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Title: The validity of the Canadian clinical scores for occupational asthma in European populations

Running title: Validating clinical scores for occupational asthma

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To the Editor:

In industrialized and developing countries, occupational asthma (OA) is one of the most common chronic occupational respiratory diseases(1, 2). Worldwide, especially in developing countries, OA remains under-recognised and poorly diagnosed(2).

Based on available resources, diagnostic tests are used in a stepwise approach starting with a detailed medical and occupational history; assessment of non-specific bronchial hyperresponsiveness (NSBHR); and immunological sensitization with skin-prick tests (SPT) or specific immunoglobulin E to workplace agent when available(3). The second step includes serial assessments of NSBHR and peak expiratory flow at work and off work, or specific inhalation challenge (SIC). As the reference test for diagnosing OA, SIC is only available in a few centers around the world. Therefore, Suarthana and colleagues developed non-SIC-based diagnostic models for OA using Quebec data of 160 symptomatic subjects who completed an SIC procedure (i.e., development set)(4). These subjects were exposed to high-molecular weight (HMW) protein agents such as flour, laboratory animal allergens, and latex. OA was defined as a positive SIC, namely a sustained fall in forced expiratory volume in one second (FEV_1) >20% from baseline value after exposure to the suspected occupational agent(5).

Multivariable analysis with backward stepwise selection, using Akaike inclusion criterion of p-value <0.157(6), was performed to develop the clinical interview model and subsequently objective tests were added. The accuracy of the model was quantified using calibration and discrimination measures(7). Calibration is the agreement between predicted probabilities and observed proportions of each outcome. It was evaluated with a Brier score (i.e., the squared difference between predicted probability and actual binary outcome). A perfect model has a Brier score of 0. Discrimination was determined with the area under the receiver operating characteristics curve (AUC), which represents the probability of how well the model could correctly differentiate individuals with vs. without the outcome. AUC can range from 0.5 (no discrimination) to 1.0 (perfect discrimination: 100% sensitivity and 100% specificity).

The final predictive model included age (>40 *vs.* ≤40 years); agent type (flour vs. other HMW agents); the presence of work-related rhinoconjunctivitis (yes/no); inhaled corticosteroid use (yes/no); positive SPT reaction to the specific occupational agent(s) (yes/no); and the presence of NSBHR

(defined as the provocative concentration of histamine/methacholine causing a 20% decrease in FEV_1 (PC_{20}) ≤16 mg/ml). This final model demonstrated a good accuracy and internal validity. To facilitate its use, it was transformed into clinical scores equipped with the corresponding predicted probability of OA(4). Sum scores ≥150 with a corresponding predicted probability of OA >0.25 was recommended for referral cut-off with a sensitivity of 96%, specificity 59%, positive predicted value 72%, and negative predicted value 94%(4). It is now available as a free app on Calculate by QxMD at: https://qxcalc.app.link/occ-asthma-hmw. In this study, we externally validated this model to evaluate its generalizability so that it could be used in practice with confidence(7).

Databases from five centers in four European countries were used. As done in model development, only subjects who were exposed to HMW agents and were still at their workplace or exposed to the suspected agent(s) at work within one month prior to SIC test were included in the analysis. A total of 473 subjects met these criteria: Belgium n=164, Finland n=112, Poland n=156, and Spain n=41 (i.e., validation set). In all European centers, the study was approved by the research ethics committee and the SIC protocol complied with the European Respiratory Society recommendations(8). The level of NSBHR was assessed using validated methods(9, 10).

Among subjects exposed to HMW agents who were referred for the investigation of possible OA, the prevalence of positive SIC was 52.5% in Canadian data and 57.5% in European data (Table 1). Among OA cases, the proportions of males, atopy, exposure to flour, NSBHR in the European were significantly ($p<0.05$) lower than the Canadian population. In contrast, the European workers had significantly ($p<0.05$) longer work duration and higher percentage of workers with work-related rhinoconjunctivitis than the Canadians. Nevertheless, in both populations, male subjects with younger age and exposure to flour consistently had higher likelihood of having OA.

To externally validate the model(7), we first calculated individual probabilities in European data using the equation from the Canadian model without any adjustments (no update method). In Table 2, the model demonstrated good discrimination in European data although lower than in Canadian (AUC 0.83 vs. 0.89, respectively). The Brier score was also higher in European data (0.171 vs. 0.121), but the model was still informative (i.e. the maximum score for a non-informative model in a population with a 57.5% prevalence of OA was 0.24). Second, we recalibrated the intercept of the model. Finally, the intercept and coefficients were re-estimated (refitting method). Both methods did

not improve the discriminative ability of the model: the AUC remained the same, although the Brier score slightly improved.

We are aware that SIC is subject to false-negative results due to imprecise techniques, exposure to unknown or multiple agents, and the absence of specific BHR when workers are off-work for a prolonged period. However, SIC is currently considered as a reference test for OA(8), and therefore we used positive SIC as our OA definition. Our analysis was restricted to subjects who were still at their workplace or exposed at work within one month prior to SIC test. Moreover, technical errors causing false-negative results were less likely to have occurred, since all centers where data were derived to develop and validate the models were specialized centers for SIC with highly qualified trained staff.

In conclusion, we validated the Canadian non-SIC model specific for HMW-induced OA with a high accuracy in European data. The model could facilitate the quantification of individuals' probability of OA by specialists who have access to specific sensitization and non-specific bronchial challenge tests. It may help clinicians determine which subjects should be referred to tertiary centers for more specialized investigations. Nevertheless, separate models should be developed for subjects exposed to low-molecular-weight agents as well as subjects who were no longer exposed to the offending workplace exposure, which represent a large portion of those referred for diagnostic investigation.

Table 1. Distribution and association between the predictors and occupational asthma in the development (Canadian) and validation (European) datasets

	Development Set (Canadian)		Validation Set (European)	
	OA/Non-OA (%)	**OR (95% CI)**	**OA/Non-OA (%)**	**OR (95% CI)**
Number	**84/76**		**272/201**	**-**
SIC (OA)	52.5/47.5		57.5/42.5	
Sex (male)	75.0/38.2	4.9 (2.5-9.6)	56.6/51.2	1.2 (0.9-1.8)
Ever smoker	35.7/32.9	1.3 (0.6-2.7)	38.0/44.8	0.8 (0.5-1.1)
Duration of lower respiratory symptoms >5 years	51.3/48.7	0.8 (0.4-1.6)	34.1/39.9	0.8 (0.5-1.1)
Duration of exposure >10 years	48.1/51.9	0.7 (0.4-1.2)	67.5/76.4	0.6 (0.4-1.0)
Atopy to common allergen(s)	91.6/79.5	2.8 (1.1-7.3)	61.9/43.5	2.1 (1.4-3.1)
Low predicted FEV1 ≤80%	21.4/17.1	1.3 (0.6-2.9)	19.5/13.9	1.5 (0.9-2.5)
Predictors in the model				
Age ≤40 years	61.9/47.4	1.8 (1.0-3.4)	56.3/43.3	1.7 (1.2-2.4)
Presence of work-related rhinoconjunctivitis	27.4/13.2	2.5 (1.1-5.7)	90.2/71.6	4.1 (2.4-6.9)
Inhaled corticosteroid usage	63.1/51.3	1.6 (0.7-3.1)	64.1/46.2	2.1 (1.4-3.1)
Agent type: flour and associated agents	73.8/30.3	6.5 (3.3-13.0)	48.2/34.8	1.8 (1.2-2.5)
SPT-based sensitization to work-specific agents	93.8/41.3	21.3 (7.6-60.1)	88.9/36.0	14.2 (8.7-23.2)
NSBHR	92.9/57.9	9.5 (3.7-24.4)	79.8/43.0	5.2 (3.5-8.0)

*The results are presented in complete cases; therefore, there is no missing in data.

Abbreviations: CI: confidence interval; NSBHR: non-specific bronchial hyperresponsiveness; SPT: skin-pricked test.

Table 2. Overall performance and discriminative ability of the Canadian models for high-molecular-weight induced occupational asthma in European data

Development set (Canadian)		Validation set (European)					
		No update Method		Re-calibration of intercept		Refitting Method	
AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score	AUC (95% CI)	Brier score
0.89 (0.85-.94)	0.121	0.83 (0.79-0.87)	0.171	0.83 (0.79-0.86)	0.168	0.83 (0.79 to 0.87)	0.154

Abbreviations: AUC: the area under the receiver operating characteristics curve; CI: confidence interval.

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