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# Estimation and development of 10- and 20-year cardiovascular mortality risk models in an industrial male workers database

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ABSTRACT

We examined the performance of the Framingham Heart Study (FHS) and the European Systematic Coronary Risk Evaluation (SCORE) models for cardiovascular disease (CVD) mortality prediction in Israeli industrial workers, and developed and validated new risk prediction models for CVD mortality incidence in the same population. Our database was a longitudinal Israeli industrial cohort (CORDIS cohort) of 4809 adult males followed-up for 22 years. Performance of the FHS and the SCORE prediction models was analyzed by insertion of the CORDIS cohort measurements to each model separately. The standard prognostic variables and results obtained from the new refined Cox regression analyses were used to construct two new 10- and 20-year CVD mortality risk scoring systems: a modified FHS model (FHS/Cox) and an omnibus model with Cox regression (Omnibus/Cox). The SCORE model of high-risk and low-risk charts yielded 10-year mortality mean risks of 1.12% and 0.64%, respectively, for male subjects aged > 30 years. The new FHS/Cox and Omnibus/Cox models generated a mean predictive 10-year risk of 1.12% and 1.50%, respectively. The mean 20-year risk predicted by the new FHS/Cox and the Omnibus/Cox models was 2.66% and 3.75%, respectively. Internal validation of both models demonstrated a high and stable area under the receiver operating characteristic curve > 0.85. No significant differences were found between the two models. In conclusion, the CVD mortality risk prediction scoring systems tailored for the Israeli workers population demonstrated good performance. Additional studies to externally validate these algorithms will indicate which of these quantitative risk estimation platforms should be used in specific settings.



## 1. Introduction

The concept of risk assessment and reduction, initially introduced by the American Framingham Heart Study (FHS) > 50 years ago and refined by other models, forms the cornerstone of preventive cardiology (Pearson, 2002; National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002; Greenland et al., 2010; Perk et al., 2012). Risk factor assessment, the first step in primary cardiovascular disease (CVD) prevention, guides the therapeutic strategy as the intensity of preventive efforts is tailored to each patient's unique CVD risk status (Pearson, 2002; National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002; Greenland et al., 2010; Perk et al., 2012).

Risk prediction algorithms have been developed and used to identify high-risk individuals. The most well-established risk score algorithms are the FHS risk scores (Gibbons et al., 2013; Dawber et al., 1963) and the European Systematic Coronary Risk Evaluation (SCORE) (Conroy et al., 2003). The SCORE risk scores were calculated for high- and low-risk regions of Europe, using a database including >200,000 patients pooled from cohort studies in 12 European countries (Conroy et al., 2003). The Omnibus algorithm, published in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on the assessment of CVD risk, calculates the risk of a first atherosclerotic cardiovascular disease (ASCVD) event (Goff et al., 2014). This algorithm is based on a Cox regression model.

Several basic differences exist between the 3 models. The FHS risk scores estimate the 10-year risk of developing CHD (Gibbons et al., 2013; Dawber et al., 1963) while the SCORE, estimates the 10-year risk of a first fatal ASCVD event (i.e. CVD mortality) (Conroy et al., 2003). The Omnibus model estimates the 10-year risk of a first ASCVD event, defined as a nonfatal myocardial infarction or CHD death, or fatal or nonfatal stroke, among people free of ASCVD (Goff et al., 2014). Common prediction factors for the models include: age, gender, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) and current smoking status. Other unique variables include "belonging to high- or low-risk regions of Europe" for

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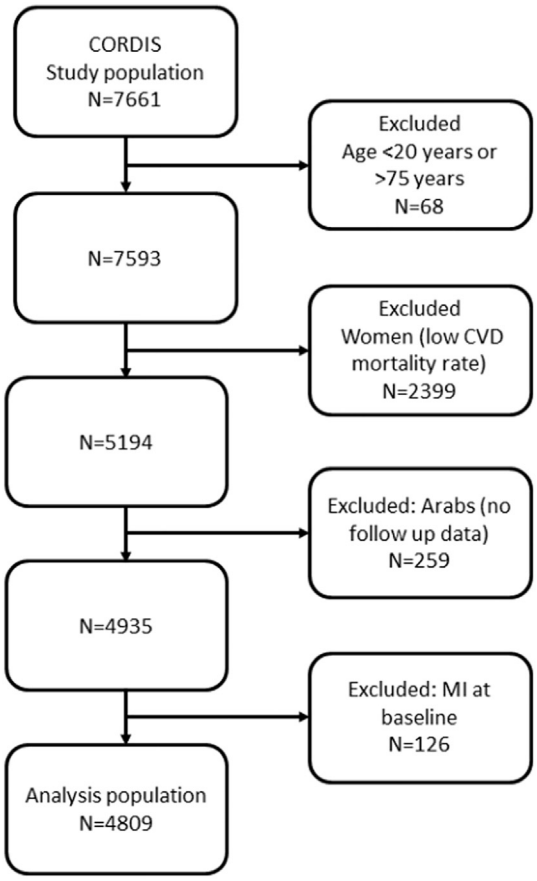


**Fig. 1.** Flow chart of the CORDIS cohort population for the study analysis.

the SCORE, and race and categorical parameters for treatment of hypertension and diabetes in the Omnibus model. Major limitations of the FHS risk algorithm include underestimation of risk in younger age groups and overestimation in older age groups as well as the fact that they are more likely to identify individuals at greater coronary heart disease (CHD) risk in higher socioeconomic groups (Ramsay et al., 2011; Hemann et al., 2007). Overestimation of CHD risk was also seen in ethnic groups such as Japanese Americans, Hispanic men, Native American women (D'Agostino et al., 2001), as well as in countries characterized by a lower incidence of coronary events (Menotti et al., 2000a). Analysis of 10-year CHD incidence data from northern and southern European cohorts showed that the absolute risk was overestimated when applying the northern European model to southern European populations and vice versa (Menotti et al., 2000b). It is therefore clear that models should be specifically adapted to each population according to its characteristics and risk factor prevalence.

**Table 1**
Baseline characteristics of the Israeli industrial cohort followed-up for 22 years.

| Parameter | CORDIS cohort N = 4809 |
|---|---|
| Age, years | 42.3 ± 12.1 |
| Cholesterol (mg/dL) | 202.1 ± 44.6 |
| High-density lipoprotein cholesterol (mg/dL) | 42.8 ± 11.3 |
| Systolic blood pressure (mm Hg) | 125.6 ± 16.0 |
| Body mass index (kg/m$^2$) | 25.7 ± 3.7 |
| Resting heart rate (beats/min) | 76.6 ± 10.8 |
| Smoker at baseline, N (%) | 1900 (39.5) |
| Diabetes mellitus at baseline, N (%) | 159 (3.3) |
| Treated for hypertension, N (%) | 334 (6.9) |

Continuous variables are displayed as mean ± standard deviation; categorical variables are displayed as N (%).

**Table 2**
Mean 10-year risk of cardiovascular disease mortality in an Israeli industrial worker-based cohort followed-up for 22 years calculated according to the Framingham Heart Study and SCORE models.

| Risk algorithm | N | Mean risk (%) | 95% CI | Min | Max |
|---|---|---|---|---|---|
| SCORE (high-risk population) | 3836 | 1.12 | 1.05, 1.18 | 0 | 26 |
| SCORE (low-risk population) | 3836 | 0.64 | 0.60, 0.68 | 0 | 15 |
| Framingham Heart Study | 3870 | 10.71 | 10.43, 10.98 | 0 | 30 |

Note: Framingham Heart Study scores predict cardiovascular disease morbidity, therefore the mean risk obtained is higher.

The Israeli population has specific characteristics in terms of lifestyle and genetics. Nonetheless, clinicians use the FHS and the SCORE risk score charts for predicting CHD risk in Israeli individuals, even though they have never been validated in this population.

Our primary objective was to examine the performance of these coronary mortality risk prediction models in the Israeli population and to develop new models better fitted to this population thus creating an adjusted and reliable quantitative risk estimation platform to be potentially used by local clinical decision-makers.

## 2. Methods

### 2.1. Study design/participants

We used the Cardiovascular Occupational Risk Factor Determination in Israel Study (CORDIS) population database to 1) analyze its performance in the FHS and SCORE risk prediction models, and 2) for the development of two new risk prediction models.

The CORDIS population included 7661 male and female workers aged 18–75, recruited from 21 industrial plants (metalwork, textiles, light industry, electronics, food manufacturing and plywood production) throughout Israel for on-site screening of cardiovascular risk factors. Approval for the study was obtained from the Ethics Committees of the National Institute of Occupational and Environmental Medicine and the Chaim Sheba Medical Center, Ramat Gan, Israel. All participants provided written informed consent.

The current analysis was restricted to 4809 male employees aged 20–75 years at baseline (excluded: <20 or ≥75 years, N = 68). Females (N = 2399) were excluded from the analysis due to the small proportion of CVD deaths reported (8 and 21 women died of CVD in the 10-year and 20-year time points, respectively). Arab men (N = 259) were excluded from the current analysis as no follow-up data was available for them; individuals who reported myocardial infarction at baseline were also excluded (N = 126) (Fig. 1).

### 2.2. Data collection

Data collection was performed as previously described (Harari et al., 2015). Briefly, data related to medical history, demographics, blood test results and cardiovascular risk factors were collected in two phases: 1985–1987 and 1988–1990. Trained technicians visited the various plants and performed computerized interviews as well as physical examinations. The CORDIS questionnaires constituted the basis for population characterization and the identification of risk factors.

**Table 3**
Mean 10- and 20-year risk of cardiovascular disease mortality in an Israeli industrial cohort followed-up for 22 years estimated according to the new models: FHS/Cox and Omnibus/Cox.

| Risk algorithm | Mean risk (%) | 95% CI | Min | Max |
|---|---|---|---|---|
| FHS/Cox (10-year) | 1.12 | 1.06, 1.18 | 0.01 | 45.49 |
| Omnibus/Cox (10-year) | 1.5 | 1.43, 1.56 | 0 | 33.09 |
| FHS/Cox (20-year) | 2.66 | 2.53, 2.8 | 0.03 | 77.75 |
| Omnibus/Cox (20-year) | 3.75 | 3.58, 3.92 | 0 | 65.09 |

N = 4809; FHS, Framingham Heart Study; CI, confidence interval.