HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Autism Res. 2017 May ; 10(5): 757–768. doi:10.1002/aur.1739.

Infant Muscle Tone and Childhood Autistic Traits:

A Longitudinal Study in the General Population

Fadila Serdarevic, MD, DSc[1,2], **Akhgar Ghassabian, MD, PhD**[2,3], **Tamara van Batenburg-Eddes, PhD**[1,2], **Tonya White, MD, PhD**[1,2,4], **Laura M.E. Blanken, MD, PhD**[1,2], **Vincent W.V. Jaddoe, MD, PhD**[1,5,6], **Frank C. Verhulst, MD, PhD**[2], and **Henning Tiemeier, MD, PhD**[2,5,7]

[1]The Generation R Study Group, Erasmus Medical Centre Rotterdam, the Netherlands [2]Department of Child and Adolescent Psychiatry, Erasmus Medical Centre-Sophia Children's Hospital Rotterdam, the Netherlands [3]Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA [4]Department of Radiology, Erasmus Medical Centre Rotterdam, the Netherlands [5]Department of Epidemiology, Erasmus Medical Centre Rotterdam, the Netherlands [6]Department of Pediatrics, Erasmus Medical Centre-Sophia Children's Hospital Rotterdam, the Netherlands [7]Department of Psychiatry, Erasmus Medical Centre, Rotterdam, the Netherlands

Abstract

Objective—In a longitudinal population-based study of 2905 children, we investigated if infants' neuromotor development was associated with autistic traits in childhood.

Methods—Overall motor development and muscle tone were examined by trained research assistants with an adapted version of Touwen's Neurodevelopmental Examination between ages 2–5 months. Tone was assessed in several positions and items were scored as normal, low or high tone. Parents rated their children's autistic traits with the Social Responsiveness Scale (SRS) and the Pervasive Developmental Problems (PDP) subscale of the Child Behavior Checklist at 6 years. We defined clinical PDP if scores were >98th percentile of the norm population. Diagnosis of autism spectrum disorder (ASD) was clinically confirmed in 30 children.

Results—We observed a modest association between overall neuromotor development in infants and autistic traits. Low muscle tone in infancy predicted autistic traits measured by SRS (adjusted beta=0.05, 95% CI for B: 0.00–0.02, p=0.01), and PDP (adjusted beta=0.08, 95% CI for B: 0.04–0.10, p<0.001). Similar results emerged for the association of low muscle tone and clinical PDP (adjusted OR=1.36, 95% CI: 1.08–1.72, p=0.01) at age 6 years. Results remained unchanged if adjusted for child intelligence. There was no association between high muscle tone and SRS or PDP. Exclusion of children with ASD diagnosis did not change the association.

Correspondence to: Henning Tiemeier, MD, PhD, Department of Child and Adolescent Psychiatry, Erasmus Medical Centre-Sophia Children's Hospital Rotterdam, the Netherlands; P.O. Box 2060, 3000 CB Rotterdam, the Netherlands; Tel: 010-7043447; h.tiemeier@erasmusmc.nl.

Conflict of Interests: For the other authors, no competing financial interest exists.

Conclusion—This large study showed a prospective association of infant muscle tone with autistic traits in childhood. Our findings suggest that early detection of low muscle tone might be a gateway to improve early diagnosis of ASD.

Lay Abstract

There is a growing awareness of the developmental importance of motor function and, in particular, muscle tone in children with autism spectrum disorder (ASD). In a longitudinal study of 2905 children, we investigated if infants' neuromotor development was associated with autistic traits in the general population. Overall motor development and muscle tone were examined by trained research assistants with an adapted version of Touwen's Neurodevelopmental Examination between ages 9–20 weeks. Tone items were scored as normal, low or high tone. Parents rated their children's autistic traits with using two validated questionnaires: Social Responsiveness Scale (SRS) and the Pervasive Developmental Problems (PDP) at 6 years. ASD diagnosis was clinically confirmed in 30 children. We observed a modest association between overall neuromotor development in infants and autistic traits. Low muscle tone in infancy predicted autistic traits. This association was not affected by a child's intelligence. We observed no association between high muscle tone and autistic traits. After exclusion of children with ASD diagnosis, the association remained unchanged. This large study showed a prospective association of infant muscle tone with autistic traits in childhood. Our findings suggest that early detection of low muscle tone might be a gateway to improve early diagnosis of ASD.

Keywords

infant muscle tone; autistic traits; autism spectrum disorder; prospective

Autism spectrum disorder (ASD) is a developmental disorder characterized by persistent impairments in social communication and interaction, and repetitive stereotyped behaviors that manifest in early childhood (American Psychiatric Association, 2013). Subclinical deficits in social communication or some degree of repetitive behaviors that do not meet the diagnostic criteria for ASD are defined as autistic traits and exist in the general population (Constantino & Todd, 2003).

Neuromotor function during infancy is an important early indicator of central nervous system development. Numerous studies in clinical or high-risk populations have demonstrated a close relationship between neuromotor development and ASD (Bhat, Galloway, & Landa, 2012; Brian et al., 2008; Flanagan, Landa, Bhat, & Bauman, 2012; LeBarton & Iverson, 2013; Lloyd, MacDonald, & Lord, 2013). For example, Landa, Gross, Stuart, and Faherty (2013) reported a worsening of fine motor performance over the first 3 years of life in infants later diagnosed with ASD. Bhat, Landa, and Galloway (2011) proposed that early motor delays within the first two years of life may contribute to the social impairments of children with ASD.

As individuals with ASD are at the high end of the distribution of autistic traits (Constantino, 2011), infant neuromotor development may also be associated with autistic traits in children from the general population. In a population-based cohort, Bolton, Golding, Emond, and Steer (2012) showed that maternal report of fine motor delays at 6 months

predicted later diagnoses of ASD, as well as autistic traits. Such motor milestones, which are typically assessed retrospectively based on caregivers report, cannot be measured reliably before age of 6 months.

Several studies reported problems with muscle tone in children with ASD. Adrien et al. (1993) rated family home movies of 12 infants who were later diagnosed as autistic and 12 typically developing infants. They observed a high prevalence of low muscle tone in children with autistic traits. Ming, Brimacombe, and Wagner (2007) investigated a cohort of children with ASD using retrospective clinical record review and found a higher prevalence of gross and fine motor impairment among 2–6 year old children with ASD. The children typically had mild to moderate hypotonia early in life.

It remains unknown if differences in infant neuromotor development, and in particular muscle tone, as early as 2–5 months may serve as a prodromal sign of autistic traits. Such information can facilitate early detection of children at risk for ASD and potentially allow for early intervention. The purpose of the current study was to explore whether variations in infant neuromotor development are associated with childhood autistic traits in the general population. We hypothesized that non-optimal neuromotor development, and in particular muscle tone, in infants are related to autistic traits in childhood.

We applied two parental rating scales to study autistic traits in childhood: the Social Responsiveness Scale (SRS) and the Pervasive Developmental Problems (PDP) scale of the Child Behavior Checklist for toddlers (CBCL/1½–5). The use of parental reports on children's social behavior provides an informative mean of examining autistic traits, as parents are familiar with everyday behavior of their children. Parental reports provide the contextual information with high ecological validity. We also obtained information on ASD diagnosis, if available.

Method

This study was conducted within the Generation R Study, a population-based cohort that follows children from fetal life onwards (Jaddoe et al., 2012; Tiemeier H, 2012). Briefly, mothers were eligible if they were living in the Rotterdam area, the Netherlands, and had a delivery date between April 2002 and January 2006. When infants were 2–5months old, their neuromotor development was assessed during a home visit by trained research assistants. Neuromotor assessment was completed in 4055 infants. These 4055 children were the eligible participants for this follow-up study. When the children were 6 years old, questionnaires were mailed to caregivers in order to assess autistic traits in the children. Information on autistic traits was available in 2905 children (72 % of 4055). The Medical Ethics Committee of the Erasmus Medical Centre approved the study and written informed consent was obtained from all adult participants.

Neuromotor and Muscle Tone Assessment

Neuromotor assessment is an accepted means of measuring the maturity and intactness of an infant's central nervous system. Its relevance is demonstrated by the fact that impaired development of the central nervous system in the first year of life is expressed mainly in

neuromotor delay (Prechtl, 1977; Touwen, 1976). Depending on the instrument neuromotor developmental measures assess muscle tone and primitive reflexes or emphases behavior and coping with environmental stimuli.

Infants underwent a neuromotor assessment at a corrected postnatal age between 9 and 20 weeks. Two versions of neuromotor assessment instrument were used: One for infants aged 9–15 weeks and the other for infants aged 15–20 weeks. We selected age-appropriate items from Touwen's Neurodevelopmental Examination, and categorized items in three groups: tone, responses, and other observations (de Groot, Hopkins, & Touwen, 1992) (Table 1). Muscle tone is the degree of passive resistance to movement (Foster, 1895). Tone was assessed in several positions –supine, horizontal, vertical, prone and sitting– and all items, such as adductor angle, were scored as normal, low or high tone. Responses were assessed in supine (e.g. asymmetrical tonic neck reflex), vertical (e.g. Moro response) or prone position (e.g. Bauer response) and were scored as present, absent or excessive. Other observations, such as following movements, were scored as present, absent or excessive. Assessment of overall neuromotor development and tone was used in this analysis. For each item, an age-appropriate response was labelled 'optimal'. If the response indicated a delayed development, it was labelled 'non-optimal'. By summing the raw values of all items, we obtained a total score, with high values indicating less optimal neuromotor development.

Research assistants were trained by a movement scientist who also was a child physiotherapist specialized in child motor development. Training consisted of a lecture about the theory of neuromotor development. Furthermore, the neuromotor assessment and the practical procedure and protocol were explained in detail. Next, research assistants carried out hands-on assessment during home visits while accompanied by a trained assistant until assessments were carried out properly. During the whole data collection period, there were schooling meetings on a regular basis. The aim of these meetings was to refresh knowledge about neuromotor assessment and discuss special cases encounter during the home visits. Research assistants were blinded of previous results. To investigate inter-observer reliability, two research assistants independently conducted a neuromotor assessment in a sample of 76 children. The intra-class correlation coefficient (ICC) was 0.64. Moreover, we performed a reliability study to test the short-interval test-retest interobserver reliability and the interobserver reliability. The short-interval test-retest interobserver reliability test (n=61) consisted of a first assessment by a research assistant, followed within one week by a second assessment by another research assistant. For the interobserver reliability test (n=76), two research assistants together went on a home visit in which they independently conducted two consecutive neuromotor assessments in the same child. The ICC's for the short-interval test-retest reliability and the interobserver reliability were .52 and .64, respectively. The ICC's for the reliability of the neuromotor assessment were in the 'modest' (.41–.60) to 'substantial' (.61–.80) range (Cohen, 1968), and in line with a study (Peters, Maathuis, Kouw, Hamming, & Hadders-Algra, 2008) who reported a moderate to good reliability of a modified Touwen examination. However, it is difficult to compare these values with a criterion as the ICC is influenced by features of the data, such as its variability (the ICC will be greater if the observations are more variable).

Over a period of approximately three years (children were born between April 2002 and January 2006) neuromotor assessments were performed by in total 15 trained research assistants. Six of them participated in the reliability study. Furthermore, the trained research assistants were blinded for gestational age of the infants.

Child Autistic Traits

Social Responsiveness Scale (SRS)—Due to length of the original questionnaire, and the need to minimize subject burden, we used a short-form SRS with 18 items for assessment of autistic traits based on parent's observation of the child's social behavior in a naturalistic setting. Each item is rated from '0' (never true) to 3 (almost always true), covering social, language, and repetitive behaviors; higher scores indicate more problems (Constantino & Todd, 2003; Roman et al., 2013). In a sample of 3857 children aged 4–18 years (part of the Social Spectrum Study, a multi-center study on social development of children referred to a mental health care institution in the South-West of the Netherlands from 2010–2012) the correlation between total scores derived from the SRS short-form (18 items) and the SRS scores derived from the complete instrument was r=0.95 ($p<0.001$). The correlation between SRS short-form and SRS total scores in Missouri Twin Study was 0.93 in monozygotic male twins (n=98) and 0.94 in dizygotic male twins (n=134).

Pervasive Developmental Problems (PDP) subscale of the CBCL/1½–5—The CBCL/1½–5 is a validated instrument to measure behavioral and emotional problems of children at young age. The Dutch version is reliable and well-validated (Tick, van der Ende, Koot, & Verhulst, 2007). The PDP is one of the five scales that can be derived from the CBCL/1½–5, consistent with the Diagnostic and Statistical Manual of Mental Disorders 4th edition diagnostic categories. The PDP has been shown to be a useful screening instrument to identify children with ASD when compared with Autism Diagnostic Observation Schedule-Generic (Sikora, Hall, Hartley, Gerrard-Morris, & Cagle, 2008). It has a good predictive validity to identify preschoolers at risk of ASD (sensitivity=0.85. specificity=0.90) (Muratori et al., 2011). At 6 years, the correlation coefficient between the PDP and SRS scores was r=0.6 ($p<0.001$, n=2275).

ASD diagnoses—Only diagnoses made by a specialist as part of the regular clinical care were used. These diagnoses were retrieved from general practitioners; in the Dutch health care system, all specialists are obliged to inform the general practitioner as the primary health care provider, who holds the central medical records. To the aim of checking general practitioners' records, we selected those children for which one of three sources of information signaled possible ASD. First, children who screened positive on the Social Communication Questionnaire (SCQ), a 40-item parent-reported screening instrument for ASD. All children who scored in the top 15th percentile on the CBCL/1½–5 total score or those in the top 2nd percentile on the PDP subscale were screened with this instrument (Berument, Rutter, Lord, Pickles, & Bailey, 1999). Second, we retrieved medical records from the general practitioners of all children who had weighted scores over 1.078 for boys and 1.000 for girls on the SRS-short form (Constantino, 2002). Third we retrieved medical records in all children of whom the mother at any contact moment up to age 8 years had reported that the child had undergone a diagnostic procedure for possible ASD. Only

children for whom a diagnosis of ASD could be confirmed by specialist medical records were considered ASD cases in the analyses. The specialist diagnoses of ASD were generally based on clinical consensus by a multidisciplinary team. The standard diagnostic work-up involves an extensive developmental case history obtained from parents, as well as school information, and repeated observations of the child.

Covariates

Characteristics such as maternal age, household income, child ethnicity, maternal educational level, as well as maternal lifestyle, were assessed by questionnaires. The child's national origin was defined based on the national origin of parents and grandparents. Dutch ethnicity was used as the reference group. The education level of the mother was assessed by the highest completed education and reclassified into 3 categories: "low" (less than 3 years of secondary school), "mid" (at most intermediate vocational training), and "high" (at least college education). Household income, defined as the total net monthly income of the household, was categorized into <1200 Euros (below social security level), 1200–2200 Euros (low income), and >2200 Euros (modal income and above). We used the Brief Symptom Inventory, a validated self-report questionnaire, to measure maternal psychopathology during pregnancy (De Beurs, 2004). Child nonverbal IQ was assessed during the child's visit to the research center at the age of 6, using two subtests of the validated Dutch test battery Snijders-Oomen Niet-verbale intelligentietest-Revisie (Tellegen, Winkel, Wijnberg-Williams, & Laros, 2005). These subtests were Mosaics (assesses spatial visualization abilities), and categories (accesses abstract reasoning abilities). Raw non-verbal IQ scores were standardized using age-defined norms. In our previous study, we showed that infant neuromotor development is not associated with verbal expressive language ability and therefore we did not include this variable as a covariate in the analysis (Serdarevic et al., 2015).

Information about birth weight and gestational age at birth as well as complications during pregnancy or delivery were obtained from the medical records and midwives' practices. Gestational age was determined by fetal ultrasound examination. Postnatal age was calculated as the difference between date of assessment and date of birth.

Statistical Analyses

Participants' characteristics are presented in Table 2. In this cohort (n=2905), 48.8% children were male and 54.5% had Dutch ethnic background; 55.0% mothers completed higher education and 79.3% families had a monthly income >2000 Euros. Neuromotor development was assessed at an average age of 12.6 weeks (SD=2) postnatally.

We included children with an assessment of neuromotor development between 2 to 5 months and at least one autistic trait measure in the analyses (n=2905). Missing values on covariates and autistic traits were imputed using multiple imputations. Five copies of the original data set were generated. Standardized effect sizes were calculated as the average effect size of five imputed data sets.

Infant's overall neuromotor development and muscle tone were determinants in all analyses. The neuromotor assessment scores were highly skewed in this non-clinical population.

Therefore, we categorized the sum scores into tertiles in line with a prior study (van Batenburg-Eddes et al., 2013). The lowest tertile represents the most optimal neuromotor development and the highest the least optimal neuromotor development. These tertiles were analyzed continuously, as well as categorically. The associations of neuromotor development and muscle tone with autistic traits were assessed with linear regression. Both outcome measures, i.e. SRS and PDP, had a skewed distribution, and were therefore transformed using a logarithm function. We also categorized PDP scores in order to facilitate the clinical interpretation of the findings. For this purpose, the 98th (clinical) percentile of a Dutch norm group was used as a cut-off score to classify children with behavioral problems within the clinical range of the PDP (Tick et al., 2007). We explored the associations of neuromotor development and muscle tone with clinical PDP using logistic regression.

To assess whether our results were driven by children in the clinical end of the spectrum, we conducted a sensitivity analysis excluding children with a confirmed diagnosis of ASD. We also explored the associations with confirmed diagnosis of ASD using logistic regression.

Selection of covariates was based on prior literature. Final models were adjusted for the child's age, gender, gestational age at birth, Apgar score at 5 minutes, child ethnicity, child IQ, household income, age-appropriate version of motor instrument, maternal age, maternal education, and maternal psychopathology during pregnancy.

Attrition Analysis—We compared child and maternal characteristics of the children included in the analysis (n=2905) with those excluded because of missing data on outcome (n=1190). Children of responding mothers were more likely to have higher IQ (mean 103.1) compared to children of nonresponding mothers (mean 96.4). They were also more likely to be Dutch (61.2% vs 34.0%, p<0.001) compared to children of nonresponding mothers. Responding mothers also had less severe psychopathology symptoms (mean 0.24) compared with nonresponding mothers (mean 0.37). However, children included scored similarly on muscle tone compared to children not included (score: 1.92 vs 1.96, p=0.54).

Results

Associations of neuromotor development and muscle tone with autistic traits measured continuously by the SRS are presented in Table 3. Overall neuromotor development and autistic traits were significantly associated in the unadjusted model (beta=0.06, 95% CI: 0.01, 0.02, p=0.001). Adjustment for maternal education, age and psychopathology attenuated the association (adjusted beta=0.04, 95% CI: 0.00, 0.02, p=0.05). Muscle tone in infants predicted autistic traits in children measured by the SRS (adjusted beta=0.05, 95%CI: 0.00, 0.02, p=0.016). This association remained significant for low muscle tone and SRS after adjustment for all confounders (adjusted beta=0.05, 95%CI: 0.00, 0.02, p=0.006), while there was no association between high muscle tone and SRS in unadjusted and adjusted analyses (adjusted beta=0.03, 95%CI:−0.004, 0.02, p=0.23).

The association between neuromotor development and autistic traits measured by PDP scores is presented in Table 4. We found an association between overall muscle tone and PDP scores in children. Less optimal muscle tone was significantly associated with PDP

scores (adjusted beta=0.05, 95%CI: 0.02, 0.09, p=0.010). Low muscle tone predicted PDP scores (adjusted beta=0.08, 95%CI: 0.04, 0.10, p<0.001), with the third tertile being strongly associated with outcome (adjusted beta=0.09, 95%CI: 0.08, 0.21, p<0.001), whereas the second tertile was not (adjusted beta=0.03, 95% CI:−0.04, 0.13, p=0.29). Results adjusted for child IQ remained essentially unchanged (Table 4). The SRS and PDP in 3 categories of low muscle tone are presented in Figures 1 and 2.

In an additional analysis, we present the association between neuromotor development and the dichotomized PDP scale using the clinical cut off. Consistent with the above results, the odds of having PDP scores in the clinical range was associated with low muscle tone in infancy (adjusted OR=1.36, 95%CI: 1.08, 1.72, p=0.01) (Table 5). Children with low muscle tone in the highest tertile had higher odds of PDP in the clinical range compared to other children. Other results were not significant.

To assess whether results were driven by children with ASD, we repeated the analyses excluding children with a confirmed diagnosis of ASD (n=30, 0.9%). This exclusion did not materially change the results (adjusted beta of the second tertile of low muscle tone=0.02, 95%CI: −0.01, 0.03, p=0.25, adjusted beta of the third tertile of low muscle tone=0.05, 95%CI: 0.00, 0.04, p =0.01).

Next, we tested the association between low muscle tone and a confirmed diagnosis of ASD. We observed that a non-optimal low muscle tone increased the odds of ASD (adjusted OR for the second tertile=1.99, 95%CI: 0.69, 5.70, p=0.20, adjusted OR for the third tertile=1.44, 95%CI: 0.54, 3.83, p=0.46), although results did not reach significance due to small number of confirmed ASD cases. In the sample of 30 children with ASD the description of the median of the SRS and PDP scores in 3 categories of low muscle tone is presented graphically (Figures 3 and 4).

Discussion

In this population-based study, we investigated whether infant neuromotor development is associated with autistic traits. Our study showed a modest association between overall neuromotor delay early in life and autistic traits in school age. In particular, low muscle tone in infants aged 2–5months was prospectively associated with autistic traits in 6 year-old children. High muscle tone during infancy did not predict autistic traits.

The majority of studies to date exploring early motor development of ASD children used case-control designs of clinically diagnosed patients with ASD (Brisson, Warreyn, Serres, Foussier, & Adrien-Louis, 2012; Papadopoulos et al., 2012). While these studies are very beneficial to help understanding of ASD, they cannot answer the question whether subtle variations in neurodevelopment precede autistic traits in the general population. In the past, videos and child care registries have been used to overcome such limitations in developmental studies of autism (Yirmiya & Charman, 2010). Also, registry studies using routine assessment of motor milestones have yielded important findings in psychopathology research, but they have several limitations, e.g. a restricted number of confounders that can be addressed and the lack of precision of results in small samples (Rosso et al., 2000; Susser

& Bresnahan, 2002). The studies assessing motor functioning in large numbers of participants relied on age of motor milestone achievement as reported by parents, whereas full neurological examinations to assess neuromotor development as a precursor of psychopathology at a later age were often conducted in small or clinical samples only (Ming et al., 2007).

Several large studies measured fine motor skills from the age of 6 months onwards in the general population or in children at high-risk for ASD (Bolton et al., 2012; Landa, Gross, Stuart, & Bauman, 2012; Landa et al., 2013). Some studies on children at high risk for autism reported differences in gross motor skills (Bhat et al., 2012), other studies observed that high risk children had delays in fine moto and grasping skills (Libertus, Sheperd, Ross, & Landa, 2014) On the other hand, Ozonoff et al. (2008) found motor abnormalities in children with developmental delays, but not ASD-specific movement abnormalities in children who later developed ASD. Importantly, the authors recommended motor screening for the detection of developmental delays in general pediatric settings. One potential explanation for these inconsistent findings is that high-risk children from multiplex families may have different risk profiles than children from the general population (Barbaro & Dissanayake, 2012; Hobbs et al., 2007; Kleinman et al., 2008). Our results are in line with studies suggesting that motor coordination deficits are pervasive across ASD subtypes and a potential core feature of ASD (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010).

Motor delays in early movement behavior are commonly reported in children with ASD, but little is known about the prospective association between early muscle tone development and autistic traits at later age (Ming et al., 2007; Rutter, Kim-Cohen, & Maughan, 2006). Our research extends the findings of two small prior studies focusing on muscle tone in children with ASD. Ming et al. (2007) found a higher prevalence of motor impairment in 2–6 year old children with ASD based on retrospective record reviews. The degree of hypotonia was mild to moderate and observed throughout the body. In a sample of 398 twin pairs (aged 8–17 years) from an Italian twin registry, Moruzzi, Ogliari, Ronald, Happe, and Battaglia (2011) showed a genetic overlap between low muscle tone and autistic traits. They hypothesized that the genes with effects in brain regions underlying autistic behaviors also affect motor development, arguing that low muscle tone might be an early, preclinical marker of autism. Alternatively, neuromotor delay in infancy could result in a developmental cascade that subsequently leads to the development of social communication problems in the child and diagnosis of autism. In other words, infants with low muscle tone may have delays in important milestones e.g., sitting, which in turns reduces opportunities for face-to-face exchanges, joint-attention, and language learning during the first year. Two studies on typically developing children reported association between onset of the independent walking and language development in 10–14 months infants (Walle & Campos, 2014). In addition, a recent longitudinal study showed a prospective association between early motor skills, in particular sitting at age 3–5 months and later receptive language development (He, Walle, & Campos, 2015; Libertus & Violi, 2016). Also a study of high risk children showed that fine motor skills in infancy might be a useful predictor of expressive language development, which is important for communicative and social development (LeBarton & Iverson, 2013). Even if hypotonicity is not necessarily autism-specific, hypotonia may be important to recognize and evaluate in children who are at risk for autism (Bhat et al., 2011). The authors

recommended measures of clumsiness as an endophenotype of disease. Some of the most consistently reported structural brain abnormalities in ASD occur within regions of the brain involved in movement, including the frontal lobe and cerebellum (Mostofsky et al., 2009). However, there are other possible explanations. For example, teratogens, like diseases or nutrition and maternal stress, could cause brain abnormalities associated with hypotonia or autistic traits during prenatal development. Alternatively, postnatal influences could underlie both poor motor development and autistic traits.

In this study, we controlled for numerous external factors in our study, e.g. gestational age or Apgar score. Importantly, we included child nonverbal IQ in our analysis and our results remained largely unaltered, which is consistent with our previous work showing no association between motor development and IQ (Serdarevic et al., 2015). Similarly, Bolte, Poustka, and Constantino (2008) showed low correlation between IQ and social responsiveness scale in children with ASD. It is possible that there is substantial degree of genetic independence between IQ and autistic symptoms (Hoekstra, Bartels, Verweij, & Boomsma, 2007) in the general population, although autistic symptoms closely co-occur with low IQ in clinical population.

Strengths and Limitations

Our study has several strengths, including the longitudinal design and large sample size recruited from the general population. The prospective nature of the study ensured that infant neuromotor development measurements were assessed blind to the eventual later autistic traits. Research nurses assessed neuromotor development using a hands-on test battery, independently of mothers, eliminating common method bias, which can affect motor mile stone research based on parent report (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Also, we were able to adjust for large number of prenatal and postnatal covariates.

The present study also has limitations. Although clinical assessment of ASD was available, no standardized formal evaluation with the Autism Diagnostic Observation Schedule, which is considered the gold standard, was performed. Selection effects were observed in our non-response analysis. The non-response may reduce the generalizability but is less likely to bias the associations between variables (Wolke et al., 2009). Some studies have shown that social or communicative therapy can influence ASD outcome; this could have slightly reduced the observed effect (MacDonald, Lord, & Ulrich, 2013; Sutera et al., 2007). Also, we do not know if any of children in our study received an intervention for neuromotor delays, but this is unlikely, as most children with subclinical traits receive no treatment. This study examined neuromotor development and autistic traits in a large sample of children from the general population. The clinical implications of the effects with modest sizes should be considered with caution.

Conclusion

Low muscle tone in infancy predicted autistic traits at age 6 years. High muscle tone was not associated with autistic traits. To the best of our knowledge, this is the first longitudinal population-based study that shows the long-term association of very early low infant muscle tone development with autistic traits in childhood. The earliest observable traits of ASD

involve motor behaviour. There is a growing awareness of the developmental importance of impaired motor function in ASD and its association with social skill. This study suggests that muscle tone as part of the motor system development might be a gateway to improving early detection of ASD. Motor problems, in particular low muscle tone in early infancy as an early symptom or precursor of autistic traits requires increased attention.

Acknowledgments

The general design of the Generation R Study is supported by the Erasmus Medical Center-Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw “Geestkracht’ programme 10.000.1003), the Netherlands Organization for Scientific Research, and the Ministry of Health, Welfare and Sport. The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond. Dr. A. Ghassabian was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). This study received support from the Simons Foundation Autism Research Initiative (SFARI - 307280) to Tonya White, MD, PhD, and ZonMw TOP grant number 91211021. The financial supporters did not influence the results of this article. The funders had no role in the study design, data collection, analysis, interpretation of the data, or writing of the report.

Dr. Frank C. Verhulst is the contributing editor of the Achenbach System of Empirically Based Assessment, from which he receives remuneration.

Abbreviations

ASD	Autism Spectrum Disorder
SRS	Social Responsiveness Scale
CBCL/1½–5	Child Behavior Checklist for toddlers
PDP	Pervasive Developmental Problems
SCQ	Social Communication Questionnaire

References

Adrien JL, Lenoir P, Martineau J, Perrot A, Hameury L, Larmande C, Sauvage D. Blind ratings of early symptoms of autism based upon family home movies. Journal of the American Academy of Child and Adolescent Psychiatry. 1993; 32(3):617–626. [PubMed: 7684363]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.; 2013.

Barbaro J, Dissanayake C. Developmental profiles of infants and toddlers with autism spectrum disorders identified prospectively in a community-based setting. Journal of Autism and Developmental Disorders. 2012; 42(9):1939–1948. [PubMed: 22310906]

Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. British Journal of Psychiatry. 1999; 175:444–451. [PubMed: 10789276]

Bhat AN, Galloway JC, Landa RJ. Relation between early motor delay and later communication delay in infants at risk for autism. Infant Behavior & Development. 2012; 35(4):838–846. doi: S0163-6383(12)00096-3 [pii] 10.1016/j.infbeh.2012.07.019. [PubMed: 22982285]

Bhat AN, Landa RJ, Galloway JC. Current perspectives on motor functioning in infants, children, and adults with autism spectrum disorders. Physical Therapy. 2011; 91(7):1116–1129. doi: ptj.20100294 [pii] 10.2522/ptj.20100294. [PubMed: 21546566]

Bolte S, Poustka F, Constantino JN. Assessing autistic traits: cross-cultural validation of the Social Responsiveness Scale (SRS). Autism Research. 2008; 1(6):354–363. [PubMed: 19360690]

Bolton PF, Golding J, Emond A, Steer CD. Autism spectrum disorder and autistic traits in the Avon Longitudinal Study of Parents and Children: precursors and early signs. Journal of the American Academy of Child and Adolescent Psychiatry. 2012; 51(3):249–260. e225. doi: S0890-8567(11)01143-9 [pii] 10.1016/j.jaac.2011.12.009. [PubMed: 22365461]

Brian J, Bryson SE, Garon N, Roberts W, Smith IM, Szatmari P, Zwaigenbaum L. Clinical assessment of autism in high-risk 18-month-olds. Autism. 2008; 12(5):433–456. [PubMed: 18805941]

Brisson J, Warreyn P, Serres J, Foussier S, Adrien-Louis J. Motor anticipation failure in infants with autism: a retrospective analysis of feeding situations. Autism. 2012; 16(4):420–429. [PubMed: 22250193]

Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychological Bulletin. 1968; 70(4):213–220. [PubMed: 19673146]

Constantino, JN. Social Responsiveness Scale (SRS), Manual. Los Angeles: Western Psychological services; 2002.

Constantino JN. The quantitative nature of autistic social impairment. Pediatric Research. 2011; 69(69(5 Pt 2)):55R–62R.

Constantino JN, Todd RD. Autistic traits in the general population: a twin study. Archives of General Psychiatry. 2003; 60(5):524–530. [PubMed: 12742874]

De Beurs, E. Brief Symptom Inventory, handleiding. the Netherlands: Leiden; 2004.

de Groot L, Hopkins B, Touwen BC. A method to assess the development of muscle power in preterms after term age. Neuropediatrics. 1992; 23(4):172–179. [PubMed: 1407383]

Flanagan JE, Landa R, Bhat A, Bauman M. Head lag in infants at risk for autism: a preliminary study. American Journal of Occupational Therapy. 2012; 66(5):577–585. [PubMed: 22917124]

Foster, M. A Text-book of Physiology. Lea Bros & Company; 1895.

Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. Motor coordination in autism spectrum disorders: a synthesis and meta-analysis. Journal of Autism and Developmental Disorders. 2010; 40(10):1227–1240. [PubMed: 20195737]

He M, Walle EA, Campos JJ. A cross-national investigation of the relationship between infant walking and language development. Infancy. 2015; 20(3):283–305.

Hobbs K, Kennedy A, DuBray M, Bigler ED, Petersen PB, McMahon W, Lainhart JE. A retrospective fetal ultrasound study of brain size in autism. Biological Psychiatry. 2007; 62(9):1048–1055. [PubMed: 17555719]

Hoekstra RA, Bartels M, Verweij CJH, Boomsma DI. Heritability of autistic traits in the general population. Archives of Pediatrics & Adolescent Medicine. 2007; 161(4):372–377. [PubMed: 17404134]

Jaddoe VW, van Duijn CM, Franco OH, van der Heijden AJ, van Iizendoorn MH, de Jongste JC, Hofman A. The Generation R Study: design and cohort update 2012. European Journal of Epidemiology. 2012; 27(9):739–756. [PubMed: 23086283]

Kleinman JM, Robins DL, Ventola PE, Pandey J, Boorstein HC, Esser EL, Fein D. The Modified Checklist for Autism in Toddlers: A follow-up study investigating the early detection of autism spectrum disorders. Journal of Autism and Developmental Disorders. 2008; 38(5):827–839. [PubMed: 17882539]

Landa R, Gross AL, Stuart EA, Bauman M. Latent class analysis of early developmental trajectory in baby siblings of children with autism. Journal of Child Psychology and Psychiatry. 2012; 53(9): 986–996. [PubMed: 22574686]

Landa R, Gross AL, Stuart EA, Faherty A. Developmental trajectories in children with and without autism spectrum disorders: the first 3 years. Child Development. 2013; 84(2):429–442. [PubMed: 23110514]

LeBarton ES, Iverson JM. Fine motor skill predicts expressive language in infant siblings of children with autism. Developmental Science. 2013; 16(6):815–827. [PubMed: 24118709]

Libertus K, Sheperd KA, Ross SW, Landa RJ. Limited fine motor and grasping skills in 6-month-old infants at high risk for autism. Child Development. 2014; 85(6):2218–2231. [PubMed: 24978128]

Libertus K, Violi DA. Sit to talk: relation between motor skills and language development in infancy. Frontiers in Psychology. 2016; 7:475. [PubMed: 27065934]

Lloyd M, MacDonald M, Lord C. Motor skills of toddlers with autism spectrum disorders. Autism. 2013; 17(2):133–146. doi: 1362361311402230 [pii] 10.1177/1362361311402230. [PubMed: 21610184]

MacDonald M, Lord C, Ulrich DA. The relationship of motor skills and social communicative skills in school-aged children with autism spectrum disorder. Adapted Physical Activity Quarterly. 2013; 30(3):271–282. [PubMed: 23860508]

Ming X, Brimacombe M, Wagner GC. Prevalence of motor impairment in autism spectrum disorders. Brain & Development. 2007; 29(9):565–570. [PubMed: 17467940]

Moruzzi S, Ogliari A, Ronald A, Happe F, Battaglia M. The nature of covariation between autistic traits and clumsiness: a twin study in a generalp sample. Journal of Autism and Developmental Disorders. 2011; 41(12):1665–1674. [PubMed: 21347613]

Mostofsky SH, Powell SK, Simmonds DJ, Goldberg MC, Caffo B, Pekar JJ. Decreased connectivity and cerebellar activity in autism during motor task performance. Brain. 2009; 132:2413–2425. [PubMed: 19389870]

Muratori F, Narzisi A, Tancredi R, Cosenza A, Calugi S, Saviozzi I, Calderoni S. The CBCL 1.5–5 and the identification of preschoolers with autism in Italy. Epidemiology and Psychiatric Sciences. 2011; 20(4):329–338. [PubMed: 22201210]

Ozonoff S, Young GS, Goldring S, Greiss-Hess L, Herrera AM, Steele J, Rogers SJ. Gross motor development, movement abnormalities, and early identification of autism. Journal of Autism and Developmental Disorders. 2008; 38(4):644–656. [PubMed: 17805956]

Papadopoulos N, McGinley J, Tonge B, Bradshaw J, Saunders K, Murphy A, Rinehart N. Motor proficiency and emotional/behavioural disturbance in autism and Asperger's disorder: another piece of the neurological puzzle? Autism. 2012; 16(6):627–640. [PubMed: 21949004]

Peters LH, Maathuis KG, Kouw E, Hamming M, Hadders-Algra M. Test-retest, inter-assessor and intra-assessor reliability of the modified Touwen examination. European Journal of Paediatric Neurology. 2008; 12(4):328–333. doi: S1090-3798(07)00164-X [pii] 10.1016/j.ejpn.2007.09.006. [PubMed: 17951085]

Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. Journal of Applied Psychology. 2003; 88(5):879–903. [PubMed: 14516251]

Prechtl, HF. The Neurological Examination of the Full-Term Newborn Infant: A Manual for Clinical Use from the Department of Developmental Neurology. Vol. 63. Cambridge University Press; 1977.

Roman GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Tiemeier H. Association of gestational maternal hypothyroxinemia and increased autism risk. Annals of Neurology. 2013; 74(5):733–742. [PubMed: 23943579]

Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T, Cannon TD. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophrenia Bulletin. 2000; 26(2):367–378. [PubMed: 10885637]

Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. Journal of Child Psychology and Psychiatry. 2006; 47(3–4):276–295. doi: JCPP1614 [pii] 10.1111/j.1469-7610.2006.01614.x. [PubMed: 16492260]

Serdarevic F, van Batenburg-Eddes T, Mouse SE, White T, Hofman A, Jaddoe VJW, Tiemeier H. Relation of infant motor development with nonverbal intelligence, language comprehension and neuropsychological functioning in childhood. a population-based study. Developmental Science. 2015 doi: DS-04-14-0133-P.R2.

Sikora DM, Hall TA, Hartley SL, Gerrard-Morris AE, Cagle S. Does parent report of behavior differ across ADOS-G classifications: Analysis of scores from the CBCL and GARS. Journal of Autism and Developmental Disorders. 2008; 38(3):440–448. [PubMed: 17619131]

Susser E, Bresnahan M. Epidemiologic approaches to neurodevelopmental disorders. Molecular Psychiatry. 2002; 7(Suppl 2):S2–S3. [PubMed: 12142930]

Sutera S, Pandey J, Esser EL, Rosenthal MA, Wilson LB, Barton M, Fein D. Predictors of optimal outcome in toddlers diagnosed with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2007; 37(1):98–107. [PubMed: 17206522]

Tellegen, PJ., Winkel, M., Wijnberg-Williams, B., Laros, JA. Snijders-Oomen Niet-Verbale Intelligentietest: SON-R 2 ½–7. Amsterdam: Boom Testuitgevers; 2005.

Tick NT, van der Ende J, Koot HM, Verhulst FC. 14-year changes in emotional and behavioral problems of very young Dutch children. Journal of the American Academy of Child and Adolescent Psychiatry. 2007; 46(10):1333–1340. [PubMed: 17885575]

Tiemeier H, V F, Szekely E, Roza SJ, Dieleman G, Jaddoe VW, Uitterlinden AG, White TJ, Bakermans-Kranenburg MJ, Hofman A, Van Ijzendoorn MH, Hudziak JJ, Verhulst FC. The Generation R Study: A review of design, findings to date, and a study of the 5-HTTLPR by environmental interaction from fetal life onward. Journal of American Academy of Child and Adolescent Psychiatry. 2012; 51(11):1119–1135.

Touwen B. Neurological development in infancy. 1976

van Batenburg-Eddes T, Henrichs J, Schenk JJ, Sincer I, de Groot L, Hofman A, Tiemeier H. Early Infant Neuromotor Assessment is Associated with Language and Nonverbal Cognitive Function in Toddlers: The Generation R Study. Journal of Developmental and Behavioral Pediatrics. 2013; 34(5):326–334. [PubMed: 23708382]

Walle EA, Campos JJ. Infant language development is related to the acquisition of walking. Developmental Psychology. 2014; 50(2):336–348. [PubMed: 23750505]

Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, Lamberts K. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. British Journal of Psychiatry. 2009; 195(3):249–256. doi: 195/3/249 [pii] 10.1192/bjp.bp.108.053751. [PubMed: 19721116]

Yirmiya N, Charman T. The prodrome of autism: early behavioral and biological signs, regression, peri- and post-natal development and genetics. Journal of Child Psychology and Psychiatry. 2010; 51(4):432–458. [PubMed: 20085609]

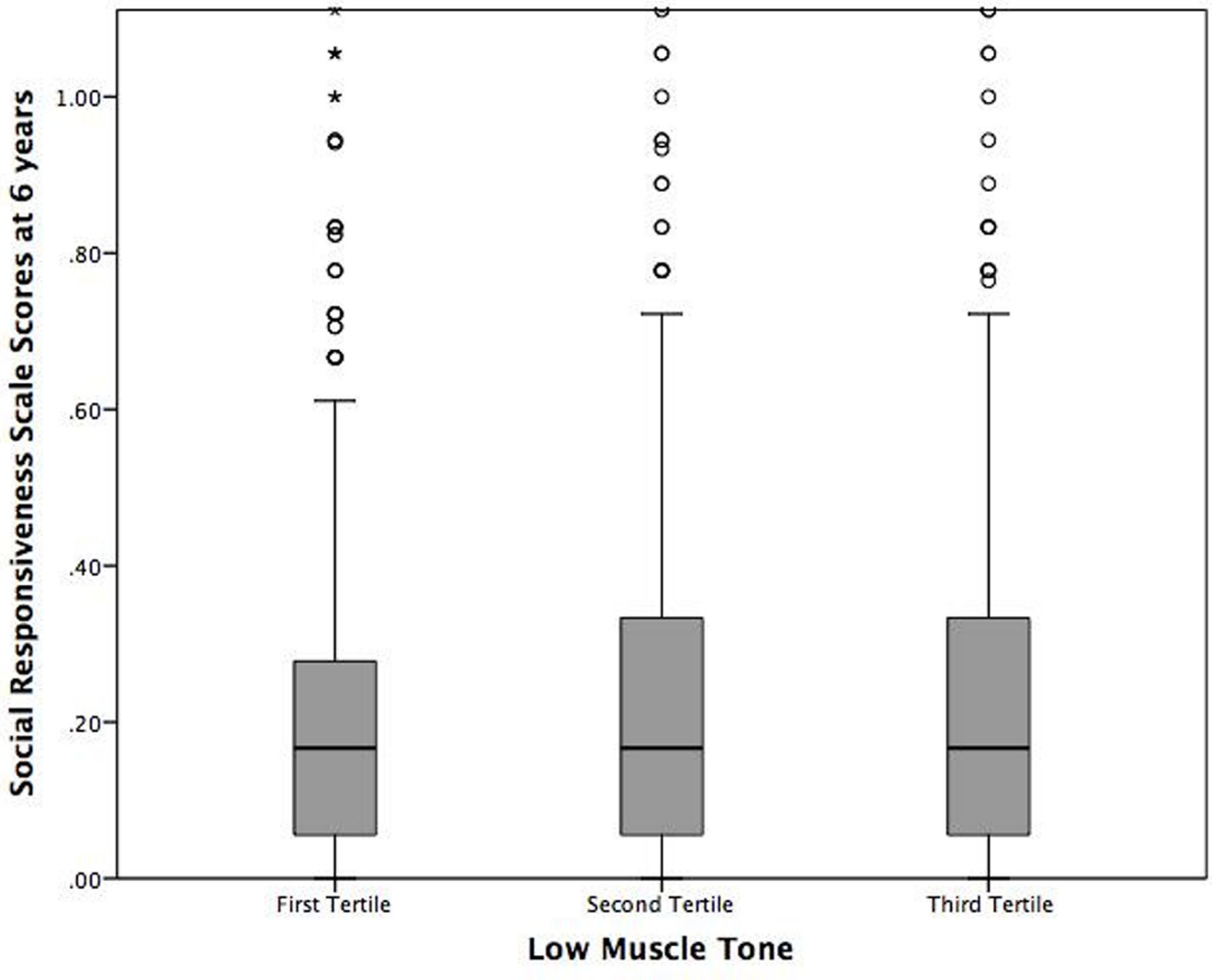

Figure 1.

Social Responsiveness Scale Scores in three categories of low muscle tone scores (n=2905). Low muscle tone was assessed Touwen's Neurodevelopmental Examination, with high values indicating less optimal neuromotor development.

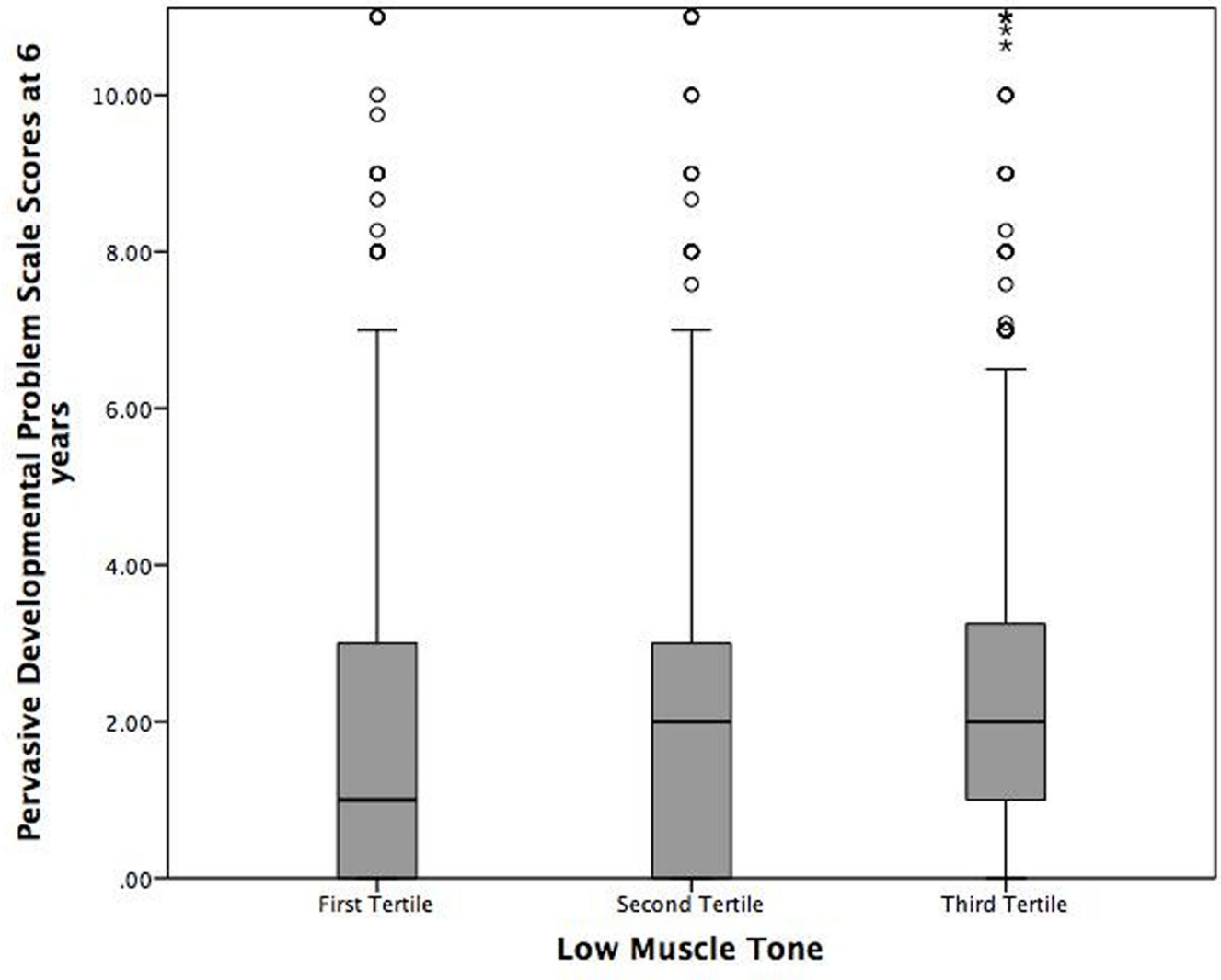

Figure 2.

Pervasive Developmental Problem Scale Scores in three categories of low muscle tone scores (n=2905)

Pervasive Development Problem Scores was assessed at age 6 years using the Child Behavior Checklist

Low muscle tone was assessed Touwen's Neurodevelopmental Examination, with high values indicating less optimal neuromotor development.

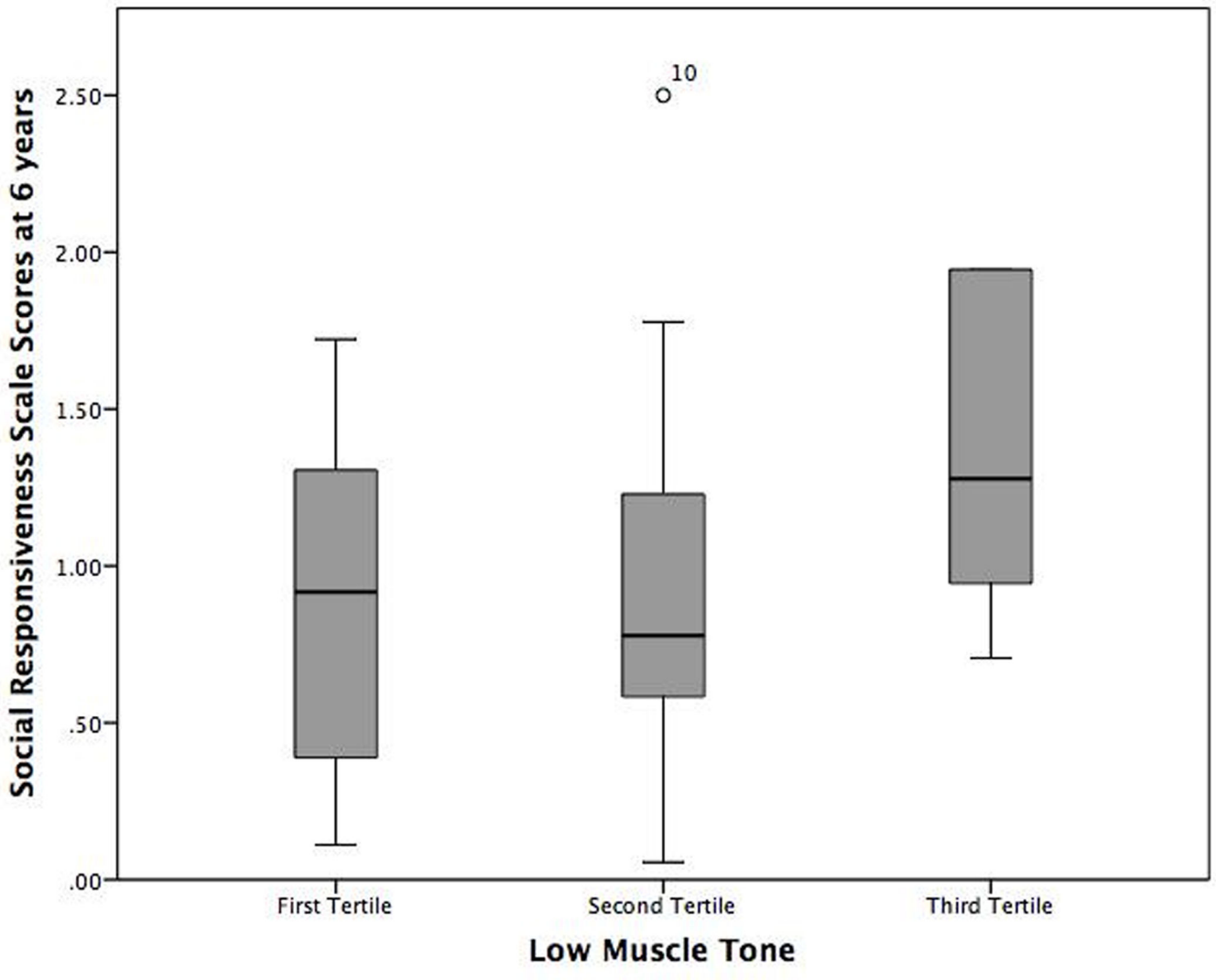

Figure 3.

Social Responsiveness Scale Scores in three categories of low muscle tone scores (in children with Autism Spectrum Disorders, n= 30).

Low muscle tone was assessed Touwen's Neurodevelopmental Examination, with high values indicating less optimal neuromotor development.

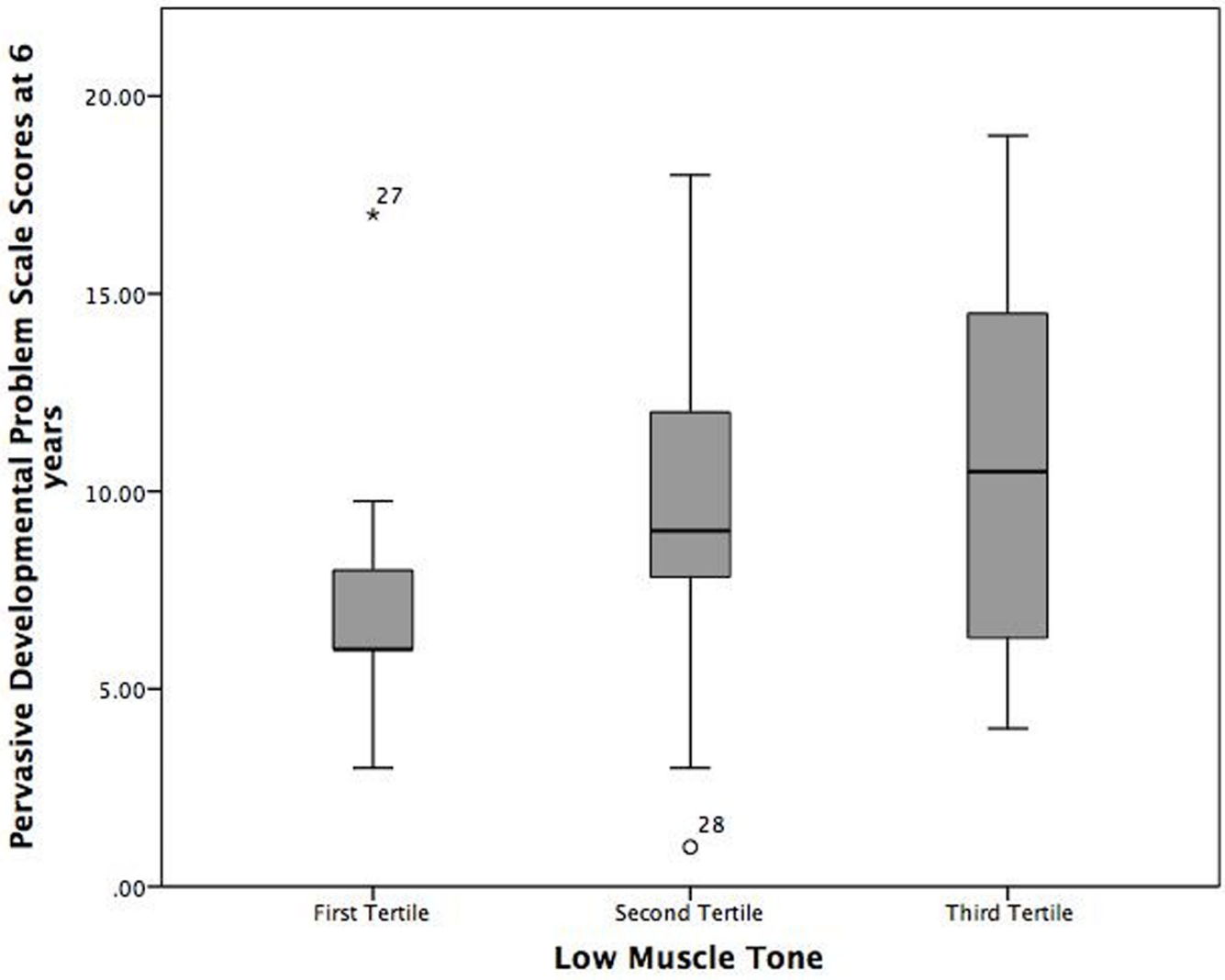

Figure 4.

Pervasive Developmental Problem Scale Scores in three categories of low muscle tone scores (in children with Autism Spectrum Disorders, n= 30).

Pervasive Development Problem Scores was assessed at age 6 years using the Child Behavior Checklist

Low muscle tone was assessed Touwen's Neurodevelopmental Examination, with high values indicating less optimal neuromotor development.

Table 1

Items on neuromotor developmental assessment (9–15 weeks version)*

Subscale	Position	Item description	Answering categories		
			Optimal	**Non-optimal**	**Non-optimal**
Tone	Supine	Resting posture	Semi-flexed legs; slight abduction at the hips	Legs flat on the surface	Legs stretched
		Adductor angle	> 80° – < 140°	> 140°	< 80°
		Popliteal angle	90°–130°	130°–180°	< 90°
		Ankle angle	> 20° – < 90°	< 20°	> 90°
		Head preference	No	Yes	
		Opening & closing hands	Yes	Sometimes closed	Always closed
		Alternating leg movements	Yes	Decreased	Absent
		Grasps with one hand	Yes	Decreased	Absent
		Hyperextension	No	Sometimes	Yes
		Dyskinesia	No	Sometimes	Yes
	Supine-to-sit	Traction response	Arms moderately flexed	Arms fully extended, no resistance	Strong resistance, flexion elbows, legs extended
		Traction response-head control	Active lift of head	Head lag	Exaggerated
	Horizontal	Ventral Tone	Normal tone	Low tone	Back and limbs stretched
	Vertical	Head	Normal tone	Low tone	High tone
		Shoulders	Normal tone	Low tone	High tone
		Trunk	Normal tone	Low tone	High tone
		Legs	Normal tone	Low tone	High tone
	Prone	Pulls arms up	Yes	No	
		Turns head	Yes	No	
		Lifts head	Yes	No	Overstretched

Subscale	Position	Item description	Answering categories		
			Optimal	Non-optimal	Non-optimal
	Sitting	Needs support	Yes	No	
		Head control	Yes	No	
		Shoulder retraction	No	Yes	
		Shape of the back	Round	Straight	Scoliosis
Responses	Supine	Asymmetrical Tonic Neck Reflex	Weak	Yes	Exaggerated
		Babinski	Yes	Exaggerated	Spontaneous
	Prone	Bauer	Yes / weak	Exaggerated	
	Vertical	Stepping movements	No	Yes	Exaggerated
		Moro intensity	Yes / weak	Exaggerated	
		Moro opening hands	Yes	No	
Other	Supine	Strabismus	No	Sometimes	Yes
		Fixation eyes	Yes	Decreased	No
		Following movements eyes	Smooth	Decreased	No
		Hearing	Yes	Moderate	No
		Sweating	No	Yes	
		Startles	No	Sometimes	Yes

*This version was used in 2341 children aged 9–15 weeks; in children aged 16–20 weeks a slightly modified version was used.

Table 2

Participant characteristics (n=2905)

Maternal characteristics	
Age at enrolment, year	31.3 (4.7)
Education %	
Primary	16.5
Secondary	28.5
High	55.0
Psychopathology score in pregnancy	0.13 (0.00, 0.87)
Household income %	
Poor	6.2
Low	14.5
Modal and above	79.3
Child characteristics	
Age at neuromotor assessment, month visit, weeks	12.6 (2.0)
Sex, boy%	48.8
Nonverbal Intelligence	102.4 (14.7)
Ethnic background %	
Dutch	57.8
Other Western	11.5
Non-Western	30.7
Gestational age at birth, week	40 (1.7)
Age at SRS assessment, year	6.0 (1.3)
Age at PDP, year	5.9 (0.4)

Numbers are mean (SD) for variables with normal distribution, median (quartile range) for not-normally distributed variables, and percentages for categorical variables.

SRS: Social Responsiveness Scale; PDP: Pervasive Developmental Problems scale of the Child Behavior Checklist for toddlers.

Table 3

Infant neuromotor development and Social Responsiveness Scale (SRS) scores in children at age 6 years (n=2905)

	Social Responsiveness Scale (SRS) scores N =2905					
	Basic		**Adjusted for covariates**		**Adjusted for child IQ**	
Predictor measure	**beta (95% CI)**	**p**	**beta (95% CI)**	**p**	**beta (95% CI)**	**p**
Overall neuromotor development, per tertile	0.063 (0.005, 0.022)	**0.001**	0.042 (0.000, 0.018)	**0.050**	0.039 (−0.001, 0.017)	**0.073**
Muscle tone, per tertile	0.057 (0.004, 0.020)	**0.003**	0.045 (0.002, 0.017)	**0.016**	0.043 (0.001, 0.017)	**0.023**
Hypertone						
High muscle tone, per tertile	0.035 (−0.001, 0.015)	0.075	0.028 (−0.004, 0.015)	0.230	0.027 (−0.004, 0.015)	0.236
First tertile	Reference		Reference		Reference	
Second tertile	0.006 (−0.013,0.017)	0.782	−0.001 (−0.015, 0.014)	0.930	−0.002 (−0.015, 0.014)	0.915
Third tertile	0.039 (−0.001, 0.030)	0.069	0.041 (−0.005, 0.034)	0.132	0.041 (−0.005, 0.034)	0.134
Hypotone						
Low muscle tone, per tertile	0.057 (0.004, 0.020)	**0.005**	0.054 (0.003, 0.019)	**0.006**	0.053 (0.003, 0.019)	**0.007**
First tertile	Reference		Reference		Reference	
Second tertile	0.030 (−0.004,0.026)	0.146	0.027 (−0.009, 0.029)	0.306	0.025 (−0.010, 0.028)	0.339
Third tertile	0.061 (0.007, 0.041)	**0.006**	0.058 (0.006, 0.039)	**0.007**	0.058 (0.006, 0.039)	**0.008**

Model I: adjusted for gender and gestational age
Model II: additionally adjusted for a child's age, ethnicity, Apgar score at 5 min, and household income, and maternal age, education, and psychopathology in pregnancy, and version of instrument for assessment of tone.
Model III: additionally adjusted for child IQ

For muscle tone first tertile was as the reference category. The SRS scores were transformed using natural logarithm. Confidence intervals are reported for B.

Table 4

Infant neuromotor development and autistic traits measured by Pervasive Developmental Problems (PDP) scores in children at age 6 years (n=2792)

	Pervasive Developmental Problems (PDP) scores N =2905					
	Basic		**Adjusted for covariates**		**Adjusted for child IQ**	
Predictor measure	**beta (95%CI)**	**p**	**beta (95% CI)**	**p**	**beta (95%CI)**	**p**
Overall neuromotor development, per tertile	0.066 (0.015, 0.082)	**0.004**	0.060 (0.024, 0.095)	**0.001**	0.058 (0.023, 0.093)	**0.001**
Muscle tone, per tertile	0.042 (0.011, 0.081)	**0.021**	0.052 (0.020, 0.090)	**0.010**	0.051 (0.020, 0.090)	**0.010**
Hypertone						
High muscle tone, per tertile	−0.003 (−0.033, 0.028)	0.878	0.024 (−0.019,0.059)	0.312	0.024 (−0.019, 0.059)	0.316
First tertile	Reference		Reference		Reference	
Second tertile	0.006 (−0.054,0.073)	0.778	0.005 (−0.055,0.071)	0.805	0.005 (−0.055, 0.070)	0.811
Third tertile	−0.003 (−0.067, 0.056)	0.858	0.032 (−0.036,0.132)	0.260	0.032 (−0.036, 0.131)	0.263
Hypotone						
Low muscle tone, per tertile	0.080 (0.036, 0.102)	<**0.001**	0.082 (0.039,0.104)	<**0.001**	0.081 (0.039, 0.104)	<**0.001**
First tertile	Reference		Reference		Reference	
Second tertile	0.011 (−0.044,0.078)	0.588	0.030 (−0.038,0.128)	0.286	0.029 (0.039,0.126)	0.300
Third tertile	0.092 (0.083, 0.216)	<**0.001**	0.089 (0.080, 0.211)	<**0.001**	0.089 (0.079, 0.211)	<**0.001**

Model I: adjusted for gender and gestational age
Model II: additionally adjusted for a child's age, ethnicity, Apgar score at 5 min, and household income, and maternal age, education, and psychopathology in pregnancy, and version of instrument for assessment of tone.
Model III: additionally adjusted for child IQ

For muscle tone first tertile was used as the reference category. The PDP scores were transformed using natural logarithm.
Confidence intervals are reported for B.

Table 5

Infant neuromotor development and Pervasive Developmental Problems within the clinical range in children at age 6 years (n=2792)

	Pervasive Developmental Problems within the clinical range at 6 years (N=114)					
	Basic		**Adjusted for covariates**		**Adjusted for child IQ**	
Predictor measure	**OR (95%CI)**	**p**	**OR (95%CI)**	**P**	**OR (95%CI)**	**p**
Overall neuromotor development, per tertile	1.240 (0.968, 1.589)	0.088	1.287 (0.983, 1.684)	0.066	1.274 (0.972, 1.668)	0.079
Muscle tone, per tertile	1.332 (1.036, 1.711)	**0.025**	1.306 (1.009, 1.692)	**0.043**	1.303 (1.006, 1.689)	**0.045**
Hypertone						
High muscle tone, per tertile	0.852 (0.676, 1.074)	0.174	0.867 (0.640, 1.174)	0.356	0.865 (0.635, 1.117)	0.354
First tertile	Reference				Reference	
Second tertile	0.933 (0.593, 1.469)	0.765	0.930 (0.584, 1.482)	0.761	0.934 (0.585, 1.491)	0.775
Third tertile	0.715 (0.445, 1.149)	0.166	0.714 (0.359, 1.420)	0.335	0.706 (0.351, 1.418)	0.326
Hypotone						
Low muscle tone, per tertile	1.355 (1.08, 1.72)	**0.011**	1.359 (1.077, 1.715)	**0.010**	1.368 (1.082, 1.729)	**0.009**
First tertile	Reference				Reference	
Second tertile	1.286 (0.802, 2.064)	0.297	1.692 (0.960, 2.982)	0.069	1.665 (0.940, 2.951)	0.081
Third tertile	1.835 (1.154, 2.918)	**0.010**	1.849 (1.159, 2.969)	**0.011**	1.873 (1.163, 3.016)	**0.010**

Model I: adjusted for gender and gestational age

Model II: additionally adjusted for a child's age, ethnicity, Apgar score at 5 min, and household income, and maternal age, education, and psychopathology in pregnancy, and version of instrument for assessment of tone.

Model III: additionally adjusted for child IQ

For muscle tone first tertile has been used as the reference category.