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Association Between Early Developmental Milestones and Autism Spectrum Disorder

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Abstract

Early diagnosis and treatment of autism spectrum disorder (ASD) has been shown to lead to better prognosis. Here, we examined the association of commonly measured early developmental milestones (DMs) with later diagnosis of ASD. We conducted a case-control study of 280 children with ASD (cases) and 560 typically developed children (controls) matched to cases by date of birth, sex, and ethnicity in a control/case ratio of 2:1. Both cases and controls were ascertained from all children whose development was monitored at mother-child health clinics (MCHCs) in southern Israel. DM failure rates during the first 18 months of life in three developmental categories (motor, social, and verbal) were compared between cases and controls. Conditional logistic regression models were used to assess the independent association of specific DMs with the risk of ASD, while adjusting for demographic and birth characteristics.

Significant case-control differences in DM failure rates were observed as early as 3 months of age ($p < 0.001$), and these differences increased with age. Specifically, cases were 2.4 times more likely to fail ≥ 1 DM at 3 months (aOR = 2.39; 95%CI = 1.41–4.06), and 15.3 times more likely to fail ≥ 3 DMs at 18 months (aOR = 15.32; 95%CI = 7.75–30.28). The most notable DM-ASD association was observed for social DM failure at 9–12 months (aOR = 4.59; 95%CI = 2.59–8.13). Importantly, the sex or ethnicity of the participants did not affect these DM-ASD associations. Our findings highlight the potential role of DMs as early signs of ASD that could facilitate earlier referral and diagnosis of ASD.

Keywords Autism Spectrum Disorder · Developmental Milestone · Early Signs · Epidemiology

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The diagnosis of autism spectrum disorder (ASD) currently relies on a clinical evaluation of a child's behavior in two main areas, social communication and interactions, and the manifestation of restrictive repetitive behaviors (American Psychiatric Association, 2013). These core symptoms of ASD are more reliably detected after the first year of life, and such an age-constraint on assessment may be a contributing factor to the mean age of diagnosis being after 2 years of age (Centers for Disease Control and Prevention, 2022; Shaw et al., 2020).

There is compelling evidence that early ASD diagnosis and intervention is associated with improved prognosis (Bradshaw et al., 2015; Gabbay-Dizdar et al., 2022; Hyman et al., 2020; Towle et al., 2020; Whitehouse et al., 2019; Zwaigenbaum et al., 2015). Cognition, language, and adaptive behavior have all been shown to improve markedly when intervention is implemented prior to 4 years of age (Dawson et al., 2010; Devescovi et al., 2016; Vivanti et al., 2016). This evidence has led the American Academy

of Pediatrics to recommend ASD screening for all children aged 18–24 months (Hyman et al., 2020), but even so, the average age of diagnosis has not fallen significantly in the past two decades (Maenner et al., 2021). While aids and barriers to ASD screening measures have been well documented (Baoum et al., 2022; Bivarchi et al., 2021; King et al., 2010; Pinto-Martin et al., 2005; Steinman et al., 2022), screening rates still remain generally low (Arunyanart et al., 2012; Zwaigenbaum et al., 2015).

A wide range of screening tools have been developed for the detection of early signs of ASD, and these aid in decisions to refer children with suspected ASD for further evaluation. Some of these screening tools aim to identify ASD in children at the population level, regardless of the child's risk level, and may be administered by persons without any formal training. For example, the Modified Checklist for Autism in Toddlers (M-CHAT), a questionnaire that contains 23 yes/no items that can be completed by parents of toddlers between 16 and 30 months of age, is an ASD screening tool that is widely used in various populations and in multiple languages (Albores-Gallo et al., 2012; Baduel et al., 2017; Brennan et al., 2016; Dai et al., 2021; Guo et al., 2019; Mohamed et al., 2016; Robins et al., 2001; Stewart & Lee, 2017). A more detailed interview form of the test, the M-CHAT-R/F (Revised with Follow-up) has also been developed for administration by parents or other non-professional users (Robins et al., 2014). Another type of ASD screening tool, e.g., the Screening for Autism in Toddlers & Young Children (STAT™) (Stone, 2000), requires constructive interaction with a trained professional and is generally implemented for validating the diagnosis in high-risk children (McCarty & Frye, 2020; Towle & Patrick, 2016).

The prognostic benefits of early ASD detection followed by extensive intervention have prompted research into early developmental signs of ASD. Several studies based on retrospective parent reports have identified developmental concerns in children with ASD prior to 12 months of age based on social, motor, attention, and temperament (De Giacomo & Fombonne, 1998; Gillberg et al., 1990). Use of video analysis has also revealed atypical development in ASD during infancy (Goldberg et al., 2008; Ozonoff et al., 2011). Other longitudinal prospective studies have been conducted to avoid recall bias associated with retrospective studies and have monitored developmental trajectories in ASD by tracking high-risk siblings' cohorts (Estes et al., 2015; Landa et al., 2007; Sullivan et al., 2007; Zwaigenbaum et al., 2005). While most of these studies found that atypical development could not be reliably detected in children with ASD until 12 months of age, Estes et al. (2015) concluded that atypical sensorimotor development was associated with ASD in high-risk infants as early as 6 months of age. Replication of these studies in other populations is thus needed to identify significant trends in ASD developmental trajectories.

Previous data from Israel have revealed atypical developmental trajectories in motor and language/communication milestones at 9 months of age in children later diagnosed with ASD (Davidovitch et al., 2018). Children included in the study sample were registered under Maccabi Health Care, a health maintenance organization serving ~ 25% of the Israeli population and whose membership shows underrepresentation of low-socioeconomic non-Jewish populations (Davidovitch et al., 2020). Effects of sex and ethnicity on the findings were also not evaluated.

In the current study, we examined developmental measures (DMs) of children belonging to Clalit Health Services (CHS), the largest HMO in Israel, which provides health services to > 50% of the Israeli population, with the dual goal of identifying early DMs from birth until 18 months of age that are associated with later diagnosis of ASD and of testing the effect of the children's sex and ethnicity on such associations.

Methods

We conducted a retrospective case-control study in a population of children living in the Negev region of southern Israel, examining the children's acquisition of DMs applicable to five developmental stages: 6 weeks–3 months, 3–6 months, 6–9 months, 9–12 months, and 12–18 months.

Study Setting

The Negev is home to approximately one million residents belonging to two major ethnic groups, Jews and Bedouin Arabs (Central Bureau of Statistics of Israel, 2021). In this region, there are approximately 16,000 live births each year, distributed evenly between these two ethnic groups. The early-stage growth and development of these newborns is routinely monitored from birth until the age of 6 years at 47 government-funded mother-child health clinics (MCHCs) distributed across the region. Attendance at these MCHCs is extremely high, with 95–99% of all newborns attending MCHCs for developmental assessments, standard vaccinations, and other services during infancy (Bin Nun et al., 2010; Israel Ministry of Health, 2022). The universal healthcare system in use in Israel today also contributes to high attendance due to ease of accessibility to services. Trained nurses assess the child's acquisition of gross and fine motor skills, language, and social-emotional behaviors both by direct observation and testing, as well as by parent report regarding these skills. Should a child fail to master a particular milestone, s/he is scheduled for another, more

thorough evaluation. If, during these visits to the MCHC, concern is raised regarding the proper development of the child, s/he is referred for a more extensive evaluation at a Child Developmental Center (Israel Ministry of Health, 2022). There, these children go through rigorous ASD assessment according to DSM-5 criteria. During this assessment, the child psychiatrist or pediatric neurologist may ask the parents about their child's development and/or use the MCHC patient file to make a diagnosis according to DSM-5 criteria and clinical evaluation.

Case-Control Ascertainment

Cases were randomly ascertained from all children with ASD who are registered in the database of the Azrieli National Center for Autism and Neurodevelopment Research (ANCAN) and who are members of the CHS, which provides health services to ~75% of the population of southern Israel. ASD diagnosis of these children was determined by either child psychiatrists or pediatric neurologists at Soroka University Medical Center (SUMC) according to DSM-5 criteria (American Psychiatric Association, 2013, DSM-5) after rigorous interdisciplinary clinical evaluation as described previously (Meiri et al., 2017) Controls were children without ASD or any other diagnosis of developmental delay. Controls were matched to cases in a 2:1 ratio based on date of birth (±3 months), sex (male/female) and ethnicity (Jewish/Bedouin). Exclusion criteria for both cases and controls included children who had been lost to follow-up (missing ≥ 2 checkups) and children who had been referred for further evaluation due to a possible developmental delay, but who had not yet been diagnosed with ASD at the time of data collection. Overall, the study sample included 280 cases and 560 controls born between 2014 and 2017.

Table 1 Characteristics of the study sample

Variable		ASD	Non-ASD	p-value
Gender (male), N (%)		219 (78.2%)	438 (78.2%)	1[a]
Ethnicity (Jewish), N (%)		215 (76.8%)	430 (76.8%)	1[a]
Social-economic status, N (%)	Low	95 (33.9%)	180 (32.1%)	< 0.001[a]
	Moderate	175 (62.5%)	255 (45.5%)	
	High	10 (3.6%)	125 (22.3%)	
Maternal age at birth (years), mean ± SD		30.58 ± 5.99	29.68 ± 5.53	0.031[b]
Paternal age at birth (years), mean ± SD		33.86 ± 6.91	32.69 ± 6.53	0.020[b]
Type of birth, N (%)	Spontaneous	169 (71.3%)	382 (81.6%)	Ref
	Cesarean section	68 (28.7%)	86(18.4%)	0.002[a]
	Assisted delivery	7 (4%)	32 (7.7%)	0.093[a]
Birth week, mean ± SD		38.50 ± 2.91	39.54 ± 1.33	< 0.001[b]
Premature delivery (< 37 weeks), N (%)		46 (17.2%)	26 (4.7%)	< 0.001[a]
Birth weight (grams), mean ± SD		3.06 ± 0.676)	3.31 ± 0.388	< 0.001[b]

[a] Chi-square test

[b] Two-sided unpaired t-test

Data Collection

Data were gathered prospectively by trained MCHC healthcare personnel, while data analysis was conducted retrospectively through use of MCHC charts. Demographic, birth, and developmental data were collected from the MCHC charts and included the following variables: ethnicity (Jewish/Bedouin), socio-economic status, paternal and maternal ages, date of birth, sex, gestational age, birth delivery type, and birth weight. In addition, the acquisition of DMs at five developmental assessment appointments were classified by healthcare personnel as either "passed" or "failed" according to the Israel Ministry of Health's (MOH) guidelines that specify the exact range of months within which a child with typical development is expected to achieve a given milestone. Full details of these milestones are provided in Supplementary Table S1.

Data Analysis

The numbers, cumulative numbers, and proportions of DM failures were computed for each child at five assessment sessions. Rates of DM failure and demographic and birth characteristics were compared between cases and controls by using standard univariate statistics (e.g., t-test, Chi-Square test). Conditional logistic regression models were used to assess the independent association of DM failures at specific ages and in specific developmental categories (motor, social, and verbal) with risk of ASD, while adjusting for different demographic and birth characteristics. These logistic regression models were also applied separately to males and females and separately to Jewish and Bedouin children, with adjustment for various demographic and birth characteristics. The Breslow-Day test was used to determine the homogeneity of the odds ratios (OR) across these groups.

Results

The characteristics of the study sample are given in Table 1. Of the 840 children in the study, 78.2% were males and 76.8% were Jewish. Families of ASD children tended to be of lower socio-economic status compared to families of non-ASD children ($p < 0.001$). In addition, both maternal and paternal ages of ASD children were significantly higher than the respective ages of the parents of non-autistic

children (30.58 ± 5.99 vs. 29.68 ± 5.53 years; p = 0.031, and 33.86 ± 6.91 vs. 32.69 ± 6.53 years; p = 0.020 for maternal and paternal ages, respectively). ASD children were more likely to be born by Cesarean Sect. (28.7% vs. 18.4%; p = 0.002) and/or to be born prematurely (17.2% vs. 4.7%; p < 0.001) and at lower birthweights (3.06 ± 0.676 vs. 3.31 ± 0.388; p < 0.001) compared to their non-ASD counterparts.

An examination of the number and types of DM failures at five developmental assessment appointments revealed that the children in the study sample attended these appointments at the average ages of 2, 4, 6, 9 and 12 months, with no significant differences between cases and controls, except for the third checkup, in which controls were on average ~ 2 days older than cases at the time of the appointment (Supplementary Table S2). Notably, children later diagnosed with ASD (cases) had, on average, a significantly higher number of DM failures than controls at each of the assessment appointments (p < 0.001), and these case-control differences increased with assessment age (Fig. 1).

Figure 2 presents the rates of DM failures for the study sample for different ages and different developmental areas. Overall, failure rates were higher in children later diagnosed with ASD compared to controls at each of the examined ages. Specifically, 18.1% of the cases failed to master at least one DM at the first developmental checkup (ages 6 weeks–3 months), which is more than twice the 8.4% observed in children with typical development (Fig. 2A; p < 0.001). Similar case-control differences were observed for all other developmental assessments, with the rates of children failing ≥ 1 DM increasing with age for both groups and reaching 66.6% and 43.1% for cases and controls, respectively, at the last assessment at age 12–18 months. Similar trends were observed for the different DM categories (i.e., motor, social and communication; Fig. 2C-D), suggesting that the developmental delay seen in children later diagnosed with ASD is not restricted to specific ages or specific developmental areas.

The independent association of DM failure at different ages with ASD diagnosis was assessed using conditional logistic regression models, while adjusting for several sociodemographic and clinical characteristics. Failure to master DMs at all ages, except those appropriate for

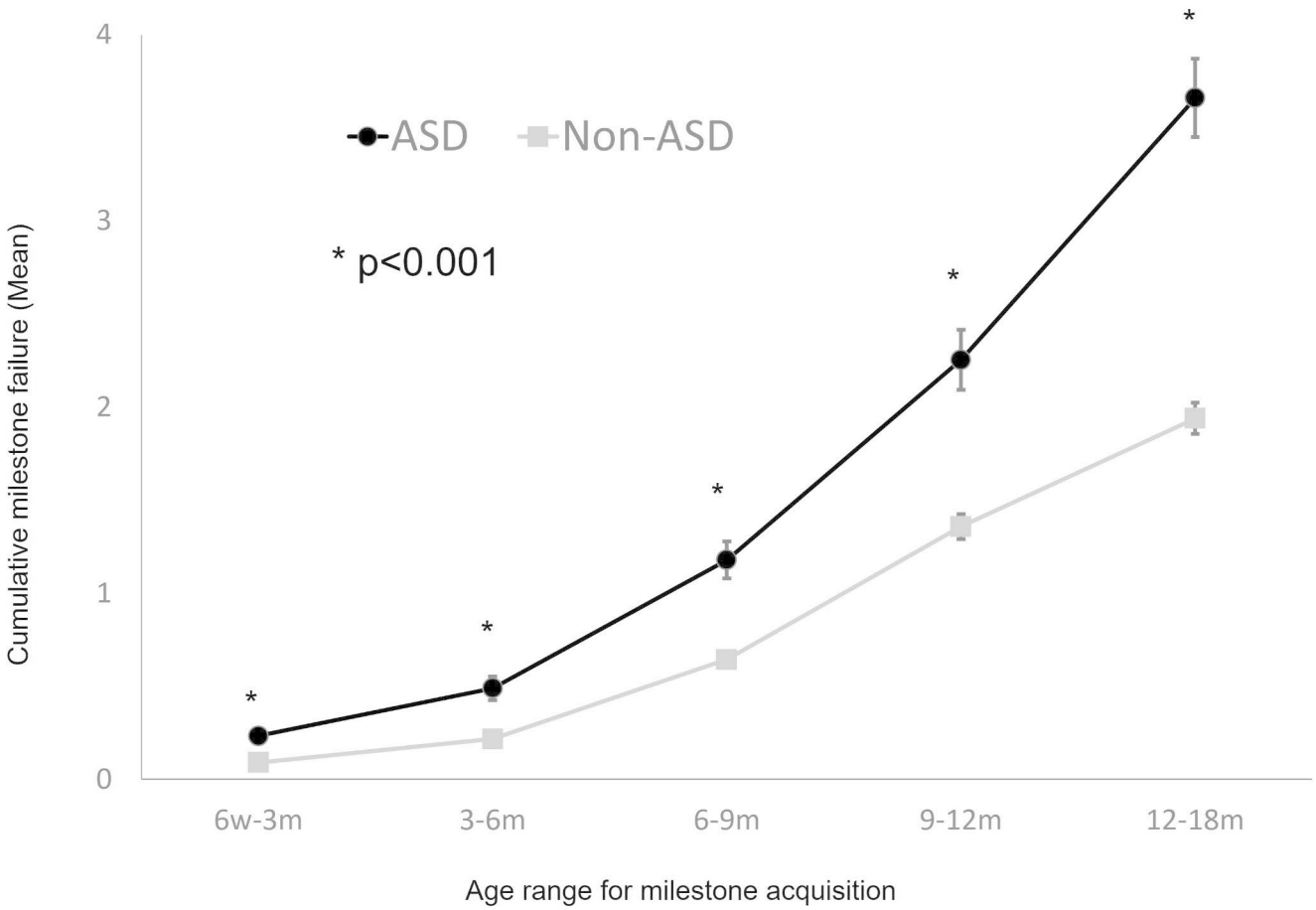

Fig. 1 Cumulative developmental milestone (DM) failure. The mean and standard errors of the cumulative numbers of DM failure from 6 weeks to 18 months of age are plotted for children with ASD (black dots) and children without ASD (gray squares). Asterisks indicate statistically significant differences between groups at p < 0.001

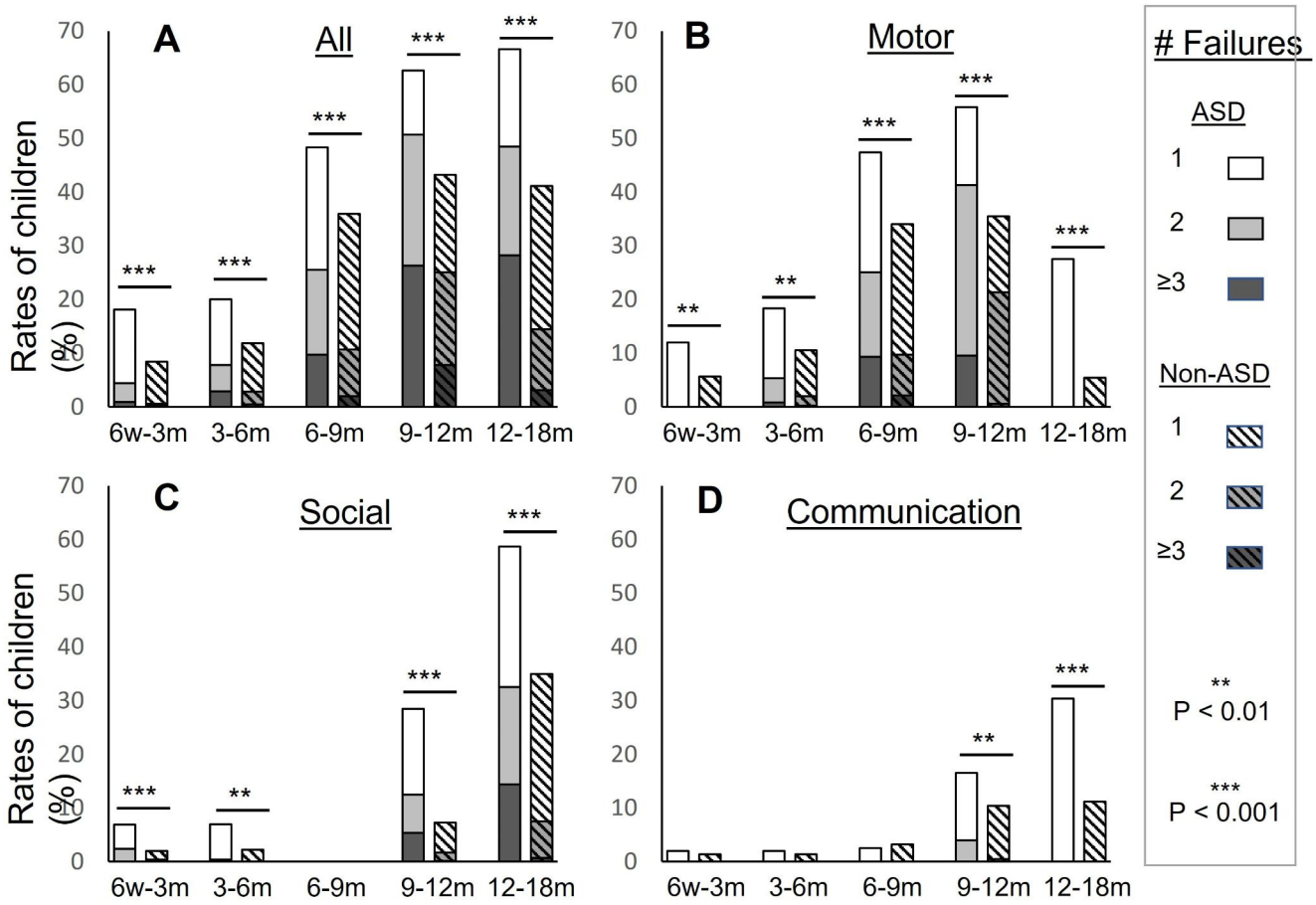

Fig. 2 Rates of children with developmental milestone (DM) failure. The percentage of ASD and non-ASD children who failed 1, 2, or ≥3 DMs at ages 6 weeks–3 months, 3–6 months, 6–9 months, 9–12 months, and 12–18 months are depicted in the columns. **(A)** Any DM; **(B)** Motor DMs; **(C)** Social DMs; and **(D)** Communication DMs

ages 3–6 months, was significantly associated with ASD (Table 2). Specifically, failure to master ≥ 1 DM in the first 3 months of age was significantly associated with a more than twofold risk of a subsequent ASD diagnosis (OR = 2.39, 95%CI = 1.41–4.06), with this risk being similar for motor and social milestones (OR = 2.24, 95%CI = 1.21–4.14; and OR = 2.81, 95%CI = 1.16–7.08, respectively). Similarly, failure to master ≥ 1 DM at the 6- to 9-month, 9- to 12-month, and 12- to 18-month assessments was also associated with an increased risk for a diagnosis of ASD (OR = 1.50, 95%CI = 1.01–2.23; OR = 2.37, 95%CI = 1.47–3.83; and OR = 2.32, 95%CI = 1.41–3.82, respectively). Failures to master the social DMs at the 9- to 12-month assessment and the motor DMs at the 12- to 18-month assessment were the factors most strongly associated with ASD risk (OR = 5.59, 95%CI = 2.59–8.13; and OR = 3.91, 95%CI = 1.98–7.71, respectively). Notably, these associations between DMs and ASD did not differ significantly between males and females (Supplementary Table S3) or between Jewish and Bedouin children (Supplementary Table S4), thus suggesting that there was no significant effect of sex and/or ethnic background on our findings.

Finally, the association of ASD diagnosis with the number of failed DMs at each age was examined by using similar logistic regression models (Table 3). Overall, the numbers of DM failures at each age were positively associated with the risk of ASD, namely, higher numbers of failed DMs were associated with a higher risk of ASD. This association was particularly noticeable at the age of 12–18 months, at which stage there was no association between ASD risk and failing 1 DM, but the risk of ASD increased exponentially with failing 2 and 3 DMs (OR = 3.14, 95%CI = 1.88–5.24; and OR = 15.32, 95%CI = 7.75–30.28, respectively). Notably, the risk of ASD associated with the cumulative number of DM failures did not increase with age, suggesting the importance of evaluating each DM according to its appropriate age range in order to determine developmental deviation.

Table 2 Association between developmental milestone failures from 6 weeks to 18 months of age and ASD

Age range for milestone acquisition	Milestone area	Failed ≥ 1 milestones		Adjusted[a] odds ratio (CI 95%)	p-value
		ASD	Non-ASD		
6 weeks–3 months (246 ASD; 556 non-ASD)	General	41 (%18.1)	46 (%8.4)	**2.39 (1.41–4.06)**	**0.001**
	Motor	30 (12%)	31 (5.6%)	**2.24 (1.21–4.14)**	**0.010**
	Social	17 (6.9%)	11 (2%)	**2.81 (1.16–7.08)**	**0.022**
	Language	5 (2%)	8 (1.4%)	1.32 (0.34–5.18)	0.687
3–6 months (239 ASD; 557 non-ASD)	General	41 (%20)	55 (11.8%)	1.30 (0.75–2.23)	0.350
	Motor	45 (18.2%)	58 (10.4%)	1.53 (0.90–2.61)	0.114
	Social	16 (7%)	12 (2.2%)	0.73 (0.18–2.93)	0.656
	Language	5 (2%)	8 (1.4%)	1.32 (0.34–5.18)	0.687
6–9 months (222 ASD; 556 non-ASD)	General	104 (48.4%)	174 (35.9%)	**1.50 (1.01–2.23)**	**0.042**
	Motor	102 (47.4%)	165 (34%)	**1.57 (1.07–2.23)**	**0.021**
	Social	-	-	-	-
	Language	6 (2.5%)	18 (3.2%)	0.84 (0.29–2.43)	0.744
9–12 months (154 ASD; 550 non-ASD)	General	105)62.5%(	222 (43.3%)	**2.37 (1.47–3.83)**	**< 0.001**
	Motor	100 (55.9%)	192 (35.4%)	**2.14 (1.36–3.36)**	**0.001**
	Social	48 (28.4%)	38 (7.3%)	**4.59 (2.59–8.13)**	**< 0.001**
	Language	29 (16.5%)	57 (10.4%)	1.63 (0.90–2.92)	0.105
12–18 months (212 ASD; 554 non-ASD)	General	158)66.7%(	225 (41.1%)	**2.32 (1.41–3.82)**	**0.001**
	Motor	68 (27.5%)	30 (5.4%)	**3.91 (1.98–7.71)**	**< 0.001**
	Social	139 (58.6%)	195 (35.1%)	**1.94 (1.24–3.03)**	**0.004**
	Language	75 (30.4%)	62 (11.2%)	**3.10 (1.82–5.29)**	**0.013**

[a] Conditional logistic regression adjusted to maternal and paternal age at child's birth, type of birth, social-economic status, and premature birth

Numbers in bold are statistically significant at $p < 0.05$

Table 3 Association between the number of developmental milestone failures from 6 weeks to 18 months of age and ASD

Age range for milestone acquisition	Number of failed milestones	Adjusted[a] odds ratio (CI 95%)	p-value
6 weeks–3 months	1	**2.04 (1.14–3.65)**	**0.017**
	2	4.50 (0.80-25.26)	0.088
	≥ 3	3.49 (0.28–43.12)	0.329
	Cumulative	**1.93 (1.24–2.99)**	**0.004**
3–6 months	1	1.43 (0.80–2.56)	0.233
	2	1.31 (0.41–4.16)	0.651
	≥ 3	2.46 (0.44–13.88)	0.308
	Cumulative	**1.37 (1.07–1.75)**	**0.011**
6–9 months	1	1.07 (0.69–1.66)	0.760
	2	**1.83 (1.05–3.18)**	**0.034**
	≥ 3	**4.13 (1.72–9.91)**	**0.002**
	Cumulative	**1.26 (1.09–1.45)**	**0.001**
9–12 months	1	0.96 (0.52–1.78)	0.906
	2	**1.98 (1.20–3.28)**	**0.008**
	≥ 3	**4.11 (2.26–7.46)**	**< 0.001**
	Cumulative	**1.16 (1.06–1.26)**	**0.001**
12–18 months	1	1.22 (0.76–1.96)	0.408
	2	**3.14 (1.88–5.24)**	**< 0.001**
	≥ 3	**15.32 (7.75–30.28)**	**< 0.001**
	Cumulative	**1.23 (1.15–1.32)**	**< 0.001**

[a] Conditional logistic regression adjusted to maternal and paternal age at birth, birth form, social-economic status, and premature birth

Numbers in bold are statistically significant at $p < 0.05$

Discussion

The results of this study suggest that children with ASD are more likely to fail age-appropriate DMs than children with typical development, even at ages below 3 months, and that this tendency to fail DMs increases with age. Furthermore, the findings showed that the higher likelihood of DM failure in children with ASD pertained to all developmental areas, with failure of motor and social DMs being associated with ASD at all ages, and failure of language DMs being associated with ASD after the first year of age. Finally, it was found that the association of DM failures with ASD was not affected by the sex or ethnicity of the study participants.

In general, our findings are consistent with the results of the study of Davidovitch et al. (2018), which explored the same DMs in a different Israeli population, and which also found significant differences in DM failure that increased with age between children later diagnosed with ASD and other children. Yet, there are a few important differences between the two studies. First, we identified significant differences in DM failure between ASD children and other children at all developmental assessments, while Davidovitch et al. (2018) identified significant differences between groups only after 9 months of age. Second, we showed no significant effect of sex and ethnicity on our findings, whereas Davidovitch et al. (2018) did not investigate these effects, thus limiting the generalizability of their results. In addition, we compared the DM failure between ASD and typically developing children, while Davidovitch et al. (2018) also included non-ASD developmentally impaired (DI) controls.

As apparent differences in the developmental trajectory of ASD and DI children were indeed detected, it is possible that some of the DMs that were associated with ASD in our study may not sufficiently discriminate between ASD and DI children. Thus, subsequent studies should include comparison groups of children with DIs other than ASD with the aim to distinguish a unique behavioral profile for ASD.

Evidence for the association of DM failure with ASD diagnosis generated in our study is consistent with prevailing data on the developmental profile of ASD in the first 18 months. Recent studies have noted the link between ASD and an increased failure to respond to name and to initiate joint attention—both DMs used to track social development prior to 12 months of age (Miller et al., 2017; Nyström et al., 2019). An earlier study by Ozonoff et al. (2010) indicated that children later diagnosed with ASD were less likely to demonstrate certain interactional behaviors at 12 months of age when compared to typically-developed children. Behaviors assessed in the study included directed gaze to face, shared smiles, and vocalization at 12 months of age, all of which were assessed in the present study. However, in contrast to our study, they found no significant differences between ASD and non-ASD children at 6 months of age (2010). Differences in results of the two studies may be attributed to differences in data collection methods, with Ozonoff et al. (2010) using video analysis in addition to parent report, while the present study used direct observation in addition to parent report. In addition, the findings of Ozonoff et al. were based on a small behavioral sample collected during developmental testing in the lab in a span of 5–10 min (2010) while the current study included observation of the child's behavior across settings and over longer periods of time, thus indicating differences in the degree of objectivity/subjectivity as well as time scale used in the studies. Another study by Sacrey et al. (2015) solely relied on parent report and found that social communication did not predict ASD diagnosis until after 12 months. The differences in findings may indicate that direct clinical observation may help identify possible ASD symptoms at a younger age than in other methods. In keeping with our results indicating an association between language DM failure and ASD at 12 months of age, Landa et al. (2013) concluded that children with early-onset ASD (diagnosed prior to 14 months) attained significantly lower language scores than late-onset ASD and non-ASD children by 14 months of age. Thus, it is possible that the differences in DM failure between ASD and non-ASD children in the first year of life seen in our study was driven largely by early-onset ASD children. Yet, we could not examine this hypothesis, as data about the severity of ASD symptoms and/or age of diagnosis were not available for the children in our study. Furthermore, while motor control impairment is not specific to ASD according to DSM-5 (American Psychiatric Association, 2013), our findings support growing evidence suggesting a failure to meet motor DMs prior to one year of age is indeed associated with a diagnosis of ASD (Bhat et al., 2012; Flanagan et al., 2012; Estes et al., 2015; Libertus et al., 2014; Sacrey et al., 2015).

Our study found no effect of sex or ethnicity on the association between DM failures and ASD. This finding is extremely important given the remarkable sex and ethnic bias in ASD diagnosis (Meiri et al., 2017; Levaot et al., 2019) and the reported effect of these variables on DM acquisition: For example, Gabis et al. (2020) found that a higher proportion of girl children with ASD vs. boy children had a motor delay (60% vs. 47%) or a global developmental delay (GDD) (49% vs. 36%) in early childhood, where GDD was defined as a delay in two or more developmental areas (motor, social, language) of ≥ 2 standard deviations below age norms. Concurrently, Harrop et al. (2021) observed sex differences in language DMs, with ASD girls preceding their male peers with first words and phrases, although in that study no sex differences were found in the motor DM tested (walking). In addition, it has been reported that minority toddlers have lower language/communication and motor scores than their non-minority counterparts on standardized tests (Tek & Landa, 2012). Additional studies should further investigate sex and ethnicity differences in developmental trajectories and their association with ASD risk, as such data are essential in informing health professionals so as to minimize disparities in ASD screening.

A considerable strength of the current study is that it relied on practices already in place in the Israeli healthcare system. Regular assessments at MCHCs can serve as a tool in determining divergence from the typical developmental trajectory in the general population. By simply screening for social, motor, and language milestones, healthcare providers may be in a position to initiate earlier referral for further evaluation, diagnosis, and intervention of children considered to be at risk of having ASD. As reported previously, the screening efficiency based on these DM failures is less sensitive than other established ASD screening measures, such as M-CHAT tool, and the referral decisions of nurses at the MCHC are variable (Kerub et al., 2020). Furthermore, it should be noted that while the social and language DMs included in assessment do not directly model DSM-5 criteria, they indicate the same persistent deficits in social communication and social interaction across multiple contexts (social-emotional reciprocity, nonverbal communicative behaviors, and relationship development) (American Psychiatric Association, 2013). An important limitation of this study is its case-control setting that may lead to selection bias. Indeed, cases in this study appeared to have lower socioeconomic status, older parents and different birth

characteristics. However, the resulting associations between DM failure and ASD from the logistic regression models (Table 3), were adjusted for these case-control differences, thus were less affected by such bias. An additional limitation of the study was its retrospective nature: while the developmental data were collected prospectively by clinic staff, it was analyzed retrospectively, thus restricting the possibility for further follow-up. Furthermore, participants were not tested at the oldest age possible for each assessment. However, an adjustment was made for this limitation, as the ages were equivalent for the two study groups. Finally, it is important to note that ASD is an extremely variable condition with symptoms that may appear in other developmental disorders, especially at younger ages (Brewer et al., 2020; Landa, 2008). Thus, it is possible that the failure in DM that were associated with ASD in this study are not specific to this developmental condition.

Conclusions

Overall, our results suggest that children who fail to master early DMs are at higher risk for a later diagnosis of ASD. Thus, routine developmental assessments of DM acquisition may facilitate earlier referral and diagnosis of children with ASD. The particular importance of this conclusion lies in the conventional wisdom that early diagnosis of ASD enhances the effectiveness of available interventions, thus improving the quality of life for both children with ASD and their families.

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Compliance with Ethical Standards

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of study formal consent is not required.

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