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ABSTRACT

This study examined associations between ASD diagnosis retention and non-ASD co-occurring conditions (CoCs) by child sex. The sample included 7077 males and 1487 females who had an ASD diagnosis documented in their school or health records in a population-based ASD surveillance system for 8-year-old children. ASD diagnosis retention status was determined when an initial ASD diagnosis was not later ruled out by a community professional. We found that ASD diagnosis remains fairly stable, with only 9% of children who had an initial documented ASD diagnosis later being ruled-out. Although most of the associations between the ASD diagnosis retention status and CoCs are similar in both sexes, the co-occurrence of developmental diagnoses (e.g., intellectual disability or sensory integration disorder) was predictive of ASD diagnostic changes in males, whereas the co-occurrence of specific developmental (e.g., personal/social delay) and neurological diagnosis (e.g., epilepsy) was associated with ASD diagnostic change in females. More ASD-related evaluations and less ASD-related impairment were associated with later ASD rule outs in both sexes. Our findings highlight that CoCs can complicate the diagnostic picture and lead to an increased likelihood of ambiguity in ASD diagnosis. Using sensitive and appropriate measures in clinical practice is necessary for differential diagnosis, particularly when there are co-occurring developmental conditions.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social interaction and communication, and restricted, repetitive patterns of behaviors, interests or activities (American Psychiatric

Abbreviation: ASD, autism spectrum disorder; ID, intellectual disability; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; OCD, obsessive–compulsive disorder.

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Association, 2013). The most recent prevalence estimate of ASD among 8-year-old children in the United States (US) is 14.7 per 1000 children (1 in 68 children) (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014). Persons with ASD were previously defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR) (American Psychiatric Association, 1994) as those diagnosed with Autistic Disorder (AD), Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) or Asperger's Disorder. All of these diagnoses are now subsumed under one label of ASD in the Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Although ASD symptoms typically appear in the first 3 years of life, other developmental, psychiatric and neurologic disorders frequently co-occur with ASD (Close, Lee, Kaufmann, & Zimmerman, 2012; Levy et al., 2010) and differentiation between the core features of ASD and co-occurring conditions can be challenging and may have a significant impact on the accurate identification of children with ASD. As the number of children being diagnosed with ASD is growing, it is important to explore cases in which the diagnosis of ASD changed to non-ASD, as well as the role co-occurring non-ASD diagnoses play in changing diagnostic status in order to inform early identification and intervention.

Past research examining the retention rate of ASD diagnosis is inconsistent, and it is unclear what role early intervention and subsequent symptom improvement play in the developmental outcomes of youth with ASD. High rates of ASD diagnosis retention for overall spectrum of ASDs (91–100%) have been reported between 2–4 years of age (Banach et al., 2009; Chawarska, Klin, Paul, Macari, & Volkmar, 2009; Van Daalen et al., 2009) and 88–90% between 2 and 9 years of age (Kleinman et al., 2008; Lord et al., 2006), whereas the retention rate of the subtypes diagnoses within the autism spectrum (AD or PDD-NOS) has been more variable (54–88%) compared with the retention rate of entire category of autism spectrum (Chawarska et al., 2009; Daniels et al., 2011; Malhi & Singhi, 2011; Turner, Stone, Pozdol, & Coonrod, 2006; Van Daalen et al., 2009; Wiggins et al., 2012). Furthermore, recent studies showed that almost half of ASD siblings children (41–63%) who were not diagnosed at 18 or 24 months of age received an ASD diagnosis at 36 months of age (Ozonoff et al., 2015; Zwaigenbaum et al., 2015). Other research showed 12% of ASD siblings children may change from non-ASD diagnosis at age 3 to an ASD diagnosis in middle childhood (Brian et al., 2015). Although these findings suggest that some children with an initial diagnosis of ASD no longer meet ASD diagnostic criteria at a later time or vice versa, most studies collected information from small clinic-referred samples (Banach et al., 2009; Kleinman et al., 2008; Van Daalen et al., 2009; Wiggins et al., 2012), high-risk ASD siblings (Brian et al., 2015; Ozonoff et al., 2015; Zwaigenbaum et al., 2015) or provided estimates only for a specific spectrum of ASD (e.g. AD, PDD-NOS) (Chawarska et al., 2009; Malhi & Singhi, 2011; Turner et al., 2006). These differences in study design likely contribute to the varying estimates on diagnosis retention rate. Investigation of diagnosis retention for children with ASD in a large and population-based sample is essential to provide a clearer picture of the diagnostic pattern in ASD.

Previous studies consistently report a sex difference in the prevalence of ASD of 4.5:1 males to females (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014; Newschaffer et al., 2007). Research has also found discrepancies in clinical presentation: males with ASD are more likely to exhibit repetitive and stereotyped behaviors (Carter et al., 2007; Hartley & Sikora, 2009; Hattier, Matson, Tureck, & Horovitz, 2011; Rubenstein, Wiggins, & Lee, 2015), whereas females with ASD have higher rates of severe cognitive and developmental delays (intellectual quotient [IQ] $\leq$ 70) (Banach et al., 2009; Nicholas et al., 2008; Rubenstein et al., 2015; Volkmar, Szatmari, & Sparrow, 1993). A few studies also found a sex discrepancy in timing of ASD evaluation and diagnosis: females may be referred for evaluation of ASD at earlier ages than males; however girls had a longer delay between first evaluation and ASD diagnosis than boys (Wiggins, Baio, & Rice, 2006) and are ultimately diagnosed with ASD at later ages (Shattuck et al., 2009). Although previous studies suggest that the timing of ASD evaluation and diagnosis varies between the sexes, no epidemiologic studies have further explored possible sex differences in ASD diagnosis retention.

In addition, previous studies revealed that co-occurring conditions (CoCs) and other diagnostic-related factors are associated with the change in ASD classification from ASD to non-ASD (Close et al., 2012; Wiggins et al., 2012). Wiggins et al. (2012) reported that children receiving ASD diagnoses at young ages and those with co-occurring specific developmental delays are more likely to experience a change of ASD classification. Furthermore, presence of CoCs, such as learning disability, developmental delay, speech or hearing problem, anxiety and epilepsy, can distinguish children who had a previous and current ASD diagnosis from those children with a past but not current ASD diagnosis (Close et al., 2012). Although these studies support the relationship between CoCs and changes in classification from ASD to non-ASD, possible variation in the associations between ASD diagnosis retention and CoCs based on child sex was not investigated in previous studies. Whether child sex plays a role in the association between specific CoCs and ASD diagnosis retention warrants further investigation.

In this study, we examined a large sample of children from the Autism and Developmental Disabilities Monitoring (ADDM) Network, an ongoing, population-based, multisite surveillance program established by the Centers for Disease Control and Prevention (CDC) to estimate the prevalence of ASD among children aged 8 years. Our aim was to describe the nature of ASD diagnosis retention and change according to child sex. Specifically, we examined factors that were associated with ASD diagnostic change, including presence of CoCs and ASD diagnosis-related factors in male and female children who retained an ASD diagnosis (i.e., child with past ASD diagnosis that was not later ruled-out in health or education records) and who did not retain an ASD diagnosis (i.e. child with past ASD diagnosis that was later ruled-out in health or education records).

2. Methods

2.1. Participants

Participants were drawn from the ADDM Network database for surveillance years of 2000, 2002, 2004, 2006, and 2008. The ADDM Network utilizes health and education records to classify children as meeting case definition of ASD based on ADDM clinician reviewer's assessment on the records, regardless of existing diagnosis in their records. Approximately 77–80% of children who were classified with ASD by ADDM had a previously documented ASD classification by a community professional (e.g., MD developmental pediatrician, MD neurologist or psychologist) (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators, 2007; Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators, 2009; Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators, 2012).

2.2. Procedures of data collection in ADDM Network

The ADDM Network methods are summarized briefly here and are described in detail elsewhere (Van Naarden Braun et al., 2007). Children classified with ASD by ADDM were identified in a two-phase review of developmental evaluations at community health and education sources. Eligible children were 8 years of age and resided in a defined geographic area during the surveillance year. In the first phase, children's records were screened for a diagnostic or special education classification of ASD, suspected ASD, or descriptions of social impairment relevant to ASD. Developmental evaluations meeting the screening criteria were abstracted for behavioral descriptions, developmental history or concerns, and existing diagnoses. In the second phase, all abstracted evaluations were reviewed by trained reviewers to determine ASD case status. A child was determined as meeting the surveillance case definition for ASD if behaviors described in the evaluations were consistent with the DSM-IV, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) diagnostic criteria for any ASD. Although ADDM uses ASD classification to describe a child who has a documented diagnosis or service-based (i.e., special education) eligibility for an ASD, this analysis was limited to examining diagnostic changes among children with an ASD diagnosis only (i.e., an ASD/PDD diagnosis specified in an evaluation record or diagnostic code of 299.0 or 299.8).

2.3. Determination of ASD diagnosis retention status

Documented ASD and other diagnoses were reviewed from the initial evaluation up to any evaluations completed by age 8. ASD status was considered retained (ASD-R) if the earliest ASD diagnosis noted by a community professional was never ruled out in subsequent evaluations. ASD status was considered not retained (ASD-NR) if the earliest ASD diagnosis noted by a community professional was later ruled-out by the same or another community professional (99%), or they did not meet ADDM case definition for ASD (1%). Even if diagnostic impressions were from different professionals, their clinical impressions and summaries still represent community practices and perceptions of children with ASD. In cases where an ASD diagnosis was ruled out, the community professional had to specifically state that the child did not meet diagnostic criteria for any ASD (e.g., "this child no longer meets criteria for any ASD" or "symptoms are better accounted for by other diagnosis rather than an ASD").

2.4. Variables used in the study

Surveillance variables assessed include surveillance year (i.e., 2000, 2002, 2004, 2006, and 2008), source of surveillance record (education or health records, or both). A child's gestational age and birth weight were included when available from birth certificates ($N = 5626$). Demographic variables included child race, maternal age at child's birth, and maternal education. Documented CoCs were categorized into developmental, psychiatric, neurologic, and possibly causative medical diagnoses, following the classification used by Levy et al. (Levy et al., 2010). Only those conditions confirmed and documented in the records are included in this study. Categories of co-occurring developmental delays included multiple domains of developmental delay (DD): DD in general (DD-general), DD in adaptive behavior (DD-adaptive), DD in motor (DD-motor), DD in personal/social (DD-personal/social), DD in play (DD-play); and diagnoses of language disorder, intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), learning disability, sensory integration and non-verbal learning disorder. The co-occurring psychiatric diagnoses included oppositional defiant disorder (ODD), anxiety disorder, emotional disorder, mood disorder, obsessive–compulsive disorder (OCD), depression, bipolar disorder, mutism, behavior disorder, psychosis, conduct disorder, reactive attachment disorder, personality disorder, and schizophrenia. The co-occurring neurologic diagnoses included epilepsy, encephalopathy, cerebral palsy, visual impairment, hearing loss, Tourette syndrome, and brain injury. The co-occurring possibly causative medical diagnoses included Down syndrome, Fragile X syndrome, tuberous sclerosis, and fetal alcohol syndrome.

The variables related to diagnostic evaluation included the earliest known age of ASD diagnosis, type of professional(s) who gave the ASD diagnosis (i.e., developmental pediatrician, neurologist, MD other, psychologist, speech-language pathologists, occupational therapist, EDD or EDS educators, and professional not stated), the number of evaluations by community professionals, and the impairment level associated with ASD as assigned by ADDM reviewers based on behaviors

described in the records. For children with ASD-NR, the age when ASD was ruled out, the time period between the first diagnosis and ASD rule-out, and the type of professionals who ruled out the diagnosis, were the variables that were included in the subset analysis.

2.5. Statistical analysis

Descriptive statistics, including surveillance year, birth, and demographic variables were compared, stratified by sex, between the ASD-NR children and ASD-R children. For the ASD-NR group, the age of first ASD diagnosis and the time period between age of first ASD diagnosis and age when ASD diagnosis was ruled out were examined between males and females using *t*-tests. Furthermore, the rates of each CoC and several diagnostic evaluation-related variables were examined between

Table 1
Surveillance, birth and demographic characteristics by ASD diagnosis retention status in males and females.

Characteristics	Male ($n = 7077$)			Female ($n = 1487$)		
	ASD classification not retained ($n = 653$) *n* (%)	ASD classification retained ($n = 6424$) *n* (%)	OR (95% CI)[a]	ASD classification not retained ($n = 138$) *n* (%)	ASD classification retained ($n = 1349$) *n* (%)	OR (95% CI)[a]
Child race						
Non-Hispanic white	447 (68)	3798 (59)	1.00	94 (68)	833 (62)	1.00
Non-Hispanic black or African-American	124 (19)	1450 (23)	**0.73 (0.59–0.90)**	25 (18)	268 (20)	0.83 (0.52–1.31)
Hispanic, Asian, American Indian, or Alaskan Native	54 (9)	791 (12)	**0.58 (0.43–0.78)**	12 (9)	182 (13)	0.58 (0.31–1.09)
Other or missing race	28 (4)	385 (6)	**0.62 (0.42–0.92)**	7 (5)	66 (5)	0.94 (0.42–2.11)
Source of surveillance records						
Education-only	29 (4)	732 (11)	**0.35 (0.24–0.51)**	12 (9)	136 (10)	0.91 (0.48–1.72)
Health-only	226 (35)	2188 (34)	0.90 (0.76–1.07)	55 (38)	482 (36)	1.17 (0.81–1.70)
Both education and health	393 (60)	3437 (54)	1.00	70 (52)	716 (53)	1.00
Unknown	5 (1)	67 (1)		1 (1)	13 (1)	
Surveillance year						
2000	23 (3)	576 (9)	1.00	9 (7)	127 (9)	1.00
2002	143 (22)	1390 (22)	**2.58 (1.64–4.04)**	31 (22)	309 (23)	1.42 (0.66–3.06)
2004	65 (10)	749 (11)	**2.17 (1.33–3.54)**	14 (10)	162 (12)	1.22 (0.51–2.90)
2006	180 (28)	1484 (23)	**2.04 (1.95–4.74)**	28 (20)	312 (23)	1.27 (0.58–2.76)
2008	242 (37)	2225 (35)	**2.72 (1.76–4.22)**	56 (41)	439 (33)	1.80 (0.87–3.74)
Maternal age at child birth						
<20	24 (4)	292 (5)	0.76 (0.49–1.17)	9 (7)	51 (4)	2.09 (0.94–4.63)
20–29	213 (33)	1956 (30)	1.00	32 (23)	379 (28)	1.00
30–39	199 (30)	1803 (28)	1.01 (0.83–1.24)	39 (28)	400 (30)	1.15 (0.71–1.88)
40+	18 (3)	131 (2)	1.26 (0.76–2.11)	3 (2)	37 (3)	0.96 (0.28–3.29)
Missing	199 (30)	2242 (35)		55 (40)	482 (36)	
Maternal education						
<12 years	46 (7)	490 (8)	0.76 (0.54–1.07)	12 (9)	96 (7)	1.16 (0.57–2.36)
12 years	119 (18)	1203 (19)	0.80 (0.63–1.02)	21 (15)	262 (19)	0.75 (0.42–1.34)
13–15 years	105 (16)	988 (15)	0.86 (0.67–1.11)	20 (14)	221 (16)	0.84 (0.47–1.52)
16 + years	180 (28)	1458 (23)	1.00	30 (22)	279 (21)	1.00
Missing	203 (31)	2285 (35)		55 (40)	491 (36)	

ADDM, Autism and Developmental Disabilities Monitoring; ASD, autism spectrum disorders; ID, intellectual disability. Significant findings are bolded ($p < 0.05$).

[a] The association with the change of ASD classification from ASD to non-ASD.

the two groups (i.e., ASD-NR and ASD-R) by child sex. Univariate and multivariable logistic regression were used to estimate the unadjusted and adjusted association between ASD diagnosis retention status and covariates by child sex. Odds ratios (OR) and the 95% confidence intervals (CI) were reported to indicate the association.

3. Results

3.1. Sample characteristics

Records of a total of 8564 children (7077 males and 1487 females) were reviewed and abstracted. These are children who had a documented ASD diagnosis made by a community professional and an associated age of first ASD diagnosis noted in health or school records, and were included in the subsequent analyses. The majority (60%) of the children were non-Hispanic white, followed by 22% non-Hispanic black or African-American, 12% Hispanic or Asian or Pacific Islander, and 6% other or missing race. Overall, 653 or 9% of males and 138 or 9% of females had a documented ASD diagnosis in their school or health records that was subsequently ruled out by a community professional (ASD-NR).

Surveillance, demographic, and birth characteristics for each of the two study groups (ASD-NR and ASD-R) stratified by sex are presented in Table 1. Males who were non-Hispanic black or African-American (OR = 0.73, 95% CI: 0.59–0.90), Hispanic or Asian (OR = 0.58, 95% CI: 0.43–0.78), or Other/Missing Race (OR = 0.62, 95% CI: 0.43–0.92) were less likely than males who were non-Hispanic white to be ASD-NR. Similarly, males who only had education records (OR = 0.35, 95% CI: 0.24–0.51) were less likely to be ASD-NR than males for whom both educational and clinical records were available. Furthermore, males in the surveillance years 2002 through 2008 had higher odds of being classified as ASD-NR than males in surveillance year 2000 (ORs range from 2.04–2.72).

3.2. Sex difference in ASD-NR children

Among children in the ASD-NR group, no significant difference was seen in the median age at which ASD diagnosis was ruled out in males (63 months) and females (59.5 months) (Table 2), whereas males had a shorter time interval between the initial diagnosis and the time when the diagnosis was ruled out than females (16.9 vs. 20.2 months, $p = 0.03$). Of the diagnoses that were ruled out, nearly two-thirds of the initial ASD diagnoses were ruled out by either psychologists (46% males and 43% females) or developmental pediatricians (28% males and 28% females).

3.3. Co-occurring conditions (CoCs) and ASD diagnosis retention in males and females

The rates of CoCs and their associations with ASD diagnosis retention status are presented in Table 3. Statistical analysis was not performed among subgroups with sample size < 5. After adjusting for child race, source of surveillance record, and surveillance year, both ID and sensory integration disorder were associated with ASD-NR in males, whereas DD-personal/social was associated with ASD-NR in females. Both males and females who had co-occurring DD-general, DD-motor, language disorder, ADHD, learning disability, or any co-occurring developmental diagnosis were more likely to be ASD-NR. In addition, analysis of data on psychiatric and neurological diagnoses showed both males and females with co-occurring ODD, anxiety, or mood disorder or any psychiatric diagnoses were more likely to be classified as ASD-NR than males and females without these conditions; whereas epilepsy or any co-occurring neurological diagnoses were associated with ASD-NR only in females.

Table 2
Change of ASD classification from ASD to non-ASD between males and females.

	ASD classification not retained ($n = 791$)		*P* value[a]
	Males ($n = 653$)	Females ($n = 138$)	
Age of an ASD ruled-out, median (range), months	63.0 (16–106)	59.5 (16–105)	0.45
Time between the first diagnosis and an ASD ruled-out, mean ± SD (in months)	16.9 ± 16.5	20.2 ± 17.9	0.03
Professionals who ruled out an ASD diagnosis, *n* (%)			
MD developmental pediatrician	176 (28)	38 (28)	
MD neurologist	74 (11)	19 (14)	
MD other[b]	41 (6)	10 (7)	
Psychologist	301 (46)	60 (43)	
Other professional[c]	55 (8)	8 (6)	
Professional not stated	6 (1)	3 (2)	

[a] *t* test.
[b] MD other: MD psychiatry, MD genetics, MD rehabilitation medicine, MD neonatology, and MD family medicine.
[c] Other professional: language pathologists, occupational therapists and EDD or EDS educators.

Table 3
Associations between co-occurring conditions and ASD diagnosis retention status.

Co-occurring conditions[a]	Male (n = 7077)				Female (n = 1487)			
	ASD classification not retained (n = 653)	ASD classification retained (n = 6424)	Unadjusted analysis	Adjusted analysis[b]	ASD classification not retained (n = 138)	ASD classification retained (n = 1349)	Unadjusted analysis	Adjusted analysis[b]
	n (%)	n (%)	OR (95% CI)	OR (95% CI)	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Developmental diagnoses								
Intellectual disability	222 (34)	1,778 (28)	**1.35 (1.14–1.60)**	**1.31 (1.10–1.57)**	53 (38)	486 (36)	1.11 (0.77–1.59)	1.13 (0.78–1.65)
Sensory integration disorder	47 (7)	231 (4)	**2.08 (1.50–2.88)**	**1.75 (1.26–2.44)**	11 (8)	55 (4)	**2.04 (1.04–2.99)**	1.91 (0.97–3.76)
DD-personal/social	149 (23)	1,200 (19)	**1.29 (1.06–1.56)**	1.17 (0.96–1.43)	35 (25)	240 (18)	**1.57 (1.04–2.36)**	**1.55 (1.02–2.36)**
DD-general	208 (32)	1,570 (24)	**1.45 (1.21–1.72)**	**1.37 (1.15–1.64)**	54 (39)	413 (31)	**1.46 (1.02–2.09)**	**1.49 (1.03–2.14)**
DD-motor	218 (33)	1,627 (25)	**1.48 (1.24–1.76)**	**1.31 (1.09–1.56)**	58 (42)	376 (27)	**1.88 (1.31–2.69)**	**1.86 (1.29–2.70)**
Language disorder	486 (74)	3,659 (57)	**2.20 (1.83–2.64)**	**2.03 (1.69–2.46)**	110 (80)	806 (60)	**2.65 (1.72–4.06)**	**2.75 (1.77–4.28)**
ADHD	232 (36)	1,255 (20)	**2.27 (1.91–2.70)**	**2.08 (1.75–2.48)**	39 (28)	206 (15)	**2.19 (1.47–3.26)**	**2.14 (1.43–3.21)**
Learning disability	55 (8)	210 (3)	**2.72 (2.00–3.71)**	**2.57 (1.88–3.51)**	12 (9)	50 (4)	**2.48 (1.28–4.77)**	**2.51 (1.29–4.87)**
DD-adaptive	166 (25)	1,334 (21)	**1.30 (1.08–1.57)**	1.21 (0.99–1.46)	40 (29)	288 (21)	**1.50 (1.02–2.22)**	1.49 (0.99–2.23)
DD-play	20 (3)	147 (2)	1.35 (0.84–2.17)	1.15 (0.71–1.85)	7 (5)	29 (2)	**2.43 (1.05–5.66)**	2.36 (1.00–5.56)
Any developmental diagnosis[c]	607 (93)	5,038 (78)	**3.63 (2.67–4.93)**	**3.31 (2.43–4.52)**	127 (92)	1,085 (80)	**2.81 (1.50–5.28)**	**2.89 (1.52–5.48)**
Psychiatric diagnoses								
OCD	22 (3)	109 (2)	**2.02 (1.27–3.22)**	**1.90 (1.18–3.03)**	2 (1)	22 (2)	NA	NA
Bipolar disorder	14 (2)	51 (1)	**2.74 (1.51–4.98)**	**2.25 (1.23–4.11)**	1 (1)	11 (1)	NA	NA
ODD	62 (9)	211 (3)	**3.09 (2.30–4.15)**	**2.73 (2.02–2.68)**	8 (6)	32 (2)	**2.53 (1.14–5.61)**	**2.39 (1.07–5.34)**
Anxiety disorder	49 (8)	267 (4)	**1.87 (1.36–2.57)**	**1.60 (1.16–2.20)**	12 (9)	50 (4)	**2.48 (1.28–4.77)**	**2.28 (1.17–4.45)**
Mood disorder	22 (3)	74 (1)	**2.99 (1.85–4.85)**	**2.53 (1.56–4.13)**	8 (6)	21 (2)	**3.89 (1.69–8.96)**	**3.44 (1.48–8.01)**
Emotional disorder	11 (2)	56 (1)	**1.95 (1.02–3.74)**	1.88 (0.97–3.64)	3 (2)	9 (1)	NA	NA
Depression	7 (1)	36 (1)	1.92 (0.85–4.34)	1.66 (0.73–3.76)	2 (1)	11 (1)	NA	NA
Behavior disorder	8 (1)	59 (1)	1.33 (0.64–2.81)	1.16 (0.55–2.47)	3 (2)	13 (1)	NA	NA
Any psychiatric diagnosis[d]	148 (23)	710 (11)	**2.36 (1.93–2.88)**	**2.10 (1.72–2.58)**	33 (24)	151 (11)	**2.49 (1.63–3.82)**	**2.35 (1.52–3.63)**

Table 3 (*Continued*)

Co-occurring conditions[a]	Male ($n = 7077$)				Female ($n = 1487$)			
	ASD classification not retained ($n = 653$)	ASD classification retained ($n = 6424$)	Unadjusted analysis	Adjusted analysis[b]	ASD classification not retained ($n = 138$)	ASD classification retained ($n = 1349$)	Unadjusted analysis	Adjusted analysis[b]
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)	*n* (%)	*n* (%)	OR (95% CI)	OR (95% CI)
Neurologic diagnosis								
Hearing loss	16 (2)	83 (1)	**1.92 (1.12–3.30)**	**1.82 (1.05–3.14)**	4 (3)	26 (2)	NA	NA
Epilepsy	34 (5)	275 (4)	1.23 (0.85–1.77)	1.11 (0.77–1.61)	18 (13)	107 (8)	**1.74 (1.02–2.97)**	**1.75 (1.02–3.00)**
Encephalopathy	53 (8)	411 (6)	1.29 (0.96–1.74)	1.07 (0.79–1.45)	18 (13)	112 (9)	1.66 (0.97–2.82)	1.56 (0.91–2.69)
Cerebral palsy	11 (2)	83 (1)	1.31 (0.70–2.47)	1.22 (0.64–2.30)	3 (2)	29 (2)	NA	NA
Any neurologic diagnosis[e]	110 (17)	799 (12)	**1.43 (1.15–1.77)**	1.24 (0.99–1.55)	35 (25)	235 (17)	**1.61 (1.07–2.42)**	**1.56 (1.03–2.37)**

DD, Developmental Delay; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; OCD, obsessive–compulsive disorder. Significant findings are bolded ($p < 0.05$). aOR: adjusted odds ratio.

[a] Co-occurring conditions in individual cells with the sample size <5 for males and females was not shown.

[b] Adjusting for surveillance year, source of surveillance record, and child race.

[c] Any developmental diagnosis (e.g., DD-general, DD-adaptive, DD-motor, DD-personal/social, DD-play, language disorder, ADHD, learning disability, sensory integration disorder, and non-verbal learning disorder).

[d] Any psychiatric diagnosis (e.g., obsessive–compulsive disorder, bipolar disorder, oppositional defiant disorder, anxiety disorder, mood disorder, emotional disorder, depression, mutism, behavior disorder, psychosis, conduct disorder, reactive attachment disorder, personality disorder, and schizophrenia).

[e] Any neurologic diagnosis (e.g., hearing loss, epilepsy, encephalopathy, cerebral palsy, vision impairment, Tourette syndrome, brain injury).

3.4. Factors related to ASD diagnosis retention in males and females

Table 4 presents the unadjusted and adjusted associations between ASD diagnostic factors and ASD diagnosis retention by child sex. Confounding variables, such as child race, source of surveillance record, and surveillance year were adjusted in the multivariable models. Both males and females who received 11 or more evaluations had significantly higher odds of being classified as ASD-NR than children with 1–10 evaluations. Males and females with higher degree of impairment level were less likely to be classified as ASD-NR than those with a lower degree of impairment. In addition, males first diagnosed at 31 months or older (vs. at 30 months or younger) were more likely to be classified as ASD-NR (aOR = 1.36, 95% CI: 1.03–1.79) compared to those males first diagnosed at 30 months or younger. Males first diagnosed by other professionals, such as speech-language pathologists, occupational therapists and EDD or EDS educators, (vs. psychologists) were less likely to be classified as ASD-NR (aOR = 0.74, 95% CI: 0.56–0.79). Similar association patterns were also observed in females, although did not reach statistical significance.

4. Discussion

Our findings show that ASD diagnosis remains fairly stable with only 9% of children with a documented ASD diagnosis having ASD later ruled out by a community professional. In other words, >90% of children with ASD retained their ASD diagnosis into middle childhood and likely required continued treatment and support (Banach et al., 2009; Chawarska et al., 2009; Van Daalen et al., 2009). Although most CoCs were associated with a change in ASD diagnosis in both sexes, the co-occurrence of developmental diagnoses (e.g., ID or sensory integration disorder) was predictive of ASD diagnostic instability in males, whereas the co-occurrence of specific developmental (e.g., personal/social delay) or neurological diagnosis (e.g., epilepsy) was associated with a change of ASD diagnosis in females. Moreover, some factors such as the number of evaluations and degree of impairment associated with ASD were associated with ASD diagnosis retention in both sexes, whereas age of first diagnosis and the professional type who recorded the first diagnosis were differentially associated with diagnosis retention in males and females. These findings suggest that the co-occurrence of certain non-ASD diagnoses may increase the likelihood of an ASD diagnosis eventually being ruled out, regardless of the sex of the child. Furthermore, it highlights the need for clinicians to be aware of the challenges of differentiating ASD and CoCs, as CoCs can complicate the diagnostic picture and lead to increased likelihood of ASD diagnostic instability.

Table 4
Associations between ASD diagnostic factors and diagnosis retention status in males and females.

Diagnostic factors	Male ($n = 7077$)				Female ($n = 1487$)			
	ASD classification not retained ($n = 653$)	ASD classification retained ($n = 6424$)	Unadjusted analysis	Adjusted analysis[a]	ASD classification not retained ($n = 138$)	ASD classification retained ($n = 1349$)	Unadjusted analysis	Adjusted analysis[a]
	n (%)	*n* (%)	OR (95% CI)	aOR (95% CI)	*n* (%)	*n* (%)	OR (95% CI)	aOR (95% CI)
Age of first ASD diagnosis	60.3 ± 22.2	57.2 ± 22.4	***t* = -3.45, *P* = 0.0006**		56.8 ± 22.9	56.4 ± 22.3	$t = -0.16$, $P = 0.87$	
Timing of first ASD diagnosis								
30 months or younger	62 (9)	753 (12)	1.00	1.00	17 (12)	167 (12)	1.00	1.00
31 months or older	591 (91)	5671 (88)	1.27 (0.96–1.66)	**1.36 (1.03–1.79)**	121 (88)	1,182 (88)	1.01 (0.59–1.71)	1.02 (0.60–1.75)
Community professional who recorded the first ASD diagnosis								
MD developmental pediatrician	185 (28)	1378 (22)	**1.30 (1.07–1.60)**	1.14 (0.93–1.40)	40 (29)	288 (21)	1.47 (0.93–2.31)	1.44 (0.90–2.30)
MD neurologist	95 (14)	857 (13)	1.08 (0.84–1.38)	0.94 (0.73–1.21)	23 (16)	223 (17)	1.09 (0.64–2.85)	1.07 (0.62–1.84)
MD other[b]	45 (7)	539 (8)	0.81 (0.58–1.13)	0.72 (0.51–1.01)	9 (7)	105 (8)	0.91 (0.43–1.91)	0.87 (0.41–1.87)
Psychologist	247 (38)	2395 (37)	1.00	1.00	44 (32)	485 (34)	1.00	1.00
Other professional[c]	70 (11)	881 (14)	0.77 (0.58–1.02)	**0.74 (0.56–0.97)**	14 (10)	193 (14)	0.77 (0.41–1.43)	0.77 (0.41–1.44)
Professional not stated	11 (2)	376 (6)			8 (6)	75 (6)		
Number of evaluations by community professional								
1–10	486 (74)	5674 (88)	1.00	1.00	102 (74)	1,162 (86)	1.00	1.00
11–19	143 (22)	623 (10)	**2.68 (2.19–3.29)**	**2.43 (1.97–2.99)**	29 (21)	157 (11)	**2.10 (1.35–3.28)**	**2.12 (1.33–3.36)**
20+	24 (4)	120 (1.9)	**2.34 (1.49–3.65)**	**1.94 (1.23–3.05)**	7 (5)	29 (2)	**2.75 (1.18–6.43)**	**2.64 (1.12–6.26)**
Missing		7 (0.1)				1 (1)		
Impairment level associated with ASD								
1 (least impaired)	123 (19)	696 (11)	1.00	1.00	24 (17)	135 (10)	1.00	1.00
2	229 (35)	1398 (22)	0.90 (0.73–1.18)	0.88 (0.69–1.13)	36 (26)	285 (21)	0.71 (0.41–1.24)	0.71 (0.40–1.24)
3	122 (19)	1442 (22)	**0.48 (0.37–0.63)**	**0.41 (0.31–0.54)**	30 (22)	304 (23)	**0.56 (0.31–0.99)**	**0.47 (0.26–0.86)**
4	51 (8)	921 (14)	**0.31 (0.22–0.44)**	**0.24 (0.16–0.34)**	12 (9)	190 (14)	**0.36 (0.17–0.74)**	**0.29 (0.14–0.62)**
5 (most impaired)	15 (2)	383 (6)	**0.22 (0.13–0.38)**	**0.16 (0.09–0.29)**	4 (3)	70 (5)	**0.32 (0.11–0.96)**	**0.25 (0.08–0.78)**
Not stated	113 (17)	1584 (25)			32 (23)	365 (27)		

Data presented as mean ± SD or n (%). Significant findings are bolded ($p < 0.05$). aOR: adjusted odds ratio.
[a] Adjusting for surveillance year, source of surveillance record and child race.
[b] MD other: MD psychiatry, MD genetics, MD rehabilitation medicine, MD neonatology, and MD family medicine.
[c] Other professional: language pathologists, occupational therapists and EDD or EDS educators.

Most males and females with an ASD diagnosis at younger ages retain an ASD diagnosis over time. Although the diagnosis of ASD is highly stable, we found that many CoCs were associated with ASD-NR in both sexes, which is consistent with past research (Close et al., 2012; Wiggins et al., 2012). For males but not females, our results revealed that two specific developmental diagnoses, co-occurring ID and sensory integration disorder were associated with ASD diagnostic changes. These results suggest that differential diagnosis between ASD and other developmental disorders may be particularly

difficult when males present with cognitive and other delays, or neurodevelopmental disabilities that influence sensory processing. Consequently, clinicians should consider core symptoms that distinguish ASD from other neurodevelopmental disabilities, preferably by administering a standardized diagnostic instrument that differentiates ASD social symptoms from other developmental delays.

Conversely, females with DD-personal/social were more likely to be ASD-NR than males with DD-personal/social. This finding may reflect different social expectations of females than males at young ages. Females with epilepsy or any neurological diagnosis were also more likely to be determined as ASD-NR than males with neurological diagnoses, again indicating sex-specific issues with differential diagnoses based on CoCs. An earlier ADDM report found that females with an ASD diagnosis had higher rates of neurological problems than males (Giarelli et al., 2010) and this observation has been supported in other population-based and clinic-based studies (Amiet et al., 2008; Ben-Itzchak, Ben-Shachar, & Zachor, 2013). Thus, the challenge of making an accurate diagnosis of ASD appears to increase for females with co-occurring neurological symptoms. Currently studies and evidence-based guidelines recommend that clinicians or families should look out for symptoms or behaviors concerning for epilepsy and that if these concerns are present, the child should be referred to a neurologist for further evaluation. (El Achkar & Spence, 2015; Kagan-Kushnir, Roberts, & Snead, 2005). Electroencephalography screening is recommended if there is a clinical concern for possible epilepsy (Filipek et al., 2000; Kagan-Kushnir et al., 2005). Clinicians evaluating children with complex CoCs should thus be sensitive to these diagnostic challenges that may be particularly salient in females.

We were unable to determine whether ASD-NR children were first misclassified as ASD or if their symptoms changed over time and they no longer meet ASD diagnostic criteria. We found that males had a 3-month shorter time interval between earliest ASD diagnosis and subsequent ASD rule-out than females. One possible explanation is that males with ASD-NR were rated by ADDM clinicians to be less impaired than females (54% vs. 43% with impairment levels < 3, shown in Table 4), possibly suggesting that more diagnostic challenges in higher-functioning male children. Our results also showed that males with CoCs first diagnosed with ASD at older ages (31 months or older) were more likely to change from ASD to non-ASD status, which suggests that males who were diagnosed earlier and have fewer CoCs are more likely to retain an ASD diagnosis. Overall, these findings indicate that the change of ASD diagnosis from ASD to non-ASD may be related to degree of impairment associated with ASD, timing of first ASD diagnosis and the complexity of CoCs. These results highlight the need for ongoing clinician awareness of potential factors that may influence differential diagnosis of ASD, such as sex and the presence of CoCs.

Child race, source of surveillance records, surveillance year, and the professional who noted the first ASD diagnosis were significantly associated with ASD retention status in males but not in females. Because both sexes have similar estimated effect size, it is likely that the non-significant estimates in females is due to smaller sample size, and therefore less power to detect significant effects, in ASD-NR group. The general pattern of results show that males and females whose initial ASD diagnosis was later ruled out were more likely to be non-Hispanic white, have surveillance records from a health source, and have an earlier ASD diagnosis documented by professionals such as MD developmental pediatrician, neurologist, or psychologist. Additionally, children from more recent surveillance years (that is, more recent birth cohorts) were more likely to have ASD ruled out than children in earlier surveillance years. While ASD diagnoses have become more common over time, professionals may benefit from targeted training to help distinguish ASD from other conditions in early childhood.

The results of this study should be interpreted with several limitations in mind. First, we were unable to assess reasons for change from ASD to non-ASD. Possible reasons for change in ASD diagnosis include initial misdiagnosis such as attributing delays to ASD rather than ID or global developmental delays. Since information regarding interventions the child received was not collected in ADDM, we were also not able to assess whether classification changes were due to successful intervention efforts and future studies should consider the possible influence of intervention on change in ASD diagnosis. Second, ADDM collects documentation from professional assessments that describe a child's developmental status. These evaluations can be conducted by a range of professionals who are in the position to observe and document the child's development. ADDM collects descriptors from developmental evaluations, whether an actual diagnostic evaluation as a licensed psychologist or certain physicians would provide, or from other allied health or educational professionals. Based on their profession and credentialing, the information included and the conclusions reached may vary. Third, there remains the possibility that some children who really no longer have ASD may have been missed if they didn't return to clinic for a re-assessment. In this case, the proportion of children who really no longer have ASD (i.e. ASD-NR) may have been underestimated. Fourth, although this study includes a large female sample, the female sample in the ASD-NR group is relatively small and therefore might influence the robust estimation of group difference and the relationship between CoCs and diagnosis retention status. Data collection in the ADDM Network is ongoing and future cohorts will enable additional validation of our results in a larger sample. Despite these limitations, these findings contribute to a broader understanding of ASD diagnosis retention and factors that may influence ASD diagnostic instablility in males and females.

The high retention rate of ASD diagnoses among male and female children indicates a need for continued support and treatment for children and families. Although similar proportions of males and females retained their ASD diagnosis through age 8, certain CoCs may differentially influence a change from ASD to non-ASD status in males versus in females. Our findings highlight the need for clinicians to be aware of challenges concerning differential ASD diagnosis and CoCs that may complicate an early and appropriate diagnosis of ASD.

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Conflicts of interest

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