**Title**: Neurodevelopmental features among infants with congenital hypotonia in high southern latitudes: An observational cross-sectional study.

**Authors**: Patricio Barría,1 Matías Castillo-Aguilar2,3, Katherine Harris2,3, Cristian Núñez-Espinosa3,4 \*

1 Rehabilitation Center, Punta Arenas, Chile.

2 Kinesiology Department, Magallanes University, Punta Arenas, Chile.

3 Chilean Austral Integrative Neurophysiology Group ([NIM-ACh](https://nimach.org)), Centro Asistencial de Docencia e Investigación (CADI-UMAG), Punta Arenas Chile

4 School of Medicine, Magallanes University, Punta Arenas, Chile.

### \*Autor de correspondencia

Cristian Núñez-Espinosa, School of Medicine, Magallanes University, Punta Arenas, Chile. Centro Asistencial de Docencia e Investigación CADI-UMAG, Chile. e-mail: [cristian.nunez@umag.cl](mailto:cristian.nunez@umag.cl). Address: Avenida Bulnes 01855, Box 113-D. Phone: +56 61 2201411

## Abstract

**Objective**: To describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on the *Ages and Stages Questionnaire* scores in infants diagnosed with congenital hypotonia (CH). **Material and methods**: […]. **Results**: When modelling the effect of corrected age on developmental domains we found a significant overall effect on communication skills ( = -2.36, CI95%[-3.47, -1.25]), gross motor function ( = 1.95, CI95%[0.66, 3.25]) and problem-solving skills ( = -1.87, CI95%[-3.17, -0.57]). fine motor skills did not exhibit an overall linear effect ( = 0.04, CI95%[-0.45, 0.52]), however, they showed a non-linear effect ( (2.59, 226.77) = 4.2, *p* = 0.005); unlike the personal-social domain, which did not present any variation across corrected age ( (1, 231.58) = 1.16, *p* = 0.282). **Conclusion**: After adjusting for possible confounders, we found between-subjects fluctuations in neurodevelopmental traits across age in hypotonic infants in the form of non-linear and domain-specific variations. Further research is warranted to determine how these findings apply in the presence of other context-mediated social factors and populations.

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

# Introduction

Both physical and psychological signs of early childhood development have been shown to be representative and relevant markers for the identification and monitoring of overall growth in early life ([Di Rosa et al., 2016](#ref-di2016predictive)) and can, therefore, be used in the screening of children at risk of developmental delay to support early referral and need further assessment to determine if they are eligible for early intervention services ([Bruder, 2010](#ref-bruder2010early); [Guralnick, 2017](#ref-guralnick2017early)).

Currently, a plethora of tools have been proposed to assess the developmental continuum of infants. In this sense, the Ages and Stages Questionnaire, Third Edition (ASQ-3) has been proposed as a global screening tool, parent/caregivers-oriented, that assesses five domains of development in children aged from 0 to 5.5 years old ([Singh, Yeh, & Blanchard, 2017](#ref-singh2017ages)). Current evidence suggests that the ASQ-3 is an accurate, cost-effective yet parent-friendly instrument for screening, monitoring children up to pre-school age, and can help identify and exclude neurodevelopmental impairments in very preterm-born children ([Ballantyne, Benzies, McDonald, Magill-Evans, & Tough, 2016](#ref-ballantyne2016risk); [Kerstjens et al., 2015](#ref-kerstjens2015ages); [Singh et al., 2017](#ref-singh2017ages)).

Hypotonia has been defined both as decreased muscle tone or floppiness, involving a wide range and levels of progression ([Gabis et al., 2021](#ref-gabis2021weak); [Harris, 2008](#ref-harris2008congenital)). There are multiple forms of neuromuscular, metabolic and genetic conditions associated with hypotonia and it may be a sign of neurodevelopmental delay, that may predispose to cognitive impairment in some cases ([Riou, Ghosh, Francoeur, & Shevell, 2009](#ref-riou2009global)). Given that hypotonia, and the hyperlaxity and motor delay associated with it, may impair the infant’s capacity to engage with its surroundings, critical visual cues may be ignored, potentially leading both to an impairment of learning and cognitive development ([Harris, 2008](#ref-harris2008congenital)), hence the need to explore the neurodevelopmental attributes of infants with hypotonia.

Accordingly, benign congenital hypotonia (CH) is usually considered an exclusion diagnosis, and is usually made in the absence of other signs and symptoms, after every other evaluative resources have been exhausted ([Gabis et al., 2021](#ref-gabis2021weak); [Leyenaar, Camfield, & Camfield, 2005](#ref-leyenaar2005schematic)), however this is not true for at least one author that suggest that CH can not be considered a diagnosis as such ([Thompson, 2002](#ref-thompson2002benign)). CH is considered a non-progressive neuromuscular disorder that does not progress but tends to improve with time and early intervention.

Nevertheless, and to the best of our knowledge, there is no robust evidence characterising the observed variation in developmental traits in infants with known CH across age. Therefore, our main objective in this study was to describe and model the relationship between sociodemographics, prematurity and neurodevelopmental levels based on ASQ-3 scores in infants with diagnosed CH.

# Material y methods

## Study design

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

¿Los datos vienen de algún grupo de estudio, cohorte o de algún proyecto en particular? Detalles de donde vino la muestra

Los pacientes que ingresan a la institución desde 1 mes hasta los 60 meses son evaluados al ingreso, control y alta. La evaluación la realiza una enfermera con experiencia en el instrumento. La encuesta es orientada por la enfermera del programa de ingreso. La fechas de los datos están contenidas en los timestamps de la matriz de datos que envié originalmente.

Los conjunto de datos no son una muestra, sino que es que universo de pacientes evaluados en el periodo.

¿Qué resguardos éticos se consideran? Comité de ética y otros permisos que sean pertinentes

Con respecto al test, el instrumento no presenta riesgos de aplicación, sin embargo, los usuarios son invitados a responder de manera voluntaria.

Con respecto a los datos de investigación, se dispone de un consentimiento de autorización para el uso de los datos clínicos instrumentales como de ficha clínica de cada paciente.

Finalmente, de acuerdo con la normativa de investigación nacional, se dispone de autorización escrita por parte del director institucional para el uso de base de datos para fines académicos. Sin embargo, los datos deben ser anonimizados. El fin de la obtención de estos datos se enfoca a la elaboración de un diagnostico continuo de la situación clínica de los usuarios y así mejorar los procesos y tomar acciones pertinentes.

## Participants

¿Cómo, cuando y bajo qué condiciones fueron reclutados los sujetos? Criterios de elegibilidad, tipo de muestreo, etc.

No hubo un reclutamiento, ya que la evaluación es parte del proceso regular de ingreso.

Las fechas de evaluación están informadas en el fichero Excel.

El único criterio de inclusión para el instrumento es la edad de los usuarios que va de 1 mes a 60 meses.

No hubo muestreo.

¿Cómo, cuando y quien hizo el diagnóstico de hipotonía congénita? ¿Fue igual para todos? ¿La información vino de parte de terceros?

Con respecto al diagnóstico de hipotonía congénita existen 4 orígenes del diagnóstico:

* Médico pediatra de atención primaria, quien deriva con dicho diagnostico a nuestra institución y se procede a ingresar al centro.
* Médico pediatra de clínicas privadas, quien deriva con dicho diagnostico a nuestra institución y se procede a ingresar al centro.
* Neuropediatría de Hospital clínico, quien deriva con dicho diagnostico a nuestra institución y se procede a ingresar al centro.
* Medico Fisiatra de la institución, quien puede asignar el diagnostico a un paciente si corresponde con la semiología.

## 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) ([Squires, Bricker, Twombly, et al., 2009](#ref-squires2009ages)). The ASQ is cost-effective and widely used in the United States and other countries ([Heo, Squires, & Yovanoff, 2008](#ref-heo2008cross); [Sarmiento Campos, Squires, & Ponte, 2011](#ref-sarmiento2011universal)). It has been translated into several languages, and the number of international studies on its psychometric properties with diverse cultural environments is increasing ([Heo et al., 2008](#ref-heo2008cross); [Sarmiento Campos et al., 2011](#ref-sarmiento2011universal)). It has shown adequate psychometric properties (75% sensitivity and 81% specificity) in Chilean term and preterm infants ([Schonhaut, Armijo, Schönstedt, Alvarez, & Cordero, 2013](#ref-schonhaut2013validity)).

## Procedures

### Collection of demographic data

¿Como, cuando y quién recolectó los datos demográficos?

Los datos demográficos de cada usuario se cargan al sistema informático institucional (CRIWEB) durante el ingreso a la institución. El ingreso administrativo es realizado por las secretarias de la unidad de coordinación de usuarios, registrando nombre, rut, fecha de nacimiento, diagnostico. Posteriormente los datos de edad se actualizan automáticamente con los algoritmos del sistema informatico.

### Assessment with ASQ-3

¿Cómo se evaluó el ASQ-3? ¿Con qué protocolo? ¿Que consideraciones se tuvieron en la evaluación? ¿Algo más que podría ser relevante para agregar respecto a la evaluación o corrección del cuestionario?

El instrumento ASQ3 se aplica según el protocolo establecido por el propio instrumento, siendo valido una aplicación presencial o mediante telemedicina. El protocolo se encuentra en los manuales del instrumento que están a cargo de la enfermera del programa.

Algunas consideraciones importantes de la administración son:

* Debe responder cuidador principal
* En caso de dudas del cuidador sobre a conducta evaluada, se corrobora la información mediante una prueba in situ con el usuario.
* En relación a la corrección, este procedimientos esta estandarizado por el propio test.

## Statistical analysis

Data is presented as median (*Mdn*) and interquartile range (*IQR*) for continuous variables; for categorical/discrete variables, the absolute and relative sample size was reported.

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

In order 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 () and independence of factors ().

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 ([Wood, 2011](#ref-wood2011fast)). Restricted maximum likelihood method was used for the estimation of the smoothing parameters, and thin-plate regression splines as the smoothing basis, as they are the optimal smoother of any given basis dimension/rank ([Wood, 2003](#ref-wood2003thin)). In the final models, infants’ sex, clinician and infants’ relationship with caregivers were added as random effects in the form of penalized parametric terms to account for the variability arising from these variables in the fixed effects analysed ([Wood, N., Pya, & S"afken, 2016](#ref-wood2016smoothing)). To describe the smooth terms by means of quasi-linear segments, we used approximative derivatives with 95% confidence intervals (CI95%).

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 ([R Core Team, 2021](#ref-rlanguage)). GAMs and the corresponding model estimates were computed using the *mgcv* and *modelbased* packages ([Makowski, Ben-Shachar, Patil, & Lüdecke, 2020](#ref-dominique2020estimation); [Wood, 2017](#ref-wood2017generalized)). Complementary R packages were used for visualization purposes ([Lüdecke et al., 2021](#ref-daniel2021see); [Wickham, 2016](#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 modelling the effect of chronological age on developmental domains, corrected for prematurity, we observed a significant non-linear relationship on CM scores ( (5.2, 224.04) = 13.43, *p* < 0.001), that reflect an overall negative marginal effect ( = -2.36, CI95%[-3.47, -1.25], (224.04) = -4.2, *p* < 0.001), however, this was not true when assessing the direction of the effect in the age range between 0 to 6.8 ( = 0.49, CI95%[-0.89, 1.86], (224.04) = 0.45, *p* = 0.319), neither in the 18.4 to 48 months old group ( = 0.45, CI95%[-1.32, 2.23], (224.04) = 0.42, *p* = 0.593), 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 1](#fig1).

When analysing the motor skills domain, we found a significant non-linear effect of corrected age on GM scores, (5.24, 226.75) = 6.19, *p* < 0.001, which had an overall positive effect ( = 1.95, CI95%[0.66, 3.25], (226.75) = 2.97, *p* = 0.003), however, the slope varied as a function of age, with a negative effect in the 0 to 6.8 age range ( = -2.94, CI95%[-4.55, -1.34], (226.75) = -3.7, *p* = 0.004), but in the 9.7 to 15.5 interval, this relationship was inverted ( = 1.86, CI95%[0.61, 3.11], (226.75) = 2.93, *p* = 0.009), however, in the rest of the age range the slope was non-significant and virtually zero (Age[7.3, 9.2], = 0.02, CI95%[-1.12, 1.17], (226.75) = 0.06, *p* = 0.45; Age[16, 48], = -0.02, CI95%[-2.05, 2.01], (226.75) = 0.07, *p* = 0.646).

Despite the fact that a similar non-linear effect was observed when inspecting the influence of corrected age in the FM domain scores ( (2.59, 226.77) = 4.2, *p* = 0.005), it was not possible to estimate a significant overall effect different from zero ( = 0.04, CI95%[-0.45, 0.52], (226.77) = 0.14, *p* = 0.886), nevertheless, it was only in the 22.3 to 38.3 age range where a significant and negative effect was observed ( = -0.79, CI95%[-1.45, -0.12], (226.77) = -2.34, *p* = 0.022).

CG abilities were significantly influenced by corrected age ( (5.66, 227.01) = 3.65, *p* = 0.001), with an overall negative effect ( = -1.87, CI95%[-3.17, -0.57], (227.01) = -2.83, *p* = 0.005), and just like the other domains, this relationship was modified across 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 2.81 points ( = 2.81, CI95%[1.18, 4.44], (227.01) = 3.49, *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 1.59 points could be expected in the same domain ( = -1.59, CI95%[-2.82, -0.37], (227.01) = -2.55, *p* = 0.015). The other age intervals did not have a slope that deviated significantly from zero (Age[6.3, 8.7], = 0.05, CI95%[-1.1, 1.2], (227.01) = 0.06, *p* = 0.395; Age[14.5, 48.0], = 0.03, CI95%[-1.99, 2.04], (227.01) = -0.06, *p* = 0.55).

Unlike the others, PS domain was not influenced by corrected age ( (1, 231.58) = 1.16, *p* = 0.282). Accordingly, prematurity (measured in weeks) was not associated with any developmental domain within ASQ-3 assessment (significance for smooth terms: CM, *p* = 0.715; FM, *p* = 0.987; GM, *p* = 0.357; CG, *p* = 0.292; PS, *p* = 0.131).

# 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 in the PS domain, there was no variation observed across corrected age.

This findings might be associated with the described motor impairments of hypotonia in the early stages of life, which compromise the infant’s ability to explore and interact with his or her environment ([Gabis et al., 2021](#ref-gabis2021weak); [Harris, 2008](#ref-harris2008congenital)). A reflection of the aforementioned would be expressed in an 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 a reduced interaction with their environment and peers ([Bodensteiner, 2008](#ref-bodensteiner2008evaluation)). In a recent systematic review ([Gonzalez, Alvarez, & Nelson, 2019](#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, favour 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 ([Gonzalez et al., 2019](#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 key motor milestones in infants ([Bodensteiner, 2008](#ref-bodensteiner2008evaluation); [Gabis et al., 2021](#ref-gabis2021weak); [Harris, 2008](#ref-harris2008congenital)).

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, institutionalisation, exposure to social violence, maternal education and breastfeeding ([Walker et al., 2011](#ref-walker2011inequality)). All together, 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 to an underexplored aspect of congenital myopathies, with robust statistical methods that made it possible 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 explained the observed variability in neurodevelopment. Further research is warranted to determine how these findings apply when controlling for context-mediated social factors and in other 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.

# Funding

Añadir financiamiento si fuese aplicable

No existe financiamiento extraordinario a la aplicación del instrumento.

# Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Acknowledgment

[…]

# References

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

Bodensteiner, J. B. (2008). The evaluation of the hypotonic infant. *Seminars in Pediatric Neurology*, *15*, 10–20. Elsevier.

Bruder, M. B. (2010). Early childhood intervention: A promise to children and families for their future. *Exceptional Children*, *76*(3), 339–355.

Di Rosa, G., Cavallaro, T., Alibrandi, A., Marseglia, L., Lamberti, M., Giaimo, E., … Gagliano, A. (2016). Predictive role of early milestones-related psychomotor profiles and long-term neurodevelopmental pitfalls in preterm infants. *Early Human Development*, *101*, 49–55.

Gabis, L. V., Shaham, M., Leon Attia, O., Shefer, S., Rosenan, R., Gabis, T., & Daloya, M. (2021). The weak link: Hypotonia in infancy and autism early identification. *Frontiers in Neurology*, *12*, 612674.

Gonzalez, S. L., Alvarez, V., & Nelson, E. L. (2019). Do gross and fine motor skills differentially contribute to language outcomes? A systematic review. *Frontiers in Psychology*, *10*, 2670.

Guralnick, M. J. (2017). Early intervention for children with intellectual disabilities: An update. *Journal of Applied Research in Intellectual Disabilities*, *30*(2), 211–229.

Harris, S. R. (2008). Congenital hypotonia: Clinical and developmental assessment. *Developmental Medicine & Child Neurology*, *50*(12), 889–892.

Heo, K. H., Squires, J., & Yovanoff, P. (2008). Cross-cultural adaptation of a pre-school screening instrument: Comparison of korean and US populations. *Journal of Intellectual Disability Research*, *52*(3), 195–206.

Kerstjens, J. M., Nijhuis, A., Hulzebos, C. V., Van Imhoff, D. E., Wassenaer-Leemhuis, A. G. van, Van Haastert, I. C., et al.others. (2015). The ages and stages questionnaire and neurodevelopmental impairment in two-year-old preterm-born children. *PLoS One*, *10*(7), e0133087.

Leyenaar, J., Camfield, P., & Camfield, C. (2005). A schematic approach to hypotonia in infancy. *Paediatrics & Child Health*, *10*(7), 397–400.

Lüdecke, D., Patil, I., Ben-Shachar, M. S., Wiernik, B. M., Waggoner, P., & Makowski, D. (2021). see: An R package for visualizing statistical models. *Journal of Open Source Software*, *6*(64), 3393. <https://doi.org/10.21105/joss.03393>

Makowski, D., Ben-Shachar, M. S., Patil, I., & Lüdecke, D. (2020). Estimation of model-based predictions, contrasts and means. *CRAN*. Retrieved from <https://github.com/easystats/modelbased>

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

Riou, E. M., Ghosh, S., Francoeur, E., & Shevell, M. I. (2009). Global developmental delay and its relationship to cognitive skills. *Developmental Medicine & Child Neurology*, *51*(8), 600–606.

Sarmiento Campos, J. A., Squires, J., & Ponte, J. (2011). Universal developmental screening: Preliminary studies in galicia, spain. *Early Child Development and Care*, *181*(4), 475–485.

Schonhaut, L., Armijo, I., Schönstedt, M., Alvarez, J., & Cordero, M. (2013). Validity of the ages and stages questionnaires in term and preterm infants. *Pediatrics*, *131*(5), e1468–e1474.

Singh, A., Yeh, C. J., & Blanchard, S. B. (2017). Ages and stages questionnaire: A global screening scale. *Boletı́n Médico Del Hospital Infantil de México (English Edition)*, *74*(1), 5–12.

Squires, J., Bricker, D. D., Twombly, E., et al. (2009). *Ages & stages questionnaires*. Paul H. Brookes Baltimore, MD.

Thompson, C. E. (2002). Benign congenital hypotonia is not a diagnosis. *Developmental Medicine and Child Neurology*, *44*(4), 283–286.

Walker, S. P., Wachs, T. D., Grantham-McGregor, S., Black, M. M., Nelson, C. A., Huffman, S. L., et al.others. (2011). Inequality in early childhood: Risk and protective factors for early child development. *The Lancet*, *378*(9799), 1325–1338.

Wickham, H. (2016). *ggplot2: Elegant graphics for data analysis*. Springer-Verlag New York. Retrieved from <https://ggplot2.tidyverse.org>

Wood, S. N. (2003). Thin-plate regression splines. *Journal of the Royal Statistical Society (B)*, *65*(1), 95–114.

Wood, S. N. (2011). Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society (B)*, *73*(1), 3–36.

Wood, S. N. (2017). *Generalized additive models: An introduction with r* (2nd ed.). Chapman; Hall/CRC.

Wood, S. N., N., Pya, & S"afken, B. (2016). Smoothing parameter and model selection for general smooth models (with discussion). *Journal of the American Statistical Association*, *111*, 1548–1575.

**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**. 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.