abstract

OBJECTIVE: To investigate the risk of emergency respiratory hospital admission during childhood associated with gestational age at birth and growth restriction in utero.

METHODS: The study included a total population electronic birth cohort with anonymized record-linkage of multiple health and administrative data sets. Participants were 318,613 children born in Wales, United Kingdom, between May 1, 1998, and December 31, 2008. The main outcome measure was emergency respiratory hospital admissions.

RESULTS: The rate of admission in the first year of life ranged from 41.5 per 100 child-years for infants born before 33 weeks’ gestation to 9.8 per 100 child-years for infants born at 40 to 42 weeks’ gestation. The risk of any emergency respiratory admission up to age 5 years increased as gestational age decreased to <40 weeks. Even at 39 weeks’ gestation, there was an increased risk of emergency hospital admissions for respiratory conditions compared with infants born at 40 to 42 weeks (adjusted hazard ratio 1.10; 95% confidence interval 1.08–1.13). Small for gestational age (<10th centile for gestation and gender-specific birth weight) was independently associated with an increased risk of any emergency respiratory admission to hospital (adjusted hazard ratio 1.07; 95% confidence interval 1.04–1.10).

CONCLUSIONS: The risk of emergency respiratory admission up to age 5 years decreased with each successive week in gestation up to 40 to 42 weeks. Although the magnitude of increased risk associated with moderate and late preterm births is small, the number of infants affected is large and therefore presents a significant impact on health care services. Pediatrics 2013;132:e1562–e1569
Preterm birth is associated with adverse respiratory, neurodevelopmental, and educational outcomes. Preterm birth rates have increased over the past decade, and the longer-term consequences for health are a concern for pediatricians and public health. A recent review reported that many studies have focused on outcomes for very preterm births (<32 weeks’ gestation), but there are few data for late preterm infants (34–36 weeks’ gestation), who account for 6% to 7% of all births and up to 75% of preterm infants. Compared with full-term infants, preterm infants are at risk for long-term deficits in lung function (% forced expiratory volume in 1 second) in later life. Data from a longitudinal study suggested that very (25–32 weeks) and moderately (33–34 weeks) preterm born infants have greater deficits in lung function during childhood compared with late preterm (35–36 weeks) born infants. The inclusion of infants born at 32 and 34 weeks in the very and moderately preterm categories in this latter study reflects the classification inconsistencies in the literature. It is not known how reduced lung function translates into health care utilization, although the risk of other adverse outcomes in childhood (such as lower educational attainment) has been shown to increase with every week reduction in gestational age from 40 weeks, including within the term category of 37 to 40 weeks. There are no comprehensive population-based analyses of the risk of hospital admissions across the range of gestational age and birth weight; previous studies have grouped together broad ranges of gestational age, making it difficult to distinguish between prematurity and the effects of growth restriction. Such data are required to provide accurate information to parents, inform clinical decisions, and develop care pathways for children. We hypothesized that the risk of emergency respiratory hospital admission during childhood decreases with increasing gestational age at birth and is higher for infants who were small for gestational age within each category of gestational age. We tested this hypothesis using data from a total population electronic birth cohort characterized by the anonymized linkage of multiple routine health and administrative data sets.

METHODS

Data Source: The Wales Electronic Cohort for Children

The Wales Electronic Cohort for Children (WECC) includes 804,290 children born between January 1, 1990 and December 31, 2008, with a mother or child usually residing in Wales. Eligible participants are identified from the Wales Demographic Service, an administrative register of all individuals living in Wales and registered with a General Medical Practitioner. WECC anonymously record-links routinely collected data held in health care and social data sets within the Secure Anonymised Information Linkage (SAIL) databank at the Health Information Research Unit, Swansea University, United Kingdom. For each data set within the SAIL databank, an individual is assigned an Anonymised Linking Field based on their National Health Service number, which is used to link across data sets. In this analysis, we used record-linked data from the databases shown in Table 1. The time period for this analysis was January 1, 1998 through December 31, 2008 due to availability of data on hospital admissions from the Patient Episode Database for Wales. Data were censored for migration out of Wales (ascertained by using the Wales Demographic Service) and death during infancy or childhood (ascertained by using the All-Wales Perinatal Survey data set and Public Health mortality files).

With regard to outcome measures, we defined each emergency hospital admission for respiratory disease recorded on Patient Episode Database for Wales by using the following International Classification of Diseases, 10th Revision, codes in the primary coding position: acute upper respiratory tract infection (J00–J06, J10.1, J10.8, J11.1, J11.8), influenza and pneumonia (J10.0, J11.0, J12–J18), acute lower respiratory tract infections (J20–J22), acute bronchiolitis (J21), and asthma (J45–J46).

Definition of Exposed Groups

Gestational age was based on the best estimate of gestation at the time of delivery in completed weeks, normally based on the postmenstrual age, but this could be modified on the basis of antenatal ultrasound scan or from the postnatal estimate of maturity. We categorized gestational age into the following categories: <33, 33 to 34, 35 to 36, 37, 38, 39, and 40 to 42 weeks. We defined small for gestational age as birth weight below the 10th percentile, calculated for each stratum based on gender and gestational age in weeks, using Altman’s method to model the relationship between birth weight and gestational age across the whole range of gestational age.

Statistical Analysis

We calculated the child-year incidence of emergency hospital admission for any respiratory disease up to age 1 year and between ages 1 to 5 years. We used time to event Cox’s regression analysis to obtain crude and adjusted hazard ratios (HRs) for the first emergency hospital admission for any respiratory disease in each gestational age category compared with the reference category of 40 to 42 weeks. We adjusted for small for gestational age, maternal...
TABLE 1 Data Sources for WECC

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health Birth files from the Office for National Statistics (from 2003)</td>
<td>Data on all births in Wales or to mothers who are usually resident in Wales. A national database of all children resident in Wales or born in a Welsh hospital, containing data collected at birth such as parity, mode of delivery, gestation, birth weight, gender, breastfeeding, and Apgar Score.</td>
</tr>
<tr>
<td>National Community Child Health Database (from 1987)</td>
<td></td>
</tr>
<tr>
<td>Public Health Mortality files from the Office for National Statistics (from 2002)</td>
<td>Data on all deaths in Wales or of individuals who are usually resident in Wales. Demographic and clinical data on all inpatient and day-case admissions in National Health Service Wales hospitals and all Welsh residents treated in other UK countries.</td>
</tr>
<tr>
<td>Patient Episode Dataset for Wales (from 1998)</td>
<td></td>
</tr>
<tr>
<td>All Wales Perinatal Survey (from 1993)</td>
<td>A database of perinatal and infant mortality in Wales including infants from 20 weeks’ gestation to 1 year of age, who die in a Welsh hospital or whose mother is usually resident in Wales.</td>
</tr>
<tr>
<td>Congenital Anomaly Register and Information Service (from 1998)</td>
<td>A population-based register of any fetus or infant who has a congenital anomaly whose mother is usually resident in Wales at the time of birth; congenital anomalies are defined by the European network of population-based registries for the epidemiologic surveillance of congenital anomalies.</td>
</tr>
</tbody>
</table>

Ethics and Information Governance

The WECC received approval from an independent Information Governance Review Panel, with membership from a range of government, regulatory, and professional agencies. WECC has been assessed by the Research Ethics Committee for Wales and judged to be an anonymized research database that does not require ethical review in line with National Ethics Committee guidance.

RESULTS

There were 318,613 children born in Wales between 1998 and 2008 in the WECC cohort eligible for inclusion in this analysis. The total length of follow-up for this cohort was 1,156,415 child-years (mean 3.63 child-years, SD 1.69 child-years). Overall, 17.6% of children in the cohort had ≥1 emergency respiratory hospital admission. The rate of admission in the first year of life was 12.2 per 100 child-years, 5.3 per 100 child-years for children aged between 1 and 5 years in the whole cohort, and 4.8 per 100 child-years for children aged 1 to 5 years who were born between 1998 and 2003 (ie, with follow-up for 5 years after birth to allow for the decrease in risk of admission as age increases). The rate of emergency hospital admission for respiratory conditions decreased with increasing gestational age at birth but was consistently higher for infants who were small for gestational age within each category of gestational age (Table 2).

The most common reasons for admission in the first year of life were acute upper respiratory tract infection (n = 16,475, 45.1% of admissions) and acute bronchiolitis (n = 16,172, 44.4% of admissions). For children aged between 1 and 5 years, the majority (57.4%, n = 261,911) of emergency respiratory admissions were for acute upper respiratory tract infections. For children aged <1 year, the rate of...
emergency admission for speci-
fic respiratory conditions was 5.5 per 100 child-years for acute upper respiratory tract infection, 3.0 per 100 child-years for influenza and pneumonia, 5.4 per 100 child-years for acute lower respiratory tract infections (including bronchiolitis), 4.8 per 100 child-years for bronchiolitis and 0.4 per 100 child-years for asthma. For children aged between 1 and 5 years the rate was 3.0 per 100 child-years for acute upper respiratory tract infection, 0.4 per 100 child-years for influenza and pneumonia, 0.6 per 100 child-years for acute lower respiratory tract infections (including bronchiolitis), 0.1 per 100 child-years for bronchiolitis, and 0.7 per 100 child-years for asthma.

Figure 1 shows the survival function curves for time to the first emergency respiratory hospital admission according to gestational age categories. The HR for any emergency respiratory admission up to age 5 increased as gestational age decreased (Table 3). Small for gestational age was independently associated with an increased risk of any emergency respiratory admission to hospital (adjusted HR 1.07, 95% confidence interval [CI] 1.04–1.10), but there was no strong evidence that the effect of growth restriction (P = .06 for interaction) or caesarean delivery (P = .19 for interaction) varied according to gestational age. Caesarean delivery, neonatal admission to hospital, younger maternal age, and living in areas of higher social deprivation were each independently associated with increased risk of emergency respiratory admissions, whereas breastfeeding was protective (adjusted HR 0.89, 95% CI 0.88–0.91). The risk of emergency respiratory hospital admission was higher for infants born April to June (adjusted HR 1.05, 95% CI 1.03–1.08), July to September (adjusted HR 1.19, 95% CI 1.17–1.22), and October to December (adjusted HR 1.22, 95% CI 1.19–1.25), compared with infants born between January and March. Similar patterns were seen when analyses were repeated for specific types of respiratory admissions; the seasonality effects were greater for lower compared with upper respiratory disease (Table 4).

### TABLE 2 Emergency Hospital Admissions for Respiratory Disease by Gestational Age Categories (N = 318,613)

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>% Infants With Any ERA in Before Age 1 y AGA</th>
<th>% Infants With Any ERA in Age 1–5 y AGA</th>
<th>Mean No. of ERAs per 100 Child-Years Before Age 1 y AGA</th>
<th>Mean No. of ERAs per 100 Child-Years Age 1–5 y AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 wk (AGA n = 451/SGA n = 555)</td>
<td>23.6 23.4</td>
<td>19.4 18.4</td>
<td>41.5 48.0</td>
<td>13.5 15.0</td>
</tr>
<tr>
<td>33–34 (AGA n = 4580/SGA n = 480)</td>
<td>16.6 19.8</td>
<td>14.4 17.7</td>
<td>23.7 30.5</td>
<td>8.0 9.4</td>
</tr>
<tr>
<td>35–36 (AGA n = 11457/SGA n = 1432)</td>
<td>13.5 14.5</td>
<td>12.6 14.4</td>
<td>18.8 22.5</td>
<td>6.9 7.9</td>
</tr>
<tr>
<td>37 (AGA n = 15118/SGA n = 1912)</td>
<td>11.8 13.9</td>
<td>11.9 11.9</td>
<td>15.6 18.8</td>
<td>6.2 6.1</td>
</tr>
<tr>
<td>38 (AGA n = 37187/SGA n = 4067)</td>
<td>10.2 11.2</td>
<td>11.1 12.1</td>
<td>13.2 15.4</td>
<td>5.5 6.5</td>
</tr>
<tr>
<td>39 (AGA n = 59197/SGA n = 6416)</td>
<td>8.9 10.5</td>
<td>10.0 10.8</td>
<td>11.5 14.1</td>
<td>5.1 5.4</td>
</tr>
<tr>
<td>40–42 (AGA n = 155110/SGA n = 16751)</td>
<td>7.8 9.4</td>
<td>9.6 10.7</td>
<td>9.8 12.0</td>
<td>4.7 5.4</td>
</tr>
<tr>
<td>Overall (n = 318,613)</td>
<td>9.3 10.5</td>
<td>12.2 5.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AGA, appropriate for gestational age; ERA, emergency respiratory admission; SGA, small for gestational age.
DISCUSSION

Our results show a clear pattern of increased risk of emergency hospital admissions for respiratory conditions with decreasing gestational age; this risk further increased for infants who were small for gestational age. Even at 39 weeks’ gestation, infants had a 10% increase in risk of emergency hospital admissions for respiratory conditions compared with those born at 40 to 42 weeks, and a further 7% increase in risk if they were small for gestational age. These findings add support to the recent call to redefine "full-term" pregnancy from 37 to 42 weeks to a narrower interval of 39 to 42 weeks. However, given the additional morbidity observed for infants born at 39 weeks, our results suggest that term should be defined as 40 to 42 weeks.

Intrauterine factors that adversely affect fetal growth are associated with increased risk of chronic respiratory diseases in adulthood. Prematurity is associated with immature lung development and consequently diminished lung function during childhood, but the effect of growth restriction in utero on lung function has not been systematically studied across the full range of gestational age. Several studies have tried to examine associations between fetal growth restriction, which manifests as small for gestational age, and lung function during childhood but have reported conflicting findings. Some studies of infants born small for gestational age reported reduced forced expiratory volume in 1 second and respiratory symptoms, possibly due to small airway size relative to lung size. However, others have not found this association, concluding that diminished lung function in small infants was attributable to prematurity rather than growth restriction, but these were all small studies from selected populations (ie, infants admitted to hospital for neonatal care). One longitudinal study reported that children born at 33 to 34 weeks had decreased lung function at 8 to 9 years, but this improved by age 14 to 17 years. Some used low birth weight to define their study population, which does not allow for distinguishing the effects of prematurity (and hence physiologic immaturity of the lung) from growth restriction in a physiologically mature infant. A recent systematic review has shown that compared with full-term infants, all preterm infants are at risk for diminished lung function during childhood, although it is not clear how this may impact on health care services. Most previous studies have focused on hospital admissions in general or specifically for asthma and reported an increased risk associated with prematurity or low birth weight, but none have investigated acute upper respiratory tract infection, the most common reason for hospital admission during childhood. To our knowledge, our study is the largest...
population-based study of the risk of emergency hospital admissions for respiratory disease across the range of gestation at birth. A previous study of maternal and perinatal factors on hospital admissions for asthma in children using a record-linked study of 248,612 births in the Oxford region between 1970 and 1989 found that maternal asthma, male gender, preterm birth, low birth weight, caesarean delivery, and maternal smoking were independent risk factors.9 We did not have data on maternal asthma, but our results are consistent with this study for male gender and preterm birth. However, the Oxford study used a broad range of gestation (24–37 weeks) to define preterm birth and therefore did not explore the magnitude of increased risk associated with weekly gestational ages.9 Algert et al studied a population of 240,511 births between 2001 and 2003 in Australia and reported that 3% of children aged 2 to 5 years had ≥1 admission for asthma; the risk of admissions for asthma decreased by 5% for every 1-week increase in gestational age.26 More recently, Boyle et al analyzed data from the UK Millennium Cohort Study on 18,818 births and reported an increase in the proportion of children with at least 3 hospital admissions between age 9 months and 5 years with decreasing gestation at birth, although hospital admission was based on parental report.4 Consistent with this study, we found that the increased risk of hospital admission was highest for infants born before 33 weeks’ gestation. However, the gradient of increased risk from 33 to 40 weeks applies to the majority (at least 75%) of infants born preterm and will therefore have a significant impact on health care services. The increased risk of respiratory hospital admissions in infants born in the summer months is consistent with known risk factors of hospitalization for bronchiolitis.27

We also found a protective effect associated with breastfeeding, consistent with other studies.4,28 Despite high levels of breastfeeding initiation in the United Kingdom (81%), only 22% of mothers continue to breastfeed at 6 months.29 Because breastfeeding rates are higher among more affluent populations, effective public health interventions are needed to increase breastfeeding rates, especially in more deprived areas.

Strengths and Limitations
The strength of this study is that it is a large whole population study using routinely collected data over a 11-year period. Data on maternal and birth characteristics, including gestational age and birth weight, used to define exposed groups and outcome data (hospital admissions) were collected independently on separate databases and record-linked. The size of the data set available for analysis allowed for the exploration of hospital admissions across the range of respiratory causes by each week of gestational age, avoiding the need for broader categories that limited previous studies.

There are some limitations. As with all analyses of routinely collected data sets there is potential for misclassification in the coding of diagnoses for hospital admissions and in the recording of exposure variables such as gestational age. However, this is likely to be misclassification at random, not related to exposure or outcome variables of interest, because these were collected on separate data sets. Another limitation was the high percentage of missing data on maternal smoking during pregnancy and lack of data on smoking in the household during childhood, although the effect of this is likely to be to reduce the apparent effect of smoking on respiratory admissions. Lack of data meant we were unable to adjust for pregnancy complications for the mother or comorbidities in children in the analysis nor could we explore the effect of the duration of breastfeeding. We used a standard method of multiple imputation to account for missing data. However, a separate analysis using only
the complete data on maternal smoking resulted in similar hazard ratios for the gestational age effects, so it is unlikely that the high proportion of missing data for this variable has biased the results. During the 11-year study period, there have been changes in neonatal care, particularly in respiratory management, with a trend toward less invasive and shorter duration of ventilatory support for the most preterm infants, and possibly wider variation in neonatal respiratory management for more mature preterm infants. These changes over time might be important influencing factors with respect to childhood respiratory disease, but it was not possible to explore this within our data set.

This secondary analysis of routine data cannot address the question of whether admission is appropriate. It is not possible to infer whether a high admission rate represents a high need for admission or variation in medical practice. Admission rates may be higher from localities with easy access to hospital or vary with clinical and parental thresholds for admission and organization of out of hours primary care services. The rate of emergency hospital admission for respiratory infections in children has increased over the past decade in the United Kingdom. The majority were short-stay admissions, suggesting that these were for minor illness episodes that could have been managed in the community. Additional investigation is required to identify differences in health-seeking behavior and thresholds for admission, and presentation, to hospital.

CONCLUSIONS
We have demonstrated the utility of using large-scale record-linked data sets to describe the epidemiology of health care utilization in children, particularly focusing on gestation at birth. Our key finding is that the gradient of decreasing risk of respiratory emergency admissions with increasing gestational age extends to 40 weeks’ gestation. Although the magnitude of increased risk appears small, large numbers of infants are affected with significant implications for health services.

ACKNOWLEDGMENTS
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