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Derivation and Calibration of a Cardiovascular Risk Score for Occupational Medicine

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***Abstract* - Cardiovascular disease (CVD) is one of the most prevalent causes of long-term sickness absence from work, and the working environment can contribute to its impact on workers' health. The aim of this study is to develop, validate, and compare scores to measure the risk of diagnosis of unsuitability for work. A cohort of workers employed by the municipalities of Naples was examined, as part of their scheduled occupational health surveillance, at the occupational health outpatient clinic of the Department of Public Health of the University of Naples "Federico II" between January 2006 and December 2016. Cox proportional hazards models were used in the cohort to derive risk equations for the assessment of the 10-year risk of diagnosis of unsuitability for work. Two models were developed: (i) Model A, including all the variables of the Multivariable Cox Model, and (ii) Model B, with only the variables statistically significant at the .05. The Akaikes Information Criterion was used to compare fit and performance of the different models in the derivation cohort. The above analysis proved that the model B was the better predictor of diagnosis of unsuitability for work and should be used as a clinical tool for the assessment of fitness for work in health surveillance.**

1. Introduction

Each year cardiovascular disease (CVD) causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union (EU) [1].

Gender, obesity, smoking, physical inactivity, uncontrolled diabetes, uncontrolled stress and anger are among the most common risk factor of cardiovascular disease.

CVD is also one of the most prevalent causes of long-term sickness absence from work, and the working environment can contribute to its impact on workers' health [2]. The working environment can expose workers to elevated physical and psychological work stress, which is related to elevated risk of CVD and consequent working disability. Therefore, these factors must be taken into consideration when assessing the fitness for work during the targeted scheduled medical examinations as part of the occupational health surveillance. The aim of this study is to validate the use of a new score to predict the risk of a diagnosis of unsuitability for work when assessing the fitness for work during health surveillance in a cohort of workers living in the Campania region of Italy.

2. MATERIAL AND METHODS

A. Study Design

This is a cohort study evaluating the use of a new score to predict the risk of unsuitability for work.

Considering that all clinical assessments were part of clinical practice in a university setting and the complete anonymity of the data, specific ethical approval was not required. All subjects signed the general informed consent form, authorizing the use of observational clinical data for research purposes.

B. Study Population

A cohort of 11079 workers employed by the municipalities of Naples has been examined, as part of their scheduled occupational health surveillance, at the occupational health outpatient clinic of the Department of Public Health of the University "Federico II" of Naples between January 2006 and December 2016.

According to Italian occupational medicine legislation and considering the different level of occupational risk and job strain, workers were classified into four groups, which reflected into a different periodicity of their scheduled occupational health surveillance visit (every one/two/three/five years) [12].

Socio-demographic and clinical history data, as well as laboratory and instrumental data (ECG, ergovision test, spirometry) are routinely collected during health surveillance visits.

The health surveillance diagnosis has three possible outcomes: (i) suitability; (ii) partial unsiutability, with a consequent reduction of the job strain for the worker; (iii) total unsuitability, with a radical change of activities within the job.

The Study covariates were: Demographic (age, sex); Risk Factors (smoking status, systolic bloom pressure, diastolic bloom pressure, diagnosis of hypertension, diagnosis of diabetes, use of oral blood glucose lowering drugs, use of anti-hypertensive medications, presence of Ischemic heart

disease, presence of mental illness (bipolar disorder and moderate/severe depression)); Anthropometric Measures (height, weight).
The occupational risk classification also has been considered. Therefore, four groups according to frequency of health surveillance examination and the workers' type of job have been generated [5].

C. Statistical Analysis

Multiple imputation with chained equations to replace missing values for body mass index, systolic blood pressure and diastolic blood pressure have been used [13] [14].
The statistical description of the variables after multiple imputation are shown in Table 1 and Table 2.

Table 1. Baseline characteristics of workers.
Only binary covariates are shown.

Covariates	Freq (N = 11079)	Perc
Sex		
Female	4659	42.05%
Male	6420	57.95%
Smoker	4609	41.60%
Diabetes	474	4.28%
IHD	350	3.16%
Cerebral Ischemia	10	0.09%
Stroke	30	0.27%
Valvulopathy	113	1.02%
Bipolar Disorder	3	0.03%
Hypertension	2128	19.21%
Anxiety-Depressive Disorder	199	1.80%
Anti-hypertensive	1708	15.42%
Oral Blood Glucose Lowering	330	2.98 %
Risk Classes		
Class1	699	6.31%
Class2	5878	53.06%
Class3	3639	32.85%
Class4	863	7.79%

Five imputations have been carried out, as this has a relatively high efficiency and was a pragmatic approach accounting for the size of the data set and capacity of the available servers and software. The imputed data set for all the derivation analyses has been used.

Table 2. Baseline characteristics of workers. Only continuous covariates are shown.

Covariates	Mean	SD
Age	52.35	8.46
Weight	75.25	15.53
Height	1.66	0.17
Systolic Blood Pressure	126.78	16.02
Diastolic Blood Pressure	80.30	9.16

The Rubin rule to combine the results across the imputed datasets has been used.
Cox proportional-hazards regression to predict the risk of a diagnosis of unsuitability for work during a follow-up period of 10 years has been implemented.

$$h(t) = h_o(t)e^{(b_0x_0+b_1x_1+b_ix_i+...+b_Nx_N)}$$

Where $h(t)$ is the hazard function and it is defined as the instantaneous risk that a worker is evaluated as unsuitability for work, within a very narrow time frame. $h_0(t)$ is the baseline or underlying hazard function and corresponds to the probability of unsuitability for work when all the explanatory variables are zero.
In order to choose covariates to include in Cox's multi-variables regression model, for each risk factors, Hazard Ratio of uni-variable Cox's model has been evaluated.

$$HR = \frac{h(t)}{h_0(t)} = e^{(b_ix_i)}$$

Variables that had an hazard ratio of less than 0.90 or more than 1.10 (for binary variables) and were statistically significant at the 0.01 have been included in the model.

These criteria were included in conjunction with clinical judgment to ensure that candidate variables were likely to be clinically important and to reduce the over-fitting and optimism of the model [6] [15] [16].

The interactions between predictor variables and age at study entry have been examined and then significant interactions have been included in the final models.
All the continuous variables were naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations [3].
Two main Multi-variable Cox models have been developed. Model A included all covariates above (Table 4), Model B was the same as model A except that it included only variables that were statistically significant at the 0.05 in the Multi-variable Cox Model (Table 3).

3. RESULTS

Between January 2006 and December 2016, 11079 workers were examined for health surveillance by trained physicians at the Occupational Medicine Outpatient Clinic of "Federico II" University Hospital. The 57.95% were men, mean age was 52.35($\pm$ 8.46), the 6.31% belonged to the first risk Class, the 53.06% belonged to the second risk Class, the 32.85% belonged to the third risk Class and the 7.79% belonged to the fourth risk class.
Figure 1 shows the performance of the hazard function as a function of follow-up time using model A and model B respectively, considering the different four risk classes. For both models, the highest values of the instantaneous risk of a diagnosis of unsuitability for work are associated with the highest occupational risk class.

Table 3. Adjusted hazard ratios (95% confidence interval) in the derivation cohort for model B. Notes: SBP, “Systolic Blood Pressure”; DBP, “Diastolic Blood Pressure”; BMI, “Body Max Index”; IHD,”Ischaemic heart disease”; ADD, ”Anxiety-Depressive Disorde”; OBGL,” Oral Blood Glucose Lowering ”

Covariates	**Haz. Ratio**	**p-value**
	[95% Conf. Interval]	
Sex	0.691	0.000
	[.568, .840]	
ln(Age)	2.433	0.005
	[1.301, 4.551]	
ln(Height)	0.091	0.008
	[.015, .538]	
DBP	3.039	0.000
	[1.875, 4.924]	
ln(BMI)	1.739	0.007
	[1.165, 2.594]	
Smoker	1.172	0.021
	[1.023 , 1.341]	
Diabetes	1.607	0.000
	[1.279, 2.020]	
IHD	2.549	0.000
	[2.009, 3.234]	
Cerebral Ischemia	4.339	0.004
	[1.611, 11.686]	
Valvulopathy	2.765	0.000
	[2.028, 3.766]	
Bipolar Disorder	4.450	0.015
	[1.341, 14.758]	
Hypertension	0.726	0.004
	[.585, .9004]	
ADD	2.262	0.000
	[1.625, 3.146]	
Anti-hypertensive	1.366	0.013
	[1.069, 1.745]	
Risk Classes		
Class 1	8.332	0.000
	[4.438, 15.642]	
Class 2	2.516	0.003
	[1.360, 4.653]	
Class 3	1.893	0.043
	[1.019, 3.516]	

The risk model B provides valid measure of risk in the population of workers, as shown by Akaikes Information Criterion in table 5.

Table 5. **Akaike Information Criterion**: The risk model B provides valid measure of risk in thepopulation of workers

	Model A	**Model B**
AIC	13632.222	13631.694

Table 4. Adjusted hazard ratios (95% confidence interval) in the derivation cohort for models A. Notes: SBP, “Systolic Blood Pressure”; DBP, “Diastolic Blood Pressure”; BMI, “Body Max Index”; IHD,”Ischaemic heart disease”; ADD, ”Anxiety-Depressive Disorde”; OBGL,” Oral Blood Glucose Lowering ”

Covariates	**Haz. Ratio**	**p-value**
	[95% Conf. Interval]	
Sex	0.687	0.000
	[.564 , .835]	
ln(Age^2)	2.385	0.007
	[1.269, 4.481]	
ln(Height)	0.091	0.008
	[.015, .540]	
SBP	2.894	0.000
	[1.633, 5.127]	
DBP	1.136	0.719
	[.567, 2.273]	
ln(BMI)	1.758	0.006
	[1.175, 2.628]	
Smoker	1.173	0.021
	[1.024, 1.342]	
Diabetes	1.661	0.002
	[1.201, 2.297]	
IHD	2.520	0.000
	[1.983, 3.203]	
Cerebral Ischemia	4.346	0.004
	[1.613, 11.707]	
ICTUS	2.167	0.051
	[.997, 4.710]	
Valvulopathy	2.791	0.000
	[2.048, 3.804]	
Bipolar Disorder	4.500	0.014
	[1.349, 15.009]	
Hypertension	0.706	0.002
	[.567, .879]	
ADD	2.270	0.000
	[1.629, 3.162]	
Anti-hypertensive	1.401	0.008
	[1.093, 1.795]	
OBGL	0.920	0.699
	[.603, 1.403]	
Risk Classes		
Class 1	8.317	0.000
	[4.430, 15.613]	
Class 2	2.521	0.003
	[1.363, 4.661]	
Class 3	1.896	0.043
	[1.02, 3.521]	

4. DISCUSSION

The study proposed a new cardiovascular risk score in occupational medicine. The new score was developed using the Cox regression model, already used widely in

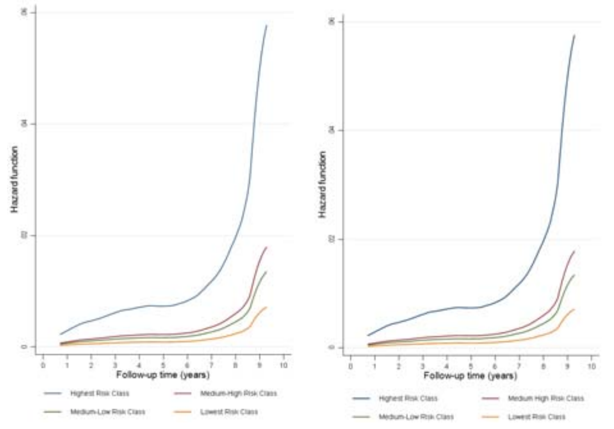

Fig. 1. **Hazard Function of Model A and Model B**: Trend of the hazard function of Model A (left) and Model B (right), as a function of follow-up time (10 years) depending on occupational risk classes. The trend of the hazard functions reflects the classification methodology of workers by Italian occupational medicine legislation

the literature to advance new proposals of cardiovascular risk score [3–9]. To our knowledge, this is the first study to develop a tool to predict the risk of a diagnosis of inadequacy at work due to cardiovascular diseases, using a heterogeneous cohort of workers.

Majority of cardiovascular risk scores were created to evaluate the risk of cardiovascular diseases either in a general population or in a certain occupational cohort (i.e.industrial male, government officials) and using, as linkage with work activity, only the psychological job demand and occupational stressors [10, 11].

In this study, Cox's regression model was used to predict the risk of a diagnosis of unsuitability for work, due to cardiovascular diseases. The study's leading innovation is the inclusion of workplace variables, in addition to established risk factors of cardiovascular diseases

In addition, is the first time that the job conditions were weighed assessing both occupational risks(chemical, physical and biological risks) and job strain. Studies in preventive medicine setting affirm that workplace stressors may increase the burden of disability due to cardiovascular diseases [11, 18]. These results support the trend of the hazard function depending on work risk classes (figure1, figure**??**). In fact, for both score, the highest values of the instantaneous risk of a diagnosis of unsuitability for work are associated with the highest occupational risk class.

While most studies consider mental health to be the leading cause of unfitness for work [19, 20], we included several mental disorders in a single covariate minimizing its weight.

In addition, study limitations include the presence of missing data for clinical variables such as body mass index, systolic blood pressure, diastolic blood pressure and height. However, we overcame the latter issue by using multiple imputation by chained equations.

Finally, most studies support ineffectiveness of model to changes of ethnic group, instead, we considered only Caucasian population. However, external validation should be conducted to estimate model predictiveness and validity.

5. POLICY IMPLICATIONS

CVD is one of the most prevalent causes of long sickness absence from work and may involve a radical change of activity for work for individuals. Therefore, the introduction of a new tool to immediately evaluate the unsuitability for work and so worker's cardiovascular risk would be useful.This would give an improvement of work performance and an increase in the frequency of health surveillance visit for better clinical management of workers at high risk of CVD.

6. CONCLUSIONS

The present investigation presents a multivariable risk factor score that could be used to assess risk of unfitness for work due to cardiovascular diseases.

Model B had a better goodness of fit, therefore, further analyses should be conducted to estimate its predictiveness and validity.

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