainment in clinical settings where ASD would be an identified condition [Christensen et al., 2016] and is relatively similar to the median prevalence estimates in Western developed nations [Elsabbagh et al., 2012]. A base rate of 1.5% is similar to surveillance data with broader ascertainment from the Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring Network [Baio, 2012; Baio et al., 2018]. Base rates of 2.0% to 2.5% are consistent with recent research that has utilized total population ascertainment from health and medical records [Myers et al., 2019; Schendel & Thorsteinsson, 2018]. This resulted in estimated numbers of possible individuals with ASD in the 3- to 21-year-old age range for each Rhode Island Census tract. The actual number of participants in the RI-CART study with an ASD diagnosis in the 3- to 21-year-old age range for each tract was then divided by the estimated number of individuals with ASD, based on prevalence measures, resulting in an approximation of the percentages of people with ASD ascertained per Rhode Island Census block. Information about the population within each geographic unit, including age, sex, number of households, representation of different races and ethnicities, and poverty indicators was obtained [Missouri Census Data Center, 2016].

Statistical analysis

Study data were managed using Research Electronic Data Capture tools [Harris et al., 2009]. For each section, descriptive statistics are reported for all obtained variables within the total sample and, where appropriate, subgroups based on the degree of concordance between community

diagnosis and results of the ADOS-2. In general, chi-square tests and analyses of variance were conducted to examine differences across diagnostic subgroups. For instances in which follow-up correlation or regression analyses were conducted, more detailed methods regarding statistical analyses are described in table legends.

Results

Overall RI-CART Study Participant Demographics

The data presented here reflect the first 1,000 participants enrolled in the RI-CART study (Table 1). The majority (67%, $n = 671$) had a formal diagnosis by a clinical professional of ASD at the time of enrollment. The remainder (33%) did not report a formal diagnosis at the time of enrollment. Age at enrollment ranged from 21 months to 64 years (Fig. 1 and Table 1). Approximately 78% (78.3%) of the participants were male. In terms of ethnicity, 72.8% identified as Not Hispanic/Latino, as compared to 73.3% as measured by the U.S. Census for the state of Rhode Island [U.S. Census Bureau, 2017]. Similarly, 12.4% of RI-CART study participants identified as Hispanic/Latino, as compared to 14.9% by U.S. Census measures. Identification of race was as follows for RI-CART study participants vs. U.S. Census data for the state of

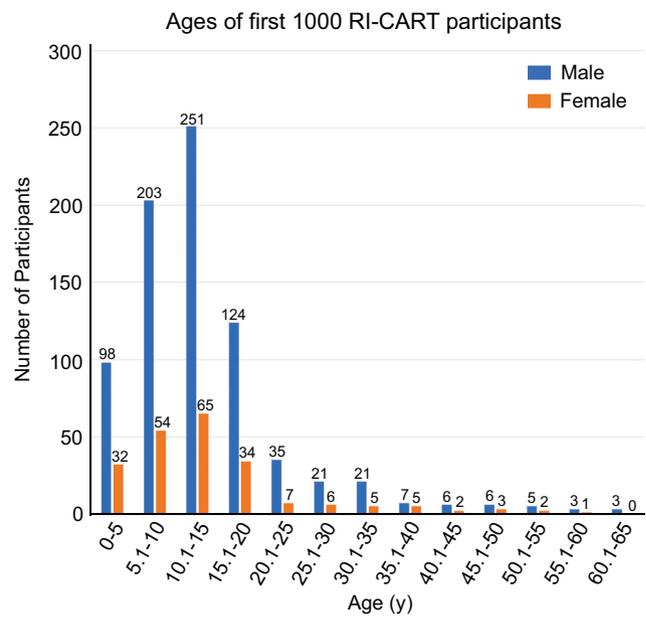


Figure 1. Ages of study participants at the time of enrollment. For the first 1,000 participants in the RI-CART study, ages at enrollment ranged from 21 months to 64 years, with a mean age of 13.62 ± 9.63 years for the overall sample. Participants were largely male, reflecting 78.3% of the sample population, and the male to female ratio was approximately 4:1.

Table 1. Demographic Characteristics of All RI-CART Study Participants

Characteristic	Overall Group	Community Dx and positive ADOS: ASD	Community Dx or positive ADOS: ASD-Inclusive	Neither community Dx or positive ADOS: Non-ASD
Participants, n	1000 ^a	533	318	101
Age, mean (SD), y	13.62 (9.63)	13.15 (9.02)	13.97 (9.84)	15.40 (11.80)
Sex, n (%)				
Male	783 (78.3)	429 (80.5)	243 (76.4)	68 (67.3)
Female	217 (21.7)	104 (19.5)	75 (23.6)	33 (32.7)
Ethnicity, n (%)				
Not Hispanic/Latino	728 (72.8)	429 (80.5)	223 (70.1)	71 (70.3)
Hispanic/Latino	124 (12.4)	70 (13.1)	39 (12.3)	14 (13.9)
Information not provided	148 (14.8)	34 (6.4)	56 (17.6)	16 (15.8)
Race, n (%)				
American Indian/Alaskan Native	5 (0.5)	2 (0.4)	3 (0.9)	0 (0.0)
Asian	10 (1.0)	6 (1.1)	3 (0.9)	1 (1.0)
Black or African American	30 (3.0)	22 (4.1)	5 (1.6)	3 (3.0)
White	718 (71.8)	424 (79.5)	221 (69.5)	67 (66.3)
Multiracial	82 (8.2)	46 (8.6)	25 (7.9)	11 (10.9)
Other	20 (2.0)	10 (1.9)	6 (1.9)	4 (4.0)
Information not provided	135 (13.5)	23 (4.3)	55 (17.3)	15 (14.9)
Community autism-related diagnosis, n (%)				
Autism	189 (18.9)	160 (30.0)	29 (9.1)	0 (0.0)
Asperger syndrome	122 (12.2)	91 (17.1)	31 (9.7)	0 (0.0)
PDD-NOS	131 (13.1)	98 (18.4)	33 (10.4)	0 (0.0)
ASD	229 (22.9)	184 (34.5)	45 (14.2)	0 (0.0)
No diagnosis	189 (18.9)	0 (0.0)	109 (34.3)	80 (79.2)
Unknown	140 (14.0)	0 (0.0)	71 (22.4)	21 (20.8)

Abbreviations: Dx, diagnosis; PDD-NOS, pervasive developmental disorder-not otherwise specified; SD, standard deviation.

^aNeither an ADOS-2 nor a community diagnosis was available for 48 individuals in the registry. Therefore, these individuals were not included in any of the subgroups.

Rhode Island: White/Caucasian, 71.8% vs. 84.4%; Black/African American, 3.0% vs. 8.1%; Asian alone, 1.0% vs. 3.6%; and Multiracial, 8.2% vs. 2.7%.

ASD Diagnostic Subgroupings and ASD Features of Participants Assessed With ADOS-2

RI-CART study diagnostic subgroups: ASD, ASD-Inclusive, and Non-ASD. Of the 671 participants who had a prior autism-related diagnosis given by their community-based clinician, specific diagnoses were reported as autism (28.2%), Asperger syndrome (18.2%),

pervasive developmental disorder-not otherwise specified (19.5%), or ASD (34.1%) (Table 1). Most large-scale, population-based studies do not incorporate in-person autism assessments. As part of the RI-CART study, we were able to administer the ADOS-2 [Lord et al., 2012] by a research-reliable ADOS-2 assessor. Participants were, thereby, stratified according to their community diagnosis at the time of enrollment and their ADOS-2 score at the study visit. In addition to the Overall Group ($n = 1,000$), this resulted in three subgroups of participants, as can be seen in Table 1: (1) ASD ($n = 533$), participants with a community diagnosis of ASD that was confirmed with a positive ADOS-

Table 2. Phenotypic Presentation of RI-CART Study Participants

Variable	Overall Group	Subgroup comparisons				P value ^a
		ASD		ASD-Inclusive	Non-ASD	
Participants, <i>n</i>	1000 ^b	533		318	101	
Age at diagnosis, mean (SD), y	5.92 (6.0)	5.71 (5.8)	<	6.80 (6.6)	N/A	0.083
Age at enrollment, mean (SD), y	13.7 (9.6)	13.2 (9.0)	≈	14.0 (9.8)	≈	15.4 (11.8)
VABS-II, mean (SD)						
Communication	71.5 (22.0)	68.05 (20.8) ^f	<	75.23 (21.7) ^e	≈	81.66 (24.5) ^e
Daily living skills	73.35 (21.2)	70.37 (20.3) ^f	<	77.69 (21.7) ^e	≈	79.28 (20.9) ^e
Social skills	65.95 (19.7)	63.19 (18.2) ^f	<	69.50 (20.8) ^e	≈	72.49 (21.2) ^e
Motor skills ^c	79.85 (19.3)	79.35 (18.9)	≈	79.80 (20.9)	≈	85.08 (18.0)
ABC	68.64 (19.1)	65.59 (17.7) ^f	<	72.53 (20.0) ^e	≈	75.96 (19.7) ^e
ADOS-2, mean (SD)						
Severity	6.25 (2.5)	7.31 (1.7) ^g	>	5.47 (2.4) ^f	>	2.10 (0.8) ^e
ADOS-2 classification, <i>n</i> (%)						
Autism	600 (60.0)	469 (88.0)		131 (56.0)	0 (0.0)	<0.001 (χ^2)
ASD	113 (11.3)	64 (12.0)		49 (20.9)	0 (0.0)	
Non-spectrum	141 (14.1)	0 (0.0)		54 (23.1)	87 (86.1)	
Data not available	146 (14.6)			84 (26.4)	14 (13.9)	
SRS-2, mean (SD)						
RRB	76.01 (11.7)	77.04 (10.5) ^f	≈	74.97 (12.2)	≈	73.16 (15.3) ^e
SCI	74.35 (11.2)	75.13 (10.1) ^f	≈	74.09 (11.6) ^f	>	70.56 (15.1) ^e
Total	75.35 (11.1)	76.24 (9.9) ^f	≈	74.82 (11.4)	≈	71.70 (15.2) ^e
Expressive language by parent report, <i>n</i> (%)						
Verbal	746 (74.8)	422 (83.9)		236 (88.7)	88 (95.7)	0.025 (χ^2)
Nonverbal	109 (11.0)	76 (15.1)		29 (10.9)	4 (4.3)	
Unsure	6 (0.6)	5 (1.0)		1 (0.4)	0 (0.0)	
Data not available	136 (13.6)	30 (5.6)		52 (16.4)	9 (8.9)	
Expressive language by ADOS-2 item A1, <i>n</i> (%) ^d						
Minimally verbal	115 (11.5)	94 (17.6)		19 (6.0)	2 (2.0)	<0.001 (χ^2)
Single-word speech	92 (9.2)	66 (12.4)		21 (6.6)	5 (5.0)	
Phrase speech	125 (12.5)	92 (17.3)		29 (9.1)	4 (4.0)	
Complex speech	523 (52.3)	281 (52.7)		165 (51.9)	77 (76.2)	
Data not available	145 (14.5)			84 (26.4)	13 (12.9)	

Note. Significance between subgroup post hoc tests with significant pairwise comparisons (Tukey) is indicated by differing letter notations (“e”, “f”, and “g”) and by appropriate notation between columns (>, <, or ≈) to indicate the direction of differences between subgroups.

Abbreviations: Dx, diagnosis; N/A, not applicable; SCI, social communication and interaction; SD, standard deviation.

^aP values for overall tests are reported. Tests of mean differences utilized ANOVA. Chi-square tests are denoted in the table.

^bNeither an ADOS-2 nor a community diagnosis was available for 48 individuals in the registry. Therefore, these individuals were not included in any of the subgroups.

^cMotor skills scores were only collected for a subset of participants, namely, those who were either <6 years old or >50 years old.

^dLanguage level from ADOS-2 was defined as follows from item A1 on each module. Minimally verbal: Module 1 scores 4 or 3; Single word speech: Module 1 scores 2 or 1, Module 2 score 3; Phrase speech: Module 2 scores 2, 1, or 0, Modules 3 and 4 scores 2 or 3; Complex speech: Modules 3 and 4, scores 1 or 0.

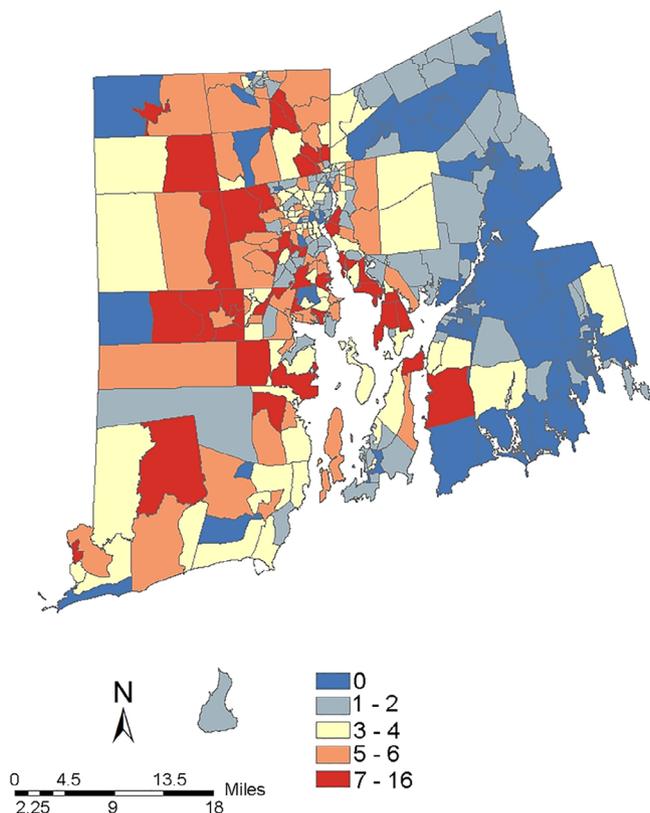
2 score; (2) ASD-Inclusive (ASD-I; $n = 318$), participants with either (a) a community diagnosis that could not be confirmed with a positive ADOS-2 score (either because the ADOS-2 score was negative or could not be obtained) or (b) a positive ADOS-2 score without a community diagnosis at the time of enrollment; and (3) Non-ASD ($n = 101$), participants who did not have or did not report a community diagnosis, and who did not have a positive ADOS-2 score. Notably, there was generally high concordance between community and research ASD diagnoses: 90.8% of participants with a community ASD diagnosis met diagnostic criteria for ASD based on the ADOS-2 (Tables S1 and S2; see Supporting Information for detailed analyses).

Regarding the ASD-I subgroup, this subgrouping reflects complex inclusion for patients with different types of evidence of ASD. This subgroup constitutes: participants with a community diagnosis of ASD but with a negative ADOS-2 score ($n = 54$ participants); participants with a community diagnosis of ASD but for whom RI-CART staff were not able

to obtain an ADOS-2 score ($n = 84$ participants); and participants with a positive ADOS-2 score but lacking a community diagnosis, because a diagnosis was not received, was unclear, or was not reported ($n = 180$ participants).

Diagnostic subgroups were significantly different in many scores on clinical measures (Table 2). There was an overall relationship between diagnostic subgroup and functional abilities, as measured by the VABS-II. Post hoc tests revealed that the ASD subgroup was the most impaired in functional skills, followed by the ASD-I subgroup and then the Non-ASD subgroup. Differences in language abilities were found between subgroups. The Non-ASD subgroup had greater expressive language abilities as compared to the ASD or ASD-I subgroups, based on both the parent report and the observer ratings from the ADOS-2 administrations. Phenotypic variation across the three categories of participants within the ASD-I subgroup is presented in Tables S3 and S4.

A Count of study participants in Rhode Island and Southeast Massachusetts by U.S. Census tract



B Percent ascertainment of the ASD population age 3 to 21 years old in Rhode Island

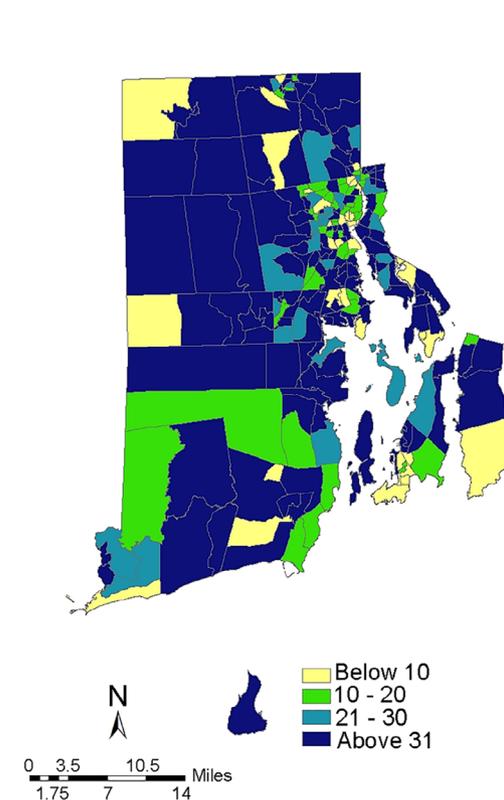


Figure 2. Geographic distribution across Rhode Island and neighboring towns in Massachusetts of study participants and enrollment depth of sample. **(A)** Numbers of study participants, as reflected by registry enrollees, of all ages by the U.S. Census tract for Rhode Island and neighboring geographic regions of Massachusetts. **(B)** Variation in rate of ascertainment (i.e., depth of enrollment), as reflected by the number of RI-CART study enrollees in the ASD or ASD-I subgroups relative to the estimated number of cases, age 3 to 21 years old and assuming a base rate prevalence of 1.5%, for each given Census block (see Section 2).

Depth of ASD Sampling Across Rhode Island

Age-restricted RI-CART study diagnostic subgroups: ASD and ASD-I. In order to estimate the proportion of ASD cases across Rhode Island that were enrolled in the RI-CART study and the extent to which enrollment sampled neighborhood diversity in the state, participants were geocoded to point locations based on home street address at the time of enrollment. The current sample is restricted to participants ranging in age from 3 to 21 years old who had a community diagnosis of ASD and/or an above threshold score on the ADOS-2 and who resided in Rhode Island. Thus, the ASD and ASD-I subgroups were classified as cases and counted in

the numerator for these analyses. Using 2010 decennial U.S. Census data, estimates of the number of people in this age range predicted to be diagnosed with ASD in each Rhode Island Census tract were generated (denominator). Four estimates were calculated, representing different ASD prevalence statistics (i.e., 1.0%, 1.5%, 2.0%, and 2.5%; see Section 2). As presented in Figure 2A, the number of participants recruited per Rhode Island Census tract varied, with the preponderance of participants in the Providence urban core, but with higher pockets of enrollment in some more geographically distant areas.

Ascertainment rates were somewhat positively skewed, indicating that, while ascertainment was high in some

Table 3. Psychiatric and Medical Co-Occurring Conditions in RI-CART Study Participants

Variable	Total Sample	Community Dx and positive ADOS: ASD	Community Dx or positive ADOS: ASD-Inclusive	Neither community Dx nor positive ADOS: Non-ASD	P value ^a
Participants, <i>n</i>	879	518	268	88	
Neurodevelopmental, <i>n</i> (%)					
ADHD	294 (33.4)	146 (28.1)	106 (40.0)	42 (47.7)	<0.001
Intellectual disability	170 (19.3)	109 (21.0)	49 (18.3)	13 (14.7)	0.431
Any neurodevelopmental	413 (47.0)	228 (44.0)	136 (50.7)	49 (55.7)	0.090
Psychiatric, <i>n</i> (%)					
Eating disorder	32 (3.6)	21 (4.0)	9 (3.4)	2 (2.3)	0.685
Bipolar disorder	44 (5.0)	16 (2.9)	20 (7.5)	8 (9.1)	0.005
Depression	133 (15.1)	50 (10.0)	61 (22.8)	22 (25.0)	<0.001
Anxiety disorder	312 (35.5)	157 (30.3)	116 (43.3)	39 (44.3)	<0.001
OCD	106 (12.1)	56 (10.8)	38 (14.2)	12 (13.6)	0.348
ODD	82 (9.3)	33 (6.4)	36 (13.4)	14 (15.9)	<0.001
CD	33 (3.8)	14 (2.7)	12 (4.5)	7 (8.0)	0.064
Any psychiatric	388 (44.1)	197 (38.0)	143 (53.4)	48 (54.5)	<0.001
Neurological, <i>n</i> (%)					
Epilepsy	40 (4.6)	27 (5.2)	10 (3.7)	3 (3.4)	0.551
Seizures	105 (11.9)	69 (13.3)	23 (8.6)	12 (13.6)	0.131
Tics	225 (25.6)	132 (25.5)	70 (26.1)	25 (28.4)	0.912
Migraines	112 (12.7)	59 (11.4)	33 (12.3)	21 (23.9)	0.004
General medical, <i>n</i> (%)					
Vision or hearing problems	426 (48.5)	230 (44.4)	144 (53.7)	54 (61.4)	0.001
Skin problems	285 (32.4)	175 (33.8)	81 (30.2)	29 (32.9)	0.631
Sleep problems	455 (51.8)	264 (51.0)	143 (53.4)	49 (55.7)	0.579
GI problems	459 (52.2)	200 (38.6)	110 (41.0)	41 (46.6)	0.302
Feeding problems	234 (26.6)	152 (29.3)	63 (23.5)	19 (21.6)	0.110
Allergies	445 (50.6)	259 (50.0)	138 (51.5)	49 (55.7)	0.554
Any general medical	794 (90.3)	473 (91.3)	242 (90.3)	82 (93.1)	0.705
Other behavioral, <i>n</i> (%)					
Self-injury	80 (9.1)	35 (6.8)	37 (13.8)	8 (9.0)	0.001
Sensory processing problems	205 (23.3)	131 (25.3)	61 (22.8)	13 (14.8)	0.056
Any other behavioral	250 (28.4)	146 (28.2)	87 (32.5)	17 (19.3)	0.016
Medications ^b <i>n</i> (%)					
Antidepressants	223 (25.5)	129 (24.9)	74 (31.1)	23 (26.1)	0.599
AEDs/mood stabilizers	69 (7.9)	43 (8.3)	23 (8.6)	5 (5.7)	0.681
Antipsychotics	135 (15.4)	78 (15.1)	53 (19.8)	9 (10.2)	0.041
Stimulants	168 (19.2)	86 (16.6)	61 (22.8)	22 (25)	0.035
Alpha-2 agonists	75 (8.6)	42 (8.1)	31 (11.6)	3 (3.4)	0.042
Anxiolytics	31 (3.5)	22 (4.2)	9 (3.4)	1 (1.1)	0.743
Any psychiatric medication	446 (51.0)	254 (49.0)	154 (57.8)	44 (50)	0.026

Abbreviations: CD, conduct disorder; Dx, diagnosis; GI, gastrointestinal.

^aP values for overall tests are reported.

^bFor this variable, *n* = 874.

areas, a number of Rhode Island Census tracts existed with proportionally fewer children with ASD represented in the RI-CART study sample. Variation in ascertainment rate by Census tract is represented in Figure 2B. Here, the ascertainment rates are based on an assumed base rate prevalence of 1.5%. These analyses demonstrated some reduced ascertainment in populations with low SES (see Supporting Information). Overall, the median state ascertainment estimates (as percentages of families sampled) were as follows for the four assumed base rate prevalence levels of ASD: 49% ascertainment at 1.0% prevalence, 35% ascertainment at 1.5% prevalence, 24% ascertainment at 2.0% prevalence, and 20% ascertainment at 2.5% prevalence.

High Rate of Co-Occurring Medical and Psychiatric Conditions in ASD Participants

Notably, of the 879 total RI-CART study participants with available data, 47.0% of the participants reported another neurodevelopmental disorder (i.e., attention-deficit/hyperactivity disorder (ADHD) or intellectual disability), 44.1% reported a psychiatric disorder (i.e., bipolar disorder, depression, anxiety, obsessive-compulsive disorder

(OCD), oppositional defiant disorder (ODD), conduct disorder, or eating disorder), 42.7% reported a neurological condition (i.e., seizures/epilepsy, migraines, tics), 92.5% reported at least one general medical condition (i.e., non-neurological and non-psychiatric), and 28.4% reported other behavioral problems (i.e., self-injurious behavior or sensory processing problems) (Table 3). The rate of intellectual disability across the sample was low (19.3%) relative to other cohorts [Baio, 2012; Baio et al., 2018], which may reflect underreporting as discussed below. Intellectual disability was higher (24%) in families wherein there was only one child affected (i.e., simplex families). (Comparison of simplex and multiplex families is described in greater detail in Supporting Information, and related data are presented in Table S5).

Analyses of co-occurring conditions across ASD subgroups revealed significant subgroup differences in psychiatric diagnoses (Table 3), with significant differences being found for bipolar disorder, depression, anxiety disorder, ODD, ADHD, self-injurious behavior, migraines, and vision or hearing problems. Across these conditions, the ASD subgroup predominantly had the lowest rate of the given condition and the Non-ASD subgroup had the highest rate of the given condition. The exception was for self-injury, where the ASD-I subgroup had the highest

Table 4. ASD Symptoms and Adaptive Function by Sex in the Combined ASD and ASD-Inclusive Subgroups

Characteristic	<i>n</i>	Males (<i>n</i> = 672)	Females (<i>n</i> = 179)	<i>t</i> / χ^2	<i>P</i> value
Age at enrollment, mean (<i>SD</i>), <i>y</i>	851	13.36 (9.17)	13.84 (9.97)	-0.612	0.541
Age at diagnosis, mean (<i>SD</i>), <i>y</i>	574	5.67 (5.57)	6.95 (7.29)	-2.031	0.043
Verbal "Yes" (parent report), <i>n</i> (%)	658	512 (85.2)	146 (90.1)	2.616	0.106
ADOS-2, mean (<i>SD</i>)					
Severity	683	6.70 (2.21)	6.85 (1.96)	-0.699	0.485
Social affect/Communication + reciprocal social interaction	767	10.84 (4.6)	10.97 (4.5)	-0.320	0.749
RRB/Stereotyped behaviors and restricted interests	767	3.52 (2.2)	3.26 (2.2)	1.353	0.176
ADOS-2 classification, <i>n</i> (%)	767			2.624	0.269
Autism	600	470 (77.2)	130 (82.3)		
Autism spectrum	113	92 (15.0)	21 (13.3)		
Non-spectrum	54	47 (7.8)	7 (4.4)		
Expressive language by ADOS-2 item A1, <i>n</i> (%)	740			0.909	0.823
Minimally verbal	105	86 (14.6)	19 (12.8)		
Single-word speech	86	71 (12.0)	15 (10.1)		
Phrase speech	103	82 (13.9)	21 (14.1)		
Complex speech	446	352 (59.6)	94 (63.1)		
SRS-2, mean (<i>SD</i>)					
Total	701	75.59 (11.01)	76.89 (10.24)	-1.311	0.190
SCI	701	74.65 (11.14)	75.77 (10.38)	-1.117	0.264
RRB	701	76.07 (11.39)	77.79 (11.49)	-1.644	0.101
VABS-II, mean (<i>SD</i>)					
ABC	632	67.85 (18.84)	68.09 (18.66)	-0.128	0.898
Communication	656	70.41 (21.11)	70.73 (22.32)	-0.159	0.874
Daily living skills	653	73.04 (21.46)	72.08 (19.70)	0.483	0.629
Socialization	640	64.91 (19.46)	66.70 (18.81)	-0.977	0.329
Motor skills	165	80.68 (19.29)	74.44 (19.15)	1.647	0.101

Abbreviations: SCI, social communication and interaction; SD, standard deviation.

rate. Additionally, mood and anxiety disorders generally increased with age (Fig. S1).

Approximately one half of the participants were prescribed one psychiatric medication at the time of enrollment (51.0%). The majority of these medications were prescribed to adolescents and adults, with 74.3% of adolescents and 64.4% of adults taking at least one prescription psychiatric medication or antiepileptic drug (AED). However, a substantial number of preadolescent children in the RI-CART study cohort were also being prescribed these medications (i.e., 38.2% of children in the sample were taking at least one prescription psychiatric medication or AED; Table S6).

Statistically significant subgroup differences in medication were found for antipsychotics, stimulants, alpha-2 agonists, and any psychiatric medication (Table 3). Specifically, the ASD-I subgroup was more likely to have been prescribed these medications than the other two subgroups, perhaps reflecting the diagnostic and behavioral complexity of this subgroup. To understand this in a greater depth, we analyzed the different subgroups, including specific categories of the ASD-I subgroup, for co-occurring conditions and medications (Table S7). Notably, the subgroup with the highest antipsychotic use was the subgroup with a community ASD diagnosis but for whom an ADOS-2 score was not available or ADOS-2 assessment was not tolerable, likely reflecting their behavioral acuity. This group also had the highest rate of intellectual disability (30.0%), bipolar disorder (9.5%), and OCD (24.3%).

Older Age at Diagnosis in Females With Autism, Potentially due to More Advanced Language Abilities

Approximately 78% (78.3%) of total study participants were male (representing a 3.5:1 male to female ratio; Table 1). This ratio was 4.13:1 for the ASD subgroup; 3.24:1 for the ASD-I subgroup; and 2.06:1 for the Non-ASD subgroup. Notably, across the ASD and ASD-I subgroups combined, we observed no significant differences in ASD symptoms based on sex, although there was a trend toward an increased rate of nonverbal males with ASD (Table 4). Similarly, there were few notable differences in psychiatric or medical comorbidities in comparing males and females with ASD (Table 5).

Importantly, however, there was a statistically significant sex-based difference in age at the first ASD diagnosis for the combined ASD and ASD-I subgroups (Table 4). Namely, on average, males received their diagnosis nearly 1.5 years earlier than females. Males ($n = 672$) were diagnosed by age 5.67 ± 5.57 years on average, whereas females ($n = 179$) were not diagnosed until an approximate age of 7 years old (age 6.95 ± 7.29 years) ($t[572] = -2.031$; $P = 0.043$). Notably, this earlier age at the time of diagnosis seemed to be driven largely by the ASD subgroup, as the

Table 5. Psychiatric and Medical Co-Occurring Conditions by Sex in the Combined ASD and ASD-Inclusive Subgroups

Variable	Males	Females	<i>P</i> value ^a
Participants, <i>n</i>	672	179	
Neurodevelopmental, <i>n</i> (%)			
ADHD	200 (29.8)	52 (29.1)	0.815
Intellectual disability	129 (19.2)	29 (16.2)	0.398
Any neurodevelopmental	295 (43.9)	69 (38.5)	0.229
Psychiatric, <i>n</i> (%)			
Eating disorder	22 (3.3)	8 (4.5)	0.424
Bipolar disorder	31 (4.6)	5 (2.8)	0.292
Depression	83 (12.4)	28 (15.6)	0.196
Anxiety disorder	214 (31.8)	59 (33.0)	0.918
OCD	74 (11.0)	20 (11.2)	0.962
ODD	54 (8.0)	15 (8.4)	0.845
CD	24 (3.6)	2 (1.1)	0.093
Any psychiatric	269 (40.0)	71 (39.6)	0.888
Neurological, <i>n</i> (%)			
Epilepsy	26 (3.9)	11 (6.1)	0.185
Seizures	75 (11.2)	17 (9.5)	0.524
Tics	169 (25.2)	33 (18.4)	0.061
Migraines	70 (10.4)	22 (12.3)	0.473
General medical, <i>n</i> (%)			
Vision or hearing problems	286 (42.6)	88 (49.2)	0.114
Skin problems	211 (31.4)	45 (25.1)	0.105
Sleep problems	319 (47.5)	88 (49.2)	0.687
GI problems	256 (38.1)	54 (30.2)	0.050
Feeding problems	177 (26.4)	38 (21.3)	0.162
Allergies	315 (46.9)	83 (46.4)	0.904
Any general medical	572 (85.1)	148 (82.7)	0.422
Other behavioral, <i>n</i> (%)			
Self-injury	52 (7.7)	20 (11.2)	0.137
Sensory processing problems	154 (22.9)	38 (21.2)	0.702
Any other behavioral	184 (27.4)	49 (27.4)	0.999

Abbreviations: CD, conduct disorder; GI, gastrointestinal.

^a*P* values for overall tests are reported.

ASD subgroup alone showed the strongest effect of female sex on age at diagnosis, and the ASD-I subgroup did not reveal a statistically significant result when analyzed alone (Tables S8 and S9).

We conducted a linear regression analysis of clinical predictors of age at ASD diagnosis across the entire sample, including those variables with suggestive evidence of differences between sexes such as verbal status and RRB, based on ADOS-2 assessment. This analysis revealed verbal status (but not RRB) to be an important predictor of age at ASD diagnosis ($\beta = 0.177$, $P = 0.005$) (Table 6). Notably, verbal status was found to be a strong predictor in males but not in females ($\beta = 0.198$, $P = 0.004$ in males vs. $\beta = 0.135$, $P = 0.394$ in females). These data suggest that more prominent language phenotypes in males with ASD may lead to earlier diagnosis. In order to account for language development that may be highly variable prior to age 5 years, we also conducted this regression analysis in participants 5 years old or greater and found similar results (Table S10). Other predictors did not differ between males and females, but an increased number of nonverbal males with ASD existed as

Table 6. Linear Regression Analyses of Clinical Predictors of Age at ASD Diagnosis

Variable	Total sample (<i>n</i> = 296)			Males (<i>n</i> = 240)			Females (<i>n</i> = 56)		
	Model <i>R</i> ²	β	<i>P</i> value	Model <i>R</i> ²	β	<i>P</i> value	Model <i>R</i> ²	β	<i>P</i> value
Overall model	0.108		<0.001	0.118		<0.001	0.119		0.161
ADOS-2 RRB		-0.114	0.062		-0.082	0.221		-0.248	0.115
VABS-II ABC		-0.119	0.051		-0.108	0.109		-0.180	0.232
Verbal "Yes"		0.177	0.005		0.198	0.004		0.135	0.394
Number of psychiatric Dx		0.168	0.005		0.195	0.003		0.065	0.676

Abbreviation: Dx, diagnoses.

compared to females (14.8% nonverbal males vs. 9.9% nonverbal females; $t/\chi^2 = 2.616$, $P = 0.106$; Table 4). To further examine the hypothesis that females are diagnosed at a later age due to more advanced language abilities than males, we conducted a logistic regression to test whether participant sex predicted verbal status in the whole RI-CART sample ($n = 1,000$). The overall model was statistically significant ($\chi^2[2] = 25.544$, $P < 0.001$; correctly classified 87.2% of cases), with both participant age (Wald = 15.043, $P < 0.001$) and participant sex (Wald = 4.449, $P = 0.035$) predicting verbal status. In addition, we conducted an analysis of covariance to examine sex differences in age at ASD diagnosis after controlling for age at enrollment and verbal status, due to the concern that these variables may be confounding age at ASD diagnosis findings. After controlling for age at enrollment ($F = 297.497$, $P < 0.001$) and verbal status ($F = 8.45$, $P = 0.004$), there was a significant sex difference in age at ASD diagnosis ($F[1,563] = 5.116$ years, $P = 0.024$; estimated marginal means: males = 5.7 [0.22] years and females = 6.9 [0.45] years). Overall, our data support an interpretation of a delay in recognition of ASD in females in the RI-CART study sample, potentially due to more advanced verbal abilities in girls.

Discussion

This study presents results from the first phase and the first 1,000 participants enrolled in the RI-CART study. The objective of the RI-CART study is to establish a densely sampled, well-phenotyped, population-based cohort with ASD representative of the U.S. population. This study is relatively unique, as it involves a sizable geographic population and reports a strong depth of sampling, estimated at 20% to as high as 49%, depending on the ASD base rate prevalence used, of pediatric age persons in Rhode Island. ASD research methodologies have faced many challenges with regard to recruitment. The RI-CART study utilizes a broad recruitment strategy that captures a heterogeneous range of clinical presentations, thereby providing an alternative method of investigation as compared to registries and cohorts with specific and more narrow case definitions. Strengths of this study

include a large sample size (an initial sample of 1,000 individuals with enrollment continuing) that extends across the life span (21 months to 64 years of age), the inclusion of both community diagnosis and research criteria for ASD, and a geographically constrained area that primarily utilizes two collaborative health care systems.

RI-CART represents a recruitment method and scope that is complementary to other U.S. cohorts. For example, the Study to Explore Early Development [Schendel et al., 2012] recruited a sizable and representative epidemiologic sample of children with ASD within a specific birth cohort (births between 2003 and 2006) and is optimized to examine potential early risk factors for ASD diagnosis. Similarly, influential studies from the Kaiser Health system in Northern California have been able to utilize large samples of individuals with ASD in a broad catchment area using medical records data [e.g., Croen et al., 2015; Kuzniewicz et al., 2014; Zerbo et al., 2015]. The RI-CART study complements these other approaches by enrolling individuals with ASD across a broad age range and with demographic characteristics that are representative. The age range will support explorations of age-related trends in ASD presentation and will lay the foundation for longitudinal studies during a variety of developmental transition periods (e.g., from childhood to adolescence; from adolescence to early adulthood).

Development of a patient registry that includes in-person assessments of participants spanning a broad population from within a specific geographic area requires grassroots enrollment and maintenance of relationships with community organizations. This creates challenges for developing demographic representativeness but has the benefit of developing relationships to support recontact and subsequent engagement of participants in ongoing research. We involved community stakeholders by making them partners in the entire research process. Important aspects of this were partnering with The Autism Project, a family support organization in Rhode Island, and also providing research outreach events designed to address interests in the community.

One focus of this study was to assess the ability to recruit a representative sample of individuals with ASD

from across the state of Rhode Island. The sample is demographically comparable to the Rhode Island population in categories such as Not Hispanic/Latino (72.8% vs. 73.3% for study sample vs. Rhode Island Census) and Hispanic/Latino (12.4% vs. 14.9% for study sample vs. Rhode Island Census), while demonstrating relatively lower rates of participants expected to self-identify as black/African American or Asian [U.S. Census Bureau, 2017]. However, it is noted that Rhode Island has a smaller proportion of residents who identify as black than the overall U.S. population [U.S. Census Bureau, 2017]. In addition, it is noted that a substantial number of participants identified as multiracial (8.2%) or did not report race or ethnicity (13.5% overall). Maternal educational attainment was higher in the RI-CART study sample vs. the general Rhode Island population (e.g., high school diploma or higher: 91.1% vs. 85.4%; bachelor's degree or higher: 46.4% vs. 31.4%) (see Supporting Information).

Utilizing location mapping with GIS and cross-referencing this information with demographic data at the level of U.S. Census tracts, case ascertainment was determined to be lower from neighborhoods with greater levels of poverty, which are also neighborhoods with higher proportions of minority residents [U.S. Census Bureau, 2017]. These findings are consistent with prior research demonstrating lower ASD ascertainment rates in minority racial and ethnic groups and lower SES [Dickerson et al., 2017]. The underrepresentation of racial/ethnic minorities and impoverished individuals is unfortunately not uncommon in clinical research or medical care, yet this has critical implications for ASD research and treatment [Mandell et al., 2009]. Initial efforts to systematically enhance ascertainment to specific minority groups (e.g., Latinos) have shown promise [Zamora et al., 2016]. In the RI-CART study, we have subsequently implemented more aggressive ascertainment of Spanish-speaking populations. Implementation of such efforts into future population-based studies remains imperative, and the location data and mapping methods described in this study can be used to develop specific strategies to enhance future recruitment in underrepresented communities.

Importantly, our cohort and research approach have allowed for the study of agreement, or lack thereof, between community and research ASD diagnoses. We observed a high concordance between community diagnosis and research criteria for ASD, as 90.8% of those participants with a community diagnosis of ASD exceeded the ASD threshold on the ADOS-2. This is consistent with prior validation on the utility of the ADOS-2 in the ASD diagnostic evaluation process [Lord et al., 2012]. Our results are also not consistent with gross over-diagnosis of ASD by community clinicians. The 9.2% of participants with community diagnosis of ASD that did not

have a positive ADOS-2 score were characterized by higher adaptive functioning, later age at the time of ASD diagnosis, and less likely to be identified as white. This may suggest that this cohort manifests as a milder phenotype, although the role of white/non-white status may also suggest some involvement of cultural or demographic factors. Of note, in this study, we defined the ASD-I subgrouping. While a subset of the ASD-I subgroup may have a milder ASD phenotype, it is notable that there was a high rate of caregiver-reported psychiatric diagnoses in this subgroup. Thus, in addition to the presence of individuals with a milder phenotype, participants within the ASD-I subgroup could also represent diagnostic uncertainties related to complex presentations.

We observed a male to female ratio of 4.13:1 for the ASD subgroup. However, in the overall sample, a 3.5:1 ratio was observed, which is more similar to the recent meta-analytic results indicating the strongest estimate of biologic sex ratio in ASD is 3:25–3:32:1 [Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015; Loomes, Hull, & Mandy, 2017]. Importantly, with regard to ASD features, we found no significant differences between males and females. That is, we did not find distinct cross-sectional ASD symptomology in males as compared to females, with the exception of a higher rate of nonverbal autism in males. Notably, a significant difference existed in age at first ASD diagnosis, as males on average had an earlier age at diagnosis (nearly 1.5 years younger). This effect seemed largely driven by the definitive ASD subgroup (Tables S2 and S3). The effects of biologic sex on clinical presentation, as reported in the literature, appear highly dependent on recruitment approaches [Howe, Yatchmink, Viscidi, & Morrow, 2014]. The lack of sex differences in clinical symptoms has also been noted in some well-powered, larger studies more recently [Mussey, Ginn, & Klinger, 2017]. In large, population-based studies (1,000+ participants), detection of differences between males and females in age at diagnosis has been somewhat inconsistent, with some studies identifying statistically significant differences between sexes [Begeer et al., 2013; May & Williams, 2018; Rosenberg, Landa, Law, Stuart, & Law, 2011; Shattuck et al., 2009], while others have not identified such differences [Giarelli et al., 2010; Hiller, Young, & Weber, 2016; Mandell et al., 2010; Mazurek et al., 2014]. Our large, broad, population-based cohort is most consistent with no sex-based differences in autism phenotype at the age of enrollment; however, our data support sex-based differences in language development. Studies of sex differences in autism warrant a more developmental approach, as opposed to cross-sectional study designs, as suggested by our observations of distinct ages at first diagnosis. The first diagnosis of ASD in females at a later age is clearly of urgent clinical importance. Our initial analyses of predictors of age at diagnosis suggest that a reduced rate of nonverbal females may mean that

fewer females are flagged early by the lack of language. More aggressive and deliberate methods to diagnose ASD in females at earlier ages may be warranted.

Medical and psychiatric co-occurring conditions represent a sizable burden on participants and their families [Croen et al., 2015; Jokiranta-Olkonemi et al., 2016; Soke, Maenner, Christensen, Kurzius-Spencer, & Schieve, 2018]. Information reported was as follows: 74% with at least one co-occurring neurodevelopmental, psychiatric, or neurological condition and 93% with at least one general medical condition. This overall rate of co-occurring neuropsychiatric conditions among individuals with ASD is in line with rates reported by prior smaller population-based studies [Abdallah et al., 2011; Simonoff et al., 2008], as is the high percentage of the sample reporting medical co-occurring symptoms, with gastrointestinal problems, sleep problems, and allergies being among the most common [Bauman, 2010]. The rates of individual neuropsychiatric conditions were generally consistent with prior population-based rates among individuals with ASD [Hudson, Hall, & Harkness, 2019; Simonoff et al., 2008], with the exception of intellectual disability (19%). This reported rate is approximately half of the previously reported prevalence rate (38%) [Baio, 2012]. Limitations of community, clinical assessments of intellectual disability, reduced reporting to parents of such diagnoses, and/or reduced parental report of intellectual disability are likely, perhaps, due in part to stigma. Whereas only 19% of participants were reported to have intellectual disability, nearly 50% were reported to have achieved only phrase speech or less. Also, a substantial percentage of the RI-CART study sample had ABC scores in the low or impaired range. Together, these data suggest that the reported rate of intellectual disability underestimates the significant degree of developmental impairments represented in the study sample.

Also, importantly, over half of the sample reported being prescribed at least one psychotropic medication, consistent with prevalence estimates in the United States for psychotropic medications that range from 34% to 81%, depending on age [Coury et al., 2012; Esbensen, Greenberg, Seltzer, & Aman, 2009; Frazier et al., 2011]. These findings also support current recommendations by the medical community for a careful medical or psychiatric workup in individuals with ASD, as clinically indicated [Isaksen et al., 2013].

When analyzing psychiatric co-occurring conditions of subgroups, the Non-ASD subgroup also reported high rates of neurodevelopmental and psychiatric conditions, especially ADHD, bipolar disorder, depression, and ODD. The ASD-I subgroup reported higher amounts of self-injurious behavior and high rates of psychiatric medication use.

In summary, we have presented the first observations on autism phenotypes in a clinically broad and deeply

sampled, population-based cohort with ASD. The information gathered from these initial 1,000 participants in the RI-CART study extends our knowledge of the vast heterogeneity of autism. Our findings of high rates of co-occurring neuropsychiatric disorders in individuals with ASD reflect provider challenges in diagnosing ASD in a clinically complex presentation, as well as the heterogeneity of ASD presentation. The nature of this well-sampled, population-based cohort, therefore, mirrors contemporary clinical challenges regarding autism, which in turn affect diagnosis, treatment, and long-term outcomes. Future research on more aggressive and earlier diagnosis in females seems warranted, given the apparent risk of delayed diagnosis for this population.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1: Supporting information