Charles University in Prague, 1^{st} Faculty of Medicine

Cardiovascular Disease Risk Estimations Based on Data from Epidemiological Studies

Ph.D. Thesis

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Contents

Preface

The thesis *Cardiovascular disease risk estimations based on data from epidemiological studies* summarizes what has been published on estimations of a cardiovascular risk, and explores the validity of cardiovascular risk estimations in the Czech population. The text of the thesis is mainly comprised of the published papers in which I participated. These publications are listed in Appendix B and cited in References. Abbreviations and acronyms used in the thesis are summarized in Appendix A.

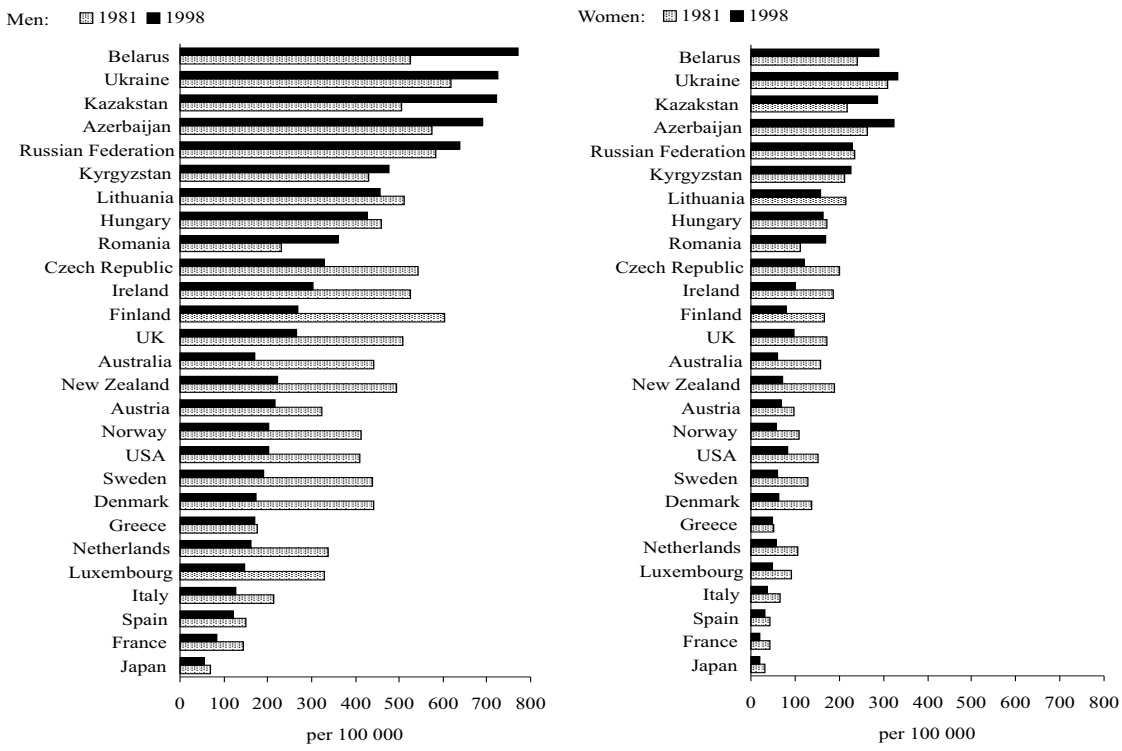
The thesis has six chapters. In *Introduction* I briefly explain causes and possible prevention strategies of cardiovascular diseases. The most frequent used statistical models that estimate an individual's cardiovascular risk are introduced here too. The second chapter specifies *Aims of the thesis*. A design of the longitudinal primary prevention study of atherosclerotic risk factors (STULONG) is demonstrated in *Material and methods*. In addition to that, used statistical methods for data analysis are described here. The chapter *Results* includes main results of validation studies, which have been realized within the STULONG study. In *Discussion* the results are compared with other validation studies. Finally, *Conclusions* are set out.

I acknowledge that the thesis could not have been written without help and support my supervisor Prof. RNDr. Jana Zvárová, DrSc., who I thank for that. I also thank to Prof. MUDr. František Boudík, DrSc. and MUDr. Marie Tomečková, CSc., with whom I collaborated on the publications cited here. Finally, I thank for the support to institutional research plan AV0Z103000504 of the Institute of Computer Science the Academy of Sciences of the Czech Republic, the project 1ET200300413 of Academy Science of the Czech Republic, and the grant LN00B107 of the Ministry of Education of the Czech Republic.

RNDr. Jindra Reissigová

1 Introduction

Diseases of the heart and the circulatory system, so-called cardiovascular diseases (CVD), are the main cause of death in Europe: accounting for over 4 million deaths each year [19]. The main cause of CVD is a disease of arteries, called atherosclerosis, in which plaque (a fatty substance) is deposited on the inside of the artery walls. Atherosclerosis is a disease starting in childhood. As a person getting older, atherosclerosis is likely to worsen. Depositing plague gradually causes narrowing the arteries. This narrowing prevents the blood from flowing properly through the arteries.



[1] Standardized using the European standard population

[2] CHD coded as 410–414 of ICD-8 and ICD-9, as I20–I25 of ICD-10, ICD International Classification of Diseases (8th, 9th and 10th Revisions)

[3] For the Czech Republic 1986 instead of 1981

Data source: [19]

Figure 1: Age-directly standardized[1] mortality from coronary heart disease[2](CHD), for adults aged 35-74 years, 1981[3], 1998

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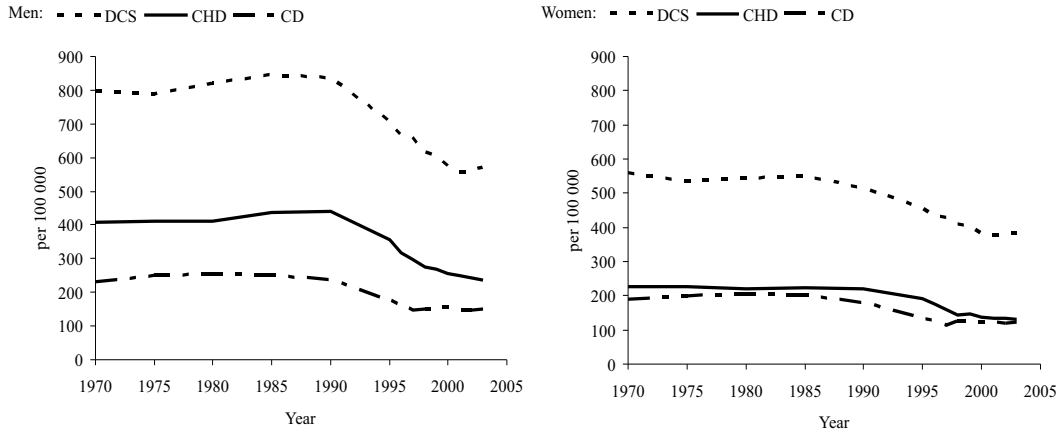
Coronary arteries are special blood vessels that supply the heart with necessary oxygen

and nutrients. If they are being narrowed, the heart does not function properly without enough oxygen and nutrients. The result is coronary heart disease (CHD), also known as ischemic heart disease or coronary artery disease. As the flow of blood to the heart can slow, it can result in e.g. chest pain (stable angina) or shortness of breath. If the flow of blood to the heart stops, the result is heart attack. If the blood flow to the heart is not quickly restored, a part of the heart will die and cause permanent disability or death of a person. Similarly, stroke (cerebrovascular disease) occurs when a part of the brain stops working because of problems with the blood supply.



[1] Standardized using the European standard population

[2] DCS codes 390–459 of ICD-8 and ICD-9, I00–I99 of ICD-10, ICD International Classification of Diseases (8th, 9th and 10th Revisions)

[3] CHD codes 410–414 of ICD-8 and ICD-9, I20–I25 of ICD-10

[4] CD codes 430–438 of ICD-8 and ICD-9, I60–I69 of ICD-10

Data source: [15]

Figure 2: Age-standardized[1] mortality from diseases of the circulatory system[2] (DCS), coronary heart diseases[3] (CHD) and cerebrovascular diseases[4] (CD) in the Czech Republic, 1970, 1975, 1980, 1985, 1990, 1995–2003

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CHD belongs to the most frequent forms of CVD [19]. In the Czech Republic, age-directly standardized mortality (computed per 100 000 European standard population) from CHD decreased from 543 in 1986 to 328 in 1998 in men aged 35–74 years and from 202 to 120 in women. Figure 1 shows the specific-country mortality from CHD in 1981 (1986 for the Czech Republic) and 1998. Despite the fact that an essential decrease was registered in CHD mortality in a majority of the countries, CHD belongs to the main causes of death. In the Czech Republic, the most frequent cause of death in 2003 was chronic coronary heart disease

(I25 - code of diagnosis in ICD-10) both in men (5 913 cases) and women (7 008 cases) [15]. Figure 2 shows the development of CHD mortality in the Czech Republic in comparison with mortality from diseases of circulatory system and cerebrovascular diseases.

Table 1: Risk factors of coronary heart disease (CHD)

Major risk factors	Cigarette smoking
	Elevated blood pressure
	Elevated serum total (and LDL[1]) cholesterol
	Low serum HDL[2] cholesterol
	Diabetes mellitus
	Advancing age
Predisposing risk factors	Obesity[3]
	Abdominal obesity[4]
	Physical inactivity
	Family history of premature CHD
	Ethnic characteristic
	Psychosocial factors
Conditional risk factors	Elevated serum triglycerides
	Small LDL particles
	Elevated serum homocysteine
	Elevated serum lipoprotein(a)
	Prothrombotic factors (e.g. fibrinogen)
	Inflammatory markers (e.g. C-reactive protein)

[1] Low-density lipoprotein
[2] High-density lipoprotein
[3] Obesity defined as Body Mass Index (weight[kg]/height[m]^2) > 30.0 kg/m^2
[4] Abdominal obesity defined as waist circumference >102 cm for men,and >88 cm for women
Source: [20]

Risk factors of CHD are summarized in Table 1 [20]. A lot of guidelines for prevention of CVD have been published by different organizations, for instance by the European Society of Cardiology [16]. A successful cardiovascular preventive programme should result in a decrease of cardiovascular incidence, and consequently, mortality. The two aims should be targeted:

1. to popularize health life style in population, and
2. to identify persons with cardiovascular risk factors already present and to intervene their risk factors. The modifiable risk factors can be controlled by changing lifestyle or by pharmacotheraphy.

The question is how to find high-risk cardiovascular persons to be targeted by a preventive programme. Epidemiologists, statisticians and other health workers have been working

on statistical models which produce an absolute risk estimation of developing CVD. The absolute risk is the probability of developing CVD event within a given time period; the ratio of absolute risks in two different groups of people is called the relative risk. These statistical models are increasingly used to identify a population at high risk.

1.1 Studies of cardiovascular risk estimations

Well-known statistical models are those derived in the Framingham heart study (FHS). While this study is based on a population of the United States, other studies estimate the absolute CHD risk for European populations. Some of these studies are described bellow. Risk calculators are available e.g. in web pages *http://www.scopri.ch/* of Commitment to Evidence for Primary Care, and in web pages cited in the text later.

Framingham heart study

As written in *http://www.nhlbi.nih.gov/about/framingham/design.htm*, FHS is the prospective cohort study started in 1948 and continuing up to this day. The original objective of FHS was to identify the risk factors of CVD developing. The original study cohort consisted of 5 209 respondents of a random sample of 2/3 of adults at the age of 30 to 62 years resisting in Framingham (Massachusetts, USA) in 1948. The offspring study was started in 1971 with the aim to assess cardiovascular risk factors in young adults. A sample of 5 135 men and women, consisting of the offspring of the original cohort and their spouses, was established. A third generation (the children of the Offspring Cohort) is currently being established with the aim to further analyse how genetic factors are associated with cardiovascular diseases.

Nowadays the Framingham statistical models derived in the 90th years of the 20th century and at the beginning of the 21st century are mainly used for the CHD risk estimations. The risk functions were derived from data on gender-age specific populations and estimate the absolute risk of CHD within different long periods, Table 2. For instance, the Framingham risk functions (1991) estimates the risk of CHD or fatal CHD, respectively, within the period from 4 to 12 years, and the Framingham risk function (1998) estimates the 10-year absolute CHD risk. The estimations of the CHD risk are based on values of the explanatory variables marked with + in Table 2. For more information see the publications cited in the heading

Table 2: Coronary heart disease risk estimations based on the Framingham heart study (FHS)

Study (year) [citation]	FHS (1991) [2]	FHS (1991) [3]	FHS (1998) [47]	FHS (2000) [13]	FHS (2000) [13]
POPULATION	General USA (Framingham)	General USA (Framingham)	General USA (Framingham)	General USA (Framingham)	General USA (Framingham)
Baseline examination	1968–1975	1968–1975	1971–1974	1968–1987	1971–1974
Gender (sample size)	Men(2 590) Women(2 983)	Men(2 590) Women(2 983)	Men(2 489) Women(2 856)	Men(4 823) Women(5 333)	Men(2 439) Women(2 812)
Age [yrs]	30–74	30–74	30–74	35–74	30–74
RISK FUNCTION					
Failure of interest[1]	CHD	Fatal CHD	CHD	CHD	Hard CHD
Time until failure [yrs]	4–12	4–12	10	1–4	5, 10
Statistical method[2]	Weibull non-proportional hazards regression	Weibull non-proportional hazards regression	Cox proportional hazards regression	Weibull non-proportional hazards regression	Cox proportional hazards regression
Explanatory variables[3]					
Gender	+	+	+	+	+
Age	+	+	+	+	+
Menopause				+ (for women)	
BP			+		+
SBP/DBP	+	+		+ (SBD)	
Antihypertensive theraphy				+	
Cigarette smoking	+	+	+	+	+
Total cholesterol	+	+	+	+	+
HDL-cholesterol	+	+	+	+	+
LDL-cholesterol			(+)		
Triglycerides				(+) (for women)	
Diabetes mellitus	+	+	+	+	+
Left ventricular hypertrophy	+	+			
Alcohol				+ (for women)	

Abbreviations: Appendix A (page 52)

[1] CHD involves angina pectoris, coronary insufficiency, myocardial infarction, and fatal CHD, Fatal CHD involves coronary death, Hard CHD involves fatal CHD and non-fatal myocardial infarction

[2] See Table 4

[3] The explanatory variables marked with + were used for modelling the risk, (+) explained in the text

of the table. By the way, the models with total-cholesterol and without LDL-cholesterol and vice versa were derived in FHS (1998), and the model with and without triglycerides derived for women in FHS (2000) (these variables are marked with (+) in Table 2).

A lot of risk tables and charts based on the Framingham risk functions have been devel-

Table 3: Coronary heart disease (CHD) risk estimations based on other studies than the Framingham heart study

Study (year) [citation]	Copenhagen (2001) [43]	PROCAM–Score (2002) [4]	PROCAM–Algorithm (2002) [34]	SCORE (2003) [8]
POPULATION	General	Emoloyees	Emoloyees	General, partly employees
	Denmark	German (Münster and Northern Ruhr Area)	German (Münster and Northern Ruhr Area)	12 European studies
Baseline examination[1]	Follow-up period 1977–1993	Before the end of 1985 (Recruiment 1979–1991)	Recruiment 1979–1991	Recruiment 1967–1991
Gender (sample size)	Men(5 797)	Men(5 389)	Men(4 818)	Men (117 098)
	Women(5 968)		Women(2 810)	Women (88 080)
Age [yrs]	22–93	35–65	35–65 (Men) 45–65 (Women)	45–64
RISK FUNCTION				
Failure of interest[2]	MI	ACE	ACE	Fatal CVD
				Fatal CHD
				Fatal non-coronary CVD
Time until failure [yrs]	10	10	10	10
Statistical method[3]	Cox proportional hazards regression	Cox proportional hazards regression	Cox proportional hazards regression	Weibull proportional hazards regression
Explanatory variables[4]				
Gender	+	+	+	+
Age	+	+	+	+
SBP	+	+	+	+
Antihypertensive theraphy				
Cigarette smoking	+	+	+	+
Total cholesterol	+			+
HDL-cholesterol	+	+	+	(+)
LDL-cholesterol		+	+	
Triglycerides		+	+	
Diabetes mellitus	+	+	+	
Body mass index	+			
Personal history of MI	+			
Family history of MI	+	+	+	

Abbreviations: Appendix A (page 52)

[1] Not exactly stated in the reference, the follow-up period or the recruiment into the study is presented

[2] ACE includes fatal and non-fatal MI and sudden cardiac death, Fatal CVD includes cardiovascular death defined as ICD-9 codes 401-414, 426-443 (with the exception of the following ICD9-codes for definitely non-atherosclerotic causes of death: 426.7, 429.0, 430.0, 432.1, 437.3, 437.4 and 437.5), 798.1 (instantaneous death) and 798.2 (death within 24h of symptom onset), Fatal CHD includes coronary death, Fatal non-coronary CVD includes fatal non-coronary cardiovascular death

[3] See Table 4

[4] The explanatory varaibles marked with + were used for modelling the risk, (+) explained in the text

oped, and are summarized e.g. in the publication [26]. There were also derived Framingham risk functions which estimate an individual's absolute risk of developing e.g. myocardial infarction, stroke or CVD [3]. Models for individuals with a history of CVD, who have survived the acute period after the event, have been also developing [12]. Sheridan et al. [40] examined the features of available Framingham-based risk calculation tools and review their accuracy and feasibility in clinical practice.

Danish population study

Two Danish population studies, the Glostrup population studies and the Copenhagen city heart study, were originally aimed at a cardiovascular survey. As written in the publication [43], the Glostrup population studies were started in 1964, and included several randomly sampled age fixed cohorts examined within the same well-defined suburban area at different time. The Copenhagen city heart study from the center of Copenhagen contained single cohort of a random sample of persons over 20 years of age, examined between 1976–1978. The pooled cohorts included 24 508 persons.

The data of these studies were used to derive a Copenhagen risk score for fatal and non-fatal myocardial infarction (MI) and a model for calculating the effect of intervention. The follow-up period was from 1977 to 1993. The prevention of cardiovascular diseases (PRECARD) computer program calculating the Copenhagen risk score and the effects of risk factor changes on total risk was developed. For more detail information on which the Copenhagen risk score and PRECARD are based see Table 3.

Prospective cardiovascular Münster heart study

The Prospective cardiovascular Münster heart (PROCAM) study (also known as the Münster heart study) was focused on cardiovascular risk profile, cardiovascular event including myocardial infarction and stroke, and mortality among working people. Recruitment was started in 1979 and completed in 1991, during which about 25 000 volunteers (approximately one third women, two third men) aged 16–65 years were enrolled from the blue- and white-collar employees of 52 companies and local government authorities in Münster and the Northern Ruhr Area [10].

Data on 5 389 men was used to estimate the absolute 10-year risk of acute coronary event defined as sudden cardiac death and fatal and nonfatal myocardial infarction [4]. The estimation is based on measurements of the nine explanatory variables, Table 3. Besides this so-called the PROCAM-Score, the PROCAM-Algorithm was also derived on base of data on 4 818 men aged 35–65 years and 2 810 women aged 45–65 years [34]. The PROCAM-Algorithm estimates the absolute 10-year risk of acute coronary event and, in addition, calculates the effects of treatment on coronary risk. The PROCAM-Algorithm also avoids the distorsion that may occur when risk is estimated in persons with risk factors lying at the border between two risk factor categories. Due to the small total number of myocardial infarction in women in the 10-year period, the PROCAM-Algorithm for women should be applied with caution. Excluding a Cox regression, neural networks were also used to estimate the risk of coronary events [45]. For more information see *http://www.chd-taskforce.de/*.

European SCORE project

The SCORE project was initiated to develop a risk scoring system based on data from European population [8]. The project pooled datasets from 12 European studies (namely, studies from Finland, Russia, Norway, two studies from UK, Denmark, Sweden, Belgium, Germany, Italy, France and Spain). Three of the studies included only men. The majority of the studies were population-based cohort studies, but occupational studies were also included. Totaly, there were 205 178 persons recruited into the studies from 1967 to 1991, Table 3. Subjects were excluded from the development of the risk estimation if they had a previous history of heart attack. Besides the age, the risk estimation is based on measurements of other three variables (total cholesterol, systolic blood pressure, cigarette smoking). The model based on total cholesterol/HDL cholesterol ratio instead of total cholesterol was also developed (marked with (+) in Table 2). Separate estimation risks were also calculated for fatal CHD and for fatal non-coronary CVD. These were calculated for high-risk and low-risk regions of Europe.

As stated in *http://www.escardio.org/HeartScore/*, HeartScore is a electronic counterpart to the SCORE risk chart. It operates with the same explanatory variables and end-points, in addition to, the expected effect of intervention is calculated.

1.2 Regression models estimating cardiovascular risk

As you can see in Tables 2 and 3, Weibull and Cox regression models have been mainly used for risk estimations [1], [31]. In Table 4, there are equations how the risk of an outcome event is estimated according to these models. The Weibull proportional hazards regression model (parametric model), the non-proportional hazard Weibull accelerated failure time model (parametric model) and the Cox proportional hazards regression model (semiparametric model) were used to estimate the risk within the specific periods. The risk of a failure within a time interval t (e.g. 10 years), computed under assumption that the individual has survived up (free of the failure) to the beginning the time interval, is called the hazard.

Table 4: Risk estimation by regression models

Models	Risk estimation[1]
Weibull proportional hazards regression model	$1 - exp(-(\sum_{i=1}^{k} \beta_i x_i t)^{\alpha})$
Nonproportional hazards Weibull accelerated failure time regression model	$1 - exp(-exp(\frac{\ln(t) - \sum_{i=1}^{k} \beta_i x_i}{\sigma}))$
Cox proportional hazards regression model	$1 - S_0(t)^{exp(\sum_{i=1}^{k} \beta_i x_i - \sum_{i=1}^{k} \beta_i \overline{x}_i)}$

[1] t denotes the time until the event of interest (e.g. 10 years until CHD event); α, β_i and σ represent estimated parameters, $S_0(t)$ is the average survival at time t - for their values see the publications cited in Tables 2–3; x_i represents the explanatory variable of an individual (e.g. x_1 might be age in years)

The Cox and Weibull proportional hazards regressions assume that the hazards are proportional. It means that the hazard of a disease at time t changes proportionately with the explanatory variables and the proportionality constant is the same for all t. In other words, the two equally-aged individuals with different levels of explanatory variables will have different hazards for developing a disease. These probabilities may increase with age, but the hazard ratio between their sets of the explanatory variables is constant over time. The non-proportional hazards Weibull accelerated failure time model is without the assumption of proportional hazards. In the case of the Weibull regression, the failure time is assumed to follow the Weibull distribution. While in the Cox regression, no specific assumptions are made about the distribution.

2 Aims of the thesis

Although statistical models are developed for specific sub-populations, there are also applied in other populations, i.e. in people in other settings and at other times. Generalization of the statistical models to external populations should be done cautiously. The aim of epidemiological studies is to evaluate the validity of CVD risk estimations in other populations than that they were derived from. None of validation studies has been done in the Czech Republic yet. The aim of this work is

- to analyse cardiovascular risk factors in the Czech Republic, and above all
- to validate predictive models based on both Framingham and European populations in the Czech Republic.

On fulfilling these aims we ran up against a problem not having enough information on cardiovascular risk factors in the Czech Republic, and consecutively, the occurrence of CVD. Validation studies are pursued within cohort (longitudinal) studies, and we had at the disposal only one longitudinal study conducted in the Czech Republic. This study, described in Materials and methods, surveyed main cardiovascular risk factors and the occurrence of CVD in middle-aged men from Prague. Based on the data from this study we were able to validate the following risk functions (Tables 2–3):

- the Framingham CHD risk function (1991) [2],
- the Framingham CHD risk function (1998) [47],
- the SCORE fatal CVD risk function (2003) [8].

3 Material and methods

3.1 Design of the STULONG study

The longitudinal primary prevention study of atherosclerotic risk factors, so-called the STULONG study, was conducted by 2nd Dep. of Internal Medicine, 1st Faculty of Medicine and General Faculty Hospital, Charles University in Prague 2 in 1975–1999 (project leader František Boudík, project coordinator Marie Tomečková). Originally, STULONG was a part of a national wide study "National primary preventive multifactorial study of myocardial infarction and stroke" in former Czechoslovakia (in the study more than 10 000 subjects should be included) [27].

The design of the STULONG study we have described e.g. in publications [6], [37]. In 1975 total 2370 men aged 38–49 living in the 2nd district in the centre of Prague (Prague 2) were randomly selected from the electoral register. It was the 50 % sample of men of that age who were living in Prague 2 in 1975. Of 2370 invited men, 1417 (59.8 %) men answered the invitation and underwent entry examination in 1975–1979. *The entry questionnaire* included questions on demographic and personal data (marital status, education, working physical activity, leisure physical activity, smoking, alcohol drinking, coffee drinking, tee drinking, personal and family history, chest pain, lower limbs pain, breathlesness) and results of physical (height, weight, systolic blood pressure (BP), diastolic BP, skinfolds), laboratory (cholesterol level, triglyceridy, uric acid) and ECG (electrocardiography) measurements.

Definition of the groups: Each man was classified into one of three groups (normal, risk, pathological) according to health status and occurrence of the risk factors of atherosclerosis at the entry into the study; definition of risk factors is corresponding to the period of the beginning of the study (Table 5). The design of the STULONG study is pictured in Figure 3.

Normal Group (NG) included men without any risk factors of atherosclerosis mentioned in Table 5, without CVD, without diabetes mellitus, without other serious disease not enabling long term follow-up and without pathological finding on ECG curve at the entry into the study. NG was randomly divided into two groups: normal group regularly examined (NGE, $n = 40$) and normal group unexamined regularly (NGN, $n = 236$). NGE was yearly

Table 5: Risk factors of atherosclerosis at the entry into STULONG in 1975–1979

Positive family history	Mother or father died from cardiac infarction, stroke or suddenly (excluding accident) at the age $\leq$ 65 years
Obesity	Brocca index (BI)$\geq$115 %, where BI=weight[kg]/(height[m] $-$ 100) $\cdot$ 100 %
Cigarette smoking	Number of cigarettes a day $\geq$15, or ex-smoker less than one year who smoked $\geq$15 cigarettes a day before
Hypertension	Blood pressure $\geq$160 and/or 95 mm Hg in 2 of 3 measurements (2 measurements at the entry into the study, 3rd measurement within 190 days from the entry), or hypertension in anamnesis
Hypercholesterolaemia	Total cholesterol $\geq$260mg/100ml (6.7 mmol/l)

examined by specialists from 2nd Department of Internal Medicine. If the risk factors of atherosclerosis (obesity, smoking, hypertension, hyperlipaemia) were detected specialists initiated pharmacological and non pharmacological (feeding habits, physical activity, smoking etc.) intervention of the risk factors of atherosclerosis. NGE was examined by specialists from 2nd Dep. of Internal Medicine once in 8th–13th year from the entry into the study.

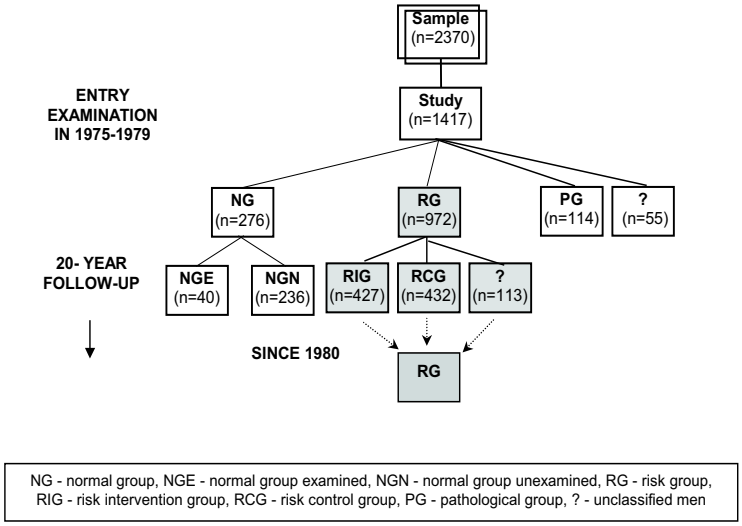

Figure 3: Design of the longitudinal primary prevention study of atherosclerotic risk factors (STULONG)

Risk group (RG) included men with at least one of the risk factors of atherosclerosis (Table 5), without CVD, without diabetes mellitus and without other serious disease not enabling long term follow-up and without pathological finding on ECG curve at the entry

into the study. RG was randomised into two subgroups: risk intervention group (RIG, $n = 427$) and risk control group (RCG, $n = 432$). Pharmacological and non-pharmacological intervention of the risk factors of atherosclerosis in RIG was performed by specialists from 2nd Dep. of Internal Medicine, RCG was under health care of general practitioners. Since early eighties of the last century, the groups RIG and RCG had been merging, mainly for ethic reasons [37].

Pathological group (PG) included men with CVD, with diabetes mellitus or with other serious disease not enabling long term follow-up or with pathological finding on ECG curve at the entry into the study.

Evaluation of risk factors: During the follow-up, control questionnaires were fulfilled by specialists from 2nd Dep. of Internal Medicine. *The control questionnaire* was consistent with the entry questionnaire except a question on family history excluded in the control questionnaire, and a question on feeding habits extra included in the control questionnaire.

Blood pressure was measured by a mercury sphygmomanometer. Total cholesterol (T-cholesterol) and HDL-cholesterol were measured by the so-called Liebermann-Burchard chemical method in 1975–1989 and enzymatically using the cholesterolesterase-cholesteroloxidase assay in 1990–1999. Diabetes mellitus was classified as present if a man was under a pharmacological treatment.

End-points: During the 20-year follow-up period the first occurrence of atherosclerotic CVD was recorded. Atherosclerotic CVD were coded as D410–D414, D427, D430–D438, D440–D444 according to ICD-8 (1975–1978), 410–414, 426–428, 431–438, 440–443 according to ICD–9 (1979–1993), and I20–I25, I44–I50, I60–I67, I69, I70 according to ICD-10 (1994–1999). CHD included ICD–8 codes D410–D414, ICD– codes 410–414, and ICD-10 codes I20–I25.

In 1999–2001, information on survival of men withdrawing or dropping out the study was ascertained (sources: outpatient departments, postal questionnaire). For deceased, date and cause of death were identified (sources: registry offices, Institute of Health Information and Statistics of the Czech Republic, relatives).

3.2 Validation studies within the STULONG study

Each man of the STULONG study who met the following criteria was included in the validation study of the Framingham risk functions (1991, 1998) [2], [47]:

- Classified into NG or RG at the entry into the study.
- Free of CHD at a control examination, and having information about the variables (Table 2) needed for the estimation risk . If more such control examinations were available, the first control examination, which met these conditions, was taken as a baseline.

We calculated individuals' 10-year absolute risk of CHD by the Framingham risk functions (1991, 1998) on basis of their control examinations instead of their entry examination, because the level of HDL-cholesterol wasn't measured at the entry. The Framingham risk model (1991) requires information on the occurrence of left ventricular hypertrophy to estimate the 10-year absolute CHD risk. However, left ventricular hypertrophy was not surveyed at control examinations. Due to the fact that none of men from NG and RG suffered from left ventricular hypertrophy at the entry examinations, the risk was estimated on the assumption that left ventricular hypertrophy was not present at the control examinations.

Each man of the STULONG study who met the following criteria was included in the validation study of the SCORE risk function (2003) [8]:

- Classified into NG or RG at the entry into the study.
- At the entry into the study, having all information about the variables (Table 3) needed for the estimation of the risk of fatal CVD. Note that HDL-cholesterol is not required for the 10-year absolute fatal CVD risk estimation by this function.

3.3 Statistical methods

A Web-based calculator for ROC curves [12], STATISTICA (StatSoft 1995), Egret (Cytel Software Corporation 1999) and R (Development Core Team 2003) software were used for

statistical analysis of data. An attained level of significance $p<0.05$ was considered as a statistical significant; p-value for a two-tailed hypothesis test.

Association methods:

The Cox proportional hazards regression was used to determine baseline explanatory variables related to survival free of fatal atherosclerotic CVD. An important assumption of the Cox model is that hazards are proportional. This assumption was graphically assessed (the plot of log(time) versus the scaled Schoenfeld residuals), and statistically tested (the Pearson and Spearman correlation coefficients between log(time) and the scaled Schoenfeld residuals, and the test of significance of the interaction between log(time) and each explanatory variables).

The Kaplan-Meier method was used to estimate the survival free of fatal atherosclerotic CVD. The log rank test was applied to compare survival functions of groups defined according to the number of present risk factors at the entry. The analysis of variance (ANOVA) test was used to compare mean age in the groups defined according to the number of present risk factors at the baseline.

Validation methods:

Overall goodness of fit evaluated by tests of calibration and discrimination measures the degree of the accuracy of the prediction of a model.

Calibration of a model (also known as reliability of a model) describes the degree of correspondence between the observed number of the outcome variable and that estimated by the statistical model. The calibration was measured with the Hosmer-Lemeshow (H-S) goodness of fit test (besides H-S goodness of fit test, other goodness of fit tests have been developed [25]). For each man the risk was estimated by the risk function. Afterwards men were grouped together in quintiles of risk (rather than into deciles because of the relatively small number of the observed outcome events). It means that each of the group contained approximately 20 % of the total number of subjects. In each quintile, the number of CHD events was estimated by the sum of the individual's absolute risks. Then the estimated and

observed numbers of CHD events across quintiles were compared by the Hosmer-Lemeshow goodness of fit test [24]

$$\chi^2_{HL} = \sum_{i=1}^{k} \frac{(o_i - n_i\widehat{p}_i)^2}{n_i\widehat{p}_i},$$

where n_i is the total frequency of subjects in the ith group, o_i is the total frequency of observed outcome events in the ith group, and $\widehat{p}_i$ is the average estimated risk (probability) of an outcome event in the ith group. Under the null hypothesis that the fitted model is correct, when $n = \sum_{i=1}^{k} n_i$ is large and the expected counts ($n_i\widehat{p}_i$) in each group are $\geq$5, the Hosmer-Lemeshow statistics with k groups has approximately chi-square distribution with $k-2$ degrees of freedom (χ^2_{k-2}). The value of $\chi^2_{HL} \geq \chi^2_{k-2}(\alpha)$ indicates a lack of fit of the model; the value of α is the desired level of significance. A version of the Hosmer-Lemeshow statistics for survival data was also applied in our statistical analysis of data [14]. Trend in the occurrence of CHD and fatal CVD, respectively, across quintiles of the estimated risk was analysed by a chi-square test for trend, and by a Poisson regression model.

If the lack of fit model is detected, the model can be *recalibrated*, i.e. adjusted for prevalence of risk factors and underlying rates of outcome in the external population. In the STULONG study, the Framingham risk function (1998) was recalibrated for mean age, prevalence of risk factors and survival rate according to the methods described in publication by D'Agostino et al. [13]. Note that recalibration does not influence discrimination.

Discrimination of a model expresses the ability of model to distinguish observations with a positive and a negative outcome. Discrimination was evaluated by a co-called Receiver Operating Characteristics (ROC) curve. The ROC curve plots sensitivity of the model (the proportion of individuals with disease in whom the model indicates disease present) against specificity (the proportion of individuals without disease in whom the model indicates disease absent) over all the possible values of the absolute risk estimated by the model. Area under ROC shows how well the model distinguishes between possible outcomes. Its values vary between 0.0 and 1.0. If the area under ROC is equal to 1.0 the model can perfectly distinguish between possible outcomes. The model is no better than chance if the area of 0.5.

The area under the ROC curve was estimated by the Wilcoxon statistic W [22]. The Wilcoxon statistic measures the probability θ that randomly chosen subjects with disease-present and with disease-absent will be correctly ranked. Let's denote n_i^P and n_i^A, respectively, the number of subjects with disease-present and with disease-absent in ith group, $i = 1 \dots k$ (the groups e.g. defined on the basis of the quintiles of the risk), and $n^P = \sum_{i=1}^{k} n_i^P$, $n^B = \sum_{i=1}^{k} n_i^A$. Then

$$W = \widehat{\theta} = \frac{1}{n^A n^P} \sum_{i=1}^{k} (n_i^A \sum_{j=i+1}^{k} n_j^P + \frac{1}{2} n_i^A n_i^P),$$

where $\sum_{j=i+1}^{k} n_j^P = 0$ for $j > k$. The standard error of W is

$$\mathrm{SE}(W) = \sqrt{\frac{W(1-W)+(n^P-1)(Q_1-W^2)+(n^A-1)(Q_2-W^2)}{n^A n^P}},$$

where

$$Q_1 = \frac{\sum_{i=1}^{k} n_i^A [(\sum_{j=i+1}^{k} n_j^P)^2 + (\sum_{j=i+1}^{k} n_j^P) n_i^P + \frac{1}{3}(n_i^P)^2]}{n^A (n^P)^2},$$

and $n_j^P = 0$ for $j > i$.

$$Q_2 = \frac{\sum_{i=1}^{k} n_i^P [(\sum_{j=1}^{i} n_j^A)^2 + (\sum_{j=1}^{i} n_j^A) n_i^A + \frac{1}{3}(n_i^A)^2]}{(n^A)^2 n^P},$$

and $n_j^A = 0$ for $j = i$.

The web-based calculator for ROC curves [17] was used to generate ROC curves with 95% confidence intervals. Besides the Wilcoxon statistic, the area under the ROC curve was also estimated by a method for survival data [33].

When validating the Framingham risk function (1998), the regression coefficients of this function was also estimated using the data from the STULONG study. Afterward *the estimations of the regression coefficients were compared* between the Framingham and STULONG models by the test statistic z [13]

$$z = \frac{b(F)-b(S)}{\sqrt{\mathrm{SE}(F)^2+\mathrm{SE}(S)^2}},$$

where $b(F)$ and $b(S)$ are, respectively, the regression coefficient estimations of the Framingham and STULONG models, and the denominator is the standard error of the difference in the coefficients (SE(F) and SE(S) are, respectively, the standard errors of the regression coefficients in the Framingham and STULONG studies). If $\mid z \mid > z(\alpha)$, where $z(\alpha)$ is critical value for standard normal distribution, we reject the null hypothesis about the equality of the two compared regressions coefficients $b(F)$ and $b(S)$.

Finally, homogeneity of risk factors' distribution between the STULONG and FHS studies was tested by the Pearson chi-square test, and the test on standardized residuals. The Student t-test was used to compare mean age between the STULONG and FHS studies.

4 Results

4.1 Cardiovascular risk factors in the Czech Republic

Prevalence of the atherosclerosis risk factors (defined in Table 5) at the entry into the study in 1975–1979 is pictured in Figure 4. Table 6 shows prevalence of the atherosclerosis risk factors stratified by the groups. According to the definition, men from NG were without the atherosclerosis risk factors.

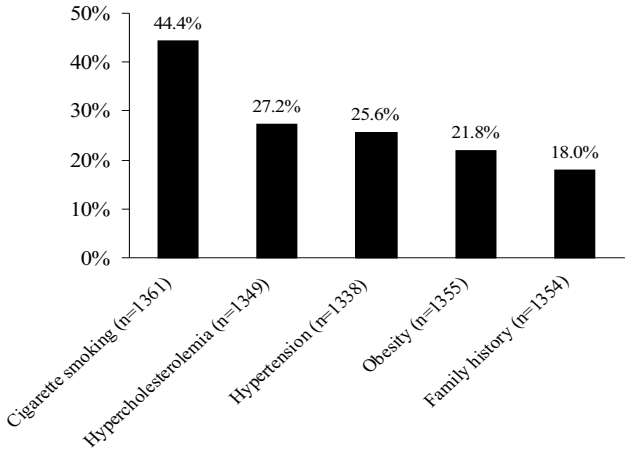

Figure 4: Prevalence of atherosclerosis risk factors at the entry into the study, 1975–1979

Table 6: Prevalence of atherosclerosis risk factors in normal (NG), risk (RG) and pathological (PG) groups at the entry into the study, 1975–1979 (in brackets a total number of men)

Risk factor	NG		RG		PG	
Cigarette smoking	0 %	(276)	57.5 %	(971)	40.4 %	(114)
Hypercholesterolemia	0 %	(276)	33.9 %	(961)	36.6 %	(112)
Hypertension	0 %	(276)	30.9 %	(951)	44.1 %	(111)
Obesity	0 %	(276)	27.4 %	(967)	26.8 %	(112)
Family history	0 %	(276)	22.2 %	(966)	26.8 %	(112)

Figure 5 demonstrates Kaplan-Meier survival curves. They show the survival free of fatal atherosclerotic CVD in men from RG stratified according to the number of the atherosclerosis risk factors at study entry. A total of 910 men had the information on all the surveyed risk factors at the entry into the study. Out of 910 men, 22.3 % had a positive family

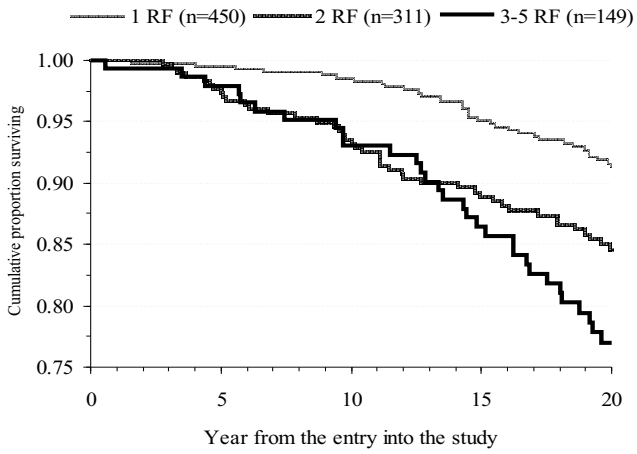

Figure 5: Kaplan-Meier survival free of fatal atherosclerotic CVD according to the number of risk factors (RF) in the risk group

Table 7: Results of the Cox regression model: the numbers of men from RG in each category (n), hazard ratio (HR) of death from atherosclerotic CVD with 95% confidence interval (CI)

Variable		n	HR	95% CI	*p*-value
Age [yrs]		926	1.1	1.1–1.2	<0.001
Education	Elementary	110	1.0		
	Apprenticeship	274	0.7	0.4–1.3	0.273
	Secondary	292	0.6	0.3–1.0	0.050
	University	250	0.3	0.2–0.6	<0.001
Cigarette smoking	<15 cigarettes daily	396	1.0		
	≥15 cigarettes daily	530	3.0	2.0–4.6	<0.001
Blood pressure[1]	<140/90 [mm Hg]	525	1.0		
	140/90–159/94 [mm Hg]	211	1.5	0.9–2.3	0.125
	≥160/95[mm Hg]	190	2.8	1.8–4.3	<0.001
T-cholesterol	<202 [mg/dl]	199	1.0		
	202–259 [mg/dl]	412	1.4	0.8–2.5	0.182
	≥260[mg/dl]	315	1.8	1.0–3.1	0.043

[1] If only one value (systolic or diastolic blood pressure (BP)) exceeds the limit, patient belongs into the higher category (e.g. patient with BP 130/92 mm Hg belongs into the category 140/90–159/94 mm Hg), BP - mean of two measurements

history, 26.0 % were obese, 56.7 % smoked, 30.7 % had hypertension, and 33.8 % had hypercholesterolemia. 50.5 % of men had at least two risk factors. Interestingly the groups did not differ (p=0.759) in mean age (46.2 years in all groups). There was a significant (Anova, p <0.001) decrease in the survival with the increasing number of the risk factors.

At 20 years study entry, subjects with one risk factor had cumulative CVD event free survival of 91.1 %, with two risk factors 84.2 %, and with three or more risk factors 77.0 %.

Selected risk factor variables were included into a Cox regression model to analyse survival free of fatal atherosclerotic CVD among men from RG with all pertinent variables recorded. The final model adjusted for the age was highly statistically significant (p <0.001), see Table 7. Obesity and family history were insignificant, so the final Cox regression model was applied without these two variables. The significant variables were included in the model (n=926): education, smoking cigarettes, blood pressure and total cholesterol. Heavy smokers (at least 15 cigarettes daily) had hazard significantly higher than men with lower cigarette consumption, men with hypertension (blood pressure ≥160/90 mm Hg) had hazard significantly higher than men with blood pressure <140/90 mm Hg. Men with hypercholesterolemia (plasma cholesterol ≥260 mg/dl, i.e. ≥6.7 mmol/l) had hazard significantly higher than men with the level of cholesterol up to 202 mg/dl (i.e. 5.2 mmol/l). Men with university education had hazard significantly lower than men with elementary education.

4.2 Validation of cardiovascular risk estimations in the Czech Republic

4.2.1 Framingham risk function (1991)

Table 8: Baseline risk factors, FHS (1991)

Risk factors	n	Mean	Std.Dev.	Median	Min	Max
At the entry into the study[1]						
Age [yrs]	916	46.1	3.6	46.5	38.0	53.0
Systolic blood pressure [mm Hg]	916	130.4	17.3	127.5	80.0	210.0
Diastolic blood pressure [mm Hg]	916	83.4	11.2	82.5	50.0	132.5
T-cholesterol [mg/dl]	916	234.9	45.8	231.0	112.0	470.0
At the control examination						
Age [yrs]	540	51.1	3.6	51.0	44.0	62.0
Systolic blood pressure [mm Hg]	540	133.0	16.9	130.0	90.0	200.0
Diastolic blood pressure [mm Hg]	540	85.6	10.1	85.0	60.0	115.0
T-cholesterol [mg/dl]	540	224.6	40.2	222.0	128.0	391.0
HDL-cholesterol [mg/dl]	540	53.9	14.2	52.0	16.0	114.0

[1] Blood pressure - mean of two measurements, HDL-cholesterol not measured

Among 1 417 men aged 38–53 years at the entry, 1 248 men were from NG and RG, i.e.

Table 9: Absolute 10-year coronary heart disease (CHD) risk estimations and numbers of CHD, FHS (1991)

Quintile		10-year CHD risk				Number of CHD		
of risk	n	Mean	Std.Dev.	Min	Max	Observed	Estimated	Observed/Estimated
1	108	4.6 %	1.1 %	0.7 %	6.1 %	8	4.9	162.5 %
2	108	7.4 %	0.8 %	6.1 %	8.8 %	17	8.0	212.4 %
3	108	10.2 %	0.8 %	8.8 %	11.7 %	17	11.1	153.8 %
4	108	13.5 %	1.1 %	11.7 %	15.6 %	23	14.6	157.8 %
5	108	20.0 %	4.5 %	15.6 %	36.0 %	30	21.6	138.9 %
Total	540	11.1 %	5.8 %	0.7 %	36.0 %	95	60.1	158.0 %

without evidence of CHD, without pathological findings on ECG, without diabetes mellitus and without other serious disease. From these 1 248 men, 916 (176 men from NG, and 740 from RG) had the complete 10-year follow-up (CHD event within 10 years or the control examination at 10-year follow-up, or later), and the information on the risk factors, excluding HDL-cholesterol, needed for the estimation of an individual's absolute 10-year CHD risk by the Framingham risk function (1991). 387 (42.2 %) of 916 men were nonsmokers (as defined in Table 5).

In 1979–1988, 540 of 916 men were without evidence of CHD having the complete follow-up of 10-year and all information on the risk factors, excluding left ventricular hypertrophy, needed for the estimation of the risk. All 540 men were without diabetes mellitus, and 271 (50.2 %) were actual nonsmokers (at least one cigarette a day). Statistical characteristics of men at the control examination (the baseline) are presented in Table 8.

When estimating the risk within 10 years from the baseline, the risk of CHD was estimated under the assumption that left ventricular hypertrophy was not present. At 10-year follow-up the estimated number of CHD events (60.1) was lower than observed (95), Table 9. The Framingham risk function significantly underestimated the CHD risk observed across all quintiles of the risk (H-L goodness of fit test, p <0.001), Figure 6. The trend in the proportion of CHD was significantly increasing across quintiles (chi-square test for trend, p <0.001).

Figure 7 shows the true positive fraction (sensitivity) of the Framingham risk function versus the false positive fraction (1−specificity) with the 95% confidence interval of the fitted

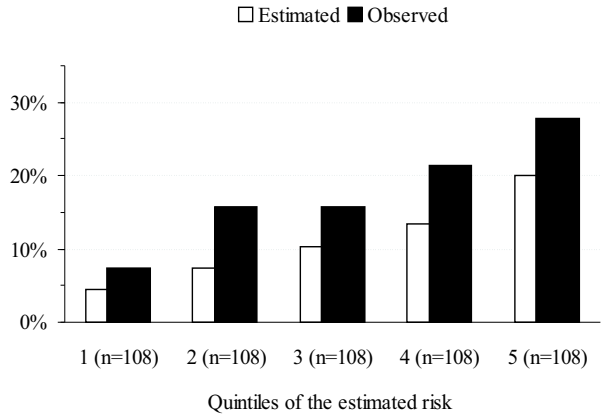

Figure 6: Observed and estimated risks of coronary heart disease (CHD) within 10 years, FHS (1991)

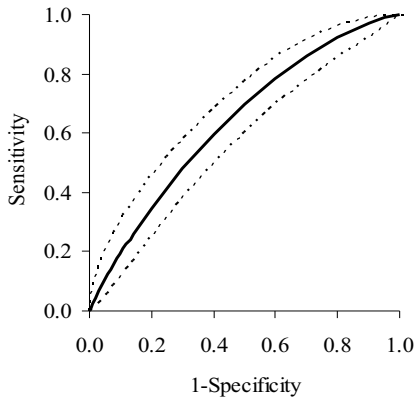

Figure 7: Receiver operating curve with 95% confidence interval (n=540), FHS (1991)

ROC curve. Each point on the ROC curve is associated with a specific 10-year CHD risk. At about 11 % of the risk the ROC curve is closest to the upper-left-hand corner. The sensitivity of the Framingham risk with a 11% threshold is 60.0 %, and the specificity 59.3 %. According to the ROC analysis the Framingham risk function classified men at the baseline into those with and without developing CHD in the 10-year period with the accuracy of 62.8 % (95% CI 56.3 %, 69.3 %).

4.2.2 Framingham risk function (1998)

A total of 646 men underwent the control (baseline) examination in 1979–1988. They were significantly different in the background risk factors from those from Framingham. In STU-

LONG, there was a higher prevalence of hypertensives, smokers, and men with hypercholesterolemia and with a higher HDL-cholesterol level, Table 10. None of men in STULONG suffered from DM. Note that blood pressure (ignoring blood pressure therapy) in Table 10 was categorized into groups [47]: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal blood pressure (systolic 120 to 129 mm Hg and diastolic 80 to 84 mm Hg), high normal blood pressure (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg), hypertension stage I (systolic 140 to 159 mm Hg or diastolic 90 to 99 mm Hg), and hypertension II–IV (systolic 160 mm Hg or diastolic 100 mm Hg). When systolic and diastolic pressures fell into the different groups, blood pressure was classified into the higher group.

Out of 646 men, 450 men were censored at 10-year follow-up, 99 were censored before the 10-year follow-up without CHD, and 97 men were diagnosed with CHD in 10-year follow-up.

Table 11 shows the age-adjusted Cox proportional hazards regression model (so-called the Framingham risks function) derived from FHS data for estimating 10-year CHD risk. The model with the same covariates was derived from STULONG data. Unlike FHS, total cholesterol and HDL-cholesterol levels were not significantly associated with CHD risk in STULONG (95% confidence intervals not overlapped the value of one). Smokers had significantly higher hazard of CHD event than non-smokers (a 1.68 times higher hazard in FHS, a 2.84 times higher hazard in STULONG). The difference in the hazard ratio of smokers to non-smokers between FHS and STULONG was significant (z-test, p=0.036). The 10-year survival free of CHD events was 90.0 % for FHS, and 83.6 % for STULONG.

For each man of 646, 10-year absolute risk of CHD was estimated according to the Framingham risk function (Table 11). The mean 10-year absolute risk of CHD was of 12.8 % (n=646). A total of 646 men were categorized into five groups according to quintiles of the estimated risk. Their risk factors across quintiles are shown in Table 12. There was the significant difference between the observed and estimated risk of CHD across quintiles (H-L goodness of fit test for survival data, p=0.013), Figure 8. Overall 12.8 % CHD events were estimated and 16.4 % observed in 10-year follow-up. The occurrence of CHD events observed in 10-year follow-up was significantly increasing across quintiles of the estimated risk (Poisson regression model, p <0.001).

Prevalence of risk factors and mean age in men from STULONG (Table 10) were used

Table 10: Baseline risk factors in FHS compared with STULONG, FHS (1998)

Risk factors	FHS (n=2489)	STULONG (n=646)	p-value[1]
Mean age (SD)	48.6 (11.7)	51.2 (3.7)	0.999
Blood pressure [mm Hg]			
Optimal	**20.0** %	**11.3** %	
Normal	**24.0** %	**17.8** %	
High normal	20.0 %	16.1 %	<0.001
Hypertension stage I	**22.8** %	**39.0** %	
Hypertension stage II–IV	13.1 %	15.8 %	
Cigarette smoking [No/Yes]			
No	59.5 %	48.9 %	
Yes	40.5 %	51.1 %	<0.001
Diabetes mellitus [No/Yes]			
No	94.8 %	100.0 %	
Yes	5.2 %	0.0 %	<0.001
T-cholesterol [mg/dl]			
<160	**7.4** %	**4.2** %	
160–199	**31.2** %	**21.1** %	
200–239	38.9 %	41.2 %	<0.001
240–279	**16.7** %	**25.7** %	
≥280	5.8 %	7.9 %	
HDL-cholesterol [mg/dl]			
<35	**19.3** %	**6.5** %	
35–44	**35.5** %	**20.1** %	
45–49	14.9 %	16.3 %	<0.001
50–59	**19.6** %	**26.9** %	
≥60	**10.7** %	**30.2** %	

[1] Student t-test used when comparing mean age; homogeneity of risk factors' distribution compared by chi-square test, for risk factors with more than two categories bold font indicates the categories significantly (at least p <0.05 by test on standardised residuals) contributed to chi-square test significance

to recalibrate the Framingham risk function. The recalibrated Framingham risk function is in Table 13. The estimated risk of CHD by this recalibrated function was insignificantly different from that observed across quintiles of risk (H-L goodness of fit test for survival data, p=0.320), Figure 8.

Figure 9 shows true positive fraction (sensitivity) of the Framingham risk versus false positive fraction (1-specificity) with the 95% confidence interval of the fitted ROC curve (n=547). Men who did not complete the 10 years of follow-up without having a CHD event

Table 11: Hazard rate (HR) of coronary heart diesease (CHD) in FHS compared with STULONG, FHS (1998)

	FHS (n=2 489)		STULONG (n=544)		
Risk factors	HR	95% CI	HR	95% CI	p-value[1]
Age [yrs]	1.05	1.04–1.06	1.05	0.99–1.11	0.999
Blood pressure [mm Hg]					
Normal (including optimal)	1.00	Referent	1.00	Referent	
High normal	1.31	0.98–1.76	1.85	0.96–3.56	0.346
Hypertension stage I	1.67	1.28–2.18	1.72	0.97–3.03	0.927
Hypertension stage II–IV	1.84	1.37–2.49	3.36	1.77–6.37	0.094
Cigarette smoking [No/Yes]					
No	1.00	Referent	1.00	Referent	
Yes	1.68	1.37–2.06	2.84	1.82–4.41	0.036
Diabetes mellitus [No/Yes]					
No	1.00	Referent	1.00	Referent	
Yes	1.50	1.06–2.13	-	-	
T-cholesterol [mg/dl]					
<200	1.00	Referent	1.00	Referent	
200–239	1.31	1.01–1.68	0.92	0.54–1.57	0.243
≥240	1.90	1.47–2.47	1.35	0.79–2.28	0.260
HDL-cholesterol [mg/dl]					
<35	1.47	1.16–1.86	0.85	0.38–1.87	0.201
35–59	1.00	Referent	1.00	Referent	
≥60	0.56	0.37–0.83	0.72	0.45–1.15	0.432

[1] HRs compared by z-test

Table 12: Risk factors in quintiles of the estimated risk of CHD (mean ± std.dev.), FHS (1998)

Quintiles	1	2	3	4	5
n	130	129	128	133	126
Age [yrs]	49.5 ± 3.4	50.3 ± 3.7	51.4 ± 3.6	52.0 ± 3.5	52.8 ± 3.3
Systolic blood pressure [mm Hg]	124.2 ± 14.8	129.7 ± 15.8	134.8 ± 17.3	135.4 ± 17.8	141.5 ± 17.8
Diastolic blood pressure [mm Hg]	81.1 ± 9.7	83.7 ± 9.7	86.7 ± 10.8	86.6 ± 9.7	89.9 ± 9.6
Cigarette smoking [%]	23.1 ± 3.7	47.3 ± 4.4	43.0 ± 4.4	69.2 ± 4.0	73.0 ± 4.0
T-cholesterol [mg/dl]	198.7 ± 34.6	218.6 ± 40.1	229.3 ± 35.3	233.6 ± 35.5	245.3 ± 38.0
HDL-cholesterol [mg/dl]	61.3 ± 13.2	58.6 ± 14.5	54.9 ± 13.7	50.6 ± 10.9	41.9 ± 8.4

were excluded from this analysis. Each point on the ROC curve is associated with a specific 10-year CHD risk. At about 12 % of the risk the ROC curve is closest to the upper-left-hand corner. The sensitivity of the Framingham risk greater than 12 % is 64.9 %, and the

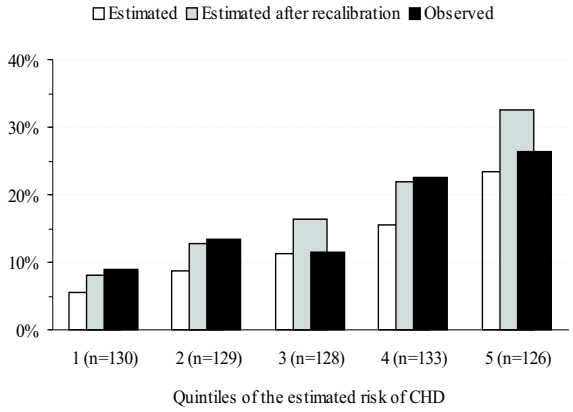

Figure 8: Observed and estimated risks of coronary heart disease (CHD) within 10 years, FHS (1998)

Table 13: Recalibrated Framingham risk function (1998)

P=1-$S(10)^{\exp\{f(x)-f(M)\}}$, where[1]

$S(10)$=0.83604 is the 10-year survival rate (probability of not suffering from HCCHD to 10 years, x=(x_1,... x_k), k=15, represents individuals' risk factors,M=(M_1,... M_k) their mean values and prevalences, respectively, and

$f(x,M)$=0.04826x(age-51.21053)-0.00226x($bp1$-0.11300)+0.28320x($bp3$-0.16099)+0.52168x($bp4$-0.39009)+ 0.61859x($bp5$-0.15789)+0.52337x($smoking$-0.51084)+0.42839x($diabetes$-0.00000)-0.65945x($tch1$-0.04180)+ 0.17692x($tch3$-0.41176)+0.50539x($tch4$-0.25697)+0.65713x($tch5$-0.07895)+0.49744x($hdl1$-0.06502)+ 0.24310x($hdl2$-0.20124)-0.05107x($hdl4$-0.26935)-0.48660x($hdl5$-0.30186)

[1] Age refers to the man's age in years, and other risk factor categories are dichotomous (1 if a man si classified into the category, 0 not classified), e.g. for a smoker is $smoking$=1, otherwise $smoking$=0. The categories of blood pressure ($bp1$, $bp2$, $bp3$, $bp4$, $bp5$), T-cholesterol ($tch1$, $tch2$, $tch3$, $tch4$, $tch5$), and HDL-cholesterol ($hdl1$, $hdl2$, $hdl3$, $hdl4$,$hdl5$)refer to those defined in Table 10, respectively. For instance, if T-cholesterol of 205 mg/dl then $tch1$=0, $tch2$=0, $tch3$=1, $tch4$=0, $tch5$=0.

specificity 59.8 %. The Framingham risk of CHD classified men free of CHD at the entry into those with and without CHD over 10 years with 63.2% accuracy (the area under the ROC curve), 95% CI (57.2 %, 69.3 %). When all men (n=646) were included into the ROC analysis, the discrimination accuracy was of 63.8 %, 95% CI (58.4 %, 69.1 %). So that, discrimination accuracy was approximately same as for the complete data.

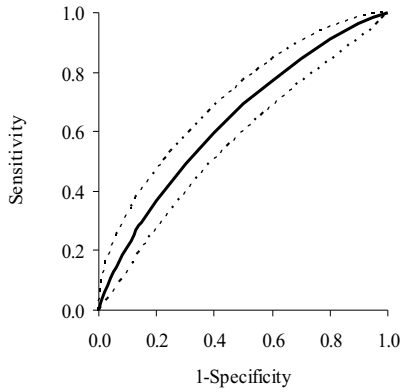

Figure 9: Receiver operating curve with 95% confidence interval (n=547), FHS (1998)

4.2.3 SCORE risk function (2003)

In the STULONG study, there were 1129 men free of CVD at the entry into the study, and having all information on variables needed to estimate the fatal CVD risk by the SCORE risk function, Table 14. A total 53.5 % of them were actual smokers (at least one cigarette a day).

Table 14: Baseline risk factors, SCORE (2003)

Risk factors	n	Mean	Std.Dev.	Median	Min	Max
Age [yrs]	1129	46.1	3.6	46.0	38.0	53.0
Systolic blood pressure[1] [mm Hg]	1129	130.5	17.6	130.0	80.0	220.0
Diastolic blood pressure[1] [mm Hg]	1129	83.4	11.2	82.5	50.0	142.5
T-cholesterol [mg/dl]	1129	233.4	45.1	230.0	112.0	470.0

[1] Mean of two measurements

1129 men completed the 10 years follow-up (fatal CVD event within 10 years, or the control examination at 10-year follow-up or later). In the 10-year follow-up from the entry, the estimated number of fatal CVD was significantly differed from that observed (H-L goodness of fit test, p=0.006). There were a total of 45 fatal CVD events observed and 28.0 estimated, Table 15.

The largest difference was in the fifth quintile in which 24 fatal CVD events were observed and 12.5 estimated. The smallest difference was in the third quintile. There were 4 fatal

Table 15: Absolute 10-year fatal cardiovascular disease (CVD) risk estimations and numbers of fatal CVD, SCORE (2003)

Quintile		10-year fatal CVD risk				Number of fatal CVD		
of risk	n	Mean	Std.Dev.	Min	Max	Observed	Estimated	Observed/Estimated
1	225	0.7 %	0.2 %	0.2 %	1.1 %	2	1.6	121.3 %
2	227	1.3 %	0.2 %	1.1 %	1.6 %	4	3.0	133.4 %
3	226	2.0 %	0.2 %	1.6 %	2.3 %	4	4.4	89.9 %
4	225	2.9 %	0.3 %	2.4 %	3.4 %	11	6.4	171.0 %
5	226	5.5 %	2.8 %	3.5 %	23.5 %	24	12.5	192.7 %
Total	1129	2.5 %	2.1 %	0.2 %	23.5 %	45	28.0	160.8 %

CVD events observed and 4.4 estimated. The proportion of fatal CVD event observed in the 10-year follow-up was significantly increasing (chi-square test for trend, p <0.001) across quintiles of the estimated risk, Figure 10.

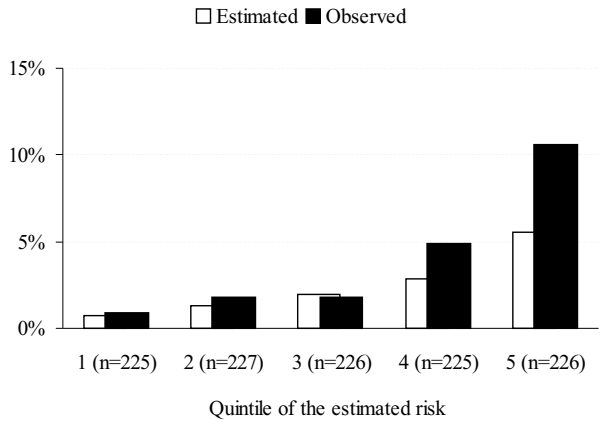

Figure 10: Observed and estimated risks of fatal cardiovascular diseases (CVD) within 10 years, SCORE (2003)

Figure 11 shows the ROC curve with the 95% confidence interval. The fatal CVD risk estimated by the SCORE risk function classified men free of CVD at the entry into those with and without fatal CVD in the 10-year follow-up with 73.6% accuracy, 95% CI (66.4 %, 80.8 %). The ROC curve is closest to the upper-left-hand corner at about 2.8 % of the risk. The sensitivity of the SCORE risk greater than 2.8 % is 68.9 %, and the specificity 70.9 %.

When we added to 1129 men 81 men who were censored before the 10-year follow-up, calibration and discrimination accuracies of the SCORE risk function (n=1210) were similar

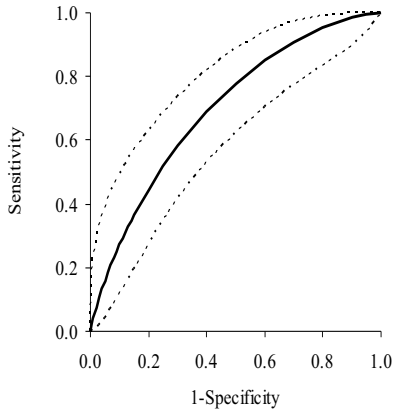

Figure 11: Receiver operating curve with 95% confidence interval (n=1129), SCORE (2003)

as those for the complete data (n=1129): the risk function underestimated the observed risk of fatal CVD (H-L goodness of fit test for a survival data, p=0.006), with discrimination accuracy of 74.3 %, 95% CI (67.0 %, 81.5 %).

5 Discussion

Cardiovascular prediction models derived from a specific population may not hold for another population. It can happen if the two populations are not homogenous with respect to cardiovascular risk factors, and consequently, in the occurrence of cardiovascular events. In this thesis we evaluate the accuracy of the Framingham CHD prediction models (1991, 1998) [2], [47] and the SCORE fatal CVD prediction model (2003) [8] in Czech men from Prague. The Framingham model (1998) we explored in more detail in the comparison with the Framingham model (1991) and the SCORE model (2003). The reason is that we had complete information to estimate the risk by this model unlike the resting models. In the case of the Framingham model (1991), we assumed left ventricular hypertrophy not present, and in the case of the SCORE model (2003), the definition of cardiovascular diseases in the SCORE and STULONG studies was not fully same. While the Framingham models are based on subjects (almost all Caucasian) from the town of Framingham (a suburb west of Boston, USA), the SCORE model on subjects from the European countries.

In our long-term 20-year follow-up data from middle-aged men multivariate analysis reaffirms the importance of high cholesterol >6.7 mmol/l, hypertension >160/95 mm Hg, and cigarette smoking on survival free of fatal atherosclerotic CVD in risk men [6]. University education was highly protective factor compared with primary education (Table 7). There was detected a significant decrease in the survival free of fatal CHD event with the increasing number of the risk factors (Figure 5).

5.1 Validation studies in the Czech Republic

The Framingham (1991, 1998) and SCORE (2003) models underestimated the real absolute risk of the disease of the interest in STULONG. When recalibrating (i.e. adjusting) the Framingham CHD risk function (1998) for mean age, prevalence of risk factors and survival rate in the STULONG study, the observed and estimated risks of CHD were insignificantly different. However, recalibration does not influence discrimination. Discrimination ability of a model expresses its ability to distinguish observations with a positive or a negative end-point. Discrimination accuracy of the Framingham and SCORE models in STULONG

was over 60 %. Generally, the discrimination ability of 90 %–100 % is regarded as excellent, 80 %–90 % as good, 70 %–80 % as fair, and 60 %–70 % as acceptable.

Note that the results of the tests of calibration and discrimination were similar for the complete data (men who did not complete the 10 years of follow-up without having an event were excluded from the analysis) and survival data (men who did not complete the 10 years of follow-up without having an event were included into the analysis). The methods how to measure calibration and discrimination for survival data have been developing recently. In our work we used the methods described in the publications [14], [33].

Discrepancy between the observed and expected risks

The interactions between genes, lifestyle, and environmental factors may play an important part in the differences in the observed and estimated risks in the present validation study. The accuracy of the risk functions depends on the risk profile of population that it is applied to. Prevalence of the risk factors used for the estimation of the CHD risk by the Framingham risk function (1998) was not homogenous in the FHS and STULONG populations (Table 10). The Framingham population was at a lower risk than that STULONG population, except HDL-cholesterol, and DM. In STULONG the hazard of CHD for smokers was essentially higher than that in FHS (Table 11).

The data on the risk factors were gathered in 1971–1974 in FHS, in 1967–1991 in the SCORE study, and in 1975–1988 in the STULONG study. The directly age-standardized mortality from CHD in men from the Czech Republic in 1986 was comparable (543 per 100 000 European standard population aged 35–74 years) with that in the USA in 1975 (558 per 100 000), however, higher than that in the USA in 1986 (323 per 100 000). Mortality from CHD was also higher in the Czech Republic than in a great number of European countries [9], [19].

The estimation of the risk by Framingham risk function (1991) may have been more precise, if the occurrence of left ventricular hypertrophy (LVH) was surveyed (LVH needed to estimate the CHD risk was assumed not to be present). On the other hand, Anderson et al. [2] say that the estimated effect of the left ventricular hypertrophy is very large but with a large standard error because of the small prevalence of left ventricular hypertrophy

in FHS. In the case of the SCORE model, the definition of fatal CVD included somewhat different diseases than in the STULONG study (the definition of the diseases in Table 3 for SCORE, and on the page 19 for STULONG). The difference was in ICD-9 codes 426.7, 432.1, 437.3 and 437.4 comprised in CVD, and codes 401-404, 798.1, 798.2 excluded from CVD in the STULONG study unlike the SCORE project. Despite this fact, the definitions largely overlapped. The largest difference might cause codes 401-404 (death from hypertension) that we did not consider as causes of death, but only non-fatal diseases causing complication.

Besides the difference in the end-points, there were also some (in most cases only minor) differences in measurements of risk factors in the studies. It is only worth mentioning that persons who smoked regularly during the previous 12 months were classified as smokers in Framingham risk function (1991, 1998), while in STULONG persons who smoked at least one cigarette a day.

Lastly, the absolute risks of CHD and fatal CVD were estimated using the risk functions based on the Cox proportional hazards models. The important assumption of a Cox model is the assumption of proportional hazards, i.e. the ratio of hazard functions for two subjects with different values of explanatory variables does not depend on time. In STULONG, this assumption was fulfilled. On the other hand, STULONG was the primary preventive study. The discrepancy between the 10-year observed and estimated risks of CHD and fatal CVD, respectively, can indicate, among other things, that levels of the risk factors were non-randomly changing over the 10-year period. As it was shown by Boudík et al. [6], we can speculate about the efficiency of the intervention: by design a true control group was lacking, nevertheless, the age-specific CVD mortality in the risk group decreased over time in relation to the general population. Even if the efficiency of the intervention wasn't clearly improved, the regular examinations by cardiologists could influence the behaviour of the validation population compared with the general population (so-called attention bias).

Limitations of validation studies

The men from STULONG involved into the validation study do not represent all men from the Czech Republic. The STULONG study recruited middle-aged men from the centre of Prague, and a respondence rate was of 59.8 % in 1975–1979.

In the STULONG study, diabetic men were excluded from the follow-up study according to the initial protocol. All subjects with diabetes identified during 20 years of follow-up were referred to outpatients for diabetic department, but remain part of our survey. However, none diabetic man was recorded into the validation study. In 2002 diabetes afflicts 6.5 % of the Czech population, while in 1993 it was only 4.8 % [11].

5.2 Other validation studies

Tables 16–19 show studies that validate the Framingham risk functions in external (i.e. non-Framingham) populations. Some of them used the Framingham functions to estimate CHD risk beyond the designed period and age range (e.g. the validation studies by Ramachandran et al. [36]). A great number of the validation studies restricted to a narrower age range

Table 16: Validation study of the Framingham CHD risk function (1991) [2]

First author (year) [citation]	Menotti (2000) [29]	Ramachandran (2000) [36]	Bastuji-Garin (2002) [5]	Boudík (2005) [6]	Wang (2005) [46]
POPULATION	Italian rural-Seven countries study of CVD	North east English (Whickham)	Northern and Southern treated hypertensives-INSIGHT study	Czech urban (Prague)-STULONG study	Aboriginal Australian (Northern Territory)
Baseline examination	In the 1960s	1972–1974	1994–1996	1979–1988	1992–1995
Gender (sample size)	Men (1 656)	Men (751) Women (949)	Men (1 971) Women (2 436)	Men (540)	Men (356) Women (331)
Age [yrs]	40–59	30–75	55–74	44–62	20–74
FAILURE OF INTEREST	CHD	CHD	CHD	CHD	CHD
Time until failure [yrs]	10	20	A median follow-up 3.7 years	10	8–11
Calibration	Overestimation	Underestimation in the low-risk group ($\leq$ 1.5 %)	Overestimation	Underestimation	Underestimation, most marked in women and younger adults
Recalibration	Not done, new model developed	Not done	Not done	Not done	Not done
Discrimination (ROC curve)	Not done	Not done	Not done	0.63	Not done
COMMENTS	The risk chart derived from FRF (1991) validated	The 20-year risk estimated for 30–75 years aged (FRF (1991) derived for 4–12 years and 30–74 years aged); HDL-cholesterol not collected but assumed 1.15 mmol/l in men, 1.14 mmol/l in women	The CHD risk within 3.7 years estimated and considered by authors as valid (FRF (1991) derived for 4–12 years)	Primary preventive study; LVH status not collected, but assumed not present	The risk for 20–74 years aged estimated (FRF (1991) derived for 30–74 years aged); LVH status not collected, but approximated

Abbreviations: Appendix A (page 52)

than FHS. Some studies verified the risk estimation in samples recruited from structurally different populations than was the Framingham population. Remind that the FHS study recruited participants from residents of the town Framingham, however, some validation studies from e.g. rural populations and employees (e.g. the validation study by Menotti et al. [29]). Generally, there were a large geographic variation in coronary morbidity and mortality across the validation studies.

Table 17: Validation study of the Framingham fatal CHD risk function (1991) [3]

First author (year) [citation]	Brindle (2003) [7]	Hense (2003) [23]
POPULATION	British urban - British regional heart study	German inhabitans and employees - MONICA Augsburg and PROCAM studies
Baseline examination	1978–1980	MONICA: 1984/1985,1989/1990 PROCAM: 1979–1985
Gender (sample size)	Men (6 643)	MONICA: Men (2 861) Women (2 925) PROCAM: Men (5 527) Women (3 155)
Age [yrs]	40–59	35–64
FAILURE OF INTEREST	Fatal CHD, CHD	Fatal CHD plus non-fatal MI
Time until failure [yrs]	10	7–13
Calibration	Overestimation for both fatal CHD and CHD	Overestimation of sum of non-fatal MI and fatal CHD
Recalibration	Good	Not done
Discrimination (ROC curve)	Not done	MONICA: 0.78 (Men) 0.88 (Women) PROCAM: 0.73 (Men) 0.77 (Women)
COMMENTS	None	None

Abbreviations: Appendix A (page 52)

As seen in Table 16, the Framingham risk function (1991) [2] overestimated the risk of CHD for the Italian rural man population [29], and Western Europe [5]. While in the Czech population and aboriginal Australians [46], the Framingham risk function underestimated the absolute CHD risk. In England the Framingham risk function underestimated the 20-year

absolute CHD risk for subjects with the lower absolute risk [36]. However, the Framingham function was derived to estimate the risk within 4–12 years, and here used for the 20-year period. The Framingham risk function (1991) overestimated the CHD and fatal CHD risk in British men [7], and the risk of fatal CHD and non-fatal myocardial infarction in Germany [23], Table 17.

Table 18: Validation study of the Framingham CHD risk function (1998) [47]

First author (year) [citation]	Orford (2002) [32]	Suka (2002) [41]	Empana (2003) [18]	Reissigová [39]
POPULATION	USA healthy veterans (Boston)-NAS study	Japanese workers	Northern Ireland (Belfast) and France urban-PRIME study	Czech urban-(Prague)-STULONG study
Baseline examination	Not stated precisely (NAS started 1961 and lasted 30 years)	1991–1993	1991–1993	1979–1988
Gender (sample size)	Men (1 393)	Men (5 611)	Northern Ireland Men (2 399) France Men (7 359)	Men (646)
Age [yrs]	30–74	30–59	50–59	44–62
FAILURE OF INTEREST	CHD	CHD	CHD	CHD
Time until failure [yrs]	10	5–7	Over 5	10
Calibration	Underestimation in the low-risk (< 5 %) group and overestimation the high-risk (> 40 %) group	Good	Overestimation	Underestimation
Recalibration	Not done	Not needed	Not done	Not done
Discrimination (ROC curve)	0.60	0.62	Northern Ireland 0.66 France 0.68	0.64
COMMENTS	None	The CHD risk within 5–7 years estimated (FRF (1998) derived for 10 years)	The 5-years CHD risk estimated (FRF (1998) derived for 10 years)	Primary preventive study

Abbreviations: Appendix A (page 52)

As shown in Table 18, the Framingham risk function (1998) [47] underestimated the absolute risk of CHD in the low-risk group and overestimated in the high-risk group in healthy veterans in Boston (USA) [32], and overestimated the risk in men in Northern Ireland and France [18]. The Framingham risk model appropriately estimated the risk of CHD in Japanese man workers [41]. However, the Framingham risk function (1998) was developed to provide the 10-year CHD risk, and Japanese men were followed-up from 5 to 7

years.

Table 19: Validation study of the Framingham hard CHD risk function (2001) [13]

First author (year) [citation]	D'Agostiano (2001) [13]	Marrugat (2003) [30]	Liu (2003) [28]
POPULATION	White, blacks, Native American, Japanese American men, Hispanic men- Six prospective studies	North East Spanish (Gerona)	Chinese urban and rural- Chinese multi-provincial cohort study
Baseline examination	Not stated precisely (recruitments into studies in 1965–1991)	1995 - cross-sectional study	Follow-up 1992–2002
Gender (sample size)	Men (20 985)	Men (709) Women (771)	Men (16 065) Women (14 056)
Age [yrs]	40–59	30–74	35–64
FAILURE OF INTEREST	Hard CHD	Hard CHD	Hard CHD
Time until failure [yrs]	5	8 - population registry 1990–1997	10
Calibration	Good excluding overestimation in Japanese American, men, Hispanic men and native American women	Overestimation	Overestimation
Recalibration	Good	Good	Good
Discrimination (ROC curve)	0.63–0.75 (Men) 0.66–0.83 (Women)	Not done	0.705 (Men) 0.742 (Women)
COMMENTS		Applied to Gerona registry population, but prevalence of risk factors estimated on the base of cross-sectional study; the hard CHD risk within 8 years estimated (FRF (2001) derived for 5 and 10 years)	Hard CHD events comprised acute MI, sudden death, and other coronary death (Hard CHD in FRF (2001) comprised fatal CHD and non-fatal MI)

Abbreviations: Appendix A (page 52)

As seen in Table 19, the estimation of the hard CHD risk, by the Framinhgam risk function (2001), within 5 years of follow-up for white and black men and women from the Atherosclerosis risk in communities study (a study in the United States), was reasonably good [13]. However, overestimation was observed in Japanese American and Hispanic men, Native American women [13], Chinese population [28], and Northeast Spain [30]. In the last mentioned study, the Framingham risk function was applied to the Gerona (Northeast Spain) population, but the prevalence of risk factors was estimated on the base of a cross-sectional study.

The Framingham risk functions were successfully recalibrated in some of the above mentioned studies, Tables 16–19 The discrimination ability, when calculated, was at least of 60 % in these studies. So that, even if calibration accuracy of the Framingham risk functions were not satisfying, the Framingham risk functions were able to rank individuals according to risk from low-risk to high-risk groups, with discrimination of 60 % and more.

As regard the SCORE model, we did not identify any study on external validation for the SCORE risk function by the reason that the model was issued only in 2003.

6 Conclusions

The Framingham (1991, 1998) and SCORE (2003) risk functions significantly underestimated an individual's 10-year absolute risk of CHD and fatal CVD, respectively, in middle and upper aged men (age range 44–62 years) from the Czech Republic (Prague). It seems that the underestimation was largely caused by differences in the background risk factors and frequency in the occurrence of disease outcome in populations under investigation. Recalibration of the Framingham risk function (1998) essentially increased the accuracy of the estimate of the CHD risk.

Despite these facts, the proportion of disease events was significantly increasing across quintiles of te estimated risk for both the Framignam and SCORE functions. The functions were able to rank individuals according to risk from low-risk to high-risk groups with the discrimination ability over 60 %. On the other hand the discrimination ability varying about 60 % can be debatable because it is not high.

The results have policy implications concerning the cardiovascular prediciton models. Generally speaking, it is not surprising that the risk functions derived for a specific population will not be accurate in other populations. They can underestimate or overestimate the real absolute risk of a disease of the interest, if the populations are not homogenous with respect to risk factors (traditional, non-traditional) for cardiovascular diseases, and consequently, in the occurrence of cardiovascular diseases events. Then the risk functions must be recalibrated, or a new risk function derived. The risk functions can partly help in searching a population at high cardiovascular risk, if discrimination ability is sufficiently high.

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Appendix

Appendix A: Abbreviations and acronyms

ACE	Acute coronary event
BP	Blood pressure
BI	Brocca index
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Elektrocardioghraphy
FHS	Framingham heart study
FRF	Framingham risk function
HDL-cholesterol	High-density lipoprotein cholesterol in serum
ICD-10	International classification of diseases, 10th revision (similarly ICD-8, ICD-9)
INSIGHT	Goal in hypertension treatment
LDL-cholesterol	Low-density lipoprotein cholesterol in serum
MI	myocardial infarction
MONICA	Monitoring trends and determinants of cardiovascular disease
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NAS	Normative aging study
NG	Normal group
NGE	Normal group regularly examined
NGN	Normal group regularly unexamined
PG	Pathological group
PRIME	Prospective epidemiological study of myocardial infarction
PROCAM	Prospective cardiovascular cardiovascular Muenster
ROC	Receiver operating chracteristics
RCG	Risk control group
RG	Risk group
RIG	Risk intervention group
STB	Systolic blood pressure
STULONG	Longitudinal primary prevention study of atherosclerotic risk factors

Appendix B: Publications and presentations of the author

There are enclosed *the publications* on which the author of the present thesis participated:

1. Reissigová J, Tomečková M. Intervention of the Risk Factors of Atherosclerosis and Cardiovascular Mortality. A 20-year Primary Prevention Study from a Statistician's Point of View. *Cor et Vasa*, 45:249–255, 2003 (in Czech).

2. Reissigová J, Tomečková M. State of the Art Coronary Heart Disease Risk Estimations Based on the Framingham Heart Study *Central European Journal of Public Health*, 13:180–186, 2005.

3. Boudík F, Reissigová J, Hrach K, Tomečková M, Bultas J, Anger Z, Aschermann M, Zvárová J: Primary Prevention of Coronary Artery Disease Among Middle Aged Men in Prague: Twenty-Year Follow-up Results. *Atherosclerosis*, 184:86–93, 2006. (Translated into Czech: *Vnitřní lékařství* (in press), 2006.)

4. Reissigová J, Zvárová J. The Framingham Risk Function Underestimated Absolute Coronary Heart Disease Risk in Czech Men. *Methods of Information in Medicine* (to be published).

Note that the results were also presented in conferences and seminars:

1. Reissigová J. Validation of Coronary Heart Prediction. Proceedings of the IX. PhD. Conference, Institute of Computer Science Academy of Sciences of the Czech Republic (Paseky nad Jizerou, Czech Republic, September 25–26, 2003), MATFYZPRESS, ISBN 80-86732-16-9, 89-95, 2003.

2. Reissigová J, Tomečková M, Zvárová J. External Validation of the Framingham Risk Function in Men with Coronary Heart Disease from the Czech Republic. Proceedings of the International Joint Meeting EuroMISE 2004 (Prague, Czech Republic, April 12–15, 2004), EuroMISE, ISBN 80-903431-0-4, 29, 2004.

3. Reissigová J. Estimations of Cardiovascular Disease Risk - A survey of our Results from 2004. Proceedings of the IX. PhD. Conference, Institute of Computer Science Academy

of Sciences of the Czech Republic (Paseky nad Jizerou, Czech Republic, September 29–October 1, 2004), MATFYZPRESS, ISBN 80-86732-30-4, 101–106, 2004.

4. Reissigová J. Does the Accuracy of the Estimation of Coronary Heart Diseases Risk by the Framingham Risk Function Depend on HDL-Cholesterol? Proceedings of the Seminar of Informal Technology in Health Care (Prague, Czech Republic, December 6, 2004), EuroMISE, spol. s r.o., ISBN 80-903431-1-2, 135–141, 2004.