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Early motor trajectories in infants at increased genetic likelihood for autism

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Introduction: Infants with an older sibling with autism spectrum disorder (ASD) (EL-AutSib) and infants with tuberous sclerosis complex (EL-TSC), a genetic neurodevelopmental syndrome highly associated with ASD, exhibit motor and other developmental differences in the first year of life. Despite the prevalence of gross motor impairments in these populations and the need for early clinical monitoring, there is little conclusive evidence of the onset of motor differences between these groups, specific patterns of delay, and how these might relate to a future ASD diagnosis. In this study, we used a detailed gross motor infant assessment, the Alberta Infant Motor Scale (AIMS), to assess motor trajectories in the first year of life in EL-AutSib, EL-TSC, and a comparison group with low-likelihood of autism (LL).

Methods: Participants included 51 EL-AutSib, 26 LL, and 16 EL-TSC infants who were assessed on motor ability at 3, 6, 9, and 12 months of age using the AIMS. EL-AutSib participants were further categorized into autism (ASD) or no autism (nASD) groups based on clinical best estimate at 24 or 36 months of age. AIMS total scores were analyzed using a linear mixed-model to assess differences in motor development between groups over time.

Results: EL-AutSib-ASD, EL-AutSib-nASD, and LL groups exhibited comparable growth in motor ability over 3–12 months of age. Though non-significant, LL participants on average had the highest AIMS total scores across timepoints, followed by EL-AutSib-nASD and EL-AutSib-ASD, respectively. EL-TSC participants scored significantly lower on the AIMS compared to the EL-AutSib-ASD group ($ß = -7.92$, $p < 0.001$), with slower growth over time ($ß = -0.80$, $p = 0.04$).

Discussion: These findings identify distinct motor trajectories between two populations with an elevated genetic likelihood of developing ASD. EL-AutSibs displayed converging motor trajectories with the LL group irrespective of ASD outcomes, suggesting that motor milestones, even when examined more granularly, may not capture the full range of motor differences in EL-AutSibs. However, the AIMS captured early and persistent motor delays in EL-TSC infants, highlighting the clinical utility of this measure for populations with more significant developmental delays.

KEYWORDS
autism spectrum disorder, infancy, motor development, neurodevelopmental disorders, tuberous sclerosis complex

1 Introduction

Longitudinal studies of infants with an older sibling with autism spectrum disorder (ASD) have increased our understanding of some of the earliest signs of autism. Compared to prevalence estimates in the general population, the recurrence rate of ASD is significantly elevated in families who already have one or more autistic children, up to 21% in infants with one older sibling with ASD and 36% in multiplex families (McDonald et al., 2020; Ozonoff et al., 2024; Shaw et al., 2025). Studies utilizing an infant sibling design have followed babies born into these families from shortly after birth through 2–3 years of age when ASD can typically be diagnosed [hereafter referred to as elevated likelihood-autism siblings (EL-AutSib)]. Early development in autism has also been studied in infants with genetic syndromes that are highly penetrant for ASD and identifiable prenatally or in early infancy, such as tuberous sclerosis complex (TSC; hereafter referred to as EL-TSC infants). TSC is a rare disorder involving a single gene mutation in TSC1 or TSC2 and is characterized by hamartoma formation in the brain and other organs, along with high rates of epilepsy, developmental delays, and intellectual disability (Northrup et al., 1999; Crino et al., 2006; Curatolo et al., 2008). Approximately 50% of children with TSC go on to develop ASD, with autism symptoms often emerging within the first year of life (Jeste et al., 2016; McDonald et al., 2017). EL-AutSibs and EL-TSC constitute two groups of infants with an increased genetic likelihood for autism, yet the genetic liability for ASD arises from different mechanisms. Investigating variations in early atypical developmental markers in these groups can begin to elucidate how these mechanisms influence early developmental profiles.

Studies on EL-AutSib and EL-TSC infants have largely focused on detecting early social communication markers that are associated with a later ASD diagnosis, such as lack of joint attention and imitation in infancy (Zwaigenbaum et al., 2005; Bryson et al., 2007; Capal et al., 2017b). Motor impairments are also prevalent in these populations and other infant populations at elevated likelihood for autism, with these impairments crossing multiple motor domains (e.g., gross motor, fine motor, motor coordination). Motor differences have been posited to be one of the earliest signs of atypical development in those that go on to have ASD (Teitelbaum et al., 1998; Landa and Garrett-Mayer, 2006; Brian et al., 2008; Esposito et al., 2009; Bhat et al., 2011; Flanagan et al., 2012; Landa et al., 2013; Estes et al., 2015; Sacrey et al., 2018; Leezenbaum and Iverson, 2019). In the gross motor domain, for instance, EL-AutSib infants were found to have reduced duration of independent sitting and standing at 6 and 14 months, respectively, compared to infants with no family history of autism, with more prominent postural delays in a small cohort of those later diagnosed with ASD (Nickel et al., 2013). Studies on major motor milestones, such as crawling and walking, have had mixed results, with some finding that EL-AutSibs reach these milestones at later time points and others reporting a typical range for age of onset (Ozonoff et al., 2008; West et al., 2019; Patterson et al., 2022).

Prospective studies in the EL-TSC population have largely focused on overall developmental trajectories and verbal/non-verbal communication, with much less known about infant motor development in TSC compared to EL-AutSibs. One study found that gross motor skills in infants with TSC fell significantly behind typically-developing peers as early as 9 months of age (Jeste et al., 2014). In older cohorts, toddlers with TSC and ASD had similar motor and autism profiles to those with idiopathic autism, but with more prominent delays than TSC toddlers without ASD (Jeste et al., 2014, 2016; Capal et al., 2021). Another study found greater deficits in social and adaptive functioning in TSC toddlers with ASD compared to their peers without autism at 36 months, though no differences were noted in motor skills measured by the Vineland Adaptive Behavioral Scales (Goodman et al., 2025).

Though various motor differences have been described through these studies, more research is needed to establish whether specific longitudinal patterns of motor delays in the first year of life are present in a larger sample of EL-AutSibs with autism outcomes and whether these delays manifest differently in EL-TSC infants, who have a unique mechanism related to higher likelihood of ASD. Additionally, new methods to explore motor trajectories in these groups are needed. Most prior studies in EL-TSC and EL-AutSib populations have evaluated motor skills using broader measures of development, such as the Mullen Scales of Early Learning and the Bayley Scales of Infant and Toddler Development, or with caregiver report (e.g., Vineland) (Mullen, 1995; Sparrow et al., 2016). These assessments are not solely focused on ascertainment of motor skills but rather include subscales to assess specific aspects of gross and fine motor function, such as major motor milestone acquisition or complex motor tasks (e.g., crawl on all fours, stack blocks, thread beads). Furthermore, these measures are largely binary in scoring or have a small range of scores, capturing little variation in motor abilities. These assessments do not evaluate early motor maturation in infancy, such as the motor control and coordination needed to develop emerging postures and intermediate motor skills that enable larger motor milestones (Wilson et al., 2018). Examination of more detailed infant motor skills, longitudinally, can allow for the identification of more subtle phenotypic variability, particularly in more heterogenous infant populations such as the groups presented here. Furthermore, evaluation of motor trajectories can better identify the onset of a developmental divergence rather than a single snapshot of developmental delay. Ultimately, this approach can better inform when clinicians should employ more frequent developmental monitoring and perhaps even the introduction of more pre-emptive interventions. Thus, in this study, we examined motor trajectories using the Alberta Infant Motor Scale (AIMS), which includes more detailed aspects of infant gross motor movements, motor strength, control, and their progression compared to other commonly used standardized assessments (Piper et al., 1992). The AIMS has been widely used to evaluate motor delays in clinical settings to indicate the need for referral to motor interventions and in studies of high-risk medical populations, such as infants with extreme prematurity and Down syndrome (Eliks and Gajewska, 2022; Ko and Lim, 2023). In this study, we utilized the AIMS to longitudinally assess infant motor development over the first 12 months in EL-AutSib infants, EL-TSC infants, and infants without a neurogenetic diagnosis or family history of ASD [low likelihood (LL)].

There have been three prior studies of EL-AutSib infants using the AIMS and none within EL-TSC. One study described only EL-AutSib infants who did not go on to receive an ASD diagnosis (EL-AutSib-nASD), finding higher rates of gross motor delays between 5 and 10 months of age compared to expected population norms (LeBarton and Iverson, 2016). The remaining two studies compared EL-AutSib and LL infants in the first 6 months of life. Bhat et al. compared AIMS total score and prone / supine subscales, finding that EL-AutSib infants exhibited significant delays at 3 and 6 months of age, though limited follow-up prevented analysis by autism outcomes (Bhat et al., 2012). Heathcock et al. retrospectively scored the AIMS using infant videos taken at 2, 4, and 6 months of age, finding significantly lower total scores in EL-AutSib infants at 4 months and preliminary trends supportive of more prominent delays in their final sample of 5 EL-AutSib-ASD infants (sample size limiting statistical analysis) (Heathcock et al., 2015).

The present study addresses limitations of prior studies and meaningfully advances our knowledge of early motor development in autism by evaluating the trajectories of AIMS scores from 3 to 12 months of age in a larger sample of LL and EL-AutSib infants stratified by autism outcomes (EL-AutSib-ASD and EL-AutSib-nASD), along with a novel cohort of EL-TSC infants. To our knowledge, this is the first study to use the AIMS to evaluate infant motor development in TSC, allowing us to begin investigating how early gross motor impairments present in this population and may differ between two populations with distinct genetic pathways contributing to an increased likelihood of autism. Given the prevalence of motor impairments in ASD, we hypothesized that LL and EL-AutSib-nASD infants would attain higher AIMS scores and a greater rate of growth in motor skills over time compared to EL-AutSib-ASD and EL-TSC. In alignment with previous findings in EL-TSC toddlers and toddlers with idiopathic ASD, we predicted that EL-TSC infants would score lower and exhibit a slower increase in motor ability over time compared to the EL-AutSib-ASD group.

2 Methods

2.1 Participants

A total of 107 participants (EL-AutSib $n = 65$, LL $n = 26$, EL-TSC $n = 16$) were enrolled in two studies approved by the Institutional Review Board (IRB#17-001265, IRB #19-000863) at the University of California, Los Angeles. Written informed consent was obtained from all caregivers prior to infant participation and publication of these results. Infants were recruited through referrals from specialty clinics/healthcare providers in the greater Los Angeles area.

Inclusion criteria for EL-AutSib participants was having an older sibling with ASD, which was confirmed through review of documentation of diagnosis and caregiver completion of the Social Communication Questionnaire (Rutter et al., 2003a). Exclusion criteria for LL participants included having a first- or second-degree relative with a diagnosis of ASD or other neurodevelopmental disorders. Exclusion criteria for EL-AutSib and LL groups were also severe birth trauma and a previous diagnosis of a neurological condition. EL-TSC participants had a clinical diagnosis of TSC1 or TSC2, with information on genetic testing collected when available. There were no exclusions for medical conditions or epilepsy given high rates of comorbid medical conditions.

2.2 Procedure

Data collection occurred between 2017 and 2025. There were significant disruptions to the study due to the COVID-19 global pandemic. Data collection procedures were modified to ensure compliance with research-related shutdowns at the University of California, Los Angeles and to ensure validity of outcome assessments. These disruptions necessitated the use of remote phenotyping, as well as ASD outcome measures that could be conducted without a mask and yield reliable and valid results. The EL-AutSib and LL infants were enrolled by 6 months of age. Three TSC participants enrolled at the 12-month time point due to pandemic-related delays in recruitment, which included difficulty participating in in-person research due to medical fragility. Infants were assessed at 3, 6, 9, and 12 months, with outcome assessments at 24 or 36 months of age as described below. Sample size by timepoint and measure is described in Supplementary Figure 1.

2.3 Measures

2.3.1 Developmental assessments

The Mullen Scales of Early Learning (MSEL) is a standardized developmental assessment designed for birth to 69 months (Mullen, 1995). Subscales include Gross Motor (up to 33 months of age), Visual Reception, Fine Motor, Receptive Language, and Expressive Language, with the last four subscales combining to form the Early Learning Composite (ELC). The MSEL was collected at 24 and/or 36 months.

The Vineland Adaptive Behavior Scales, 3rd Edition (VABS-3) was collected through caregiver interviews (usually via Zoom/phone call) at the 12-month timepoint and at the 24- and/or 36-month visit for outcome assessments. The VABS-3 assesses four main domains (Communication, Daily Living Skills, Socialization, Motor), and provides an overall Adaptive Behavior Composite (ABC) score (based on first three scales) as a measure of adaptive function (Sparrow et al., 2016). Results from the VABS-2 were included from a small cohort of participants who were enrolled in an earlier phase of the study ($n = 5$).

2.3.2 Motor assessment

Motor skills were measured at 3, 6, 9, and 12 months of age using the Alberta Infant Motor Scale (AIMS), which includes 58 total items across four subscales: prone (21 items), supine (nine items), sit (12 items), and stand (16 items) (Piper and Darrah, 1994). A trained examiner scored infants on a binary scale ("observed" or "not observed") based on specific descriptors of posture, weight-bearing, and anti-gravity movements for each item, with full credit given to items below the least

advanced observed position in each subscale. Raw subscale and total scores were obtained from summing the achieved items, with percentile scores available for the total score (see Supplementary Figure 2 for the distribution of percentile scores by group).

AIMS sessions were conducted in-person within a laboratory setting prior to the COVID-19 pandemic, during which assessments shifted to remote observation over Zoom in the participant's home. Administering the AIMS over teleconferencing has been shown to have high concurrent validity to in-person observations (Passamani et al., 2024). The same administration procedures were followed for both settings, with infants scored and observed in 20-to-30-min sessions in both settings. Within our final sample, $n = 45$ participants completed the AIMS fully in-person (i.e., at every timepoint they were assessed), $n = 31$ fully remote, and $n = 30$ had a mix of in-person and remote assessments across timepoints. To ensure concordance between our two methods of administration, we separately analyzed correlations of AIMS scores from all participants to parent report of gross motor ability on the VABS at the 12-month timepoint. Gross Motor v-scale scores on the VABS were strongly and similarly correlated with both in-person ($n = 35$, $r = 0.687$, $p < 0.001$) and remote ($n = 49$, $r = 0.765$, $p < 0.001$) AIMS total scores.

2.3.3 Autism assessment

A subset of participants completed the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2), a standardized measure of reciprocal social interaction and stereotyped/repetitive behaviors, at the 24 and/or 36-month timepoint (Lord et al., 2012a,b). The Toddler Module, Module 1, or Module 2 were administered based on participant age and language level. Research reliable examiners scored the ADOS-2 to produce an algorithm score that corresponded to a clinical cutoff or range of concern and a calibrated severity score.

To comply with safety protocols after the onset of the COVID-19 pandemic, the Brief Observation of Autism Symptoms (BOSA) was administered in-person or over Zoom (using standard materials sent to the family's home). The BOSA assesses social communication behaviors and autism symptoms elicited through short parent-child interactions using standardized materials and prompts (Dow et al., 2022). The Minimally Verbal or Phrase Speech-Young Fluent version was administered based on the child's language level, with a trained, ADOS research reliable examiner scoring autism-associated behaviors to produce an algorithm total score and range of concern.

2.4 Clinical best estimate

Outcome classifications were made by an expert clinician based on all clinically available data gathered for each participant, including parent report of behavior and early development via the Autism Diagnostic Interview-Revised (Rutter et al., 2003b) and the results of direct developmental and autism assessments at 24 and/or 36-month timepoints. For children who underwent assessments at both timepoints, data from the 36-month assessment was used to determine final outcomes. Eighty-four participants completed outcome assessments: 24 children at 24 months of age ($n = 6$ EL-AutSib-ASD, $n = 9$ EL-AutSib-nASD, $n = 3$ LL, $n = 6$ EL-TSC) and 60 children at 36 months ($n = 11$ EL-AutSib-ASD, $n = 25$ EL-AutSib-nASD, $n = 18$ LL, $n = 6$ EL-TSC).

Of the 51 EL-AutSib participants who completed outcome assessments, 17 met DSM-5 criteria for ASD (33%), 12 had other concerns (24%; broader autism phenotype $n = 9$, non-ASD behavioral concerns or developmental delays $n = 3$), and 22 had typical development (43%). For outcome comparisons, we combined the latter two groups into a non-ASD group, resulting in a total $n = 34$ EL-AutSib-nASD (Wilson et al., 2024b). The data from the 14 EL-AutSib participants who were unable to complete outcome assessments due to the pandemic or external family circumstances were excluded from further analyses except for AIMS-Vineland correlations.

Twenty-one LL participants completed outcome assessments in this study. None met criteria for ASD, though two were noted to have mild developmental/speech and language delays. The five LL infants without outcome assessments had no developmental concerns at the timepoint of their latest visit and were included in subsequent analyses based on their lack of family history and genetic diagnosis, as well as historically low prevalence rates of autism within this population (Shaw et al., 2025). A sensitivity analysis excluding these five participants was also conducted (Supplementary Table 1).

The EL-TSC cohort was not further stratified for group comparisons due to sample size limitations and limited outcome data related to the COVID-19 pandemic, though autism outcomes are reported here for descriptive purposes (distribution of AIMS total scores by outcome depicted in Supplementary Figure 3). Of the 12 EL-TSC participants with sufficient outcome data, seven met criteria for ASD, three had other concerns (developmental delay $n = 2$, broader autism phenotype $n = 1$), and two were typically developing.

2.5 Statistical analysis

Descriptive statistics summarize sample characteristics by cohort (Table 1). Differences between cohorts were evaluated using chi-squared or Fisher's exact tests as appropriate for qualitative characteristics, and one-way ANOVA tests for quantitative characteristics.

AIMS total score trajectories were analyzed using a linear mixed-model. Raw total score was used for analyses to provide a continuous measure of absolute motor performance for each group. The model included fixed effects for group (EL-AutSib-nASD, LL, and EL-TSC v. EL-AutSib-ASD), a linear time term centered at 7.5 months (midpoint of the 3–12 month assessment interval), and the interaction of these terms. Child random effects were used to account for repeated measurements. Coefficients

TABLE 1 Participant characteristics.

Variable	EL-AutSib-ASD ($n = 17$)	EL-AutSib-nASD ($n = 34$)	LL ($n = 26$)	EL-TSC ($n = 16$)	Test statistic
Gender, *n* (column %)					
Male	10 (58.8%)	21 (61.8%)	14 (53.8%)	8 (50.0%)	χ^2 (3, $N = 93$) = 0.76
Race, *n* (column %)					
White	10 (58.8%)	21 (61.8%)	16 (61.5%)	9 (56.3%)	Fisher's exact test $p = 0.50$
Asian	2 (11.8%)	6 (17.6%)	2 (7.7%)	2 (12.5%)	
Multiracial[a]	2 (11.8%)	3 (8.8%)	8 (30.8%)	4 (25%)	
Unknown/not-reported	3 (17.6%)	4 (11.8%)	0 (0.0%)	1 (6.3%)	
Ethnicity, *n* (column %)					
Hispanic/Latino	7 (41.2%)	7 (20.6%)	6 (23.1%)	3 (18.8%)	Fisher's exact test $p = 0.33$
Not Hispanic/Latino	8 (47.1%)	24 (70.6%)	20 (76.9%)	12 (75.0%)	
Unknown/not-reported	2 (11.8%)	3 (8.8%)	0 (0.0%)	1 (6.3%)	
Household income, *n* (column %)					
Less than $50,000	5 (29.4%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	Fisher's exact test $p < 0.001$
$50,000 to $99,999	2 (11.8%)	0 (0.0%)	6 (23.1%)	3 (18.8%)	
$100,000 and above	7 (41.2%)	29 (85.3%)	18 (69.2%)	11 (68.8%)	
Unknown/not-reported	3 (17.6%)	5 (14.7%)	1 (3.8%)	2 (12.5%)	
Birth history[b] [mean (SD), range]					
Gestational age (weeks)	38.5 (2.29), 33–41	37.9 (2.1), 31–41	39.0 (1.1), 37–41	38.8 (1.3), 36–41	$F_{(3,81)} = 1.90$
Birth weight (lbs)	8.1 (0.9), 6.1–9.5	7.0 (1.1), 4.1–8.9	7.9 (1.1), 5.9–10.1	7.2 (1.1), 4.8–8.8	$F_{(3,84)} = 5.83^{**}$
MSEL early learning composite at outcome age [mean (SD), range]					
Standard score ($n = 69$)	90.2 (27.6), 49–135	109.9 (13.9), 77–138	123.8 (10.5), 109–146	62.1 (24.9), 49–115	$F_{(3,65)} = 21.95^{***}$
VABS adaptive behavior composite at outcome age [mean (SD), range]					
Standard score ($n = 80$)	74.5 (12.8), 43–94	95.4 (12.6), 76–129	101.6 (12.5), 81–127	74.3 (20.7), 48–118	$F_{(3,76)} = 17.9^{***}$
Walking onset[c] [mean (SD), range]					
Age (months)	12.1 (2.3), 9–18	12.8 (2.1), 9–18	12.1 (2.2), 8–18	16.4 (2.8), 13–21	$F_{(3,73)} = 7.4^{***}$

$^{**}p < 0.01$.

$^{***}p < 0.001$.

[a]American Indian/Alaska Native and White (n = 1 LL, n = 1 EL-TSC), Black/African American and White (n = 1 EL-TSC), Asian and White (n = 1 EL-AutSib-ASD, n = 3 EL-AutSib-nASD, n = 6 LL, n = 2 EL-TSC), Black/African American and Asian (n = 1 EL-AutSib-ASD, n = 1 LL).

[b]Birth history data is unknown for n = 2 EL-AutSib-nASD, n = 1 LL, and n = 2 EL-TSC. Another n = 2 EL-AutSib-ASD and n = 1 AutSib-nASD participants had confirmed full-term pregnancies and known birth weights, but unknown gestational ages.

[c]Age of walking is unknown for n = 2 EL-AutSib-ASD, n = 2 EL-AutSib-nASD, n = 2 LL, and n = 9 EL-TSC.

on the cohort fixed effects were used to evaluate differences in AIMS total score, averaged over time (level differences), while interaction coefficients were used to evaluate differences in AIMS total score trajectories (slope differences). Statistical significance was defined as a *p*-value less than 0.05. All analyses were performed using R v. 4.1.0 (http://www.r-project.org/). The EL-AutSib-ASD group was chosen as the main reference group to allow for a fuller comparison across autism outcomes in a familial risk group (v. EL-AutSib-nASD) and to assess differences compared to a genetic risk group (v. EL-TSC). A sensitivity analysis was conducted adjusting for birthweight. We also ran a version of the model with LL as the reference group and note the findings below. AIMS subscale scores were analyzed utilizing the same model as above for exploratory purposes.

3 Results

Participant demographics and descriptive results are presented in Table 1. Differences in sample size at each timepoint is largely due to differences in enrollment age (e.g., infants enrolled at 3 vs. 6 months). Group membership was not found to be significantly related to gestational age, gender, race, or ethnicity. There were significant group differences in birthweight, with EL-AutSib-nASD infants having a lower average birthweight compared to EL-AutSib-ASD ($p < 0.01$) and LL ($p < 0.05$). Family income was also significantly related to group membership, with a greater proportion of EL-AutSib-nASD infants belonging to higher-income households compared to the EL-AutSib-ASD ($p < 0.001$) and LL ($p < 0.01$) groups. EL-TSC infants lagged significantly

behind their EL-AutSib-ASD ($p < 0.001$), EL-AutSib-nASD ($p < 0.01$), and LL ($p < 0.001$) peers in walking onset.

All groups differed from one another on developmental outcome measures, with the exception of LL and EL-AutSib-nASD groups scoring similarly on both the MSEL and the VABS, and TSC and EL-AutSib-ASD having comparable performance on the VABS.

3.1 Level differences

Relative to the EL-AutSib-ASD group, LL ($ß = 2.32$, $p = 0.16$) and EL-AutSib-nASD infants ($ß = 0.73$, $p = 0.64$) exhibited comparable gross motor performance on the AIMS (Table 2; Figure 1). EL-TSC participants scored significantly lower ($ß = -7.92$, $p < 0.001$). On subscale analysis, the EL-TSC group had significantly lower scores on the prone ($ß = -3.14$, $p < 0.001$), sit ($ß = -1.39$, $p = 0.003$), and stand ($ß = -2.69$, $p < 0.001$) scales (Supplementary Table 3). LL infants had higher average prone scores ($ß = 1.60$, $p = 0.03$) than EL-AutSib-ASD infants.

3.2 Slope differences

Similar to the group effect findings, LL ($ß = -0.05$, $p = 0.86$) and EL-AutSib-nASD ($ß = 0.05$, $p = 0.85$) growth trajectories on the AIMS did not significantly differ from the EL-AutSib-ASD group. EL-TSC participants had a significantly slower rate of motor gains on total score ($ß = -0.80$, $p = 0.04$) and the stand subscale ($ß = -0.61$, $p = 0.001$) over time (Supplementary Figure 4).

The model with LL as the reference group similarly indicated that EL-TSC was the only group that differed significantly with both level ($ß = -10.24$, $p < 0.001$) and slope ($ß = -0.75$, $p = 0.03$) effects (Supplementary Table 4). Sensitivity analyses adjusting for birthweight and excluding the five LL infants without outcomes did not meaningfully diverge from results that included the full sample (Supplementary Tables 1, 2).

TABLE 2 AIMS total score trajectory analyses.

Group	Beta (β)	Standard error (SE)	p-value
Level differences (vs. EL-AutSib-ASD)			
EL-AutSib-nASD	0.73	1.57	0.64
LL	2.32	1.65	0.16
EL-TSC	−7.92	1.99	<0.001
Slope differences per month (vs. EL-AutSib-ASD)			
EL-AutSib-nASD	0.05	0.25	0.85
LL	−0.05	0.26	0.86
EL-TSC	−0.80	0.38	0.04

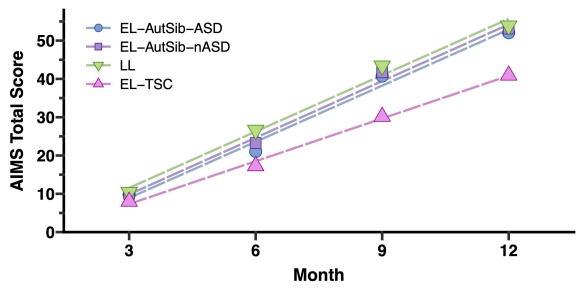

FIGURE 1
AIMS total score trajectories.

4 Discussion

This study utilized the Alberta Infant Motor Scale to examine detailed gross motor development in the first year of life in infants with an elevated familial likelihood of autism stratified by future autism outcomes (EL-AutSib-ASD and EL-AutSib-nASD), a diagnosis of tuberous sclerosis complex (EL-TSC), and a comparison group of infants without a close family history of ASD or genetic diagnoses (LL).

We found that EL-AutSibs that went on to receive an ASD diagnosis specifically performed poorer on the prone subscale compared to LL infants. Unexpectedly, no other differences were noted between these two groups, or compared to EL-AutSibs without autism. The prone subscale examines the ability to lift the head, support oneself on the forearms, and pivot the body and reach with upper extremities while the head and upper trunk are lifted. Differences between EL-AutSib-ASD and LL groups were specifically driven by the 6-month timepoint, which could indicate deficits in gross motor strength and ability in the EL-AutSib-ASD group that are apparent in early infancy. Compared to LL infants who were reaching with forearm support and pivoting, EL-AutSib-ASD infants were, on average, just beginning to maintain forearm support and roll without trunk rotation at this age. This indicates that infants that go on to receive an ASD diagnosis may specifically diverge in gross motor control at 6 months, but these differences may dissipate as infants achieve more advanced skills such as sitting independently, which is captured by similar subscale scores between EL-AutSib-ASD and LL at 9 and 12 months of age. It is possible that if we were able to further stratify our analyses of the EL-AutSib-ASD group by autism symptom severity, then we may have found that distinct groups have lower motor trajectories. We were unable to do this due to our use of both the ADOS and BOSA, which was necessary due to the COVID-19 pandemic. One large study of EL-AutSibs has utilized the ADOS Calibrated Severity Score (CSS) to stratify outcome groups of EL-AutSib-ASD and EL-AutSibs with high or low ADOS scores without meeting full criteria for ASD. They found that fine motor (but not gross motor) scores at 6 months of age significantly predicted ADOS CSS at 3 years in EL-AutSibs, though this was using the MSEL and there was no evidence of early motor differences associated with a later ASD diagnosis (Iverson et al., 2019). However, another study, also utilizing "high and low" ASD groupings, found that EL-AutSib-ASD infants with high ADOS scores demonstrated less advanced gross motor and visual reception skills at 6 months of age on the MSEL (Estes et al., 2015). Thus, examination of autism symptom severity may help identify more subtle motor differences compared

to global groupings of ASD vs. no ASD. This pattern of findings suggests that gross motor impairments in infancy may serve as an indicator of those who go on to have higher support needs.

Alternatively, our null findings in EL-AutSibs may also be a product of how the AIMS assesses motor ability. Though the AIMS includes intermediate skills leading up to major locomotive movements, it is still scored on a binary scale based on item achievement, similar to other developmental measures. Our group has utilized other tools to objectively capture and quantify detailed aspects of movement in EL-AutSibs. Using these methods, we have identified differences in movement patterns that differentiate EL-AutSib-ASD from EL-AutSib-nASD, finding that lower motion complexity in the first year of life is correlated with later ASD diagnosis, with a later study highlighting that these motor differences are highly predictive by 18 months of age (Wilson et al., 2021, 2024b). In toddlers with autism, we have utilized quantitative analysis of locomotion and found that toddlers with ASD exhibited slower walking pace compared to their typically-developing peers despite normal age of walking onset (Wilson et al., 2024a). Therefore, it is possible that motor differences in the EL-AutSib-ASD and EL-AutSib-nASD participants in this study may have manifested in a more qualitative way outside of the timeline of attaining skills, such as slower transition movements between postures or requiring more attempts to eventually achieve an item within a session, as studies on older children have shown that those with ASD have impaired motor planning and delayed movement initiation (Dowd et al., 2012; Bäckström et al., 2021). Thus, the addition of more objective methods and evaluating how an infant executes a task may uncover different patterns of atypical motor behavior more specific to EL-AutSibs and particularly EL-AutSib-ASD.

On the other hand, the EL-TSC infants stood out with a markedly lower level of motor skills on the AIMS over the first year, with particular difficulty and slow growth in developing the skill to stand. In addition to broader motor supports, this finding suggests that EL-TSC infants likely need additional monitoring and intervention in this area. Though we are limited in our ability to comment on these differences without ASD outcome data, it is interesting that EL-TSC infants on a whole scored lower than their EL-AutSib-ASD peers given previous findings that EL-TSC toddlers without ASD have comparable developmental functioning compared to toddlers with non-syndromic autism (Jeste et al., 2016). The majority of our EL-TSC cohort reported a history of seizures (10/16), and thus we were not able to stratify AIMS scores by epilepsy status. Poorer developmental trajectories have been well-documented in individuals with TSC and epilepsy (Capal et al., 2017a; Tye et al., 2020; Lindsay et al., 2024), and thus the presence of seizures as well as a genetic diagnosis likely contributed to our findings on motor trajectories between these groups. Interestingly, contrary to the above studies, there was a recent study that showed seizure burden did not account for differences in social, emotional, and behavioral developmental trajectories in those with TSC with and without ASD (Goodman et al., 2025). Hence, it is possible that our evaluation of the EL-TSC cohort in infancy has uncovered more impacted developmental trajectories compared to examination of toddlers and children with TSC. Also, infants with rare *de novo* or inherited genetic mutations will likely demonstrate more visible developmental motor delays compared to infants with a familial history of ASD (Buja et al., 2018). These data can help to inform early developmental trajectories in these infants, and potential concern for genetic disorders and referral for genetic evaluation in the first year of life.

We note that both remote and in-person AIMS scores showed a strong correlation with parent report of gross motor skills on the VABS parent interview, highlighting a unique ability of this measure to serve as an accurate direct assessment of infant motor skills using remote methods. Robust remote assessment methods are necessary to overcome barriers to accessing studies for individuals from rural or underserved areas that cannot travel to major academic settings for assessment. These findings have important clinical and research implications that warrant further consideration of how remote assessment may increase accessibility and validity of motor assessment.

There are limitations to our study. Most of the participants in each cohort identified as White and reported relatively high household incomes, limiting the generalizability of our findings. Challenges with participant follow-up and data collection during the COVID-19 pandemic also contributed to missing outcomes in our final sample and the use of two different ASD outcome assessments. As noted above, our EL-TSC cohort was limited in outcome follow-up. Thus, we were not able to stratify AIMS scores by ASD outcome. It is possible that the magnitude of difference in scores between EL-AutSib-ASD and EL-TSC groups would be stronger if we were able to factor in this variable.

5 Conclusions

This study has added to previous investigations into early gross motor and developmental differences into infants with a family history of ASD and infants with TSC during the first year of life. Interestingly, compared to previous studies with smaller sample sizes, we did not find that EL-AutSibs or EL-AutSib-ASD infants show significantly slower motor trajectories on the AIMS. This may indicate that methods utilizing more quantitative approaches to evaluate patterns of motor behavior are needed in addition to the AIMS to detect atypical motor development beyond delays in timing of motor skill achievement. However, we did find that there are differences in early prone positions in infants that went on to have an ASD diagnosis. These findings warrant further investigation in future studies of infant populations that are at elevated likelihood for autism. Our study is the first to investigate motor differences in TSC in infancy using the AIMS. The ability of the AIMS to readily capture persistent delays in the EL-TSC group highlights a strong potential for clinical and research utility to more granularly measure motor ability in populations that present with more substantial delays. Overall, further investigations utilizing multi-modal assessments of motor ability, including more objective instruments like wearable technologies, are important to provide additional insight into the emergence of motor delays in populations with elevated likelihood for ASD to better understand early manifestations of ASD.

Data availability statement

The datasets presented in this article are not readily available. Requests for raw, de-identified datasets will be reviewed by the corresponding author and be made available upon reasonable request.

Ethics statement

The studies involving humans were approved by University of California, Los Angeles Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

SW: Data curation, Writing – original draft, Visualization. SA: Writing – review & editing, Writing – original draft, Data curation. SV: Data curation, Writing – original draft, Formal analysis, Writing – review & editing. NM: Supervision, Writing – review & editing, Data curation, Investigation. RW: Writing – original draft, Funding acquisition, Data curation, Methodology, Conceptualization, Writing – review & editing, Investigation, Supervision.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declared that generative AI was not used in the creation of this manuscript.

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