Reasons for Rehospitalization in Children Who Had Neonatal Abstinence Syndrome

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abstract

BACKGROUND AND OBJECTIVES: Neonatal abstinence syndrome (NAS) occurs after in utero exposure to opioids, but outcomes after the postnatal period are unclear. Our objectives were to characterize childhood hospitalization after NAS.

METHODS: Population-based linkage study of births, hospitalization, and death records of all children registered in New South Wales (NSW), Australia, between 2000 and 2011 to a maximum of 13 years. Infants with an *International Statistical Classification of Disease and Related Problems, 10th Edition, Australian Modification*, coding of NAS (P96.1, n = 3842) were compared with 1 018 421 live born infants without an NAS diagnosis.

RESULTS: Infants with NAS were more likely to be admitted into a nursery (odds ratio 15.6, 95% confidence interval: 14.5–16.8) and be hospitalized longer (10.0 vs 3.0 days). In childhood, they were more likely to be rehospitalized (1.6, 1.5–1.7), die during hospitalization (3.3, 2.1–5.1), and be hospitalized for assaults (15.2, 11.3–20.6), maltreatment (21.0, 14.3–30.9), poisoning (3.6, 2.6–4.8), and mental/behavioral (2.6, 2.1–3.2) and visual (2.9, 2.5-3.5) disorders. Mothers of infants with NAS were more likely to be Indigenous (6.4, 6.0–7.0), have no antenatal care (6.6, 5.9–7.4), and be socioeconomically deprived (1.6, 1.5–1.7). Regression analyses demonstrated that NAS was the most important predictor of admissions for maltreatment (odds ratio 4.5, 95% confidence interval: 3.4–6.1) and mental and behavioral disorders (2.3, 1.9–2.9), even after accounting for prematurity, maternal age, and Indigenous status.

CONCLUSIONS: Children with NAS are more likely to be rehospitalized during childhood for maltreatment, trauma, and mental and behavioral disorders even after accounting for prematurity. This continues to adolescence and emphasizes the critical need for continued support of this vulnerable group after resolution of NAS.

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WHAT'S KNOWN ON THIS SUBJECT: Infants with neonatal abstinence syndrome are hospitalized for longer after birth and are more likely to be from highly vulnerable families. Determining long-term outcomes is difficult because this is a large and chaotic population.

WHAT OUR STUDY ADDS: After neonatal abstinence syndrome, children are twice as likely to require hospitalization, to die in hospital, and be admitted for maltreatment, visual, mental, and behavioral problems. Strategies to reduce these risks will improve safety and outcomes of these vulnerable children.

Neonatal abstinence syndrome (NAS) results from in utero exposure to opioids.[1] Although the effects of NAS are usually short-term, poor childhood[2–4] outcomes have been described even though many infants with NAS are provided with intensive social and medical support immediately after birth.[5–7] Despite this, unfavorable social and environmental problems associated with parental drug use[8,9] make long-term health and social surveillance of these infants and families difficult to track after discharge from the hospital of birth. Adding to this is a rapid increase of NAS in many countries from both legal and illegal opioid exposure, which further compounds strain on available support services.[5,9]

The health of children after prenatal opioid exposure is thus unclear. Opioids may interfere with neurologic development, resulting in physiologic,[10] psychological,[11] and behavioral[11] dysfunction up to adolescence.[11] The addition of environmental stress, due to chaotic home environments, parental dysfunction, and economic deprivation such as poverty and malnutrition may further affect child health and development,[12,13] which in turn could lead to future and more serious adult outcomes, even until old age.[14]

Early identification and treatment of health issues in childhood in the important "first 1000 days from conception to 2 years of age" may significantly modulate adult health outcomes.[15] This is a particularly important concept for the vulnerable NAS population. Postnatal data for this population is difficult to obtain, and existing studies examine children born almost 2 decades ago, when management of perinatal drug exposure was different from contemporary care.[11] Current hospitalization data could therefore be used to identify specific areas of health care needs affecting this elusive population[16] and to develop strategies for improving the outcomes of children with NAS beyond the postnatal period.

In this study, linkage methods were used to determine the health of children beyond the postnatal period of NAS by combining perinatal, hospitalization, and mortality data for all infants born in the state of New South Wales (NSW), Australia, between 2000 and 2011. These results were compared with details from children without a diagnosis of NAS. We hypothesized that children with NAS would have increased risk of rehospitalization after discharge from the birth hospital and that hospitalization would be caused by external and potentially preventable factors such as trauma, accidents, and maltreatment.

METHODS

Study Design and Setting

This study analyzed linked information from routinely collected government population databases to obtain birth, hospitalization, and mortality data until December 2013 for all children born in NSW, Australia, between 2000 and 2011. We obtained hospitalization and mortality data from a minimum of 2 years to a maximum of 13 years of age. Similar databases are collected from every state in Australia, but only information for NSW children were used for this study.

Databases

Perinatal Data Collection of NSW

The Perinatal Data Collection (PDC) was used as the primary database and provides maternal, infant, and birth information for any child born in NSW to NSW and non-NSW residents. Notifications to the PDC are required for all births attended by a doctor or midwife, but registration is not compulsory. Differences between PDC and total registered live births varies between 0.4% and 5.0% depending on parental registration trends for any particular year.[17]

The Admitted Patient Data Collection

The Admitted Patient Data Collection (APDC) informs on all separations (discharges, transfers, and deaths) and occasions of service in public and private hospitals, multipurpose facilities, and private day procedure centers in and outside of NSW to NSW residents. Linkage is available from July 1, 2000. Diagnoses contributing to episodes of care are coded by each hospital according to the *International Statistical Classification of Diseases, 10th Revision* (ICD-10), *Australian Modification*. The APDC has 95% to 99% coding concordance with the PDC[18] and other clinical databases[19] depending on the disease.

Australian Bureau of Statistics Cause of Death

The Australian Bureau of Statistics codes cause of death for all registered deaths in NSW and to NSW residents occurring outside NSW. Identifiable uncoded text information from the Medical Certificate of Cause of Death is coded according to the ICD-10.[17]

NICUS Data Collection

This is a population-based prospective statewide audit of newborn infants admitted to any of the 10 NICUs (8 perinatal centers and 2 children's hospitals) in NSW and the Australian Capital Territory with ≥1 of the following problems: (1) <32 weeks' gestation, (2) ≤1500 g birth weight and/or who require, during the first 28 days of life (3) mechanical ventilation (including continuous positive airway pressure) for ≥4 hours, (4) major surgery (opening of a body cavity), (5) insertion of a central venous catheter, (6) Humidified High Flow air/oxygen >1L/min, and (7) therapeutic hypothermia.

Record Linkage

Identified extracts of patient records were linked by the Centre for Health Record Linkage,[20] an independent data linkage facility for research and

audit purposes. Each patient was provided with a unique Patient Project Number by the Centre, which was used by the research team to amalgamate information from different databases. No personal identifiers were provided to the researchers.

Patient Selection

The ICD-10, Australian Modification, code P96.1 corresponding to a diagnosis of NAS[1] in any episode of care was used to differentiate children with and without NAS. Each episode of hospital care was characterized by a principal diagnosis and up to 55 subsidiary diagnoses. Stillbirths or infants born ≤23 weeks' or ≥44 weeks' gestation were excluded from analysis. NAS management is guided by local hospital as well as state guidelines.[21] Some aspects of care (such as nursery admission criteria) may not be standardized because they are dependent on local resources.

Data Analysis

The characteristics of children with an ICD-10 coding of NAS (P96.1) were compared with those without NAS for perinatal details and hospitalization information (for those surviving hospital discharge after birth). Missing data were considered random (ie, most likely entered incorrectly) and treated by listwise deletion. Demographic characteristics, hospitalization outcomes, and specific ICD-10 diagnoses were compared by using χ^2 and Fisher exact tests, t tests, the Mann-Whitney U test, and nonparametric median tests, where appropriate. Data are expressed as number (%) with odds ratio (OR) and 95% confidence interval (CI), median (range), or mean ± SD where appropriate. Crude rates of diagnosis were calculated using the total number of individual children receiving a diagnosis as a percentage of the total population group. Binary logistic regression with backward elimination (likelihood ratio) was undertaken to analyze the contribution of various factors including prematurity, rural birth, Indigenous status, and NAS to hospitalizations in general and for assaults and maltreatment. Kaplan-Meyer risk of readmission and 95% CIs were calculated in days censoring children who could not be followed beyond the study period. The level of statistical significance for all analyses was set at $P < .05$ using 2-tailed comparisons. Statistical analyses were performed by using SPSS (Release 22.0; IBM, Chicago, IL).

Ethics Approval

The project was approved by the NSW Population and Health Service Research (2012/09/415). AH&MRC Ethics Committee approval was attained.

RESULTS

Patient details are provided in Fig 1. Of the 1 022 263 live born infants notified to the NSW PDC between July 1, 2000, and December 21, 2011, 3842 (0.38%) were diagnosed with NAS (P96.1) during the birth admission. Five (0.1%) NAS and 1856 (0.2%) non-NAS infants died before discharge from hospital after birth ($P < .001$). Surviving children (NAS = 3837; non-NAS = 1 016 565) received 5154 and 887 227 episodes of care respectively over the follow-up period. The number of episodes of care per child were significantly higher in children with NAS (2009 rehospitalized, 2.6 episodes per child) than without NAS (408 993 rehospitalized, 2.2 episodes per child, $P < .001$). Forty-five (1.2%) children with NAS died by the end of the study period, compared with 3665 (0.4%) non-NAS children ($P < .001$). Mean (SD) age of live children with NAS at the end of the study period NAS was 6.5 (3.3) years versus 6.1 (3.3), $P < .001$.

Maternal Demographics

Details are in Table 1. Compared with mothers of infants without NAS, mothers of infants with NAS were younger, had less antenatal care, and were more likely to have smoked in pregnancy and be multiparous. More (13.7% vs 8.9%, $P < .01$) were in the lowest socioeconomic bracket.

Infant Characteristics

Details are in Table 2. Infants with NAS were born at lower birth weights and gestation and were more likely to require resuscitation at birth

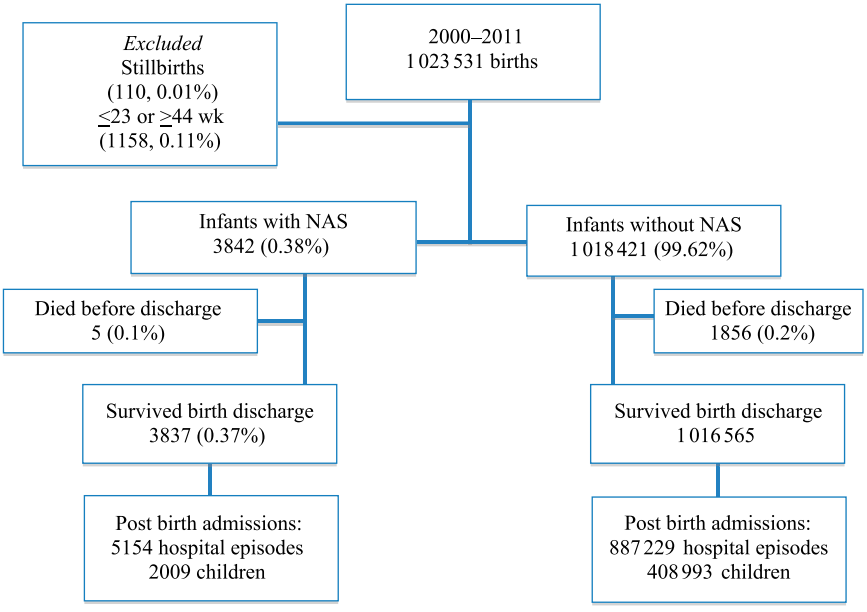

FIGURE 1
Characteristics of children included in the study.

TABLE 1 Maternal Characteristics

	NAS (n = 3803)	No NAS (n = 1 003 012)	OR (95% CI)	P
Mean maternal age, y	29.1 (5.8)	30.4 (5.6)	—	<.001
Young mother (<20 y at delivery)	174 (4.5)	37 714 (3.8)	1.23 (1.05–1.43)	.008
Older mother (>35 y at delivery)	646 (17.0)	214 280 (21.4)	0.75 (0.69–0.82)	<.001
Indigenous Australian	595 (15.6)	28 108 (2.8)	6.43 (6.00–7.03)	<.001
Primiparous	1043 (27.4)	420 839 (42.0)	0.52 (0.49–0.56)	<.001
Cigarette smoking	2926 (76.9)	124 431 (12.4)	23.56 (21.84–25.41)	<.001
No antenatal care	321 (8.4)	13 816 (1.4)	6.60 (5.88–7.41)	<.001
Mean gestation at first antenatal visit, wk	16.7 (9.1)	11.7 (6.1)	—	<.001
Caesarean delivery	844 (22.2)	253 217 (25.2)	0.85 (0.72–0.91)	<.001
Instrumental delivery	215 (5.7)	97 533 (9.7)	0.56 (0.49–0.64)	<.001
Private hospital birth	12 (0.3)	240 991 (24.0)	0.01 (0.01–0.02)	<.001
Pregnancy complications				
Preeclampsia	71 (1.9)	29 484 (2.9)	0.63 (0.50–0.79)	<.001
Gestational diabetes	56 (1.5)	48 395 (4.8)	0.30 (0.23–0.38)	<.001
Maternal discharge status				
Discharged alive	3730 (98.1)	973 599 (97.1)	1.54 (1.22–1.95)	<.001
Transferred	70 (1.8)	29144 (2.9)	0.63 (0.50–0.79)	<.001
Died in hospital	1	24	10.99 (1.49–81.27)	.09
SEIFA Quintile				
First (lowest)	503 (13.3)	88 763 (8.9)	1.57 (1.43–1.73)	<.001
Fifth (highest)	852 (22.5)	328 695 (33.0)	0.59 (0.55–0.64)	<.001

Data expressed as n (%) or mean (SD) unless otherwise stated. SEIFA, Socioeconomic Indexes for Area; —, analysis not applicable, not conducted, or data not available.

(Table 2). Five-minute Apgar scores were lower, and almost 75% were admitted to a nursery (vs 15.8%, $P <$ .001). They were less likely (49.4% vs 63.6%) to be born in nontertiary obstetric hospitals. Most (99.9%) were discharged alive. The duration of hospitalization after birth was threefold longer in infants with NAS (median: 10.0 vs 3.0 days, $P <$ .001).

Characteristics of Hospitalization After Discharge From the Birth Hospital

Infants who died before discharge from the hospital of birth were not considered for further analyses. After discharge from the birth hospital, infants with NAS had more episodes of care per child than children without NAS (median: 2 vs 0, $P <$ .001) and were more likely to be transferred to another hospital or die during these episodes. More hospitalization episodes for infants with NAS occurred between 28 days and 1 year of age (32.6% vs 26.0%, $P <$ .001), but they were less likely to be admitted between 1 and 4 years (36.8% vs 42.4%; $P <$ .001). Median age of admissions for children after NAS was lower (20.6 vs 23.2 months, $P <$ .001; Table 3). Significantly more children with NAS were readmitted throughout the duration of study compared with those without NAS (χ^2: 43.7, df 1, $P <$ .001). From age 23 days, the risk of readmission to hospital was significantly higher in the NAS group, and readmission rates remained higher throughout childhood. By age 10 years, the risk of readmission (95% CI) was 61.6% (59.8–63.7) vs 50.0% (49.9–50.2) for children without NAS (Fig 2).

TABLE 2 Infant Characteristics

	NAS (n = 3842)	No-NAS (n = 1 018 421)	OR (95% CI)	P
Male gender	2017 (52.5)	523 676 (51.4)	1.04 (0.98–1.11)	.18
Rural residence at birth	684 (17.8)	191 720 (18.8)	0.93 (0.86–1.02)	.11
Mean birth weight, g	2868 ± 593	3386 ± 569	—	<.001
Low birth weight (<2500 g)	961 (25.0)	58 825 (5.8)	5.44 (5.06–5.86)	<.001
Mean gestational age, wk	37.9 ± 2.5	39.0 ± 1.9	—	<.001
Preterm birth (<37 wk gestation)	860 (22.4)	68 165 (6.7)	4.02 (3.73–4.34)	<.001
Multiple birth[a]	74 (1.9)	30 640 (3.0)	0.63 (0.50–0.80)	<.001
Resuscitation at birth	1658 (43.2)	388 383 (38.1)	1.23 (1.16–1.31)	<.001
Apgar <7 at 5 min	139 (3.7)	13 790 (1.4)	2.77 (2.33–3.28)	<.001
Admission to nursery	2866 (74.6)	161 079 (15.8)	15.63 (14.53–16.81)	<.001
Admission to an NICU	270 (7.0)	23958 (2.4)	3.14 (2.77–3.55)	<.001
Admission for birth defect	3 (0.1)	1359 (0.1)	—	.35
Birth in nontertiary obstetric hospital[b]	1899 (49.4)	492 412 (63.6)	0.56 (0.53–0.60)	<.001
Transferred after birth[c]	169 (4.4)	29 586 (2.9)	1.54 (1.32–1.80)	<.001
Died before discharge from birth hospital	5 (0.1)	1856 (0.2)	0.71 (0.30–1.72)	.45
Median length of stay after birth, d	10.0	3.0	—	<.001

Data expressed as number (%) or mean ± SD unless otherwise stated. —, analysis not applicable, not conducted, or data not available.

[a] Number of individual infants born as part of twin, triplet, or quadruplet birth.

[b] Nontertiary hospital defined as hospital obstetric level 1–5.[35] Private hospital births not included in this comparison.

[c] Transferred refers to infants transferred to another hospital after birth.

Reasons for Admission

A total of 198 (5.1%) of children with NAS were readmitted for NAS treatment (total of 246 episodes of care). Diagnoses made upon episodes of care are shown in Table 4. The number of children receiving each diagnosis upon episode of care is shown in Table 5. Children with NAS were more likely to be admitted with respiratory disease (OR, 95% CI: 1.5, 1.4–1.6) and infections (1.5, 1.4–1.7), including subcutaneous tissue infections (2.1, 1.7–2.6) such as impetigo (4.5, 2.9–7.0). Injuries (1.9, 1.8–2.1), including burns (2.6, 1.9–3.6), poisoning (3.6, 2.6–4.8), maltreatment (21.0, 14.3–30.7), accidents (1.9, 1.7–2.1) and assault (15.2, 11.3–20.6), were also more likely and occurred at younger ages than in children without NAS (mean ages of hospitalization for external causes of injury or accidents: 3.6 versus 10.2 months, $P <$ .001; and

TABLE 3 Episodes of Care After Discharge From Hospital of Birth

	Number of Episodes (%)		OR (95% CI)
	NAS	Non–NAS	
Age			
0–28 d	238 (4.6)	50 225 (5.7)	0.81 (0.71–0.92)*
28 d–1 y	1678 (32.6)	231 052 (26.0)	1.37 (1.29–1.45)*
1–4 y	1899 (36.8)	376 570 (42.4)	0.79 (0.75–0.84)*
>4 y	1339 (26.0)	229 380 (25.9)	1.01 (0.95–1.07)
Total	5154 (100)	887 227 (100)	—
Duration of hospitalization per episode of care (d)[a]			
Age 0–28 d	3 (46)*	2 (1318)	—
Age 28 d–1 y	2 (77)*	1 (1679)	—
Age 1–4 y	1 (53)*	1 (721)	—
Age >4 y	1 (76)***	1 (465)	—
Total	1 (78)*	1 (1679)	—
Admission after birth hospital discharge (%)			
Yes	2009 (52.4)	408 993 (40.2)	1.63 (1.53–1.74)*
Episodes of care per child[b]			
Median (range)	2 (68)*	0 (504)	—
Separation mode (%)			
Discharge home	4680 (90.8)	827 015 (93.2)	0.72 (0.65–0.79)*
Transferred to another hospital	370 (7.2)	45 483 (5.1)	1.43 (1.29–1.59)*
Died	20 (0.4)	1063 (0.1)	3.25 (2.09–5.06)*

*$P < .001$. **$P < .01$. ***$P < .05$. —, analysis not applicable, not conducted, or data not available.

[a] Median (range).

[b] Refers to the number of episodes of care encounters occurring after initial discharge after birth admission.

social problems (eg, respite care): 12.0 versus 69.2 months, $P < .001$).

There were also conditions for which children with NAS were hospitalized for at older ages, including ophthalmologic conditions (strabismus, 7.9, 6.3–10.0; nystagmus, 12.5, 6.8–22.9), mean age 33.9 versus 24.0 months, $P < .05$. Admissions for mental and behavioral disorders, including autism, conduct disorders, and adjustment disorders were more common in children with NAS (2.6, 2.1–3.2), again at older ages (mean: 64.3 vs 41.3 months, $P < .001$). Details are in Fig 3.

Factors Influencing Hospitalization for Assault and Maltreatment and Mental And Behavioral Disorders

Table 5 contains details of regression analyses that were conducted to determine the effects of known risk factors (male gender, NAS, lowest socioeconomic quintile for the mother, young mother (aged <20 years old at delivery), residence in a rural area, Indigenous Australians, any smoking during pregnancy, and prematurity) on hospitalization for assault/maltreatment and for mental and behavioral disorders. Hospitalizations as a result of assault and maltreatment were increased by all factors including an almost fivefold increase by NAS and maternal smoking (OR 4.5 and 4.6, respectively). Hospitalization for mental and behavioral disorders (F00–F98) was increased by all of factors, notably NAS (OR 2.3) and prematurity (OR 1.8).

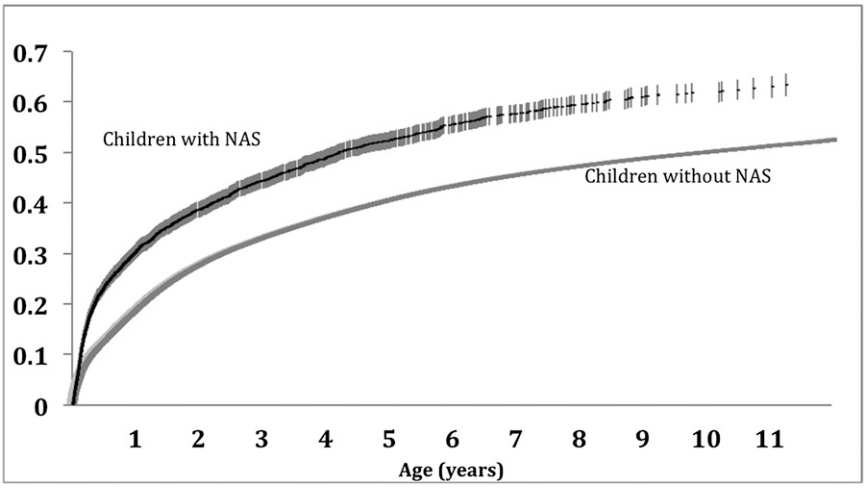

FIGURE 2
Proportion of infants readmitted to hospital during the study period.

DISCUSSION

Our study demonstrates significantly increased childhood hospitalization for children after NAS compared with those without, even until adolescence and even after accounting for prematurity as an independent risk factor for poor childhood health and hospitalization.[22] After NAS, children were more likely to be admitted for potentially preventable conditions (such as injury from burns, poisonings and accidents, maltreatment, and abuse) and for medical conditions that could affect optimal adult functioning. For example, they were up to 12-fold more likely to be admitted for strabismus and nystagmus. The underlying cause of visual disturbances in opioid-exposed children are unclear[23] but, if untreated, may lead to difficulties with self-image and social adjustment that intensifies to adulthood.[24]

After NAS, children were also admitted more frequently for conditions that usually develop insidiously and which may not be apparent in early infancy, when medical and social surveillance of the high-risk mother and child is at its most intense. OR for admissions for

TABLE 4 Episode of Care After Discharge From the Birth Hospital

ICD-10 Classification	Episodes of care (%)		OR (95% CI)	
	NAS (n = 5154)	No NAS (n = 887 229)	Unadjusted	Adjusted[a]
Infections and parasitic disease (A00–B99)	857 (16.6)	147 632 (16.6)	0.98 (0.93–1.08)	1.02 (0.96–1.08)
Intestinal infection (A00–A9)	319 (6.2)	60 258 (6.8)	0.09 (0.81–1.01)	—
Neoplasms (C00–D48)	43 (0.8)	26 394 (3.0)	0.27 (0.20–0.37)*	0.68 (0.56–0.82)*
Malnutrition or nutritional deficiency (E40–64)	3 (0.1)	899 (0.1)	0.57 (0.19–1.78)	0.34 (0.21–0.55)*
Mental and behavioral disorders (F00–99)	381 (7.4)	19 081 (2.2)	3.63 (3.27–4.04)*	2.08 (1.92–2.25)*
Adjustment disorder (F43.2)	58 (1.1)	224 (0)	45.07 (33.72–60.24)*	6.70 (5.09–8.83)*
Anxiety disorder, unspecified (F41.9)	105 (2.0)	1860 (0.2)	9.90 (8.12–12.07)*	3.77 (3.09–4.61)*
Mental Retardation (F70–79)	16 (0.3)	2175 (0.2)	1.27 (0.77–2.07)	—
Disorders of psychological development (F80–89)	72 (1.4)	7827 (0.9)	1.59 (1.26–2.01)*	1.29 (1.14–1.45)*
Disorder of speech/language	16 (0.3)	1384 (0.2)	1.99 (1.22–3.27)**	—
Autism	21 (0.4)	1813 (0.2)	2.00 (1.30–3.08)*	—
Behavioral and emotional disorders with onset in childhood or adolescence (F90–99)	198 (4.0)	7259 (0.8)	4.84 (4.19–5.59)*	3.35 (3.02–3.72)*
Disturbance to attention and activity (F90.0)	42 (0.8)	2566 (0.3)	2.83 (2.09–3.85)*	1.68 (1.40–2.01)*
Conduct disorder (F91)	138 (2.7)	5102 (0.6)	4.76 (4.01–5.65)*	3.13 (2.73–3.58)*
Oppositional defiant disorder (F91.3)	130 (2.6)	4178 (0.5)	5.47 (4.58–6.53)*	3.67 (3.16–4.26)*
Mixed conduct and emotional disorders (F92)	13 (0.3)	167 (0)	13.43 (7.63–23.63)*	3.13 (2.73–3.58)*
Emotional disorder (childhood) (F93)	44 (0.9)	429 (0)	17.80 (13.04–24.30)*	22.28 (18.11–27.41)*
Cerebral palsy	98 (1.9)	6183 (0.7)	2.76 (2.26–3.38)*	—
Diseases of the eye and adnexa (H00–59)	174 (3.4)	18 286 (2.1)	1.66 (1.43–1.93)*	1.44 (1.32–1.58)*
Strabismus (H50)	87 (1.7)	3317 (0.4)	4.58 (3.69–5.67)*	3.13 (2.72–3.59)*
Nystagmus (H55)	12 (0.2)	346 (0)	5.98 (3.36–10.64)*	4.61 (3.43–6.20)*
Diseases of respiratory system (J00–99)	1629 (31.6)	275 108 (31.0)	1.03 (0.97–1.09)	0.85 (0.80–0.90)*
Chronic lower respiratory diseases (J40–47)	455 (8.8)	63 320 (7.1)	1.26 (1.14–1.39)*	—
Asthma (J45)	359 (7.0)	50 557 (5.7)	1.24 (1.11–1.38)*	1.22 (1.14–1.31)*
Respiratory infection (J00–22)	455 (8.8)	65 814 (7.4)	1.21 (1.10–1.33)*	—
Diseases of digestive system (K00–93)	176 (3.4)	28 545 (3.2)	1.06 (0.92–1.24)	1.10 (1.01–1.19)***
Diseases of the skin and SC tissue (L00–99)	244 (4.7)	32 619 (3.7)	1.30 (1.14–1.48)*	1.14 (1.06–1.24)*
Infection of skin and subcutaneous tissues (L00–08)	117 (2.3)	13 922 (1.6)	1.46 (1.21–1.75)*	—
Impetigo (L01)	23 (0.4)	1258 (0.1)	3.16 (2.09–4.77)*	1.62 (1.30–2.03)*
Diseases of musculoskeletal and CT (M00–99)	58 (1.1)	13 336 (1.5)	0.75 (0.58–0.97)**	0.62 (0.54–0.73)*
Diseases of the genitourinary system (N00–99)	139 (2.7)	35 298 (4.1)	0.67 (0.57–0.79)*	0.87 (0.79–0.96)**
Perinatal conditions (P00–96)	326 (6.3)	29 507 (3.3)	1.96 (1.75–2.20)*	1.90 (1.76–2.05)*
Injury, poisoning, and other consequences of external causes (S00–T98)	629 (12.2)	92 006 (10.4)	1.20 (1.11–1.31)*	1.17 (1.10–1.24)*
Injury (S00–T75; T79)	582 (11.3)	79 824 (9.0)	1.29 (1.18–1.40)*	—
Burns and corrosions (T20–32)	53 (1.0)	7022 (0.8)	1.30 (0.99–1.71)	1.28 (1.07–1.53)**
Poisoning by drugs, medicaments, and toxic substances (T36–50)	52 (1.0)	3568 (0.4)	2.52 (1.92–3.32)*	1.39 (1.17–1.66)*
Benzodiazepines (T42.4)	15 (0.0)	426 (0.0)	6.08 (3.63–10.18)*	—
Narcotic/psycholeptics (T40)	19 (0.4)	218 (0)	13.95 (8.38–23.24)*	—
Opioid (T40.1–0.4)	15 (0.0)	183 (0)	14.15 (8.35–23.97)*	—
Maltreatment syndrome (T74)	31 (0.6)	381 (0)	14.09 (9.76–20.33)*	3.38 (2.87–4.26)*
Neglect/abandonment (T74.0)	12 (0.2)	125 (0)	16.56 (9.15–29.97)*	3.27 (2.36–4.52)*
Physical abuse (T74.1)	3 (0.1)	140 (0)	3.69 (1.18–11.59)**	0.51 (0.19–1.38)
Unspecified maltreatment (T74.9)	10 (0.2)	62 (0)	27.82 (14.26–54.28)*	—
External causes of mortality and morbidity	686 (13.8)	100 854 (11.9)	1.19 (1.10–1.29)*	—
Accidents (V01–X59)	563 (11.3)	81 951 (9.6)	1.19 (1.09–1.30)*	1.26 (1.18–1.34)*
Assault (X85–Y09)	44 (0.9)	865 (0.1)	8.74 (6.45–11.85)*	4.20 (3.58–4.93)*
Factors influencing health status and contact with health services	816 (15.8)	109 118 (12.3)	1.34 (1.24–1.45)*	—
Social environmental problems (Z60)	87 (1.7)	679 (0.1)	22.42 (17.90–28.07)*	6.08 (5.34–6.92)*
Loss of love relationship (Z60.1)	28 (0.5)	92 (0)	52.67 (34.47–80.48)*	—
Negative life event in childhood (Z61)	16 (0.3)	950 (0.1)	2.91 (1.77–4.77)*	1.11 (0.82–1.49)
Physical abuse problems (Z61.6)	8 (0.2)	110 (0.0)	12.54 (6.11–25.71)*	—
Problem with primary support group (Z63)	203 (3.9)	4206 (0.5)	8.61 (7.46–9.94)*	4.67 (4.23–5.16)*

*$P < .001$. **$P < .01$. ***$P < .05$. —, analysis not applicable, not conducted, or data not available.

[a] Adjusted for gender, young mother (<20 y old), maternal smoking, prematurity, low Socioeconomic Indexes for Area, rural residence, Indigenous Australian.

TABLE 5 Number of Children Affected After Discharge From the Birth Hospital

ICD-10 Classification	Number of Children (%)		OR (95% CI)	
	NAS (n = 3837)	No NAS (n = 1 016 565)	Unadjusted	Adjusted[a]
Infections and parasitic disease (A00–B99)	622 (16.2)	113 441 (11.2)	1.54 (1.41–1.68)*	1.01 (0.92–1.11)*
Intestinal infection (A00–A9)	266 (6.9)	51 048 (5.0)	1.41 (1.24–1.60)*	0.89 (0.58–1.38)
Neoplasms (C00–D48)	23 (0.6)	6055 (0.6)	1.01 (0.67–1.52)	0.98 (0.63–1.53)
Malnutrition or nutritional deficiency (E40–64)	3 (0.1)	778 (0.1)	1.02 (0.33–3.18)	0.48 (0.12–1.94)
Mental and behavioral disorders (F00–99)	96 (2.5)	9924 (1.0)	2.60 (2.12–3.19)*	2.05 (1.66–2.54)*
Adjustment disorder (F43.2)	1	42	6.31 (0.87–45.85)	2.00 (0.26–15.20)
Anxiety disorder, unspecified (F41.9)	3 (0.1)	158 (0.0)	5.03 (1.61–15.78)**	3.02 (0.93–9.80)
Mental Retardation (F70–79)	13 (0.3)	1238 (0.1)	2.79 (1.61–4.82)*	1.68 (0.96–2.93)
Disorders of psychological development (F80–89)	39 (1.1)	3592 (0.4)	2.90 (2.11–4.00)*	1.74 (1.26–2.41)*
Disorder of speech/language	12 (0.3)	887 (0.1)	3.59 (2.03–6.36)*	2.42 (1.35–4.34)**
Autism	15 (0.4)	1113 (0.1)	3.58 (2.15–6.00)*	2.48 (1.47–4.18)*
Behavioral and emotional disorders with onset in childhood or adolescence (F90–99)	32 (0.83)	2090 (0.2)	4.08 (2.88–5.80)*	2.30 (1.60–3.30)*
Disturbance to attention and activity (F90.0)	13 (0.3)	346 (0.0)	9.99 (5.73–17.39)*	3.73 (2.10–6.61)*
Conduct disorder (F91)	13 (0.3)	1009 (0.1)	3.42 (1.98–5.92)*	2.11 (1.21–3.70)**
Oppositional defiant disorder (F91.3)	6 (0.2)	225 (0.0)	7.07 (3.14–15.93)*	2.90 (1.26–6.66)***
Mixed conduct and emotional disorders (F92)	4 (0.1)	61 (0.0)	17.39 (6.32–47.85)*	6.65 (2.29–19.34)*
Emotional disorder (childhood) (F93)	4 (0.1)	208 (0.0)	5.10 (1.90–13.72)**	3.9 (1.5–10.6)
Cerebral Palsy	20 (0.5)	1703 (0.2)	3.12 (2.01–4.86)*	1.90 (1.21–2.99)**
Diseases of the eye and adnexa (H00–59)	146 (3.8)	13 497 (1.3)	2.94 (2.49–3.47)*	1.93 (1.62–2.31)*
Strabismus (H50)	75 (2.0)	2558 (0.3)	7.90 (6.27–9.97)*	4.73 (3.69–6.05)*
Nystagmus (H55)	11 (0.3)	234 (0.0)	12.49 (6.82–22.88)*	7.99 (4.15–15.40)*
Diseases of respiratory system (J00–99)	894 (23.3)	173 829 (17.1)	1.47 (1.37–1.59)*	0.85 (0.79–0.93)*
Asthma (J45)	210 (5.5)	31 615 (3.1)	1.80 (1.57–2.07)*	1.10 (0.95–1.27)
Respiratory infection (J00–22)	329 (8.6)	51 997 (5.1)	1.74 (1.55–1.95)*	1.00 (0.88–1.13)
Diseases of digestive system (K00–93)	128 (3.3)	21 647 (2.1)	1.59 (1.33–1.89)*	1.15 (0.96–1.38)
Diseases of the skin and SC tissue (L00–99)	197 (5.1)	27 020 (2.7)	1.98 (1.72–2.29)*	1.26 (1.08–1.46)**
Infection of skin and subcutaneous tissues (L00–08)	94 (2.4)	12 146 (1.2)	2.08 (1.69–2.55)*	1.14 (0.92–1.41)
Impetigo (L01)	20 (0.5)	1179 (0.1)	4.51 (2.90–7.03)*	1.90 (1.20–3.03)*
Diseases of musculoskeletal and CT (M00–99)	47 (1.2)	8927 (0.9)	1.40 (1.05–1.87)**	1.07 (0.79–1.43)
Diseases of the genitourinary system (N00–99)	101 (2.6)	25 230 (2.5)	1.06 (0.87–1.30)	0.92 (0.75–1.13)
Perinatal conditions (P00–96)	265 (6.9)	25 793 (2.5)	2.85 (2.51–3.23)*	1.97 (1.71–2.27)*
Injury, poisoning, and other consequences of external causes (S00–T98)	478 (12.5)	69 977 (6.9)	1.93 (1.75–2.12)*	1.34 (1.20–1.49)*
Burns and corrosions (T20–32)	41 (1.1)	4139 (0.4)	2.64 (1.94–3.60)*	1.52 (1.11–2.09)*
Poisoning by drugs, medicaments, and toxic substances (T36–50)	43 (1.1)	3231 (0.3)	3.56 (2.63–4.81)*	1.78 (1.30–2.42)*
Benzodiazepines (T42.4)	12 (0.3)	389 (0)	8.20 (4.61–14.57)*	3.12 (1.73–5.63)*
Narcotic/psycholeptics (T40)	17 (0.4)	195 (0.0)	23.20 (14.12–38.12)*	7.22 (3.99–13.05)*
Opioid (T40.1–0.4)	13 (0.3)	168 (0)	20.57 (11.69–36.19)*	7.10 (3.93–12.83)*
Maltreatment syndrome (T74)	28 (0.7)	355 (0.0)	21.04 (14.30–30.96)*	5.08 (3.38–7.64)*
Neglect/abandonment (T74.0)	12 (0.3)	118 (0.0)	27.02 (14.91–48.98)*	4.81 (2.58–8.97)*
Physical abuse (T74.1)	3 (0.1)	133 (0.0)	5.98 (1.90–18.79)**	1.84 (0.57–5.92)
Unspecified maltreatment (T74.9)	8 (0.2)	59 (0.0)	36.00 (17.19–75.38)*	9.26 (4.27–20.12)*
External causes of mortality and morbidity	43 (1.1)	8328 (0.8)	1.37 (1.02–1.86)**	—
Accidents (V01–X59)	440 (11.5)	64 497 (6.3)	1.91 (1.73–2.11)*	1.32 (1.18–1.47)*
Assault (X85–Y09)	45 (1.2)	791 (0.1)	15.24 (11.27–20.61)*	4.25 (3.09–5.84)*
Factors influencing health status and contact with health services	509	72 241	2.00 (1.82–2.20)*	1.60 (1.44–1.77)*
Social environmental problems (Z60)	60 (1.6)	585 (0.1)	27.59 (21.11–36.05)*	7.99 (5.96–10.72)*
Negative life event in childhood (Z61)	15 (0.4)	287 (0.0)	13.90 (8.26–23.38)*	4.27 (2.48–7.33)*
Problem with primary support group (Z63)	88 (2.3)	1849 (0.2)	12.88 (10.38–15.99)*	4.70 (3.72–5.94)*

*$P < .001$. **$P < .01$. ***$P < .05$.

[a] Adjusted for gender, young mother (<20 y old), maternal smoking, prematurity, low Socioeconomic Indexes for Area, rural residence, Indigenous Australian.

mental and behavioral disorders, for example, were up to 18-fold higher than children without NAS, and whether these conditions are due to intrauterine substance-exposure, parenting influences, or genetic predisposition is unclear. Yuan et al recently demonstrated lower brain volumes in opioid-exposed infants compared with known population values[25] and intrauterine opioid exposure impairs neural tract development,[26] neurogensis,[27] myelination,[28] and neuronal longevity.[29] This emphasizes the

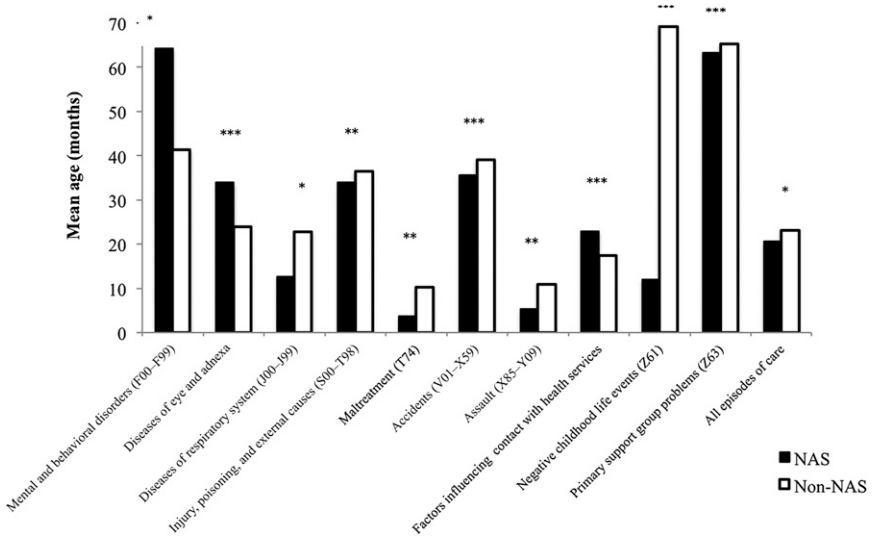

FIGURE 3
Mean age of admission for specific conditions. *$P < .05$, **$P < .005$, ***$P < .001$.

importance of extending surveillance to at least school age for children after NAS as failure to diagnose and treat these conditions in a timely manner may lead to school difficulties, poor adult productivity, and psychological function.[30]

Of great concern is the significantly increased risk of hospitalization caused by maltreatment or trauma (up to 36-fold for unspecified causes of maltreatment) that occurred significantly earlier (mostly during the first 4 months) than those without NAS (admissions closer to their first birthday). This may reflect a drop-off in support provided to substance-affected parents and caregivers in the first few weeks to months after birth but which may be difficult to maintain due to pressure on resources.[31,32] The association between maternal substance use and child maltreatment is not new. Mothers who use drugs sometimes have poor parenting and coping skills,[33] psychiatric comorbidities[34] and insufficient social support, which amalgamate to exacerbate parenting stress, poor attachment,[35] and vulnerability for child harm, particularly if the infant is discharged early from medical care before resolution of NAS (leading to an irascible and difficult infant). Our results show that NAS increases the risk of hospitalization for child maltreatment or trauma even when prematurity is taken into account. Nevertheless, the contribution of other factors that promote this risk, including young,[36] Indigenous, and poor or isolated rural mothers,[37] highlights the need to extend support for this particularly vulnerable subset of families.

Inherent differences between mothers and infants with and without NAS could also increase the risk of admission for certain conditions noted in this study. For example, mothers of children with NAS were 20 times more likely to smoke and reducing this practice may decrease the risk of childhood respiratory problems.[38] As a group, mothers of infants with NAS were younger, poorer, and had less antenatal care, which could lead to suboptimal perinatal outcomes including prematurity. Prematurity, although not a function of NAS, is an independent risk factor for problems including childhood hospitalization,[22] visual problems,[39] and child maltreatment.[40]

We were limited by the lack of data regarding maternal drug use, which was not available for our study. Because linked patient data were deidentified, it was not possible to obtain further information from medical records. We presumed that NAS resulted from exposure to maternal opioids, but whether this was due to prescription or illicit drugs or whether polydrug use was involved cannot be deduced. Most known pregnant drug users in NSW use opioids, such as heroin, methadone, and buprenorphine, but NAS can be caused by either legal or illegal opioids.[5] Additional study about the association between maternal drug use and sociodemographic factors (eg, domestic violence) can be obtained from external sources of information (eg, child protection databases), and this could further inform on the risk factors for potentially preventable causes of admissions, including poisoning and external injury.

Again, due to the deidentified nature of the study data, we were unable to verify NAS diagnosis by alternative methods (eg, medical record search). We acknowledge that drug exposure in this cohort is most likely to have been underdiagnosed for several reasons. Prematurity is more common with maternal drug use and may also be associated with less severe NAS expression, possibly resulting in underdiagnosis.[41] There are no official Australian NAS figures, but previous studies, predominantly obtained from public hospitals, estimate that 1% to 1.5% of NSW infants are born to known drug users.[42] Our data also accounts for private hospital births (~25% of NSW births),[43] and whether different disclosure rates or management pathways in these institutions affected the lower (0.38%) estimation of rates is unclear.

Finally, our results show that more children were rehospitalized after NAS than those without, even up to adolescence. In particular, the age of admissions for children who had

NAS occurred later in certain conditions (eg, mental and behavioral issues or visual problems) than children without NAS. The reasons for this are uncertain but may reflect improved vigilance when the child attends school. Delayed diagnosis, unfortunately, may reduce treatment effectiveness for many of these conditions. Also, any hospitalization will remove the child from mainstream society, particularly school. This may then lead to academic difficulties and future lifestyle problems, including a sixfold risk of illicit drug abuse even after adjustment for socioeconomic status.[43,44]

CONCLUSIONS

Our study has shown that children with NAS are more likely than those without NAS to be admitted to hospital with conditions that are potentially preventable (such as trauma and maltreatment) and that cause significant adult sequelae if untreated (such as visual, mental, and behavioral problems). Increased hospitalization continues to occur in this group until adolescence and this, in itself, can severely hamper the child's normal development. Although resources are limited, efforts to extend services for children beyond the resolution of NAS should be considered to reduce this risk, which could lead to poorer adult outcomes for this already vulnerable but rapidly growing population of children.

ABBREVIATIONS

CI: confidence interval
ICD-10: International Statistical Classification of Diseases, 10th Revision
NAS: neonatal abstinence syndrome
NSW: New South Wales
OR: odds ratio
PDC: Perinatal Data Collection of New South Wales

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Reasons for Rehospitalization in Children Who Had Neonatal Abstinence Syndrome

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