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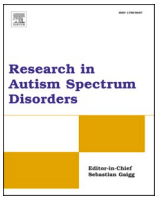

Toe walking in children and adolescents with Autism Spectrum Disorder: Relationship with sensory and motor functions, language, cognition, and autism severity

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ABSTRACT

Background: Children and adolescents with Autism Spectrum Disorder (ASD) often present motor signs and symptoms, including toe walking (TW). The pathophysiology of TW in ASD is not fully understood. In particular, it is debated whether it may represent a persistent primitive walking pattern or the result of abnormal processing of sensory input from the lower limbs and feet. The present study is aimed at assessing the association between TW and cognitive, sensory, motor and language functions, as well as autism severity.
Method: We enrolled 112 children and adolescents with ASD, 61 with TW and 51 without TW. A complete psychodiagnostic assessment was performed, including ADOS-2, ADI-R, PEP-3, IQ testing or Griffiths Mental Developmental Scales, and Short Sensory Profile.
Results: Children and adolescents with TW have significantly lower cognitive level, greater language and motor impairment, as well as greater autism severity. Instead, no difference in severity of sensory abnormalities or in sensory profile emerges between cases with and without TW.
Conclusions: the present data are most compatible with a model interpreting TW as a behavioral pattern resulting from the persistence of a primitive walking pattern (i.e. lack of heel strike, prior to the acquisition of plantar walking) or possibly of archaic tonic reflexes, rather than as a consequence primarily of abnormal sensory processing. Health practitioners should monitor the

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gait of autistic children and plan appropriate interventions, aimed at promoting the adoption of more mature plantar walking patterns.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder broadly characterized by impairment in socio-communicative interactions, restricted interests, repetitive behaviors, and abnormal sensory processing (American Psychiatric Association, 2013). Moreover, children with ASD often display co-morbid disorders, such as intellectual disability and language impairment (Persico et al., 2020).

1.1. Abnormal sensory processing in ASD

While socio-communicative deficits and behavioral symptoms have long been viewed as part of the clinical picture of ASD, sensory features have been recognized as core symptoms of ASD much more recently (Ben-Sasson et al., 2019). Abnormal sensory processing may include difficulty in integrating multisensory stimuli, limited proprioception and/or impaired body scheme, reduced sensory discrimination, inconsistent perception of stimulus intensity, impaired sensory modulation in turn leading to abnormal behavioural responses to sensory inputs (Miller et al., 2007). In particular, sensory features have been classified into three distinct patterns, namely sensory over-responsivity (SOR), sensory under-responsivity (SUR), and sensation seeking (Miller et al., 2007). Children with ASD frequently display atypical patterns of SOR, SUR and sensation seeking compared to typically developing (TD) children (Ben-Sasson et al., 2009). SOR seemingly differentiates to a larger extent individuals with ASD from TD children, but also from children with other developmental disorders, while SUR distinguishes ASD only from the TD group and higher sensation seeking is significantly moderated by age and intellectual quotient (IQ) (Ben-Sasson et al., 2019).

1.2. Abnormal motor function and toe walking in ASD

Not only abnormal sensory processing, but also delays and deficits in motor behavior have been frequently described in ASD (e.g. Ming et al., 2007), ever since the initial reports by Leo Kanner (1943) and Hans Asperger (1944). Motor impairment can range from delayed motor milestones (Provost et al., 2007), to motor incoordination (Mari et al., 2003), deficits in gross and fine motor skills (Noterdaeme et al., 2002), and difficulties in postural control (Memari et al., 2014). In addition, more recent studies have also reported an increased prevalence of toe walking (TW) in children with ASD (Accardo & Barrow, 2015). TW refers to walking on the toes or forefoot with lack of heel strike and it can be often seen in children during development, especially when they start to walk (Ruzbarsky et al., 2016; Leyden et al., 2019). The majority of children with TW will naturally achieve a normal gait within six months after starting to walk, or will resolve TW by 3–7 years of age (Shetreat-Klein et al., 2014). If TW continues beyond this period and persists for more than 6 months, children are diagnosed with “persistent toe walking”. In typically developing children, the prevalence of persistent TW has been reported at 4.5 % in a large sample of 1436 TD children 5–6 years old (Engström and Tedroff, 2012). These TD children also display a significantly greater incidence of speech/language delays, deficits in executive functions and memory, limited social skills and learning disorders (Accardo et al., 1992; Engström and Tedroff, 2012). The pathophysiology underling idiopathic toe walking (ITW) in typically developing children is still unknown (van Kuijk et al., 2014). Contributions by perinatal damage, neurological or orthopaedic impairment, or overt neuropsychiatric disorders have been excluded (van Kuijk et al., 2014). Recently, Veerkamp and colleagues (Veerkamp et al., 2024) validated a model through dynamic simulation showing how a musculotendinous contracture combined with altered neural control could result in ITW. Engström and Tedroff (2018) proposed to distinguish TW children in two groups between birth and 5 years of age: the majority display transient or idiopathic TW without secondary contracture, whereas some children already show a contracture of the triceps surae or tight heel cords. It is important to distinguish these two conditions, as they evolve differently: children with contracture will need treatment, whereas TW will resolve spontaneously by the age of 10 in 79 % of children without contracture (Engström & Tedroff, 2012). Only few studies explored the natural long-term outcome of ITW. From a physical standpoint, an abnormal development of the talus has been described (Sinclair et al., 2018). Importantly, more recent studies report a negative impact of ITW on daily life activities and on quality of life. Healthy children with ITW between 4 and 16 years, who did not take part in an active treatment for their TW within the previous 12 months, reported lower quality of life compared to their healthy peers (Caserta et al., 2022). Similar, data collected in twelve paediatric orthopaedic centres across the United Kingdom showed that ITW in children is associated with lower health related quality of life in different domains, including physical, school, play and emotions (Morrow et al., 2024).

The prevalence of persistent TW in children with ASD is significantly greater compared to TD children, and varies across studies, ranging from 20.0 % (Ming et al., 2007; Barrow et al., 2011) to 31.9 % (Valagussa et al., 2017), to 33 % or 45 % depending on whether TW is detected only by video recording or also by direct office observation (Sheatreat-Klein et al., 2014). More recently, a large retrospective database review found persistent TW in 8.4 % (484/5739) patients with ASD, compared to 0.47 % of children without ASD (Leyden et al., 2019). Interestingly, these Authors found no significant difference in prevalence of TW in autistic children with and without intellectual disability (ID), whereas Valagussa et al. (2017) reported a correlation between ID severity and the presence of TW in a group of 69 children with ASD. In the same study, also the severity of language delay was found correlated with the persistence of TW, in line with prior evidence (e.g. Barrow et al., 2011).

Table 1
Demographic and developmental characteristics of the study sample with toe walking (TW) and without toe walking (NO-TW).

Variables	ASD NO-TW group (N = 51)	ASD TW group (N = 61)	Mean difference (95 % CI low/high)	p-value
Sex (M:F)	42:9	55:6		0.27
Age category	40	54		0.2
• 0-9	10	5		
• 10-18	1	2		
• >=19				
Age at enrollment	6.86 ± 4.19 (1.8-20.0)	6.55 ± 4.25 (2.1-25.3)	0.31 (−1.28/1.90)	0.77
Age at first visit (yrs)	2.54 ± 0.98 (0.6-5.0)	2.45 ± 1.64 (1-13.4)	0.01 (−0.48/0.50)	0.97
Birth weight (kg)	3.13 ± 0.61 (1.8-4.5)	3.21 ± 0.64 (1.9-4.7)	0.06 (−0.18/0.31)	0.60
Motor development (months):	3.26 ± 1.43 (2-12)	3.64 ± 1.58 (2-11)	0.44 (−0.164/1.05)	0.16
• Age at head control				
• Age at trunk control	6.55 ± 2.13 (5-18)	6.84 ± 1.84 (4-15)	0,39 (−0,39/1,17)	0.33
• Age at autonomous walking	14.64 ± 3.70 (10-30)	14.70 ± 2.76 (9-22)	0.16 (−1.07/1.40)	0.79
Language development (months):	30.00 ± 14.98 (10-72)	24.57 ± 17.03 (8-84)	-5.23 (−12.79/2.34)	0.18
• Age at first words				
• Age at first sentences	53.28 ± 21.80 (18-108)	43.95 ± 28.04 (12-132)	-9.38 (−25.81/7.05)	0.27

Note. Quantitative data are presented as mean ± standard deviation (range); p-values refer to between-group comparisons.

1.3. Possible pathophysiology of toe walking in ASD

Several different hypotheses have been formulated to explain the association between ASD and TW. On the one hand, TW could result from the persistence of primitive reflexes, automatic patterns of motor response to a specific sensory stimulus (Capute et al., 1978; Gieysztor et al., 2022), which should disappear around 4–6 months of postnatal life. as the maturation of the central nervous system progresses. Hence, the persistence of primitive reflexes indicates a neuromotor immaturity in children. Young children with ASD often tend to arch when picked up and cuddled. Hence, this unusual posture together with toe walking have been interpreted as a sign of persistent primitive reflexes, Moreover, ASD has been associated in some children with a persistent tonic labyrinthine reflex, whereby extension of the head over the neck produces a full body extension, with arching of trunk, legs and feet accompanied by the abduction of shoulders and arms (Capute et al., 1978; Barrow et al., 2011; Accardo & Barrow, 2015). A persistent asymmetrical tonic neck reflex could also trigger toe walking (Teitelbaum et al., 2004). The persistence over time of these two primitive reflexes, paired with the absence of other primitive reflexes, such as the allied protective reflexes, has been proposed to represent an early developmental marker of an ASD diagnosis (Teitelbaum et al., 1998; Teitelbaum et al., 2004). The persistence of even one primitive reflex negatively impacts the development of motor skills and voluntary movements, including gait (Gieysztor et al., 2022). The persistence of TW yields secondary orthopedic deformity, pain in legs, feet and the lumbar region, as well as frequent falling, complicating the management of ASD children (Barrow et al., 2011; Davies et al., 2018). Moreover, TW can negatively impact quality of life, by affecting functional activities and social interactions (van Kuijk et al., 2014) and it is correlated with language and cognitive development (Valagussa et al., 2017). Thus, considering that in ASD children the rates of spontaneous resolution for TW within 10 years of diagnosis are low (i.e., clinical intervention is required in 63.6 % of ASD patients compared to 19.3 % of TD children) (Leyden et al., 2019), the presence of TW represents a risk factor for later developmental milestones, level of adaptive functioning and quality of life which indeed deserves to be considered by clinicians and addressed in timely fashion.

On the other hand, both motor skills and language depend on the sensory system (Liu et al., 2013; Valagussa et al., 2017) and deficits in these functions could also stem from impaired sensory modulation (Accardo & Barrow, 2015; Valagussa et al., 2017). In reference to TW, deficits in sensory information processing could impact sensorimotor integration from the foot and leg, consequently affecting also motor planning and movement execution. The influence of sensory information on TW has been shown by Valagussa et al. (2017), reporting that hard floor surfaces stimulate toe standing and TW much more than soft surfaces, but only in the TW group of autistic children. Others have found Short Sensory Profile (SSP) and Movement ABC-2 scale scores significantly correlated to each other in ASD (Liu, 2013). Furthermore, children with ASD and TW tend to fulfill the "under-responsive/seeks sensation" profile at the SSP significantly more often than ASD children without TW (Valagussa et al., 2022). Hence, within this conceptual framework, some ASD children would appear to use TW to increase their proprioceptive sensory input and/or to decrease their foot surface area of tactile stimulation.

1.4. Study aim

The aim of the present study is to characterize the cognitive, language, motor and sensory profile of autistic children and adolescents with and without TW, in order to begin validating these interpretative models in a new large independent sample.

2. Methods

2.1. Participants

The sample includes 112 children and adolescents with a diagnosis of ASD (age range: 1.6–24.0 years; M:F=6.5:1). This sample includes 61 individuals with TW (TW group) and 51 without TW (NO-TW group). All patients fulfilled DSM-5 criteria for a clinical diagnosis of ASD (American Psychiatric Association, 2013). Children with comorbid disorder or medical conditions that could have an impact on gait (i.e. upper motor neuron syndromes, cerebral palsy, muscular dystrophy, trisomy 21, tethered spinal cord, spinal muscular atrophy) were excluded. None of the ASD subjects with TW had received active treatment for TW. No age range limitation was set, in order to maximize sample size and statistical power, but analyses restricted to children aged 0–9 y.o. were also performed, yielding results superimposable to those of the entire sample (data not shown). Patients were recruited at the Service for Neurodevelopmental Disorders at Campus Bio-Medico University Hospital in Rome (Italy), and at the Interdepartmental Program "Autism 0–90" of the "G. Martino" University Hospital in Messina (Italy). The demographic and developmental characteristics of the study sample are summarized in Table 1. The TW and NO-TW groups did not differ significantly in any demographic or developmental variable (Table 1).

All parents gave written informed consent for themselves and for their children. The consent form and data collection methods were approved by the Institutional Review Board of University "Campus Bio-Medico'' of Rome, Italy (prot. n. 14/98, first approval on April 28, 1998 and subsequent amendments) and the Ethics Committee of Messina, Italy (prot. n. 22/17, approved on June 19, 2017). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration (2000).

2.2. Materials and study design

Children and adolescents with ASD were recruited during the course of their first evaluation or of a control visit. Initially, data on the child's development and clinical history were collected; during follow-up visits, the evolution over time of the clinical profile was evaluated. All participants were subsequently assessed with psychodiagnostic testing, which was divided into 2 or 3 sessions, depending on the level of attention and collaboration of the patient. The clinical diagnosis of ASD was confirmed in all patients using both the Autism Diagnostic Observation Schedule (ADOS, ADOS-2) (Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al., 2003). Cognitive level was assessed using the Wechsler Intelligence Scales for children (WISC-III, WISC-IV) (Orsini & Picone, 2006; Orsini, Pezzuti, & Picone, 2012), the Wechsler Intelligence Scales for adolescents and adults (WAIS-III, WAIS-IV Orsini & Laicardi, 1993; Orsini & Pezzuti, 2013), the Leiter International Performance Scale R (Roid & Miller, 1997; Italian), the Leiter International Scale-third edition (Roid et al., 2013; Cornoldi et al., 2016), or the k Mental Developmental Scales (Griffiths, 1996) depending on age and language development. A "composite IQ" variable was also employed, importing for each subject his/her IQ or DQ, regardless of the test administered. The different domains of acquired and emerging functions were assessed using the Psycho educational Profile-Third Edition (PEP-3) (Schopler et al., 2005). Parents were asked to fill the Short Sensory Profile questionnaire (McIntosh et al., 1999) in the clinic, while their child was undergoing evaluation. Prior to the inclusion of the child in the study, the presence of TW was determined on the basis of direct clinical observation during motor activities (i.e. running, standing position, walking) and by parental report. To be included in the "TW group", children and adolescents had to have a persistent TW, either directly observed by clinicians or reported by parents as present in the past for an estimated minimum of 6 months, during most days and for most time during the day. On the contrary, subjects were included in the "NO-TW group" if TW was never observed by

Table 2
Comparison in language abilities, motor skills, IQ and autism severity between autistic individuals with (TW) and without (NO-TW) toe walking.

Variables	ASD NO-TW group (N = 51)	ASD TW group (N = 61)	Mean difference (95 % CI low/high)	p-value
PEP-3 scales:	57.51 ± 19.55 (28-110; N = 34)	44.28 ± 20.18 (14-90; N = 45)	-11.51 (−20.27/−2.75)	**0.01**
• Cognitive Pre-Verbal				
• Expressive Language	37.83 ± 16.87 (13-84; N = 34)	30.81 ± 16.29 (10-68; N = 45)	-5.60 (−12.88/1.67)	0.14
• Receptive Language	50.77 ± 24.11 (22-125; N = 34)	38.37 ± 20.35 (9-92; N = 45)	-11.32 (−21.22/−1.42)	**0.03**
• Fine Motor	54.37 ± 17.80 (28-89; N = 34)	44.34 ± 16.84 (11-74; N = 45)	-8.32 (−15.47/−1.17)	**0.02**
• Gross Motor	51.14 ± 15.92 (24-93; N = 34)	44.25 ± 14.76 (11-74; N = 45)	-5.63 (−11.46/0.20)	0.06
• Visual-Motor Imitation	50.52 ± 18.10 (27-100; N = 34)	40.62 ± 18.81 (16-90; N = 45)	-7.83 (−15.24/−0.43)	**0.04**
Griffiths Global Quotient	53.61 ± 23.63 (20-100; N = 18)	47.19 ± 19.92 (20-94; N = 34)	-5.83 (−18.19/6.52)	0.36
Leiter-3 Total IQ	71.52 ± 14.48 (41-104; N = 21)	61.47 ± 10.85 (41-84; N = 15)	-11.40 (−19.47/−3.33)	**0.01**
Composite IQ	66.13 ± 22.36 (20-119; N = 48)	54.56 ± 20.66 (20-102; N = 60)	-11.36 (−19.56/−3.17)	**0.01**
ADOS-2:	11.23 ± 4.40 (2-20; N = 43)	13.21 ± 4.85 (4-20; N = 53)	1941 (0.02/3.86)	0.05
• Social Affect				
• Restrictive, Repetitive Behaviour	2.10 ± 1.73 (0-5; N = 43)	2.6 ± 1.83 (0-8; N = 53)	0589 (−0.14/1.32)	0.12
• Total Score	13.33 ± 5.19 (5-22; N = 43)	15.81 ± 5.62 (6-28; N = 53)	2530 (0.30/4.76)	**0.03**

Note. Quantitative data are presented as mean ± standard deviation (range, N); mean difference and p-values refer to between-group comparisons; significant results are highlighted in bold

Table 3
Between-group comparison of Short Sensory Profile (SSP) scale scores.

Variables	ASD NO-TW group (N = 51)	ASD TW group (N = 61)	Mean difference (95 % CI low/high)	p-value
Tactile sensitivity	29.79	29	-0.70 (−2,69/1.29)	0.49
Taste Olfactory sensitivity	15.12	13.27	1.81 (−4.12/0.47)	0.13
Movement sensitivity	13.06	12.18	0.94 (−2.21/0.34)	0.15
Hyporeactivity	24.62	23.59	0.81 (−3.54/1.91)	0.56
Auditory filtering	19.94	19.76	0.02 (−1.95/1.20)	0.98
Low energy	25.39	23.43	-1.78 (−4.56/0.99)	0.21
Visual auditory sensitivity	20.16	19.35	-0.97 (−2.88/0.93)	0.32
Total score	147.53	141.43	-5.62 (−15.99/4.75)	0.29

clinicians during the evaluation or follow-up visits, and if parents reported the complete absence or occasional appearance of TW (i.e., children walked on their toes only intermittently for a period of less than 6 months, and for a very limited time during the day).

2.3. Data analysis

Descriptive statistics were computed for each variable: numerical variables are reported as mean±standard deviation (SD), or as median±interquartile range (IQR); categorical variables were reported as absolute frequencies and percentages. The association between TW and each variable of interest was investigated using multivariable generalized regression models, based on the characteristic of each outcome. Dichotomous and count variables were modelled through Poisson regression models and the results are reported in terms of Relative Risk (RR); ordinal categorical variables were analysed using ordinal logistic regression models and the results are reported as Odds Ratio (OR). Finally, linear regression models were used to detect association with respect to numerical outcome variables and results are provided in terms of Mean Difference (MD). Sex and age were also included in all models as covariates, to take into account their effect on the relationship between TW and each outcome variable considered. The estimates obtained from each model are presented with 95 % confidence intervals (CI) and p-values. In the cases of Poisson regression models, 95 % CI and p-values were obtained using robust standard errors, obtained applying Sandwich estimator (Zeileis, 2006). P-values are considered significant when < 0.05. All analyses were carried out using R Statistical software (The R Foundation for Statistical Computing) version 4.2.2 (R Core Team, 2022).

3. Results

3.1. Demographic data

The TW group includes 61 ASD cases, encompassing 49 cases with current TW directly observed by the clinician and 12 patients with prior persistent TW reported by parents. The NO-TW group is composed of 51 ASD cases, including 40 patients who never presented any TW, and 11 cases with prior history of occasional TW (Table 1). The TW and NO-TW groups did not differ in any demographic and developmental characteristic, including age distribution and mean age in years, which were 6.55 ± 4.25 (range 2.1–25.3) and 6.86 ± 4.19 (range 1.8–20.0), respectively (Table 1).

3.2. Differences in language and motor function between the TW and NO-TW groups

Contrasts in variables pertaining to the language and motor function domains are presented in Table 2. Compared to the NO-TW group, ASD children and adolescents with TW obtained significantly lower scores in all PEP-3 scales, reaching statistical significance ($P < 0.05$) in receptive language ($P = 0.03$), fine motor ($P = 0.02$) and visual motor imitation scores ($P = 0.04$).

3.3. Differences in cognitive level between the TW and NO-TW groups

Scores obtained in the cognitive pre-verbal scale of the PEP-3 by the TW group were significantly lower than the scores of the NO-TW group ($P = 0.01$). Differences in cognitive level also emerged with the Leiter-R IQ, or computing a "composite IQ", which were significantly lower in children and adolescents with TW compared with to the NO-TW group (both $P < 0.01$) (Table 2).

3.4. Differences in autism severity between the TW and NO-TW groups

Significant differences in ASD severity were detected, with higher mean ADOS2 total score in TW cases compared with the NO-TW group ($P = 0.03$) (Table 2). Although none of the two subscales reached significance, greater contributions to this difference were seemingly provided by the Social-Affect subscale, reaching a $P = 0.05$, than by the Restrictive, Repetitive Behavior subscale, reaching a $P = 0.12$ (Table 2).

3.5. No difference in Short Sensory Profile between the TW and NO-TW groups

Contrary to language, motor, cognitive and autism measures, Short Sensory Profile mean scores were very similar in the two groups (Table 3). Differences between the TW and NO-TW groups were small and never approached statistical significance ($p > 0.05$) (Table 3). Age-specific analyses restricted to children aged 0–9 yielded superimposable results for all of the above-mentioned parameters (data not shown).

4. Discussion

Persistent TW is frequently associated with ASD and represents a relevant clinical issue. It can lead to tight heel cords requiring Achilles tendon lengthening surgery, with complicated post-surgical management in children and adolescents with autism (Barrow et al., 2011). Moreover, persistent TW can generate with time an equinus deformity, which in turn has been associated with a range of orthopaedic pathologies (i.e acquired flatfoot and metatarsalgia) (see the review by Bemmel et al., 2013). Finally, TW represents a risk factor for a worse developmental trajectory in terms of language, IQ and ASD severity (Gong et al., 2020; Valagussa et al., 2017) and affects the possibility of environmental exploration, favoring rigid patterns of behavior and communication (Bhat et al., 2011). Hence the evaluation of TW in ASD children and adolescents should be included in their clinical assessment and TW should be a target for early intervention.

The present study aims to understand the association between TW and ASD, by defining the functional domains which best differentiate autistic individuals with and without TW. In particular, we focused on a set of functional variables previously found associated with TW, including IQ, language abilities, motor skills, sensory issues, and autism severity. Our results support an association between TW and lower IQ, greater impairment in verbal language and motor skills, and greater autism severity (Table 2). Instead, we find no difference in sensory profile between cases with and without TW (Table 3). Hence, the present data are most compatible with the model interpreting TW as a behavioral pattern resulting from the persistence of a primitive walking pattern or possibly of archaic reflexes, rather than as a consequence primarily of abnormal sensory processing.

4.1. Toe walking is associated with greater language impairment

TW appears to characterize a subset of autistic children and adolescents with more profound ASD (Table 2). In addition to lower IQ, expressive language is mostly lacking and receptive language is typically limited to short sentences and single commands. In our sample, ASD children with TW appear to have more difficulties in receptive language compared to ASD children without TW, whereas differences in expressive language do not reach statistical significance (Table 2). We think these results are unlikely to reflect greater impairment in receptive over expressive language in the presence of TW. Mean scores at the PEP-3 appear more compatible with a "ceiling" effect present for expressive, but not for receptive language in our sample. Indeed, expressive language is severely affected in both the TW and the NO-TW samples, limiting the variance of this parameter (Table 2). Instead, receptive language is less impaired in the NO-TW group, allowing for between-group differences to emerge (Table 2). A similar trend has been previously described in ASD children (Accardo & Barrow, 2015; Valagussa et al., 2017), whereas differences in language quotient between typically developing children with and without TW remain significant, precisely for a lack of this ceiling effect (Accardo et al., 1992).

4.2. Toe walking is associated with greater impairment in motor skills

In addition to its cognitive and symbolic component, speech and language skills clearly encompass a motor praxic component. Interestingly, our cases with TW display not only more severe difficulties in language comprehension, but also in fine motor skills (Table 2). In the present study, motor skills were assessed using the PEP3, which is a valid alternative to tests requiring the comprehension of verbal instructions, like the Movement-ABC2, in children with ASD and communication disabilities (Craig et al., 2021). Our results support the association between greater motor delay and TW on the one hand, with more severe language impairment on the other hand, as described by Valagussa et al. (2017), and supports their view of motor and language milestones stimulating each other's progress along the developmental trajectory. Indeed, motor milestones (e.g. sitting, reaching, walking) precede and can predict language acquisition both in typically developing children (Iverson & Wozniak, 2007; Walle & Campos, 2014), and in ASD children (Valagussa et al., 2017; Bedford et al., 2016). More broadly, motor impairment can limit the child's experience of environmental stimuli and participation in interactive activities, hampering the development of behavioral, cognitive, social, and communication skills (Bhat et al., 2011, 2022). Gait abnormalities were found to be linked to the core symptoms of ASD and in particular to social impairment, in fifty-eight autistic children 4–6-year-old (Gong et al., 2020). Moreover, motor and gait difficulties are detectable even before social and communication deficits in children later diagnosed with ASD and are linked to later adaptive behaviour, daily living skills and adaptive social and communicative skills (McDonald et al., 2013). Interestingly, Uljarević et al. (2017) found a predictive role of early motor milestones on restricted and repetitive behaviours. Hence, according to one hypothesis, difficulties in motor skills (standing and walking) may limit the child during the exploration of the environment, reducing opportunities for learning and diminishing self-regulation and cognitive flexibility. An alternative hypothesis underscores the possible existence of a common neural basis affecting both motor control and executive functions, on the one hand, and social cognition on the other, likely involving the cerebellum, fronto-striatal circuits, and broader white matter connectivity (Ridler et al., 2006; Yerys et al., 2015). Indeed, granule cell migration in the cerebellum, the structuring of mossy and climbing fiber circuits, the shaping of connectivity within the cerebellum and with the prefrontal cortex (i.e., cortico-cerebellar circuits) are all believed to play a pivotal role in

supporting both motor and language development during early infancy in typically developing children and, when developmentally disrupted, in producing both language and motor deficits in children with ASD (Fatemi et al., 2012; D'Mello & Stoodley, 2015). Similarly, hypoconnectivity involving frontal regions critical to executive functions, but also part of the theory-of-mind network (Courchesne and Pierce, 2005; Cheng et al., 2015), as well as imbalanced hypo/hyper-connectivity in motor and limbic fronto-striatal circuits, respectively, relevant to stereotypic behaviors (Abbott et al., 2018) also represent neurofunctional links between deficits in social cognition, verbal communication and motor function active in many ASD patients. Finally, studies applying diffusion tensor imaging (DTI) have consistently demonstrated delayed white matter maturation, particularly in neural pathways underlying language, such as the arcuate and uncinate fasciculus, but also in regions involved in motor coordination, such as corpus callosum, cerebellum and brain stem (Zhang et al., 2018).

4.3. Toe walking and lower IQ

In order to assess possible correlations between TW and cognitive level, depending on age we measured DQ or IQ and merged them into a single "composite IQ" measure for statical purposes (Table 2). Both the TW group and the NO-TW group included children and adolescents ranging from normal IQ to profound Intellectual Disability/severe Global Developmental Delay (Table 2). However, TW was associated with significantly greater cognitive difficulties or more severe developmental delay, in line with previous evidence (Accardo & Barrow, 2015; Valagussa et al., 2017). In the vast majority of young children, global developmental delay predicts a diagnosis of Intellectual Disability after 5 years of age (Moeschler et al., 2014). Conversely, it is not surprising that in older children and adolescents a more severe form of Intellectual Disability may be more likely to encompass less mature motor/sensory schemes and persistent primitive reflexes. Interestingly, intellectual disability/global developmental delay represents the most frequent co-morbidity in patients primarily diagnosed with movement disorders (ataxias, stereotypies, dystonia, etc) due to chromosomal copy number variants (Soliani et al., 2023). The lower cognitive level recorded here among autistic individuals with TW compared to those without TW thus seems to represent just one of many clinical paradigms reflecting the profound bilateral link between cognitive and motor functions.

4.4. Toe walking and greater ASD severity

In the present study, children and adolescents with TW have significantly higher ADOS-2 total scores compared to cases in the NO-TW group (Table 2). Greater ASD severity may be due to more profound impairment in socio-communicative skills ($P = 0.05$), compared to stereotypic behaviors ($P = 0.12$) (Table 2). However, differences between the two subscales should be viewed with caution at this stage, because neither subscale reaches full statistical significance and most of all because this may represent an artifact due to the wider range of SA scores compared to RRB scores (Table 2). Meanwhile, our results differ from those of two other studies reporting no significant difference in ADOS scores between ASD children with and without TW (Valagussa et al., 2017; Valagussa et al., 2022). These studies recruited 7 and 14 matched patients per group (total $N = 14$ and 28 patients in Valagussa et al., 2017 and in Valagussa et al., 2022, respectively). The discrepancy between our results and the outcome of these studies may be likely due to the need of larger sample sizes to grant sufficient statistical power, by sampling a broader and more representative distribution of autism severity scores.

4.5. Lack of association with sensory profile

We did not find any major difference in sensory features between ASD cases with and without TW, although the profile of patients with TW tends to be slightly more compromised (Table 3). Our findings partially contrast to those of Valagussa et al. (2022), recently reporting a significantly higher rate of the SSP pattern "under-responsive/seeks sensation" among ASD children with TW compared to the NO-TW group. They are also not in agreement with another study that investigated typically developing children age 4–8 years with and without idiopathic persistent TW (Williams et al., 2014). Using the parent-report Sensory Profile the authors found that subjects of the idiopathic toe walking group potentially have a difficulty in the modulation or normalisation of sensory responses. Thus, children with sensory challenges may unconsciously use TW to change or challenge especially tactile, vestibular, and proprioceptive sensory inputs. In line with this hypothesis, abnormal sensory responses to tactile stimulus have also been described in ASD children with TW (Valagussa et al., 2017). Our data do not support a strong relationship between TW and sensory processing. In addition to a sampling bias and to the well-known interindividual variability present in ASD, at least two other possible explanations for this discrepancy appear plausible. First, results from typically developing children with idiopathic TW may not directly apply to autistic children, due to a much greater involvement of motor circuits in the neurodevelopmental processes deranged in ASD. In practical terms, TW aimed at normalizing an abnormal proprioceptive or tactile sensory threshold appears as a much more adequate, adaptive, "normal" motor response, as compared to the persistence of a primitive walking pattern in a child with severe intellectual disability and profound ASD. Indeed, we cannot exclude that excessive tactile sensitivity and/or decreased proprioceptive perception may trigger TW in ASD children, but most likely only if central motor systems are not developed sufficiently to prevent the appearance of this primitive postural/walking pattern. Secondly, anxiety has been shown to decrease the sensory threshold in typically developing children (Williams et al., 2014). This may add another layer of complexity, whereby there may be two autistic subgroups, one displaying TW throughout the wake period due to the persistence of a primitive postural and walking motor pattern, another displaying TW during most of the day but not always, due to severe anxiety in many (but not all) contexts increasing tactile sensitivity and triggering TW, possibly in interaction with a partial, but not complete consolidation of a plantar walking pattern over more primitive

motor patterns. In this second scenario, an "anxiety x sensory x motor" interaction would result in TW present occasionally, or during most of the day. Clearly, dissecting pathophysiologies with this degree of complexity requires very large samples and hypothesis-driven studies designs using appropriate measures. Nonetheless, collectively our data do not support abnormal sensory processing as representing the primary trigger and/or the most relevant component in the pathophysiological cascade leading to TW in ASD.

4.6. Study strengths and limitations

Our study has several strengths and limitations. One strength is the sample size, which is larger than most prior studies addressing the issue of TW in ASD. Another strength is the use of standardized measures for IQ, adaptive behaviors, sensory profile and autism severity. Among the limitations of our study, which must be duly acknowledged, the TW and NO-TW samples are very similar in demographic and clinical characteristics (Table 1), but are not the result of a tight 1-to-1 age- and sex-matching. Another limitation is represented by the lack of use of a standardized scale to define "toe walking" and the reliance on parental report to quantify its pervasiveness, when not directly observed during medical visits or psychodiagnostics testing. Moreover, the SSP remains an indirect measure of sensory-related behaviors based on parental report, whereas direct objective measures would be much more precise and reliable, especially in non-verbal children and adolescents, to quantify and characterize abnormal sensory processing, as well as inappropriate motor program selection and execution. Finally, a longitudinal design is needed to better elucidate the nature of the association between TW, cognitive, language, and motor skills, especially in reference to the extent these parameters co-vary over time in ASD with and without active interventions on TW.

5. Conclusion

Children, adolescents, and adults with ASD frequently display a range of motor impairments, also including TW. If not corrected at an early age, TW does produce significant orthopedic complications (Barrow et al., 2011; Davies et al., 2018) and negatively impacts quality of life in multiple ways, such as hampering participation in sport activities and limiting social inclusion (van Kuijk et al., 2014; Williams et al., 2014). In addition, TW appears indeed associated with an unfavourable developmental trajectory characterized by more profound cognitive impairment, language deficits, and autism severity. Hence health practitioners should soon pay attention to the orthostatic posture and gait of autistic children, and promptly prescribe appropriate interventions, whenever necessary. Our results are most compatible with TW stemming from the persistence of a primitive walking pattern present also in typically developing children during the first few months after the acquisition of independent walking (Ruzbarsky et al., 2016; Leyden et al., 2019). Consequently, promoting the development of a more mature plantar walking pattern by applying physiatric and behavioral strategies appears more justified by these results than attempting to improve TW by primarily modulating the sensory input from feet and lower limbs. Future research will need to define and test targeted therapeutic interventions based on these assumptions and on the functional profile of autistic children with TW.

Language use statement

In this paper, we have used identity-first terminology in line with the published preferences of the autistic community (e.g., Kenny et al., 2016; Bottema-Beutel, 2021). However, we acknowledge and respect the preference of others for person-first language.

CRediT authorship contribution statement

Maria Boncoddo: Data curation, Investigation. **Roberto Sacco:** Conceptualization, Data curation, Methodology. **Michela Camia:** Conceptualization, Investigation, Validation, Writing – original draft. **Antonio M. Persico:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Roberto D'Amico:** Conceptualization, Formal analysis, Methodology. **Riccardo Cuoghi Costantini:** Formal analysis, Methodology. **Pasquale Tomaiuolo:** Data curation, Software. **Laura Turriziani:** Data curation, Investigation. **Arianna Ricciardello:** Data curation, Investigation. **Francesca Cucinotta:** Data curation, Investigation. **Fabiana Bellomo:** Data curation, Investigation.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that they have not used generative AI in any of the writing that appears in the present manuscript.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

Abbott, A. E., Linke, A. C., Nair, A., Jahedi, A., Alba, L. A., Keown, C. L., … Müller, R. A. (2018). Repetitive behaviors in autism are linked to imbalance of corticostriatal connectivity: a functional connectivity MRI study. *Social cognitive and affective neuroscience, 13*(1), 32–42. https://doi.org/10.1093/scan/nsx129

Accardo, P. J., & Barrow, W. (2015). Toe Walking in Autism: Further Observations. *Journal of Child Neurology, 30*(5), 606–609. https://doi.org/10.1177/0883073814521298

Accardo, P., Morrow, J., Heaney, M. S., Whitman, B., & Tomazic, T. (1992). Toe walking and language development. *Clinical pediatrics, 31*(3), 158–160. https://doi.org/10.1177/000992289203100306

American Psychiatric Association. (2013). Diagnostic and statisti-cal manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association. ISBN-13 978–0890425558.

Asperger, H. (1944). Die 'Autistischen Psychopathen' im Kindesalter. *Archiv fur Psychiatrie und Nervenkrankheiten, 117*, 76–136. Translated in English as "Autistic psychopathy in childhood", by Frith U. (1991) Autism and Asperger's Syndrome. Cambridge (UK): Cambridge University Press.

Barrow, W. J., Jaworski, M., & Accardo, P. J. (2011). Persistent toe walking in autism. *Journal of Child Neurology, 26*(5), 619–621. https://doi.org/10.1177/0883073810385344

Bedford, R., Pickles, A., & Lord, C. (2016). Early gross motor skills predict the subsequent development of language in children with autism spectrum disorder. *Autism Research, 9*(9), 993–1001. https://doi.org/10.1002/aur.1587

Ben-Sasson, A., Gal, E., Fluss, R., Katz-Zetler, N., & Cermak, S. A. (2019). Update of a meta-analysis of sensory symptoms in ASD: A new decade of research. *Journal of Autism and Developmental Disorders, 49*, 4974–4996.

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S. A., Engel-Yeger, B., & Gal, E. (2009). A meta-analysis of sensory modulation symp*-toms in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*(1), 1–11. https://doi.org/10.1007/s1080 3-008-0593-3.

Bhat, A. N., Boulton, A. J., & Tulsky, D. S. (2022). A further study of relations between motor impairment and social communication, cognitive, language, functional impairments, and repetitive behavior severity in children with ASD using the SPARK study dataset. *Autism Research, 15*(6), 1156–1178. https://doi.org/10.1002/aur.2711

Bhat, A. N., Landa, R. J., & Galloway, J. C. (2011). Current perspectives on motor functioning in infants, children, and adults with autism spectrum disorders. *Physical Therapy, 91*(7), 1116–1129. https://doi.org/10.2522/ptj.20100294

Capute, A. J., Accardo, P. J., Vining, E. P., Rubenstein, J. E., Ronald Walcher, J., Harryman, S., & Ross, A. (1978). Primitive reflex profile: A pilot study. *Physical Therapy, 58*(9), 1061–1065. https://doi.org/10.1093/ptj/58.9.1061

Caserta, A., Reedman, S., Morgan, P., & Williams, C. M. (2022). Physical activity and quality of life in children with idiopathic toe walking: a cross sectional study. *BMC pediatrics, 22*(1), 544. https://doi.org/10.1186/s12887-022-03583-w

Cheng, W., Rolls, E. T., Gu, H., Zhang, J., & Feng, J. (2015). Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. *Brain, 138*(*Pt 5*), 1382–1393. https://doi.org/10.1093/brain/awv051

Core Team, R. (2022). R: A language and environment for statistical computing. *R Foundation for Statistical Computing* (URL: https://www.R-project.org/).

Cornoldi, C., Giofrè, D., & Belacchi, C. (2016). Leiter-3 Leiter International Performance Scale Tirth Edition. Standardizzazione italiana.

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology, 15*(*2*), 225–230. https://doi.org/10.1016/j.conb.2005.03.001

Craig, F., Crippa, A., Ruggiero, M., Rizzato, V., Russo, L., Fanizza, I., & Trabacca, A. (2021). Characterization of Autism Spectrum Disorder (ASD) subtypes based on the relationship between motor skills and social communication abilities. *Human Movement Science, 77*, Article 102802. https://doi.org/10.1016/j.humov.2021.102802

Davies, K., Black, A., Hunt, M., & Holsti, L. (2018). Long-term gait outcomes following conservative management of idiopathic toe walking. *Gait & Posture, 62*, 214–219. https://doi.org/10.1016/j.gaitpost.2018.02.014

D'Mello, A. M., & Stoodley, C. J. (2015). Cerebro-cerebellar circuits in autism spectrum disorder. *Frontiers in Neuroscience, 9*, 408. https://doi.org/10.3389/fnins.2015.00408

Engström, P., & Tedroff, K. (2012). The prevalence and course of idiopathic toe-walking in 5-year-old children. *Pediatrics, 130*(2), 279–284. https://doi.org/10.1542/peds.2012-0225

Engström, P., & Tedroff, K. (2018). Idiopathic toe-walking: prevalence and natural history from birth to ten years of age. *JBJS, 100*(8), 640–647. https://doi.org/10.2106/JBJS.17.00851

Fatemi, S. H., Aldinger, K. A., Ashwood, P., Bauman, M. L., Blaha, C. D., Blatt, G. J., Chauhan, A., Chauhan, V., Dager, S. R., Dickson, P. E., Estes, A. M., Goldowitz, D., Heck, D. H., Kemper, T. L., King, B. H., Martin, L. A., Millen, K. J., Mittleman, G., Mosconi, M. W., Persico, A. M., Sweeney, J. A., Webb, S. J., & Welsh, J. P. (2012). Consensus paper: pathological role of the cerebellum in autism. *The Cerebellum, 11*, 777–807. https://doi.org/10.1007/s12311-012-0355-9

Gieysztor, E., Kowal, M., & Paprocka-Borowicz, M. (2022). Primitive reflex factors influence walking gait in young children: an observational study. *International Journal of Environmental Research and Public Health, 19*(7), 4070. https://doi.org/10.3390/ijerph19074070

Gong, L., Liu, Y., Yi, L., Fang, J., Yang, Y., & Wei, K. (2020). Abnormal gait patterns in autism spectrum disorder and their correlations with social impairments. *Autism Research, 13*(7), 1215–1226. https://doi.org/10.1002/aur.2302

Griffiths, R. (1996). *Griffiths mental developmental scale- revised: birth to 2 years (GMDS-R)*. Firenze: Hogrefe.

Iverson, J. M., & Wozniak, R. H. (2007). Variation in vocal-motor development in infant siblings of children with autism. *Journal of Autism and Developmental Disorders, 37*, 158–170. https://doi.org/10.1007/s10803-006-0339-z

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child, 2*(3), 217–250.

Leyden, J., Fung, L., & Frick, S. (2019). Autism and toe-walking: Are they related? Trends and treatment patterns between 2005 and 2016. *Journal of Children's Orthopaedics, 13*(4), 340–345. https://doi.org/10.1302/1863-2548.13.180160

Liu, T. (2013). Sensory processing and motor skill performance in elementary school children with autism spectrum disorder. *Perceptual and Motor skills, 116*(1), 197–209. https://doi.org/10.2466/10.25.PMS.116.1.197-209

Lord, C., Rutter, M., DiLavore, P.C., Risi, S., Gotham, K., & Bishop, S. Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part I): Modules 1–4. Torrance, CA: Western Psychological Ser-vices; 2012.

MacDonald, M., Lord, C., & Ulrich, D. (2013). The relationship of motor skills and adaptive behavior skills in young children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 7*(11), 1383–1390. https://doi.org/10.1016/j.rasd.2013.07.020

Mari, M., Castiello, U., Marks, D., Marraffa, C., & Prior, M. (2003). The reach–to–grasp movement in children with autism spectrum disorder. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences, 358*(1430), 393–403. https://doi.org/10.1098/rstb.2002.1205

McIntosh, D. N., Miller, L. J., & Shyu, V. (1999). Development and validation of the short sensory profile. In W. Dunn (Ed.), *Sensory Profile: User's Manual* (pp. 59–73). The Pscyhological Corporation.

Memari, A. H., Ghanouni, P., Shayestehfar, M., & Ghaheri, B. (2014). Postural control impairments in individuals with autism spectrum disorder: a critical review of current literature. *Asian Journal of sports Medicine, 5*(3). https://doi.org/10.5812/asjsm.22963

Miller, L. J., Anzalone, M. E., Lane, S. J., Cermak, S. A., & Osten, E. T. (2007). Concept evolution in sensory integration: A proposed nosology for diagnosis. *The American Journal of Occupational Therapy, 61*(2), 135. https://doi.org/10.5014/ajot.61.2.135.

Ming, X., Brimacombe, M., & Wagner, G. C. (2007). Prevalence of motor impairment in autism spectrum disorders. *Brain and Development, 29*(9), 565–570. https://doi.org/10.1016/j.braindev.2007.03.002

Moeschler, J. B., Shevell, M., & Committee on Genetics. (2014). Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics, 134*(3), e903–e918. https://doi.org/10.1542/peds.2014-1839

Morrow, E., Harris, J., Gelfer, Y., Cashman, J., Kothari, A., & FOOTT-UK Collaborators. (2024). Health-related quality of life in Idiopathic Toe Walkers: A multicenter prospective cross-sectional study. *Journal of Pediatric Orthopaedics*, 10–1097. https://doi.org/10.1097/BPO.0000000000002620

Noterdaeme, M., Mildenberger, K., Minow, F., et al. (2002). Evaluation of neuromotor deficits in children with autism and children with a specific speech and language disorder. *European Child & Adolescent Psychiatry, 11*, 219–225. https://doi.org/10.1007/s00787-002-0285-z

Orsini, A., & Laicardi, C. (1993). *WAIS-R: contributo alla taratura italiana*. Firenze, Italy: Organizzazioni Speciali.

Orsini, A., & Pezzuti, L. (2013). WAIS IV). *Italian validation of the Wechsler adult intelligence scale*. Giunti OS.

Orsini, A., Pezzuti, L., & Picone, L. (2012). Edizione Italiana. *Wechsler Intelligence Scale for Children IV*. Giunti OS.

Orsini, A., & Picone, L. (2006). *WISC-III. Contributo alla taratura italiana.* Organizzazioni Speciali.

Persico, A.M., Cucinotta, F., Ricciardello, A., & Turriziani, L.. Chapter 3. Autisms. In: "Comprehensive Developmental Neuroscience. Neurodevelopmental Disorders", 1st Edition (Rubenstein JLR and Rakic P, Senior Eds; Chen B and Kwan K, Eds; Wynshaw-Boris A, Section Ed). Academic Press/Elsevier Inc., pag. 35–77, 2020 (ISBN: 978–0-12–814409-1).

Provost, B., Lopez, B. R., & Heimerl, S. (2007). A comparison of motor delays in young children: autism spectrum disorder, developmental delay, and developmental concerns. *Journal of Autism and developmental Disorders, 37*, 321–328. https://doi.org/10.1007/s10803-006-0170-6

Ridler, K., Veijola, J. M., Tanskanen, P., Miettunen, J., Chitnis, X., Suckling, J., & Bullmore, E. T. (2006). Fronto-cerebellar systems are associated with infant motor and adult executive functions in healthy adults but not in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 15651–15656. https://doi.org/10.1073/pnas.0602639103

Roid, G. H., Miller, L. J., & Koch, C. (2013). *Leiter international performance scale.* Stoelting.

Rutter, M., LeCouteur, A., & Lord, C. (2003). *ADI-R, autism diagnostic interview-revised.* Western Psychological Services.

Ruzbarsky, J. J., Scher, D., & Dodwell, E. (2016). Toe walking: causes, epidemiology, assessment, and treatment. *Current Opinion in pediatrics, 28*(1), 40–46. https://doi.org/10.1097/MOP.0000000000000302

Schopler, E., Lansing, M.D., Reichler, R.J., & Marcus, L.M. (2005). PEP-3, Psychoeducational profile. Pro-ed.

Shetreat-Klein, M., Shinnar, S., & Rapin, I. (2014). Abnormalities of joint mobility and gait in children with autism spectrum disorders. *Brain and Development, 36*(2), 91–96. https://doi.org/10.1016/j.braindev.2012.02.005

Sinclair, M. R., Lind, A. A., & Knowlton, J. Q. (2018). The effect of persistent toe walking on the skeletal development of the pediatric foot and ankle. *Journal of Pediatric Orthopaedics B, 27*(1), 77–81. https://doi.org/10.1097/BPB.0000000000000461

Soliani, L., Alcalá San Martín, A., Balsells, S., Hernando-Davalillo, C., & Ortigoza-Escobar, J. D. (2023). Chromosome microarray analysis for the investigation of deletions in Pediatric Movement Disorders: A Systematic Review of the Literature. *Movement Disorders Clinical Practice, 10*(4), 547–557. https://doi.org/10.1002/mdc3.13711. PMID: 37070051; PMCID: PMC10105116.

Teitelbaum, O., Benton, T., Shah, P. K., Prince, A., Kelly, J. L., & Teitelbaum, P. (2004). Eshkol–Wachman movement notation in diagnosis: The early detection of Asperger's syndrome. *Proceedings of the National Academy of Sciences, 101*(32), 11909–11914. https://doi.org/10.1073/pnas.0403919101

Teitelbaum, P., Teitelbaum, O., Nye, J., Fryman, J., & Maurer, R. G. (1998). Movement analysis in infancy may be useful for early diagnosis of autism. *Proceedings of the National Academy of Sciences, 95*(23), 13982–13987. https://doi.org/10.1073/pnas.95.23.13982

Uljarević, M., Hedley, D., Alvares, G. A., Varcin, K. J., & Whitehouse, A. J. (2017). Relationship between early motor milestones and severity of restricted and repetitive behaviors in children and adolescents with autism spectrum disorder. *Autism Research, 10*(6), 1163–1168. https://doi.org/10.1002/aur.1763

Valagussa, G., Purpura, G., Nale, A., Pirovano, R., Mazzucchelli, M., Grossi, E., & Perin, C. (2022). Sensory Profile of Children and Adolescents with Autism Spectrum Disorder and Tip-Toe Behavior: Results of an Observational Pilot Study. *Children, 9*(9), 1336. https://doi.org/10.3390/children9091336

Valagussa, G., Trentin, L., Balatti, V., & Grossi, E. (2017). Assessment of presentation patterns, clinical severity, and sensorial mechanism of tip-toe behavior in severe ASD subjects with intellectual disability: A cohort observational study. *Autism Research, 10*(9), 1547–1557. https://doi.org/10.1002/aur.1796

van Kuijk, A. A., Kosters, R., Vugts, M., & Geurts, A. C. (2014). Treatment for idiopathic toe walking: a systematic review of the literature. *Journal of Rehabilitation Medicine, 46*(10), 945–957. https://doi.org/10.2340/16501977-1881

Veerkamp, K., van der Krogt, M. M., Waterval, N. F., Geijtenbeek, T., Walsh, H. J., Harlaar, J., … Carty, C. P. (2024). Predictive simulations identify potential neuromuscular contributors to idiopathic toe walking. *Clinical Biomechanics, 111*, Article 106152. https://doi.org/10.1016/j.clinbiomech.2023.106152

Walle, E. A., & Campos, J. J. (2014). Infant language development is related to the acquisition of walking. *Developmental Psychology, 50*(2), 336–348. https://doi.org/10.1037/a0033238

Williams, C. M., Tinley, P., Curtin, M., Wakefield, S., & Nielsen, S. (2014). Is idiopathic toe walking really idiopathic? The motor skills and sensory processing abilities associated with idiopathic toe walking gait. *Journal of Child Neurology, 29*(1), 71–78. https://doi.org/10.1177/0883073812470001

Yerys, B. E., Antezana, L., Weinblatt, R., Jankowski, K. F., Strang, J., Vaidya, C. J., … Kenworthy, L. (2015). Neural correlates of set-shifting in children with autism. *Autism Research, 8*(4), 386–397. https://doi.org/10.1002/aur.1454

Zeileis, A. (2006). Object-oriented Computation of Sandwich Estimators. *Journal of Statistical Software, 16*(9), 1–16. https://doi.org/10.18637/jss.v016.i09

Zhang, F., Savadjiev, P., Cai, W., Song, Y., Rathi, Y., Tunç, B., & O'Donnell, L. J. (2018). Whole brain white matter connectivity analysis using machine learning: An application to autism. *Neuroimage, 172*, 826–837. https://doi.org/10.1016/j.neuroimage.2017.10.029