



Published in final edited form as:

J Pediatr. 2013 March ; 162(3): 606–611.e1. doi:10.1016/j.jpeds.2012.09.011.

Living at higher grounds reduces child neurodevelopment— Evidence from South America

George L. Wehby, MPH, Ph.D. [Associate Professor]

Department of Health Management and Policy, College of Public Health, University of Iowa, 105 River Street, N248 CPHB, Iowa City, IA 52242, Phone: 319-384-3814

George L. Wehby: george-wehby@uiowa.edu

Abstract

Objective—To study the effects of altitude on infant neurodevelopment in the first two years of life.

Study design—Data from a unique study of normal infant neurodevelopment in five South American countries are used. The sample includes 2,116 infants 3–24 months of age who were evaluated for neurodevelopmental problems by study physicians during their routine well-child visits at 31 pediatric practices. We employ regression models with country fixed-effects that compare the neurodevelopment of children born at different altitudes within the same country to avoid confounding. The regressions adjust for several socioeconomic and demographic factors. We also evaluate altitude effects stratifying by sex, age, and household wealth. Infant neurodevelopment was evaluated by physicians using the Bayley Infant Neurodevelopment Screener (BINS). The primary outcome is an indicator for whether the infant is at high risk for neurodevelopmental problems based on the BINS norms.

Results—Altitude significantly increases the probability of being at high risk for neurodevelopmental problems (100-meter increase in altitude: OR= 1.02; 95% CI: 1.001–1.037; high altitude greater than 2,600 meters versus low altitude less than 800 meters: OR=2.01; 95% CI: 1.36–2.973). The effects are larger for females and for second than first year of life. The largest effect is for females 12–24 months of age (high versus low altitude: OR=4.147; 95% CI: 1.466–12.013). There are no significant differences in altitude effects by household wealth.

Conclusions—Altitude may significantly increase the risk of neurodevelopmental problems during the first two years of life, especially for females during their second year of life.

Keywords

Altitude; neurodevelopment; fetal growth; hypoxia; South America

Several previous studies have reported that altitude may have adverse effects on fetal and child growth, particularly on physical outcomes such as birth weight and gestational age.[1–3] Recently, a large study using South American data reported significant declines in birth weight (BW) with altitude increases not just at high ranges but also at relatively low ranges

© 2012 Mosby, Inc. All rights reserved.

The authors declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(less than 1200 meters),[4] confirming previous results from South American and other populations. [5–7] Little is known about how altitude may affect neurological development early in life, other than through its effects on physical growth. Only a few studies have evaluated the effects of altitude on some measures of infant and child neurodevelopment.[8–11] All of these are descriptive, lack appropriate control groups, and include very small samples (less than 100 infants). Understanding the effects of altitude on neurodevelopment is important given that large populations reside at high altitudes, especially in South America. We employ a unique sample from five South American countries to assess the effect of residential altitude within a range of 5 to 3,600 meters on neurodevelopment early in life.

Methods

The study sample includes 2,116 infants born in the following five South American countries between 2005 and 2006: Argentina (662 infants), Brazil (487), Bolivia (116), Chile (387) and Ecuador (464). The infants were enrolled between ages 3 and 24 months including 1,156 infants at less than 12 months and 960 infants at 12–24 months in a study of neurodevelopment of infants without health complications during their well child visits to 31 pediatric practices.[12–14] The geographic location of the study sites, their altitude, and distributions of infants' ethnic ancestries are shown in the Appendix (available at www.jpeds.com). To be eligible for the main study at the time of screening, infants had to be singleton births with birth weight \geq 2500 grams, gestational age \geq 37 weeks, and Apgar scores \geq 6. Infants with the following major complications were ineligible at screening: needing oxygen after birth, admission to neonatal intensive care, spending more than 5 days in the hospital before discharge after birth, chronic illness requiring regular treatment and/or medicine for more than two weeks (except otitis media and allergies), major surgery, previously documented developmental delay, and maternal hospitalization for complications during pregnancy with the infant.

The study physicians (mostly pediatricians) were identified through an epidemiological and birth defect surveillance network called the Latin American Collaborative Study of Congenital Malformations (ECLAMC),[15] with which they were affiliated. The physicians screened infants for eligibility and collected demographic, socioeconomic, and health data from interviews with mothers of enrolled infants at the time of their routine care visits, using the same procedures and data collection instruments across all study sites. The study used a cross-sectional design where most infants completed one study visit (about 10% completed a second visit within two weeks for test-retest reliability assessment). The physicians assessed the neurodevelopment of the infants using the same instrument as described below. The study physicians received training in enrollment procedures and data collection before the initiation of the study.

Outcome Measures

Infant neurodevelopment was evaluated using the Bayley Infant Neurodevelopmental Screener (BINS).[16] The BINS is a standardized instrument designed to screen infants between ages 3 and 24 months for risk of neurodevelopmental problems in four main domains of ability: basic neurological, expressive, receptive, and cognitive functioning. The BINS has good psychometric properties including internal consistency of 0.73–0.85, test-retest reliability 0.71–0.84, and an inter-rater reliability of 0.79–0.96, and is predictive of the child's performance on diagnostic neurodevelopmental instruments including the Bayley Scales of Infant Development (BSID).[16, 17] Before study initiation, the study physicians received standard training in administering the BINS and were evaluated for their reliability in evaluating expert-scored cases, which was 84% on average. [14]The test-retest reliability

of the BINS in this study was 0.8–0.93. [14] The BINS instrument was translated into and administered in Spanish and Portuguese.

Depending on the infant's age, the BINS involves completing 11–13 items that are each scored by 0 (1) if the infant fails (passes) the task/question. Based on the instrument's established norms, the total score ranging from 0 (for failing all items) to 11–13 (for passing all items) can be assigned into a categorical measure indicating the level of risk for neurodevelopmental problems. [16, 17] We use the binary indicator of high versus low risk following the BINS pre-established norm-based thresholds as the neurodevelopment measure for our analysis. [16, 17] The established thresholds for defining BINS risk categories based on the US norms were found in previous work to be appropriate for this South American sample.[14] We also evaluate the infant's score on each of the four BINS domains. These scores are percentages of the highest possible score for each domain (given the child's age) and are calculated by dividing the infant's total score for a certain domain (number of passed items) by the total number of items of that domain for the child's age (multiplied by 100).

Altitude Measures

Altitude is measured at the level of the pediatric practices where the infants were enrolled. We first use a continuous measure of altitude which allows for utilizing the entire altitude variation observed in the sample. This continuous measure does not impose an arbitrary categorization of altitude into low or high thresholds. Furthermore, this measure allows for only using within country variation in altitude, which controls for unobserved differences between countries that relate to both altitude and neurodevelopment. In a separate model, we employ an alternative measure based on a binary indicator for altitude above 2,600 meters versus altitude lower than 800 meters. We choose this threshold as an indicator for high altitude mainly for two reasons: 1- there are no observations in the sample at altitudes between 800 and 2,600 meters; 2- the partial pressure of oxygen drops significantly at altitude above 2,000 meters indicating a greater decrease in arterial oxygen saturation. [18, 19]

Statistical Analyses

We used logistic regression to evaluate the effects of altitude on child neurodevelopment, adjusting for several conceptually relevant covariates. For the continuous altitude measure, we first estimate a conditional fixed-effect logistic regression with country-level fixed effects.[20] By using only within-county variation, this model can account for country differences in both altitude and unobserved factors that are relevant for infant neurodevelopment, such as healthcare characteristics, economic effects, and cultural factors that are not captured by the covariates controlled for in the model. In other words, this model does not compare infants from different countries to each other; it only compares infants from the same country living at different altitudes and estimates an “averaged” effect across all countries using the total sample. In order to evaluate the extent to which unobserved country differences may confound altitude effects on neurodevelopment when ignored, we estimate for comparison to the fixed-effect model a random-effect logistic regression that treats country-level differences as being unrelated to altitude. The random-effect model utilizes both within- and between-country variation.

For the binary indicator for high altitude, we only estimate a random-effect model. We do not estimate a fixed-effect model with the binary indicator because most countries have observations in only one altitude category (ie, all are in low or high altitude); only one country in the sample, Ecuador, has observations at both low and high altitude categories. Because Ecuador has the most within-country variation in altitude in the sample, we re-

estimate the effects of the continuous and high altitude measures separately for Ecuador. This allows us to partially evaluate if the random-effect estimate of the high altitude indicator using the whole sample is biased.

We adjust in the regressions for several conceptually relevant background characteristics that may correlate with both altitude and infant neurodevelopment and that were collected by the study physicians from interviewing the mothers or abstracting clinical records. In addition to theory, the selection of these covariates is also motivated by an extensive literature showing their relevance for child health and development. These include maternal demographic and socioeconomic characteristics: maternal age, marital status, education, and employment/occupational status, all mother-reported. Also included is a household wealth index from principal component analysis of asset ownership and household quality conditions reported by the mother. [12, 13, 21, 22] The index items include: owning a radio, television, refrigerator, and car; employing a worker in the household; working on the family's agricultural land; source of drinking water; type of toilet facility; principal house flooring, roofing and wall material; and number of household individuals per sleeping room. We also adjust for the numbers of the infant's siblings and adult household members (mother-reported). Finally, we also include infant's ethnic ancestry, sex, birth weight, and gestational age. The mother was asked to report all the ancestries that the child has. Following previous studies, the ancestry measure is recoded into three mutually exclusive categories: African (reporting African ancestry with or without other ancestries), Native (reporting Native ancestry with or without other ancestries but no African ancestry), and other ancestries (non-African non-Native ancestries). [6, 12, 13, 21] Even though the sample is limited to infants with birth weight $\geq 2,500$ grams and gestational age ≥ 37 weeks, the study sample still has variation in these measures (Table I) which may correlate with neurodevelopment. Therefore, we adjust for birth weight and gestational age in order to isolate altitude effects on neurodevelopment other than through these two outcomes.

In addition to the main analyses, we also estimate models stratified by infant's age and sex and by household wealth in order to explore their interactions with altitude. Specifically, we evaluate if altitude effects on neurodevelopment vary between the first and second year of life and accumulate over time. Differences in altitude effects by sex may occur due to either biologic or socioeconomic and cultural factors. Finally, we compare altitude effects between poorer households (with a wealth index below median) and richer households (with wealth index above median) in order to evaluate if altitude effects occur mainly through biologic or socioeconomic pathways.

Finally, we descriptively evaluate the relationship between altitude and each of the four BINS domains in order to understand if certain aspects of neurodevelopment are more sensitive to altitude than others. Specifically, we compare the means of the scores for each domain between low and high altitudes using a t-test.

Results

Table I reports a description of the study variables. The sample infants lived at altitudes ranging from 5 to 3,600 meters, with an average altitude of about 750 meters. About one fifth of the sample lived above 2,600 meters. In Ecuador, about 34% of the sample were close to sealevel (average altitude of 72 meters) and 66% were at high altitude (average altitude of 2,831 meters; range from 2,620 to 3,096 meters; Appendix). The sample from Bolivia has only observations at high altitude, and the other three countries have observations only at low altitude. About 10% of the infants had African ancestry and another 43% had Native ancestry. The BINS evaluation indicated that about 20% of the total sample

infants were at high risk of having neurodevelopmental problems (18% of those at low altitude compared with 29% of those at high altitude).

Altitude Effects

The effects of altitude on neurodevelopment risk using the total sample are reported in Table II. Starting with the continuous altitude measure and the country fixed-effect model utilizing within-country variation, altitude has a significant adverse effect on child neurodevelopment; a 100-meter increase in altitude increases high risk for neurodevelopment problems by 1.02 times ($p=0.033$). This effect is comparable with the random-effect model utilizing both within- and between-country variation. The similarity between the fixed and random-effects suggests no unobservable country-level factors that confound the altitude effects in the random-effect model. Next, we evaluate the effect of high altitude ($>2,600$ meters) compared with low altitude (<800 meters) in the total sample using the random-effect model. Compared with low altitude, high altitude doubles high neurodevelopment risk ($p<0.001$).

We also evaluate the effects of the continuous altitude measure and high altitude indicator specifically for Ecuador (Table II). We find overall similar effects to the main sample; a 100-meter increase in altitude increases high risk for neurodevelopmental problems by 1.02 times ($p=0.044$), and high altitude almost doubles this risk ($p=0.049$).

Next, we report in Table III the altitude effects stratified by infant's sex and age and by household wealth. For continuous altitude, we report estimates from both the fixed- and random- effect models. Altitude has larger effects for females than males; a 100-meter increase in altitude significantly increases the risk of neurodevelopment problems among females by 1.03–1.04 times, but the effect for males is smaller ($OR=1.01$ – 1.02) and insignificant in the fixed effects model. The difference by sex is also observed in the effects of the high altitude, which increases the risk of neurodevelopment problems by 3 times for females and 1.9 times for males. Altitude has larger effects at ages 12–24 months than first year of life; a 100-meter increase in altitude increases high risk for neurodevelopmental problems by 1.04 times at ages 12–24 months, but has a smaller effect in the first year (effect is insignificant in the fixed-effect model). Similarly, high altitude ($>2,600$ meters) has larger effects in the second than first year of life (OR of 2.6 and 1.9, respectively). Given these results, we estimate the altitude effects specifically for females in the second year of life, and find larger altitude effects than the previously described estimates. In this group, a 100-meter increase in altitude increases high risk by 1.05 times, and high altitude ($>2,600$ meters) quadruples high risk. Finally, when stratified by wealth, altitude has overall similar effects between poorer and wealthier households.

In Table IV, we show the means of each BINS domain scores separately for the low- and high-altitude groups. There are no differences in neurological functioning/intactness between the two groups. However, there are significant differences in receptive and expressive functioning and a marginally significant difference in cognitive functioning, with lower scores in the high-altitude group. The largest difference is for expressive functioning (7.3 percentage-points) followed by receptive functioning (5.9 percentage-points). Cognitive functioning scores are lower in the high-altitude group by 3 percentage-points.

Discussion

We found that altitude has significant adverse effects on infant neurodevelopment. The effects are larger among females and are more pronounced during the second year of life, suggesting that they accumulate over time. The largest effects are for females aged 12–24 years old, for whom high altitude increases high risk for neurodevelopment problems by 4

times. Also, altitude appears to mostly affect expressive and receptive functions and to have a smaller effect on cognitive functioning.

There are several pathways through which altitude may affect fetal and infant neurodevelopment. Lower oxygen levels and reduced uterine blood flow at higher altitude, resulting in lower oxygen flow to the fetus may lead to permanent neurological impairments that are manifested after birth during early childhood. High altitude may also adversely affect maternal health such as by increasing the risks of pre-eclampsia and gestational hypertension which in turn may affect fetal development. [5] Altitude may also affect fetal and infant neurodevelopment through less direct biologic pathways. For example, through its effects on agriculture and dietary intake, altitude may reduce maternal and infant nutrition.[23, 24] Previous work reported a decrease in maternal body iron with high altitude (>3000 meters) but overall there was no consistent iron decrease with altitude among children. [24] Infant iron deficiency may increase the risk of neurodevelopmental complications. [25] Another less studied potential pathway may be the exposure to environmental hazards such as heavy metals in communities close to mining sites at higher altitude. The differences in altitude effects by infant's sex and age that we observe and the overall similar altitude effects by household wealth suggest that altitude affects infant neurodevelopment mostly through biologic rather than socioeconomic pathways, although these are not ruled out as potential contributors to some of the altitude effects. All these potential pathways deserve future work in order to understand the mechanisms underlying the relationship between altitude and infant neurodevelopment.

The observed effects are important for infant health and development but are not too large to be unrealistic, which provides some validity for the findings. Also, the overall similarity between the results based on within-county variation alone and those that compare children across different countries provides further validity. The findings emphasize the need for healthcare providers and policy makers to recognize that altitude may increase developmental risks not just for physical growth as has been reported,[4] but for neurological and cognitive development. Furthermore, the adverse effects on neurodevelopment are not occurring through altitude effects on physical fetal growth or health problems, as our sample is limited by construction to children without health complications and with birth weight $\geq 2,500$ grams and gestational age ≥ 37 weeks, and we control for variation in birth weight and gestational age above these thresholds. Because altitude effects are likely to be highly biologic and knowledge of their pathways is currently unknown, preventing these risks may be challenging. However, one approach for reducing these risks may involve earlier screening of infants living at high altitude for neurodevelopmental problems and increasing household investments in child neurodevelopment in order to compensate for any deficiencies. Such investments have been found to be effective in enhancing neurodevelopment in South America, especially among infants with lower neurodevelopment.[12] Of course, further research is needed to understand how altitude affects neurodevelopment and to identify the effectiveness of household investments and other interventions in reversing altitude-related neurodevelopmental delays.

Only a few studies have evaluated the effects of altitude on infant neurodevelopmental measures.[8–11] These descriptive and small-sample studies have produced mixed results. Only one study used the BINS and found no elevated risks.[11] However, that study used a much smaller sample (52 infants). Therefore, we are unable to directly compare our results to the literature. Our study sample was recruited in 31 sites in 27 cities (in 22 provinces) in 5 countries and has significant geographic diversity and variation in socioeconomic and demographic characteristics (Table I and the Appendix). This geographic and socioeconomic diversity is expected to enhance the sample representativeness. However, the

pediatric practices were not randomly selected as they were part of an existing network, which may limit the generalizability of the results to the entire infant populations in the study countries. Replicating this study in additional samples and populations would be needed for understanding the generalizability of the study results.

Another limitation is potential measurement error in altitude because it is assigned based on the pediatric practices visited by the infants and not their living addresses. Also, we do not have information on whether the study infants were born and raised in the same area. Differences in altitude between the pediatric practices and infants' homes, as well as between the infants' birth place and current residence (or study pediatric practice), are likely to be limited because parents usually seek the nearest available practices and are likely to reside in the same or nearby city and we studied infants during the first two years of life. However, some infants may reside at higher or lower altitudes than the pediatric practice. This measurement error may attenuate the estimated effects of altitude towards 0, suggesting that the effects may be larger than what we estimate. Therefore, this potential limitation does not change the main inference of the study.

Acknowledgments

The collection of the data used in this paper was supported by NIH/NICHD grant U01 HD0405-61S1.

The author thanks Dr Eduardo E. Castilla and ECLAMC's coordinators and physicians for their efforts in data collection, and Drs Jeffrey C. Murray and Ann Marie McCarthy for providing access to the parent study data.

The outcome data in this work are "derived from the Bayley Infant Neurodevelopment Screener. Copyright © 2004. Harcourt Assessment Inc. Used with Permission. All rights Reserved."

Abbreviations

ECLAMC	Latin American Collaborative Study of Congenital Malformations
BINS	Bayley Infant Neurodevelopmental Screener

References

- Hartering S, Tapia V, Carrillo C, Bejarano L, Gonzales GF. Birth weight at high altitudes in Peru. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2006; 93:275–81. [PubMed: 16678829]
- Moore LG, Young D, McCullough RE, Droma T, Zamudio S. Tibetan protection from intrauterine growth restriction (IUGR) and reproductive loss at high altitude. *American journal of human biology: the official journal of the Human Biology Council*. 2001; 13:635–44. [PubMed: 11505472]
- Unger C, Weiser JK, McCullough RE, Keefer S, Moore LG. Altitude, low birth weight, and infant mortality in Colorado. *Journal of American Medical Association*. 1988; 259:3427–32.
- Wehby GL, Castilla EE, Lopez-Camelo J. The impact of altitude on infant health in South America. *Economics & Human Biology*. 2010; 8:197–211. [PubMed: 20594925]
- Keyes LE, Armaza JF, Niermeyer S, Vargas E, Young DA, Moore LG. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. *Pediatric research*. 2003; 54:20–5. [PubMed: 12700368]
- Lopez Camelo JS, Campana H, Santos R, Poletta FA. Effect of the interaction between high altitude and socioeconomic factors on birth weight in a large sample from South America. *Am J Phys Anthropol*. 2006; 129:305–10. [PubMed: 16323195]
- Jensen GM, Moore LG. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am J Public Health*. 1997; 87:1003–7. [PubMed: 9224184]
- Barker PT. Human adaptation to high altitude. *Science*. 1969; 163:1149–56. [PubMed: 5765326]

9. Bender DE, Auer C, Baran J, Rodriguez S, Simeonsson R. Assessment of infant and early childhood development in a periurban Bolivian population. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation*. 1994; 17:75–81. [PubMed: 7525498]
10. Saco-Pollitt C. Birth in the Peruvian Andes: physical and behavioral consequences in the neonate. *Child Dev*. 1981; 52:839–46. [PubMed: 7285656]
11. Hogan AM, Virues-Ortega J, Botti AB, Bucks R, Holloway JW, Rose-Zerilli MJ, et al. Development of aptitude at altitude. *Developmental science*. 2010; 13:533–44. [PubMed: 20443973]
12. Wehby G, McCarthy AM, Castilla EE, Murray JC. The Impact of Household Investments on Early Child Neurodevelopment and on Racial and Socioeconomic Developmental Gaps in South America. *Forum for Health Economics & Policy*. 2011:14.
13. Wehby, Prater K, McCarthy AM, Castilla EE, Murray JC. The Impact of Maternal Smoking during Pregnancy on Early Child Neurodevelopment. *Journal of Human Capital*. 2011; 5:207–54. [PubMed: 22272363]
14. McCarthy AM, Wehby GL, Barron S, Aylward GP, Castilla EE, Javois LC, et al. Application of neurodevelopmental screening to a sample of South American infants: The Bayley Infant Neurodevelopmental Screener (BINS). *Infant Behav Dev*. 2012; 35:280–94. [PubMed: 22244313]
15. Castilla EE, Orioli IM. ECLAMC: the Latin-American collaborative study of congenital malformations. *Community Genet*. 2004; 7:76–94. [PubMed: 15539822]
16. Aylward, GP. Bayley Infant Neurodevelopmental Screener San Antonio. The Psychological Corporation; 1995.
17. Aylward GP, Verhulst SJ. Predictive utility of the Bayley Infant Neurodevelopmental Screener (BINS) risk status classifications: clinical interpretation and application. *Dev Med Child Neurol*. 2000; 42:25–31. [PubMed: 10665972]
18. Mortola JP, Frappell PB, Aguero L, Armstrong K. Birth weight and altitude: a study in Peruvian communities. *J Pediatr*. 2000; 136:324–9. [PubMed: 10700688]
19. Subhi R, Smith K, Duke T. When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. *Arch Dis Child*. 2009; 94:6–10. [PubMed: 18829620]
20. Wooldridge, JM. *Econometric analysis of cross section and panel data*. Cambridge and London: MIT Press; 2002.
21. Wehby GL, Murray JC, McCarthy AM, Castilla EE. Racial Gaps in Child Health Insurance Coverage in Four South American Countries: The Role of Wealth, Human Capital, and Other Household Characteristics. *Health Services Research*. 2011; 46:2119–38. [PubMed: 21210797]
22. Wehby GL. Child health insurance and early preventive care in three South American countries. *Health Policy Plan*. 2012
23. Niermeyer S, Andrade Mollinedo P, Huicho L. Child health and living at high altitude. *Arch Dis Child*. 2009; 94:806–11. [PubMed: 19066173]
24. Cook JD, Boy E, Flowers C, del Daroca CM. The influence of high-altitude living on body iron. *Blood*. 2005; 106:1441–6. [PubMed: 15870179]
25. Baker RD, Greer FR. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010; 126:1040–50. [PubMed: 20923825]

Table 1

Study Variables

Variable	Description	Mean (SD) or %	Min	Max
High neurodevelopment risk ^a	0/1 indicator for being at high risk of neurodevelopmental problems	20.18	0	1
Neurological ^a	Score of neurological functioning/intactness	98.48 (10.31)	0	100
Receptive ^a	Score of receptive functioning	82.63 (34.10)	0	100
Expressive ^a	Score of expressive functioning	77.63 (20.00)	0	100
Cognitive ^a	Score of cognitive functioning	80.71 (27.79)	0	100
Continuous altitude	Altitude in 100-meter units	7.53 (11.74)	0.05	36
High altitude	0/1 indicator for altitude > 2600 meters versus altitude < 800 meters	19.99	0	1
Birth weight	Infant's birth weight in grams	3295.32 (425.11)	2500	5560
Gestational age	Infant's gestational age in weeks	39.33 (1.01)	37	42
Maternal age	Maternal age in years	27.14 (6.52)	14	47
Single ^b	0/1 indicator for single mothers	15.26	0	1
Stable ^b	0/1 indicator for single mothers	34.97	0	1
Household wealth index	PCA derived wealth index based on asset ownership and household quality	0.00 (1.09)	-5.4	2.43
Primary school incomplete ^c	0/1 indicator for incomplete primary schooling or less	0.52	0	1
Completed primary school ^c	0/1 indicator for mother completing primary schooling	10.63	0	1
Secondary school incomplete ^c	0/1 indicator for mother attending not completing secondary schooling	14.13	0	1
Secondary school complete ^c	0/1 indicator for completing secondary schooling	18.67	0	1
Maternal university incomplete ^c	0/1 indicator for mother attending but not completing university	30.34	0	1
Unqualified worker ^d	0/1 indicator for mother having an unskilled blue collar occupation	6.14	0	1
Qualified worker ^d	0/1 indicator for mother having a skilled blue collar occupation	3.5	0	1
Independent worker ^d	0/1 indicator for mother being an independent workers	5.15	0	1
Clerk ^d	0/1 indicator for mother having a clerical (white collar) occupation	13.66	0	1
Boss, chief, owner ^d	0/1 indicator for mother being a boss, chief, or owner	0.85	0	1
Professional, executive ^d	0/1 indicator for mother being a professional or executive	6.38	0	1

Variable	Description	Mean (SD) or %	Min	Max
African ^e	0/1 indicator for infant having African ancestry	10.16	0	1
Native ^e	0/1 indicator for infant having Native ancestry	42.72	0	1
Male	0/1 indicator for a male child	50.05	0	1
Total siblings	Total number of infant's siblings	0.92 (1.21)	0	8
Total adults	Total number of adults living in the household	3.4 (2.03)	0	21

All statistics are for the 2,116 infants except for the cognitive functioning score which is based on 1,766 infants as there are no cognitive functioning items in the BINS for infants 3–4 months of age.

^aDerived from the Bayley Infant Neurodevelopment Screener. Copyright © 2004. Harcourt Assessment Inc. Used with Permission. All rights Reserved.

^bThe reference category is married.

^cThe reference category is completed university.

^dThe reference category is unemployed.

^eAfrican includes infants reported to have African ancestry (with or without other ancestries). Native includes infants reported to have Native ancestry with or without other ancestries excluding African ancestry). The reference category is other non-African non-Native ancestry (mostly European).

Table 2

Main Altitude Effects on High Neurodevelopment Risk Status

Model	Continuous altitude measure OR [95% CI]	Binary indicator for high versus low altitude OR [95% CI]
Total sample – fixed effects logistic regression	1.019 ** [1.001,1.037]	-
Total sample – random effects logistic regression	1.020 *** [1.006,1.034]	2.011 *** [1.360,2.973]
Ecuador – standard logistic regression	1.025 ** [1.001,1.049]	1.939 ** [1.002,3.752]

**
p < 0.05,

p < 0.01.

Table 3

Altitude Effects on High Neurodevelopment Risk Status Stratified by Selected Characteristics

Model	Continuous altitude measure		Binary indicator for high versus low altitude	Sample Size
	Fixed Effects OR [95% CI]	Random Effects OR [95% CI]	Random Effects OR [95% CI]	
Females	1.032 ** [1.005,1.059]	1.038 *** [1.018,1.059]	3.061 *** [1.644,5.700]	1057
Males	1.011 [0.987,1.035]	1.023 *** [1.006,1.039]	1.872 ** [1.132,3.096]	1059
Infant's age < 12 months	1.009 [0.988,1.030]	1.021 *** [1.005,1.037]	1.909 *** [1.179,3.092]	1156
Infant's age 12–24 months	1.044 ** [1.009,1.081]	1.036 *** [1.017,1.054]	2.649 *** [1.466,4.788]	960
Females in second year of life	1.050 * [0.991,1.113]	1.053 *** [1.018,1.089]	4.147 *** [1.431,12.013]	488
Below median wealth	1.019 [0.996,1.042]	1.029 *** [1.007,1.051]	1.999 [0.872,4.585]	1059
Above median wealth	1.018 [0.988,1.049]	1.027 *** [1.008,1.046]	2.173 *** [1.258,3.752]	1057

* $p < 0.1$,

** $p < 0.05$,

*** $p < 0.01$

Table 4

BINS Domain Scores by Altitude Level

BINS domain	Low-altitude	High-altitude	P-value
Neurological	98.62	97.92	0.21
Receptive	83.82	77.90	0.001
Expressive	79.09	71.76	1.241×10^{-11}
Cognitive	81.31	78.309	0.069

Appendix

Study Sites

City	Province	Country	Altitude in 100-meter units	Infant ancestry			Number of infants
				African (%)	Native (%)	Other (%)	
San Miguel	Tucumán	Argentina	4.36	0.0%	91.11%	8.89%	45
Rosario	Santa Fe	Argentina	0.24	0.0%	27.27%	72.73%	33
Bahia Blanca	Buenos Aires	Argentina	0.05	0.0%	15.79%	84.21%	38
La Plata	Buenos Aires	Argentina	0.1	0.0%	16.46%	83.54%	79
Gualeduaychu	Entre Ríos	Argentina	0.11	0.0%	56.06%	43.94%	66
El Bolson	Río Negro	Argentina	2.5	0.0%	12.96%	87.04%	108
Bahia Blanca	Buenos Aires	Argentina	0.05	0.0%	94.12%	5.88%	51
Isidro Casanova	Buenos Aires	Argentina	0.05	0.0%	71.43%	28.57%	7
Buenos Aires	Buenos Aires	Argentina	0.05	0.0%	91.46%	8.54%	82
Esquel	Chubut	Argentina	5.33	0.0%	91.94%	8.06%	62
Buenos Aires	Federal Capital	Argentina	0.05	0.0%	56.04%	43.96%	91
La Paz	Murillo	Bolivia	36	0.0%	100.00%	0.00%	44
La Paz	Murillo	Bolivia	36	0.0%	45.83%	54.17%	72
Sao Paulo	Sao Paulo	Brazil	7.31	45.2%	16.67%	38.10%	42
Porto Alegre	Rio Grande do Sul	Brazil	0.11	44.0%	29.33%	26.67%	75
Joao Pessoa	Paraiba	Brazil	0.05	43.4%	0.00%	56.58%	76
Salvador	Bahia	Brazil	0.05	86.6%	9.76%	3.66%	82
Porto Alegre	Rio Grande do Sul	Brazil	0.1	24.1%	39.66%	36.21%	58
Campinas	Sao Paulo	Brazil	6.93	50.0%	43.90%	6.10%	82
Florianopolis	Santa Catarina	Brazil	0.24	0.0%	0.00%	100.00%	72
Linares	Linares	Chile	1.78	0.0%	91.18%	8.82%	68
Rancagua	Cachapoal	Chile	5	0.0%	3.30%	96.70%	91
Curico	Curico	Chile	2.14	0.0%	42.86%	57.14%	133
Talca	Maule	Chile	2.76	0.0%	95.77%	4.23%	71
Santiago	Santiago	Chile	6	0.0%	100.00%	0.00%	24
Azogues	Cañar	Ecuador	28.83	0.0%	57.50%	42.50%	80

City	Province	Country	Altitude in 100-meter units	Infant ancestry			Number of infants
				African (%)	Native (%)	Other (%)	
Chone	Manabi	Ecuador	1.1	1.2%	0.00%	98.78%	82
Quito	Pichincha	Ecuador	28.5	0.0%	17.11%	82.89%	76
Ibarra	Imbabura	Ecuador	26.2	3.1%	7.29%	89.58%	96
Cañar	Cañar	Ecuador	30.96	0.0%	100.00%	0.00%	55
Portoviejo	Manabi	Ecuador	0.3	0.0%	53.33%	46.67%	75