Altitude, birth weight, and infant mortality.

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ABSTRACT

Birth weight decreases with increasing altitude. However, some argue that there is no corresponding increase in infant mortality, implying that birth weight is not on the causal pathway to mortality. This research statistically examines the relationship between altitude, birth weight, and infant mortality using 1995-2002 linked birth/death files: European-American cohorts from high altitude Colorado and low altitude Iowa. Socioeconomic variation is controlled for by education. CDDmlr is used, which identifies "direct" and "indirect" effects of altitude on mortality in two latent birth categories interpreted as "normal" and "compromised" births. Mean birth weight declines in "normal" births 156-185 grams. The variance declines 484-787 $grams^2$ in "normal" births and 11,025-22,201 $grams^2$ in "compromised" births. There is one significant increase in mortality in male, low socioeconomic, "normal" births. There are no indirect effects of birth weight on mortality indicating that birth weight distribution shifts are not involved in the change in mortality.

INTRODUCTION

Many studies have found that birth weight decreases with increasing altitude and further, that this decline is not associated with other low birth weight risk factors (for example, Jensen and Moore, 1997). However, the relationship between birth weight, altitude, and mortality is more complex. It is often assumed that infant mortality will increase if birth weights decrease and this assumption underlies the US national health policy of reducing infant mortality (US-DOHHS, 2000). In contrast, other studies have found declining mean birth weight with no increase in mortality with increasing altitude, especially in high risk infants (Paranka et al, 2001). Wilcox (2001) observes that high altitude births have lower mortality at lower birth weights and higher mortality at higher birth weights compared to low altitude births. By standardizing the birth weight distributions and re-plotting the mortality curves, he then observes that the two mortality curves almost coincide. He concludes that for the case of altitude, the mortality curve shift corresponds to the birth weight distribution shift and therefore there is no change in overall mortality between high and low altitude births, implying that birth weight is not on the causal pathway to mortality. If birth weight is on the causal pathway to infant mortality, we would expect to see an uncoupling of birth weight and mortality, that is, we would see an additional horizontal shift in the mortality curve after standardizing the birth weight distribution and the overall mortality between the two groups would be different. This would represent an indirect effect of altitude on mortality that is mediated through birth weight. If an exogenous variable, like altitude, acts independently of birth weight, we expect to see a vertical shift of the mortality curve, which would be a direct effect of altitude on mortality. This research tests this hypothesis by statistically examining the relationship between altitude, birth weight, and infant mortality.

DATA AND METHODS

The data analyzed is from the US national 1995-2002 linked birth/infant death files: male and female European-American births. Socioeconomic variation associated with altitude is controlled for by maternal education level. The high altitude group is from Colorado (births geo-coded from 5,000-10,000 feet) and the low altitude group is from Iowa (births from 472-1,640 feet). Descriptive statistics of the sample population can be found in Table 1.

Table 1 about here

These four birth cohorts are examined using Covariate Density Defined mixtures of logistic regressions (CDDmlr), which identifies "direct" (independent of birth weight) and "indirect" (through birth weight) effects of altitude on mortality in two latent birth categories. There are eight total cases to test the existence of direct and indirect mortality effects (sex X education X latent category).

The model (f; Eq. 1) used in this analysis is an extension of Gage et al (2004) two-subpopulation CDDmlr model of infant mortality, which decomposes the birth weight distribution into two subpopulations by using standard mixtures of Gaussian distributions and simultaneously fits a separate birth weight specific mortality curve to each latent subpopulation. This model is extended by making the parameters functions of a dichotomous variable z which represents altitude (z = 0, low altitude; z = 1 , high altitude). Birth weight data is represented by x and mortality data is represented by y.

The birth weight density submodel (f_1; Eq. 2) has mixture parameters for each latent subpopulation represented by θ: mean birth weight, standard deviation of birth weight, and the proportion of births belonging to the secondary subpopulation (π_s). The majority subpopulation is referred to as the primary subpopulation and the minority subpopulation is referred to as the secondary subpopulation which are interpreted as "normal" and "compromised" births and fetal development respectively. The mortality submodel (f_2; Eq. 4) has parameters represented by β. The mortality is modeled as a quadratic logistic to allow for a reverse J-shaped birth weight specific mortality in each subpopulation. The mortality submodel is the product of the probability of death in the primary or secondary subpopulation and the conditional probability that an infant belongs to that subpopulation.

The likelihood function for the CDDmlr model with altitude as an exogenous covariate of infant mortality (y) is a product of the conditional mortality submodel $f_2(y \mid x;\theta,\beta)$ and the birth weight (x) density submodel $f_1(x;\theta)$:

$$f(x,y;\theta,\beta) = f_2(y \mid x;\theta,\beta) f_1(x;\theta) \qquad \text{(Eq. 1)}$$

$$\begin{aligned} f_1(x \mid z;\theta = (\pi_s,\mu_s,\sigma_s,\mu_p,\sigma_p)) \\ = \pi_s(z) \times N_{500}(x;\mu_s(z),\sigma_s(z)) + [1-\pi_s(z)] \times N_{500}(x;\mu_p(z),\sigma_p(z)) \end{aligned} \qquad \text{(Eq. 2)}$$

$$\pi_s(z) = log\,it(\eta_s(z)) = log\,it(\alpha_0 + z \times \alpha_1) \qquad \text{(Eq. 3)}$$

$$f_2(y \mid x;\theta,\beta) = q_s(x;\theta) \times P_s(y \mid x;a_s,b_s,c_s) + [1-q_s(x;\theta)] \times P_p(y \mid x;a_p,b_p,c_p) \qquad \text{(Eq. 4)}$$

π_s, the mixing proportion, is defined as the proportion of births belonging to the less numerous of the two subpopulations, that is, the secondary subpopulation (s) as opposed to the primary subpopulation (p). For i = p and s, $N_{500}\left(x;\mu_i,\sigma_i^2\right)$ represents the Gaussian density, truncated at 500 grams, with mean μ_i and variance σ_i^2.

Births at low altitudes are the default and the altitude effect is defined as an indicator variable (z) on each of the 11 parameters in the CDDmlr model. Birth weight is standardized according to the respective subpopulation density characteristics (i.e. mean and standard deviation) and then used in the corresponding logistic regression function. Therefore,

$$\mu_i(z) = \gamma_{i0} + z \times \gamma_{i1} \qquad \text{(Eq. 5)}$$

$$\sigma_i(z) = \lambda_{i0} + z \times \lambda_{i1} \qquad \text{(Eq. 6)}$$

$$P_i(y \mid x_i, z; \beta_i = (a_i, b_i, c_i)) = \frac{\exp[a_i(z) + x_i \times b_i(z) + (x_i)^2 \times c_i(z)]}{1 + \exp[a_i(z) + x_i \times b_i(z) + (x_i)^2 \times c_i(z)]} \qquad \text{(Eq. 7)}$$

$$a_i(z) = a_{i0} + z \times a_{i1} \qquad \text{(Eq. 8)}$$

$$b_i(z) = b_{i0} + z \times b_{i1} \qquad \text{(Eq. 9)}$$

$$c_i(z) = c_{i0} + z \times c_{i1} \qquad \text{(Eq. 10)}$$

The entire model includes 22 parameters, 11 representing the characteristics of low altitude births, and 11 representing the altitude effect, that is, differences of high altitude compared to low altitude birth outcomes. The 5 indicator variable terms in the density submodel (i.e. α_1 , $\mu_{i,1}$, and $\sigma_{i,1}$ for i=s and p) account for the effects of altitude on the birth weight distribution, and the 6 indicator variable terms in the mortality submodel (i.e. $a_{i,1}$, $b_{i,1}$, and $c_{i,1}$, for i=s and p) account for the altitude difference in the standardized birth weight specific mortality curves.

The relative risk of high altitude births compared to low altitude births with respect to the overall infant mortality of the ith subpopulation is given by:

$$RR_i = \frac{\overline{P_i(y=1 \mid z=1, \beta_i)}}{\overline{P_i(y=1 \mid z=0, \beta_i)}} = F_{i1} \times F_{i2} \qquad \text{(Eq. 11)}$$

where F_{i1} is the direct factor that is independent of birth weight (does not contain birth weight terms) and F_{i2} is the indirect factor which contains all the terms multiplied by birth weight.

The model (Eq. 1) is fitted using the method of maximum likelihood to individual level data using the function ms() in the SPLUS statistical library. Bias-adjusted 95% confidence intervals of each parameter are estimated with 200 bootstrap samples.

RESULTS

The results indicate that the birth weight distribution changes significantly with altitude. Mean birth weight declines in “normal” births and the variance declines in both “normal” and “compromised” births. The proportion of births in the secondary population do not change between the “normal” and “compromised” subpopulations (Table 2 and Figure 1).

Table 2 about here

Figure 1 about here

There is one significant increase in mortality out of the eight cases tested; in male, low socioeconomic, “normal” births, mortality increases by 1.3 deaths/1000. There is also a marginally insignificant increase in mortality of female, high socioeconomic, “normal” births of 0.6 deaths/1000 (Table 2 and Figure 2).

Figure 2 about here

With respect to direct and indirect effects, there are no cases where the indirect effects of birth weight on mortality are significant. In male, high education births, there are significant direct effects in the “compromised” subpopulation (Table 3).

Table 3 about here

DISCUSSION

While the data presented here included only a comparison of Colorado and Iowa, Kansas and Missouri were also used as low altitude baseline populations. The replicates in Kansas and Missouri also show sporadic significant direct effects. However, these are not completely consistent across comparisons.

It is possible that there are minor increases in mortality with altitude birth cohorts, however, there is no evidence that the shifts in the birth weight distribution associated with altitude are involved. It appears that birth weight is not on the causal pathway to infant mortality.

Acknowledgements

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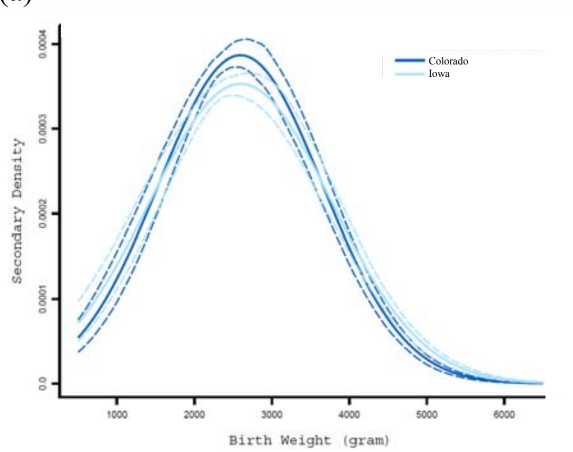
FIGURE CAPTIONS

Figure 1. Graphical representation of the birth weight submodel for male, low education, births with 95% confidence intervals (dotted lines). Panel (a) is the secondary or “compromised” subpopulation, panel (b) is the primary or “normal” subpopulation, and panel (c) is the total population.

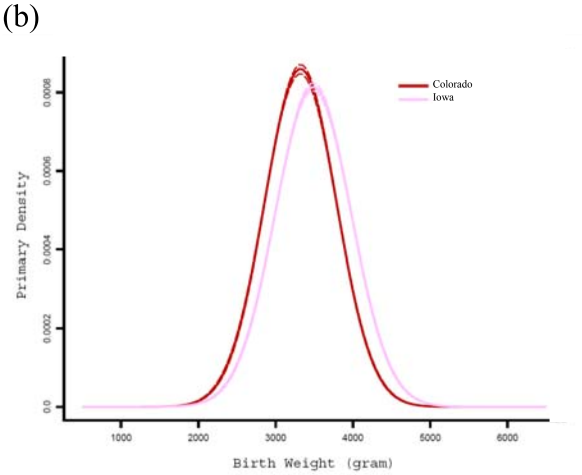
Figure 2. Graphical representation of the mortality submodel for male, low education, births with 95% confidence intervals (dotted lines). Panel (a) is the secondary or “compromised” subpopulation, panel (b) is the primary or “normal” subpopulation, and panel (c) is the total population.

(a)



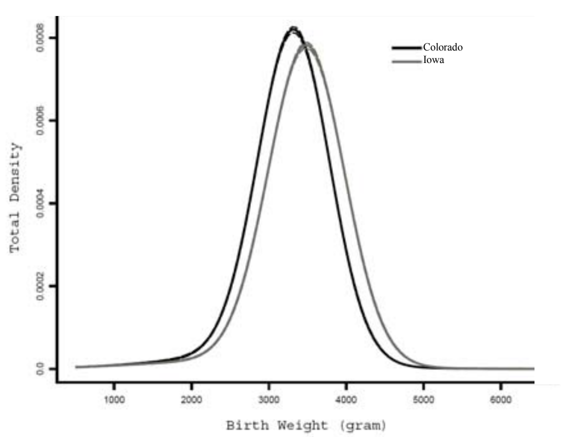
Colorado
Iowa
Secondary Density
0.0
0.0001
0.0002
0.0003
0.0004
1000
2000
3000
4000
5000
6000
Birth Weight (gram)

(b)



Colorado
Iowa
Primary Density
0.0
0.0002
0.0004
0.0006
0.0008
1000
2000
3000
4000
5000
6000
Birth Weight (gram)

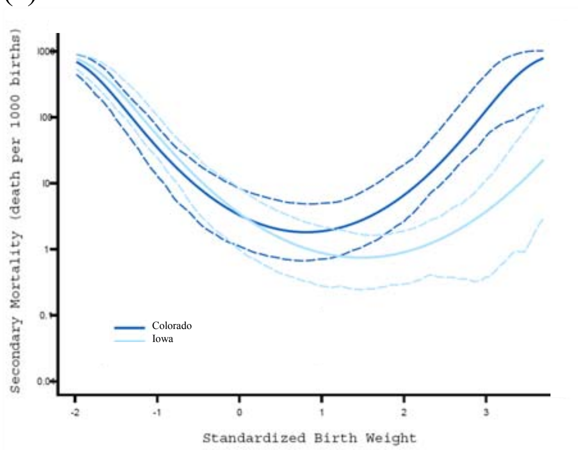
(c)



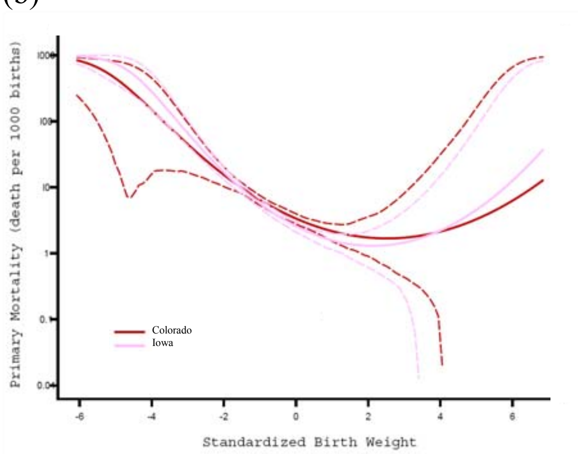
Colorado
Iowa
Total Density
0.0
0.0002
0.0004
0.0006
0.0008
1000
2000
3000
4000
5000
6000
Birth Weight (gram)

Figure 1

(a)


Secondary Mortality (death per 1000 births)
Standardized Birth Weight
Colorado
Iowa

(b)


Primary Mortality (death per 1000 births)
Standardized Birth Weight
Colorado
Iowa

(c)

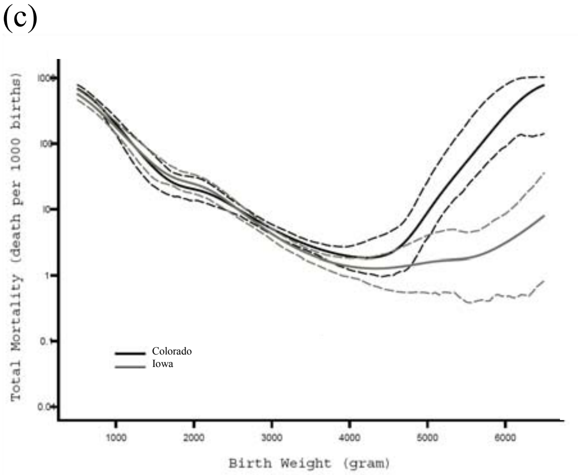

Total Mortality (death per 1000 births)
Birth Weight (gram)
Colorado
Iowa

Figure 2

Table 1 Descriptive statistics for the sample populations (non-Hispanic European Americans)

State	Gender	Maternal Education#	# Births	# Deaths	CDR	Birth Weight (grams)		
						Min	Mean	Max
Iowa	Females	0	46630	188	4.0	505	3322	6152
		1	67462	147	2.2	510	3442	6215
	Males	0	49081	249	5.0	500	3441	6040
		1	71123	213	3.0	500	3556	5982
Colorado*	Females	0	52750	276	5.2	510	3159	5216
		1	91000	256	2.8	510	3257	5443
	Males	0	55738	403	7.2	510	3276	5613
		1	95637	325	3.4	510	3376	6350

*: Colorado residents living between 5000 ft and 1000 ft

#: 0 - high school and below; 1 - college and above

CDR = Crude death rate (deaths per 1000 births)

Table 2 Model-estimated birth weight distribution and mortality characteristics with bias-adjusted 95% confidence intervals

		Maternal Education: High School and Below		Maternal Education: College and Above	
		Iowa	Colorado	Iowa	Colorado
Females					
"Normal"	Direct Factor	94.3 (93.3 ; 95.3)	93.2 (92.0 ; 94.3)	95.5 (94.6 ; 96.2)	94.3 (93.6 ; 95.2)
	Indirect Factor	3357 (3352 ; 3362)	3201 (3197 ; 3206) *	3470 (3465 ; 3473)	3285 (3281 ; 3288) *
	Standard Deviation (g)	464 (458 ; 470)	442 (436 ; 447) *	446 (441 ; 450)	424 (419 ; 427) *
	Death Rate (deaths/1000)	2.9 (2.3 ; 3.4)	3.8 (3.1 ; 4.5)	1.5 (1.1 ; 1.8)	2.1 (1.7 ; 2.5)
	Direct Factor	67.7 (58.4 ; 75.5)	70.8 (62.7 ; 77.7)	66.0 (50.8 ; 75.1)	71.6 (63.1 ; 78.1)
	Indirect Factor				
"Compromised"	Percent of Total Population	5.7 (4.7 ; 6.7)	6.8 (5.7 ; 8.0)	4.5 (3.8 ; 5.4)	5.7 (4.8 ; 6.4)
	Mean Birth Weight (g)	2678 (2521 ; 2798)	2530 (2395 ; 2626)	2799 (2696 ; 2913)	2653 (2556 ; 2744)
	Standard Deviation (g)	1138 (1074 ; 1222)	1003 (952 ; 1051) *	1133 (1067 ; 1196)	984 (946 ; 1030) *
	Death Rate (deaths/1000)	22.7 (15.6 ; 32.5)	21.4 (14.1 ; 29.0)	16.4 (11.1 ; 24.5)	13.9 (10.0 ; 19.1)
	Percent of Total Death Rate	32.3 (24.8 ; 41.6)	29.2 (22.3 ; 36.7)	34.0 (25.1 ; 49.1)	28.4 (21.9 ; 37.0)
Total Population Death Rate		4.0 (3.4 ; 4.6)	5.0 (4.3 ; 5.7)	2.2 (1.8 ; 2.5)	2.8 (2.4 ; 3.2)
Males					
"Normal"	Percent of Total Population	94.3 (93.2 ; 95.0)	92.8 (91.4 ; 93.9)	93.8 (92.7 ; 94.6)	93.0 (91.9 ; 93.7)
	Mean Birth Weight (g)	3486 (3481 ; 3491)	3322 (3317 ; 3327) *	3598 (3594 ; 3602)	3415 (3410 ; 3419) *
	Standard Deviation (g)	490 (484 ; 496)	464 (458 ; 470) *	469 (464 ; 474)	441 (437 ; 445) *
	Death Rate (deaths/1000)	3.3 (2.7 ; 3.8)	4.6 (3.8 ; 5.3) *	2.1 (1.8 ; 2.5)	2.1 (1.6 ; 2.5)
	Percent of Total Death Rate	60.9 (53.4 ; 68.6)	63.6 (55.3 ; 71.4)	67.0 (58.4 ; 74.1)	56.9 (48.3 ; 65.5)
"Compromised"	Percent of Total Population	5.7 (5.0 ; 6.8)	7.2 (6.1 ; 8.6)	6.2 (5.4 ; 7.3)	7.0 (6.3 ; 8.1)
	Mean Birth Weight (g)	2597 (2450 ; 2727)	2595 (2473 ; 2714)	2877 (2750 ; 2972)	2744 (2680 ; 2831)
	Standard Deviation (g)	1174 (1117 ; 1244)	1056 (999 ; 1106) *	1076 (1025 ; 1123)	971 (931 ; 1004) *
	Death Rate (deaths/1000)	34.5 (26.2 ; 45.7)	34.0 (25.2 ; 46.0)	16.0 (11.9 ; 21.9)	20.8 (15.4 ; 26.1)
	Percent of Total Death Rate	39.1 (31.3 ; 46.4)	36.4 (28.7 ; 44.2)	33.0 (25.8 ; 41.4)	43.1 (34.5 ; 51.9)
Total Population Death Rate		5.0 (4.5 ; 5.6)	6.7 (6.0 ; 7.6) *	3.0 (2.7 ; 3.5)	3.4 (3.0 ; 3.7)

*: significantly different between Iowa and Colorado

Table 3 Decomposition analysis of altitude effects on infant mortality by gender with bias-adjusted 95% confidence intervals

Gender	Females	Females	Males	Males
Maternal Education Level	high school and below	college and above	high school and below	college and above
"Normal" Subpopulation				
Direct Factor	1.24 (0.77 ; 1.75)	1.35 (0.90 ; 2.07)	1.30 (0.27 ; 3.24)	1.32 (0.84 ; 2.00)
Indirect Factor	1.06 (0.77 ; 1.56)	1.03 (0.69 ; 1.51)	1.09 (0.46 ; 5.03)	0.73 (0.50 ; 1.05)
Sub-total (Relative Risk)	1.32 (1.03 ; 1.69) *	1.39 (1.09 ; 1.84) *	1.41 (1.12 ; 1.79) *	0.96 (0.72 ; 1.24)
"Compromised" Subpopulation				
Direct Factor	0.97 (0.03 ; 10.06)	0.29 (-0.08 ; 4.54)	2.43 (0.48 ; 12.74)	6.27 (2.05 ; 50.43) *
Indirect Factor	0.97 (0.13 ; 11.85)	2.89 (0.89 ; 21.13)	0.41 (-0.02 ; 7.54)	0.21 (-0.02 ; 1.14)
Sub-total (Relative Risk)	0.94 (0.55 ; 1.49)	0.85 (0.45 ; 1.54)	0.99 (0.70 ; 1.49)	1.30 (0.88 ; 1.92)

*: Relative risk is significantly different from 1