Journal of Developmental Origins of Health and Disease (2017), **8**(2), 188–195.

doi:10.1017/S2040174416000751

ORIGINAL ARTICLE

Age at menarche in relation to prenatal rainy season exposure and altitude of residence: results from a nationally representative survey in a tropical country

E. C. Jansen[1]*, O. F. Herrán[2], N. L. Fleischer[1,3], A. M. Mondul[1] and E. Villamor[1,4]

[1]*Nutritional Sciences Department, University of Michigan School of Public Health, Ann Arbor, MI, USA*
[2]*School of Nutrition and Dietetics, Faculty of Health, Industrial University of Santander, Bucaramanga, Colombia*
[3]*Center for Social Epidemiology and Population Health, University of Michigan, School of Public Health, Ann Arbor, Michigan*
[4]*Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan*

Intrauterine exposure to the rainy season in the tropics may be accompanied by high rates of infection and nutritional deficiencies. It is unknown whether this exposure is related to the extrauterine timing of development. Our aim was to evaluate the relations of prenatal exposure to the rainy season and altitude of residence with age at menarche. The study included 15,370 girls 10 to <18 years old who participated in Colombia's 2010 National Nutrition Survey. Primary exposures included the number of days exposed to the rainy season during the 40 weeks preceding birth, and altitude of residence at the time of the survey. We estimated median menarcheal ages and hazard ratios with 95% confidence interval (CI) according to exposure categories using Kaplan–Meier cumulative probabilities and Cox proportional hazards models, respectively. All tests incorporated the complex survey design. Girls in the highest quintile of gestation days exposed to the rainy season had an earlier age at menarche compared with those in the lowest (adjusted hazard ratios (HR) = 1.08; 95% CI 1.00–1.18, *P*-trend = 0.03). Girls living at altitudes ⩾2000 m had a later age at menarche compared with those living <1000 m (adjusted HR = 0.88; 95% CI 0.82–0.94, *P*-trend <0.001). The inverse association between gestation days during the rainy season and menarche was most apparent among girls living at altitudes ⩾2000 m (*P*, interaction = 0.04). Gestation days exposed to the rainy season and altitude of residence were associated with the timing of sexual maturation among Colombian girls independent of socioeconomic status and ethnicity.

Received 29 July 2016; Revised 23 November 2016; Accepted 25 November 2016; First published online 24 January 2017

Key words: altitude, menarche, puberty, rainy, season

Introduction

The age at menarche, or timing of a girl's first menstrual period, is a reliable marker of puberty. An earlier age at menarche is related to adverse health outcomes including breast cancer and all-cause mortality.[1,2] The timing of menarche is relevant from a public health perspective because it could be responsive to environmental conditions occurring as early as the prenatal period.[3]

In tropical climates there is a rainy season characterized by increased precipitation, reductions in temperature and sunlight,[4] higher transmission rates of some infections,[5] and decreased availability of food.[6] When pregnancy overlaps with the rainy season, mothers and fetuses may be at high risk of infections and nutritional deficiencies.[7] Intrauterine exposure to these factors could act as a prediction of prevailing extrauterine conditions and signal the offspring to alter their development plan in a way that maximizes survival and reproductive potential.[8] Accelerating the timing of sexual maturation could constitute one of those adaptations. Some studies conducted in temperate climates found associations between the season of birth and onset of puberty in the offspring.[9,10] For example, a study among Polish women reported a slightly earlier mean age at menarche among those born in summer compared with those born in other seasons (13.1 years for summer-born women *v.* 13.4 years for winter-born, 13.3 years for spring-born, and 13.2 years for fall-born; $P < 0.01$).[9] Another study among women from the U.S. reported a statistically significant earlier average age at menarche among women born in February (12.7 years) compared with those born in December (13.2 years; $P < 0.04$).[10] However, this has not been investigated in tropical climates where the effects of season on health could be substantial.

Altitude of residence is another environmental factor that may affect the timing of sexual maturation. Studies in Peru and Bolivia found that girls living at altitudes >3000 m had older ages at menarche compared with girls living in elevations <500 m; these observations were attributed to the lower oxygen availability at higher compared with lower elevations.[11–13] Nevertheless, some argued that these variations could be explained by differences in socioeconomic status (SES) and access to nutrition rather than altitude.[14]

The aim of this study was to assess whether a higher number of gestation days exposed to the rainy season was related to an

---

*Address for correspondence: E. C. Jansen, Department of Nutritional Sciences, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109, USA.
(Email janerica@umich.edu)

earlier age at menarche. We also examined the association of altitude of residence with age at menarche. In addition, as seasonality may differ according to altitude, we ascertained whether the relation between gestation days exposed to the rainy season and age at menarche was modified by altitude of residence.

Methods

Study population

The Colombian National Nutrition Survey (ENSIN) was conducted in 2010 by the Colombian Institute of Family Welfare [Instituto Colombiano de Bienestar Familiar (ICBF)] in conjunction with the Colombian Demographic and Health Survey (ENDS). The survey methodology has been described in detail elsewhere.[15] Briefly, a multistage stratified sampling scheme was employed to select participants representing 99% of the Colombian population. All municipalities from the 32 departments in the country were grouped into strata based on similar geographic and sociodemographic characteristics. One municipality was randomly chosen from each stratum with the probability of being chosen proportional to the population size. Clusters of about 10 households were randomly selected within strata and all household members were invited to participate. A total 50,670 households were included.

Trained personnel administered questionnaires to the head of each household to obtain sociodemographic information of all family members. Girls aged 10 to <18 years were asked to recall the age in years and months when their first menstrual period had occurred or if it had not yet occurred. Geographic information on the households including region and altitude of residence was abstracted from the National Department of Statistics [Departmento Administrativo Nacional de Estadistica (DANE)] and included in the survey datasets.

Data sources

The survey included 188,599 people; 16,940 were girls 10 to <18 years of age. We excluded 1570 girls with missing information on menarche or date of birth or who answered 'don't know' to either of these questions. Thus, the final sample comprised 15,370 girls born from 1992–2000.

The primary outcome was age at menarche, estimated in decimal years from the age of occurrence reported in years and months. There were two primary exposures: gestation days exposed to the rainy season and altitude of residence at the time of the survey.

To calculate gestation days exposed to the rainy season, we assumed as the exposure period the 40 weeks before and including the birthdate. Each day coinciding with the rainy season within the exposure period contributed to a summary measure for each girl. This assignment was region-specific, depending on the weather pattern of the region. There are five major geographic regions in Colombia: Andean, Pacific, Atlantic, Orinoquian and Amazonian. Based in part on rainfall data collected from 1972 to 1998, rainy seasons in the Andean and Pacific regions occur from April to May and September to November, whereas there is only one rainy season in the Atlantic (May to October), Eastern Andean piedmont (July to August), and Orinoquian (April to November) regions.[16,17] The Amazonian region does not experience much variability in rainfall throughout the year, although from December to May the precipitation is slightly higher (according to data averaging years 1964–2003);[18] thus, we assigned exposure to the rainy season to the gestation days that occurred between December and May in the Amazonian region. The number of gestation days exposed to the rainy season was categorized into quintiles, weighted according to the complex survey design. It was also considered as a continuous variable, expressed per 30 days of gestation.

Altitude of residence (in meters) at the time of the survey for each girl was abstracted from the ENSIN data set and categorized into altitude of residence zones as 0–999, 1000–1999 or ⩾2000 m. It was also considered as a continuous exposure, expressed per 500 m. We assumed that altitude of residence at the time of the survey was a proxy for altitude of residence during gestation.

Other covariates were year of birth, race/ethnicity, maternal education, wealth index and geographic region. Race/ethnicity, maternal education and wealth index were defined as previously described.[19] Although wealth index and maternal education were measured at the time of the survey, we assumed that they were proxies for the SES of the girls' family environment during her intrauterine life.

Statistical analysis

Analyses were conducted with the use of the complex survey design routines of Stata statistical software package version 13 (StataCorp, College Station, TX, USA).

We first compared the distribution of sociodemographic predictors of age at menarche according to the primary exposures. For categorical predictors, we estimated proportions ± S.E. in each category of the primary exposure, and performed Rao-Scott χ^2-tests. For continuous characteristics, we estimated means ± S.E. We performed tests for linear trend using linear regression models in which a variable representing the quintiles of gestation days exposed to the rainy season or altitude of residence zone was introduced as a continuous predictor.

To analyze the relations between the primary exposures and age at menarche, we employed time-to-event analytic techniques, including the Kaplan–Meier method and Cox proportional hazards models, which consider as the outcome the time from birth to the age when menarche occurred. These methods allow the combination of information on menarcheal age from post-menarcheal girls with the last known age when menarche had not occurred (age at the survey interview) from pre-menarcheal girls in the estimation of the population median age at menarche and hazard ratios (HR). The 'right censoring' of the data that arises from the inclusion of pre-menarcheal girls is appropriately accounted for.[20] In bivariate analysis, we estimated the weighted median age at menarche by exposure categories using Kaplan–Meier cumulative probabilities. For girls who had not yet experienced menarche, the censoring time was age at interview, estimated as date of interview minus birthdate. Cox proportional hazards models were used to estimate HR and 95% confidence intervals (CI), accounting for the complex survey design. Hazards represent the instantaneous rate of the event at any given time point for a given exposure group. HRs <1 indicate a later age at menarche compared with the reference group, whereas HRs >1 represent an earlier age. We conducted tests for linear trend by introducing into the models a variable representing ordinal categories of each exposure as a continuous covariate. The proportional hazards assumption was verified with the use of terms for the interaction between time and covariates. This assumption was met in all models.

Next, we estimated adjusted HRs and 95% CI with a model that included indicator variables for the gestation days exposed to rainy season quintiles in addition to year of birth, race/ethnicity, wealth index and geographic region (Amazonian and Orinoquian regions were collapsed into one category due to small sample sizes). For altitude of residence, HRs and 95% CI were adjusted for race/ethnicity, maternal education and wealth index. We did not include geographic region due to issues of collinearity.

We also examined whether the relation of gestation days exposed to the rainy season and age at menarche differed according to altitude of residence zones. We used a Cox proportional hazards model that included gestation days exposed to the rainy season as a continuous exposure, altitude of residence zone as an ordinal variable and their interaction terms. Estimates were adjusted for year of birth, race/ethnicity and wealth index. The interaction between gestation days exposed to the rainy season and altitude of residence was tested with the use of Type III Wald's tests. All tests incorporated the complex survey design.

Results

The mean ± s.d. age of girls at the time of the interview was 13.9 ± 2.3 years. In total, 33% of the girls had not experienced menarche and were censored.

The weighted mean ± s.e. number of gestation days that occurred during the rainy season was 115.3 ± 0.4. Girls born 1992–1993 had fewer gestation days during the rainy season than girls born after 1993. Also, girls of Mestizo-Caucasian ethnicity had fewer gestation days during the rainy season compared with those of Afro-Colombian or Indigenous ethnicity (Table 1). The number of gestation days during the rainy season was non-monotonically inversely related to household wealth index. In addition, it was higher in girls from

Table 1. *Sociodemographic characteristics according to weighted quintiles of gestation days exposed to the rainy season among Colombian girls born 1992–2000*[a]

Characteristics	Q1[b] (*n* = 2656)	Q2 (*n* = 3157)	Q3 (*n* = 2517)	Q4 (*n* = 2926)	Q5 (*n* = 4114)	*P*[c]
Gestation days exposed to the rainy season	69 ± 0.6	95 ± 0.1	112 ± 0.2	138 ± 0.2	169 ± 0.4	
Year of birth (%)						0.01
1992–1993	22.4 ± 0.9	18.2 ± 0.9	17.5 ± 1.0	16.1 ± 0.9	17.6 ± 0.8	
1994–1995	24.0 ± 1.0	25.9 ± 1.0	24.1 ± 1.0	25.3 ± 1.0	27.0 ± 1.0	
1996–1997	23.3 ± 0.9	25.6 ± 1.0	26.0 ± 1.1	25.9 ± 1.1	25.6 ± 0.9	
1998–2000	30.2 ± 1.0	30.3 ± 1.0	32.4 ± 1.2	32.7 ± 1.2	29.8 ± 1.0	
Race/ethnicity (%)						<0.001
Mestizo-Caucasian	89.2 ± 0.7	86.7 ± 0.8	82.5 ± 1.0	81.3 ± 1.0	80.4 ± 0.1	
Indigenous	2.6 ± 0.4	4.1 ± 0.4	4.8 ± 0.5	5.5 ± 0.6	5.7 ± 0.5	
Afro-Colombian	8.2 ± 0.6	9.2 ± 0.7	12.7 ± 0.9	13.3 ± 0.8	13.9 ± 0.9	
Maternal education (years)	7.8 ± 0.08	7.6 ± 0.07	7.8 ± 0.08	7.9 ± 0.08	7.8 ± 0.08	0.41
Wealth index[d]	2.9 ± 0.04	2.7 ± 0.04	3.0 ± 0.04	3.0 ± 0.04	2.6 ± 0.04	0.006
Geographic region						<0.001
Andean	78.5 ± 0.9	60.6 ± 1.1	61.8 ± 1.3	59.0 ± 1.2	26.3 ± 1.2	
Pacific	0.3 ± 0.1	26.9 ± 1.0	14.4 ± 0.8	16.4 ± 0.8	52.4 ± 1.2	
Atlantic	18.0 ± 0.9	6.9 ± 0.6	22.8 ± 1.1	23.5 ± 1.0	11.5 ± 0.7	
Amazonian	0.0	1.9 ± 0.2	1.0 ± 0.1	0.8 ± 0.0	2.8 ± 0.2	
Orinoquian	3.2 ± 0.3	3.8 ± 0.4	0.0	0.4 ± 0.0	7.0 ± 0.4	

[a] Values are weighted proportions or means ± SE.

[b] Weighted quintiles of gestation days that occurred during rainy season, based on region of residence and date of birth.

[c] For categorical characteristics, *P*-values are from Rao-Scott χ^2-tests. For continuous characteristics, tests for trend are from a linear regression model in which a variable representing weighted quintiles of gestation days exposed to the rainy season was introduced as a continuous predictor.

[d] The wealth index is a composite measure of the household's living standard. It is constructed from principal component analysis of a number of household assets including type of flooring, number of bedrooms, type of toilet and mode of transportation.

the Pacific, Amazonian and Orinoquian regions compared with those from other geographic regions.

The weighted mean ± S.E. altitude of residence was 1194 ± 16 m. Girls of Afro-Colombian ethnicity were more likely to reside in the lowest altitude zone compared with girls of other ethnicities (Table 2). In addition, altitude of residence was positively related to maternal education, wealth index and living in the Andean region.

The weighted median age at menarche was 12.6 years (interquartile range (IQR) 12.0–13.5). In bivariate analysis, the number of gestation days exposed to the rainy season was related to earlier menarche (HR for Q5–Q1 = 1.09, 95% CI 1.02–1.18; *P*, trend = 0.002, Table 3). After adjustment for year of birth, ethnicity, wealth index and geographic region, girls in the highest weighted quintile had a 8% higher probability of menarche compared with those in the lowest quintile (HR for Q5–Q1 = 1.08, 95% CI 1.00–1.18, *P*, trend = 0.03).

In bivariate analysis, altitude of residence was not related to age at menarche (Table 3). However, after adjustment for ethnicity, maternal education, and wealth index, altitude of residence was significantly related to later age at menarche. Girls living at an altitude $\geqslant$2000 m had a 12% lower probability of menarche compared with girls living at an altitude <1000 m (HR = 0.88, 95% CI 0.82–0.94; *P*, trend <0.001).

The association between gestation days exposed to the rainy season and age at menarche varied according to altitude of residence (Table 4). There was no association between gestation days exposed to the rainy season and menarche at an altitude of residence <2000 m, whereas there was an 8% higher hazard of menarche for every 30 gestation days exposed to the rainy season among girls living at an altitude $\geqslant$2000 m (HR = 1.08, 95% CI 1.03–1.14, *P*, interaction = 0.04).

Discussion

In this nationally representative sample of Colombian girls born 1992–2000, we found that a higher number of gestation days exposed to the rainy season was related to an earlier age at menarche, whereas a higher altitude of residence was associated with a later age at menarche. We also noted that the inverse relation between gestation days exposed to the rainy season and menarche was mostly apparent among girls residing at altitudes $\geqslant$2000 m.

Our finding on the relation between prenatal rainy season exposure and age at menarche in the context of a tropical climate is novel. A few studies have examined whether season of birth is associated with age at menarche in temperate regions, although results are mixed.[9,10,21–24] One recent study among 1,697 Polish women found that those who were born during summer months (June to August) reported an average age at menarche that was 0.1, 0.3 and 0.2 years earlier than did women born during fall, winter and spring, respectively ($P < 0.01$).[9] In another study among 950 women from the United States, those born in February had an average age at menarche that was 0.5 years earlier than the menarche of women born in December ($P < 0.04$).[10] This difference was

Table 2. *Sociodemographic characteristics according to altitude of residence among Colombian girls born 1992–2000*[a]

	Altitude of residence			
Characteristics	0–999 m (*n* = 9982)	1000–1999 m (*n* = 3378)	$\geqslant$2000 m (*n* = 2010)	*P*[b]
Year of birth (%)				0.78
1992–1993	18.0 ± 0.5	18.6 ± 0.8	19.1 ± 0.9	
1994–1995	25.6 ± 0.5	25.5 ± 0.9	24.3 ± 1.1	
1996–1997	25.3 ± 0.5	24.6 ± 0.8	25.9 ± 1.1	
1998–2000	31.1 ± 0.6	31.4 ± 1.0	30.6 ± 1.1	
Race/ethnicity (%)				<0.001
Mestizo-Caucasian	77.3 ± 0.8	87.2 ± 1.0	93.8 ± 0.8	
Indigenous	4.6 ± 0.3	4.4 ± 0.7	4.4 ± 0.7	
Afro-Colombian	18.1 ± 0.7	8.4 ± 0.8	1.8 ± 0.4	
Maternal education (years)	7.6 ± 0.05	7.6 ± 0.08	8.3 ± 0.09	<0.001
Wealth index	2.5 ± 0.03	2.8 ± 0.05	3.5 ± 0.04	<0.001
Geographic region				<0.001
Andean	31.3 ± 0.9	74.2 ± 1.2	89.9 ± 1.0	
Pacific	42.6 ± 0.9	3.8 ± 0.6	1.3 ± 0.5	
Atlantic	17.4 ± 0.7	22.0 ± 1.1	8.9 ± 0.9	
Amazonian	2.7 ± 0.1	0.0	0.0	
Orinoquian	6.0 ± 0.3	0.0	0.0	

[a] Values are weighted proportions or means ± SE.

[b] For categorical characteristics, *P*-values are from Rao-Scott χ^2-tests. For continuous characteristics, tests for trend are from a linear regression model in which a variable representing altitude of residence zone was introduced as a continuous predictor.

Table 3. *Age at menarche according to gestation days exposed to the rainy season and altitude of residence among Colombian girls born 1992–2000*

	n	Median age at menarche (years)[a]	Unadjusted hazard ratio (95% CI)[b]	Adjusted hazard ratio (95% CI)[c]
Gestation days exposed to rainy season (weighted quintiles)				
Q1 (median = 75 days)	2656	12.8	1.00	1.00
Q2 (median = 97 days)	3157	12.7	1.03 (0.96, 1.11)	1.02 (0.95, 1.11)
Q3 (median = 112 days)	2517	12.6	1.05 (0.97, 1.13)	1.02 (0.94, 1.10)
Q4 (median = 137 days)	2926	12.5	1.11 (1.04, 1.20)	1.08 (1.00, 1.17)
Q5 (median = 177 days)	4114	12.6	1.09 (1.02, 1.18)	1.08 (1.00, 1.18)
P (trend)[d]			0.002	0.03
Per 30 days			1.03 (1.01, 1.04)	1.02 (1.00, 1.04)
P[e]			0.008	0.10
Altitude of residence				
0–999 m	9982	12.6	1.00	1.00
1000–1999 m	3378	12.8	0.92 (0.88, 0.98)	0.88 (0.83, 0.93)
⩾2000 m	2010	12.5	0.98 (0.91, 1.04)	0.88 (0.82, 0.94)
P (trend)			0.27	<0.001
Per 500 m			1.00 (0.98, 1.01)	0.97 (0.96, 0.99)
P[e]			0.52	<0.001

[a] From Kaplan–Meier survival probabilities.

[b] From a Cox proportional hazards models with age at menarche as the outcome and indicator variables for weighted quintiles of gestation days during the rainy season as the predictor or a continuous variable for days of exposure.

[c] Estimates for gestation days exposed to the rainy season were from a Cox proportional hazards model adjusted for year of birth, race/ethnicity, wealth index and geographic region. Estimates for altitude of residence were from a Cox proportional hazards model adjusted for race/ethnicity, maternal education and wealth index.

[d] From a Cox proportional hazards model in which a variable representing ordinal categories of the exposure was introduced as a continuous predictor and tested with an adjusted Wald's test.

[e] From an adjusted Wald's test.

Table 4. *Age at menarche per 30 gestation days exposed to the rainy season, stratified by altitude of residence among Colombian girls born 1992–2000*

	Unadjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Altitude of residence	Per 30 gestation days exposed to the rainy season	Per 30 gestation days exposed to the rainy season
0–999 m	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
1000–1999 m	1.02 (0.96, 1.07)	1.00 (0.95, 1.06)
⩾2000 m	1.11 (1.05, 1.16)	1.08 (1.03, 1.14)
P (interaction)	0.001	0.04

[a] From a Cox proportional hazards model with age at menarche as the outcome and predictors that included gestation days occurring during the rainy season (continuous), altitude of residence (categorical) and their interaction terms.

[b] From a Cox proportional hazards model adjusted for year of birth, race/ethnicity and wealth index.

only statistically significant when the analyses were restricted to women born before 1970. In contrast, studies in the United Kingdom, United States, Denmark and Italy reported no association between season of birth and age at menarche.[21–24]

The rainy season in tropical climates is characterized by lower sunlight exposure[25] which could be related to vitamin D deficiencies[26] or decreases in photoperiod-mediated melatonin concentrations.[27] The rainy season is also marked by higher transmission rates of infectious diseases including dengue,[28] malaria[29] and respiratory infections.[30] In addition, it may be linked to food shortages.[31] Hence, the finding that a higher number of gestation days exposed to the rainy season was associated with an earlier menarche is consistent with the notion that adverse early-life conditions may be related to earlier onset of sexual maturation. There are a few specific pathways that may contribute to explain this association. Lower serum vitamin D levels during middle childhood were related to an earlier age at menarche in a prospective study of girls from Bogotá, Colombia.[32] Although there is no evidence for an effect of vitamin D deficiency during pregnancy on the onset of puberty, a recent study among 977 U.K. women showed that gestational vitamin D deficiency was related to higher adiposity in the offspring at age 4 and 6 years.[33] Childhood obesity is a predictor of earlier age at menarche.[34] Another potential mechanism related to decreased sunlight exposure during pregnancy involves photoperiod effects. Some studies have suggested that higher sunlight exposure in peripubertal years may trigger menarche.[10] It is plausible that rhythmicity in exposure to photoperiods during pregnancy affects the development of the fetal circadian system,[27] altering the offspring's response to light cycles around the time of puberty. Our finding could also have to do with a higher rate of infectious disease transmission or lower availability of food during the rainy season compared with the dry season. One consequence of these insults is reduced nutrient availability to the fetus.[35] This could act as a prediction of nutrient scarcity in the extrauterine environment, leading to an acceleration in the timing of puberty as an adaptive mechanism to optimize reproductive success.[36] Although human studies are lacking, experimental animal research supports the notion that undernutrition during pregnancy may result in accelerations in the timing of sexual maturation of the offspring.[37] In addition, some epidemiological studies have linked prenatal undernutrition with higher incidence of adult obesity.[38] An earlier menarche is related to increased risk of adult obesity.[39]

We found that girls residing at higher altitudes had later menarche than girls living at lower altitudes independent of socioeconomic conditions. This finding is in agreement with results from studies in Peru and Bolivia.[11–13] In these studies, girls residing at altitudes >3000 m had later ages at menarche than girls residing at altitudes <500 m. For example, among 4142 Peruvian girls, those living at an altitude of 3400 m had a mean menarcheal age of 13.7 years, whereas girls living at sea level had a mean age at menarche of 12.2 years.[12] Later sexual maturation among high altitude dwellers has been explained as an energy trade-off to allow for accelerated growth of the lungs and chest.[40] Thus, the observed association with altitude may not necessarily be due to exposure to a higher altitude during pregnancy, but throughout childhood.

We also found that the relation between gestation days exposed to the rainy season and menarche was mostly apparent at altitudes ⩾2000 m. This could be due to more seasonal variation at higher altitudes. For example, the seasonal incidence of respiratory infections could be more marked at higher elevations.[9] It is also plausible that cooler overall temperatures at high altitudes are correlated with greater differences in seasonal behavior among pregnant women, which could affect exposure to sunlight (e.g. through clothing choices).

Our study has several strengths. The 2010 ENSIN survey provided adequate statistical power; in addition, the estimates are nationally representative. Few nation-wide studies have collected information on age at menarche. The ability to adjust for important socioeconomic variables was also a strength, particularly in the analysis of altitude. There were also limitations. We lacked information on gestational age at delivery; thus, exposure to rainy season days could have been misclassified in girls delivered pre- or post-term. If girls delivered pre-term had later ages at menarche[41] and had fewer gestation days during the rainy season than assigned, estimates might represent an underestimation of the true underlying effect. The lack of information on gestational age at delivery also prevented us from examining effects of rainy season exposure during each trimester of pregnancy. We did not have access to rainfall data during the specific birth years of the participants; rather, we used historical weather data spanning from 1972 to 1998 (or 1964 to 2003 for Orinoquian region). This is another source of potential misclassification of the number of gestation days exposed to the rainy season. There is also a possibility of outcome misclassification, although research in a similar setting suggests that the short-term recall of menarche is reliable.[42] Furthermore, we would not expect that recall of menarche would be differential with respect to the exposures examined. Girls <10 years were not asked about menarche. This could result in selection bias if there was a meaningful number of girls born after 2000 with menarche <10 years who differed with respect to exposure status from girls ⩾10 years of age. However, there are likely very few girls with menarche before 10 years of age; among girls born 1992–2000, only 0.9% had menarche before their 10th birthday. Some girls came from the same households and this could violate the assumption of independence in the estimation of variances. Nevertheless, the within-household component of the variances is likely negligible compared with that arising from clustering of households as sampling units,[43] which was fully accounted for. Causal inference may also be hindered by residual confounding of the estimates due to ethnic composition or SES. Our measures of SES were only a proxy for socioeconomic conditions during the girls' intrauterine life, as they were measured at the time of the outcome measurement. Nonetheless, they are likely to be reasonable proxies because intragenerational social mobility in Colombia was relatively low during this period.[44] Similarly, we do not have knowledge on whether altitude of residence at the time of the survey was reflective of that during gestation. Notwithstanding, if altitude of residence at the time of the survey resulted in random misclassification of altitude during gestation and/or childhood, it could mean that the estimates obtained were attenuated compared with the true estimates. Finally, we did not have information on maternal pre-pregnancy body mass index or physical activity levels, which prevented us from considering them as potential adjustment variables.

In summary, a higher number of gestation days exposed to the rainy season was related to an earlier age at menarche in a nationally representative sample of Colombian girls; this finding was mostly apparent among girls residing in altitudes ⩾2000 m. Conversely, higher altitude of residence in this Colombian population was related to a later age at menarche after adjustment for SES indicators.

Acknowledgments

The following organizations participated in the Colombian National Nutrition Survey and the National Demographic and Health Survey (ENDS): Ministry of Health and Social Protection (Ministerio de Salud y Protección Social), National Institute of Health (Instituto Nacional de Salud), Profamilia, Association of Nutrition and Dietetic Schools (Asociación de Facultades de Nutrición y Dietética), Administrative Department of Recreational Sport, Physical Activity, and Use of Free

Time (Departamento Administrativo del Deporte la Recreación, la Actividad Física y el Aprovechamiento del Tiempo Libre), National Administrative Department of Statistics (Departamento Administrativo Nacional de Estadística), Panamerican Health Organization, World Food Program, International Organization for Migration, and United States Agency for International Development (USAID).

Financial Support

This research received no specific grant from any funding agency or from commercial, or not-for-profit sectors.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. The Research Ethics Review Board at the Colombian Institute of Family welfare approved the survey protocol and all participants provided written informed consent. The Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan determined that analyses of these anonymized data were exempt from review.

References

1. Horn J, Opdahl S, Engstrom MJ, *et al.* Reproductive history and the risk of molecular breast cancer subtypes in a prospective study of Norwegian women. *Cancer Causes Control*. 2014; 25, 881–889.
2. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *Am J Epidemiol*. 2014; 180, 29–40.
3. Cole TJ. Secular trends in growth. *Proc Nutr Soc*. 2000; 59, 317–324.
4. Instituto Geografico Agustin Codazzi. Imprenta Nacional de Colombia: Bogota, Cundinamarca, Colombia, 49–50.
5. Ramirez AP, Mendoza AR, Montoya JM, *et al.* Mortality associated with peak seasons of influenza virus circulation in Bogota, Colombia, 1997-2005. *Rev Panam Salud Publica*. 2009; 26, 435–439.
6. Ntwenya JE, Kinabo J, Msuya J, Mamiro P, Majili ZS. Dietary patterns and household food insecurity in rural populations of Kilosa district, Tanzania. *PLoS One*. 2015; 10, e0126038.
7. Moore SE, Cole TJ, Poskitt EM, *et al.* Season of birth predicts mortality in rural Gambia. *Nature*. 1997; 388, 434.
8. Gluckman PD, Beedle AS, Hanson MA, Low FM. Human growth: evolutionary and life history perspectives. *Nestle Nutr Inst Workshop Ser*. 2013; 71, 89–102.
9. Klis K, Jarzebak K, Borowska-Struginska B, *et al.* Season of birth influences the timing of first menstruation. *Am J Hum Biol*. 2015; 2, 226–232.
10. Matchock RL, Susman EJ, Brown FM. Seasonal rhythms of menarche in the United States: correlates to menarcheal age, birth age, and birth month. *Womens Health Iss*. 2004; 14, 184–192.
11. Gonzales GF, Villena A. Body mass index and age at menarche in Peruvian children living at high altitude and at sea level. *Hum Biol*. 1996; 68, 265–275.
12. Freyre EA, Ortiz MV. The effect of altitude on adolescent growth and development. *J Adolesc Health Care*. 1988; 9, 144–149.
13. Greksa LP. Age of menarche in Bolivian girls of European and Aymara ancestry. *Ann Hum Biol*. 1990; 17, 49–53.
14. Wiley AS. *An Ecology of High-Altitude Infancy: A Biocultural Perspective*. 2004. Cambridge University Press: New York, USA.
15. *Encuesta Nacional de la Situacion Nutricional en Colombia 2010*. Bogotá: ICBF, Instituto Colombiano de Bienestar Familiar; 2011.
16. Poveda G, Alvarez DM, Rueda OA. Hydro-climatic variability over the Andes of Colombia associated with ENSO: a review of climatic processes and their impact on one of the Earth's most important biodiversity hotspots. *Climate Dynam*. 2011; 36, 2233–2249.
17. Pacheco Y, Leon-Aristizabal G. Clasificación climática de la Orinoquia Colombiana a partir de los patrones de circulación atmosférica. *Meteorol Colomb*. 2001; 4, 117–120.
18. Villar JCE, Ronchail J, Guyot JL, *et al.* Spatio-temporal rainfall variability in the Amazon basin countries (Brazil, Peru, Bolivia, Colombia, and Ecuador). *Int J Climatol*. 2009; 29, 1574–1594.
19. Jansen EC, Herran OF, Villamor E. Trends and correlates of age at menarche in Colombia: results from a nationally representative survey. *Econ Hum Biol*. 2015; 19, 138–144.
20. Kleinbaum D, Klein M. *Survival Analysis: A Self-Learning Text*, 3rd edn, 2012. Springer Science and Business Media: New York, NY.
21. Jongbloet PH, Kersemaekers WM, Zielhuis GA, Verbeek AL. Menstrual disorders and month of birth. *Ann Hum Biol*. 1994; 21, 511–518.
22. Cagnacci A, Pansini FS, Bacchi-Modena A, *et al.* Season of birth influences the timing of menopause. *Hum Reprod*. 2005; 20, 2190–2193.
23. Maisonet M, Christensen KY, Rubin C, *et al.* Role of prenatal characteristics and early growth on pubertal attainment of British girls. *Pediatrics*. 2010; 126, e591–e600.
24. Boldsen JL. Season of birth and recalled age at menarche. *J Biosoc Sci*. 1992; 24, 167–173.
25. Graham EA, Mulkey SS, Kitajima K, Phillips NG, Wright SJ. Cloud cover limits net CO2 uptake and growth of a rainforest tree during tropical rainy seasons. *Proc Natl Acad Sci U S A*. 2003; 100, 572–576.
26. Parisi AV, Turnbull DJ, Downs NJ. Influence of high levels of cloud cover on vitamin D effective and erythemal solar UV irradiances. *Photochem Photobiol Sci*. 2012; 11, 1855–1859.
27. Reiter RJ, Tan DX, Korkmaz A, Rosales-Corral SA. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. *Hum Reprod Update*. 2014; 20, 293–307.
28. Polwiang S. The seasonal reproduction number of dengue fever: impacts of climate on transmission. *PeerJ*. 2015; 3, e1069.
29. Oringanje C, Meremikwu M, Ogar B, Okon A, Udoh A. Patterns of cord, placental and post-delivery maternal malaria parasitemia. *Acta Obstet Gynecol Scand*. 2010; 89, 1206–1209.
30. Rodriguez-Martinez CE, Rodriguez DA, Nino G. Respiratory syncytial virus, adenoviruses, and mixed acute lower respiratory infections in children in a developing country. *J Med Virol*. 2015; 87, 774–781.

31. Graham MA. "No somos iguales": the effect of household economic standing on women's energy intake in the Andes. *Soc Sci Med*. 2004; 58, 2291–2300.
32. Villamor E, Marin C, Mora-Plazas M, Baylin A. Vitamin D deficiency and age at menarche: a prospective study. *Am J Clin Nutr*. 2011; 94, 1020–1025.
33. Crozier SR, Harvey NC, Inskip HM, *et al*. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. *Am J Clin Nutr*. 2012; 96, 57–63.
34. Lee JM, Appugliese D, Kaciroti N, *et al*. Weight status in young girls and the onset of puberty. *Pediatrics*. 2007; 119, e624–e630.
35. Di Renzo GC, Spano F, Giardina I, *et al*. Iron deficiency anemia in pregnancy. *Womens Health (Lond)*. 2015; 11, 891–900.
36. Uauy R, Kain J, Corvalan C. How can the developmental origins of health and disease (DOHaD) hypothesis contribute to improving health in developing countries? *Am J Clin Nutr*. 2011; 94, 1759S–1764SS.
37. Khorram O, Keen-Rinehart E, Chuang TD, Ross MG, Desai M. Maternal undernutrition induces premature reproductive senescence in adult female rat offspring. *Fertil Steril*. 2015; 103, 291–8 e2.
38. Correia-Branco A, Keating E, Martel F. Maternal undernutrition and fetal developmental programming of obesity: the glucocorticoid connection. *Reprod Sci*. 2015; 22, 138–145.
39. Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int J Obes (Lond)*. 2013; 37, 1036–1043.
40. Frisancho AR. Developmental functional adaptation to high altitude: review. *Am J Hum Biol*. 2013; 25, 151–168.
41. Hui LL, Leung GM, Lam TH, Schooling CM. Premature birth and age at onset of puberty. *Epidemiology*. 2012; 23, 415–422.
42. Castilho SD, Nucci LB, Assuino SR, Hansen LO. The importance of memory bias in obtaining age of menarche by recall method in Brazilian adolescents. *Arq Bras Endocrinol Metabol*. 2014; 58, 394–397.
43. Lepkowski JM, Mosher WD, Groves RM, *et al*. Responsive design, weighting, and variance estimation in the 2006–2010 National survey of family growth. *Vital Health Stat 2*. 2013; 158, 1–52.
44. Azevedo V, Bouillon C. *Social Mobility in Latin America: A Review of Existing Evidence*. 2009. Inter-American Development Bank: Washington, DC.