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Early Autism Diagnosis in the Primary Care Setting

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As the prevalence of autism spectrum disorder (ASD) has increased in recent years, so too has the body of research describing the importance of early diagnosis and early intervention. Unfortunately, a large proportion of children with the disorder do not receive a diagnosis until after their fourth birthday. Various reasons exist for late diagnosis, including limited understanding of nuanced early warning signs and limited knowledge of effective early detection mechanisms among healthcare providers. Since early diagnosis enables access to treatment, and early intensive intervention improves long-term developmental outcomes, early detection by pediatric healthcare providers is critical. This article will review ASD prevalence rates, describe correlates and factors that might influence prevalence estimates, and highlight recent advances in early detection methods and intervention services.
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Introduction

Autism spectrum disorder (ASD) — once regarded as a relatively rare condition — is now one of the more common neurodevelopmental disorders diagnosed in childhood. Since the beginning of the century, the prevalence of ASD has increased threefold, with it now being estimated that 1 in 54 children has the disorder. Pediatric healthcare providers (PHPs) are therefore more likely than ever to have a patient who is on the autism spectrum. While prevalence continues to increase, the average age of ASD diagnosis continues to hover around age 4 years. Later diagnosis means a child misses the opportunity to benefit from early intervention, which does not have to be the case.

PHPs are an incredibly important component of early ASD detection and are in a unique position to influence the age of diagnosis. For PHPs to effect the most change in lowering the age of detection, it is important that they understand nuanced features of the disorder and characteristics of individuals with ASD who may be missed or diagnosed later in life. PHPs must also be knowledgeable about various effective early screening methods. A better understanding of subtle differences related to ASD and knowledge of different mechanisms of detection measurement will likely improve screening practices among PHPs and help lower the age that children are referred for evaluation. The purpose of this paper is to highlight current estimates and trends in ASD prevalence, and to delineate recent advances in early detection methods.

ASD Prevalence: CDC and Beyond

Prevalence estimates of ASD have been calculated using different methodologies and data sources (see Table 1). The most frequently cited estimates come from the Centers for Disease Control and Prevention (CDC). The CDC has been monitoring the prevalence of autism since 2000 through an active surveillance system: The Autism and Developmental Disabilities Monitoring (ADDM) Network. Currently, eleven sites comprise the ADDM Network: Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin.[1] Surveillance by the CDC involves record review and abstraction of evaluations from community-based health and education providers. Clinicians determine ASD case status using coding schemes based on DSM-IV-TR and DSM-5 guidelines. CDC estimates are calculated only for children aged 8 years whose caregivers reside in one of the ADDM Network sites. ASD prevalence has also been estimated using population-based

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Table 1 Prevalence of ASD Estimated Using Different Methodologies and Data Sources

	Data Source		
	ADDM[a]	**NHIS[b]**	**NSCH[c]**
Data collection approach	Record review/abstraction of evaluations from health and education providers.	In-person interview with caregivers.	Caregiver completed mail-based questionnaire.
Sample size (surveillance year)	275,419 children (2016)	40,220 households (2016)	67,047 households (2016)
States included	11	50 + DC	50 + DC
Sample age (years)	8	3-17	3-17
Prevalence of ASD (%)	1.85	2.47	2.50
Among white children	1.85	2.76	2.57
Among black children	1.83	2.49	2.79
Among Hispanic children	1.54	1.82	2.43
Male-to-female ratio	4.3:1	3.8:1	2.9:1

[a]Autism and Developmental Disabilities Monitoring Network.
[b]National Health Interview Survey.
[c]National Survey of Children's Health.

data sources, such as the National Health Interview Survey (NHIS) and the National Survey of Children's Health (NSCH).

The NHIS is a nationally-representative survey of children's health that is administered as an in-person interview with caregivers in their home. The NHIS sample is selected from defined clusters of households in each state using a probability design. The sample size for the 2016 NHIS was 40,220 households.[2] For the NHIS, a child is identified as having ASD if a caregiver reports receiving a diagnosis from a doctor or health professional. Similar to the NHIS, the NSCH is a nationally-representative survey of children's health and well-being based on caregiver report. NSCH data are collected from state-level samples of households that are selected from the Census Master Address File. In 2016, the sample size was 67,047 households.[3] Unlike the NHIS, the NSCH is a mail-based questionnaire. For the NSCH, a child is identified as having ASD if a caregiver reports (1) that a doctor or health professional has told them that their child has ASD, and (2) that their child currently has the disorder.

Prevalence Estimates

The most recent CDC report[1] estimated that 1.85% of children aged 8 years had ASD. Higher estimates have been found from other sources: 2.47% of children aged 3-17 years were estimated to have ASD based on data from the NHIS.[4] Similarly, the prevalence of ASD has been estimated to be 2.50% among children aged 3-17 years when using NSCH data.[5] Discrepancies in estimates likely reflect differences between systems with regard to: (1) methodologies (ie, records review [CDC] vs in-person interviews [NHIS] vs mail surveys [NSCH]), (2) populations (ie, 11 ADDM sites [CDC] vs all of US [NHIS and NSCH]), and (3) ages of children studied (ie, 8 years [CDC] vs 3-17 years [NHIS and NSCH]). Despite these differences, one thing is clear: regardless of data sources, prevalence estimates have increased in recent years. CDC estimates have tripled since the early 2000s, from one in 166 children in 2004 to one in 54 most recently,[1] while NHIS estimates have increased from one in 169 in 2004[6] to one in 41 most recently.[4] The extent to which this represents a genuine increase in the number of children with ASD is unknown. Temporal differences in estimates may also be due, at least in part, to better detection methods, and increased awareness and advocacy, especially among minority children and girls.[7]

Race and Ethnicity

ASD prevalence estimates have historically been higher for non-Hispanic white (hereafter, white) children than for non-Hispanic black (hereafter, black) children and Hispanic children. Currently, the prevalence of ASD is estimated to be 1 in 54 (1.85%) among white children, 1 in 55 (1.83%) among black children, and 1 in 65 (1.54%) among Hispanic children.[1] Similar trends, yet slightly higher prevalence rates, have emerged from NHIS data, where 2.76% of white children, 2.49% of black children, and 1.82% of Hispanic children were estimated to have ASD.[4] In recent years, greater increases in prevalence rates have been found among black and Hispanic children, which in turn have resulted in a smaller prevalence ratio between each of these groups and white children.[1] Indeed, the most recent CDC estimates have, for the first time, found no significant difference in prevalence among black and white children.[1] Reduced racial disparities in ASD prevalence are likely a result of increased outreach efforts in minority communities and in response to improved identification methods, which have also impacted the male-to-female prevalence ratio.

Gender

The prevalence of ASD has been estimated to be one in 34 boys and one in 145 girls, representing a 4.3:1 male-to-female ratio.[1] Smaller ratios of 3.8:1 and 2.9:1 have been estimated using NSCH data and NHIS data, respectively.[4,5] Although a male bias in prevalence has consistently been found across data sources, decreases in the male-to-female

ratio have emerged in recent years, resulting from greater increases in ASD prevalence among girls than boys. Currently, it is unclear if differences in prevalence rates represent true differences, or if females are underdiagnosed due to gender differences in phenotypic presentation.[8] Emerging research suggests, for example, that gender differences in language development, and gendered parental concerns and expectations, may result in females with more advanced language skills being missed by current diagnostic practices.[9] Despite differences in prevalence for boys and girls, the most recent CDC report found no significant gender difference in average age at first diagnosis.[1]

Average Age of Diagnosis

Although research suggests autism symptoms can be identified by 12-months,[10,11] the average age of diagnosis continues to be disconcertingly high, with a substantial proportion of children not identified until after 6 years of age.[12] According to the most recent CDC report, the median age of earliest ASD diagnosis is 51 months.[1] Surprisingly, only 44% of children with ASD received a comprehensive evaluation by age 3 years; 37% did not receive an evaluation until after age 4 years.[1] This is unfortunate, as children who receive late diagnosis miss the opportunity to benefit from early intervention services during a critical period of development.

Early Intervention for ASD

Over the past 3 decades, a growing body of research has emerged showing that early intervention can alter the course of ASD and result in improved long-term outcomes.[13] While there are no curative treatments for ASD, the FDA has approved aripiprazole and risperidone for comorbid symptoms of irritability and aggression,[14,15] although neither pharmacotherapy targets core symptoms. Since the disorder is behaviorally defined, programs based on applied behavioral analytic principles are considered the gold-standard for ASD treatment.

Applied Behavioral Analysis

Based on the principles of operant conditioning proposed by B.F. Skinner, interventions incorporating Applied Behavioral Analysis (ABA) attempt to facilitate skill development through continuous functional assessment.[16] Early intensive behavioral intervention (EIBI) was one of the first ABA-based treatments created specifically for individuals with ASD.[17] EIBI is typically delivered to children who are younger than 6 years of age for up to 40 hours per week in a 1:1 setting.[18] The guiding tenet of EIBI — discrete-trial training (DTT) — involves breaking down behaviors into specific, simpler tasks that are taught sequentially through repetition.[19] Depending on the child's response, reinforcement or correction follows. As a child develops more advanced skills, treatment becomes less structured and targets more complex behaviors.

Despite EIBI's overall effectiveness,[18] the intervention has been criticized as being inefficient. EIBI requires many hours, and at times many repetitive trials, to produce small gains that may not generalize. EIBI has also been criticized as being overly structured and adult-centered (ie, using select materials chosen by adults). Disregarding a child's choice of tasks and materials is thought to have a direct, negative impact on child motivation, which in turn can lead to decreases in responsiveness and concomitant increases in disruptive behaviors.[20] In response to these criticisms, less structured and more naturalistic forms of ABA-based therapies were developed, such as Pivotal Response Treatment.

Pivotal Response Treatment (PRT), similar to EIBI, is an ABA-based treatment that is used to develop and shape behaviors. Unlike DTT, however, PRT is a more flexible, play-based approach that targets "pivotal" areas of development using child-directed methods, instead of targeting individual behaviors. Core pivotal areas include motivation, self-regulation, responding to numerous cues, and initiations.[21] PRT is guided by the assumption that improvement in pivotal areas leads to widespread positive collateral changes in other untargeted behaviors.[21]

Whereas DTT methods require strict adherence to processes using prescribed tasks, PRT is guided by a child's choice of activities and materials. PRT is also less rigid in terms of task learning: whereas DTT sessions focus exclusively on target behaviors, PRT sessions can incorporate already mastered tasks along with new tasks. When taken together, these characteristics are thought to promote maintenance and generalization of behaviors across situations and settings.[20] As with DTT, PRT is most effective when it is provided early in a child's life.[11]

Importance of Early Intervention

The underlying motivation for early intervention is that during the first years of life, a critical period of synaptogenesis occurs, where a surge of synapse formation and refinement takes place. Peak synaptic density in the prefrontal cortex occurs by age 3 years, after which synaptic remodeling and elimination takes place.[22] A growing body of work has reported neural dysfunction and overgrowth of connections in the frontal regions of the brain during the early postnatal period in individuals with ASD.[23, 24] Aberrant neuroplasticity, namely abnormal synaptic pruning, is thought to lead to the accumulation of damaged neurons and result in an abnormal neural network of defective connections.[25] Research suggests that environmental factors and experiences influence both the construction of specific neural circuits and the elimination of excess synapses.[26] Thus, neurofunctional outcomes for toddlers with ASD should be optimized if interventions are provided as early as possible, before neural circuits have been formed.

Providing early environmental enrichment to children during the first years of life has been found to alter the trajectory of both biological and behavioral development. Specifically, research has found early comprehensive behavioral

intervention to be effective in improving adaptive behavior, language, and IQ among children with ASD.[18,27] Moreover, EEG measurements taken 2 years after children with ASD received early intervention found normalized patterns of brain activity related to social behavior.[28] Finally, children who receive early intensive intervention have been found to require fewer services later on, resulting in overall long-term cost savings.[29] Given the reported benefits of early intervention, efforts to lower the age of diagnosis have intensified in recent years and led to the development of innovative models for early identification.

Attempts to Improve Early Diagnosis

Emerging evidence on the importance of early intervention has resulted in efforts to promote very early identification of ASD. Various novel approaches to early detection have been undertaken, ranging from the use of biomarkers to the implementation of universal screening programs.

Despite the American Academy of Pediatrics' (AAP) recommendation that general developmental screenings should be conducted at all well-child visits, and autism specific screenings at 18- and 24-month visits,[30] many pediatricians do not adhere strictly to these guidelines. Some pediatricians may screen at 18-month but not 24-month. Others may screen at both ages, but without using validated tools, relying solely on clinical judgment, which can vary widely with experience. This disparity is unfortunate, given that standardized screening is more accurate than clinical judgment alone in identifying children with developmental delays, and autism in particular.[31, 32]

For routine standardized screening to be successful, pediatric offices need to implement systemic efforts to ensure procedural policies are in place, and to get buy-in from all staff. Without staff training and procedural guidance, the full benefit of early screening will not be obtained. University-based researchers in San Diego tested the effectiveness of adding structure to early screening by developing and implementing the 1-year Well-Baby Checkup Approach.[10] As part of the approach, a network of 137 pediatric healthcare providers (PHPs) in San Diego County was developed, and PHPs were trained uniformly on (1) early warning signs for autism, (2) the benefits of early detection, and (3) screening and referral procedures. PHPs agreed to screen universally at the 12-month well-check with a standardized questionnaire. All failed screens, regardless of parent or PHP concerns, were referred to the university or another community-based clinic, based on the parents' choice, for further evaluation. As a result of the program, developmental evaluations were completed for 184 toddlers, of whom 32 were identified with ASD. Children with ASD were, on average, referred for treatment at 17 months and started treatment at 20 months of age. Comparing these findings to the CDC's estimate of the median age of earliest ASD diagnosis (ie, 51 months) reveals the potential of universal standardized screening for lowering the age of diagnosis, and subsequently the start of treatment, for some children.

Despite the obvious benefits of routine screening, critics have argued that additional, more objective detection methods are needed given that screening tools rely solely on using observable behaviors. Indeed, taking into account the heterogeneity in presentation of symptoms and severity of symptomatology, tools that only assess observable traits may be ill equipped to detect toddlers with less obvious and less impaired behaviors. Inconsistencies in the age and pattern of symptom onset further complicate issues of screening for ASD at specific ages. Although a subset of children will start to show symptoms as early as 12 months, some may not manifest symptoms until their second or third birthday.[33] Other children may develop appropriately up until around 24 months then suddenly experience developmental regression, where previously mastered skills and abilities are lost and ASD symptoms emerge.[34] Yet another subgroup of "late-diagnosed" children may present with a mild phenotype early, but only satisfy diagnostic criteria after an extended progression of symptom development (eg, after 60 months of age).[35] Attempting to overcome these issues, research has recently focused on studying biological markers to detect ASD before clinical symptoms emerge.[36] Eye tracking is one approach to studying biomarkers that has gained increased attention in recent years as emerging evidence suggests inconsistent eye contact and atypical visual attention may be preclinical signs of ASD.[37]

Eye tracking devices were developed to measure various forms of visual engagement, including gaze, amount of time spent looking at social and nonsocial stimuli, and areas of the face that receive preferential attention. Eye tracking studies have confirmed, with objective quantifiable data, that individuals with ASD have abnormal eye contact and aberrant gaze patterns to social and nonsocial information.[38] Specifically, studies have found that toddlers with ASD, compared with their neurotypically developing counterparts, fixate significantly more on geometric images than on social images[39] and spend significantly less time attending to eye and mouth regions.[40] Moreover, symptom severity, as measured across a range of developmental areas (eg, cognitive, language, adaptive functioning) has been found to be significantly associated with percent fixation on geometric images.[41] In other words, children with a higher percent fixation on geometric images are more likely to have more severe symptomatology. Importantly, atypical visual engagement has been observed beginning around the first 6 months of life in toddlers later diagnosed with ASD.[42]

Despite the promising potential of eye tracking, the field is still in its infancy, and current approaches are far from optimal with regard to correctly identifying toddlers with the disorder. Pierce et al[39,41] estimated the sensitivity of their eye tracking technique for ASD to be 21%. Although the specificity was estimated to be 98%, the relatively low sensitivity, coupled with the association found between symptom severity and percent fixation on geometric images, suggests eye tracking may be most useful for identifying children with more impaired symptoms. Encouragingly, several researchers

are currently undertaking rigorous studies with more robust eye tracking devices. Until results from these studies start to emerge, it is imperative that pediatricians screen all children for ASD using validated, standardized screening tools at multiple ages.

Pediatrician Screening Habits and Behaviors

Pediatricians in many instances are the "first line of defense" when it comes to identifying children with ASD.[43] Recognizing this, in 2007 the American Academy of Pediatrics published updated autism screening guidelines that recommended ASD specific screenings at 18- and 24-month well-visits using validated, standardized tools.[30] Inherent within the AAP recommendations is the notion that early screening for ASD by pediatricians can lower the age that children are referred for formal evaluation, which subsequently can lower the age of diagnosis and the start of appropriate interventions. It is important to highlight that the AAP's recommendation stresses early routine screening using ASD-specific tools, as opposed to early screening using clinical judgment alone. Although some pediatricians may have demonstrably acute clinical judgment, research suggests that pediatricians identify more children with ASD when they use formal screening tools. [30,31,32,44] Despite this, alarmingly low rates of ASD screening using standardized tools are reported by pediatricians.

Rates of ASD Screening

Estimates of screening practices for ASD vary considerably. Dosreis et al[45] mailed surveys to a random sample of pediatricians in Maryland and Delaware to examine screening practices and habits. Only 8% of the 225 respondents reported screening for ASD. Gillis[46] used a modified version of the questionnaire used in Dosreis et al's study to survey pediatricians and family physicians in Alabama and Mississippi. Of the 51 respondents, 28% reported using ASD screeners, and only 1 pediatrician reported routinely screening for ASD at 18- and 24-month well-checks.

Arunyanart et al[47] examined rates of ASD screening by emailing a link to a web-based questionnaire to pediatricians who were fellows of the AAP in 6 states: Connecticut, Hawaii, Massachusetts, Michigan, New Jersey, and New York. Of the 281 respondents, 59.8% reported that they always used standardized autism screening tools at 18-month visits, and 50.2% reported always using ASD screeners at 24-month visits. Moreover, 72.7% of respondents reported using standardized autism screening tools more often than they did 5 years prior. Reported reasons for this increase included: wanting to maintain a standard of care, publication of the AAP policy statement, and improved reimbursement for screening.

Most recently, Self et al[48] surveyed pediatricians and family physicians in Kansas, Oklahoma, and Iowa to examine ASD screening habits. Among the 396 respondents, 58% reported using ASD screening tools at 18-month visits or 24-month visits. Only 17% of respondents reported screening routinely for ASD in accordance with the AAP recommended schedule (ie, at 18- and 24-month well-child visits).

Although rates of ASD-specific screenings among pediatricians appear to have increased in recent years, more work needs to be done to promote consistent screening of autism using formal tools as outlined by the AAP. Efforts to promote universal screening should start by understanding, and addressing, common barriers and concerns reported by pediatricians.

Barriers to ASD Screening and Recommendations

The US Preventive Services Task Force (USPSTF) recently published a controversial report on universal screening for ASD that concluded that, "the current evidence is insufficient to assess the balance of benefits and harms of screening for autism spectrum disorder (ASD) in young children for whom no concerns of ASD have been raised by their parents or a clinician."[49] The underlying message from the report is that we currently do not have sufficient robust evidence (ie, from randomized controlled trials) to demonstrate that the overall benefits of universal screening outweigh potential harms (eg, false-positive results leading to parental stress). It cannot be denied that more research is needed to examine outcomes specifically for children who fail screenings and whose parents or clinical providers have no concerns; however, conducting research in this area using research designs recommended by the USPSTF would be both infeasible and unethical (eg, withholding early screening from toddlers).[50] As it stands, research has consistently shown that screening using a standardized tool has predictive validity (which was acknowledged by the USPSTF), and pediatricians have been shown to identify symptoms of ASD more consistently and earlier when they use screening tools.[30,31,32,44] While it does not explicitly recommend against universal screening, it is disconcerting to think of the possible misinterpretations and negative effects of the report. Recognizing this, the AAP has urged pediatricians to screen universally for ASD despite the USPSTF recommendation. Unfortunately, even prior to publication of the USPSTF, not all pediatricians have adhered to AAP guidelines because of numerous reported barriers.

One of the more commonly reported barriers to screening is unfamiliarity with appropriate and valid ASD screening tools.[45,46,51] Strikingly, over half (58%) of the respondents in Self et al's[48] study reported that they were not familiar with ASD screening tools, and 44% reported that they had insufficient training to screen. This finding demonstrates the need for preprofessional education and continuing education and training on ASD. In particular, education should highlight the importance of early screening using formal tools and provide information on valid screening instruments. The utility

of screening tools as an accompaniment to clinical observation should be stressed, given that some pediatricians have a perceived belief that early screeners are ineffective, and clinical judgment alone is sufficient.[45,48,51] Moreover, continuing education should review updated research on screening tools, including psychometric properties of the tools, as this is an area that is constantly changing. Without increased education, pediatricians may continue to use outdated tools.

Time constraints and insufficient reimbursement have also been voiced by pediatricians as barriers to screening.[45,46,48,51] Several free screeners (eg, the M-CHAT, CSBS-DP-ITC) are brief report measures that can be completed by parents in approximately 5 minutes while they are waiting to see their pediatrician. Scoring of these tools is quick and easy, taking a few minutes to complete. Results can thus be shared with medical providers and incorporated into office visits, facilitating, when necessary, referrals for further developmental evaluation or treatment services. In many instances, pediatrician offices can bill for administering screeners, provided that the tool is validated and the scored results have been reviewed with the family.[51]

A more complicated challenge presents itself in the larger screening process when it comes to next steps. The process of screening is only as effective as the referral processes in place for diagnostic and intervention services. Limited understanding of referral options is often cited as a challenge to screening. Developing relationships with community partners (eg, autism centers, researchers) is one way to educate pediatricians about appropriate and available resources for children who flag screening questionnaires. At a more fundamental level, strong relationships between pediatricians and specialists can increase pediatrician awareness of autism detection and facilitate practice improvement to promote early routine screening.[12] This was demonstrated by Pierce et al[10] in San Diego who developed a supportive relationship with a network of pediatricians (as mentioned in the previous section). Pediatricians in the network were provided education, simple screening tools (the CSBS-DP-IT), and guidelines for referral for both evaluation and treatment. Infants who saw one of the pediatricians for a 12-month well-visit were screened and referred, when appropriate, to the study center for further developmental evaluation. Thus, questions surrounding appropriate referral options were eliminated, and ultimately resulted in children who were later identified as having autism starting treatment at 20 months of age.

These findings demonstrate the feasibility of developing and maintaining supportive relationships between pediatricians and community partners to facilitate formal screening and referral processes. On a larger level, these findings highlight the critical importance of collaborative, interdisciplinary efforts to autism research and practice. Regardless of the approach taken (universal standardized screening, biomarkers, etc.), our odds of success at lowering the age of ASD detection and treatment will only go up if we share our expertise and work together across disciplines.

Conclusion

Over the past 2 decades, the number of individuals diagnosed with ASD has increased significantly, with it now being estimated that almost 2% of the population has the disorder. As the prevalence of the disorder has increased over time, so too has the body of literature demonstrating the importance of early intervention. Unfortunately, the average age of ASD diagnosis continues to be far too high, at around age 4 years. At this age, children miss the opportunity to benefit from early intervention services. Naturally, early intervention cannot begin without early diagnosis. To support early diagnostic efforts, it is important that early detection and referral mechanisms are in place in the community. Given the role of PHPs in monitoring the development of children from a young age, they are in unique position to directly influence the age of ASD diagnosis by promoting early detection efforts. While there are various approaches to early detection, screening in the primary care setting using validated tools is currently the most promising approach, with some studies showing this method can lower the average age of diagnosis by almost 3 years. To be successful, PHPs should screen consistently at periodic intervals using currently validated tools, as recommended by the AAP. PHPs should also be knowledgeable about referral options for further developmental evaluation for families whose children flag the screening tool. Without this knowledge, the potential of early screening for lowering the age of diagnosis will not be fully maximized.

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