Paediatric Respiratory Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

A systematic review of early life factors which adversely affect subsequent lung function

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ARTICLE INFO

Keywords:
Paediatrics
Lung function
Asthma
COPD
Infection
Bronchiolitis
Prematurity
Bronchial hyper-reactivity

SUMMARY

It has been known for many years that multiple early life factors can adversely affect lung function and future respiratory health. This is the first systematic review to attempt to analyse all these factors simultaneously. We adhered to strict *a priori* criteria for inclusion and exclusion of studies. The initial search yielded 29,351 citations of which 208 articles were reviewed in full and 25 were included in the review. This included 6 birth cohorts and 19 longitudinal population studies. The 25 studies reported the effect of 74 childhood factors (on their own or in combinations with other factors) on subsequent lung function reported as percent predicted forced expiration in one second (FEV_1). The childhood factors that were associated with a significant reduction in future FEV_1 could be grouped as: early infection, bronchial hyper-reactivity (BHR) / airway lability, a diagnosis of asthma, wheeze, family history of atopy or asthma, respiratory symptoms and prematurity / low birth weight. A complete mathematical model will only be possible if the raw data from all previous studies is made available. This highlights the need for increased cooperation between researchers and the need for international consensus about the outcome measures for future longitudinal studies.

INTRODUCTION

The two respiratory diseases with the largest burden on patients and on society as a whole are asthma and chronic obstructive pulmonary disease (COPD). Both have their origins in early childhood [1–4]. The early life factors that have been implicated in poor future lung health include environmental tobacco smoke, antenatal nutrition, premature birth, respiratory infections in early life, air pollution, social deprivation, obesity and asthma [5–8]. To reduce the global burden of respiratory disease we should target modifiable early life factors known to be associated with subsequent respiratory disease.

The purpose of this review was to (a) systematically assess early life factors which have been reported in association with low lung function and if the data allowed (b) develop a mathematical model to simultaneously assess the relative contribution of each factor.

Studies are limited in which subjects exposed to risk factors early in life have had lung function measured into early or later adult life. Despite this, observational cohort studies have demonstrated "tracking" of low lung function in early childhood through adolescent years [9,10] and into adult life [11]. The assumption that children with reduced lung function will continue to have poor respiratory health is supported by the Melbourne Asthma Cohort in that those with severe asthma added to the study at the age of 10 years already then demonstrating low lung function, were much more likely to develop COPD by 55 years of age [12,13].

AIMS

There have been no comprehensive systematic reviews on this important area. We undertook this review to address this omission. The aims of our review were:

1. Systematically review the medical literature to identify longitudinal, observational studies reporting associations between known early life risk factors for poor future respiratory health and lung function.

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http://dx.doi.org/10.1016/j.prrv.2016.03.003
1526-0542/

2. Undertake statistical analysis to quantify the size effects of those risk factors on lung function.
3. If possible, to develop a mathematical model to simultaneously assess the relative contribution of each risk factor together with any interactions.

METHODOLOGY

To ensure that the temporal association between putative risk factors and lung function was consistent with a causal relationship, an *a priori* decision was made to exclude cross-sectional studies [14]. Only longitudinal studies which estimated the association of a factor or factors ascertained before forced expiratory volume in one second (FEV_1) was measured were included. By definition systematic reviews involving lung function are required to select a single index to enable comparison between studies. Forced expiratory volume in one second (FEV_1) measurements have been the most widely reported and best understood lung function indices in the paediatric medical literature. They can be reported as FEV_1 volume, percentage predicted FEV_1, FEV_1 z scores or FEV_1: forced vital capacity (FVC) ratios. No individual measure is perfect but it is necessary to correct for growth, gender, ethnicity and age when combining studies which involve children. It was therefore decided *a priori* to use percentage predicted FEV1 as our end point.

A search of Medline, using the search strategy described in Appendix S1 (*Date for search – from 1946 up until October 2014; Type of studies – Human. Language – English*), was performed and papers identified were imported into Reference Manager (Thomson Reuters, Carlsbad, CA). After removal of duplicate papers, titles and abstracts of all identified studies were screened by two independent reviewers (AK and VB) to select publications that met the following 3 criteria:

1. They included COPD and/or asthma
2. They were longitudinal population-based cohorts recruited at birth or in early childhood (<5 years of age).
3. Lung function was measured after assessment of exposure to early life risk factors.

Where there was uncertainty as to whether all 3 criteria were met, the full article was obtained and scrutinised. Disagreement between reviewers was resolved by discussion between AK and VB and, if necessary, a third person (AP) acted as arbitrator.

The remaining papers that were relevant to the research question were obtained and screened to discover if all the following data were available:

4. Early life exposure to a defined risk factor.
5. Lung function reported as percent predicted FEV_1 or data available from which this index could be derived.
6. FEV_1 data (mean and standard deviation [SD] or 95% confidence intervals [CI] or standard error of measurement [SEM] or median and interquartile range [IQR]) were reported separately for subjects exposed and non-exposed to the relevant risk factors.

The authors of the papers excluded from this review (n = 30), because they did not meet criteria 4-6, were contacted and asked if they were willing to provide data to enable their inclusion.

Quality assurance

The methodological quality of the studies was formally assessed using a quality assurance tool from the Critical Appraisal Skills Programme (CASP) (http://www.casp-uk.net/#!casp-tools-checklists/c18f8) which consists of nine questions [15]. See Box 1. Each question could be answered "Yes", "No" or "Do not know". If the answer was "Yes" a score of 1 was given and if the answer was "No" a score of 0 was given. If the answer was "Do not know" the original authors were contacted for clarification. If a clarification was provided the previous scoring rule was applied. If clarification was not available then a score of 0 was given. Each study therefore had a quality assurance score out of nine. The questions that were most relevant when assessing the quality of longitudinal-cohort and birth-cohort studies were 1,2,3,5,6,7. Studies were only selected if the answer was "yes" to all these questions.

Box 1. Critical Appraisal Skills Programme Questions

1. Were the factors that affected lung function clearly described?
2. Was a method of screening used to confirm exposure to factor(s)?
3. Did the study have a control cohort?
4. Was there confirmation that the control cohort had no exposure to any of the risk factors?
5. Were the measures used appropriate?
6. Were one or more measurements taken at a defined time point in both groups?
7. Were both point measures (e.g. mean/median) and measures of dispersion (e.g. SD, IQR, etc.) reported at each measurement point?
8. Were drop-out rates reported?
9. Were all important confounding factors identified?

Box 2. Calculation of Mean Difference

$$MD = (\text{mean predicted } FEV_1 \text{ from exposed sample}) - (\text{mean predicted } FEV_1 \text{ from non exposed sample})$$

$$95\%\ CI = MD \pm t'_{(1-\frac{\alpha}{2})} * \sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}$$

Key: MD – Mean Difference; 95% CI – 95% Confidence Interval; $\mathbf{t'_{(1-\alpha/2)}}$ – reliability factor estimated using the previously described procedure [16]; and was estimated s_1 – Standard deviation of the predicted FEV_1 in the exposed population; n_1 – Sample size of the exposed population; s_2 – Standard deviation of the predicted FEV_1 in the non-exposed population; n_2 – Sample size of the non-exposed population.

Data extraction and synthesis

For each paper, differences between the means of the percent predicted FEV_1 and the 95% CI of the difference between the exposed and unexposed sample were calculated for each risk factor using the formula above. Unequal variance was assumed [16]. For calculation of mean difference see Box 2.

When the SEM was given, the SD was estimated by multiplying the SEM by the square root of the number of participants in the group. When median and IQR were presented the mean was estimated to be equal to the median and the SD was estimated to be the inter quartile range divided by 1.35 [16].

A structured approach was used to assess if the data available in the selected articles allowed for a mathematical model to be developed. This is described below. The risk factor reported in each paper was identified as a binary outcome, once this was done the corresponding percent predicted FEV_1 data for those exposed and