## Abstract

**Aim**: To describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on the *Ages and Stages Questionnaire* (ASQ-3) scores in infants diagnosed with congenital hypotonia (CH). **Method**: A total of 234 patients diagnosed with CH participated in this study (median age, 8 years; 94 (40.2%) females and 140 (59.8%) males). Neurodevelopmental status was assessed with the ASQ-3 at admission, as well as sociodemographic and obstetric data obtained through the initial clinical interview. **Results**: When modeling the neurodevelopmental status of each domain, an overall negative effect of corrected age on communication and problem-solving skills was observed, whereas the overall effect tends to be positive in gross motor function. Fine motor skills did not exhibit a linear relationship with corrected age but a non-linear effect, unlike the personal-social domain, which did not present significant variations across age corrected for prematurity. **Interpretation**: After adjusting for possible confounders, we found between-subjects fluctuations in neurodevelopmental traits across age in hypotonic infants. These fluctuations were present in the form of non-linear and domain-specific variations.

What this paper adds:

* Describes the levels of variations observed in neurodevelopmental traits across age in hypotonic infants.
* Provides the estimated probability of developmental delay according to the ASQ-3 across age in hypotonic infants.
* The variations observed in developmental domains are not solely attributable to prematurity, where age corrected for prematurity best explains the variability observed in neurodevelopment.

**Keywords**: Developmental traits, Congenital hypotonia, Ages and Stages Questionnaire (ASQ), Infants.

Early childhood development’s physical and psychological signs are representative and relevant markers for identifying and monitoring overall growth in early life.[1](#ref-di2016predictive) Therefore, both can be used in screening children at risk of developmental delay to support early referral and identify the need for further assessment to determine if they are eligible for early intervention services.[2](#ref-bruder2010early),[3](#ref-guralnick2017early)

Currently, many tools have been proposed to assess the continued development of infants. In this sense, the Ages and Stages Questionnaire, Third Edition (ASQ-3), has been presented as a global screening tool aimed at parents/caregivers, assessing five developmental domains in children aged 0 to 5.5 years.[4](#ref-singh2017ages) Current evidence suggests that the ASQ-3 is an accurate, cost-effective, and parent-friendly instrument for screening and monitoring children through pre-school age, helping to identify and eliminate neurodevelopmental deficits in children born very premature.[4](#ref-singh2017ages)–[6](#ref-ballantyne2016risk)

Multiple neuromuscular, metabolic, and genetic conditions have been associated with hypotonia. Hypotonia is the decreased muscle tone or flaccidity and may represent a sign of delayed neurological development in the child, which may predispose to cognitive impairment in some cases.[7](#ref-riou2009global) Because the baby’s growth-associated hypotonia, hypermobility, and motor delay can affect her ability to relate to her environment, critical visual cues are not always interpreted, leading to impaired learning and cognitive development.[8](#ref-harris2008congenital) Hypotonia implies a wide range and levels of muscle flaccidity, which should be explored in the cognitive development of the infant.[8](#ref-harris2008congenital),[9](#ref-gabis2021weak) There are multiple causes of hypotonia, one of them being congenital hypotonia (CH). Some authors suggest that CH cannot be referred to as a diagnosis.[10](#ref-thompson2002benign) Those who do consider it point it out as a diagnosis of exclusion in the investigation, considering it only when it is established in the absence of other signs and symptoms.[9](#ref-gabis2021weak),[11](#ref-leyenaar2005schematic) However, its research is fundamental since it is a non-progressive neuromuscular disorder, which tends to improve with time and early intervention.[9](#ref-gabis2021weak)

To our knowledge, there is no substantial evidence characterizing the observed variation in developmental traits in infants with diagnosed CH across ages. Therefore, our primary goal in this study was to describe and model the relationship between sociodemographic characteristics, prematurity, and neurodevelopmental levels as a function of ASQ-3 estimates in infants diagnosed with CH.

# Material y methods

## Ethics

Participating subjects gave their permission, and legal guardians provide informed consent before participation. The Ethics Committee approved this study of the Corporación de Rehabilitación Club de Leones Cruz del Sur, Chile (code: CorporacionRCLCS010322), following the regulations established by the Declaration of Helsinki on ethical principles in human beings.

## Study design

We conducted an observational, cross-sectional study under a quantitative approach.

## Participants

A total of 234 patients were enrolled as part of an intervention program carried out by the Cruz del Sur Rehabilitation Center (Punta Arenas, Chile), admitted from one month to 60 months old, and evaluated at admission, control and discharge. Participating patients were diagnosed based on clinical criteria confirmed by a neurologist and a physiatrist. The total files of the patients diagnosed with CH, and admitted to the institution’s program, were analyzed, and the evaluation of the subjects was carried out and guided by a nurse trained in the application of the ASQ-3.

In this context, it is worth noting that the data, as well as the patient registry, are part of institutional strategies aimed at the diagnosis and continuous monitoring of the clinical situation of users, which are used to improve care processes and clinical decision-making.

The diagnosis of CH is based on four sources: 1) primary care pediatrician, who refers the diagnosis to the institution where admission to the program is made; 2) pediatricians from private clinics, who refer the diagnosis; 3) neuropediatricians from the clinical hospital, who refer the diagnosis to the program; 4) physiatrist from the institution, who assigns the diagnosis if it corresponds to the semiology.

## Measures

### The Ages and Stages Questionnaire, third edition (ASQ-3)

The ASQ-3 is a parent-reported initial level developmental screening instrument consisting of 21 intervals, each with 30 items in five areas: i) communication (CM), ii) gross motor (GM), iii) fine motor (FM), iv) problem-solving (CG), and v) personal-social (PS).[12](#ref-squires2009ages) The ASQ is cost-effective and widely used in the United States and other countries.[13](#ref-heo2008cross),[14](#ref-sarmiento2011universal) It has been translated into several languages, and international studies on its psychometric properties in diverse cultural environments are increasing.[13](#ref-heo2008cross),[14](#ref-sarmiento2011universal) It has shown good psychometric properties (75% sensitivity and 81% specificity) in Chilean term and preterm infants.[15](#ref-schonhaut2013validity)

## Procedures

For the collection of research data, authorization consent was obtained for the use of instrumental clinical data as well as the clinical record of each patient. Subsequently, and following national research regulations, written authorization was obtained from the institutional director to use the forms and database for research purposes. To this end, the data were anonymized during data processing and subsequent analyses.

### Collection of demographic data

Each patient’s demographic data were collected and made available throughout the study by the institutional electronic systems at the time of entry to the program. The administrative registration was done by the secretaries of the user coordination unit, recording name, ID number, date of birth and diagnosis. In addition, age data was automatically updated by the computer system’s algorithms.

### Assessment with ASQ-3

The ASQ-3 was applied according to the protocol established by the instrument itself, with a face-to-face or telematic application being valid. The protocol can be found in the instrument’s manuals, which the program nurse administered. Some important considerations of the administration are that i) the primary caregiver must answer, ii) in case of doubts of the caregiver about the assessed behavior, the information is corroborated by in situ tests with the user, and iii) in relation to the correction, the test itself standardizes these procedures.

## Statistical analysis

Data are presented as median (*Mdn*) and interquartile range (*IQR*) for continuous variables; for categorical/discrete variables, the absolute and relative sample size was reported. There was no missing data.

A non-parametric approach was used since the underlying distribution of continuously measured outcomes, assessed through analytical and graphical methods, did not follow a Gaussian distribution.

In order to assess the differences in developmental scores between males and females, the *Wilcoxon* rank-sum test was used, meanwhile the chi-square test () was used to evaluate goodness-of-fit ().

Generalized additive models (GAM) were used to describe linear and non-linear relationships in the form of smooth terms between developmental characteristics, represented through penalized regression splines.[16](#ref-wood2011fast) The restricted maximum likelihood method was used to estimate the smoothing parameters, and thin-plate regression splines as the smoothing basis, as they are the optimal smoother of any given basis dimension/rank.[17](#ref-wood2003thin) We used approximative derivatives with 95% confidence intervals (CI95%) to describe the smooth terms by means of quasi-linear segments.[18](#ref-dominique2020estimation)

In order to assess the influence of confounding variables, we fitted different models using the variables: i) sex of the infant, ii) clinician ID and iii) the relationship of the infant to the respondent (i.e., whether the respondent was the infant’s mother, father, uncle or grandparent) as random effects in the form of penalized parametric terms.[19](#ref-wood2016smoothing) Varying random effects structures models can be seen in the section *Random effects structures* of the supplementary file.

Based on the technical report of the ASQ-3, we’ve been able to estimate the threshold of possible delay based on the total score for each developmental domain. In this sense, a logistic regression, within GAM framework, was used to estimate the predicted probability of having a possible delay in developmental domains given the corrected age.

A probability of committing a type I error () of less than 5% (*p* < 0.05) was considered sufficient evidence for statistical significance in hypothesis testing. All the statistical analyses were computed and implemented in the R programming language.[20](#ref-rlanguage) GAMs and the corresponding model estimates were calculated using the *mgcv* and *modelbased* packages.[18](#ref-dominique2020estimation),[21](#ref-wood2017generalized) Complementary R packages were used for visualization purposes.[22](#ref-daniel2021see),[23](#ref-hadley2016ggplot2)

# Results

From a total of 234 subjects with congenital hypotonia, 94 (40.2%) were females and 140 (59.8%) males ( (1) = 9.04, *p* = 0.003). The developmental characteristics of the sample can be seen in [Table 1](#tab1).

When modeling the effect of chronological age on developmental domains, different random effects structures were compared when assessing model estimates, these estimates can be seen in [Figure 1](#fig1).

After fitting a GAM to assess the effect of corrected age on CM scores, we observed a significant non-linear relationship between them ( (5.1, 224.74) = 13.88, *p* < 0.001), that reflect an overall negative marginal trend ( = -2.39, CI95%[-3.46, -1.32], (224.74) = -4.4, *p* < 0.001), however, this was not true when assessing the direction of the effect in the age range between 0 to 6.8 ( = 0.38, CI95%[-0.96, 1.72], (224.74) = 0.33, *p* = 0.351), neither in the 18.4 to 48 months old group ( = 0.44, CI95%[-1.27, 2.16], (224.74) = 0.42, *p* = 0.577), whereas the effect tend to be positive but non-significant. The relationship between developmental domains, corrected age and their effect derivatives can be seen in [Figure 2](#fig2).

When analyzing the motor skills domain, we found a significant non-linear effect of corrected age on GM scores, (5.25, 226.82) = 5.6, *p* < 0.001, which had an overall positive effect ( = 1.86, CI95%[0.57, 3.16], (226.82) = 2.83, *p* = 0.005), however, the slope varied as a function of age, with a negative effect in the 0 to 6.8 age range ( = -3.02, CI95%[-4.63, -1.42], (226.82) = -3.81, *p* = 0.003), but in the 10.2 to 15.5 interval, this relationship was inverted ( = 1.83, CI95%[0.57, 3.08], (226.82) = 2.87, *p* = 0.008), however, in the rest of the age range the slope was non-significant and virtually zero (Age[7.3, 9.7], = 0.13, CI95%[-1.02, 1.27], (226.82) = 0.23, *p* = 0.387; Age[16, 48], = -0.06, CI95%[-2.09, 1.97], (226.82) = 0.01, *p* = 0.701).

Although a similar non-linear effect was observed when inspecting the influence of corrected age in the FM domain scores ( (2.56, 228.03) = 4.11, *p* = 0.006), it was not possible to estimate a significant overall effect different from zero ( = 0.01, CI95%[-0.47, 0.49], (228.03) = 0.03, *p* = 0.977), nevertheless, it was only in the 22.3 to 37.3 age range where a significant and negative effect was observed ( = -0.75, CI95%[-1.4, -0.11], (228.03) = -2.32, *p* = 0.023).

CG abilities were significantly influenced by corrected age ( (5.69, 225.93) = 3.7, *p* = 0.001), with an overall negative effect ( = -1.93, CI95%[-3.24, -0.63], (225.93) = -2.91, *p* = 0.004), and just like the other domains, this relationship was modified across the corrected age. In this sense, from the 0 to 5.8 age interval, we found that for every increase in one month in corrected age, we can expect a proportional increase in 2.8 points ( = 2.8, CI95%[1.17, 4.43], (225.93) = 3.48, *p* = 0.002) in the CG domain, while in the age range 9.2 to 14.1 the relationship changes inversely, mainly because in this age range we observe that for every one-month increase in the corrected age, a decrease of 1.64 points could be expected in the same domain ( = -1.64, CI95%[-2.86, -0.41], (225.93) = -2.62, *p* = 0.014). The other age intervals did not have a slope that deviated significantly from zero (Age[6.3, 8.7], = 0.06, CI95%[-1.09, 1.2], (225.93) = 0.07, *p* = 0.388; Age[14.5, 48.0], = 0.04, CI95%[-1.98, 2.07], (225.93) = -0.05, *p* = 0.564).

Unlike the others, the PS domain was not influenced by corrected age ( (1, 230.4) = 1.06, *p* = 0.304). Accordingly, prematurity (measured in weeks) was not associated with any developmental domain within ASQ-3 assessment (significance for smooth terms: CM, *p* = 0.639; FM, *p* = 0.918; GM, *p* = 0.33; CG, *p* = 0.323; PS, *p* = 0.152).

When analyzing the probability of having a developmental delay based on the scores for each domain, we found a significant non-linear effect for CM ( (7.73) = 32.11, *p* < 0.001), whereas in this domain we observed that for every one-month increase in the corrected age in the 13.6 to 18.9 age range, the odds of a possible developmental delay increases by 60% (OR = 1.6 CI95%[1.16, 2.23], (224.56) = 2.89, *p* = 0.01), as well with the 28.6 to 29.6 age range, whereas the odds of delay increases by 36% in this domain (OR = 1.36 CI95%[1.00, 1.86], (224.56) = 1.98, *p* = 0.049). Similar to CM, an overall linear effect of corrected age in the GM domain was observed ( (1) = 6.86, *p* = 0.009), whereas for every one-month increase the odds of a possible developmental delay decrease by a 3.9% (OR = 0.96, CI95%[0.50, 0.99], (232) = -2.62, *p* = 0.009). The probability associated with a possible delay according to the total score for each developmental domain in response to corrected age can be observed in [Figure 3](#fig3).

# Discussion

Our study aimed to describe and model the relationship between sociodemographic data, prematurity and neurodevelopmental levels based on ASQ-3 scores in infants diagnosed with CH. Our main findings suggest a non-linear effect of age, corrected for prematurity, with a marked decrease in scores for all neurodevelopmental traits at different age frames, even after adjusting for caregiver relationship, sex and inter-rater influence. However no variation was observed across the corrected age in the PS domain.

These findings confirm the described motor impairments of hypotonia in the early stages of life, which compromise the infant’s ability to explore and interact with their environment.[8](#ref-harris2008congenital),[9](#ref-gabis2021weak) A reflection of those mentioned above would be expressed in altered development of GM function in the first months of life, with a consequent limitation in FM skills later on, which would have a subsequent negative impact on the communicative competence of infants, secondary to reduced interaction with their environment and peers.[24](#ref-bodensteiner2008evaluation) In a recent systematic review,[25](#ref-gonzalez2019gross) differences in the predictive abilities of gross and FM skills on communication skills in infants and early childhood were reported. Whereas GM skills, such as crawling and walking, favor exploration with their environment and caregivers, while FM skills, expressed through tasks such as drawing and handling utensils, could lead to improvements in language through mechanisms yet to be explored.[25](#ref-gonzalez2019gross) These milestones may be impaired in the face of poorer head and trunk control in CH, which have been shown to delay the achievement of crucial motor milestones in infants.[8](#ref-harris2008congenital),[9](#ref-gabis2021weak),[24](#ref-bodensteiner2008evaluation)

It is worth noting that other context-mediated social factors may also have influenced our results, mainly due to the role that other variables would also play in the neurodevelopment of our study sample, which could have an impact on many of the developmental traits assessed here, such as intrauterine growth restrictions, maternal depression, institutionalization, exposure to social violence, maternal education and breastfeeding.[26](#ref-walker2011inequality) Altogether, these represent the main limitations in our study design, which need to be addressed in future research, exploring the variations observed in different developmental traits in hypotonic infants. However, our study sheds light on an underexplored aspect with robust statistical methods that enabled us to capture and model the complex relationships seen early in life.

# Conclusion

The present study shows that the marked variations observed in neurodevelopmental traits are present across age in hypotonic infants, mainly in the form of non-linear and domain-specific variations, even after adjusting for the effect that caregiver relationship, sex and evaluators might exert. Moreover, we show that the observed variations in developmental domains are not solely attributable to prematurity, where age corrected for prematurity best explains the observed variability in neurodevelopment. Future research may determine how these findings apply when controlling for context-mediated social factors and other clinical populations.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

# Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

# Conflicts of interest

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

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# References

1. Di Rosa G, Cavallaro T, Alibrandi A, et al. Predictive role of early milestones-related psychomotor profiles and long-term neurodevelopmental pitfalls in preterm infants. *Early Human Development* 2016; **101**: 49–55.

2. Bruder MB. Early childhood intervention: A promise to children and families for their future. *Exceptional children* 2010; **76**: 339–55.

3. Guralnick MJ. Early intervention for children with intellectual disabilities: An update. *Journal of Applied Research in Intellectual Disabilities* 2017; **30**: 211–29.

4. Singh A, Yeh CJ, Blanchard SB. Ages and stages questionnaire: A global screening scale. *Boletı́n Médico Del Hospital Infantil de México (English Edition)* 2017; **74**: 5–12.

5. Kerstjens JM, Nijhuis A, Hulzebos CV, et al. The ages and stages questionnaire and neurodevelopmental impairment in two-year-old preterm-born children. *PLoS One* 2015; **10**: e0133087.

6. Ballantyne M, Benzies KM, McDonald S, Magill-Evans J, Tough S. Risk of developmental delay: Comparison of late preterm and full term canadian infants at age 12 months. *Early Human Development* 2016; **101**: 27–32.

7. Riou EM, Ghosh S, Francoeur E, Shevell MI. Global developmental delay and its relationship to cognitive skills. *Developmental Medicine & Child Neurology* 2009; **51**: 600–6.

8. Harris SR. Congenital hypotonia: Clinical and developmental assessment. *Developmental Medicine & Child Neurology* 2008; **50**: 889–92.

9. Gabis LV, Shaham M, Leon Attia O, et al. The weak link: Hypotonia in infancy and autism early identification. *Frontiers in Neurology* 2021; **12**: 612674.

10. Thompson CE. Benign congenital hypotonia is not a diagnosis. *Developmental medicine and child neurology* 2002; **44**: 283–6.

11. Leyenaar J, Camfield P, Camfield C. A schematic approach to hypotonia in infancy. *Paediatrics & child health* 2005; **10**: 397–400.

12. Squires J, Bricker DD, Twombly E, et al. Ages & stages questionnaires. Paul H. Brookes Baltimore, MD, 2009.

13. Heo KH, Squires J, Yovanoff P. Cross-cultural adaptation of a pre-school screening instrument: Comparison of korean and US populations. *Journal of Intellectual Disability Research* 2008; **52**: 195–206.

14. Sarmiento Campos JA, Squires J, Ponte J. Universal developmental screening: Preliminary studies in galicia, spain. *Early Child Development and Care* 2011; **181**: 475–85.

15. Schonhaut L, Armijo I, Schönstedt M, Alvarez J, Cordero M. Validity of the ages and stages questionnaires in term and preterm infants. *Pediatrics* 2013; **131**: e1468–74.

16. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society (B)* 2011; **73**: 3–36.

17. Wood SN. Thin-plate regression splines. *Journal of the Royal Statistical Society (B)* 2003; **65**: 95–114.

18. Makowski D, Ben-Shachar MS, Patil I, Lüdecke D. Estimation of model-based predictions, contrasts and means. *CRAN* 2020. <https://github.com/easystats/modelbased>.

19. Wood SN, N., Pya, S"afken B. Smoothing parameter and model selection for general smooth models (with discussion). *Journal of the American Statistical Association* 2016; **111**: 1548–75.

20. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2021 <https://www.R-project.org/>.

21. Wood SN. Generalized additive models: An introduction with r, 2nd edition. Chapman; Hall/CRC, 2017.

22. Lüdecke D, Patil I, Ben-Shachar MS, Wiernik BM, Waggoner P, Makowski D. [see: An R package for visualizing statistical models](https://doi.org/10.21105/joss.03393). *Journal of Open Source Software* 2021; **6**: 3393.

23. Wickham H. ggplot2: Elegant graphics for data analysis. Springer-Verlag New York, 2016 <https://ggplot2.tidyverse.org>.

24. Bodensteiner JB. The evaluation of the hypotonic infant. In: Seminars in pediatric neurology. Elsevier, 2008: 10–20.

25. Gonzalez SL, Alvarez V, Nelson EL. Do gross and fine motor skills differentially contribute to language outcomes? A systematic review. *Frontiers in psychology* 2019; **10**: 2670.

26. Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: Risk and protective factors for early child development. *The lancet* 2011; **378**: 1325–38.

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**Table 1**. Overall baseline and developmental characteristics of the sample and grouped by sex. 1 Data is presented as sample size, and *Mdn* (*IQR*); 2 p-values are computed from the *Wilcoxon* rank-sum test.

**Figure 1**. Predicted scores on developmental domains using corrected age as an independent variable, comparing different random effects structures on the estimated score.

**Figure 2**. Relationship between corrected age (in months) and developmental domains. Left panel: regression lines represent predicted values estimated from GAM models (bold red lines) and 200 bootstrap replicates (faded red lines), points and error bars represent the mean and standard error at 5-month age intervals. Right panel: effect derivatives and their CI95%, representing how the effect of corrected age (in months) in developmental domains changes across corrected age. Significant areas consider CI95% that do not cross zero.

**Figure 3**. Predicted probability of having a possible delay according to the total score for each developmental domain in response to corrected age. Fitted models were estimated using logistic regression within GAM framework and adjusted for possible confounders as already described. The p-values of smooth terms, associated with the main effect of corrected age on developmental delay, are shown within each panel.