A Systematic Review of Serial Peak Expiratory Flow Measurements in the Diagnosis of Occupational Asthma

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ABSTRACT

This paper systematically reviews literature on the application of serial peak expiratory flow (PEF) measurements in the diagnosis of occupational asthma and calculates summary estimates of the sensitivity, specificity, and feasibility of serial PEFs.

Methods

Papers were searched for on the Medline database via the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) and on the Birmingham Chest Clinic departmental website www.occupationalasthma.com from 2004 until April 2009 using the search terms ''Peak flow AND occupational asthma'' and ''Peak flow AND work related asthma''. Abstracts were screened to select those justifying a full paper review. Papers used in the British Occupational Health Research Foundation (BOHRF) guidelines (current until June 2004) were also reviewed. Case studies and narrative reviews were excluded. Type of analysis, quality of paper, sensitivity, and specificity of serial PEFs compared with reference tests and return rates were documented. Results were pooled from all studies to produce overall estimates.

Results

A total of 80 abstracts were reviewed, leading to 23 full papers for further review plus 15 papers from the 2004 BOHRF review. Seven papers were excluded (mostly for duplicate data), leaving 31 papers for inclusion. The pooled sensitivity of serial PEF fulfilling minimum data quantity requirements for a diagnosis of occupational asthma was 82% (95% CI 76–90%), and the pooled specificity was 88% (95% CI 80–95%). Return rates were similar between PEFs requested through workplace studies (85%) and those requested in a clinical setting (78%), with 61% being interpretable for a diagnosis of occupational asthma from either setting.

Conclusion

Based on a systematic literature search, serial PEF measurement is a feasible, sensitive, and specific test for the diagnosis of occupational asthma, when potential sources of error are understood.

Keywords: occupational asthma, peak expiratory flow, sensitivity, specificity, return rate, adequate data quantity

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INTRODUCTION

Occupational asthma is asthma mainly caused by an agent in the workplace environment. According to population-based studies, as much as 10–20% of adult asthma may be work related [1–3]. When comparing this proportion with the numbers of occupational asthma cases reported in registries [4–9], there seems to be a problem of underdiagnosing work-related asthma. Thus, more focus should be paid to methods that facilitate the recognition and diagnosis of work-related asthma.

For a diagnosis of occupational asthma, it is important to establish a relationship objectively between the workplace exposure and asthma symptoms and signs. Physiologically, this can be achieved by monitoring airflow limitation in relation to occupational exposure(s). If there is an effect of a specific workplace exposure, airflow limitation should be more prominent on work days compared with days away from work (or days away from the causative agent). Airflow limitation can be measured by spirometry, with peak expiratory flow (PEF) and/or forced expiratory volume in 1 s (FEV1) being the most useful for observing changes in airway caliber. PEF is more a reflection of the caliber of larger airways, whereas FEV1 reflects both the large and the small airways. It has been suggested previously that FEV1 could be a more sensitive measure for asthmatic changes than PEF [10] and, as a consequence of this, FEV1 is usually used in specific inhalation challenge testing, which is the gold standard confirmatory test for diagnosing occupational asthma. However, the FEV1 maneuver may be more difficult to accomplish reliably when unsupervised personally by health-care personnel [11], and could therefore be less reproducible when performing unsupervised serial lung function measurements for diagnostic purposes at home and at work.

Serial PEF monitoring is currently recommended as a confirmatory test for occupational asthma by several guidelines [12–14], but not all diagnostic centers have agreed about its value. Previous reviews of diagnostic methods for occupational asthma have been published [12, 15] but, to our knowledge, this is the first systematic review of serial PEF measurements in diagnosing occupational asthma, with focus on the feasibility, sensitivity, and specificity of this method.

Work-related patterns of PEF

Work-relatedness of PEF values can be evaluated by assessing deterioration of mean values at work compared with mean values away from work [16–18] and/or by within-day variability (i.e., diurnal variation), being larger during work days than on rest days or being ⩾20% for more work days than rest days [11, 19–21]. Diurnal variability has been calculated as (daily maximum PEF–daily minimum PEF)/mean daily PEF or predicted PEF or daily maximum PEF.

There are several patterns that can emerge from measuring PEF across work and rest days that are compatible with occupational asthma. These include immediate decreases in PEF (within an hour of arriving at work or being exposed to a specific exposure at work), delayed decreases in PEF (either starting later in the working day or after leaving work), cumulative decreases in PEF over the working week (with PEF deteriorating further with each day at work), non-cumulative decreases (similar falls each day), and on rare occasions a tolerance developing to work exposure can be seen where PEF falls dramatically on the first day of exposure and becomes less as the working week progresses. Recovery usually shows two types of pattern, either immediate or delayed. In the case of immediate recovery, workers make a full recovery within a few hours of leaving work, whereas with delayed recovery, it may take several days to return to the individual's baseline values [16].

Plotting and analysis of serial PEFs

Diagnostic centers around the world plot and analyze serial PEFs for the diagnosis of occupational asthma in different ways. Methods can be statistical or non-statistical, hand plotted or computer generated. For non-occupational asthma, graph-type charts are mostly used creating a line graph. This is useful when the aim is to evaluate asthma control, but may be harder to interpret occupational effect. **Figure 1** shows a serial PEF record that has been plotted in this fashion for a worker exposed to oil mists. This type of line graph can be modified to show a line for the maximum and the minimum each day and labeling for days at work and days away from work (rest). Information on the diurnal variation each day can also be shown and can be used in the assessment of an occupational effect. An example of this is shown in **Figure 2** (data are from the same PEF record as **Figure 1**). Plotting can be ''day interpreted'' [22], with each work day starting with the first reading at work (rather than the waking reading) and finishing with the last reading before work on the following day. This is the preferred method as the first reading taken before work in the morning will be influenced by the previous day's exposure. Plotting can be done to create a maximum and minimum daily PEF with or without a mean PEF. **Figure 3** shows the same PEF record as shown in **Figures 1 and 2** plotted using a computer-based program known as Oasys (Occupational Asthma System). It is easier to see work-related deterioration in this record.

As with plotting, there are several ways to analyze serial PEF records. Records can be analyzed visually by experts, they can undergo statistical analysis, or other computer-based analysis can be utilized. Features influencing expert interpretation include changes in mean daily PEF related to work exposure and the extent of changes in diurnal variation. Statistical analyses of PEF variability have shown significant differences between work and rest days in several studies [19, 23, 24]. However, the sensitivity and specificity of differences in diurnal variation analyzed statistically are often not as high as

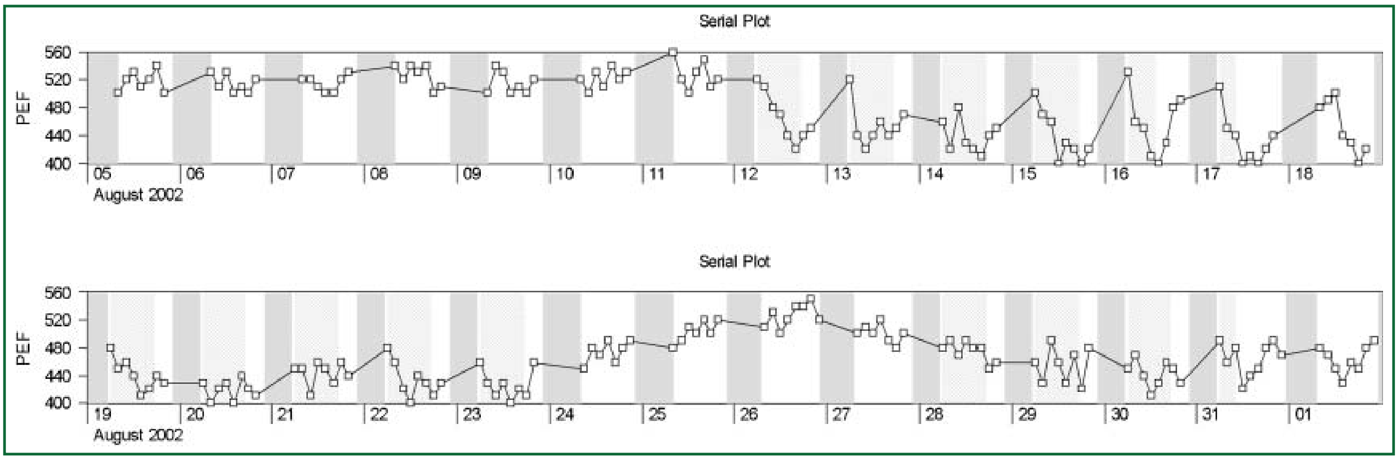

Figure 1. Serial plot of PEF measurements for a worker exposed to oil mists. Working times have diagonal back slash bars (day shifts), times away from work are blank, and times when the worker is asleep are block grey. The highest PEF readings per measurement session (approximately 2-hourly) made throughout each day are plotted

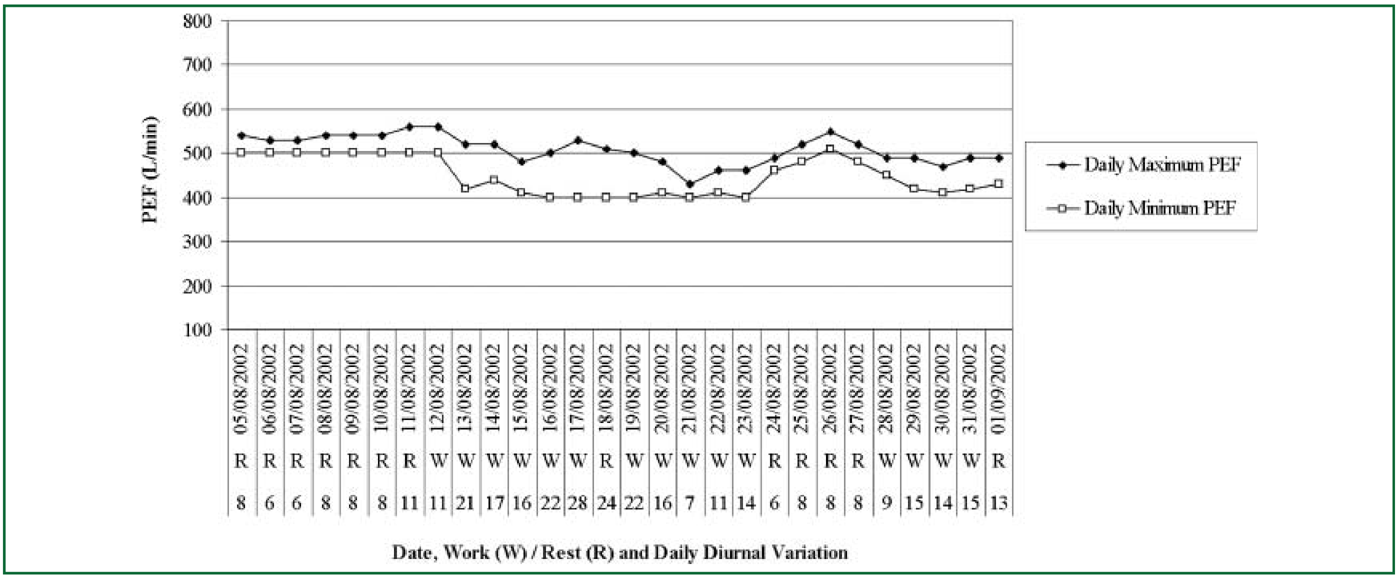

Figure 2. Quantitative analysis plot based on comparison of diurnal variation in PEF between work days and rest days. Plotted for the same worker as in Figure 1

expert evaluation or other computer-based analysis [11, 16–21, 25, 26]. A further analysis utilizes Shewart's control charts [21, 27]. Two types of analysis have been suggested: the first compares the individual's lower limit on work days with their personal best on rest days (this method detects high diurnal variation rather than a work-related decrease in PEF); the second compares diurnal variation on work days (in L/min) with diurnal variation on rest days. A 15% increase in work day variation constitutes a positive result [17, 22, 26, 28, 29]. Neither method has been tested in prospective studies.

Oasys

The Oasys 2 program is a computer-based PEF analysis tool freely available from www.occupationalasthma.com. It was first developed in 1995 by Gannon *et al* [17] and was based on expert interpretation of hand-plotted PEF records. It uses discriminant analysis (non-statistical) to determine whether each work–rest–work period or rest–work–rest period (known as complexes) shows a pattern compatible with an occupational effect. In the updated version of Oasys, several other analyses have been developed such as the area between curves (ABC) score [26], timepoint analysis [28], and work–rest PEF score [30]. The ABC score utilizes the 2-hourly plot of average lung function on rest days and work days and creates a score from the area between the mean work day and mean rest day curves plotted by either clock time or time from waking up [26]. **Figure 4** shows this plot for the same worker as in **Figure 1**. The timepoint analysis is a statistical method identifying measurements at a single timepoint which are below the 95% confidence interval (CI) for the mean rest day measurements [28]. This has similarities to the first Shewart's chart method, but is less influenced by increased diurnal variation in occupational asthmatics compared with control subjects.

Aims

In this paper, all types of analysis method for serial PEFs have been included. The aims of this article are to systematically review studies published on serial PEF measurements used for the diagnosis of occupational asthma and to calculate summary estimates of the sensitivity, specificity, and feasibility of serial PEF measurements for diagnosing occupational asthma in clinical and workplace settings.

METHODS

Articles published on serial PEFs as a diagnostic test for occupational asthma were systematically searched for from 2004 until April 2009 on the Medline database via the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) using the search terms "Peak flow AND occupational asthma" and "Peak flow AND work related asthma". The Birmingham Chest Clinic departmental website (www.occupationalasthma.com) was also searched using the same search terms. Abstracts were screened to select those that justified a full paper review. These included: (1) those that investigated serial peak flow/forced expiratory volume in 1 s (FEV1) measurements plus another confirmatory test for occupational asthma; and (2) those that investigated the achievability of serial PEFs or FEV1s in the clinical or workplace setting. Single case reports and narrative reviews were excluded. For the remaining abstracts, the full paper was obtained. In addition to these selected papers, the research articles used in the British Occupational Health Research Foundation (BOHRF) guidelines were also reviewed. The literature search for the BOHRF guidelines had been performed in a similar way, by systematically searching Medline and Embase from 1966 and 1974, respectively, to the end of June 2004 [14].

Information on the country where the study took place, the year of the study, the reference confirmatory test, methodol-

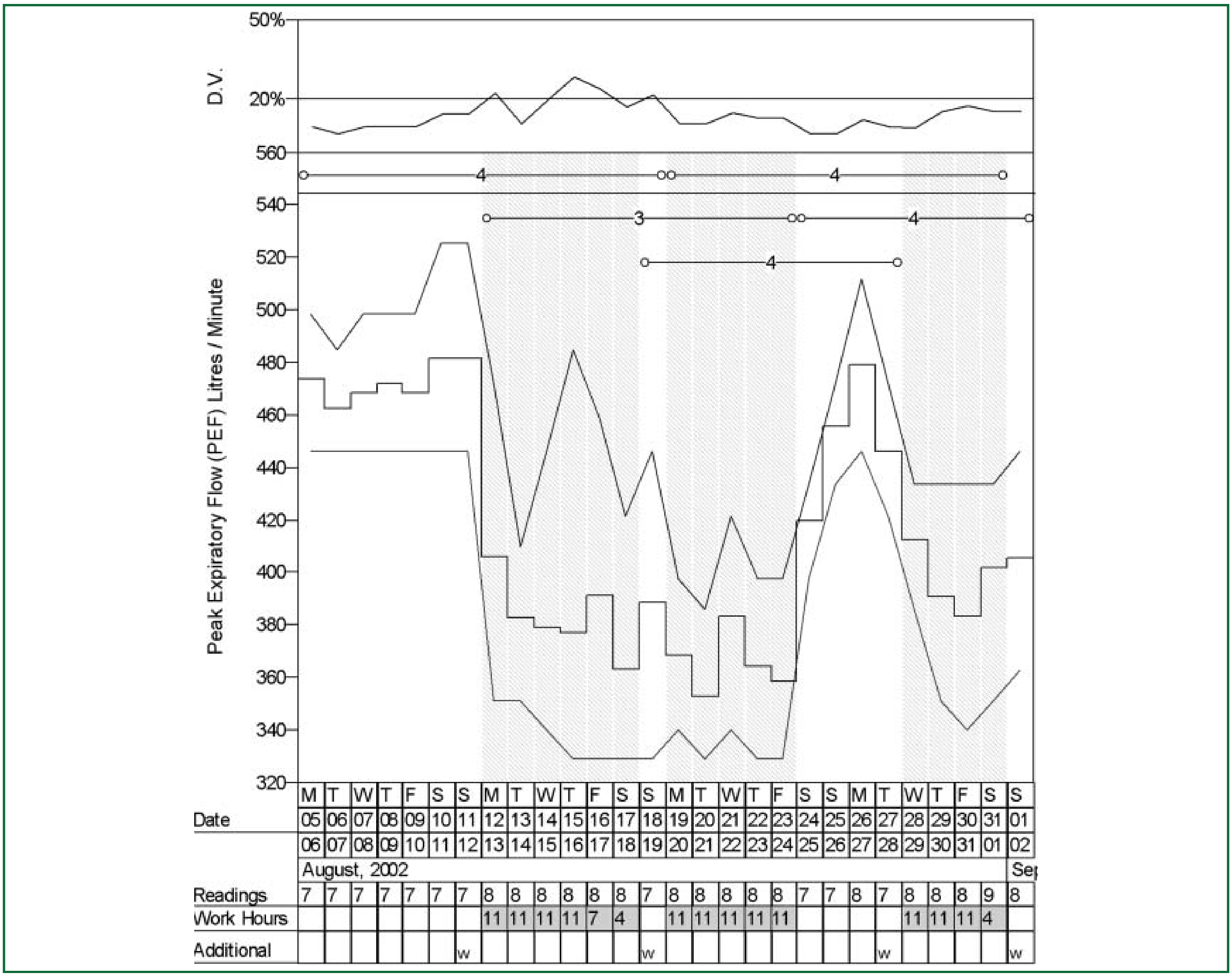

Figure 3. Maximum, mean, and minimum PEF plot from the Oasys program for the same record as in **Figure 1**. The top part of the chart shows the diurnal variation (DV) for each day. The middle of the chart shows the maximum, mean, and minimum peak flow for each day. The black continuous line is the mean PEF, the upper line the maximum PEF, and the lower line the minimum PEF for each day. The work periods are the shaded areas (diagonal back slash bars are day shifts) and the rest periods are blank areas. The horizontal lines containing numbers in this part of the chart are scores for the work–rest–work and rest–work–rest complexes (six complexes in total in this record). The bottom of the record shows the days and dates of the record. The Oasys score of this record is 3.89 (almost definite occupational asthma)

ogy and data needed for a quality assessment using Scottish Intercollegiate Guidelines Network (SIGN) methodology [31], and results on sensitivity, specificity, data quantity, and return rates were recorded. Data were pooled to represent summary findings. For the pooled sensitivity and specificity, studies with more than one visual assessor were treated separately. For all other types of analyses (i.e., computer based or quantitative), the index with the highest sensitivity and specificity being tested was used. Pooled results were calculated using raw data from the studies. The total number of all those who were correctly identified as having occupational asthma were divided by the total number of reference test positives for sensitivity, and the total number of those who were correctly identified as not having occupational asthma were divided by the total number of reference test negatives for specificity.

Oasys minimum data quantity criteria were used for computer-based analyses [29]; these require ⩾4 readings per day, ⩾3 consecutive work days in any work period, and ⩾3 complexes (approximately 3 weeks) of data. For visual analysis, the recommendations by Bright and Burge [18] and Malo *et al* [32] were used; these require 2 weeks at work and 2 weeks away from work with ⩾4 readings per day. In the papers discussing Shewart's control charts, minimum data were taken as records that were usable for this method [21, 27]. Records were deemed to be acceptable/interpretable based on the requirements defined by each study itself. That is, if records were able to be scored by any method and analyzed to give a diagnostic outcome of whether they showed occupational asthma or not, they were considered to be acceptable or interpretable. If the study reported data for records failing to fulfill data quantity standards, these were analyzed separately [29].

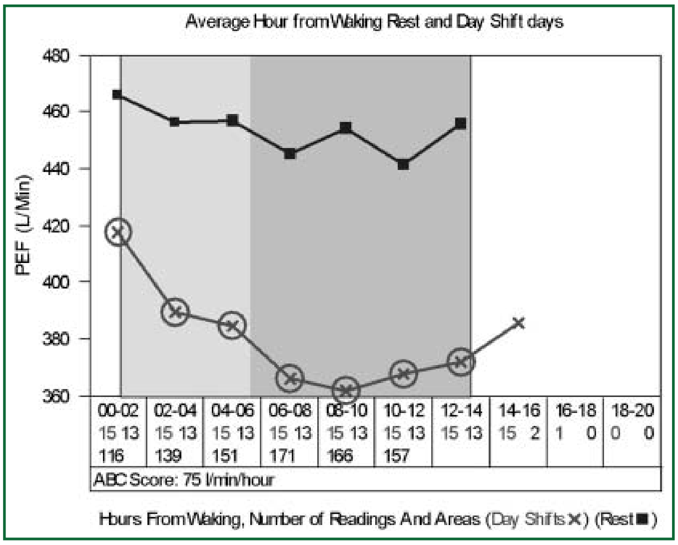

Figure 4. A 2-hourly plot of the average PEF on rest days and work days analyzed by the Oasys program for the same worker as in **Figure 1**. Mean PEF measurements taken at the following times: between 0 and 2, >2–4, >4–6 h, and so on from the waking time are plotted based on all work days and all rest days. The black upper line (square markers) shows the average peak flow for rest days by 2-h segments from 0 to 24 h from waking. The grey lower line (cross markers) shows the same for work days. The circles relate to the timepoint analysis (significant drops). The gray area shows information about the times of starting and stopping work (mode, minimum, and maximum). The legend shows the start and end of the 2-h time segments, the number of readings used to calculate the work and rest day average PEFs, the area between the rest and work day PEF curves (ABC) on the graph for each time segment, and the total area between the lines divided by the number of hours for which there are measurements (ABC score). This record gives an ABC score of 75 L/min/h (shown on the plot) (interpreted as occupational asthma)

Papers were reviewed applying quality criteria according to SIGN methodology for diagnostic studies, which scores studies as ++, +, or – according to how reliable the conclusions of the study were [31]. Only studies with ++ or + scores were included in pooled calculations.

RESULTS

A total of 79 abstracts were found in the Medline (PubMed) database search using the search terms ''Peak flow AND occupational asthma'' or ''Peak flow AND work related asthma''. One further abstract was found on the www.occupationalasthma.com database. The flow diagram in **Figure 5** shows how papers were excluded leaving 31 articles, 17 of which were from this systematic review from 2004 until April 2009 and 14 papers from those used previously for the BOHRF 2004 guidelines.

Articles reviewed for the purpose of calculating the pooled sensitivity and specificity of diagnosis of occupational asthma based on serial PEF measurements are summarized in **Table 1**. Papers reviewed for the purpose of calculating the pooled return rates of serial PEF records and/or the numbers of acceptable/interpretable PEFs returned are summarized in **Table 2**.

Table 3 gives an overview of each article's country of origin and results of the pooled analyses. The majority of the articles were published in Canada (31%) and the UK (25%), with the rest being conducted in the USA, Finland, Spain, and other European countries including Turkey. The pooled sensitivity from all studies was 75%, and the pooled specificity was 79%. Two articles presented data for sensitivity only. When

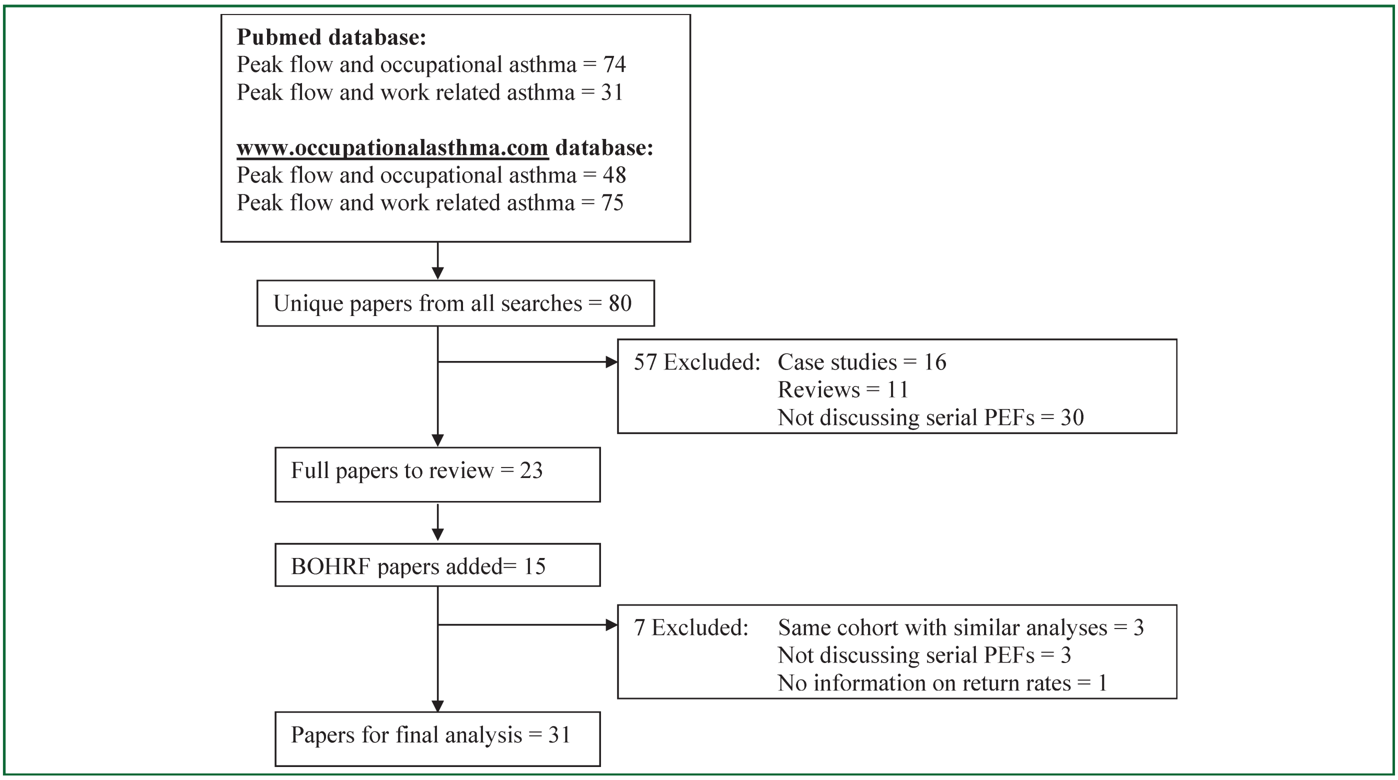

Figure 5. Flow diagram of the selection process for inclusion of papers

Table 1. Articles identified for Sensitivity and Specificity of the Diagnosis of Occupational Asthma based on serial PEF Measurements

First author, year [ref.]	Country	Included	Paper quality	PEF data quality	No. of subjects	Analysis type	Sensitivity (%)	Specificity (%)	Reference test
Girard 2004 [33]	Canada	Yes	++	Inadequate	49	Computer-based Oasys 2 score and visual	Oasys score:	Oasys score:	23 SIC +ve
							34.8	65.2	26 SIC –ve
							Visual:	Visual:	
							63.1	61.9	
							78.9	52.9	
							82.3	55.0	
							77.7	47.6	
							86.6	50.0	
Hannu 2007 [34]	Finland	Yes	+	Unknown	9	Visual	83.3	NA	SIC
Moore 2009 [26]	UK	Yes	++	Inadequate	112 (test set)	Computer-based Oasys ABC score	72.2	100	54 SIC/NSBR change/ specific IgE +ve
									58 asthmatics not at work
Hayati 2006 [27]	USA	Yes	+	Adequate	45	Other— Shewart's control chart	85.7	87.5	21 SIC +ve
									24 SIC –ve
Chiry 2007 [23]	Canada	No—same cohort as Girard paper with same analyses							
Anees 2004 [29]	UK	Yes	++	Presents adequate and inadequate data	122 (test set)	Computer-based Oasys 2 score	78.1 (⩾min. data)	91.7 (⩾min. data)	74 SIC/NSBR change/ specific IgE +ve
							63.6 (<min. data)	83.3 (<min. data)	60 asthmatics not at work
Kennedy 2007 [35]	Canada	No—same cohort as Girard [33] with same analyses; discusses costs of tests							
Munoz 2004 [36]	Spain	Yes	+	Unknown	5	Visual	80		SIC

Table 1. Continued

First author, year [ref.]	Country	Included	Paper quality	PEF data quality	No. of subjects	Analysis type	Sensitivity (%)	Specificity (%)	Reference test
Hayati 2008 [21]	USA/Canada	Yes	+	Adequate	36	Other—Shewart's control chart (DV)	94 .4	61 .1	18 SIC +ve
									18 SIC –ve
Park 2009 [37]	UK	Yes	++	Adequate	40 (test set)	Computer-based Oasys 2 score and other quantitative (mean PEF)	Oasys: 83.3	Oasys: 91	18 SIC +ve
							Other: 66.7	Other: 100	22 asthmatics not at work
Cote 1990 [24]	Canada	No—same cohort and analyses as Cote 1993 [19]							
Cote 1993 [19]	Canada	Yes	++	Adequate	25	Visual and other quantitative (Max.–min. PEF)	Visual: 86.7	Visual: 90	15 SIC +ve
							Other: 93.3	Other: 90	10 SIC –ve
Leroyer 1998 [11]	Canada	Yes	++	Inadequate	20	Visual and other quantitative (DV)	Visual:	Visual:	11 SIC +ve
							72.7	88.9	9 SIC –ve
							72.7	100	
							81.8	100	
							Other:	Other:	
							36.3	77.7	
Malo 1993 [32]	Canada	Yes	++	Adequate	74	Visual	72	78	33 SIC +ve
									41 SIC –ve
Bright 2001 [25]	UK	Yes	++	Adequate	67 (test set)	Computer-based Oasys 3 score and visual	Computer:	Computer:	35 SIC/NSBR change/ specific IgE +ve
							82	94	32 asthmatics not at work or asymptomatic post office workers
							Visual:	Visual:	
							100	93	

Table 1. Continued

First author, year [ref.]	Country	Included	Paper quality	PEF data quality	No. of subjects	Analysis type	Sensitivity (%)	Specificity (%)	Reference test
Burge 1982 [16]	UK	Yes	++	Inadequate	46	Visual	70	92	33 SIC +ve
									13 no work effect after returning to work after a break or workers with OA not exposed
Liss 1991 [38]	Canada	Yes	++	Inadequate	37	Visual	72	53	18 History plus NSBR change or NSBR <8 plus SPT or SIC
									19 normal subjects (NSBR >8 or SIC –ve)
Perrin 1992 [20]	Canada	Yes	++	Inadequate	61	Visual and other quantitative (DV)	Visual:	Visual:	25 SIC +ve
							81	74	36 SIC –ve
							Other:	Other:	
							60	78	
Gannon 1996 [17]	UK	Yes	++	Adequate	67 (test set)	Computer-based Oasys 2 score	75	94	35 SIC/NSBR change/ specific IgE +ve
									32 asthmatics not at work or asymptomatic post office workers

NA, not available; SIC, specific inhalation challenge test; NSBR, significant improvement in non-specific bronchial reactivity away from work; IgE, immunoglobulin E; Oasys 2, discriminant analysis using the Oasys software; Oasys ABC, area between the curves of work and rest day PEF 2-hourly plots using the Oasys software.

Visual analysis is the opinion of an expert from a plotted PEF record, computer-based analysis is the results of Oasys 2 and Oasys ABC scores, Shewart's control chart is based on a statistical analysis that forms part of the Shewart's system, and quantitative analysis was mostly based on diurnal variation differences between work and rest day measurements. Those relying on differences in mean PEF on work and rest days are identified separately.

Table 2. Articles showing Return Rates of Serial PEF Records, comparing Records requested at Workplace Surveys and those requested following Clinic Referral

First author, year [ref.]	Country	Included	No. of subjects	OA clinic (1) or workplace study (2)	PEFs returned (%)	Acceptable/interpretable PEFs returned (%)
Girard 2004 [33]	Canada	Yes	94	OA clinic	81	49
Hannu 2007 [34]	Finland	Yes	9	OA clinic	100	67
Medina-Ramón 2006 [39]	Spain	Yes	80	Workplace	64	46
Arbak 2004 [40]	Turkey	Yes	64	Workplace	100	NA
Bolen 2007 [41]	USA	Yes	178	Workplace	76	53
Eifan 2005 [42]	Turkey	Yes	36	Workplace	78	61
Turgut 2005 [43]	Turkey	Yes	22	Workplace	95	NA
Huggins 2005 [44]	UK	Yes	158 postal instructions	OA clinic	56	42
			86 personal instructions		85	65
Sauni 2009 [45]	Finland	Yes	76	OA clinic	NA	53
Minov 2007 [46]	Macedonia	Yes	5	Workplace	100	NA
Robertson 2007 [47]	UK	Yes	191	Workplace	87	NA
Hayati 2006 [27]	USA	Yes	48	OA clinic	NA	94
Chiry 2007 [23]	Canada	No—same cohort as Girard [33]				
Munoz 2004 [36]	Spain	Yes	5	OA clinic	100	NA
Hayati 2008 [21]	USA/Canada	Yes	45	OA clinic	NA	80
Cote 1993 [19]	Canada	Yes	29	OA clinic	100	86
Henneberger 1991 [48]	USA	Yes	26	Workplace	77	54
Hollander 1998 [49]	The Netherlands	Yes	398	Workplace	90	52
Leroyer 1998 [11]	Canada	Yes	20	OA clinic	100	NA
Malo 1995 [50]	Canada	Yes	21	OA clinic	NA	71
Quirce 1995 [51]	Canada	Yes	17	OA clinic	76	65
Revsbech 1989 [52]	Denmark	Yes	139	Workplace	NA	95
Redlich 2001 [53]	USA	Yes	75	Workplace	NA	87
Liss 1991 [38]	Canada	Yes	78	OA clinic	NA	64
Perrin 1992 [20]	Canada	Yes	61	OA clinic	100	72

OA, occupational asthma; PEF, peak expiratory flow; NA, not available.

confined to PEF records fulfilling the minimum data quantity, the sensitivity was even better at 82% (95% CI 76–90%), with specificity at 88% (95% CI 80–95%). Visual analyses seemed to be slightly more sensitive (78%) than computer-based analysis (71%), but specificity was better with computer-based analysis (91%) vs visual analysis (69%). Other quantitative methods of analysis gave a sensitivity of 74% and a specificity of 82%.

The return rate of serial PEF recordings was good overall at 83%, with 61% containing interpretable and acceptable PEF data. The return rate was slightly better when requested in a workplace study (85%) compared with an occupational respiratory clinic (78%), but the rate of interpretable and acceptable PEF data was similar between these two types of studies (62% vs 61% respectively).

DISCUSSION

This systematic review shows that serial PEF measurements are achievable, and have a good sensitivity and specificity for diagnosing occupational asthma. Acceptable and interpretable serial PEF recordings can be achieved by 61% of people asked to carry them out because of suspicion of occupational asthma. The pooled sensitivity and specificity of serial PEF recordings were 82% and 88%, respectively, when the minimum data requirements were satisfied.

Table 3. Overall Results from the Articles identified in the Systematic Search

Articles identified	%	Confidence interval	Likelihood ratio	No. of studies
Location				
Canada	31	–	Na	8
UK	25	–	Na	8
Turkey	10	–	Na	3
Others	39	–	Na	12
Articles including data on sensitivity of serial PEFs for independent diagnosis of OA	Sensitivity %			16
Pooled sensitivity	75	69–81	3.6	16
PEFs fulfilling minimum data quantity	82	76–90	6.8	8
PEFs not fulfilling minimum data quantity	69	61–78	2.5	7
Unknown data quantity	82	61–100	–	2
Computer-based analysis	71	54–85	7.9	6
Visual analysis	78	72–85	2.5	9
Other quantitative analyses	74	49–96	4.1	6
Articles including data on specificity of serial PEFs for independent diagnosis of OA	Specificity %			14
Pooled specificity	79	73–87	0.3	14
PEFs fulfilling minimum data quantity	88	80–95	0.2	8
PEFs not fulfilling minimum data quantity	72	65–85	0.4	7
Unknown data quantity	–	–	–	–
Computer-based analysis	91	78–99	0.3	6
Visual analysis	69	64–86	0.3	9
Other quantitative analyses	82	65–93	0.3	6
Reference confirmatory test	%			
Specific inhalation challenge (SIC)	74	–	NA	11
Mixed (SIC, fourfold change in NSBR, IgE)	26	–	NA	5
Papers discussing feasibility of serial PEFs	Return rate %			24
Pooled return rates	83	80–94	NA	17
Pooled return rates for interpretable/acceptable PEFs	61	58–74	NA	19
Pooled return rates for PEFs requested through an occupational respiratory clinic	78	77–100	NA	8
Return rate for interpretable/acceptable PEFs	61	58–77	NA	11
Pooled return rates for PEFs requested through a workplace study	85	76–95	NA	9
Return rate for interpretable/acceptable PEFs	62	47–82	NA	7

NA, not available; NSBR, significant improvement in non-specific bronchial reactivity away from work; IgE, immunoglobulin E; OA, occupational asthma; PEF, peak expiratory flow.

The pooled return rate of PEF recordings was 83%. According to a previous study from the UK, return rates can be improved from 56% to 85% by giving personal instructions in an occupational clinic rather than sending instructions by post only [44]. Results are improved by using specialized record cards, which require times of waking and going to sleep, and times of starting and stopping work. They provide better results than the standard asthmatic charts which simply graph PEF (often every 4 h or less) [44], where details of times of working and sleeping are often missing. Workers seen in occupational clinics who are going through their diagnostic pathway yield similar return rates and acceptability to those who have taken part in specific work-based studies.

Visual analysis by an expert is the most sensitive method for deciding whether a PEF record shows a pattern compatible with occupational asthma or not, but it has been found to show only moderate repeatability within observers (kappa 0.47), which is reflected in lower specificity. Within-observer agreement is further reduced when PEFs are of poorer quality, [54, 55]. Agreement between observers is moderate to high (kappa values mostly from 0.6 to 1, but one study reported a kappa value of 0.19) [11, 20, 32, 33, 38, 54–56]. Computer-based interpretation overcomes observer disagreements; they have shown a slightly lower sensitivity (71%) but a better specificity (91%) compared with visual analysis (78% sensitivity and 69% specificity) for records with adequate quantity of data [17, 25, 29]. Computer-based interpretation can be used in any type of clinic, specialist or not, and does not usually require an expert to be present, as long as the interpreters are aware of potential sources of error in measurements. Analyses utilizing methods such as the Shewart's control chart also display these attributes [21, 27]. However, these methods have not been tested in prospective studies. Combining serial PEF records with induced sputum analysis improved sensitivity and specificity of the diagnosis of occupational asthma in one study that had an unusually low sensitivity when using computer-based analysis [33]. Combining serial PEFs with non-specific bronchial reactivity (NSBR) measurements showed either no improvement over PEF recordings alone or an improvement in sensitivity and a decrease in specificity [20, 24].

There are differences of opinion about the minimum diurnal variation and the magnitude of difference between mean PEF on work and rest days required for a diagnosis of occupational asthma [11, 16, 18–21, 33]. Some centers require the diurnal variation in PEF to be >20% during work days, at least in part of the record. Diurnal variation is increased in asthmatics, and cutoffs of 20% and 15% have been suggested previously [57, 58]. In a population sample, the sensitivity of diurnal variation has been shown to be very low (32%) at a specificity of 90% for detecting asthma [59]. Many workers with occupational asthma show increased diurnal variation in PEF on work days compared with days away from work, but this may not always be the case, as the acrophase (peak) PEF may be suppressed by work exposures, which would reduce work day diurnal variation, even if the values at work are lower. The magnitude of changes in PEF can be altered by treatment. The only papers that have assessed the effect of asthma medication on serial PEFs are from the 1980s and early 1990s when the PEF analysis methods were being developed. The changes seen in patients taking disodium cromoglycate or low-dose inhaled steroids were smaller than those seen off treatment and initially led to reduced visual assessment scores [60]. Malo *et al* [32] found little difference in the visual analysis of PEFs in patients using inhaled corticosteroids (ICS) compared with those using beta agonists alone. These studies preceded the use of long-acting beta agonists and high-dose inhaled steroids that are used today rather commonly in the treatment of asthma. Asthma treatments are likely to influence the methods based on numerical differences between work and rest periods more than those based on pattern recognition and discriminant analysis, although the latter are also likely to be influenced. Studies of non-occupational asthmatics and normal workers exposed to high levels of irritants have shown that 16 L/min is the upper 95% confidence limit for differences in mean PEF between work and rest days in workers off treatment [30, 37]. If PEF monitoring does not show a work-related effect while taking regular long-acting beta agonist or prophylactic asthma treatment, it is worth repeating the measurements off treatment or with minimal inhaled steroid medication required from the clinical point of view, if there is still a suspicion of occupational asthma based on symptom patterns. This is based on expert opinion and experience rather than on published studies.

When investigating the sensitivity and specificity of a physiological test, a positive and negative reference test needs to be used. Specific inhalation challenge (SIC) testing is most commonly used as the gold standard for occupational asthma, as this most closely represents a single exposure at work, thereby identifying a specific cause for occupational asthma. Many studies use a positive result in a SIC as the positive reference standard and a negative SIC as the negative reference. However, this does have some drawbacks as false-negative results may be obtained if the amount of exposure used in the specific challenge test was too small compared with real-life conditions, a wrong agent was chosen to be tested in SIC, or if the exposure is difficult to reproduce under laboratory conditions [61]. The last may be the case if a mixture of occupational exposures is more relevant for developing occupational asthma than any single exposure alone. The opposite may also occur, in that false-positive results can be obtained if exposures in SIC are too high compared with real-life exposures and reach levels to which any general asthmatic would react.

Some authors use workplace challenge tests as the reference standard alongside specific challenge tests [23, 32]. Workplace challenges allow supervision of exposures and lung function monitoring but, like serial PEF measurements, do not usually identify the specific cause of the occupational asthma. Other authors have included tests such as changes in non-specific bronchial reactivity between a period of occupational exposure and a period of no such exposure (measured after at least 1 week away from work) and/or specific immunoglobulin (Ig)E to a relevant substance combined with a work-related symptom history as their reference standards [17, 25, 26, 28, 38]. The former has been shown to have a moderate sensitivity and specificity for occupational asthma diagnosis compared with SIC [20, 24, 62]. The latter is the only method that is exclusive of any lung function measurements. Specific IgE indicates sensitization to a specific agent rather than disease, and validation of asthma is also required when it is used as a reference standard for occupational asthma. Such an approach has been validated for a limited number of agents [63–66]. In the current review, the reference test for occupational asthma was based on SIC test in 74% of the studies and a combination of SIC and other tests in 26% of the studies. The sensitivity of the studies with adequate PEF data using SIC vs all methods was similar at

81% and 83% respectively. The corresponding specificity was 82% and 94%. It should be noted that Oasys score or Oasys ABC was used for all studies using the mixed method reference standards, so the high specificity reflects these methods.

Sources of error in PEF measurements

High sensitivity and specificity of PEF records has been found despite the many potential sources of error in PEF measurements, including suboptimal effort, fabricated measurements, variable asthma treatment, and potential effects of other exposures that might affect airway caliber apart from workplace agents. Respiratory tract infections in particular may lower PEF independently of work exposures. To cause a systematic error in the interpretation of serial PEFs, i.e., to cause a bias, these factors need to be systematically different on work compared with rest days. Two potential errors need particular attention: the use of more bronchodilator treatment on work days may mask work effects; and lower readings taken during sickness absence due to respiratory infections may obscure improvement on rest days. It is important to try to keep asthma treatment the same during the entire period of serial PEF measurements, always make measurements before taking bronchodilating medication, and record any respiratory tract infections occurring during the serial PEFs, as suggested in diagnostic guidelines [12]. These sources of error can be assessed by inspecting the record and removing the affected sections of serial PEFs from the final analysis of records.

Other potential sources of error that need to be taken into consideration include meter precision and meter/person accuracy. Recording reliability should be checked before interpretation; at least three measurements should have been carried out at each measurement session with the best two differing by less than 20 L/min. Fabrication should be suspected if all three measurements are exactly the same or the same results are recorded many times on each day [30]. Most often, such fabrication is an attempt to compensate for forgotten recordings rather than purposefully to invent work-related changes. Errors related to fabrication can be eliminated using data-logging instruments (unless someone else has blown into the meter). However, there are still other issues as to whether the measurements are precise and accurate. The ways to improve these are to ensure that the meter conforms to certain standards, to understand how the meter logs the results, and to train the patients so that they understand how to do their best readings and what to record on the chart. It should also be emphasized that the same meter should be used at work and away from work, as there are differences between individual meters. Differences between types of logging meters include the fact that some models save only the highest of three measurements taken regardless of quality, whereas other models save only measurements that are deemed adequate based on preprogrammed quality criteria. Some models allow unlimited measurements within a session, while others only allow a set number of measurements. Some meters log every measurement session, whereas other meters will overwrite measurements taken within the hour. Getting the worker to write down as much information about their occupational and other exposures, exercise, and use of short-acting bronchodilators is the best way of trying to identify other factors that may affect the PEF recordings. Dedicated forms with space to write information on occupational and other exposures alongside working times, asthma treatment, and recordings of 2-hourly measurements of PEF facilitate interpretation of serial PEFs [44]. Suitable forms are downloadable, for example from http://www.occupationalasthma.com/resources/dataentryform.pdf.

Other issues related to serial PEFs in diagnosing occupational asthma

Serial measurements of PEF often involve the repeated exposure to an agent to which the worker is sensitized. It is not suitable to carry out such recordings in those who have a history of severe work-related reactions and, in these cases, carefully controlled specific challenge tests in hospital are preferable. Records should be made as early in the diagnostic process as possible, preferably when the suspicion of occupational asthma has been raised, and before exposures have been modified or the worker has been relocated. Because of this, serial PEF measurements should be started when first seen in primary care or occupational health departments. Serial PEFs can also be used to check the adequacy of relocation away from exposure to the causative agent after the diagnosis of occupational asthma has been made. The records are more sensitive if performed before asthma treatment is started [16]. Treatment may however be needed first if the asthma is severe or very variable.

PEF records cannot differentiate between reactions due to allergic or irritant or other mechanisms by which occupational exposures may have their effects. PEF records would be expected to show work-related changes in regular work-aggravated asthma, for example due to exercise, sulfur dioxide, or cold air. PEF records do not usually identify the specific cause of occupational asthma [23], but are better at identifying reactions caused by a mixture of occupational exposures compared with SIC. They do not replace the need for SIC testing, but do reduce the numbers for which these are required, as SIC testing needs much more resources.

The question concerning the significance of SIC testing showing a positive result when there are no PEF changes seen from usual work exposures, or showing a negative result when there are obvious work-related changes in PEF, warrants some further discussion. It should be remembered that the overall sensitivity of serial PEFs of 75% (including records of adequate and inadequate data quantity) means that the PEF recordings will not show diagnostic changes in 25% of workers who actually have occupational asthma. Non-diagnostic records may occur early in the disease when work reactions are small or infrequent. Repeating the record after a few months (together with spirometry and NSBR) is the most appropriate next step. Records with high PEF variability are also difficult to interpret, but including periods at work with an intervening 1- to 2-week period away from work may then aid interpretation [67]. Alternatively, the worker may be temporarily relocated away from exposure and comparisons then made between the two work periods with different occupational exposures. When serial PEF shows work-related changes, but SIC is negative, it should be remembered that the sensitivity of SIC is in reality also less than 100%, for example if the period between the last occupational exposure situation and the challenge testing is long, or when the SIC has been performed with the wrong agent or with a smaller amount of exposure than that encountered in real life. Another explanation may be that the work-related changes in PEF result from non-specific exposures at work rather than specific causal agents. However, if serial PEFs repeatedly show a pattern consistent with occupational asthma in the absence of any obvious non-specific exposures, the value of a single negative SIC should be questioned.

We think it is valid to pool the results from all papers assessed as being of adequate quality using the SIGN quality criteria. This is an accepted method and has been used in other systematic reviews [15]. Most studies used SIC testing as their reference standard, and those that included fourfold changes in NSBR and/or a symptom history compatible with occupational asthma together with documentation of asthma and a positive IgE to a relevant allergen showed sensitivity and specificity similar to those validated by SIC testing within the same study [26, 38]. We believe that the main differences in sensitivity and specificity between different studies relate to the quality of the PEF records. The improved effect related to good-quality PEF records was shown in our results.

Summary estimates based on systematic reviews are always liable to publication bias, i.e., bias resulting from a tendency to publish positive studies more readily than negative results. However, there are centers around the world which believe that the results of SIC are more reliable for the diagnosis of occupational asthma than serial peak flow measurements that might bias the results in the other direction to those observed in this review [61]. Also, there is a difference between PEF records that are truly negative and those that are equivocal. However, the consistency of results between studies from different parts of the world, studies using different methods of PEF analysis, and countries with different health and compensation schemes add confidence to the validity of our conclusions.

CONCLUSIONS

Serial PEF measurements are a useful objective confirmatory test for a diagnosis of occupational asthma, when potential sources of error are understood. They can be achieved by approximately two-thirds of those asked to do them and have an overall sensitivity of 82% and specificity of 88% when minimum data quantity requirements for the method of analysis used are fulfilled. They do not usually identify the precise cause of the occupational asthma in an individual, and complementary information on specific exposures is needed. They have been better validated against independent standards than any other method of occupational asthma diagnosis, including SIC testing.

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