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Associations between ECG abnormalities and death or myocardial infarction. A 25 year follow up of middle-aged men employed in a Swedish automotive industry

Degree Project in Medicine

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List of abbreviations

CI = Confidence interval

CVD = Cardiovascular disease

ECG = Electrocardiography

ECGA = Electrocardiography Abnormality

FRI = Framingham Risk Index

FRS = Framingham Risk Score

HR= Hazard Ratio

ICD = International classification of diseases

MC = The Minnesota Code Classification System for Electrocardiographic Findings

MI = Myocardial infarction

OR= Odds ratio

Pseudo-R² = Calculation of how much of the outcome variation is explained by the model.

P-Value = Probability value

QRS-complex = An ECG pattern that symbolizes the depolarization of ventricles

QTc= An ECG pattern that measures the time between ventricles depolarization and ventricles repolarization corrected for pulse rate.

RR=Relative Risk

STJ= ST-junction = An ECG pattern symbolizes phase 2 of ventricular repolarization.

T-Wave = An ECG pattern symbolizes phase 3 of ventricular repolarization

USPSTF = United States' Preventive Services Task Force

WHO=World Health Organization

Abstract

Background: The Coeur Project started in 1992 as a joint medical project between two automotive companies, one located in Sweden (the Volvo Corporation) and one located in France (Renault Automotive Group). The original design of the Coeur study had 3 steps. In 1993, baseline data was collected from 1,000 randomly selected men aged 45-50 years from each of the two enterprises. In 1995, a second step involved special investigations of 100 high and 100 low risk individuals according to Framingham risk index. These included diet, ultrasonographic and blood viscosimetry investigations. All participants underwent new examinations, In a third step, 1998, all baseline participants were offered a full nurse-led health assessment to evaluate cardiovascular end-points after five years. The objective of the fourth step of the longitudinal cohort study was to investigate associations between various potential risk factors and death or myocardial infarctions (MI) during the following 25 years. A factor of particular interest was abnormalities found in the resting Electrocardiogram (ECG), which was recorded in 1993 as well as 1998.

This study aims to investigate if there are statistical associations between ECG findings and the cumulative risk of death and MI as well as how much the information about ECG abnormalities (ECGA) adds to that which can be obtained using the well-known Framingham Risk Index (FRI) for the risk of MI or death. That is, how much certainty in prediction of these events is gained if we know the result of ECG investigations. The study is limited to the Swedish cohort of workers.

Methods: The answers to the questionnaire and laboratory data from the health survey at baseline (1993) were used to estimate the risk of cardiovascular disease according to Framingham Risk Index (FRI) and to obtain information of known riskfactors, some included in the FRI and some not. The ECG examinations in 1993 and 1998 were analyzed using the Minnesota Code Classification System for Electrocardiographic findings (MC). In 2018 we obtained information

about deaths from the National Board of deaths register for the Swedish participants. In 2019 data was collected from the National myocardial infarction registry, Swedeheart. The basic tools for the statistical analyse were conventional basic statistical analysis and logistic regression with death or MI as the dependent variable. We used five sets of independent, explanatory variables (Models1-4 below):

1. ECG abnormality (ECGA) only
2. FRI quintiles only (for reference, the ECGA variable not included)
3. ECGA and FRI quintiles
4. ECGA and the variables constituting FRI.
5. As in 3 above with a number of additional variables

Pseudo-R² according to McFadden was used to describe the prognostic value of the models.

Nelson –Aalen curves were used to illustrate the cumulative risk for death and MI.

Results: Seventy-nine of the 977 participants with baseline information had at least one ECG abnormalities 1993 or 1998, 790 participants had two normal ECG, 108 had one normal ECG and missed the other ECG examination. Death data showed that 157 participants had died before 2019. The data from Swedeheart showed that 100 participants had a first MI over the 25 years. The Odds ratio (OR) for having a MI in the group that had one or more ECG abnormality compared with the group with two normal ECGs (Model 1) was estimated to 3.16 (CI (1.74;5.73), p-value 0.000).

For death no statistically significant difference was shown between the group with at least one ECG abnormality and the group with two normal ECG (model 1) OR 1.52 (CI (0.83-2.76).

For MI, Model 1 had a Pseudo-R² of 2%, Model 2 had 9%, Model 3 had 14 % and Model 4 reached 25%. The corresponding percentages for death were all lower.

Conclusions:

Our study confirms what other studies have shown i.e. ECG abnormalities are statistically associated with increased risk of suffering from an MI but not for death. However, larger studies are needed to evaluate the importance of specific types of ECG abnormalities.

Introduction:

The Coeur study started in 1992 in a joint cooperative project between the occupational health departments of Renault (France) and Volvo (Sweden) about the French paradox. Data exist from 1993 (baseline) and 1998 (first follow-up) from 1,000 middle-aged Swedish men and 1,000 Frenchmen

In the present study we do a follow-up of the Swedish cohort with focus on ECG abnormalities and their subsequent associations with myocardial infarction (MI) and death for 25 years.

The causes of death vary over time and between countries. In the 1970's Ancel Keys and colleagues followed 11,579 middle-aged men in seven countries for 15 years. Six hundred and eighteen (27%) died from coronary heart disease [1]. In 2011, cardiovascular disease (CVD) was the main cause of mortality responsible for over 3.9 million deaths a year in Europe, or 45% of all deaths, and for 1 of every 3 deaths in the United States [2,3].

The map of the burden of disease exhibits disparities within and among populations [4].

In 2015, unadjusted life expectancy was for Swedish men 80.1 years versus 78.8 for Frenchmen [5].

Ancel Keys groundbreaking study of seven countries, with populations that varied in relation to their physical characteristics and lifestyle was the start of cardiovascular epidemiology. He found that atherosclerotic diseases correlated with dietary fat, high blood pressure and smoking [6].

Consequently, the Monitoring trends and determinants in cardiovascular disease (MONICA) collaboration published a comparison of the epidemiology of myocardial infarction (MI) and coronary deaths in 21 countries in four continents [7].

They confirmed that the annual age standardized coronary event rates of MI for the period 1985-1987 for men was lower in Mediterranean countries such as France (France, Toulouse) 240/100 000; 95% CI 225-255 as compared to Nordic countries such as Sweden (Sweden, Gothenburg) 406/100 000; 95% CI 380-432 [7]. This difference coined the French Paradox because Frenchmen with a higher fat consumption (such as cheese), and wine compared to Swedish men paradoxically had a lower rate of MIs.

Myocardial infarction

MI, commonly known as a heart attack, occurs when the blood flow decreases or stops to some part of the heart, causing damage to the heart muscle. Most MIs occur due to coronary artery disease also called ischemic heart disease [8].

Ischemic heart disease is according to the World Health Organization (WHO) the leading cause of death globally (2016) and was responsible for 9.4 millions of death or 16% of all deaths worldwide 2016 [9]. Even in Sweden Ischemic heart disease is the leading cause of death [10].

Ischemic heart disease includes stable angina, unstable angina, myocardial infarction, and sudden cardiac death [11]. There are different instruments to calculate the risk of cardiovascular events using risk factors, for examples SCORE, Qrisk and Framingham Risk Score [12-15]. In 1998 the first version of Framingham risk score (FRS), developed from data of the Framingham Heart Study was published [16]. It calculates an individual's 10-years risk for cardiovascular events. The Framingham Risk score has been validated for Americans, and subgroups of Americans (both gender, European Americans, African Americans) [17].

The Framingham Heart study showed several factors associated with increased risk of myocardial infarction. These include older age, male sex, high blood pressure, current smoking, abnormal lipid levels, diabetes, obesity, and physical inactivity [18].

ECG as risk assessment

Electrocardiography (ECG) is a common examination in both annual health checks and as a part of the diagnostics when patients have suspected symptoms from the heart e.g. chest pain. ECG is used as a screening instrument in some profession such as pilots, and train drivers

ECG is a non-invasive test that measures the electrical activity of the heart beat and also provides information about heart muscle damage, types and kinds of arrhythmias and signs of a heart attack.

In 2017, a population-based retrospective cohort study in Canada found that ECG taken during annual health examinations was common, in 22% [19]. ECG is also used as a screening method in some professions (e.g. air pilots) [20]. And there is a plenty of private options for those who want to undergo a health check including ECG, e.g. google gives 17 millions hits if you search for “private ecg” [21].

In 2018, the US Preventive Services Task Force (USPSTF) published its recommendations on screening for cardiovascular disease risk using electrocardiography (ECG). USPSTF recommends against screening low risk adult with ECG. For adults with higher risk, they conclude that there is insufficient evidence for making a recommendation [22].

The USPSTF submitted a report reviewing the association of ECG and cardiovascular endpoints.

Regarding resting ECG, they found 9 cohort studies (n = 66 407) that showed adding a resting ECG to traditional risk factors produced small improvements in risk assessment [23]

One cohort study from the Netherlands concludes “Performing a resting ECG in a primary care population does not seem to improve risk classification” [24].

Contrary to this several studies that showed that specific and unspecific ECG abnormalities can help predict cardiovascular events, MI and death [25-34].

Several studies indicate that prolonged QRS-complexes are associated with higher risk for MI/Death [25-28, 30]. In the largest of these studies they evaluated the 12-lead ECGs of 10 899 Finnish middle-aged subjects from the general population and it showed that “Prolonged QRS duration predicted all-cause mortality (multivariate-adjusted relative risk [RR] 1.48; 95% confidence interval [CI] 1.22–1.81; $P < 0.001$), cardiac mortality (RR 1.94; CI 1.44–2.63; $P < 0.001$), and sudden arrhythmic death (RR 2.14; CI 1.38–3.33; $P = 0.002$)”[26].

In the National Health and Nutrition Examination Survey—III which Included 8,527 patients with ECG data they found “The addition of the QRS duration in 10-millisecond increments to the Framingham Risk Score model resulted in 4.4% overall net reclassification improvement (95% CI 0.02 to 0.04; $p = 0.00006$). In conclusion, increased QRS duration was found to be an independent predictor of CV mortality in this cross-sectional US population. A model including QRS duration in addition to traditional risk factors was associated with improved CV risk prediction.” [27]

A few studies show that T-wave inversion is associated with all-cause and cardiac mortality

[25,29-31]. In the PRIME Study they recorded 10 600 ECG from men. Later a study showed that Isolated negative T waves (INTW) after multivariate adjustment that “INTW ≥ 1 mm in lateral or anterior leads were associated with a higher incidence of myocardial infarction [HR 2.75, 95% CI (1.29–5.88) and HR 3.20 95% CI (1.68–6.09) respectively]. The association of INTW ≥ 1 mm in leads V1 to V5 with mortality remained highly significant [HR 3.17 95% CI (1.77–5.65)] after multivariate adjustment” [31].

Furthermore some studies show that unspecific as well as any major ECG abnormalities are associated with death/CVD/MI in specific patient populations [32-35].

Among the coding systems for classification of electrocardiographic (ECG) abnormalities, the Minnesota Code (MC), introduced in the early 1960s, is the most widely used in epidemiologic studies and clinical trials [36-38].

Volvo, Renault and a study of the French paradox.

In the beginning of the 90s the two automobile manufacturers Volvo (Sweden) and Renault (France) were planning to merge. Both companies' health care units decided to start a study of the French paradox [39]. The question was why myocardial infarction is more common in Swedish men than in French, despite the Frenchmen had a less healthy lifestyle, particularly more cheese and wine. This query was the basis for a comparative study of middle-aged men at Renault and Volvo.

Cardiovascular morbidity is hypothesized to vary with differences in environmental factors, individual life style, and diet. The aim of the study was to compare the risk factors of sub-groups thereby creating hypotheses about causality. The result would hopefully serve to direct the

preventive work of occupational health services.

In 1993 1,000 men between 45-50 years from each company/country were chosen to undergo an extensive nurse-led investigation of health including a resting ECG, laboratory samples, and a survey with 144 questions. In the baseline questionnaire, the family history of a heart attack question was worded: "Before the age of 70, has anyone in your family (parents, sisters, brothers) been affected by a heart attack?". The risk for cardiovascular events was calculated by the Framingham Risk Index.

In 1995, a special study of pathogenetic mechanisms included ultrasonography of the heart and blood vessels, blood viscosity measurements, hormone analyses, and a diet interview was performed in sub-groups from the population. These sub-groups were selected to include 90 individuals with high and 90 with low Framingham Risk Index from each country [40].

In 1998 a five-year follow-up was performed. 95% of the Swedes and 74% of the French were reached for the follow up. In the Swedish cohort both subjective (self-reported) and objective (register verified) end-points were collected. In the French cohort only, subjective end-point were collected. A full nurse-lead medical examination including a second ECG was also offered.

The Swedish cohort reported triple the rate of subjective end-points compared to the French. The study showed that differences in alcohol intake, female social support, and detection and treatment of traditional risk factors might partly explain the national differences of cardiovascular end-points in this cohort [41].

The Swedish Cohort

The merger of Volvo and Renault was never fully accomplished, and after the 5-year follow-up, the French cohort was thus not available for any more follow-ups. This left us with the Swedish cohort including 980 Swedes from the baseline available for follow-up. Today (2019) all men born between 1943 and 1948 should be between 70-75 years old. The group were all employees at the start of the study, white-collar 61% and blue-collar workers 39%.

In 2015, this cohort was revisited, and incident MIs were identified using postal questionnaires, hospital records, and the Swedish national MI and death registers. This study concluded that traditional risk factors were confirmed but explained a modest proportion of the risk. The French paradox was not contradicted, but the mechanism behind it remains unclear. [42]

The long follow-up period (25 years) and the baseline documentation of a multitude of traditional and non-traditional risk factors allow for of the additional risk estimate of ECG-Abnormalities. This type of follow up in a relatively healthy male working population will add important information on the interpretation of often neglected ECG findings at routine health examinations

AIM

The aims of this study were:

- To investigate statistical associations between ECG abnormality (ECGA) found in resting ECG of healthy Swedish working men aged 45 to 50 years and risk of death or MI during 25 years.
- To investigate how much the information about ECG findings adds to that which can be obtained using the Framingham index for prognosis of death and MI. Shortly, how much better can the prognosis be made if we know about ECG abnormality.

Material and methods

The present study is part of the Coeur project a prospective longitudinal study started in 1993 where survey and laboratory baseline data (including a 12-lead ECG) were collected from 1000 randomly selected Caucasian men born between 1 January 1943 and 1 January 1948 from two enterprises Volvo and Renault. The main goal was to investigate the French paradox – Why Frenchmen have less cardiovascular events than Swedes even do the higher burden of risk factors. [39]

The Swedish cohort from 1993

In 1993, all Caucasian men born between 1 January 1943 and 1 January 1948 in the participating Volvo units were extracted from the personnel files. From this cohort of about 4000 men, every third person from the top of the list down was asked to participate in the study, until 1000 volunteers had been selected out of the 1144 men who were approached [41]. Information was obtained by extensive laboratory examinations and a self-administered questionnaire. Cardiovascular risk was estimated for all participants using the Framingham risk index according to Andersson [43]. The formula that was used can be found in appendix 1.

The following baseline data was used for the present analysis: age; married/single/divorced; smoking status (Yes/No); systolic blood pressure (SBP) in mmHg; pulse rate in beats/min; serum high-density lipoprotein cholesterol (HDL-C) in mmol/L; serum triglycerides (TG) in mmol/L, diabetes mellitus; left ventricular hypertrophy; Framingham risk index; alcohol intake in g/week; body mass index (BMI) in kg/m²; sagittal abdominal diameter in cm and ECG.

At baseline, all employees completed a self-administrated standardized questionnaire. Marital status was categorized as married/single/divorced. Smoking habits were compiled by the question

about current smoking (yes/no) defined as “Do you presently smoke”

Registered anthropometric measures, standardization of blood pressure and heart rate measurements together with venous blood tests, lipoproteins and ECG are detailed in a previous report [39].

ECG collection and analysis 1993 in the Swedish cohort

The 12-lead resting ECGs and the examinations were performed by two nurses (one in Gothenburg and one in Trollhättan). All ECGs were read and coded by the same laboratory technician [39]. The ECG investigation was conducted under a strict protocol, developed by professor Sverker Jern. All ECG were classified by The Minnesota Code Classification System for Electrocardiographic Findings (MC).

<i>Minnesota Code</i>	<i>ECG abnormality</i>
1-1-1 1-3-6	Q waves
2-1 2-5	QRS axis deviation
3-1 3-3	High amplitude R waves
4-1-1 4-4	ST junction (J) and segment depression
5-1 5-4	T wave items
6-1 6-8	A-V conduction defect
7-1-1 7-8	Ventricular conduction defect
8-1-1 8-9	Arrhythmias
9-1 9-8-2	Miscellaneous including ST segment elevation (9-2)

Codes 1, 4, 5, and 9-2 (ST elevation) are grouped by leads, resulting in three subclassifications of anterolateral, posterior (inferior) and anterior.

Figure 1: An overview of The Minnesota Code Classification System for Electrocardiographic ECG Findings

The Swedish cohort from 1993 first follow-up and new ECGs in 1998.

In 1998 step three the Coeur project was performed [40]. All 1000 Swedish participant were called in for a new health check-up including a new ECG. The same ECG protocol as the one used 1993 was used and each ECG was classified by the same nurse at the department of physiology at Östra Sjukhuset according to The Minnesota Code Classification System for Electrocardiographic Findings.

The 25-year follow-up, end-point information

In 2019 we contacted The National Board of Health and Welfare (Socialstyrelsen), to gain access to the Cause of Death Register and to identify who out of our 1,000 participants had passed away, and for what cause according to the ICD manual.

Furthermore, we contacted the Swedish national myocardial infarction registry, also known as Swedeheart to obtain information about heart attacks in our cohort. Swedeheart is a national database that was started in 2009 by combining four already existing databases, thus creating the largest heart disease registry in Sweden. The registry collects information from all Swedish hospitals that care for patients with acute coronary artery disease and all patients undergoing coronary angiography, catheter intervention, or open-heart surgery [44]. To define myocardial infarction, we used code 410 of the International Classification of Diseases Ninth Revision, and codes I21-I23 of the Tenth Revision.

Variable definitions

Outcomes, endpoints (dependent variable):

Death 157, deaths reported

First Myocardial Infarctions, 100 MI reported

Explanatory (independent) variables, components of Framingham Risk Index:

Systolic blood pressure (mmHg)

Smoking (Yes/No)

HDL Cholesterol/ Tot Cholesterol

Left ventricular Hypertrophy

Age

Diabetes (Yes/No)

Additional explanatory variables

Diastolic blood pressure (mmHg)

Heart rate (beats/min)

Triglycerides (mmol/l)

Glycemia (mmol/l)

Body mass index BMI

Waist/Hip ratio

Sagittal diameter (dm)

Total alcohol consumption (g/week)

Blue Collar Workers (Yes/No)

Married or cohabiting (Yes/No)

Noisy work environment (Yes/No)

Hypertension (Yes/No)

Family heart attack (Yes/No)

STATISTICAL ANALYSIS

The cumulative incidence from baseline to the end of follow-up was estimated as a percentage with confidence limits estimated using the conventional method. Confidence intervals were estimated using exact probability methods when requested due to small numbers

To study the associations between ECG abnormalities (ECGA) and other risk factors by category, we used conventional means with confidence limits, again with exact methods when necessary.

To study different models with the dichotomous variables Death or MI as dependent variable and different combinations of risk factors as independent variables, logistic regressions were used.

All such models except one, included the dichotomous ECGA. One model contained only the FRI variable as independent. Continuous variables like FRI, SBP, BMI etc. were represented in the model with dummy variables for the five quintiles of the variable distribution

The results considered in the logistic models were the Odds Ratios (OR) and a Pseudo R². The Odds of an event is the risk for the event divided by 1 minus the risk, i.e. the probability for the event divided with the probability for non-occurrence. If the risk is low, we can say that the OR is a fair approximation of the Risk Ratio (RR) or relative risk. The estimates of OR are given with appropriate confidence intervals.

The logistic regression uses a generalized linear model. We cannot use the traditional R² to assess the goodness-of-fit of the model. Several Pseudo R² have been proposed. The one used here is the one proposed by (Mc Fadden) [45], that can be interpreted similarly to the R² for a linear model. The Pseudo-R² results are expressed as percentages in this paper.

The Nelson-Aalen curve was used to illustrate the occurrences of death and MI over time. It uses the same information as the more commonly used Kaplan-Meier curve and gives the same information. The N-A starts from the whole group and shows how individuals leave as events occur. The K-M starts from totality and shows what is left at different time points. When the incidence of events is low and we don't want to censor the y-axis the K-M curve(s) do not deviate too much from unity and can become problematic to read. The N-A uses the graph space more fully.

Calculations were performed using the software Stata version 15.

Ethics

The Research Ethics Committee of Gothenburg University approved the study protocol on 11 February 1993, and the Swedish Data Inspection on 26 January 1993. The Research Ethics Committee of Gothenburg University renewed their approval of a changes study protocol on 19 February 2019. Applications to the national death registry and Swedeheart were also approved. Participation was voluntary, and the partakers could withdraw at any time. Data were only analyzed at the group level and the participants were anonymized using attributed Id-numbers.

Results

The study participants and ECG outcome

The sample selected for the baseline survey included 1000 men aged 45-50 years. Of these 3 did not provide any information. Another 20 had substantial numbers of missing values, particularly they did not have results from any of the two ECG investigations in 1993 and 1998. (Table 1) Totally 108 participants had only one ECG, 72 in 1993 and 36 in 1998. ECG means electrocardiogram. ECGA means electrocardiogram with abnormality.

Table 1. Electrocardiographic abnormalities (ECGA) of the 977 cohort participants, men aged 45-50, in 1993 (baseline) and at follow up in 1998

ECG 1993 \ ECG 1998	ECGA no	ECGA yes	Missing	Total
ECGA no	790	29	72	891
ECGA yes	19	15	7	41
Missing	36	9	(23)*	45
Total	845	53	79	977 (1000)**

* 23 non-informative

** 1000-23 informative

Classification of ECG outcomes

The 977 participants were classified into three ECG categories as follows:

ECG Category 0 ECG performed 1993 and 1998, no ECGA, (n= 790)

ECG Category 1 ECG performed 1993 and/or 1998 One or more abnormalities. (n= 79)

ECG Category 9 ECG performed 1993 or 1998 without abnormality. (n= 108)

Table 2. Estimated cumulative incidences (percentages) and absolute numbers of deaths and first MI for participants followed for 25 years by category. (95% confidence intervals in brackets)

ECG Category	Death (n=157) Cumulative percentage	Infarction (n=100) Cumulative percentage	Deaths Number of cases	First MI Number of cases
0 (n=790)	13.9 (11.5;16.3)	8.35 (6.42;10.3)	110	66
1 (n=79)	20.8 (11.5;30.0)	22.4 (13.8;31.9)	16	17
9 (n=108)	27.6 (18.5;36.6)	12.6 (5.83;19.4)	27	12
Total	15.6 (13.3; 17.57)	10.2 (8.3; 12.1)	153*	95**

* 4 deaths among the 23 non-informative

** 5 MIs among the 23 non-informative

Note: ECG Category 0 ECG performed 1993 and 1998, no ECGA

ECG Category 1 ECG performed 1993 and/or 1998 with one or more abnormalities

ECG Category 9 ECG performed 1993 or 1998 without abnormality

As shown in Table 2 surprisingly the category 9 with only one registered and normal ECG compared to category 0 with two normal ECGs had a significantly higher risk of death, but not of MI. As expected, category 1 with one or more ECG abnormalities had over double cumulative percentage than category 0

Table 3. Estimated means with 95% confidence intervals in brackets for continuous baseline risk factors by ECG category

Risk factor	ECG Category 0 (n=790)	ECG Category 1 (n=79)	ECG Category 9 (n=108)
Framingham risk index	0.089 (0.085-0.093)	0.108 (0.091-0.128)	0.094 (0.080-0.108)
Systolic blood pressure (mmHg)	116 (115- 118)	124 (120-128)	116 (113- 119)
Diastolic blood pressure (mmHg)	75 (74-75)	79 (76-83)	74 (71-76)
Heart rate (beats per minute)	63 (63-64)	63 (61-66)	62 (61-65)
HDL chol/ total cholesterol	0.212 (0.207-0.216)	0.226 (0.197-0.255)	0.207 (0.193-0.222)
Triglycerides (mmol/l)	1.52 (1.46-1.58)	1.53 (1.31-1.74)	1.60 (1.38-1.82)
Glycemia (mmol/l)	5.47 (5.40-5.54)	5.58 (5.27-5.89)	5.39 (5.22-5.57)
Body mass index BMI	25.8 (25.5-26.0)	25.4 (24.6-26.2)	25.0 (24.4-25.6)
Waist/hip ratio	0.933 (0.929-0.937)	0.923 (0.910-0.936)	0.930 (0.919-0.941)
Sagittal diameter (dm)	2.03 (2.02-2.05)	2.02 (1.95-2.08)	1.98 (1.93-2.02)
Alcohol consump (g/week)	51.5 (47.4-55.6)	52.2 (41.1-63.3)	54.3 (41.7-66.9)

Note: ECG Category 0 ECG performed 1993 and 1998, no ECGA

ECG Category 1 ECG performed 1993 and/or 1998 with one or more abnormalities

ECG Category 9 ECG performed 1993 or 1998 without abnormality

Table 3 only shows statistically significant differences in higher blood pressure (systolic and diastolic) between those with normal ECGs (category 0) and those with ECG abnormalities (category 1).

Table 4. Estimated percentages of “yes” response, with confidence intervals in brackets for dichotomous risk factors by ECG category.

Risk factor	ECG Category 0 (n=790)	ECG Category 1 (n=79)	ECG Category 9 (n=108)
Blue collar workers	39 (36-43)	39 (27-50)	36 (26-46)
Married or cohabiting	77 (74-80)	79 (69-88)	74 (65-83)
Noisy work environment	3.7 (2.4-5.0)	8.0 (1.7-14.3)	5.3 (0.69-9.83)
Smoker	28 (25-31)	26 (16-36)	30 (20-39)
Diabetes at baseline	0.008 (0.001-0.014)	0.039 (0.000-0.084)	0.042 (0.000-0.0832)
Hypertension at baseline	8.8 (6.79-10.7)	21 (11.6-30.4)	9.5 (3.48-15.4)
Family heart attack	23 (20.0-25.8)	29 (18.8-39.9)	27 (18.2-36.4)

Note: ECG Category 0 ECG performed 1993 and 1998, no ECGA

ECG Category 1 ECG performed 1993 and/or 1998 with one or more abnormalities

ECG Category 9 ECG performed 1993 or 1998 without abnormality

Table 4 shows a statistically significantly higher percentage of baseline hypertension in those with ECGA (category 1) compared to those with normal ECG (category 0).

No statistically significant risk difference between Category 1 and Category 0 was seen for blue collar workers (OR =1.02; p=0.93)

Regression models

The results from Logistic regression models are presented in Tables 5 and 6. The two tables have identical structure and content. Table 5 gives the results for the estimation in a series of models for the outcome, dependent, variable death whereas Table 6 shows the corresponding for the outcome “first MI”.

The independent variables in the models 1-5, from top to bottom in the two tables, are:

1. Category of ECG
2. Quintiles of the FRI
3. Category of ECG together with FRI
4. Quintiles of ECG together with the variables that are included in the FRI, here considered separately in linear form.
5. Quintiles of ECG, the FRI variables in linear form and the additional; total alcohol, Heart rate, BMI, Waist/Hip ratio and Sagital diameter.

For the two last models the tables contain only the estimates for ECGA and total model Pseudo R².

Table 5. Results for regression models with death as dependent variable with ECGA and additional independent variables of the 977 cohort participants of men aged 45-50 at baseline in 1993 followed for 25 years

Death Model	Independent variable(s)	Estimated OR	95% confidence interval for OR	p-value for OR	Pseudo-R2 for model %
ECGA only (Model 1)	ECGA =0 ECGA =1 ECGA =9	Referens 1.52 2.09	(0.83; 2.76) 1.26 3.46	0.106 0.001	1.4
FRI Only (Model 2)	FRI=1 FRI=2 FRI=3 FRI=4 FRI=5	Referens 0.68 0.77 1.51 2.16	(0.35; 1.31) (0.40; 1.46) (0.66; 2.67) (1.25; 3.73)	0.248 0.418 0.154 0.006	2.9
ECGA and FRI (Model 3)	ECGA =0 ECGA =1 ECGA =9 FRI=1 FRI=2 FRI=3 FRI=4 FRI=5	Referens 1.58 1.84 Referens 0.68 0.69 1.40 2.12	(0.85; 2.93) (1.06; 3.20) (0.35; 1.32) (0.36; 1.34) (0.75; 2.51) (1.22; 3.69)	0.146 0.030 0.256 0.272 0.246 0.007	3.8
ECGA and FRI variables (Model 4)	ECGA =0 ECGA =1 ECGA =9	Referens 1.41 1.84	(0.73; 2.73) (1.01; 3.37)	0.301 0.048	8.3
ECGA and all explanatory variables (Model 5)	ECGA =0 ECGA =1 ECGA =9	Referens 1.42 2.52	(0.69; 3.02) (1.27; 4.97)	0.247 0.021	13.8

The main interest is the association between death and ECG abnormality. We don't find a statistically significant association in any of the models in Table 5. The lack of statistical significance with OR between 1.4 and 1.6 is largely due to the small number of ECGA. The significant OR comparing the categories coded 0 and 9 is difficult to interpret since the last category is problematically defined.

The Pseudo-R²s are generally low even for the largest model (13.8). It shall be noted though, that the ECGA variable has some importance. However, even at the low level, the model with ECGA and the individual FRI variables is better than the model where the calculated FRI is used.

Table 6. Results for regression models with first MI as dependent variable with ECGA and additional independent variables of the 977 cohort participants of men aged 45-50 at baseline in 1993 followed for 25 years

Infarct Models	Independent variable(s)	Estimated OR	95% confidence interval for OR	p-value for OR	Pseudo-R2 for model %
ECGA only (Model 1)	ECGA =0	Referens			2.11
	ECGA =1	3.16	(1.74; 5.73)	0.000	
	ECGA =9	1.59	(0.82; 3.06)	0.168	
FRI Only (Model 2)	FRI=1	Referens			8.57
	FRI=2	6.35	(1.40; 28.8)	0.017	
	FRI=3	9.27	(2.11; 40.7)	0.003	
	FRI=4	14.3	(3.24; 61.5)	0.000	
	FRI=5	25.4	(6.02; 106)	0.000	
ECGA and FRI (Model 3)	ECGA =0	Referens			10.6
	ECGA =1	2.82	(1.51; 5.28)	0.001	
	ECGA =9	1.43	(0.70; 2.89)	0.324	
	FRI=1	Referens			
	FRI=2	6.22	(1.36; 28.3)	0.018	
	FRI=3	7.98	(1.79; 35.5)	0.006	
	FRI=4	14.1	(3.28; 60.6)	0.000	
	FRI=5	24.3	(5.77; 103)	0.000	
	ECGA and FRI variables (Model 4)	ECGA =0	Referens		
ECGA =1		3.43	(1.74; 6.76)	0.000	
ECGA =9		1.24	(0.57; 2.70)	0.579	
ECGA and all explanatory variables (Model 5)	ECGA =0	Referens			24.6
	ECGA =1	4.22	(1.85; 9.64)	0.001	
	ECGA =9	1.18	(0.47; 2.96)	0.719	

For MI the OR for comparisons of ECGA=0 and ECGA=1 are all statistically significant whereas those comparing ECGA=0 and ECGA=9 are not. ECG investigation is statistically significantly associated with MI but not with death. The OR for ECGA are all fairly high, between 2.8 and 4.2, regardless of model.

The R2s are higher for MI than for death and the model with individual FRI is higher than the model with computed FRI, same as for death. The highest R2 is almost 25% which is higher than for the 13% for death. Both however, shall be considered as fairly low.

The tables 7 and 8 shows the distributions of ECG abnormalities by types according to the Minnesota classification”.

Table 7 Number of ECG deviations in 1993 Electrocardiographic abnormalities and myocardial infarction and death in 964 middle-aged, employed men in 1993 followed for 25 years

Minnesota code	Explanation	Investigated persons	Observed findings	Findings with death	Findings with infarct	p-value death	p-value infarct	ECG findings both in 1993 and 1998
Q and QS patterns								
1:1	Q and QS pattern	964	3	1	2		.000	2
1:2	Q, QS and QSR pattern	964	10	1	2			5
STJ and segment depression								
4:1 or 4:2	STJ depression	947	5	4	3	.000	.000	1
T wave items								
5:1 or 5:2	T wave negative or biphasic	947	7	3	2	.004	.075	3
AV conduction defect								
6:1	Complete AV block	964	0					
6:4:1	Wolf-Parkinson-White pattern	964	0					
6:8	Artificial pacemaker	964	0					
Ventricular conduction defect								
7:1:1	Complete left bundle branch	964	1	0	0			0
7:2:1	Complete right bundle branch	964	7	1	2			4
7:3	Incomplete RBB	964	23	1	5			11
7:4	Intraventricular block	962	11	4	1	.004		0
7:6	Incomplete LBB	919	8	1	1			

The p-values refer to death and infarct risk comparisons between persons with and without ECG abnormalities. Only p-values smaller than .100 are shown. Note that the p-values themselves are due to variation. Even one single finding more or less might change the p-value substantially.

Table 8 Number of ECG deviations in 1998 Coeur ECG Preliminary results 1998 Follow-up

Minnesota code	Explanation	Investigated persons	Observed findings	Findings with death	Findings with infarct	p-value death	p-value infarct
Q and QS patterns							
1:1	Q and QS pattern	944	15	2	3		
1:2	Q, QS and QSR pattern	942	16	1	3		
STJ and segment depression							
4:1 or 4:2	STJ depression	926	18	4	4	.054	.041
T wave items							
5:1 or 5:2	T wave negative or biphasic	924	19	4	5	.072	.006
AV conduction defect							
6:1	Complete AV block	945	0				
6:4:1	Wolf-Parkinson-White pattern	945	0				
6:8	Artificial pacemaker	945	0				
Ventricular conduction defect							
7:1:1	Complete left bundle branch block	945	1	0	0		
7:2:1	Complete right bundle branch block	945	9	1	2		
7:3	Incomplete RBB	945	26	3	5		
7:4	Intraventricular block	944	4	0	0		
7:6	Incomplete LBB	919	5	1	1		

The p-values refer to death and infarct risk comparisons between persons with and without ECG abnormalities. Only p-values smaller than .100 are shown. Note that the p-values themselves are due to variation. Even one single finding more or less might change the p-value substantially.

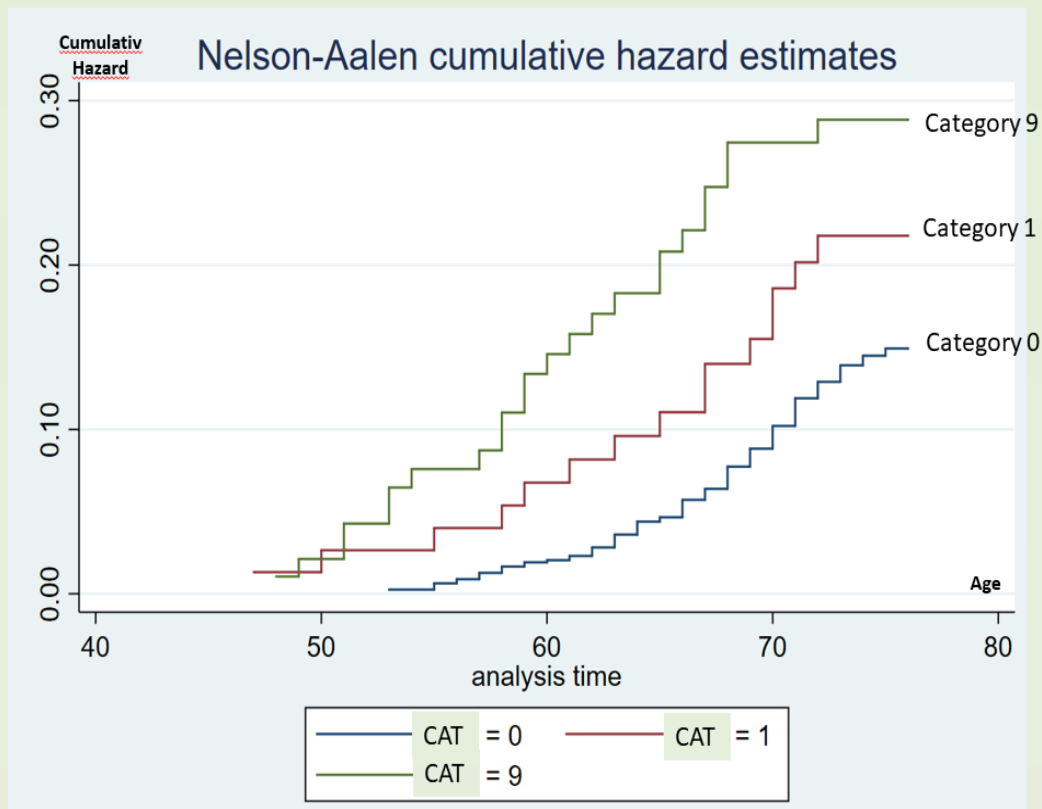


Figure 2 Nelson-Aalen Cumulative Risk Estimates for Death by category in 977 men.

Note: ECG Category 0 ECG performed 1993 and 1998, no ECGA

ECG Category 1 ECG performed 1993 and/or 1998 with one or more abnormalities

ECG Category 9 ECG performed 1993 or 1998 without abnormality

The study started in 1993 when the participants were 45-50 years old and finished in 2018, when they were 70-75 years old. The Cumulative deaths, all causes, by age at death in category 9 (only first ECG) compared to category 1 (first and second ECG with at least 1 abnormal) and category 0 (two normal ECGs) indicate that category 9 over the 25 years follow up was at highest risk, shown in Figure 2.

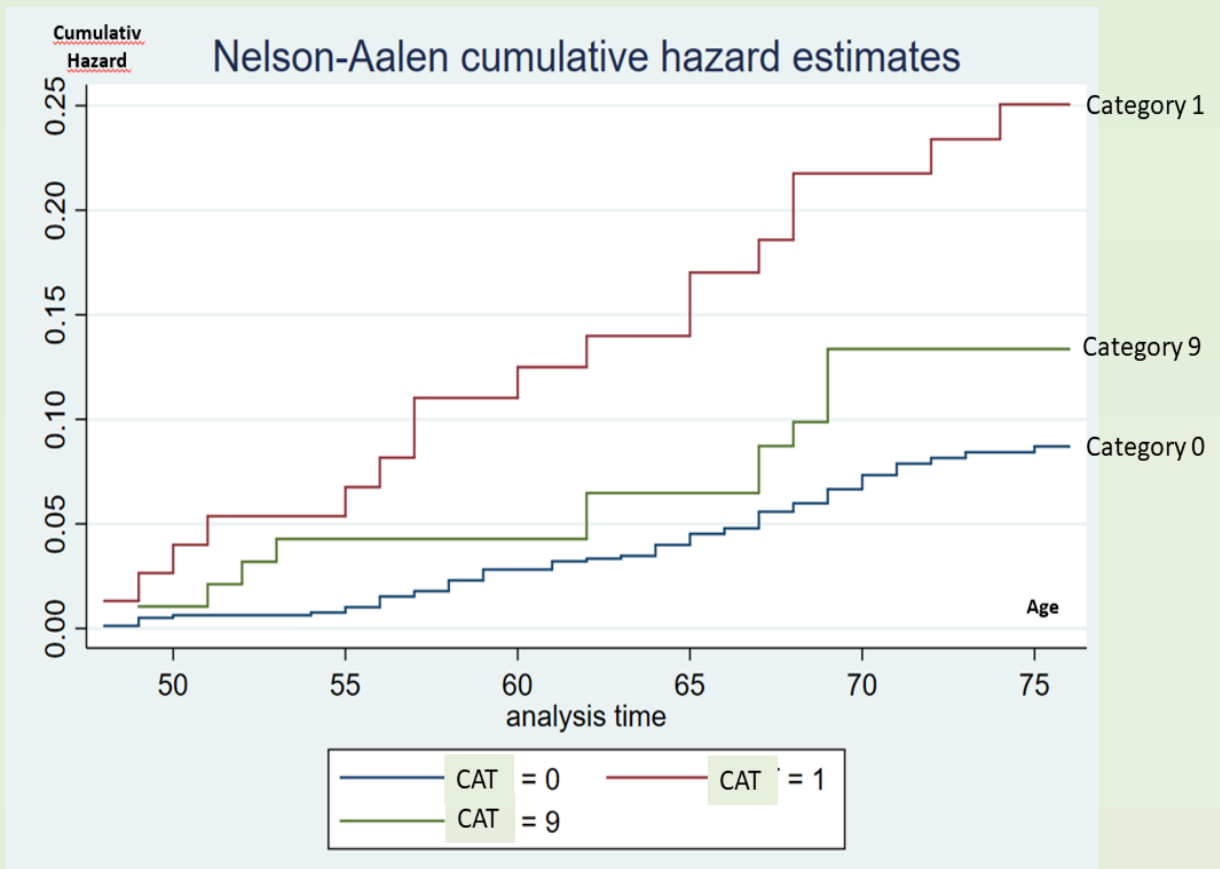


Figure 3 Nelson-Aalen Cumulative Risk Estimates for MI by category in 977 men.

Note: ECG Category 0 ECG performed 1993 and 1998, no ECGA

ECG Category 1 ECG performed 1993 and/or 1998 with one or more abnormalities

ECG Category 9 ECG performed 1993 or 1998 without abnormality

Contrary to the cumulative deaths and correspondingly Figure 3 shows the significant outcome of MIs highest in category 1 (at least one abnormal ECG)

Discussion and analysis

Main Findings

A main finding from the present study is that there is a statistically significant difference between the cumulative incidences of myocardial infarction (MI) after the 25-year follow-up comparing the group of participants that had an ECG abnormality with the group that had not. The ORs quantifying the comparisons are all high, between 2.8 and 4.2, regardless of the regression model used. The risk for having an MI is about tripled if there is an ECG abnormality. There is no statistically significant association between ECGA and the outcome death.

The US Preventive Services Task Force (USPSTF) in 2018 published a recommendation not to use ECG for screening [22]. Our study and others [24-33] though, indicate that using ECGs provide some increased information when we estimate a patient's risk of myocardial infarction in clinical work.

It is important to realize the difference between using ECG for screening of an assumed healthy population and using it as a tool among others in clinical practice. In the former case the USPSTF recommendation is justified. Using the present data as an example, a population screening would have a sensitivity of about 20% i.e. only one in five will be classified as potential MI patients.

Further there will be about 75 % false positive, unnecessarily requiring some attention.

Population screening aims at finding potential cases early and an important requirement also is that there is some action that can be taken which is hardly the case in the present study.

In clinical work the assumptions are different with higher sensitivity and less false positive due to higher prevalence of persons with really high risk. It can be clinically relevant to examine healthy

45-50 years old men with an ECG as one component among others when judging the risk for MI. A question though, is how much weight an abnormal ECG shall be given when estimating the risk of an MI. Since no specific remedy exists for unspecific ECG abnormalities, such findings can mainly be used to emphasize the important prevention of a healthy life-style. This study shows that if a professional working man between 45-50 years, has an ECG abnormality, his risk of suffering a heart attack is increased more within the next 25 years than if he had not, but it is not really possible to say how much.

Due to the few cases in the subgroups of the ECG abnormalities it is not meaningful to evaluate statistically the impact of most Minnesota code subgroups on the specific risk. Earlier studies suggest that prolonging QRS complexes [25-28+30] and negative T-waves [25,29-31] lead to increased risks. In table 7 and 8 we study this in our cohort. That this cohort is too small for this kind of stratification. Even though some p-values are smaller than 0.05, it shall be noted that the p-values themselves are due to variation. Even one single case more or less might change the p-value substantially.

Our results are in line with previously findings that some specific ECG abnormalities are associated with increased risk for MI but no increased risk of death. This applies to both widespread QRS complexes and negative T-waves. In addition, we also find that STJ depression shows an increased risk for both death and MI.

Prolonged QTc (pulse-corrected QT-time) has been seen to be associated with higher risk of MI and death [46-49]. Prolonged QTc is not classified in the Minnesota code and has therefore not been studied here.

Regarding the second aim, finding out what value information about ECGA has compared to the Framingham risk index information, it is clear that there is a some added value. This may be interpreted so that the mechanism creating the ECGA does not follow the same arteriosclerotic mechanism as the FRI. On the other hand, only a small proportion of the infarct risk variations are explained by FRI (Pseudo-R2 8.6 %).

We also see in the in the regression models of MI, OR for ECGA are between 3-4 compared with normal ECG with small p-numbers and this might suggest ECG abnormalities have a prognostic value in identifying risk patients for myocardial infarction. All OR are over 2.8 when comparing those with at least one ECGA registered at either of the two screening occasions compared with the reference group with normal ECGs. However, the Pseudo-R2 for ECGA was only 2.1% compared to Framingham risk index (FRI) that had 8.5%. The model combining ECGA and FRI has a Pseudo-R2 at 11%. The Pseudo-R2 values in general are fairly low even if the ECGA adds risk-information in all the modules [Table 6].

The strength of this finding can be questioned when Pseudo-R2 is only 2.1%, but it must of course be stated that even the Framingham's risk score only shows a Psudo-R2 of merely 8.6 % and compared with any of the six variables included variables in Framingham Risk Score a Psuedo-R2 at 2.1% seems pretty good.

Other findings

An unexpected finding was that ECG the Category 9 participants, one ECG without abnormality, had a statistically significantly higher risk of death, 28% vs 14%. We have no satisfactory explanation for this. One thought was that if this could have been a cause of death between -93 and -98 (the two examinations) but as you see in fig 2 (Nelson) this is not the explanation. Some participants abstaining from the second follow up may have been skeptical or lacked confidence in the individual use of the study. However, this can only be a speculation. In the regression models of death, Category 9 is associated with significantly higher odds ratio than Category 1, the p-value is less than 0.048 for all the modules.

Another finding shown in table 5 and 6 is that there is more information found in the variables included in FRI if they are studied separately then in the combined risk index (FRI). The Pseudo-R² for MI goes from 11% to 15% and for death 3.8% to 8.3%. This suggests that the various adjustment factors used in the index are not fully appropriate for the participants of this particular cohort. The FRI is calculated using constants from some original data in a specific context and therefore be less appropriate in another context.

Study strengths

The original 1000 men were randomly selected from a well-defined population. Very few rejected to participate. Careful training and supervision of the field work at the baseline survey was secured. The procedures for baseline information acquisition was designed using carefully tested approaches. Accurate information about end-points is available in Sweden. The registers providing end-point information, deaths and MI, come from well-established official institutions that can be considered to contain valid data. The internal validity of the study and its results have throughout been carefully secured.

Study Limitations

The external validity i.e. validity for other populations and with other contextual structures is clearly limited. The study is confined to males in a certain age range in a particular industry and a particular country. The comparable small sample size and, as a consequence, the small number of outcomes events is limited is a problem to some extent.

The study was also limited by the use of the Framingham risk index in the original Coeur study.

The Framingham risk index has since been superseded by better predictive tools such as QRISK2 [50] and the use of biomarkers [51], but in a 25-year longitudinal study the analysis is necessarily restricted to the original risk measure. Another limitation is that the Minnesota Code doesn't register QTc.

Confounding

The main research question concerns the statistical association between risk and result of ECG-investigation. This association can be confounded by several variables. Many of these were observed at baseline e.g. age, smoking status, alcohol consumption, weight, height and systemic blood measurements. Most of these are correlated each other and with the risk. Therefore, the crude correlation between risk and ECG is confounded by a manifold of variables. Among these some are known and possible to observe. Others are known but not possible to observe and yet others have not even been imagined. The first mentioned group can be adjusted for using different regression models. For this paper we have tried several models. An important finding is that the OR for ECG abnormality remains reasonably stable, OR about 3 – 4, regardless of model. This is an indication that the main results are not seriously confounded by the variables used in

the study.

Bias

A bias is a systematic error that has similar size and direction for a group of measurements

Several biases could influence the results. For example, laboratory results might be biased due to incorrect calibrations, questions for self-reporting can be formulated to give biased information.

Avoidance of bias is a matter of careful planning and testing of the equipment and questionnaires.

Once data has been collected little can be done about biases.

In longitudinal studies it is possible for both confounding and biases to occur since it is difficult to account for changes in individual's habits or health status over the whole, in this case 25-year, period. Confounding factors in this study would include not accounting for the eventuality that participants' behaviors might change over time, for example smoking less or loss of weight as well as medical treatment of cholesterol and hypertension making the prognostic value of baseline risk factor obsolete in some cases. This has been seen in existing studies [50], which show secular changes (smoking less, lower cholesterol but higher BMI and sedentary lifestyle) in cardiovascular risk factors over time (50 years). Although we do not have secular longitudinal data of a 50-year period the findings presented in [52] are likely to be applicable to our cohort. Furthermore, another confounding factor could be the addition of medication during this period, which may have changed the prognosis of some endpoints.

Conclusions

The study showed that there was an about 3 to 4-fold risk for MI in persons with at least one ECG abnormality (ECGA) compared with those with normal ECGs found in resting ECGs of healthy Swedish working men aged 45 to 50 years and MI over the following 25 years observed. A parallel statement for death could not be made.

Information about ECG findings adds some information of MI risk variation to that which can be obtained using the Framingham Risk Index only, thus bettering the prognosis for MI.

The highest Pseudo-R² observed in the study is found for a MI model with about 20 independent variables. It reaches almost 25%, however meaning that we must assume that there is still a large number of variables, not observable or totally unknown that influence the risks.

Populärvetenskaplig sammanfattning på svenska.

Bakgrund: I ett medicinskt samarbetsprojekt mellan Volvo (Sverige) och Renault (Frankrike) som inleddes 1992 undersöktes 1000 slumpmässigt utvalda anställda män från vardera land i åldern 45–50 år med frågeformulär och en stor hälsoundersökning inklusive omfattande laboratorieprover och Elektrokardiogram (EKG). Kända riskfaktorer klassificerades bl.a. enligt Framinghams riskindex (FRI) som är ett sammanvägt riksmått grundad på traditionella riskfaktorer såsom blodtryck, kolesterol, rökning, övervikt mm. Vid en uppföljning 1998 noterades alltför få personer med hjärt-kärlsjukdom eller död för att kunna genomföra en meningsfull statistisk analys avseende riskfaktorernas betydelse. Samarbetet mellan Volvo och Renault har sedan dess upphört Vi har emellertid tillgång till den svenska gruppens data.

Syfte & Medicinsk relevans: Hjärt-kärlsjukdom var 1993 den ledande dödsorsaken i världen totalt såväl som i Sverige. Vår arbetsfrågeställning var; vilken prognostisk betydelse har en EKG avvikelse för att drabbas av hjärtinfarkt och död inom 25 år? Hur förhåller sig denna skattade risk till risken som vi uppskattat enbart med hjälp av FRI?

Vetenskaplig frågeställning: Det finns betydande stöd i litteraturen för att vissa specifika EKG avvikelser från det normala är associerade med högre risk för att drabbas av plötslig död och hjärtinfarkt. I en longitudinell studie av friska medelålders arbetsföra män har vi nu haft möjlighet att studera associationen mellan en EKG avvikelse observerad i ett EKG tagit i vila och hjärtinfarkt eller död inom 25 år. Vi har även möjlighet att studera hur mycket information som en EKG avvikelse tillför till riskskattningen som kan skattas med hjälp av FRI.

Metod: År 1993 insamlades data med hjälp av frågeformulär, Lab-prover och en hälsoundersökning inklusive ett vilo-EKG. Risken för hjärnkärl-sjukdom uppskattades med hjälp av FRI, man samlade även in information om andra kända riskfaktorer som inte ingår i FRI. År 1998 vid en första uppföljning togs ytterligare ett vilo-EKG på alla deltagare. Alla EKG

klassificerades med hjälp av Minnesota EKG kod (The Minnesota Code Classification System for Electrocardiographic Findings). Data gällande dödfall samlades in från Socialstyrelsens dödsorsaksregister och data gällande hjärtinfarkter samlades in från hjärtinfarktregistret (Swedeheart).

Resultat och Analys: Sjuttionio av de 977 deltagarna i studien hade minst en EKG-avvikelse 1993, 1998 eller vid båda tillfällena, 790 hade två normala EKG, 108 hade ett normalt EKG men missade en av undersökningarna. Data från dödsorsaksregistret visade att 157 av deltagarna hade avlidit under uppföljningsperioden, 25 år. Data från hjärtinfarktregistret visade att 100 personer drabbats av sin, så vitt känt, första hjärtinfarkt. Risken att drabbas av en hjärtinfarkt givet minst en EKG-avvikelse är tre gånger så stor som risken utan sådan.

Inga signifikanta skillnader ses mellan gruppen med en eller flera EKG-avvikelser och gruppen med två normala EKG avseende död, däremot observerar man att i gruppen med en missad EKG undersökning är risken för död grovt sett dubblerad (Oddsquot =2.35, P-value=0.001). Vår studie konfirmerar det andra studier visat att EKG avvikelser verkar ha en prognostisk betydelse för risken att få en hjärtinfarkt men fler och större studier krävs för att förstå hur stor riskökningen är och hur den ska användas kliniskt. I vår studie på arbetande medelålders män är risken större än vad andra studier visat och oberoende av andra kända traditionella riskfaktorer som högt blodtryck, övervikt och höga blodfetter. Då ingen behandling av orsakerna till flertalet EKG avvikelser finns, är det av största vikt att förbättra livsstil och behandla kända traditionella riskfaktorer för att i denna grupp förebygga hjärtinfarkt.

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Appendix 1

Framingham risk index was calculated in steps according to Andersson (1991). The formulae used were:

$$\begin{aligned}A &= 11.11220.9119 * \text{LOG}(A169)^{0.2767} * A4^{0.7181} - \text{LOG}(A175/A176) * 0.5865 * \\ &\text{POLVH} \\ M &= A1.4792 * \text{LOG}(A4)^{0.1759} * A84; \\ MU &= 4.4181 + M; \\ \text{SIGMA} &= \text{EXP}(0.3155 + 0.2784 * M); \\ U &= (\text{LOG}(10) * MU) / \text{SIGMA}; \\ \text{RISKINDEX} &= 1 + \text{EXP}(\text{EXP}(U));\end{aligned}$$

Where:

A169 = systolic blood pressure

A40 = smoking

A175 = total cholesterol

A176 = HDL cholesterol

POLVH = possible left ventricular hypertrophy

A4 = age

A84 = reported diabetes

(natural logarithms)