

ORIGINAL ARTICLE

Novel clinical scores for occupational asthma due to exposure to high-molecular-weight agents

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ABSTRACT

Objective Specific inhalation challenge (SIC) as the reference diagnostic test for occupational asthma (OA) is not widely available worldwide. We aimed to develop non-SIC-based models for OA.

Methods Of 427 workers who were exposed to high-molecular-weight agents and referred to OA clinic at Montréal Sacré-Cœur Hospital between 1983 and 2016, we analysed 160 workers who completed non-specific bronchial hyper-responsiveness (NSBHR) tests and still worked 1 month before SIC. OA was defined as positive SIC. Logistic regression models were developed. The accuracy of the models was quantified using calibration and discrimination measures. Their internal validity was evaluated with bootstrapping procedures. The final models were translated into clinical scores and stratified into probability groups.

Results The final model, which included age ≤ 40 years, rhinoconjunctivitis, inhaled corticosteroid use, agent type, NSBHR, and work-specific sensitisation had a reasonable internal validity. The area under the receiver operating characteristics curve (AUC) was 0.91 (95% CI 0.86 to 0.95), statistically significantly higher than the combination of positive NSBHR and work-specific sensitisation (AUC=0.84). The top 70% of the clinical scores (ie, the high probability group) showed a significantly higher sensitivity (96.4%vs86.9%) and negative predictive value (93.6%vs84.1%) than the combination of positive NSBHR and work-specific sensitisation (p value <0.001).

Conclusions We developed novel scores for OA induced by high-molecular-weight agents with excellent discrimination. It could be helpful for secondary-care physicians who have access to pulmonary function test and allergy testing in identifying subjects at a high risk of having OA and in deciding on appropriate referral to a tertiary centre.

Key messages

What is already known about this subject?

- The diagnosis of occupational asthma (OA) remains a challenge in clinical practice.
- Specific inhalation challenge (SIC) as the reference diagnostic test is only available in a few specialised centres around the world. No diagnostic model currently quantifies the diagnostic value of clinical and exposure characteristics, coupled with work-specific sensitisation and non-specific bronchial hyper-responsiveness tests for estimating the individual probability of having OA in the clinical setting.

What are the new findings?

- We developed non-SIC-based models for identifying OA induced by high-molecular-weight agents that had excellent discriminative ability and reasonable internal validity.
- The models are the first to include easily available clinical and exposure characteristics, coupled with work-specific sensitisation and/or non-specific bronchial hyper-responsiveness tests.

How might this impact on policy or clinical practice in the foreseeable future?

- Our models could facilitate the quantification of individuals' probability of OA with a high accuracy and the detection of at-risk workers in a timely manner.
- These are novel tools that could help to diagnose OA in workers exposed to high-molecular-weight agents in centres around the world where there is no access to SIC.

INTRODUCTION

Occupational asthma (OA) is the most common chronic occupational respiratory diseases in industrialised countries and second most common in developing countries.^{1,2} Hundreds of different agents in the workplace have been identified as causing OA,³ including high-molecular-weight (HMW) agents (mostly proteins) and low-molecular-weight (LMW) agents (mostly chemical agents). The most common causal HMW agents include flour and laboratory animal allergens, to which bakers and laboratory animal workers are respectively exposed. The most

common LMW aetiological agents include cleaning products, isocyanates and wood dust, which may be present in occupations such as healthcare, cleaning, car painting and carpentry.⁴ Since OA is associated with work impairment, impaired quality of life and psychological distress, its diagnosis is crucial without undue delay.^{5,6}

A stepwise approach is recommended for diagnosing OA. It starts with taking a full history (symptoms and their correlation to work, description of job and potential direct or indirect exposure to sensitisers); assessing non-specific bronchial



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hyper-responsiveness (NSBHR; with methacholine or histamine challenge test) and immunological sensitisation (with skin prick tests [SPTs] or specific immunoglobulin E [IgE] to workplace agent) when available. The second step includes serial peak expiratory flow recordings, NSBHR test off-work versus at work or specific inhalation challenge (SIC).⁷

Overall, diagnosing OA remains challenging due to delayed referral by general practitioners,⁸ or specialists' failure to take proper diagnostic steps.^{8,9} Worldwide, especially in developing countries, OA remains under-recognised and poorly diagnosed.² SIC as the reference test⁷ is only available in a few specialised centres worldwide. In Canada, SIC is recommended to confirm the diagnosis of OA in Quebec, but not in other provinces.¹⁰

Diagnostic models and clinical scores can improve secondary prevention by helping physicians to detect individuals with work-related disease, choose appropriate diagnostic tests and decide to refer workers for further evaluation.¹¹ Pralong *et al*¹² evaluated the capacity of a self-administered questionnaire (the Occupational Asthma Screening Questionnaire) to identify patients suspected of having OA in a clinical setting in Canada. Jonaid *et al*¹³ used information from a self-administered questionnaire and the medical history to develop prediction models for bakers' asthma in the Netherlands.

Currently, no diagnostic model quantifies the value of clinical and exposure characteristics, coupled with various objective tests for estimating the individual probability of having OA in the clinical setting. We aimed to develop the first non-SIC-based models and clinical scores, using information from the clinical interviews, skin-prick test (SPT), spirometry and NSBHR tests. Development and validation of such models could facilitate the quantification of individuals' probability of OA and the detection of workers with a high probability in a timely manner.¹¹

METHODS

Study design and population

We performed a retrospective study, based on Standards for Reporting Diagnostic Accuracy guidelines,¹⁴ and analysed a database of 427 workers referred to the Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada, between 1983 and 2016 with suspected OA. They presented with lower respiratory symptoms, including dyspnoea, cough, wheezing and/or chest tightness possibly attributable to exposure in their workplaces. The database contains information about symptoms, exposure characteristics and the results of different tests performed during the diagnostic work-up, including spirometry, SPT, methacholine challenge and SIC. The process of data extraction has been explained by Pralong *et al*,¹⁵ who examined the same population of workers and demonstrated that the negative predictive value (NPV) of the methacholine challenge test is >97% when done while a patient was still working. Thus, we finally included 160 workers who had been exposed to HMW agents and were still working 1 month prior to SIC. Online supplementary figure shows the selection of the study population.

Outcome and potential predictors

OA was defined as having a positive SIC, namely a sustained fall in forced expiratory volume in 1 s (FEV₁) >20% of the baseline value after exposure to the suspected occupational agent.¹⁶

For predictors, we analysed subjects' demographic, clinical and exposure characteristics: age (>40/≤40 years and as a continuous variable), sex (male/female), smoking habits (current smoker, ever smoked and never smoked), the presence of rhinoconjunctivitis (yes/no), duration of lower respiratory symptoms (≤5/>5

years and as a continuous variable), inhaled corticosteroid use (yes/no) and exposure duration (≤10/>10 years and as a continuous variable). Restricted cubic spline was used to determine the cut-off for dichotomisation of the continuous variables.¹⁷ Atopy and specific sensitisation to occupational agents were defined as having a positive SPT reaction to at least one of 11 common aeroallergens and to the specific occupational agent(s), respectively.¹⁸ Reduced pulmonary function at the time of SIC evaluation was defined as percentage predicted FEV₁ ≤80%. NSBHR was defined as the provocative concentration of methacholine causing a 20% decrease in FEV₁ (PC20) ≤16 mg/mL. Due to the order of the tests, the physician who interpreted the SIC results were aware of the specific SPT and baseline NSBHR challenge results. However, the technicians who administered these two tests were not aware of the SIC results. No adverse event was reported from performing the above tests.

STATISTICAL ANALYSIS

Model development and evaluation

Logistic regression analysis was carried out to develop models with clinical and exposure characteristics (ie, model 1, clinical interview model).¹⁹ Different objective tests were added to model 1 to create new models: specific sensitisation in model 2; NSBHR in model 3; both specific sensitisation and NSBHR in model 4. Further detail on statistical analysis is described in the online supplementary file.

The accuracy of the models was quantified using calibration and discrimination measures.¹⁹ Calibration was evaluated with a Brier score, which measures the difference between predicted and observed outcomes. A Brier score of 0 represents a perfect model. Discriminative ability of models was determined with the area under the receiver operating characteristics curve (AUC). An AUC of 1.0 reflects perfect discrimination. The differences between the AUC of the models were calculated using the Hanley and McNeil method.²⁰ The final model was selected based on the greatest increase of the corrected AUC compared with model 1. Models were validated internally using bootstrap method, which gives a correction factor for both the models' AUCs and for the regression coefficients of the predictors.¹⁹ A correction factor of 1.0 reflects perfect internal validity.

Clinical scores production and stratification

To facilitate the clinical application of the final model, it was transformed to easy-to-use scores. To help with referral decision, the sum scores were subsequently divided to stratify subjects into groups with a high and a low probability of having OA. Several cut-offs (top 20% through 70% of the sum scores) were evaluated. The diagnostic properties of each cut-off were calculated and compared with the combination of positive specific sensitisation and NSBHR tests using McNemar's test.²¹ Details on the production of clinical scores and treatment of missing data are described in the online supplementary file.

Analyses were performed using SPSS V.24.0 for Windows, S-Plus 8.0.1 for Windows (Insightful Corp) and R-Studio Version 1.1.442 software.²²

RESULTS

Positive SICs confirming OA were observed in 84 of 160 (52.5%) subjects. Subjects with OA presented more rhinoconjunctivitis and had a longer duration of lower respiratory symptoms compared with subjects without OA (table 1). Compared with workers with a negative SIC, the majority of subjects with a positive SIC had a higher proportion of positive NSBHR (58%

Table 1 Distribution and association between the predictors and occupational asthma*

	OA N (%)	Non-OA N (%)	Total N (%)		
Diagnosed OA	84 (52.5)	76 (47.5)	160 (100.0)	OR	95% CI
Clinical and exposure characteristics					
Sex (male)	63 (75.0)	29 (38.2)	92 (57.5)	4.9	2.5 to 9.6
Age (year)†	37.6 (9.9)	41.5 (11.5)	39.5 (10.8)	0.97	0.93 to 0.99
Age ≤40 years	52 (61.9)	36 (47.4)	72 (45.0)	1.8	1.0 to 3.4
Smoking habits					
Current smoker	21 (25.0)	15 (19.7)	36 (22.5)	1.5	0.7 to 3.4
Ever smoked	30 (35.7)	25 (32.9)	55 (34.4)	1.3	0.6 to 2.7
Never smoked	33 (39.3)	36 (47.4)	69 (43.1)	REF	REF
Presence of rhinoconjunctivitis	23 (27.4)	10 (13.2)	33 (20.6)	2.5	1.1 to 5.7
Duration of lower respiratory symptoms‡	3.0 (0.0–26.0)	2.0 (0.0–35.0)	2.0 (0.0–35.0)	1.0	0.9 to 1.1
Duration of lower respiratory symptoms >5 years	58 (51.3)	55 (48.7)	113 (71.5)	0.8	0.4 to 1.6
Inhaled corticosteroid usage	53 (63.1)	39 (51.3)	92 (57.5)	1.6	0.7 to 3.1
Duration of exposure¶	11.0 (0.7–48.0)	8.0 (0.0–53.0)	10.0 (0.0–53.0)	1.0	0.9 to 1.0
Duration of exposure >10 years	37 (48.1)	40 (51.9)	77 (48.7)	0.7	0.4 to 1.2
Agent type: flour and associated agents	62 (73.8)	23 (30.3)	85 (53.1)	6.5	3.3 to 13.0
Objective tests					
Atopy to common allergen(s)§	76 (91.6)	58 (79.5)	134 (85.9)	2.8	1.1 to 7.3
Sensitisation to work-specific agents**	75 (93.8)	26 (41.3)	101 (70.6)	21.3	7.6 to 60.1
NSBHR	78 (92.9)	44 (57.9)	122 (76.3)	9.5	3.7 to 24.4
Low predicted FEV ₁ ≤80%	18 (21.4)	13 (17.1)	31 (19.4)	1.3	0.6 to 2.9

*Evaluated in subjects exposed to high-molecular-weight agents who were still working 1 month prior to SIC.

†Mean (SE), median (maximum–minimum)=38.6 (21.0–63.0).

‡Missing=2, median (minimum–maximum).

§ Missing=4.

¶Missing=2, median (minimum–maximum).

**Missing=17.

FEV₁, forced expiratory volume in 1 s; NSBHR, non-specific bronchial hyper-responsiveness; OA, occupational asthma.

vs 93%) or specific sensitisation to workplace agents (41% vs 94%).

Half (53.1%) of the subjects were exposed to flour and associated agents (flour, cereal and so on), 14.4% to animal allergens, 8.1% to latex and 24.4% to a mixture of proteins and/or other HMW agents. Sixty-two of 85 (72.9%) of subjects exposed to flour and associated agents and 8 of 13 (61%) subjects exposed to latex had positive SIC. The proportion of positive SIC in other agent type categories ranged from 11% to 50%. Therefore, we defined two categories of exposure as exposed to flour and associated agents or exposed to other HMW agents.

The diagnostic properties of each predictor and their AUCs, along with 95% CI, is provided in the online supplementary table. Among the objective tests, the highest sensitivity and NPV

belonged to sensitisation to work-specific agents (94% and 90%, respectively).

Model development and evaluation

Four models were developed (table 2). Age ≤40 years, rhinoconjunctivitis, inhaled corticosteroid use and agent type were selected as model 1. Adding both NSBHR and specific sensitisation to model 1 (ie, model 4) resulted in the highest increase of AUC compared with adding only one of the tests (ie, model 2 and model 3). Model 4 also had the best overall performance (ie, lowest Brier score). From bootstrap validation, this model also had a correction factor of 0.86, indicating a reasonable internal validity.

Clinical scores production and stratification

Table 3A shows the sum of scores and the corresponding predicted probability of the presence of OA in every worker, calculated according to his/her individual clinical characteristics, as well as the results of objective tests. Table 3B shows a few real examples from our dataset.

Table 4 displays the diagnostic parameters of different cut-offs of the sum scores for referral purposes. For all cut-offs, the mean predictive probability in the high probability group was close to the observed OA rate indicating a good calibration (ie, agreement between the predicted probabilities and observed proportion of OA). Should sum scores of ≥149 be chosen as the referral cut-off, the first four sample cases in table 3B would be referred to a tertiary centre with facilities for performing SIC test to confirm the diagnosis of OA, while the fifth case would preferably be re-evaluated before being referred for further investigation in a tertiary centre.

Sensitivity analysis

In our study, occupational asthma was more prevalent among male workers than female workers (OR=4.9). The majority of subjects exposed to flour were men (70/85; 82.4%) and 76% (53/70) of them had positive SIC. In an additional analysis, we found a weak correlation (coefficient 0.4) between sex and agent type. Furthermore, adding sex to model 1 did not enhance the discriminative ability of the final model (corrected AUC=0.89). Adding their interaction to the model also did not improve the model's performance (p=0.691).

An additional model was developed to assess the discriminative ability of combining the positive methacholine challenge test and work-specific sensitisation without clinical and exposure characteristics (table 2: model 5). The AUC was 0.84 (95% CI 0.77 to 0.90): it was lower than the final model 4 (delta AUC=0.06, 95% CI 0.01 to 0.11). Figure 1 shows the comparison of the ROC curves of models 1, 4 and 5. As shown in table 4, sum scores cut-off ≥149 had a significantly higher sensitivity (96.4% vs 86.9%) and NPV (93.6% vs 84.1%) than the combination of the two tests (p value <0.001). Sum scores cut-off ≥208 had a significantly higher specificity (88.2% vs 76.3%) and positive predictive value (PPV; 88.2% vs 80.2%) than the two tests in pair (p value <0.001).

We also developed two models to evaluate the added value of FEV₁ ≤80% and atopy to common allergens. However, since the AUCs of these models were not significantly different with model 1, the results were not presented.

DISCUSSION

We developed the first non-SIC-based models for occupational asthma in a population of workers exposed to HMW agents who

Table 2 Multivariable models in workers exposed to high-molecular-weight agents*

	Clinical interview	Model 1+specific sensitisation	Model 1+NSBHR testing	Model 1+specific sensitisation+NSBHR	Specific sensitisation+NSBHR
Corrected ^B	Model 1	Model 2	Model 3	Model 4	Model 5
Intercept	−1.66	−3.64	−3.09	−5.03	−3.84
Age ≤40 years	0.57	0.36	0.53	0.22	–
Rhinoconjunctivitis symptoms	0.90	1.00	0.78	0.88	–
Inhaled corticosteroid usage	0.65	0.79	0.41	0.54	–
Agent type: flour and associated agents	1.70	1.61	1.72	1.63	
Sensitisation for work-specific agents	–	2.76	–	2.67	2.99
NSBHR	–	–	2.02	2.14	2.22
AUC (95% CI)	0.77 (0.70 to 0.85)	0.86 (0.81 to 0.93)	0.83 (0.77 to 0.90)	0.91 (0.86 to 0.95)	0.84 (0.77 to 0.90)
Brier score	0.189	0.139	0.164	0.121	0.143
Corrected AUC (95% CI)	0.75 (0.68 to 0.83)	0.85 (0.80 to 0.91)	0.81 (0.75 to 0.87)	0.89 (0.85 to 0.94)	0.83 (0.77 to 0.89)

*Delta AUC of model 1 and model 2=0.10; 95% CI 0.05 to 0.16; delta AUC of model 1 and model 3=0.06; 95% CI −0.001 to 0.12; delta AUC of model 1 and model 4=0.14, 95% CI 0.08 to 0.20; delta AUC of model 2 and model 3=0.04; 95% CI −0.02 to 0.10; delta AUC of model 2 and model 4=0.04, 95% CI −0.004 to 0.08; delta AUC of model 3 and model 4=0.08, 95% CI 0.03 to 0.13; delta AUC of model 4 and model 5=0.06, 95% CI 0.01 to 0.11. The AUC difference between models 1 and 5 was 0.08, but no significant correlation was found between the prediction probabilities of two models among diseased and non-diseased cases.

B, intercept; AUC, area under the curve; NSBHR, non-specific bronchial hyper-responsiveness.

were referred to a tertiary centre for work-related asthma. The final model showed excellent discriminative ability and reasonable internal validity in predicting OA. For practical use, it was transformed into clinical scores. For referral purposes, several cut-offs of the sum scores were proposed and compared with the diagnostic performance of the combined positive work-specific sensitisation and NSBHR.

Model development and validation

The protocol and tests used for diagnosing OA depend on available resources in the country and region. Our model was

developed in an existing database that was collected retrospectively and included objective tests commonly and routinely done in Quebec province to establish an OA diagnosis. Induced sputum was not done before 2000 and the number of subjects with this test was too small for developing the model. SPT-based atopy and lung function did not show significant added value to the clinical interview model. Our final model shows that adding both NSBHR and specific sensitisation tests to the clinical interview model resulted in the highest discriminative ability for diagnosing OA. This emphasises the necessity of performing

Table 3A Clinical scores of the final model in workers exposed to high-molecular-weight agents

Predictors	Value	Clinical scores
Age	>40 years	0
	≤40 years	8
Rhinoconjunctivitis symptoms	Present	33
	Absent	0
Inhaled corticosteroid usage	Yes	20
	No	0
Agent type	Flour and associated agents	61
	Other HMW agents	0
Sensitisation to work-specific allergens	Positive	100
	Negative	0
NSBHR (PC20 ≤16 mg/mL)	Positive	80
	Negative	0
Sum scores	0	80 100 120 141 161 180 200 221 241 261 282 302
Predicted probability of OA	0.01	0.05 0.09 0.14 0.22 0.33 0.45 0.58 0.71 0.81 0.88 0.92 0.95

From the model, the individual probability of having occupational asthma can be estimated using the following formula:

$P(\text{occupational asthma}) = 1 / (1 + \exp(-((0.22 \times \text{age}) + (0.88 \times \text{rhinoconjunctivitis symptoms}) + (0.54 \times \text{inhaled corticosteroid usage}) + (1.63 \times \text{agent type}) + (2.67 \times \text{sensitisation for work specific agent}) + (2.14 \times \text{NSBHR}) - 5.03)))$. Each predictor is valued as 1 when present and 0 when absent.

FEV₁, forced expiratory volume in 1 s; HMW, high molecular weight; NSBHR, non-specific bronchial hyper-responsiveness; PC20, the concentration of methacholine needed to produce a 20% fall in FEV₁ from baseline; OA, occupational asthma.

Table 3B Examples of calculations of sum of scores and individuals' probability of occupational asthma according to individual characteristics

Predictors	Case 1		Case 2		Case 3		Case 4		Case 5	
	Value	Clinical scores	Value	Clinical scores	Value	Clinical scores	Value	Clinical scores	Value	Clinical scores
Age (years)	25	8	33	8	37	8	41	0	43	0
Rhinoconjunctivitis symptoms	+	33	+	33	+	33	–	0	+	33
Inhaled corticosteroid use	+	20	+	20	–	0	–	0	+	20
Agent type	Flour	61	Flour	61	Flour	61	Multiple agents	0	Animal allergens	0
Sensitisation to work-specific allergens	+	100	+	100	–	0	+	100	–	0
NSBHR (PC20 ≤16 mg/mL)	+	80	–	0	+	80	+	80	+	80
Sum of scores	302		222		182		180		133	
Probability of OA (%)	95		71		46		45		19	

+/-, positive/negative; FEV₁, forced expiratory volume in 1 s; NSBHR, non-specific bronchial hyper-responsiveness; OA, occupational asthma; PC20, the concentration of methacholine needed to produce a 20% fall in FEV₁ from baseline.

both tests in workers exposed to HMW agents. This is in agreement with a systematic review by Beach and colleagues,²³ which concluded that the diagnosis of OA in the absence of SIC should preferably be determined by a combination of NSBHR and specific sensitisation tests. Vandenplas and colleagues⁷ proposed NSBHR and specific SPT tests as the first step of the stepwise approach for diagnosing OA, and the American College of Occupational and Environmental Medicine²⁴ also strongly recommended these two tests in diagnosing OA.

Clinical and exposure characteristics selected in the final model were in agreement with the published literature. Some studies reported that smoking at diagnosis did not seem to increase the risk of occupational asthma.^{25–26} In line with these results, smoking was not selected in the final model due to its weak association with SIC. Sensitivity analysis showed that

the over-representation of men in the category of exposure to flour and associated agents (or having jobs such as bakery and pastry making) would not influence the discriminative ability of the model and could possibly be explained by the gender-specific choice of profession (ie, bakers are mostly men).^{27–28} Accordingly, a systematic review by Maestrelli *et al*²⁵ reported that the effect of sex on the development of occupational asthma was inconsistent.

Dichotomisation of continuous variables at their medians may result in loss of information, reduction of power and underestimation of variations in outcome between groups.²⁹ Given the non-linear relationship between the continuous predictors (age, duration of lower respiratory symptoms and duration of exposure) and outcomes (positive SIC), we used the recommended restricted cubic splines method.³⁰ The suggested cut-offs for duration of exposure and duration of symptoms were 10 years and 5 years, respectively. However, none of the continuous and/or dichotomised variables remained in model 1 after stepwise selection. Most studies in subjects exposed to various HMW and LMW agents also did not find an association between duration of exposure and occupational asthma outcome.²⁵ The resulting cut-off point for age was 40 years old, which was close to the mean age in this population and in the literature.^{31–34}

Clinical application

Our proposed diagnostic model for HMW-induced occupational asthma targets the secondary levels of prevention (ie, early diagnosis and prompt treatment). In places without access to SIC evaluations, an estimation of the probability of occupational asthma for individuals based on their unique characteristics by this model can guide physicians at the secondary care level (specialists: ie, respirologists, occupational medicine physicians) in deciding whether: (A) they could remove workers from the exposing agents in the workplace and initiate treatment or (B) they should consider further evaluation of the clinical characteristics and order other test to confirm the diagnosis (eg, serial measurement of peak expiratory flow and/or NSBHR and/or induced sputum at work and off work).⁷ Furthermore, this model could be used to assess workers with workers' compensation claims.

In places where SIC is available, this model can guide physicians at the secondary care level whether they should refer a patient with suspected OA to a tertiary centre where SIC is done. However, it is less beneficial in places such as Quebec where SICs are systematically performed to confirm OA diagnosis.

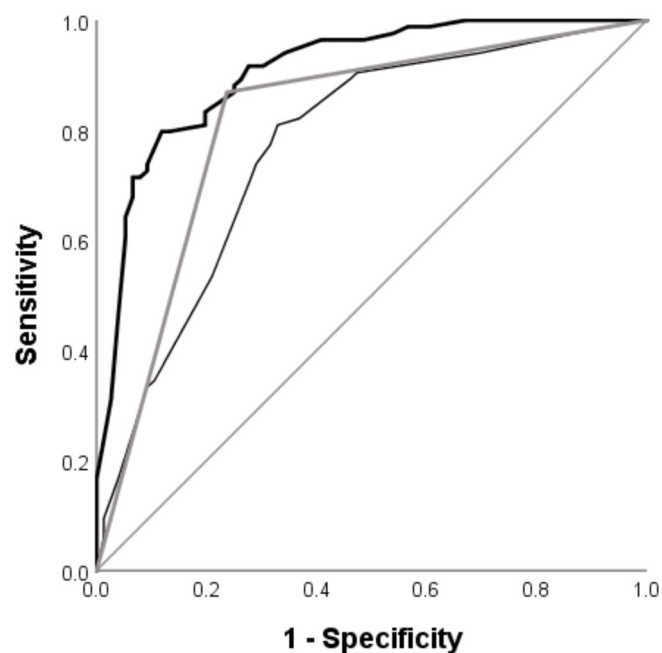


Figure 1 Comparison of the ROC curves of Model 1 (interview), Model 4 (interview + specific sensitization + non-specific bronchial challenge tests), and Model 5 (the combined positive specific sensitization + non-specific bronchial challenge tests). The thin black line represents Model 1; the thick black line shows Model 4; the thick gray line shows Model 5; the diagonal gray line represents the reference. ROC, receiver operating characteristic

Table 4 Diagnostic parameters of clinical scores groups versus standard diagnostic tests

Sum scores	Clinical scores cut-off									Standard diagnostic tests *
	Top 20%	Top 30%	Top 40%	Top 45%	Top 50%	Top 55%	Top 60%	Top 65%	Top 70%	
	≥261	≥249	≥233	≥208	≥200	≥188	≥180	≥169	≥149	
N	42	55	65	76	83	92	98	105	113	91
Observed OA (N)	39	51	60	67	68	73	77	79	81	73
Observed OA (%)	92.9	92.7	92.3	88.2	81.9	79.3	78.6	75.2	71.7	80.2
Mean predictive probability (%)	90.4	88.7	87.3	84.2	82.0	78.9	76.8	74.2	71.2	78.6
Positive predicted value (%)	92.9	92.7	92.3	88.2	81.9	79.3	78.6	75.2	71.7	80.2
Negative predicted value (%)	61.9	68.6	74.7	79.8	79.2	83.8	88.7	91.0	93.6	84.1
Sensitivity (%)	46.4	60.7	71.4	79.8	80.9	86.9	91.7	94.1	96.4	86.9
Specificity (%)	96.0	94.7	93.4	88.2	80.3	75.0	72.4	65.8	57.9	76.3
Positive likelihood ratio (+LR)	11.8	11.5	10.9	6.7	4.1	3.5	3.3	2.7	2.3	3.7
Negative likelihood ratio (–LR)	0.6	0.4	0.3	0.2	0.2	0.2	0.1	0.1	0.1	0.2
McNemar test†	<0.001	<0.001	<0.001	<0.001	0.039	1.000	0.016	<0.001	<0.001	–

*Positive sensitisation to work-specific agents and NSBHR challenge test

†Comparing diagnostic parameters between the clinical scores group versus specific sensitisation and NSBHR.

LR, likelihood ratio; NSBHR, non-specific bronchial hyper-responsiveness; OA, occupational asthma.

The diagnostic procedures of OA are complex and time consuming; it could be several months before the diagnosis is established. Therefore, providing patients with a more accurate risk assessment combined with an appropriate insight about the prognosis of the disease would allow workers to make a more educated decision about whether to undergo further diagnostic testing. Physicians can adapt an appropriate risk communication strategy about the hazards of delay in reaching a definite diagnosis and starting treatment appropriately, especially considering that patients with occupational asthma may develop irreversible deterioration in their respiratory health even after removal from offending agents in the workplace.

For decision-making purpose, the choice of the cut-off point is an important issue. It must be based on the balance between the acceptable proportion of missed cases and the reduction of unnecessary tests.³⁵ When there is no reference cut-off, usually we choose a cut-off point with a corresponding predicted probability higher or equal to the disease prevalence in the population. The OA prevalence in our study is high (52.5%), resulting in a high PPV and rather low NPV. However, sensitivity and specificity are not affected by disease prevalence. Given the impact of occupational asthma, the choice of referral cut-off must lead to a high level of case detection (high sensitivity) and at the same time a reasonably low level of unnecessary referrals. With a low cut-off (eg, sum scores ≥149, sensitivity=96%), we would be able to catch 8 (11%) cases more at the cost of referring 22 (24%) more subjects compared with referring only subjects with combined positive-specific sensitisation and NSBHR. Conversely, if we chose a higher cut-off (eg, sum scores ≥208 with a corresponding predicted probability of 64%), we would refer fewer subjects with high specificity at the cost of missing some OA cases. Either way, our final model offered better diagnostic parameters than the combined positive-specific sensitisation and NSBHR.

Study strengths and limitations

This study has some limitations. The highly selective population of this study may limit the application of models to clinical settings. Our previous study suggests that the NPV of the methacholine challenge test is at highest in subjects who still worked 1 month prior to SIC¹⁵ and, therefore, our current models were developed in this selected group. Sensitivity analyses confirmed

that models that were developed in subjects who were still working 1 month prior to the SIC had better discriminations (AUCs) compared with the models developed in the total population of workers (results not shown). Nevertheless, we could not confirm if these workers were currently or recently exposed to the causative agents in the workplace because they might have been relocated from exposure at work.¹⁵

The interview model alone composed of easily available clinical and exposure characteristics, which makes it more appealing as it could be used by any physicians, especially in less developing countries where even access to work-specific sensitisation and methacholine challenge is scarce.² It has a good discriminative ability (AUC 0.75), but as in the case of questionnaires in general, it is subject to a low specificity⁷ as shown in figure 1. The use of the final model with objective tests would be restricted to physicians with access to both SPT to specific allergen such as flour and methacholine challenge tests.

As SIC is considered as the reference test for OA, we used positive SIC as our OA definition. However, SIC is subject to false-negative results due to imprecise techniques, exposure to unknown or multiple agents and the absence of specific bronchial hyper-responsiveness when workers are off work for a prolonged period.^{16 36 37} An increase in the false-negative rate may decrease the power of the test and the sensitivity of the prediction model. Technical errors causing false-negative results were less likely to have occurred, since the Hôpital du Sacré-Cœur de Montréal (HSCM) is a specialised centre for the SIC with highly qualified trained staff.

Our model may not be applicable to subjects exposed to LMW agents. Although a few have been associated with the production of specific IgE antibodies, most occupational LMW agents induce asthma through mechanisms that are poorly understood.³⁸ Therefore, as a future project, we will develop separate models for the LMW-induced OA.

The strength of this study lies in using a database with a relatively high number of workers with positive SIC (n=84). There were seven predictors in the final model; therefore, the 10:1 cases per predictor ratio was maintained.³⁹ A correction factor of ≥0.86 after the bootstrapping procedure also indicates reasonable internal validity.¹⁹ When we develop a new model, external validation is crucial for confirming the satisfactory performance of the model and its generalisability to other worker populations

before it can be used with complete confidence.⁴⁰ In a separate article, we demonstrated external validation of the models in data from European countries.⁴¹ Our models performed well in population where symptomatic workers who were exposed to HMW agents were referred directly to a tertiary centre for work-related asthma, such as in Poland.

CONCLUSION

The novelty of our model lies in its ability to calculate individuals' probability of OA in workers exposed to HMW agents, given easily available clinical and exposure characteristics from clinical interviews, specific sensitisation to work-related agents and NSBHR tests. The model has an excellent discriminative ability and has been validated. For practical use, it was transformed into clinical scores and several cut-offs with good diagnostic performance were proposed for referral purposes. Given SIC is not widely available around the world, this model has a potential to help diagnose occupational asthma globally.

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Contributors JA-P initiated the study. AC, CL and JA-P took part in the acquisition and management of data. MT performed the analysis under the supervision of ES, PS-C and GM assisted model evaluation. ES and MT drafted and revised the manuscript. AC, CL, JA-P, PSC, GM and RC critically reviewed the manuscript.

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Correction: *Novel clinical scores for occupational asthma due to exposure to high-molecular-weight agents*

Taghiakbari M, Pralong J, Lemière C, *et al.* Novel clinical scores for occupational asthma due to exposure to high-molecular-weight agents. *Occup Environ Med* 2019;**76**:495–501. doi: 10.1136/oemed-2018-105593.

In the published version the term “Rhinoconjunctivitis symptoms”, used in texts and tables should be “Work-related rhinoconjunctivitis symptoms”. The latter is the correct variable that is used in data analysis of this paper.

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