

## ORIGINAL ARTICLE

Effect of preterm birth on later FEV<sub>1</sub>: a systematic review and meta-analysis

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## ABSTRACT

**Background** Increasing evidence suggests that preterm birth affects later lung function. We systematically reviewed the literature to determine whether percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) is lower in later life in preterm-born subjects, with or without bronchopulmonary dysplasia (BPD), compared with term-born controls.

**Methods** Studies reporting %FEV<sub>1</sub>, with or without a term-born control group, in later life for preterm-born subjects (<37 weeks gestation) were extracted from eight databases. Data were analysed using Review Manager and STATA. The quality of the studies was assessed.

**Results** From 8839 titles, 1124 full articles were screened and 59 were included: 28 studied preterm-born children without BPD, 24 with BPD<sub>28</sub> (supplemental oxygen dependency at 28 days), 15 with BPD<sub>36</sub> (supplemental oxygen dependency 36 weeks postmenstrual age) and 34 born preterm. For the preterm-born group without BPD and for the BPD<sub>28</sub> and BPD<sub>36</sub> groups the mean differences (and 95% CIs) for %FEV<sub>1</sub> compared with term-born controls were –7.2% (–8.7% to –5.6%), –16.2% (–19.9% to –12.4%) and –18.9% (–21.1% to –16.7%), respectively. Pooling all data on preterm-born subjects whether or not there was a control group gave a pooled %FEV<sub>1</sub> estimate of 91.0% (88.8% to 93.1%) for the preterm-born cohort without BPD, 83.7% (80.2% to 87.2%) for BPD<sub>28</sub> and 79.1% (76.9% to 81.3%) for BPD<sub>36</sub>. Interestingly, %FEV<sub>1</sub> for BPD<sub>28</sub> has improved over the years.

**Conclusions** %FEV<sub>1</sub> is decreased in preterm-born survivors, even those who do not develop BPD. %FEV<sub>1</sub> of survivors of BPD<sub>28</sub> has improved over recent years. Long-term respiratory follow-up of preterm-born survivors is required as they may be at risk of developing chronic obstructive pulmonary disease.

## INTRODUCTION

Evidence suggests that being born preterm has adverse effects on later lung function, especially if associated with the development of bronchopulmonary dysplasia (BPD) in infancy.<sup>1 2</sup> BPD, often also called chronic lung disease of prematurity, is a common disease of extremely preterm-born infants characterised by prolonged supplemental oxygen dependency and dysregulated lung growth. While there have been several studies of lung function outcomes in preterm-born subjects, most have focused on those who developed BPD. Some studies have investigated later lung function

## Key messages

## What is the key question?

- Is percentage forced expiratory volume in 1 s (%FEV<sub>1</sub>) lower in later childhood and adulthood in preterm-born subjects (<37 weeks gestation), with or without bronchopulmonary dysplasia (BPD), compared with term-born subjects (≥37 weeks)?

## What is the bottom line?

- Preterm-born subjects of <37 weeks who do not develop BPD in infancy have moderate deficits of %FEV<sub>1</sub> of approximately –7.2% compared with term-born controls; infants who develop BPD, defined as supplemental oxygen dependency at 28 days of age or until at least 36 weeks postmenstrual age, have greater deficits in %FEV<sub>1</sub> of –16.2%, and –18.9%, respectively, compared with term-born controls.

## Why read on?

- Our findings suggest that all preterm-born survivors are at risk of long-term deficits in %FEV<sub>1</sub>; however, there has been an improvement in %FEV<sub>1</sub> over the last three decades for the group with supplemental oxygen dependency at 28 days.

outcomes of low birth weight infants (<2.5 kg) but do not distinguish between preterm-born and term-born infants with evidence of intrauterine growth restriction.<sup>3</sup> It is clearly important to distinguish between the two as different mechanisms lead to lung function deficits.

Studies reporting respiratory outcomes of preterm birth have produced inconsistent results, which may be explained partly by poorly defined populations, including comparison groups, differences in the gestational ages of the preterm-born subjects and methodological differences. Furthermore, there have been temporal changes in the medical management of preterm-born infants, especially the routine use of antenatal corticosteroids, introduction of surfactant therapy and gentler modes of mechanical ventilation that may have altered the relationship between prematurity, BPD and lung function over time.

Although a systematic review of outcomes in young adults (≥18 years) who had BPD in infancy

has recently been published, a formal meta-analysis was not possible due to the heterogeneous nature of the studies.<sup>4</sup> To our knowledge, there has not been a systematic review with meta-analyses of all studies reporting later percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) for children or adults born preterm with or without BPD. We therefore conducted a systematic review to determine whether %FEV<sub>1</sub> in later childhood and adulthood is lower in preterm-born subjects (<37 weeks gestation) with or without BPD compared with term-born subjects (≥37 weeks gestation).

## METHODS

We developed a search strategy using the keywords and medical subject headings (MeSH) terms given in online supplementary appendix 1 for eight databases: CINAHL, Embase, HMC Health Management Consortium, Medline, Scopus, OpenSIGLE, Web of Knowledge (Science Citation Index Expanded, Social Science Citation Index, ISI proceedings). The databases were searched in May 2010 and October 2011. Websites of Action Medical Research, SPARKS and the Wellcome Trust were also searched and references in the included studies were also screened for inclusion.

## Eligibility criteria

Published studies were eligible for inclusion if they reported %FEV<sub>1</sub> in later life for preterm-born infants, defined as a gestation of <37 weeks, with and without BPD. The comparison with infants born at term, defined as a gestation of ≥37 weeks, was made by comparing with a contemporaneous term-born control group; comparison was also made using historical controls by using the percentage predicted values with the notional 100% representing an average in the population. We included only papers which had already calculated the percentage predicted FEV<sub>1</sub> and did not discriminate on the basis of which reference values were used, assuming the authors would have used the most appropriate reference values for their populations. We included studies that recruited based on the subjects' birth weight, but only included studies which reported the %FEV<sub>1</sub> of preterm-born infants (whether recruited on gestational age or birth weight). BPD was defined as dependence on supplementary oxygen either at 28 days of life or at 36 weeks postmenstrual age (PMA). Childhood was defined as <18 years and adulthood ≥18 years of age. The lung function measure primarily studied was %FEV<sub>1</sub> obtained by spirometry, hence mainly used for children ≥5 years. Studies that reported other measures of lung function were eligible but were not included in the meta-analyses. Studies in all languages and from all countries were included.

## Study selection

Two reviewers (SJK and MOE) independently screened each reference title and abstract (if available) using the inclusion criteria. Complete papers were obtained for those that met the inclusion criteria. Abstracts that did not meet the inclusion criteria were excluded. Both reviewers then screened the full paper against the inclusion criteria. For any disagreement, a third reviewer (SK) made a final decision.

## Data collection process

A data extraction form (see online supplementary appendices 2 and 3) was initially piloted independently on 10 papers by SJK, WJW, SP, FD, SK and MOE. SJK and MOE extracted data from the remaining articles. The authors of articles were contacted if possible for further details if the information was presented

only graphically or if the data were not extractable (eg, if data for term-born and preterm-born children were combined). Multiple articles from the same cohort were reviewed by SK and SJK and the article reporting the most complete data from the highest number of subjects was included in the analysis. Data from included papers were extracted and entered into Review Manager V.5.1 and STATA V.10 (Stata Corporation, Texas, USA) for analysis.

## Assessment of study quality and risk of bias

A proforma shown in online supplementary appendix 3 was used to assess study quality based on relevant criteria from the Newcastle Ottawa criteria and the Cochrane risk of bias tool, focusing on the risks of selection, measurement and attrition bias. This was piloted and data extracted as detailed above. Each study was assessed and scored for representativeness of the cohort, appropriate selection of the non-exposed group, exposure ascertainment and demonstration that the outcome of interest was not present at the start of the study, outcome assessment and adequacy of follow-up. The minimum possible score was 6 and the maximum possible score was 20.

## Outcome measures

Mean %FEV<sub>1</sub> was the principal outcome.

## Statistical analysis

Statistical analyses were performed using Review Manager for studies including a term-born control group and STATA for pooling all the data on preterm-born subjects, with or without a control group. The method of Hozo *et al* was used to convert the medians to means where possible for included articles reporting median values.<sup>5</sup> For graphically presented data, the graphs were read as accurately as possible.

After initial exploration of the data we used random effects meta-analyses to provide a pooled estimate of the mean difference in %FEV<sub>1</sub> between preterm-born subjects and term-born controls to allow for heterogeneity for the following groups:

1. Preterm-born subjects without BPD.
2. BPD<sub>28</sub> (defined as supplemental oxygen dependency at 28 days of life in preterm-born infants).
3. BPD<sub>36</sub> (defined as supplemental oxygen dependency at 36 weeks PMA in preterm-born infants).
4. Preterm-born subjects (general populations which may include BPD cases).

Separate analyses were performed for those studies that included term-born controls and those not including term-born controls but reporting %FEV<sub>1</sub> based on historical control (reference value) data. For the latter, separate meta-analyses provided pooled estimates of the mean %FEV<sub>1</sub> for preterm-born subjects; this could be compared with 100% as a notional control mean.

Studies which presented FEV<sub>1</sub> results not expressed as percentage predicted were excluded as insufficient information was available to calculate predicted values. We performed a sensitivity analysis to assess the effect of study quality by including only studies which scored ≥12 in each grouping. A funnel plot was used to assess if there was a risk of publication bias. We also explored if there was an association between year of birth, surfactant use or age at time of FEV<sub>1</sub> testing and later %FEV<sub>1</sub> using linear weighted regression in the BPD groups only. The studies were weighted inversely by the variance of the estimate of the mean. Linearity was checked by examining residuals. In studies which recruited subjects over a number of years, we used the midpoint between the first and last year of birth in the analysis.

## RESULTS

## Study selection

The search strategy identified 8839 titles and abstracts; 1124 full articles were screened and 206 met the inclusion criteria (figure 1). Of these papers, 59 studies reporting on %FEV<sub>1</sub> for the preterm-born groups were included in the meta-analysis (E1–29, E51–E60, E71, E73–92; online supplementary data). Some were included in more than one analysis. Twenty-eight studies compared a term-born group with a preterm-born group without BPD (E1–E29; online supplementary data); 24 with a BPD<sub>28</sub> group (E3, E4, E10, E14, E16, E18, E19, E21, E23–E26, E28, E29, E51–E60; online supplementary data); 15 with a BPD<sub>36</sub> group (E1, E5, E6, E8–E13, E15, E16, E20, E22, E27, E29, E71; online supplementary data); and 34 with a general preterm-born group (including some subjects with BPD) (E1–E4, E6, E7, E9, E14, E15, E17, E20, E22, E24, E26, E73–E92; online supplementary data). Five of the 1124 full

articles were excluded as the FEV<sub>1</sub> was not reported as percentage predicted values. Five of 10 articles reporting median %FEV<sub>1</sub> were included as means could be calculated and are included in the 59 included studies.

## Study characteristics

The characteristics of the included articles are given in online supplementary tables E1–E4. Studies included subjects born between 1964 and 2000; their ages ranged from 5 to 23 years and the preterm-born subjects were born between 24 and 36 weeks gestation. Term-born control groups in general were of a similar age to the preterm-born children. For the preterm-born subjects, rates of ventilation and surfactant administration varied widely.

## Risk of bias across studies

Overall, the studies were of moderate quality with scores ranging from 6 to 19 (median 12). Across the studies there was a moderate risk of selection bias. In 33 studies no information was given about how gestation at birth was measured, so possibly there was a high risk of bias in the domain of exposure ascertainment. In 16 studies data were collected retrospectively so exposure ascertainment would not have been independent of outcome status. In the majority of studies no description was provided about how outcomes were ascertained, so it was not possible to reliably judge the potential for risk of bias in this domain.

## Synthesis of results

The primary comparison was between preterm-born and control groups as some of the sources of heterogeneity are removed by this within-study comparison. In the preterm-born group without BPD, the mean difference for %FEV<sub>1</sub> was –7.2% (95% CI –8.7% to –5.6%) compared with term-born controls. The comparisons between the BPD and term-born groups showed larger differences (mean difference for BPD<sub>28</sub> and BPD<sub>36</sub> groups –16.2% (95% CI –19.9% to –12.4%) and –18.9% (95% CI –21.1% to –16.7%), respectively). The mean difference for %FEV<sub>1</sub> was –8.7% (95% CI –11.0% to –6.4%) for the preterm-born subjects (including BPD cases) compared with term-born controls (figures 2–5).

Pooling all the data on preterm-born subjects whether or not there was a control group gave a pooled estimate of the mean % FEV<sub>1</sub> of 91.0% (95% CI 88.8% to 93.1%) for the preterm-born cohort without BPD, 83.7% (95% CI 80.2% to 87.2%) for the BPD<sub>28</sub> group, 79.1% (95% CI 76.9% to 81.3%) for the BPD<sub>36</sub> group and 89.4% (95% CI 87.0% to 91.7%) for the preterm-born subjects (including BPD cases) (see online supplementary figures E1–E4). These differences using 100% as a notional comparator were slightly larger than when comparing with a control group. Including studies which estimated means from the medians had little impact on the results.

## Additional analysis

Funnel plots showed a low risk of publication bias. Including only the higher quality articles made very little difference to the results (see online supplementary data). We examined the effect of year of birth, surfactant use and age at lung spirometry on later %FEV<sub>1</sub> in the BPD groups only. Age at time of FEV<sub>1</sub> testing appeared to have little effect on later %FEV<sub>1</sub> (data not shown). Additional information would be obtained from longitudinal studies, but there were insufficient numbers of these studies to reach a reliable conclusion. There was inadequate data to examine the effect of surfactant. %FEV<sub>1</sub> for the BPD<sub>28</sub> group may have improved over the years (figure 6).

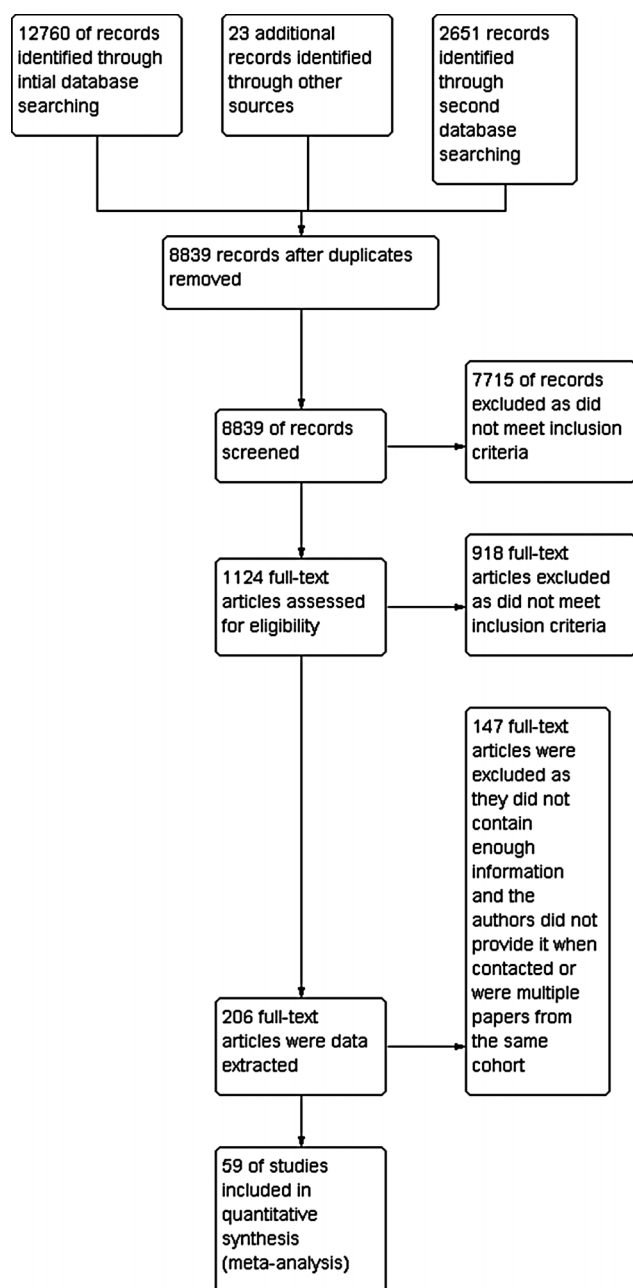
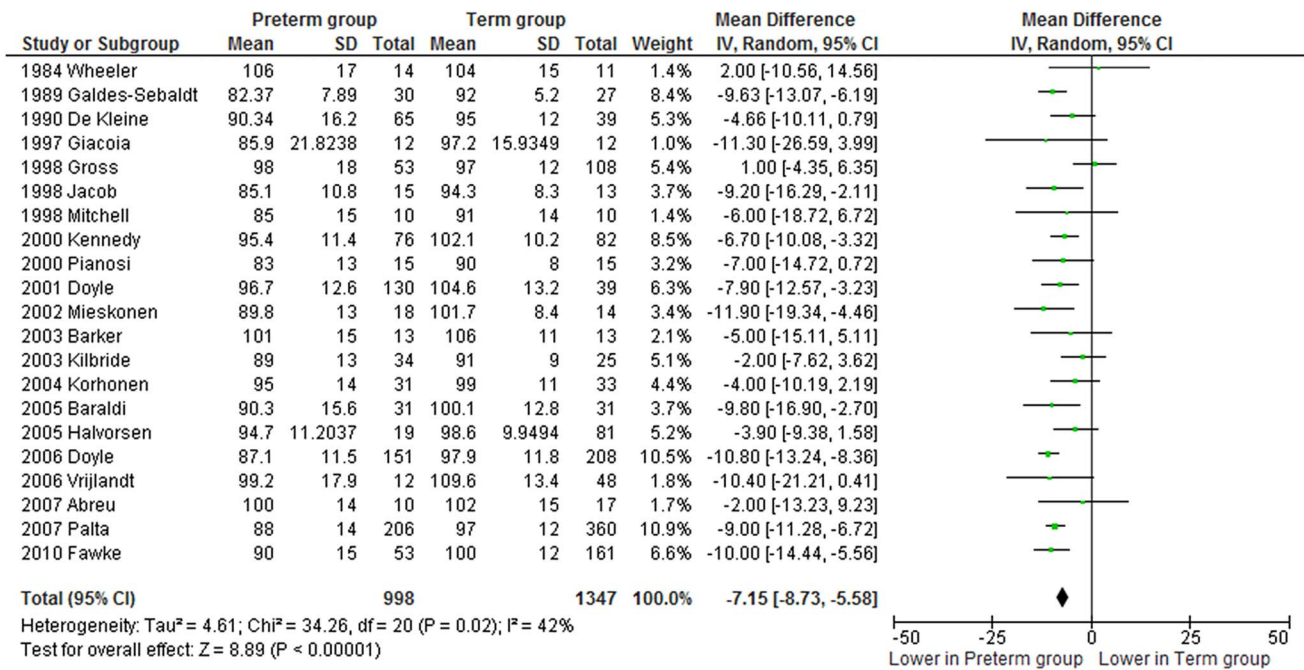


Figure 1 Study selection results.





**Figure 2** Percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) of the premature group (no bronchopulmonary dysplasia, BPD) compared with term control group.

The estimated change per year of %FEV<sub>1</sub> for the BPD<sub>28</sub> group was 0.57% and 0.01% for the term-born controls. No such improvement was apparent in the BPD<sub>36</sub> group, although there were fewer studies reporting this outcome (data not shown).

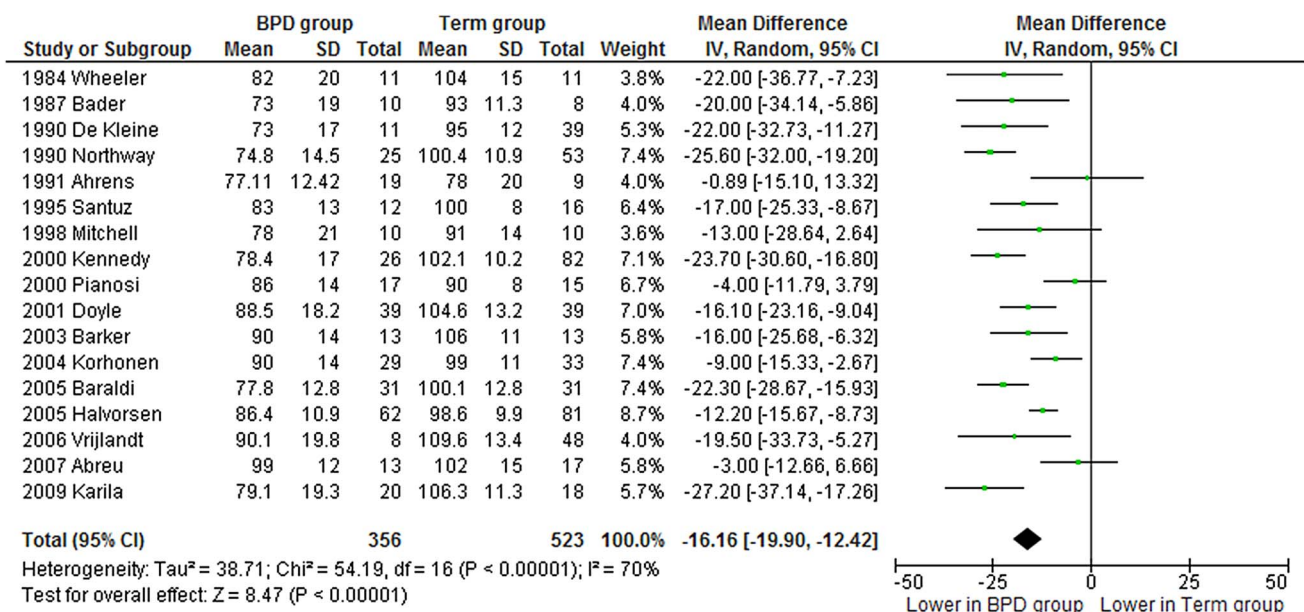
## DISCUSSION

### Summary of evidence

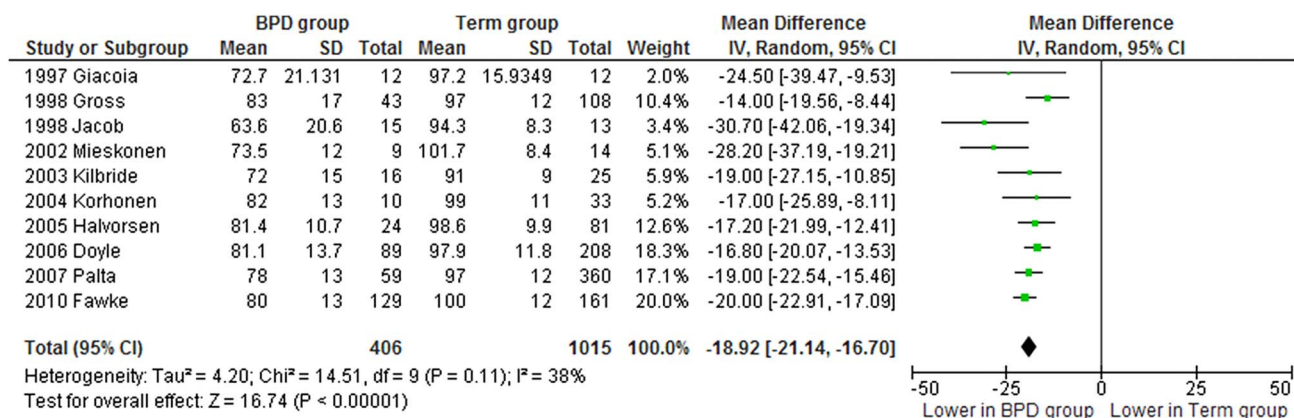
To our knowledge, this is the first systematic review and meta-analysis that included all available evidence on later %FEV<sub>1</sub> of preterm-born infants with and without BPD, although a previous descriptive systematic review reported lung function in adult survivors of BPD.<sup>4</sup> With increasing rates of preterm births<sup>6</sup> and improved survival, it is important to

investigate the long-term consequences associated with being born during a critical stage of lung development.<sup>7</sup> Our analyses show that preterm-born subjects without BPD had moderate deficits in their %FEV<sub>1</sub> of approximately -7.2%, while the BPD<sub>28</sub> and the BPD<sub>36</sub> groups had greater deficits in %FEV<sub>1</sub> of -16.2% and -18.9%, respectively. It is of great interest to note that there was an improvement in %FEV<sub>1</sub> over the three decades in the BPD<sub>28</sub> group.

Prematurity is associated with delivery at an immature stage of lung development, especially for the very preterm-born infants born at <32 weeks gestation,<sup>7</sup> but even those born at <37 weeks are vulnerable to increased rates of respiratory illness in infancy.<sup>8</sup> The modern management of preterm-born



**Figure 3** Percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) of the bronchopulmonary dysplasia (BPD) group (supplemental oxygen-dependency at 28 days of life) compared with term control group.

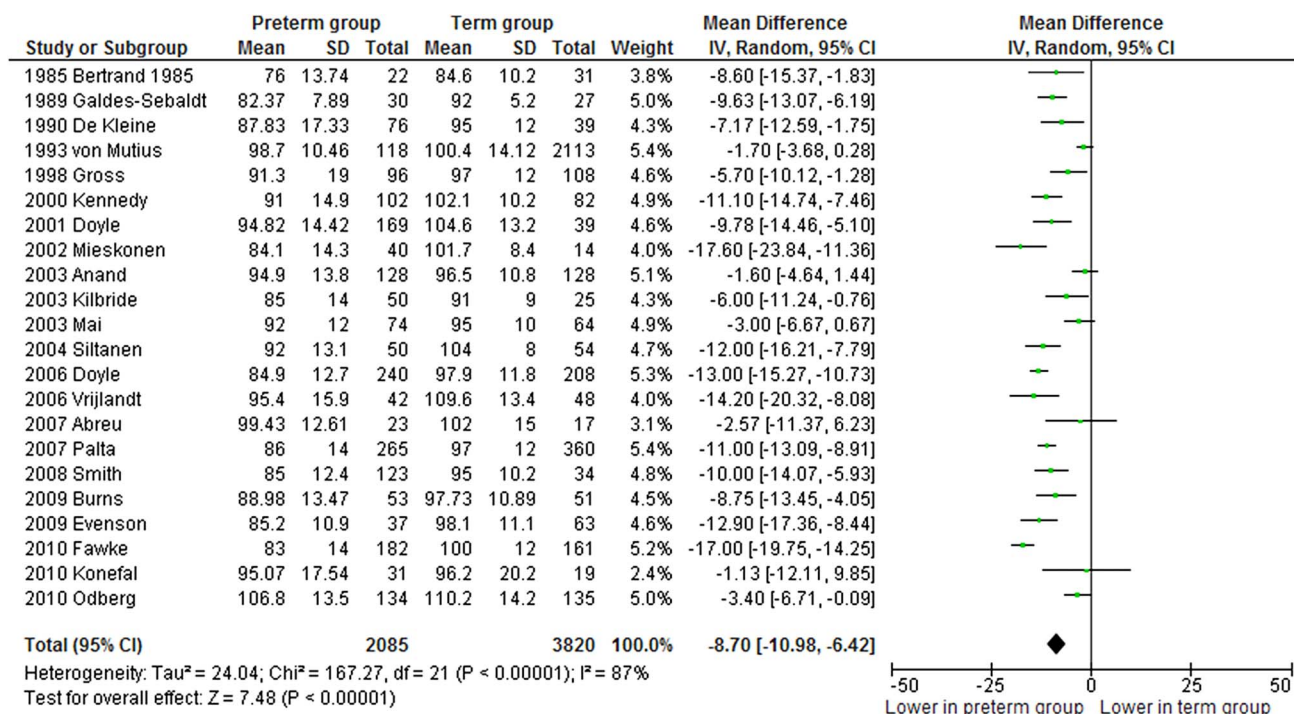


**Figure 4** Percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) of the bronchopulmonary dysplasia (BPD) group (supplemental oxygen dependency 36 weeks postmenstrual age) compared with term control group.

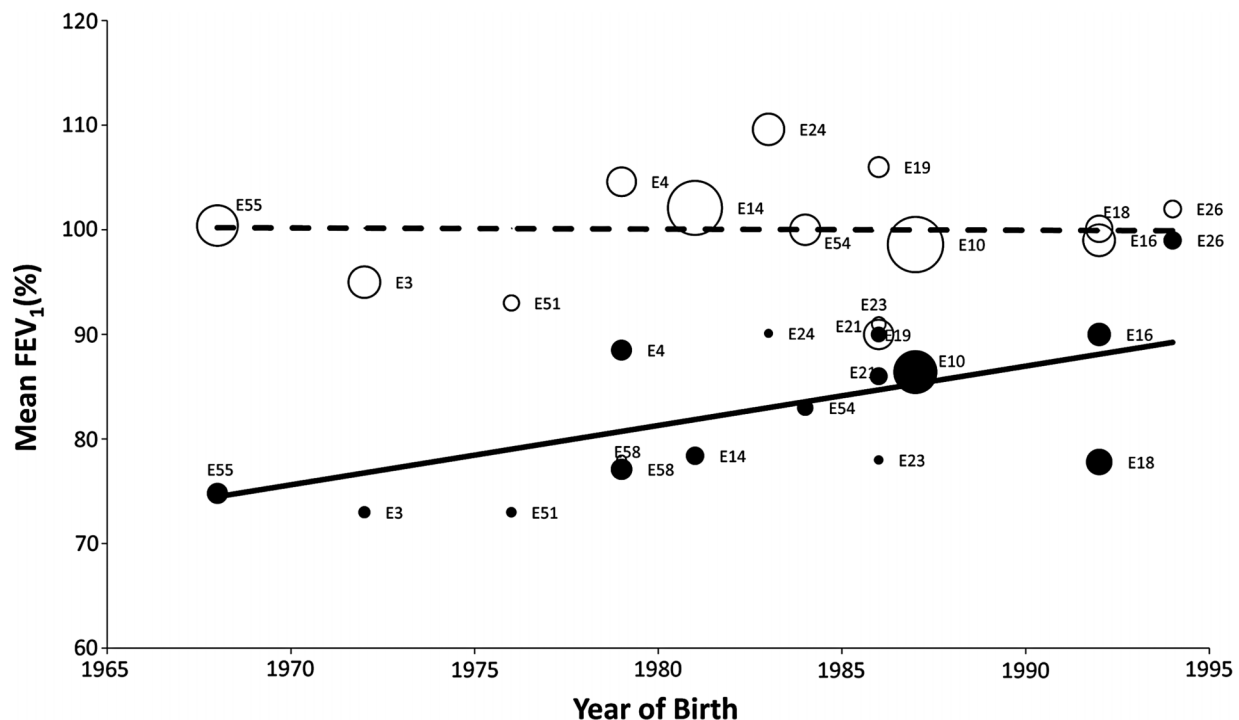
infants, including the routine use of antenatal corticosteroids, surfactant treatment and gentle mechanical ventilation, has undoubtedly improved survival, especially of more immature infants, and has possibly led to improved later %FEV<sub>1</sub>. Perhaps not surprisingly, preterm-born infants who develop BPD in infancy continue to have respiratory function deficits as has been consistently reported in many studies. However, of particular note is the improvement in %FEV<sub>1</sub> for the BPD<sub>28</sub> group over the decades despite survival of increasingly preterm-born infants. While our data suggest that %FEV<sub>1</sub> may have improved in the BPD<sub>28</sub> group over the last few decades, the data need to be interpreted with caution as other factors such as selection bias of the worst survivors of prematurity and small numbers, especially for the early studies, may explain the reported lower %FEV<sub>1</sub> values. Due to a smaller number of studies, confirmation was not possible for the BPD<sub>36</sub> group. One possible factor for this potential improvement is the introduction of surfactant

which improves lung compliance markedly in the neonatal period, but insufficient data were available to perform a meta-regression to assess its role in future lung function.

Barker's hypothesis postulates that low birth weight as a consequence of fetal undernutrition is associated with respiratory, cardiac and metabolic disease in adults.<sup>9–11</sup> However, low birth weight includes both immature infants of appropriate growth for gestation and growth retarded infants who may be physiologically mature at birth. Since the mechanisms that lead to %FEV<sub>1</sub> deficits are likely to be different in these two conditions, it is important to separate these in future studies. In our meta-analyses, preterm-born subjects without BPD had a deficit of -7.2%, which is significantly different from term-born infants. This is an important observation, especially as lung function is thought to track throughout life. Low lung function in early life is likely to lead to failure to attain peak lung function in early adulthood, and we speculate that the natural



**Figure 5** Percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) of the preterm group (including groups with bronchopulmonary dysplasia, BPD) compared with term control group.



**Figure 6** Effect of year of birth on percentage predicted forced expiratory volume in 1 s (%FEV<sub>1</sub>) for the bronchopulmonary dysplasia (BPD) group supplemental oxygen dependency at 28 days (closed circles) and the term control group (open circles). Weighting was based on two separate models, one for the BPD<sub>28</sub> group and one for the term control group. Weighting was defined by variance which differs for the term control and BPD<sub>28</sub> group. Bubble sizes show relative contributions based on individual weighting of term control and BPD<sub>28</sub> group. The E-numbers refer to references which are given in the online data supplement.

decline in %FEV<sub>1</sub> from that point onwards will be accelerated by any additional injuries encountered by preterm-born subjects may encounter, for example, tobacco smoking. There is increasing interest in the possibility that chronic obstructive pulmonary disease (COPD) may have its origins in such early life events.<sup>12</sup>

Preterm-born children (with and without BPD) may experience increased respiratory symptoms often reported as asthma and have increased reported bronchodilator use and increased health utilisation including hospitalisation, especially in early childhood.<sup>13</sup> Children who had BPD in infancy may also have increased exercise-induced bronchoconstriction and, importantly, may have reversible bronchoconstriction at rest, as recently reported.<sup>7, 14</sup> It is not currently known whether the deficit in %FEV<sub>1</sub> shown for preterm-born subjects without BPD is reversible. We would also have liked to investigate further the influence of gestational age on later %FEV<sub>1</sub>, but we were unable to classify the group of preterm-born infants without lung disease into different gestational groups as data were not available. It is likely, as we recently reported, that different gestational groups including the very preterm-born and moderately preterm-born groups (33–34 weeks gestation) have greater deficits of lung function in later life than those born at 35–36 weeks gestation.<sup>15, 16</sup> In addition, even infants identified as having BPD will have been exposed to ever-changing interventions and also changing pathology of ‘old’ versus ‘new’ BPD. Our data on changes in %FEV<sub>1</sub> over the last 2–3 decades shows an improvement, which may reflect improvements in the management of these infants but may also reflect the changing pathology of the underlying multifactorial disease we recognise as BPD. Identifying the deficits in lung function is important as children born preterm may have life-long consequences including being potential candidates for the development of COPD, especially if

they are exposed to noxious substances such as tobacco smoke or increased environmental pollution. Furthermore, it is unclear if the deficits in %FEV<sub>1</sub> that we have reported are translated into increased respiratory symptoms or, indeed, are reversible with bronchodilators. However, it is clear that further studies are required to determine whether these children and young adults would benefit from closer follow-up and treatment in childhood and beyond.

### Study limitations

Since some studies did not include a control group but reported %FEV<sub>1</sub> against prevalent reference values at the time of publication, we performed two separate analyses to compare the results obtained when comparisons with a term-born control group or with historical reference values were reported. The pooled effects for the latter were slightly greater and, as expected, there was greater heterogeneity between the studies as systematic differences between populations and methods of calculating predicted values affect this synthesis. In addition, the reference values used may not be contemporaneous, changing only every few decades; and we accepted the reference values used and have not attempted to standardise them which could be another source of heterogeneity. As with all systematic reviews, we were limited by the quality and quantity of information presented in the included articles. This led us to exclude five papers where the results were presented as medians. Further studies which did not report results as percentages of predicted values were also excluded. In a small number of articles we estimated %FEV<sub>1</sub> results from graphically presented data which may have led to small errors, but these are unlikely to have a major effect on the findings. We were only able to contact the authors of the recently published articles, which may be another source of



bias. The articles included were heterogeneous, as expected. This could arise for many reasons. The subjects were of different ages when FEV<sub>1</sub> was measured, although age did not appear to influence %FEV<sub>1</sub> at least for the BPD analyses. An additional factor that may have influenced the results is the age of the child at testing as age is independently associated with FEV<sub>1</sub> (E39). However, since our initial analyses included only papers containing a control group, this influence of age is unlikely to have affected our conclusions. Subjects were born in different decades and treatments have changed over time, which may have led to cohort effects. For example, in some studies a proportion of infants were treated with surfactant to improve their infant lung function, survival and prevent lung injury. The methods for calculating percentage predicted FEV<sub>1</sub> varied between studies. We acknowledge that the preterm-born group containing BPD cases is a very heterogeneous group. The results from this group should be treated with caution, although they were broadly consistent with the results in the tightly defined preterm without BPD population. The other three groups are defined more precisely and included only preterm-born subjects from studies which clearly identified the BPD status. We were therefore able to categorise confidently the preterm-born subjects into groups for analysis.

## CONCLUSIONS

This comprehensive systematic review has quantified the deficits in %FEV<sub>1</sub> in later life of a number of different groups of subjects born preterm and has shown that, even in subjects without BPD, later %FEV<sub>1</sub> is lower than in the population born at term. Future research should follow up these cohorts into middle age and beyond to see if these %FEV<sub>1</sub> deficits translate into higher rates of COPD. Efforts should also be made to identify subgroups at higher risk of poorer lung function in later life and to devise interventions to ameliorate the impact of being born preterm.

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**Contributors** All authors led by SK were involved in the concept and protocol design of the systematic review. SJK and MOE screened the titles and abstracts and data extracted the articles. FD and WJW were primarily responsible for statistical

analyses. SP was primarily involved in the interpretation of the quality data. All the authors contributed to interpreting the results. SJK wrote the initial drafts of the paper to which all the authors contributed. SK is the guarantor.

**Competing interests** None.

**Ethics approval** Ethics approval was not required as this is a systematic review using previously published studies and no new subjects were studied.

**Provenance and review** Not commissioned; externally peer reviewed.

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