Low Birth Weight and Respiratory Disease in Adulthood

A Population-based Case-Control Study

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Rationale: The proportion of low and very low birth weight births is increasing. Infants and children with a history of low and very low birth weight have an increased risk of respiratory illnesses, but it is unknown if clinically significant disease persists into adulthood.

Objectives: To determine if a history of low birth weight is associated with hospitalization for respiratory illness in adulthood.

Methods: This study was a population-based, case-control study. Cases were adults 18 to 27 years of age who were hospitalized for a respiratory illness from 1998 to 2007 within Washington State who could be linked to a Washington State birth certificate for the years 1980 to 1988. Four control subjects, frequency matched by birth year, were randomly selected from Washington State birth certificates for each case patient. Control subjects who died before age 18 were excluded.

Measurements and Main Results: Two levels of exposure were identified: (1) very low birth weight (birth weight <1,500 g) and (2) moderately low birth weight (birth weight, 1,500–2,499 g). Normal birth weight individuals (2,500–4,000 g) were considered unexposed. Respiratory hospitalizations were defined using discharge diagnosis codes. Logistic regression was used to calculate the odds ratio for hospitalization comparing exposed and unexposed individuals. A total of 4,674 case patients and 18,445 control subjects were identified. The odds ratio for hospitalization for respiratory illness was 1.83 for very low birth weight (95% confidence interval, 1.28–2.62; $P = 0.001$) and 1.34 for moderately low birth weight (95% confidence interval, 1.17–1.53; $P < 0.0005$). This association remained after adjustment for birth year, sex, maternal age, race, residence, and marital status.

Conclusions: Adults with a history of very low birth weight or moderately low birth weight were at increased risk of hospitalization for respiratory illness.

Keywords: infant; low birth weight; very low birth weight; respiratory tract diseases; adult; survivors

Since the mid-1980s, the proportion of low birth weight (LBW) and very low birth weight (VLBW) births has increased over 20% in the United States. In 2005, there were over 330,000 LBW and 60,000 VLBW births in the United States (approximately 8.2 and 1.5% of all births, respectively) (1). With improved neonatal care, survival of infants with below normal birth weight has improved (2, 3) and many are now surviving into adulthood (4–6). Survival to adulthood was approximately 65% for infants born less than 32 weeks gestational age in a recent longitudinal study from Norway (5). In the United States, this would

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Infants and children with a history of low birth weight (LBW) are at increased risk of respiratory illness. Long-term follow-up studies in adolescents and young adults with a history of LBW have reported decreased pulmonary function testing and increased respiratory symptoms compared with those with a history of normal birth weight. It is unknown if LBW is associated with clinically significant respiratory disease in adulthood.

What This Study Adds to the Field

We report an increased risk of hospitalization for respiratory disease among adults with a history of LBW compared with adults with a history of normal birth weight. As birth weight decreased, the risk of adult hospitalization increased.

represent more than 200,000 new adult survivors each year. The increased prevalence of LBW and improved survival has led to an increase in the incidence of chronic illnesses associated with LBW (3, 7–9). Bronchopulmonary dysplasia (BPD) is a chronic lung disease associated with prematurity. BPD is defined as oxygen dependence for at least 28 postnatal days for infants 32 weeks or greater postmenstrual age or oxygen dependence at 36 weeks postmenstrual age for infants born before 32 weeks (10). The increasing incidence of extreme prematurity and improved survival has led to an increase in BPD (3, 6, 9, 10), including a threefold increase in one study (3).

Survivors of VLBW with and without a history of BPD have been found to have abnormal pulmonary function testing as infants (11–13), children (14, 15), and adolescents (16–19). Less is known about the effects of LBW on adult respiratory disease. We sought to determine if adults with a history of VLBW were at increased risk of hospitalization for respiratory illness using a population-based, case-control design. We also sought to see if an association was present for specific respiratory diagnoses including asthma, respiratory infection, and acute respiratory failure. Additionally, we evaluated the exposure of moderately low birth weight (MLBW) (i.e., birth weight 1,500–2,499 g) to see if a similar association existed for this intermediate exposure category. Some of the results of these studies have been previously reported in the form of an abstract (20).

METHODS

Patient Selection

We conducted a population-based, case-control study. Potential cases were identified from the Washington (WA) State Comprehensive Hospital Abstract Reporting System (CHARS) discharge database and defined as individuals hospitalized from January 1, 1998 to December 31, 2007, who were 18 years of age or older at the time of

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hospitalization and who received a discharge diagnosis of a respiratory illness. Respiratory illnesses were defined using specific International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes representing acute and chronic respiratory disease, respiratory infections, respiratory symptoms, and nonoperative mechanical ventilation (see Table E1 in the online supplement). Selection was limited to individuals with a respiratory diagnosis code present among the first four listed discharge diagnoses. Individuals thus identified from CHARS were retained as cases if they could be linked to a birth certificate in the WA State Birth Certificate database for the years 1980 to 1988. Linkage was performed using date of birth and the first two letters of the first and last names. Potential cases that matched to two or more different birth certificates were excluded.

Control subjects were randomly selected from the WA State birth certificate database (excluding cases) and frequency matched to cases by birth year. Four times as many control subjects as cases were selected. Control subjects were filtered through the WA State Department of Health death file to exclude individuals who were known to have died before 18 years of age. This study was approved by the Institutional Review Board at the University of Washington.

Outcomes and Exposure

The primary outcome was hospitalization for respiratory disease between 18 and 27 years of age. The primary exposure was LBW. LBW was classified as VLBW (birth weight <1,500 g) and MLBW (birth weight 1,500–2,499 g). Normal birth weight (NBW) (i.e., birth weight 2,500–4,000 g) individuals were considered unexposed. Individuals with macrosomia (birth weight >4,000 g) were excluded. Exploratory analyses were performed for three *a priori* identified subgroups of respiratory illness hospitalizations: asthma, respiratory infection, and respiratory failure requiring mechanical ventilation. Subgroups were defined using ICD-9 discharge codes and are described in the online supplement (Table E2).

Clinical Variables

Clinical variables potentially associated with birth weight and subsequent respiratory illnesses were identified from birth certificate data. They included birth year, sex, maternal age, and maternal race/ethnicity. Birth year was modeled continuously and maternal age categorically. Additional variables included maternal smoking status, maternal marital status, induction of labor, delivery type, and maternal residence. Clinical variables are further described in the online supplement.

Statistical Analysis

All statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX). Crude odds ratios (OR) comparing risk of hospitalization in subjects with a history of VLBW or MLBW to subjects with a history of NBW were calculated using logistic regression with robust standard errors. Variables with a two-sided *P* value of less than 0.1 in univariate analyses were included in multivariable analyses. In addition, because cases and control subjects were frequency matched on birth year, this was included in multivariable analyses. Mantel-Haenszel stratified analyses and logistic regression were used to evaluate for confounding and effect modification by covariates. The likelihood ratio test was used to assess for interactions between birth weight and maternal smoking status and birth weight and birth year. A two-sided *P* value of less than 0.05 was considered statistically significant.

RESULTS

From 1980 to 1988, there were 628,508 live births (mean, 69,834 births/yr) in WA State (21). From 1998 to 2007, 11,437 patients were identified through CHARS as having been hospitalized for a respiratory illness between the ages of 18 to 27. Of these patients, 5,777 were born in WA as determined by linkage to the Birth Certificate database. After excluding duplicate linkages (*n* = 358; 6.2%), 5,419 cases were identified. Cases were excluded for macrosomia (*n* = 730; 13.5%), missing birth weight (*n* = 14; 0.3%), and implausible birth weight (BW = 113 g; *n* =

1). A total of 21,659 control subjects were randomly selected. Control subjects were excluded for macrosomia (*n* = 3120, 14.4%) and missing birth weight (*n* = 94, 0.4%). Maternal and delivery characteristics of cases (*n* = 4674) and control subjects (*n* = 18,445) are described in Table 1. Cases were more likely to be female, to have mothers who were younger, to be African American, to be unmarried, and to have smoked during pregnancy. Hyaline membrane disease was more likely among cases (*P* = 0.005 when missing data included; *P* = 0.002 when excluded). Patients missing data at one or more covariates of interest were excluded in subsequent analyses (*n* = 517 [2.2%] for the entire cohort; *n* = 796 [8.4%] for 1984–1988 analyses).

Primary Outcome

Individuals with a history of VLBW or MLBW were more likely to be hospitalized for a respiratory illness as young adults (VLBW: OR, 1.83; 95% confidence interval [CI], 1.28–2.62; *P* = 0.001; MLBW: OR, 1.34; 95% CI, 1.17–1.53; *P* < 0.0005). The trend of an increased risk of hospitalization as birth weight decreased was statistically significant (*P* < 0.0005). After

TABLE 1. MATERNAL AND INFANT CHARACTERISTICS OF CASES AND CONTROL SUBJECT

	Cases (<i>n</i> = 4,674) (%)	Control (<i>n</i> = 18,445) (%)	<i>P</i> Value
Birth weight			<0.0005
NBW	4,312 (92.3)	17,379 (94.2)	
LBW	315 (6.7)	961 (5.2)	
VLBW	47 (1.0)	105 (0.6)	
Sex			0.002
Male	2,189 (46.8)	9,098 (49.3)	
Female	2,485 (53.2)	9,347 (50.7)	
Mother's age, years			<0.0005
<20	723 (15.5)	2,217 (12.0)	
20–34	3,690 (79.0)	15,267 (82.8)	
>35	259 (5.5)	953 (5.2)	
Unknown	2 (< 0.1)	8 (< 0.1)	
Mother's ethnicity			<0.0005
Caucasian	3,966 (84.9)	15,990 (86.7)	
African-American	262 (5.6)	671 (3.6)	
Other	429 (9.2)	1,699 (9.2)	
Unknown	17 (0.4)	85 (0.5)	
Mother's marital status			<0.0005
Married	3,480 (74.5)	15,203 (82.4)	
Unmarried	1,181 (25.3)	3,191 (17.3)	
Unknown	13 (0.3)	51 (0.3)	
Maternal residence			<0.0005
Urban	3,763 (80.5)	14,731 (79.9)	
Rural	870 (18.6)	3,404 (18.5)	
Unknown	41 (0.9)	310 (1.7)	
Maternal smoking*			<0.0005
Yes	644 (13.8)	1,869 (10.1)	
No	1,136 (24.3)	5,178 (28.1)	
Unknown	2,894 (61.9)	11,398 (61.8)	
Induction of labor			0.700
Yes	101 (2.2)	379 (2.1)	
No	4,573 (97.8)	18,064 (97.9)	
Unknown	0 (0)	2 (< 0.1)	
Delivery type			0.185
Cesarean section	748 (16.0)	2,768 (15.0)	
Vaginal	3,926 (84.0)	15,675 (85.0)	
Unknown	0 (0)	2 (< 0.1)	
Hyaline membrane disease			0.005
Yes	39 (0.8)	85 (0.5)	
No	4,381 (93.7)	17,284 (93.7)	
Unknown	254 (5.4)	1,076 (5.8)	

Definition of abbreviations: LBW = low birth weight; NBW = normal birth weight; VLBW = very low birth weight.

* Smoking data available only from 1984 to 1998.

adjustment the odds of hospitalization were largely unchanged (VLBW: OR, 1.68; 95% CI, 1.16–2.42; $P = 0.006$; MLBW: OR, 1.26; 95% CI, 1.10–1.44; $P = 0.001$; $P < 0.0005$ for trend) (Table 2).

Recording of maternal smoking status on birth certificates began in 1984. Limiting the analysis to those born after 1983 decreased the number of cases and control subjects by 60% to 1,852 and 7,331, respectively. Maternal smoking during pregnancy was associated with an increased risk of her child being hospitalized for respiratory disease as an adult (OR, 1.56; 95% CI, 1.39–1.74; $P < 0.0005$). There was no evidence of effect modification by smoking as determined by the Breslow-Day test of homogeneity ($P = 0.25$). Using the subset of patients from 1984 to 1988 and including the same covariates as for the full sample, the adjusted OR for hospitalization for a respiratory illness was 1.30 and 1.33 for VLBW and MLBW survivors, respectively. After further controlling for maternal smoking, the adjusted ORs were 1.29 and 1.27, respectively (Table 3). The linear trend test for LBW remained significant in both analyses ($P = 0.010$ and 0.027 , respectively).

Secondary Outcomes

In unadjusted subgroup analyses, a history of VLBW or MLBW was associated with hospitalization for asthma, respiratory infections, and respiratory failure requiring mechanical ventilation (Table 4). Specifically, individuals with a history of MLBW had a 39% increased odds of hospitalization for asthma. The odds in those with a history of VLBW were increased twofold. In MLBW survivors the ORs for respiratory infection and respiratory failure were 1.5-fold higher. For VLBW survivors, the odds of respiratory infection were increased twofold, and the odds of respiratory failure requiring mechanical ventilation were increased 2.6-fold. After adjustment, ORs were attenuated slightly but remained significant for all analyses except for respiratory infections in VLBW survivors ($P = 0.059$). The linear trend of an increased risk of hospitalization as birth weight decreased remained significant for all adjusted and unadjusted subgroup analyses.

To further adjust for maternal smoking in each subgroup, the cohort was limited to births from 1984 to 1988. A trend of an increased risk of hospitalization as birth weight decreased was again seen for respiratory infections (OR, 1.57; 95% CI, 1.18–2.09; $P = 0.002$) and respiratory failure (OR, 1.86; 95% CI, 1.30–2.65; $P = 0.001$). There was no longer a significant trend between the odds of hospitalization for asthma and birth weight category (OR, 1.02; 95% CI, 0.77–1.36; $P = 0.877$) (Table E5).

TABLE 2. ODDS RATIOS FOR HOSPITALIZATION FOR RESPIRATORY ILLNESS FROM AGES 18 TO 26 AS A FUNCTION OF BIRTH WEIGHT

Exposure	n (%)	Unadjusted Estimated Association			
		OR	95% CI	P Value	P Value
NBW	21,229 (93.9)	Referent	–	–	
MLBW	1,233 (5.5)	1.34	1.17–1.53	<0.0005	<0.0005
VLBW	140 (0.6)	1.83	1.28–2.62	0.001	
Exposure	n (%)	Adjusted Estimated Association*			
		OR	95% CI	P Value	P Value
NBW	21,229 (93.9)	Referent	–	–	
MLBW	1,233 (5.5)	1.26	1.10–1.44	0.001	<0.0005
VLBW	140 (0.6)	1.68	1.16–2.42	0.01	

Definition of abbreviations: CI = confidence interval; LBW = low birth weight; NBW = normal birth weight; OR = odds ratio; VLBW = very low birth weight.

* Adjusted for birth year, sex, maternal age, race, residence, and marital status.

TABLE 3. ADJUSTED ODDS RATIOS FOR HOSPITALIZATION RESTRICTED TO THOSE BORN FROM 1984 TO 1988, WITH AND WITHOUT ADJUSTMENT FOR MATERNAL SMOKING STATUS

Exposure	n (%)	Estimated Association*			
		OR	95% CI	P Value	P Value
NBW	8,104 (93.9)	Referent	–	–	
MLBW	478 (5.5)	1.33	1.07–1.65	0.009	0.010
VLBW	45 (0.5)	1.30	0.66–2.56	0.448	
Exposure	n (%)	Estimated Association, Adjusted for Smoking†			
		OR	95% CI	P Value	P Value
NBW	8,104 (93.9)	Referent	–	–	
MLBW	478 (5.5)	1.27	1.02–1.57	0.029	0.027
VLBW	45 (0.5)	1.29	0.65–2.56	0.465	

See Table 2 for abbreviations.

* Adjusted for birth year, sex, maternal age, race, residence, and marital status.

† Adjusted for birth year, sex, maternal age, race, residence, marital status, and smoking status.

DISCUSSION

We report the largest population based study to date of respiratory illness in adults with a history of LBW. VLBW survivors had 83% higher odds of hospitalization for respiratory illnesses as young adults when compared with NBW individuals. For MLBW survivors, the odds were 34% higher. This risk remained present after adjusting for maternal socio-demographic characteristics including age, race, marital status and urban/rural residence, and infant factors, including sex and birth year. VLBW survivors were at greater risk for hospitalization for respiratory disease than MLBW survivors. This graded risk, with infants of lower birth weight at greater risk of later lung disease, is biologically plausible. Infants with a lower birth weight are more likely to be born at an earlier gestational age and are known to be at higher risk of lung injury and BPD (9, 10, 22–24). We were unable to determine if gestational age modified the effect of birth weight on adult hospitalizations, as has been hypothesized (25). Gestational age according to last menstrual period was available in our data but was not felt to be accurate. Others have reported the inaccuracies in estimation of gestational age estimation using the last menstrual period as well (26–28). An increased risk of hospitalization was present across all three subgroups of respiratory illness: asthma, respiratory infections, and respiratory failure. Although the number of events was low, LBW survivors were at a particularly high risk of the most severe condition of respiratory failure requiring mechanical ventilation.

Maternal smoking may explain a small amount of the association between birth weight and risk of hospitalization. Adjustment for smoking status attenuated the OR for MLBW from 1.33 to 1.27 and for VLBW from 1.30 to 1.29 (Table 3). However, birth weight remained significantly associated with adult hospitalizations after adjustment for maternal smoking in MLBW survivors. The trend also remained significant.

The increased risk of hospitalization may be explained by poor lung development among LBW infants. Poor lung function in healthy term infants is associated with decreased lung function in young adults (29). It is reasonable to assume this relationship would also be true for LBW survivors. Although we were unable to assess for a history of BPD, some LBW survivors in our study would have been at risk for “old” BPD. Old BPD is characterized by diffuse alveolar damage and neutrophilic inflammation leading to fibrosis (6, 9). Abnormal pulmonary anatomy has been seen on computed tomography scans in adult survivors of moderate to severe BPD (30). The sequelae of lung injury may alter respiratory anatomy and

TABLE 4. ESTIMATED ASSOCIATIONS BETWEEN BIRTH WEIGHT AND THE RISK OF HOSPITALIZATION FOR ASTHMA, RESPIRATORY INFECTION, OR RESPIRATORY FAILURE AS A YOUNG ADULT

Exposure	Cases, n (%)	Control Subjects, n (%)	Unadjusted Estimated Effect		Adjusted Estimated Effect*	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Asthma						
NBW	1,674 (92.0)	16,978 (94.3)	Referent	—	Referent	—
MLBW	127 (7.0)	924 (5.1)	1.39 (1.15–1.69)	0.001	1.26 (1.03–1.53)	0.022
VLBW	19 (1.0)	96 (0.5)	2.01 (1.22–3.29)	0.006	1.82 (1.06–3.13)	0.030
Respiratory infection						
NBW	1,060 (91.2)	16,978 (94.3)	Referent	—	Referent	—
MLBW	90 (7.8)	924 (5.1)	1.56 (1.25–1.95)	<0.0005	1.47 (1.18–1.84)	0.001
VLBW	12 (1.0)	96 (0.5)	2.00 (1.10–3.66)	0.024	1.80 (0.98–3.30)	0.059
Respiratory failure						
NBW	541 (91.2)	16,978 (94.3)	Referent	—	Referent	—
MLBW	44 (7.4)	924 (5.1)	1.49 (1.09–2.05)	0.012	1.48 (1.08–2.04)	0.014
VLBW	8 (1.4)	96 (0.5)	2.62 (1.26–5.41)	0.009	2.40 (1.15–5.01)	0.020

See Table 2 for abbreviations.

* Adjusted for birth year, sex, maternal age, race, residence, and marital status.

physiology for years to come. This may predispose survivors to air trapping, poor airway clearance, or gas exchange disorders. LBW survivors may also be more likely to have upper airway problems, such as tracheal stenosis, tracheomalacia, or vocal cord paralysis placing them at higher risk of respiratory illness. Additionally, LBW in the absence of BPD may confer an increased risk of adult respiratory disease because hyaline membrane disease, which is associated with old BPD, was relatively uncommon in our study.

Young adult survivors of BPD have been reported to have abnormal pulmonary function. In 1990, Northway and colleagues reported mild airflow obstruction, airway hyperresponsiveness, and air trapping in 26 young adult survivors (31). Others have reported mild airflow obstruction in extremely LBW (16) and VLBW survivors (17). Low normal range exercise capacity has been reported in LBW survivors (32). Others have not found significant differences in pulmonary function between LBW survivors and NBW control subjects. Narang and colleagues recently reported that mean z-scores for FEV₁ and FVC were slightly below normal among LBW survivors and NBW control subjects, but there were no significant differences between the two groups (25). In addition to abnormal PFTs, LBW survivors have reported a greater prevalence of respiratory symptoms and doctor-diagnosed asthma compared with NBW survivors (16, 19, 25).

Our data should be interpreted with some caution. We were unable to assess for differential migration out of WA in our control group. It is possible that NBW infants were more likely to move out of the state than LBW infants. If these control subjects had been hospitalized as young adults in other states, we would have missed these hospitalizations. However, we estimate that 14% of NBW control subjects would need to have been hospitalized outside of WA to eliminate the observed excess in respiratory disease hospitalizations for VLBW survivors. This seems unlikely because only about 0.3% of young adults are hospitalized for diseases of the respiratory system in any given year (33). The use of linked databases has limitations. However, it seems unlikely that birth weight would have been recorded any differently for cases and control subjects, and any misclassification would tend to bias our estimates toward the null.

We were only able to assess maternal socio-economic status indirectly. Nevertheless, after adjustment for maternal age and sociodemographic characteristics, results were largely unaffected. We were also unable to assess for smoking exposure in adult survivors. If LBW survivors had smoked more than NBW survivors, they may have been at increased risk of respiratory disease. However, it is unknown if differences in smoking

behavior exist between these two groups. Smoking has been reported to be more prevalent among LBW survivors compared with NBW survivors, although lung function did not differ between the groups (25). Others have not found differences in smoking behavior between the two groups (8). Finally, similar to all long-term follow-up studies, we identified a study population born in an era before the routine use of antenatal corticosteroids and surfactant therapy. These practices have decreased the incidence of old BPD. The incidence of “new” BPD, however, is increasing. New BPD is primarily a result of immature lung development and is associated with fewer, larger alveoli and disrupted capillary development. It is unknown if these survivors will have the same risk of adult respiratory illness as our study population.

We report a previously unrecognized excess risk of hospitalization for respiratory illness in young adults with a history of LBW. Our findings suggest that not only are VLBW and MLBW survivors at increased risk of long-term respiratory disorders but that these disorders are clinically significant and associated with increased health care utilization. In our study, the population attributable risk percent, the percentage of disease in a population attributable to a particular exposure, was estimated to be 1.8%. If this were extrapolated to the 1.2 million U.S. hospitalizations for respiratory illnesses per year for ages 18 to 44, low birth weight may account for over 21,000 adult hospitalizations per year, with charges in excess of \$225 million per year (33–35). The number of excess hospitalizations may grow in view of the improving survival and increasing prevalence of BPD. If confirmed, these findings suggest that internists, and not just pediatricians, need to be aware of their patient’s birth history. Future studies should focus on identifying other risk factors that may modify this risk so that interventions can be designed to improve outcomes and reduce health care utilization costs.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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