Extended Abstract

The Effect of Birth Weight on Childhood Obesity

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ABSTRACT

Conventional linear analyses indicate higher birth weight predicts subsequent obesity (a risk factor for cardiovascular diseases). Paradoxically, a reduced risk of cardiovascular diseases is associated with higher birth weight. This study explores the association between birth weight and BMI (a measurement of obesity) at age seven by applying Covariate Density Defined mixture of linear regressions (CDDmlr) to the 1958 British birth cohort. Our analysis identifies two latent subpopulations ("normal" and "compromised" fetal development) and accounts for significant unmeasured heterogeneity in childhood BMI. Overall, 87-88% of the births are "normal" and their BMIs increase with birth weight. The remaining "compromised" births, though significantly smaller at birth, have higher BMIs and account for the majority of obese at age seven, compared to "normal" births. By demonstrating the association between faster postnatal growth rates with "compromised" births, our analysis offers a rational explanation for the birth weight and obesity paradox.

INTRODUCTION

It is well established that obesity has numerous adverse health effects on general. In particular, it is a major risk factor for cardiovascular diseases (Poirier, Giles et al. 2006; Lavie, Milani et al. 2009) and this risk has also been documented in obese children (Teixeira, Sardinha et al. 2001). In adults, overweight is defined as a body mass index (BMI) 25 to 29.9 kg/m^2 and obese as BMI $\geq$ 30 kg/m^2. A series of studies have shown that generally there is a positive relationship between birth weight and child/adult BMI (Parsons, Power et al. 2001; Ong 2006). However, this positive relation of birth weight and BMI in later life contradicts with the finding that people with high birth weight are less susceptibility to cardiovascular diseases (Rich-Edwards, Stampfer et al. 1997; Frontini, Srinivasan et al. 2004; Rich-Edwards, Kleinman et al. 2005; Claris, Beltrand et al. 2010).

Gage and colleauges (Gage and Therriault 1998; Gage 2002; Fang, Stratton et al. 2007) extended the finite mixture of logistic regressions model by defining the mixing parameter as a continuous function of the marginal distribution of a covariate. When applied to birth weight and infant mortality, two subpopulations (interpreted as births undergoing "normal" and "compromised" fetal development) are identified, which accounts for statistically significant, yet unmeasured, heterogeneity in infant mortality. In particular, "compromised" births have significantly lower mean birth weight and lower birth weight specific mortality compared to "normal" births. These results resolve the pediatric paradox (Gage, Bauer et al. 2004; Gage, Fang et al. 2008), that is

disadvantaged populations (as to race, smoking, altitude, social economical level, and etc.) have lower mortalities at low birth weights despite a higher overall mortality.

Some studies demonstrate a J-shaped, or even U-shaped, correlation between birth weight and BMI with a higher prevalence of obesity for low birth weight and macrosomic births (Parsons, Power et al. 2001; Claris, Beltrand et al. 2010). These results suggest that the association between birth weight and obesity may be much more complex. One possible explanation is that there is unmeasured heterogeneity in postnatal growth rate and consequent obesity similar to the case of infant mortality. Therefore, in this study, we extend Gage's statistical methodology (Gage and Therriault 1998; Gage 2002; Fang, Stratton et al. 2007) and develop the model of Covariate Density Defined mixture of linear regressions (CDDmlr). Then we use the longitudinal data from the 1958 British birth cohort study to investigate the relation between birth weight and childhood obesity (in particular, BMI at age seven) with CDDmlr. In particular, we intend to explore the J-shaped BMI by birth weight curve reported by Parsons et al. (2001) using the same birth cohort while controlling for potential heterogeneity in postnatal growth.

METHODS

Source of Data

The 1958 longitudinal British birth cohort includes all infants born in England, Scotland, and Wales during March 3rd-9th, 1958 (Power and Elliott 2006). Follow up of surviving children was conducted at age seven. Birth weight was originally recorded in

pounds and ounces and converted to grams in this study. At age seven, heights (to the nearness inch) and weights (in underclothes, to the nearness pound) were measured by trained medical personnel. Summary statistics for the samples used in this study are presented in Table 1.

Table 1 about here

Statistical Model - CDDmlr

Following (Gage 2002), the CDDmlr model includes two steps. First, the birth weight (x) density is modeled as a mixture of two Gaussian distributions:

$$f_1(x;\theta) = \pi_s \cdot N\left(x;\mu_s,\sigma_s^2\right) + (1-\pi_s)\cdot N\left(x;\mu_p,\sigma_p^2\right) \qquad \text{(Eq. 1)}$$

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 (s) subpopulation as opposed to the primary (p) subpopulation. For $i = s$ and p, $N\left(x;\mu_i,\sigma_i^2\right)$ represents the Gaussian distribution with mean μ_i and variance σ_i^2.

Second, a weighted estimation technique is applied to the regression of BMI (y) by birth weight (x). In particular, the BMI of the total population at each birth weight is a weighted sum of the BMIs of the secondary and the primary subpopulations at each particular birth weight:

$$f_2\left(y \mid x;\beta_s,\beta_p,\theta\right) = q_s(x;\theta)\cdot g_s\left(y \mid x;\beta_s\right) + \left(1-q_s(x;\theta)\right)\cdot g_p\left(y \mid x;\beta_p\right) \qquad \text{(Eq. 2)}$$

$q_s(x;\theta)$ is the posterior probability of latent group membership (i.e. the probability of being a secondary birth) given a particular birth weight. The birth weight density submodel (Eq. 1) determines that:

$$q_s(x;\theta) = \frac{\pi_s \cdot N(x;\mu_s,\sigma_s^2)}{\pi_s \cdot N(x;\mu_s,\sigma_s^2) + (1-\pi_s)\cdot N(x;\mu_p,\sigma_p^2)} \quad \text{(Eq. 3)}$$

For $i = s$ and p, the subpopulation specific BMI by birth weight association is modeled by a 2nd-order linear regression:

$$g_i(y \mid x;\beta_i = (\beta_{i,0},\beta_{i,1},\beta_{i,2})) = \beta_{i,0} + \beta_{i,1}\cdot x + \beta_{i,2}\cdot x^2 \quad \text{(Eq. 4)}$$

Model Fitting

The models (Eq. 1 and 2) are fitted sequentially using the method of maximum likelihood to individual level data using ms() in the SPLUS statistical library. Bias-adjusted 95% confidence intervals of each parameter are estimated by using 1000 bootstrap samples. Also Hierarchical analysis is carried out to determine the significance of parameters.

RESULTS

The birth weight distribution characteristics of 1958 British birth cohort are presented in Table 2 and Figure 1. The secondary subpopulation accounts for 12% and 13% of the female and males births, respectively. Compared to primary births of the same sex, secondary births have a significantly lower mean birth weight (by 424-498 grams, estimated using numbers in Table 2), but a significantly larger standard deviation (by 487-524 grams). Consequently, the primary subpopulation is largely confined to the normal birth weight range and it is generally interpreted as births with "normal" fetal growth, while the secondary subpopulation accounts for most births in both the lower and upper tails of the birth weight distribution as well as some birth in

the normal birth weight range and it is interpreted as "compromised" births, which are under some sort of stress during fetal development. This interpretation of the latent subpopulations is similar to that used in Gage's study of infant mortality (Gage and Therriault 1998; Gage 2002; Gage, Bauer et al. 2004).

Table 2 about here

Figure 1 about here

Standard chi-square tests (H_0: $\beta_s = \beta_p$, df = 3, p-value << 10^{-3}) show that there is significant heterogeneity in the association of BMI at age seven by birth weight between "compromised" and "normal" births in both sexes. For the "normal" subpopulation, its BMI at age seven appears to be a positive linear function of birth weight (Table 2 and Figure 2(a)). The average BMI at age seven for "normal" births is predicted to be 15.5 and 15.7 kg/m^2 for females and males, respectively. Interestingly, the birth weight specific BMI curve of the "compromised subpopulation is ∩-shaped (Table 2 and Figure 2(a)). Its BMI at age seven is significantly higher between 2000-5000 grams and changes more rapidly with birth weight compared to the "normal" subpopulation. Despite being smaller at birth (Table 2 and Figure 1(a)), "compromised" births have a higher mean BMI (18.2 and 17.5 kg/m^2 for females and males, respectively) and thus account for most obese individuals at age seven.

The model-predicted curve of BMI at age seven by birth weight for the total birth cohort is presented in Figure 2(b). In general, it shows a positive correlation between birth weight and BMI as is often observed (Seidman, Laor et al. 1991; Parsons, Power et al. 2001; Ong 2006). However, there is a bump around 2000 grams which might not be

detected if binned birth weight is used in the analysis. Between 2000-5000 grams, the curve is U-shaped and this is a results of the "compromised" subpopulation, which has higher BMI (Figure 2(a)) and accounts for the majority of births at low and high birth weights (Figure 1(b)).

Figure 2 about here

DISCUSSION

The Barker Hypothesis (1990) posits that "compromised" growth in utero may be associated with differential organ development (the severity and effects depending upon the timing of the insult) with increased allocation of nutrients to adipose tissue during development. This may then result in an accelerated weight gain during childhood, which could contribute to a relatively greater risk of various illnesses (including cardiovascular diseases) later in life. Our result that the "compromised" subpopulation has a faster postnatal growth rate during childhood (Figure 1(a)) supports the Barker Hypothesis (1990) and tends to resolve the paradox among birth weight, obesity, and cardiovascular diseases. Therefore CDDmlr is a very useful tool for studying the fetal programming hypothesis.

Our CDDmlr analysis of birth weight and childhood obesity identifies precisely those (i.e. "compromised" births) that are considered to be at highest risk of chronic adult disorders from birth weight information alone. Furthermore, the "compromised" subpopulation is at much higher risk of infant death (Gage 2002; Gage, Bauer et al. 2004; Gage, Fang et al. 2008). Thus the historical decline in infant mortality (Singh and Yu

1995) may play a role in the rise of obesity and chronic adult diseases (Rudolf, Greenwood et al. 2004; Yang 2008).

A major limitation of the current analysis is the potential bias due to the unavoidable losses through death and/or emigration as well as avoidable sample attrition (e.g. failure in follow up and refusal to participate further) (Atherton, Fuller et al. 2008), which occurs in any longitudinal study. For the 1958 British birth cohort, the losses of births with lower and higher (macrosomic) birth weight seem to occur more frequently than births with normal birth weights. The loss of these "compromised" births is likely due to death during infancy. On the other hand, these members of the birth cohort are most likely to be associated with adverse outcomes in childhood and adulthood due to fetal programming if they survive. Therefore, the "compromised" subpopulation appears to be underrepresented and the statistical power of this analysis of BMI by birth weight correlation for "compromised" births may be reduced. We are currently developing an EM algorithm approach which should resolve this issue.

ACKNOWLEDGEMENT

This work is supported by NIH grant R01 HD037405 and R24 HD044943.

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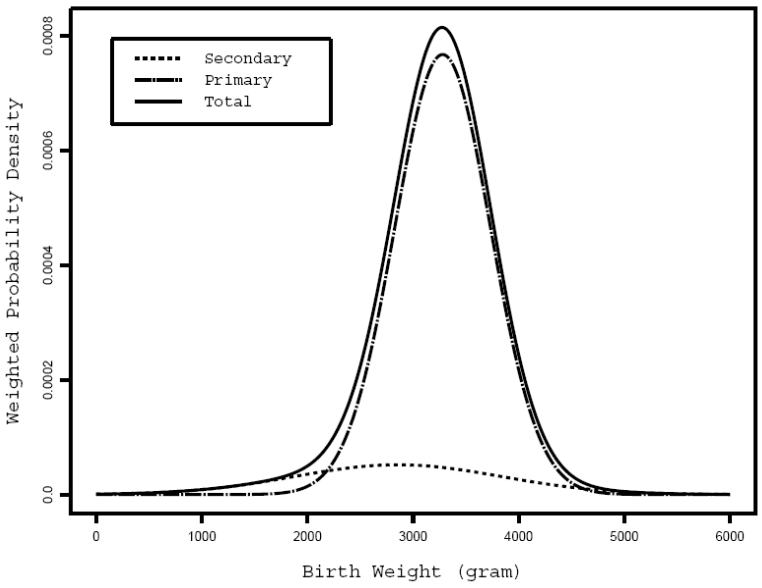
Figure Captions

Figure 1 Model-predicted birth weight distributions: Females of 1958 British birth cohort. Results for males are similar.

Figure 2 Model-predicted BMIs at age seven: Females of 1958 British birth cohort. Results for males are similar.

(a)


Secondary
Primary
Total
Weighted Probability Density
0.0
0.0002
0.0004
0.0006
0.0008
0
1000
2000
3000
4000
5000
6000
Birth Weight (gram)

(b)

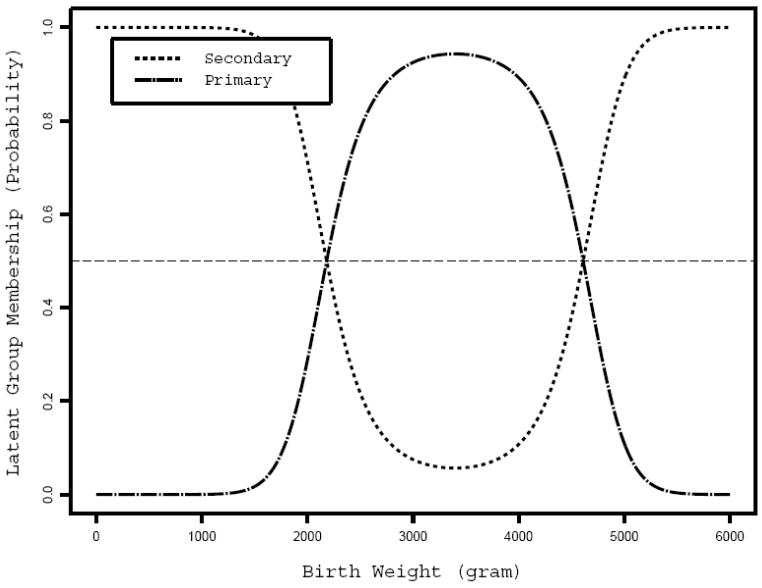
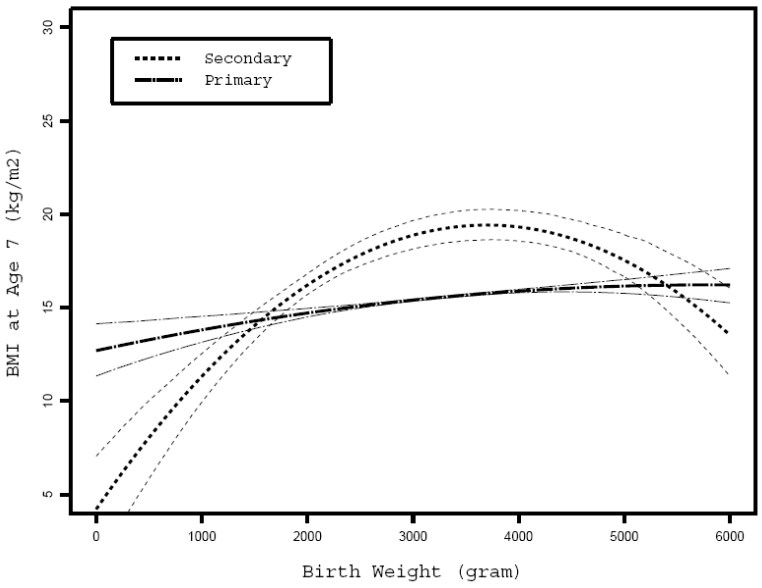

Secondary
Primary
Latent Group Membership (Probability)
0.0
0.2
0.4
0.6
0.8
1.0
0
1000
2000
3000
4000
5000
6000
Birth Weight (gram)

Figure 1

(a)


Secondary
Primary
BMI at Age 7 (kg/m2)
Birth Weight (gram)
5
10
15
20
25
30
0
1000
2000
3000
4000
5000
6000

(b)

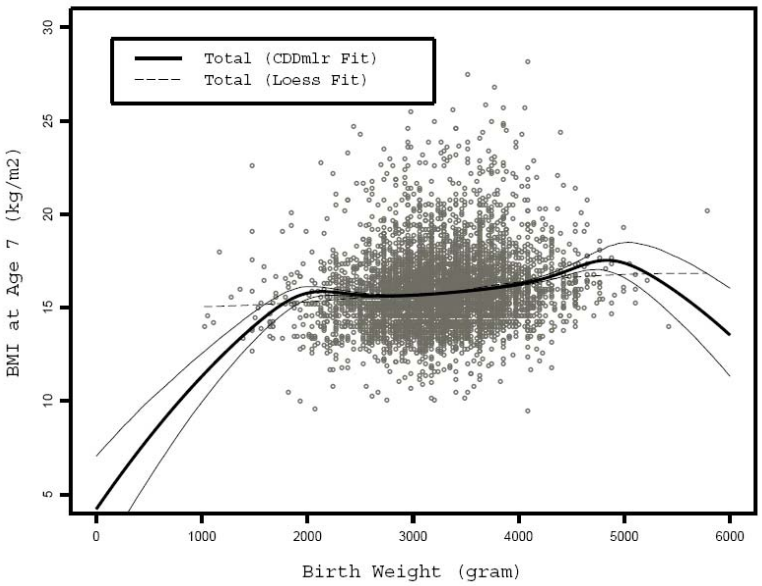

Total (CDDmlr Fit)
Total (Loess Fit)
BMI at Age 7 (kg/m2)
Birth Weight (gram)
5
10
15
20
25
30
0
1000
2000
3000
4000
5000
6000

Figure 2

Table 1 Statistical description of birth weight (gram) and body mass index (BMI, kg/m^2) at age seven # for members of the 1958 British birth cohort by gender

	Females		Males	
	Birth Weight	BMI	Birth Weight	BMI
sample size	8143	6041	8637	6419
minimum	369	9.5	312	9.3
5^{th} percentile	2296	13.4	2381	13.8
25^{th} percentile	2920	14.6	3033	15.0
50^{th} percentile	3232	15.6	3402	15.8
75^{th} percentile	3600	16.7	3742	16.7
95^{th} percentile	4082	19.3	4252	18.7
maxium	6010	28.2	5727	29.0
mean	3225	15.9	3362	15.9
stdev	567	1.9	584	1.6
skewness	-0.6	1.3	-0.6	1.2
kurtosis	2.2	3.9	1.9	4.9

#: members with birth weight information available as well

Table 2 Parameter estimates and bias-adjusted 95% confidence intervals

Parameter	Females				Males			
	Estimate	LCI	UCI		Estimate	LCI	UCI	
marginal birth weight distribution								
π_s	0.13	0.10	0.16		0.12	0.09	0.16	
μ_s	2855	2714	2972		2922	2764	3041	
σ_s	978	924	1031		968	904	1026	
μ_p	3279	3267	3291		3420	3407	3434	
σ_p	453	438	468		481	467	496	
subpopulation-specific 2nd-order linear regression coefficients								
$\beta_{s,0}$	4.21	1.04	7.04		8.27	5.04	10.82	
$\beta_{s,1}$	8.22E-03	6.23E-03	1.04E-02		4.86E-03	2.99E-03	7.09E-03	
$\beta_{s,2}$	-1.11E-06	-1.43E-06	-7.93E-07		-5.82E-07	-9.02E-07	-2.74E-07	
$\beta_{p,0}$	12.70	11.34	14.14		14.87	13.68	16.09	
$\beta_{p,1}$	1.22E-03	3.74E-04	2.06E-03		4.01E-06	-7.16E-04	6.99E-04	#
$\beta_{p,2}$	-1.05E-07	-2.31E-07	1.42E-08	# *	7.19E-08	-3.09E-08	1.75E-07	# *

: not significantly different from zero based on bias-adjusted 95% confidence interval

*: not significantly different from zero based on hierarchical analysis