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High Altitude Continues to Reduce Birth Weights in Colorado

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Abstract

Objectives Colorado's relatively high altitudes have been reported to lower birth weight but the most recent studies were conducted 20 years ago. Since then, the accuracy for assigning altitude of residence has been improved with the use of geocoding, and recommendations for pregnancy weight gain have changed. We therefore sought to determine whether currently, residence at high altitude (≥ 2500 m, 8250 ft) lowers birth weight in Colorado. *Methods* Birth certificate data for all live births (n = 670,017) to Colorado residents from 2007 to 2016 were obtained from the Colorado Department of Public Health and Environment. Geocoded altitude of maternal residence for the current birth was assigned to each birth record. Linear and logistic regression models were used to examine the effects of altitude on birth weight or low birth weight (< 2500 g) while controlling for other factors affecting birth weight, including pregnancy weight gain. *Results* Compared to low altitude, infants born at high altitude weighed 118 g less and were more often low birth weight (8.8% vs. 11.7%, $p < 0.05$). After accounting for other factors influencing birth weight, high altitude reduced birth weight by 101 g and increased the risk of low birth weight by 27%. The only factors with larger impacts on birth weight were hypertensive disorders of pregnancy and cigarette use during pregnancy. *Conclusions for Practice* High altitude remains an important determinant of elevated LBW rates in Colorado, and likely contributes to Colorado's comparative resistance towards meeting the Healthy People 2010/2020 nationwide goal to reduce the low birth weight rate to 7.2% by 2020.

Keywords Low birth weight · Hypoxia · Hypertensive disorders of pregnancy

Significance

Low birth-weight rates in the State of Colorado have consistently exceeded the Healthy People 2010/2020 goal of 7.2%. Using individual-level assessment of maternal altitude of residence and expanded birth-certificate data, our findings demonstrate that high-altitude remains an important contributor to reduced birth weights in the State of Colorado and provides rationale for further study to investigate the mechanisms underlying such effects.

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Introduction

Birth weight is a major contributor to infant morbidity and mortality (Wilcox and Skjaerven 1992). Low birth weight (< 2500 g) may result from preterm delivery, fetal growth restriction, or both. While much of the association between infant morbidity or mortality and low birth weight is attributable to prematurity, birth weight adjusted for gestational age remains strongly associated with infant health and survival (Wilcox and Skjaerven 1992). In addition to the negative impacts of low birth weight during infancy, a continuous j-shaped relationship between birth weight and susceptibility to cardiovascular and metabolic disease later in life exists, with both low and very high birth weights compromising adult health outcomes (Barker 2006; Hales et al. 1991).

Therefore, the effects of birth weight on immediate and long-term health of the affected offspring have important public health implications and impose a substantial economic burden due to the costs of acute care and long-term disability (Meis et al. 1987, 1998).

The incidence of low birth weight in the United States exceeds that of almost every other high-income country, and has been steadily increasing (United Nations Children's Fund and World Health Organization, 2004). From 1998 to 2016, the United States' low birth weight rate rose from 7.6 to 8.2% despite a major US public health initiative (Healthy People 2000/2010) that established the ambitious goal of reducing the low birth weight rate to 5.0% nationwide by 2010. Healthy People 2010/2020 relaxed this goal, seeking to reduce the low birth weight rate to 7.8% of live births by 2020, from a baseline of 8.2% in 2007 (Healthy People 2020).

Population-based studies in the United States and elsewhere demonstrate that maternal residence at high altitude (≥ 2500 m, 8250 ft) has one of the most powerful effects on lowering birth weight, which is due primarily to slowed fetal growth rather than shortened gestation (Jensen and Moore 1997; Lichtyet al. 1957; Unger et al. 1988). Supporting fetal growth restriction, rather than the babies being constitutionally small, are Doppler indices of fetal brain sparing and a greater reduction in birth weight than length (Browne et al. 2015; Soria et al. 2013) The effect of altitude on birth weight is pervasive, affecting all high-altitude populations studied to date, although being of lesser magnitude in populations that have lived at high altitude for millennia (Julian et al. 2007; Moore et al. 2004; Tripathy and Gupta 2005). Previous studies demonstrate that differences in health-care access, socioeconomic status, number of prenatal visits, parity, maternal height or hypertensive complications of pregnancy do not explain the altitude-associated reduction (Giussani et al. 2001; Jensen and Moore 1997) Consequently, high-altitude residents are the largest at-risk population for this major contributor to perinatal morbidity and mortality worldwide (Gilbert and Danielsen 2003; Villar et al. 2003; Walker 2000).

Colorado has the highest mean altitude (2073 m) of any state, with approximately 250,000 people living above 2500 m. The incidence of low birth weight in Colorado is consistently greater than the United States average (9.0% vs. 8.2%), despite premature-delivery rates being well below the national mean (8.9% vs. 9.9%) (Center for Disease Control). While the chronic hypoxia of high-altitude residence is a prominent contributor to reduced birth weights in Colorado, other factors such as insufficient maternal weight gain and smoking during pregnancy have also been shown to play a role (Letson et al. 2016). While the transfer of high-risk pregnancies from high-altitude locations to advanced care hospitals at lower altitudes has effectively eliminated the altitude-associated increase in neonatal mortality in Colorado (McCullough et al. 1977; Unger et al. 1988) low birth weight and other neonatal complications including respiratory distress syndrome and pulmonary hypertension remain more common (Niermeyer et al. 2009).

Since the most recent study was conducted more than 20 years ago and expanded information on maternal altitude of residence—based on geocoding rather than county averages—as well as pre-pregnant body weight and body mass index has become available, we sought to determine whether residence at high altitude continues to independently lower birth weight in Colorado. Awareness of altitude's effect on birth weight together with the influences of other factors is important for health-care providers serving the growing numbers of residents and visitors to Colorado's high country.

Methods

The Colorado Multiple Institutional Review Board and the ethical oversight group for the Colorado Department of Public Health and Environment approved the acquisition of de-identified statewide birth certificate data for the present study, declaring its use exempt from IRB oversight and Health Insurance Portability and Accountability Act requirements and in compliance with Center for Health and Environmental Data release policies.

Dataset

Birth-certificate data for all live births (n = 670,017) from 2007 to 2016 among Colorado-resident women were obtained from the Center for Health and Environmental Data, Colorado Department of Public Health and Environment. The 10 year period was selected given that a statewide electronic birth registration system was implemented in 2007 and, at the same time, additional data fields (e.g., maternal body mass index and weight gain during pregnancy) were incorporated in accordance with National Center for Health Statistics' 2003 revisions of United States birth certificate standards. These changes allowed for a more complete assessment of the relative contribution of high altitude to the increased incidence of low birth weight seen in Colorado.

The specific variables abstracted for each record included maternal age, marital status, ethnicity, height, pre-pregnancy body mass index, pregnancy weight gain, cigarette or alcohol use during pregnancy, use of Women, Infant and Children's (WIC) benefits, family income (expressed on a 6 point scale, < $15,000; $15,000–$24,999; $25,000–$34,999; $35,000–$49,999; $50,000–$74,999; $75,000+), complications of pregnancy (listed as pregnancy-induced hypertension, gestational diabetes, eclampsia), infant sex, gestational age at delivery in weeks, preterm or term delivery (preterm < 37 weeks, full term > 37 weeks), birth weight in grams, and birth weight category (low birth weight, < 2500 g; very low birth weight < 1500 g or birth weight > 2500 g). Adequate weight gain during pregnancy was calculated using criteria established by the Institute of Medicine for the categories of pre-pregnancy body mass index of underweight (gain of 28–40 lb), normal weight (gain of 25–35 lb), overweight (gain of 15–25 lb), and obese (gain of 11–20 lb) (Institute of Medicine and National Research Council 2009).

Altitude Assessment

Geocoded elevation of maternal residence at the time of birth (i.e. the z-coordinate accompanying the latitude and longitude was assigned by the Colorado Department of Public Health and Environment) was used to increase the accuracy of altitude assignment for each birth record. Compared to the use of county mean elevations of residence, based on the weighted averages for all incorporated and unincorporated entities within a given county, individual-level altitude assignments are more accurate, provide a continuous variable, and permit the aggregation of individual data by altitude category rather than geopolitical boundaries. Geographic coordinates for rooftop, latitude and longitude were ascribed to the maternal residence listed on each birth certificate using geocoding Centrus and MapMarker Desktop software (Pitney Bowes, NY) and assigning altitude by overlaying the locations (latitude, longitude) onto the United States Geological Survey 7.5 min (1:24,000 scale) 30 M Digital Elevation Model using Arc Geographic Information Systems (ArcGIS) software (ESRI, California). Colorado Department of Public Health and Environment birth-certificate geocoding coverage consistently reaches 97% statewide, and averages 98, 92, and 88% in urban, rural and frontier counties (which include the highest elevations), respectively (K. Bol, personal communication). Only records with geocoded elevation-assignments were included for primary analysis. However, because fewer birth certificates from rural and frontier counties were geocoded, comparisons of key outcome variables were made between geocoded and non-geocoded records to assure that the records used for the primary dataset were representative of statewide data. In keeping with prior usage and the observation that arterial oxygen saturation begins to decline more markedly at elevations above 2500 m, we defined high altitude as ≥ 2500 m and low altitude as < 2500 m.

Data Analysis

Using maternal altitude of residence as a dichotomous variable (< 2500 m or ≥ 2500 m) and birth-record data including demographic and medical information, descriptive statistics were used to characterize the study population, and births compared between elevation groups using independent t-tests and Chi square analysis, as appropriate. Bivariate associations between maternal altitude of residence and birth weight were examined using t-tests and Chi square analysis. Linear and logistic regression models were used to examine relationships between altitude of residence (< 2500 m and ≥ 2500 m) groups and birth weight or birth-weight categories, respectively, while controlling for background factors and accounting for pregnancy weight gain. For both types of regression analysis background factors were entered stepwise, with pregnancy weight gain and altitude of maternal residence being entered on the final two steps. All analyses were conducted using SPSS 24.0 (IBM Corp, Armonk, NY) and considered statistically significant when $p < 0.05$. Data are reported as the mean plus or minus standard error of the mean (SEM) or 95% confidence intervals. Sample sizes and statistical tests are noted for each table and figure, as appropriate.

Results

The initial dataset included all live births in Colorado over a 10 year period (2007–2016), representing a total of 670,017 woman-newborn dyads. Geocoded elevation of maternal residence was missing for 1.5% (n = 17,989) of records, leaving a total of 652,028 dyads for primary analysis. A minimal amount of missing data existed, but as all primary variables but income, for which 11.7% were missing, were at least 98% complete, the full sample of 652,028 was retained with missing cases excluded pairwise for each analysis. Of the final sample, 1.5% (n = 10,069) resided at an altitude of 2500 m or greater, while the remainder resided below 2500 m. For women living ≥ 2500 m, average altitude of residence was 2752 m (range 2500–3518), compared to 1698 m (range 1033–2499) for women living < 2500 m.

Compared to low altitude, high-altitude residents more often lived in rural locations (11.5% vs. 63.9%, respectively). However, unlike reports from other regions (Bailey and Cole 2009), rurality in Colorado is not associated with an increased rate of adverse pregnancy and newborn outcomes. Specifically, in the current sample, women with rural zip codes (13.2%) had significantly lower rates of preterm delivery than non-rural women (8.6% vs. 9.1%, $p < 0.001$), and similar rates of low birth weight newborns (8.8% vs. 8.9%, p = ns). Additionally, rural women were no more likely than non-rural women to have existing (1.1% vs. 1.0%, p = ns) or pregnancy induced (4.2% vs. 4.2%, p = ns) hypertension. Compared to low-altitude, women living at high-altitude were older, more likely to be married, less likely to be Hispanic, and have a higher household income, lower pregnancy BMI, and greater pregnancy weight gain (Table 1). An equivalent proportion (26.1%) of women at each altitude

Table 1 Maternal characteristics by altitude of residence during pregnancy

	Low altitude *n* = 641,959	High altitude *n* = 10,069	t/χ2	P
Demographics				
Maternal age (years)	28.5 ± 6.0	30.6 ± 6.0	31.46	< .001
Maternal marital status, % married	75.9%	80.6%	119.07	< .001
Women receiving WIC[a] benefits (%)	30.3%	20.7%	377.21	< .001
Family income, 6-point scale[b]	2.6 ± 2.0	3.0 ± 1.9	17.26	< .001
Maternal ethnicity, % hispanic	29.5%	18.6%	569.82	< .001
Maternal height (inches)	64.4 ± 2.9	64.7 ± 2.8	11.61	< .001
Maternal pre-pregnancy BMI[c]	25.7 ± 5.9	24.2 ± 4.9	28.81	< .001
Pregnancy-related characteristics				
Pregnancy weight gain (lbs)	29.6 ± 14.2	30.4 ± 13.0	5.79	< .001
Number of previous pregnancies	1.5 ± 1.6	1.3 ± 1.4	12.57	< .001
Cigarette use in pregnancy (%)	7.5%	6.1%	30.45	< .001
Alcohol use in pregnancy 0.5+ drinks/day[d] (%)	0.2%	0.3%	3.45	NS
Pregnancy induced hypertension (%)	4.2%	5.1%	18.40	< .001
Gestational diabetes (%)	4.0%	3.2%	13.52	< .001
Eclampsia (%)	0.5%	0.8%	9.73	< .01
Infant gender (% male)	48.8%	49.2%	.88	NS
Gestational age at delivery (weeks)	38.6 ± 2.1	38.7 ± 2.0	1.22	NS
Preterm delivery (%)	9.0%	9.3%	.98	NS
Birth weight (grams)	3199 ± 558	3081 ± 529	20.85	< .001
Low birth weight (%)	8.8%	11.7%	100.34	< .001
Very low birth weight (%)	1.3%	1.2%	.01	NS
Singleton delivery (%)	96.7%	96.7%	.01	NS

[a]Federal Women Infant and Children's benefits eligible to low income families

[b] < $15,000; $15,000–$24,999; $25,000–$34,999; $35,000–$49,999; $50,000–$74,999; $75,000+

[c]Body Mass Index = weight in kg/height in m^2

[d]Definition of pregnancy risk drinking = 0.5 drinks/day or more

gained an inadequate amount of weight in relation to their pre-pregnancy BMI. In addition, women at higher altitudes had experienced fewer previous pregnancies, were less likely to smoke during pregnancy, had higher rates pregnancy-induced hypertension and eclampsia, and had lower rates of gestational diabetes. Other potential birth weight confounders including pre-pregnancy hypertension and diabetes rates were rare (< 1% at low altitude and high altitude) and were not different for the altitude groups.

As noted, geocoded altitude was missing for 1.5% of the sample. Records with complete data were compared to records with missing data for all variables in Table 1. Statistical, but not likely clinically-significant, differences existed for only a few characteristics; namely, missing cases were 0.4 years older, 1.5% more likely to be married, 3.8% less likely to be Hispanic, had a 0.13-point lower pre-pregnancy BMI, gained 0.28 fewer pounds during pregnancy, had a 0.06 higher parity, and were 1.4% more likely to smoke. Additionally, records with missing altitude data were 0.7% more likely to deliver preterm, had newborns weighing 25 g less at birth, had 1% higher rates of low birth weight, and were 0.3% more likely to deliver a singleton infant.

Overall, higher maternal altitude of residence considered as a continuous variable was modestly but significantly related to lower birth weight ($r = -0.04$, $p < 0.001$) (Fig. 1), with each 1000 m increase in elevation resulting in a 94 g decrease in birthweight (unstandardized regression coefficient = − 094 in uncontrolled linear regression analysis) and a 91 g decrease when linear regression analysis controlled for all significant potential confounders in Table 1. When altitude of residence was considered categorically (< 2500 m vs. ≥ 2500 m), infants born to high-altitude residents weighed 118 g less than infants born to women residing at lower altitudes and were 33% more likely to be of low birth weight (< 2500 g) (Table 1). The effect of altitude to reduce birth weight and increase the proportion of LBW infants was equivalent between male and female infants. However, our findings do not indicate an altitudinal difference in gestational age at delivery, the proportion of premature deliveries, or the frequency of multiple (e.g., twins, etc.) births.

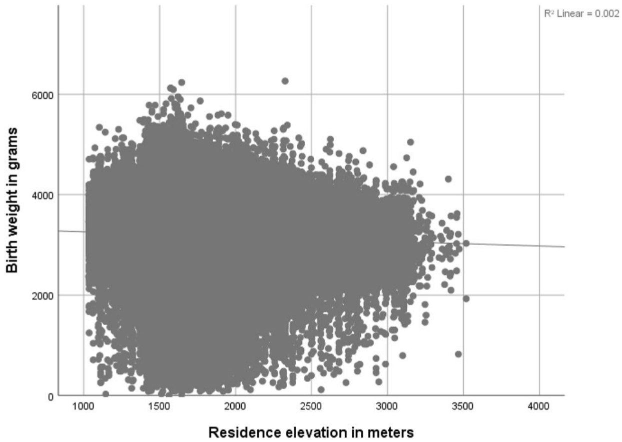

Fig. 1 Scatterplot with fit line of birth weight by elevation of residence

Since low maternal weight gain was previously identified as an important contributor to Colorado's higher rate of low birth weight infants (Letson et al. 2016), we used linear regression analysis to examine the association between altitude of residence (< 2500 m vs. ≥ 2500 m) and birth weight while taking absolute pregnancy weight gain into account. Table 2 presents the linear-regression results for predicting birth weight as a continuous variable, while Table 3 presents the results using low birth weight status as a categorical variable (i.e., < 2500 g vs. ≥ 2500 g). After controlling for potential confounders (i.e., the significant background and pregnancy-related factors in Table 1) and pregnancy weight gain, elevation of maternal residence remained a significant, negative predictor of birth weight (Table 2). Compared to infants born to women residing at low altitude and adjusting for the birth-weight effects of pregnancy-induced hypertension or eclampsia, advanced maternal age, and smoking during pregnancy, infants born to high-altitude women had a 101 g lower adjusted birth weight. The effect of altitude remained significant whether birth weight was treated as a continuous or dichotomous variable. Maternal and pregnancy-related factors positively associated with birth weight included maternal height, pre-pregnancy BMI, pregnancy weight gain, Hispanic ethnicity, family income, and the number of prior pregnancies (Table 2). After controlling for background factors and pregnancy weight gain, women living ≥ 2500 m had a 27% increased risk of delivering a low birth weight baby. When these analyses were restricted to singleton, full-term deliveries and pregnancy weight gain considered as adequate versus inadequate relative to

Table 2 Linear regression results predicting continuous birth weight from dichotomous altitude of residence adjusting for pregnancy weight gain and background factors

Independent variable	Unstandardized regression coefficient (b)	Standardized regression coefficient (β)	t	P
Maternal height	25.50	.13	94.54	< .001
Pre-pregnancy BMI	14.67	.16	113.48	< .001
Pregnancy induced hypertension[a]	– 307.11	– .11	– 84.92	< .001
Cigarette use during pregnancy[b]	– 171.27	– .08	– 59.76	< .001
Eclampsia[c]	– 571.57	– .08	– 56.93	< .001
Marital status[d]	52.80	.04	26.34	< .001
Ethnicity[e]	43.98	.04	23.65	< .001
Family income	10.52	.04	18.97	< .001
Maternal age	– 1.18	– .01	– 7.61	< .001
Number of previous pregnancies	6.13	.02	11.98	< .001
WIC[f]	8.11	.01	4.03	< .001
Pregnancy weight gain	7.39	.19	138.50	< .001
Elevation of maternal residence[g]	– 101.06	– .02	– 16.72	< .001

All significant variables from Table 1 were included as potential covariates in the model. Covariates were entered stepwise in the first step, followed by entry of pregnancy weight gain in the second step, and altitude of residence in the final step. Individual variable values above are from the final step of the model with all variables entered

Overall model: $R^2 = .091$, $F = 4038.52$, $p < .001$

[a]0 = Did not develop hypertension during pregnancy, 1 = did develop hypertension during pregnancy

[b]0 = Non-smoker during pregnancy, 1 = smoked at some point during pregnancy

[c]0 = Did not develop eclampsia, 1 = did develop eclampsia

[d]0 = Unmarried, 1 = married

[e]0 = Non-hispanic, 1 = hispanic

[f]0 = Did not receive Women Infants and Children benefits in pregnancy, 1 = did receive benefits

[g]0 = < 2500 m, 1 ≥ 2500 m

Table 3 Logistic regression results predicting low birth weight from dichotomous altitude of residence adjusting for pregnancy weight gain and background factors

Independent variable	Unstandardized regression coefficient (b)	Wald	Adjusted odds ratio	95% CI
Maternal height	− .07	1234.48	.94	.93–.94
Pre-pregnancy BMI	− .04	1548.49	.96	.96–.97
Pregnancy induced hypertension[a]	1.29	5027.67	3.64	3.52–3.78
Cigarette use during pregnancy[b]	.57	1156.23	1.77	1.71–1.83
Eclampsia[c]	1.99	2264.11	7.34	6.76–7.97
Marital status[d]	.19	205.81	1.21	1.18–1.25
Ethnicity[e]	− .20	238.53	.82	.80–.84
Family income	− .05	201.35	.95	.94–.96
Maternal age	.02	369.11	1.02	1.02–1.02
Number of previous pregnancies	.02	20.37	1.02	1.01–1.02
WIC[f]	.06	18.91	.94	.92–.97
Gestational diabetes[g]	.09	14.21	1.10	1.05–1.15
Pregnancy weight gain	− .02	3466.78	.98	.98–.98
Elevation of maternal residence[h]	.24	39.86	1.27	1.18–1.37

All significant variables from Table 1 were included as potential covariates in the model. Covariates were entered stepwise in the first step, followed by entry of pregnancy weight gain in the second step, and altitude of residence in the final step. Individual variable values above are from the final step of the model with all variables entered

Overall model: $R^2 = .059$; $\chi 2 = 13{,}813.89$, $p < .001$; 91.5% correctly classified

[a]No pregnancy hypertension is reference group

[b]Non-smoker during pregnancy is reference group

[c]No eclampsia is reference group

[d]Married is reference group

[e]Non-Hispanic is reference group

[f]Not receiving WIC benefits is reference group

[g]No gestational diabetes is reference group

[h]Elevation < 2500 m is reference group

pre-pregnant BMI, maternal altitude of residence retained its negative association with birth weight, and remained a significant predictor of low birth weight even after accounting for the significant altitude-associated increase in the incidence of pregnancy-induced hypertension or eclampsia, and the reduced rate of smoking during pregnancy at high altitudes in Colorado.

Discussion

Using individual-level assessment of altitude or maternal residence and expanded birth-certificate data, our findings demonstrate that high altitude remains an important contributor to the increased incidence of low birth weight in the State of Colorado. The 670,017 birth records considered here comprise the largest sample of births analyzed to date, and at least twice as many high-altitude births as in previous reports (Jensen and Moore 1997; Soria et al. 2013; Yip 1987). Importantly, the effect of high altitude on reducing birth weight persisted after accounting for the known influences of maternal weight gain, hypertensive disorders of pregnancy, and smoking. For the more than 650,000 live births occurring over the 10 syear period with geocoded elevations available, the only factors with a larger impact on birth weight and low birth weight than maternal altitude of residence (− 101 g) were pregnancy-induced hypertension (− 307 g), eclampsia (− 572 g) and cigarette use during pregnancy (171 g). Importantly, the major known covariates of birth weight, including altitude of residence, only explained 9% of the variance in birth weight, demonstrating that most of the variance in birth weight is due to individual factors or other predictors not yet understood.

Using population attributable fraction analyses, recent work estimated the proportion of low birth weight cases that could be prevented by eliminating known risk factors (including altitude of maternal residence) for singleton births in Colorado for the years 1995–97 and 2007–09 (Letson et al. 2016). In that report, the factors with the greatest impact on the occurrence of low birth weight were considered as inadequate weight gain, smoking, and premature rupture of membranes. However, very few high-altitude births were considered (< 100 births/yr) given that high altitude was defined as ≥ 3048 m (10,000 ft), which is a higher cutoff value than used in most reports and higher than the altitude (2500 m) at which the reduction in birth weight becomes apparent (Mortola et al. 2000). While very few women in Colorado live ≥ 3048 m (n = 1100 or 0.2%), more than 10,000 live above 2500 m.

High-altitude residence is associated with lower obesity rates (Voss et al. 2014). Colorado has consistently had one of the lowest obesity rates in the nation (Centers for Disease Control and Prevention 2014), which has often been attributed at least in part to altitude of residence. We therefore thought that the pregnancy-associated weight gain might be reduced among women living at high altitude and could influence the altitude-associated decline in birth weight. In contrast to our expectation, the high-altitude women on average gained more weight during pregnancy than their low-altitude counterparts and an equivalent proportion of women gained an insufficient amount of weight during pregnancy relative to their pre-pregnancy BMI. While maternal weight gain was positively associated with birth weight at each altitude, its protective effect did not offset the negative influence of altitude.

One limitation of the current analysis is the assumption that the location of the maternal residence noted on the birth certificate accurately reflected where she lived during her entire pregnancy. While it is unlikely that many women changed their altitudes of residence substantially during their pregnancies, we do not know whether the woman spent her entire pregnancy at the altitude noted on her infant's birth record. A second factor is that even though nearly all (97%) of Colorado birth records were successfully geo-coded, records that were not were disproportionately located in the rural and higher-altitude locations of the state. However, as we have reported for this sample, rural women in Colorado do not experience the increase in adverse pregnancy and birth outcomes seen in other rural areas, and premature delivery is less common in rural compared to non-rural women. Finally, Colorado lacks a sea-level reference group, given that its lowest elevation is 1010 m, and the largest portion of Colorado's residents live in the Denver metropolitan region at an altitude is 1609 m, where birth weights are ~ 200 g lower than at sea level (Galan et al. 2001). Thus the birth-weight difference detected here between low and high altitudes in Colorado would be amplified if the high-altitude births were compared to sea-level births.

Public Health Implications

Low birth-weight rates in the State of Colorado have consistently exceeded the Healthy People 2010/2020 goal of 7.2%. Reducing this rate requires knowing the factors having the greatest impact on birth weight and determining how their impact can be reduced. Previous reports have separated risk factors into modifiable versus non-modifiable risks, with altitude of residence being considered as non-modifiable (Letson et al. 2016). However, altitude is not necessarily non-modifiable since cases diagnosed with intrauterine growth restriction or other pregnancy complications can be and routinely are transferred from the high- to low-altitude regions of the state. Oxygen supplementation too is sometimes used in Colorado's high-altitude regions. However, we are not aware of any documentation as to whether fetal growth is improved following transfer to lower altitudes or oxygen use. Such studies are needed so as to be able to better advise clinicians and their patients as to how to improve health outcomes, especially considering the large numbers of studies demonstrating the importance of birth weight for the risk of cardiovascular and other diseases later in life. In addition, since not all infants born at high altitude are of low birth weight, studies at high altitude afford the opportunity to identify factors protecting against hypoxia-associated fetal growth restriction. Indeed, existing evidence suggests that multigenerational, Tibetan and Andean high- altitude residents are relatively protected from altitude-associated reductions in birth weight and that such protection is, at least in part, genetic (Bigham et al. 2014; Julian et al. 2011). Identifying the biological pathways by which such protection is conferrred offers the chance to identify new treatments for such disorders and possibly even means means for their prevention.

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