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Hospitalisations from one to six years of age: Effects of Gestational Age and Severe Neonatal Morbidity

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Abstract

Background: To investigate whether the adverse infant health outcomes associated with early birth and severe neonatal morbidity (SNM) persist beyond the first year of life and impact on paediatric hospitalisations for children up to six years of age.

Methods: The study population included all singleton live births, >32 weeks gestation in New South Wales, Australia in 2001-2005, with follow-up to six years of age. Birth data were probabilistically linked to hospitalisation data (n=392,964). The odds of hospitalisation, mean hospital length of stay (LOS) and costs, and cumulative LOS were evaluated by gestational age and SNM using multivariable analyses.

Results: A total of 74,341 (18.9%) and 41,404 (10.5%) infants were hospitalized once and more than once, respectively. SNM was associated with increased odds of hospitalisation once (adjusted odds ratio (aOR) 1.16 [95% CI 1.10, 1.22]), and more than once (aOR 1.51 [1.42, 1.60]). Decreasing gestational age was associated with increasing odds of hospitalisation more than once from aOR 1.19 at 37-38 weeks to 1.49 at 33-34 weeks. Average LOS and costs per hospital admission were increased with SNM but not with decreasing gestational age. Cumulative LOS was significantly increased with SNM and decreasing gestational age.

Conclusions: Adverse effects of SNM and early birth persist between one and six years of age. Strategies to prevent early birth and reduce SNM, and to increase health monitoring of vulnerable infants throughout childhood may help reduce paediatric hospitalisations.

Health outcomes of babies are closely linked to foetal maturation, with preterm birth the single most important perinatal indicator of infant morbidity and mortality.[1-4] Even infants born at 37-38 weeks gestation have poorer health outcomes than infants born at 39-40 weeks gestation, experiencing increased rates of respiratory complications, newborn sepsis and admission to neonatal intensive care units.[5-7] Paediatric hospitalisation following discharge home from the birth admission is a leading indicator of childhood morbidity and is strongly predicted by gestational age.[5, 8-10] A range of other perinatal risk factors for increased hospitalisation and health-care utilization following birth have been identified and include severe neonatal morbidity,[5] low birth weight,[11] maternal smoking,[12] maternal age,[13] primiparity,[14] and socioeconomic status.[13]

The literature identifying perinatal risk factors for infant morbidity and mortality has largely focused on outcomes occurring within the first year of life,[1, 2, 5, 8-10] with few studies investigating child health outcomes. The aim of this study was to examine the potential longer term effects of timing of birth and severe neonatal morbidity on child health outcomes, specifically paediatric hospitalisation, up to six years of age. In particular, we aimed to elucidate the long term outcomes of infants born at early term (37-38 weeks), a group that represents a sizeable proportion of all births (e.g. >25% in Australia in 2011[15] and in the USA in 2010[16]) and previously considered to be low risk.[17]

Methods

Study population and data sources

The study population included all singleton live births in New South Wales (NSW), Australia, of at least 33 weeks gestation between 1 January 2001 and 31 December 2005. The population was restricted to infants who survived to at least one year of age without major congenital anomalies. The study cohort was followed up to the child's sixth birthday or death by 31 December 2011.

Data were obtained from the NSW Perinatal Data Collection (PDC), the NSW Admitted Patient Data Collection (APDC) and the NSW Registry of Births, Deaths and Marriages (RBDM) death registrations. The PDC is a population-based surveillance system that records all births in NSW that are ≥ 20 weeks gestation or ≥ 400 grams birth weight and includes information on medical conditions, maternal and infant characteristics, and obstetric data. The APDC is a census of all hospital separations from public and private hospitals in NSW and is based on information collected at discharge. Diagnoses associated with admissions in the APDC are coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM).[18] The NSW RBDM is a register of vital statistics for NSW residents, which include information on all deaths.

PDC records were probabilistically linked to APDC maternal and infant records and RBDM death records by the Centre for Health Record Linkage (CheReL). Infant APDC hospital records were available up to the age of six years. The linkage rate between the PDC and infant and mother's APDC was high (~98%) and the proportion of missing data was small. Deaths during birth admission or hospitalisation were identified from the APDC and deaths following

discharge from hospital were ascertained from the RBDM. This study was approved by the NSW Population and Health Services Research Ethics Committee.

Study outcomes and predictive factors

The main outcomes assessed in the study were frequency of hospitalisation, cumulative number of days spent in hospital as an admitted patient, and mean acute care costs and length of stay (LOS) per hospital admission for all children aged between one and six years. Cumulative LOS provides an estimate of the mean amount of time an infant was hospitalized between one and six years of age, and is akin to summing the total number of hospitalized days for all infants and dividing by the total number of infants. Mean LOS provides an estimate of the expected amount of time spent in hospital on each occasion an infant is admitted to hospital and only considers infants that are hospitalized. Hospitalisations due to injuries (21,545, 5.5%) were excluded from the study because they were unlikely to be associated with the study factors. The most common health conditions associated with hospitalisation were identified from the APDC based on primary ICD-10-AM diagnosis codes.

The main predictive factors were severe neonatal morbidity and gestational age at birth. Severe neonatal morbidity was defined using the Neonatal Adverse Outcome Indicator (NAOI) of Lain et al, 2012.[19] Briefly, the NAOI is a composite indicator which uses information from the PDC and data on diagnosis and procedure codes from the APDC, and covers a range of conditions commonly observed in severely ill infants. The use of a composite indicator addresses the under-ascertainment associated with the use of individual diagnosis and procedure codes to identify infants born with severe neonatal morbidity.[19] Gestational age at birth was obtained from the PDC and categorized into five groups (33-34, 35-36, 37-38, 39-40 and 41+ weeks gestation)

for analysis. In the PDC, gestational age is reported in completed weeks of gestation, as determined by the best clinical estimate including early ultrasound and last menstrual period. Reporting of gestational age has been shown to have excellent agreement with medical records with a kappa value of 0.81.[20] Other maternal and infant risk factors were based on those previously reported in the literature,[5, 11-14] and ascertained from the PDC including maternal age, socioeconomic status, private or public hospital status, labour onset (spontaneous or planned), and smoking during pregnancy. An indicator of marital status was obtained from mother's APDC records around the time of birth.

Socioeconomic status was derived from the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage, 2006.[21] The index was assigned to maternal postcode of residence at the time of birth and infants were classified into three categories: 1) "disadvantaged" (≤ 20th percentile); 2) "average" (21st-80th percentile); and 3) "advantaged" (> 80th percentile). Similarly, matching on postcode was used to assign an urban or rural area of residence to each infant based on the Accessibility and Remoteness Index of Australia Plus (ARIA+).[22]

Estimates of acute care costs for each hospital stay were derived according to the NSW Cost of Care Standards 2009/10.[23] Acute care costs are based on Australian Refined Diagnosis Related Groups which classify hospital admissions with similar clinical conditions into groups that reflect comparable usage of hospital services and resources. Adjustments for day-stays, extended lengths of stay, in-hospital deaths, private health insurance status and transfers were also made. Costs in Australian dollars ($AUD) were escalated to 2013 levels by multiplying estimated costs by Sydney, NSW health care sector rates of inflation for the financial years 2010 to 2012.

Statistical analysis

Descriptive statistics of the study population and their outcomes from age one to six years were calculated. The association between the main predictive factors (severe neonatal morbidity and gestational age) and paediatric hospital admissions between one and six years of age were assessed using multivariable multinomial logistic regression models. The outcome variable had three categories: 0, 1, and 2 or more hospital admissions during the follow-up period, with 0 used as the reference category. The mean cost per hospital admission was estimated using linear regression with generalized estimating equations to account for the correlation among repeat hospital stays. Negative binomial regression with generalized estimating equations was used to assess mean LOS when hospitalized. Cumulative LOS in hospital between one and six years of age was examined using negative binomial regression. To reduce the effects of extreme outliers, cumulative LOS greater than the 99th percentile (20 days) was truncated to this value.

Multivariable analysis was used to assess the effects of the main predictive factors on study outcomes while adjusting for important birth and maternal risk factors. All covariates with $P < 0.05$ were deemed to significantly improve model fit and retained in final multivariable models. Two-way interactions between the main predictive factors were tested in all statistical models and retained in final models if their overall P was < 0.05. For all components of the study, statistical model fits were assessed using log-likelihood ratio chi-square and deviance statistics. Data manipulations and statistical analyses were performed in SAS 9.3 software (SAS Institute, Cary NC).

Results

Over the period 2001-2005, there were 392,964 singleton live births in NSW who survived to at least one year of age and linked to an APDC birth record. The proportion of children hospitalized by year of age declined steadily with increasing age, decreasing from 16.4% within the first year of life to 5.2% between 5 and 6 years of age (data not shown). Between the ages of one and six years, 115,745 (29.4%) children were hospitalized (excluding admissions for injuries), including 74,341 (18.9%) who were hospitalized once and 41,404 (10.5%) more than once. Table 1 reports descriptive maternal and infant birth characteristics by hospitalisation category. Children who were hospitalized were more likely to have been born with severe neonatal morbidity, at a younger gestational age, to younger mothers, mothers who smoked, and mothers who were not married or in a de facto relationship around the time of birth (Table 1). Maternal, birth and socio-demographic characteristics were similar between children hospitalized once and more than once, except for severe neonatal morbidity and births at 38 weeks gestation or less, which were over-represented in infants admitted to hospital more than once (Table 1).

Severe neonatal morbidity was significantly associated with increased odds of being hospitalized once (adjusted odds ratio (aOR) 1.16 [95% CI 1.10, 1.22]) or more than once (aOR 1.51 [1.42-1.60]) between one and six years of age (Figure 1). Likewise, earlier birth was linked to increasing odds of hospitalisation with children born at early term (37-38 weeks) having greater odds of one (aOR 1.08 [1.06, 1.11]) or more than one hospitalisation (aOR 1.19 [1.16, 1.22]) than infants born at 39-40 weeks gestation (Figure 1).

The most common conditions associated with paediatric hospitalisation were respiratory illnesses including asthma, tonsillitis and pneumonia; and gastrointestinal infections such as diarrhoea, gastroenteritis and rotavirus enteritis. Between one and six years of age, 12.5% and 4.6% of the cohort were hospitalized at least once for respiratory illnesses (ICD10-AM codes J00-J99) and gastrointestinal infections (A00-A09), respectively. Other infections (A10-B99) represented the next most frequent diagnosis at hospitalisation (2.5%).

After adjusting for covariates, estimated mean LOS per hospital admission ranged from 1.6 days to 1.7 days for infants born without severe neonatal morbidity and was similar across the different gestational age groups (Table 2). Estimated LOS was slightly elevated in those with severe neonatal morbidity (approximately 8-9%) for infants born at 37 weeks gestation or later, but not for infants born at 33-34 and 35-36 weeks gestation where mean LOS was similar to those without morbidity (Table 2). Like LOS, adjusted mean costs per hospital admission between one and six years of age were similar across different gestational age groupings, ranging from $AUD2576 to $AUD2651 in those without severe neonatal morbidity (Table 2). With severe neonatal morbidity, mean costs per admission ranged from $AUD2519 to $AUD2865 and were on average approximately 8-10% higher than those without severe neonatal morbidity for infants born at 37 weeks gestation or more, but marginally lower for those born at 33-34 weeks gestation and marginally higher for those born at 35-36 weeks gestation (Table 2).

Mean cumulative LOS in hospital per infant between one and six years of age was significantly related to the two major study factors (Figure 2). Gestational age displayed a decreasing trend in cumulative LOS in infants born without severe neonatal morbidity, ranging from a mean of 1.0 days per infant at 33-34 weeks gestation to 0.7 days at 41+ weeks gestation. For infants with severe neonatal morbidity, mean cumulative LOS ranged from a maximum of

1.3 days at 37-38 weeks gestation to a minimum of 1.0 days at 41+ weeks gestation. The gestational-age-specific relative increases in mean cumulative LOS with severe neonatal morbidity ranged from 25% to 59% and were more pronounced in the older gestational age groups. Unlike infants born without severe neonatal morbidity, no gradient of decreasing cumulative LOS with increasing gestation was observed in infants born with severe neonatal morbidity.

Comments

In this study, we have shown that decreased gestational age was significantly associated with increased likelihood of hospitalisation between one and six years of age, indicating that adverse outcomes of preterm and even early term birth persist beyond the first year of life. Regardless of gestational age, severe neonatal morbidity was also linked to heightened odds of hospitalisation between one and six years of age, displaying effect sizes similar to babies born at 33-34 weeks gestation. Although decreased gestational age and severe neonatal morbidity were not associated with increased mean costs or LOS per hospital admission, both study factors were associated with increased total accrued time spent hospitalized between one and six years of age. These results suggest that increased health care burden associated with early birth and severe neonatal morbidity occurred predominantly through increased frequency of hospitalisation and not through extended lengths of stay when admitted to hospital.

An important finding from our study was that the adverse effects of severe neonatal morbidity and decreased gestational age persisted into early childhood. Equally revealing was the fact that, when compared with the first year of life,[5] the effects were reduced in magnitude suggesting an attenuation of risk and the ability for infants to recover over time. These findings are consistent with Boyle *et al,* who showed that the effect of early birth at 34-38 weeks gestation on the odds of three or more hospitalisations was reduced between 9 months and 5 years of age (OR = 1.9) compared with the first 9 months of life (OR = 5.1), supporting a dampening of adverse effects over time.[24]

The stronger relative effect of severe neonatal morbidity on cumulative LOS in the older gestational age groups (37+ weeks gestation) suggests that severe neonatal morbidity is more

likely to be caused by pathology at older gestations, and immaturity at younger gestations. The interrelationship between physiological immaturity and pathology is complex, with pathology likely to contribute towards birth at early gestation and early birth likely to exacerbate the effects of pathology.[25, 26] This complex relationship makes it difficult to estimate the independent effects of pathology and immaturity. However, Basso and Wilcox estimated that approximately 49% of neonatal deaths across all gestational ages were due to the effects of pathological conditions. Their study also showed that the contribution of pathology to neonatal mortality lessens with decreasing gestation, suggesting that the adverse effects of physiological immaturity become more pronounced with earlier birth.[25] Our observations are supportive of such a relationship.

Few published studies have examined the effects of prematurity on health outcomes beyond one year of age (e.g.[24, 27]) and, to our knowledge, we are the first to examine longer term effects of both severe neonatal morbidity and infant prematurity on paediatric hospitalisation and resource utilization outcomes concomitantly. Significantly, earlier birth has also been shown to affect school performance[28] and behaviour[27] suggesting that the adverse effects of preterm and early term birth, and severe neonatal morbidity may extend to other aspects of development. Furthermore, both the short and longer term community-based healthcare burden, such as general practitioner attendance and the use of prescription medicines associated with increased perinatal risk, are likely to be considerable with decreased gestational age and severe neonatal morbidity.[29] It is hoped that the results of our study together with similar current research demonstrating prolonged increased risk of adverse health outcomes with early gestation will help guide perinatal policy and clinical practice. Specifically, the need to closely monitor the long-term health of vulnerable infants born with severe neonatal morbidity and/or at early gestations, and,

where possible, avoid early births particularly in light of recent trends in some nations towards birth at earlier gestations.[30-33]

Respiratory and gastrointestinal infections were the most common reasons for hospitalisation, suggesting that severe neonatal morbidity and decreased gestational age lead to increased risk of infection, possibly due to perturbed/reduced immune function.[34] Such data suggest that a possible strategy to address and reduce the adverse effects of these conditions is to focus on preventing infections by promoting improved family health through increased awareness/monitoring of child health status, completing vaccination schedules, providing adequate nutrition, and having appropriate lifestyle and living conditions. Other risk factors for hospitalisation, including maternal age, marital status, rural area of residence and maternal smoking,[5, 12, 13] should also be taken into consideration. Specific strategies for the management of these pregnancies and subsequent follow-up after birth would help improve health outcomes and reduce hospitalisations in high-risk infants.

A major strength of our study was the fact that the analyses were carried out on a very large, linked population-based dataset, permitting adjustment for a range of maternal, birth and socio-demographic factors in the statistical analyses. The linked dataset enabled longitudinal and comprehensive follow-up of children up to six years of age for over 98% of all births, providing information on multiple diagnoses and hospitalisation costs. Limitations of the study include the absence of information on other important risk factors such as lifestyle, nutritional, developmental and family factors that were not available in the routinely collected administrative datasets. The inability to track infants born in NSW who subsequently left the state is another limitation. However, the proportion leaving the state annually is estimated to be small (< 2%).[35]

Conclusions

In conclusion, our study investigated the longer term impacts of severe neonatal morbidity and earlier timing of birth providing important information to guide paediatric and clinical policy and practice. The effects of severe neonatal morbidity and decreasing gestational age persisted between one to six years of age, but at reduced levels. Crucially, even babies born early term at 37-38 weeks gestation displayed prolonged increased risk of hospitalisation and cumulative time spent in hospital between one and six years of age. Future strategies to ensure reduction and prevention of infants born with severe neonatal morbidity and/or at earlier gestations before the due date are essential. In addition, comprehensive follow up and monitoring of vulnerable infants are required throughout childhood to ensure optimal health and development.

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Table 1: Characteristics of study population and percentage of infants admitted zero, once or more than once to hospital between 1 and 6 years of age, NSW, 2001-2011

	Admission to hospital, n (%)		
Birth Characteristic	**None**	**Once**	**Two or more**
	N = 277219	N = 74341	N = 41404
Severe neonatal morbidity			
No	270828 (97.7)	72243 (97.2)	39817 (96.2)
Yes	6391 (2.3)	2098 (2.8)	1587 (3.8)
Gestational age (weeks)			
33-34	2402 (0.9)	875 (1.2)	601 (1.5)
35-36	8344 (3.0)	2595 (3.5)	1726 (4.2)
37-38	55069 (19.9)	15814 (21.3)	9595 (23.2)
39-40	155546 (56.1)	40678 (54.7)	22030 (53.2)
41 or more	55858 (20.1)	14379 (19.3)	7452 (18.0)
Parity			
Primipara	112594 (40.6)	32257 (43.4)	18545 (44.8)
Multipara	164434 (59.4)	42036 (56.6)	22840 (55.2)
Maternal age (years)			
< 20	10809 (3.9)	3426 (4.6)	1929 (4.7)
20-34	211634 (76.4)	57544 (77.4)	32091 (77.5)
≥ 35	54697 (19.7)	13353 (18.0)	7368 (17.8)
Hospital type			
Public	211845 (76.4)	55766 (75.0)	30229 (73.0)
Private	65374 (23.6)	18575 (25.0)	11175 (27.0)
Labor			
Spontaneous	171823 (62.0)	44376 (59.7)	23568 (56.9)
Planned delivery	105373 (38.0)	29961 (40.3)	17830 (43.1)
Smoking status			
No	235786 (85.1)	62283 (83.8)	34577 (83.6)
Yes	41319 (14.9)	12032 (16.2)	6808 (16.5)
Marital status			
Married/de facto	224509 (81.6)	59024 (79.9)	32564 (79.2)
Not married	50617 (18.4)	14804 (20.1)	8553 (20.8)
Socioeconomic status			
Disadvantaged	45350 (16.4)	12232 (16.5)	6851 (16.5)
Average	168622 (60.8)	45309 (60.9)	25013 (60.4)
Advantaged	63247 (22.8)	16800 (22.6)	9540 (23.0)
Remoteness			
Urban	247045 (89.1)	65325 (87.9)	36373 (87.8)
Rural	30174 (10.9)	9016 (12.1)	5031 (12.2)

Table 2: Mean adjusted[a] length of stay [95% CI] and cost per childhood hospital admission between one and six years of age by gestational age and severe neonatal morbidity, NSW, 2001-2011

	Gestational age group (weeks)				
Outcome	**33-34**	**35-36**	**37-38**	**39-40**	**41 or more**
LOS (days)	1.7 [1.6-1.8]	1.7 [1.7-1.8]	1.7 [1.6-1.7]	1.6 [1.6-1.7]	1.6 [1.6-1.7]
LOS with SNM (days)	1.6 [1.5-1.7]	1.8 [1.6-1.9]	1.8 [1.7-1.9]	1.8 [1.7-1.9]	1. 8 [1.6-2.0]
Cost ($AUD)	2645 [2527-2763]	2651 [2593-2709]	2610 [2581-2639]	2591 [2568-2614]	2576 [2546-2605]
Cost with SNM ($AUD)	2519 [2405-2631]	2725 [2584-2866]	2865 [2725-3005]	2830 [2710-2948]	2799 [2637-2960]

[a]Adjusted for area of residence (urban or rural), public or private hospital status, socioeconomic disadvantage, maternal smoking, maternal age, parity, labor onset, age at admission and marital status

LOS: Length of stay; SNM: Severe neonatal morbidity; CI: Confidence Interval

Figure legends

Figure 1. Odds ratio of one and more than one hospitalization (relative to none) by severe neonatal morbidity and gestational age classifications. Error bars represent 95% confidence intervals and the reference category for gestational age is 39-40 weeks. Analysis adjusted for area of residence, private hospital status, maternal smoking and age, parity, labor onset and marital status.

Figure 2. Mean adjusted cumulative length of stay (cLOS) in hospital per infant between one and six years of age by gestational age and severe neonatal morbidity. Percentage (%) represents relative increase in cLOS associated with severe neonatal morbidity at each gestational age. Estimates were adjusted for area of residence, private hospital status, socioeconomic disadvantage, maternal smoking, maternal age, parity, labor onset and marital status.

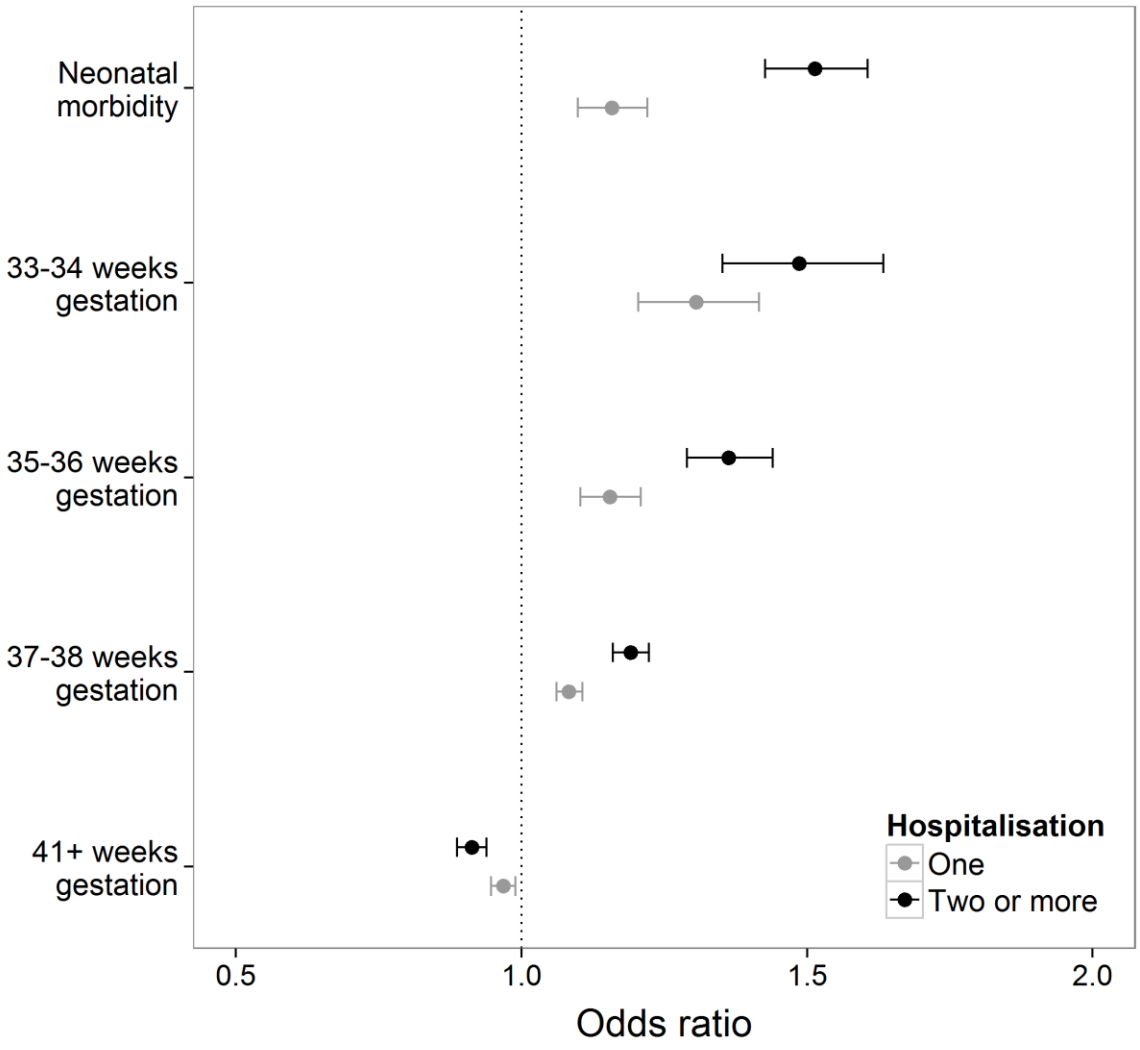
Neonatal morbidity
33-34 weeks gestation
35-36 weeks gestation
37-38 weeks gestation
41+ weeks gestation
Hospitalisation
One
Two or more
0.5
1.0
1.5
2.0
Odds ratio

Figure 1

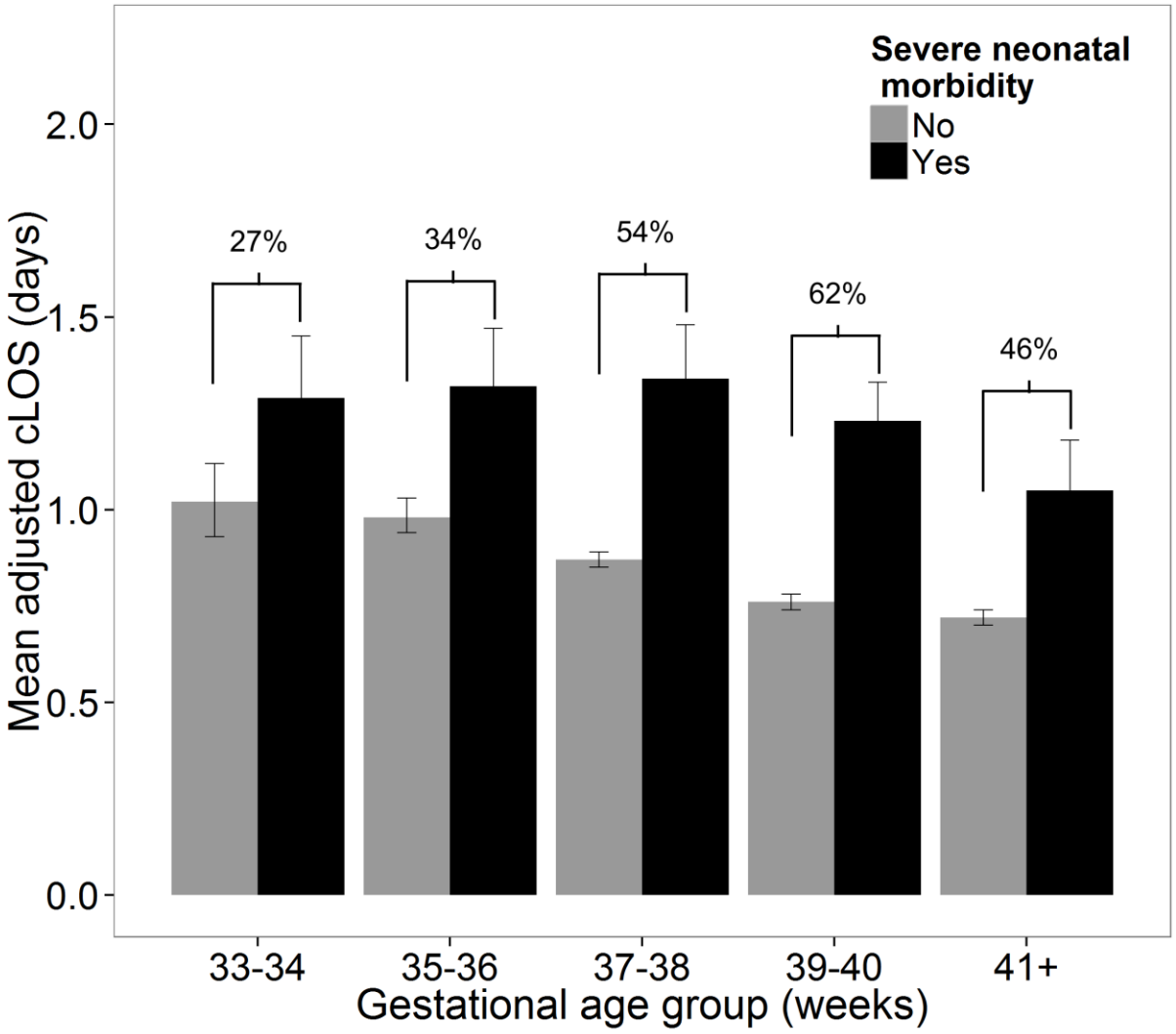
Severe neonatal morbidity
No
Yes
Mean adjusted cLOS (days)
2.0
1.5
1.0
0.5
0.0
27%
34%
54%
62%
46%
33-34
35-36
37-38
39-40
41+
Gestational age group (weeks)

Figure 2