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USE OF FRAMINGHAM RISK SCORE AS A CLINICAL TOOL FOR THE ASSESSMENT OF FITNESS FOR WORK: RESULTS FROM A COHORT STUDY.

--Manuscript Draft--

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Abstract:	Objective The aim of this study is to validate the use of the Framingham Risk Score (FRS) as clinical tool to predict the risk of diagnosis of unsuitability for work in a cohort of Italian workers. Methods A cohort of workers has been followed from January 2006 to March 2014. FRS was calculated at each visit. Health surveillance diagnosis of unsuitability for work was selected as outcome. Results 2857 workers were followed, 58.9% were men, mean age was 51.6 (±6.7), the mean FRS was 15.1% (±10.7%). Increased values of FRS at baseline were associated with increased rate of diagnosis of unsuitability for work (HR 11.2, 95% CI 3.3-37.8). Conclusions FRS is a strong 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.

1st April 2016

Dear Editor,

As the corresponding and guarantor author, I'm pleased to submit our Paper titled "The use of Framingham risk score to predict the risk of diagnosis of unsuitability for work: results from a cohort study" for your consideration for publication in Journal of Occupational and Environmental Medicine. As highlighted in the title, the present study examines the use of Framingham risk score in worker's health assessment during scheduled medical visits for health surveillance to predict the risk of diagnosis of unsuitability for work. Health assessment during health surveillance is a very difficult process because often the available clinical information are fragmented and not always workers are willing to share information related to their health status. Furthermore the cardiovascular risk assessment plays a key role in the entire health assessment and the use of a sensitive, clinical tool is essential. Using a combination of multilevel analyses and multivariate Cox regression models with a subsequent formal comparison of the predictive power of the model, this study demonstrated that the use of the Framingham Risk Score as clinical tool to evaluate the cardiovascular risk profile of workers, rather than evaluate all the cardiovascular risk factors separately, would be desirable.

The study has not been published previously, it is not under consideration for publication elsewhere, and if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors take full responsibility for the data analyses and interpretation, and the conduct of the research. Each author has full access to all of the data, approved the manuscript and declared no conflict of interest. We authorize the right to publish any and all data. On behalf of my co-authors and myself, we appreciate your time and consideration, and we look forward to hearing from you.

Sincerely,

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Dear Editor,

Please find enclosed a revised version of the manuscript. We have sought to address all Reviewer comments and believe that the paper is greatly improved. Please find our responses to individual comments below.

<u>Reviewer comments:</u>

P1. Study title, It is a little awkward to use the words 'diagnosis of unsuitability for work.' If an employee receives such a diagnosis of unsuitability for work, does he or she should quit the job in your country? Is there a difference between partial and full unsuitability? Please explain more on occupational background in the introduction section.

We apologize about the lack of clarity in the title. The diagnosis of suitability/unsuitability for work is only the last part of the more general process of assessment of fitness for work during the health surveillance. Therefore, we have revised the title as follows:
“Use of Framingham Risk Score as clinical tool for the assessment of fitness for work: results from a cohort study”
We agree that more details about the assessment of fitness for work would improve the contextualization of the research questions and the clarity of the manuscript. Therefore, we have edited the introduction and the material and methods - other study variables sections as follows:

<u>Introduction:</u>

"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. 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. Other factors associated with increased risk of CVD-related working disability are excessive working hours and working over-time. 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".

Material and methods – other study variables:

"At the end of each visit of health surveillance, according to Italian occupational medicine guidelines a health surveillance diagnosis to assess fitness for work was made by the occupational medicine physician and later confirmed by a senior occupational medicine consultant. The health surveillance diagnosis has three possible outcomes: i) suitability for work ii) partial unsuitability for work, with a consequent reduction of the job strain for the worker (i.e. avoiding night shifts for a watchman), or iii) total unsuitability for work, with more radical change of activities within the job. The main outcome of this study was the health surveillance diagnosis of partial or total unsuitability for work coded as binary variable (diagnosis of partial or total unsuitability for work was coded as 1 in both cases)".

P3. Study population. More specific explanations are needed that the four groups are categorized based on which characteristics. You mentioned the occupational risk classification done according to frequency of health surveillance examination and the worker's type of job (p 5). A more detailed description is necessary for that.

We apologize for the lack of clarity. We revised the methods - study population section as follows:

“According to Italian occupational medicine legislation, and considering the different level of occupational risk and job strain, workers were classified into four groups. Workers in the lower group were subjected to a higher occupational risk and greater job strain (Appendix Table 1) and, therefore, their medical surveillance was scheduled more frequently. Level of occupational risk and job strain were progressively decreasing from the first to the fourth group (Appendix Table 1), with a consequent decrease in the frequency of scheduled medical examination as well”.

P4. Composing elements are differed those from [13]D'Agostino's et al.(2008). HDL cholesterol level was not included in your modifiable risk factors. If there is no data left out for HDL-chol., you must mention it as an important limitation in your study in terms of estimating the cardiovascular general risk.

We agree with the Reviewer that this is an important limitation. Although the Framingham Risk Score (FRS) based on non-laboratory predictors has been proved to have similar predictive power than the score based on laboratory predictors (Green et al., 2012), it is important to highlight this difference. Therefore, we moved this limitation to the second paragraph of the study limitations section. We also rephrased the sentence to give more emphasis to this important limitation.

P6. Discussion. More specific discussions are needed based on previous studies of FRS. Discussion is too short compared to limitation section that weakens the

strength of your study.

We agree with the Reviewer. Although no previous study looked at the use of FRS in health surveillance, discussion of previous studies, which evaluated the cardiovascular risk profile in workers using the FRS, is important. Therefore, the discussion section has been expanded with the following paragraph:

"To authors' knowledge this is the first study that aimed to validate the use of FRS as routine, clinical tool to assess fitness for work in occupational health surveillance. However, the FRS has already been used in occupational medicine to assess the CVD risk. Furthermore, FRS components like BMI and smoking status have been previously found to be associated to increased job strain. These findings support the use of the FRS in health surveillance as numerous studies found that job strain is associated with consistent, increased risk of cardiovascular events incidence and consequent increased risk of unsuitability for work"

P8. Typing error. Delete a 'non' from non non-laboratory predictor

We apologize about the typo, which has been corrected.

Figure1. Please put specific reasons for exclusion in boxes. Please move the sentences that describe the tables to the result section or need to be shorten. For example, Table 2. Results from ~March 2014. It is not necessary.

We thank the Reviewer for these suggestions. Reasons for exclusions from the study have been rephrased in the legend of the figure 1, whilst titles of table 1 and 2 have been shortened. Additional information has been inserted in the notes section of both tables.

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Green, B. B., Anderson, M. L., Cook, A. J., Catz, S., Fishman, P. A., McClure, J. B., & Reid, R. (2012). Using body mass index data in the electronic health record to calculate cardiovascular risk. *Am J Prev Med, 42*(4), 342-347. doi:10.1016/j.amepre.2011.12.009

Title Page (include all author information)

USE OF FRAMINGHAM RISK SCORE AS A CLINICAL TOOL FOR THE ASSESSMENT OF FITNESS FOR WORK: RESULTS FROM A COHORT STUDY.

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Running title

THE FRAMINGHAM RISK SCORE AND THE ASSESSMENT OF FITNESS FOR WORK

Contributors

RP and MT conceived the article. RP conducted the statistical analysis. RP, OC, IT and MT wrote first draft of the paper. All the authors revised critically the paper before the submission.

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Conflict of interest

The authors declare there are no conflicts of interest.

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ABSTRACT

Objective

The aim of this study is to validate the use of the Framingham Risk Score (FRS) as clinical tool to predict the risk of diagnosis of unsuitability for work in a cohort of Italian workers.

Methods

A cohort of workers has been followed from January 2006 to March 2014. FRS was calculated at each visit. Health surveillance diagnosis of unsuitability for work was selected as outcome.

Results

2857 workers were followed, 58.9% were men, mean age was 51.6 (±6.7), the mean FRS was 15.1% (±10.7%). Increased values of FRS at baseline were associated with increased rate of diagnosis of unsuitability for work (HR 11.2, 95% CI 3.3-37.8).

Conclusions

FRS is a strong 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.

KEY TERMS: PREVENTION, CARDIOVASCULAR DISEASE, CARDIOVASCULAR RISK, FITNESS FOR WORK, OCCUPATIONAL RISK.

INTRODUCTION

The burden of cardiovascular Disease (CVD) is increasing in Europe [1-3]. The rate of hospital admission for CVD causes is rising and the CVD mortality rate is reported as constantly high [1, 2, 4]. Increasing obesity, physical inactivity, calorific diet, and ageing superimposed on a genetic predisposition are all factors that contribute to the burden of CVD in Europe [1, 2].

CVD is also one of the most prevalent causes of long-term sickness absence from work [5], and the working environment can contribute to its impact on workers' health. 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 [6-10]. Other factors associated with increased risk of CVD-related working disability are excessive working hours and working over-time [11, 12]. 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[13].

Therefore, the importance of the CVD risk assessment and prevention is well acknowledged in occupational health surveillance. The simplified 10-year Framingham General Cardiovascular Disease Risk Score (FRS), a standardized algorithm based on non-laboratory predictors estimating the 10-year likelihood of cardiovascular events [14], has been used as valid CVD risk exposure measure in different healthcare settings [14-16], but not in occupational medicine. Aim of the present study is to validate the use of FRS as a comprehensive, clinical tool to predict the risk of diagnosis of unsuitability for work when assessing the fitness for work during health surveillance in a cohort of Italian workers.

MATERIAL AND METHODS

Study design

This is a retrospective cohort study evaluating the use of FRS based on non-laboratory predictors as comprehensive, clinical tool in workers' health surveillance 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 anonymization of the data, specific ethical approval was not required. All subjects signed the general informed consent form, authorising the use of observational clinical data for research purposes. The study was performed in accordance with good clinical practices and the Declaration of Helsinki.

Study population

Workers were identified during period targeted scheduled medical examination for health surveillance at the Occupational Medicine Outpatient Clinic of "Federico II" University Hospital in Naples between January 2006 and December 2010, with a follow-up period until March 2014. Only workers with at least one follow-up visit were considered for the study. Workers with history of coronary heart disease were excluded, as well as those with history of diseases possibly having an impact on working disability such as malignant tumour or clinical major depression. According to Italian occupational medicine legislation [17], and considering the different level of occupational risk and job strain, workers were classified into four groups. Workers in the lower group were subjected to a higher occupational risk and greater job strain (Appendix Table 1) and, therefore, their medical surveillance was scheduled more frequently. Level of occupational risk and job strain were progressively decreasing from the first to the fourth group (Appendix Table 1), with a consequent decrease in the frequency of scheduled medical examination as well.

Framingham risk score assessment

Data about age, gender, smoking status, body mass index (BMI), systolic blood pressure, type II diabetes, and use of antihypertensive medication are routinely collected during medical examination. Therefore, it was possible to calculate the FRS based on non-laboratory predictors, an individualised percentage risk score estimating the 10-year likelihood of cardiovascular events (coronary, cerebrovascular, peripheral arterial disease and heart failure)[14]. The FRS single item evaluation was performed as previously suggested [14, 18, 19].

Considering that the FRS is composed of both modifiable (smoking, BMI, systolic blood pressure, type II diabetes and use of antihypertensive medication) and not-modifiable (age, gender) risk factors, statistical analysis has been adjusted for age and gender in order to better understand the impact of modifiable cardiovascular risk factors on the outcome.

Other study variables

At the end of each visit of health surveillance, according to Italian occupational medicine guidelines[17], a health surveillance diagnosis to assess fitness for work was made by the occupational medicine physician and later confirmed by a senior occupational medicine consultant. The health surveillance diagnosis has three possible outcomes: i) suitability for work ii) partial unsuitability for work, with a consequent reduction of the job strain for the worker (i.e. avoiding night shifts for a watchman), or iii) total unsuitability for work, with more radical change of activities within the job. The main outcome of this study was the health surveillance diagnosis of partial or total unsuitability for work coded as binary variable (diagnosis of partial or total unsuitability for work was coded as 1 in both cases). Study covariates were: single items used to calculate the FRS (age, gender, smoking status, BMI, systolic blood pressure, presence of diabetes, use of anti-hypertensive medications), and the occupational risk classification (categorised in four groups according to frequency of health surveillance examination and the workers' type of job, Appendix Table 1).

Power analysis

A sample size of 2800 was considered sufficient for a study power of 0.8 (alpha 0.05, standard deviation 0.5, hazard ratio 1.5, estimated probability of diagnosis of unsuitability for work 5%).

Statistical analysis

Analysis of covariance (ANCOVA) was used to test differences in the FRS mean among workers of different occupational risk categories at baseline. Cox regression model was used to study the association between FRS at first visit and health surveillance diagnosis of unsuitability for work over time. Mixed logistic regression analysis was fitted to assess the association between the change of the FRS over time (FRS considered as a time-varying variable) and the likelihood of receiving a diagnosis of unsuitability for work. To account for different job-specific occupational risks, a sensitivity analysis was performed for the multilevel analysis considering the type of job as an additional level in the hierarchical model. Finally, in order to evaluate the predictive power of the Cox model, a cross-validation of the model was performed by comparing the main model (using the FRS) with a second one excluding the FRS and including the single items composing the FRS separately: the dataset was divided into two subsets (training and test sets) using a stratified semi-random selection of the two sets accounting for sex and occupational risk category. Harrell's C was the parameter used to compare the predictive power of the two models [20].

Stata 12.0 was used for data processing and analysis. Variables were tested for normal distribution by using both statistical and graphical methods when appropriate. Results were considered statistically significant for $P < 0.05$.

RESULTS

Between January 2006 and December 2010 4,421 workers were examined for health surveillance by trained physicians at the Occupational Medicine Outpatient Clinic of "Federico II" University Hospital. 1,564 workers were excluded from this study because they did not meet the inclusion criteria, therefore, a final sample of 2,857 workers was included (Figure 1). Follow-up visits were available until March 2014 (follow-up visits 1.9±1.0). Baseline characteristics are shown in Table 1. Mean value of FRS at the baseline was 15.1% (±10.7) with those in the higher occupational risk group with significantly higher FRS values than the other groups after correcting for age and sex (table 1).

Diagnoses of unsuitability for work at follow-up were 275 (cumulative incidence 9.6%). The multivariable Cox-model showed that 1% increasing of FRS at baseline was associated with increasing rate of diagnosis of unsuitability for work (HR 11.2, 95%CI 3.3-37.8) (Table 2). Likewise, increased value of FRS over time was more likely associated with having a diagnosis of unsuitability for work over time (AOR 7.8, 95% CI 1.6-37.0). Results were also confirmed by the sensitivity analysis (AOR 7.7 95%CI 1.6-36.2, Table 2).

At the cross-validation analysis the Harrell's parameter for the model considering the FRS was significantly greater than the one for the model considering the single items composing the FRS separately (main model: coeff. 0.73 95%CI 0.67-0.78; difference: coeff. 0.03 95%CI 0.01-0.05; Table 2).

DISCUSSION

Our findings showed that FRS is a strong predictor of diagnosis of unsuitability for work. Increased values of FRS at baseline and follow-up are associated with increased risk of diagnosis of unsuitability for work. Considering the FRS in the model rather than the single items composing the score was demonstrated to have a greater predictive power.

To authors' knowledge this is the first study that aimed to validate the use of FRS as routine, clinical tool to assess fitness for work in occupational health surveillance. However, the FRS has already been used in occupational medicine to assess the CVD risk[21]. Furthermore, FRS components like BMI and smoking status have been previously found to be associated to increased job strain [6]. These findings support the use of the FRS in health surveillance as numerous studies found that job strain is associated with consistent, increased risk of cardiovascular events incidence [6, 8, 22, 23] and consequent increased risk of unsuitability for work. Our findings confirm these results as workers in higher occupational risk groups, more likely to be subjected to higher job strain, had increased values of FRS and subsequent increased risk of diagnosis of unsuitability for work. Discordant results have been found in previous studies regarding the impact of gender on CVD outcomes in workers, with some showing increased risk in women [24], others in men [25, 26], others reporting similar effect estimates between sexes [6, 8, 27]. Our findings are in line with those showing men as at increased risk of cardiovascular events as in our study men were found to have increased FRS at baseline with subsequent increased risk of diagnosis of unsuitability for work.

Study limitations

Several caveat merit discussion. The main study limitation is that the FRS estimates the 10-year risk of cardiovascular events, while in our case the study duration was less than 8 years. Moreover, despite a study sample considered sufficient to detect an acceptable statistical power, relatively small numbers of events for the outcome reflected on quite large confidence intervals when estimating risk of unsuitability for work. For the same reason we had to combine for our study outcome diagnoses of partial and total unsuitability for work, regardless the difference in severity between them. Another important limitation to address is that we could not calculate the FRS based on laboratory predictors, as it includes HDL and total cholesterols, which are not routinely measured in our protocol for occupational medicine visits. However, we used the FRS based on non-laboratory predictors which has been proved to have similar predictive power, especially for those who do not have a high CVD risk profile [14, 28]. Additionally, a baseline average FRS of 15% for our study population is already high, suggesting that the study was performed on a population at quite high CVD risk, probably due to older age and high job strain. Therefore, additional studies on a population with a lower CVD risk at baseline, with longer follow-up period and greater sample size would be needed for a better generalization of our findings. Furthermore, the FRS calculation is partially based on self-reported information (i.e. previous diagnosis of diabetes or hypertensive treatment) and this can introduce possible errors due to inability to recall or unwillingness to reveal a condition, particularly for persons from lower socio-economic and education background who may be more likely to under-report, in fact the prevalence of people with diabetes in this study was lower than the estimated national and international prevalence [1]. However, this bias might result into an under-estimation of the FRS calculation which unlikely had a positive impact on our findings. Another possible bias to address is the selection bias, as workers in higher occupational risk categories, more likely to have cardiovascular events due to being subjected to higher job strains, had a higher frequency of scheduled visits and more representative of the longitudinal sub-sample. Moreover by controlling our models for age we addressed that one additional limitation of the use of the FRS in clinical practice is that the score assumes constant effects of the risk factors at differing ages and levels of the other risk factors [30, 31]. Finally, although information about work-related stress are recorded during health surveillance visits (and taken into account for the final diagnosis) it was not possible to link them with clinical data. However workers with clinical diagnosis of major depression were excluded as this condition could have affected the diagnosis greatly.

Policy Implications

Cardiovascular disease is one of the main causes of long sickness absence and diagnosis of unsuitability for work [5-8, 22], but its assessment in workers can be difficult due to the multiple factors to consider and the discontinuity of the relationship between workers and occupational medicine physicians. The introduction of the FRS in routine clinical practice during medical visits for health surveillance would be a useful and comprehensive tool to immediately evaluate the worker's global cardiovascular risk profile and provide life-style counselling. This would give the possibility to increase the frequency of health surveillance visits for a better clinical management of workers considered at high risk of CVD and to refer those workers to local based prevention programs with the aim to reduce the global cardiovascular risk and the subsequent risk of diagnosis of unsuitability for work.

Conclusions

FRS was found to be a strong predictor of diagnosis of unsuitability for work. Therefore, it should be used as clinical tool for comprehensive and accurate global cardiovascular risk assessment during targeted medical examinations for health surveillance, as well as a long-term predictor of occupational risk assessment.

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Figure 1: Study tree showing workers who have been included in the present cohort study.

Notes: Workers were included if visited during health surveillance between January 2006 and December 2010 and if meeting the inclusion criteria.

Reasons for exclusion from the study could be the following: * not meeting the clinical inclusion criteria (history of coronary heart disease or diseases having an impact on working disability, e.g. malignant tumour or clinical major depression); ** no follow-up visit available.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Appendix Table 1: List of jobs and their classification in four occupational risk groups (I as the highest, IV as the lowest).

ABSTRACT

Objective

The aim of this study is to validate the use of the Framingham Risk Score (FRS) as clinical tool to predict the risk of diagnosis of unsuitability for work in a cohort of Italian workers.

Methods

A cohort of workers has been followed from January 2006 to March 2014. FRS was calculated at each visit. Health surveillance diagnosis of unsuitability for work was selected as outcome.

Results

2857 workers were followed, 58.9% were men, mean age was 51.6 (±6.7), the mean FRS was 15.1% (±10.7%). Increased values of FRS at baseline were associated with increased rate of diagnosis of unsuitability for work (HR 11.2, 95% CI 3.3-37.8).

Conclusions

FRS is a strong 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.

KEY TERMS: PREVENTION, CARDIOVASCULAR DISEASE, CARDIOVASCULAR RISK, FITNESS FOR WORK, OCCUPATIONAL RISK.

INTRODUCTION

The burden of cardiovascular Disease (CVD) is increasing in Europe [1-3]. The rate of hospital admission for CVD causes is rising and the CVD mortality rate is reported as constantly high [1, 2, 4]. Increasing obesity, physical inactivity, calorific diet, and ageing superimposed on a genetic predisposition are all factors that contribute to the burden of CVD in Europe [1, 2].

CVD is also one of the most prevalent causes of long-term sickness absence from work [5], and the working environment can contribute to its impact on workers' health. 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 [6-10]. Other factors associated with increased risk of CVD-related working disability are excessive working hours and working over-time [11, 12]. 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[13].

Therefore, the importance of the CVD risk assessment and prevention is well acknowledged in occupational health surveillance. The simplified 10-year Framingham General Cardiovascular Disease Risk Score (FRS), a standardized algorithm based on non-laboratory predictors estimating the 10-year likelihood of cardiovascular events [14], has been used as valid CVD risk exposure measure in different healthcare settings [14-16], but not in occupational medicine. Aim of the present study is to validate the use of FRS as a comprehensive, clinical tool to predict the risk of diagnosis of unsuitability for work when assessing the fitness for work during health surveillance in a cohort of Italian workers.

MATERIAL AND METHODS

Study design

This is a retrospective cohort study evaluating the use of FRS based on non-laboratory predictors as comprehensive, clinical tool in workers' health surveillance 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 anonymization of the data, specific ethical approval was not required. All subjects signed the general informed consent form, authorising the use of observational clinical data for research purposes. The study was performed in accordance with good clinical practices and the Declaration of Helsinki.

Study population

Workers were identified during period targeted scheduled medical examination for health surveillance at the Occupational Medicine Outpatient Clinic of "Federico II" University Hospital in Naples between January 2006 and December 2010, with a follow-up period until March 2014. Only workers with at least one follow-up visit were considered for the study. Workers with history of coronary heart disease were excluded, as well as those with history of diseases possibly having an impact on working disability such as malignant tumour or clinical major depression. According to Italian occupational medicine legislation [17], and considering the different level of occupational risk and job strain, workers were classified into four groups. Workers in the lower group were subjected to a higher occupational risk and greater job strain (Appendix Table 1) and, therefore, their medical surveillance was scheduled more frequently. Level of occupational risk and job strain were progressively decreasing from the first to the fourth group (Appendix Table 1), with a consequent decrease in the frequency of scheduled medical examination as well.

Framingham risk score assessment

Data about age, gender, smoking status, body mass index (BMI), systolic blood pressure, type II diabetes, and use of antihypertensive medication are routinely collected during medical examination. Therefore, it was possible to calculate the FRS based on non-laboratory predictors, an individualised percentage risk score estimating the 10-year likelihood of cardiovascular events (coronary, cerebrovascular, peripheral arterial disease and heart failure)[14]. The FRS single item evaluation was performed as previously suggested [14, 18, 19].

Considering that the FRS is composed of both modifiable (smoking, BMI, systolic blood pressure, type II diabetes and use of antihypertensive medication) and not-modifiable (age, gender) risk factors, statistical analysis has been adjusted for age and gender in order to better understand the impact of modifiable cardiovascular risk factors on the outcome.

Other study variables

At the end of each visit of health surveillance, according to Italian occupational medicine guidelines[17], a health surveillance diagnosis to assess fitness for work was made by the occupational medicine physician and later confirmed by a senior occupational medicine consultant. The health surveillance diagnosis has three possible outcomes: i) suitability for work ii) partial unsuitability for work, with a consequent reduction of the job strain for the worker (i.e. avoiding night shifts for a watchman), or iii) total unsuitability for work, with more radical change of activities within the job. The main outcome of this study was the health surveillance diagnosis of partial or total unsuitability for work coded as binary variable (diagnosis of partial or total unsuitability for work was coded as 1 in both cases). Study covariates were: single items used to calculate the FRS (age, gender, smoking status, BMI, systolic blood pressure, presence of diabetes, use of anti-hypertensive medications), and the occupational risk classification (categorised in four groups according to frequency of health surveillance examination and the workers' type of job, Appendix Table 1).

Power analysis

A sample size of 2800 was considered sufficient for a study power of 0.8 (alpha 0.05, standard deviation 0.5, hazard ratio 1.5, estimated probability of diagnosis of unsuitability for work 5%).

Statistical analysis

Analysis of covariance (ANCOVA) was used to test differences in the FRS mean among workers of different occupational risk categories at baseline. Cox regression model was used to study the association between FRS at first visit and health surveillance diagnosis of unsuitability for work over time. Mixed logistic regression analysis was fitted to assess the association between the change of the FRS over time (FRS considered as a time-varying variable) and the likelihood of receiving a diagnosis of unsuitability for work. To account for different job-specific occupational risks, a sensitivity analysis was performed for the multilevel analysis considering the type of job as an additional level in the hierarchical model. Finally, in order to evaluate the predictive power of the Cox model, a cross-validation of the model was performed by comparing the main model (using the FRS) with a second one excluding the FRS and including the single items composing the FRS separately: the dataset was divided into two subsets (training and test sets) using a stratified semi-random selection of the two sets accounting for sex and occupational risk category. Harrell's C was the parameter used to compare the predictive power of the two models [20].

Stata 12.0 was used for data processing and analysis. Variables were tested for normal distribution by using both statistical and graphical methods when appropriate. Results were considered statistically significant for $P < 0.05$.

RESULTS

Between January 2006 and December 2010 4,421 workers were examined for health surveillance by trained physicians at the Occupational Medicine Outpatient Clinic of "Federico II" University Hospital. 1,564 workers were excluded from this study because they did not meet the inclusion criteria, therefore, a final sample of 2,857 workers was included (Figure 1). Follow-up visits were available until March 2014 (follow-up visits 1.9±1.0). Baseline characteristics are shown in Table 1. Mean value of FRS at the baseline was 15.1% (±10.7) with those in the higher occupational risk group with significantly higher FRS values than the other groups after correcting for age and sex (table 1).

Diagnoses of unsuitability for work at follow-up were 275 (cumulative incidence 9.6%). The multivariable Cox-model showed that 1% increasing of FRS at baseline was associated with increasing rate of diagnosis of unsuitability for work (HR 11.2, 95%CI 3.3-37.8) (Table 2). Likewise, increased value of FRS over time was more likely associated with having a diagnosis of unsuitability for work over time (AOR 7.8, 95% CI 1.6-37.0). Results were also confirmed by the sensitivity analysis (AOR 7.7 95%CI 1.6-36.2, Table 2).

At the cross-validation analysis the Harrell's parameter for the model considering the FRS was significantly greater than the one for the model considering the single items composing the FRS separately (main model: coeff. 0.73 95%CI 0.67-0.78; difference: coeff. 0.03 95%CI 0.01-0.05; Table 2).

DISCUSSION

Our findings showed that FRS is a strong predictor of diagnosis of unsuitability for work. Increased values of FRS at baseline and follow-up are associated with increased risk of diagnosis of unsuitability for work. Considering the FRS in the model rather than the single items composing the score was demonstrated to have a greater predictive power.

To authors' knowledge this is the first study that aimed to validate the use of FRS as routine, clinical tool to assess fitness for work in occupational health surveillance. However, the FRS has already been used in occupational medicine to assess the CVD risk[21]. Furthermore, FRS components like BMI and smoking status have been previously found to be associated to increased job strain [6]. These findings support the use of the FRS in health surveillance as numerous studies found that job strain is associated with consistent, increased risk of cardiovascular events incidence [6, 8, 22, 23] and consequent increased risk of unsuitability for work. Our findings confirm these results as workers in higher occupational risk groups, more likely to be subjected to higher job strain, had increased values of FRS and subsequent increased risk of diagnosis of unsuitability for work. Discordant results have been found in previous studies regarding the impact of gender on CVD outcomes in workers, with some showing increased risk in women [24], others in men [25, 26], others reporting similar effect estimates between sexes [6, 8, 27]. Our findings are in line with those showing men as at increased risk of cardiovascular events as in our study men were found to have increased FRS at baseline with subsequent increased risk of diagnosis of unsuitability for work.

Study limitations

Several caveat merit discussion. The main study limitation is that the FRS estimates the 10-year risk of cardiovascular events, while in our case the study duration was less than 8 years. Moreover, despite a study sample considered sufficient to detect an acceptable statistical power, relatively small numbers of events for the outcome reflected on quite large confidence intervals when estimating risk of unsuitability for work. For the same reason we had to combine for our study outcome diagnoses of partial and total unsuitability for work, regardless the difference in severity between them. Another important limitation to address is that we could not calculate the FRS based on laboratory predictors, as it includes HDL and total cholesterols, which are not routinely measured in our protocol for occupational medicine visits. However, we used the FRS based on non-laboratory predictors which has been proved to have similar predictive power, especially for those who do not have a high CVD risk profile [14, 28]. Additionally, a baseline average FRS of 15% for our study population is already high, suggesting that the study was performed on a population at quite high CVD risk, probably due to older age and high job strain. Therefore, additional studies on a population with a lower CVD risk at baseline, with longer follow-up period and greater sample size would be needed for a better generalization of our findings. Furthermore, the FRS calculation is partially based on self-reported information (i.e. previous diagnosis of diabetes or hypertensive treatment) and this can introduce possible errors due to inability to recall or unwillingness to reveal a condition, particularly for persons from lower socio-economic and education background who may be more likely to under-report, in fact the prevalence of people with diabetes in this study was lower than the estimated national and international prevalence [1]. However, this bias might result into an under-estimation of the FRS calculation which unlikely had a positive impact on our findings. Another possible bias to address is the selection bias, as workers in higher occupational risk categories, more likely to have cardiovascular events due to being subjected to higher job strains, had a higher frequency of scheduled visits and more representative of the longitudinal sub-sample. Moreover by controlling our models for age we addressed that one additional limitation of the use of the FRS in clinical practice is that the score assumes constant effects of the risk factors at differing ages and levels of the other risk factors [30, 31]. Finally, although information about work-related stress are recorded during health surveillance visits (and taken into account for the final diagnosis) it was not possible to link them with clinical data. However workers with clinical diagnosis of major depression were excluded as this condition could have affected the diagnosis greatly.

Policy Implications

Cardiovascular disease is one of the main causes of long sickness absence and diagnosis of unsuitability for work [5-8, 22], but its assessment in workers can be difficult due to the multiple factors to consider and the discontinuity of the relationship between workers and occupational medicine physicians. The introduction of the FRS in routine clinical practice during medical visits for health surveillance would be a useful and comprehensive tool to immediately evaluate the worker's global cardiovascular risk profile and provide life-style counselling. This would give the possibility to increase the frequency of health surveillance visits for a better clinical management of workers considered at high risk of CVD and to refer those workers to local based prevention programs with the aim to reduce the global cardiovascular risk and the subsequent risk of diagnosis of unsuitability for work.

Conclusions

FRS was found to be a strong predictor of diagnosis of unsuitability for work. Therefore, it should be used as clinical tool for comprehensive and accurate global cardiovascular risk assessment during targeted medical examinations for health surveillance, as well as a long-term predictor of occupational risk assessment.

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Figure 1: Study tree showing workers who have been included in the present cohort study.

Notes: Workers were included if visited during health surveillance between January 2006 and December 2010 and if meeting the inclusion criteria.

Reasons for exclusion from the study could be the following: * not meeting the clinical inclusion criteria (history of coronary heart disease or diseases having an impact on working disability, e.g. malignant tumour or clinical major depression); ** no follow-up visit available.

LIST OF SUPPLEMENTAL DIGITAL CONTENT

Appendix Table 1: List of jobs and their classification in four occupational risk groups (I as the highest, IV as the lowest).

Figure 1

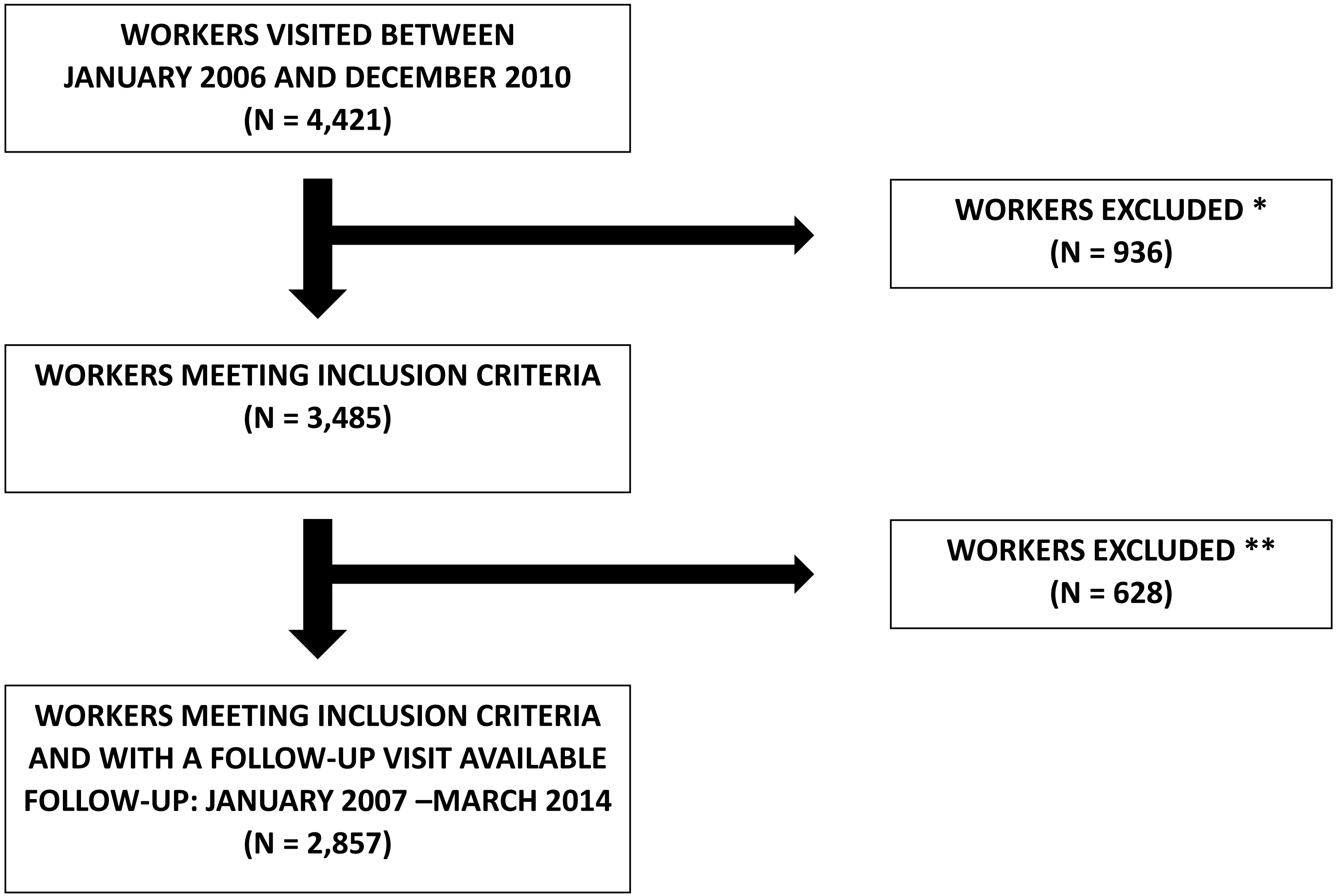
WORKERS VISITED BETWEEN
JANUARY 2006 AND DECEMBER 2010
(N = 4,421)
WORKERS EXCLUDED *
(N = 936)
WORKERS MEETING INCLUSION CRITERIA
(N = 3,485)
WORKERS EXCLUDED **
(N = 628)
WORKERS MEETING INCLUSION CRITERIA
AND WITH A FOLLOW-UP VISIT AVAILABLE
FOLLOW-UP: JANUARY 2007 –MARCH 2014
(N = 2,857)

Table 1

Table 1: Baseline characteristics of a cohort of workers undergoing medical examinations for health surveillance in Naples (Italy) between January 2006 and December 2010.

COVARIATES	SAMPLE CHARACTERISTICS (N = 2,857)		FRS	p-value
SMOKER	44.9%			
DIABETES	2.7%			
SYSTOLIC BLOOD PRESSURE	127.5 mmHg	± 15.7		
TREATMENT FOR HYPERTENSION	14.9%			
BMI	27.6	± 4.7		
AGE	51.6	± 6.7		
MALE	58.9%			
OCCUPATIONAL RISK				
I group	25.5%		23.1% ±9.2	<0.001
II group	33.1%		13.2% ±9.6	
III group	30.9%		10.7% ±9.3	
IV group	10.5%		14.9% ±10.8	

Notes: BMI: “Body Mass Index”; FRS “Framingham Risk Score”; Hg “mercury”.

Results are showed as percentage or mean and standard deviation. Difference in the mean FRS between occupational risk groups is explored using the analysis of covariance and correcting for age and gender.

Table 2

Table 2: Association between FRS and diagnosis of unsuitability for work.

I MODEL				
	AHR	**95% CI**		**p value**
FRAMINGHAM RISK SCORE	11.18	3.31	37.81	0.000
II MODEL				
Main Analysis				
	AOR	**95% CI**		**p value**
FRAMINGHAM RISK SCORE	7.77	1.63	37.00	0.010
Sensitivity Analysis				
	AOR	**95% CI**		**p value**
FRAMINGHAM RISK SCORE	7.69	1.63	36.18	0.010
CROSS-VALIDATION OF THE II MODEL				
	Coeff.	**95% CI**		**p value**
FRAMINGHAM RISK SCORE	0.73	0.67	0.78	0.000
SINGLE ITEMS COMPOSING FRS	0.70	0.64	0.75	0.000
DIFFERENCE	0.03	0.01	0.05	0.009

Notes: Time period: January 2006 – March 2014.

I MODEL shows results from a Cox regression model exploring the association between FRS at first visit and rate of diagnosis of unsuitability for work. II MODEL shows results from a mixed model logistic regression exploring the association between change of the FRS over time and diagnosis of unsuitability for work. In the sensitivity analysis the type of job has been considered as an additional hierarchical level. Cross-validation of the model I was performed by comparing the use of the FRS in the main model and the use of each item composing the FRS separately in the second case. Harrell's C was the parameter used to compare the predictive power of the two models. All analyses have been adjusted for age, sex, and occupational risk groups. AHR = Adjusted Hazard Ratio, AOR = Adjusted Odds Ratio, CI = Confidence Intervals, Coeff. = Harrell's Coefficient.

Clinical Significance

Assessment of fitness for work in workers can be difficult due to the multiple factors to consider and the discontinuity of the relationship between workers and occupational medicine physicians. The introduction of the Framingham Risk Score in health surveillance would be a comprehensive tool to evaluate workers' global cardiovascular risk profile and it might help identifying those who might benefit from life-style counselling.