The cost of Neonatal Abstinence Syndrome: an economic analysis of English national data held in the National Neonatal Research Database

Philippa Rees MBBCh MPhil[1], Ben Carter PhD[2], Chris Gale PhD[3], Stavros Petrou PhD[4], Beverley Botting PhD[1], Alastair Sutcliffe PhD[1]

Affiliations:
1. Population Policy and Practice, Institute of Child Health University College London, London, UK

2. Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

3. Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, Chelsea and Westminster campus, London, UK

4. Nuffield Department of Primary Care and Health Science, Oxford University, Oxford, UK

Address correspondence to: Dr Philippa Rees, Population Policy Practice 1st Floor, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London, WC1N 1EH.
Tel: +44 7794669436
E-mail: p.rees@ucl.ac.uk

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Author contributions:
Dr Rees designed the study, undertook the analysis, interpreted the data, and drafted and revised the manuscript.
Dr Carter was the lead statistician; he was involved in the analysis and interpretation of data, and revising the manuscript for important intellectual content.
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Dr Botting was involved in the concept and design of the study, interpretation of results, supervision of the study, and revising the manuscript for intellectually important content.
Professor Petrou was the study health economist; he was involved in the concept and design of the study, interpretation of results, supervision of the study, and revising the manuscript for intellectually important content.
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Objective: To determine the incidence of Neonatal Abstinence Syndrome (NAS) across neonatal units, explore healthcare utilisation and estimate the direct cost to the NHS.

Design: Population cohort study.

Setting: NHS neonatal units, using data held in the National Neonatal Research Database.

Participants: Infants born between 2012-2017, admitted to a neonatal unit in England, receiving a diagnosis of NAS (n=6411).

Main outcome measures: Incidence, direct annual cost of care (£, 2016-17 prices), duration of neonatal unit stay (discharge hazard ratio), predicted additional cost of care, and odds of receiving pharmacotherapy.

Results: Of 524,334 infants admitted during the study period, 6,411 had NAS. The incidence (1.6/1000 live births) increased between 2012-2017 (β 0.07 95%CI (0, 0.14)) accounting for 12/1000 admissions and 23/1000 cot days nationally. The direct cost of care was £62,646,661 over the study period. Almost half of infants received pharmacotherapy (n=2631; 49%) and their time-to-discharge was significantly longer (median 18.2 versus 5.1 days; adjusted Hazard Ratio (aHR) 0.16 95%CI (0.15, 0.17)). Time-to-discharge was longer for formula-fed infants (aHR 0.73 (0.66, 0.81)), and those discharged to foster care (aHR 0.77 (0.72, 0.82)). The greatest predictor of additional care costs was receipt of pharmacotherapy (additional mean adjusted cost of £8,420 per infant).

Conclusions: This population study highlights the substantial cot usage and economic costs of caring for infants with NAS on neonatal units. A shift in how healthcare systems provide routine care for NAS could benefit infants and families whilst alleviating the burden on services.

INTRODUCTION

Neonatal abstinence syndrome (NAS) is a clinical withdrawal syndrome experienced by babies when exposure to certain substances that cross the placenta is abruptly halted after birth. [1 2] These substances include illicit opioids such as heroin, maintenance opioids such as methadone, and prescription medications such as codeine.[1 2] Clinically, these infants require monitoring for withdrawal symptoms and those with severe symptoms require treatment with opioids, anticonvulsants or sedatives.

NAS has become a global public health problem.[3 4 5] Putative explanations for the rise in NAS include the effects of economic downturns leading to increased illicit drug use, increased prescription of opioids in pregnancy, and the development of new and more potent opioids.[2 6 7] Affected countries have seen increasing healthcare resource use amongst this population, with high accompanying costs of care. In the USA neonatal unit admissions for NAS have increased from 7 to 27 per 1000 admissions, and they accounted for 4% of USA neonatal intensive bed days in 2013.[8]

The neonatal care component of NAS has not been described at a national level in the UK. We therefore determined the incidence of NAS across neonatal units in England, characterised healthcare utilisation and explored the associated healthcare costs with a view to estimating the economic burden of NAS.

METHODS

We conducted a retrospective observational cohort study of all infants admitted to a neonatal unit in England, born between January 1st 2012 and December 31st 2017, who received a diagnosis of NAS. The study objectives were:

- To explore the characteristics of infants affected by NAS on the neonatal unit
- To determine the annual incidence of NAS on neonatal units
- To calculate the annual direct cost of neonatal unit care for infants with NAS
- To explore factors associated with time-to-discharge, increased cost of care, and pharmacotherapy on the neonatal unit

This study received Research Ethics Committee approval (18/LO/0665). We followed an a-priori protocol (available on request).

The database

Data were extracted from the National Neonatal Research Database (NNRD), which holds data from all infants admitted to NHS neonatal units in England since 2012. The NNRD includes over 450 defined data items. Validation studies have confirmed data completeness and accuracy.[9-11] All variables pertaining to our included study population were obtained from the NNRD.[12] The neonatal dataset is a clinical dataset within the NHS data dictionary searchable at the following webpage:
https://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_neonatal_data_set/national_neonatal_data_set_-_episodic_and_daily_care_fr.asp?shownav=1

Study population

The study included infants who had observable NAS (signs and symptoms that may or may not require pharmacological treatment) at any point during their stay (Supplement 1). This included admission and discharge diagnoses of NAS identified through ICD 10 codes, (with a positive predictive value of 91% for NAS) in keeping with previous population studies.[4 6 13-16] All such infants were included in incidence figures. However, those with major co-morbidities were excluded from subsequent analyses, as their admission was likely attributable to other factors. These included preterm infants (<34 weeks), infants with low birth weights (<1800g), confirmed sepsis, and brain injuries.[17]

Data analysis

The characteristics of included infants with NAS and their mothers were explored using descriptive statistics and compared to the general population using publicly available data. Incidence was determined by dividing the number of NAS cases by the number of live births in England annually. The proportion of NAS admissions per 1,000 and attributable cot days were calculated using denominator data from the NNRD. A linear regression was fitted to estimate the change in incidence over time with 95% Confidence Intervals (CIs). Time-to-discharge from the neonatal unit was examined using the Kaplan-Meier plot of survival function for covariates detailed in Table 1. Covariates were chosen on the basis of clinical importance and as mediators of the study outcomes.

Health economic costing

The annual direct costs of care were calculated using NHS reference costs, valued at 2016-2017, for the number of cot days, the highest level of daily care, and the number of inter-hospital transfers.[18] This was done using daily data, which includes Healthcare Resource Group (HRG) codes for the highest level of care received by individual infants each day, and episodic data. NHS reference costs are calculated on a full absorption basis accounting for variable costs such as drugs and consumables, semi-fixed costs such as staff and fixed costs such as depreciation.[18] NHS reference costs do not account for non-routine investigations or high-cost treatments. However, these are not generally required for the monitoring or treatment of NAS. Linked maternity data were unavailable for the infants with NAS.

Statistical analysis

Using a semi-parametric Cox proportional baseline hazards model, fitting hospital as a frailty (random intercept effect), the time-to-discharge was analysed with the covariates. The proportionality assumption was evaluated visually using log-log plots. Both crude hazard ratios

(HRs) and adjusted HRs (aHR) were estimated and presented alongside 95% CIs. Total cost data were transformed using a natural logarithm [$\log_n$(cost)]. All analyses were undertaken on this scale. Total cost was fitted using a mixed-effects linear model, with a random intercept for hospital. A crude mean difference, alongside the adjusted mean difference was fitted in a multivariable linear model. Crude and adjusted log additional costs were reported with 95% CIs, alongside back-transformed costs. A mixed effect logistic regression model was used to explore the characteristics associated with receipt of pharmacotherapy for NAS. Missing items were coded as unknown. An intention-to-treat population was used for all analyses.

RESULTS

During the study period 524,334 infants were admitted to neonatal units across England (Supplement 2). Of these, 6,411 met our definition for NAS. Infants were predominantly term with a median gestational age of 38 weeks and birth weight of 2820g.

Incidence and healthcare utilisation

Between 2012-2017, the incidence of NAS across neonatal units increased from 1.49 to 1.91 per 1000 live births (β 0.07; 95%CI (0, 0.14)) (Supplement 3). A sensitivity analysis (excluding 2017 data) suggested a true increasing incidence (β 0.28 95%CI (-0.01, 0.07)). During this time, 1.2% of infants admitted to the neonatal unit were diagnosed with NAS, accounting for 2.3% of neonatal unit cot days (Supplement 4).

Direct annual cost

Table 1 details the characteristics of infants with NAS but without major co-morbidities (n=5,336). Most infants (n=4951; 92.8%) had admission or discharge diagnoses related to NAS or social services involvement. The direct annual cost of care was £10,440,444, with a median cost of £7,715 per infant (Table 2). Although the incidence of NAS across neonatal units increased over the time period studied, the overall time-to-discharge reduced, therefore direct annual costs did not change.

Time-to-discharge

Most admissions to the neonatal unit occurred on the day of delivery (n=4070; 76.3%), at a median age of 4.2 hours (interquartile range 0.97 to 22 hours). The median time-to-discharge for infants with NAS was 10.2 days (interquartile range 4.8 to 20.0): reducing from 12 days in 2012 to 7.5 days in 2017. Time-to-discharge varied from a median of 12.4 days for those born to mothers who smoked, to a median of 7.6 days for those born to mothers who did not smoke (Figure 1). Additionally, those discharged to foster care had a median time-to-discharge of 14.9 days compared to 7.8 days for those discharged elsewhere (Figure 1). Infants receiving formula at discharge had a median time-to-discharge of 12 days compared to 6.2 days for those receiving mixed feeds and 5.1 days for those receiving breast milk (Figure 1). Also, infants receiving pharmacological treatment for NAS had a median time-to-discharge of 19.2 days compared to 5.1 days for those not receiving pharmacotherapy (Figure 1).

After fitting the Cox model, NAS pharmacotherapy was seen to be the most prominent characteristic associated with length of stay, with infants receiving pharmacotherapy staying considerably longer (aHR 0.16, (95%CI 0.15, 0.17)). Other factors significantly affecting hazard of discharge were: formula feed on discharge (aHR 0.73 (95%CI 0.66, 0.81)); and discharge to foster care (aHR 0.77 (95%CI 0.72, 0.82)) all leading to longer admissions (Table 3). Earlier gestation also significantly impacted hazard of discharge: those born 34-35 weeks had a lower hazard of discharge (aHR 0.51 (95%CI 0.45, 0.57)), although this was likely influenced by prematurity. There was no evidence of a breach in the baseline proportionality assumption.

These findings demonstrate that time-to-discharge was considerable longer due to factors associated with receiving NAS pharmacotherapy, which was mirrored in the total cost analysis. The additional adjusted cost of an infant requiring NAS pharmacotherapy was £8,420 (95%CI £7,164, £9,891): whereas those discharged to foster care were predicted to cost an additional £845 (95%CI £626, £1,113), and those receiving formula on discharge an additional £495 (95%CI £270, £782) (Table 3).

Pharmacotherapy

Almost half of infants admitted to a neonatal unit with NAS received pharmacotherapy (n=2631; 49%): reducing from 56% in 2012 to 40% in 2017. The mean duration of therapy was 7.5 days (SD 11.5). Of those receiving pharmacotherapy for NAS, the most common recorded medication was morphine (n=2521; 95.8%) (Supplement 5). Infants most likely to receive pharmacotherapy were: exposed to smoking in pregnancy (aOR 1.22 (95%CI 1.04, 1.43)); born to mothers resident in areas of high deprivation (IMD quintile 1)[12] (aOR 1.31 (95%CI 1, 1.71)); term infants (38-39 weeks) (aOR 1.95 (95%CI 1.57, 2.43)) or post-term infants (>40 weeks) (aOR 2.73 (95%CI 2.17, 3.43)). Receipt of pharmacotherapy was also associated with discharge to foster care (aOR 1.84 (95%CI 1.62, 2.1)) and formula feeds on discharge (aOR 2.72 (95%CI 2.21, 3.35)) (Table 4).

DISCUSSION

This is the first national study to model NAS associated healthcare utilisation in the UK. We highlight a steadily increasing incidence of infants with NAS admitted to neonatal units between 2012-2017. These admissions directly cost the NHS over £10 million annually and many were potentially avoidable.

Strengths and limitations

A key strength of this study is the population-level national coverage of NHS neonatal unit admissions afforded by using data held in the NNRD.[9] This enabled reliable ascertainment of neonatal unit data for infants with NAS although we could not reliably capture postnatal ward data. The extensive data held within the NNRD and the validity of that data enabled detailed analysis including health economic analyses.[8] The utility and reliability of the NNRD for economic analyses has been validated.[8] However, there is likely a degree of population heterogeneity. We excluded infants with major co-morbidities from our cost-analysis, however some remaining infants may have had additional diagnoses such as hypoglycaemia, impacting their admission. This could have led to an over-estimation of the attributable cost. Conversely, the number of cot days was derived from daily data, which include each completed 24-hour day. This would therefore not capture partial cot days, such as the day of discharge, underestimating costs. We did not have access to linked maternity data (e.g. maternal length of stay) nor antenatal information such as nature of drug use. There is therefore likely a degree of imprecision in the estimated costs presented.

Context of current literature

Davies et al. compared the incidence of NAS in four countries and found a relatively stable incidence across UK hospitals up to 2012 (2.7 /1000).[4] Our findings however show increasing numbers of infants admitted to neonatal units in England with NAS since 2012. This may represent a true increase in incidence, improved detection, or increasing proportions of admissions amongst the population.[4]

Our study highlights that infants who received formula on discharge had an increased odds of receiving pharmacotherapy and longer neonatal unit admissions. Breastfed infants have been consistently shown to have less severe NAS.[19-23] This is thought to be due to the presence of low-dose opioids in breast milk, in addition to the benefits of skin-to-skin contact and improved maternal bonding, which are considered non-pharmacological treatments.[19-24] Rates of breastfeeding amongst this population were low compared to the general population.[25] This may be underpinned by a range of factors including separation of mother and baby affecting lactation and bonding, lack of knowledge around breastfeeding safety in this context, and uncoordinated sucking seen in NAS.[26]

We highlight that term infants were more likely to receive pharmacotherapy. Preterm infants have been shown less likely to suffer from severe NAS.[4 22 27-30] This association may be the result of biased detection rates, as NAS scoring tools are not validated for use in preterms. Alternative explanations concern the relative immaturity of CNS development amongst preterm infants in conjunction with reduced total intra-uterine drug exposure and reduced placental transfer of opioids in early pregnancy.[28 29] Several studies have also highlighted an association between antenatal smoking and severe NAS, which is mirrored in our study, although the reason is unclear.[22 31-33] Discharge to foster care was associated with longer admissions and receipt of pharmacotherapy however the underpinning factors and direction of correlation are unclear.

Implications

This study highlights substantial direct costs of routinely caring for infants with NAS on the neonatal unit; many of these admissions may have been avoidable. The infants included in this study were admitted within hours of birth, despite NAS typically occurring after 24 hours, and only half received pharmacotherapy.[1] Therefore considerable neonatal unit bed days are potentially used for monitoring and discharge planning, activities that could take place on the postnatal ward. Neonatal unit care is a high-cost service that requires healthcare workers with high-level skills and specialist resources. There is a lack of evidence around the most appropriate care setting for infants with NAS.[24 26 34] Many argue that admission to neonatal units, with their high clinical activity and separation of baby and mother, can be detrimental to infants with NAS. There is increasing evidence that infants with NAS benefit from rooming-in: encouraging family-centred care, breastfeeding and skin-to-skin:[35 36] which in turn, can reduce need for pharmacotherapy, admission duration and economic costs.[24 34 36-40] In parts of the UK and USA, infants with NAS are cared for and even given pharmacotherapy (once on a stable dose) by carers in the community.[26 41] Testing of this approach in different contexts, to ensure safety and effectiveness, with a view to scaling-up and spreading nationally, could offer considerable benefits given that receipt of pharmacotherapy was associated with additional costs.[42]

Future research is needed to determine the optimum care environment for infants with NAS and to explore the feasibility of standardised transitional rather than neonatal unit care. The efficacy, safety and cost-effectiveness of such an approach would require evaluation. The potential cost-savings of this approach could be substantial particularly when considering additional savings from shorter admissions secondary to breastfeeding, bonding and skin-to-skin.[34]

CONCLUSION

This is the first national population-level study describing the cost of NAS in infants admitted to NHS neonatal units. Costs associated with caring for infants with NAS on the neonatal unit are substantial, and a proportion may be avoidable. A re-think of how healthcare systems provide routine care for NAS could benefit infants and families, alleviate the burden on neonatal services and produce substantial cost savings.

What is already known on this topic:

- The global opioid crisis has resulted in a NAS epidemic
- Infants with NAS require prolonged monitoring and sometimes treatment with opioids, anticonvulsants or sedatives
- The most appropriate care setting for infants with NAS, and the necessity of costly neonatal unit care is undetermined

What this study adds:

- Costs associated with caring for infants with NAS on the neonatal unit are substantial, a proportion may be avoidable, and receipt of pharmacotherapy was the greatest predictor of additional costs
- Future studies exploring the provision of pharmacotherapy outside of the neonatal unit are warranted
- Review of local and national policy is necessary to investigate the feasibility of standardised transitional rather than neonatal unit care for infants with NAS

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Figure 1: Kaplan-Meier plots of estimated time-to-discharge by maternal smoking status, discharge destination, discharge feeds and treatment group

Table 1: the characteristics of included infants with NAS (but without major comorbidities) and their mothers from the National Neonatal Research Database (NNRD) compared to the general population using Office for National Statistics (ONS) and NHS Digital data

Characteristics	Infants with NAS n=5336 (%)	General population* (%)
Birth weight	**NNRD**	**ONS, England 2015**
<1500g	0 (* <34 weeks excluded)	6,919 (1)
1500-2499g	1,188 (22.3)	39,503 (5.9)
2500-3999g	3959 (74.0)	534,671 (80.5)
>4000g	189 (3.5)	73,247 (11)
Gestation	**NNRD**	**ONS, England and Wales 2015**
34-35 weeks	443 (8.3)	17,100 (2.5)
36-37 weeks	1,324 (24.8)	70,768 (10.2)
38-39 weeks	2,097 (39.3)	265,773 (38.2)
>40 weeks	1,472 (27.6)	324,259(46.6)
Sex	**NNRD**	**ONS, England and Wales 2015**
Male	2,906 (54.5)	358,136 (51.3%)
Female	2,427 (45.5)	339,716 (48.7%)
Unknown	3 (0.1)	-
Smoking in pregnancy	**NNRD**	**Health & Social Care Information Centre, England 2014-2015**
Smoker	3,198 (59.9)	70, 879 (11.4)
Non-smoker	942 (17.7)	533,178 (85.6%)
Missing	1,196 (22.4)	18,586 (3%)
Maternal ethnicity	**NNRD**	**ONS, England and Wales 2015**
White	3,902 (73.1)	507, 829 (72.9)
Black	108 (2)	29,447 (4.2)
Asian	95 (1.8)	59,613 (8.6)
Mixed and other	120 (2.3)	77,435 (11.1)
Missing	1,111 (20.8)	22,041 (3.2)
Maternal age	**NNRD**	**ONS, England and Wales 2015**
<20 years	82 (1.5)	23,925 (3.5%)
20-24 years	586 (11.0)	107,603 (15.6%)
25-29 years	1,321 (24.8)	196,363 (28.5%)
30-34 years	1,669 (31.3)	214,870 (31.2%)
>35 years	1, 461(27.4)	146,990 (21.3%)
Missing	217 (4.07)	**-**
Index of multiple deprivation quintile	**NNRD**	**ONS, England 2015**
1 (most deprived)	2,141 (40.1)	177,794 (26.8)
2	1,151 (21.6)	150,445 (22.7)
3	732 (13.7)	125,666 (19.0)
4	478 (9.0)	111,210 (16.8)
5 (least deprived)	280 (5.3)	97,844 (14.8)
Missing	554 (10.4)	-
Feed on discharge	**NNRD**	**NHS Digital, England 2010 (infant feeding survey; feed at day 7)**
Breast milk exclusively and mixed	1,191 (22.3)	3,553 (72%)
Formula	3,904 (73.2)	1, 382 (28%)
Other	241 (4.5)	-

*England-only data used where available, where England-only data unavailable combined England and Wales data used. The groups may not sum to the total number of births for that year due to differences in the completeness of variables between data sources. The total births recorded within the ONS for each year also differ depending on the data source used.

Table 2: The direct and average costs of care for infants with NAS admitted to a neonatal unit in England between 2012-2017 (excluding infants with major co-morbidities other than NAS).

Year of birth	Total annual direct cost of care (£)	Mean cost of care per baby (£)	Median cost of care per baby (£)
2012	11,427,983	12,812	9,230
2013	11,569,927	13,178	9,455
2014	10,655,676	12,625	8,364
2015	9,445,081	11,311	7,346
2016	9,983,039	11,409	7,087
2017	9,560,955	9,448	5,593
Total direct cost	62,642,661	-	-
Mean direct cost over study period	10,440,444	11,740	7,715[Y]

[Y] median costs

Table 3: Cox proportional hazard of discharge, general linear modelling of costs for a subgroup of infants with NAS and crude and adjusted $\log_n$ transformed coefficients of additional costs of care for this subgroup (after excluding those with major co-morbidities and adjusting for hospital) *p<0.05 **p<0.01

Characteristic	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)$^{\gamma}$	Mean cost of care per patient (SD)	Mean adjusted additional cost of care per patient (95% CI)$^{\gamma}$	$\log_n$ transformed crude coefficient (95% CI)	$\log_n$ adjusted coefficient (95% CI)
Sex						
Male	1.01(0.96, 1.07)	0.97 (0.92, 1.03)	£11,764(12, 122)	£10 (-76, 122)	-0.01 (-0.06,0.4)	0 (-0.03, 0.04)
Female	Reference	Reference	£11,716 (11,547)	Reference	Reference	Reference
Smoking in pregnancy						
Non-smoker	Reference	Reference	£10,202 (12,772)	Reference	Reference	Reference
Smoker	0.7 (0.65, 0.76)**	0.87 (0.8, 0.94)**	£13,180 (12,095)	£344 (173, 563)*	0.36 (0.29, 0.43)*	0.11 (0.07, 0.16)**
Index of multiple deprivation quintile 2015						
1 (most deprived)	0.78 (0.68, 0.89**)	0.91 (0.8, 1.05)	£12,318 (12,107)	£115 (-110, 418)	0.25 (0.13, 0.38)**	0.04 (-0.04, 0.12)
2	0.81 (0.7, 0.93)	0.89 (0.77, 1.02)	£12,454 (12,899)	£186 (-55, 508)	0.22 (0.09, 0.34)**	0.06 (-0.02, 0.15)
3	0.85 (0.74, 0.98)	0.9 (0.78, 1.04)	£11,417 (11,633)	£170 (-75, 500)	0.16 (0.03, 0.3)*	0.06 (-0.03, 0.15)
4	0.95 (0.82, 1.11)	0.96 (0.82, 1.12)	£10,954 (11,193)	£35 (-199, 356)	0.07 (-0.08, 0.21)	0.01 (-0.08, 0.11)
5 (least deprived)	Reference	Reference	£9,611 (9,325)	Reference	Reference	Reference
Gestation						
34-35 weeks	0.97 (0.87, 1.08)*	0.51 (0.45,0.57)**	£11,803 (10,644)	£1,170 (811,1624)**	0.12 (0.01, 0.21)*	0.34 (0.28, 0.41)**

36-37 weeks	1.16 (1.07, 1.25)**	0.9 (0.83, 0.97)**	£10,512 (10,445)	£133 (-4, 311)	-0.14 (-0.21, -0.07)**	0.05 (0, 0.26)*
38-39 weeks	1.1 (1.02, 1.17)*	1.09 (1.02, 1.17)*	£11,792 (12,730)	-£145 (-229, -32)*	-0.12 (-0.18, -0.06)**	-0.05 (-0.09, -0.01)*
>40 weeks	Reference	Reference	£12,750 (12,030)	Reference	Reference	Reference
Ethnicity						
White	Reference	Reference	£12,157 (12,038)	Reference	Reference	Reference
Black	1.42 (1.16, 1.75)**	1.05 (0.85, 1.3)	£11,806 (12,734)	-£263 (-506, 88)	-0.31 (-0.5, -0.13)**	-0.1 (-0.22, 0.03)
Asian	0.82 (0.66, 1.01)	0.61 (0.49, 0.77)**	£15,593 (14,250)	£382 (-12, 922)	0.14 (-0.06, 0.33)	0.13 (0, 0.26)
Mixed	1.24 (0.99, 1.55)	1.24 (0.99, 1.55)	£11,692 (11,221)	£-146 (-438, 279)	-0.17 (-0.37, 0.04)	-0.05 (-0.19, 0.08)
Other	0.95 (0.68, 1.34)*	0.66 (0.47, 0.95)*	£15,101 (17,198)	£108 (-407, 899)	-0.02 (-0.34, 0.29)	0.04 (-0.17, 0.25)
Discharge to out of home/ foster care						
Not discharged to foster care	Reference	Reference	£10,080 (11,220)	Reference	Reference	Reference
Discharged to foster care	0.65 (0.61, 0.69)**	0.77 (0.72, 0.82)**	£15,226 (12,402)	£845 (626, 1113)	0.53 (0.48, 0.58)**	0.26 (0.22, 0.3)**
Maternal age						
<20 years	1.14 (0.9, 1.43)	1.16 (0.92, 1.47)	£8,951 (12,864)	-£341 (-598, 41)	-0.44 (-0.65, -0.12)**	-0.13 (-0.27, 0.01)
20-24 years	1.16 (1.05, 1.28)**	1.14 (1.03, 1.26)*	£10,655 (12,670)	-£198 (-317, -36)*	-0.18 (-0.27, -0.09)**	-0.07 (-0.13, -0.01)*
25-29 years	1.03 (0.96, 1.12)**	1.08 (1, 1.17)	£11,926 (11,662)	-£98 (-201, 38)	-0.06 (-0.13, 0.01)	-0.04 (-0.08, 0.01)
30-34 years	0.96 (0.9, 1.03)	1.04 (0.96, 1.11)	£12,275 (12,028)	£5 (-106, 150)	0.03 (-0.04, 0.1)	0 (-0.04, 0.05)

>35 years	Reference	Reference	£12,185 (11,617)	Reference	Reference	Reference
Discharge feed τ						
Breast milk	Reference	Reference	£6,463 (7,714)	Reference	Reference	Reference
Mixed	0.76 (0.69, 0.87)**	0.98 (0.87, 1.11)	£8,152 (9,567)	£95 (-98, 352)	0.18 (0.08, 0.29)**	0.03 (-0.04, 0.1)
Formula	0.47 (0.43, 0.52)**	0.73 (0.66, 0.81)**	£13,049 (12,326)	£495 (270, 782)**	0.6 (0.52, 0.69)**	0.16 (0.1, 0.22)**
NAS treatment						
No treatment	Reference	Reference	£4,725 (4,553)	Reference	Reference	Reference
Treatment	0.18 (0.17, 0.19)**	0.16 (0.15, 0.17)**	£18,951 (12,704)	£8,420 (7,164, 9,891)**	1.43 (1.4, 1.47)**	1.38 (1.34, 1.41)**

T ‘other’ feed type not included within the table due to low numbers

Y The covariates included within the multivariate model were sex, smoking status, IMD quintile, gestation, ethnicity, discharge to out of home care, maternal age, feed at discharge and NAS treatment

Table 4: Crude and adjusted Odds Ratios (ORs) for receipt of pharmacological treatment for NAS during neonatal stay (after excluding those with major co-morbidities) *p<0.05 **p<0.01

Characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)^{Y}
Sex		
Male	0.98 (0.88, 1.09)	1.02 (0.91, 1.15)
Female	Reference	Reference
Smoking in pregnancy		
Non-smoker	Reference	Reference
Smoker	1.72 (1.49, 2)**	1.22 (1.04, 1.43)*
Index of multiple deprivation quintile 2015		
1 (most deprived)	1.6 (1.24, 2.06)**	1.31 (1, 1.71)*
2	1.44 (1.1 1.87)**	1.25 (0.94, 1.65)
3	1.28 (0.97, 1.69)	1.17 (0.87, 1.57)
4	1.23 (0.92, 1.66)	1.15 (0.84, 1.58)
5 (lease deprived)	Reference	Reference
Gestation		
34-35 weeks	Reference	Reference
36-37 weeks	1.2 (0.96, 1.5)	1.4 (1.07, 1.7)*
38-39 weeks	1.61 (1.3, 1.98)**	1.95 (1.57, 2.43)**
>40 weeks	2.09 (1.68, 2.6)**	2.73 (2.17, 3.43)**
Maternal age		
<20 years	0.36 (0.22, 0.59)**	0.35 (0.21, 0.57)**
20-24 years	0.68 (0.56, 0.83)**	0.63 (0.51, 0.77)**
25-29 years	0.95 (0.82, 1.11)	0.91 (0.78, 1.07)

30-34 years	1.04 (0.9, 1.19)	1 (0.86, 1.16)
>35 years	Reference	Reference
Ethnicity		
White	Reference	Reference
Black	0.6 (0.4, 0.87)*	0.64 (0.42, 0.97)*
Asian	1.24 (0.82, 1.87)	1.38 (0.9, 2.12)
Mixed	0.76 (0.49, 1.17)	0.7 (0.44, 1.11)
Other	0.89 (0.46, 1.73)	1.09 (0.54, 2.19)
Discharge to out of home/ foster care		
Not discharged to foster care	Reference	Reference
Discharged to foster care	2.19 (1.95, 2.47)**	1.84 (1.62, 2.1)**
Discharge Feed $^{\tau}$		
Breast milk	Reference	Reference
Mixed	1.58 (1.23, 2.02)**	1.55 (1.2, 2)**
Formula	3.4 (2.79, 4.215)**	2.72 (2.21, 3.35)**

T ‘other’ feed type not included within the table due to low numbers
Y The covariates included within the multivariate model were sex, smoking status, IMD quintile, gestation, ethnicity, discharge to out of home care, maternal age, feed at discharge and NAS treatment