Behavioural outcomes at 3 years of age among late preterm infants admitted to neonatal intensive care: a cohort study

Boylan, J., Alderdice, F. A., McGowan, J. E., Craig, S., Perra, O., & Jenkins, J. (2014). Behavioural outcomes at 3 years of age among late preterm infants admitted to neonatal intensive care: a cohort study. Archives of Disease in Childhood - Fetal and Neonatal Edition, 99(5), 359-365. DOI: 10.1136/archdischild-2013-304785

Published in:
Archives of Disease in Childhood - Fetal and Neonatal Edition

Document Version:
Peer reviewed version

TITLE PAGE

Title: Behavioural Outcomes at three years of age among Late Preterm Infants Admitted to Neonatal Intensive Care: A Cohort Study

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Abbreviations:

LPI – Late preterm infant
LP – Late preterm
NIC – Neonatal Intensive Care
NI – Northern Ireland
SCO – Special Care Only

Key words: late preterm infants, neonatal intensive care, early childhood, behavioural outcomes, follow-up

Word Count:

ABSTRACT

Objective: Examine the behavioural outcomes at age 3 years of Late Preterm Infants (LPIs) who were admitted to Neonatal Intensive Care (NIC) in comparison with LPIs who were not admitted.

Method: This cohort study prospectively recruited 225 children born late preterm (34-36^{+6} weeks gestation) in 2006 in Northern Ireland, now aged 3 years. Two groups were compared: LPIs who received NIC (Study; n=103) and LPIs who did not receive NIC (Control; n=122). Parents/guardians completed the Child Behaviour Checklist/1½-5 (CBCL/1½-5). Descriptive maternal and infant data were also collected.

Results: As expected LPI children admitted to NIC had higher medical risk than the non admitted comparison group (increased Caesarean Section, born at earlier gestation, lower birthweight and an episode of resuscitation at birth). LPIs admitted to NIC scored higher on the CBCL/1½-5 compared to control children indicating more behavioural problems; this was statistically significant for the Aggressive Behaviour Subscale (z = -2.36) and the Externalising Problems Scale (z = -2.42). The group difference on the Externalising Problems Scale was no longer significant after controlling for gender, gestational age, and deprivation score.

Conclusions: This study provides valuable data on the behaviour at age 3 of LPIs admitted to NIC compared to LPIs not admitted to NIC. Further research would be beneficial to explore medical and psychosocial explanations for observed differences between groups using large prospective cohort studies

INTRODUCTION

Most research examining the longer term outcomes of infants who receive neonatal intensive care (NIC) has been conducted on those born very preterm (< 28 weeks gestation) or very low birthweight (<1500g). Yet, Late Preterm Infants (LPIs: born at 34-36^{+6} weeks gestation) account for 20-25% of all admissions [1-2]. Emerging evidence suggests that LPIs have poorer health, neurodevelopmental, cognitive, developmental and educational outcomes when compared to full term infants [3-12]. Furthermore, a systematic review of early childhood outcomes of LPIs concluded that LPIs are at increased risk of adverse developmental outcomes and academic difficulties up to 7 years of age in comparison to term infants [13].

Research to date regarding the behavioural outcomes of LPIs, has been inconclusive. Some research has indicated that LPIs may display more behavioural problems [14-21], with van Barr *et al* [15] reporting that moderately preterm children (mean gestational age 34.7 weeks) who did not receive NIC displaying more behaviour problems when compared with term children at eight years of age. Furthermore, when the sample was divided into two subgroups (32 - 33 vs. 34 - 36 weeks' gestation) more behaviour problems were assessed by mothers in the 34 - 36 weeks' gestation subgroup. Others report no significant difference in behavioural outcomes for LPIs when compared to term controls [22-24]. Ketharanathan *et al* [24] assessed behavioural problems in children born between 32 and 36 weeks' gestation that were not admitted to NIC but were admitted to their hospitals neonatology ward, at 2 - 5 years of age and concluded that the overall occurrence of behavioural problems did not differ from the general term-born paediatric population. As low birth weight babies have a well document risk of increased behaviour problems[17] it is important to explore explanations for this variation further. While the reasons for these problems are unclear one possibility is that the experience of NIC, with accompanying separation and medical risk, may interfere with parent attachment.

It is important to understand the unique problems that the growing population of LPIs may experience [25]. It is also recognised that the consequences of postnatal care of LPIs warrants further research [5], however most previous studies do not consider the neonatal status of LPIs (i.e., whether they were admitted to NIC). Furthermore, a comparison group of infants born within the same gestational age range has not been utilised to date. Prior to this study the three year behavioural outcomes of LPIs who receive NIC have not been fully examined. The purpose of this paper was to report on the behavioural outcomes of LPIs who received NIC compared with LPIs who did not receive NIC, thus providing important, new information on LPIs.

METHOD S

There were 1032 consecutive live births between 1st January and 31st December 2006 in Northern Ireland, of infants with a gestational age range of 34 weeks $^{+0}$ days to 36 weeks $^{+6}$ days at birth (LPIs). There were two groups of LPIs; study children (received any episode of NIC) and control children (did not receive NIC or did receive Special Care Only (SCO) for ≤ 3 days); as defined by the British Association of Perinatal Medicine [26]. Exclusion criteria included children who received SCO for greater than 3 days and those with congenital abnormalities. Details of infant eligibility can be found in Figure 1 and further detail on recruitment and methods can be found in McGowan *et al* [27].

Recruitment and data collection took place between March 2008 to March 2009, when the children were aged 3 years. Registry data were accessed to ensure that parents/guardians with a child who died in infancy were not contacted. Parents/guardians received an invitation letter and two reminder letters from the Consultant Neonatologist at the hospital where their child was born; a handwritten flyer was included and a thank-you gift voucher was offered for participation. Data

collection took place in the parents/guardians home, with the researcher blinded with regards to the perinatal details of the child. Written informed consent was obtained from parents/guardians of all children.

Parents/guardians completed the Child Behaviour Checklist (CBCL/1½-5) [28]which is a well validated questionnaire that measures the frequency of various types of behavioural and emotional problems that occur in children aged 1 ½ to 5 years old. It consists of 99 items plus space for 3 additional self-reported problem behaviours. There are two sets of scales (1) Problem Scales (used in this study) and (2) DSM-Oriented Scales (not used in this study). The Problem Scales are derived from 67 of the 99 items and are categorized as the following 7 subscales (1) Emotionally Reactive, (2) Anxious/Depressed, (3) Somatic Complaints, (4) Withdrawn, (5) Sleep Problems, (6) Attention Problems, (7) Aggressive Behaviour. Scores for Internalising, Externalising and Total Problems Scales are also calculated. Items are scored on a 3-point Likert scale (0= "not true", 1= "somewhat or sometimes true", and 2= "very true or often true"), based on the preceding 2 months. Items are summed to give a raw score for each subscale. Higher scores indicate greater presence and severity of symptoms. Scores for Internalising, Externalising and Total Problems Scales are also calculated. Please see the results section for how many items are included in these subscales and scales and how they are calculated.

Demographic and perinatal data describing maternal and infant characteristics were collected. The Office for Research Ethics in Northern Ireland (ORECNI; Reference: 08/NIR02/116) approved the study.

< Insert figure 1 here >

There were a total number of 23895 live births in 2006. 135 born ≤ 28 weeks; 420 ≤33 weeks; 1098 between 34-36 weeks; and 22,242 ≥ 37 weeks [2]. A total of 1098 LPIs were live born, however only those born at a hospital with a Neonatal Unit were eligible for recruitment, resulting in 1032 potentially eligible LPIs for the study group (see figure 1).

Table 1: Clinical characteristics of LPIs born in 2006 admitted to NIC and Special Care

Infant Clinical Characteristic	Number
Infant died	8/497
Congenital abnormalities	39/497
Any respiratory support	146/497
Mechanical ventilation	37/497
Respiratory Distress Syndrome	93/496 (1 unknown)
Continuous Positive Airway Pressure (CPAP)	136/497
Transient Tachypnoea of the newborn (TTN)	116/497
Hypoglycaemia on admission	193/447 (50 unknown)
Temperature > 36.5C	178/481 (16 unknown)
Sepsis early onset	12/484 (13 unknown)
Sepsis late onset	17/497
Seizures	4/450 (27 unknown)

Source: NICORE Database [29]

Table 1 presents the reasons for admission to neonatal care for all LPIs born in Northern Ireland in 2006. These cannot be compared with non admissions as medical problems that lead to NIC admission are inherent in the study group.

SAMPLE SIZE CALCULATION

A sample size calculation stipulated 144 children per group to detect a 5 point difference on the CBCL/1½ -5 assuming an α level of 0.05, a power of 80%, and a two-sided hypothesis.

STATISTICAL ANALYSIS

Three sets of analyses were undertaken. First, descriptive characteristics of those children and their mothers who took part the study are reported: most data were categorical and $\chi 2$ analysis/Fisher's Exact Test were undertaken to compare the characteristics between groups.

Second, scores from the CBCL/1½-5 Problem Subscales, and Internalising, Externalising and Total Problems Scales were analysed. Data from the CBCL/1½-5 were highly skewed and not normally distributed therefore the non-parametric Mann Whitney U test for two group comparison was undertaken using SPSS for Windows 17.0 [SPSS Inc, Chicago, IL].

Third, a regression analysis was conducted on the Externalising Problem scores as this was the main outcome where the two groups significantly varied. Group (control vs. study) was entered as the predictor variable, with gestational age (34; 35; 36 weeks); gender (male; female) and deprivation (coded in five categories; most to least deprived using the Northern Ireland Multiple Deprivation Index, 2010 [30]) considered as covariates in the models. Models were estimated using Mplus Version 7 [31]. To allow for the non-normal distribution of the outcomes the Maximum Likelihood Parameter (MLM) estimator was used, indicating MLM estimates with standard errors and a mean-adjusted chi-square test statistic that are robust to non-normality. The unadjusted standardised parameters relative to each covariate are reported. Following this all the covariates were entered and the adjusted standardised parameters are reported (model 1); these represent the relationship between the covariate and the outcome while controlling for the other covariates.

RESULTS

A total of 225 children took part in the study (103 in the study group and 122 in the control group). Table 2 outlines the characteristics of the study and control children. Equal numbers in each group were male (47.5% study and 51.5 % control). There was significant variation of gestational age of children in

each group ($p \leq .001$), with 41% of study children and 15% of control children born at 34 weeks gestation. More children in the control group were born at 36 weeks gestation than study children (30.3% and 29.1% respectively). Levels of deprivation, based on postcode, did not vary significantly between the groups.

Table 2: Maternal Perinatal Factors and Characteristics of Children by Group (n=225)

	Late Preterm Infant Group		χ^2	p*
	Study (n=103)	Control (n=122)		
Mode of Delivery				
Vaginal	31 (30.1)	75 (61.5)	26.83	<.001
Caesarean	72 (69.9)	41 (33.6)		
Missing	0	7 (4.9)		
Reason for caesarean delivery				
Emergency	52 (72.2)	25 (65.0)	0.63	.43
Elective	20 (27.8)	16 (35.0)		
Resuscitation				
Resuscitation required+	46 (44.7)	19 (15.6)	16.11	<.001
No resuscitation	56 (54.3)	82 (67.2)		
Missing	1 (1.0)	21 (17.2)		
Birth weight				
≤2500g	60 (58.3)	44 (36.1)	8.71	0.003
>2500g	43 (41.7)	71 (58.2)		
Missing	0	7 (5.7)		
Male Gender	53 (51.5)	58 (47.5)	0.34	0.558
Deprivation				
Quintile 1 (most deprived)	16 (15.5)	14 (11.5)	2.25	0.69
Quintile 2	20 (19.4)	27 (22.1)		
Quintile 3	25 (24.3)	25 (20.5)		
Quintile 4	17 (16.5)	27 (22.1)		
Quintile 5 (least deprived)	22 (21.4)	29 (23.8)		
Unknown	3 (2.9)	0		

NB. Data are n (%) and children in unknown categories were excluded from statistical analysis.
*p calculated using Chi-Square Analysis or Fishers Exact test if any cell = <5
+Includes face-mask oxygen, positive pressure, cardiopulmonary resuscitation

Study children were significantly more often born by Caesarean Section delivery and had lower birthweights than control children. Significantly more study children required an episode of resuscitation

at birth (including facial oxygen, positive pressure, CPR). Further details regarding this cohort are tabulated in McGowan *et al* [27].

Table 3: CBCL/1½-5 Mean Behavioural Problem Scores by Group: Descriptive Data (n=221)

		Late Preterm Infant Group				
	CBCL/1.5-5: Problem Subscales & Scales	Study (n=102)+	95% CI	Control (n=119)++	95% CI	Normative (n=700)+++
		Mean		Mean		Mean
	Subscales					
1	Emotionally Reactive (9 items)	2.4	1.9-2.9	1.7	1.4-2.1	2.4
2	Anxious/Depressed (8 items)	2.4	2.0-2.8	2.0	1.7-2.4	2.9
3	Somatic Complaints (11 items)	2.3	1.8-2.8	1.7	1.3-2.0	1.8
4	Withdrawn (8 items)	1.2	0.9-1.5	1.1	0.9-1.4	1.5
5	Sleep Problems (7 items)	2.9	2.3-3.5	2.6	2.1-3.2	2.8
6	Attention Problems (5 items	2.5	2.1-2.9	2.1	1.7-2.5	2.5
7	Aggressive Behaviour (19 items)	9.2	8.0-10.5	7.4	6.3-8.5	10.4
	Scales					
i	Internalising Scale (Subscales 1-4)	8.3	6.9-9.6	6.9	5.7-7.5	8.6
ii	Externalising Scale (Subscales 1-4 + 6 + 7)	11.7	10.1-13.3	9.5	8.1-10.9	12.9
iii	Total Problems Scale (Subscales 1-7 + 32 items classified as "other problems"+ 1 additional problem*)	31.5	27.3-35.7	26.1	22.9-29.2	33.3

NB: Sleep problems (subscale 5) are treated as a separate syndrome and not included in the Internalising or Externalising Problems Scales
CI: Confidence Interval
* the highest scoring item added by parent/guardian (from the 3 additional problems they have the option to complete)
+ no data for 1 child
++ 3 children were removed from analysis due to being outliers (2 of these children had a diagnosis of autism, as reported by their parent/guardian)
+++ Achebach & Rescorla (2001) normative data

Mean scores on the CBCL/1½-5 revealed that children in the study group scored marginally higher on all 7 Problem Scales' subscales and the 3 overall Total Scales (Internalising, Externalising, and Total Problems Scales) than children in the control group (table 3). Both the control and study group children's mean scores were in the same range as comparative data [28].

Table 4: CBCL/1½-5 Median Behavioural Problem Scores by Group: Mann-Whitney U Tests (n=221)

		Late Preterm Infant Group				
	CBCL/1.5-5: Problem Subscales & Scales	Study (n=102)+		Control (n=119)++		
		Median	Mean Rank	Median	Mean Rank	Z score
	Subscales					
1	Emotionally Reactive	2	119.49	1	103.72	-1.87
2	Anxious/Depressed	2	115.65	2	107.02	-1.01
3	Somatic Complaints	1	119.57	1	103.66	-1.89
4	Withdrawn	1	111.29	1	110.75	-0.07
5	Sleep Problems	2	114.22	2	108.24	-0.71
6	Attention Problems	2	118.91	2	104.22	-1.73
7	Aggressive Behaviour	8	121.93	6	101.63	-2.36*
	Scales					
i	Internalising Scale (Subscales 1-4)	7	117.62	6	105.32	-1.43
ii	Externalising Scale (Subscales 1-4 + 6-7)	10	122.23	8	101.37	-2.42*
iii	Total Problems Scale (Subscales 1-7 + 32 items classified as "other problems")	26.5	118.55	23	104.53	-1.63

** p<.05*

\+ no data for 1 child

++ 3 children were removed from analysis due to being outliers (2 of these children had a diagnosis of autism, as reported by their parent/guardian)

95% Confidence Interval

Mann-Whitney U tests were conducted to evaluate the hypothesis that children in the control group would score lower (i.e. have fewer behaviour problems), on average, than study group children on the behavioural outcomes of the CBCL/1½-5 (table 4). The median scores were generally lower for the control group suggesting that they may score lower than the study group. Raw scores were transformed to ranks in order to perform the Mann-Whitney U test. The mean ranks differ in the same direction as the medians (see Table 4). Results were in the expected direction for all subscales and scales, these were significant for the Aggressive Behaviour subscale ($z=-2.36$, $p < .05$), study children had an average rank of 121.93 and control children had a lower average rank of 101.63 and the Externalising Problems

scale (z = -2.42, *p.* < .005), study children had an average rank of 122.23 while control children had a lower average rank of 101.37.

Table 5: CBCL/1½-5 Externalising Problem Scale Scores: Regression Standardised Parameters and their 95% CI (n=221)

		Unadjusted Parameters	*Model1 Adj. Parameters*
Group	Control+	*reference*	*reference*
	Study++	0.14* (.01 .27)	0.11 (-.04 0.25)
Gender	Female	*Reference*	*reference*
	Male	0.11** (-.02 . 24)	0.13** (-.001 .25)
Deprivation	Most deprived	*Reference*	*reference*
	2	-0.13 (-.33 .07)	-0.11 (-.30 .09)
	3	-0.18** (-.38 .02)	-0.19** (-.38 .01)
	4	-0.25 * (-.41 -.09)	-0.25* (-.41 -.10)
	Least deprived	-0.19* (-.36 -.02)	-0.18* (-.35 -.01)
	Missing information	-0.07 (-.08 .21)	0.05 (-.11 .21)
Gestational Age	34	0.03 (-.13 .18)	0.00 (-.16 .16)
	35	-0.03 (-.18 .12)	-0.02 (-.17 .13)
	36	*Reference*	*reference*

** p < .05 ** p < .10*

\+ 3 children were removed from analysis due to being outliers (2 of these children had a diagnosis of autism, as reported by their parent/guardian)

++ no data for 1 child

Further analysis showed that children from the study group had an increase of 0.14 standard deviation (SD) unit (less than a fifth of a SD unit) in the Externalising Problem Scale scores (table 5). Deprivation also displayed some association but neither gender nor gestational age were significantly associated with Externalising Problem Scale scores.

When controlling for other covariates (model 1), the association between group and Externalising Problem Scale scores was no longer significant. However the association between deprivation and Externalising Problem Scale scores remained significant; being from the two least

deprived backgrounds was associated respectively with 0.25 and 0.18 SD unit decrease compared to children from the most deprived background.

DISCUSSION

The aim of this study was to consider the three year behavioural outcomes of late preterm infants (LPIs) who were admitted to NIC (study group).Our first main finding indicated that LPIs who received NIC scored marginally higher on all behavioural outcomes (subscales and total scales of the CBCL/1½-5) than LPIs who did not, indicating that LPIs who received NIC are displaying more behavioural problems than LPIs who did not. However this was only significant for the Aggressive Behaviour Subscale and the Externalising Problems Scale. It is important to note that the Aggressive Behaviour Subscale is used in calculating the Externalising Problems Scale and may actually account for this significant finding for the Externalising Problems Scale. It is also reassuring to note that both groups of LPIs were scoring within the normative range for the CBCL/1½-5 [28]. This would suggest that LPIs, regardless of their neonatal status are displaying behaviour similar to the normative population in contrast to what previous research has suggested [14-21]. However it is important to note that the comparative norms are from American children which may influence the comparability of our data with these norms.

Our second main finding indicated that although there were differences between the two LPI groups on their Externalising Problem Scale scores, when gestational age, deprivation and gender were controlled for this difference was no longer significant. Gender and deprivation remained significant, with males and LPIs from the most deprived backgrounds scoring higher on the Externalising Problem Scale. These findings suggest caution when attributing differences in behavioural outcomes among preterm populations to neonatal status: male gender or increased deprivation, rather than neonatal status may be influential. While gender and deprivation have been found to be influential in studies of

behaviour in low birthweight children [17] ,research regarding the influence of gender on the behavioural outcomes of moderately preterm children has been inconclusive. Bul and van Baar [21] examined behavioural outcomes for moderately preterm children (32-36 weeks gestation) and reported that male gender was important in the teacher's assessments of behavioural problems (but not the parents), whilst Pojtik et al [16] reported that moderately preterm birth affected girls more than boys. Deprivation and gender influence on behavioural outcomes are clearly areas for further research.

Our research provides some support for the assertion that LPIs do not differ from term children with regards to behavioural problems [22-24], however we did not have a term control group so this observation is based on the comparative norms [28]. Ketharanathan *et al* [24] used the CBCL/1½-5 with children born 32 - 36 weeks gestation who were admitted to their hospitals neonatology ward, at 2 - 5 years of age. Similar to the current study, they reported that the CBCL/1½-5 scores were within the validated normal range, however their study population scored higher on Emotionally Reactive, Somatic Complaints and Attention Problems when compared to the normative data [28]; yet the overall occurrence of behavioural problems did not differ from the general term-born paediatric population.

LIMITATIONS

Not all those who were invited to take part responded to the invitation, McGowan *et al* [27] reported analyses of those non-responders (from the LPI NIC group), reporting that fewer young mothers, more smokers and single parents chose not to take part in the study. Furthermore, mothers in more deprived areas were also marginally less likely to take part. However, comparison of the sociodemographic characteristics of children who were recruited to the study was largely similar between the two LPI groups.

It may also be the case that the CBCL/1½-5 was not sensitive enough to detect subtle but significant differences in the behavioural outcomes at age three years for the children in this study.

The sample size for both groups may have been too small to detect a significant difference in scores. A sample size calculation recommended 144 children per group in order to detect a 5 point difference. However this study did not meet the requirements of this calculation (102 vs. 119). This may have affected the significance of the findings.

CONCLUSION

This subgroup of premature infants has increasingly become the focus of research in recent years, however research examining neonatal status using an LPI comparison group is sparse. This study aimed to fill that gap in the literature. Our results are reassuring for parent and clinicians involved in the care of LPIs. Even though LPIs who received NIC scored higher than those who did not on the CBCL/1½-5, this was only significant for one subscale and one total scale, and the scores were also similar to the comparative norms, suggesting that LPIs, regardless of neonatal status seem to behave similarly to the general paediatric population.

Late preterm children experience a wide range of morbidities in the neonatal period; indeed these morbidities in association with their place of neonatal care, may contribute to their longer term behavioural outcomes. The finding that male gender or levels of deprivation rather than neonatal status may account for the increase in Externalising Problem Scales warrants further exploration. Furthermore life events and experiences may also contribute to behavioural outcomes over and above neonatal status. Whilst the findings from this study should reassure parents and clinicians, three years of age is not a reliable end point for assessment of these children; it is recommended that they are followed until

school age and beyond before strong conclusions could be made regarding their longer term behavioural outcomes.

ACKNOWLEDGEMENTS

The authors thank Emma McCall, NICORE Database Manager; Dr Christopher Cardwell, Statistician; Clinical Facilitators: Dr N. Lipscomb, Dr D. Brown, Dr S. Bali, Dr C. Corkey, Dr P Quinn, Dr A. Black and clinical administrative support.

We are also indebted to the families who took part in this follow-up study.

COMPETING INTERESTS

None

FUNDING

Department of Health, Social Services and Public Safety (DHSSPS) funded the study. J McGowan received a PhD Studentship from the Department for Employment and Learning, Northern Ireland; the other authors have no financial disclosures relevant to this article.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Research suggests that late preterm infants (LPIs) have poorer longer term outcomes when compared to children born at full term.
- Research has been inconclusive regarding their behavioural outcomes. Some report higher levels of behavioural problems, others report no significant differences, compared to term controls.
- The longer term behavioural outcomes of LPIs who received neonatal intensive care (NIC) have not been fully explored to date.

WHAT THIS STUDY ADDS

- This study provides new information on the potential impact admission to NIC, as a proxy for medical risk, has on behavioural outcomes of LPIs at age three years.
- LPIs admitted to NIC displayed more behavioural problems when compared to those who were not; however this was statistically significant only for Aggressive Behaviour and Externalising Problems.
- Being male and from a more deprived backgrounds were the best predictors of higher scores on the Externalising Problems scale in this LPI group.

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