OBJECTIVE: Delayed onset of independent walking is common in intellectual disability (ID). However, in children with autism spectrum disorders (ASD), delayed walking has not been reported as frequently, despite the high rate of concurrent ID in ASD. This study directly examined the relationship between delayed walking and severity of ID in children with ASD versus other non-ASD diagnoses.

METHOD Participants were 1185 individuals (ASD, n = 903; non-ASD, n = 282) who received an assessment at age 4 to 12 years (6.89 ± 2.25) that yielded an estimate of nonverbal IQ (NVIQ) and retrospectively reported age of walking from the Autism Diagnostic Interview–Revised. The relationship between diagnostic group and delayed walking (defined as occurring at ≥16 months) as a function of NVIQ was explored using the Cox proportional hazards model.

RESULTS: Children with ASD were less likely to exhibit delayed walking than those with non-ASD diagnoses, and this difference was larger at lower levels of NVIQ (P = .002). For example, rates of delayed walking for ASD and non-ASD were 13% and 19%, respectively, in those with NVIQ >85 but 31% and 60% in children with NVIQ <70.

CONCLUSIONS: Although lower IQ scores were associated with increased rates of late walking in both ASD and non-ASD groups, children with low IQ were more likely to show delayed walking in the absence of ASD. This raises the possibility of separate etiological pathways to ID in children with and without ASD.
Delay in independent walking, defined as walking at or after 16 months, has been established as a marker of atypical development. According to the World Health Organization, 97% of both male and female children begin to walk before the age of 16 months, and ~95% of children walk within the time frame of 9 to 16 months. Thus, for clinicians and parents, onset of independent ambulation signifies an important milestone. Compared with other developmental events, such as age of first words, age of walking is also a particularly reliable parent-reported milestone.

Many influences on the attainment of gross motor milestones such as independent walking have been identified, including prenatal, perinatal, and postnatal environmental factors (e.g., nutrition, cultural practices). One consistently identified association is between delayed walking and later intellectual disability (ID). Based on clinical reports of delayed walking in children later diagnosed with ID, early studies hypothesized a negative linear relationship between age of walking and IQ. However, studies in both typically developing and developmentally delayed populations have indicated no clear linear relationship, as children with high IQ do not necessarily walk early, and children with ID do not always walk late.

On the other hand, individuals with ID are more likely to experience delays in walking compared with individuals in the general population. In 1 study of 185 consecutive referrals with ID, half or fewer of children with moderate (47%), severe (51%), and profound (35%) ID walked by the age of 15 months. Another study of 87 children with profound ID reported that fewer than a quarter walked by the age of 14 months, and only two-thirds started walking before their second birthdays. The likelihood of delayed walking is also associated with degree of cognitive delay within several specific neurologic disorders (e.g., Duchenne muscular dystrophy). Studies of specific genetic syndromes, including Phelan-McDermid syndrome, Prader-Willi syndrome, and Angelman syndrome, highlight the extent of gross motor delay, where rates of walking late are very high, and many children at the most profound levels of ID do not ever walk independently.

Delayed walking has also been reported in other specific developmental disabilities, including autism spectrum disorder (ASD). In fact, Kanner’s first accounts of autism included descriptions of the children as having some gross motor clumsiness, including 1 child who “began to walk [at age 2 years] without any preliminary crawling or assistance by chairs.” Since then, numerous studies have pointed more generally to the potential role of the motor system in the development of ASD. In addition, retrospective studies have suggested a higher rate of late walking and other gross motor milestone delays in children with ASD compared with the general population, although these rates appear to be lower than in other disorders associated with ID.

To date, very little has been done to explicitly investigate delayed walking in relation to ID within ASD. Existing research dates back to the 1970s and 1980s and includes samples that are small by today’s standards. Nevertheless, the apparently lower rate of late walking in ASD compared with ID reported in these early studies is both perplexing and intriguing, given that a high proportion of children with ASD are also eventually determined to have ID. One of the many questions this dissociation raises is what other features co-occur when gross motor milestones (such as walking) are abnormal in ASD.

Using a large sample of children with neurodevelopmental disorders, we asked the following research questions: (1) Is there a difference in rates of delayed walking between children with ASD and non-ASD diagnoses, and does this change as a function of IQ? (2) What characteristics are associated with delayed walking in ASD versus non-ASD? and (3) In particular, is there a relationship between delayed walking and factors such as gender and epilepsy, which have been previously found to be relevant in biological investigations of ASD?

METHODS

Participants were drawn from an existing database of children assessed ≥1 times in 3 autism specialty clinics (54%) or as part of research projects conducted at 4 universities. Data from 1 assessment, including both the behavioral evaluation and parent-reported historical information, were used for each participant. Participants were eligible for the current analyses only if their assessment had included the Autism Diagnostic Interview–Revised (ADI-R), a comprehensive parent interview designed to elicit information about ASD-related symptoms and behaviors; the Autism Diagnostic Observation Schedule (ADOS), a direct observation measure of social-communication impairments and restricted and repetitive behaviors associated with ASD; and a nonverbal IQ (NVIQ) test. Information about age of walking was obtained from question 5 on the ADI-R, which asks "At what age did [subject] walk without holding on?" For participants who were assessed multiple times, we selected the first assessment that occurred between the ages of 4 and 12 years. The lower age limit was selected to allow adequate time for the child to begin walking. The upper age limit was selected to avoid the confounding...
variable of ratio IQ at older ages. NVIQ, used in this study as a trait variable reflecting severity of ID, was used instead of verbal or full-scale IQ to minimize the effects of language in measuring intellectual abilities in this population. NVIQ was estimated using ratio IQ from the Mullen Scales of Early Learning or standard scores from the Differential Ability Scales or the Wechsler Intelligence Scale for Children, depending on the ability level of the child.

Diagnoses of ASD (defined as Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnoses of autistic disorder, pervasive developmental disorder not otherwise specified, or Asperger disorder) were made by expert clinicians using information from the ADI-R, ADOS, and cognitive tests, in combination with other validated measures of language and behavior. For some studies, children with known genetic syndromes were eligible or were specifically recruited as non-ASD controls, but given the high rate of motor abnormalities associated with these syndromes, participants with known genetic syndromes (31 with Down syndrome, 8 with Williams syndrome, and 1 with fragile X syndrome) were excluded from the current study. Children with a known diagnosis of cerebral palsy were also excluded. Children who did not receive any Diagnostic and Statistical Manual of Mental Disorders diagnosis at the time of the assessment (eg, typically developing controls) were also excluded. As shown in Table 1, the final sample comprised 903 children with primary clinical diagnoses of ASD, with varying IQ levels, and 282 with non-ASD primary diagnoses, such as ADHD, language disorders, or ID.

### ANALYSIS

We used survival analysis to evaluate the relationship between age of walking and diagnosis, as a function of severity of ID. In this case, the survival event modeled was parent-reported age of walking. We then examined whether ID severity, indexed by current NVIQ,
was associated with age of walking attainment (eg, different survival experiences) and whether this relationship differed by ASD versus non-ASD diagnostic status. These variables, as well as the individual’s gender and parent-reported history of seizures, were entered into a Cox proportional hazards model. A hazard is the instantaneous event rate for an individual who has survived (ie, not walked) up to a given time. The Cox proportional hazards model is nonparametric, but with noncensored data such as these, it does assume proportional hazards, which were evaluated and satisfied. Relative model fit was assessed by using the likelihood ratio, which follows a $\chi^2$ distribution.

All analyses were completed by using SAS/STAT software, version 9.3 for Windows.$^{25}$ $\alpha$ was set to 0.05.

### RESULTS

Participant characteristics are presented in Table 1. The rate of late walking ($\geq 16$ months) differed significantly between the ASD group ($n = 201$, 22%) and the non-ASD group ($n = 85$, 30%) ($P = .007$). Age of walking was modeled using survival analysis; diagnostic group, NVIQ, and their interaction were simultaneously entered into the model (Table 2). This model had a significantly better fit than the null model according to the likelihood ratio test ($P < .001$). The interaction between group and NVIQ was statistically significant ($P < .001$) and was characterized by a greater likelihood of walking in the ASD group relative to the non-ASD group, especially when the level of functioning was low (see Fig 1). For example, Fig 1D shows that the predicted probability of having achieved independent walking by 18 months was the same for ASD and non-ASD (~85%) when NVIQ was held constant at 85. However, when NVIQ was held constant at 50 (Fig 1B), the predicted probability of having achieved independent walking by 18 months was ~80% for ASD compared with ~60% for non-ASD.

Two additional correlates were added to the model (Table 2): gender was entered first and significantly improved model fit ($P < .005$), followed by history of seizures, which did not improve model fit ($P > 0.10$) and was discarded. Males were more likely to have walked at a given time.

**TABLE 2** Results of Survival Analyses

<table>
<thead>
<tr>
<th>Model</th>
<th>Wald $\chi^2$</th>
<th>$P$</th>
<th>$-2LL$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 0 (null)</td>
<td>14 673.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>14 592.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>11.25</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>NVIQ</td>
<td>32.30</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Group × NVIQ</td>
<td>7.63</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>14 583.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>8.96</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>11.68</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>NVIQ</td>
<td>32.64</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Group × NVIQ</td>
<td>8.37</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>14 581.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>1.96</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>8.52</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>10.73</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>NVIQ</td>
<td>29.73</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Group × NVIQ</td>
<td>7.52</td>
<td>.006</td>
<td></td>
</tr>
</tbody>
</table>

Parent-reported seizure data were missing for $n = 105$ (12%) participants with ASD and $n = 10$ (3%) non-ASD participants. For the purposes of these analyses, missing data were coded as “no seizures” so that the full sample could be retained for Model 3. Sensitivity analyses were performed to ensure that the results were identical when Models 1 to 3 were evaluated in the sample with the full complement of data ($n = 1070$).

![FIGURE 1](https://example.com/figure1.png)

**FIGURE 1** Significant interaction between diagnostic group and later NVIQ in Cox proportional hazards model ($n = 1185$). Estimated survival probability (y axis) reflects the probability of having not walked by a given time, controlling for NVIQ. The interaction of diagnostic group (ASD versus non-ASD) and later NVIQ was statistically significant: $\chi^2 = 7.63, P = .0006$. Shown are the survival curves for each diagnostic group, held constant at various levels of NVIQ. The successively smaller distance between the curves in A through D illustrate the convergence in hazards between groups as NVIQ increases. The point estimates of the hazard ratios for ASD versus non-ASD (with 95% confidence interval) were as follows: A, 1.94 (1.35–2.79); B, 1.65 (1.27–2.14); C, 1.40 (1.18–1.66); and D, 1.24 (1.08–1.42). Higher hazard ratios indicate greater hazard of the event (walking) for an individual in the ASD group, relative to the non-ASD group, at any given time.
point than females (hazard ratio 1.23, 95% confidence interval 1.07–1.44). No significant interactions with gender were observed.

DISCUSSION

The results of this study build on data from much earlier studies of small samples suggesting that the relationship between delayed walking and later ID differs between children with and without ASD. For children with IQs in the average range, rates of delayed walking were similar between those with ASD and those with other neurodevelopmental disorders (eg, attention deficit hyperactivity disorder, language disorder), with rates in both groups moderately elevated (13% and 19%, respectively) compared with general population samples of children with average IQ. On the other hand, for children with below-average IQ, and especially for those in the range of ID, the rate of delayed walking was lower in those with ASD. We found that as NVIQ decreased, the gap between the survival curves for ASD and non-ASD widened, reflecting earlier attainment of walking in ASD compared with non-ASD.

This difference in delayed walking between children with ASD and ID relative to ID alone raises the question of whether some children with ASD arrive at their ID via a different route than other children with ID with or without accompanying ASD. Given that late walking in ASD appears to be relatively less common than what would be expected at comparable levels of non-ASD ID, how significant is late walking when it does occur? A specific hypothesis that can be explored is whether delayed walking in ASD is associated with a greater likelihood of identifiable genetic mutations. In line with this hypothesis is the finding that in the overall group, females showed higher rates of delayed walking than males, and that there was a trend for this effect to be stronger in ASD than in non-ASD. Given that recent genetics studies in ASD have reported higher rates of de novo mutations\(^{26,27}\) and more penetrant copy number variations\(^{28}\) in ascertained females than in males, these findings add to the broader differential liability hypothesis that suggests phenotypic differences may relate to sex (female)-specific protective factors.\(^{29,30}\)

Studies of genetic abnormalities in ASD have increasingly implicated IQ as an important stratification variable.\(^{27}\) The weaker association between age of walking and ID in ASD compared with non-ASD in this study suggests that markers of abnormal gross motor development such as late walking may be useful in further stratifying individuals with ASD into more etiologically similar subgroups. Precedence for this stratification exists in the ID literature, in which delayed walkers with ID are characterized by a higher rate of known etiology, other dysmorphic features, and medical comorbidities.\(^{8}\) These factors, which may be influenced by both genetics and the environment,\(^{31}\) are often not known or identified in individuals diagnosed with ID or ASD. Thus, as more detailed neurologic evaluations of individuals with ASD and ID are now being conducted clinically and through research, associations with delayed walking (which may differ based on sex) may become clearer.

Researchers in ASD are faced with many challenges in developing consistent and replicable phenotypes. Recent research has been less fruitful than hoped in the pursuit of phenotypes that link behavior with etiology. There are many potential explanations for the lack of identified correlates to date, most notably the reliance on behavioral measures that change within and across individuals over time.\(^{32}\) For this reason, an early developmental marker of neurobiological abnormality, such as delayed walking, is an attractive construct. Late walking can be accurately assessed at a single point in time and may link more readily to etiologic subgroups than other phenotypic variables that are more susceptible to retrospective reporting effects (eg, age of first words, regression)\(^{4,33}\) or that change over time (eg, social-communication symptoms, restricted and repetitive behaviors). Indeed, it is precisely that late walking is not specifically found to be associated with autism per se that it may be akin to one of the minor physical anomalies enumerated in complex autism, which was recently linked to a higher rate of genetic abnormalities.\(^{34}\)

Other recent investigations suggest that measures of multiple motor skills, rather than 1 milestone, may be more powerful in predicting outcomes.\(^{35}\) In the current study, we were not focused on predicting developmental trajectories, but rather on whether we can conceptualize a single, important milestone as having differential relationships with cognitive functioning in different diagnostic groups. Eventually, considering both early motor development and behavioral trajectories (including later motor development) together will likely be most helpful in elucidating more biologically meaningful phenotypes.

Although retrospective parent report of age of walking is reliably recalled in both general population and ASD samples,\(^{3,4}\) the use of a single motor milestone may be a limitation, especially compared with detailed prospective analysis of motor problems in infant sibling studies\(^{36}\) or retrospective analysis of videorecorded motor behaviors.\(^{37}\) These detailed evaluations have revealed significant motor delays and differences in infants who later develop autism, with more subtle
delays not necessarily reflective of a lower IQ later.38,39 On the other hand, because the ASD sample in the current study was large and was recruited for various purposes, our results may be more generalizable to the broad ASD population than smaller targeted prospective infant studies. Also, whereas infant sibling studies and other studies of high-risk samples use “low-risk” controls, our control group is more relevant in terms of understanding issues related to differential diagnosis and etiology of ASD and ID.

Nevertheless, because the sample was not obtained with epidemiologic methods, there are a number of potential sampling/referal biases that should be considered, including potential bias in how children are diagnosed with specific neurodevelopmental problems based on their early motor delays. Motor delays are often the first discernible sign of more global developmental problems,40 so it is possible that children with significant early motor delays were routed toward medical professionals (ie, neurology or genetics) for first evaluation, rather than ASD specialty clinics. Given that a substantial number of the ASD children in this study were ascertained from such clinics, late walkers with ASD may be underrepresented. Similarly, children with very significant motor delays may have been flagged with other dysmorphic features and, as a result, received genetic testing and subsequent genetic syndrome diagnoses. At the same time, although children with known genetic conditions were excluded from this study, genetic testing may not be part of most clinic or research protocols, so it is likely that some members of both the ASD and non-ASD groups had unidentified specific genetic abnormalities. Future studies that use more epidemiologically diverse data from Centers for Disease Control and Prevention prevalence studies41 or from birth cohort studies that specifically monitor ASD and other developmental disorders42 would be useful in providing a more complete understanding of how delayed walking relates to NVIQ in children with and without ASD, as well as in children with and without identifiable genetic abnormalities.

CONCLUSIONS
Our findings suggest that at least 1 major motor milestone, on-time walking, is conserved more often than expected in children with ASD. Among children with ID, a greater proportion of those with ASD began walking within the normal time frame compared with those without ASD. These findings are important because they provide a relatively straightforward avenue for beginning to explore the relationship between early motor delays and later functioning, within the broader population of neurodevelopmental disorders. Further exploration of this topic, incorporating genetic and neurobiologic approaches, is warranted to determine whether on-time and delayed walkers with ASD and ID differ from one another in etiologically significant ways.

ACKNOWLEDGMENTS
The authors are extremely grateful to all the families who participated in the research, as well as the clinicians and researchers who assisted in the collection and preparation of data included in the current study. We also thank Cherry Youn for her assistance in the preparation of this manuscript.

ABBREVIATIONS
ADI-R: Autism Diagnostic Interview—Revised
ADOS: Autism Diagnostic Observation Schedule
ASD: autism spectrum disorder
ID: intellectual disability
NVIQ: nonverbal IQ

FUNDING: This project was supported by grants from the Health Resources and Services Administration (HRSA, R40MC28145) and National Institute of Child Health and Human Development (NICHD; R01HD085277) to Dr Bishop and the National Institute of Mental Health (R01MH081873-01A1 and R01-MH06496) and NICHD (U19-HD 35482) to Dr Lord.

POTENTIAL CONFLICT OF INTEREST: Dr Lord receives royalties from Western Psychological Services (WPS) for publication of the Autism Diagnostic Interview—Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS)/Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2). Dr Bishop receives royalties from the ADOS-2. All royalties they received related to this project were given to a not-for-profit agency. Drs Farmer and Thurm report no conflicts of interest.

REFERENCES


**Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking**

Somer L. Bishop, Audrey Thurm, Cristan Farmer and Catherine Lord

*Pediatrics* 2016;137;
DOI: 10.1542/peds.2015-2959 originally published online February 3, 2016;

<table>
<thead>
<tr>
<th><strong>Updated Information &amp; Services</strong></th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/137/3/e20152959">http://pediatrics.aappublications.org/content/137/3/e20152959</a></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>References</strong></td>
<td>This article cites 34 articles, 2 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/137/3/e20152959.full#ref-list-1">http://pediatrics.aappublications.org/content/137/3/e20152959.full#ref-list-1</a></td>
</tr>
</tbody>
</table>
| **Subspecialty Collections** | This article, along with others on similar topics, appears in the following collection(s):
  - Developmental/Behavioral Pediatrics
    [http://classic.pediatrics.aappublications.org/cgi/collection/developmental_behavioral_issues_sub](http://classic.pediatrics.aappublications.org/cgi/collection/developmental_behavioral_issues_sub)
  - Autism/ASD
    [http://classic.pediatrics.aappublications.org/cgi/collection/autism_asd_sub](http://classic.pediatrics.aappublications.org/cgi/collection/autism_asd_sub) |
| **Permissions & Licensing** | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: [https://shop.aap.org/licensing-permissions/](https://shop.aap.org/licensing-permissions/) |
| **Reprints** | Information about ordering reprints can be found online: [http://classic.pediatrics.aappublications.org/content/reprints](http://classic.pediatrics.aappublications.org/content/reprints) |
Autism Spectrum Disorder, Intellectual Disability, and Delayed Walking
Somer L. Bishop, Audrey Thurm, Cristan Farmer and Catherine Lord
Pediatrics 2016;137;
DOI: 10.1542/peds.2015-2959 originally published online February 3, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/3/e20152959