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REVIEW

Contribution of host factors and workplace exposure to the outcome of occupational asthma

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ABSTRACT: The outcome of occupational asthma after diagnosis is often poor. The identification of factors associated with a worse outcome may help in the management of the disease, determining its prognosis and assessing the permanent impairment attributable to occupational exposure.

The aim of this systematic review was to provide the available evidence from the medical literature to answer the question: ''What is the contribution of host factors and workplace exposure to the risk of a bad outcome of occupational asthma?''

A systematic literature search was conducted in March 2010. We retrieved 177 abstracts. Of these, 67 were assessed as potentially relevant. After full text evaluation, 35 articles that were actually relevant for the question were included in the analysis.

The information obtained was sufficient to establish that older age, high-molecular-weight agents, impaired lung function and longer duration of exposure to the offending agent at the time of diagnosis had a negative role on the outcome of occupational asthma. Atopy and smoking at diagnosis did not seem to influence the outcome of occupational asthma. A limited number of studies considered sex and the pattern of asthmatic reaction on specific inhalation challenge and their findings were contradictory.

KEYWORDS: Atopy, cigarette smoke, duration, lung function, occupational exposure, prognosis

The outcome of occupational asthma after diagnosis is often poor. The identification of factors associated with a worse outcome may help in planning appropriate management of the disease, determining its prognosis and in assessing the permanent impairment attributable to occupational exposure. The issue of risk factors associated with the outcome of occupational asthma was considered by recent guidelines but not in a systematic manner. The American College of Chest Physicians (ACCP) [1], the British Occupational Health Research Foundation (BOHRF) [2] and the Agency for Healthcare Research and Quality (AHRQ) [3] agreed that longer symptomatic exposure is related to a worse outcome of occupational asthma. BOHRF concluded that better lung function at diagnosis is related to a better outcome of occupational asthma [2].

The aim of this systematic review was to provide the available evidence from medical literature to answer the key question: ''What is the contribution of host factors and workplace exposure to the risk of a bad outcome of occupational asthma?'' We considered eight risk factors, in order to determine their respective influence on the prognosis of occupational asthmas: 1) lung function at the time of diagnosis; 2) duration of exposure to the offending agent; 3) atopic status; 4) smoking status at diagnosis; 5) sex; 6) age; 7) type of causing agent; and 8) the pattern of asthmatic reaction on specific inhalation challenge (SIC).

METHODS

Appropriate search terms were adapted to search Medline *via* PubMed (table 1).

The final literature search with PubMed was conducted in March 2010. Additional papers were retrieved by cross-referencing. The abstract of each title was independently screened by two occupational medicine specialists for consistency

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TABLE 1 Terms used for the PubMed search

First term(s)	AND	AND
General risk factors		
"Risk factors"[Mesh]	("Prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Outcome"[all] OR "Prognosis"[all] OR "Prognostic value"[all] OR "Follow-up studies"[Mesh])	"Asthma"[Mesh] AND ("Occupational diseases"[Mesh] OR "Occupational health"[Mesh] OR "Occupational exposure"[Mesh] OR "Occupational groups"[Mesh] OR "Workplace"[Mesh] OR "Work related"[all] OR "Work aggravated"[All]) AND "Humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh]
Smoking		
("Smoking"[Mesh] OR "Tobacco Smoke Pollution"[Mesh] OR "Tobacco Use Cessation"[Mesh])	As above	"Asthma"[Mesh] AND ("Occupational diseases"[Mesh] OR "Occupational health"[Mesh] OR "Occupational exposure"[Mesh] OR "Occupational groups"[Mesh] OR "Workplace"[Mesh] OR "Work related"[all] OR "Work aggravated"[All]) AND "Humans"[MeSH Terms] NOT ("Child"[Mesh] OR "Parity"[Mesh] OR "Risk factors"[Mesh])
Atopy		
("Atopy"[all] OR "Atopic status"[all])	As above	As above
Impaired lung function		
("Respiratory function tests"[Mesh] AND ("Impairment"[all] OR "Decrease"[all] OR "Decline"[all] or "Lower"[all]))	As above	As above
Duration and cessation		
("Duration of exposure"[all] OR "Exposure duration"[all] OR "Exposure cessation"[all] or "Long-term cessation"[all])	("Prognosis"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Outcome"[all] OR "Prognosis"[all] OR "Prognostic value"[all] OR "Follow-up studies"[Mesh] OR "Recovery of Function"[Mesh])	As above

with the aim of the search (P. Mason and V. Schlünssen). The full text of potentially relevant articles was examined according to pre-determined criteria using standardised forms. Two reviewers independently assessed each article. The quality of the studies relevant to the key question was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) grading system (from 1++, highest quality, to 4, lowest quality). Disagreement among reviewers was resolved by discussion and/or consulting a third party, if needed. The heterogeneity of the studies prevented the use of sophisticated analytical methods. Nonetheless, in the synopsis of the data we were able to sufficiently homogenise the information provided and use it for the formulation of statements graded according to the Royal College of General Practitioners (RCGP) three-star system. The evidence and clinical relevance of the recommendations were classified according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system adapted by the American Thoracic Society [4]. The methods are extensively described in the paper by BAUR *et al*. [5]. Search results, as well as the list of considered articles, are included in the evidence tables and are presented in table O3 in the supplementary material in the paper by BAUR *et al*. [5].

RESULTS

148 titles were identified in the systematic literature search. An additional 29 titles that were not included in the search were obtained by cross-referencing the review article by RACHIOTIS *et al*. [6]. In total, 177 abstracts were considered. Of these, 67 were assessed as potentially relevant for the key question. After full text evaluation, we selected 36 papers that were actually relevant for the key question. The study by AMEILLE *et al*. [7] was subsequently excluded as the findings were based on results from two papers that were already included [8, 9]. The evidence table of the 35 papers is included in the study by BAUR *et al*. [5] (supplementary material, table O3). For each investigated factor, the number of subjects in the positive and negative studies was calculated by adding the number of subjects at follow-up in each study that considered the investigated factor included in the review by RACHIOTIS *et al*. [6] and in the extended literature search.

Lung function impairment at diagnosis

Among the 18 articles reviewed, 15 studies detected a significant relationship between low indices of lung function at baseline (nonspecific bronchial hyperresponsiveness (NSBHR): n=10; forced expiratory volume in 1 s (FEV_1) or forced vital capacity (FVC): n=9; SIC: n=2) and a worse asthma outcome at follow-up (table 2). One study found that increased bronchial hyperresponsiveness (BHR) at baseline favours a good outcome at follow-up [24]. In contrast, five studies did not find associations between low indices of lung function at baseline (NSBHR: n=4; FEV_1 or FVC: n=4) and a worse asthma outcome at follow-up. If the evaluation was restricted to well-conducted studies (grading 2+ and 2++), the

TABLE 2 Lung function impairment at diagnosis and outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
MERGET [10]	No relationship (NSBHR)	2-	Cohort study	Platinum salts	275
TARLO [11]	+ (NSBHR, FEV_1, FVC)	3	Descriptive study of register	Isocyanates	235
COTE [12]	+ (SIC), no relationship (FEV_1, FVC, NSBHR)	2+	Longitudinal	Plicatic acid (Western red cedar)	48
SORGDRAGER [13]	+ (FEV_1)	2-	Longitudinal	Fluorides	122
PISATI [14]	No relationship (FEV_1, VC, NSBHR)	2-	Longitudinal	TDI	25
PERFETTI [15]	+ (NSBHR, FEV_1)	2-	Longitudinal	Various HMW and LMW agents	99
PARK [16]	+ (NSBHR)	2-	Longitudinal	TDI	35
CHANG-YEUNG [17]	+ (NSBHR, FEV_1,FVC)	2-	Longitudinal	Western red cedar	125
MAGHNI [8]	+ (NSBHR)	2+	Longitudinal	Various HMW and LMW agents	133
LOZEWICZ [18]	+ (NSBHR, FEV_1)	2+	Longitudinal	Isocyanates (TDI, MDI)	56
HUDSON [19]	+ (FEV_1)	2-	Longitudinal	Crab; various HMW and LMW agents	63
MALO [20]	+ (NSBHR, FEV_1)	2+	Longitudinal	Various HMW and LMW agents	80
PARK [21]	+ (NSBHR)	2-	Longitudinal	TDI	41
MAPP [22]	+ (SIC), no relationship (FEV_1, NSBHR)	2-	Longitudinal	TDI	35
LABREQUE [23]	+ (NSBHR, FEV_1)	2-	Longitudinal	Isocyanates	79
PADOAN [9]	+ (NSBHR, FEV_1)	2++	Longitudinal	TDI	87
SOYSETH [24]	- (Higher NSBHR at baseline favours good prognosis), no relationship (FEV_1)	2+	Longitudinal	Fluorides	38
MOSCATO [25]	+ (FEV_1)	2+	Longitudinal	Various	29

SIGN: Scottish Intercollegiate Guidelines Network; NSBHR: nonspecific bronchial hyperresponsiveness; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SIC: specific inhalation challenge; VC: vital capacity; TDI: toluene diisocyanate; HMW: high molecular weight; LMW: low molecular weight; MDI: methylene diphenyl diisocyanate. +: relationship between worse lung function at baseline (FEV_1, FVC, VC, NSBHR and SIC) and worse asthma status at follow-up; - : relationship between worse lung function at baseline (FEV_1, FVC, VC, NSBHR and SIC) and better asthma status at follow-up.

number of studies reporting a significant relationship between low indices of lung function at baseline and a worse asthma outcome at follow-up was six *versus* two studies that reported no relationship (table 2).

Duration of occupational exposure

In addition to the study by RACHIOTIS *et al.* [6], which includes 14 papers related to the duration of occupational exposure before diagnosis, we evaluated seven papers that detected a significant relationship between duration of exposure and outcome of occupational asthma [11, 13, 14, 21, 26–28]. In contrast, four articles did not find a relationship between duration of exposure and outcome of occupational asthma [24, 29–31]. If the evaluation is restricted to well-conducted studies (2+, 2++ or 1-), two studies found a positive association compared to three which did not find any association (table 3). However, the number of subjects in the positive studies (excluding those with grade 3 evidence) largely exceed (>3,000) the number of subjects in the negative studies (~500).

Atopy

None of the articles reported a relationship between atopy and outcome of occupational asthma (table 4).

Smoking at diagnosis

11 articles did not find a significant relationship between smoking at diagnosis and outcome of occupational asthma [12, 16, 18, 20, 22–24, 28, 29, 31, 39]. This group includes most of the studies with better (2+) grading. In contrast, four articles reported a relationship between smoking and worse outcome of occupational asthma (table 5) [10, 13, 32, 38].

Sex

Two papers found no significant relationship between sex and outcome of occupational asthma [21, 31]. However, two other studies found a significant relationship between sex and outcome of occupational asthma [20, 39]. MALO *et al.* [20] found female sex to favour good prognosis, while GASSERT *et al.* [39] found male sex to favour good prognosis (table 6).

Age at diagnosis

The papers selected by the systematic review were already included in the study by RACHIOTIS *et al.* [6], which identified an effect of age on asthma outcome (table 7). The number of subjects (~1,700) evaluated in the papers reporting an association between older age at diagnosis and worse outcome of occupational asthma (excluding those with grade 3

TABLE 3 Duration of occupational exposure and outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
Descatha [28]	+ (2)	2+	Case series	Various HMW and LMW agents	227
Chang-Yeung [32]#	+ (1)(2)	2-	Longitudinal	Western red cedar	38
Tarlo [11]	+ (1)(2)	3	Descriptive study of disease register	Isocyanates	235
Orriols [27]	+ (2)	3	Longitudinal	Isocyanates	21
Valentino [29]	No relationship (1)(2)	2+	Longitudinal	TDI	50
Sorgdrager [11]	+ (2)	2-	Longitudinal	Fluorides	122
Saric [30]	No relationship (2)	3	Longitudinal	Fluoride/SO_2	30
Rachiotis [6]	+ (1)(2)	1-	Systematic review	Various	2376
Pisati [14]	+ (1)	2-	Longitudinal	TDI	25
Pisati [33]#	No relationship (1)(2)	2+	Longitudinal	TDI	60
Perfetti [34]	+ (2)	2-	Longitudinal	Various HMW and LMW agents	99
Park [16]	+ (1)	2-	Longitudinal	TDI	35
Lemière [35]#	No relationship (2)	3	Longitudinal	Various HMW and LMW agents	15
Chang-Yeung [17]#	+ (2)	2-	Longitudinal	Western red cedar	125
Lozewicz [18]#	No relationship (2)	2+	Longitudinal	Isocyanates (TDI, MDI)	56
Anees [31]	No relationship (related to cessation) (1)(2)	2+	Longitudinal	Various HMW and LMW agents	156
Allard [36]#	+ (1)(2)	2-	Longitudinal	Various HMW and LMW agents	28
Marabini [37]#	+ (2)	2-	Longitudinal	Plicatic acid (Western red cedar)	128
Hudson [19]#	+ (1)(2)	2-	Longitudinal	Crab; various HMW and LMW agents	63
Malo [20]	No relationship (2)	2+	Longitudinal	Various HMW and LMW agents	80
Merget [26]	+ (1)	3	Longitudinal	Platinium salts	83
Labreque [21]	+ (2)	2-	Longitudinal	Isocyanates	79
Padoan [9]#	+ (2)	2++	Longitudinal	TDI	87
Soyseth [24]	No relationship (2)	2+	Longitudinal	Fluorides	38
Moscato [25]#	+ (1)(2)	2+	Longitudinal	Various	29
Merget [38]#	No relationship (1)	2-	Longitudinal	Platinum salts	24

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; TDI: toluene diisocyanate; MDI: methylene diphenyl diisocyanate. +: positive relationship between duration of exposure and asthma outcome (shorter exposure results in better outcome); (1): symptomatic exposure before diagnosis; (2): total duration of occupational exposure. #: these articles are included in the review by Rachiotis *et al.* [6].

evidence) largely exceeds, the number of subjects (~500) included in the studies that did not find such a relationship.

Type of causative agent

Three studies [19, 34, 39] and the study by Rachiotis *et al*. [6] found a significant relationship between type of agent and outcome of occupational asthma. Gassert *et al.* [39] found occupational asthma from the industrial sector to have a worse outcome compared to other sectors. Rachiotis *et al.* [6] and Perfetti *et al.* [34] found that patients who are exposed to high-molecular-weight agents are more likely to have persistent BHR. Four studies found no relationship between the type of agent and outcome of occupational asthma [11, 20, 28, 35]. The number of studies is limited, but the body of data supporting a positive relationship in the studies graded 2+ or 1- is substantial compared to data revealing no relationship (~2,000 *versus* ~500 subjects) (table 8).

Pattern of asthmatic reaction on specific inhalation challenge: late versus *early*

Three papers did not find any significant relationship between type of response and outcome of occupational asthma [11, 29, 35]; the grading of these articles is generally low. However, two studies have found late response to worsen the outcome of occupational asthma [22, 40], and Cote *et al.* [12] detected a relationship with the severity of either early or late asthmatic reactions (table 9).

TABLE 4 Effect of atopy on outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
Merget [10]	No relationship	2-	Cohort study	Platinium salts	275
Descatha [28]	No relationship	2+	Case series	Various HMW and LMW agents	227
Cote [12]	No relationship	2+	Longitudinal	Plicatic acid (Western red cedar)	48
Valentino [29]	No relationship	2+	Longitudinal	TDI	50
Park [16]	No relationship	2-	Longitudinal	TDI	35
Lozewicz [18]	No relationship	2+	Longitudinal	Isocyanates (TDI, MDI)	56
Anees [31]	No relationship	2+	Longitudinal	Various HMW and LMW agents	156
Park [21]	No relationship	2-	Longitudinal	TDI	41
Mapp [22]	No relationship	2-	Longitudinal	TDI	35
Merget [38]	No relationship	2-	Longitudinal	Platinium salts	24

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; TDI: toluene diisocyanate; MDI: methylene diphenyl diisocyanate.

DISCUSSION

The information retrieved from the systematic literature search was sufficient to establish the role of lung function at the time of diagnosis, duration of exposure to the offending agent, atopic status, smoking status at diagnosis, age and type of causative agent on the outcome of occupational asthma. In contrast, a limited number of studies considered sex and the pattern of asthmatic reaction on SIC, and their findings were contradictory.

The following statements summarise the results of our systematic analysis (refer to table O3 in the Task Force report [5]). The evidence was graded according to the RCGP three-star system.

1) There is a substantial body of data that indicates that lower lung volumes, higher NSBHR or stronger asthmatic response to specific inhalation challenge at diagnosis are risk factors for a bad occupational asthma outcome (moderate evidence: **).

The statement is based on 18 articles; seven had SIGN grade 2+ or 2++ (table 2) [8, 9, 12, 18, 20, 24, 25]. This statement is in agreement with the conclusions of BOHRF [2]. The issue was not considered by ACCP [1] or AHRQ [3].

2) There is a substantial body of data that suggests that a longer symptomatic exposure relates to a worse outcome of occupational asthma (moderate evidence: **).

The statement is based on 26 articles, 10 with SIGN grade 2+, 2++ or 1- (table 3) [6, 9, 18, 20, 21, 25, 28, 29, 31, 33]. This statement is in agreement with the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

TABLE 5 Effect of smoking at diagnosis on outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/occupation	Subjects n
Merget [10]	+	2-	Cohort study	Platinum salts	275
Descatha [28]	No relationship	2+	Case series	Various HMW and LMW agents	227
Chang-Yeung [32]	+	2-	Longitudinal	Western red cedar	38
Cote [12]	No relationship	2+	Longitudinal	Plicatic acid (Western red cedar)	48
Valentino [29]	No relationship	2+	Longitudinal	TDI	50
Sorgdrager [13]	+	2-	Longitudinal	Fluorides	122
Park [16]	No relationship	2-	Longitudinal	TDI	35
Lozewicz [18]	No relationship	2+	Longitudinal	Isocyanates (TDI, MDI)	56
Anees [31]	No relationship	2+	Longitudinal	Various HMW and LMW agents	156
Malo [20]	No relationship	2+	Longitudinal	Various HMW and LMW agents	80
Mapp [22]	No relationship	2-	Longitudinal	TDI	35
Gassert [39]	No relationship	2-	Longitudinal	Various	55
Labreque [23]	No relationship	2-	Longitudinal	Isocyanates	79
Soyseth [24]	No relationship	2+	Longitudinal	Fluorides	38
Merget [38]	+	2-	Longitudinal	Platinum salts	24

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; TDI: toluene diisocyanate; MDI: methylene diphenyl diisocyanate. +: relationship between smoking at diagnosis and worse asthma outcome.

TABLE 6 Effect of sex on outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
Anees [31]	No relationship	2+	Longitudinal	Various HMW and LMW agents	156
Malo [20]	+ (Female sex favours good prognosis)	2+	Longitudinal	Various HMW and LMW agents	80
Park [21]	No relationship	2-	Longitudinal	TDI	41
Gassert [39]	+ (Male sex favours good prognosis)	2-	Longitudinal	Various	55

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; TDI: toluene diisocyanate. +: effect of sex on asthma outcome.

3) There is no relationship between atopy and the outcome of occupational asthma (strong evidence: ***).

The statement is based on 10 articles, five with SIGN grade 2+ (table 4) [12, 18, 28, 29, 31]. Atopy was not included in the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

4) Smoking at the time of diagnosis is not related to the outcome of occupational asthma. Although it is well established that smoking cessation is beneficial for the prognosis of asthma *per se*, smoking at the time for diagnosis of occupational asthma does not seems to have a major impact on the prognosis (moderate evidence: **).

The statement is based on 15 articles, seven with SIGN grade 2+ (table 5) [12, 18, 20, 24, 28, 29, 31]. Smoking was not included in the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

5) There is a limited body of data that considered sex in the outcome of occupational asthma and the evidence is contradictory (contradictory evidence: *).

The statement is based on four articles, two with SIGN grade 2+ (table 6) [20, 31]. Sex was not included in the conclusions of ACCP [1], BOHR [2] and AHRQ [3].

6) There is a sufficient body of data that indicates that an older age of the patients is associated with poorer prognosis of occupational asthma (moderate evidence: **).

The statement is based on six articles, three with SIGN grade 2+ or 1- (table 7) [6, 25, 28]. Age was not included in the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

7) There is a substantial body of data that indicates an effect of the type of causing agents on occupational asthma outcome. High-molecular-weight agents seem to cause longer duration of NSBHR compared to low-molecular-weight allergens (moderate evidence: **).

The statement is based on eight articles, three with SIGN grade 2+ or 1- (table 8) [6, 20, 28]. This statement is in agreement with the conclusions of ACCP [1]. The issue was not included in the conclusions of BOHRF [2] or AHRQ [3].

8) From the low number of papers it is not clear whether the pattern of asthmatic response affects the prognosis for occupational asthma (limited evidence: *).

The statement is based on six articles, three with SIGN grade 2+ (table 9) [12, 29, 40]. The issue was not included in the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

The statements on lung function at diagnosis and duration of exposure to the offending agent before diagnosis are based on a significant number of studies. However, the strength of evidence remains moderate since there is some inconsistency in the results. The conclusion of BOHRF [2] that ''the likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have a relatively normal lung function at the time of diagnosis'' is in agreement with our statement. The issue was not considered by ACCP [1] or AHRQ [3].

All recent guidelines have concluded that the probability of a better outcome of occupational asthma is greater in those who have a shorter duration of symptomatic period before diagnosis, and avoid exposure to the offending agent after the diagnosis.

TABLE 7 Effect of age at diagnosis on outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/occupation	Subjects n
Descatha [28]	No relationship	2+	Case series	Various HMW and LMW agents	227
Rachiotis [6]	+	1-	Systematic review	Various	2376
Chang-Yeung [17]#	+	2-	Longitudinal	Western red cedar	125
Park [21]#	No relationship	2-	Longitudinal	TDI	41
Mapp [22]#	No relationship	2-	Longitudinal	TDI	35
Moscato [25]#	+	2+	Longitudinal	Various	29

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; TDI: toluene diisocyanate. +: effect of age on asthma outcome. #: these articles are included in the review by Rachiotis *et al.* [6].

TABLE 8 Effect of type of causing agent on outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
Descatha [28]	No relationship	2+	Case series	Various HMW and LMW agents	227
Tarlo [11]	No relationship	3	Descriptive study of disease register	Isocyanates	235
Rachiotis [6]	+ (HMW persistent BHR)	1-	Systematic review	Various	2376
Perfetti [34]	+ (HMW persistent BHR)	2-	Longitudinal	Various HMW and LMW agents	99
Lemiere [35]#	No relationship	3	Longitudinal	Various HMW and LMW agents	15
Hudson [19]#	+ (Crab occupational asthma better outcome compared to other agents)	2-	Longitudinal	Crab; various HMW and LMW agents	63
Malo [20]	No relationship	2+	Longitudinal	Various HMW and LMW agents	80
Gassert [39]	+ (Occupational asthma industrial sector worse outcome compared to other sectors)	2-	Longitudinal	Various	55

SIGN: Scottish Intercollegiate Guidelines Network; HMW: high molecular weight; LMW: low molecular weight; BHR: bronchial hyperresponsiveness. +: effect of the type of causing agent on asthma outcome. #: these articles are included in the review by Rachiotis *et al.* [6].

Although it is well established that atopy is a risk factor for occupational asthma due to high-molecular-weight agents, whereas it is not so for low-molecular-weight causes of occupational asthma, the analysis of data indicated that once occupational asthma has developed, being atopic does not modify the prognosis of the disease irrespective of the nature of the occupational agent. The evidence that the outcome of occupational asthma is not related to the presence of atopy is strong, since the literature is concordant on this conclusion. However, it should be considered that among the studies evaluated, there was an imbalance in favour of occupational asthma due to low-molecular-weight agents. Atopy was not included in the conclusions of ACCP [1], BOHRF [2] and AHRQ [3].

There was evidence, albeit moderate, that being a smoker at the time of diagnosis of occupational asthma did not influence the prognosis of the disease. This may be surprising considering that asthmatic smokers have an accelerated decline in lung function and poorer response to corticosteroid treatment compared to nonsmokers. Probably the effect of other variables, in particular on persistence or cessation of exposure to the causing agent, on the course of the disease is sufficiently strong to obscure that of cigarette smoke in the small cohorts examined in the studies on occupational asthma. Since pathophysiology and treatment of occupational asthma are comparable to those of non-occupational asthma, it is reasonable to offer the option of smoking cessation to smoking workers when the diagnosis of occupational asthma is made.

There is evidence that older age is related to poorer prognosis of occupational asthma. It remains to be seen whether age is a risk factor *per se* or that the effect is seen because older workers had been exposed to the workplace environment for longer. Neither smoking habit nor age were considered in previous guidelines by the ACCP [1], BOHRF [2] and AHRQ [3]. The ACCP [1] adopted the findings of Rachiotis *et al.* [6] and stated that the prevalence of persisting NSBHR was significantly higher among those with occupational asthma caused by high-molecular-weight agents compared with those with occupational asthma from low-molecular-weight agents. These conclusions have been confirmed by our extended analysis. The relationship between type of causal agent (high molecular weight *versus* low molecular weight) and outcome of occupational asthma should be taken cautiously, since Rachiotis *et al.* [6] found that patients exposed to high-molecular-weight agents are more likely to have persistent NSBHR, but the recovery rate after cessation of

TABLE 9 Pattern of asthmatic reaction on specific inhalation challenge (late *versus* early) and outcome of occupational asthma

First author [ref.]	Main conclusion	SIGN grade	Study type	Exposure/ occupation	Subjects n
Tarlo [11]	No relationship	3	Descriptive study of disease register	Isocyanates	235
Cote [12]	+ (Severity of early and late)	2+	Longitudinal	Plicatic acid (Western red cedar)	48
Valentino [29]	No relationship	2+	Longitudinal	TDI	50
Lemière [35]	No relationship	3	Longitudinal	Various HMW and LMW agents	15
Marabini [40]	+ (Late)	2+	Longitudinal	TDI	40
Mapp [23]	+ (Late)	2-	Longitudinal	TDI	35

SIGN: Scottish Intercollegiate Guidelines Network; TDI: toluene diisocyanate; HMW: high molecular weight; LMW: low molecular weight. +: effect of the pattern of asthmatic reaction on asthma outcome.

TABLE 10 Recommendations

Recommendation	Strength of recommendation	Level of evidence
Health practitioners should consider that an early recognition and diagnosis of occupational asthma is recommended, since shorter symptomatic periods after diagnosis are associated with a better outcome	Strong	High
Smoking habit and atopy should not be taken into account in assessing prognosis for medical legal purposes	Strong	Moderate
More research is needed in order to assess the effects of sex and type of asthmatic response to specific bronchial challenge test on the outcome of occupational asthma	Strong	Moderate

exposure did not differ in the two groups. The type of causing agent was not considered by BOHRF [2] and AHRQ [3].

Future aspects

More research is needed in order to assess the prognostic value of sex and type of asthmatic response to specific bronchial challenge test at diagnosis. Furthermore, knowledge on the level of exposure is needed in order to assess the effect of duration of exposure in a more qualified way. Finally, most research on risk factors for a bad outcome is performed on a limited number of exposures, *i.e.* isocyanates and Western red cedar. It is crucial to include other exposures in the research field as well.

In conclusion, based on this systematic review some recommendations can be made regarding risk factors for a bad outcome of occupational asthma (table 10).

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