Mini Review

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Systematic review of the long-term effects of postnatal corticosteroids

https://doi.org/10.1515/jpm-2023-0297
Received July 19, 2023; accepted August 6, 2023;
published online August 23, 2023

Abstract

Background: Dexamethasone administration can reduce bronchopulmonary dysplasia, our objective was to identify long term adverse effects.
Content: A systematic review was performed to determine the childhood and adolescent cardiopulmonary and cognitive effects of dexamethasone systemically administered to preterm infants during neonatal intensive care. Relevant studies were identified by searching two electronic health databases and the grey literature. Spirometry assessments were used as respiratory outcomes, blood pressure and echocardiography assessments as cardiovascular outcomes and cognitive and motor function as cognitive outcomes. From 1,479 articles initially identified, 18 studies (overall 1,609 patients) were included (respiratory n=8, cardiovascular n=2, cognitive n=10); all were observational cohort studies. Dexamethasone exposure was associated with worse pulmonary outcomes in children and adolescents (more abnormal FVC and FEV1:FVC z scores). Dexamethasone exposure was associated in one study with lower IQ scores compared to preterm controls (mean 78.2 [SD 15.0] vs. 84.4 [12.6], [p=0.008]) and in two others was associated with lower total and performance IQ when compared to term controls (p<0.001).
Summary and outlook: Postnatal dexamethasone exposure has a negative influence on pulmonary and cognitive outcomes in childhood and adolescence. Medications with a better benefit to risk profile need to be identified.

Keywords: cardiac function; cognitive function; dexamethasone; lung function

Introduction

Bronchopulmonary dysplasia (BPD) is an important complication of preterm birth as it is associated with significant morbidity and mortality [1]. Systemic administration of dexamethasone can improve extubation success and reduce BPD [2] but does have adverse effects [3]. Follow up at two years corrected age demonstrated that dexamethasone given systemically postnatally increased respiratory morbidity [4], neuro-developmental impairment [5] and was associated with hypertrophic cardiomyopathy [6]. It is important, however, to determine if there are long term adverse effects of postnatal dexamethasone on respiratory, cognitive and cardiovascular function in older children and adolescents to give a more accurate risk benefit ratio. We, therefore, have performed a systematic review to examine the long-term health effects of administering dexamethasone during neonatal intensive care.

Methods

Literature search

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations, we performed a systematic search of the following databases: Medline and EMBASE. The search strategies for Medline and EMBASE are included in the Supplementary (Appendix 1). A search of grey literature (first 100 hits in Google scholar and PubMed) and reference lists of relevant review articles were manually checked. The literature search was conducted on articles published between January 2000 and February 2023.

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Article inclusion and exclusion criteria

Two authors independently screened all studies identifying duplicates, screening titles and abstracts and completing full text reviews. A third reviewer adjudicated over reviewer disagreements.

Articles were deemed eligible if they included details of respiratory, cardiac or cognitive assessment of children and/or adolescents (aged between 3 and 19 years) exposed to dexamethasone during neonatal intensive care and included both preterm dexamethasone exposed infants and control groups. The controls differed according to the study design. In some studies Preterm a prematurely born infants (a gestational age of less than 37 weeks) were included as the comparator group in other studies term born infants were used as the controls (a gestational age of greater than 37 weeks). Only articles in the English language were included.

The following types of articles were excluded after reviewing titles and abstracts: duplicates, letters, editorials, commentaries, reviews and meeting abstracts. Preclinical studies, pharmacodynamics and pharmacokinetics articles were also excluded.

Analysis

For the meta-analysis of respiratory reported outcomes, the included articles were required to report data on FVC z score, FEV_1 z score, FEV_1 % predicted and FEV_1:FVC z score using spirometry. Data were treated as continuous variables and for each parameter a random-effects analysis was performed in Review Manager (RevMan, version 4.5).

Results

The electronic literature search identified 1,473 studies; 586 studies were immediately removed as duplicates. Screening by title, then abstract excluded a further 843 studies. The full text of the remaining 44 articles was then assessed with three additional articles found in the search of grey literature (Google Scholar) and reference lists. The PRISMA diagram detailing the screening process can be found in the Supplementary (Appendix 2).

Eighteen studies were included in the systematic review (Table 1). Nine studies reported outcomes at follow-up from randomised controlled trials (RCT) of dexamethasone; five of the studies were placebo controlled double blind RCTs. All 18 studies were observational cohort studies (Table 1). The total number of patients in the original studies was 3,539 and the total number in the follow up studies was 1,609. In most of the studies the reported populations had a gestational age of less than 32 weeks and/or a birthweight of less than 1500 g. The studies by Karemaker et al. [7], and Romagnoli et al. [8, 9] did not specify a gestational age or birthweight for inclusion, but their reported median/mean gestational age and birthweight were below the above limits (Table 1). In three studies there were significant differences in the demographics of the exposed and unexposed groups (Table 1). Most studies reported the dexamethasone regimen used (17 of 18); the dose, frequency and length of treatment varied (Table 1).

Respiratory assessment

Spirometry was performed in eight studies; in seven FEV_1, FVC, FEV_1:FVC, FEF_{25-75} were assessed, but in one study only PEFR was measured. Significantly inferior lung function in those exposed to dexamethasone was reported in half the studies (Table 2). A total of five articles were eligible for meta-analysis (Figure 1A–D).

Cognitive outcomes

Cognitive outcomes were assessed in 10 studies, with the Weschler Intelligence Scale for Children used in six (Table 3). Other assessments used were the Differential Ability Scales [10], the British Ability Scales and the Stanford-Binet Scale of Intelligence (third version) [8, 9]. When compared to term populations, children exposed postnatally to dexamethasone had a significantly lower IQ in two studies (Table 3) [11, 12]. When compared to a matched preterm population, Yeh et al. [13] found that dexamethasone exposed children had significantly lower verbal and performance IQ scores and scores for perceptual organization, freedom from distractibility, processing speed, immediate visual memory and visual-motor integration than dexamethasone unexposed infants. Compared with preterm peers, Crotty et al. found motor skills were poorer, but the total IQs were similar [10].

Cardiovascular assessment

Only one study [14] performed echocardiography at follow up and found no significant differences in cardiac volumes or markers of pulmonary hypertension (tricuspid regurgitation and mean pulmonary artery peak flow velocity). Two studies reported blood pressure measurement results with no significant differences between groups [15, 16].

Discussion

Children and adolescents born preterm exposed to dexamethasone during neonatal intensive care had inferior lung function at follow up. In the two largest studies inferior lung function was found at 11–14 years [17] and 16–19 years [18]. At both time points, there was a dose dependent reduction in lung function, an effect which persisted after adjustment for

Table 1: Summary of studies and participant demographics.

Author	Age at follow up	Type of study	Original study participants	Follow up study participants	BW (dex exposed)	BW (control)	GA (dex exposed)	GA (control)	Dexamethasone dose regime
Romagnoli et al. [8]	3–4	Follow up of RCT[b]	50	30	850 (183)	948 (239)	27.5 (1.4)	27.1 (1.4)	0.5 mg/kg/day for the first six days, 0.25 mg/kg/day for the next six days, and 0.125 mg/kg/day for the last two days (total dose 4.75 mg/kg)
Romagnoli et al. [9]	3–4	Follow up of RCT[b]	50	45	940 (590–1,250)	940 (610–1,250)	28.2 (25–31)	28.4 (25–30)	0.5 mg/kg/d for the first 3 days, 0.25 mg/kg/d the next 3 days, and 0.125 mg/kg/d on the seventh day)
Mieskonen et al. [14]	8–10	Follow up of RCT[c]	23	16	905 (700–1,460)	830 (600–980)	25.9 (25.3–29)	25.8 (24.1–28.1)	0.5 mg/kg per day, divided into two doses, for one week
Jones et al. [25]	13–17	Follow up of RCT[b]	287	150	1,041 ± 340	998 ± 284	22–36	24–34	0.6 mg/kg/day for 1 week
Jones et al. [16]	13–17	Follow up of RCT[b]	287	150	1,041 ± 340	998 ± 284	22–36	24–34	0.6 mg/kg/day for 1 week
Gross et al. [26]	14–15	Follow up of RCT[c]	36	22	Dex42 851 (776–926) Dex18 810 (620–100)	948 (721–1,175)	Dex42 26 (25–27) Dex18 26 (24–28)	27 (24–29)	0.5 mg/kg/day, with taper
Yeh et al. [13]	5–11	Follow up of RCT[c]	262	146	1,398 ± 340	1,371 ± 343	29.8 ± 2.3	29.4 ± 2.5	0.25 mg/kg D1-7; 0.12 mg/kg 8–14, 0.05 mg/kg 15-21
Wilson et al. [15]	4–9	Observational cohort	570	60	Dex (early) 1,032 (252) Dex (late) 1,107 (368)		Dex (early) 27.6 (1.6) Dex (late) 27.5 (2.2)		0.05 mg/kg/day 3/7, then 0.25 mg/kg 3/7, then 0.10 mg/kg/day 3/7, and finally 0.05 mg/kg for 3/7 [Total 12/7]
O'Shea et al. [27]	4–11	Follow up of RCT[c]	N/A	84	758 (530–1,050)	784 (515–1,267)	25 (23–28)	26 (24–29)	0.25 mg/kg BD for 3/7, then 0.15 mg/kg BD for 3/7, then a 10 % reduction in the dose every 3/7 until the dose of 0.1 mg/kg on day 34. After 3 days on this dose, 0.1 mg/kg qod was given until 42 days after entry.
Nixon et al. [28]	8–11	Follow up of RCT[c]	118	68	743 (523–1,172)	789 (557–1,293)	25 (23–28)	26 (23.6–29.9)	0.5 mg/kg/day that was tapered over 42 days

Table 1: (continued)

Author	Age at follow up	Type of study	Original study participants	Follow up study participants	BW (dex exposed)	BW (control)	GA (dex exposed)	GA (control)	Dexamethasone dose regime
Karemaker et al. [7]	7–9	Observational cohort	208	139	Dex 972 ± 237	1,095 ± 193	Dex 27.8 ± 1.9	28.6 ± 1.0	0.5 mg/kg/day tapering off to 0.1/kg/day over 21/7 period
Smith et al. [29]	9–11	Observational cohort	N/A	102	999	999	999	999	N/A
Crotty et al. [10]	5–7	Observational cohort	N/A	228	720.4 (132.06)[a]	830.9 (103.9)[a] [ELBW] 3,500 (423.43)[a] [term]	25.2 (1.58)[a]	27.4 (2.39) [ELBW][a] 39.2 (0.97) [term][a]	0.1 mg/kg BD eight doses, then 0.05 mg/kg BD six doses
Wolbeek et al. [30]	14–17	Observational cohort	208	101	Dex 1,004 (249)	1,083 (239)	Dex 27.73 (1.69)[a]	28.42 (1.35)	0.5 mg/kg/day tapering off to 0.1/kg/day over 21/7 period
Hitzert et al. [11]	8–11	Observational cohort	77	53	920 (480–1,570)	N/A	27.1 (24–32)	N/A	0.5 mg/kg/d for 3/7 then A) 10 day taper OR B) 42 day taper
Harris et al. [17]	11–14	Observational cohort	797	179	810 (±175)[a]	939 (±205)[a]	25.6 ± 1.3[a]	26.7 ± 1.2[a]	0.25 mg BD for 3/7, then 0.15 mg BD for 3/7, then 0.05 mg BD for 3/7
Kraft et al. [12]	6–13	Observational cohort	56	27	830 (750–960)	N/A	26.7 (25.5–27.2)	N/A	0.25 mg/kg/d for 3/7 then A) 6 day taper (1.125 mg/kg) OR B) 14 day taper (2.075 mg/kg)
Harris et al. [18]	16–19	Observational cohort	797	159	782 (173.1)[a]	943 (217)[a]	25.9 (1.3)	27.3 (1.3)	0.25 mg BD for 3/7, then 0.15 mg BD for 3/7, then 0.05 mg BD for 3/7

BW, birthweight; GA, gestational age; Dex, dexamethasone; ELBW, extremely low birth weight; N/A, missing data; [a]statistically significant difference reported between groups. Data are presented as median (IQR) or mean (± standard deviation) (%) or mean difference (95 % CI). [b]Unblinded RCT, [c]placebo controlled double blind RCT.

neonatal factors. Importantly, there was a significant deterioration in FEF_{75} and FEV_1 between the ages of 11–14 and 16–19 years, when an improvement in lung function would have been expected during puberty. Over 90 % of the children and adolescents in those populations were exposed to antenatal corticosteroids and postnatal surfactant, so the results are relevant to the current era of neonatal care. The generally accepted lung function threshold for developing symptoms in COPD is a FEV_1:FVC ratio below 70 % of the predicted value [19] which corresponds to a z-score of –2.19. The dexamethasone exposed group in the cohort studied by Harris et al. had an FEV_1/FVC ratio z-score of –1.83 at 16–19 years [18] which is above the threshold but very close to it suggesting an increased risk of early onset COPD. Indeed, with a standard deviation of 1.25 some of the cohort would be at high risk.

Ten studies compared cognitive performance in preterm infants with or without postnatal corticosteroid exposure. The largest study reporting cognitive outcomes found that preterm infants who had corticosteroid exposure had significantly lower full IQ, verbal IQ, performance IQ as well as motor skills, coordination and visual motor integration scores at 5–11 years of age [13]. Two further studies including term controls found the dexamethasone exposed preterm populations to have poorer cognitive performance. Whilst there has been neurodevelopmental outcome reporting in

Table 2: Summary of respiratory outcomes.

Author	Respiratory measurement	Dexamethasone exposed	Control	RR or difference	
Mieskonen et al. [14]	FVC, % predicted	1.74 (0.38)	1.42 (0.36)[a]; 2.01 (0.46)[b]		p<0.05[a]
	FEV1, % predicted	81.8 (17.1)	77.5 (16.4)[a]; 102 (7.6)[b]		p<0.01[b]
	FEF_{50} % predicated	62.3 (25)	58.4 (23)[a]; 102 (15)[b]		p<0.01[b]
	ΔFEV1 post bronchodilator	9.9 (4.9)	9.4 (8)[a]; 1.3 (4.0)[b]		p<0.001[b]
Jones et al. [16]	FVC, z score	−0.32 (1.10)	−0.41 (1.15)[b]	Difference: 0.09 (0.32–0.50)	NS
	FEV1 z score	−0.74 (1.17)	−1.02 (1.2)[b]	Difference: 0.28 (−0.14 to 0.07)	NS
	FEV1/FVC ratio	0.79 (0.76–0.83)	0.78 (0.71–0.85)[b]	Difference: 0.02 (−0.02 to 0.04)	NS
	PEF, z score	−0.58 (1.2)	−0.79 (1.17)[b]	Difference: 0.21 (−0.21 to 0.63)	NS
	$FEF_{25-75\,\%}$ % of predicted value	4.7 (4.0)	6.6 (4.8)[b]	Difference: 6.0 (−2 to 0.04)	NS
	FVC>2 SD below mean			RR: 0.95 (0.27–3.35)	NS
	FEV1>2 SD below mean			RR: 0.77 (0.32–1.86)	NS
Gross et al. [26]	FVC, % predicted	106 (97–114)[d]; 83 (71–94)[e]	96 (79–114)[c]		p<0.01
	FEV1, % predicted	90 (78–102)[d]; 71 (54–87)[e]	73 (45–101)[c]		p<0.05
	$FEF_{25-75\,\%,}$ % predicated	81 (59–104)[d]; 66 (35–99)[e]	53 (12–94)[c]		NS
	RV % predicted	133 (103–164)[d]; 132 (97 vs. 167)[e]	176 (67–284)[c]		NS
Nixon et al. [28]	FVC % predicted	94	89[a]		NS
	FEV1 % predicted	86	76[a]		NS
	FEV1/FVC % predicted	81	80[a]		NS
	$FEF_{25-75\,\%,}$ % predicted	68	61[a]		NS
	ΔFEV1 post bronchodilator	3	7[a]		NS
Smith et al. [29]	FVC, z score	93.9 (13.1)	98.5 (12.3)[b]	Difference: −4.6 (−9.6 to 0.4)	0.07
	FEV1 z score	81.5 (11.4)	88.3 (12.6)[b]	Difference: −6.7 (−11.5 to −1.9)	0.01
	FEV1/FVC ratio	80.6 (8.9)	83.3 (7.6)[b]	Difference: −2.6 (−5.9 to 0.6)	0.11
	PEF z score	84.9 (16)	92.9 (16.9)[b]	Difference: −8.0 (−14.6 to −1.5)	0.02
	$FEF_{25-75\,\%,}$ z score	64.6 (19.7)	78 (23.5)[b]	Difference: −13.4 (−22.0 to −4.7)	0.003
Harris et al. [17]	FVC, z score	−0.24 (0.96)	−0.73 (1.11)[b]	Difference: −0.46 (0.74 to −0.18)	p=0.001
	FEV1 z score	−0.55 (1.03)	−1.44 (1.03)[b]	Difference: −0.86 (−1.2 to 0.53)	p<0.001
	FEV1/FVC ratio	−1.17 (1.69)	−2.32 (2.11)[b]	Difference: −0.86 (−1.20 to 0.53)	p<0.001
	PEF, % predicted	86 (14)	77 (13)[b]	Difference: −8.34 (−113.06 to −3.62)	p=0.001
	$FEF_{25-75\,\%,}$ z score	−1.24 (1.07)	−1.98 (1.05)[b]	Difference: −0.07 (−1.06 to −0.35)	p<0.001
	FRC_{pleth} z score	−0.11 (1.25)	0.39 (1.39)[b]	Difference: 0.49 (0.004–0.94)	p=0.031
	RV z score	0.26 (1.09)	1.29 (1.67)[b]	Difference: 0.99 (0.53–1.45);	p<0.001
Harris et al. [18]	FVC, z score	−0.15 (1.36)	−0.46 (1.28)[b]	Difference: −0.01 (−0.62 to 0.06)	0.984
	FEV1 z score	−0.72 (1.28)	−1.74 (1.14)[b]	Difference: −0.65 (−1.19 to −0.10)	0.023
	FEV1/FVC ratio	−0.89 (1.1)	−1.83 (1.25)[b]	Difference: −0.08[a]	0.003
	PEF z score	−1.08 (1.00)	−0.22 (1.05)[b]	Difference: −0.75 (−1.13 to −0.38)	0.003
	$FEF_{25-75\,\%,}$ z score	−1.12 (1.16)	−2.3 (1.22)[b]	Difference: −0.08[a]	0.003
	FRC_{pleth} z score	0.39 (1.28)	1.24 (1.39)[b]	Difference: 0.78[a]	0.011
	RV_{pleth} z score	1.75 (1.57)	0.81 (1.18)[b]	Difference: 0.90 (0.32–1.48)	0.003

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; $FEF_{n\%}$, forced expiratory flow at n% of the vital capacity; RV, residual volume; FRC, functional residual capacity; PEFR, peak expiratory flow rate; Data are presented as median (IQR) or mean (± standard deviation) (%) or mean difference (95 % CI). [a]Placebo control group; [b]preterm control group; [c]term control group; Δ, change in %; [d]42 day tapering course; [e]18 day tapering course.

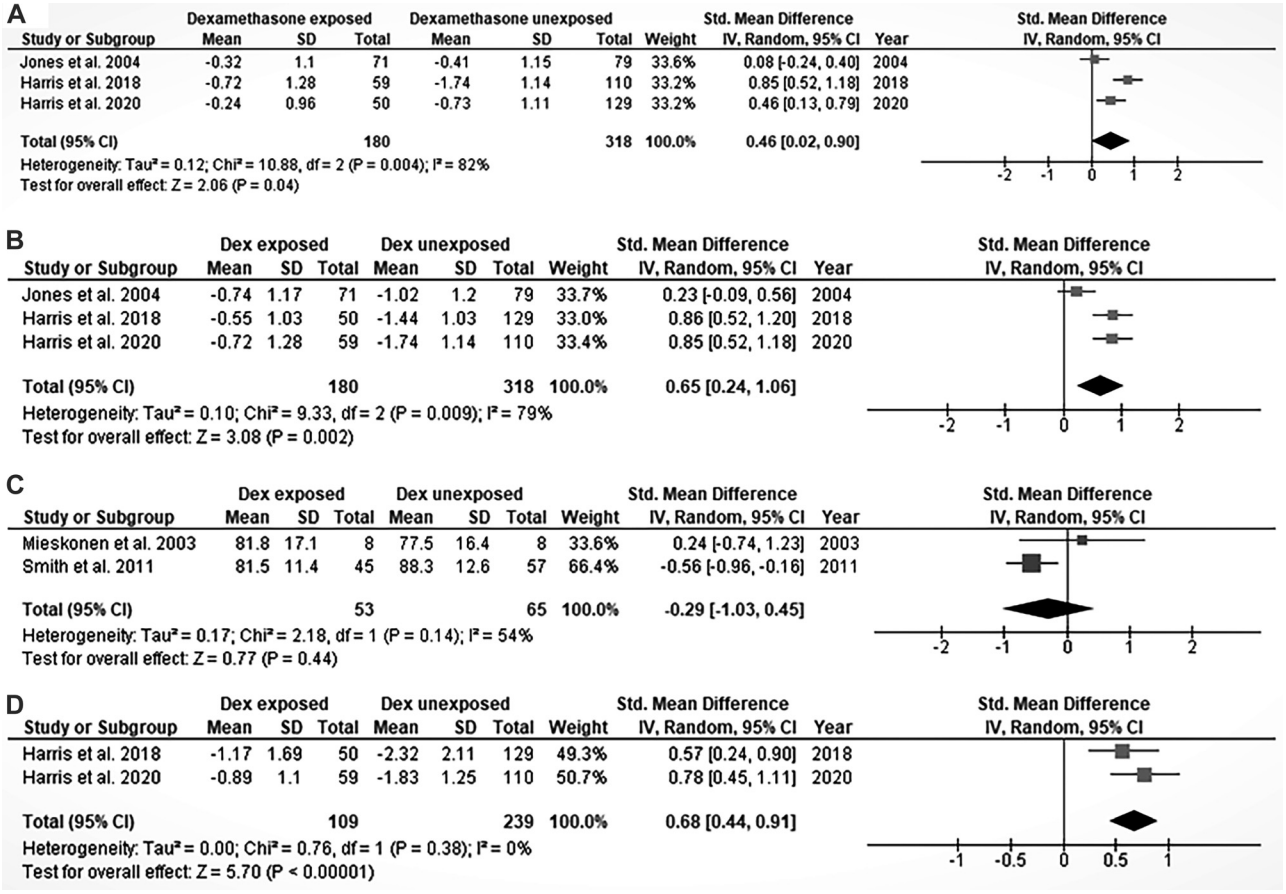

Figure 1: Meta-analysis of respiratory outcomes. (A) Standard mean difference in FVC z score between dexamethasone exposed and unexposed. (B) Standard mean difference in FEV_1 z score between dexamethasone exposed and unexposed. (C) Standard mean difference in FEV_1 % predicted between dexamethasone exposed and unexposed. (D) Standard mean difference in FEV_1:FVC z score between dexamethasone exposed and unexposed. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 min.

children and adolescents born extremely premature [20, 21], this is the first time that administration of corticosteroids during neonatal intensive care has been shown to contribute a negative impact on cognitive outcomes in children and adolescents born extremely prematurely.

These adverse effects have biological plausibility. In preclinical models, systemically administered postnatal corticosteroids have been shown to result in delayed alveolarization and emphysematous changes resulting in fewer air spaces [22]. Dexamethasone has also been shown to increase brain apoptosis and defective myelination in neonatal rats [23, 24].

An effect of systemically administered postnatal corticosteroid use is hypertrophic cardiomyopathy because of abnormal cardiomyocyte maturation [6]. While this effect is reported as transient, there is no available evidence on the long-term effects on cardiac structure or function following postnatal corticosteroid exposure. No significant differences in blood pressure results at follow-up were reported between those exposed or not exposed [15].

This review is the first to summarise the long-term effects of systemically administered postnatal corticosteroids and there was a large number of included participants. A limitation of this review is the heterogeneity of outcome reporting, as well as the variability in the dosing regimes (Table 1). As a result, a meta-analysis of cognitive outcomes was not possible. Many of the studies were cohort studies from previous RCTs and loss to follow up was common as was selection bias with only those alive and capable of performing the outcome measures included.

Conclusions

The long-term effects of postnatal corticosteroids in childhood and adolescence have infrequently been reported, but include impaired respiratory and cognitive outcomes. There has been a move towards using inhaled corticosteroids to avoid the side-effects of systemically administered

Table 3: Summary of cognitive outcomes.

Author	Assessment tools		Dex exposed	Dex unexposed	
Romagnoli et al. [8]	Scale of Intelligence Stanford-Binet	IQ score	84.2 (12.4)	83 (15.6)	NS
Romagnoli et al. [9]	Scale of Intelligence Stanford-Binet	IQ score	85.8 (13.9)	85.6 (16.3)	NS
Gross et al. [26]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	85 (77–93)[b]; 69 (51–86)[c]	73 (45–101)	NS
		Verbal IQ	89 (77–101)[b]; 74 (56–92)[c]	78 (48–108)	NS
		Performance IQ	83 (76–91)[b]; 68 (53–84)[c]	70 (40–100)	NS
Yeh et al. [13]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	78.2 (15.0)	84.4 (12.6)	p=0.008
		Verbal IQ	84.1 (13.2)	88.4 (11.8)	p=0.04
		Performance IQ	76.5 (14.6)	84.5 (12.7)	p=0.001
	Movement ABC-2, age-band 3	Total score	19.2 (12.4)	11.6 (10.3)	p<0.001
	Beery-Buktenica test of visual-motor integration	Motor co-ordination	6.7 (2.3)	8.2 (2.5)	p<0.001
		Visual perception	6.5 (2.4)	7.9 (2.1)	p=0.02
		Visual-motor co-ordination	7.1 (2.4)	7.9 (1.8)	p=0.02
Wilson et al. [15]	British ability scales, second edition		86 (16)[d]; 90 (19)[e]		NS
	Strength and difficulties questionnaire		10 (5)[d]; 11 (6)[e]		NS
	Child Behaviour Checklist for children 4–18 years of age		45 (10)[d]; 41 (10)[e]		NS
O'Shea et al. [27]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	90 (48–115)[a]	85 (63–111)[a]	NS
		Verbal IQ	94 (56–118)[a]	90 (62–125)[a]	NS
		Performance IQ	86 (47–110)[a]	86 (66–106)[a]	NS
	Kaufman survey of early academic and language skills and the Vineland Adaptive Behavioural Scales (VABS)	Verbal	95 (50–118)[a]	85 (52–115)[a]	NS
		Nonverbal	84 (47–109)[a]	79 (43–102)[a]	NS
		General cognitive	88 (52–103)[a]	81 (45–105)[a]	NS
Crotty et al. [10]	Differential ability scales	General conceptual ability	94.2 (17.67)	99.5 (15.79)	
		Verbal composite	96.4 (18.61)	98.9 (15.34)	
	Beery-Buktenica test of visual-motor integration		87.0 (13.77)	95.3 (12.81)	p=0.009
Wolbeek et al. [30]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	86 (16)	90 (15)	NS
	Movement ABC-2, age-band 3,	Total score	4.38 (2.45)	5.69 (2.62)	NS [p=0.08]
Hitzert et al. [11]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	88 (14)[f]		
		Verbal IQ	91 (15)		NS
		Performance IQ	86 (17)		NS
	Motor function: Movement ABC-2, age-band 3	Total score	N/A[g]	N/A[g]	
Kraft et al. [12]	Wechsler Intelligence Scale for Children, third edition (WISC-III)	Full scale IQ	87 (75–87)[h]	0.18 (−0.30 to 0.65)	p<0.001[h]
		Verbal IQ	95 (85–109)		NS
		Performance IQ	77 (70–95)[h]		p<0.001[h]
	Movement ABC-2, age-band 3	Total score	16.5 (12.5–19.5)[h]	−1.16 (−1.51 to 0.82)	p<0.05[h]

Data are presented as median (IQR) or mean (± standard deviation) (%) or mean difference (95 % CI) or [a]median (5th–95th centile). [b]42-day dexamethasone tapering dose; [c]18-day dexamethasone tapering dose; [d]early dexamethasone; [e]late dexamethasone; [f]compared to the norm population, more DXM-treated children had total, verbal and performance IQs below 85 (p<0.001, p=0.002, p<0.001, respectively), and more children had a performance IQ below 70 (p=0.001); [g]compared to the norm population, DXM-treated children scored worse on all scales of the Movement-ABC; [h]dex group w/lower total and performance IQs than norm population (p<0.001) but not preterm group; full scale IQ mean z-score −0.29 to −1.12 in dex group compared to norm population; motor mean z-score − 1.81 in dex group vs. 'norm population'.

corticosteroids. A promising approach is using surfactant as the vehicle to deliver intra-tracheal budesonide, importantly the corticosteroid dose is much smaller [31]. Safer and effective treatments to prevent and ameliorate BPD need to be urgently identified.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: AG, TD and AJ designed the systematic review, AJ and OK independently screened all possible studies and AG adjudicated if there were disagreements. All authors were involved in the preparation of the manuscript. The authors accept responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

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Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/jpm-2023-0297).