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PEDIATRICS

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Neonatal Abstinence Syndrome and High School Performance

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abstract

BACKGROUND AND OBJECTIVES: Little is known of the long-term, including school, outcomes of children diagnosed with Neonatal abstinence syndrome (NAS) (*International Statistical Classification of Disease and Related Problems* [10th Edition], Australian Modification, P96.1).

METHODS: Linked analysis of health and curriculum-based test data for all children born in the state of New South Wales (NSW), Australia, between 2000 and 2006. Children with NAS (n = 2234) were compared with a control group matched for gestation, socioeconomic status, and gender (n = 4330, control) and with other NSW children (n = 598 265, population) for results on the National Assessment Program: Literacy and Numeracy, in grades 3, 5, and 7.

RESULTS: Mean test scores (range 0–1000) for children with NAS were significantly lower in grade 3 (359 vs control: 410 vs population: 421). The deficit was progressive. By grade 7, children with NAS scored lower than other children in grade 5. The risk of not meeting minimum standards was independently associated with NAS (adjusted odds ratio [aOR], 2.5; 95% confidence interval [CI], 2.2–2.7), indigenous status (aOR, 2.2; 95% CI, 2.2–2.3), male gender (aOR, 1.3; 95% CI, 1.3–1.4), and low parental education (aOR, 1.5; 95% CI, 1.1–1.6), with all Ps < .001.

CONCLUSIONS: A neonatal diagnostic code of NAS is strongly associated with poor and deteriorating school performance. Parental education may decrease the risk of failure. Children with NAS and their families must be identified early and provided with support to minimize the consequences of poor educational outcomes.

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Dr Oei developed the project idea, obtained ethics approval and linkage data, performed the statistical analysis, and drafted the initial manuscript; Dr Melhuish provided statistical advice, contributed intellectual content, and revised the manuscript; Ms Uebel and Ms Azzam assisted with data cleaning; Drs Breen and Burns, Ms Bajuk, Drs Ward and Feller, Ms Falconer, Ms Clews, and Dr Eastwood contributed intellectual content and reviewed and revised the manuscript; Ms Hilder revised the manuscript and provided statistical supervision; Dr Abdel-Latif and

WHAT'S KNOWN ON THIS SUBJECT: Children with neonatal abstinence syndrome (NAS) may be at risk for neurodevelopmental and cognitive problems, but their performance at a population level in school in comparison with their peers is unknown because of difficulties in long-term follow-up.

WHAT THIS STUDY ADDS: Australian children with NAS perform poorly at school from grade 3, and results deteriorates even more by high school, suggesting that children with NAS must be supported beyond withdrawal to minimize the risk of school failure and its consequences.

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Neonatal abstinence syndrome (NAS) is one of the fastest-growing public health problems in the world,[1] especially in the United States, where it is estimated that an infant with NAS is born every 25 minutes.[2] Clinical and research efforts to improve the care of babies with NAS are considered major priorities by the US Congress,[3] the March of Dimes Foundation,[4] and the World Health Organization,[5] with significant financial, social, and health expenditures. These costs are attributed mostly to perinatal problems, including low birth weight, prematurity, and withdrawal.[6,7] With prompt recognition and appropriate treatment, NAS is an uncommon direct cause of death, and there are now a rapidly increasing number of children and adults with a neonatal history of NAS.

Recently, Uebel et al[8] showed in a group of 3842 Australian children that NAS was associated with a higher risk of health, social, and psychological problems even into the teenage years. Whether these poor outcomes were a direct consequence of intrauterine exposure to drugs of addiction during critical periods of fetal development[9] or related to the socioeconomic and other environmental adversities associated with parental drug use is unclear.[10] Long-term follow-up of this large and often chaotic population of children is difficult, and tangible evidence of long-term functional outcomes after resolution of NAS therefore remains elusive and concerning.

School performance is 1 of the most important outcomes of childhood. Around the world, the ability to do well in school is consistently related to adult success. Children who fail at school are at risk for many poor adult outcomes, including psychiatric and physical illness,[11] unemployment, delinquency,[12] crime,[13] drug use,[14] and intergenerational disadvantage.[15] On a global scale, school underachievement costs trillions of dollars every year in social support, lost earnings, and poor health.[16] The early identification of children at risk for school failure is often difficult. Learning problems may not be recognized until the child enters school, and the later a child is provided support and intervention, the less effective such strategies will be. Nevertheless, comparatively simple and cost-effective strategies are strikingly beneficial in improving educational and social outcomes, and effects may last well into adulthood and extend to affect even subsequent generations.[15]

Considering the known risks, evidence for school outcomes in children with NAS is limited. Children with NAS can be identified from birth, and factors associated with poor outcomes, including educational achievement, can theoretically be addressed early in life so that intervention and support can be provided in a timely manner for both the child and the family. Because long-term follow-up of any child, let alone children on a large scale, is difficult, we used data linkage to determine the relationship between a hospital discharge diagnosis of NAS (International Statistical Classification of Disease and Related Problems (10th Edition), Australian Modification [ICD-10-AM] P96.1)[17] and school performance in compulsory, standardized curriculum-based tests for 2236 children with NAS who were born in the state of New South Wales (NSW), Australia, between 2000 and 2006. We hypothesized that children with a diagnosis of NAS would perform more poorly at school than other NSW children even after we controlled for other factors influencing school outcomes, such as socioeconomic and perinatal factors.

METHODS

Study Design and Setting

This study used information from Australian administrative databases that was collected from children born in NSW between July 1, 2000 and December 31, 2006 (n = 605 094). Three mutually exclusive groups were created from this cohort: those with a hospital discharge diagnosis of NAS (ICD-10-AM P96.1,[17] n = 2234); controls matched in a 2:1 ratio for factors that were decided a priori to influence school outcomes, including male gender,[18] gestational age,[19] year of birth,[20] and socioeconomic status (n = 4330);[21] and other NSW children (n = 598 265). The records for each child were linked via common identifiers such as names, dates of births, addresses, and hospital identification numbers with probabilistic methods by the Centre for Health Record Linkage, a dedicated data linkage facility that provides data for research and other purposes.[22]

Australian Education System

Australian children must start school in the calendar year that they turn 6 years of age. There are 3 main education sectors that adhere to a single, standard national curriculum: Government (free except for nominal costs), Independent (fee-based and includes home schooling), and the National Catholic Education Commission (fee-based).[23]

National Assessment Program: Literacy and Numeracy

The National Assessment Program: Literacy and Numeracy (NAPLAN)[24] test was introduced in 2008 to serve as a compulsory, curriculum-based test for children in all Australian schools, including those located overseas. It is composed of 5 domains of testing: reading, writing, numeracy, spelling, and grammar/punctuation. Each test is scored out of 1000, which is then graded into 10 standard achievement bands. The scores are scaled to reflect the same level of performance, so that a child who scores 350 out of 1000 (or a band 3) in grade 3, for example, is considered to have the same ability

as a child who has the same score in grade 5.

Exemptions from testing are granted very infrequently (eg, new immigrant from a non–English speaking country, moral objections from the guardians for the test). Each child sits for the test 4 times in their school career, in grades 3, 5, 7, and 9 (at ages 8–9, 10–11, 12–13, and 14–15, respectively). Each grade level has a predetermined National Minimum Standard (NMS: band 1 in grade 3, band 3 in grade 5, band 5 in grade 7). Children who do not meet the NMS are considered to not have the necessary skills to progress to the next level of education and to need focused intervention and additional support. Nonattendees are considered not to meet NMS.

Databases

- *Perinatal Data Collection (PDC):* Details of the mother, infant, and the birth, including gestation, birth weight, parity, and delivery details.
- *The Admitted Patient Data Collection:* Details on separations (discharges, transfers, and deaths) for all NSW residents within and outside NSW from 2000 onwards. It was used to identify children with a diagnosis of NAS (P96.1).[17]
- *Australian Bureau of Statistics Cause of Death:* Details on the cause of death for NSW residents (ICD-10-AM).[25] These data were used to identify and exclude children who died before 2008 (the inaugural NAPLAN test year). Children who died after sitting for a test were included in analysis for that particular grade level.
- *The NAPLAN database*.[24] Details on the age of child at test, parental education, Indigenous status, school location (ie, metropolitan or rural), and test scores. Nonattendance was assigned a blank score and designated as failure to meet NMS. Parental education levels were by self-report and consisted of 2 discrete variables: high school (from grade 9 to 12) and nonschool qualification (from no nonschool qualification to bachelor level or above).

Participant Selection

Children with a diagnosis of neonatal withdrawal from maternal use of drugs of dependency, corresponding to the ICD-10-AM code P96.1,[17] were selected from the Admitted Patient Data Collection database and compared with matched controls and with other children in NSW. Stillbirths, infants born at <23 or >44 weeks' gestation or of unknown gestational age, and those who died before the first test in 2008 were excluded from analysis.

Data Analysis

Missing data were treated by listwise deletion. Demographic characteristics and NAPLAN outcomes were compared via χ^2 and Fisher exact tests for categorical data of proportions, Student's *t* test, and analysis of variance (ANOVA) for approximately normal data (eg, maternal age, gestations, birth weights, test scores), with pairwise comparisons of 3 study groups also examined via Scheffe's post hoc multiple comparison test. The Mann–Whitney *U* test was used for nonnormal continuous data (eg, duration of hospitalization). Binary logistic regression with factors determined a priori to be associated with poor outcomes, including gender,[18] prematurity (<37 weeks' completed gestation),[19] Indigenous status (a person of Australian Aboriginal or Torres Strait Islander origin),[26,27] school remoteness,[28] and parental education levels (lower than grade 9 and nonschool: yes or no)[29] was conducted to assess influences on failure to meet NMS at each grade level because previous data show that these factors are associated with poorer school outcomes. Educational information for the primary parent or guardian (assumed to be the mother in >90% of cases)[24] was used in the analysis because not all children had 2 parents. Mean (SD) composite scores (ie, average of scores for each domain of testing) for children born between 2000 and 2001 were examined longitudinally from grades 3, 5, and 7 because this group was eligible to sit for all 3 tests. Results were compared between children with NAS, control children without NAS, and other NSW children. All were referenced to results published by the Department of Education and Training.[24] Statistical significance for all analyses was set at $P < .05$.

Ethics Approval

Ethics approval was obtained from the research ethics committees of the NSW Population and Health Services (2012/09/415), Aboriginal Health and Medical Research Council (1001/14), and all Australian educational sectors: the Board of Studies (for government schools), the Australian Independent Schools, and the Catholic Education Commission (D2014/120797).

RESULTS

Linkage was obtained between PDC records and at least ≥1 NAPLAN test result for 468 239 of 604 829 (77.4%) NSW children. Linkage rates were similar between control (3359 of 4330, 77.6%) and other NSW children (463 192 of 598 265, 77.4%; $P = .83$) but were significantly lower in children with NAS (1688 of 2234, 75.6%; $P = .03$) (Fig 1).

Patient Demographics

Compared with both control and other mothers in NSW, the mothers of children with NAS were younger, had more previous pregnancies, and were more likely to be Indigenous and to have had no antenatal care. They were more likely to deliver in a tertiary hospital and less likely

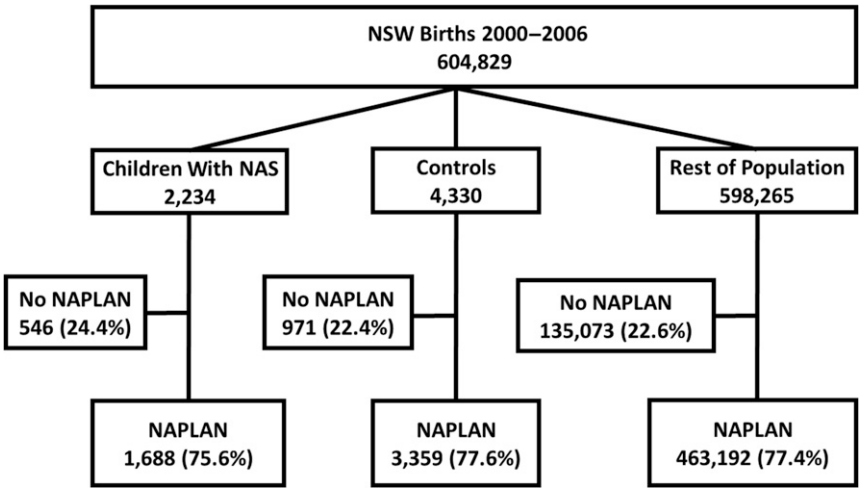

FIGURE 1
Linkage rates between children with NAS, control, and rest of NSW population to NAPLAN results.

to undergo cesarean delivery. Compared with control and other NSW infants, those with NAS were more likely to have lower 5-minute Apgar scores and lower birth weights (even when matched for gestation) and were more likely to be admitted to a nursery (Table 1).

Parental and School Characteristics

Almost half (44.0%) of the primary parents of children with NAS either did not disclose high school education levels or had a high school education below grade 9 (vs 18.4% control and 17.1% population parents, $P < .001$). More primary parents of NAS children did not have nonschool qualifications (70.6% vs 44.8% controls and 39.5% population, $P < .001$), only 4.3% of NAS parents had a bachelor's degree (vs 19.5% controls and 23.3% population, $P < .001$). More children with NAS were educated in government schools (88.3%) compared with control (71.0%) and other NSW (68.1%) children ($P < .001$).

Test Scores

Numerical scores (maximum score 1000) and the proportion of children not reaching NMS for each grade of testing and for each test domain are shown in Table 2. Children with NAS had significantly lower scores than either matched controls or other NSW children in every grade and every domain of testing. By grade 7, 37.7% of children with NAS did not meet NMS in ≥1 domain (vs 18.4% control and 14.5% other NSW children). Mean serial composite scores were consistently lower in children with NAS from grades 3 to 7 compared with the other 2 groups. This difference was progressive. By the time the children reached grade 7, scores for children with NAS were lower than scores for other children in grade 5 (Fig 2).

Logistic regression was conducted at each grade level of testing to determine the effects of perinatal and school factors on failure to meet NMS in the overall population, in children with NAS only (Table 3). In children with NAS, Indigenous status (adjusted odds ratio [aOR] 1.7), male gender (aOR 1.3), and having a primary parent without

TABLE 1 Patient Demographics

	NAS, $n = 2234$	Control, $n = 4330$	Population, $n = 598265$	NAS vs Control	NAS vs Population	Control vs Population	ANOVA F, df
Mother							
Maternal age, y	28.4 (5.7)	29.6 (5.8)	30.2 (5.5)	$P <.001$	$P <.001$	$P <.001$	128.1, 2*
Previous pregnancies	1.7 (1.6)	1.1 (1.3)	1.0 (1.1)	$P <.001$	$P <.001$	$P <.001$	371.3, 2*
Indigenous	336 (15.0%)	164 (3.8%)	15289 (2.6%)	3.9 (3.3–4.7)*	5.9 (5.3–6.5)*	1.5 (1.3–1.8)*	—
No antenatal care	318 (14.2%)	202 (4.7%)	15472 (2.6%)	3.4 (2.8–4.1)**	6.3 (5.5–7.0)**	5.3 (4.6–6.2)**	—
Tertiary hospital birth	1148 (51.3%)	1251 (28.9%)	161943 (27.1%)	2.6 (2.3–2.8)**	2.8 (2.6–3.1)**	1.1 (1.0–1.2)**	—
Rural residence	320 (14.3%)	732 (16.9%)	86353 (14.4%)	1.0 (0.9–1.2)**	1.7 (1.4–1.9)	1.6 (1.4–1.8)**	—
Cesarean delivery	504 (22.5%)	1333 (30.8%)	157995 (26.4%)	0.6 (0.5–0.07)*	0.8 (0.7–0.09)*	1.2 (1.1–1.3)*	—
Infant							
5-min Apgar	8.8 (0.9)	8.9 (1.1)	9.0 (0.9)	$P <.001$	$P <.001$	$P <.001$	56.5, 2*
Gestation, wk	37.9 (2.4)	37.9 (2.4)	39.0 (1.9)	$P =.78$	$P <.001$	$P <.001$	1053.2, 2*
Birth wt, g[a]	2852 (580)	3147 (682)	3386 (580)	$P <.001$	$P <.001$	$P <.001$	1297.1, 2*
Male	1175 (52.5%)	2303 (53.2%)	308166 (51.4%)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	1.1 (1.0–1.1)**	—
Nursery admission	1705 (76.3%)	1232 (28.4%)	100285 (16.8%)	8.1 (7.2–9.1)*	15.9 (14.4–17.6)*	4.7 (4.4–5.1)*	—

Values are expressed as mean (SD) or n (%); pairwise comparisons are expressed as odds ratio (95% CI). A $P < .05$ is considered significant. *df*, degrees of freedom. —, not applicable.
[a] Numbers represent total number of children who sat for a NAPLAN test during the study period in all 3 grades (3, 5, and 7).
* $P < .001$.
** $P < .05$.

TABLE 2 Test Scores for Each Domain and Grade

	Grade 3	Grade 5	Grade 7
NAS	*N* = 1663	*N* = 1104	*N* = 499
Controls	*N* = 3251	*N* = 2160	*N* = 992
Population	*N* = 447 536	N = 300 178	*N* = 160 154
Reading			
Mean (SD) score			
NAS	360.8 (81.8)	449.2 (72.9)	493.5 (68.3)
Controls	410.3 (86.6)	490.3 (77.5)	533.8 (74.7)
Population	422.9 (88.9)	501.3 (79.9)	546.7 (73.8)
ANOVA	$F = 63.4$,* *df* 2	$F = 85.3$,* *df* 2	$F = 109.8$,* *df* 2
NSW 2013 data[a]	424.0 (79.1)	506.4 (65.0)	544.1 (67.5)
Below NMS			
NAS	168 (10.1%)	150 (13.6%)	71 (14.2%)
Controls	143 (4.4%)	122 (5.6%)	53 (5.3%)
Population	15 515 (3.5%)	15 731 (5.2%)	6057 (3.8%)
NSW data[a]	2.1%	1.6%	3.9%
NAS vs controls	3.1 (2.4–3.9)*	2.6 (2.0–3.4)*	2.9 (2.0–4.3)*
NAS vs population	3.8 (3.2–4.6)*	2.8 (2.5–3.4)*	4.2 (3.3–5.4)*
Controls vs population	2.7 (2.4–3.0)*	1.1 (0.9–1.3)	1.4 (1.1–1.9)**
Numeracy			
Mean (SD) score			
NAS	350.1 (65.5)	440.3 (61.6)	489.8 (54.4)
Controls	393.1 (75.2)	485.2 (74.1)	536.6 (76.1)
Population	405.4 (78.1)	486.8 (78.5)	549.2 (79.9)
ANOVA	$F = 83.9$,* *df* 2	$F = 96.2$,* *df* 2	$F = 110.5$,* *df* 2
NSW 2013 data[a]	403.6 (67.4)	493.1 (76.8)	547.5 (77.4)
Below NMS			
NAS	145 (8.7%)	143 (12.9%)	52 (10.4%)
Controls	131 (4.0%)	118 (5.5%)	41 (4.1%)
Population	14 628 (3.3%)	13 610 (4.5%)	4387 (2.7%)
NSW data[a]	2.0%	4.6%	3.5%
NAS vs controls	2.2 (1.8–2.9)*	2.6 (1.9–3.3)*	2.7 (1.8–4.1)*
NAS vs population	2.8 (2.3–3.3)*	3.1 (2.6–3.7)*	4.1 (3.1–5.5)*
Controls vs population	1.2 (1.0–1.5)**	1.2 (1.0–1.5)**	1.5 (1.1–2.0)**
Writing			
Mean (SD) score			
NAS	365.1 (78.2)	428.7 (72.9)	442.4 (100.8)
Controls	415.3 (69.4)	474.8 (67.9)	501.2 (81.3)
Population	423.1 (68.9)	485.1 (69.0)	516.5 (79.1)
ANOVA	$F = 110.6$,* *df* 2	$F = 125.2$,* *df* 2	$F = 182.1$,* *df* 2
NSW 2013 data[a]	422.2 (68.1)	483.7 (68.4)	516.6 (76.3)
Below NMS			
NAS	136 (8.2%)	200 (18.1%)	131 (26.1%)
Controls	89 (2.7%)	131 (6.1%)	93 (9.4%)
Population	10 032 (2.2%)	16 457 (5.5%)	12 378 (7.7%)
NSW data[a]	3.1%	5.3%	9.4%
NAS vs controls	3.2 (2.4–4.2)*	3.4 (2.7–4.3)*	3.4 (2.6–4.6)*
NAS vs population	3.9 (3.3–4.6)*	3.8 (3.3–4.4)*	4.2 (3.5–5.2)*
Controls vs population	1.2 (0.9–1.5)**	1.1 (0.9–1.3)	1.1 (0.9–1.4)
Grammar			
Mean (SD) score			
NAS	357.2 (96.8)	446.9 (79.9)	490.7 (77.5)
Controls	417.2 (96.8)	496.5 (86.5)	530.4 (83.7)
Population	430.7 (97.2)	508.6 (88.7)	547.1 (85.5)
ANOVA	$F = 89.3$,* *df* 2	$F = 97.6$,* *df* 2	$F = 95.8$,* *df* 2
NSW 2013 data[a]	436.7 (81.1)	508.0 (70.5)	541.0 (78.4)
Below NMS			
NAS	232 (14.0%)	177 (46.4%)	86 (239%)
Controls	161 (4.9%)	138 (17.8%)	92 (11.7%)
Population	19 844 (4.4%)	17 027 (5.7%)	11 101 (6.9%)
NSW data[a]	1.9%	2.6%	7.1%
NAS vs controls	3.1 (2.5–3.8)*	3.1 (2.5–3.8)*	2.0 (1.5–2.8)*
NAS vs population	3.5 (3.0–4.0)*	3.5 (3.0–4.0)*	2.8 (2.2–3.5)*

TABLE 2 Continued

	Grade 3	Grade 5	Grade 7
Controls vs population	1.1 (0.8–1.5)	1.1 (0.9–1.3)	1.4 (1.1–1.7)**
Spelling			
Mean (SD) score			
NAS	356.5 (82.1)	447.3 (79.1)	504.2 (81.9)
Controls	412.3 (82.3)	496.4 (75.1)	544.9 (72.6)
Population	421.9 (82.3)	504.3 (74.9)	559.7 (71.8%)
ANOVA	$F = 92.6$,* df 2	$F = 98{\cdot}7$,* df 2	$F = 100.0$,* df 2
NSW 2013 data[a]	423.4 (78.7)	505.4 (75.3)	540.6 (66.3)
Below NMS			
NAS	235 (14.1%)	181 (16.4%)	82 (22.6%)
Controls	120 (3.7%)	108 (5.0%)	60 (7.6%)
Population	15 174 (3.4%)	13 211 (4.4%)	7507 (5.6%)
NSW data[a]	2.9%	4.1%	3.8%
NAS vs controls	4.3 (3.4–5.4)*	3.7 (2.8–4·8)*	3.1 (2.2–4.4)*
NAS vs population	4.7 (4.1–5.4)*	4.3 (3.6–5·0)*	4.1 (3.2–5.2)*
Controls vs population	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.3 (1.0–1.6)**
Any occasion below NMS			
NAS	479 (28.8%)	406 (36.7%)	189 (37.7%)
Controls	399 (12.3%)	341 (15.8%)	183 (18.4%)
Population	43 931 (9.8%)	40 589 (13.5%)	23 304 (14.5%)
NAS vs controls	2.4 (2.1–2.7)*	2.3 (2.1–2·6)*	2.1 (1.7–2.4)*
NAS vs population	1.2 (1.2–1.3)*	2.7 (2.5–2·9)*	3.6 (2.9–4.3)*
Controls vs population	2.9 (2·7–3.2)*	1.2 (1.1–1.3)**	1.3 (1.1–1.4)*

Values are expressed as mean (SD) or *n* (%); comparisons are expressed as odds ratio (95% CI). A $P < .05$ is considered significant. *Df*, degrees of freedom.

[a] NSW population data.[24]

* $P < .001$.

** $P < .05$.

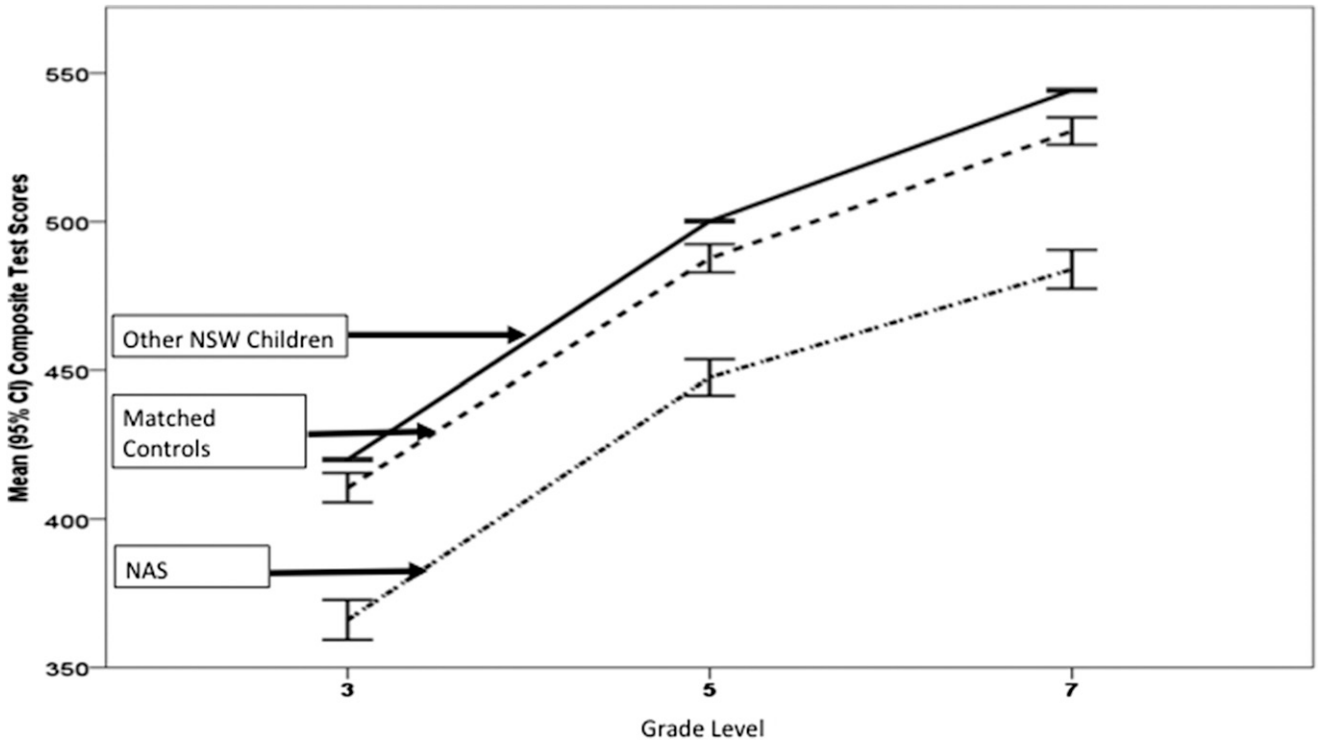

FIGURE 2
Composite NAPLAN test scores between children with NAS, control, and other NSW children.

TABLE 3 Associations With Failure to Meet NMS

Characteristic	Grade 3	Grade 5	Grade 7	Any Occasion Below NMS
For children with NAS (data expressed as aOR, 95% CI)				
Indigenous	1.3 (2.3–17.5)*	1.9 (1.3–2.7)*	1.3 (0.9–2.1)	1.7 (1.4–2.1)*
Male	0.8 (0.5–1.2)	1.7 (1.3–2.2)*	2.1 (1.5–3.1)	1.3 (1.2–1.6)*
Mother >30 y old	0.8 (0.5–1.3)	1.2 (0.9–1.6)	1.3 (0.9–1.9)	1.2 (0.9–1.4)
Preterm (<37 wk)	1.1 (0.6–1.9)	1.0 (0.7–1.4)	1.3 (0.8–2.0)	1.1 (0.9–1.3)
Parental education less than grade 9	1.0 (0.6–1.7)	1.2 (0.8–1.6)	1.9 (1.4–2.9)**	1.3 (1.0–1.5)**
Parent without nonschool education	1.3 (0.8–2.3)	1.6 (1.1–2.2)**	1.1 (0.7–1.7)	1.3 (1.1–1.6)**
For all children (data expressed as odds ratio [95% CI])				
NAS	3.5 (2.8–4.4)*	2.8 (2.4–3.2)*	2.4 (1.9–2.9)*	2.5 (2.2–2.7)*
Indigenous	2.9 (2.8–3.1)*	3.0 (2.9–3.1)*	3.1 (2.9–3.3)*	2.2 (2.2–2.3)*
Male	1.3 (1.3–1.4)*	1.5 (1.5–1.6)*	1.9 (1.9–2.0)*	1.3 (1.3–1.4)*
Mother >30 y old	0.6 (0.5–0.6)*	0.6 (0.5–0.6)*	0.6 (0.5–0.6)*	0.7 (0.7–0.8)*
Preterm (<37 wk)	1.3 (1.2–1.4)*	1.4 (1.3–1.4)*	1.4 (1.3–1.5)*	1.2 (1.2–1.3)*
Parental education less than grade 9	1.0 (0.9–1.0)	1.2 (1.1–1.3)*	1.4 (1.3–1.4)*	1.1 (1.0–1.2)*
Parent without nonschool education	1.9 (1.9–2.0)*	1.8 (1.7–1.9)*	1.8 (1.7–1.8)*	1.5 (1.5–1.6)*

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

grade 9 or nonschool education (aOR 1.3) increased the risk of failure to meet NMS. In the overall population, NAS (aOR 2.5), Indigenous status (aOR 2.2), male gender (aOR 1.3), prematurity (<37 weeks' gestation, aOR 1.2), and parental education below grade 9 (aOR 1.1) or no nonschool parental qualification (aOR 1.5) increased risk of failure to meet NMS.

DISCUSSION

This is the first report of academic outcomes at a population level for children with a history of NAS. Our results show that a diagnosis of NAS is associated with poorer performance in standardized and compulsory curriculum-based tests from as early as 8 or 9 years of age in grade 3 of school when compared with other NSW children, including those who were matched for gender, gestation, and socioeconomic status. Indeed, by the first year of high school, children with NAS performed even more poorly than other children in grade 5 who were, on average, 2 years younger. By grade 7, 44% of children with NAS had failed to meet NMS in ≥1 domain of testing.

This finding is of great concern because school failure increases the risk of myriad poor adult outcomes, including depression in women,[11] criminal activity,[13] and drug use.[14] We showed that children with NAS performed more poorly in all 5 test domains, including reading or literacy skills, 1 of the most important predictors of school success. Children who cannot read at expected levels by grade 3 are less likely to enroll in college or graduate high school.[30] In the United Kingdom, two-thirds of prisoners have a reading age <11 years.[31] Furthermore, test results in children with NAS worsened as they entered high school.

The cause for these effects is uncertain. NAS is caused by transplacental exposure to drugs of addiction or dependency that interfere with brain function and development. Opioids impair adult brain function and cognitive skills even after only a few days of use,[32] and their effects on the developing brain are subtle but long-lasting[33] and include alterations to neuronal apoptosis,[34] dendritic morphogenesis,[35] and neurotransmitter homeostasis.[36] We did not have information on the specific drugs used by the mothers, including psychotherapeutic agents, but multiple drug use is common[37] and includes use of legal substances such as alcohol[38] and nicotine.[39] Future studies should be designed to assess the impact of these variables on school performance in drug-exposed children and the impact of specific agents on children's learning abilities.

Postnatal factors may also compound poor outcomes. Infants with NAS may be treated for days to weeks with the same classes of drugs that initially caused the withdrawal,[40] and these drugs also have similar neurologic effects despite being legally prescribed.[32] There are no data evaluating the impact of postnatal NAS treatment on long-term outcomes, which is currently based on subjective clinical assessment, and infants are medicated with a variety of drugs depending on local practice.[37,40] Families affected by drug use disorders may be more socially chaotic,[41] with increased occasions of out-of-home care,[42] school mobility,[43] and other stressors such as poverty, poor nutrition, and poor parenting skills.[44] In a group of children born to heroin-using mothers, Ornoy et al[45] found that intellectual and learning abilities of children between ages 5 and 12 who were raised from an early age in foster homes were significantly better than that of children who remained with heroin-dependent parents, but reduced performance

on intelligence testing persisted, suggesting that early life stressors were of great importance in future outcomes. Efforts to assess the impact of out-of-home care on children with NAS are warranted because almost 50% of NSW children of methadone-using mothers are removed from their biological parents at birth, and another 25% are removed by 5 years of age.[42]

Two mitigating factors against school failure were maternal age and parental education levels. Having an older mother (>30 years) and having a primary parent with high school education above grade 9 or with some type of nonschool qualification significantly decreased the risk of failing to meet NMS, and this is a potentially modifiable public health factor. Encouraging women from high-risk families to extend education[46] and delay their first pregnancy[47] will be instrumental in improving childhood educational and health outcomes, even after biological risk factors such as prematurity are accounted for.[46]

Advantage must be taken of the fact that children with NAS can be identified from birth. Up to 16% of children have learning difficulties that are not identified before school,[47] and interventions are much more effective if they are instituted earlier. Campbell et al[15] showed that early support of vulnerable African American infants from 6 weeks of age prolonged education (13·5 vs 12·3 years), improved education achievements (more received a bachelor's degree, 23% vs 6%), and increased employment rates (75% vs 53%) even at the age of 30. Furthermore, learning difficulties and other behavioral problems, such as attention-deficit/hyperactivity disorder, are more common in children after intrauterine drug exposure,[45] and these problems must be taken into consideration.

We were limited by the inability to verify the coding of NAS or to identify infants who were not medicated because doing so would have necessitated deidentification for a medical record review. We also chose to match on a priori variables known to be associated with poorer school outcomes but acknowledge that other strategies for matching, such as propensity score matching (PSM), are options to preprocess data for causal inference. In observational studies such as this, the data generation process is rarely standard or uniform, so attempts to use PSM may increase imbalance, inefficiency, model dependence, research discretion, and statistical bias in both real data and data that are generated to meet the requirements of PSM modeling.[48] For these reasons the PSM approach was rejected. Regardless, 1 of the strengths of our study is the high linkage rate; other studies have obtained data only from government schools and achieved linkage rates of <50%.[26]

CONCLUSIONS

To date these are the only data demonstrating long-term school outcomes for children with a history of NAS. Similar data for children born from the current opioid epidemic gripping much of the Northern Hemisphere,[1] assuming linkage is possible, will be available only in 7 to 10 years. Although this study was conducted in Australia, the high risk of poor academic performance in this vulnerable group of children is applicable to all countries, and strategies to address this risk and prevent poor adult outcomes and intergenerational vulnerability must be urgently addressed.

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ABBREVIATIONS

ANOVA: analysis of variance
aOR: adjusted odds ratio
CI: confidence interval
ICD-10-AM: International Statistical Classification of Disease and Related Problems (10th Edition), Australian Modification
NAPLAN: National Assessment Program, Literacy and Numeracy
NAS: neonatal abstinence syndrome
NMS: National Minimum Standard
NSW: New South Wales
PDC: Perinatal Data Collection
PSM: propensity score matching

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