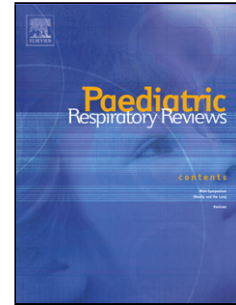


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A systematic review of early life factors which adversely affect subsequent lung function.

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Abstract

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.
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 FEV₁ or data available from which this index could be derived.
6. FEV₁ 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?

Data extraction and synthesis

For each paper, differences between the means of the percent predicted FEV₁ and the 95% CI of the difference between the exposed and unexposed sample were calculated for each risk factor using the formula below. Unequal variance was assumed.[16]

Box 2: Calculation of Mean Difference

$$MD = (\text{mean predicted FEV}_1 \text{ from exposed sample}) \\ - (\text{mean predicted FEV}_1 \text{ from non exposed sample})$$

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

Key: MD – Mean Difference; 95% CI – 95% Confidence Interval; $t'_{(1-\alpha/2)}$ – reliability factor estimated using the previously described procedure [16]; and was estimated s_1 – Standard deviation of the predicted FEV₁ in the exposed population; n_1 – Sample size of the exposed population; s_2 – Standard deviation of the predicted FEV₁ in the non-exposed population; n_2 – Sample size of the non-exposed population.

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 FEV₁ data for those exposed and those not exposed was documented for every measurement time point. It is important to note that there were missing values (i.e. not all risk

factors had a measure taken at every reported time point). Where missing values were identified we contacted respective authors to provide us with the required data.

Results

The initial search yielded 29,351 citations. After removal of duplicates and screening for relevance, 208 articles were selected for full review, of which 55 met the inclusion criteria (criteria 1-3 above). Twenty five studies met additional inclusion criteria (4-6 above), thus enabling comparison between papers. See Figure 1. They comprised 6 birth cohorts[17–22] and 19 population-based longitudinal studies.[12,13,23–39] Tables 1 and 2 give an overview of the included studies. The reasons for rejecting the remaining 30 papers [9,10,40–67] are summarised in Table 3. When the 25 selected articles were analysed, the published data were not suitable for the development of an explanatory model. All relevant authors were contacted but no additional data were made available.

Figure 1: PRISMA flowchart showing numbers of articles reviewed for the systematic review

Article	Factors Investigated	Sample size	FEV ₁ Measured	Quality Assurance Score
Collins 20-11 [17]	Asthma at 6-14 years Atopy at 6-14 years BHR at 6-14 years	1510	6 - 14 years	8/9
Grischkan 2004 [18]	Prematurity Asthma at 8-11 years	251	8 - 11 years	8/9
Guilbert 2011 [19]	Parental allergy and asthma Wheezing <3years	238	5 - 8 years	8/9
Hollams 2014 [20]	Maternal smoking in pregnancy Smoking at age 14 years	1129	14 years	8/9
Mullane 2013 [21]	Lung function at 1 month Wheezing at 18 years	150	18 years	7/9
Vonk 2004 [22]	LRTI aged <1year BHR / atopy 20 years	597	20 years	8/9

Table 1: Summary of birth cohort studies included in systematic review

Article	Factors Investigated	Sample size	FEV1 Measured	Quality Assurance Score
Cassimos 2008 [23]	Bronchiolitis < 1 year Asthma at 7.5 years	189	7.5 years	7/9
De Goojer 1993 [24]	Family history of atopy Respiratory symptoms 8-11 years	60	8-11 years 36 years	8/9
Goksor 2007 [25]	Pre / post-natal smoke exposure Hospitalised with wheeze <2 years	101	17-20 years	7/9
Goksor 2008 [26]	Pre / post natal smoke exposure Asthma 17-20 years	101	17-20 years	8/9
Kim 2013 [27]	History of bronchiolitis Exposure to high levels of ozone	1743	6.8 years	7/9
Korppi 2004 [28]	RSV bronchiolitis <2 years	127	18-20 years	7/9
Kwinta 2013 [29]	Extreme low birth weight Wheeze	81	6.7 years	8/9
Mai 2003 [30]	Prematurity <36 weeks	138	12 years	7/9
Mikalsen 2012 [31]	Bronchiolitis < 1 year RSV +ve / RSV -ve Asthma at 11 years	121	11 years	6/9
Murray 1992 [32]	Clinical bronchiolitis <1 year	73	5 years	7/9
Oswald 1997 [33]	Mild wheezy bronchitis at 7 years Wheezy bronchitis at 7 years Asthma at 7 years Severe asthma at 7-10 years	286	35 years	6/9
Piippo-Savolainen 2004 [34]	Hospitalised with bronchiolitis <2 years Hospitalised with pneumonia <2 years	88	18-21 years	7/9
Rasmusen 2000 [35]	Airway lability at 14 years Airway lability at 19 years	271	14-19 years	7/9
Sigurs 2005 [36]	RSV < 6 months	47	13 years	7/9
Siltanen 2004 [37]	Preterm (<34 weeks) and BW <1.5 kg	72	10 years	8/9
Tai 2014 [12]	Mild wheezy bronchitis at 7 years Wheezy bronchitis at 7 years Asthma at 7 years Severe asthma at 7-10 years	197	50 years	8/9
Tai 2014 [13]	Wheezy bronchitis and asthma 7 years Asthma readmission at 50 years Asthma at 50 years COPD at 50 years	197	50 years	8/9
Tamesis 2013 [38]	Doctor diagnosis of asthma at 7 years BHR at 7 years Asthma at 7 years	177	7 years	7/9
Wilson 2004[39]	Atopic parent Wheeze <4 years Wheeze >4 years	49	10 years	8/9

Table 2: Summary of Longitudinal Studies included in systematic review

Table 3: Summary of studies that were rejected

Article	Factors Investigated	Lung Function	Reason for Rejection
Castro-Rodríguez 2001 [9]	Lower respiratory illness in first 3 years	6 & 11 years	1
Castro-Rodríguez 2001 [10]	Asthma symptoms, BMI and skin tests at 6 years	11 years	1
Stein 1999 [40]	Lower respiratory tract illness in first 3 years	Up to 13 years	1
Krantz 1990 [41]	Whooping cough as infant	6-13 years	1
Bisgaard 2012 [42]	BHR as neonate	6 years	1
Kurukulaaratchy 2003 [43]	BHR at 1,2,4 & 10 years	10 years	1
Lodge 2014 [44]	Wheeze phenotypes, asthma and respiratory symptoms	12 & 18 years	1
Narang 2008 [45]	Preterm delivery	21 years	1
Pike 2013 [46]	Asthma, wheeze and atopy at 6, 12, 24 & 36 months	6 years	1
Illi 2006 [47]	Allergen exposure at 6 & 18 months and 3, 4 & 5 years	7, 10 & 13 years	1
Granell 2013 [48]	Early wheezing phenotypes, doctor-diagnosed asthma and atopy at 7 years	8 years	1
Kreiner-Moller 2013 [49]	Diagnosis of asthma	6 years	1
Pike 2012 [50]	Wheeze phenotype at 6, 12, 24 & 36 months. Infant adiposity gain 0-6 months.	6 years	1
Ware 1984 [51]	Exposure to indoor and outdoor air pollutants		1
Morales 2014 [52]	Intrauterine and early postnatal exposure to outdoor air pollution	4 years	1
Torjussen 1992 [53]	Exposure to environmental tobacco smoke and pets	10 years	1
Chen 2014 [54]	Physical fitness, sedentary time, obesity measures and asthma aged 9 to 12 years	9 to 12 years	2
Singleton 2003 [55]	Hospitalised with RSV at <2 years	5 & 8 years	2
Martinez 1995 [56]	Wheezing phenotypes, markers of atopy	6 years	2
Turner 2009 [57]	Airway responsiveness at 1, 6 & 12 months. Asthma at 11 years	11 years	2
Chawes 2010 [58]	Asthma, eczema, food sensitization, markers of atopy and bronchial responsiveness	7 years	2
Hallberg 2010 [59]	Presence of asthma at 1, 2, 4 and 8 years	8 years	2
Eenhuizen 2013 [60]	Long-term average air pollution concentrations	4 years	2
Van der Gugten 2013 [61]	Respiratory symptoms and presence of respiratory viruses	<1 year	2
Voraphani 2014 [62]	RSV LRTI < 3 years	26 years	2
Belgrave 2014 [63]	Wheeze and atopy phenotypes at 3, 8 & 11 years	3, 8 & 11 years	2
Elliott 2013 [64]	Wheeze phenotypes	0-1 & 2-3 years	2
Wills 2013 [65]	25(OH)D concentrations in pregnancy. Wheeze, asthma, atopy, eczema, hayfever, at 7-8 years	9 years	3
Kerkhof 2014 [66]	Environmental tobacco smoke	6-8 years	3
Halonen 2013 [67]	Eczema and wheezing < 1 year, physician-diagnosed asthma <9 years and asthma in the parents	9 years	3

Reason for rejection: 1- Data not presented as percent predicted FEV₁
2- Data not presented as FEV₁
3- Missing data

All 25 selected papers answered “Yes” to the six key quality questions (1,2,3,5,6,7). The total quality score for each paper can be seen in Tables 1 and 2. Although the risk of bias was minimal it was not eliminated as it was not possible to clearly identify potential confounding factors (questions 4 & 9) in all papers selected.

The 25 papers included in the review reported the association of 74 childhood factors (either individually or in combination) together with subsequent percent predicted FEV₁. Full details of these exposures are shown in Appendix 2. A number of childhood factors were associated with a significant reduction in subsequently measured FEV₁ as defined by the 95% CI of the mean difference (MD) from unexposed subjects excluding zero. These factors could be broadly grouped into: early childhood infection, bronchial hyper-responsiveness (BHR) / airway lability, wheeze, family history of atopy or asthma, a diagnosis of asthma, respiratory symptoms and prematurity / low birth weight. The childhood factors that were significantly associated with future lung function are summarised in Figure 2.

Figure 2: Summary of childhood factors associated with a significant reduction in subsequent lung function

Discussion

Although it is widely recognised that a number of early life factors can adversely affect lung function and therefore future respiratory health [1–4], to our knowledge this is the first comprehensive, systematic review on this topic. A number of risk factors including early childhood infection, BHR / airway lability, a childhood diagnosis of asthma, wheeze, family history of atopy or asthma, respiratory symptoms and prematurity / low birth weight were associated with low percent predicted FEV₁ when measured later in childhood or in adult life in some but not all of the

papers identified. These were variously reported individually or in combination with other factors. The most frequently reported data were for childhood infection, BHR / airway lability and a childhood diagnosis of asthma.

We adhered to strict a priori inclusion and exclusion criteria for studies. This strengthened our results but necessitated the exclusion of some potentially informative studies. Cross-sectional studies were excluded as they cannot assess the temporal direction of associations, making the inference of causality impossible. The quality assurance tool confirmed that the included studies were of a high quality with a low risk of bias. Despite this, we were not able to fully quantify the risk of bias associated with confounders (in both the study and the control cohorts) or with missing values as these were not always documented.

A priori we chose percent predicted FEV₁ as the outcome measure and therefore excluded studies that did not report this value or provide the raw data to allow its calculation. This decision was subsequently justified as it was the most frequently reported lung function outcome measure in the relevant studies. We accept that percent predicted FEV₁ is not the perfect lung function outcome. The equations used to generate the percentage values can impact on results.[68] It may also be less sensitive than Lung Clearance Index in detecting early lung disease [69] and not be as accurate as FEV₁ z scores. Unfortunately, neither of these outcome measures has been used in many longitudinal studies.

It might be assumed that environmental tobacco smoke before birth, and in the early years of life, is a very important risk factor for future respiratory health. Indeed, there are many studies culminating in a systematic review by Cook et al. (1998) which concluded that maternal smoking was associated with a small but statistically significant deficit in lung function in school aged children.[6] Unfortunately, most studies included in that review were cross-sectional and the longitudinal studies included did not present data as percent predicted FEV₁. None of those

studies therefore met our inclusion criteria. The effects of maternal smoking on lung function are mainly seen in early childhood, the differences becoming less apparent with time. There has been a similar debate about the possible effects of environmental pollution and lung growth but relevant papers were not included in our review as they were cross-sectional or did not provide outcome data as percent predicted FEV₁. The seminal paper on lung growth and pollution showed adverse effects on lung development in children 10 to 18 years old leading to clinically significant deficits in attained FEV₁ as they reached adulthood.[70] In addition, 2 large paediatric [71,72] and one adult study[73] have identified small deficits in lung function associated with exposure to particulate matter.

In our study 7 of 22 risk factor combinations which included early childhood infections were associated with a low percent predicted FEV₁ in later life. Acute viral bronchiolitis and viral illnesses associated with wheeze in young children are common but the terminology used to define them is variable. Two combinations which included early childhood infection had very wide confidence intervals (ID 43 & 45) suggesting there were other unexplored confounding factors contributing to the observed differences. In some studies early respiratory viral infections have been associated with the subsequent development of asthma [23,32,34,36] but not in others.[40,74] It has been suggested that RV infections in early life are more likely to cause reduced lung function than RSV infections.[19] Birth cohort studies suggest that lung damage caused by infection may be dependent on the lung already being abnormal due to genetic, immunological or developmental issues as identified by reduced lung function at birth.[40,75,76] This suggests that other risk factors such as prematurity may interact with early infection.

Seven of 8 risk factor combinations that included BHR or airway lability showed a significant reduction in percent predicted FEV₁. Although not present in all patients, BHR is an important feature of asthma and it may also contribute to COPD phenotype.[77] It is caused by an influx of

inflammatory cells and improves when treated with inhaled corticosteroids.[78] The triggers can be nonspecific such as viral infections or specific such as allergen inhalation. The exact relationship between BHR in childhood and the later development of respiratory disease (with or without BHR) is unclear. Some articles included in our review investigated the association between childhood asthma and the subsequent development of COPD.[17,18,23,26,31,33] Six of 13 risk factor combinations included in these articles had a significant reduction in percent predicted FEV₁. We had envisaged including more long term asthma cohort studies within our review but most have not measured FEV₁ percent predicted. The paediatric asthma study with the longest duration of follow-up is from Melbourne, which reported FEV₁ percent predicted at 50 years with a number of participants having been diagnosed with COPD.[12,13] The vast majority of those with COPD aged 50 years came from the severe asthma group recruited at 10 years of age.

Prematurity and extreme prematurity have been highlighted as risk factors for reduced lung function in childhood and for increased severity of viral respiratory infections in infancy. Four studies were included in our review. Three of the five risk factor combinations investigated showed a significant association with subsequent low lung function.[18,29,30,37] The longest duration of follow-up in those studies was 12 years. A 21 year follow-up study of babies born extremely prematurely has reported that any differences in lung function compared with term-born controls during childhood disappears in adult life.[45] This may be linked to suggestions from recent imaging studies that alveolarisation continues through to adolescence.[79] Although studies included in our review did not show lower FEV₁ in atopic compared with non-atopic children, the Multicentre Allergy Study (not included as did not present data on percent predicted FEV₁) found that 90% of children with wheeze but no atopy lost their symptoms at school age and

retained normal lung function at puberty. In contrast, those sensitised to perennial allergens in the first 3 years of life had reduced lung function at school age.[47]

We began this review with the aim of prioritising factors in early life which adversely affect lung function and future lung health. We chose FEV₁ percent predicted as our outcome measure as this was the most widely reported lung function measurement. We soon realised, however, that the data on FEV₁ were much more limited than we had hoped. We also recognised that many risk factors for subsequent low FEV₁ were not reported as independent variables. Therefore a complex picture began to emerge in which multiple factors interacted to affect subsequent lung function. Such interactions have not previously been well discussed. An example of this is early childhood infection. In isolation, acute viral infections in infancy are associated with subsequent low FEV₁ values but the incidence and severity of such infections are affected by other factors such as prematurity, social deprivation, atmospheric pollution and secondary tobacco smoke exposure. In turn, prematurity may be influenced by maternal diet, socio-economic status, maternal smoking and a host of genetic and epigenetic factors, some of which are not fully understood. This complex web of interactions means it is almost impossible to quantify the effect of a single childhood risk factor for future respiratory health. It also suggests it is impossible or impractical to design and implement a sufficiently rigorous birth cohort study to model this outcome.[80]

Conclusion

This systematic review has confirmed that a number of childhood factors significantly adversely affect subsequent lung function. These include: early infection, BHR / airway lability, asthma, wheeze, a family history of atopy or asthma, respiratory symptoms and prematurity / low birth weight {Figure 2}. The different outcome measures reported by cohort studies and our inability to obtain their raw data meant that it was not possible to develop a mathematical model to prioritise

the effects of the various early life factors. The interaction between these factors means that any such model would be extremely complex. If we are to further elucidate the role of early childhood factors that affect future respiratory health it essential that the data from all previous studies are made freely available.[81] Collaborations to share the data from cohort studies such as the Study Team for Early Life Asthma Research (STELAR)[82] represent an important new direction for future research.

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Conflict of Interests

Since completing this project WL has retired from his full time post at Royal Stoke University Hospital and is working part-time as a Respiratory Paediatrician in the Medical Expert Team of GlaxoSmithKlein in the Global Respiratory Franchise.

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Figure 1: PRISMA flowchart showing numbers of articles reviewed for the systematic review

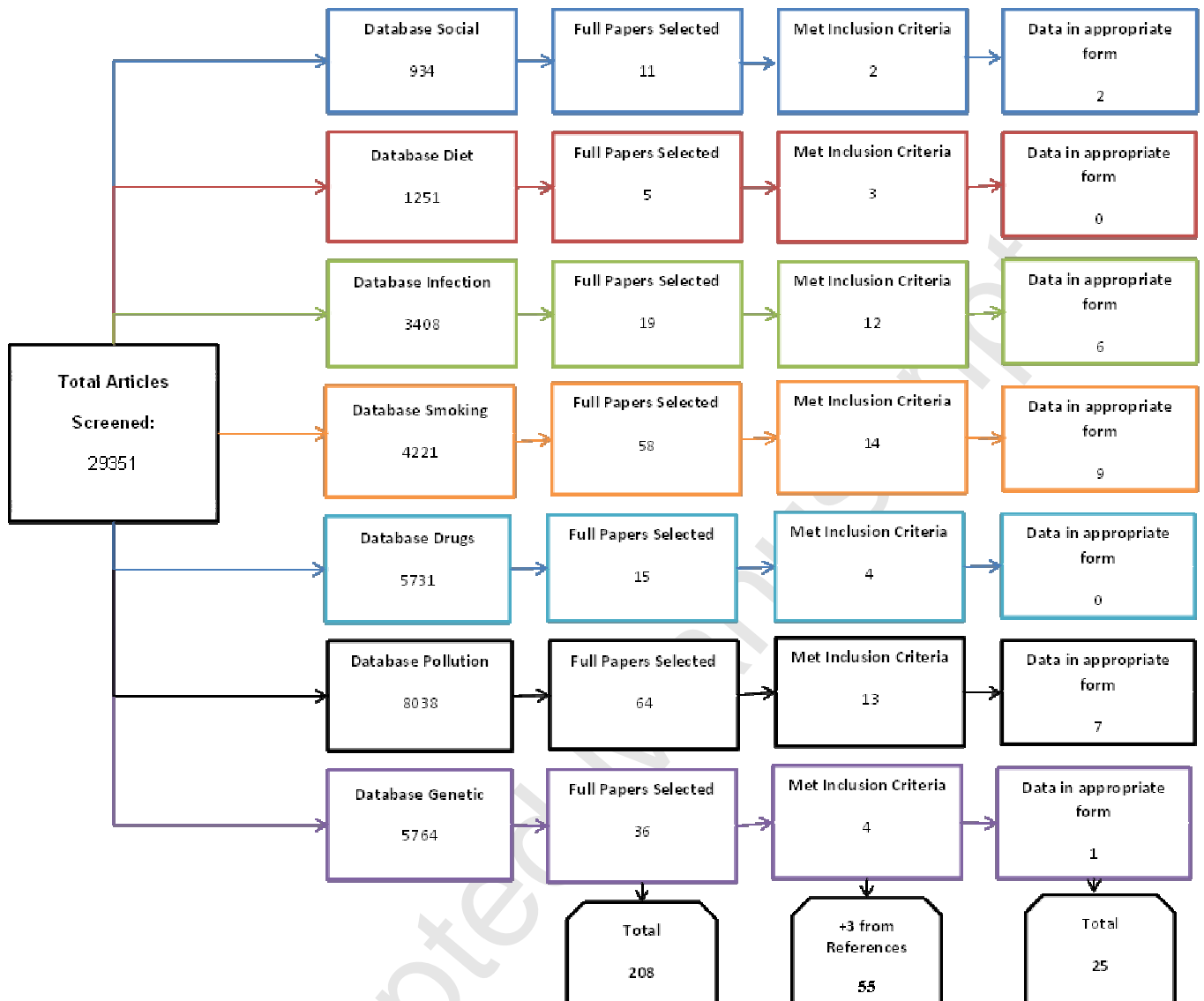
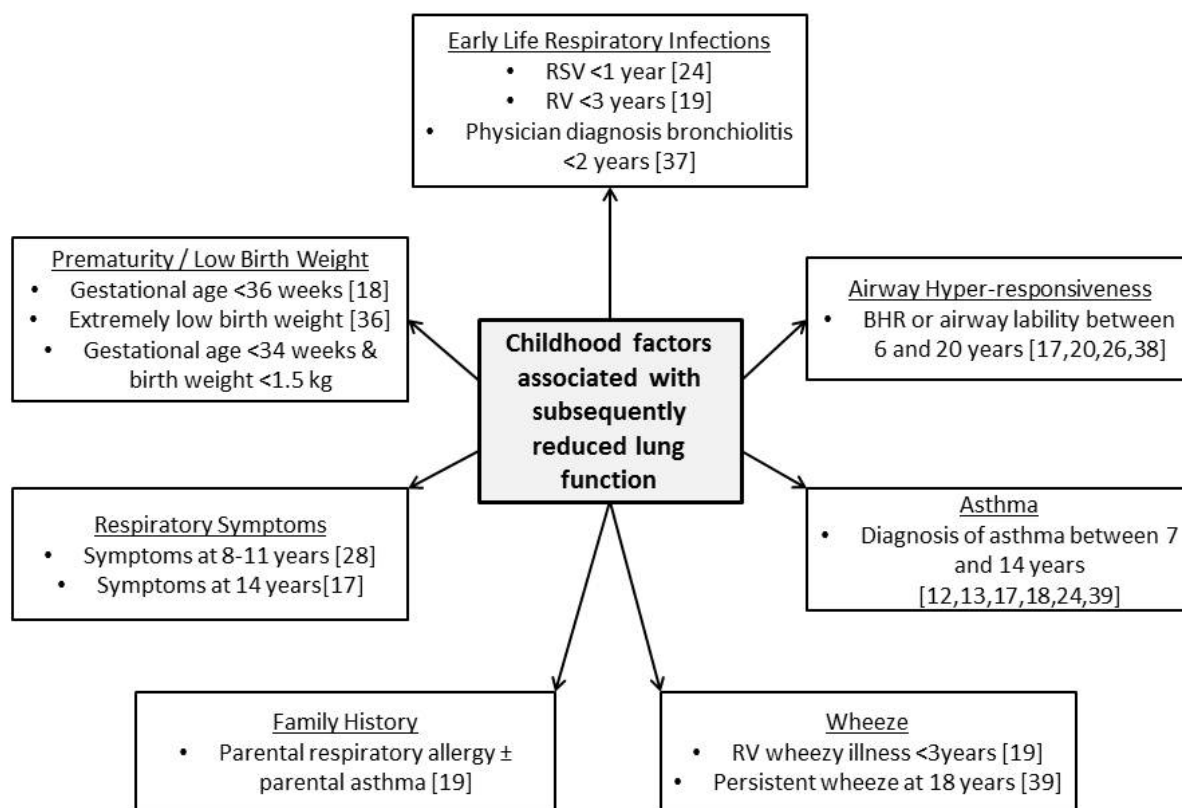


Figure 2: Summary of childhood factors associated with a significant reduction in subsequent lung function



RSV: Respiratory syncytial virus, RV: Rhinovirus, BHR: bronchial hyper-responsiveness