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4 authors, including:

Mary L Hediger
U.S. Department of Health and Human Ser…

Mary D Overpeck

Birthweight and gestational age effects on motor and social development

Mary L. Hediger[a], Mary D. Overpeck[a,b], W. June Ruan[a] and James F. Troendle[a]

[a]*Division of Epidemiology, Statistics, and Prevention Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, and* [b]*Maternal and Child Health Bureau, Health Resources and Services Administration, Rockville, MD, USA*

Correspondence:
Dr Mary L. Hediger, DESPR/NICHD/NIH, Building 6100, Room 7B03, 9000 Rockville Pike, Bethesda, MD 20892-7510, USA.
E-mail: hedigerm@exchange.nih.gov

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Summary

The number of children at risk for delays in motor and social development (MSD) associated with preterm delivery and low birthweight is increasing, but such children are generally not seen as being in need of evaluation. The objective of these analyses was to determine whether there are independent effects of birthweight and gestational age on MSD and the magnitude of effects. Subjects were a representative sample of 4621 US-born singleton children, aged 2–47 months, examined in the third National Health and Nutrition Examination Survey (1988–94). MSD was assessed using an age-appropriate scale. Birthweight and gestational age were taken from birth certificates. Mexican–American and 'other' race/ethnicity (other than non-Hispanic white, non-Hispanic black or Mexican–American), low parental education level, older maternal age, higher birth order, low birthweight (LBW, <2500 g) and preterm delivery (<37 weeks) were all found to be associated with significant ($P < 0.01$) delays in MSD. Three percent of the infants and children were preterm LBW and 2.2% term LBW (<2500 g, 37–44 weeks). Adjusting for socio-demographic factors, preterm LBW children had lower MSD scores (–1.5 ± 0.3 points, $P < 0.0001$) through early childhood, as did term LBW children (–0.8 ± 0.4 points, $P < 0.03$). For females, LBW was the most important perinatal predictor of a lowered score (–0.9 ± 0.3 points compared with normal birthweight, $P < 0.04$). For males, scores were additionally decreased by –0.1 ± 0.03 points/week ($P = 0.001$) of early delivery. LBW children had less muscle mass, but adjusting for muscularity did not diminish the effects of birth size on MSD. LBW status and preterm delivery are associated independently with small, but measurable, delays in MSD through early childhood and should be considered along with other known risk factors for development delays in determining the need for developmental evaluation.

Introduction

As the survival of infants born very preterm or growth retarded has improved,[1–3] it has become important to determine the expected consequences of perinatal factors on infant and child motor and social development (MSD). However, it is often difficult to disentangle effects that are attributable to preterm delivery or intrauterine growth retardation from those attributable to other environmental, socio-demographic or maternal factors that are associated with developmental delays.[4] Risk factors for preterm delivery (<37 completed weeks) and low birthweight (LBW, <2500 g), such as low socio-economic status and parental education, are also more common among children at risk of developmental delays.[5] The subtle deficits and delays associated with mild intrauterine growth retardation or moderate preterm delivery are particularly difficult to detect.

Studies looking at the effects of very preterm (<33 weeks' gestation) or moderately preterm delivery (33–36 weeks) and very low birthweight (VLBW <1500 g) or LBW status on later developmental outcome have tended to focus on the outcomes for the most extreme cases (very preterm delivery and/or VLBW), who are likely to have the most severe developmental delays.[6,7] Alternatively, they have followed children born to women generally at risk of poor pregnancy outcome and therefore already at risk of having children with developmental differences.[8,9]

Less attention has been paid to the developmental follow-up of infants born moderately LBW (1500–2499 g) or moderately preterm (33–36 weeks), because these infants are perceived to be at much lower risk of significant morbidity. Nevertheless, there has been a trend towards medical induction of labour or delivery by caesarean section at moderately preterm gestational ages, especially when the pregnancy is complicated by pregnancy-induced hypertension, gestational diabetes or pre-eclampsia. Early delivery is thought to be more benign than continued fetal development in a compromised intrauterine environment. The increase in the US singleton preterm birth rate from 97.0 (per 1000 liveborn infants) in 1989 to 97.3 in 1996 has been almost entirely driven by a near doubling (9.1% in 1989 to 17.1% in 1996) in the number of infants born moderately preterm after medical induction.[10] Over this same time period, although the rates of moderately preterm delivery increased (74.8 per 1000 in 1989 to 76.5 in 1996), the rates of very preterm and extremely preterm delivery (20–28 weeks) declined. Consistent with the US data, comparable trends in preterm delivery have been noted in Canada.[11,12] This means that the number of children at risk of developmental delays associated with moderate preterm delivery may be increasing.

Questions also remain about the relative impact of maturity status at birth on MSD, with its implied neurological complications, compared with birth size (fetal growth restriction).[13] Whether there are effects of fetal growth restriction independent of maturity status, particularly, is not well known. Studies of the body composition of infants born small-for-gestational-age (SGA, both preterm and term) have shown that lean body mass (muscle) and bone mineral content are significantly reduced in the SGA infant compared with infants born appropriate- (AGA) or large-for-gestational-age (LGA).[14–16] In previous analyses from the third National Health and Nutrition Examination Survey (NHANES III), we have shown that infants born small remain smaller through early childhood and that the deficit in weight is primarily attributable to deficits in lean body mass (i.e. muscle).[16–18] MSD scales, because they necessarily focus on motor development in infancy, may be affected by these differences in muscularity associated with birth status. That is, whether or not cognitive skills are affected, the acquisition of appropriate motor skills might be delayed among infants and young children born SGA or LBW at term who have reduced musculature. Some evidence for this exists; in comparison with term and preterm AGA infants, preterm SGA infants have been shown to have poorer quality upright locomotion in childhood.[19]

However, there have been no studies examining the effects of perinatal factors on MSD for a representative sample of US infants and children over the entire range of perinatal outcomes and at younger ages. The objective of these analyses is therefore to examine the effects of birthweight and gestational age on MSD, accounting for differences in muscularity, in a nationally representative, cross-sectional sample of infants and children, aged 2–47 months. The infants and children were assessed using a specially designed MSD scale as participants in NHANES III, and the information from NHANES III was linked to birth certificates for US-born infants and children to determine status at birth.

Methods

Design and sample

The third National Health and Nutrition Examination Survey (NHANES III; 1988–94), conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (NCHS/CDC), is a cross-sectional, health examination survey of nearly 40 000 people, aged 2 months and older, representative of the US civilian, non-institutionalised population.[20] Infants and children from 2 to 71 months at interview were oversampled, as were Blacks and Mexican–Americans. The analyses reported here are on infants and children examined between 2 and 47 months of age.

Informed consent was obtained from parents or guardians at the time of the household interview to seek birth certificates for these infants and children (n = 5965). Health examinations, including an anthropometric measurement component, were given to 5629 of these children (94.4%), usually within 2–4 weeks of interview.

Birth certificates

Birth certificates for the years 1985–94 were positively matched for 5183 US-born infants and children who were both interviewed and examined. Excluded at this point were four cases with missing birthweights, one where sex was discrepant between the birth certificates and NHANES III, and 120 children who were twins or triplets. Although twins or triplets might be expected to be at particular risk because they are more likely to be born preterm and LBW, there were too few multiples in the NHANES III sample for separate analyses.

Length of gestation from the mother's last menstrual period (LMP) was examined on the certificates for completeness and validity.[17,18,21] Gestational age was considered invalid for 90 cases when >44 weeks and for 80 cases when, at gestational ages of ≤35 weeks, birthweight was inconsistent (too high).[22,23] Length of gestation was missing for 116 cases and could not be replaced by clinical estimates because clinical estimates were not reported on birth certificates before 1989. Of the 286 cases excluded for missing or invalid gestational age, 7.2 ± 2.1% (% ± SE) were LBW, 82.5 ± 2.9% normal weight (2500–3999 g) and 10.3 ± 2.2% high birthweight (≥4000 g), such that the distribution of birthweight groupings for the excluded cases did not differ much from that of the analysed sample.

Birthweight and gestation indices

Infants were categorised as low birthweight (LBW) at <2500 g, normal at birthweights between 2500 and 3999 g and high ≥4000 g. Very preterm delivery was defined as delivery <33 completed weeks, preterm as 33–36 weeks and term as ≥37 weeks.

Infants were categorised by birthweight-for-gestational-age (BWGA) using a reference derived for singleton infants from US vital statistics where length of gestation was also based on the LMP.[23] Infants were categorised separately by race/ethnicity (non-Hispanic white, Mexican–American, non-Hispanic black), infant sex and maternal parity. Those belonging to the 'other' racial/ethnic group were categorised using the reference percentiles for non-Hispanic whites. Small-for-gestational-age (SGA) was defined as <10th percentile of BWGA, appropriate-for-gestational-age (AGA) from the 10th to the 89th percentile and large-for-gestational-age (LGA) as ≥90th percentile.

Estimates of gestational age by specific week from the LMP that form the basis for classification of BWGA may be in error, especially at preterm gestations. However, the ability to identify term births correctly using the LMP is over 95%.[24,25] Therefore, a modified Yerushalmy index combining birthweight and gestational age was created.[26] The categories defined were: very preterm (<33 weeks), preterm LBW (33–36 weeks, <2500 g), term LBW (37–44 weeks, <2500 g) and all others not born LBW (not LBW, ≥2500 g). Too few VLBW infants (n = 27) were in the sample to warrant a separate category. In multiple regression analyses, the very preterm and preterm LBW categories were combined to increase sample size.

Motor and social development (MSD) score

The MSD scale was administered by interview as part of the NHANES III Household Youth Questionnaire for infants and children under 4 years at interview.[20] The principal respondent was predominantly the mother (91.2 ± 0.7%). In fewer cases, the father (6.5 ± 0.7%), grandparent (1.4 ± 0.2%) or other relative (0.9 ± 0.2%) was interviewed. The interview was conducted in Spanish for 6.3 ± 0.9%; most (93.1 ± 1.0%) were conducted in English and a handful (0.6 ± 0.4%) in a language other than English or Spanish.

MSD items in NHANES III were derived from standard measures of child development, including the Bayley Scales of Infant Development,[27] the Gesell scale[28] and the Denver Developmental Screening Test (DDST).[29,30] The items selected for the scale are standard questions with face validity that have performed as expected with respect to many of the other independent variables. A nearly identical composite scale was used first in the Child Health Supplement to the 1981 National Health Interview Survey,[31] and then modified for use in the National Longitudinal Survey of Youth (NLSY).[32] The composite scale was modified and amplified for the NHANES III. Similar to the DDST, the NHANES III scale was designed for administration by home interview and for the assessment of children aged 2–47 months.

Based on the child's age, the scale assesses 15 or 16 age-appropriate items out of 48 MSD markers (Appendix). The assessment had eight components. Part 1 relates to infants aged 0–3 months, and Part 8 is addressed to children aged 22–47 months. The scale is heavily focused on motor development at the youngest ages. In the initial age interval (0–3 months), 73.3% of the 15 items assess gross and fine motor skills. Cumulatively through the 47 months, 56.2% of the total of 48 items are fine or gross motor items.

All items are dichotomous (0 = not achieved, 1 = passed), and the total raw score is obtained by summation. Raw scores range from 0 to 15 for ages 0–21 months and from 0 to 16 for ages 22–47 months. The youngest age represented in NHANES III is 2 months. For these analyses, a new continuous score (MSD score) was created with a raw score range of 0–48 that was dependent on age. Items previous to those considered appropriate for a given age range were scored as 'passed'. Fourteen narrow age groups[29] were defined to control for the effects of age in analyses, and age group was included as a covariate in all subsequent analyses (Appendix). This approach should yield similar results to one using an age-standardised score as the dependent variable, given that the standard deviations of the MSD scores appear to be approximately constant across age–sex strata. No attempt was made to classify infants and children into diagnostic categories (i.e. normal, questionable, abnormal) because the aim was to look at relative development, and the diagnostic sensitivity of some of the underlying scales (Gesell, DDST) in identifying LBW children as abnormal is low.[33] A total of 151 cases were excluded because scoring for two or more items was missing, leaving a final analytic sample of 4621 infants and children.

Anthropometric measurements

The measurements considered were those used to develop indices of muscularity, that is mid-upper arm circumference (cm) and triceps skinfold thickness (mm), measured using standard anthropometric protocols.[34,35] Mid-upper arm muscle area (cm^2) was derived from the mid-upper arm anthropometry[36] to determine the effect of musculature on the development of motor skills.

Other variables

Other variables, used as exclusion criteria and in analysis, were taken from either the birth certificates or NHANES III. Infant sex, infant plurality (twin or triplet birth), maternal parity and infant birth order were taken from the birth certificate.[21]

Race/ethnicity as self-reported in NHANES III was based on US Bureau of the Census categories.[20] Bureau of the Census definitions were used in NHANES III to define type of residence (metropolitan and non-metropolitan county) and region of residence (north-east, mid-west, south and west), with the exception that Texas was included in the south as opposed to the west census region. The definition of metropolitan counties is central or fringe counties of metropolitan areas of 1 million population or more.

Information on mother's age and smoking during pregnancy were taken from NHANES III questionnaires, and the education of the family reference person (FRP) in NHANES III was used to measure education level in the household.

Statistical methods

Statistical sample weights for examined children were used to account for the oversampling and unit non-response.[37] SUDAAN software was used to estimate standard errors (SE) of the descriptive and prevalent characteristics for the final analytic sample.[38] Means (± SE) for the total MSD score by age group and sex were computed using SUDAAN; standard deviations (SD) of the total MSD score adjusted for the sampling weights were estimated using SAS for Windows.[39]

SUDAAN linear regression procedures were used to determine the univariate relationships between MSD score and various predictors, adjusting for age group, and to develop multiple regression models with the MSD score or anthropometric outcomes as the dependent variable. Results are presented as regression coefficients (β) ± SE in MSD score points or the unit of anthropometric measurement. The coefficients are tested for statistical significance from zero ($\alpha = 0.05$). SUDAAN procedures yield more conservative estimates of variation than conventional parametric statistics, so that statistical significance is not inflated because of the large sample size.

Results

Sample characteristics

The final analytic sample was 4621 infants and children, aged 2–47 months. After applying the statistical sample weights, the sample was predominantly non-Hispanic white, although nearly a third were ethnic minorities (Table 1). Other factors potentially related to the MSD score were sufficiently prevalent and were included in multiple regression models. About 40% of the infants and children were first-born, and roughly 20% were born either to teenage mothers (<19 years,

Table 1. Sample characteristics,[a] 4621 infants and children, aged 2–47 months, NHANES III, 1988–94

Characteristic (source)	Unweighted	Weighted
	n	% ± SE
Age group (months) (NHANES III)		
2–3	346	4.7 ± 0.4
4–6	504	6.5 ± 0.3
7–9	505	6.7 ± 0.3
10–12	388	5.6 ± 0.3
13–15	245	6.6 ± 0.4
16–18	261	6.3 ± 0.5
19–21	230	6.0 ± 0.6
22–24	278	7.1 ± 0.6
25–27	267	6.6 ± 0.5
28–30	259	6.9 ± 0.5
31–34	357	8.9 ± 0.5
35–38	317	8.6 ± 0.6
39–42	301	8.0 ± 0.6
43–47	363	11.6 ± 0.6
Race/ethnicity (NHANES III)		
Non-Hispanic white	1980	65.1 ± 2.0
Non-Hispanic black	1190	16.2 ± 1.2
Mexican–American	1165	8.8 ± 0.9
Other race/ethnicity	286	10.0 ± 1.6
Sex (NHANES III, birth certificate)		
Male	2329	51.9 ± 1.0
Female	2292	48.1 ± 1.0
Birth order (birth certificate)		
First born	1849	41.0 ± 1.1
Second born	1484	34.7 ± 1.0
Third or higher born	1288	24.3 ± 1.1
Census region of residence (NHANES III)		
North-east	617	18.2 ± 1.2
Mid-west	990	25.4 ± 1.4
South	1884	34.3 ± 2.7
West	1130	22.0 ± 3.7
Residence (NHANES III)		
Metropolitan county	2344	48.6 ± 5.1
All other areas	2277	51.4 ± 5.1
Mother's age (years) (NHANES III)		
<19	436	7.5 ± 0.6
19–34	3799	83.2 ± 0.8
≥35	376	9.3 ± 0.8
Maternal smoking during pregnancy (NHANES III)		
No	3642	76.7 ± 1.0
Yes	971	23.3 ± 1.0
Education of family reference person (years) (NHANES III)		
<9	680	8.9 ± 1.0
9–11	810	14.5 ± 0.7
12	1576	33.9 ± 1.3
13–15	771	20.1 ± 1.3
16–17	699	22.6 ± 1.6
Birthweight (birth certificate)		
Low (<2500 g)	260	5.1 ± 0.5
Normal (2500–3999 g)	3882	83.3 ± 0.8
High (≥4000 g)	479	11.6 ± 0.8
Gestation at delivery (birth certificate)		
Very preterm (<33 weeks)	47	1.2 ± 0.3
Preterm (33–36 weeks)	329	6.1 ± 0.5
Term (37+ weeks)	4245	92.7 ± 0.6
Birthweight-for-gestational-age (birth certificate)		
Small (<10th percentile)	485	9.5 ± 0.8
Appropriate (10–89th percentile)	3686	80.6 ± 0.8
Large (≥90th percentile)	450	9.9 ± 0.8
Gestation and birthweight index (birth certificate)		
Very preterm	47	1.2 ± 0.3
Preterm LBW	92	1.8 ± 0.3
Term LBW	124	2.2 ± 0.3
Not LBW	4358	94.9 ± 0.5

[a]The statistics are percentage ±SE estimated using the statistical weights for examined children to account for the NHANES III sample design. Sample sizes for individual characteristics may vary slightly because of missing data.

7.5%) or to women of advanced maternal age (≥35 years, 9.3%). Just under a quarter of the mothers smoked during pregnancy, and >40% of the FRP had some college education.

Looking at birth status, 5.1% were LBW (0.7% VLBW, 4.4% moderately LBW), whereas 7.3% were preterm (1.2% very preterm, 6.1% moderately preterm). The prevalence of SGA and LGA categories was close to the expected 10%; 9.5% were SGA, 9.9% LGA. However, less than a third (28.8%) of SGA infants were also LBW, and the preponderance of the SGA infants were born at term (93.5%). On the other hand, 79.4% of LGA infants had high birthweights, with 89.6% born at term. Combining birthweight and gestational age, 3.0% were born either very preterm (1.2%) or preterm LBW (1.8%), whereas another 2.2% were both term and LBW. The preterm LBW and term LBW infants were fairly uniformly distributed across the age categories, such that no one age category was bereft or had a significant surfeit of preterm or term LBW infants.

Univariate relationships with the MSD score

The associations of the MSD score with individual factors were assessed, and a number of socio-demographic and maternal characteristics were associated with the MSD score. In models adjusting for age group, Mexican–Americans and those of 'other' race/ethnicity had average MSD scores that were significantly lower over this age range (Table 2). The average MSD scores for non-Hispanic blacks were not different compared with the scores for non-Hispanic whites. When the education level of the FRP was less than high school (12 years), MSD scores were significantly lower. The infants and children of older mothers (≥35 years) had lower total MSD scores (–0.6 points, $P = 0.009$). Overall, males had lower scores (–0.6 points, $P < 0.0001$) than females, and second or higher born infants and children had lower scores than the first-born. Residence and maternal smoking during pregnancy were not related to MSD score.

There were significant linear effects of both birthweight and length of gestation on the MSD score up to 47 months (Table 2). The MSD score was increased by 0.3 points per kg of birthweight ($P = 0.012$) and by 0.1 points per week of accrued gestational age ($P < 0.0001$).

Although trending in the expected directions, BWGA showed little significant association with the MSD score, whereas both birthweight and gestational age categories alone were significantly associated with the MSD score. LBW was associated with a significantly lower MSD score (–1.1 points, $P < 0.0001$). There was a dose–response effect of gestational age with those born very preterm having scores lower by –1.4 points ($P = 0.008$), as would be expected as nearly all (98.3%) were also LBW. However, even those born moderately preterm had scores significantly lower by –0.4 points ($P = 0.014$), despite the fact that only 29.5% were LBW.

Combining birthweight and gestational age (modified Yerushalmy index) provided the most informative index, with the categories of very preterm (–1.4 points), preterm LBW (–1.2 points) and term LBW (–0.8 points) capturing a dose–response effect.

Multiple regression models

To determine whether there were effects of birthweight and gestational age on the MSD score, independent of its association with other socio-demographic and maternal factors, a multiple regression model was constructed adjusting for race/ethnicity, mother's age, birth order and the education of the FRP (Table 3). Also included in the model were age group, sex and the interaction of age group and sex (Wald $F = 6.48$, $P < 0.0001$). Adjusting for socio-demographic and maternal factors, the coefficients for Mexican–Americans and 'other' race/ethnicity were no longer significant, whereas the MSD scores for non-Hispanic blacks were significantly greater (0.3 ± 0.1 points, $P = 0.01$) than those for non-Hispanic whites. The significant negative effects of higher birth order and low FRP education on the MSD score remained in the multiple regression model. The positive effect of young maternal age (<19 years) became statistically significant, whereas the negative effect of older maternal age (≥35 years) was diminished but also remained significant.

The effects of birthweight and gestational age remained, even after adjusting for the other socio-demographic and maternal factors. Infants and children born preterm LBW had scores lower by –1.5 points ($P < 0.0001$); those born term LBW had scores lower by –0.8 points ($P = 0.024$).

Analyses were stratified by sex because of the significant interaction between age group and sex with differential effects of birthweight and gestational age for males and females. For females, there was a significant effect of LBW (–0.9 ± 0.3 points, $P = 0.034$) compared with normal birthweight, but no additional contribution for length of gestation, indicating that LBW status (birth size) was the most important perinatal predictor of MSD score in females. For males, although the effect of LBW was significant (–0.8 ± 0.3 points, $P = 0.018$) compared with normal birthweight, length of gestation was also highly significant (0.1 ± 0.03 points per accrued week of gestational age, $P = 0.001$). Maturity, as well as birth size, is associated with the rate of MSD for males.

Age trends by sex

In the multiple regression model, male infants had higher MSD scores than females infants at age 2–3 months, but scores were similar through the rest of the first year. After the first year, scores for female children were higher than those for males. Table 4 presents the weighted means for males and females by age group to illustrate the interaction between age group and sex. The weighted means are similar to the least square means estimated from the multiple regression model.

Through the first year, when there is most emphasis on motor development in the scale, male infants had MSD scores comparable with those of females. After 12 months, males had MSD scores consistently lower,

Table 2. Univariate relationships for the total motor and social development (MSD) score, 4621 infants and children, NHANES III, 1988–94

Characteristic	Coefficient (β) ± SE[a]	*P*
Race/ethnicity		
Non-Hispanic white	0.00 Reference	
Non-Hispanic black	+0.15 ± 0.12	0.208
Mexican–American	–0.39 ± 0.12	0.003
Other race/ethnicity	–0.53 ± 0.26	0.046
Education of family reference person (FRP) (years)		
<9	–0.98 ± 0.24	0.0002
9–11	–0.48 ± 0.20	0.018
12	–0.15 ± 0.17	0.377
13–15	0.00 Reference	
16–17	–0.12 ± 0.19	0.521
Residence		
Metropolitan county	+0.02 ± 0.10	0.851
Non-metropolitan county	0.00 Reference	
Mother's age (years)		
<19	+0.39 ± 0.20	0.056
19–34	0.00 Reference	
≥35	–0.64 ± 0.23	0.009
Mother's smoking during pregnancy		
No	0.00 Reference	
Yes	+0.12 ± 0.12	0.296
Sex		
Male	–0.58 ± 0.10	<0.0001
Female	0.00 Reference	
Birth order		
First born	0.00 Reference	
Second born	–0.55 ± 0.10	<0.0001
Third or higher born	–0.77 ± 0.17	<0.0001
Birthweight (pt/kg)	+0.26 ± 0.10	0.012
Gestation (pt/wk)	+0.12 ± 0.02	<0.0001
Birthweight-for-gestational-age (BWGA)		
Small (<10th percentile)	–0.24 ± 0.17	0.172
Appropriate (10–89th percentile)	0.00 Reference	
Large (≥90th percentile)	–0.03 ± 0.24	0.899
Birthweight		
Low (<2500 g)	–1.05 ± 0.22	<0.0001
Normal (2500–3999 g)	0.00 Reference	
High (≥4000 g)	–0.02 ± 0.21	0.937
Gestation		
Very preterm (<33 weeks)	–1.36 ± 0.49	0.008
Preterm (33–36 weeks)	–0.44 ± 0.17	0.014
Term (37+ weeks)	0.00 Reference	
Gestation and birthweight index		
Very preterm	–1.38 ± 0.49	0.007
Preterm LBW	–1.17 ± 0.28	0.0001
Term LBW	–0.76 ± 0.36	0.04
Not LBW	0.00 Reference	

[a]The results are from linear models, adjusting for age group.

with the greatest discrepancy (–1.3 points) beginning from 22 to 27 months. Using a scale in which motor development is emphasised early and social and language skills are emphasised at later ages, males appear to develop at similar rates to females in the first year of life, but develop more slowly after the first year as the acquisition of social and language skills becomes more important as milestones.

Table 3. Multiple regression coefficients[a] predicting the total MSD score

	Coefficient (β) ± SE	*P*
Race/ethnicity		
Non-Hispanic white	0.00 Reference	
Non-Hispanic black	+0.32 ± 0.12	0.01
Mexican-American	–0.07 ± 0.19	0.71
Other race/ethnicity	–0.27 ± 0.19	0.18
Education of family reference person (FRP) (years)		
<9	–0.83 ± 0.24	0.001
9–11	–0.45 ± 0.17	0.01
12	–0.16 ± 0.15	0.30
13–15	0.00 Reference	
16–17	–0.03 ± 0.17	0.87
Mother's age (years)		
<19	+0.41 ± 0.19	0.032
19–34	0.00 Reference	
≥35	–0.50 ± 0.20	0.016
Birth order		
First born	0.00 Reference	
Second born	–0.52 ± 0.10	<0.0001
Third or higher born	–0.62 ± 0.14	<0.0001
Gestation and birthweight index		
Preterm LBW	–1.51 ± 0.25	<0.0001
Term LBW	–0.82 ± 0.35	0.024
Not LBW	0.00 Reference	

[a]From a linear model (R^2 = 0.958), adjusting for age group, sex and the interaction of age group and sex (Wald F = 6.48, P < 0.0001).

Joint effects

The delay in MSD attributable to LBW or preterm delivery is not by itself large. However, the joint effects of the other factors should be considered, although there are myriad possible combinations. For example, based on the multiple regression analysis, an infant or child born preterm LBW to a mother aged 35 years or older would have an MSD score about –2 points or –0.75 SDU below the mean for age, translating into their achieving two items less than a child without risk factors on the age-appropriate scale (Appendix). An infant or child born term LBW to an older mother would be expected to have a score –1.3 points or –0.5 SDU. Of those preterm LBW, 7.7% were also born to a mother 35 years of age or older, and 4.7% of term LBW infants and children were born to an older mother. Second or higher born preterm LBW children, accounting for 37.4% of those born preterm LBW, would also be expected to have a score –0.75 SDU below the mean, and second or higher born term LBW children (60.9% of those born term LBW) –0.5 SDU. There are comparable joint effects of birth status and the FRP having achieved an educational level of 11 years or less, and 28.0% of preterm LBW and 43.6% of term LBW infants and children fall into this category. The third child born to an older mother where the FRP had less than

Table 4. Mean total MSD score by infant or child sex and age group

Age group (months)	Males			Females			Difference Male–Female
	n	Mean[a] ± SE	SD	*n*	Mean ± SE	SD	
2–3[b]	167	10.4 ± 0.2	2.0	179	10.2 ± 0.2	2.2	+0.2
4–6	271	15.5 ± 0.1	2.2	233	15.4 ± 0.1	2.2	+0.1
7–9	258	21.6 ± 0.2	3.0	247	21.9 ± 0.2	2.5	–0.3
10–12	186	27.6 ± 0.3	2.6	202	27.5 ± 0.3	2.6	+0.1
13–15	130	31.6 ± 0.2	2.2	115	32.0 ± 0.2	1.7	–0.4
16–18	131	33.7 ± 0.2	2.2	130	34.2 ± 0.2	1.9	–0.5
19–21	115	35.7 ± 0.2	2.2	115	36.2 ± 0.2	2.1	–0.5
22–24	134	38.8 ± 0.3	2.6	144	40.1 ± 0.3	2.7	–1.3
25–27	135	40.8 ± 0.3	2.8	132	42.1 ± 0.3	2.6	–1.3
28–30	132	42.4 ± 0.3	2.7	127	43.3 ± 0.3	2.4	–0.9
31–34	199	43.5 ± 0.2	2.6	158	44.6 ± 0.2	2.2	–1.1
35–38	151	44.9 ± 0.3	2.5	166	45.0 ± 0.3	2.4	–0.1
39–42	149	45.4 ± 0.4	2.3	152	46.2 ± 0.2	1.9	–0.8
43–47	171	45.9 ± 0.2	1.9	192	46.7 ± 0.1	1.5	–0.8

[a]The means are given as mean ± SE, which have been estimated in SUDAAN using the statistical weights for examined children to account for the NHANES III sample design. The SD were also estimated using the statistical weights with SAS for Windows software.
[b]Although the target age for the interval is 0–3 months, the starting age in the sample is 2 months.

Table 5. Coefficients from models predicting mid-upper arm muscle area measurements in infancy and childhood

	Males	Females
	Coefficient[a] ± SE	Coefficient ± SE
Mid-upper arm muscle area (cm^2)		
Preterm LBW	–1.37 ± 0.27**	–0.84 ± 0.34*
Term LBW	–1.02 ± 0.52*	–1.35 ± 0.28**
Not LBW	0.00 Reference	0.00 Reference

[a]Coefficients (±SE) are from models including age group, race/ethnicity, mother's age, mother's smoking during pregnancy, birth order, the education of the family reference person and the gestation and birthweight index.
*$P \leq 0.05$, **$P \leq 0.001$.

a ninth grade education, who is also born preterm and LBW, may be expected to have an MSD score –4 points (achieving four items less at age level) or –1.5 SDU below the mean for age.

Mid-upper arm muscle area

There was an approximate 1 cm^2 deficit in mid-upper arm muscle area through early childhood associated with LBW status (Table 5). To determine whether diminished muscularity associated with being born LBW could account for the lower MSD scores, the final multiple regression model was adjusted further by using mid-upper arm muscle area (cm^2) as a continuous variable (R^2 = 0.96). Mid-upper arm muscle area was strongly associated with MSD score (0.1 ± 0.02 points/cm^2, $P < 0.001$) but, in this model, the coefficients for the preterm LBW (–1.3 ± 0.3 points, $P < 0.0001$) and term LBW groups (–0.8 ± 0.4 points, $P = 0.043$) were slightly diminished, although still statistically significant. Although differences in muscle attributable to being born LBW did account for some of the deficit in the MSD score attributable to birth status, there remained a substantial independent effect of birth status on MSD score.

Discussion

In these analyses, we assessed the independent effects of birthweight and gestational age on MSD in a nationally representative sample of 4621 singleton infants and children, aged 2–47 months. The directions of the associations between the MSD scale administered in NHANES III and various socio-demographic and maternal characteristics compare favourably with the NLSY findings where a similar MSD scale was administered.[32] In both national studies, the youngest black children scored higher than other young children, MSD scores were higher for females, and children of parents with less education scored lower. Both mother's age and birth order affected MSD scores, with scores being higher for first-born children and children of young mothers and lower for later born children and children of older mothers.

There were significant independent linear effects of birthweight and length of gestation on the MSD score. Even after adjusting for factors including muscularity, infants and children born preterm LBW had MSD scores lower by –1.5 points; those born term LBW had scores lower by –0.8 points. Based on the average standard deviation (SD) of 2.4 points for any given age group, there is a difference of –0.6 SD units (SDU) for children born preterm LBW and –0.3 SDU for term LBW children.

Although it might be argued that the delay in MSD that has been identified as attributable to LBW status or preterm delivery is not by itself very large or meaningful, the joint effects of the other factors should be considered along with other perinatal factors in determining magnitude of risk and identifying subgroups at particular risk. There are significant joint effects of preterm delivery and LBW status with maternal age, birth order and an indicator of household education. In the worst case scenario, an infant or child, born as the third child of an older mother with a household education index of less than the ninth grade, who is also born preterm and LBW, may be expected to have an MSD score almost –4 points or –1.5 SDU below the mean for age. This means achieving four items less than same-age children with no other risk factors (Appendix). This degree of delay would almost certainly be clinically meaningful.

In stratified analyses, there was a differential impact of birthweight and gestation by sex. For females, there was a significant effect of LBW (–0.9 points), but no additional contribution for length of gestation, indicating that LBW status was the most important perinatal predictor of MSD score in females. For males, although the effect of LBW was significant (–0.8 points), gestational age was also highly significant (0.1 points per week accrued gestational age). Maturity, as well as birth size, was associated with the rate of MSD for males, such that even delivery early by only 3 or 4 weeks should have a measurable impact. This is not surprising as males, in general, appear to be more affected by early delivery and growth retardation than females. Male infants born very preterm are less likely to survive the neonatal period than females,[1] and they show more signs of minimal neurological dysfunction if born small.[5]

Our findings are in agreement with the few studies that have looked at developmental outcomes in large or national samples, although direct comparison among studies is complicated by differing definitions of birth status and developmental scales used. Markestad *et al*.[40] compared the development of term, SGA (<15th percentile birthweight for gestation) and non-SGA Norwegian and Swedish infants at 13 months of age, using the Bayley Scales of Infant Development, and found that SGA infants had significantly lower mental scores at 13 months, although the discrepancy was slight. The only other significant predictor of Bayley scores was mother's education. We were unable to detect a significant effect of SGA across a broader age range, but this may be accounted for by the fact that the preponderance of the SGA infants were born at term (94%), and few were significantly growth restricted (29% LBW).

In a longer follow-up, Strauss and Dietz[41] compared over 43 000 term normal birthweight with over 2700 term LBW children from the Collaborative Perinatal Project and found that, at age 7 years, the height, weight, intelligence quotient (IQ) and visual-motor development of the term LBW children were all significantly lower. In the longest follow-up of functional outcomes of those born SGA at term (primarily LBW), Strauss[42] found that, after 26 years, adults born SGA still had small, but statistically significant, deficits in academic achievement compared with those born AGA, but there were no long-term social consequences. Although adults born SGA at term may not be seriously functionally impaired, the effects of these perinatal events may linger through to adulthood. Additional studies with long periods of follow-up are needed to verify that measures of infant MSD indeed predict future measures or abilities.

Our findings are also consistent with studies looking at the differential effects of preterm birth and fetal growth restriction on later development. In a longitudinal follow-up of children at 8–9 years who were born at less than 33 weeks' gestation and at or below 2000 g, Hutton *et al*.[6] found that children born SGA (estimated using the birthweight ratio) had lower cognitive ability (IQ), whereas motor ability was additionally associated with the timing of preterm birth. Gestational age, as opposed to birthweight, appears to be the better predictor of developmental outcomes associated with maturation.

There are several limitations to this study. The NHANES III MSD scale was not meant for use in clinical settings, but it is similar to the standardised DDST with overlap to standard questions in the Bayley and Gesell scales. The MSD appears to have face validity, and the age, sex and racial/ethnic trends found are identical to those found for the NLSY,[32] which was also a national sample. The MSD scale performed within the study as expected with respect to many of the independent variables that have previously been associated with infant development. Thus, although the amount of specific advancement or delay expected on other scales cannot be anticipated,[27–30] the relative associations with birthweight, length of gestation and other socio-demographic and maternal factors should hold.

Because of small numbers in the NHANES III sample, we were not able to examine the effects of birthweight and gestation on the MSD of twins or higher order multiples. This is unfortunate because multiples are more likely to be born both preterm and LBW.[43,44] In the US (1995–97), compared with an LBW rate of 6.1% for singletons, 53.4% of twins were LBW and 93.1% of triplets.[43] Looked at another way, in 1997, twins accounted for 19.1% of all LBW births nationally and 13.0% of all preterm deliveries.[44] Thus, studies are needed to determine whether the developmental course of twins is similar to that of singletons.

In this cross-sectional study, we were also unable to examine a number of other intervening perinatal, home or environmental factors that may affect or moderate the course of fetal, infant and child development (e.g. maternal infection, drug use, positive home environment, preschool attendance),[9] basing our analyses instead on those common socio-demographic and maternal factors that might be used prospectively to determine risk. Longitudinal follow-up studies that track development from prenatal life through childhood are needed to determine the importance of perinatal, home or environmental factors.

Although the rates of very preterm delivery in the US and Canada have generally been decreasing, the rates of moderate preterm delivery have actually been increasing.[10] At the same time, many of the socio-demographic indicators associated with an MSD delay have also been increasing, such as the percentage of singleton infants born to women aged 35 years or older (8.4% in 1989 to 12.0% in 1996)[10] and the second birth rate for women aged 35–39 years (50.7 per 1000 in 1990 to 59.7 in 1997).[45] Many more infants and children are at increased risk of developmental delays associated with moderate preterm delivery or moderate LBW status than ever before. We have shown that intrauterine growth retardation, as evidenced by LBW, and preterm delivery are associated independently with small, but measurable, delays in MSD through early childhood, and their effect should be considered when evaluating the MSD of infants and children.

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Appendix

Motor and social development items[a,b] administered and scoring protocol

0–3 months
On stomach, lifted head
On stomach, turned head
Eyes followed moving object
Eyes followed side to side
On stomach, raised head and chest
Turned head to look
Pulled to sit, head held stiffly — 4–6 months
Laughed out loud
Held moderately sized object
Rolled over on purpose
Looked around for toy — 7–9 months
Smiled spontaneously
Enjoyed looking in mirror
Picked up small objects
Sat alone with no help
Said recognisable words — 10–12
Knows names of common objects — months
Walked two steps with help
Sat 10 min alone, no help
Crawled — 13–15
Pulled to stand, with help — months
Waved good-bye
Pulled to stand, no help
Stood alone 10 s — 16–18
Walked two steps without holding — months
Indicated by pointing
Said name of familiar object — 19–21
Crawled up two steps — months
Said two words (not mama, dada)
Bothered by wet or soil
Walk up two steps, holding — 22–47
Ever run — months
Make line with crayon/pencil
Fed self
Spoke sentence (3+ words)
Said first and last name
Walked up stairs, no holding
Counted three objects
Walked up stairs, one foot/stair
Know own age and sex
Said names of 4+ colours
Pedalled a tricycle 40′+
Done a somersault
Washed hands by self
Dressed self
Gone to toilet alone
Counted out loud to 10
Drawn a picture of person, two parts and head

Scoring protocol

Months	Part	No. of items administered	Score (points)	Range
0–3	1	15	Number passed	0–15
4–6	2	15	Number passed +7	7–22
7–9	3	15	Number passed +11	11–26
10–12	4	15	Number passed +17	17–32
13–15	5	15	Number passed +21	21–36
16–18	6	15	Number passed +25	25–40
19–21	7	15	Number passed +28	28–43
22–24	8	16	Number passed +32	32–48
25–27	8	16	Number passed +32	32–48
28–30	8	16	Number passed +32	32–48
31–34	8	16	Number passed +32	32–48
35–38	8	16	Number passed +32	32–48
39–42	8	16	Number passed +32	32–48
43–47	8	16	Number passed +32	32–48

[a]Individual items are scored as 1 = passed, 0 = not achieved.
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