Neonatal caffeine treatment and respiratory function at 11 years in children <1251 g birth weight

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Contributor's statements

Lex Doyle – wrote the first draft of the manuscript, conception and design of the study, data analysis and interpretation, drafting and revising the article; and approval of the final manuscript as submitted.

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At a Glance Commentary

Scientific Knowledge on the Subject: Caffeine treatment of preterm newborn infants reduces apnea of prematurity, shortens the need for assisted ventilation and reduces lung injury in the short-term. Long-term effects on respiratory health are unknown.

What This Study Adds to the Field: This study shows, within the context of a randomized controlled trial, that neonatal caffeine compared with placebo improves expiratory flow rates at 11 years of age. This is an additional longer-term respiratory benefit of neonatal caffeine therapy. Given the known short- and long-term benefits of neonatal caffeine therapy, with no evidence for any harmful effects, such a placebo-controlled randomized trial is unlikely to ever be repeated.

Abstract

Rationale: Caffeine in the newborn period shortens the duration of assisted ventilation and reduces the incidence of bronchopulmonary dysplasia, but its effects on respiratory function in later childhood are unknown.

Objectives: To determine if children born <1251 g birthweight who were treated with neonatal caffeine had improved respiratory function at 11 years of age compared with children treated with placebo.

Methods: Children enrolled in the Caffeine for Apnea of Prematurity randomized controlled trial and assessed at the Royal Women's Hospital in Melbourne at 11 years of age had expiratory flow rates measured according to the standards of the American Thoracic Society. Values were converted to z-scores predicted for age, height, ethnicity and sex. Parents completed questionnaires related to their child's respiratory health.

Results: 142 children had expiratory flows measured. Expiratory flows were better in the caffeine group, by approximately 0.5 SD for most variables (e.g. forced expired volume in one second; mean z-score -1.00 vs. -1.53; mean difference 0.54, 95% confidence interval [CI] 0.14, 0.94, P=0.008). Fewer children in the caffeine group had values for the forced vital capacity <5th centile (11% vs 28%; odds ratio 0.31, 95% CI 0.12, 0.77, P=0.012). When adjusted for bronchopulmonary dysplasia, the differences in flow rates between groups diminished.

Conclusions: Caffeine treatment in the newborn period improves expiratory flow rates in mid-childhood, which it seems to achieve by improving respiratory health in the newborn period. Follow up lung function testing in adulthood will be vital. Future placebo-controlled randomized trials of neonatal caffeine are unlikely.

Word count: 250

Introduction

Infants born very preterm (<32 weeks' gestational age) or very low birthweight (<1500 g) have worse expiratory air flow in childhood and adulthood than those born at term or of normal birthweight.[1] Among preterm infants, those who develop bronchopulmonary dysplasia (BPD) in the newborn period have even worse lung function in later life than those who did not have BPD.[1-5]

There are few treatments in the newborn period that can reduce the rates of BPD, and caffeine is one of them. In the Caffeine for Apnea of Prematurity (CAP) randomized controlled trial, 2006 infants with birthweights <1251 g and who were less than 10 days after birth were randomly allocated to either caffeine citrate or placebo if their treating doctor considered they were likely to have apnea of prematurity.[6] Infants in the CAP trial who were treated with caffeine had assisted ventilation ceased approximately one week earlier than those treated with placebo, and a reduction in the rate of BPD (i.e. supplemental oxygen at 36 weeks' postmenstrual age) from 47% to 36%.[6] However, the effects of early caffeine on pulmonary function and respiratory health in later childhood are unknown.

The aims of this study were to determine if children born <1251 g birthweight and who were treated with caffeine in the newborn period as part of the CAP trial had improved respiratory health, including expiratory airflows, at 11 years of age compared with children treated with placebo, and if the effect of caffeine on long-term airflow in the lung was independent of its effects on the rate of BPD in the newborn period. We hypothesized that respiratory function would be better in children in the caffeine group.

Methods

The Royal Women's Hospital in Melbourne, Australia, was one of the 35 hospitals that participated in the CAP study; of the total of 2006 infants enrolled in the CAP study, 199

(10%) infants were recruited from our hospital. The details of the CAP study design, caffeine treatment and outcomes in the newborn period have been described elsewhere.[6] Briefly, infants of 500-1250 g birthweight aged less than 10 days after birth who were considered candidates for treatment with caffeine by their treating clinicians were randomly allocated either to caffeine citrate 20 mg/kg loading and 5-10 mg/kg/day maintenance, or to an equal volume of saline placebo. Treatment was continued until the treating clinicians considered it was no longer required, which mostly occurred after 34 weeks of postmenstrual age. The CAP trial is registered on ClinicalTrials.gov (NCT00182312). Surviving children in the CAP study were assessed at 18 months,[7] 5 years[8] and 11 years[9] of age as part of the overall study design, with the emphasis on determining the neurological and cognitive consequences of caffeine treatment, results of which have been reported elsewhere.[7-9] The Royal Women's Hospital participated in each of these follow-up phases. At the 11-year assessment parents completed questionnaires related to health of their child, including respiratory health[10] and medications related to asthma treatment.

Lung function tests

At the 11 year assessment, in addition to the assessments required by the overall study,[9] children who were assessed by the team at the Royal Women's Hospital in Melbourne also had expiratory flow rates measured according to the standards of the American Thoracic Society and the European Respiratory Society.[11] None of the other CAP centers participating in the 11-year assessment performed pulmonary function tests. Values for the forced expired volume in 1 second (FEV_1), forced vital capacity (FVC), the ratio of the two (FEV_1/FVC), and the forced expired flow from 25% to 75% of the FVC ($FEF_{25-75\%}$) were converted to z-scores and % predicted for age, height, ethnicity and sex using the reference equations of the Global Lungs Initiative.[12] The proportions with z-scores <5th centile (<-1.645 SD) were calculated. Children had repeated expiratory flows measured after receiving a standard dose

of bronchodilator. A significant bronchodilator response was defined as >12% increase in the FEV_1.[13]

Ethical considerations

Ethical aspects of the study were approved by the Human Research Ethics Committee at the Royal Women's Hospital, Melbourne. Parents gave written informed consent for their children to participate at all ages.

Statistical analyses

Data were analyzed using STATA version 14.2.[14] Generalized Estimating Equations with robust (sandwich) estimates of standard errors were used to allow for clustering of siblings within a family.[15] Baseline perinatal variables (outborn status [birth outside the Royal Women's Hospital], antenatal corticosteroids, multiple pregnancy, mode of delivery, gestational age, birth weight, sex, and exogenous surfactant), and variables after randomization, including BPD (defined as oxygen dependency at 36 weeks' postmenstrual age), were contrasted between caffeine and placebo groups. Expiratory flows were compared between caffeine and placebo groups, firstly unadjusted, and then adjusted for potentially confounding baseline perinatal variables. To determine if caffeine had an effect on expiratory flows independent of effects on BPD, both variables and an interaction term were entered into regression models with expiratory flows as the dependent variables. In addition, in view of a recent report highlighting differences between the sexes of children aged 10-14 years in expiratory flow z-scores calculated using the GLI reference equations,[16] we further compared differences between the treatment groups both unadjusted and adjusted for sex and height at 11 years of age. Comparisons are presented as mean differences or odds ratios (ORs), with 95% confidence intervals (CI) and P-values.

Results

Of the 199 infants enrolled into the CAP study at the Royal Women's Hospital, 182 survived to 11 years of age, 137 (75%) of whom had adequate respiratory function test results at that age. An additional 5 children who had neonatal care in other CAP centers were assessed by our team and had respiratory function test results available for analysis. The perinatal characteristics of the children assessed at 11 years with and without respiratory function data were similar (Supplementary Table 1).

Of the 142 children with respiratory function data, 74 (52%) had been treated with caffeine and 68 (48%) with placebo. More children in the placebo group entered the study with the main intent to facilitate extubation compared with the main intent being either for apnea prophylaxis or to treat apnea, whereas the three main intents were approximately equal in the caffeine group (Table 1). The duration of study drug was shorter in the caffeine group by approximately one week (Table 1). Of baseline perinatal variables prior to randomization, the rate of being exposed to antenatal corticosteroids was higher, and there was a trend for the proportion of males to be lower in the caffeine group; other baseline variables were not substantially different between the two groups (Table 1). Of perinatal variables occurring after randomization, the rates of having a patent ductus arteriosus requiring treatment, of BPD, and of requiring home oxygen therapy were substantially lower in the caffeine group (Table 1). The postmenstrual ages when the child was last intubated and when they last received assisted ventilation were lower in the caffeine group (Table 1). The proportion of children in the caffeine group who received postnatal corticosteroids was lower than in the placebo group (Table 1). Age, height, weight and ethnicity were similar in the two groups when expiratory flows were measured (Table 1).

Expiratory flows were significantly better in the caffeine group by approximately 0.5 SD for the FEV_1, FVC, and $FEF_{25-75\%}$ when expressed as z-scores, but by a lesser amount for the FEV_1/FVC z-score (Table 2). Identical conclusions applied to results expressed as %

predicted, as would be expected. None of the other baseline perinatal variables was independently related to any of the airflow variables, apart from birth weight which was positively related to FVC. Adjustment for baseline perinatal variables had little effect on the differences between groups (Table 2). Fewer children in the caffeine group had flow rates <5th centile, with the strongest evidence for a difference between the groups in the rates of low FVC z-scores (Table 2). Adjustment for baseline perinatal variables had little effect on any differences between the caffeine and placebo groups (Table 2).

Adjustment of expiratory flow z-scores for height and sex reduced the differences between treatment groups by a small amount (Supplementary Table 2).

Children in both treatment groups had substantial bronchodilator responses (caffeine, mean increase in FEV_1 of 8.3%, 95% CI 6.2-10.3%, P<0.001; placebo, mean change 8.2%, 95% CI 5.8-10.7%, P<0.001), but there was little difference between the groups in the average bronchodilator responses (mean difference 0.2%, 95% CI -2.9, 3.3%, P=0.91). There was little difference in the rates of clinically important bronchodilator responses between the groups (caffeine, 20% [14/69]; placebo 25% [15/60]; odds ratio 0.80, 95% CI 0.35, 1.81, P=0.59).

Children who had BPD in the newborn period had substantially lower z-scores for FEV_1 (mean difference -0.93; 95% CI -1.32, -0.53; P<0.001), FVC (mean difference -0.75; 95% CI -1.15, -0.35; P<0.001), and $FEV_{25-75\%}$ (mean difference -0.72; 95% CI -1.12, -0.31; P=0.001) compared with children who did not have BPD, but the reduction in the FEV_1/FVC ratio was not as large (mean difference -0.43; 95% CI -0.83, 0.03, P=0.07). If BPD was added as a covariate to the regression models alongside the treatment group variable, the beneficial effect of caffeine was reduced and was no longer statistically significant for any of the flow rates (mean differences in z-scores [95% CI]; FEV_1 0.24 [-0.15, 0.62] P=0.24; FVC 0.17 [-0.24, 0.58] P=0.41; FEV_1/FVC 0.11 [-0.36, 0.57] P=0.44; $FEF_{25-75\%}$. 0.23 [-0.17, 0.62]

P=0.26. There were no significant interactions between caffeine and BPD for any expiratory flow rate (all P>0.05).

In the children with lung function data, there were fewer children in the caffeine group who received treatment for wheezing symptoms at 11 years of age (11% [8/74] compared with 19% [13/68] in the placebo group), but the evidence for a difference was weak (OR 0.52, 95% CI 0.21, 1.26; P=0.14). In all children seen at 11 years in our center in whom the respiratory questionnaire data were complete, regardless of whether they had expiratory flow data or not, 11% (10/88) of the caffeine group received treatment for wheezing at 11 years of age compared with 21% (17/80) in the placebo group, but the evidence for a difference remained weak (OR 0.50, 95% CI 0.23, 1.10; P=0.08).

Discussion

The major finding of this study is that expiratory flow rates were better at 11 years of age in children born weighing <1251 g who had been treated with caffeine in the newborn period than in those who had been treated with placebo. Caffeine substantially reduced the rate of BPD in the newborn period, and the caffeine effects on expiratory flows were reduced when BPD was added as a covariate. There was little evidence of an additional effect of caffeine on expiratory flows independent of its effects via reducing BPD. Although there was imbalance in some pre-randomization variables favoring the caffeine group, adjusting for these variables altered no conclusions concerning the long-term effects of early caffeine treatment on expiratory flows at 11 years of age. There are no other randomized controlled trials of caffeine in the newborn period where lung function has been reported in later childhood with which to compare our results. Given the known benefits of caffeine in the newborn period in improving not only respiratory function but also neurological outcomes,

particularly motor function in childhood,[7,9,17] further placebo-controlled trials of neonatal caffeine versus placebo are unlikely to be repeated.

In the CAP trial overall, positive airway pressure through an endotracheal tube, the use of any positive airway pressure, and oxygen therapy were each discontinued approximately one week earlier for infants in the caffeine group than for infants in the placebo group,[6] whereas the reductions were larger and closer to 3 weeks within the subgroup reported here. In addition, in the CAP trial overall, the use of postnatal corticosteroids was reduced from 20% in the caffeine group to 14% in the placebo group, rates in both groups being higher than observed in our subgroup. However, the short-term benefits of caffeine in our sub study are magnified because the original CAP trial results included infants who died before 36 weeks,[6] whereas our study reports results only from survivors, and hence we cannot compare the two studies directly.

How might caffeine in the newborn period improve expiratory flows in later childhood? In the short-term caffeine is a respiratory stimulant. In one study Davis et al[18] reported a 37% increase in minute ventilation one hour following 10 mg/kg of caffeine given to 16 infants with bronchopulmonary dysplasia (BPD). They also reported a substantial drop in pulmonary resistance and an improved pulmonary compliance in the same study.[18] Similar improvements in pulmonary resistance and pulmonary compliance have also been reported in newborn baboons 12 and 24 hours of age after treatment with caffeine given at 1 and 12 hours of age.[19] In another study in preterm infants diaphragmatic activity substantially increased within 5 minutes of injection of caffeine, which was sustained for 120 minutes.[20] Short-term effects of caffeine in stimulating breathing seem to translate into reductions in the need for ongoing assisted ventilation. In the CAP trial, caffeine treatment improved respiratory function in the newborn period, manifest as substantially lower postmenstrual ages at which infants no longer required an endotracheal tube (from a median of 30.0 weeks

to 29.1 weeks), received any positive airway pressure (from 32.0 to 31.0 weeks), and received any supplemental oxygen (from 35.1 to 33.6 weeks).[6] Moreover, caffeine reduced rates of a patent ductus arteriosus requiring medical or surgical treatment, and of BPD in the CAP trial.[6] Reductions in patent ductus arteriosus requiring treatment and BPD were also evident in our cohort that participated in the CAP study, but to an even larger extent, as were improvements in shortening the durations of intubation, of any positive pressure, or any oxygen. When BPD was added to the analyses, the independent effect of caffeine on expiratory flows diminished and became non-significant, with little evidence of an important interaction between BPD and caffeine. It thus appears that neonatal caffeine improves expiratory flow rates in childhood largely by reducing ventilator and oxygen dependency, possibly related to its acute effects on stimulating respiration and improving lung compliance, and hence reducing lung injury in the short-term, rather than having any independent direct effect on airway structure.

Other treatments that improve neonatal lung disease include exogenous surfactant and postnatal corticosteroids. Exogenous surfactant reduces the severity of respiratory distress syndrome and the rates of mortality and BPD.[21,22] However, there are limited data on lung function from the many RCTs of surfactant that were reported during its development as a clinical treatment. In one study of only 17 surfactant treated and 12 control children at 6 ½ years of age, there were no substantial differences between the groups in several lung function measures including expiratory flow rates.[23] In another study of 40 preterm children, comprising two groups treated with surfactant and a placebo group, children treated with surfactant had better expiratory flow than the placebo group at 7-12 years of age.[24] In our study surfactant therapy was not associated with any substantial change in expiratory flow rates. Postnatal corticosteroids reduce rates of BPD, but again there are limited data on lung function in childhood.[25,26] In one report from a randomized controlled trial of postnatal

corticosteroids, mean values for expiratory flow variables were not substantially different between treatment groups at ages 8-11 years.[27] However, the proportion with below-normal values for FEV_1, defined as $<5^{th}$ centile, was lower (40%) in 35 children who had been treated with dexamethasone compared with 68% in 28 children who had received placebo in the newborn period.[27]

The major strengths of our study are that it reports the results from a randomized controlled trial in an area where there are no other reported data, and the children were all assessed blinded to knowledge of treatment, using respiratory function tests that complied with strict guidelines for measuring expiratory flows in children. Since caffeine had clear short-term and long-term benefits, with no evidence of any harmful effects, there is little likelihood that there will be any future placebo-controlled randomized trials of caffeine, which therefore limits the ability to determine later lung function related to neonatal caffeine treatment as in the current study. A limitation is that the respiratory function tests were restricted to expiratory flows. The children were being assessed primarily for cognitive and neurological outcomes as part of the overall 11-year assessment of the CAP study, thus leaving little time for more detailed lung function testing.[9] Thus we were unable to examine other areas of respiratory function, such as ventilation inhomogeneity that might shed more light on the mechanisms of the effects of early caffeine exposure on expiratory flows in childhood. In addition, it would have been preferable if respiratory function had also been measured at other study sites involved in the CAP study to be able to confirm our findings. This is important because, as discussed earlier, the reduction in the rate of BPD with neonatal caffeine was much larger within our cohort (i.e. from 62% to 27%), compared with the reduction from 47% to 36% in the CAP study overall,[6] which may have led to an overestimate of the effect of neonatal caffeine on expiratory airflow at 11 years. Another

limitation is the possible inaccuracy of the GLI equations for children aged 10-14 years of age, particularly for males.[16]

In conclusion, it is reassuring that the short-term benefits of caffeine on the lung in the newborn period translated into better lung function and respiratory health later in childhood. Given that children born preterm are not likely to reach their full adult lung growth potential,[1,28] it will be important to assess lung function in adulthood in survivors from the CAP trial to determine if caffeine treatment in the newborn period will reduce airway obstruction even later in life and potentially reduce the chance of preterm survivors developing adult chronic obstructive pulmonary disease.

Table 1. Perinatal and demographic characteristics contrasted between caffeine and control groups in those with lung function data

Characteristics	**Caffeine 74**	**Control 68**	**Statistics***
Study drug			
Primary indication			
• Apnea prophylaxis, n (%)	24 (32)	18 (26)	P=0.013‡
• Facilitate extubation, n (%)	22 (30)	36 (53)	
• Treat apnea, n (%)	28 (38)	14 (21)	
Duration of treatment – days, mean (SD)	47.4 (15.8)	54.8 (22.4)	-7.4 (-13.8, -1.0) P=0.023
Events before randomization			
Outborn,† n (%)	17 (23)	15 (22)	1.05 (0.48, 2.32) P=0.90
Antenatal corticosteroids, n (%)	73/73 (100)	61 (90)	Fisher's Exact P=0.005
Multiple birth, n (%)	25 (34)	19 (28)	1.32 (0.64, 2.69) p=0.45
Vaginal delivery, n (%)	25 (34)	22 (32)	1.02 (0.85, 1.24) P=0.79
Gestational age at birth - weeks, mean (SD)	27.7 (1.7)	27.3 (1.8)	0.3 (-0.1, 0.7) P=0.19
Birthweight - grams, mean (SD)	967 (182)	926 (181)	36 (-25, 98) P=0.25
Male, n (%)	31 (42)	41 (60)	0.56 (0.29, 1.06) P=0.08
Exogenous surfactant, n (%)	42 (57)	48 (71)	0.60 (0.31, 1.18) P=0.14
Events after randomization			
Patent ductus arteriosus, n (%)	15 (20)	31 (46)	0.33 (0.15, 0.69) P=0.003
Postmenstrual age when last intubated – weeks, mean (SD)	28.5 (1.6)	31.3 (4.7)	-2.7 (-3.9, -1.6) P<0.001
Postmenstrual age when assisted ventilation ceased – weeks, mean (SD)	30.3 (2.1)	33.9 (4.5)	-3.5 (-4.7, -2.3) P<0.001
Postnatal corticosteroids, n (%)	3 (4)	9 (13)	0.25, 0.06, 0.99 P=0.048
Bronchopulmonary dysplasia, n (%)	20 (27)	41 (62)	0.26 (0.13, 0.53) P<0.001
Postmenstrual age when oxygen ceased – weeks, mean (SD)	34.5 (8.1)	37.5 (4.9)	-3.1 (-5.3, -0.9) P=0.005
Home oxygen therapy, n (%)	4 (5)	14 (21)	0.22 (0.07, 0.72) P=0.012
At 11 years of age			
Age – years, mean (SD)	11.4 (0.4)	11.4 (0.6)	0.0 (-0.2, 0.2) P=0.97
Height – cm, mean (SD)	147.4 (7.9)	145.0 (8.8)	2.5 (-0.3, 5.3) P=0.08
Weight – kg, mean (SD)	41.4	39.4	2.0 (-1.8, 5.9)

	(11.7)	(11.4)	P=0.29
Ethnicity			
– White, n (%)	72 (96)	61 (91)	P=0.32§
– Black, n (%)	1 (1)	1 (1)	
– NE Asia, n (%)	0 (0)	0 (0)	
– SE Asia, n (%)	0 (0)	2 (3)	
– Other/mixed, n (%)	1 (1)	3 (4)	

*either odds ratio (95% confidence interval [CI]), or mean difference (95% CI), allowing for clustering of multiple births within the same family, unless otherwise stipulated; †born outside a tertiary maternity hospital; ‡Chi-square test over all three categories; §Chi-square test over all five categories

Table 2. Expiratory flow variables contrasted between caffeine and control groups

Expiratory flow variable	**Caffeine n=74**	**Control n=68**		
			Mean difference (95% CI) P-value*	Mean difference (95% CI) P-value†
$zFEV_1$ – mean (SD)	-1.00 (1.17)	-1.53 (1.35)	0.54 (0.14, 0.94) P=0.008	0.49 (0.07, 0.91) P=0.023
FEV_1 – % predicted – mean (SD)	88.4 (13.7)	82.0 (15.8)	6.4 (1.7, 11.2) P=0.008	6.0 (1.0, 11.0) P=0.018
zFVC – mean (SD)	-0.51 (1.15)	-0.95 (1.30)	0.44 (0.04, 0.83) P=0.031	0.38 (-0.02, 0.77) P=0.06
FVC – % predicted – mean (SD)	94.2 (13.2)	89.2 (15.0)	5.0 (0.4, 9.5) P=0.032	4.2 (-0.3, 8.7) P=0.07
$zFEV_1$/FVC – mean (SD)	-0.73 (1.37)	-0.97 (1.39)	0.24 (-0.21, 0.68) p=0.30	0.23 (-0.24, 0.70) p=0.33
$zFEF_{25-75\%}$ – mean (SD)	-1.30 (1.14)	-1.75 (1.27)	0.45 (0.05, 0.84) P=0.028	0.42 (0.002, 0.85) P=0.049
$FEF_{25-75\%}$ – % predicted – mean (SD)	74.0 (22.1)	65.7 (22.7)	8.4 (1.0, 15.7) P=0.026	8.4 (0.4, 16.3) P=0.039
			Odds ratio (95% CI) P-value*	Odds ratio (95% CI) P-value†
$zFEV_1$ <5th centile – n (%)	17 (23)	25 (37)	0.51 (0.24, 1.08) P=0.08	0.59 (0.25, 1.39) P=0.23
zFVC <5th centile – n (%)	8 (11)	19 (28)	0.31 (0.12, 0.77) P=0.012	0.27 (0.10, 0.74) P=0.011
$zFEV_1$/FVC <5th centile – n (%)	17 (23)	21 (31)	0.72 (0.34, 1.53) P=0.40	0.67 (0.29, 1.56) p=0.36
$zFEF_{25-75\%}$ <5th centile – n (%)	23 (33)	31 (47)	0.57 (0.29, 1.12) P=0.10	0.62 (0.32, 1.28) P=0.20

CI=confidence interval; SD=standard deviation; FEV_1=forced expired volume in 1 second; FVC=forced vital capacity; $FEF_{25-75\%}$= forced expired flow from 25% to 75% of the FVC
*allowing for clustering of multiple births within the same family
†allowing for clustering of multiple births within the same family and adjusted for baseline variables (outborn status, antenatal corticosteroids, mode of delivery, multiple birth, sex, gestational age, birthweight, surfactant)

Figure 1. Plots of z-scores for expiratory flow variables comparing caffeine (C) and placebo (P) groups. Size of circles proportional to sample size. Expected mean value of zero shown as solid line; mean value for each subgroup shown as short solid line. 5^{th} centile shown as dotted line; percentages $<5^{th}$ centile shown for each subgroup.

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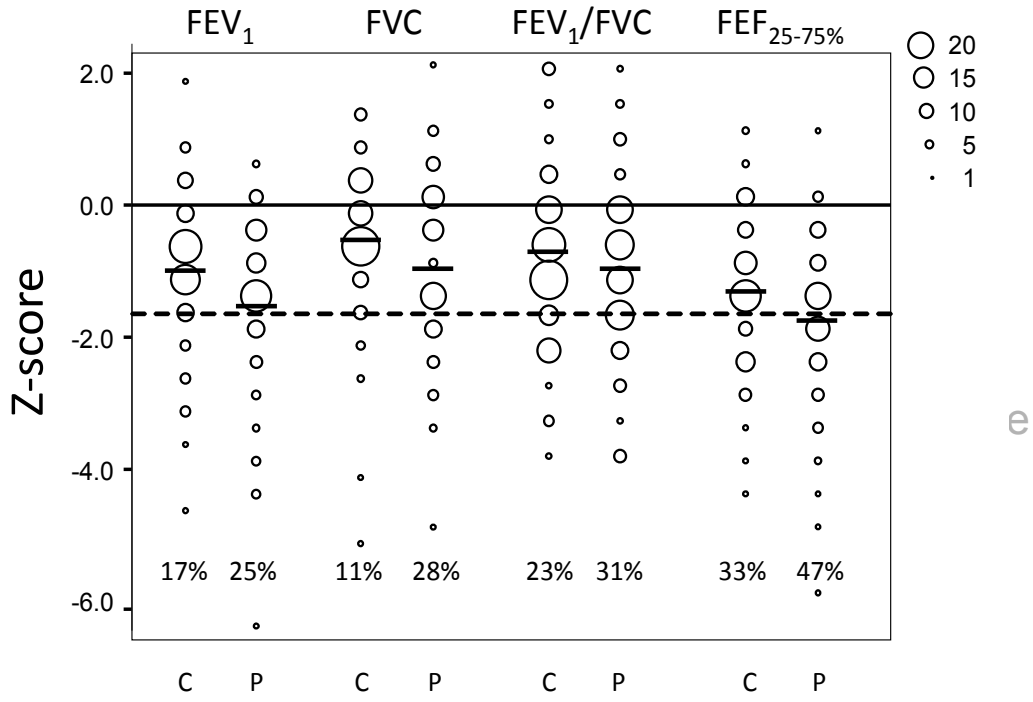
Figure 1


FEV1
FVC
FEV1/FVC
FEF25-75%
20
15
10
5
1
2.0
0.0
-2.0
-4.0
-6.0
Z-score
17%
25%
11%
28%
23%
31%
33%
47%
C
P
C
P
C
P
C
P

Supplementary Table 1. Perinatal and demographic characteristics

Characteristics	**Lung function**		**Statistics***
	yes	no	
	142	42	
Perinatal variable)			
Outborn,† n (%)	32 (23)	11 (26)	0.82 (0.37, 1.81) P=0.62
Antenatal corticosteroids, n (%)	134/141 (95)	39 (93)	1.47 (0.36, 6.03) P=0.53
Multiple birth, n (%)	44 (31)	13 (31)	1.00 (0.48, 2.11) p=1.0
Vaginal delivery, n (%)	47 (33)	20 (48)	0.46 (0.22, 0.96) P=0.038
Gestational age at birth - weeks, mean (SD)	27.5 (1.7)	27.8 (1.7)	-0.1 (-0.8, 0.5) P=0.72
Birthweight - grams, mean (SD)	947 (182)	999 (178)	-52 (-114, 10) P=0.10
Male, n (%)	72 (51)	22 (52)	0.83 (0.40, 1.72) P=0.62
Exogenous surfactant, n (%)	90 (63%)	23 (55%)	1.33 (0.64, 2.76) P=0.44
Patent ductus arteriosus, n (%)	46 (32)	16 (38)	0.79 (0.39, 1.59) P=0.50
In oxygen at 36 weeks' postmenstrual age, n (%)	62 (44)	18 (43)	1.03 (0.51, 2.09) P=0.93
Primary indication for caffeine			
Apnea prophylaxis, n (%)	42 (30)	15 (36)	P=0.68‡
Facilitate extubation, n (%)	58 (41)	17 (40)	
Treat apnea, n (%)	42 (30)	10 (24)	

*either odds ratio (95% confidence interval [CI]), or mean difference (95% CI); †born outside a tertiary maternity hospital; ‡Chi-square Test

Supplementary Table 2. Expiratory flow z-scores contrasted between caffeine and control groups, before and after adjustment for sex and height at 11 years of age.

Expiratory flow variable	**Caffeine n=74**	**Control n=68**		
			Mean difference (95% CI) P-value*	Mean difference (95% CI) P-value†
$zFEV_1$ – mean (SD)	-1.00 (1.17)	-1.53 (1.35)	0.54 (0.14, 0.94) P=0.008	0.43 (0.03, 0.83) P=0.034
zFVC – mean (SD)	-0.51 (1.15)	-0.95 (1.30)	0.44 (0.04, 0.83) P=0.031	0.29 (-0.08, 0.66) P=0.12
$zFEV_1$/FVC – mean (SD)	-0.73 (1.37)	-0.97 (1.39)	0.24 (-0.21, 0.68) p=0.30	0.23 (-0.23, 0.69) p=0.33
$zFEF_{25-75\%}$ – mean (SD)	-1.30 (1.14)	-1.75 (1.27)	0.45 (0.05, 0.84) P=0.028	0.38 (-0.01, 0.78) P=0.057

*allowing for clustering of multiple births within the same family
†allowing for clustering of multiple births within the same family and adjusted for sex and height at 11 years of age