Measuring the Impact of Deprivation on Learning Difficulties and Behaviour Among Infants born Preterm: A Cohort Study

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Short Title: Impact of Deprivation on LD in Preterms

Abstract

Background: Preterrm birth and social deprivation are known risk factors for learning difficulties. However there has been little work looking into the interaction between these two risks. We aimed to identify if children born preterm to families with higher levels of social deprivation are disproportionately more likely to have learning difficulties than those with lower levels of social deprivation.

Methods: Data from the RANOPS (Respiratory And Neurological Outcomes in children born Preterm Study) was used to assess prevalence of learning difficulties. The effects of preterm birth and deprivation were reviewed. Multi-level logistic regression models were used to examine if gestational age and deprivation impacts interacted after adjustment for possible confounders. Primary outcome measure was parent-reported learning difficulties. Secondary outcome measures were parent-reported behavioural problems and a statement of special educational need.

Results: We investigated the developmental outcomes of 6,691 infants with a median age of 5 years at time of survey (IQR 5). Deprivation decile (OR 1.08 (1.03,1.12)) and preterm birth (OR 2.67 (2.02,3.53)) were both associated with increased risk of learning difficulties. There was little evidence for any interaction between preterm birth and deprivation (p=0.298) and the risk of learning difficulties.

Conclusions: Deprivation and preterm birth have significant associations with learning difficulties. While deprivation does not appear to have potentiated the impact of preterm birth, preterm infants in the most deprived areas have the highest risk of learning difficulties with almost 1 in 3 extremely premature infants with a learning difficulty in the most deprived areas.

Keywords

Child Development, Epidemiology, Neonatology, Public Health, Statistics

Abbreviations

ANOVA- analysis of variance

RANOPS - Respiratory and neurological outcomes in children born preterm study

SES- Socioeconomic status

SD- Social Deprivation

WIMD- Welsh Index of Multiple Deprivation

SEN- Statement of Educational Needs

Introduction

1 in 10 children are born preterm(1) representing a major target for interventions to benefit public health(2-5). Preterm birth is associated with an increased risk of neurological impairment of varying severity(6-9). These neurological sequelae of prematurity can manifest as learning difficulties in later life(10-14).

Socioeconomic status (SES) has a well-established relationship with health outcomes. Increasing social deprivation (SD) is related to increased risk of preterm labour, preterm birth, low birth weight and neonatal mortality(15-17). Children with deprived SES are more likely to have intellectual and developmental disability (18). Increasing risk of intellectual disability is associated with increasing SD(19).

SD is commonly adjusted for in analyses of prematurity and neurodevelopmental outcomes(20). Lower parental education attainment, as proxy for SES, is a negative prognostic factor for neurodevelopment in preterm birth(21). There is also evidence that SD may increase risk after preterm birth on early(22) and later(23) academic performance. However, limited work has investigated the relationship between preterm birth, a deprived environment, and neurodevelopmental outcomes(24, 25). It is unclear if the substantial impact of preterm birth is relatively unaffected by deprivation, or if the environment has an even more important role to play for these vulnerable infants.

Aims

To identify if outcomes related to learning difficulties and behavioural problems are disproportionately worse for children born preterm to families living in areas of high social deprivation than those living in areas with lower deprivation

Material and Methods

Cohort

Data was drawn from the RANOPS (respiratory and neurological outcomes in children born preterm study), a cross-sectional survey in Wales of children born preterm from 2003-2011. Participants were aged between 1 and 10 at time of survey. RANOPS identified a total of 13,373 preterm infants (less than 37 weeks gestation) matched with 13,369 term controls next born on their date of birth of the same sex and in the same locality(26)contacting 26,742 families in 2013. 7,149 responded to self-completed questionnaires regarding respiratory and neurological outcomes(26-28). Parents of term and preterm children received the same questionnaires. Post-term infants (42 or more weeks' gestation) and infants with birthweights below and above the 0.4^{th} and 99.6^{th} centiles for gestation were excluded leaving 6,761 eligible infants.

Exposure

Exposure measures were gestational age at birth and a geographic measure of deprivation. Preterm birth was defined as gestation of less than 37 weeks. Deprivation was defined using the Welsh Index of Multiple Deprivation (WIMD) derived from the child's address at the time of the survey. WIMD is a measure of relative deprivation for small areas with the same population in each in Wales created by the Welsh Government(29). WIMD is similar to other indices of multiple deprivations in the United Kingdom but varies in some indicators and is specific to Wales. Therefore, Townsend score, was used as a secondary definition measure of deprivation (30).

Outcomes

Primary outcome was learning difficulties as reported by parents at questionnaire (see supplementary materials). Measures of parental report of statement of educational need

(SEN) or behaviour problems were secondary outcomes. Parents were asked at the survey 'does your child have any learning difficulties?' with free text to record details of the specific learning difficulty. A composite measure of learning difficulties, where one or more of these were present, was used as the primary outcome. A subsequent analysis of the specific domains of learning difficulty described in parent's free text responses was used as a secondary outcome. These were categorised into the following sub domains: global developmental delay, speech and communication difficulties, autism, dyslexia and generalised learning difficulty.

Possible confounders were defined *a priori* and divided into two groups:

- Demographic (maternal age at birth, sex and ethnicity)
- Clinical (Pregnancy and intrapartum: smoking in pregnancy, multiple birth, mode of delivery; Infant and postpartum: birthweight, breast feeding at birth)

Statistical Analysis

Initially, we compared the characteristics of children included in analyses, with those who were excluded for missing data. Next, we investigated the characteristics of the included population, for example median age at time of survey, split categorically as term and preterm children and deprivation measured by WIMD rank. WIMD was categorised into deciles. We reviewed the association between the two exposures of interest. For preterm and term infants, we tested for evidence of increasing numbers of term or preterm born infants related to deprivation decile using a Poisson regression.

We then reviewed the independent association between the two exposures and the presence of learning difficulties. Frequencies for each gestational age and deprivation decile were derived. Comparisons were made using Chi^2, t-test, p for trend and ANOVA as appropriate.

Finally, we assessed the association between the preterm birth, increasing decile of deprivation measure and learning difficulties using a logistic regression model. We compared preterm born children to term born children and more deprived children to those living in the least deprived decile. Initially, a univariate, multivariable random-effects model was developed between the exposures and the outcome, using the age of the child at the time of the survey as the random effects variable. We then adjusted for potential confounders by adding them to the model in groups of common variables . We tested to see if the association between gestational age or deprivation differed depending on the other exposure by using an interaction term. Models were compared using the likelihood ratio test. Models were then tested for secondary outcomes. To test if SEN support was modified by deprivation, the analyses using SEN as the outcome was repeated restricted to those children with reported learning difficulties.

Sensitivity analyses were performed; analysis using the WIMD deprivation measure at the time of birth, using the Townsend score (30), using 5 gestational age groups divided into late (36 weeks), moderately (32-35 weeks), very (28-31 weeks), and extremely preterm (below 28 weeks) .

Statistical analyses were performed using Stata/SE 16.1 (Statacorp LLC).

Ethics

Ethical approval was sought at initiation of the RANOPS and approved by South East Wales Research Ethics Committee (Research Ethics Committee 12/WA/0155 Project 91349)(26, 28).

Results

Of 6,761 eligible children, 26 lacked data on learning difficulties and 44 children lacked information regarding deprivation (Appendix 1). This left 6,691 in the cohort for the primary analysis with a median age of 5 years at time of survey (IQR 5, see appendix 2). 19 lacked data on behavioural problems and 3,335 missing data on SEN and consequently the number of children in each analysis varied with outcome assessed. Infants in the primary cohort for analysis were more likely to be male than those not analysed due to missing data (p=0.02) but were otherwise similar in terms of demographics (appendix 3).

Children born preterm were more likely to be male (p=0.05), more likely to be born to a mother who smoked (p=0.01), from multiple pregnancies (p<0.001) and be born by unplanned LSCS (p<0.001); they had lower birthweights (p<0.001) and were less likely to have started breast feeding at birth (p<0.001). Children in the more deprived deciles had younger mothers (p<0.001), were of a younger age at time of survey and were more likely to be of an ethnic minority group (p<0.001). They were more likely to be born to mothers who smoked (p<0.001), from a singleton pregnancy (p=0.01) and by normal vaginal delivery (p<0.001). More deprived children had lower birthweights (p<0.0001) and were less likely to have started breast feeding at birth (p<0.001) (Table 1).

There was strong evidence (p<0.001) that term infants were more likely to live in the less deprived areas and some less strong evidence of a relationship with deprivation for preterm infants (p=0.05) (Figure 1, data in appendix 5).

[Fig. 1]

In univariable analysis, preterm infants were more likely than term infants to have a learning difficulty (10.5% vs 4.5%, p<0.001), a SEN (7.3% vs 2.5%, p<0.001) and a behaviour problem (11.3% vs 5.8%, p<0.001) (Table 2). There was evidence for a high risk of global developmental delay and general learning difficulties (both p<0.001) in preterm infants, but insufficient evidence for an association with specific speech or communication problems, autism or dyslexia (Table 2).

Children living in more deprived areas also had a higher prevalence of learning difficulties, SEN and behaviour problems (each $p<0.001$). There was strong evidence that global developmental delay (p=0.02), general learning difficulties (p=0.002) and autism (p=0.01) were associated with increasing deprivation. There was weak evidence of increasing speech or communication needs (p=0.06) but less dyslexia (p=0.05) in more deprived deciles. The combined results are shown in Figure 2.

[**Fig. 2**]

In the logistic regression, compatible with the univariable model, preterm infants (OR 2.57 (2.08,3.17)) and children in increasingly deprived areas (OR 1.08 (1.05,1.12), $p<0.001$) had increased odds of learning difficulties (Table 3). There was no evidence of interaction between the two exposures ($p_{interaction}=0.4$). There was little change in the point estimates with the addition of potential confounders to the model and little evidence of interaction in the final adjusted model ($p_{interaction}=0.3$).

In the fully adjusted model, there was strong evidence that preterm babies were more likely to have global developmental delay ($p<0.001$), general learning difficulties ($p<0.001$) and dyslexia (p=0.03) but no clear association with speech delay (p=0.2) or autism (p=0.9). Deprivation appeared to be associated with global developmental delay (p=0.01) and autism (p=0.004) but not speech disorders (p=0.5) or dyslexia (p=0.09).

There was some evidence that the relationship between preterm birth and autism (p=0.02) and dyslexia (p=0.05) was modified by deprivation. The relationship between autism and deprivation was seen in term (OR 1.54 (1.18,2.00)) but not preterm infants (OR 1.09 (0.93,1.29)). In contrast, the relationship between lower rates of dyslexia with increasing deprivation was seen in preterm (OR 0.84 (0.73,0.97)) infants but not in term infants (OR 1.11 (0.87,1.40)).

Comparable patterns were seen with the analysis of the secondary outcomes. In the logistic regression, preterm infants had an increased odds of SEN (OR 4.08 (1.68,9.88)) as did children in increasingly deprived areas (OR 1.14 (1.01,1.28)). Preterm birth increased the odds of behavioural problems (OR 2.36 (1.45,3.85)) as did living in increasingly deprived areas (OR 1.21 (1.14,1.29)). There was no evidence of interaction between the exposures for SEN (p=0.2) and behavioural problems (p=0.1).

There was little evidence for any interaction between preterm birth and deprivation and the risk of SEN($p_{interaction}$=0.6) when restricting the cohort to those with learning difficulties. Sensitivity analyses for primary outcome gave compatible results to the main analyses; using Townsend score ($p_{interaction}$=0.3) or the WIMD rank at birth ($p_{interactiont}$=0.5) as the measure of deprivation, or using gestaional age split into five levels ($p_{interaction}$=0.7).

Discussion

The results of this study provide further strong evidence of increased risk of learning difficulties in preterm-born children, and those children living in socially deprived areas. However, there was little to suggest preterm-born children, living in more deprived areas, have the impact of preterm birth potentiated by their perinatal journey in terms of learning difficulties and behavioural problems. However, the additive nature of the impacts does mean that these children still have the highest individual risk. Equally, we found no evidence that having a SEN was related to deprivation in those children reported to have learning difficulties.

Although learning difficulties were based on parental reports a similar relationship was seen in the more objective measure of parent report of having a statement of educational need. A SEN is analogous more modern descriptors like Individual Development plans and Education, Health and Care plans. Amongst those with a reported learning difficulty, preterm birth did not appear to be a risk factor for SEN but this is likely due to altered population in this subanalysis. Substantial confounding appears unlikely with unadjusted and adjusted measures reporting similar point estimates. This study is limited by its outcome measures being derived from parental report. In addition to this, a SEN requires input from educational and healthcare services so would not be measurable in very young children who had not enrolled in school. Further correlation with more objective assessments such as Bayley scales would be of benefit in future work.

Repeating the analysis with different measures of deprivation also produced similar results although uncontrolled and residual confounding is always possible in such observational studies; although the results of the models did not appear particularly sensitive to adjustment to the covariates we did have available. Of note some of the covariates (e.g. breastfeeding) may be consequences of our primary outcomes and so our anayalysis may be considered overconservative but are consequently likely to be robust. While there was little to suggest that missing data is a significant issue, the generalisability of the work to recent preterm births should be considered, alongside the representative nature of the sample. Like most studies of this kind, only a proportion of the eligible population was enrolled in the initial study(26, 28) . There was variation in demographics between those who responded to the survey and did not (appendix 2) with the parents of preterm children, younger children and families living in less deprived areas being more likely to respond; although whether this would bias the association between deprivation and preterm births, and their neurodevelopmental outcome is unclear. We did not undertake statistical adjustment or weighting for non response. However as our primary outcome measure was interaction it is unlikely the effect of non response would be different the outcomes of depriavation and prematurity. Overall, the initial study was able to recruit a large number of preterm and term infants, controlling for a number of confounders.

As premature birth overall, and survival after it, increases(1, 3, 4) a better understanding of the effects the environment has beyond the neonatal intensive care unit becomes increasingly important. Previous studies have shown variable evidence of an interaction between parental education as a measure of deprivation and developmental delay in ex-preterm infants(24). Ex-preterm children, living in challenging environments, appear to face multiple challenges to their chance of a good neurodevelopmental outcome (7, 10, 18, 19, 31) (32) but if, and how, these factors combine is difficult to answer. Early intervention programmes may help support neurodevelopmental outcomes for ex-preterm infants, at least until early school ages(33) and "catch up" with their peers in school outcomes over the early years of education looks possible and modifiable(11). Previous investigations of structured development programmes are often adjusted for socioeconomic status, and consideration that targeted programs may work differentially should be considered. Indeed, even the impacts of significant brain injury appear to be modified by a parent-based intervention(32); but given the lack of interaction here, it may be that targeted interventions, rather than broad changes to environment reducing overall social deprivation , may be needed.(32)

The finding of possible interaction for just two domains (autism and dyslexia) should be interpreted with caution. Learning difficulties, including autism and dyslexia, are diagnoses more likely to be made at school age and a significant proportion of our cohort were under 5 years old. However, there is evidence autism can be reliably diagnosed in preschool children(34). Autistic spectrum disorder and their traits(35) have been reported as more common in preterm children although some studies have suggested this may be due to confounding (36). Equally, some work has suggested a relationship between deprivation and increased risk of autism(37), but others have not(38). These findings may reflect differences in access to services or clinician bias. In this work, the lack of an association between deprivation and autism in preterm children may represent a real finding, the effect of prematurity outweighing that of deprivation or a relative lack of diagnosis in this vulnerable group and warrants further investigation. The reduction in dyslexia, as deprivation increases, in preterm infants shown in our model should also be interpreted cautiously.t. Decreased SES is associated with poorer language outcomes(39), as is premature birth(40). This finding may represent an underdiagnosis in more deprived areas, or diagnosis being related to educational level; confirmation of this finding would be important, alongside deeper investigation into its possible implications.

Conclusion

While there remains an association between living in a deprived area and learning difficulties, this doesn't appear to be disproportionately worse in those children born preterm. Preterm birth is the single biggest impact on the risks seen for developing learning difficulties, requiring a SEN and having behavioural problems, in this cohort, but these risks increase further in those preterm-born children living in the most deprived areas. We also identified interactions with autism and dyslexia and the role of gestational age at birth and the social deprivation in their local environment, which may identify groups with unmet need.

However, preterm infants in deprived areas have the highest individual risks of all groups investigated and represent a group in which evidence-based targeted interventions, both neurodevelopmental and socioeconomic, may have a substantial impact.

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Statements and Declarations

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose

Availability of data and material

As per the ethical approval given for this research, all data must be held securely at Cardiff University. Anonymous data will be available from the Child Health department at Cardiff University to bona fide researchers as long as ethical approval is obtained from a research ethics committee in the UK for any suggested studies. Requests for data access should be sent to Sailesh Kotecha (Kotechas@cardiff.ac.uk)

Code availability

All statistical analyses were performed using Stata/SE 16.1 (Statacorp LLC). Syntax is available upon request from the corresponding author.

Author contributions

Thomas Isaac conceived and designed this work, wrote statistical analysis plan, cleaned and analysed data, drafted first manuscript, revised draft manuscript and edited and updated final paper

David Odd conceived and designed this work, wrote statistical analysis plan, analysed data and drafted first manuscript, revised draft manuscript and edited and updated final paper

Martin Edwards, Sarah Kotecha and Sailesh Kotecha conceived, designed, performed original RANOP study including data collection, revised draft manuscript and edited and updated final paper

Mallinath Chakraborty and Dawn Odd revised draft manuscript and edited and updated final paper

Ethical approval

Ethical approval was sought at initiation of the RANOPS and approved by South East Wales Research Ethics Committee (Research Ethics Committee 12/WA/0155 Project 91349.

Consent to participate

Parents/guardians provided written consent to participate for their children.

Consent to publication

Not applicable. Individual data or images have not been published.

References

1. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob. 2019;7(1):e37-e46.
2. Platt MJ. Outcomes in preterm infants. Pub Health. 2014;128(5):399-403.
3. Moser K, Macfarlane A, Chow YH, Hilder L, Dattani N. Introducing new data on gestation-specific infant mortality among babies born in 2005 in England and Wales. Health Stat Q. 2007;35(35):13-27.
4. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ. 2012;345:e7976.
5. Pierrat V, Marchand-Martin L, Arnaud C, Kaminski M, Resche-Rigon M, Lebeaux C, et al. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. BMJ. 2017;358:j3448.
6. Litt J. EPICE cohort: 2-year neurodevelopmental outcomes after very preterm birth. Arch. Dis. Child. Fetal Neonatal Ed. 2020;105(4):344-5.
7. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early Childhood Development of Late-Preterm Infants: A Systematic Review. Pediatrics. 2011;127(6):1111-24.
8. Pettinger KJ, Kelly B, Sheldon TA, Mon-Williams M, Wright J, Hill LJB. Starting school: educational development as a function of age of entry and prematurity. Arch Dis Child. 2020;105(2):160-5.
9. Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol. 2008;21(2):123-8.
10. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA. 2002;288(6):728-37.
11. Odd D, Evans D, Emond AM. Prediction of school outcome after preterm birth: a cohort study. Arch Dis Child. 2019;104(4):348-53.
12. Odd DE, Emond A, Whitelaw A. Long-term cognitive outcomes of infants born moderately and late preterm. Dev Med Child Neurol. 2012;54(8):704-9.
13. Peacock PJ, Henderson J, Odd D, Emond A. Early school attainment in late-preterm infants. Arch Dis Child. 2012;97(2):118-20.
14. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379(9814):445-52.
15. Weightman AL, Morgan HE, Shepherd MA, Kitcher H, Roberts C, Dunstan FD. Social inequality and infant health in the UK: systematic review and meta-analyses. BMJ Open. 2012;2(3).
16. Hesselman S, Wikström AK, Skalkidou A, Sundström-Poromaa I, Wikman A. Neighborhood deprivation and adverse perinatal outcomes in Sweden: A population-based register study. Acta Obstet Gynecol Scand. 2019;98(8):1004-13.
17. Smith LK, Manktelow BN, Draper ES, Springett A, Field DJ. Nature of socioeconomic inequalities in neonatal mortality: population based study. BMJ. 2010;341:c6654.
18. Emerson E. Deprivation, ethnicity and the prevalence of intellectual and developmental disabilities. J. Epidemiology Community Health. 2012;66(3):218-24.
19. Leonard H, Petterson B, De Klerk N, Zubrick SR, Glasson E, Sanders R, et al. Association of sociodemographic characteristics of children with intellectual disability in Western Australia. Soc. Sci. Med. . 2005;60(7):1499-513.

20. Wong HS, Edwards P. Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. Matern. Child health J. . 2013;17(9):1689-700.
21. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight: A Systematic Review. JAMA Pediatrics. 2015;169(12):1162-72.
22. Richards JL, Chapple-McGruder T, Williams BL, Kramer MR. Does neighborhood deprivation modify the effect of preterm birth on children's first grade academic performance? Soc. Sci. Med. . 2015;132:122-31.
23. Ekeus C, Lindström K, Lindblad F, Rasmussen F, Hjern A. Preterm Birth, Social Disadvantage, and Cognitive Competence in Swedish 18- to 19-Year-Old Men. Pediatrics. 2010;125(1):e67-e73.
24. Potijk MR, Kerstjens JM, Bos AF, Reijneveld SA, de Winter AF. Developmental delay in moderately preterm-born children with low socioeconomic status: risks multiply. J Pediatr. 2013;163(5):1289-95.
25. Beauregard JL, Drews-Botsch C, Sales JM, Flanders WD, Kramer MR. Preterm Birth, Poverty, and Cognitive Development. Pediatrics. 2018;141(1):e20170509.
26. Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Management of Prematurity-Associated Wheeze and Its Association with Atopy. PLoS One. 2016;11(5):e0155695.
27. Edwards M, Kotecha S, Lowe J, Watkins WJ, Henderson AJ, Kotecha S. Respiratory and neurological outcomes in children born preterm study (RANOPs): Preterm outcomes. Eur Respir J. 2014;44(Suppl 58):P1253.
28. Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Early-term birth is a risk factor for wheezing in childhood: A cross-sectional population study. J Allergy Clin Immunol. 2015;136(3):581-7.e2.
29. WIMD 2014 Executive Summary 2014 [Available from: https://gov.wales/sites/default/files/statistics-and-research/2019-05/welsh-index-of-multiple-deprivation-wimd-2014-executive-summary.pdf.
30. Mackenbach JP. Health and deprivation. Inequality and the North: by P. Townsend, P. Phillimore and A. Beattie (eds.) Croom Helm Ltd, London, 1987 221 pp., ISBN 0-7099-4352-0, pound sign 8.95. Health Policy. 1988;10(2):207-6.
31. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-Analysis of Neurobehavioral Outcomes in Very Preterm and/or Very Low Birth Weight Children. Pediatrics. 2009;124(2):717-28.
32. Benavente-Fernández I, Synnes A, Grunau RE, Chau V, Ramraj C, Glass T, et al. Association of Socioeconomic Status and Brain Injury With Neurodevelopmental Outcomes of Very Preterm Children. JAMA Netw. Open. 2019;2(5):e192914-e.
33. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane Database of Syst Rev. 2015(11).
34. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007;120(5):1183-215.
35. Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis. Pediatrics. 2018;142(3):e20180134.
36. Maimburg RD, Væth M. Perinatal risk factors and infantile autism. Acta Psychiatrica Scandinavica. 2006;114(4):257-64.
37. Xinjun Li and Cecilia Sjöstedt and Kristina Sundquist and Bengt Zöller and Jan S. Neighborhood deprivation and childhood autism: A nationwide study from Sweden. J of Psych Res. 2014;53:187-92.
38. Thomas P, Zahorodny W, Peng B, Kim S, Jani N, Halperin W, et al. The association of autism diagnosis with socioeconomic status. Autism. 2012;16(2):201-13.

39. Peterson RL, Pennington BF. Developmental Dyslexia. Annu Rev of Clin Psychol. 2015;11(1):283-307.
40. Ene D, Der G, Fletcher-Watson S, O'Carroll S, MacKenzie G, Higgins M, et al. Associations of Socioeconomic Deprivation and Preterm Birth With Speech, Language, and Communication Concerns Among Children Aged 27 to 30 Months. JAMA Netw. Open. 2019;2(9):e1911027-e.

Table 1. Characteristics of study group split by gestational age and deprivation measure

Measure	Number with data	Preterm (n=4023)	Term (n=2668)	P value	1st and 2nd WIMD decile (Most deprived) (n=1158)	3rd and 4th (n=1322)	5th and 6th (n=1397)	7th and 8th (n=1348)	9th and 10th (Least Deprived) (n=1466)	P value
Demographic										
Maternal age (years)	5956	30.2 (6.0)	30.4 (5.6)	0.3*	28.105 (6.1)	29.040(6.1)	30.503(5.7)	31.223(5.3)	31.979(5.2)	<0.001†
Sex (Male)	6691	2223 (55.3%)	1408 (52.8%)	0.05	626 (54.1%)	719 (54.4%)	766 (54.8%)	749 (55.6%)	771 (52.6%)	0.6
Ethnic minority groups	5974	214 (6.0%)	148 (6.1%)	0.8	94 (8.9%)	81 (6.7%)	47 (3.8%)	63 (5.3%)	77 (5.9%)	<0.001
Age at survey (y)-median (IQR)	6691 (100%)	5 (5)	5 (5)	0.4**	3 (5)	5 (5)	4(5)	4 (5)	4 (5)	0.008††
Pregnancy										
Smoking in pregnancy	6409	541 (14.0%)	299 (11.8%)	0.03	270 (24.4%)	223 (17.6%)	159 (11.8%)	104 (8.1%)	84 (6.0%)	<0.001
Multiple pregnancy	6691	894 (22.2%)	41 (1.5%)	<0.001	133 (11.5%)	194 (14.7%)	179 (12.8%)	197 (14.6%)	232 (15.8%)	0.01
Mode of Delivery	5956			<0.001						<0.001
Normal Vaginal Delivery		1494 (41.7%)	1446 (61.0%)		564 (53.7%)	589 (49.7%)	605 (49.2%)	559 (47.2%)	623 (47.6%)	
Breech		83 (2.3%)	10 (0.42%)		21 (2.0%)	19 (1.6%)	19 (1.6%)	17 (1.4%)	17 (1.3%)	
Instrumental		270 (7.5%)	279 (11.8%)		64 (6.1%)	107 (9.0%)	115 (9.4%)	114 (9.6%)	149 (11.4%)	
Elective CS		553 (15.4%)	307 (13.0%)		133 (12.7%)	193 (16.3%)	172 (14.0%)	154 (13.0%)	208 (15.9%)	
Unplanned CS		1185 (33.0%)	329 (13.9%)		268 (25.5%)	277 (23.4%)	318 (25.9%)	338 (28.6%)	313 (23.9%)	
Infant and postpartum										
Birthweight (kg)	6691	2.216 (0.63)	3.439 (0.48)	<0.0001*	2.616 (0.8238)	2.668 (0.8234)	2.713 (0.8049)	2.762 (0.8439)	2.744 (0.8428)	<0.0001†
Breast feeding initiated at birth	5693	2050 (61.8%)	1630 (68.7%)	<0.001	468 (46.2%)	644 (57.6%)	806 (67.9%)	819 (73.1%)	943 (75.3%)	<0.001

Values are numbers (%) or mean (SD)unless otherwise stated. Comparisons are made by Chi^2 ,*t-test, †ANOVA, **Mann-Whitney U and ††Kruskal-Wallis, as appropriate

Table 2. Gestational age, and deprivation decile, and the risk of learning difficulties or developmental problems.

	Gestation					Deprivation by WIMD Decile					
	N total	**n per group**	**Preterm**	**Term**	**P value**	**1st and 2nd**	**3rd and 4th**	**5th and 6th**	**7th and 8th**	**9th and 10th**	**p_{trend}**
Learning Difficulties						Least				Most	
All Learning Difficulties	6691	541	421 (10.5%)	120 (4.5%)	<0.001	128 (23.7%)	112(20.7%)	110(20.3%)	91 (16.8%)	100 (18.5%)	<0.001
GDD*		149	128 (3.2%)	21(0.8%)	<0.001	36 (24.2%)	32 (21.5%)	29 (19.4%)	26 (17.5%)	26 (17.5%)	0.02
Speech/Communication		89	56 (1.4%)	24(0.9%)	0.07	20 (25%)	10 (12.5%)	27 (33.8%)	12 (15%)	11 (13.8%)	0.06
Autism		47	30 (0.8%)	17(0.6%)	0.6	11 (23.4%)	14 (29.8%)	12 (25.5%)	3 (6.4%)	7 (14.9%)	0.01
Learning difficulty (general)		201	162 (4.0%)	39(1.5%)	<0.001	53 (26.4%)	45 (23.4%)	32 (15.9%)	33 (16.4%)	38 (18.9%)	0.002
Dyslexia		65	46 (1.1%)	19 (0.7%)	0.08	8 (12.3%)	11 (16.9%)	10 (15.4%)	17 (26.1%)	19 (29.2%)	0.05
Other Outcomes											
Education Statement	3356	179	145 (7.3%)	34 (2.5%)	<0.001	42(23.5%)	38(21.2%)	40(22.3%)	25(14.0%)	34(19.0%)	0.001
Behavioural Problem	6672	611	456(11.3%)	155(5.8%)	<0.001	181(29.6%)	158(25.9%)	117(19.1%)	84(13.8%)	71(11.6%)	<0.001

Values are number (%)

***GDD= Global developmental delay**

Comparisons are by Chi^2 or extended Wilcoxon rank-sum test as appropriate.

Table 3. Associations between both gestational age, and deprivation measures, and developmental outcomes; along with measures of interaction/modification between the two exposures.

Neurodevelopmental Measure	Unadjusted model		Adjusted for demographics factors*		Adjusted for demographics* and clinical factors**	
	OR (95% CI)	**$P_{interaction}$**	**OR (95% CI)**	**$P_{interaction}$**	**OR (95% CI)**	**$P_{interaction}$**
Learning Difficulties	n=6691		n=5443		n=4563	
All Learning Difficulties						
Preterm birth	2.52 (2.04,3.12)	0.4	2.64 (2.07,3.37)	0.5	2.67 (2.02,3.53)	0.3
WIMD Decile	1.08 (1.04-1.11)		1.07 (1.03,1.11)		1.08 (1.03-1.12)	
GDD						
Prematurity	4.06 (2.55,6.46)	0.5	4.80 (2.79,8.28)	0.4	4.88 (2.73,8.74)	0.3
WIMD Decile	1.06 (1.00,1.13)		1.08 (1.01,1.15)		1.10 (1.02,1.18)	
Speech						
Preterm birth	1.53 (0.95,2.49)	0.2	1.58 (0.91,2.75)	0.2	1.53 (0.79,2.95)	0.2
WIMD Decile	1.09 (1.01,1.18)		1.09 (1.00,1.20)		1.04 (0.94,1.16)	
LD (general)						
Preterm birth	2.91 (2.04,4.17)	0.8	2.78 (1.83,4.23)	0.4	2.72 (1.68,4.40)	0.5
WIMD Decile	1.10 (1.04,1.16)		1.07 (1.01,1.14)		1.07 (1.00,1.15)	
Autism						
Preterm birth	1.14 (0.63,2.08)	0.2	1.00 (0.52,1.91)	0.04	0.94 (0.44,2.12)	0.02
WIMD Decile	1.14 (1.03,1.27)		1.18 (1.04,1.34)		1.23 (1.06,1.40)	
Dyslexia						
Preterm birth	1.72 (1.001,2.96)	0.02	2.14 (1.12,4.08)	0.04	2.38 (1.08,5.23)	0.05
WIMD Decile	0.94 (0.86,1.02)		0.87 (0.78,0.97)		0.90 (0.80,1.02)	
Educational Statement	n=3356		n=2594		n=2062	
Preterm birth	2.99 (2.04,4.38)	0.2	2.68 (1.75,4.11)	0.6	2.44 (1.50,3.98)	0.5
WIMD Decile	1.09 (1.03,1.15)		1.11 (1.05,1.19)		1.14 (1.06,1.23)	
Educational statement in Children with Learning Difficulties	n=389		n=291		n=231	
Preterm birth	1.45 (0.87,2.43)	0.8	1.26 (0.70,2.29)	0.4	1.06 (0.54,2.11)	0.6
WIMD Decile	1.04 (0.97,1.12)		1.13 (1.04,1.25)		1.14 (1.02,1.28)	
Behavioural problems	n=6672		n=5429		n=4550	
Preterm birth	2.01 (1.67,2.44)	0.1	2.14 (1.73,2.67)	0.1	2.07 (1.62,2.65)	0.3
WIMD Decile	1.19 (1.15,1.22)		1.14 (1.11,1.19)		1.11 (1.07,1.16)	

Values are OR (95% CI) from the multi-level logistic regression model (random effects variable was the age at the time of the survey).* Adjusted for maternal age at birth, sex and ethnicity ** Adjusted for smoking in pregnancy, multiple births, mode of delivery, birthweight and whether breast feeding was initiated at birth

Figure Legends

Figure 1- Percentage of children living in each WIMD decile split by preterm and term birth. P value reported are p for trend.

Figure 2- Proportion of children with a learning difficulty by gestational age in weeks and WIMD decile

Figures

Figure 1

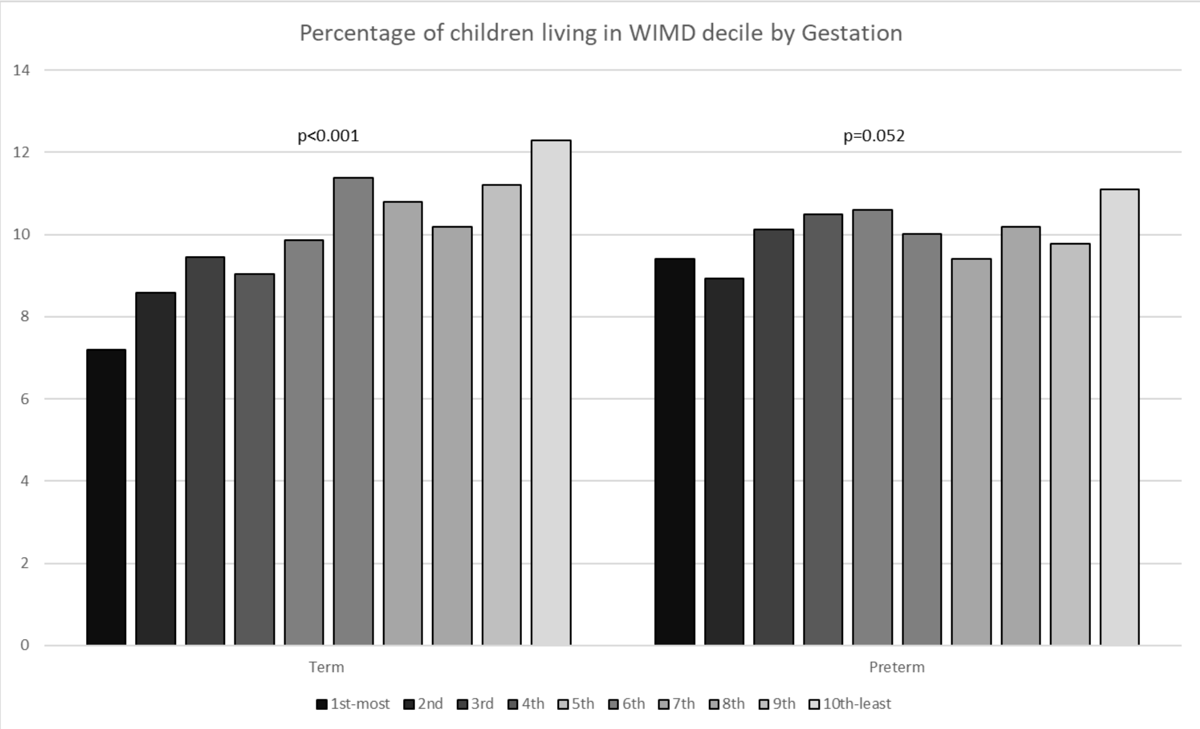
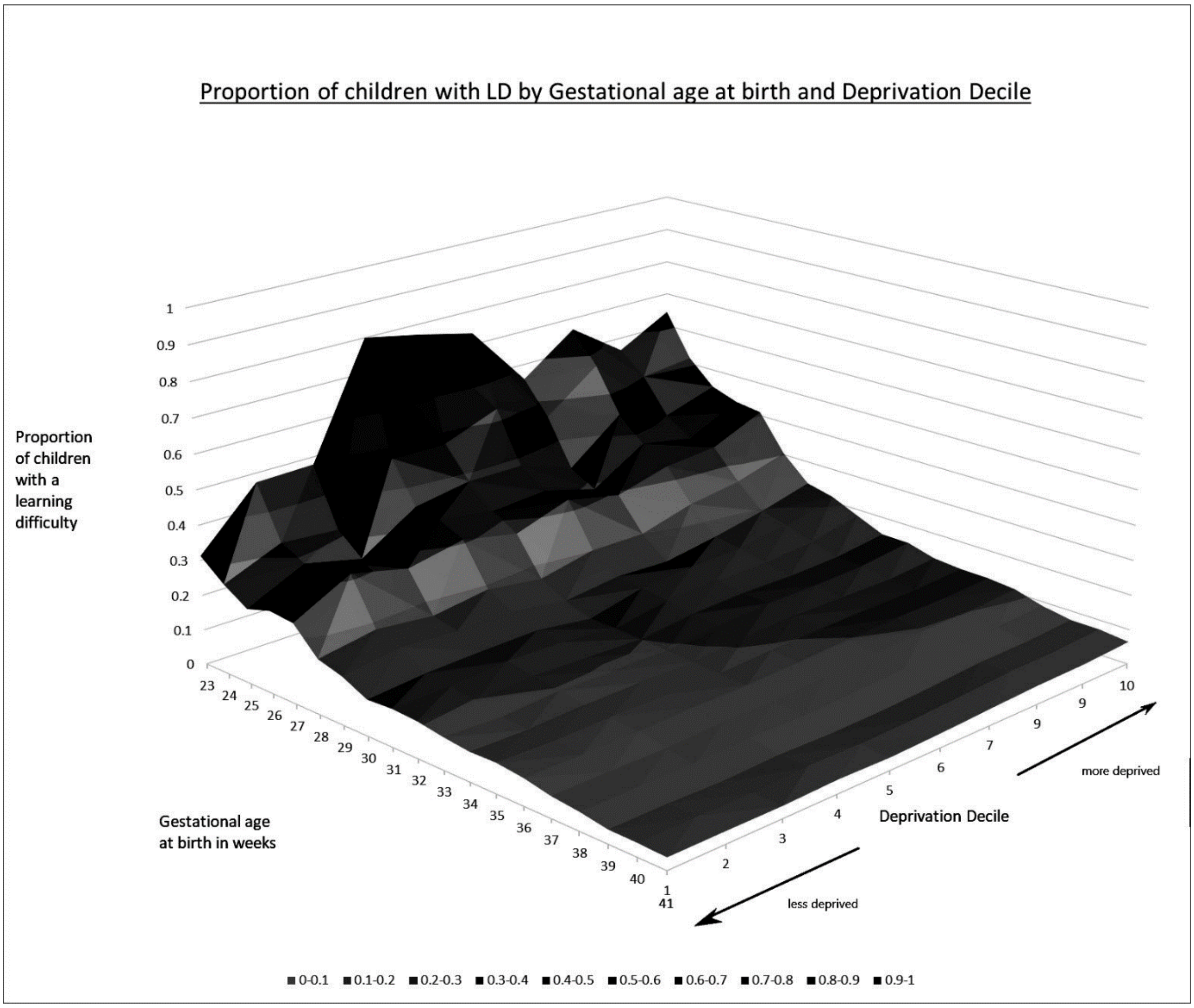
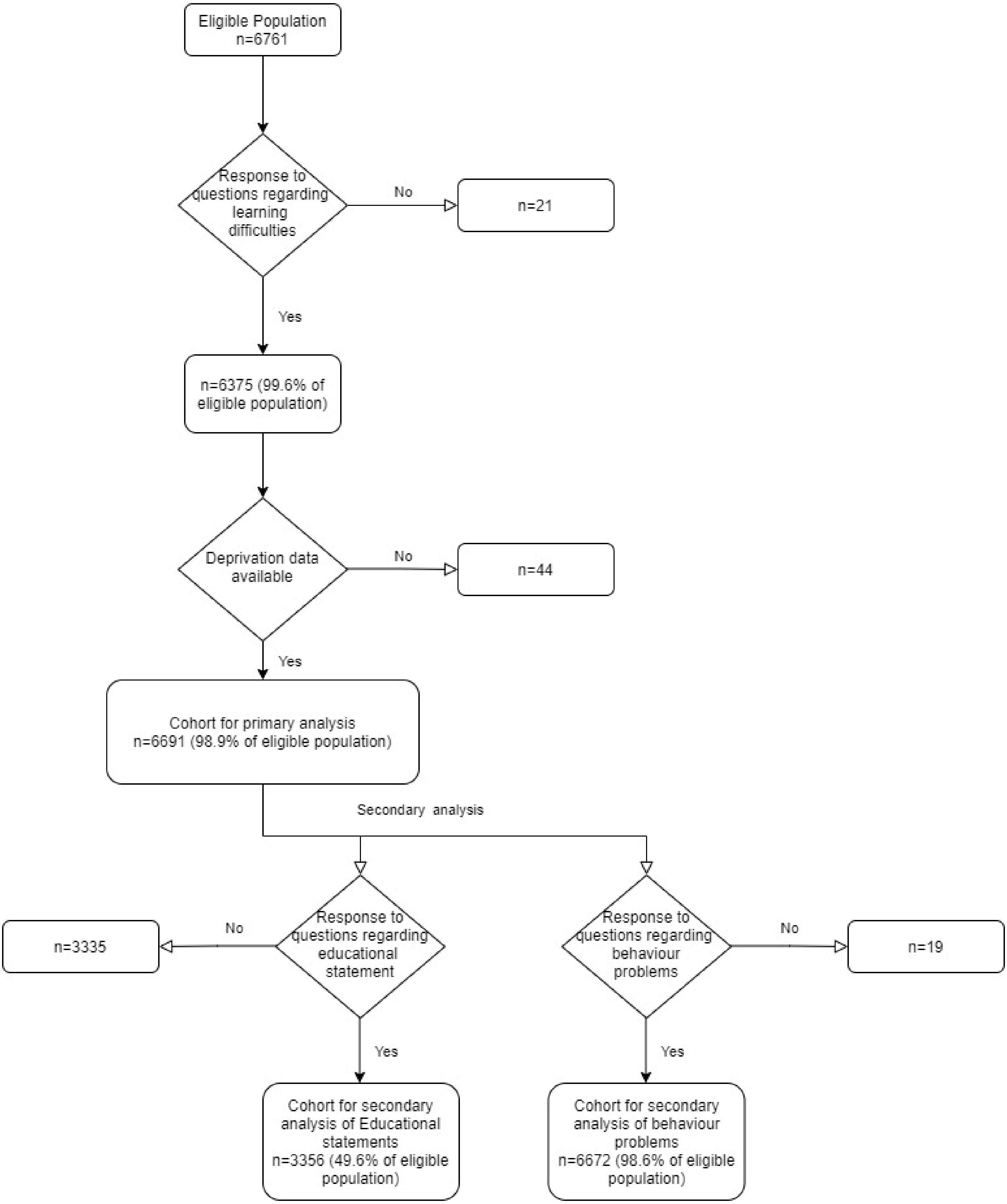


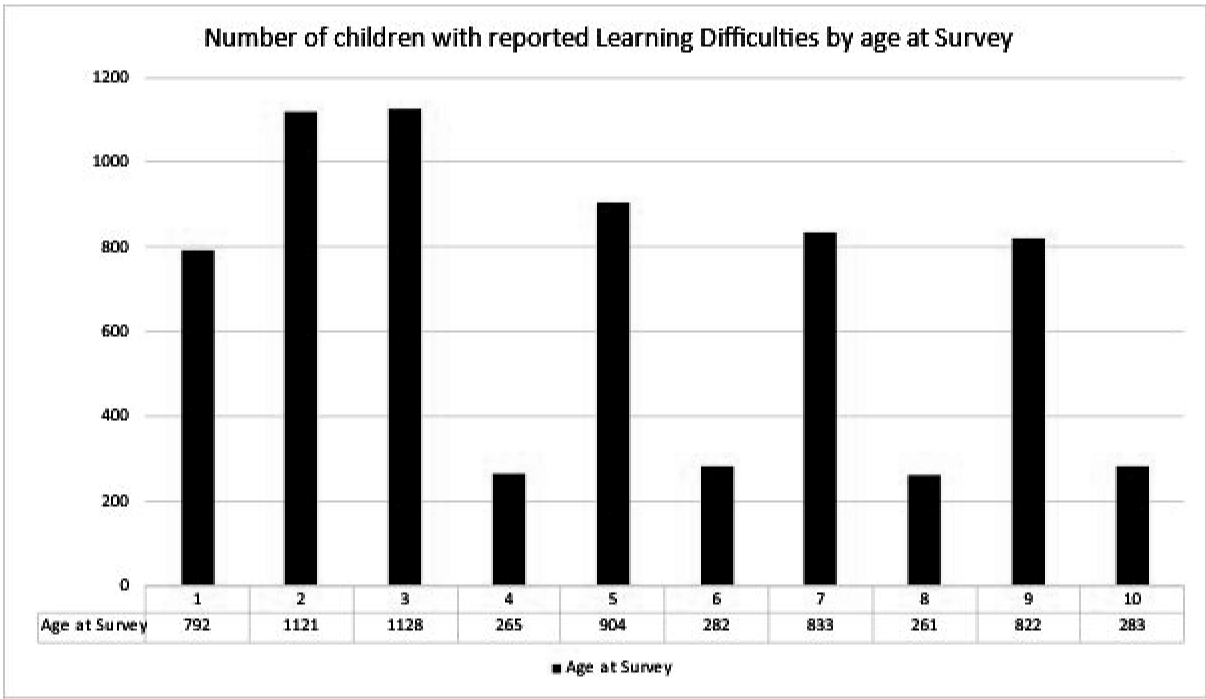
Figure 2


Proportion of children with LD by Gestational age at birth and Deprivation Decile
Proportion of children with a learning difficulty
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Gestational age at birth in weeks
1 2 3 4 5 6 7 9 9 10
Deprivation Decile
more deprived
less deprived
0-0.1 0.1-0.2 0.2-0.3 0.3-0.4 0.4-0.5 0.5-0.6 0.6-0.7 0.7-0.8 0.8-0.9 0.9-1

Appendix 1. Study Population and generation of the cohort for analysis



Appendix 2- Data regarding Age at time of survey in combined tabular and graphical format



Appendix 3- Comparison of Responders and Non Responders in the original study

Measure	**Responders** n=7149	**Non-Responders** n=19593	**p**
Preterm	**4284 (59.9%)**	**9090 (46.4%)**	**<0.001**
Living in most deprived 50%	**3357 (47.0%)**	**12068 (61.6%)**	**<0.001**
Age at time of survey (All) Preterm Term	**4.7 (2.8)** **4.7 (2.8)** **4.8 (2.9)**	**5.3 (2.8)** **5.3 (2.8)** **5.3 (2.8)**	**<0.001** **<0.001** **<0.001**
Male Sex	**3862 (54.0%)**	**10666 (54.4%)**	**0.6**
Birthweight in kg	**2.74 (0.86)**	**2.91 (0.81)**	**<0.001**

Numbers are number (%) or mean (SD) as appropriate.

Appendix 4. Comparison of Eligible cohort to those excluded

Measure	Analysed cohort (n=6761)	Participants with missing data (n=70)	p
Preterm	4023 (60.1%)	38 (54.3%)	0.3
Maternal age in years	30.256 (5.8)	30.375 (6.3)	0.9
Minority ethnicity	362 (6.1%)	1 (1.6%)	0.1
Male sex	3631 (54.3%)	28 (40.0%)	0.02
Smoking during pregnancy	840 (13.1%)	11 (16.2%)	0.5
Breastfeeding initiated at birth	3680 (55.0%)	32 (45.7%)	0.1
Delivery by NVD	2940 (49.4%)	30 (46.9%)	0.4

Numbers are number (%) or mean (SD) as appropriate.

Appendix 5. Number of children with Learning disability split by gestational group and deciles of deprivation measure (WIMD), combined deciles and groups to reduce identifiability

Deprivation Decile	Term (>37 weeks)	Late preterm (36 weeks)	Moderate preterm (32 to 35 weeks)	Very preterm (28 to 31 weeks)	Extreme preterm (less than 28 weeks)
9th/10th (Least Deprived)	22 (3.51%)	22 (7.33%)	32 (9.58%)	13 (9.35%)	11 (16.92%)
7th/8th	23 (4.11%)	19 (7.04%)	22 (6.73%)	12 (8.11%)	15 (34.88%)
5th/6th	20 (3.53%)	24 (8.82%)	41 (11.29%)	17 (11.11%)	8 (19.04%)
3rd/4th	23 (4.67%)	25 (8.47%)	36 (10.43%)	17 (12.59%)	11 (20.37%)
1st/2nd (Most Deprived)	32 (7.60%)	21 (8.30%)	38 (12.62%)	21 (15.91%)	16 (31.37%)

Values are number (%)