S1 File: Supplement

Effect of dexamethasone exposure on the neonatal unit on adolescent lung function

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Further Baseline data (S1 file: Online supplement. Tables A-C)

Table A shows lung function at follow up in children with or without complete data and shows little evidence of bias in our dataset.

Table B shows reasonable balance according to whether follow-up lung function data were or were not available.

Table C gives mean FEF_{75} z-score by neonatal factors and shows that most neonatal factors had a limited effect on later lung function. This supports our suggestion that the observed effects of dexamethasone are unlikely to be fully explained by uncontrolled confounding.

26 S1 File: Online supplement. Table A: Lung function at follow up of children with and without
27 complete data.

Lung Function	N	Complete covariate data Mean(SD) (n=179)	Missing covariate data Mean(SD) (n=69)	p-value
FEF_{75} z score	248	-1.09 (0.89)	-1.03 (0.87)	0.748
FEF_{50} z score	248	-1.22 (0.92)	-1.20 (0.85)	0.837
FEF_{25} z score	248	-1.02 (0.95)	-0.95 (0.89)	0.403
FEF_{25-75} z score	231	-1.46 (1.11)	-1.46 (0.97)	0.995
FEV_1 z score	248	-0.80 (1.10)	-0.71 (0.95)	0.563
FVC z score	248	-0.38 (1.02)	-0.32 (0.84)	0.769
FEV_1:FVC z score	248	-1.49 (1.88)	-1.33 (1.50)	0.527
PEF percentage predicted	247	83.6 (14.9)	82.9 (16.3)	0.991
RV z score	211	0.54 (1.35)	0.06 (0.96)	0.018
FRC_{pleth} z score	218	0.03 (1.31)	-0.40 (1.11)	0.034
FRC_{he} z score	229	-0.64 (1.07)	-0.77 (1.06)	0.469
DL_{CO} z score	210	-0.94 (1.09)	-0.97 (1.03)	0.941
Respiratory resistance - percentagepredicted				
At 5 Hz	237	97.2 (23.0)	91.3 (19.6)	0.098
At 20 Hz	237	93.2 (23.0)	89.76 (22.5)	0.380

28 S1 file: Online supplement. Table B: Baseline characteristics of the infants included and not included due to missing lung function data

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Characteristics	Sample analysed with complete data N=179	Sample not analysed with incomplete data N=223	Comparison of complete and incomplete samples
	% (n) or mean (SD)	% (n) or mean (SD)	p-value
Birth weight	882 (208)	912 (211)	0.15
Gestational age	26.5 (1.3)	26.2 (1.4)	0.06
Male sex	51% (91)	54% (125)	0.57
Multiple birth	25% (44)	22% (52)	0.59
Postnatal dexamethasone use	28% (50)	30% (70)	0.64
Oxygen dependency at 28 days	82% (147)	81% (188)	0.71
Oxygen dependency at 36 weeks PMA	59% (105)	58% (135)	0.88
Oxygen dependency at hospital discharge	24% (43)	21% (50)	0.50
Major ultrasound abnormality in neonatal period	13% (23)	15% (36)	0.46
Maternal smoking in pregnancy	23% (41)	27% (58)	0.31

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31   S1 File: Online supplement. Table C: Mean FEF_{75} z-score by neonatal factors (n=179)

	Mean FEF_{75} z-score (SD)	p-value
Birth weight <860g (89) ≥860g (90)	-1.12 (0.95) -1.07 (0.83)	0.71
Birthweight standard devaion score <-0.5 (90) ≥-0.5 (89)	-1.16 (0.86) -1.02 (0.91)	0.28
Gestational age 23-25wk (42) 26-28wk (137)	-1.11 (0.95) -1.09 (0.87)	0.91
Sex Girl (88) Boy (91)	-1.00 (1.03) -1.18 (0.71)	0.18
Multiple birth Singleton (135) Multiple (44)	-1.22 (0.82) -0.70 (0.98)	<0.001
Oxygen dependency at 36 weeks PMA No (74) Yes (105)	-0.95 (0.84) -1.19 (0.91)	0.08
Neonatal cranial ultrasound Normal (156) Abnormal (23)	-1.09 (0.91) -1.11 (0.72)	0.92
Airleak No (158) Yes (21)	-1.10 (0.89) -1.02 (0.87)	0.68
Patent ductus arteriosus No (125) Yes (54)	-1.11 (0.92) -1.05 (0.80)	0.72
Pulmonary haemorrhage		

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No (169)	-1.07 (0.89)	0.15
Yes (10)	-1.48 (0.85)	
Mode of ventilation		
CV (90)	-1.19 (0.79)	0.13
HFOV (89)	-0.99 (0.96)	
Apgar score at 5 mins		
<9 (82)	-1.06 (0.95)	0.66
≥9 (97)	-1.12 (0.83)	
Maternal smoking in pregnancy		
No (138)	-1.01 (0.86)	0.65
Yes (41)	-1.04 (0.99)	
Antenatal steroids		
No (17)	-1.09 (0.67)	0.98
Yes (161)	-1.09 (0.91)	

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Propensity Score Matching (S1 File: Online supplement. Table D)

Since the use of postnatal dexamethasone is so highly confounded by neonatal factors, we also used propensity score matching for

dexamethasone exposure (yes/no) [S4] as an alternative way of adjustment in addition to linear mixed model regression. Propensity score (PS)

matching works differently to multiple regression in that it matches the subjects as closely as possible using baseline factors prior to analysis so

that the study closely resembles a randomised trial

The matching algorithm used was up to three nearest neighbours for each case. This approach was used because it leads to less bias than if the

single nearest neighbour approach is used without replacement [S4]. Logistic regression models were used to assign a probability of steroid use

to each child based on their baseline characteristics. The model included data collected prior to the initiation of steroid use, namely: sex, birth

weight, birth weight z-score, gestational age in weeks (in keeping with the original trial's randomisation strata), smoking in pregnancy, multiple

birth, ventilation group and Apgar score at five minutes. Children who received dexamethasone, were then matched to three children who did not

receive dexamethasone with the closest propensity scores.

The main challenge of the PS method is to obtain close matches for all subjects. Inspection of the table of variables by groups before and after

matching showed substantial improvement achieved by PS with no significant imbalance for any variable. It was not possible to use propensity

score matching for three measures of dexamethasone exposure, that is timing of administration, number of courses and days of exposure due to

the small numbers in the different dexamethasone-use categories. For this reason, only adjustment by multivariable logistic regression was

49   undertaken for those measures. A further limitation of PS matching in this context is that it is difficult to adjust for clustering within propensity

50   score models.

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52   S1 File: Online supplement. Table D: Lung function and postnatal dexamethasone exposure: sensitivity analyses adjusted for confounding using propensity
53   score matching
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Lung Function	N	No dexamethasone exposure Mean (SD)	Dexamethasone exposure Mean (SD)	Adjusted using multiple regression (main analysis) Difference (95% CI)	p-value	Adjusted using propensity score matching (sensitivity) Difference (95% CI)	p-value
FEF_{75} z score	179	-0.95 (0.91)	-1.45 (0.71)	-0.53* (-0.85 to -0.21)	0.002	-0.51 (-0.89 to -0.13)	0.009
FEF_{50} z score	179	-1.04 (0.89)	-1.71 (0.81)	-0.74 (-1.05 to -0.43)	<0.001	-0.54 (-0.93 to -0.14)	0.006
FEF_{25} z score	179	-0.82 (0.91)	-1.53 (0.86)	-0.75 (-1.07 to -0.44)	<0.001	-0.51 (-0.78 to -0.24)	<0.001
FEF_{25-75} z score	169	-1.24 (1.07)	-1.98 (1.05)	-0.70 (-1.08 to -0.33)	<0.001	-0.55 (-0.99 to -0.11)	0.014
FEV_1 z score	179	-0.55 (1.03)	-1.44 (1.03)	-0.87 (-1.24 to -0.51)	<0.001	-0.62 (-1.00 to -0.24)	0.002
FVC z score	179	-0.24 (0.96)	-0.73 (1.11)	-0.38 (-0.75 to -0.01)	0.043	-0.23 (-0.59 to 0.14)	0.221
FEV_1:FVC z	179	-1.17 (1.69)	-2.32 (2.11)	-1.43 (-2.09 to -0.78)	<0.001	-1.16 (-1.98 to -0.34)	0.006
PEF % pred*	178	86.07 (14.64)	77.36 (13.98)	-10.74 (-16.06 to -5.41)	<0.001	-7.42 (-11.5 to -3.4)	<0.001
RV z score	152	0.26 (1.09)	1.29 (1.67)	0.86 (0.36 to 1.36)	0.001	0.67 (0.27 to 1.07)	0.001
FRC_{pleth} z	157	-0.11 (1.25)	0.39 (1.39)	0.39 (-0.11 to 0.90)	0.128	0.37 (0.01 to 0.73)	0.042
FRC_{he} z score	168	-0.73 (1.09)	-0.42 (1.00)	0.27 (-0.13 to 0.66)	0.186	0.30 (-0.06 to 0.67)	0.106
DL_{CO} z score	149	-0.93 (1.11)	-1.04 (1.02)	0.09 (-0.33 to 0.52)	0.658	-0.01 (-0.61 to 0.59)	0.968
At 5 Hz	170	96.06 (21.38)	100.11 (27.03)	9.57 (1.13 to 18.02)	0.026	1.22 (-5.42 to 7.86)	0.719
At 20 Hz	170	93.94	91.28	2.49	0.578	-1.57	0.669

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| | | (19.82) | (4.46) | (-6.27 to 11.25) | | (-8.79 to 5.64) | |

Further details on statistical analysis (S1 File: Online supplement. Tables E and F)

Since differences in mean z-scores can be difficult to interpret, we have additionally

presented the equivalent difference in the proportion of children with abnormal lung function.

To do this we have used the 5th centile for normal to define the cut-off between 'normal' and

'abnormal'. Since in healthy children the z-score has a Normal (Gaussian) distribution, the

cut-point for abnormality is defined as $z < -1.645$, the 5th centile of the Normal Distribution.

The proportion abnormal is not calculated using the data values themselves but using a

statistical model to gain precision. These calculations are similar to those performed to

calculate reference ranges. The calculations used a statistical method called the

'distributional approach'[table 3] The distributional approach provides more precise values

than we would obtain had we used the data alone. In the present study, the adjusted estimates

from the multivariable mixed model analyses were used to estimate the difference in the

proportion of children who have abnormal lung function in those children who were and

were not exposed to steroids. The calculations use the same adjusting factors to allow for

confounding neonatal factors as the main analyses [table 3].

The differences for all analyses in main paper Table 2 are shown in Table 3. They show that

what may seem to be quite small differences in mean z-score, eg, 0.53 standard deviations for

FEF_{75}, translate into quite substantial differences in the percentage that have abnormal lung

function results, 22 percentage points, and so the additional data help to make the results

more clinically meaningful.

77   Table S5 is a further sensitivity analysis that adjusts for antenatal steroids and postnatal

78   surfactant. This table shows no appreciable effect of this change in the modelling. Table S6

79   gives the random effects estimates for the mixed effects models shown in the main paper,

80   table 2.

S1 File: Online supplement. Table E: Sensitivity analyses adjusting for antenatal steroids and postnatal surfactant

Lung Function	N	No dexamethasone exposure Mean (SD)	Dexamethasone exposure Mean (SD)	Adjusted using original variables (Table 2 in text) Difference (exposed-unexpo) (95% CI)	Adjusted using original variables + antenatal steroids, postnatal surfactant Difference (exposed-unexpo) (95% CI)
FEF_{75} z score	179	-0.95 (0.91)	-1.45 (0.71)	-0.53 (-0.85 to -0.21)	-0.52 (-0.84 to -0.20)
FEF_{50} z score	179	-1.04 (0.89)	-1.71 (0.81)	-0.74 (-1.05 to -0.43)	-0.73 (-1.04 to -0.43)
FEF_{25} z score	179	-0.82 (0.91)	-1.53 (0.86)	-0.75 (-1.07 to -0.44)	-0.77 (-1.09 to -0.46)
FEF_{25-75} z score	169	-1.24 (1.07)	-1.98 (1.05)	-0.70 (-1.08 to -0.33)	-0.68 (-1.06 to -0.31)
FEV_1 z score	179	-0.55 (1.03)	-1.44 (1.03)	-0.87 (-1.24 to -0.51)	-0.88 (-1.24 to -0.51)
FVC z score	179	-0.24 (0.96)	-0.73 (1.11)	-0.38 (-0.75 to -0.01)	-0.40 (-0.77 to -0.02)
FEV_1:FVC z	179	-1.17 (1.69)	-2.32 (2.11)	-1.43 (-2.09 to -0.78)	-1.42 (-2.08 to -0.75)
PEF % pred*	178	86.07 (14.64)	77.36 (13.98)	-10.74 (-16.06 to -5.41)	-10.75 (-16.15 to -5.35)
RV z score	152	0.26 (1.09)	1.29 (1.67)	0.86 (0.36 to 1.36)	0.86 (0.38 to 1.39)
FRC_{pleth} z	157	-0.11 (1.25)	0.39 (1.39)	0.39 (-0.11 to 0.90)	0.40 (-0.12 to 0.91)
FRC_{he} z score	168	-0.73 (1.09)	-0.42 (1.00)	0.27 (-0.13 to 0.66)	0.21 (-0.18 to 0.61)
DL_{CO} z score	149	-0.93 (1.11)	-1.04 (1.02)	0.09 (-0.33 to 0.52)	0.06 (-0.36 to 0.49)
At 5 Hz	170	96.06	100.11	9.57	8.60

		(21.38)	(27.03)	(1.13 to 18.02)	(0.10 to 17.10)
At 20 Hz	170	93.94 (19.82)	91.28 (4.46)	2.49 (-6.27 to 11.25)	1.84 (-7.02 to 10.71)

1   S1 File: Online supplement. Table F: Random effects estimates from adjusted models presented in
2   table 2 main paper

Lung Function	SD Intercept	SD Residual
FEF_{75} z score	0.54	0.62
FEF_{50} z score	0.60	0.54
FEF_{25} z score	0.52	0.63
FEF_{25-75} z score	0.80	0.55
FEV_1 z score	0.58	0.74
FVC z score	0.58	0.76
FEV_1:FVC z score	1.25	1.19
PEF % pred*	10.96	8.55
RV z score	0.70	0.93
FRC_{pleth} z	0.80	0.97
FRC_{he} z score	0.62	0.78
DL_{CO} z score	0.73	0.70
At 5 Hz	16.41	14.14
At 20 Hz	15.42	16.13

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References

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