Cardiovascular risk prediction in Central and Eastern Europe and former Soviet Union

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Thesis submitted for the degree of Doctor of Philosophy

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Declaration

I, Olga Vikhireva, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

SCORE scale assesses the risk of fatal atherosclerotic cardiovascular disease (CVD), based on traditional risk factor levels. The high-risk SCORE version is recommended for Central & Eastern Europe/former Soviet Union (CEE/FSU). The aim of the thesis was to evaluate SCORE performance in CEE/FSU, using evidence from two large CEE/FSU studies.

These studies – MONICA and HAPIEE – include cohorts from CEE/FSU countries which have relatively high but heterogeneous CVD mortality. MONICA subjects were followed for ≥10 years from the mid-1980s. Ongoing HAPIEE follow-up (baseline 2002-2004) allowed preliminary assessment of SCORE performance in contemporary CEE/FSU settings. The present study included Czech, Polish-Warsaw, Polish-Tarnobrzeg, Lithuanian, and Russian MONICA samples (n=15,027), plus Czech, Polish, and Russian HAPIEE samples (n=20,517). Predicted 10-year CVD mortality was calculated with high-risk SCORE; observed mortality data came from local registers.

While SCORE calibration was good in most MONICA samples (predicted to observed (P/O) mortality ratios approached 1.0), mortality risk was under-estimated in Russian men and women. In Cox regression analysis, SCORE ≥5% significantly predicted 10-year CVD mortality: hazard ratios (HR) ranged from 1.7 to 6.3. The shorter HAPIEE follow-up meant that P/O ratios exceeded 1.0. These ratios were 2-3 times higher in Czech and Polish vs. Russian participants. Estimates of 10-year HAPIEE mortality confirmed this gap between Czech and Polish vs. Russian samples. SCORE significantly predicted CVD mortality in each HAPIEE sample (HR 2.6-10.5). Values of Harrell's C-statistic, a summary discrimination measure, reached 0.6-0.7 in MONICA and HAPIEE. Adding socioeconomic parameters or alcohol consumption characteristics to the SCORE model failed to improve its predictive performance.

High-risk SCORE discrimination was satisfactory in most MONICA and HAPIEE samples, despite risk under-estimation in Russian MONICA. HAPIEE data suggest that in contemporary Czech and Polish populations, high-risk SCORE might over-estimate CVD risk. SCORE extension by additional predictors did not improve its performance.

Contents

List of tables

List of figures

Abbreviations

AH – arterial hypertension

ARIC – Atherosclerosis Risk in Communities

AUROC – area under the receiver operating characteristic curve

BMI – body mass index

BP – blood pressure

BRHS – British Regional Heart Study

CEE – Central and Eastern Europe

CHD – coronary heart disease

CI – confidence interval

CINDI – Countrywide Integrated Non-communicable Diseases Intervention Program

CVD – cardiovascular disease

CZ – the Czech Republic

DALYs – disability-adjusted life years

DBP – diastolic blood pressure

DM – diabetes mellitus

EPV – events per variable

ESC – European Society of Cardiology

EU – European Union

EURIKA – European Study on Cardiovascular Risk Prevention and Management in Daily Practice

FHS – Framingham Heart Study

FSU – former Soviet Union

GF – graduated frequency

GGT – gamma-glutamiltransferase

HAPIEE – Health, Alcohol and Psychosocial factors In Eastern Europe

HDL-CH – high-density lipoprotein cholesterol

HR – hazard ratio

hsCRP – high-sensitivity C-reactive protein

ICD – International Classification of Disease

IDI – integrated discrimination improvement

IL – interleukin

IPD – individual participant data

KORA – Cooperative Health Research in the Augsburg Region study

LDL-CH – low-density lipoprotein cholesterol

LLH – Living Conditions, Lifestyles and Health

LR+ – likelihood ratio positive

LR- – likelihood ratio negative

LRC – Lipid Research Clinics

LRT – likelihood ratio test

LT – Lithuania

MI – myocardial infarction

MONICA – MONitoring of trends and determinants in CArdiovascular disease

MORGAM – MONICA, Risk, Genetics, Archiving, and Monograph

MORGEN – Monitoring Project on Chronic Disease Risk Factors

MP-CVDRF – Monitoring Project on Cardiovascular Disease Risk Factors

NPV – negative predictive value

NRT – net reclassification index

OR – odds ratio

PAR – population-attributable risk

P/E – predicted to estimated risk ratio

PL – Poland

P/O – predicted to observed risk ratio

PPV – positive predictive value

PRIME – Prospective Epidemiological Study of Myocardial Infarction

PROCAM – PROspective CArdiovascular Munster Study

RCTs – randomised controlled trials

RR – relative risk

RU – Russia

SBP – systolic blood pressure

SCORE – Systematic COronary Risk Evaluation

SD – standard deviation

SHHEC – Scottish Heart Health Extended Cohort

SHIP – Study of Health in Pomerania

SIMD – Scottish Index of Multiple Deprivation

TCH – total cholesterol

TNF-alpha – tumour necrosis factor-alpha

WHO – World Health Organisation

Acknowledgements

First, I would like to thank my supervisors, Dr Hynek Pikhart and Professor Martin Bobak, who guided my work throughout this research project. Without their encouragement and support, constructive criticism, and invaluable help in so many aspects – from obtaining access to the MONICA and HAPIEE data to reading pages and pages of endless draft chapters – this PhD would not be possible.

I am also grateful to the HAPIEE Study team – both the researchers at the UCL Department of Epidemiology and Public Health, including Professor Michael Marmot as a co-PI of the HAPIEE Study, and local collaborators in the Czech Republic, Poland, Lithuania, and Russia. Their hard work, supported by the grants from the Wellcome Trust (grant numbers 064947/Z/01/Z and 081081/Z/06/Z) and the MacArthur Foundation (Health and Social Upheaval network), made HAPIEE one of the most promising research projects undertaken in Central and Eastern Europe and the former Soviet Union. I would also like to thank the MONICA Study teams from the Czech Republic, Poland, Lithuania, and Russia, for performing the study which still remains one of the major sources of cardiovascular data in the region of interest, and for allowing me to analyse the relevant data. My acknowledgements additionally go to all HAPIEE and MONICA participants, who took part in these epidemiological studies during a period of major societal transition.

I am thankful to all my colleagues from the UCL Cent-East research group, who taught me about HAPIEE, the international work environment, and life in general – my supervisors, Dr Anne Peasey, Christina Chung, Simone Croezen, Rosanna Seels, Natalia Bobrova, and Sinead Boylan. The same is true for my fellow PhD students – and my special thanks go to Jitka and Catalina. I would also like to thank Professor Svetlana Shalnova, Professor Alexander Alexandrov, and Dr Alexander Deev – my colleagues from Moscow – for the honour to have worked with them for seven years, and for their ongoing support. I have been funded throughout the PhD by the UCL Overseas Research Scholarship alongside with a departmental scholarship; many thanks to the funding bodies for enabling me to pursue my research goals.

Last, but by no means least, I am grateful to my friends in Russia, UK, and beyond, and to my family – my mum, dad, and Matthew – for their wisdom, inspiration, loyalty, patience, and love.

Chapter 1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality, morbidity, and disability throughout the world.[1-4] To prevent further increases in the CVD burden, assessing present rates and monitoring population trends should be combined with cardiovascular risk prediction and management, with a focus on individuals and groups at higher risk, who are most likely to benefit from preventive measures.[4-7] Multifactorial concept of CVD infers that multiple risk factors should be considered in combination when identifying individuals at increased total risk.[8-16]

There are numerous scores and algorithms to predict the future risk of cardiovascular events in individuals who are currently free of clinical CVD. These scores are based on established cardiovascular risk factors – core demographic (age and sex), behavioural (smoking), physiological and clinical characteristics, such as blood pressure (BP), blood lipids, and diabetes mellitus (DM). Multiple scales have been developed to predict various fatal and/or non-fatal cardiovascular events over different time periods. All the currently existing, prospective data-based risk scores have been derived from Western European and North American cohorts, and differ by their prognostic accuracy when applied to external populations.[5;9;10;13;17;18]

The best known and most widely used instruments are the Framingham risk model[19] and the SCORE (Systematic COronary Risk Evaluation) scale.[20] The latter, based on prospective data from 12 European cohorts, estimates 10-year risk of fatal CVD and uses age, gender, blood lipids, BP, and smoking as risk predictors. SCORE exists in two versions created specifically for high and low-risk countries of Europe. The European Society of Cardiology (ESC) recommends applying the high-risk SCORE to all populations of Central and Eastern Europe (CEE) and former Soviet Union (FSU), although this version was derived without using any local data.

Of note, CEE/FSU countries have experienced a particularly heavy CVD burden, with high rates of cardiovascular mortality and morbidity. While CVD mortality has declined in most CEE states after the disintegration of the Soviet bloc in 1989, many FSU countries continue to suffer from high rates of circulatory disease, and CVD remains an important health problem throughout the region.[21;22] Therefore, these populations particularly need to have their cardiovascular risk assessed and managed by efficient,

reliable, and relatively inexpensive tools, such as SCORE, which can be implemented in healthcare systems with limited resources.[17;23;24]

However, the universal applicability of a single high-risk modification of SCORE to all CEE/FSU populations appears questionable. It is not entirely clear how well SCORE performs in CEE/FSU, since it has never been properly adjusted, or recalibrated, to these populations. Importantly, CVD rates across CEE/FSU countries are heterogeneous, with two to three-fold differences between areas with the highest and lowest mortality, and it is possible that more than one risk score version is needed. As classical risk factors only partly explain the differences in CVD rates between populations, one would expect that the predictive ability of traditional risk determinants captured by SCORE is also limited (for example, there may be over-estimation of risk in countries with lower CVD rates, such as the Czech Republic and Poland, and risk under-estimation in countries with higher rates, such as Russia). To my knowledge, no prospective individual-level data have been used thus far to investigate the predictive potential of SCORE in CEE/FSU settings.

In addition to and independently from risk factors included in existing, widely used algorithms, such as Framingham or SCORE scales, numerous other parameters predict cardiovascular risk. Recently, there have been ongoing attempts to improve the performance of CVD scales by adding novel risk determinants, such as various biological, genetic, or environmental characteristics (e.g.[8;9;25-41]). In the region of interest, socioeconomic disadvantage and hazardous alcohol consumption appear to be the most likely candidates for inclusion in the cardiovascular risk models, together with conventional risk factors. These extended models might estimate CVD risk in CEE/FSU populations more accurately than the original high-risk SCORE version.

Reflecting the current gaps in knowledge about CVD risk assessment in CEE/FSU, the overall aim of this thesis is to assess the prognostic performance of the SCORE instrument in the populations of interest. Specifically, it will examine (i) how reliably SCORE predicts fatal cardiovascular events in CEE/FSU populations with different levels of absolute risk (i.e. mortality levels); and (ii) whether inclusion of socioeconomic parameters or alcohol consumption characteristics improves the predictive performance of the SCORE instrument in these populations.

This thesis uses individual-level data from four CEE/FSU countries: the Czech Republic, Poland, Lithuania, and Russia. Although sharing some socioeconomic and public health-related characteristics, these states are heterogeneous in terms of recent CVD trends, socioeconomic trajectories, and alcohol consumption patterns. The data come from two existing studies – MONICA and HAPIEE. The MONICA study (MONitoring of trends and determinants in CArdiovascular disease) investigated the dynamics of CVD rates and risk factors from the mid-1980s to at least the mid-1990s[42], while the ongoing HAPIEE (Health, Alcohol, and Psychosocial factors in Central and Eastern Europe) project collects prospective data on cardiovascular outcomes.[43] These studies provide a unique opportunity to compare the predictive role of traditional, SCORE-captured cardiovascular risk factors, as well as socioeconomic characteristics and alcohol consumption parameters, across CEE/FSU populations and over time.

The thesis has been structured into ten chapters. ***Chapter 2*** reviews the concept of total cardiovascular risk prediction, the main characteristics of the existing risk scales, and the major features of the CVD epidemic in CEE/FSU. The emphasis is on the widely used SCORE model, as the instrument officially recommended for all European countries, and on the SCORE applicability to CEE/FSU settings. The importance of cardiovascular risk assessment in CEE/FSU populations facing high CVD rates, the inadequate explanatory potential of classical risk determinants, and the role of other risk predictors, such as socioeconomic parameters and alcohol consumption characteristics, are also discussed. The research aims and objectives are presented in ***Chapter 3***. ***Chapter 4*** describes the study methodology, including information about the study population and samples, measurements of the main SCORE components and additional risk determinants, and the overall strategy and specific steps of statistical analyses.

Chapters 5-9 present the study results. First, MONICA and HAPIEE samples are described in terms of the levels of classical risk factors, additional risk determinants, and atherosclerotic CVD mortality (***Chapter 5***). The prognostic performance of the original, non-extended SCORE across MONICA and HAPIEE samples is then evaluated (***Chapter 6***). Calibration and discrimination of the SCORE models extended by additional risk determinants, namely socioeconomic characteristics or alcohol consumption parameters, are also investigated (***Chapters 7-8***). Finally, the overall strength of the association between SCORE and fatal CVD is assessed, employing the

random effects meta-analysis technique for pooling the sample-specific effect estimates, before and after adjustment for additional risk factors (***Chapter 9***).

In ***Chapter 10***, the summary of the results is followed by a discussion of the methodological limitations and strengths of the thesis. A critical review of the findings and their comparison with the external evidence is also presented, focusing on the predictive performance of the original SCORE and the cardiovascular risk models extended by socioeconomic parameters or alcohol consumption characteristics. The chapter then outlines the future directions of CVD risk assessment and reduction, such as SCORE recalibration and further "evolution" as a prognostic model, the role of socioeconomic measures and drinking parameters as CVD risk determinants, the extension of risk models with novel predictors, and the importance of targeting lifestyle risk factors for cardiovascular prevention. The research and policy implications, together with the overall conclusions of the thesis, are presented in the final part of ***Chapter 10***.

Chapter 2. Background

In this chapter, the concept of total cardiovascular risk assessment and the existing instruments for cardiovascular risk prediction are reviewed, with an emphasis on the SCORE model. The main features of CVD epidemic in CEE/FSU are described, together with the importance and potential problems of total cardiovascular risk evaluation in these populations. The predictive role of classical cardiovascular risk factors, as well as non-conventional risk determinants, such as socioeconomic characteristics and alcohol consumption parameters, is discussed. Finally, the possible ways to optimise CVD risk prediction in CEE/FSU are considered.

2.1. Total cardiovascular risk assessment

In the following section, the current views on total CVD risk assessment are outlined, including methodology and specific risk scales. Among numerous risk models, the SCORE scale is described in more detail.

2.1.1. Total cardiovascular risk assessment: rationale, concept, benefits, and methodology

Cardiovascular disease is a major public health problem and the leading cause of mortality, morbidity, and disability throughout the world.[1-4] The well-known Global Burden of Disease project[2] demonstrated that, in 2001, two major components of CVD, coronary heart disease (CHD) and cerebrovascular disease, were, respectively, the first and second leading causes of death. In combination, they were responsible for over 20% of all deaths worldwide, where CHD accounted for 7.06 million lives lost, and cerebrovascular disease claimed 5.39 million. Moreover, CHD and cerebrovascular disease accounted, respectively, for 84.27 million and 72.02 million DALYs (disability-adjusted life years) lost, and were, when combined, the primary cause of global disease burden.

In Europe as a whole, CVD claims over 4.3 million lives every year, which is almost one-half (48%) of all European deaths.[22] Circulatory disease is the leading cause of death among women in all European states and men in most European countries. Specifically, CHD and stroke account for one half and one third of all CVD deaths, and claim 1.92 and 1.24 million lives per year, respectively. In 2010, the latest year in the WHO Health for All database with the all-European data available, age-standardised death rates were 385.2 per 100,000 for CVD, 178.1 per 100,000 for CHD, and 102.2 per

100,000 for cerebrovascular disease.[21] Even though CVD incidence data for the entire European region are unavailable, morbidity levels could be assessed indirectly, via hospital discharge statistics. In 2010, the number of hospital discharges was as high as 2,505.0 per 100,000 for CVD, 800.5 per 100,000 for CHD and 441.9 per 100,000 for cerebrovascular disease. Similar to other regions, in Europe CVD is not only the leading cause of mortality and morbidity, but also the principal cause of years lost due to early death. It is responsible for 23% (over 34 million) of DALYs lost annually.[22]

According to the WHO projections, the global death toll from non-communicable causes, half of which will be related to CVD, might increase by 17% between 2006 and 2015.[4] The global burden of CHD is expected to rise from approximately 47 million DALYs in 1990 to 82 million in 2020, while the stroke burden is projected to increase from 38 million to 61 million DALYs.[3] The latest WHO estimates suggest that the currently observed annual CVD mortality (approximately 17 million deaths in 2008) will increase by 6 million in 2030.[44]

To prevent further increases in CVD mortality, morbidity, and disability, assessing present rates and monitoring population trends should be combined with cardiovascular risk prediction and management. Ideally, cardiovascular prevention should have universal coverage, targeting whole populations as well as every individual, but in real-world settings with limited healthcare resources, preventive measures need to be focused on individuals and groups at higher risk, i.e. those most likely to benefit.[5;6] This targeted prevention approach aims to "save the greatest number of lives at lowest cost".[4] Therefore, over the last five decades, the general principles of total CVD risk assessment have been developed, and numerous risk prediction instruments were created. The former will be summarised in the rest of this section, while the latter will be described in ***Sections 2.1.2*** and ***2.1.3***.

The main principles of total CVD risk assessment were first formulated in the 1960-1970s.[45;46] Although these principles were introduced before obtaining the vast evidence on strengths and benefits of total risk evaluation, they remain relevant half a century later. Despite the tremendous progress of cardiology, epidemiology, and other biomedical disciplines over the last decades, no single factor is yet known which would either provide complete prevention from CVD, or inevitably lead to cardiovascular pathology. In other words, no single factor can predict cardiovascular risk ideally. Individual risk factors act as component causes, and clinical evidence shows that none

of the currently known factors could qualify as a necessary component cause, elimination of which would completely eradicate CVD. Multifactorial, or multicausal, concept of CVD implies that various risk factors should be considered in combination when identifying individuals at higher total risk.[8-16] The exact impact of a specific risk factor depends on the particular cardiovascular outcome of interest. However, these factors are common enough, due to atherosclerosis parallelism in different vascular territories, to create a single instrument assessing general CVD risk.[47;48]

The varied clinical course of CVD means that a substantial proportion of events are registered in previously asymptomatic patients. This reflects a continuum of cardiovascular risk in the population, with young, risk-free individuals and patients with manifested CVD at the opposite ends of the spectrum, and people with predisposing risk factors and asymptomatic atherosclerosis in the intermediate position.[5;6] Therefore, timely prevention and treatment implies identifying individuals at increased risk among people currently free of symptomatic CVD and not receiving risk-lowering interventions. Typically, risk prediction is based on combined levels of the core demographic (age and sex), behavioural (smoking), physiological and clinical factors, such as blood pressure (BP), blood lipids, and diabetes mellitus (DM). The same factors also determine the level of total cardiovascular risk in patients with established and symptomatic CVD, i.e. across the continuum of risk and atherosclerosis in the population.[5;17] According to the aims of the present research, its primary focus is cardiovascular risk assessment in CVD-free individuals.

Cardiovascular risk factors are rarely observed in isolation. In fact, most people who develop atherosclerotic CVD have several risk factors, which, when combined, produce the total risk. In clinical practice, high cardiovascular risk more often results from a combination of moderately elevated risk factors than from extremely high levels of single factors. Moreover, the risk associated with any specific factor partly depends on the amount of clustering.[11;14;47;49] Even though the risk fraction attributable to a particular factor may be of interest *per se*, the combined, total CVD risk appears to be even more important, both clinically and epidemiologically.

The above-mentioned general principles of total cardiovascular risk assessment underlie its multiple benefits. The main benefit is that risk groups are identified more effectively. Under-treatment of high-risk people with multiple marginal risk factors is prevented, and over-treatment of low-risk subjects with one isolated risk factor is avoided. In

addition, as focusing on a single risk determinant would result in substantial over-estimation of its population-attributable risk[50], the multivariable approach also more accurately evaluates population-level consequences of the risk factor distribution. As a result, more efficient clinical decision-making allows a more targeted and cost-effective allocation of limited healthcare resources, focusing on individuals and groups at the highest risk.[7;12;51;52] Moreover, since shared risk factors predict virtually all the individual CVD outcomes, controlling these factors would prevent multiple outcomes, although to a varying extent. For example, antihypertensive therapy not only reduces BP, but also cuts the risks of CHD, stroke, and heart failure[47;48], with the maximal benefits among those at the highest baseline risk. Finally, more accurate prognostic information improves risk communication and prevention/treatment compliance. Better compliance, in turn, will further improve the effectiveness of cardiovascular risk-reducing interventions.[53;54]

To utilise the above-mentioned benefits of total CVD risk assessment, the high accuracy of risk scales is important. Otherwise, these instruments are no more efficient than traditional, single risk factor-based approaches.[14;55] The two main components of predictive performance, namely calibration and discrimination, are briefly described below (for details, see ***Section 4.5.3*** in the ***Methods*** chapter).

The calibration ability of a risk score reflects how close predicted and observed risks are, and is typically operationalized via the observed to predicted risk ratio, or via the Hosmer-Lemeshow χ^2 statistic.[56-59] A model could be truly predictive only if generalizable to external settings. Since CVD rates vary substantially across populations[60], any model will over- or under-predict risk in lower or higher-risk populations, respectively.[9;10;18;20] To some extent, the problem of generalizability could be resolved by recalibration. Recalibration procedure adjusts existing scales to external settings, by introducing population-specific event rates and risk factor means, while keeping the original regression coefficients for risk factors.[9;10] Relative risk estimates are considered similar for both genders, across populations, and over time.[20;23;61] Typically, the recalibrated models perform well in different populations (e.g.[61-67]; see ***Section 2.1.3***).

Another parameter of the model prognostic performance is discrimination – the ability of a score to separate the participants who will experience events from those who will remain event-free, over a defined time period.[55;58;59;68] Threshold measures of

discrimination include sensitivity (probability of high-risk score for people with subsequent events), specificity (probability of low-risk score for people without subsequent events), true to false positive ratio (likelihood ratio positive, LR+, or sensitivity/1 - specificity), false to true negative ratio (likelihood ratio negative, LR-, or (1-sensitivity)/specificity), positive predictive value (PPV, outcome probability in the high-risk group), and negative predictive value (NPV, outcome probability in the low-risk group). These measures are calculated for a certain cut-off point, which is typically recommended as the drug treatment threshold in the clinical guidelines. However, these threshold characteristics of discrimination are often inadequately described in the recommendations and are assumed to be taken for granted by clinicians. Furthermore, these thresholds differ between guidelines, are often selected arbitrarily, and fail to reach a balance between sensitivity and specificity, which reflects the probability-based nature of any risk scale. By contrast, summary discrimination measures are more useful for comparing the overall predictive performance of different instruments, or for assessing the impacts of different threshold values.[58] An example of summary discrimination measures is the area under the receiver operating characteristic (AUROC) curve. This curve plots the proportion of true positives (sensitivity) versus false positives (1 - specificity) across all risk thresholds. Therefore, AUROC, or the Harrell's C-statistic (AUROC equivalent for survival models), estimates the probability that the scale assigns a higher risk to those developing the event than to those event-free.[10;58;69-71] A recently introduced discrimination measure for survival models is Royston's R^2 index, which denotes the amount of the outcome variation accounted for by risk predictors.[72]

Although the combination of traditional calibration and discrimination parameters reflects statistical performance of the risk models better than either calibration or discrimination alone, its usefulness for clinical decision making and, ultimately, for clinical outcome improvement, is still limited.[71;73] Moreover, the conventional calibration and discrimination measures are relatively insensitive to adding new markers to the model, unless independent, significant associations between new risk factors and the outcome are exceptionally strong.[39;71;74;75] Therefore, the use of novel model performance measures was suggested for evaluating the new risk markers.[34;39;68;71;76-79]

The additional prognostic information, provided by extra risk predictors, could be assessed by comparing the original and extended models and be operationalized via

such discrimination measures as likelihood ratio (LR) test *p* values and/or via risk reclassification indices. In particular, Cook and colleagues proposed risk stratification tables as a tool for assessing the benefit of adding a new marker to a pre-established set of predictors.[68;80;81] The risks calculated from models with and without the new predictor are cross-tabulated, and the proportions of individuals stratified into high vs. low-risk groups, or those in whom intervention is recommended or not, are presented. The summary of the reclassification table is the net reclassification index (NRI), or the net proportion of people who cross the risk threshold as a result of adding a new risk predictor. In other words, it is the difference between the proportions of those moving up and down the risk categories among people who develop events, plus the difference between the proportions moving down and up among event-free participants.[9;39;71;79] The NRI risk categories could be formed on clinically relevant thresholds. The summary reclassification parameter – integrated discrimination improvement (IDI) – is independent of risk thresholds and risk category numbers. IDI quantifies the separation between the individuals who develop an event and those who do not, in terms of the average predicted risks for these two groups, across all possible cut-offs. In other words, IDI represents the extended model's ability to improve average sensitivity without affecting average specificity.[39;71;79;82-85] Reclassification measures are considered the most clinically relevant parameters of prognostic performance, since the adjustment of risk levels, based on the additional risk determinants, could affect clinical decision making, such as starting or withholding pharmacological treatment, and, hence, influence clinical outcomes.[70;73;84;86]

Therefore, the heavy CVD burden is the main rationale for total cardiovascular risk estimation. Assessing and controlling total risk levels could prevent future events more effectively than a single risk factor approach. To achieve this aim, risk scales should have adequate prognostic performance, i.e. acceptable calibration and discrimination. The most widely used instruments for CVD risk prediction, including the SCORE scale as the main risk algorithm of interest, will be described in the rest of ***Section 2.1***.

2.1.2. Scales for predicting total cardiovascular risk

In the last 30 years, several instruments for total CVD risk assessment have been developed. The characteristics of the most popular risk scales, including their predictive performance, strengths and limitations, are discussed in this section. In particular, the main features of the Framingham, PROCAM, ASSIGN, and QRISK/QRISK2 models

are presented. The SCORE scale, officially recommended by the ESC for use in all European populations, is the focus of ***Section 2.1.3***.

Among the variety of currently available instruments for cardiovascular risk evaluation, the oldest one is the Framingham risk function. The Framingham Heart Study (FHS), which started in 1948, is an ongoing prospective, single-centre study of a community-based adult cohort from Framingham, USA. The Framingham risk model, presented by Anderson and colleagues in 1991[19], was derived from the 12-year follow-up of 5,573 FHS and Framingham Offspring Study participants – 30-74-year-old men and women, free of CVD at baseline. The score estimated the five-year and 10-year risk of fatal and non-fatal CHD, based on age, sex, levels of total cholesterol (TCH) and high-density lipoprotein cholesterol (HDL-CH), systolic BP (SBP), current smoking, DM, and electrocardiography signs of left ventricular hypertrophy. Absolute 10-year risk of ≥20% was recommended as an intervention threshold. A modification of this model could be used to estimate the 4-12-year risk of six separate outcomes, namely myocardial infarction (MI), CHD, CHD death, stroke, CVD, and CVD death[87]. Wilson's modification of the Framingham function is similar to that proposed by Anderson and colleagues, but it uses TCH, low-density lipoprotein cholesterol (LDL-CH), and SBP as categorical, rather than continuous variables.[88]

Later modifications of the Framingham risk function applied Cox proportional hazards regression to the 12-year follow-up data on 8,491 Framingham study participants and 1,174 CVD events.[48] The sex-specific risks of any first CVD event (CHD, cerebrovascular or peripheral vascular disease, and heart failure) were predicted by age, TCH, HDL-CH, SBP, treatment for AH, smoking, and DM. With simple adjustments, the model could also be used for assessing the risks of each component of the general CVD risk. Additionally, a total coronary risk score based only on non-laboratory predictors was created. It included body mass index (BMI), instead of TCH and HDL-CH, and performed reasonably well, when compared to the original risk function.[48] The recent version of the Framingham scale predicts 30-year risk of "hard" CVD (coronary death, MI, or stroke), adjusting for competing risk of non-CVD death.[89]

The discriminative ability of Framingham models can be regarded as satisfactory. For instance, the earliest Framingham risk score correctly identified 10% of the asymptomatic population at the highest risk who accounted for approximately one-fifth of CHD events and one-third of stroke and peripheral vascular events over the following

eight years.[90] The later models for coronary risk prediction demonstrated that in Framingham men and women, AUROC was 0.76-0.79 and 0.79-0.83, respectively, compared to 0.63-0.75 in men and 0.66-0.83 in women from six multi-ethnic American studies.[48;61] In non-American populations, the Framingham model discrimination was also adequate. For example, in two German cohorts, namely MONICA Augsburg cohort and PROCAM cohort, respective AUROC values were 0.78 and 0.73 for men and 0.88 and 0.77 for women.[91] In Northern Irish and French men, the Framingham C-statistic was 0.66 and 0.68, respectively[92], while among the participants of the Chinese Multi-provincial Cohort Study, it reached 0.71 for men and 0.74 for women.[93]

However, since the Framingham risk functions were developed in a white middle-class sample, at the peak of CVD incidence in the USA, their generalizability was problematic, especially for populations with lower background risk. Multiple studies demonstrated that original, non-calibrated Framingham algorithms over-estimated coronary risk not only in low-risk Mediterranean populations (e.g.[62;94-96]), but also in Western and Northern Europe (for instance[91;92;97-101]), Native, Japanese or Hispanic Americans[61], and Asian populations[93]. A systematic review by Brindle and co-authors, including 27 studies and 71,727 participants, demonstrated a substantial variability of the original Framingham score calibration in different settings. Coronary risk was under- or over-estimated in high and low-risk populations, respectively: predicted to observed risk ratios varied from 0.43 to 2.87.[18] Nonetheless, recalibrated Framingham models typically performed well in different settings and populations (e.g.[23;61;62;65;93;94;102]).

When used in European populations, the original Framingham model has been criticised not only for risk over- or under-prediction, but also for its specific definitions of some non-fatal end-points (incident effort angina and unstable angina), which were barely applicable to other settings.[20] These limitations stimulated the development of alternative risk instruments, the most widely used of which are presented below.

The German PROCAM scale was derived from the PROspective CArdiovascular Munster Study data (325 acute coronary events in 5,389 35-65-year-old men followed for 10 years). This scale includes age, LDL-CH, HDL-CH, SBP, smoking, and DM, as well as several additional risk factors, such as triglycerides and family history of premature CHD. The instrument predicts 10-year probability of coronary death or first MI in middle-aged men.[103] The PROCAM scale showed good discrimination (AUROC

0.82) and calibration (Hosmer-Lemeshow χ^2 6.5) in the original dataset. However, PROCAM demonstrated worse discrimination and inadequate calibration when applied to external male populations. Among middle-aged men from Northern Ireland, France, and England/Scotland, respective C-statistic values were 0.61, 0.64, and 0.63, and predicted to observed event ratios were 1.78, 2.76, and 2.17.[92;101] Another limitation of the original PROCAM model is its impossibility to provide reliable coronary risk predictions for women, since the proportion of women in the PROCAM cohort was very low.

The Scottish ASSIGN score was derived from the Scottish Heart Health Extended Cohort (SHHEC) study, with 6,540 men and 6,757 women, aged 30-74 years and free from CVD at baseline, who were followed for fatal and non-fatal CVD over the next 10 years.[104] ASSIGN includes not only conventional risk factors (sex, age, TCH, HDL-CH, SBP, the number of cigarettes smoked daily, and DM), but also the area-based Scottish Index of Multiple Deprivation (SIMD) and family history of premature CVD. Demonstrating slightly better discrimination than the Framingham scale (respective AUROC values were 0.73 vs. 0.72 for men, and 0.77 vs. 0.74 in women), the ASSIGN score identified 20% of the population accounting for approximately 45% of CVD events in the next 10 years. The ASSIGN predictions, lower on average than the Framingham risk values, still over-estimated the risk, by 23% in men and 45% in women. Despite its limited calibration potential, ASSIGN reflected the socioeconomic gradient in CVD risk more effectively, compared to the Framingham score. This approach, facilitating better fairness of cardiovascular risk evaluation and management, will be discussed in more detail in ***Section 2.3.2***.

The recently developed CVD risk instrument, QRISK, and its latest modification, QRISK2, are based on the routinely collected data from contemporary UK general practices, encompassing 2.3 million patients aged 35-74 years, over 16 million person-years, and 140,000 incident CVD events.[105] Risk factors included in the QRISK2 scale are age, sex, ethnicity, TCH:HDL-CH ratio, SBP, smoking, BMI, family history of premature CHD, Townsend deprivation score, treated AH, Type 2 DM, renal disease, atrial fibrillation, and rheumatoid arthritis. Compared to the Framingham risk scale[87], QRISK2 demonstrated improved discrimination and calibration. Thus, out of the 112,156 patients classified as high-risk group (≥20% risk over 10 years) by the Framingham score, 41.1% would be reclassified at low risk by QRISK2. Out of the

78,024 patients classified at high risk by QRISK2 (≥20%), 15.3% would be categorised into low-risk group by the Framingham score. Importantly, patients identified at high risk by QRISK2 had higher observed rates of CVD events than patients classified as high-risk by the Framingham scale. The AUROC values for QRISK2 were 0.79 in men and 0.82 in women, compared to 0.78 and 0.80 for the Framingham scale.

The QRISK/QRISK2 instrument was also better calibrated than the Framingham model and the ASSIGN scale. For instance, the predicted QRISK score was very close to the observed risk in both male and female validation cohorts, while the Framingham score was 47% and 18% higher than the actual risk in men and women, respectively, and ASSIGN over-estimated the risk by 35% in men and 38% in women. Similarly, the predicted to observed risk ratios were very close to 1.0 for the QRISK2 estimates, but exceeded 1.0 (risk over-estimation) for the Framingham scale.[105-107] In the independent validation study, QRISK2 under-estimated the risk by 13% and 10% in male and female UK patients from the THIN database (www.thin-uk.com), respectively, while the risk over-prediction by the Framingham scale reached 32% and 10%. Moreover, AUROC values were slightly higher for QRISK2 (0.76 in men and 0.78 in women) than for the Framingham instrument (0.74 and 0.76, respectively).[108] The latest QRISK modification estimates lifetime risk of CVD, based on QRISK2 predictors and controlled for competing risk of non-cardiovascular death.[109]

At present, the QRISK/QRISK2 instrument is the only risk scale developed using the routinely collected data, which explains a greater size and lower selectivity of the original sample. On the other hand, as the model validation was UK-based, involving a one-third random sample of the original cohort and an alternative electronic primary care practice system[108], its international generalizability is unclear. Moreover, a substantial amount of data was missing (for example, blood lipid measurements were unavailable for 60-70% of the participants), and multiple imputation of the missing values for TCH:HDL ratio, SBP, smoking, and BMI was performed. The risk assessment validity and clinical decision potential of the data which were mostly imputed, rather than recorded, might be regarded as questionable. The better performance of QRISK/QRISK2, compared to that of the Framingham model, could be partly explained by additional variables in the former scale (including a socioeconomic parameter; for details, see ***Section 2.3.2***). Other explanations may include the use of data from contemporary UK populations, as well as the cohort-derived nature of the

Framingham scale.[110] Any instrument based on the data from treatment-naïve cohorts, such as the Framingham score, will inevitably over-predict risk in the general population, where treatment "contamination" effects are increasingly common. However, this strength of the QRISK/QRISK2 also mirrors its limitation: this population-derived instrument might inaccurately assess the risk in non-treated individuals.

Less popular, but still worth mentioning are the scores such as PRECARD, derived from the pooled Danish Glostrup Population Studies and the Copenhagen City Heart Study data[99;111], and FINRISK, based on the 10-year follow-up of the 1982 and 1987 cohorts from eastern and south-western Finland.[112] Using the data from the UK Heart Disease Prevention Project and the Scottish Heart Health Study, the Dundee risk function measures modifiable coronary risk from TCH, BP, and smoking, by sex and age.[113] Based on the British Regional Heart Study (BRHS) results, the risk function by Shaper and colleagues uses BP, smoking, self-reported CHD or DM, history of parental death, and the presence of angina to predict the risk of acute MI or sudden ischemic death in men only.[114] The Reynolds score was developed using the follow-up data of over 25,000 female American health professionals, to predict the 10-year composite risk of MI, ischemic stroke, coronary revascularisation, and cardiovascular death, using age, SBP, smoking, TCH, HDL-CH, high-sensitivity C-reactive protein (hsCRP), family history of CVD, and glycated haemoglobin in diabetics.[115] Later, an equivalent score was developed for men.[116] Most of these instruments performed adequately in the original cohorts, but achieved relatively little international acceptance.

Therefore, numerous scores and algorithms have been developed for total cardiovascular risk prediction in individuals currently free of manifested CVD, but having various combinations of cardiovascular risk factors. Most of these scores are based on traditional risk factors, such as age, gender, smoking, blood lipids, BP, and DM. The risk assessment scales differ not only by risk determinants included in the model, but also by outcomes and time-windows for predicted risk. All the currently existing, prospective data-based scores have been derived from Western European and North American populations, and vary by their discrimination and calibration ability when applied externally. The SCORE model, created specifically for different types of external populations and widely used across Europe, is described in the next section.

2.1.3. SCORE model for fatal CVD risk assessment

The main reason for presenting the SCORE instrument in a separate section is its advanced approach to generalizability of risk assessment functions, which resulted in two versions of the original model. Moreover, SCORE is currently the risk scale officially recommended by the European Society of Cardiology (ESC) for any European country.[17] This puts SCORE in a unique position of being the gold standard in cardiovascular risk assessment for European populations and a current acme point in the evolution of European clinical guidelines on CVD prevention.

Over the last few decades, separate guidelines on the management of specific risk factors, such as AH or dyslipidemia, have been gradually replaced by more complex cardiovascular prevention guidelines, incorporating various risk prediction scales. Initially, European guidelines and recommendations on CVD/CHD prevention were based on the Framingham risk model. In 1994, European recommendations presented the Framingham risk function graphically, in a form of a Coronary Risk Chart – a table containing absolute risk estimations for various levels of risk factors.[117] In 1998, a colourful version of these charts was introduced in the Joint European clinical recommendations on CHD prevention.[118] The current guidelines by the ESC and collaborators contain the SCORE risk charts, based on the original European data from the SCORE Project.[17;119]

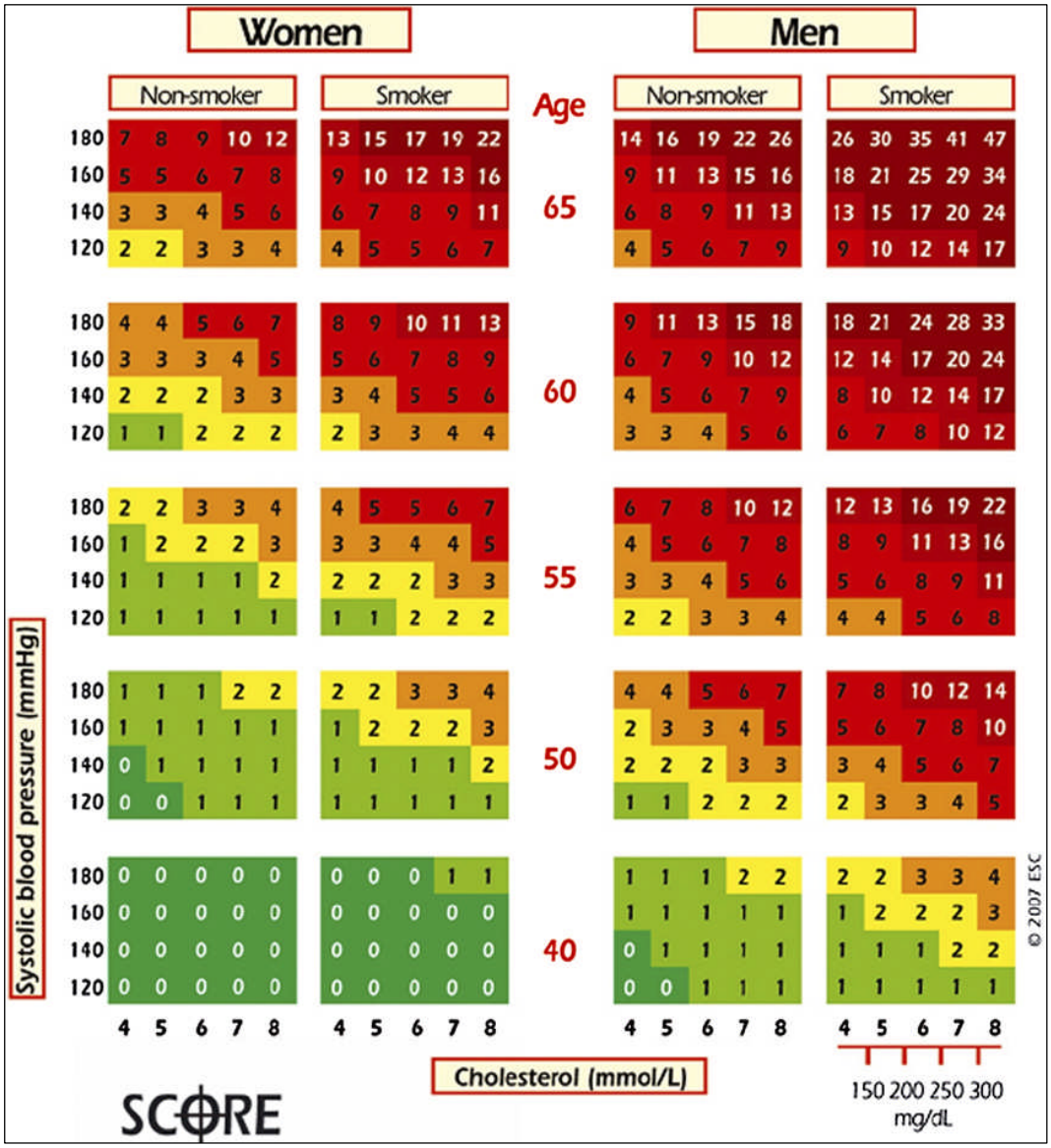
Recommended for wide clinical use throughout Europe, these risk charts and the underlying risk prediction algorithms are the main focus of ***Section 2.1.3***. In particular, after the general description of the SCORE scale, the evidence on calibration and discrimination of the original, non-calibrated SCORE is presented. The limitations of this instrument are summarised, and the prognostic performance of recalibrated SCORE is described.

a) SCORE description

The SCORE (Systematic COronary Risk Evaluation) Project encompassed 12 European cohorts with varying background risk, 205,178 individuals, over 2.7 million years of follow-up, and 7,934 CVD deaths (including 5,652 CHD fatalities) as end-points.[20] The majority of SCORE cohorts were population-based; in addition, occupational cohorts from France, Italy, and Spain were included to improve representation of low-risk regions. To reflect different levels of background risk across Europe, two separate risk charts were created – for high-risk countries, based on the data from Danish, Finnish,

and Norwegian cohorts, and for low-risk countries, based on the cohorts from Belgium, Italy, and Spain. These two charts predict the 10-year risk of fatal atherosclerotic CVD in middle-aged people and include sex, smoking, SBP, and either TCH or TCH:HDL-CH ratio (see **Figure 2.1.1** for the SCORE chart recommended for high-risk countries).

Figure 2.1.1. SCORE chart: 10-year risk of fatal CVD in populations at high risk[17;20]



In the original Weibull risk model, age was defined as a hazard function, or a measure of risk exposure time, rather than a risk factor in a traditional log-linear approach. As the performance of the charts based on TCH and TCH:HDL-CH ratio is very similar (concordance coefficients 0.99), they can be used interchangeably. People with pre-existing atherosclerotic CVD are regarded as having increased risk, irrespective of their risk factor levels. The SCORE model end-points include atherosclerotic cardiovascular

fatal events (coronary and non-coronary), which better reflects the implications of total CVD risk assessment at both individual and population levels. Non-coronary CVD represents a substantial proportion of the total cardiovascular burden in the regions with relatively low CHD rates; therefore, it is also included into the risk prediction algorithm. The prognostic performance of the original SCORE instrument is discussed in the next section.

b) Prognostic performance of original, non-calibrated SCORE

While no data on the SCORE calibration ability were presented in the original publication, the discrimination potential of this scale in SCORE cohorts could be regarded as satisfactory. Thus, the AUROC values in the SCORE Project cohorts not used to derive the risk function were 0.70-0.72 and 0.71-0.84 for high and low-risk cohorts, respectively.[20] The SCORE threshold of 5% for fatal CVD risk over the next 10 years was associated with sensitivity of 59-83% and specificity of 46-73% in high-risk cohorts, compared to 20-43% and 90-96%, respectively, in low-risk cohorts.

Although the prognostic performance of the original, non-calibrated SCORE was satisfactory in the SCORE Project cohorts, it was not ideal in external populations. For example, the performance of the non-calibrated high-risk SCORE instrument and the Framingham scale was examined in the ethnically heterogeneous population of the Newcastle Heart Project (684 South Asians and 825 Europeans), since South Asians living in the UK are known to have a higher risk of CVD mortality than their peers of European ethnicity. In all South Asian groups, the Framingham model mostly followed the patterns expected from the national cause-specific mortality statistics for England and Wales, while SCORE could under-predict CVD mortality risk by 17%, possibly due to the non-inclusion of HDL-CH and DM as risk determinants.[120] Both the Framingham stroke model and the SCORE non-coronary CVD model predicted comparatively low rates, in contrast to high national statistics-based figures: for instance, potential risk under-prediction in South Asian men could reach 29% and 20%, respectively.

In the French virtual population, based on national demographic statistics and representative observational studies (1,046,277 middle-aged men and women), the baseline risk levels, assessed with the original low-risk SCORE version and the Framingham scale, were compared to the cardiovascular mortality estimates from the national vital statistics.[121] As the individual-level record linkage was not performed, the discrimination of CVD risk scales could not be evaluated. However, the indirect

assessment of calibration showed that SCORE could slightly under-predict the risk (the ratios of predicted to estimated risk were 0.94 in men and 0.85 in women), while the Framingham scale might over-predict it (respective ratios were 1.48 and 1.27).

The performance of the non-calibrated low-risk SCORE model, the original Framingham scale, and the local Framingham adaptation – REGICOR (REgistre GIroní del COR) was investigated in the population of nine autonomous Spanish regions. The study cohort included 5,732 35-74-year-old people, CVD-free at baseline and followed for over five years.[122] Sensitivity and specificity were similar for all risk scales, while REGICOR demonstrated the highest PPV values. The percentage of participants classified as high-risk was 7.5% for REGICOR (the closest to the observed CVD risk level of 4.3%), compared to 16.6% and 8.4% for Framingham and SCORE scales, respectively. However, as the 10-year mortality data were unavailable, it was not possible to adequately assess SCORE calibration.

Among 40-65-year-old participants of the Austrian Vorarlberg Health Monitoring and Promotion Programme (n=44,649), who were examined in 1985-1991 and followed for 10 years, the observed number of cardiovascular deaths was 371 in men and 116 in women.[123] The discriminative ability of the original low-risk SCORE was good and similar in both genders (respective AUROC values 0.76 and 0.78). However, SCORE over-predicted the risk in men (predicted to observed (P/O) risk ratio 1.20) and, to a greater extent, in women (P/O ratio 1.91).

In Germany, the prognostic performance of the non-calibrated high and low-risk SCORE versions and the Framingham scale were studied, using the nationally representative data from the German National Health Interview and Examination Survey 1998, as well as the national mortality statistics.[124] In total, 1,811 men and 1,955 women, aged 30-69 years, with no previous history of CVD and no markedly elevated levels of single risk factors, were included in the study. Since no follow-up data were available for these participants, no direct calibration and/or discrimination assessment was possible. However, the high-risk SCORE model could over-estimate CVD mortality risk by 13% (87 events predicted vs. 77 estimated based on national mortality statistics), while the Framingham and the low-risk SCORE scales might under-estimate it by 20% and 39% (62 and 47 events predicted, respectively).

Data from the prospective Reykjavik Study were used to investigate the SCORE performance in Iceland – a country not included in the original SCORE database.[63] In the sample of 7,555 men and 8,277 women aged 36-64 years at baseline, median observed 10-year risk of fatal CVD was 2.44% in men, compared to 1.97% and 3.93% predicted by the low and high-risk SCORE, respectively; for women, these figures were 0.55%, 0.67%, and 1.14%, respectively. The discrimination ability of both SCORE versions was adequate (AUROC 0.80). Therefore, despite the fact that the current European recommendations on CVD prevention[17] consider Iceland as a high-risk country, the low-risk SCORE was better adjusted to Icelandic population, especially in younger men and women of any age.

Both high and low-risk SCORE models were applied to the contemporary Norwegian population – a nationally representative sample of 57,229 CVD-free individuals, aged 40-69 years at baseline (1985 and 1989). SCORE-predicted outcomes were compared to the observed CVD mortality (718 and 226 observed cardiovascular deaths in men and women, respectively).[125] The high-risk SCORE calibration was rather modest, with substantial risk over-prediction in Norwegian men of any age and older women. Specifically, P/O ratios were 1.89, 1.89, and 2.22 in men aged 40-49, 50-59, and 60-69 years, respectively, and 1.67, 2.22, and 2.70 in women from the same age groups. Discrimination of the high-risk SCORE was adequate, with AUROC values varying from 0.65 to 0.72. However, these values were somewhat lower than those for the high-risk cohorts in the original SCORE publication (0.70-0.72).[20] The low-risk SCORE function, even though officially not recommended for Norway[17], was used as a comparison and demonstrated better calibration: in the age groups of 40-49, 50-59, and 60-69 years, P/O ratios were 1.18, 1.09, and 1.27 for men and 1.12, 1.45, and 1.79 for women, respectively, while the AUROC values were similar to the values for high-risk SCORE and slightly lower than those for individual low-risk cohorts in the original SCORE publication (0.71-0.84).[20]

The above-mentioned examples illustrate the restricted predictive ability of the non-calibrated SCORE instrument across external populations. The underlying reasons for this, as well as other SCORE limitations, are discussed below.

c) SCORE limitations

The limited prognostic performance of the original SCORE in external settings could be explained by such factors as the variation of CVD risk between populations and over

time; single assessment of risk factor levels resulting in regression dilution bias; and real-world "contamination" of natural CVD clinical course, due to unaccounted risk-reducing interventions such as antihypertensive therapy.[58] Specifically, the so-called background, baseline, or reference levels of cardiovascular risk, reflecting average CVD-free survival, vary substantially across populations, due to their geographical, cultural, social, behavioural, genetic, and other characteristics. This variation is only partly explained by traditional risk factors included in the conventional risk models.[126] In most industrialized countries, CVD and CHD incidence, mortality and case-fatality have declined in the years following the SCORE data collection. As a result, SCORE will be implicitly prone to risk over-estimation in contemporary settings.[127;128] Since both the scope and the speed of this decline are highly heterogeneous across countries and regions (for details, see ***Section 2.2***), using only two variants of the risk assessment chart, which dichotomise Europe into "high" vs. "low" risk areas, might be inadequate.

The prevalence and distribution of classical risk factors also differ across populations, explaining different absolute risks, despite similar relative risks, associated with a specific factor.[129-131] As risk factor levels in SCORE cohorts were measured only at baseline, the regression dilution bias was introduced, resulting in the relative risk under-estimation for factors with high intra-individual variability. For example, the magnitude of this under-estimation for BP could be as large as one-third.[132] Particularly inaccurate prognosis is expected in individuals with extreme values of highly variable risk factors. The SCORE investigators claimed that the impact of this potential bias was "negligible"[20], although did not provide any substantial evidence to support this assumption.

Moreover, the SCORE chart does not include any indicator variables reflecting the possible "contamination" of the natural, treatment-free clinical course of the disease by various risk-reducing interventions, which are increasingly common in the real-world clinical settings.[133;134] For example, the benefits of antihypertensive therapy might go far beyond BP reduction and not be fully reflected by the risk score. Ignoring this contamination would over-estimate CVD risk when the SCORE instrument is applied to general populations, rather than to "non-contaminated" cohorts.

In addition, due to the limited availability of international morbidity data and varying definitions of non-fatal end-points, only fatal atherosclerotic CVD is regarded as an outcome in the SCORE algorithm. Consequently, the substantial burden of

cardiovascular morbidity and disability, experienced by individuals, populations, healthcare services, and society in general, could be only indirectly assessed. Since mortality risk is substantially lower than morbidity risk, this could also affect risk communication between health professionals and patients.[58]

An extra SCORE limitation is its restricted age range (40-65 years), partly stemming from the age limit compatibility of the original SCORE cohorts. From a clinical perspective, the SCORE investigators' assumption that "persons aged 30 are essentially risk free within the next 10 years"[20] seems rather unlikely, especially for the regions where CVD is widely prevalent in younger age groups, such as many CEE/FSU countries.[22]

The above-mentioned SCORE limitations affect the applicability of the non-calibrated SCORE model to the contemporary external populations. For instance, Norway is considered as one of the healthiest countries in the world. However, using the risk threshold of ≥5%, including risk extrapolation to 60 years as recommended in the European guidelines[17], results in categorising a substantial proportion of Norwegians as being at increased risk. Thus, among participants of the Nord-Tröndelag health study 1995-1997 (HUNT 2), medical treatment would be started in 22.5% of women and 85.9% of men aged 40 years. At 65 years, the respective figures would be as high as 84.0% and 91.6%, according to the Nordic Risk Group.[135] Another research team also demonstrated that the high-risk SCORE classifies a large proportion of asymptomatic middle-aged and older Norwegians as having increased risk, which could lead to unjustified medicalization of the general population.[136] Of note, the SCORE Project investigators themselves emphasised the absence of a single "perfect" level of absolute risk that would define an optimal intervention threshold, regardless of the individual characteristics.[20]

To overcome the problem of generalizability, common to both SCORE and other existing cardiovascular risk charts, risk functions should be recalibrated, adapted and updated, according to the contemporary local event rates and risk profiles. It is particularly important when populations face rapid changes in CVD incidence, case fatality, or risk factor distribution.[58;137] The prognostic performance of recalibrated SCORE in different populations is the focus of the following section.

d) Prognostic performance of recalibrated SCORE

To facilitate the process of country-specific SCORE recalibration, the SCORE research team initiated the HeartScore Project. HeartScore is an interactive web-based tool to recalibrate the risk models and charts for individual countries, using current national statistics on CVD mortality and risk factor distributions.[11;138;139] Such country-specific instruments have recently been developed for Cyprus, Germany, Greece, the Netherlands, Spain, Sweden, and Switzerland, with recalibration in progress for several other countries.

One of these recalibrated scales is SCORE-Germany, developed in 2005 and later validated in two large population-based surveys: the Study of Health in Pomerania (SHIP), Northeast Germany (n=1,956), and the Cooperative Health Research in the Augsburg Region (KORA) study, South Germany (n=2,201).[64] Among 40-65-year-old CVD-free men and women examined in 1997-2001, the predicted 10-year risk of cardiovascular death was compared to the risk extrapolated from the official CVD mortality statistics. As individual-level data on observed CVD mortality were unavailable, the direct assessment of SCORE calibration and discrimination was not possible. Nonetheless, SCORE calibration was expected to be adequate: in accordance with the estimated CVD rates, the model predicted higher risk in the SHIP cohort than in the KORA cohort. The ratio of predicted to estimated mortality rates was close to 1.0 in both cohorts, although some potential risk over-prediction was registered in women.

In Switzerland, the predictive performance of the original low-risk and the country-specific recalibrated SCORE was compared, using the data from a cross-sectional population-based study of 5,773 men and women aged 35-74 years, together with the national CVD mortality statistics for 2003.[140] The original and recalibrated risk functions classified 16.3% and 15.8% of men and 8.2% and 8.9% of women, respectively, at increased risk. Both scales adequately estimated the number of CVD deaths in 10 years: for men, 71 and 74 events were predicted by SCORE models, compared to 73 events recorded in the national statistics data; for women, these figures were 44 and 45 vs. 45, respectively. The recalibrated SCORE classified more women and fewer men at increased risk than the original instrument, and also better estimated risk in people aged over 65 years. Unfortunately, due to the cross-sectional nature of this study, no prospective data were available for the direct assessment of SCORE calibration and discrimination.

By contrast, the performance of the Belgian SCORE version was assessed using prospective individual-level data. Among 6,212 middle-aged men and women, CVD-free at baseline (the early 1980s), 274 cardiovascular deaths were registered over 10 years. Good calibration ability of SCORE was confirmed by the P/O ratio of 0.96 and the Hosmer-Lemeshow χ^2 of 8.31. SCORE sensitivity, specificity, and Harrell's C-statistic were 77%, 72%, and 0.86, respectively, as an evidence of good discrimination.[66]

Among 1,998 middle-aged Australians participating in the Blue Mountains Eye Study, who were free from CVD or DM at baseline (1988) and developed 62 fatal CVD events over the next 10 years, the recalibrated SCORE showed better prognostic performance, compared to the original high and low-risk SCORE scales. Respective Hosmer-Lemeshow χ^2 values, reflecting the model's calibration, were 2.32 vs. 32.78 and 4.40 for men and 7.43 vs. 27.25 and 12.92 for women.[67] Discrimination of the local SCORE was good and similar to that for the original high and low-risk instruments: C-statistic values were 0.75-0.76 for men and 0.70-0.71 for women.

In the Netherlands, the predictive ability of the Framingham scale and the nationally adapted SCORE instrument was compared for 39,719 20-59-year-old participants of the Monitoring Project on Cardiovascular Disease Risk Factors (MP-CVDRF), who developed 256 CVD deaths in 10 years.[141] While the discriminative ability of both models was adequate (AUROC 0.86 for Framingham and 0.85 for SCORE), their calibration was poor, as the respective Hosmer-Lemeshow χ^2 values were 64 and 35 (values under 20 are generally considered acceptable). Although the adapted SCORE instrument was still better calibrated to the local settings than the non-calibrated Framingham score, these findings suggest that the prognostic performance might be not ideal even for recalibrated SCORE.

In the Dutch subsamples of the MP-CVDRF and MORGEN (Monitoring Project on Chronic Disease Risk Factors) projects, 325 CVD deaths were observed among 32,885 37.5-62.5-year-old men and women over 10 years. Both locally adapted SCORE and the original high-risk SCORE over-estimated the risk, while the low-risk SCORE version demonstrated better calibration (respective P/O values 1.33, 1.85, and 0.90 in men, and 1.82, 1.79, and 1.05 in women).[142] No findings on SCORE discrimination were presented.

Among 22,341 middle-aged men and women from North Sweden, who developed 229 fatal CVD events in 10 years following the baseline screening (1990-1994), the national SCORE version demonstrated rather modest calibration, since it over-estimated the risk of cardiovascular mortality (P/O ratio 1.57 for men and 1.55 for women); no data on SCORE discrimination were reported.[143] As the calibration of the original SCORE was not analysed, it cannot be excluded that the local SCORE version still performed better than the non-calibrated instrument.

Therefore, the above-cited evidence[141-143] suggests that even for the locally adapted SCORE versions, prognostic performance might decline over time. This re-emphasizes the importance of SCORE recalibration as a continuous process of the model adjustment to current event rates and risk factor levels.

To summarise, only two variants of the original SCORE scale may not fully reflect the scope of background CVD risk and risk factor patterns in different European settings. Up-to-date country-specific, recalibrated SCORE modifications typically predict risk more accurately. Adequate risk assessment is particularly important for high-risk populations, such as CEE/FSU countries. The problem of CVD burden and cardiovascular risk prediction in CEE/FSU is discussed in the next section.

2.2. Cardiovascular disease in CEE/FSU

The current rates and time trends of CVD are summarised, using the data from the European Health for All database and national studies. The role of traditional risk factors as potential determinants of high CVD rates in CEE/FSU is examined. The importance of cardiovascular risk prediction, the SCORE applicability to local settings, and the opportunities for maximising its predictive potential are also discussed.

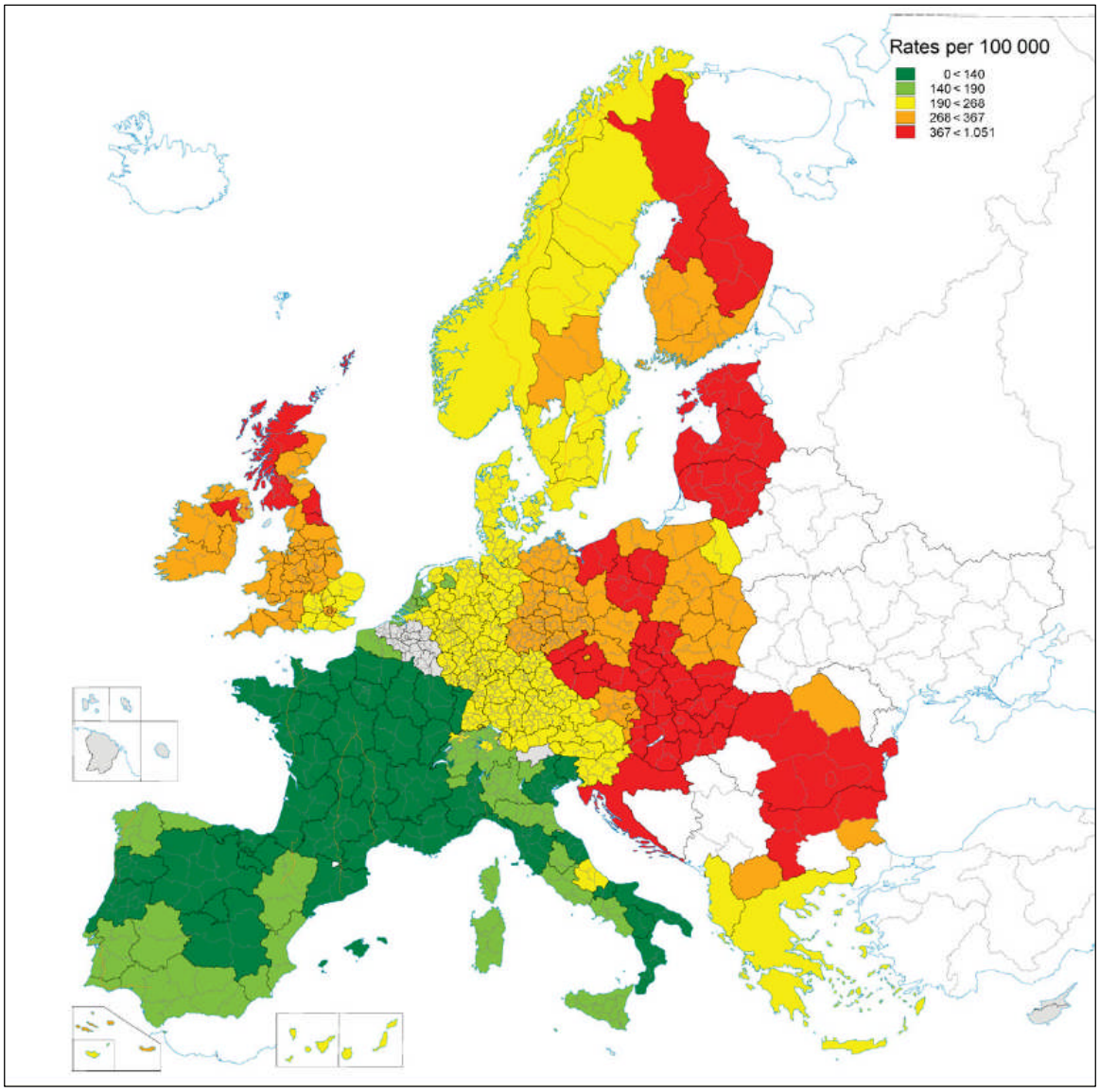
2.2.1. Cardiovascular mortality in CEE/FSU

The global burden of circulatory disease is not evenly distributed, and some countries, such as CEE and FSU states, have experienced particularly high CVD rates. The main focus of this section is on current rates and CVD trends across the CEE/FSU region, put in the context by comparison with respective rates in Western Europe. Due to the limited availability of the data on cardiovascular morbidity and disability for CEE/FSU, the review will concentrate on fatal CVD rates in this region.

Cardiovascular disease is considered the main determinant of the East-West life expectancy gap: for example, in the mid-1990s, it accounted for over 50% of the six-year difference in life expectancy between Eastern and Western Europe.[144-146] Accordingly, the recent cross-sectional estimates of CVD mortality have demonstrated the heterogeneity of Europe in terms of circulatory death rates. In particular, the Global Burden of Disease 2000 and Comparative Risk Assessment studies showed that in 45-59-year-old men from the CEE/FSU countries, the risk of cardiovascular death was three to five times higher than in their peers from Western Europe. In women, relative differences in fatal CVD were of similar magnitude.[147]

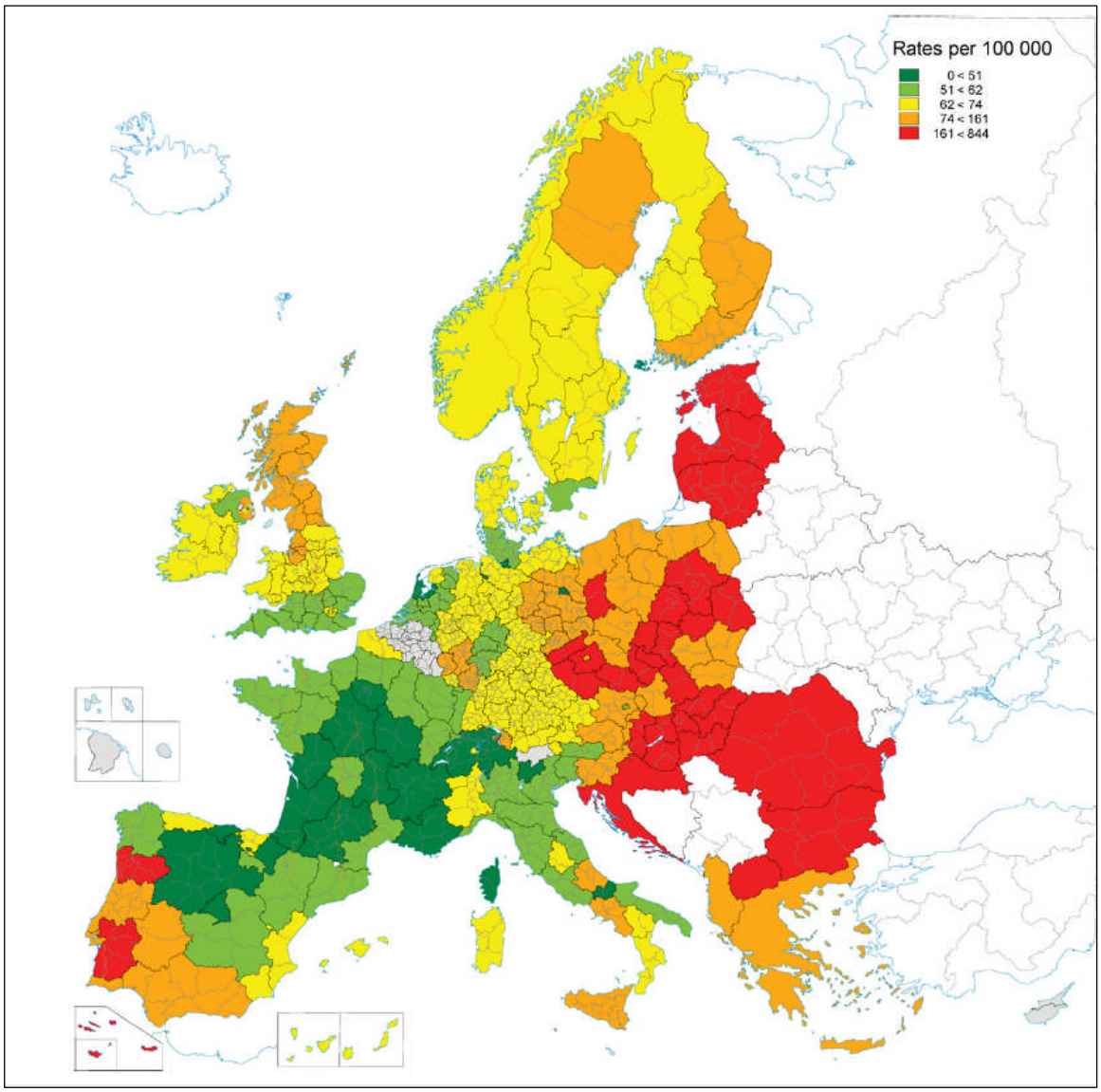
Analysing age-standardised national mortality rates for coronary and cerebrovascular disease in 2000, Muller-Nordhorn and colleagues[148] demonstrated the north-east to south-west gradient in fatal CHD – in particular, the highest vs. lowest death rates in CEE countries vs. France, Spain, or Portugal (**Figure 2.2.1** shows the coronary mortality rates in middle-aged men; the gradients for other age and gender groups were similar).

Figure 2.2.1. Age-standardised coronary mortality in European regions (45-74-year-old men, 2000)[148]



Cerebrovascular mortality was higher outside the “green” circle represented by Central Western Europe – specifically, France, North Italy, and North Spain (**Figure 2.2.2**). The cross-country patterns of coronary and cerebrovascular mortality were similar in both genders. Therefore, men and women from the CEE region were at increased risk of not only CHD, but also cerebrovascular death.[148]

Figure 2.2.2. Age-standardised cerebrovascular mortality in European regions (45-74-year-old men, 2000)[148]



In the late 2000s, according to the WHO statistics[21], age-standardised CVD mortality was the highest in the FSU republics, including Russia and Lithuania, lower in the non-FSU countries such as the Czech Republic and Poland, and the lowest in the "old" member states of the European Union (the members before May 2004, or EU-15), as presented in **Figure 2.2.3**. The distribution of coronary and cerebrovascular mortality across Europe (**Figures 2.2.4** and **2.2.5**, respectively) was similar to that for all cardiovascular deaths. Even though CVD rates in the CEE/FSU region were generally high, there were discrepancies between specific countries: for example, the relative difference in cardiovascular mortality between Russia and Poland was two-fold. For coronary and cerebrovascular mortality, the variation between CEE/FSU countries with the highest and lowest rates was even greater, almost four-fold.

The rates of fatal circulatory disease are described in more detail for the Czech Republic, Poland, Lithuania, and Russia, since this thesis is based on the existing MONICA and HAPIEE studies. These international projects have collected the data on CVD outcomes in Czech, Polish, Lithuanian, and Russian middle-aged population samples.[42;43] In particular, in 2009, the latest year for which official data are available, age-standardised Czech and Polish CVD mortality rates (per 100,000) were similar, being 1.4 times lower than the Lithuanian rates (357.0 and 356.3 vs. 496.8, respectively) and 1.9 times lower than the Russian rates (683.0).[21] To put the respective figures in the context, they were 2.1, 2.0, 2.9, and 3.9 times higher than the rates in the "old" EU states (**Figure 2.2.3**).

As shown in **Figure 2.2.4**, CHD mortality (per 100,000) in the Czech Republic (170.1) was higher than in Poland (96.9), but still substantially lower than in Lithuania (305.1) or Russia (351.7). Comparing these rates with coronary mortality in the EU-15 states produced the 2.6, 1.5, 4.7, and 5.5-fold differences, respectively. In other words, the coronary mortality gap between selected CEE/FSU countries and the EU-15 members was generally larger than that for fatal CVD. In regard to cerebrovascular mortality, Czech and Polish rates (79.1 and 72.4 per 100,000, respectively) were approximately two-thirds and one-third of the corresponding Lithuanian and Russian figures (119.5 and 220.7 per 100,000, respectively). The rates of fatal cerebrovascular disease also demonstrated marked differences between the CEE/FSU countries of interest and EU-15: the respective gaps were 2.0, 1.8, 3.0, and 5.5-fold (**Figure 2.2.5**).

Figure 2.2.3. Age-standardised CVD mortality across Europe (both genders, all ages per 100,000; 2009 or latest available year)[21]

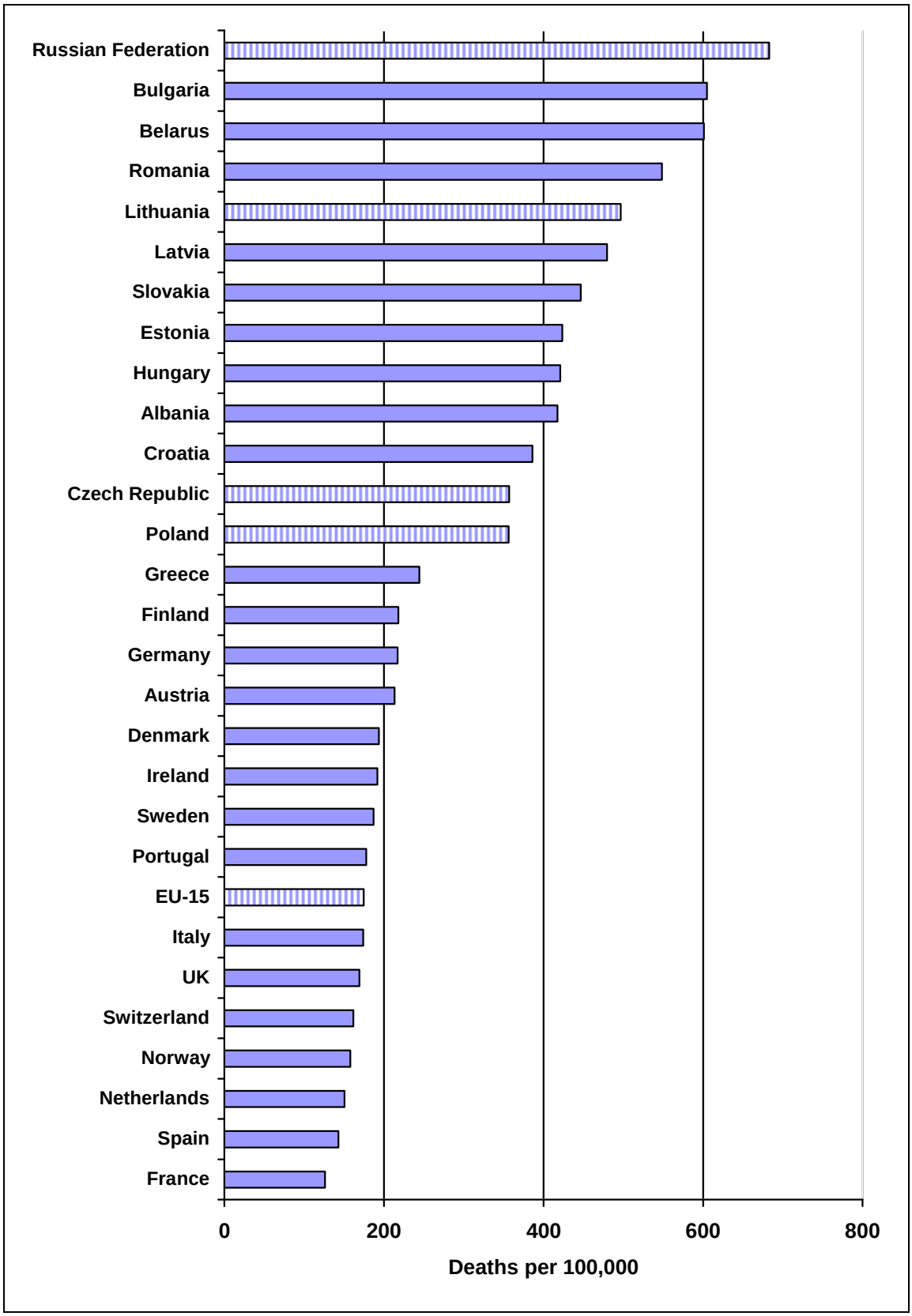


Figure 2.2.4. Age-standardised CHD mortality across Europe (both genders, all ages per 100,000; 2009 or latest available year)[21]

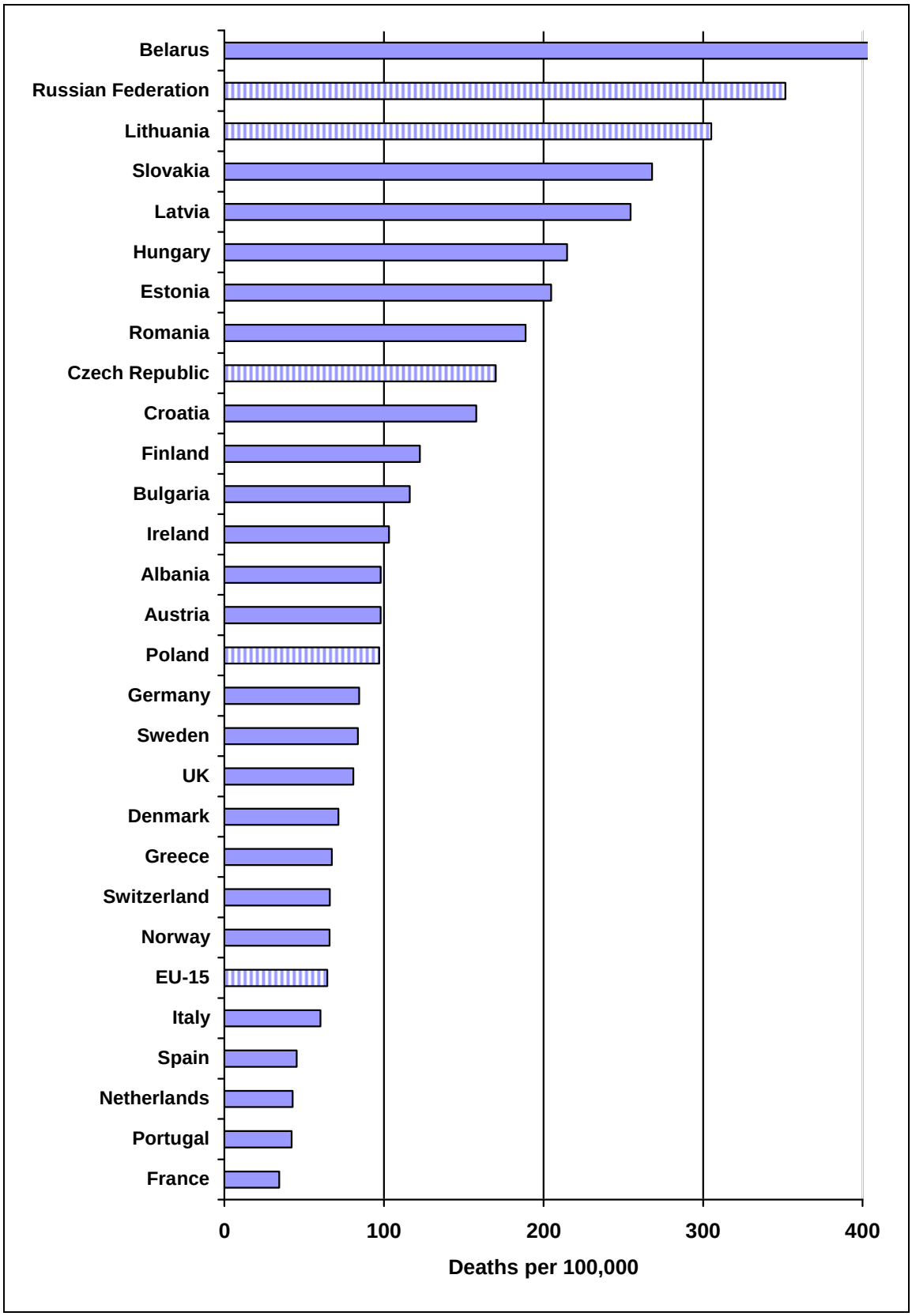
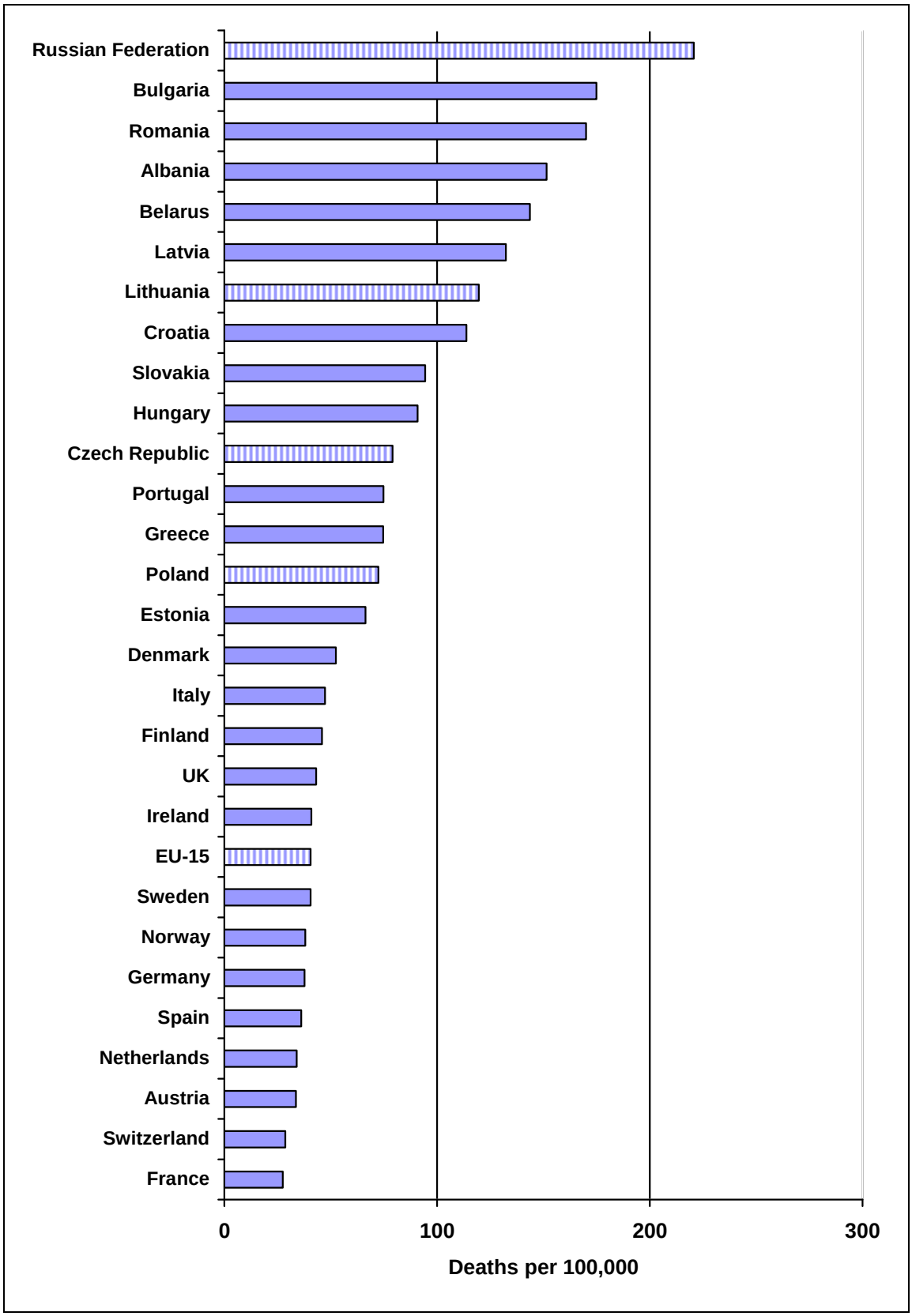


Figure 2.2.5. Age-standardised cerebrovascular mortality across Europe (both genders, all ages per 100,000; 2009 or latest available year)[21]



Thus, the cross-sectional mortality estimates showed high, but not uniform rates of fatal cardiovascular, coronary, and cerebrovascular disease across the CEE/FSU region. The differences in CVD rates appeared relatively small between the non-FSU countries, but were two to three-fold between former republics of the Soviet Union and non-FSU states. These cross-sectional estimates are consistent with the recent time trends in CVD, which are described below.

For specific countries of the CEE/FSU region, statistics on cardiovascular mortality has been systematically collected from the 1950s, when fatal CVD rates were relatively similar in CEE/FSU and Western populations. In the 1960-1970s, while cardiovascular mortality in Western Europe remained stable or gradually declined, it approximately doubled in CEE/FSU.[149-153] According to the WHO statistics, the majority of CEE/FSU countries demonstrated stagnation in cardiovascular mortality over the late 1970-1980s, its gradual decline starting in the early to mid-1990s, and later divergence of cardiovascular death rates. By contrast, CVD mortality in most Western European countries – the EU-15 members – has been continuously declining over the last four-five decades.[21]

The post-1989 heterogeneity of fatal CVD trends in CEE/FSU was mostly due to a dramatic mortality increase in the former Soviet republics and a gradual mortality decline in non-FSU states (e.g.[144;149-151;154-157]). For example, in the 1990s, coronary mortality decreased by 40% in the Czech Republic and by 30% in Poland[149], while this decrease was less pronounced in Lithuania, and Russia did not achieve any substantial reduction in CHD death rates.[22] The trends in total cardiovascular, coronary, and cerebrovascular mortality in these four countries could exemplify the general changes in CVD rates across the CEE/FSU region.

In particular, according to the European Health for All database, CVD mortality in the Czech Republic and Poland stagnated from the 1970s to the late 1980s and then declined, particularly rapidly in the Czech population.[21] Lithuanian trends in fatal CVD were similar, although the mortality decline has decelerated since the early 2000s. In Russia, a gradual increase in the early 1980s and a small decline in 1985-1987 were followed by two peaks in the mid- and late 1990s, with some decrease in 1995-1997, and a tendency towards a slow reduction starting from 2004. To compare, the EU-15 countries faced a steady decline in CVD mortality over the past 40 years (**Figure 2.2.6**).

Similar trajectories were observed for coronary and cerebrovascular mortality (**Figures 2.2.7-2.2.8**).

Specifically, Czech and Polish rates of CHD and stroke death were relatively stable in the 1970-1980s and then decreased – relatively fast and starting in the early 1990s in the Czech Republic, slowly and starting from the late 1990s in Poland. An increase in Polish rates of fatal CHD and stroke in the late 1990s, without a simultaneous elevation in total CVD mortality, could be explained by the introduction of ICD (International Classification of Disease) 10 in 1997.[158] In Russia, some mortality decline in the late 1980s and early 1990s was followed by a sharp increase in the mid-1990s, a brief and less pronounced reduction, and then another increase from the late 1990s to 2003. In 2004-2009, Russian coronary and cerebrovascular mortality levels remained high, despite some decline. In Lithuania, CHD trends were closer to Russian ones, while cerebrovascular mortality trajectories were similar to that in the Czech Republic and Poland. By comparison, a continuous decline in fatal CHD and stroke was observed for the EU-15 countries over the past four decades.

Figure 2.2.6. Trends in age-standardised CVD mortality across Europe (both genders, all ages per 100,000; 1970-2009)[21]

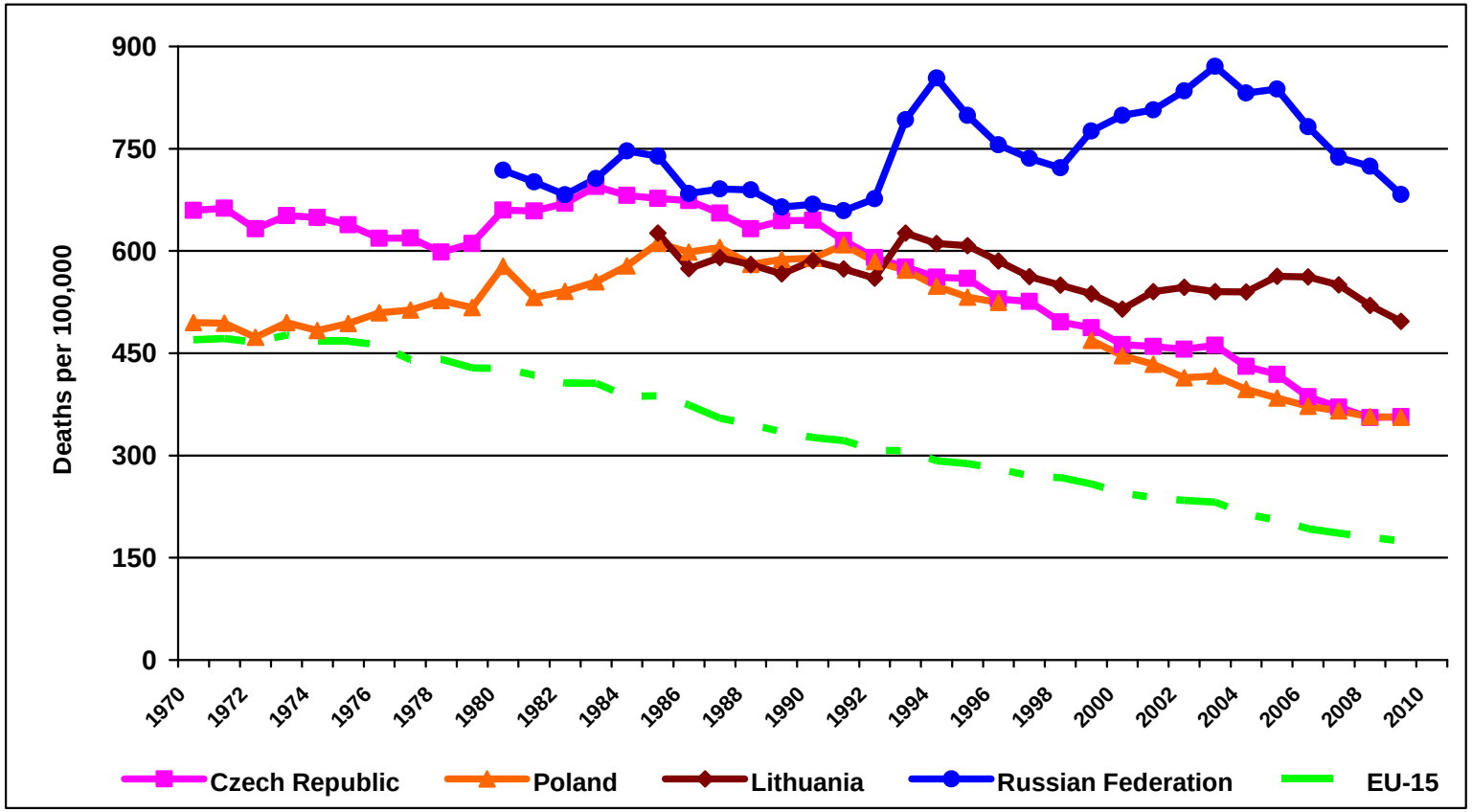


Figure 2.2.7. Trends in age-standardised CHD mortality across Europe (both genders, all ages per 100,000; 1970-2009)[21]

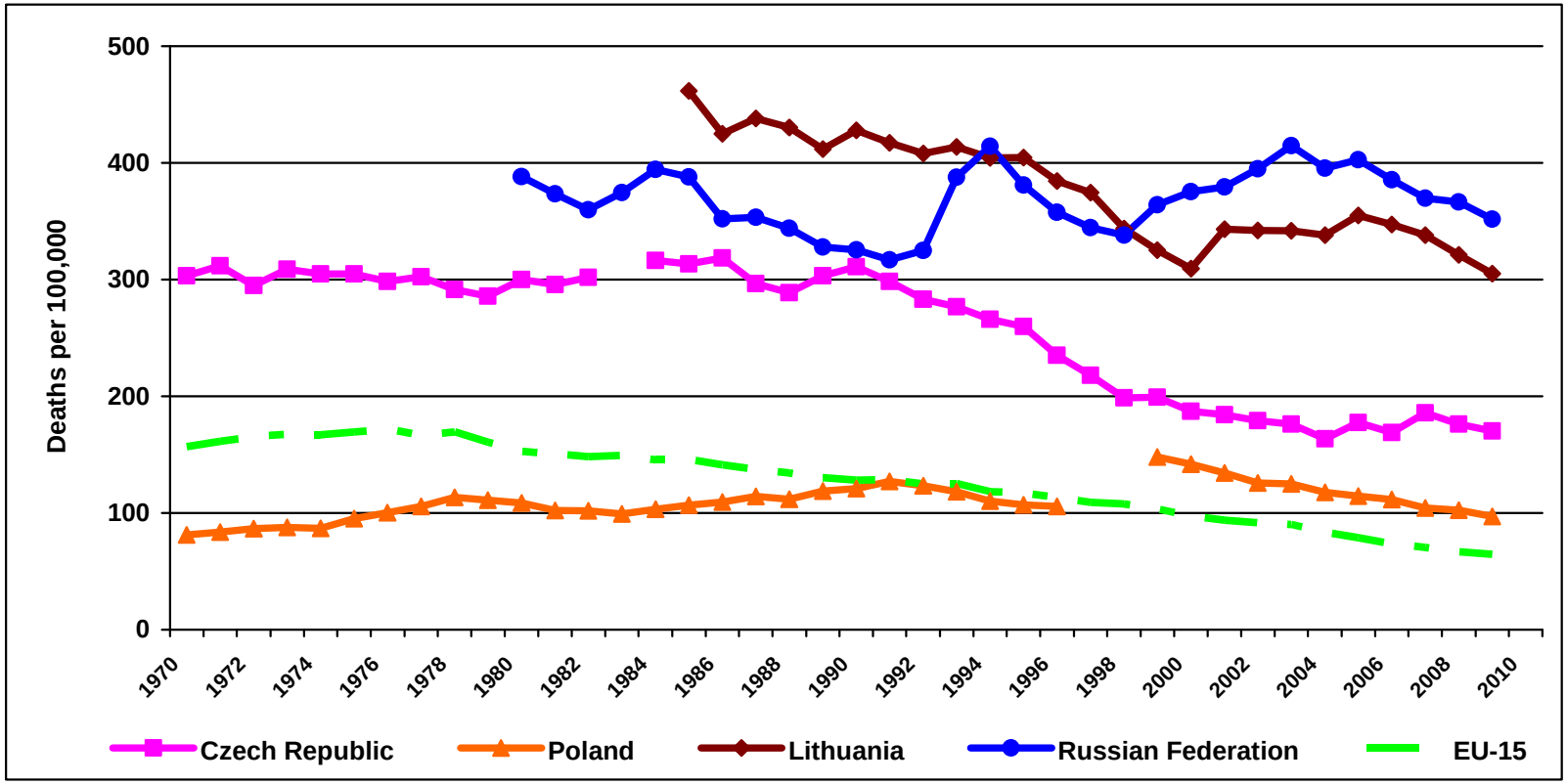
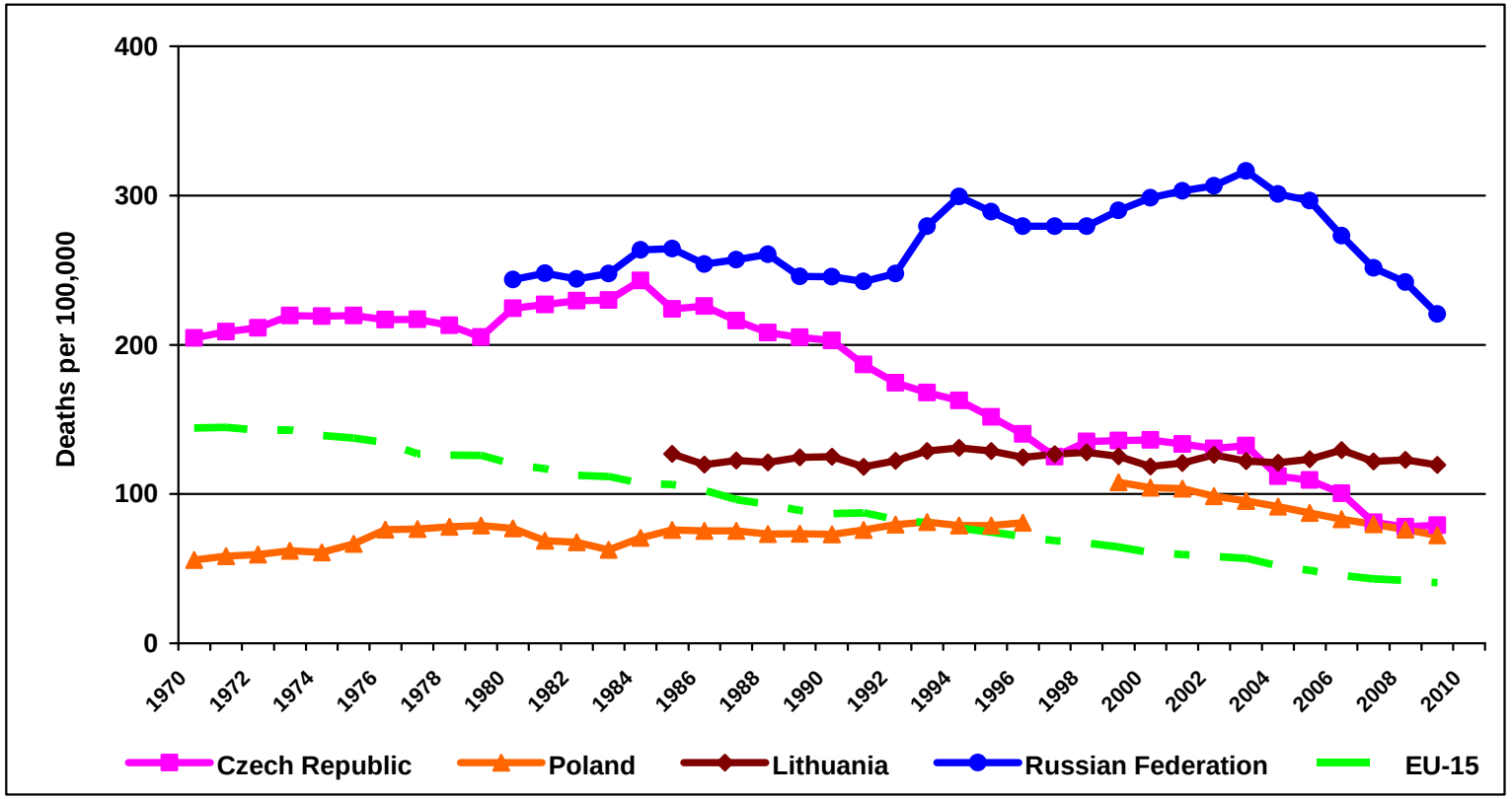


Figure 2.2.8. Trends in age-standardised cerebrovascular mortality across Europe (both genders, all ages per 100,000; 1970-2009)[21]



While several studies have investigated the recent dynamics of cardiovascular mortality in the Czech Republic[159-161], Poland[162;163], and Lithuania[164], the particularly dramatic CVD mortality fluctuations in Russia have been addressed in more detail. Thus, Leon and colleagues demonstrated that between 1984 and 1987, cardiovascular mortality in 20-69-year-old Russian men and women decreased, respectively, by 1,015 and 494 per 1,000,000.[165] On the contrary, from 1987 to 1994, CVD mortality increased by 3,149 per 1,000,000 in men and by 1,314 per 1,000,000 in women. Even though absolute differences in fatal CVD were greater in men, relative changes were of similar magnitude in men and women, with the 1984-1987 decrease of 9% and 7% and the 1987-1994 increase of 29% and 17%, respectively. Changes in fatal CHD and stroke rates, even though not presented in detail, followed the general pattern for cardiovascular mortality.

Similar results for the period between 1990 and 1994 were obtained by Notzon and colleagues, who additionally put the data in an international context. In particular, using Russian national statistics for 1990-1994, the authors showed that increasing CVD mortality accounted for 33.4% and 41.6% of the life expectancy decline in men (-6.1 years in total) and women (-3.2 years in total), respectively.[166] Between 1990 and 1994, mortality from heart disease rose by 31% in Russian men and by 17% in Russian women. Over the same period, fatal heart disease rates in U.S. men and women decreased by 8% and 6%. As a result, the ratio between heart disease mortality in Russia vs. the USA rose from 1.4 to 2.0 in men, and from 1.3 to 1.7 in women. Similarly, cerebrovascular mortality rose by 24% among Russian men and by 17% in Russian women, while in their American peers, it decreased by 4%. The between-country ratio for male and female cerebrovascular mortality increased, respectively, from 5.3 to 6.8 and from 4.7 to 5.7.

In accordance with the above-cited studies, Shkolnikov and co-authors showed an increase in adult Russian cardiovascular mortality between 1991 (the year of the Soviet Union's break-up) and 1994 (the year of minimal life expectancy). There was some improvement from 1994 to 1998 (the year with the then-latest mortality data available), even though the 1998 death rates remained higher than the 1991 levels.[167] For instance, CVD mortality rate ratios for 1994/1991, 1998/1994, and 1998/1991 reached, respectively, 1.5, 0.8, and 1.2 in 15-74-year-old men, and 1.4, 0.8, and 1.2 in women of the same age. The above-mentioned tendency of greater absolute differences in males,

but similar relative changes in both genders was also observed for coronary and cerebrovascular mortality.

Analysing more extensive national statistics data for 1991-2001, Men and colleagues also demonstrated that in seven Russian regions, cardiovascular mortality was already high in 1991 and rose further over the next 10 years, with a particularly sharp increase after the 1998 economic crisis.[168] For instance, in 35-69-year-olds, CVD mortality in 2001 was 24% higher for men and 18% higher for women than in 1998, while in 1994-1998 fatal CVD rates decreased by 22-23%. The 1998-2001 increase in CHD mortality was slightly smaller than the 1994-1998 decline: +21% vs. -26% in men, and +19% vs. -27% in women. The increase in cerebrovascular mortality during 1998-2001 was similar to the 1994-1998 drop for men (15-17%) and women (10-13%). A later analysis of the national statistics data by the same research group demonstrated that in 35-60-year-old Russian men, the rates of fatal CVD and CHD continued to increase from 2001 to 2003, remained relatively stable in 2003-2005, and in 2006 decreased to the level of 2003.[169] Thus far, no studies extensively analysing the post-2006 CVD trends, based on the Russian national data, have been published, to the best of my knowledge.

Importantly, the CEE/FSU region not only demonstrates high current CVD rates, but is also expected to face an increasing CVD burden in the future. For instance, according to the WHO estimates for 2020, coronary mortality in men and women from former socialist economies, represented mostly by CEE/FSU countries, would increase to 712,000 and 702,000 deaths per year, respectively – by 52% and 26%, compared to the 1990 levels. An increase in cerebrovascular mortality is expected to be as large as 52% in men (up to 364,000 deaths per year) and 24% in women (495,000 deaths per year).[1] However considerable, these estimates could be regarded as conservative: they are based only on expected population shifts (specifically, ageing) and do not take into account potentially increasing risk factor levels in former socialist economies.

Therefore, not only are CVD rates in CEE/FSU higher than in EU-15, but there is also marked heterogeneity in cardiovascular mortality across the CEE/FSU region. Although circulatory death rates declined in most CEE populations since 1989, the FSU countries still suffer from high CVD mortality. The extent to which the high rates of fatal CVD in CEE/FSU are explained by conventional risk factors is discussed in the following section.

2.2.2. Traditional cardiovascular risk factors and fatal CVD in CEE/FSU

The simplest explanation of high CVD rates in the CEE/FSU populations would be a higher prevalence of conventional cardiovascular risk factors. Classical risk factors are considered as the principal determinants of total CVD risk and, hence, remain the basis of the currently used scales and algorithms for cardiovascular risk assessment. However, CVD has multicausal aetiology, and as yet, there is no single risk factor acting as a necessary cause of circulatory disease (***Section 2.1.1***). Given the increasingly large number of new factors that have been independently related to elevated cardiovascular risk, it is possible that the role of traditional risk determinants, as the explanation of high CVD mortality in CEE/FSU, is important, but not exclusive.

One of the best-known international epidemiological projects which allow the comparison of conventional cardiovascular risk factors and CVD mortality across populations is the WHO MONICA (MONitoring of trends and determinants in CArdiovascular disease) initiative. In particular, this project monitored CVD events and traditional risk factors in 38 middle-aged populations (men and women aged 35-64 years). In Europe, 29 populations from 16 countries were included in the project.[42;130] Even though the MONICA follow-up took place from the mid-1980s to the mid-1990s, this study remains one of the largest all-European sources of individual-level data on CVD and cardiovascular risk factors.

In agreement with the WHO statistics presented in ***Section 2.2.1***, the cross-sectional MONICA data from the mid-1980s demonstrated that CVD rates in CEE/FSU countries were higher than in Western Europe even before the collapse of the Soviet bloc. The national age-standardized CVD and stroke mortality rates in 15 “communist” countries participating in MONICA (including the Czech Republic, Poland, Lithuania, and Russia) were on average twice as high as those in 25 “non-communist” countries.[170] Although, in general, cardiovascular risk factors were more prevalent in Central/Eastern European and Siberian centres, the East-West divide for these factors was less obvious than for CVD rates. For example, while “communist” populations had a significantly higher prevalence of AH and male smoking, the prevalence of hypercholesterolemia was lower than in non-communist populations. A later ecological analysis demonstrated that cross-sectional MONICA estimates of traditional risk factors (TCH, BP, and smoking) inadequately reflected the between-population variation in cardiovascular, coronary, and stroke mortality.[126] Specifically, in men, these risk factors explained over

39% of the stroke mortality variance, but less than 25% of the variance in fatal CVD and CHD. In women, over 33% of the cardiovascular and stroke mortality variance was explained by classical risk factors, while for coronary deaths this percentage was only 14%.

Using later MONICA data from the early 1990s, Bobak and Marmot showed that contemporary levels of traditional cardiovascular risk factors explained 30% and 45% of coronary mortality variation in men and women, respectively.[149] These percentages were higher than those obtained by Stewart and colleagues[126], but still demonstrated that over a half of between-population variation in fatal CHD remained unexplained by conventional risk determinants. Similarly, the East-West differences in coronary mortality were to some extent due to classical risk factors, but not explained away by them. For instance, the age-adjusted rates of CHD mortality in Eastern European men were 81% higher than in their Western peers; after adjustment for conventional cardiovascular risk factors, this percentage reduced to 42%. For females, the respective figures were 70% and 47%.

Importantly, the MONICA Project not only analysed cross-sectional data, but also compared the international trends in CVD and cardiovascular risk factors over time. It was shown that in populations with declining CHD mortality, two thirds and one third of this decline were explained, respectively, by coronary event rates and case fatality.[127] In turn, population-level trends in coronary event rates were partly explained by the changes in conventional risk factors – by approximately 40% in men and 15% in women.[130] However, for the CEE/FSU populations, the risk factor trends did not fully account for coronary mortality changes from the mid-1980s to the mid-1990s. In general, the strength of the association between risk factors and mortality dynamics depended on the selected statistical model, age group, and "exposure-disease" time lag.[130] Additionally, due to the ecological nature of data analysis, this association could be confounded by various non-measured covariates, which were linked to both classical risk factors and CHD. Precise estimation of the magnitude and direction of this complex confounding effect is problematic, due to the understandably limited number of potential confounders measured in MONICA populations.

The MONICA findings were confirmed in later studies from the CEE/FSU region, focusing on the further follow-up of pre-established MONICA or other cohorts. Specifically, in middle-aged men from Prague, followed for 20 years, CVD mortality

was largely explained by AH, high TCH, and smoking.[171] A marked decline in CHD and stroke mortality in the Czech population over the period from 1985 to 2007-2008 was linked to a significant reduction in population levels of SBP and TCH, although the magnitude of this impact was not reported.[159;160] In Warsaw MONICA participants, followed from 1984 for 10 years, the decline in fatal CVD by 25% in men and 33% in women was mostly explained by reduced mean SBP levels and smoking prevalence.[172] In Polish adult population, aged 25-74 years, CHD mortality halved from 1991 to 2005, which was partly (54%) due to beneficial changes in classical risk factors, such as TCH, SBP, and smoking.[158] In general, it has been shown that traditional cardiovascular risk factors demonstrate similar relative risks in CEE/FSU and Western populations.

Therefore, the evidence from local studies (predominantly from MONICA) is consistent with the important role of classical risk factors in CVD and CHD mortality variation and trends. However substantial, this impact is not exclusive; other, non-conventional determinants of cardiovascular risk, described in more detail in ***Section 2.3***, may also play a role. Despite their limitations, classical risk factors remain the major risk determinants incorporated in all CVD risk scales, including SCORE. The high-risk SCORE version is officially recommended for CEE/FSU[17], and its applicability to local settings is discussed below.

2.2.3. SCORE applicability to CEE/FSU populations

The paradigm of total CVD risk assessment implies that the benefits of risk-lowering interventions are the greatest in individuals, groups, and populations at the highest background risk. This approach is particularly relevant to post-transitional CEE/FSU countries, which face high and often increasing rates of CVD.[22;173] These populations particularly need to have their cardiovascular risk assessed and managed by efficient, reliable, and inexpensive tools, which can be readily and easily implemented in healthcare systems with limited resources.[17;23;24] The scope of the CVD problem is too substantial in CEE/FSU countries to postpone proactive risk assessment. For this reason, the existing instruments, although not validated against country-specific risk functions, are widely used – specifically, the high-risk SCORE model, recommended by the ESC guidelines on CVD prevention.[17] The SCORE strengths, limitations, and potential ways to improve its performance in the CEE/FSU settings are outlined below.

The obvious strength of the SCORE scale when applied to CEE/FSU populations is its limited number of easily measured risk factors. All SCORE risk determinants are either basic demographic characteristics (such as age and gender), or routinely measured clinical parameters (BP, blood lipids, and self-reported smoking status). Therefore, no additional resources are required for the total cardiovascular risk assessment with the SCORE instrument. However, this parsimony and closeness to the real-world clinical settings, together with the official endorsement of the SCORE use throughout Europe by the ESC and national societies, should not mask a number of important SCORE limitations.

The principal limitation is directly linked to SCORE simplicity: while classical risk factors are important in cardiovascular risk prediction, they cannot explain this risk completely (***Section 2.2.2***). Additionally, as mentioned in ***Section 2.2.1***, CVD rates and trends in the CEE/FSU region are heterogeneous. Nonetheless, according to the ESC guidelines on CVD prevention, all CEE/FSU states, including the Czech Republic, Poland, Lithuania, and Russia, are regarded as "high-risk" countries, without any further differentiation.[17] At the same time, only one Russian male cohort was included in the original SCORE database.[174] These data were obtained in the Soviet era, before the dramatic changes in CVD mortality took place in the region. In the populations used for the development of the high-risk SCORE version (Denmark, Finland, and Norway; no CEE/FSU countries), the data were collected from the late 1970s to the early 1990s.[20] Since then, CVD mortality has declined in some CEE/FSU countries, such as the Czech Republic and Poland, and increased in the others, such as Russia, with particularly striking fluctuations during the last three decades.

The risk estimates from the cohort studies which started more than 30 years ago are likely to over-predict cardiovascular risk in some CEE/FSU states (such as the Czech Republic and Poland) and under-predict it elsewhere (for example, Russia), since contemporary Czech and Polish CVD mortality is lower and contemporary Russian CVD mortality is higher than cardiovascular death rates in Scandinavian countries in the late 1970s to the early 1990s.[20;21] This could cause unnecessary medicalization of low-risk individuals, as well as insufficient intervention for higher-risk people. Both scenarios would result in human and economic losses and could further increase the burden on the already struggling healthcare systems of CEE/FSU countries.

As outlined in ***Section 2.1.3***, adjusting, or recalibrating, the original SCORE scale for specific countries makes the processes of risk prediction, reduction, and communication more efficient. This approach is particularly relevant to CEE/FSU, due to its heavy CVD burden. Recently, the country-specific SCORE models have been introduced in the Czech Republic[175] and Poland[176], while in Lithuania and Russia, a non-specific high-risk SCORE chart is widely used. To date, the Czech and Polish SCORE scales lack a detailed description of recalibration procedure and/or comparison of their predictive accuracy with the original instrument. Considering the above-mentioned limitations of the non-calibrated SCORE, its performance might be far from ideal when applied to CEE/FSU populations.

The nationally representative, updated information on event rates and risk factor patterns, necessary for a proper SCORE recalibration, is not systematically collected in CEE/FSU, since the coverage and the linkage between routine systems of health-related and demographic data collection are inadequate.[146] The approach based on the national statistics, however attractive, cannot currently substitute for individual-level data collection in cohort studies. Thus far, prospective individual-level studies, which could form an evidence base for assessing the prognostic performance and potentially recalibrating the existing CVD risk scales, have mostly been conducted outside CEE/FSU. This enhances the importance of relevant local epidemiological projects in CEE/FSU countries. In particular, MONICA and HAPIEE are among the largest international studies on cardiovascular health and CVD in the region of interest. The MONICA study investigated the dynamics of CVD and CHD rates and risk factors from the mid-1980s to the mid-1990s[42], while the ongoing HAPIEE (Health, Alcohol, and Psychosocial factors in Eastern Europe) project collects prospective data on cardiovascular outcomes, starting from the early 2000s.[43] The MONICA and HAPIEE studies provide an opportunity to investigate the impact of classical and non-conventional risk factors on fatal CVD and to assess the predictive performance of the original and extended SCORE models in CEE/FSU populations.

In summary, the high-risk SCORE scale is based on routinely measured classical risk factors, and is easy to use in CEE/FSU. However, it has not been properly assessed and/or recalibrated in these countries, and heterogeneous CVD mortality in the region suggests that several variants of the high-risk SCORE might be necessary. In addition, the prognostic potential of the classical risk factors included in SCORE is limited.

Adding non-conventional risk factors to the model could improve the accuracy of total CVD risk prediction, which is the focus of the next section.

2.3. Additional risk factors and cardiovascular risk prediction

As outlined in ***Section 2.2***, however important the classical risk determinants are in predicting total cardiovascular risk, they do not explain it completely. Therefore, recently, there have been ongoing attempts to improve the performance of CVD scales by including new, non-traditional risk factors, such as various biological, genetic, or environmental characteristics (e.g.[25-38]). In CEE/FSU, socioeconomic disadvantage and hazardous alcohol consumption appear to be the most likely candidates for inclusion in the cardiovascular risk models, together with classical risk factors. The role of these two additional factors in total CVD risk assessment will be discussed in more detail.

2.3.1. New risk factors as potential cardiovascular risk determinants

There is a general agreement that adding new variables could improve predictive ability of multivariable risk functions by identifying more people with very high or very low risk.[15;32-34;86;177] However, numerous novel risk factors are not included in the two principal CVD risk scales – the Framingham and SCORE instruments. These algorithms do not take into account such factors as socioeconomic parameters, ethnicity, family history of premature CVD, psychological stress, renal disease and microalbuminuria, alcohol consumption, low physical activity, obesity, metabolic syndrome, insulin resistance, triglycerides, fibrinogen, homocysteine, inflammation markers, and other risk determinants.[39;40;47;51] The limited number of risk factors included in the existing risk assessment models, however artificial, reflects the essential feasibility issues. Additional risk factors often improve predictive performance at the cost of extra resources necessary for their measurement. Clinical acceptability, applicability, and relevance for population screening programs are questionable for more extensive risk scales. The large number of risk predictors in a model also complicates the creation of visually displayable risk charts. Additionally, the models including new CVD risk determinants often fail to demonstrate a substantial improvement in the traditional measures of prognostic performance.[8;40;86]

In particular, there is limited potential for further improving the prognostic accuracy by adding more predictors to the model. For example, out of 57 variables investigated in the PROCAM study, eight were finally included in the eponymous risk scale.[103] Nonetheless, when the PROCAM performance was assessed in the prospective PRIME

study (Prospective Epidemiological Study of Myocardial Infarction), both the more parsimonious Framingham model and the more extended PROCAM instrument demonstrated substantial risk over-estimation in high and low-risk cohorts from Northern Ireland and France, respectively.[92] Recently, numerous studies on both primary and secondary prevention have shown that adding new biomarkers (such as C-reactive protein, N-terminal pro-brain natriuretic peptide, aldosterone, renin, insulin-like growth factor-1, fibrinogen, D-dimer, plasminogen activator inhibitor-1, homocysteine, lipoprotein-associated phospholipase A2, cystatin C, microalbuminuria, brachial flow-mediated vasodilation, and ankle-brachial index) or genetic polymorphisms (for example, for interleukin 18 or thrombomodulin), which are independent CVD predictors, on the top of conventional risk factors does not markedly improve the model performance (for instance[27;30;31;33;34;37;38;40;75;178-186]).

The problem of limited additional prognostic value is relevant for any new factors, since most of them correlate with standard risk determinants, and are less prevalent in the population than classical risk predictors.[30;74;75;80;187] Age is the strongest predictor of cardiovascular risk, which outweighs all the additional risk determinants in the multivariable risk assessment.[5;8;20;80;188] The nature of the most statistical models for multivariable risk prediction implies that once a set of "core" variables (such as age) is entered, AUROC or C-statistic, as measures of model discrimination, improve only modestly when other statistically significant predictors are added (for definitions and measures of model calibration and discrimination, see ***Section 2.1.1***; for more detailed description, see ***Methods***, ***Section 4.5.3***). Perfectly calibrated models of 10-year CVD risk demonstrate the maximal AUROC/C-statistic of 0.75-0.90 when applied to population-based cohorts.[80] This measure is also limited by competing risks and regression dilution bias, common to prospective studies.[8] However, unchanged discrimination could be matched with improved model calibration[187], particularly in those with intermediate risk, as demonstrated in the Women's Health Study.[81;115] Moreover, extended risk model could correctly reclassify substantial proportions of individuals into different risk categories: for example, people with the traditionally measured risk below the intervention threshold may be reclassified by the extended scale into the higher-risk group and, hence, be administered a risk-reducing intervention[8;31;39;40;68;86;188] (for description of reclassification measures, see ***Sections 2.1.1*** and ***4.5.3***). Therefore, a search for new cardiovascular risk determinants and the

identification of the best-performing extended models can result in a more accurate risk prediction and, ultimately, more effective risk reduction and CVD prevention.

The key steps for selecting new risk factors and incorporating them into risk models are determined by the following principles. First, the evidence from prospective studies is used for identifying independent predictors, associated with high relative risk of CVD in multiple regression models. Second, the derived risk model is compared to the already existing instruments, using traditional calibration and discrimination measures. Third, the clinically relevant reclassification of risk categories by a new model is assessed.[8;39;59;189;190] Finally, even if new risk factors do not improve the model performance, they could still benefit our knowledge on CVD pathophysiology (e.g., homocysteine[191]) and/or optimise cardiovascular prevention. For example, LDL-CH may become a relatively weak risk predictor in future models, but lowering its levels will nonetheless remain one of the key methods of cardiovascular risk reduction.[8;177]

Linking the theory and practice of this complex research area, several scientific initiatives have been launched to identify new cardiovascular risk factors and optimise the risk scales applicable to various European populations. One example is the Emerging Risk Factors Collaboration (www.phpc.cam.ac.uk/ceu/research/erfc) – a consortium of prospective studies linking fatal and non-fatal incident CVD events to lipid and/or inflammatory markers.[26] Currently, over 125 international cohorts are involved, representing more than 1.1 million participants at baseline, over 11.7 million person-years at risk, and approximately 69,000 major CVD outcomes. In future, this project will be extended to metabolic, haemostatic, and other risk predictors; however, there is no information available whether at some stage, socioeconomic parameters or alcohol consumption might be considered as exposures of interest.

Another promising research initiative is the MORGAM Project (MONICA, Risk, Genetics, Archiving, and Monograph; www.ktl.fi/morgam), prospectively studying various phenotypical parameters, several hundred genetic factors, and the interaction of genetic and environmental characteristics, based on MONICA and other relevant cohorts.[25;32] The risk component of this project aims to compare the risk coefficients for classical and, later, new cardiovascular risk factors, including socioeconomic and drinking characteristics, by age, gender and European country/region, using validated coronary and cerebrovascular end-points. In future, these coefficients will be used to derive more accurate European scores for CVD risk assessment.

Of note, several studies have attempted to extend the original SCORE model by adding extra risk determinants, in order to improve its predictive performance. Among 104,961 participants of the high and low-risk SCORE cohorts, who developed 2,463 fatal CVD events over the follow-up of 991,058 person-years, adding HDL-CH to the SCORE algorithm did not change the model calibration (P/O ratios 0.9-1.4), sensitivity (52-55% for the 5% risk cut-off), or specificity (85%). The extended model demonstrated a significant overall AUROC increase by 0.01 ($p<0.01$) and an NRI value of 2% ($p<0.01$).[192] The same research team explored the performance of the SCORE instrument extended by resting heart rate among 30,858 FINRISK study participants. Over the first 10 years of observation, 446 cardiovascular deaths were registered. For the algorithm including resting heart rate, calibration was similar to that for the original SCORE. The AUROC improvement did not exceed 0.01 in both genders and reached borderline statistical significance in women only ($p=0.05$). The overall NRI value was 0.3% (non-significant).[193]

SCORE was also extended by the markers of subclinical organ damage, such as left ventricular mass index, atherosclerotic carotid plaques, carotid/femoral pulse wave velocity, and urine albumin/creatinine ratio, using the data on 1,968 middle-aged Danish men and women who developed 81 CVD deaths over the 10-year follow-up.[194] The extended algorithm demonstrated slightly lower sensitivity (65% vs. 72% for the original SCORE) and a significantly better specificity (81% vs. 75%; $p<0.05$) (no calibration data were reported). The increase in C-statistic (0.02) was not significant, and NRI reached only 9% ($p=0.22$). In two other, recently published studies, the SCORE performance was slightly improved after extending the model by obesity and parental history of MI[195], or by ambulatory BP measurements and markers of subclinical organ damage[196]; however, the end-points used (fatal and non-fatal CVD[195] or fatal CVD, non-fatal MI, and non-fatal stroke[196]) were different from the SCORE end-point (atherosclerotic fatal CVD).

Therefore, the improvement in the extended SCORE performance, even when statistically significant, is still relatively modest in absolute terms, which questions its clinical relevance. However, the range of the additional risk predictors used for the SCORE extension has been limited (for example, to the best of my knowledge, there have been no published studies extending the SCORE model by socioeconomic

parameters or alcohol consumption characteristics), and it is possible that other factors might increase the predictive potential of SCORE to a greater extent.

As mentioned in ***Section 2.2***, accurate risk assessment is particularly important for CEE/FSU populations, with their high CVD rates only partly explained by classical risk factors (for example[1;148;197]). While healthcare quality, psychosocial factors, diet, birth cohort effect, air pollution, and other non-conventional factors affect high CVD levels across CEE/FSU, socioeconomic disadvantage and alcohol consumption appear to be the major underlying risk determinants, which are widely spread and relatively easy to measure.[145;149;152;165;198-201] The complex associations between CVD mortality and socioeconomic parameters or alcohol in CEE/FSU populations are described in the next two sections.

2.3.2. Socioeconomic factors and cardiovascular risk

This section briefly summarises the international evidence on socioeconomic inequalities in cardiovascular mortality and then presents in more detail the findings from CEE/FSU, as the region of interest in this thesis. The potential role of traditional risk factors in the socioeconomic gradient, as well as the independent impact of socioeconomic circumstances on CVD risk, is also discussed. Finally, the prognostic performance of the existing risk scales including or excluding socioeconomic parameters is compared, and the issue of the best socioeconomic predictor(s) of cardiovascular risk in the CEE/FSU settings is debated.

a) Socioeconomic inequalities in cardiovascular mortality

The results of numerous studies from the UK, USA, Canada, and other industrialised countries, summarised in several key reviews (for example[202-204]), demonstrate that starting from the second half of the 20th century, heart pathology had lost its "disease of affluence" stigma, and an inverse social gradient in fatal CVD emerged and persisted. In particular, socioeconomic disadvantage, operationalized via various measures of education, occupation, and income/wealth, has been demonstrated to be independently associated with increased CVD risk in Western populations.[203;205-209]

Although marital status is not among traditionally accessed socioeconomic parameters, it reflects to some extent the individual's socioeconomic circumstances and can influence cardiovascular risk via multiple mechanisms discussed later in this section. Thus, higher CVD and CHD mortality has been linked to non-married status among

middle-aged Dutch men[210], male Whitehall civil servants[211], middle-aged British men who participated in the BRHS Study[212], American men and women taking part in the National Longitudinal Mortality Study[213], and middle-aged Scottish men and women.[214]

Importantly, the magnitude of absolute and relative socioeconomic discrepancies in CVD varies substantially across populations.[203;206;215] For example, in the 1990s, the slope index of inequality, measuring absolute differences between CVD mortality rates in the lowest and the highest socioeconomic groups, was twice as high in Czech, Polish, and Lithuanian men as in men from England and Wales.[206] For male coronary and cerebrovascular mortality, the gap between CEE/FSU countries and Western Europe was two and three-fold, respectively. In Czech, Polish, and Lithuanian women, the slope indices of inequality for fatal CVD, CHD, and stroke were, on average, 1.5-4.5 times higher than those in Western European women.

Therefore, the findings from the West cannot be mechanically extrapolated to CEE/FSU settings, which are different in terms of both socioeconomic trajectories and cardiovascular mortality trends. The CEE/FSU states have recently experienced much more dramatic societal changes and greater fluctuations in population health than Western Europe.[144] In addition, after 1989, both all-cause and cardiovascular mortality started decreasing in CEE, but not in FSU countries. The main underlying causes of this divergence include the different economic baseline and speed of socioeconomic transformations; varying baseline health status; differences in lifetime accumulation of disadvantage and health risk; and different governmental and societal response to transition.[157;158;216] Such dissimilar socioeconomic scenarios could affect the variation in cardiovascular mortality not only across, but also within countries.

In the CEE/FSU populations, the socioeconomic gradient in fatal CVD has received relatively less attention than in the West, due to the understandable lack of complete, updated epidemiological data from the transitional CEE/FSU states.[146] Nevertheless, the available data confirm substantial socioeconomic differentials in cardiovascular risk. For example, among the workers of the Skoda factory, Pilsen, the Czech Republic, men with lower than secondary education demonstrated higher CVD rates, compared to their colleagues with secondary or university education. Based on the 11-year follow-up data (1977-1988), the adjusted rate ratios were 1.42 for all (fatal and non-fatal) CHD, 1.69 for all MI, and 2.22 for all stroke.[217] Cross-sectional analyses of the Czech MONICA data from the later period (the mid-1980s to the early 1990s) were mostly focused on

socioeconomic patterns of cardiovascular risk factors (***Section 2.3.2(b)***), rather than CVD mortality disparities across socioeconomic groups.

In a Polish cohort of over 3,000 adult Krakow residents, followed from 1968 for 13 years, CVD mortality was lower among men and women with elementary education than in their peers with higher education (rate ratios 0.87 and 0.83, respectively). This could be related to the earlier stages of Polish cardiovascular epidemic in the late 1960s and 1970s, when CVD had not completely lost its "disease of affluence" status.[218] Later, in the Warsaw MONICA sample, 10-year CVD mortality (1983-1994) demonstrated a clear inverse educational gradient: adjusted mortality rate ratio for people with low vs. high education was 1.75. Additionally, higher levels of fatal CVD were observed in non-married Polish men and women, compared to their married peers.[146]

The decline in Polish cardiovascular mortality, started from the early 1990s and linked to the increased dietary intake of vegetable oils, vegetables, and fruit, was observed for both genders and all age groups, irrespective of their socioeconomic characteristics.[162;219] However, relative educational differences in fatal CVD among 35-64-year-old Poles increased from 1990 to 2000.[155] In men, the CVD mortality rate difference between the lowest and the highest educational group was at the same level in 1990 and 2000, but the rate ratio increased from 1.88 to 2.86. This points to increasing relative inequalities, despite stable or declining absolute differences, in accordance with the "inverse equity hypothesis" proposed by Victora and co-authors.[220] Similarly, in Polish women, CVD mortality rate difference declined by 19 per 100,000, but the rate ratio increased from 2.42 to 3.34. For coronary and cerebrovascular mortality in both genders, there was a tendency of slightly increasing rate differences, but substantially growing rate ratios. As a result, in 2000, CHD and stroke death rates among lower-educated Poles were approximately three times higher than in their higher-educated peers.

In Lithuania, the analysis of the national routine statistics also demonstrated that between 1989 and 2001, relative educational inequalities in cardiovascular mortality significantly increased, due to both declining fatal CVD rates in higher-educated people and increasing mortality in lower-educated Lithuanians. Of note, in 2001, the magnitude of relative inequalities in fatal CVD was greater for Lithuanian women than for men.[221] A later, more detailed analysis of these data[155] showed that among Lithuanian men, the CVD mortality rate difference between the lowest and the highest educational stratum

increased from 187 to 422 per 100,000, while the rate ratio grew from 1.56 to 2.76. For Lithuanian women, the respective rate difference increased from 96 to 202 per 100,000, and the rate ratio rose from 2.02 to 4.67. In both genders, there was an increase in rate differences and especially rate ratios for coronary and cerebrovascular mortality. In 2001, the levels of fatal CHD and stroke were 2.67 and 2.83 times higher in lower-educated Lithuanian men than in their higher-educated peers. For women, the respective figures were 5.14 and 3.32, denoting an even more pronounced educational gradient in mortality. In addition, compared to Lithuanian married men and women, their never-married, widowed, or divorced peers had a higher risk of fatal CVD in both 1989 and 2001.[222] Over time, cardiovascular mortality rate differences increased for never-married men (from 702.2 per 100,000 in 1989 to 839.8 per 100,000 in 2001) and divorced men (from 274.6 to 515.0 per 100,000), as well as for divorced women (from 12.2 to 298.3 per 100,000). Mortality rate ratios increased in never-married men (1.77 vs. 1.88), divorced men (1.30 vs. 1.54), and divorced women (1.02 vs. 1.51).

In Russia, most studies focused on the increasing educational gradient in all-cause mortality, due to deteriorating death rates in the least educated and declining mortality in the best educated (e.g.[223-226]). Although there is relatively little evidence on socioeconomic differences in fatal CVD, this issue has been better described for Russia than for the Czech Republic, Poland, or Lithuania. In particular, the analysis of the Russian national routine statistics demonstrated that in 1989, the ratios for CVD mortality in the lowest vs. highest educational group were 1.41 and 1.56 for 20-69-year-old Russian men and women, respectively.[223] This ecological evidence is consistent with the results of prospective individual-level studies. For example, in the collaborative USA-USSR research project, the Lipid Research Clinics (LRC) Program, there was an inverse association between education and coronary mortality in initially CHD-free Moscow and St. Petersburg men, observed since 1975-1977 for 12 years. Among the least educated males, the age and clinic-adjusted relative risk (RR) of coronary death was 2.43, compared to their most educated peers.[227]

The Moscow and St. Petersburg male cohorts from the Russian LRC Study, followed from 1975 to 1997, were also compared to similar cohorts from Oslo and Helsinki. Educational inequalities in fatal CHD among Russian males were similar to those in their Norwegian and Finnish counterparts: for example, standardised rate ratio was close to 0.50 for high vs. low education. On the other hand, educational gap in stroke

mortality was greater in Russia than in Norway and particularly in Finland: respective rate ratios were 0.48, 0.52 and 0.60.[228] A study by Plavinski and colleagues, which also stemmed from the Russian LRC project, demonstrated that throughout the 1990s, CVD and CHD mortality rates rapidly increased in Russian men with lower education, but declined in those with higher education. Specifically, in two St. Petersburg cohorts, initially examined in 1975-1977 and 1986-1988, the least educated 40-59-year-old men from the later cohort had 10-year RR of 1.99 and 1.92 for cardiovascular and coronary death, respectively, compared to the earlier cohort. In men with university education, the respective RR were 0.64 and 0.57.[224]

An alternative, indirect technique for mortality analysis, based on widowhood, was used in a Russian national sample, examined in 2000. Despite methodological differences with the above-mentioned research, this study also showed an inverse educational gradient in cardiovascular death rates. Male spouses of women with primary education had 2.22 times higher CVD mortality than spouses of university-educated women. Similar trends were observed in female spouses of men with varying educational attainment.[229]

Among over 11,000 MONICA participants from Novosibirsk, who were examined in 1984, 1985-1986, 1988-1989, and 1994-1995 and had a mean follow-up duration of 10 years, the age-adjusted RR of fatal CVD and CHD for men with university vs. primary education were 0.61 and 0.55, respectively; for women, the respective values were 0.55 and 0.11.[230] In addition, divorced men, compared to their married peers, had significantly higher age-adjusted RR of cardiovascular and coronary mortality (2.03 and 2.17, respectively). In women, however, marital status was inconsistently related to fatal CVD and CHD.

Therefore, the available CEE/FSU data, although limited, confirm substantial socioeconomic differentials in fatal CVD risk. The extent, to which conventional cardiovascular risk factors account for this gradient, is discussed below.

b) Traditional risk factors and socioeconomic inequalities in CVD mortality

The inverse socioeconomic gradient in cardiovascular mortality could be, at least partly, due to a higher prevalence of traditional risk factors in lower socioeconomic groups.[204;207;215] Over the last few decades, multiple Western studies have demonstrated that a substantial part of socioeconomic inequalities in CVD is explained by the

distribution of classical risk determinants. For instance, among Norwegian men and women, CVD-free at baseline and followed for 26 years, lower education was a significant predictor of fatal CHD (age-adjusted RR 1.33 and 1.72 for men and women, respectively). After extra controlling for conventional risk determinants (smoking, SBP, diastolic BP (DBP), TCH, BMI, physical activity) and marital status, this association not only weakened, but also lost statistical significance (respective adjusted RR 1.03 for men and 1.24 for women).[231] In middle-aged men from France and Northern Ireland, who were followed for incident CHD for five years in the PRIME study, higher education was related to a significantly lower coronary risk after adjustment for age and study centre (relative odds 0.72). Nonetheless, additional controlling for smoking, DBP, TCH, DM, and fibrinogen resulted in the loss of statistical significance (relative odds 0.90).[232] Similarly, a later analysis of the 10-year PRIME follow-up data demonstrated that years of education were inversely and significantly linked to the risk of fatal and non-fatal CVD events after adjustment for age and country (hazard ratio, HR, 0.92). However, this link was no longer significant after additional adjustment for lifestyle behaviours and conventional risk factors (HR 1.00).[233] Among middle-aged participants of the Melbourne Collaborative Cohort Study, the age, gender, and country of birth-adjusted association between lower education and a higher nine-year risk of fatal CVD (RR 1.66) was substantially weakened and lost its statistical significance after additional controlling for behavioural and physiological cardiovascular risk factors (RR 1.17).[234]

The important role of conventional risk determinants was demonstrated for the CVD gradient not only by education, but also by marital status, income, and occupation. For example, in middle-aged male and female participants of the Framingham Offspring Study, the reduction in the 10-year coronary risk for married vs. non-married status did not reach statistical significance after controlling for age, SBP, TCH:HDL-CH, smoking, BMI, and DM, as demonstrated by the adjusted RR of 0.92 for men and 0.85 for women.[235] Among male participants of the Kuopio Ischemic Heart Disease Risk Factor Study, the lowest vs. highest level of income was associated with significantly higher age-adjusted relative hazards of fatal CVD.[236] Accounting for 23 biological, behavioural, psychological, and social risk factors reduced the hazards from 2.66 to 0.70, with a loss of statistical significance. In middle-aged British men – BRHS participants, who were free of CHD in the beginning of the 20-year follow-up, manual occupation was linked to a significantly higher coronary risk (age-adjusted HR 1.50).

After controlling for adult coronary risk factors and height, the link between manual occupation and CHD became non-significant (adjusted HR 1.20).[237]

Nonetheless, other studies have demonstrated that socioeconomic effects on cardiovascular mortality are not fully due to the socioeconomic patterns of traditional risk factors. In a national sample of middle-aged Americans who participated in the NHANES I (National Health and Nutrition Examination Survey), RR of fatal CVD doubled in those with the lowest vs. highest educational attainment.[238] After controlling for age, SBP, smoking, and BMI, RR were slightly reduced, but remained statistically significant in men. In a later analysis of the NHANES I data, the adjusted risk of CHD mortality associated with lower education (RR 1.5) was comparable to that for male gender, current smoking, hypercholesterolemia, and high normal SBP (no unadjusted RR values were reported).[239] Among Finnish men and women, followed for over 11 years, primary education was linked to a higher risk of fatal CVD, after accounting for age, study year, and pre-existing chronic disease (HR 1.46 for men and 2.16 for women). While behavioural risk factors (smoking, alcohol, physical activity, diet, and BMI) explained 54% and 22% of this difference in cardiovascular mortality, lower education remained a statistically significant predictor of fatal CVD: adjusted HR were 1.21 for men and 1.90 for women.[240] In the case-control INTERHEART study, modifiable lifestyle factors, such as smoking, exercise, diet, alcohol, and abdominal obesity, explained about 50% of the educational gradient for the first non-fatal acute MI. However, after controlling for age, sex, region, lifestyle, psychosocial factors, and other socioeconomic parameters (income, family possessions, and occupation), lower education (≤8 years) was still significantly associated with higher MI odds (adjusted odds ratio, OR, 1.31). Interestingly, the association between other socioeconomic parameters and MI was weak, or even absent.[241]

In addition, non-married status has been linked to higher CVD mortality, even after controlling for various cardiovascular risk factors and/or other socioeconomic characteristics. For example, in middle-aged Dutch men, free of CVD at baseline, non-married status was associated with a significantly higher 10-year risk of coronary mortality (adjusted RR 2.2), after controlling for age, smoking, DBP, TCH, education, and alcohol consumption.[210] Among 40-64-year-old male Whitehall civil servants, followed for 18 years, CVD and CHD mortality was significantly higher in widowed vs. married individuals, even after accounting for age, smoking, SBP, TCH, DM, impaired

glucose tolerance, BMI, height, lung function, disease at entry, and employment grade. The mortality ratios were 1.33 and 1.46 for CVD and CHD, respectively.[211] In 40-59-year-old British men, who were followed for 11.5 years as participants of the BRHS, single status was a significant predictor of CVD death (adjusted RR 1.5), independent of age, smoking, SBP, TCH, BMI, physical activity, forced expiratory volume in 1 second, disease/medication use at baseline, occupation, employment, and alcohol intake.[212] Among middle-aged Scottish adults, free of CVD at baseline and followed for seven years, behavioural risk factors, such as smoking, physical activity, and alcohol consumption, as well as occupation, did not fully account for a significant increase in CVD mortality risk among single men (adjusted RR 2.55), widowed men (RR 2.17), single women (RR 2.06), and separated/divorced women (RR 2.22).[214]

A well-known example of the independent impact of employment grade on CVD risk is the evidence from the Whitehall Study. In male British civil servants, an inverse association between employment grade and CHD mortality was observed, with age-adjusted 10-year risk in the lowest grade being 2.7 times higher than in the highest one.[242;243] After controlling for smoking, SBP, TCH, height, and blood glucose, the association weakened (adjusted RR 2.1), but remained significant. A later analysis of the Whitehall II data, with the follow-up length extended to 24 years, confirmed that while health behaviours (smoking, alcohol, diet, and physical activity) explained to a considerable extent the association between lower employment grade and CVD mortality (29% or 45% when assessed at baseline only, or at baseline and throughout the follow-up, respectively), the main association of interest still remained statistically significant: the respective adjusted HR were 2.22 and 1.85.[244]

The extensive evidence on the inverse associations between various socioeconomic characteristics, traditional risk factors, and CVD outcomes in Western populations has been summarised in several reviews (for example[202;203;208]), demonstrating that both conventional risk determinants and socioeconomic parameters are independently linked to cardiovascular risk. In the CEE/FSU region, most of the data on socioeconomic distribution of classical cardiovascular risk factors come from the MONICA populations. As before, the evidence from the Czech Republic, Poland, Lithuania, and Russia will be used in order to illustrate the associations between socioeconomic measures and traditional cardiovascular risk determinants in CEE/FSU settings, as well as to outline the role of these factors in CVD mortality inequalities. Although in the late

1970s to the early 1980s, these populations demonstrated a direct link between educational attainment and blood lipids[245], later studies showed inverse associations between the majority of conventional risk factors and socioeconomic parameters, which may reflect the process of socioeconomic and epidemiological transition in the CEE/FSU region.[146]

Among Czech MONICA participants, the dynamics of the main cardiovascular risk factors from the mid-1980s to the early 1990s depended on educational attainment.[246] Even though BP changes were small in all educational strata, TCH decline over 1988-1992 was significantly greater in university-educated men than in males with primary education (-0.47 vs. -0.23 mmol/l, respectively). In 1988, before the beginning of the radical societal changes in the Czech Republic, no educational gradient in TCH concentration was observed. Smoking prevalence increased only in women with primary education (+5%), while in higher-educated women, it decreased by 1-2%. As a result, in 1992, a clear inverse educational gradient in all cardiovascular risk factors was observed in Czech men and women, with the most adverse risk profiles among the least educated. In a later analysis of the cross-sectional 1992 data from the same MONICA population, lower education, but not material deprivation, was associated with higher levels of most risk factors.[247] For instance, people with primary education had mean TCH levels higher by 0.4-0.6 mmol/l than their university-educated peers. Primary education was also associated with doubled and quadrupled odds of AH and smoking, respectively. Among Czech adults participating in the Czech Health and Life Style Study (2003), current smoking was significantly associated with lower education (for instance, for university vs. primary education, adjusted OR was 0.33) and single or divorced status (adjusted OR 1.30 and 1.67, respectively).[248] Unfortunately, the cross-sectional design of these studies did not allow the investigation of the impact of the risk factor trends on CVD mortality across socioeconomic strata.

As a part of the CINDI Project (Countrywide Integrated Non-communicable Diseases Intervention Program; 2001-2002), it was shown that in the adult population of an industrial Polish town Lodz, higher education, but not higher income or married status, was associated with a significantly lower prevalence of cumulative (≥3) cardiovascular risk factors (AH, abdominal obesity, hypertriglyceridemia, low HDL-CH, and hyperglycaemia). Compared to those with primary education, university-educated men and women had OR of 0.51 and 0.14, respectively.[249]

The 1997 survey of a Lithuanian representative sample, including 20-64-year-old men and women, demonstrated that the age-adjusted odds of current smoking were significantly lower in university vs. primary educated men (OR 0.61) and in men with the highest vs. lowest income (OR 0.55). The inverse association between socioeconomic characteristics and current smoking was also observed in Lithuanian women, but it was not statistically significant. After additional adjustment for nationality, residence type, and another socioeconomic parameter, the link between smoking and either education or income failed to reach statistical significance for both genders.[250] Among Lithuanian MONICA participants, examined in 2001-2002, the prevalence of some, but not all traditional risk factors was higher in manual workers than in their peers with non-manual occupations.[251] While regular smoking was more prevalent in male manual workers (47.8% vs. 30.1%), the prevalence of AH, overweight and obesity, leisure time physical inactivity, and low HDL-CH levels was similar between these two occupational groups. In women, only obesity was significantly associated with manual occupation (47.3% vs. 36.5%), while the prevalence of other risk determinants did not differ substantially by occupation.

In Russia, smoking might be the best-examined cardiovascular risk factor in terms of its socioeconomic distribution. Some inconsistencies between specific studies could be explained not only by different study designs, but also by changing smoking trends across socioeconomic groups and progressing tobacco epidemic in the region. For instance, the results of the cross-sectional Russia Barometer Survey (1996) demonstrated a statistically significant association between current smoking and material deprivation: when comparing the most and the least deprived quartiles, the adjusted OR were 1.69 in men and 2.00 in women. At the same time, smoking was equally distributed across educational groups in both genders.[252] By contrast, among men and women from Taganrog, Southwest Russia (1998), lower education and deprivation were both linked to doubled odds of smoking.[253] In the 2001 LLH Study (Living Conditions, Lifestyles and Health), which included Russia and seven other FSU countries, education and economic position were inversely related to smoking in men, but not in women.[254] While the links between smoking and marital status were inconsistent for men, in women, being divorced, separated, or widowed vs. being married was associated with significantly higher odds of smoking (adjusted OR 1.54).

Therefore, the available evidence is generally consistent with the existence of an inverse socioeconomic gradient in conventional cardiovascular risk factors across CEE/FSU populations. The research aimed at linking risk factor differentials to CVD mortality gradients mostly comes from Russia and demonstrates rather contradictory results. Some Russian studies failed to confirm an independent association between socioeconomic characteristics and fatal circulatory disease after adjustment for behavioural risk factors. For example, a case-control study (1998-1999) from the Udmurt Republic, Central Russia, using verbal autopsy reports by proxies, showed an elevated CVD death risk in lower-educated, non-married, and unemployed men of working age. However, none of these associations, controlled for other socioeconomic parameters and behavioural risk factors, such as smoking, reached statistical significance: adjusted OR were 1.21 for lower education, 1.56 for never-married status, and 1.58 for unemployment. A borderline significance was observed for the link between cardiovascular mortality and smoking (adjusted OR 1.99).[255]

On the other hand, the findings from prospective studies support the hypothesis of an independent socioeconomic effect on fatal CVD. For instance, using the 12-year follow-up data from the above-mentioned Russian LRC Program, Dennis and colleagues showed that coronary mortality in Moscow and St. Petersburg men, who were free of CHD at baseline, was significantly higher in those least educated. Controlling for classical risk factors and alcohol intake reduced the age and clinic-adjusted RR from 2.43 to 1.89, which left unexplained 78% of the excess mortality associated with lower education. Relative risks for alcohol consumption or conventional risk determinants (SBP, HDL-CH, LDL-CH, BMI, and number of cigarettes smoked daily), were not reported.[227]

An example of the recent research on socioeconomic patterns of fatal CVD in Russia is a cohort study, conducted as a part of the Novosibirsk MONICA Project.[230] The gradient in CVD, CHD, and stroke mortality was investigated by education and marital status. Among over 11,000 men and women, who were examined in 1984, 1985-1986, 1988-1989, and 1994-1995 and followed for 10 years, higher education was associated with lower CVD and CHD mortality. Specifically, the age-adjusted RR of cardiovascular death for university vs. primary education was 0.61 in men and 0.36 in women. For coronary mortality, the respective RR were 0.55 and 0.11. After controlling for conventional risk factors, marital status, and drinking frequency, the RR changed

only slightly: in men, to 0.81 for CVD mortality and 0.70 for CHD mortality, and in women, to 0.31 for fatal CVD and 0.24 for fatal CHD. In both genders, 95% CI were relatively wide and included 1.0, possibly due to limited outcome numbers (e.g., in university-educated men, there were 48 and 26 cardiovascular and coronary deaths, respectively; in women, the respective figures were 6 and 1); however, these findings still support the inverse direction of the association between education and fatal CVD/CHD. Moreover, divorced men, compared to their married peers, had significantly higher age-adjusted RR of cardiovascular and coronary mortality (2.03 and 2.17, respectively). This increased risk was not explained away by conventional risk factors or lower education (respective adjusted RR 1.78 and 1.84). In women, marital status was inconsistently related to fatal CVD and CHD. The magnitude of risk associated with drinking frequency or with conventional risk determinants (smoking, TCH, SBP, and BMI) was not presented. No clear association was observed between socioeconomic characteristics and fatal stroke in both genders.

In men and women from Arkhangelsk, Northwest Russia, who were followed from 1999-2000 for 10 years, married status was linked to lower CVD mortality, even after accounting for conventional and novel risk factors, education, and alcohol consumption. Due to the limited outcome numbers (77 and 52 CVD deaths in men and women, respectively), adjusted 95% CI were rather wide and included 1.0, but married status was still associated with reduced cardiovascular risk (respective RR 0.75 and 0.57). The link between education and fatal CVD was non-significant and inconsistent: adjusted RR suggested a protective effect of higher education in men (0.78), but not in women (1.34). For such classical risk factors as smoking and TCH, the direct association with cardiovascular mortality failed to reach statistical significance, potentially because of relatively low outcome numbers.[256]

The above-cited evidence is supported by the results of a recent review, which included not only Czech, Polish, Lithuanian, and Russian data, but also the information from other CEE/FSU states.[257] This analysis demonstrated existing and growing inverse socioeconomic gradient in CVD mortality across the region in the 1990s, mostly due to deteriorating cardiovascular health in the lowest socioeconomic groups. However, the observed inverse gradient in classical risk factors was less consistent than that for fatal CVD.

Therefore, the existing data from both Western and CEE/FSU populations demonstrate that while traditional risk factors are differently distributed across socioeconomic groups, they do not fully account for the socioeconomic gradient in CVD mortality. The next section discusses the potential for incorporating socioeconomic predictors in cardiovascular risk assessment scales.

c) Performance of cardiovascular risk instruments which include socioeconomic parameters

As socioeconomic factors appear to have an independent impact on cardiovascular risk levels, the majority of the currently used scales, which do not include socioeconomic measures, may under-estimate the risk in those deprived or less affluent. For example, among over 13,000 participants of the SHHEC study, observed 10-year coronary risk was compared to that predicted by the Framingham scale, across the quintiles of the Scottish Index of Multiple Deprivation, SIMD.[104;205] The area-based SIMD reflects current income, employment, housing, health, education, skills and training, and geographic access to services and telecommunications. The Framingham scale over-estimated the coronary risk overall and in each SIMD quintile. At the same time, the socioeconomic gradient in CHD risk was substantially under-estimated. The observed RR, from the least to most deprived quintile, were 1.00, 1.81, 1.98, 2.22, and 2.57, in contrast to the predicted values of 1.00, 1.17, 1.19, 1.28, and 1.36, respectively.

Another prospective research project, the West of Scotland Study, examined the Framingham score performance across different socioeconomic groups in the high-risk Renfrew/Paisley cohort.[258] The Framingham function under-estimated 10-year risk of fatal CVD by 48% in manual workers and by 31% in non-manual participants; coronary mortality was under-predicted by 44% and 22%, respectively. Under-estimation of fatal CVD risk was also linked to the residence area deprivation, defined by the Carstairs-Morris index. Moreover, among middle-aged British men, free from CVD at baseline (1978-1980), the Framingham scale over-estimated the 10-year CHD risk to a greater extent in non-manual vs. manual workers (respective P/O ratios 1.84 and 1.49). Better Framingham sensitivity (56% vs. 52%) and specificity (79% vs. 73%) was observed among participants in non-manual vs. manual occupations.[259] In the same population, the high-risk SCORE demonstrated a greater over-prediction of fatal CVD among non-manual workers (P/O ratio 1.79 vs. 1.46 in manual workers), as well as better sensitivity (61% vs. 57%) and specificity (77% vs. 69%, respectively).

These examples demonstrate that the most affluent participants would be relatively over-treated, and the most deprived would receive only a fraction of the actually needed treatment, if the risk stratification process was based on the risk instrument not containing socioeconomic parameters. Hence, to better identify people at increased risk and to reduce existing socioeconomic inequalities in CVD, alternative approaches should be used, encompassing not only traditional risk predictors, but also various measures of deprivation and disadvantage.[203;239;259;260]

It was recently shown that adding socioeconomic disadvantage (operationalized as <12 years of education and/or low income) did not affect the Framingham scale discrimination, but improved its calibration in the middle-aged participants of the ARIC (Atherosclerosis Risk in Communities) cohort.[261] Specifically, predicted coronary risk changed from 3.7% to 3.1% in those from the higher socioeconomic group and from 3.9% to 5.2% in those from the lower socioeconomic group, compared to the respective observed 10-year CHD levels of 3.2% and 5.6%. The results were also validated using the NHANES III data, linked to the National Death Index. Moreover, in British middle-aged men who participated in the BRHS, adding occupational social class to the Framingham scale slightly improved risk reclassification, as demonstrated by NRI and IDI values of 0.18% and 0.10%, respectively.[259]

At present, there are two cardiovascular risk scales including socioeconomic characteristics – ASSIGN and QRISK/QRISK2 instruments, described in more detail in ***Section 2.2.2***. The Scottish ASSIGN score is based on traditional risk factors and social deprivation, operationalized via the residence postcode-specific SIMD.[104] Even though the ASSIGN calibration ability was similar to that for the Framingham scale, with risk over-estimation in both genders, the discrimination was better for the former instrument. ASSIGN correctly identified 20% of the population accounting for 45% of cardiovascular events over the next 10 years, and classified more deprived people at high risk than the Framingham score. In a study comparing performance of ASSIGN, QRISK, and Framingham scales in a UK cohort of general practice patients (THIN database), ASSIGN demonstrated the steepest, and the closest to the observed, deprivation gradient in cardiovascular risk.[262] The recently developed QRISK/QRISK2 scale includes various traditional and clinical cardiovascular risk predictors, as well as the Townsend deprivation score. Compared to the Framingham and ASSIGN instruments, QRISK/QRISK2 demonstrated better discrimination and calibration. For

instance, while the Framingham score and ASSIGN over-predicted CVD risk by at least 10%, the QRISK/QRISK2 estimations were very close to the observed risk levels, and AUROC values were also the highest for QRISK/QRISK2.[105-108]

To summarise, adding socioeconomic parameters to the cardiovascular risk models is a promising approach, as it may help to improve the accuracy of risk prediction in disadvantaged individuals and populations, and, in perspective, to optimise cardiovascular risk management and reduce both general CVD burden and CVD inequalities. Given the marked socioeconomic disparities in CVD across the CEE/FSU region, the risk scales incorporating socioeconomic characteristics may be of particular importance there. However, neither ASSIGN, nor QRISK/QRISK2 was calibrated for CEE/FSU, and the officially recommended SCORE scale does not contain any socioeconomic measures. Additionally, SIMD and Townsend deprivation score are hardly applicable to most CEE/FSU populations, as the local availability of area-level socioeconomic measures is limited. It seems reasonable to investigate the predictive potential of a new risk function, which would incorporate both traditional CVD risk determinants and relevant socioeconomic indicators. The selection of optimal socioeconomic parameters is the focus of the following section.

d) Optimal socioeconomic predictors of cardiovascular risk in CEE/FSU

Identifying the most appropriate measure(s) of socioeconomic influences on cardiovascular risk in CEE/FSU populations is a challenging task. On the one hand, the parameters should be context-specific and adequately reflect the local socioeconomic features. On the other hand, they also need to be generalizable and comparable across countries and over time, as well as be easily measured. An additional difficulty is the different meaning of formally equivalent socioeconomic characteristics in different socio-cultural environments, such as the developed countries of Western Europe and North America vs. post-transitional CEE/FSU economies.

Various socioeconomic measures reflect different pathways connecting socioeconomic circumstances and cardiovascular risk, and each indicator has its own strengths and limitations.[202;203;241;260;263-265] For instance, income/wealth is the best measure of current material circumstances, representing the access to goods and services, including healthy diet, safe housing, and adequate medical care. Occupation reflects current employment status, prestige, workplace exposures (for example, psychosocial stress, drinking or smoking “culture”) and certain lifestyle factors, such as physical activity. However,

both income and occupation are relatively unstable and easily affected, among other factors, by health status, including cardiovascular health, and by health behaviours such as problem drinking. Income, as well as other wealth measures, is hard to operationalize, and income-related questions are sensitive enough to compromise response rates. Occupational categories might be too broad to adequately represent the entire scope of work-related exposures and risk factors. By contrast, education as a socioeconomic characteristic is easily measurable, relatively stable, and not affected by later health status, behavioural factors, and other parameters. As the access to baseline education becomes more universal, the birth cohort effects, potentially affecting the education-CVD association, are declining over time. The mechanisms underlying both short and long-term effects of education on cardiovascular risk include "influencing life-style behaviours, problem-solving abilities, and values", "acquisition of positive social, psychological and economic skills and assets", and "insulation from adverse influences".[266]

In CEE/FSU populations, the potential of various socioeconomic parameters as CVD risk predictors could differ from that in the West.[209] Specifically, official income and occupation may capture the true material circumstances of individuals and households less effectively, due to the substantial role that informal economy still plays in many CEE/FSU states.[144] Education has been the socioeconomic measure most widely used in epidemiological studies in the region, and it also demonstrated the most consistent health gradients.[144;247] Early life health and health behaviours, such as excessive drinking, could affect educational attainment, and this might be particularly relevant to Russian settings.[223] Nonetheless, the health impact on socioeconomic parameters is weaker for education, compared to income/wealth or occupation, which minimises the risk of reverse causality being the main explanation of the association between socioeconomic circumstances and CVD. Importantly, in Russia and other CEE/FSU countries, health effects of education are confounded by income and occupation influences to a lesser extent than in the West. Higher education does not equal high income, and, hence, education *per se* provides health-protective action, independently from material circumstances.[223;226;247]

In addition, easily and routinely assessed, marital status has been recognized as a factor which protects against CVD via such mechanisms as social connections, a sense of social and familial role, socioeconomic support, and facilitation of health-promoting

behaviours.[214;267-271] These protective effects of marriage might be particularly important in the CEE/FSU context.[153] Importantly, across both Western and Central/Eastern European populations, non-married status has been linked to higher CVD mortality, especially in males, even after controlling for various cardiovascular risk factors or other socioeconomic characteristics.[210-214;230;256] Considering the extensive evidence on independent cardioprotective effect of married status, this measure appears highly relevant to the problem of CVD gradient in the region of interest.

Therefore, the available evidence is consistent that a combination of classical risk factors and other non-conventional risk determinants, such as socioeconomic characteristics, should be included in the instruments for cardiovascular risk prediction in CEE/FSU populations. Of note, there have been no published studies on the CEE/FSU performance of cardiovascular risk scales, such as SCORE, after their extension by socioeconomic parameters. Another additional risk factor could be hazardous alcohol consumption, due to its wide prevalence in the region and the link to CVD. The role of alcohol as a cardiovascular risk determinant in the CEE/FSU context is debated in the next section.

2.3.3. Alcohol consumption and cardiovascular risk

First, the mechanisms linking alcohol and CVD are outlined, with the emphasis on this association in CEE/FFU populations which are characterised by widespread hazardous drinking. The complex relationship between alcohol and fatal CVD in CEE/FSU is then addressed. Finally, some methodological aspects of including alcohol consumption measures in the cardiovascular risk scales are discussed.

a) Alcohol and cardiovascular risk

The international evidence on the complex association between alcohol and cardiovascular risk mostly comes from the studies performed in industrialised countries of Western Europe and North America. In particular, alcohol drinking has been linked primarily to CHD, but also to such CVD outcomes as cardiac arrhythmias, ischemic, thromboembolic and hemorrhagic stroke, and sudden cardiac death.[272-275] The amount, frequency, and patterns of drinking could all affect cardiovascular risk. In systematic reviews by Rehm and colleagues, higher average volume of alcohol consumption was associated with an increased risk of hypertensive disease and hemorrhagic stroke, and coronary risk was dependent on both drinking patterns and average volume of alcohol

consumed.[274;276] In contrast to drinking dose and patterns, alcohol beverage type seems to be unrelated to CVD risk. The evidence on the greater cardioprotective potential of wine[277] is counterbalanced by the seemingly equal cardiovascular benefits of moderately consumed wine, beer, or spirits.[278-280]

While moderate alcohol consumption protects against CVD, heavy, binge, and problem drinking increases cardiovascular risk, which results in a U or J-shaped dose-response curve (e.g.[272-274;280-288]). For instance, in a meta-analysis by Corrao and colleagues, the alcohol-CHD relationship was J-shaped, with the lowest RR of 0.8 at the drinking level of 20 g/day, a protective effect up to 72 g/day, and a significantly increased risk at ≥89 g/day.[284] The same research team also demonstrated that cardioprotective effect of alcohol is weaker in women, for fatal outcomes, and in the properly adjusted prospective studies not including ex-drinkers in the non-drinker category.[280]

If actual cardioprotective effect of alcohol is relatively modest, then in individuals and populations with hazardous drinking patterns, it would be outweighed by detrimental impact on cardiovascular risk. Specifically, in a recent meta-analysis, binge and heavy irregular drinking was shown to modify cardioprotective effect of alcohol.[289] Compared to abstainers, regular heavy drinkers and heavy irregular, binge drinkers had significantly different RR of CHD: 0.75 vs. 1.10, respectively. The dose-response relationship between alcohol consumption and CHD was also markedly different: irregular drinkers (≤2 days a week) demonstrated a J-shaped curve, with nadir around 28 g of alcohol per week, and the last protective dose of 131 g per week. For those who drank regularly, even high doses of alcohol had a protective effect, with an L-shaped dose-response curve. Moreover, in a later meta-analysis by Roerecke and Rehm, which specifically focused on irregular heavy drinking after controlling for consumption volume, this drinking pattern was associated with a significantly increased coronary risk, compared to regular moderate drinking (adjusted RR 1.45).[290]

The relationship between alcohol consumption and stroke is also complex, as demonstrated in the recent meta-analysis by Patra and colleagues.[291] Increasing alcohol consumption was associated with a monotonous increase in fatal and non-fatal hemorrhagic stroke risk. For example, compared to lifetime abstainers, men and women consuming 96 g of pure alcohol per day had RR for hemorrhagic stroke mortality of 1.94 and 4.50, respectively. However, ischemic stroke had a curvilinear relationship, similar to that for CHD: low to moderate consumption had protective effect against

stroke mortality in both genders (nadir at 12 g/day, and last protective dose of 44 g/day), but heavier drinking increased the risk. Of note, for both stroke types, risks for mortality tended to be higher than for morbidity.

The dose-response relationship between alcohol and CVD is also supported by clinical and physiological evidence. Thus, binge and irregular heavy drinking is associated with adverse changes in HDL and LDL-CH profiles, hypercoagulation, BP elevation, arrhythmia threshold reduction, and histological changes of the myocardial conducting system. Importantly, these harmful effects are not confined to the drinking episode only, but also extend to the alcohol withdrawal/cessation phase. On the other hand, moderate alcohol intake demonstrates beneficial effects on blood lipids, platelet aggregation, and fibrinolysis. Other cardioprotective mechanisms, such as reduced insulin resistance and inflammation, vasodilatation, and pro-oestrogenic effect, have been reported but are unlikely to play a key role.[272-274;276;292;293]

Therefore, the current evidence generally supports the concept of the dose-response relationship between alcohol and CVD. However, extrapolating these, predominantly Western, findings to CEE/FSU is problematic, as the substantial differences in drinking patterns between populations could result in different magnitude and even direction of alcohol effects on cardiovascular risk. The specifics of drinking patterns in CEE/FSU populations are summarised below.

b) Alcohol consumption in CEE/FSU

While CEE and FSU countries demonstrate high per capita levels of alcohol consumption, their drinking patterns are heterogeneous. For example, the Czech Republic is characterised by wide-spread, regular beer drinking, high overall alcohol consumption, and a relatively less hazardous drinking pattern. Poland, Lithuania, and Russia share a culture of spirits consumption, with more detrimental drinking patterns, such as bingeing.[287;294;295] Moreover, unrecorded per capita consumption of alcohol in Russia, Lithuania, and Poland, but not the Czech Republic, is substantially higher than the world average level, and is mostly presented by homemade, highly concentrated beverages with ethanol content ≥40%.[296]

These ecological findings have also been confirmed by the individual-level data analyses. For example, as shown in the cross-sectional HAPIEE Study survey, in 1999-2000 Russian men had a substantially lower mean annual alcohol intake and mean

drinking frequency than their Czech peers.[297] However, the mean alcohol dose per session was almost twice as high in Russian males as in Czech and Polish men. Bingeing, problem drinking, and negative consequences of drinking were twice as common in Russians as in Czechs or Poles. The LLH Project also demonstrated that in the early 2000s, Russia was characterised by relatively low frequency of alcohol consumption, but large amounts per occasion and frequent heavy drinking situations.[298] Abstention rates in Russian men and women were low (11% and 27%, respectively). The reduced proportion of female abstainers, compared to 35-51% levels from the mid-1990s surveys[299-301], might be an alarming predictor of the future increase in alcohol-related burden of disease among Russian women.

Not only the cross-sectional estimates, but also the trends in alcohol drinking across the CEE/FSU region could be described as heterogeneous. Specifically, Czech and Polish alcohol consumption levels have been relatively stable in the last few decades, while Russia experienced dramatic fluctuations, with a rapid decline in the mid-to-late 1980s followed by a marked increase.[22] Between 1994 and 2006, the recorded alcohol consumption rose by 30% in Russia, tripled in Lithuania, and hardly changed in the Czech Republic and Poland. In 2006, recorded alcohol consumption levels in the Czech Republic, Lithuania, and Russia exceeded the average European level (14.9, 12.9, and 11.1 vs. 10.7 litres per capita, respectively), while in Poland, they were only slightly lower (10.4 litres).[21]

Importantly, widespread hazardous drinking is linked to the heavy burden of alcohol-associated mortality and morbidity in the CEE/FSU region. In 2002, Russia and other FSU countries demonstrated the world's highest levels of alcohol-related burden of death and disease.[302] Alcohol accounted there for 18.6% and 5.4% of all deaths in men and women, respectively, and this burden had not decreased since 2000.[303] In Eastern European populations, alcohol was the second most important risk factor for disease burden after AH. A substantial proportion of the alcohol-related burden in men and women was presented by CVD, which was responsible, respectively, for 129,000 and 40,000 alcohol-attributable deaths, 1,192,000 and 253,000 years of life lost, and 1,309,000 and 281,000 DALYs per year.[302] In a country-specific analysis of the 2002 data, Russian and Lithuanian men had alcohol-attributed premature mortality almost eight and six times higher, respectively, than British men.[294] Even though for Russian and Lithuanian women, the absolute rates were lower, the respective mortality ratios

were high (3.6 and 3.2, compared to British women). In Czech and Polish males, alcohol-attributable premature mortality was approximately 2.5 times higher than in the UK, while Czech, Polish, and British women all had similar levels of alcohol-related premature deaths. In regard to CVD mortality, Rehm and colleagues acknowledged that their estimation of beneficial drinking effects could have resulted from inadequate extrapolation of the data from countries with typical moderate regular alcohol consumption to the countries with widespread binge drinking, such as Russia.

Therefore, the applicability of the Western data on the CVD-alcohol association to CEE/FSU populations, which are different in terms of both volume and patterns of alcohol consumption, is not straightforward. The following section presents the principal findings from the relevant CEE/FSU studies, in order to specify and explore the features of alcohol consumption as a cardiovascular risk factor in the region of interest.

c) Alcohol and cardiovascular mortality in CEE/FSU

To date, the local evidence on the association between circulatory disease and drinking in CEE/FSU settings mostly comes from Russia, due to the recent dramatic changes in the Russian CVD rates and alcohol intake. In particular, substantial fluctuations in Russian alcohol consumption due to the anti-alcohol campaign of 1985 and its collapse coincided with the changing rates of deaths of various aetiology over the late 1980s to the early 1990s.[304] It has been suggested that these striking mortality fluctuations were mostly explained by drinking and its effects not only on injuries and other alcohol-related causes, but also on CVD (e.g.[165;198;200;201;282;305-307]). According to Nemtsov, cardiovascular deaths were the second and the first causes contributing to the 1985-1986 decrease in alcohol-related mortality among Russian men and women, respectively.[305] Leon and colleagues estimated that the 1985 campaign, resulting in a 25% drinking reduction, was associated with the CVD mortality decrease of 9% in men and 6% in women, while after 1987, a substantial increase was observed in both alcohol consumption and fatal CVD.[165]

However, the proportion of heavy/problem drinkers in Russian women, even considering potential under-reporting, did not seem high enough to explain away the recent unprecedented fluctuations in female cardiovascular mortality (for example[299;300;304]). Some earlier individual-level studies, such as the Russian LRC Project, also did not support the hypothesis of alcohol as a major determinant of CVD

mortality. Specifically, no clear association was observed between alcohol intake and eight-year cardiovascular mortality in middle-aged Russians (the highest rates of fatal CVD were registered in non-drinkers), while in their American peers, alcohol was cardioprotective.[308] This study, however, did not address the effects of drinking patterns and bingeing on cardiovascular risk. Moreover, while HR for alcohol intake categories were adjusted for classical risk factors, the impact of these factors on cardiovascular risk was reported only for smoking. In particular, smoking was associated with at least doubled adjusted hazards of CVD death (HR 1.95 for men and 2.82 for women). A later analysis of the LRC data from St. Petersburg male cohorts showed that the input of high alcohol consumption in the all-cause mortality increase among the lower-educated men was relatively small (8-22%), and for CVD mortality it was expected to be even smaller.[224]

Nonetheless, a statistically significant, independent of conventional risk factors, association between hazardous drinking and CVD mortality was demonstrated in other case-control and cohort CEE/FSU studies, in agreement with the Western evidence.[273;274;280-282;284;285;289-291] For example, in working-age men from Udmurt Republic, Russia (1998-1999), the proxy-reported episodes of heavy beverage drinking in the past year were associated with four-fold odds of fatal CVD after adjustment for classical risk factors such as smoking, for education, marital status, and employment (unadjusted OR 4.21 vs. adjusted OR 3.54).[201;255] Regular alcohol consumption did not demonstrate any substantial cardioprotective effect. The link between smoking and CVD death had a borderline significance (adjusted OR 1.99). In a later case-control study of Udmurt men (2003-2005), the proxy-reported non-beverage alcohol drinking was linked to significantly increased odds of coronary and cerebrovascular mortality. The OR value was approximately 3.0 after controlling for smoking, volume of beverage alcohol, and education; however, no OR were reported for these covariates.[309]

Similarly, the findings of another case-control study performed in three Russian industrial cities (Tomsk, Barnaul, and Biysk), demonstrated that in the 1990s, adjusted risks of proxy-reported fatal acute non-MI CHD in male and female regular heavy drinkers were three and nine times higher, respectively, than in occasional non-heavy drinkers (OR 3.04 in men and 9.25 in women).[310] Adjustment was performed for age, city of residence, and smoking, but no respective OR were presented.

Among middle-aged Novosibirsk men, who were examined between the mid-1980s and the mid-1990s and had a mean follow-up of 9.5 years, frequent heavy drinking was linked to almost double risks of CVD and CHD death after controlling for classical risk factors and education.[300] The respective adjusted RR were 2.05 and 1.81. Although the latter 95% CI was relatively wide and included 1.0, due to the limited number of coronary deaths (n=23) among frequent heavy drinkers, these findings still point to the link between hazardous drinking and increased cardiovascular risk. The authors reported that smoking was the most important confounder of the alcohol-mortality associations; however, no RR values for any conventional risk determinants or education were presented.[300]

In women from Arkhangelsk, examined in 1999-2000 and followed for 10 years, binge drinking (consumption of ≥80 g of alcohol on one occasion at least once a month) was significantly related to higher CVD mortality risk, after controlling for education and marital status, as well as for conventional and novel cardiovascular risk factors (adjusted RR 5.06). In their male peers, however, there was no clear link between binge drinking and fatal CVD (adjusted RR 0.96). The relatively low number of outcomes (77 and 52 CVD deaths in men and women, respectively) could explain the fact that among the covariates of interest, lower education or high DBP were inconsistently linked to cardiovascular mortality, while for non-married status, smoking, and TCH, the link with fatal CVD did not reach statistical significance.[256]

Therefore, the latest evidence from CEE/FSU is mostly consistent that alcohol effects on CVD risk are not explained away by conventional risk factors. Including drinking measures in the cardiovascular prognostic algorithms could improve the risk assessment accuracy in CEE/FSU populations. On the other hand, it might also cause various methodological problems, which is the focus of the next section.

d) Alcohol drinking measures and CVD risk assessment

Since both drinking dose and drinking patterns affect cardiovascular risk, theoretically, they should both be included into risk scales. However, while the assessment of average ethanol intake is methodologically developed, the drinking patterns are more problematic to operationalize. Heavy episodic drinking is typically defined as consumption of ≥4-5 drinks per occasion or per day[311], but there are still no universal definitions of “patterns of drinking” or “binge/hazardous drinking”.[276] For example, in a well-known review on alcohol and CVD[282], the included cohort studies defined

heavy/binge drinking as frequent hangovers or intoxication[312;313], consumption of ≥6 bottles of beer per occasion[314], registration as a heavy alcohol abuser[315], and poor work performance because of alcohol-related problems.[316] However, none of these definitions differentiated between episodic vs. frequent heavy drinking, and this distinction is essential for adequate assessment of cardiovascular risk.

It is highly likely that in populations with different drinking patterns, different measures of alcohol consumption predict CVD more efficiently.[317] In addition, all self-reported measures of alcohol consumption are prone to random and non-random misclassification. Differential reporting of drinking may be affected by cardiovascular risk factors and outcomes, as well as by numerous other variables, but the direction and magnitude of this bias is hardly predictable.[317] Investigating multiple drinking characteristics could help to identify the most important context-specific predictors of CVD and minimise the risk of misclassification. Although this approach is acceptable for epidemiological or clinical research, in the real-world clinical practice – the key area for cardiovascular risk assessment and control – only the strongest and the most measurable predictors should be used. For example, in terms of feasibility, short questionnaires on alcohol-related problems like CAGE[318] could be more acceptable for both clinicians and patients than an informative, but rather time-consuming graduated frequency method.[319-321] On the other hand, while simple questions on binge drinking might provide the information which is the most relevant to cardiovascular risk prediction, such a "straightforward" approach could alienate patients and, hence, be avoided by clinicians. To my knowledge, no extensive comparison of drinking measures in terms of their predictive value and clinical feasibility for cardiovascular risk assessment has been performed in either Western populations or CEE/FSU countries.

To summarise ***Section 2.3.3***, the existing evidence suggests that alcohol could be one of the major determinants of high cardiovascular mortality in CEE/FSU, independently of classical risk factors. Adding drinking measures to existing prognostic algorithms, such as SCORE, could improve the accuracy of total cardiovascular risk assessment in CEE/FSU populations, although thus far, no studies have addressed this issue. The last section of the ***Background*** chapter summarises the current prospects on cardiovascular risk assessment and outlines the gaps in the knowledge, which will be addressed in this thesis.

2.4. Background summary

Cardiovascular disease remains the leading cause of mortality, morbidity, and disability throughout the world. To tackle this major public health problem effectively, future CVD cases should be prevented, by estimating and managing cardiovascular risk. Over the last five decades, the concept and methodology of total cardiovascular risk assessment have been developed, which use a combination of various conventional risk factors for the early identification of asymptomatic individuals and groups at increased risk of overt cardiovascular pathology. Among multiple existing risk assessment instruments, the SCORE scale is one of the most widely used in both research and clinical settings. It predicts the 10-year risk of fatal atherosclerotic CVD in middle-aged people, based on age, gender, smoking, blood pressure, and blood lipids. SCORE is officially recommended by the ESC for all European populations. Accounting for Europe's heterogeneity in terms of fatal CVD and classical risk factor levels, the high-risk and low-risk SCORE charts were created.

At the same time, SCORE ability to accurately predict cardiovascular risk in external settings is limited by the considerable variation in the baseline, or background, risk across populations and over time. Moreover, conventional risk factors, captured by SCORE, are important, but not exclusive determinants of cardiovascular risk. Numerous novel risk markers have been shown to independently predict CVD and, to a varying extent, to improve the prognostic performance of the risk models. These limitations have been addressed, first, by SCORE recalibration (adjustment to the local settings by introducing population-specific event rates and risk factor means) and, second, by SCORE model extension (adding selected novel risk factors to the original algorithm). While recalibrated SCORE versions typically demonstrate better prognostic performance than the non-calibrated instrument, there is a need for the continuous update and re-adjustment of local SCORE scales, particularly in populations with rapidly changing levels of cardiovascular risk factors and fatal CVD. The improvement in the prognostic performance of the extended SCORE models developed thus far was relatively modest, which justifies the ongoing search for alternative extended SCORE algorithms.

Importantly, the global burden of CVD is not evenly distributed, and some populations, such as the countries of Central and Eastern Europe (CEE) and former Soviet Union republics (FSU), face particularly high, but heterogeneous levels of cardiovascular

mortality. CEE/FSU populations have a particular need for accurate cardiovascular risk assessment and effective risk reduction. However, they also face additional gaps in the knowledge on cardiovascular risk prediction. Specifically, using only one high-risk version of the SCORE scale, currently recommended for all CEE/FSU countries, could inadequately reflect the variation of the background cardiovascular risk and risk factor patterns across the region. At present, the high-risk SCORE lacks both a prospective assessment of its predictive performance and a proper country-specific recalibration in CEE/FSU. In addition, conventional risk factors do not fully account for high CVD rates in the region of interest. Socioeconomic characteristics, such as education or marital status, and alcohol consumption, in particular hazardous drinking, have been shown to predict fatal CVD independently of conventional risk determinants in both Western and CEE/FSU contexts. Including socioeconomic characteristics or drinking parameters in the cardiovascular risk function, together with classical risk factors, might improve SCORE performance across CEE/FSU populations, but no attainable studies have as yet investigated this hypothesis.

In order to address the current gaps in the knowledge on cardiovascular risk prediction in CEE/FSU, the main aim and objectives of this thesis have been specified and will be presented in ***Chapter 3***. The methodological aspects of the study will then be discussed in ***Chapter 4***.

Chapter 3. Aims and objectives

As summarised in the previous chapter, there are gaps in the knowledge on cardiovascular risk prediction in CEE/FSU – a region with high rates of CVD mortality and morbidity and, consequently, in particular need of accurate risk assessment and effective risk management. Therefore, it is important to investigate the real-world performance of CVD risk prediction instruments officially recommended for the local settings, such as the SCORE scale.[17;20]

The overall aim of this thesis is to assess the predictive performance of the SCORE scale in CEE/FSU populations, using individual-level data from two large international population-based studies. Specifically, the SCORE algorithm is applied to Czech, Polish, Lithuanian, and Russian MONICA samples[42], as well as to Czech, Polish, and Russian HAPIEE samples[43], described in more detail in ***Chapter 4***, in order to examine:

- how reliably SCORE predicts fatal cardiovascular events in CEE/FSU populations with different levels of absolute risk (i.e. mortality levels);
- whether inclusion of socioeconomic parameters or alcohol consumption characteristics improves the predictive performance of the SCORE instrument in these populations.

The research hypotheses are as follows:

1) SCORE is a significant predictor of atherosclerotic CVD mortality in both genders, across all MONICA and HAPIEE samples.
2) While SCORE discrimination is expected to be satisfactory in most samples, it could be the case that for the CEE/FSU populations with the highest levels of fatal CVD, such as Russia, the risk might be under-estimated by the original high-risk SCORE instrument.
3) The prognostic performance of the SCORE model is expected to improve after SCORE extension by socioeconomic parameters.
4) Adding alcohol consumption characteristics to the SCORE model could improve its prognostic performance.

To achieve the study aims and to test the research hypotheses, the following specific objectives are formulated:

1) For each study-, population-, and gender-specific sample, to describe the distribution of classical and additional cardiovascular risk factors and the levels of fatal atherosclerotic CVD;
2) To explore the strength of the main association of interest, between SCORE and atherosclerotic cardiovascular mortality, across MONICA and HAPIEE samples;
3) To evaluate SCORE calibration and discrimination in MONICA and HAPIEE samples; in addition, to estimate the expected 10-year SCORE calibration in HAPIEE;
4a) To examine the role of SCORE and socioeconomic parameters as predictors of atherosclerotic CVD mortality;
4b) To investigate the calibration and discrimination of the SCORE model extended by socioeconomic characteristics;
5a) To assess the role of SCORE and drinking parameters as predictors of fatal atherosclerotic CVD;
5b) To estimate the calibration and discrimination of the SCORE model extended by drinking characteristics;
6) To evaluate the strength of the overall associations between SCORE and fatal atherosclerotic CVD before and after adjustment for extra risk determinants, using the random effects meta-analysis approach.

The methodological aspects of achieving the research aims and objectives specified above will be discussed in the next chapter.

Chapter 4. Methods

In this chapter, the selection of the study population and samples is described, namely Czech, Polish, Lithuanian, and Russian samples from the MONICA study, and Czech, Polish, and Russian samples from the HAPIEE study. The measurement of the main components of the SCORE model and the additional risk determinants (socioeconomic parameters and alcohol consumption characteristics) is outlined. The final part of the chapter presents the overall strategy of statistical analyses and their specific steps, including the assessment of the performance of the original SCORE scale and the evaluation of various measures of SCORE calibration and discrimination after adding extra risk factors to the model.

4.1. Study population, samples, and subjects

This thesis examines the performance of the SCORE risk scale in CEE/FSU populations, and, hence, it was advisable to obtain longitudinal local data on cardiovascular mortality. Two of the largest international studies focusing on CVD in CEE/FSU are MONICA and HAPIEE projects. Although the HAPIEE study provides more recent estimates of fatal CVD rates (from the early 2000s onwards), its mean follow-up is under seven years at the time of writing. Therefore, prospective data from the CEE/FSU MONICA samples, typically followed from the mid-1980s for at least 10 years, are also used in the analyses.

4.1.1. MONICA population and samples

As described in ***Section 2.2.2*** of the ***Background*** chapter, the international MONICA project monitored the trends in CHD rates and conventional coronary risk factors across age- and gender-stratified population samples from the mid-1980s to at least the mid-1990s. The data on CVD (both CHD and non-CHD) mortality were also collected.[42;126;127;130;170;322] Typically, MONICA cohorts, aged 35-64 years at baseline, consisted of several different samples, which were randomly selected from population registers (electoral lists in Russia) and screened with a three to five-year interval; the follow-up length was, therefore, maximal for the subjects from the first sample. In this thesis, the 10-year follow-up data were used, as the SCORE scale predicts the 10-year risk of fatal atherosclerotic CVD.[20] Although the MONICA populations are not completely representative of the respective countries as a whole, their characteristics are still considered to be satisfactory approximations of the national CVD rates, cardiovascular risk factors, and additional risk determinants.[42]

Czech MONICA: The cohort included 9,458 people (4,692 men, 4,766 women), who were urban and rural residents of the Praha-východ, Cheb, Chrudim, Jindřichův Hradec, Benešov, and Pardubice districts. The MONICA-1 sample (1,531 men, 1,544 women) was examined in 1985, the MONICA-2 sample (1,534 men, 1,576 women) in 1988, and the MONICA-3 sample in 1992 (1,627 men, 1,646 women). Only MONICA-3 participants are included in the present analyses, since the complete data on 10-year mortality follow-up were not available for MONICA-1 and MONICA-2 samples. The overall response rate for the MONICA-3 sample was 65%.[160]

Polish MONICA-Warsaw: The cohort from Warsaw (the capital city) consisted of 4,079 residents of two city districts (2,019 men, 2,060 women), who were followed for 10 years. Baseline screening took place in 1983-1984 for the MONICA-1 sample (1,309 men, 1,337 women), and in 1988-1989 for the MONICA-2 sample (710 men, 723 women). The response rates were 74% and 70% for MONICA-1 and MONICA-2, respectively.[323]

Polish MONICA-Tarnobrzeg: The cohort from Tarnobrzeg (a south-eastern Polish province consisting of small towns and rural communities) included 5,362 people (2,502 men, 2,860 women). The MONICA-1 sample was examined in 1983-1984 (1,250 men, 1,472 women), the MONICA-2 sample in 1987-1988 (627 men, 684 women), and the MONICA-3 sample in 1992-1993 (625 men, 704 women). The follow-up stopped in late December 1998, and no 10-year data were available for MONICA-3 participants; therefore, only MONICA-1 and MONICA-2 subjects are included in the present analyses. The response rates were 82% and 73% for MONICA-1 and MONICA-2, respectively.[323]

Lithuanian MONICA: The cohort consisted of four samples from Kaunas (the second largest Lithuanian city and an economic, academic, and cultural centre); in total, 3,575 men and 3,816 women were screened. The MONICA-1 sample (1,339 men, 1,404 women) was examined in 1983-1985, the MONICA-2 sample (924 men, 934 women) in 1986-1987, the MONICA-3 sample (681 men, 686 women) in 1992-1993, and the MONICA-4 sample (631 men, 792 women) in 2001-2002. For the MONICA-4 participants, no 10-year follow-up data were available; therefore, only subjects from the MONICA-1, 2, and 3 samples are included in the present analyses. The respective response rates were 70%, 70%, and 59%.[324]

Russian MONICA: The cohort included 9,835 residents (4,899 men, 4,936 women) of the three districts of Novosibirsk (an industrial and scientific centre in Western Siberia). The MONICA-1 sample (1,573 men, 1,602 women) was examined in 1985-1986, the MONICA-2 sample (1,721 men, 1,666 women) in 1988-1989, and the MONICA-3 sample (1,605 men, 1,668 women) in 1994-1995. For each sample, the response rate was approximately 72%.[230]

Since the SCORE instrument predicts cardiovascular risk in individuals without pre-existing atherosclerotic CVD, people with a self-reported history or medical evidence of MI, angina, or stroke are excluded from the present analyses. The subjects aged under 40 years at baseline are also excluded, as the SCORE scale predicts fatal CVD risk in people over 40.[20] For Tarnobrzeg samples, the deceased subjects with missing ICD codes (n=16) are excluded, since it was not possible to reliably define their outcome status (atherosclerotic CVD death vs. death from other causes). In total, 1,861, 2,437, 2,782, 3,806, and 5,669 MONICA participants from the Czech Republic, Poland (Warsaw and Tarnobrzeg), Lithuania, and Russia, respectively, are included in the first step of the analyses (**Table 4.1.1**, penultimate row).

Individuals with missing exposure values (classical risk factors included in SCORE and socioeconomic measures) are not excluded from descriptive analyses, and an additional "missing" category is created for these values. The survival analyses, for which the complete case approach is used (for details, see ***Section 4.5.1***), include 1,340, 2,404, 2,729, 3,301, and 5,253 MONICA participants from the Czech Republic, Poland (Warsaw and Tarnobrzeg), Lithuania, and Russia, respectively (**Table 4.1.1**, last row).

Table 4.1.1. MONICA sample selection

	Czech Republic		**Poland (Warsaw)**		**Poland (Tarnobrzeg)**		**Lithuania**		**Russia**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Whole MONICA sample	1,627	1,646	2,019	2,060	1,877	2,156	2,944	3,024	4,899	4,936
Within the study age range (40-64 years at baseline)	967	1,010	1,659	1,737	1,541	1,733	2,236	2,360	2,984	3,078
Without pre-existing CVD	898	963	1,264	1,173	1,301	1,481	1,897	1,909	2,751	2,918
Without missing ICD codes	898	963	1,264	1,173	1,279	1,466	1,897	1,909	2,751	2,918
Without missing SCORE values	636	704	1,253	1,151	1,267	1,462	1,651	1,650	2,576	2,677

4.1.2. HAPIEE population and samples

The HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe) study prospectively investigates the determinants of CVD and other chronic conditions in CEE/FSU.[43] It follows four cohorts from the Czech Republic (Havířov/Karviná, Hradec Králové, Jihlava, Kroměříž, Liberec, and Ústí nad Labem), Poland (Krakow), Russia (Novosibirsk), and Lithuania (Kaunas). Since the baseline (2002-2004), Czech, Polish, and Russian cohorts have been followed for cause-specific mortality, including fatal CVD, and for non-fatal CHD and strokes. As the Lithuanian cohort entered the study later (2005), the current absolute number of circulatory deaths is insufficient to assess CVD mortality. Therefore, only HAPIEE data from the first three countries are analysed in this thesis.

The study participants – men and women aged 45-69 years – were randomly selected from urban population registers (electoral lists in Russia). Although HAPIEE populations are not entirely representative of the respective national populations, it can still be assumed that their CVD mortality, cardiovascular risk profiles, and additional risk determinants satisfactorily approximate those in the majority of Czech, Polish, and Russian cities.[43] The actual total HAPIEE sample size was 28,947, with an overall response rate of 59% (55% in the Czech Republic, 61% in Poland, and 61% in Russia).[43]

Due to delayed participation, some subjects took part in the baseline survey at the age of 70-73 years; in the present analyses, the upper limit for baseline age is extended to 70.9 years, while older individuals (n=86) are excluded. The thesis also does not include people with a self-reported history of MI, angina, or stroke; therefore, in total, 23,265 subjects are included in the descriptive analyses: 7,633 from the Czech Republic, 8,316 from Poland, and 7,316 from Russia (**Table 4.1.2**, penultimate row). In the Czech Republic and Poland, the study questionnaire was completed at home, prior to the medical examination in a clinic, while in Russia, both parts of the study were performed in a clinic. This explains the smaller proportion of Czech and Polish participants with complete questionnaire and examination data (82% and 87%, respectively). However, individuals with missing exposure values are not excluded from descriptive analyses, and an additional "missing" category is created for these values. The survival analyses, employing the complete case approach (see ***Section 4.5.1***), included 6,018 participants

from the Czech Republic, 7,209 from Poland, and 7,290 from Russia (**Table 4.1.2**, last row).

Table 4.1.2. HAPIEE sample selection

	Czech Republic		**Poland**		**Russia**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Whole HAPIEE sample	4,124	4,732	5,230	5,498	4,269	5,094
Within the study age range (45-70 years at baseline)	4,077	4,704	5,230	5,498	4,264	5,088
Without pre-existing CVD	3,405	4,228	3,986	4,330	3,254	4,062
Without missing SCORE values	2,659	3,359	3,456	3,753	3,246	4,044

The population- and gender-specific distribution of classical and additional cardiovascular risk factors and fatal atherosclerotic CVD levels in Czech, Polish, Lithuanian, and Russian MONICA samples, as well as in Czech, Polish, and Russian HAPIEE samples, will be presented in ***Chapter 5***.

4.2. Ethical approval and informed consent

The MONICA study protocol was approved by the local ethics committees in each participating country.[42] The HAPIEE study protocol was approved by the University College London/University College London Hospital ethics committee and by the local ethics committees at each study centre.[43] Before entering the project, all potential participants received an explanatory invitation letter. All participants gave written informed consent at baseline to take part in the questionnaire survey, medical examination (including blood sample analyses), and the follow-up. This PhD project uses already existing data and, therefore, did not require separate ethical approval.

4.3. Measurements

At baseline, MONICA participants were examined and interviewed in the clinic. Among other procedures, an interview on demographic and socioeconomic parameters, health behaviours and lifestyle, as well as BP measurement, anthropometry, and blood sample collection, was performed.[42]

The baseline data collection in the HAPIEE Study included a questionnaire survey and a clinical examination. The structured questionnaire focused on demographic and socioeconomic characteristics, health status, health behaviours, lifestyle, and psychosocial factors[43]. All questions were translated from English into each local

language, back translated, and checked for accuracy. Anthropometry, measurement of BP, lung function and cognitive function, plus a fasting venous blood sample collection, were performed during the examination in the clinic. The description of BP and TCH measurement is given in ***Section 4.3.2***.

In the present analyses, only the variables relevant to the research aims and objectives are used. These variables are described below in more detail.

4.3.1. Outcome

The study outcome was atherosclerotic cardiovascular death, either coronary or non-coronary, in agreement with the SCORE end-points[20] (see **Table 4.3.1** for respective ICD-9 and ICD-10 codes).

Table 4.3.1. Atherosclerotic coronary and non-coronary causes of death

ICD-9 code	ICD-10 code	Diagnosis
401-405	I10-I13	Hypertensive disease
410-414	I20-I25	Ischemic heart disease
426	I44-I45	Atrioventricular and left bundle-branch block; other conduction disorders
N/A	I46.1	Sudden cardiac death, so described
427-429	I47-I51	Paroxysmal tachycardia, atrial fibrillation and flutter; other cardiac arrhythmias; heart failure; complications and ill-defined descriptions of heart disease
431	I61	Intracerebral haemorrhage
432-438	I63-I69	Cerebral infarction; stroke, not specified as haemorrhage or infarction; occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction; occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction; other cerebrovascular diseases; cerebrovascular disorders in diseases classified elsewhere; sequelae of cerebrovascular disease
440-443	I70-I73	Atherosclerosis; aortic aneurysm and dissection; other aneurysm; other peripheral vascular diseases
798.1	R96.0	Instantaneous death
798.2	R96.1	Death occurring less than 24 hours from onset of symptoms, not otherwise explained

For MONICA cohorts, cause-specific mortality data came from the population-specific routine systems of vital registration (national or local mortality registers) and were classified according to ICD-9 or ICD-10 before and after January 1st 1997, respectively.[42;126] In the HAPIEE study, cardiovascular mortality data are obtained from the same vital registration sources. Specifically, in the Czech Republic, the national death register is being used. In Poland, the provincial death register covers the city of Krakow and surrounding area. In Russia, the local mortality register covers selected

Novosibirsk districts, from which HAPIEE participants were recruited.[43] Typically, the mortality data, coded according to ICD-10, become available in the end of the following year.

4.3.2. SCORE risk determinants

As mentioned in ***Section 2.1.3*** of the ***Background*** chapter, the SCORE scale predicts 10-year risk of fatal CVD in middle-aged men and women without pre-existing atherosclerotic CVD.[20] Based on 12 European cohorts, two separate SCORE charts were created for low and high-risk countries, and the latter is officially recommended for CEE/FSU populations.[17] Since the recently introduced Czech and Polish SCORE versions lack a proper description of their development and/or recalibration[175;176], the original high-risk SCORE scale is used as a core model for all countries of interest. For comparison, the performance of the original low-risk scale is also investigated. The SCORE predictions of 10-year risk of fatal CVD in populations at high and low risk are presented in **Tables A4.3.1-A4.3.2** (***Appendix I***). In addition, the performance of high and low-risk non-dichotomised SCORE is assessed, by analysing individual levels of SCORE-predicted absolute risk (percentages in the respective SCORE chart cells) as a continuous variable, since it is well known that dichotomisation of continuous risk predictors may result in a considerable loss of power and residual confounding.[59;76;78;82;325-327]

For both SCORE versions, the risk determinants include age, gender, smoking status (current smokers vs. never or ex-smokers), TCH (scales based on TCH vs. TCH:HDL-CH ratio perform similarly), and SBP. In both MONICA and HAPIEE, the data on self-reported smoking status were obtained from the baseline standard questionnaire.[42;43;126;130] Those currently and regularly smoking at least one cigarette per day were regarded as current smokers; never and ex-smokers were considered non-smokers, in accordance with the SCORE criteria.[20]

SBP measurement was performed after a five-minute rest, in a quiet room with comfortable temperature, using a standard mercury sphygmomanometer (MONICA) or a digital blood pressure monitor Omron M5-I (HAPIEE). SBP was measured in a sitting position, on the right arm, with a two-minute interval between consecutive measurements (two for MONICA, three for HAPIEE), and recorded as a continuous variable, to the nearest two mm Hg.[42;43]

TCH concentration was measured in a fasting venous blood sample, taken from the antecubital vein, with the person in the sitting position and with minimal tourniquet use. In MONICA, TCH levels were measured with an enzymatic method (CHOD-PAP kits, Boehringer, Mannheim, Germany) in Czech and Lithuanian samples, while for Polish and Russian samples, the direct Liebermann-Burchard method was used. In HAPIEE, serum TCH levels for Czech, Polish, and Russian samples were measured using an enzymatic method.[43] All assay methods were calibrated, and all MONICA and HAPIEE laboratories were subjected to internal quality control. In addition, external quality control for MONICA was performed at the WHO Regional Lipid Reference Centre (Institute for Clinical and Experimental Medicine, Prague, Czech Republic).[42] In both MONICA and HAPIEE, the TCH concentration was recorded as a continuous variable (mmol/l).

4.3.3. Additional risk predictors

Based on the evidence summarised in ***Section 2.3.2*** of the ***Background*** chapter, selected socioeconomic parameters are considered as additional cardiovascular risk factors in this thesis. Specifically, in MONICA and HAPIEE samples, education was categorised as primary or less, vocational, secondary, or university level, and marital status as married/cohabiting, single, separated/divorced, or widowed.[42;43] For Polish MONICA samples from Warsaw and Tarnobrzeg, no data on marital status were available, while the information on education was obtained for all MONICA and HAPIEE samples.

Since hazardous alcohol drinking may be an additional cardiovascular risk factor (see ***Section 2.3.3***), it is also included in the analyses. The associations between alcohol and fatal CVD are investigated only for HAPIEE samples, because in MONICA, no compatible data on alcohol consumption were available for all samples. In HAPIEE, annual alcohol consumption and drinking patterns were estimated by the graduated frequency (GF) method[319-321], which assesses how often during the past 12 months more than a specific amount of alcohol (approximately 0.5 drinks, 1-2, 3-4, 5-6, 7-9, or ≥10 drinks) was consumed; the frequency is measured on a 9-point scale, ranging from "never" to "every day". Based on the GF data, alcohol drinking frequency in the last year ("never", "less than once per month", "1-3 times per month", "at least once per week"), and binge drinking (≥100 g of ethanol per drinking session at least once a month) parameters were calculated. Additionally, the presence of alcohol-related

problems in the last 12 months was assessed by the CAGE questionnaire[318], which asked whether the person had felt he/she should cut down on drinking; whether people had annoyed the respondent by criticising his/her drinking; whether the person had felt bad or guilty about his/her drinking; and whether he/she had a drink first thing in the morning. Participants with two or more positive answers are considered as CAGE-positive.

In the descriptive analyses, the original categories of socioeconomic parameters and alcohol consumption characteristics are used. As the outcome numbers across the original non-dichotomised categories are insufficient for performing analyses of adequate power, these additional risk determinants are dichotomised, while estimating the prognostic performance of the extended SCORE models (see ***Chapters 7-8***). Dichotomisation of alcohol consumption frequency was not appropriate, since this variable demonstrated a J or U-shaped association with fatal CVD; therefore, only binge drinking and CAGE were used in the analyses of the SCORE performance extended by alcohol consumption measures (***Chapter 8***).

The present research focuses on the easily measurable socioeconomic characteristics and alcohol consumption parameters, which will make the final extended models more relevant and applicable to real-world clinical and epidemiological settings.[189]

4.4. Statistical power of the study

This thesis uses already existing MONICA and HAPIEE data, and, therefore, the size of the samples could not be influenced. Considering the large sizes and relatively large outcome numbers for the majority of MONICA and HAPIEE samples, the study power is expected to be sufficient for an assessment of the association between baseline SCORE, as the main exposure of interest, and atherosclerotic cardiovascular mortality. Thus, in Czech MONICA samples, followed for 10 years, there were 75 atherosclerotic CVD deaths (among all participants, regardless of the availability of the baseline SCORE data). The total number of atherosclerotic cardiovascular deaths in the first 10 years was 110 and 82 for Polish MONICA samples from Warsaw and Tarnobrzeg, respectively, and 95 for Lithuanian MONICA samples. Among Russian MONICA participants, 295 atherosclerotic CVD deaths were registered within the first 10 years of follow-up. During the period for which the complete data on cause-specific mortality are available for HAPIEE subjects (until the end of 2009 for the Czech Republic, and

until the end of 2008 for Poland and Russia), the observed number of atherosclerotic cardiovascular deaths was 84, 71, and 147, respectively.

Since for several risk predictors, such as SBP and TCH in Czech and Polish HAPIEE samples, the data were partially missing, the complete case analyses might have decreased the number of observations and outcomes and, hence, reduced the study power. As the main association of interest is between the conventional cardiovascular risk predictors, captured by SCORE (exposure), and atherosclerotic CVD mortality (outcome), only the cases with available data on both exposure and outcome are included in the survival analyses and the analyses of SCORE prognostic performance. Therefore, the calculation of the study power is also based on the complete case approach.

In particular, assuming that the confidence level is 95% or 99%, and the lowest hazard ratio (HR) for the comparison of atherosclerotic CVD mortality in the exposed (high-risk SCORE ≥5%) vs. unexposed (SCORE <5%) participants is 1.25, the study power was calculated for the smallest male and female MONICA and HAPIEE samples, in order to obtain the most conservative estimates. For MONICA, the smallest samples were from the Czech Republic (636 men, 704 women). For HAPIEE, the Czech samples were also the smallest (2,659 men, 3,359 women; for details, see ***Section 4.1.2***). As shown in **Table 4.4.1**, for the 95% CI and the minimal HR of 1.25, statistical power was at least 80% across these four samples. As all the other MONICA and HAPIEE samples were larger, the respective study power was also higher and, hence, exceeded 80%.

Table 4.4.1. Study power calculation for Czech MONICA and HAPIEE samples

Hazard ratio	**Study power**			
	95% CI		*99% CI*	
Czech MONICA				
	Men	*Women*	*Men*	*Women*
1.25	80.3%	84.1%	59.4%	64.97%
1.50	99.9%	99.9%	99.4%	99.8%
2.00	>99.9%	>99.9%	>99.9%	>99.9%
Czech HAPIEE				
	Men	*Women*	*Men*	*Women*
1.25	>99.9%	>99.9%	99.9%	>99.9%
1.50	>99.9%	>99.9%	>99.9%	>99.9%
2.00	>99.9%	>99.9%	>99.9%	>99.9%

Therefore, despite some expected loss of power in multiple regression analyses (adjusting for socioeconomic parameters and alcohol consumption characteristics), the

analyses of the link between the high-risk SCORE ≥5% and fatal CVD have sufficient power to demonstrate efficiently even moderate associations (minimal HR 1.25) between SCORE and atherosclerotic cardiovascular mortality. In addition, the power of the random effects meta-analyses, which pool the sample-specific estimates of the SCORE-fatal CVD association and assess the overall magnitude of this link (see ***Section 4.5.4***), is higher than the power of the analyses for individual samples.

4.5. Statistical analyses

This section outlines the strategy to deal with missing data and outliers and summarises the reasons for performing complete case analyses. The statistical principles underlying the SCORE prognostic model are introduced, followed by the description of the measures that are used to assess the performance of original and extended SCORE instruments. Finally, the specific steps of MONICA and HAPIEE data analyses are described.

4.5.1. Missing data and outliers

For the MONICA samples, the percentage of missing data is generally low, with the exception of TCH and SBP values in the Czech Republic and TCH values in Lithuania (***Chapter 5***). Over 10% of SBP and TCH values are missing for Polish and Czech HAPIEE samples, since these participants were clinically examined after the questionnaire survey at home. The data range and consistency checks were also performed, and any clinically improbable or inconsistent values (outliers) were set as "missing". In the descriptive analyses, a separate, additional category is created for the missing values. For the risk prediction models, the observations with missing values are excluded, and the complete case analyses are performed. The potential limitations of this approach, as well as possible alternatives, will be addressed in the ***Discussion*** chapter. However, it should be noted that the main aim of this thesis is to study the individual-level relationship between the SCORE-predicted risk of fatal atherosclerotic CVD and observed risk, which requires having information on both the former (exposure) and the latter (outcome). Since individual SCORE values cannot be calculated for the subjects with missing data on TCH and/or SBP, these participants are excluded from the SCORE-based survival analyses and prognostic performance analyses.

The complete case approach has been extensively used in the area of cardiovascular risk prediction (for example[33;99;235;261;328-330]). It was also demonstrated that non-response at resurvey does not bias the associations between baseline cardiovascular risk factors and later CVD mortality[331], although more evidence is needed on the impact of non-response to baseline surveys. The alternative to the complete case analysis would be multiple imputation of missing data. The majority of the available multiple imputation approaches are based on the assumption of data missing at random, or completely at random.[23;332-337] If the assumption of SCORE missing at random, or completely at random, was true for MONICA and HAPIEE data, the mortality levels for subjects with missing vs. non-missing SCORE values would be relatively similar, since the missing SCORE group would represent a more or less equal mixture of individuals with risk levels <5% and ≥5%.

However, the observed levels of all-cause mortality and atherosclerotic CVD mortality across MONICA and HAPIEE samples clearly demonstrate that the risk of death from all causes, as well as the risk of cardiovascular death, was different in participants with missing SCORE values, compared to their peers with non-missing SCORE (in **Table 4.5.1**, the 10-year observed mortality and the currently observed mortality data are presented for MONICA and HAPIEE, respectively).

The degree of this discrepancy in the observed risk levels varied substantially across samples, and also differed for all-cause vs. atherosclerotic cardiovascular mortality. In particular, the ratio of all-cause mortality among subjects with missing vs. non-missing SCORE ranged from 0.83 (Tarnobrzeg) to 1.83 (Warsaw and the Czech Republic) in MONICA, and from 0.59 (Russia) to 1.99 (Poland) in HAPIEE. For fatal CVD, this ratio varied from 0.86 (Lithuania) to 2.10 (Tarnobrzeg) in MONICA, and from 1.86 (the Czech Republic) to 2.75 (Poland) in HAPIEE. As in the Russian HAPIEE sample, only 26 people had missing SCORE levels, no atherosclerotic CVD deaths were registered in these individuals. For Czech and Polish HAPIEE samples, the levels of all-cause and/or cardiovascular mortality among subjects with missing SCORE were even higher than in people with SCORE ≥5%.

Table 4.5.1. All-cause and atherosclerotic cardiovascular mortality by baseline SCORE levels: MONICA and HAPIEE

	Subsample size, N	All deaths, N (%)	Atherosclerotic cardiovascular deaths, N (%)
MONICA			
Czech Republic			
Non-missing SCORE	1,340	139 (10.37)	45 (3.36)
SCORE <5%	989	61 (6.17)	15 (1.52)
SCORE ≥5%	351	78 (22.22)	30 (8.55)
Missing SCORE	521	99 (19.00)	30 (5.78)
Poland (Warsaw)			
Non-missing SCORE	2,404	279 (11.61)	107 (4.45)
SCORE <5%	1,655	112 (6.77)	35 (2.11)
SCORE ≥5%	749	167 (22.30)	72 (9.61)
Missing SCORE	33	7 (21.21)	3 (9.09)
Poland (Tarnobrzeg)			
Non-missing SCORE	2,729	206 (7.55)	81 (2.97)
SCORE <5%	2,030	97 (4.78)	32 (1.58)
SCORE ≥5%	699	109 (15.59)	49 (7.01)
Missing SCORE	16	1 (6.25)	1 (6.25)
Lithuania			
Non-missing SCORE	3,301	271 (8.21)	84 (2.54)
SCORE <5%	2,476	121 (4.89)	34 (1.37)
SCORE ≥5%	825	150 (18.18)	50 (6.06)
Missing SCORE	505	43 (8.52)	11 (2.18)
Russia			
Non-missing SCORE	5,253	591 (11.25)	267 (5.08)
SCORE <5%	3,892	279 (7.17)	117 (3.01)
SCORE ≥5%	1,361	312 (22.92)	150 (11.02)
Missing SCORE	416	62 (14.90)	28 (6.73)
HAPIEE			
Czech Republic			
Non-missing SCORE	6,018	248 (4.12)	56 (0.93)
SCORE <5%	3,764	91 (2.42)	13 (0.35)
SCORE ≥5%	2,254	157 (6.97)	43 (1.91)
Missing SCORE	1,615	121 (7.49)	28 (1.73)
Poland			
Non-missing SCORE	7,209	265 (3.68)	50 (0.69)
SCORE <5%	4,494	80 (1.78)	13 (0.29)
SCORE ≥5%	2,715	185 (6.81)	37 (1.36)
Missing SCORE	1,107	81 (7.32)	21 (1.90)
Russia			
Non-missing SCORE	7,290	475 (6.52)	147 (2.02)
SCORE <5%	4,082	122 (2.99)	18 (0.44)
SCORE ≥5%	3,208	353 (11.00)	129 (4.02)
Missing SCORE	26	1 (3.85)	0 (0.00)

Therefore, as demonstrated in **Table 4.5.1**, the baseline SCORE values appear to be missing not at random, and the missingness patterns vary across MONICA and HAPIEE samples. The application of multiple imputation techniques, based on the assumption of data missing at random, or completely at random, to MONICA and HAPIEE data can produce biased results.[338-341] Hence, the present research will primarily focus on the

complete case analyses. To check the validity of this approach, the results of the Cox regression (the analysis of the strength of the unadjusted association between the high-risk dichotomous SCORE and fatal CVD) are compared for the complete and multiply imputed data. This comparison is performed for the samples with the highest proportion of missing SCORE values – Czech MONICA, Lithuanian MONICA, Czech HAPIEE, and Polish HAPIEE. The imputation model, which is based on the chained equations approach and generates 10 imputations, includes SCORE, additional risk factors (education and marital status for both MONICA and HAPIEE, binge drinking and CAGE for HAPIEE), atherosclerotic CVD death, and logarithm of survival time.

4.5.2. SCORE statistical analyses – general strategy

Before describing the steps of the SCORE performance assessment in MONICA and HAPIEE samples, it is important to summarise the statistical principles underlying the original SCORE algorithm. The SCORE scale predicts 10-year risk of atherosclerotic cardiovascular mortality in middle-aged individuals. The risk model has two components: one defines the shape of the baseline survival function, separately for men and women, and the other calculates relative risks for each risk factor – smoking, TCH, and SBP.[20] Risk factor coefficients were derived from the whole SCORE dataset, since their effects are assumed to be similar in both genders, across countries, and over time. The original SCORE risk functions were calculated using a Weibull proportional hazards model, stratified by cohort and sex. Age was defined as a measure of risk exposure time, rather than a risk factor in a traditional log-linear approach. However, the semiparametric Cox regression models, used for cross-checking the risk predictions, performed similarly.[9;20]

For both the Weibull and Cox-based risk estimates to be informative, it is essential to know how close the predicted and observed risks are, and how well the low and high-risk groups are differentiated. The next section, therefore, introduces various measures which denote the performance of prognostic models, such as SCORE.

4.5.3. Measures of predictive model performance

As outlined in ***Section 2.1.1***, the main measures of model performance are calibration and discrimination. Calibration ability of a risk score reflects how close the predicted and observed risks are, with a predicted to observed risk ratio of 1.0 indicating perfect calibration.[9;10;39;55;58;59;68;108;188] Predicted and observed risks could be compared not only for the whole samples, but also across age groups[108], or for individuals above and

below the established risk cut-off.[68] In a formal test of model calibration, the Hosmer-Lemeshow test, predicted risk values (typically, gender-specific) are compared to observed values within the deciles of estimated risk.[56] Lower values of Hosmer-Lemeshow χ^2 and higher *p* values indicate a smaller difference between predicted vs. observed risk, and therefore, better calibration.[56;58;73] The Gronnesby-Borgan test is an equivalent of the Hosmer-Lemeshow test for survival data analysis, based on martingale residuals.[342] However, due to the limited outcome numbers in the country- and gender-specific MONICA and HAPIEE subgroups, the Gronnesby-Borgan model would collapse on only two risk quantiles, and so the traditional Hosmer-Lemeshow test is used instead. It should be noted that the results of this test might be affected when at least two individuals have the same predicted risk levels, or when these levels are relatively low.[56;57] The test results are also sensitive to small deviations in fit when the sample size increases, and the null hypothesis of perfect fit is almost always rejected in larger samples.[343]

Calibration performance of the SCORE model in a specific external population could be improved by adjusting the baseline hazard function to the local background levels of CVD mortality and risk factors, via the recalibration procedure (not to be confused with calibration as a model performance parameter).[10;140;344-348] Thus, while model calibration appears a more flexible measure of prognostic performance, which potentially can be "fitted" to a specific population, it does not provide information on such a key, intrinsic quality of the risk-predicting algorithm as the accuracy of discrimination between subjects who will or will not develop the outcome of interest. Discrimination is considered more important than calibration by some authors, since the former cannot be improved by adjustment or recalibration of the model.[55;69;349-351]

Specifically, discrimination is the ability of a model to separate the participants who will experience events (such as fatal CVD) during the follow-up from the individuals who will remain event-free.[55;58;59;68;352] Threshold measures of discrimination include sensitivity (probability of high-risk score for people with subsequent events), specificity (probability of low-risk score for people without subsequent events), the ratio of true vs. false positives (likelihood ratio positive, LR+, or sensitivity/1 – specificity), and the ratio of false to true negatives (likelihood ratio negative, LR-, or (1-sensitivity)/specificity), for a particular risk cut-off (5% for the SCORE model). Additionally, the risk threshold could be characterised in terms of positive and negative

predictive values (PPV and NPV), which reflect the outcome probability in the high-risk group (PPV), and the probability of no outcome in the low-risk group (NPV).[68;70;71] The summary measures of discrimination are presented by the area under the receiver operating characteristic curve (AUROC) and the Harrell's C-statistic (AUROC equivalent for the survival models).[69] AUROC plots the sensitivity (true positive rate) against "1 - specificity" (false positive rate) across all consecutive cut-offs for the outcome probability. The AUROC or C-statistic values of 0.5 and 1.0 indicate minimal vs. ideal discrimination, respectively.[10;69-71;76;82;83;353]

Royston's R^2 index is a recently introduced discrimination measure for survival analysis models. R^2 statistic represents the amount of the outcome variation accounted for by risk predictors in the proportional hazards model.[59;72] In the present analyses, R^2 statistic was adjusted by the model dimension (the number of covariates), in order to facilitate the subsequent assessment of the extended SCORE performance. The bootstrap CI were calculated, using the minimal recommended replication number of 1,000.[72]

The additional prognostic information, provided by extra risk predictors, could be assessed by LR tests, where lower *p* values denote more pronounced differences between the nested baseline and extended models and, hence, better predictive performance of the latter instrument. The nested approach means that the extended model contains all of the markers from the baseline model.[39;73] The discrimination improvement of the extended model could also be quantified via risk reclassification parameters, such as net reclassification index (NRI) and integrated discrimination improvement (IDI). NRI represents the net proportion of people who move from one clinically relevant risk group to another, as a result of adding a new risk predictor.[9;39;71;79] In this thesis, the additional risk factors (socioeconomic parameters and alcohol consumption characteristics) are dichotomised, due to limited outcome numbers across the original categories, and, hence, are specific to MONICA and HAPIEE samples. Therefore, IDI, which is relatively independent of risk thresholds and categories, is used instead of NRI. IDI quantifies the separation between the individuals who will experience an outcome and those who will not, in terms of the average predicted risks for these two groups, across all possible cut-offs. In other words, this summary reclassification measure reflects the extended model's ability to improve average sensitivity without compromising average specificity.[39;71;79;82-85] Small IDI values, even if statistically significant, mean that the average individual change in the

risk predicted by the new, extended model is modest and, hence, the impact on the clinical decision making is minimal.[84;86;188;354]

After introducing the prognostic performance measures employed in the present research, the next section will describe how these measures are used when applying the original and extended SCORE scales to MONICA and HAPIEE samples.

4.5.4. Step-by-step analyses of MONICA and HAPIEE data

As summarised in ***Section 2.1.3***, the prognostic performance of the original, non-calibrated SCORE in external Western European populations was typically worse than in the cohorts used for deriving this instrument, but could be substantially improved by the adjustment/recalibration procedure.[9;10;20;64;140;141] However, to my knowledge, no published studies have investigated the performance of the original or recalibrated SCORE instruments in CEE/FSU, and no systematic attempt has been made for these populations to evaluate the prognostic value of such new cardiovascular risk factors as socioeconomic parameters and alcohol drinking when added to the SCORE risk predictors. Therefore, the present analyses include the following steps for each MONICA and HAPIEE sample, separately for men and women:

Step 1. Describing the distribution of classical CVD risk factors (age, smoking, TCH, and SBP) and additional cardiovascular risk determinants (socioeconomic parameters and alcohol consumption measures), as well as the levels of atherosclerotic CVD mortality (see ***Chapter 5***).

Step 2. Investigating the role of high and low-risk SCORE as predictors of atherosclerotic cardiovascular mortality, using the standard Cox, competing-risks, and Weibull regression models (***Chapter 6***, ***Section 6.1***).

Step 3. Assessing calibration of the original high and low-risk SCORE scales (predicted to observed risk ratio in whole samples, across age groups, and above/below the 5% risk threshold; Hosmer-Lemeshow test) (***Section 6.2***).

Step 4. Estimating the 10-year HAPIEE levels of atherosclerotic CVD mortality, based on the country-specific MONICA data or the exponential model projections; comparing the HAPIEE mortality levels predicted by high and low-risk SCORE to these estimates, in order to approximate the 10-year SCORE calibration across HAPIEE samples (***Section 6.3***).

Step 5. Assessing discrimination of the original high and low-risk SCORE (sensitivity, specificity, LR+, LR-, PPV, NPV, AUROC, Harrell's C-statistic, and Royston's R^2 index) (***Section 6.4***).

Step 6. Exploring the potential of socioeconomic variables for the SCORE model extension by evaluating the role of SCORE, education, and marital status as predictors of atherosclerotic CVD mortality, and by investigating the calibration and discrimination (measures listed for **Step 3**, plus LRT *p* values and IDI) of SCORE extended by socioeconomic characteristics (***Chapter 7***).

Step 7. Assessing the potential of alcohol consumption measures for the SCORE model extension by investigating the role of SCORE and drinking parameters as predictors of fatal atherosclerotic CVD, and by estimating the calibration and discrimination (measures listed for **Step 4**) of SCORE extended by drinking characteristics (***Chapter 8***).

Step 8. Combining the sample-specific effect estimates in the random effects meta-analyses, to assess the overall strength of the association between SCORE and atherosclerotic cardiovascular mortality before and after adjustment for socioeconomic parameters or alcohol consumption characteristics (***Chapter 9***).

For **Steps 2-8**, the use of proportional hazards regression models, primarily Cox regression, is justified by the high *p* values in Schoenfeld's test across all MONICA and HAPIEE samples. For each SCORE version (dichotomous and continuous high and low-risk instrument), *p* values were ≥0.10 and ≥0.36 for MONICA and HAPIEE samples, respectively. The strength of the main association of interest, between SCORE and atherosclerotic CVD mortality, is investigated in the classical Cox regression models, the parametric Weibull models which were originally used for the SCORE development[20], and the competing-risks models, which take into account the risk of death from causes other than atherosclerotic CVD. Specifically, the "naïve" Cox analysis could over-estimate the risk, since it assumes that in the future, the outcome of interest (such as fatal atherosclerotic CVD) could be registered even in the subjects who will actually never develop it, due to the already occurred competing outcome (such as non-CVD death). This limitation can be addressed by using the competing-risks regression approach.[355-358]

For **Steps 2-8**, the data from all MONICA waves have been pooled within samples, because for the association between the risk predicted by any SCORE version and observed atherosclerotic CVD mortality, there was no evidence of confounding by or statistical interaction with the MONICA study wave. Specifically, there were no substantial changes in the SCORE hazard ratios after adding the study wave to the model, and the LR tests comparing the models with and without the interaction produced high *p* values.

For **Step 4**, the estimation of 10-year CVD mortality for HAPIEE samples is based on the mortality patterns in the MONICA samples from respective countries. Specifically, for the MONICA-based estimates, it was assumed that the ratio between the death numbers registered at a pre-specified cut-off point (the mean follow-up time in complete years: six, five, and four years for the Czech, Polish, and Russian HAPIEE samples, respectively) and the death numbers observed during the 10-year follow-up period would be similar for MONICA and HAPIEE subjects from the same country. These ratios are calculated for Czech, Polish, and Russian MONICA samples, separately for men and women. The mortality patterns in the urban MONICA population of Warsaw are expected to be a better approximation of the respective patterns among urban Polish HAPIEE subjects (the residents of Krakow). Projecting these country- and gender-specific ratios onto the currently observed numbers of cardiovascular deaths in HAPIEE samples provides the estimates of the 10-year atherosclerotic CVD mortality among HAPIEE men and women. These estimates are used for the analyses of the expected 10-year SCORE calibration across HAPIEE samples. An alternative approach for estimating the 10-year HAPIEE mortality and calibration, based on the exponential survival model, is also presented.

For **Steps 6-7**, all the extended risk models would include significant, according to LRT *p* values, interactions between the main exposure of interest (SCORE, as a dichotomous or continuous high and low-risk scale) and additional risk predictors (socioeconomic measures or drinking characteristics). Extending the SCORE model by more than one additional risk predictor (for example, adding both education and marital status to SCORE) would be possible if the collinearity of these extra risk factors is ruled out, as denoted by low values of phi correlation coefficient (a measure of association between two binary variables). Using OR for the assessment of this association was problematic, due to the distribution of additional risk factors in the samples. Thus, the majority of

participants reported no bingeing and had CAGE score <2, while the number of so-called discordant observations (binge drinking only, or positive CAGE only) was low, particularly in women. Therefore, phi coefficients were considered a more appropriate measure to evaluate the strength of the association between education and marital status, or binge drinking and CAGE, across MONICA and HAPIEE samples. Of note, the SCORE model could not be simultaneously extended by socioeconomic parameters and alcohol consumption characteristics, as that would restrict the analyses to HAPIEE samples only (compatible data on alcohol consumption were not available for all MONICA samples), and also result in very low outcome numbers across the subgroups defined by both socioeconomic characteristics and drinking measures.

For **Step 8**, assessing the pooled impact of SCORE on atherosclerotic CVD mortality, both before and after controlling for additional cardiovascular risk predictors, the random effects, rather than fixed effects, meta-analysis technique has been chosen *a priori*, in order to obtain more conservative estimates.[359-361]

All statistical analyses are performed using Stata/IC 11.0 (StataCorp LP, Texas, USA).

To summarise, ***Chapter 4*** has described the selection of the study samples (MONICA and HAPIEE) and the measurement of the prognostic model components, including atherosclerotic CVD mortality as the outcome, SCORE as the main exposure, and socioeconomic parameters and alcohol consumption characteristics as the additional exposures of interest. The principles of the prognostic performance assessment were summarised and followed by the description of the specific analytical steps used to study SCORE performance in MONICA and HAPIEE samples, before and after extending the SCORE model by additional risk predictors. The results of the respective analyses will be presented in the next five chapters.

Chapter 5. Description of the study samples

Before investigating the prognostic performance of the original and extended SCORE instruments in MONICA and HAPIEE participants (***Chapters 6-9***), the study samples will be described in terms of their baseline demographic characteristics and the distribution of both classical, SCORE-comprising risk factors and additional risk determinants, such as socioeconomic parameters and alcohol consumption characteristics. The levels of 10-year (MONICA) and currently observed (HAPIEE) atherosclerotic CVD mortality will also be presented.

5.1. MONICA: SCORE risk factors, additional risk determinants, and fatal atherosclerotic CVD

The study population included only people aged 40 years or older at baseline, since the SCORE scale predicts cardiovascular risk in subjects aged 40-65 years. The mean age of MONICA participants was close to 50 years, varying from 50.7±7.3 years in Czech men to 52.5±6.8 years in Polish men from Tarnobrzeg. The five-year age group sizes were similar, with slightly lower proportion of people aged 60-64 years: from 14.5% to 17.1% in men from the Czech Republic and Tarnobrzeg, respectively (**Table 5.1.1**), and from 15.0% to 18.0% in Lithuanian and Russian women, respectively (**Table 5.1.2**).

The prevalence of traditional risk factors included in the SCORE instrument was relatively high. Smoking prevalence was over 30% in men from all samples, and exceeded 20% in Czech women and Polish women from Warsaw. By contrast, the proportion of smokers in women from Tarnobrzeg, Kaunas and Novosibirsk was under 10%. Mean levels of TCH tended to be slightly higher in women than in men, and were close to 6 mmol/l across all samples. The highest TCH concentrations were observed among Czech men (6.2±1.3 mmol/l) and Czech women (6.3±1.3 mmol/l). Mean SBP levels were close to 140 mm Hg in both genders, with maximal values registered in Polish men and women from Warsaw (142.3±23.9 mm Hg and 142.6±25.0 mm Hg, respectively).

Table 5.1.1. Baseline characteristics of MONICA samples (men)

Categories	**Czech Republic**		**Poland (Warsaw)**		**Poland (Tarnobrzeg)**		**Lithuania**		**Russia**	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Age groups										
40-44	258	28.73	273	21.60	223	17.44	443	23.35	480	17.40
45-49	207	23.05	262	20.73	265	20.72	373	19.66	616	22.40
50-54	161	17.93	253	20.02	276	21.58	374	19.72	569	20.70
55-59	142	15.81	285	22.55	296	23.14	417	21.98	634	23.00
60-64	130	14.48	191	15.11	219	17.12	290	15.29	452	16.40
Current smoking										
Yes	329	36.64	666	52.69	717	56.06	668	35.21	1474	53.60
No	528	58.80	598	47.31	562	43.94	1,228	64.73	1271	46.20
Missing	41	4.57	0	0.00	0	0.00	1	0.05	6	0.20
TCH										
Mean (SD)	6.22 (1.32)		5.61 (0.95)		5.47 (0.99)		5.97 (1.20)		5.58 (1.16)	
Missing	257	28.62	11	0.87	12	0.94	246	12.97	174	6.30
SBP										
Mean (SD)	140.68 (19.52)		142.25 (23.92)		136.63 (21.15)		137.51 (19.96)		136.19 (20.13)	
Missing	255	28.40	0	0.00	0	0.00	1	0.05	1	0.05
Education										
University	77	8.57	254	20.09	60	4.69	521	27.46	529	19.20
Secondary/vocational	211	23.50	423	33.47	309	24.16	642	33.84	1,026	37.30
Lower	500	55.68	587	46.44	910	71.15	731	38.53	1,179	42.90
Missing	110	12.25	0	0.00	0	0.00	3	0.16	17	0.60
Marital status										
Single	59	6.57	N/A		N/A		50	2.64	57	2.10
Married	651	72.49					1,752	92.36	2,516	91.50
Divorced	57	6.35					71	3.74	115	4.20
Widowed	20	2.23					16	0.84	54	2.00
Missing	111	12.36					8	0.42	9	0.30

Table 5.1.2. Baseline characteristics of MONICA samples (women)

Categories	**Czech Republic**		**Poland (Warsaw)**		**Poland (Tarnobrzeg)**		**Lithuania**		**Russia**	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Age groups										
40-44	229	23.78	254	21.65	268	18.28	443	23.21	548	18.80
45-49	237	24.61	253	21.57	318	21.69	394	20.64	629	21.60
50-54	165	17.13	237	20.20	313	21.35	395	20.69	602	20.60
55-59	170	17.65	245	20.89	309	21.08	391	20.48	613	21.00
60-64	162	16.82	184	15.69	258	17.60	286	14.98	526	18.00
Current smoking										
Yes	196	20.35	364	31.03	109	7.44	77	4.03	97	3.30
No	717	74.45	809	68.97	1,357	92.56	1,832	95.97	2,813	96.40
Missing	50	5.19	0	0.00	0	0.00	0	0.00	8	0.30
TCH										
Mean (SD)	6.34 (1.25)		5.74 (1.03)		5.69 (1.07)		6.29 (1.23)		5.89 (1.32)	
Missing	259	26.90	22	1.88	4	0.27	257	13.46	239	8.20
SBP										
Mean (SD)	139.58 (19.05)		142.61 (25.02)		141.64 (24.27)		137.56 (22.44)		138.69 (22.81)	
Missing	249	25.86	0	0.00	0	0.00	2	0.11	2	0.01
Education										
University	39	4.05	153	13.04	32	2.18	417	21.84	435	14.90
Secondary/vocational	264	27.41	533	45.44	264	18.01	729	38.19	1,398	47.90
Lower	559	58.05	487	41.52	1,170	79.81	754	39.50	1,065	36.50
Missing	101	10.49	0	0.00	0	0.00	9	0.47	20	0.70
Marital status										
Single	14	1.45	N/A		N/A		91	4.77	104	3.60
Married	665	69.06					1,568	82.14	2,123	72.80
Divorced	89	9.24					126	6.60	313	10.70
Widowed	94	9.76					123	6.44	367	12.60
Missing	101	10.49					1	0.05	11	0.40

Socioeconomic profile of MONICA samples was characterised by a relatively high prevalence of lower education (**Tables 5.1.1-5.1.2**). The proportion of lower-educated people was the highest in Tarnobrzeg (71.2% and 79.8% for men and women, respectively), while the percentage of men and women with university education was the highest in Lithuania (27.5% and 21.8%, respectively). The majority of the participants (≥70%) were married; however, the proportion of those divorced or widowed was higher in women than in men (for Polish samples, data on marital status were unavailable). For widowed women vs. men from the Czech Republic, Lithuania, and Russia, this difference was 4.4, 7.7, and 6.3-fold, respectively.

The proportion of participants with missing data on SCORE components (mostly TCH and SBP) varied across MONICA samples. For example, TCH values were missing in one-fourth of the Czech men and women, but available for almost all Polish participants (**Tables 5.1.1-5.1.2**). Since individual SCORE values cannot be calculated for the subjects with missing data on major risk factors, a complete case analysis was performed (***Methods***, ***Section 4.5.1***). The primary goal was to investigate the individual-level relationship between SCORE-predicted and observed risk of atherosclerotic CVD death, which requires having information on both exposure and outcome. After excluding the participants with missing SCORE values, the final MONICA samples consisted of 1,340 people from the Czech Republic, 2,404 from Warsaw, 2,729 from Tarnobrzeg, 3,301 from Lithuania, and 5,253 from Russia (**Table 5.1.3**; for detailed description of the MONICA sample selection, see ***Methods***, ***Section 4.1.1***).

In the samples including the data from two (Warsaw and Tarnobrzeg) or three MONICA waves (Kaunas and Novosibirsk), the observed mortality risk typically declined over time, particularly in men. However, for the main association of interest (between the SCORE-predicted and observed risk), there was no evidence of statistical interaction or confounding by the MONICA study wave (***Methods***, ***Section 4.5.4***). Therefore, the sample-specific data from all MONICA waves were pooled, which also maximised the outcome numbers in the analyses.

As expected, the absolute numbers of atherosclerotic CVD deaths, registered within the first 10 years of the follow-up, were higher in larger samples. Specifically, these numbers were the highest in Russian men and women (181 and 86, respectively), and the lowest in Czech men and women (32 and 13, respectively) (**Table 5.1.3**).

Table 5.1.3. Observed 10-year atherosclerotic CVD mortality in MONICA men and women

	Czech Republic		Poland (Warsaw)		Poland (Tarnobrzeg)		Lithuania		Russia	
	M	*W*	*M*	*W*	*M*	*W*	*M*	*W*	*M*	*W*
Sample size, N	636	704	1,253	1,151	1,267	1,462	1,651	1,650	2,576	2,677
Observed CVD deaths, N (%)	32 (5.03)	13 (1.85)	86 (6.68)	21 (1.82)	62 (4.89)	19 (1.30)	58 (3.51)	26 (1.58)	181 (7.03)	86 (3.21)

Among MONICA men, the percentage of atherosclerotic CVD deaths registered during 10 years was the highest in Novosibirsk (7.0%), lower in Warsaw (6.7%), the Czech Republic (5.0%) and Tarnobrzeg (4.9%), and the lowest in Kaunas (3.5%). The observed risk of fatal CVD in men was, on average, twice as high as in women from the respective samples (see Kaplan-Meier survival estimates in **Figures 5.1.1-5.1.5**). Among MONICA women, the highest and the lowest atherosclerotic CVD mortality levels were registered, respectively, in Novosibirsk (3.2%) and Tarnobrzeg (1.3%).

Figure 5.1.1. Observed 10-year atherosclerotic CVD mortality by gender in the Czech MONICA sample: Kaplan-Meier survival estimates

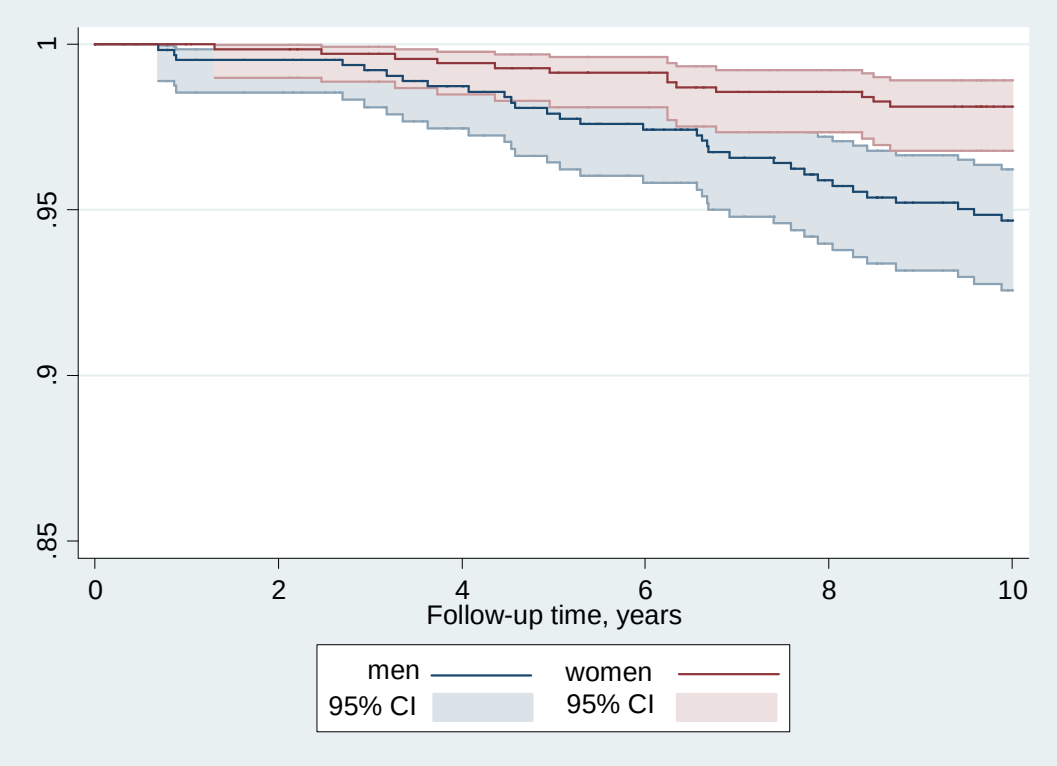


Figure 5.1.2. Observed 10-year atherosclerotic CVD mortality by gender in the Polish (Warsaw) MONICA sample: Kaplan-Meier survival estimates

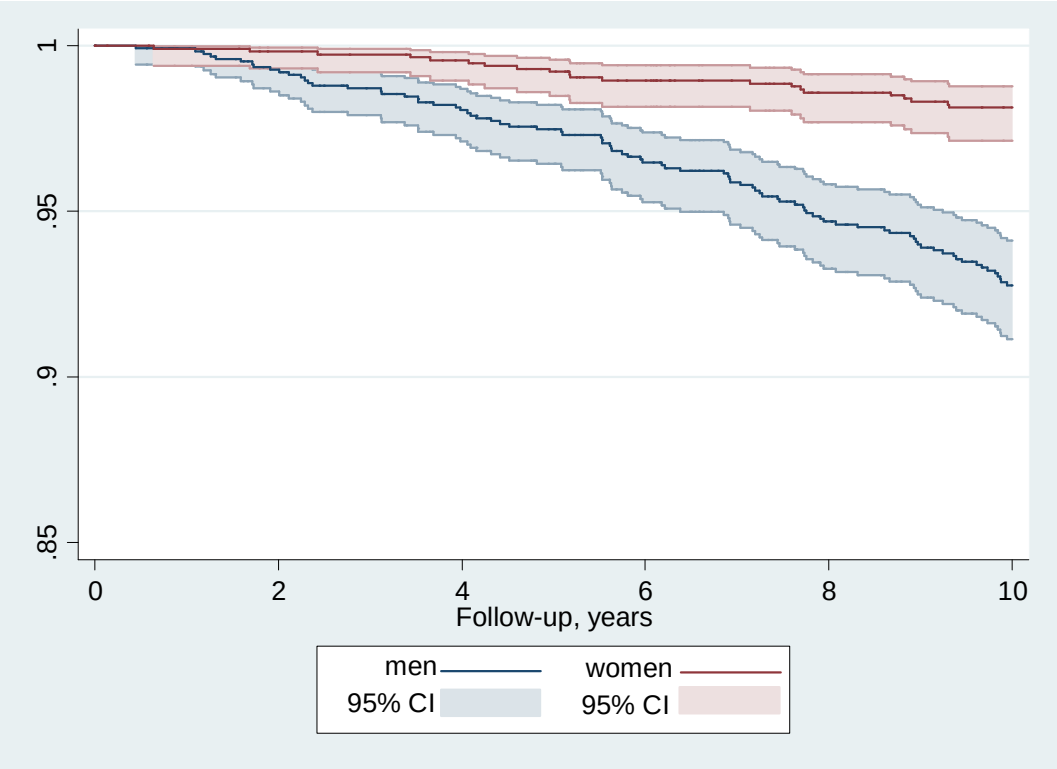


Figure 5.1.3. Observed 10-year atherosclerotic CVD mortality by gender in the Polish (Tarnobrzeg) MONICA sample: Kaplan-Meier survival estimates

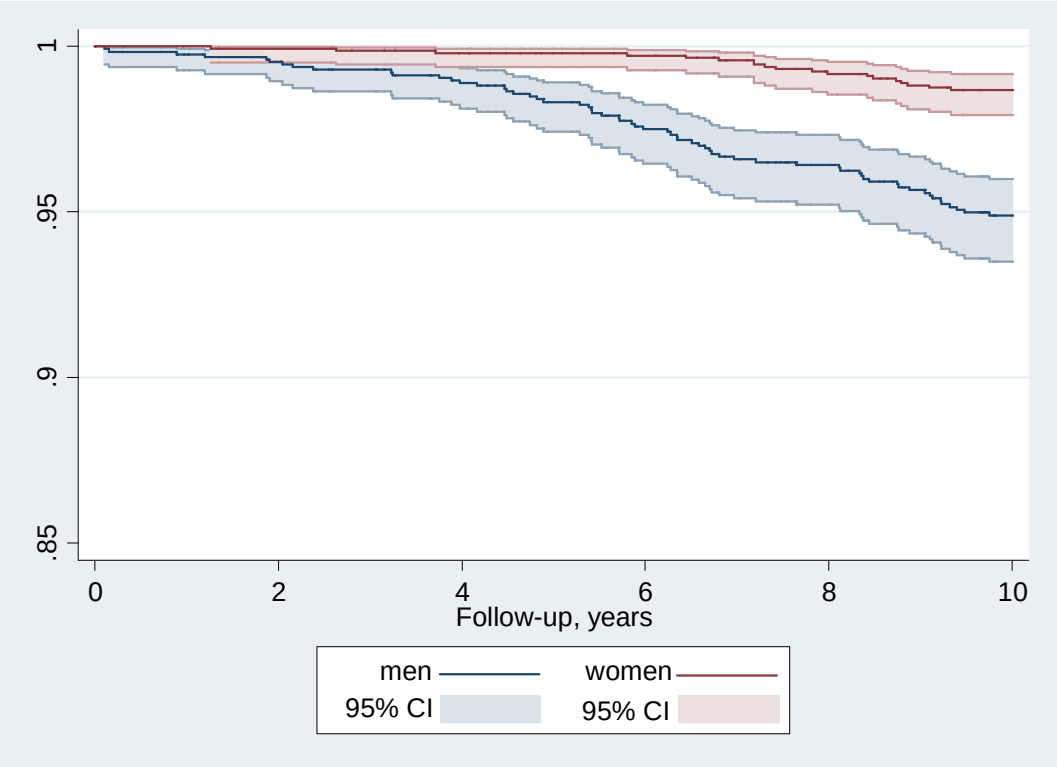


Figure 5.1.4. Observed 10-year atherosclerotic CVD mortality by gender in the Lithuanian MONICA sample: Kaplan-Meier survival estimates

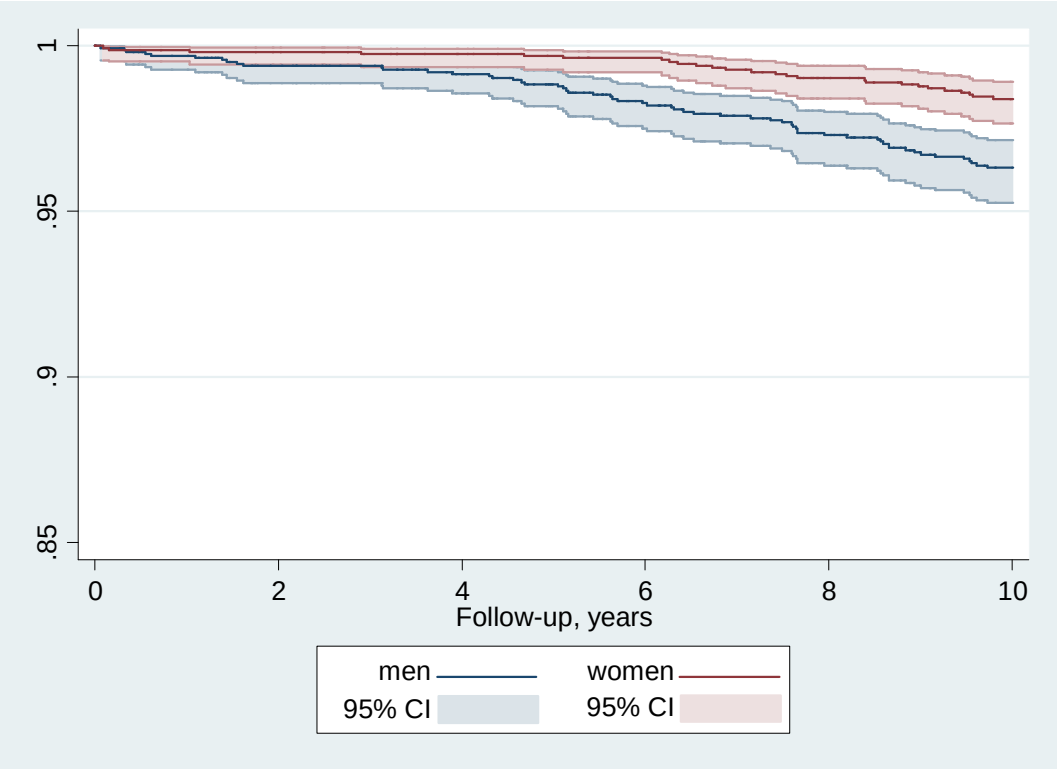
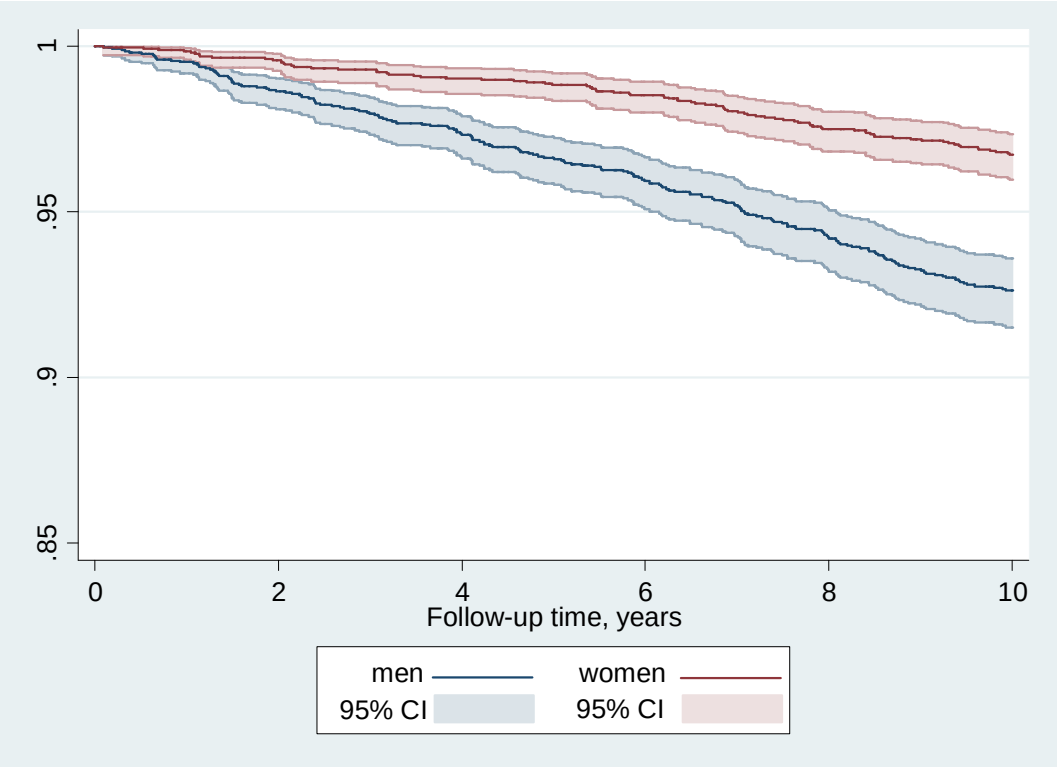


Figure 5.1.5. Observed 10-year atherosclerotic CVD mortality by gender in the Russian MONICA sample: Kaplan-Meier survival estimates



Therefore, these descriptive results demonstrated relatively high, although heterogeneous, levels of cardiovascular risk factors and atherosclerotic CVD mortality in MONICA samples. Cardiovascular mortality was particularly high in Russian men and women.

5.2. HAPIEE: SCORE risk factors, additional risk determinants, and fatal atherosclerotic CVD

Following the description of male and female MONICA samples, the data on demographic characteristics, risk factor distribution, and atherosclerotic cardiovascular mortality will be presented for contemporary HAPIEE samples. The mean baseline age of HAPIEE participants was 57.2±7.0 years, ranging from 56.6±6.9 years in Polish women to 57.7±7.1 years in Czech men. The slightly higher mean age in HAPIEE vs. MONICA subjects was due to the difference in the original lower age limits for these two studies (35 and 45 years, respectively; see ***Methods, Section 4.1***). As shown in **Table 5.2.1**, male and female HAPIEE participants were equally distributed across the five age groups.

The prevalence of classical risk factors included in the SCORE scale was high across all HAPIEE samples. Except for Russian women, both genders demonstrated high prevalence of current smoking (over 20%), which was the highest in Russian men (51.1%). TCH levels tended to be slightly higher in women than in men, and among Russian females, TCH concentration reached 6.5 mmol/l. In men, on the other hand, mean SBP levels were generally higher than in women, and slightly exceeded 140 mm Hg.

Socioeconomic characteristics of the HAPIEE samples had both common and specific features. The percentage of participants with primary education was low across all samples (<12%), with the exception of Czech women (17%). The proportion of university-educated people was higher in Poland and Russia than in the Czech Republic (for men, 32.0% and 31.0% vs. 18.7%; for women, 30.0% and 27.7% vs. 11.0%, respectively). Similar to MONICA participants, the majority of HAPIEE subjects (>60%) were married, while the percentage of those divorced or widowed for women was higher than for men. There was a 4.3, 4.7, and 5.8-fold difference in the proportion of widowed women vs. men from the Czech Republic, Poland, and Russia, respectively (**Table 5.2.1**).

Table 5.2.1. Baseline characteristics of HAPIEE samples (men and women)

Categories	**Czech Republic**				**Poland**				**Russia**			
	Men		*Women*		*Men*		*Women*		*Men*		*Women*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Age groups												
45-49	617	18.12	822	19.44	831	20.85	982	22.68	614	18.87	838	20.63
50-54	706	20.73	916	21.67	866	21.73	1,014	23.42	694	21.33	845	20.80
55-59	692	20.32	790	18.68	850	21.32	889	20.53	702	21.57	888	21.86
60-64	702	20.62	972	22.99	723	18.14	759	17.53	594	18.25	696	17.13
65+	688	20.21	728	17.22	716	17.96	686	15.84	650	19.98	795	19.57
Current smoking												
Yes	928	27.25	936	22.14	1,389	34.85	1,158	26.74	1,662	51.08	412	10.14
No	2,433	71.45	3,235	76.51	2,584	64.83	3,159	72.96	1,592	48.92	3,650	89.86
Missing	44	1.29	57	1.35	13	0.33	13	0.30	0	0.00	0	0.00
TCH												
Mean (SD)	5.66 (1.04)		5.86 (1.04)		5.78 (1.10)		5.93 (1.09)		5.99 (1.18)		6.49 (1.31)	
Missing	740	21.73	865	20.46	518	13.00	560	12.93	6	0.18	16	0.39
SBP												
Mean (SD)	143.87 (18.36)		134.23 (19.36)		141.62 (20.19)		133.15 (20.83)		141.57 (22.67)		141.59 (25.68)	
Missing	642	18.85	691	16.34	528	13.25	569	13.14	3	0.09	2	0.05
Education												
University	637	18.71	446	10.55	1,277	32.04	1,284	29.65	1,008	30.98	1,127	27.74
Secondary	1,076	31.60	1,761	41.65	1,301	32.64	1,900	43.88	1,220	37.49	1,344	33.09
Vocational	1,477	43.38	1,288	30.46	1,060	26.59	635	14.67	683	20.99	1,230	30.28
Primary	196	5.76	717	16.96	345	8.66	505	11.66	343	10.54	361	8.89
Missing	19	0.56	16	0.38	3	0.08	6	0.14	0	0.00	0	0.00
Marital status												
Married	2,854	83.82	2,906	68.73	3,466	86.95	2,894	66.84	2,859	87.86	2,461	60.59
Single	99	2.91	103	2.44	166	4.16	333	7.69	94	2.89	210	5.17
Divorced	332	9.75	647	15.30	212	5.32	405	9.35	191	5.87	595	14.65
Widowed	105	3.08	556	13.15	135	3.39	689	15.91	110	3.38	796	19.60
Missing	15	0.44	16	0.38	7	0.18	9	0.21	0	0.00	0	0.00

(continued)	Czech Republic				Poland				Russia			
	Men		*Women*		*Men*		*Women*		*Men*		*Women*	
Categories	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Drinking frequency												
Never	187	5.49	689	16.30	776	19.47	1,867	43.12	402	12.35	598	14.72
<1/month	545	16.01	1,337	31.62	731	18.34	1,199	27.69	523	16.07	2,270	55.88
1-3/month	563	16.53	996	23.56	953	23.91	773	17.85	785	24.12	847	20.85
≥ 1/week	2,016	59.21	1,034	24.46	1,499	37.61	467	10.79	1,544	47.45	347	8.54
Missing	94	2.76	172	4.07	27	0.68	24	0.55	0	0.00	0	0.00
Binge drinking												
No	2,689	78.97	3,925	92.83	3,556	89.21	4,275	98.73	2,184	67.12	4,006	98.62
Yes	622	18.27	131	3.10	43	10.11	31	0.72	1,070	32.88	56	1.38
Missing	94	2.76	172	4.07	27	0.68	24	0.55	0	0.00	0	0.00
CAGE score ≥ 2												
No	2,998	88.05	3,956	93.57	3,525	88.43	4,208	97.18	2,574	79.10	4,000	98.47
Yes	310	9.10	80	1.89	383	9.61	44	1.02	680	20.90	62	1.53
Missing	97	2.85	192	4.54	78	1.96	78	1.80	0	0.00	0	0.00

For HAPIEE samples, the data on alcohol consumption parameters, as additional predictors of cardiovascular risk, were also available. As presented in **Table 5.2.1**, the percentage of self-reported non-drinkers was the highest in Polish men and women (19.5% and 43.1%, respectively). The prevalence of alcohol consumption at least once a week was maximal in Czech men (59.2%) and women (24.5%). However, Russian men demonstrated the most hazardous drinking patterns, with the highest prevalence of binge drinking (32.9%) and CAGE score ≥2 (20.9%), which was approximately twice as high as in their Czech and Polish peers. Among Czech, Russian, and Polish women, hazardous drinking was reported by less than 4%.

The proportions of HAPIEE subjects with missing data for SCORE components, such as TCH and SBP, were higher in the Czech Republic and Poland (approximately 20% and 13%, respectively), and lower in Russia (<1%) (**Table 5.2.1**). Since this thesis is aimed at studying the individual-level relationship between SCORE-predicted risk of fatal atherosclerotic CVD (exposure) and observed risk (outcome), only the observations with complete data on both exposure and outcome were included in the survival analyses and analyses of SCORE prognostic performance (***Methods***, ***Section 4.5.1***). After excluding participants with missing SCORE values, the final HAPIEE samples consisted of 6,018 people from the Czech Republic, 7,209 from Poland, and 7,290 from Russia (**Table 5.2.2**; for detailed description of the HAPIEE sample selection, see ***Methods***, ***Section 4.1.2***).

The absolute numbers of atherosclerotic CVD deaths were the highest in Russian HAPIEE men and women (105 and 42, respectively), despite the shortest mean follow-up period (approximately 4.5 years vs. 6.2 and 5.2 years for the Czech and Polish samples, respectively) (**Table 5.2.2**).

Table 5.2.2. Observed atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic		**Poland**		**Russia**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Sample size, N	2,659	3,359	3,456	3,753	3,246	4,044
Mean follow-up, years (SD)	6.14 (0.99)	6.25 (0.78)	5.15 (0.77)	5.22 (0.59)	4.35 (1.02)	4.62 (0.78)
Observed CVD deaths, N (%)	37 (1.39)	19 (0.57)	34 (0.98)	16 (0.43)	105 (3.23)	42 (1.04)

Among Russian men, the percentage of atherosclerotic CVD deaths registered during the follow-up was two-three times higher than among their Czech and Polish peers (3.2% vs. 1.4% and 1.0%, respectively). The currently observed levels of fatal CVD in women were lower than in men from the respective countries (see Kaplan-Meier survival estimates in **Figures 5.2.1-5.2.3**), but still reflected the same ranking across the samples, being higher in Russia (1.0%) than in the Czech Republic (0.6%) or Poland (0.4%).

Figure 5.2.1. Observed atherosclerotic CVD mortality by gender in the Czech HAPIEE sample: Kaplan-Meier survival estimates

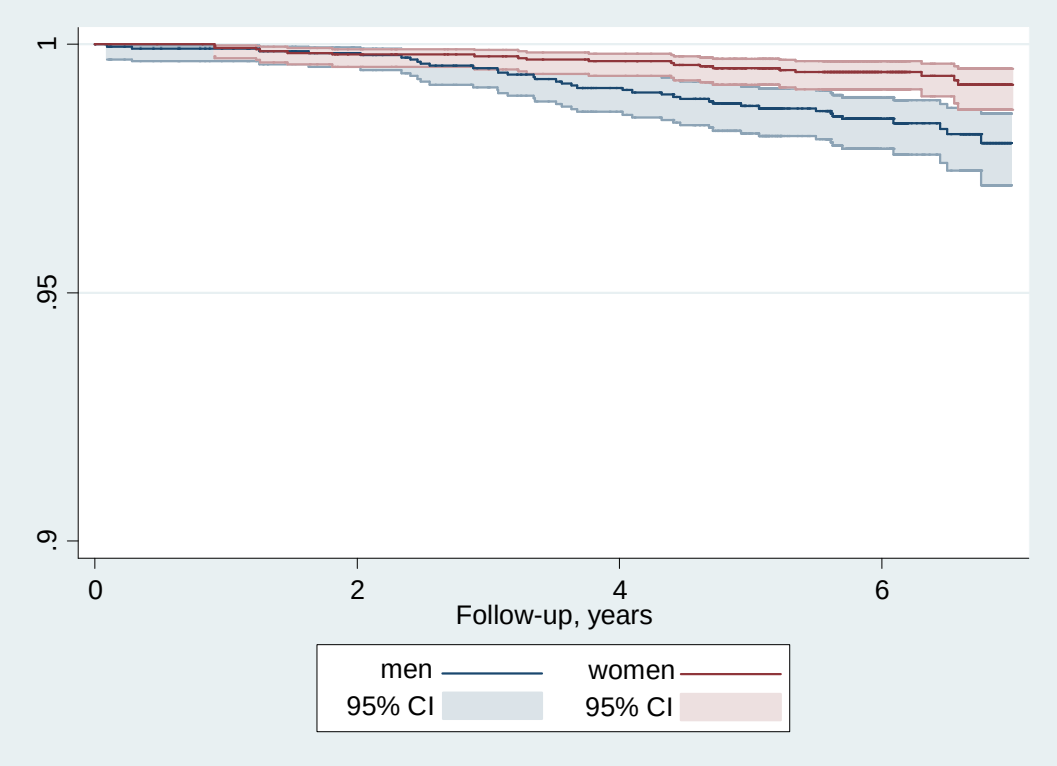


Figure 5.2.2. Observed atherosclerotic CVD mortality by gender in the Polish HAPIEE sample: Kaplan-Meier survival estimates

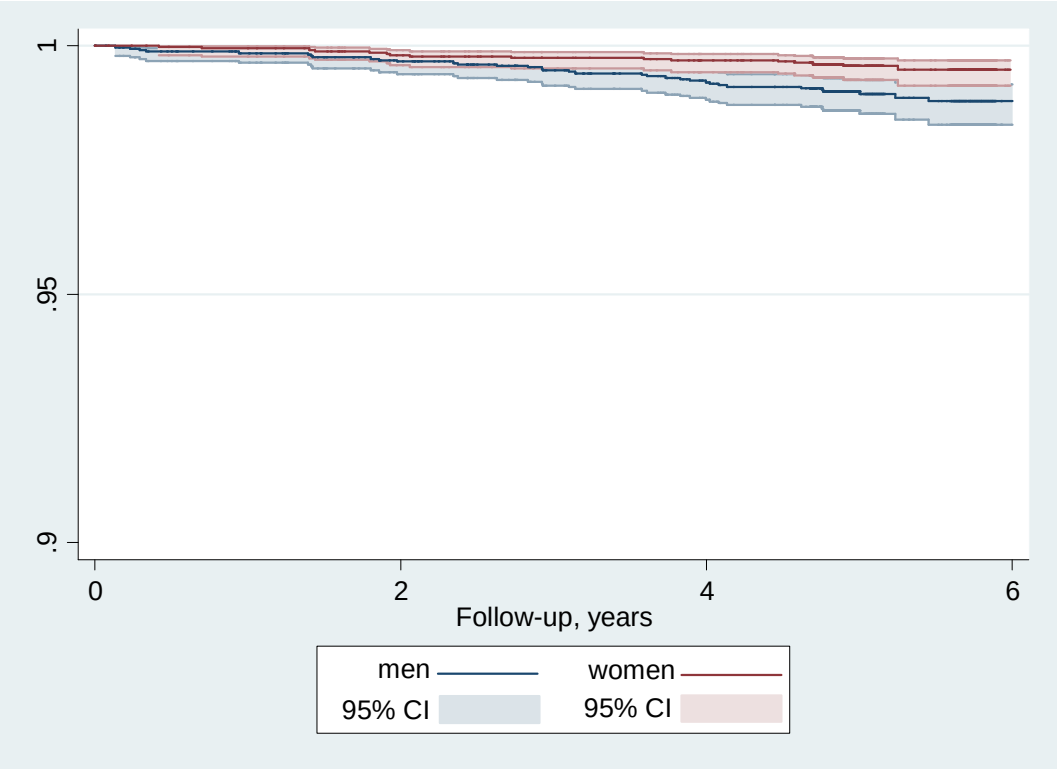
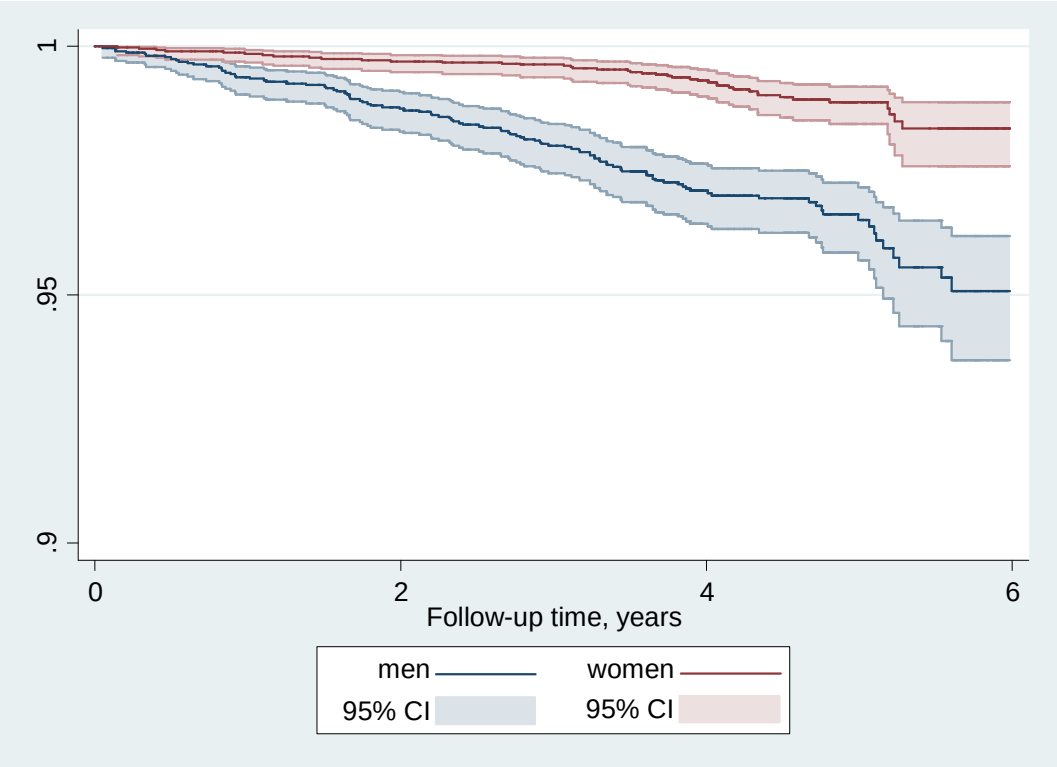


Figure 5.2.3. Observed atherosclerotic CVD mortality by gender in the Russian HAPIEE sample: Kaplan-Meier survival estimates



To summarise, the findings presented in ***Chapter 5*** have addressed the first research objective – the description of cardiovascular risk factor patterns and CVD mortality across MONICA and HAPIEE samples. Both studies demonstrated relatively high, although not uniform, levels of classical and additional cardiovascular risk factors, as well as higher levels of fatal CVD in Russian participants vs. subjects from the other CEE/FSU countries of interest. The next chapter will investigate how this heterogeneity is reflected in the prognostic performance of SCORE across study samples.

Chapter 6. Performance of the original SCORE scale

In this chapter, the strength of the main association of interest, between baseline levels of conventional cardiovascular risk factors, captured by the original, non-extended SCORE, and fatal atherosclerotic CVD, is explored across all MONICA and HAPIEE samples (***Section 6.1***). SCORE calibration (***Sections 6.2-6.3***) and discrimination (***Section 6.4***) in MONCA and HAPIEE are also evaluated.

6.1. SCORE as a predictor of atherosclerotic CVD mortality

The predictive performance of SCORE in MONICA and HAPIEE samples could be assessed, first of all, by the strength of the association between the exposure of interest (SCORE-predicted risk at baseline) and the outcome (atherosclerotic CVD death) in the survival models. The main focus of the present analyses is the performance of the high-risk dichotomous SCORE (≥5% vs. <5%), as the officially recommended and, hence, the most clinically relevant version of SCORE for CEE/FSU populations. In addition, the performance of the high-risk continuous SCORE, as well as the dichotomous and continuous low-risk SCORE, is examined. The results of survival analyses obtained with the standard Cox models, competing-risks regression models, and Weibull models were almost identical for all study samples. Therefore, the findings from the standard Cox analyses are presented in ***Section 6.1***, while the outputs from the other two models can be found in ***Appendix II***.

6.1.1. SCORE as a predictor of atherosclerotic CVD mortality in MONICA

Across all male MONICA samples, high-risk SCORE ≥5% at baseline was significantly associated with higher 10-year atherosclerotic CVD mortality, as shown in **Table 6.1.1**. The hazard ratios (HR) varied from 2.7 in Russia to 5.3 in the Czech Republic (although for Czech men, the absolute number of outcomes was the lowest, and 95% CI for HR the widest). In addition, one-point increase in SCORE was associated with a significant elevation in CVD risk, with HR for continuous SCORE close to 1.10 and 95% CI excluding 1.0 across all male samples. In most female samples, baseline high-risk SCORE ≥5% was also linked to a significant increase in fatal CVD risk (**Table 6.1.1**). The magnitude of this increase was the largest among Russian women (HR 6.3) and the smallest among Polish women from Warsaw (1.7). For both dichotomous and continuous SCORE, HR values were typically higher in women than in men from respective samples, although it should be noted that 95% CI were also wider in women, due to lower outcome numbers.

Table 6.1.1. Dichotomous and continuous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE (≥5% vs. <5%)	5.32 (2.30-12.30)	4.50 (2.68-7.56)	3.06 (1.77-5.29)	3.99 (2.24-7.10)	2.66 (1.96-3.62)
Continuous SCORE (per 1% increase)	1.09 (1.06-1.12)	1.10 (1.07-1.12)	1.11 (1.08-1.14)	1.08 (1.05-1.12)	1.11 (1.09-1.13)
Women					
Dichotomous SCORE (≥5% vs. <5%)	5.02 (1.64-15.36)	1.70 (0.57-5.06)	4.15 (1.49-11.52)	5.07 (2.20-11.66)	6.32 (4.08-9.79)
Continuous SCORE (per 1% increase)	1.23 (1.06-1.43)	1.21 (1.10-1.33)	1.33 (1.16-1.53)	1.27 (1.16-1.39)	1.34 (1.27-1.41)

The complete case-based and the multiple imputation-based approaches produced very similar results for Czech and Lithuanian participants, despite the fact that these MONICA samples had higher levels of SCORE missingness (for description of the imputation model, see ***Section 4.5.1***). For example, in Czech MONICA men, HR values for the complete case and multiple imputation-based analyses were 5.32 and 5.20, respectively (detailed results for all samples available on request). Therefore, it was unlikely that the complete case approach (**Table 6.1.1**) has substantially biased the estimates of the association between the high-risk dichotomous SCORE and fatal CVD across MONICA samples.

Similar patterns, confirming the association between baseline SCORE and atherosclerotic CVD mortality, were observed for the low-risk dichotomous and continuous SCORE in most samples (see ***Appendix II***, **Table A6.1.1**). Across MONICA samples, the results of the standard Cox, competing-risks, and Weibull regression analyses were similar (see **Tables A6.1.2-A6.1.3** for dichotomous and continuous high and low-risk SCORE). Since the 10-year risk of death from other causes (not atherosclerotic CVD) was relatively low across samples, taking it into account in the competing-risks analyses only slightly reduced the strength of the main association of interest. The exact values of SCORE HR and 95% CI were very close for all three types of survival analysis, demonstrating a clear link between the levels of predicted and observed 10-year CVD mortality.

6.1.2. SCORE as a predictor of atherosclerotic CVD mortality in HAPIEE

As mentioned earlier, the current follow-up duration for all HAPIEE samples is under 10 years. Therefore, in HAPIEE participants, the strength of the association between baseline high-risk SCORE values ≥5% and the risk of atherosclerotic CVD death over the next 4.5-6 years was analysed. Due to the shorter follow-up and lower outcome numbers, 95% CI for SCORE HR were quite wide in both genders. Nonetheless, higher risk at baseline appeared to be a significant predictor of CVD mortality in men (HR 10.5, 2.6, and 7.6 in the Czech Republic, Poland, and Russia) and women (HR 3.6, 8.8, and 7.4, respectively) (**Table 6.1.2**). One-point increase in baseline SCORE was also significantly associated with elevated cardiovascular risk: HR for continuous SCORE reached 1.1 in men and 1.2-1.3 in women.

Table 6.1.2. Dichotomous and continuous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Dichotomous SCORE (≥5% vs. <5%)	10.51 (2.53-43.71)	2.56 (1.11-5.87)	7.63 (3.35-17.40)
Continuous SCORE (per 1% increase)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
Women			
Dichotomous SCORE (≥5% vs. <5%)	3.59 (1.44-8.91)	8.79 (3.19-24.18)	7.36 (3.77-14.38)
Continuous SCORE (per 1% increase)	1.20 (1.06-1.35)	1.32 (1.22-1.43)	1.32 (1.24-1.41)

Despite a higher proportion of missing SCORE values in Czech and Polish men and women, the HR values for the dichotomous high-risk SCORE were very similar for the complete case-based and the multiple imputation-based approaches (the imputation model is described in ***Section 4.5.1***). Thus, for Polish HAPIEE men, the respective values were 2.56 and 2.66 (detailed results for all samples available on request). These findings suggest that the use of the observations with non-missing SCORE values (**Table 6.1.2**) was unlikely to substantially bias the HAPIEE findings on the link between SCORE and cardiovascular mortality.

In both genders, the dichotomous and continuous low-risk SCORE demonstrated similar patterns, confirming the significant link between the predicted and currently observed cardiovascular mortality (see ***Appendix II***, **Table A6.1.4**). The currently observed risk of death from other causes (not atherosclerotic CVD) was relatively low across HAPIEE samples, and the strength of the main association of interest was reduced only marginally in the competing-risks models. Overall, standard Cox, competing-risks, and Weibull regression analyses all provided similar results for the high-risk SCORE, as well as for its low-risk version, and showed that the higher SCORE-predicted risk was a significant determinant of fatal atherosclerotic CVD (**Tables A6.1.5-A6.1.6**).

While in most MONICA and HAPIEE samples, the association between baseline SCORE and observed cardiovascular mortality was statistically significant, the strength of this association varied across samples and did not clearly reflect the "FSU vs. CEE" gradient in fatal CVD rates, which was described in ***Chapter 5***. This lack of consistency could be due to a combination of several factors. The relative risks associated with each of the SCORE-comprising risk factors are considered to be universal across populations and over time (***Methods***, ***Section 4.5.2***), regardless of the baseline risk variation which

is reflected in the observed cross-sample mortality gradient. Therefore, SCORE HR values are expected to be relatively similar for different samples and at different points in time. However, these values were influenced by the marked variation in sample sizes and outcome numbers for both MONICA and HAPIEE.

In addition, the magnitude of the SCORE-fatal CVD link could be affected by multiple non-classical risk determinants. The impact of such measured and non-measured factors may vary across populations and over time, and, hence, could lead to heterogeneity of the sample-specific SCORE effect estimates. To assess the potential impact of some additional risk determinants, such as socioeconomic parameters and alcohol consumption characteristics, on the link between SCORE and atherosclerotic cardiovascular mortality, the association of interest was adjusted for education and/or marital status (***Chapter 7***), as well as for binge drinking and/or CAGE score (***Chapter 8***). Moreover, to provide a combined estimate of the magnitude of this association, the unadjusted and adjusted findings from individual samples were pooled in the random effects meta-analyses, as described in ***Chapter 9***.

To conclude ***Section 6.1***, SCORE was a significant predictor of fatal atherosclerotic CVD in MONICA and HAPIEE men and women, as shown by the results of standard Cox regression, competing-risks Cox analysis and Weibull analysis, for high and low-risk versions of dichotomous and continuous SCORE. These findings have addressed the second research objective (the assessment of the main association of interest, between SCORE-predicted and observed cardiovascular mortality) and demonstrated a statistically significant link between baseline SCORE and subsequent fatal CVD, which supports the first research hypothesis. This is an important step in exploring SCORE performance in the populations of interest. However, the strength of this association does not provide sufficient information on the closeness between SCORE predictions and observed mortality, or on the accuracy of separating the subjects who would develop the outcome (atherosclerotic CVD death) from those who would remain outcome-free. Therefore, the next three sections are focused on SCORE calibration and discrimination in MONICA and HAPIEE.

6.2. SCORE calibration

As described in ***Methods*** (***Section 4.5.3***), calibration is one of the performance characteristics of a prognostic model, which reflects the agreement between the predicted (P) and observed (O) risk. Calibration could be assessed with the P/O ratio,

where values of 1.0, <1.0, and >1.0 denote perfect calibration, risk under-prediction, and risk over-prediction, respectively.

6.2.1. SCORE calibration in MONICA

In all male MONICA samples, cardiovascular risk levels predicted by the high-risk SCORE version (which is officially recommended for CEE/FSU populations) were relatively high and varied from 5.0% in Kaunas to 5.8% in Warsaw (**Table 6.2.1**). Among MONICA women, predicted risk was considerably lower and approached 2%, ranging from 1.6% in Lithuania to 2.0% in Poland (Warsaw) (**Table 6.2.2**). Since age is the major determinant of cardiovascular risk, the levels of predicted risk increased, as expected, from younger to older age groups in both genders.

The closeness of predicted and observed atherosclerotic CVD mortality was satisfactory in most samples, as demonstrated by P/O ratio values close to 1.0. The risk was slightly over-predicted in Czech men, Polish men from Tarnobrzeg, and Lithuanian men (respective P/O ratios 1.05, 1.11, and 1.43), and under-predicted in men from Warsaw and Novosibirsk (0.87 and 0.76, respectively) (**Table 6.2.1**). Among women, the high-risk SCORE version slightly over-estimated mortality risk in Warsaw and Tarnobrzeg (respective P/O values 1.08 and 1.27), relatively accurately reflected it in the Czech Republic and Kaunas (0.96 and 1.01, respectively), and under-predicted the risk in Novosibirsk (0.52) (**Table 6.2.2**). Therefore, the extent of risk under-estimation was maximal in the Russian sample, for both men and women. Across age groups, as well as in subjects with SCORE levels <5% vs. ≥5%, most P/O ratios were close to the respective sample-specific values; occasional deviations could be due to low outcome numbers, or absence of outcomes, in some groups (**Tables 6.2.1-6.2.2**). For women aged 40-45 years, the number of predicted deaths was zero, as both high and low-risk SCORE versions assign these women to the category of "zero risk" (***Appendix I***, **Tables A4.3.1-A4.3.2**).

The calibration assessment was also performed for the low-risk SCORE version, even though it is not officially recommended for CEE/FSU populations. Low-risk SCORE under-estimated 10-year atherosclerotic cardiovascular mortality in all male and female MONICA samples (***Appendix II***, **Tables A6.2.1-A6.2.2**). The magnitude of this under-prediction was maximal in Russian men and women (P/O ratios 0.40 and 0.29, respectively), in agreement with the findings for the high-risk SCORE.

Table 6.2.1. Predicted (P) by high-risk SCORE and observed (O) 10-year atherosclerotic CVD mortality by age groups and SCORE level in MONICA men

	Czech Republic			**Poland (Warsaw)**			**Poland (Tarnobrzeg)**			**Lithuania**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	5.26 (5.55) N=33.5	5.03 N=32	1.05	5.78 (5.51) N=72.4	6.68 N=86	0.87	5.43 (4.80) N=69.0	4.89 N=62	1.11	5.03 (4.89) N=83.1	3.51 N=58	1.43	5.36 (4.89) N=138.1	7.03 N=181	0.76
Age groups, years															
40-44.9	1.04 (0.57) N=1.8	1.16 N=2	0.90	1.06 (0.52) N=2.9	3.32 N=9	0.32	1.02 (0.52) N=2.3	2.71 N=6	0.38	0.96 (0.52) N=3.8	1.02% N=4	0.94	0.96 (0.53) N=4.4	3.96 N=18	0.24
45-49.9	3.93 (2.33) N=5.6	4.20 N=6	0.94	3.78 (2.07) N=9.8	3.85 N=10	0.98	3.53 (1.84) N=9.3	2.28 N=6	1.55	3.24 (2.02) N=10.3	1.57 N=5	2.06	3.33 (1.91) N=19.4	4.12 N=24	0.81
50-54.9	5.37 (3.41) N=7.2	5.22 N=7	1.03	5.04 (3.31) N=12.7	5.98 N=15	0.84	4.75 (3.06) N=13.0	5.47 N=15	0.87	4.22 (2.68) N=12.6	2.68 N=8	1.58	4.52 (2.73) N=24.2	6.92 N=37	0.65
55-59.9	8.00 (4.89) N=8.1	4.95 N=5	1.62	8.34 (4.69) N=23.5	9.57 N=27	0.87	7.27 (4.34) N=21.4	5.78 N=17	1.26	7.38 (4.63) N=27.9	6.08 N=23	1.21	7.46 (4.46) N=44.5	7.55 N=45	0.99
60-64.9	12.49 (8.54) N=10.7	13.95 N=12	0.90	12.46 (7.46) N=23.6	13.23 N=25	0.94	10.63 (6.11) N=22.9	8.37 N=18	1.27	10.82 (5.98) N=28.4	6.87 N=18	1.58	11.22 (6.16) N=45.67	14.00 N=57	0.80
SCORE level															
<5%	1.98 (1.16) N=7.2	1.92 N=7	1.03	2.08 (1.15) N=13.5	2.77 N=18	0.75	2.30 (1.20) N=15.9	2.60 N=18	0.89	1.98 (1.13) N=19.1	1.66 N=16	1.19	2.25 (1.20) N=32.9	4.31 N=63	0.52
≥5%	9.67 (6.04) N=26.2	9.23 N=25	1.05	9.76 (5.57) N=59.0	11.26 N=68	0.87	9.18 (4.82) N=52.9	7.64 N=44	1.20	9.31 (4.94) N=63.9	6.13 N=42	1.52	9.44 (4.92) N=105.2	10.59 N=118	0.89

Table 6.2.2. Predicted (P) by high-risk SCORE and observed (O) 10-year atherosclerotic CVD mortality by age groups and SCORE level in MONICA women

	Czech Republic			**Poland (Warsaw)**			**Poland (Tarnobrzeg)**			**Lithuania**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	1.78 (2.11) N=12.5	1.85 N=13	0.96	1.96 (2.45) N=22.6	1.82 N=21	1.08	1.68 (1.93) N=24.6	1.30 N=19	1.29	1.60 (1.94) N=26.4	1.58 N=26	1.01	1.67 (2.00) N=44.7	3.21 N=86	0.52
Age groups, years															
40-44.9	0.00 (0.00) N=0.0	0.59 N=1	N/A	0.00 (0.00) N=0.0	0.00 (0)	N/A	0.00 (0.00) N=0.0	0.37 N=1	N/A	0.00 (0.00) N=0.0	0.25 N=1	N/A	0.00 (0.00) N=0.0	0.38 N=2	N/A
45-49.9	1.02 (0.50) N=1.8	0.00 N=0	N/A	0.91 (0.52) N=2.3	2.01 N=5	0.45	0.79 (0.53) N=2.5	0.32 N=1	2.47	0.90 (0.39) N=3.1	0.29 N=1	3.10	0.72 (0.50) N=4.2	2.04 N=12	0.35
50-54.9	1.46 (0.81) N=1.8	2.42 N=3	0.60	1.53 (1.17) N=3.6	0.00 N=0	N/A	1.17 (0.64) N=3.7	0.32 N=1	3.66	1.22 (0.68) N=4.0	0.62 N=2	1.97	1.15 (0.66) N=6.4	1.61 N=9	0.71
55-59.9	2.68 (1.58) N=3.4	3.13 N=4	0.86	3.03 (1.97) N=7.3	3.33 N=8	0.91	2.37 (1.49) N=7.3	3.25 N=10	0.73	2.44 (1.51) N=7.8	2.82 N=9	0.87	2.35 (1.39) N=12.9	4.74 N=26	0.50
60-64.9	5.12 (2.64) N=5.5	4.63 N=5	1.11	5.34 (3.41) N=9.4	4.55 N=8	1.17	4.32 (2.42) N=11.1	2.33% N=6	1.85	4.54 (2.52) N=11.6	5.10 N=13	0.89	4.54 (2.59) N=21.0	8.01 N=37	0.57
SCORE level															
<5%	1.17 (1.08) N=7.3	1.28 N=8	0.91	1.20 (1.10) N=12.1	1.69 N=17	0.71	1.21 (1.09) N=16.2	1.05 N=14	1.15	1.14 (1.08) N=17.2	1.19 N=18	0.96	1.16 (1.09) N=28.2	2.22 N=54	0.52
≥5%	6.58 (2.08) N=5.3	6.25 N=5	1.05	7.24 (2.72) N=10.5	2.76 N=4	2.62	6.76 (1.71) N=8.3	4.07 N=5	1.66	6.67 (2.05) N=9.3	5.76 N=8	1.16	6.66 (2.04) N=16.5	12.96 N=32	0.51

In addition, calibration of continuous high and low-risk SCORE was assessed with the Hosmer-Lemeshow goodness-of-fit test. This test quantifies the agreement between predicted and observed events across risk deciles (***Methods***, ***Section 4.5.3***). Since the outcome numbers in country and gender-specific subgroups were relatively low, especially in women, the results of the Gronnesby-Borgan test (equivalent of the Hosmer-Lemeshow test, recommended for survival data analysis and based on martingale residuals; ***Section 4.5.3***) were not informative, as the model collapsed on only two risk quantiles.

In most male MONICA samples, the Hosmer-Lemeshow χ^2 values were under 20 for both high and low-risk SCORE predictions, which denoted good calibration (**Table 6.2.3**). Only in Lithuanian men, the high-risk SCORE demonstrated slightly worse fit of the model (χ^2 20.9). In each sample, Hosmer-Lemeshow-assessed calibration was slightly better, as demonstrated by lower χ^2 values, for low vs. high-risk SCORE version. A similar pattern was observed among MONICA females, with slightly better calibration for low vs. high-risk SCORE in each sample, and higher χ^2 values in Lithuanian women (**Table 6.2.3**).

Table 6.2.3. Calibration of high and low-risk continuous SCORE estimated by Hosmer-Lemeshow test in MONICA men and women

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
High-risk SCORE, χ^2 (*p*)	15.41 (0.0311)	13.89 (0.0533)	4.62 (0.7059)	20.98 (0.0018)	4.56 (0.7132)
Low-risk SCORE, χ^2 (*p*)	9.41 (0.0938)	9.26 (0.0991)	4.33 (0.5025)	14.99 (0.0104)	4.53 (0.4753)
Women					
High-risk SCORE, χ^2 (*p*)	7.89 (0.0958)	8.42 (0.0722)	11.19 (0.0245)	20.89 (0.0003)	13.92 (0.0076)
Low-risk SCORE, χ^2 (*p*)	6.18 (0.1032)	8.25 (0.0411)	6.61 (0.0367)	20.52 (<0.0001)	11.62 (0.0088)

It should be noted, however, that the Hosmer-Lemeshow test results are affected when two or more individuals have the same predicted risk (especially when the estimated risk levels are relatively low) (***Methods, Section 4.5.3***). This could explain lower χ^2 values for low vs. high-risk SCORE predictions. Therefore, evaluating the calibration using P/O ratios (**Tables 6.2.1-6.2.2**) might be a more informative method to assess the agreement between predicted and observed CVD mortality in MONICA samples.

6.2.2. SCORE calibration in HAPIEE

In each male HAPIEE sample, mean levels of 10-year fatal CVD, predicted by high-risk SCORE, exceeded the cut-off value of 5% (7.5% in the Czech Republic, 7.4% in Poland, and 9.1% in Russia). Among women from the respective countries, the predicted risk was approximately three times lower, reaching 2.5%, 2.5%, and 3.1% (**Tables 6.2.4-6.2.5**). The progressive increase in predicted risk from younger to older age groups was expected, based on the key role of age as a major CVD risk determinant. Therefore, the fact that predicted levels of CVD mortality in HAPIEE samples were approximately 1.5 times higher than in respective MONICA samples could be predominantly explained by the higher mean age of HAPIEE participants.

Given the current limited duration of the follow-up (the 10-year mortality data are not yet available), the high-risk SCORE calibration cannot be adequately assessed in HAPIEE. Calibration results, based on the comparison between predicted and estimated 10-year risk of atherosclerotic cardiovascular mortality across HAPIEE samples will be presented in ***Section 6.3***. For the currently available HAPIEE data on fatal CVD, all P/O ratios exceeded 1.0, as expected (**Tables 6.2.4-6.2.5**), but their ranking was not explained by the mean follow-up length. In Russian samples, which had the shortest follow-up duration, the magnitude of risk over-estimation was substantially smaller (P/O ratios 2.81 and 2.96 in men and women, respectively) than in Czech (5.40 and 4.44) or Polish (7.52 and 5.70) samples. All P/O ratios for the subgroups defined by age, or SCORE level <5% vs. ≥5%, exceeded 1.0 and were close to the respective values for the whole samples. As expected, risk over-estimation was more pronounced in the younger age groups and people with SCORE values <5% (**Tables 6.2.4-6.2.5**).

The low-risk SCORE also over-estimated the 10-year risk of fatal atherosclerotic CVD in all HAPIEE samples, even though P/O ratios were understandably lower than for high-risk predictions (***Appendix II***, **Tables A6.2.3-A6.2.4**). For Russian men and women, P/O ratios were approaching 1.0 already (1.50 and 1.70, respectively), despite the shortest mean follow-up time of 4.5 years.

Table 6.2.4. Predicted (P) by high-risk SCORE and observed (O) atherosclerotic CVD mortality by age groups and SCORE level in HAPIEE men

	Czech Republic			**Poland**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	7.51 (5.99) N=199.7	1.39 N=37	5.40	7.37 (5.89) N=254.7	0.98 N=34	7.52	9.07 (7.27) N=294.4	3.23 N=105	2.81
Age groups, years									
<50	3.11 (1.89) N=14.3	0.22 N=1	14.14	3.24 (2.05) N=22.8	0.28 N=2	11.57	3.63 (2.00) N=22.2	0.65 N=4	5.59
50-54.9	4.19 (2.63) N=21.9	0.38 N=2	11.03	4.28 (2.84) N=32.1	0.93 N=7	4.60	4.98 (3.17) N=34.5	1.59 N=11	3.13
55-59.9	6.47 (4.04) N=35.7	1.63 N=9	3.97	7.04 (4.12) N=52.1	0.81 N=6	8.69	8.32 (5.18) N=58.3	3.14 N=22	2.65
60-64.9	10.23 (6.36) N=58.7	2.09 N=12	4.90	10.46 (5.98) N=66.3	0.79 N=5	13.24	13.68 (7.76) N=80.9	4.06 N=24	3.37
≥65	12.50 (6.69) N=69.1	2.35 N=13	5.32	12.98 (6.96) N=81.5	2.23 N=14	5.82	15.18 (7.94) N=98.7	6.77 N=44	2.24
SCORE level									
<5%	2.64 (1.05) N=25.9	0.20 N=2	13.20	2.70 (0.95) N=36.5	0.52 N=7	5.19	2.88 (0.90) N=29.7	0.58 N=6	4.97
≥5%	10.35 (5.85) N=173.8	2.08 N=35	4.98	10.38 (5.76) N=218.3	1.28 N=27	8.11	11.95 (7.14) N=264.8	4.47 N=99	2.67

Table 6.2.5. Predicted (P) by high-risk SCORE and observed (O) atherosclerotic CVD mortality by age groups and SCORE level in HAPIEE women

	Czech Republic			**Poland**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	2.53 (2.39) N=85.0	0.57 N=19	4.44	2.45 (2.41) N=92.0	0.43 N=16	5.70	3.08 (2.90) N=124.6	1.04 N=42	2.96
Age groups, years									
<50	0.72 (0.55) N=4.7	0.00 N=0	N/A	0.76 (0.53) N=6.5	(0.23%) N=2	3.30	0.85 (0.49) N=7.1	0.12 N=1	7.08
50-54.9	1.08 (0.72) N=7.7	0.28 N=2	3.86	1.16 (0.72) N=10.2	0.11 N=1	10.55	1.25 (0.76) N=10.5	0.36 N=3	3.47
55-59.9	2.05 (1.41) N=12.5	0.33 N=2	6.21	2.13 (1.44) N=16.5	0.26 N=2	8.19	2.34 (1.52) N=20.6	0.23 N=2	10.17
60-64.9	3.80 (2.38) N=30.3	0.75 N=6	5.07	4.10 (2.37) N=27.3	0.30 N=2	13.67	5.22 (2.86) N=36.3	1.44 N=10	3.63
≥65	5.12 (2.62) N=29.8	1.55 N=9	3.30	5.42 (2.89) N=31.5	1.55 N=9	3.50	6.30 (2.91) N=50.0	3.27 N=26	1.93
SCORE level									
<5%	1.64 (1.11) N=45.7	0.40 N=11	4.10	1.57 (1.07) N=49.3	0.19 N=6	8.26	1.66 (1.07) N=50.7	0.39 N=12	4.26
≥5%	6.85 (2.23) N=39.4	1.39 N=8	4.93	6.94 (2.36) N=42.5	1.63 N=10	4.26	7.45 (2.32) N=73.9	3.02 N=30	2.47

The calibration of high and low-risk continuous SCORE in HAPIEE samples was also assessed with the Hosmer-Lemeshow test, where χ^2 values <20 denote good calibration. **Table 6.2.6** presents the results of the Hosmer-Lemeshow analyses, based on predicted risk deciles. In Czech and Polish men, χ^2 values were substantially lower than 20, for both high and low-risk SCORE. In Russian men, however, the model fit was worse (χ^2 29.8 and 36.5 for high and low-risk SCORE, respectively). On the other hand, in all female samples, both versions of SCORE demonstrated good calibration, with χ^2 values ranging from 2.0 in Poland to 7.3 in the Czech Republic.

Table 6.2.6. Calibration of high and low-risk SCORE estimated by Hosmer-Lemeshow test in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men			
High-risk SCORE, χ^2 (*p*)	9.38 (0.3116)	9.06 (0.2483)	29.83 (0.002)
Low-risk SCORE, χ^2 (*p*)	6.87 (0.3332)	7.20 (0.3028)	36.52 (<0.0001)
Women			
High-risk SCORE, χ^2 (*p*)	7.30 (0.1990)	2.03 (0.7305)	5.36 (0.3738)
Low-risk SCORE, χ^2 (*p*)	3.74 (0.2907)	2.56 (0.4653)	3.00 (0.5586)

Suboptimal SCORE calibration in Russian men could be partly explained by the fact that in larger samples, Hosmer-Lemeshow test results are more sensitive to small deviations in fit (***Methods, Section 4.5.3***). In addition, a substantial number of participants had the same, relatively low levels of predicted mortality, due to the chart-based nature of SCORE instrument, which could also affect the Hosmer-Lemeshow test results. Thus, it may be more informative to assess SCORE calibration in HAPIEE by evaluating the ratios of predicted to observed levels of CVD mortality.

In summary, the high-risk SCORE demonstrated good calibration in most MONICA samples, while under-predicting the risk of fatal atherosclerotic CVD in Russian men and women. In all HAPIEE samples, the 10-year risk predictions exceeded the currently observed mortality, since the current HAPIEE follow-up is less than 10 years. The magnitude of this over-prediction was minimal in Russian samples, which suggests that at the 10-year point, high-risk SCORE can under-predict the risk of fatal CVD among Russian men and women. These findings agree with the second research hypothesis, which suggested satisfactory prognostic performance of SCORE across the majority of the samples, but risk under-prediction in the samples with higher levels of

cardiovascular mortality, such as those from Russia. Due to the present difference in the follow-up length between MONICA and HAPIEE, the direct comparison of SCORE calibration ability in these two studies is not possible. However, SCORE calibration, based on estimated 10-year CVD mortality in HAPIEE samples, will be compared to MONICA findings in the next section.

6.3. Estimated 10-year SCORE calibration in HAPIEE

As summarised in ***Section 2.1.3***, the SCORE instrument predicts the 10-year risk of fatal atherosclerotic CVD. Thus, the adequate assessment of SCORE performance requires that the populations of interest are followed up for at least 10 years. While the relevant prospective data are available for MONICA samples, the follow-up of the HAPIEE subjects is currently less than 10 years. Therefore, it has been decided to estimate the 10-year atherosclerotic mortality in HAPIEE, based on the country-specific patterns of fatal CVD distribution by the follow-up year in MONICA. An alternative approach is to use the "MONICA-independent" estimations by the exponential survival model. The estimated levels of fatal atherosclerotic CVD are then compared to predicted mortality, in order to evaluate the expected 10-year SCORE calibration.

6.3.1. MONICA-based estimates of 10-year SCORE calibration

For each male and female MONICA sample, the distribution of atherosclerotic CVD deaths across all 10 years of the follow-up is presented in **Table 6.3.1**. As expected, the absolute numbers of deaths tended to increase with longer follow-up, denoting the sample ageing. This tendency was more pronounced in men vs. women, and in larger vs. smaller samples (for example, Russian vs. Czech ones, which respectively included three vs. one study wave(s); ***Methods***, ***Section 4.1.1***).

Table 6.3.1. Observed numbers of atherosclerotic CVD deaths by follow-up year: MONICA men and women

Follow-up year	Czech Republic	Poland (Warsaw)	Poland (Tarnobrzeg)	Lithuania	Russia	All samples
Men						
1st	3	1	3	5	12	24
2nd	0	8	3	5	23	39
3rd	2	7	3	0	17	29
4th	3	8	5	4	16	36
5th	5	7	7	5	17	41
6th	3	12	10	9	17	51
7th	5	7	11	6	18	47
8th	4	14	2	9	23	52
9th	4	8	9	8	23	52
10th	3	14	9	7	15	48
TOTAL	**32**	**86**	**62**	**58**	**181**	**419**
Women						
1st	0	1	0	2	4	7
2nd	1	1	1	1	7	11
3rd	1	1	1	1	8	12
4th	2	2	1	0	7	12
5th	2	4	0	1	5	12
6th	0	3	1	1	8	13
7th	4	0	2	6	13	25
8th	0	4	6	4	14	28
9th	3	3	5	4	8	23
10th	0	2	2	6	12	22
TOTAL	**13**	**21**	**19**	**26**	**86**	**165**

Similarly, absolute numbers of deaths in HAPIEE participants tended to increase with longer follow-up and sample ageing (**Table 6.3.2**), although for the last years of the follow-up, these numbers were slightly lower. This was due to the delayed participation in the baseline survey (fewer people had six or seven complete years of follow-up) and also to the one-two-year lag between the fatal event and the register data on cause-specific mortality becoming available (***Methods***, ***Section 4.3.1***). Since this lag differed across three populations of interest, being minimal in the Czech Republic and maximal in Russia, the mean follow-up time, in complete years, varied from six among Czech participants to five in their Polish peers and four in Russian subjects (**Table 6.3.3**). Despite the shortest follow-up period, Russian men developed three times as many outcomes than their peers from the Czech Republic and Poland, while this difference was two-fold in Russian women vs. Czech or Polish females.

Table 6.3.2. Observed numbers of atherosclerotic CVD deaths by follow-up year: HAPIEE men and women

Follow-up year	Czech Republic		Poland		Russia	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
1st	2	2	5	2	20	6
2nd	2	4	6	5	20	6
3rd	7	1	6	2	23	3
4th	9	3	8	2	26	12
5th	8	4	6	4	8	11
6th	5	2	3	1	8	4
7th	4	3	-	-	-	-
TOTAL	**37**	**19**	**34**	**16**	**105**	**42**

Assuming that the ratio between the death numbers registered at a pre-specified cut-off point (six, five, and four years for Czech, Polish, and Russian samples, respectively) and the death numbers observed during the complete, 10-year follow-up period would be similar for MONICA and HAPIEE subjects from the same country, these ratios were first calculated for each MONICA sample, separately for men and women. It should be noted that only Polish participants from Warsaw were included in this analysis, since mortality patterns in this urban population were expected to be a better approximation of the respective patterns among urban Polish HAPIEE subjects (residents of Krakow City). The proportion of the atherosclerotic CVD deaths registered within the country-specific period of interest, out of the total number of deaths over 10 years, was similar in MONICA men and women from the same country (**Table 6.3.3**). Projecting these country and gender-specific ratios on the currently observed numbers of cardiovascular deaths in HAPIEE samples provided the estimates of the 10-year atherosclerotic CVD mortality among HAPIEE men and women.

Understandably, these estimates, presented in **Table 6.3.3**, cannot substitute the actually observed HAPIEE data on 10-year cardiovascular mortality, which are yet to be obtained. However, it can be noticed that the 10-year estimates for Czech and Polish HAPIEE men (2.8% and 2.7%, respectively) were substantially lower than the 10-year mortality levels observed in MONICA men from the same countries (5.0% and 6.7%; see ***Section 5.1***). Among Czech and Polish HAPIEE women, the estimated mortality (1.2% and 1.0%) was also lower than the respective MONICA levels of fatal CVD (1.9% and 1.8%). By contrast, the 10-year estimates of cardiovascular mortality for Russian HAPIEE men and women (8.6% and 3.4%, respectively) were slightly higher than the fatal CVD levels in their MONICA peers (7.0% and 3.2%). This difference might reflect the underlying heterogeneous trends in fatal CVD across CEE/FSU

populations over the last few decades (***Section 2.2.1***). In agreement with the current discrepancies between Russian vs. Czech or Polish national mortality rates[21], the 10-year estimates of fatal CVD were at least three times higher in Russian HAPIEE men and women (8.6% and 3.4%, respectively) than among their peers from the Czech Republic (2.8% and 1.2%) or Poland (2.7% and 1.0%, respectively).

Table 6.3.3. Estimation of 10-year atherosclerotic CVD mortality in HAPIEE men and women, based on observed MONICA mortality

	Czech Republic		**Poland**		**Russia**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Observed HAPIEE deaths, N (%)	37 (1.39)	19 (0.57)	34 (0.98)	16 (0.43)	105 (3.23)	42 (1.04)
Current mean HAPIEE follow-up, complete years	6		5		4	
Observed MONICA deaths in 10 years, N (%)	32 (5.03)	13 (1.85)	86 (6.68)	21 (1.82)	181 (7.03)	86 (3.21)
Observed MONICA deaths in relevant follow-up period and 10 years, N/N (%)	16/32 (50.00)	6/13 (46.15)	31/86 (36.05)	9/21 (42.86)	68/181 (37.57)	26/86 30.23)
Estimated HAPIEE deaths in 10 years, N (%)	74.0 (2.78)	41.2 (1.23)	94.2 (2.73)	37.3 (0.99)	279.3 (8.60)	139.0 (3.44)

In order to assess the expected 10-year calibration of the high-risk SCORE, these MONICA-based estimates were compared to predicted mortality levels, and the ratios of predicted to estimated (P/E) mortality were calculated for each HAPIEE sample (**Table 6.3.4**). For Czech and Polish men, the high-risk SCORE demonstrated a 2.7-fold over-prediction of the estimated 10-year cardiovascular mortality, while in their female peers, the gap between predicted and estimated risk of fatal CVD was only slightly smaller (P/E ratios 2.06 and 2.48 in Czech and Polish women, respectively). Therefore, despite the evidence of good calibration of the high-risk SCORE in Czech and Polish MONICA samples (***Section 6.2.1***), this scale appeared to over-estimate the risk in contemporary populations from respective countries. The agreement between the 10-year estimated atherosclerotic CVD mortality and the high-risk SCORE predictions was, however, good for HAPIEE men from Russia, as denoted by the P/E ratio of 1.06. Among Russian HAPIEE women, the level of predicted risk was lower than the estimated mortality (P/E ratio 0.90), although to a lesser extent than in their MONICA peers.

Table 6.3.4. Predicted (P) by high-risk SCORE and estimated (E) atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic			**Poland**			**Russia**		
	P	*E*	*P/E*	*P*	*E*	*P/E*	*P*	*E*	*P/E*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Men	7.51 (5.99) N=199.7	2.78 N=74.0	2.70	7.37 (5.89) N=254.7	2.73 N=94.2	2.70	9.07 (7.27) N=294.4	8.60 N=279.3	1.06
Women	2.53 (2.39) N=85.0	1.23 N=41.2	2.06	2.45 (2.41) N=92.0	0.99 N=37.3	2.48	3.08 (2.90) N=124.6	3.44 N=139.0	0.90

These results suggest that the use of different SCORE versions in Czech and Polish vs. Russian samples might improve the agreement between predicted and estimated risk of fatal atherosclerotic CVD. To check this possibility, the calibration of the low-risk SCORE scale was investigated across HAPIEE samples, although this SCORE version is presently not recommended for CEE/FSU populations. As seen in **Table 6.3.5**, the low-risk SCORE continued to over-predict the 10-year estimated levels of fatal CVD among Czech and Polish participants (P/E ratios from 1.19 in Czech women to 1.40 in Polish females and 1.44 in both Czech and Polish men), but to a lesser extent than the high-risk version of this instrument (respective P/E ratios 2.06-2.70). However, the low-risk SCORE was able to predict only a half of the estimated 10-year cardiovascular mortality among men and women from Novosibirsk (P/E ratios 0.56 and 0.52, respectively).

Table 6.3.5. Predicted (P) by low-risk SCORE and estimated (E) atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic			**Poland**			**Russia**		
	P	*E*	*P/E*	*P*	*E*	*P/E*	*P*	*E*	*P/E*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Men	4.00 (3.32) N=106.4	2.78 N=74.0	1.44	3.92 (3.26) N=135.5	2.73 N=94.2	1.44	4.84 (4.07) N=157.1	8.60 N=279.3	0.56
Women	1.46 (1.54) N=49.0	1.23 N=41.2	1.19	1.39 (1.56) N=52.2	0.99 N=37.3	1.40	1.77 (1.83) N=71.6	3.44 N=139.0	0.52

This is consistent with the findings for the high-risk SCORE and implies that the SCORE calibration might be improved, once the low-risk scale is used for the contemporary Czech and Polish populations, and the high-risk version is applied to Russian populations. These results, together with the data on risk under-estimation in Russian MONICA samples (***Section 6.2.1***), support the second research hypothesis of

differential SCORE calibration across CEE/FSU populations with varying levels of background risk.

6.3.2. Exponential model-based estimates of 10-year SCORE calibration

An alternative method for obtaining the 10-year estimates of HAPIEE calibration is based on the exponential model. This approach assumes a relatively constant mortality rate[362], and, hence, does not account for potential fluctuations, which are more likely in the samples with lower levels of fatal CVD, such as Czech and Polish women. However, this method provides the estimates which are not derived from the 10-15-year-old MONICA data. The estimated 10-year mortality (M_{10}) in HAPIEE samples was calculated as: $M_{10} = 1 - [1 - M_x]^{10/x}$, where M_x is mortality at x years of the follow-up.

The exponential estimates of the 10-year cardiovascular mortality in HAPIEE men and women (***Appendix II***, **Table A6.3.1**) were slightly lower than the respective MONICA-based estimates. In addition, the exponential estimates for Czech and Polish HAPIEE men (2.3% and 2.0%, respectively) were lower than the fatal CVD levels observed in MONICA men from respective countries (5.0% and 6.7%; ***Section 6.3.1***). Similarly, among Czech and Polish HAPIEE women, exponentially estimated CVD mortality (1.0% and 0.9%) was lower than the respective MONICA levels (1.9% and 1.8%). While for Russian HAPIEE women, exponentially estimated mortality (2.6%) was somewhat lower than the mortality observed in their MONICA peers (3.2%), the estimates for Russian HAPIEE men (7.9%) slightly exceeded the levels of fatal CVD observed in male MONICA participants from this country (7.0%). Consistent with the presently observed discrepancies between national Russian vs. Czech or Polish cardiovascular mortality rates[21], the exponential estimates of 10-year fatal CVD levels in HAPIEE were at least three times higher in Russian men and women (7.9% and 2.6%, respectively) than in their peers from the Czech Republic (2.3% and 1.0%) or Poland (2.0% and 0.9%, respectively).

For each HAPIEE sample, mortality predicted by the high-risk SCORE, exponentially estimated 10-year mortality, and the P/E ratio, as a measure of 10-year SCORE calibration, are presented in **Table A6.3.2** (***Appendix II***). In the Czech Republic and Poland, the high-risk SCORE demonstrated at least a 2.7-fold over-prediction of the estimated 10-year cardiovascular mortality (P/E ratios 3.25 and 2.66 in Czech men and women; 3.78 and 2.85 in their Polish peers). Among Russian men and women, the

agreement between the estimated CVD mortality and the high-risk SCORE predictions was good (respective P/E ratios 1.15 and 1.19). These results generally agree with the findings for the MONICA-based estimates of the 10-year SCORE calibration in HAPIEE and suggest that the high-risk SCORE might adequately predict cardiovascular risk in contemporary Russian populations.

With P/E ratios being at least twice as high in the Czech Republic and Poland as in Russia, the use of different SCORE versions in Czech and Polish vs. Russian samples might be advisable. Accordingly, the calibration of the low-risk SCORE was assessed in each HAPIEE sample. In Czech and Polish samples, the low-risk SCORE continued to over-predict the 10-year estimated levels of fatal CVD (P/E ratios from 1.54 in Czech women to 2.01 in Polish men), but to a lesser extent than the high-risk SCORE (P/E ratios 2.66-3.78). In Russian men and women, however, the low-risk scale predicted <70% of the estimated mortality (respective P/E ratios 0.61 and 0.69) (**Table A6.3.3**). Therefore, both exponential model-based and MONICA-based projections were consistent with the second research hypothesis and suggested that the low-risk SCORE is more appropriate for contemporary Czech and Polish settings, while the high-risk SCORE version continues to be more suitable for Russia.

Both the MONICA-derived and exponential model-derived estimates of 10-year CVD mortality in HAPIEE samples represent the aggregate projections, which cannot be extrapolated on the individual level. Thus, it was not possible to use these estimates for assessing the associations between fatal CVD and exposures of interest, or for evaluating the discrimination potential of the original SCORE scale and extended SCORE-based instruments. Nonetheless, the estimation procedure demonstrated that better calibration was achieved by the high-risk SCORE in Russian samples, and by the low-risk SCORE in Czech and Polish samples. Although no conclusion can be made before the actual 10-year data on observed HAPIEE mortality are available, it is possible that CEE/FSU populations require a further differentiation in the SCORE versions which are officially recommended to them.

6.4. SCORE discrimination

The next step of the analysis was to assess discrimination, another important aspect of SCORE performance, in both MONICA and HAPIEE. Discrimination, which reflects how accurately the risk assessment instrument separates subjects who will experience the outcome from those who will not, was assessed by sensitivity, specificity, the ratio

of true to false positives (likelihood ratio positive, LR+), the ratio of false to true negatives (likelihood ratio negative, LR-), positive and negative predictive values (PPV and NPV), area under the receiver operating characteristic curve (AUROC) and Harrell's C-statistic (AUROC equivalent for survival models), as well as by the recently introduced Royston's R^2 index (for parameter description, see ***Methods***, ***Section 4.5.3***).

6.4.1. SCORE discrimination in MONICA

As shown in **Table 6.4.1**, sensitivity of the high-risk SCORE was relatively high in all male MONICA samples, varying from 0.65 in Russia to 0.79 in Warsaw. Specificity was somewhat lower, ranging from 0.54 in Warsaw to 0.60 in Lithuania. Therefore, the high-risk SCORE correctly identified up to 80% of MONICA men who experienced an atherosclerotic CVD death within the next 10 years, and up to 60% of the men who did not develop a fatal CVD. The proportion of true positives (high-risk people with an outcome) was 1.5-1.9 times higher than the proportion of false positives (high-risk people without the outcome). Across all samples, LR- was below 1.0, as the proportion of the low-risk subjects who developed the outcome (false negatives) was small. Due to the relatively low outcome frequency, the PPV values were low in all male samples (approximately 0.10). By contrast, NPV values exceeded 0.96. In other words, while only a small proportion of high-risk men developed a CVD death within the 10-year follow-up period, almost all low-risk males remained outcome-free.

The AUROC values were over 0.50 (the value corresponding to overall discrimination no better than chance) across all male samples, being the highest for Czech men (0.69) and the lowest for Russian men (0.62). As expected, the values of Harrell's C-statistic were very close to the AUROC ones. In the subsequent analyses of extended SCORE performance, Harrell's C will be used instead of AUROC, since the former parameter allows assessing summary discrimination of multivariate models, enriched by additional risk predictors.

Table 6.4.1. Discrimination characteristics of the 5% cut-off for high-risk SCORE predicting 10-year atherosclerotic CVD mortality in MONICA men and women

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Sensitivity	25/32=0.7813	68/86=0.7907	44/62=0.7098	42/58=0.7241	118/181=0.6519
Specificity	358/604=0.5927	631/1167=0.5407	673/1205=0.5585	949/1593=0.5957	1399/2395=0.5841
LR+ (sensitivity/ 1-specificity)	78.13/40.73=1.92	70.07/45.93=1.53	70.98/44.15=1.61	72.41/40.43=1.79	65.19/41.59=1.57
LR- ((1-sensitivity)/ specificity)	21.87/59.27=0.37	20.93/54.07=0.39	29.02/55.85=0.52	27.59/59.57=0.46	34.81/58.41=0.60
PPV	25/271=0.0923	68/604=0.1126	44/576=0.0764	42/686=0.0612	118/1114=0.1059
NPV	358/365=0.9808	631/649=0.9723	673/691=0.9740	949/965=0.9834	1399/1462=0.9569
AUROC (95% CI)	0.69 (0.61-0.76)	0.67 (0.62-0.71)	0.63 (0.58-0.69)	0.66 (0.60-0.72)	0.62 (0.58-0.65)
Harrell's C	0.6900	0.6665	0.6319	0.6645	0.6188
Women					
Sensitivity	5/13=0.3846	4/21=0.1905	5/19=0.2632	8/26=0.3077	32/86=0.3721
Specificity	616/691=0.8915	989/1130=0.8752	1325/1443=0.9182	1493/1624=0.9193	2376/2591=0.9170
LR+ (sensitivity/ 1-specificity)	38.46/10.85=3.55	19.05/12.48=1.53	26.32/8.18=3.20	30.77/8.07=3.81	37.21/8.30=4.48
LR- ((1-sensitivity)/ specificity)	61.54/89.15=0.69	80.95/87.52=0.93	73.68/91.82=0.80	69.23/91.93=0.75	62.79/91.70=0.69
PPV	5/80=0.0625	4/145=0.0276	5/123=0.0407	8/139=0.0576	32/247=0.1296
NPV	616/624=0.9872	989/1006=0.9831	1325/1339=0.9895	1493/1511=0.9881	2376/2430=0.9778
AUROC (95% CI)	0.64 (0.50-0.78)	0.53 (0.45-0.62)	0.59 (0.49-0.69)	0.61 (0.52-0.70)	0.65 (0.59-0.70)
Harrell's C	0.6374	0.5354	0.5922	0.6134	0.6428

Among MONICA women, sensitivity of the high-risk SCORE was much lower than in men (from 0.19 in Warsaw to 0.39 in the Czech Republic), while its specificity was higher, approaching 0.90 in all female samples (**Table 6.4.1**). Therefore, SCORE correctly selected the majority of low-risk women who remained outcome-free, but identified only 20-40% of the women who would die from CVD in the next 10 years. Due to the low percentages of false positives in all female samples, the LR+ values were relatively high, varying from 1.5 in Warsaw to 4.5 in Novosibirsk. Women had a higher proportion of false negatives than men and, as a result, higher LR- values. Similar to men, low PPV values (≤0.13) and high NPV values (≥0.98) were observed in all female samples. AUROC and Harrell's C values were lower in women than in men, being the closest to 0.50 (inadequate discrimination) in Warsaw (0.54) and the highest in Novosibirsk (0.64).

The low-risk SCORE demonstrated lower sensitivity and higher specificity across all MONICA samples, compared to the high-risk SCORE version (***Appendix II***, **Table A6.4.1**). The values of AUROC and C-statistic for the low vs. high-risk SCORE were either similar or slightly lower.

An additional discrimination measure is the amount of the outcome variation accounted for by risk predictors. Royston's R^2 index is an indicator of explained variation specifically created for survival analysis (***Methods***, ***Section 4.5.3***). In the present study, R^2 statistic was adjusted by the model dimension (to facilitate the subsequent assessment of the extended SCORE performance), and bootstrap CI were calculated, using the minimal recommended replication number of 1,000. In male MONICA samples, the proportion of variation explained by dichotomous high-risk SCORE was the highest in the Czech Republic (R^2=0.32) and the lowest in Novosibirsk (0.13). In women, due to fewer outcomes, the proportion of explained variation was typically smaller than in men (**Table 6.4.2**). In most samples, R^2 values were higher for continuous high-risk SCORE than for its widely used dichotomous version, and reached 0.35 for Czech men and 0.47 for women from Novosibirsk.

A similar tendency, characterized by a higher proportion of explained variation in men vs. women (due to larger outcome numbers in the former), and for continuous vs. dichotomous SCORE (possibly, due to dichotomisation-caused information loss), was observed for the low-risk version of SCORE (***Appendix II***, **Table A6.4.2**).

Table 6.4.2. Discrimination of high-risk SCORE estimated by Royston's R^2 in MONICA men and women

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE	0.3169 (0.1042, 0.5817)	0.2605 (0.1354, 0.4015)	0.1593 (0.0442, 0.3247)	0.2421 (0.0905, 0.4230)	0.1336 (0.0646, 0.2261)
Continuous SCORE	0.3488 (0.1290, 0.6326)	0.2877 (0.1527, 0.4416)	0.2802 (0.1247, 0.4748)	0.1427 (0.0359, 0.2922)	0.2691 (0.1688, 0.3860)
Women					
Dichotomous SCORE	0.2452 (0.0000, 0.7025)*	0.0052 (0.0000, 0.2196)*	0.1475 (0.0000, 0.5473)*	0.2264 (0.0000, 0.5633)*	0.3376 (0.1491, 0.5235)
Continuous SCORE	0.1845 (0.0000, 0.5338)*	0.2526 (0.0000, 0.6374)*	0.3248 (0.0869, 0.5731)	0.3259 (0.1513, 0.5247)	0.4706 (0.3046, 0.6312)

* Lower confidence limits calculated as negative were regarded as 0.

In summary, the traditional risk factors comprising SCORE accounted for <50% of the outcome variation across MONICA samples, despite a significant association between SCORE and atherosclerotic CVD mortality, previously shown in ***Section 6.1.1***.

6.4.2. SCORE discrimination in HAPIEE

For HAPIEE samples, sensitivity, specificity, and other parameters of the high-risk SCORE discrimination were calculated based on the available mortality data. Since the current follow-up length for HAPIEE is less than 10 years, the results obtained should be interpreted cautiously. In male samples, the high-risk SCORE sensitivity reached 0.95, 0.80, and 0.94 in Czech, Polish, and Russian men, respectively, while its specificity was lower (0.37, 0.39, and 0.33, respectively) (**Table 6.4.3**). This means that the high-risk SCORE correctly identified at least 80% of the men who died from atherosclerotic CVD during the follow-up, but under 40% of the men who did not develop this outcome. The LR+ was 1.3-1.5, due to a relatively high percentage of outcome-free people at high risk. The LR- did not exceed 1.0 and was the lowest in Czech men (0.15). While PPV values were very low (0.01-0.05), NPV values exceeded 0.99 across all male samples. In other words, even though only a small percentage of high-risk men developed an outcome during the current follow-up period, almost all low-risk men remained event-free. The summary discrimination of high-risk SCORE was satisfactory, as denoted by relatively high values of AUROC and Harrell's C-statistic (from 0.60 in Poland to 0.66 in the Czech Republic).

In women, sensitivity of the high-risk SCORE was lower than in men, varying from 0.42 in the Czech Republic to 0.71 in Russia (**Table 6.4.3**). However, SCORE specificity was substantially higher in women, reaching 0.76-0.84. As a result, LR+ values were also higher in women. The values of LR- were relatively high, due to a considerable proportion of low-risk women who would develop the outcome. Compared to their male peers, Czech women had slightly lower AUROC and Harrell's C values. In Polish and Russian women, these parameters were higher than in men from respective samples and reached 0.73-0.74, which denoted a good summary discrimination of the high-risk SCORE.

Across all HAPIEE samples, the low-risk SCORE, compared to its high-risk version, showed lower sensitivity and higher specificity, as well as generally comparable AUROC and Harrell's C values (***Appendix II***, **Table A6.4.3**).

Table 6.4.3. Discrimination characteristics of the 5% cut-off for high-risk SCORE predicting atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men			
Sensitivity	35/37=0.9460	27/34=0.7941	99/105=0.9429
Specificity	978/2622=0.3730	1346/3422=0.3933	1024/3141=0.3260
LR+ (sensitivity/1-specificity)	94.60/62.70=1.51	79.41/60.67=1.31	94.29/67.40=1.40
LR- ((1-sensitivity)/specificity)	5.40/37.30=0.15	20.59/39.33=0.52	5.71/32.60=0.18
PPV	35/1679=0.0209	27/2103=0.0128	99/2216=0.0447
NPV	978/980=0.9980	1346/1353=0.9948	1024/1030=0.9942
AUROC (95% CI)	0.66 (0.62-0.70)	0.59 (0.52-0.66)	0.63 (0.61-0.66)
Harrell's C	0.6595	0.5964	0.6290
Women			
Sensitivity	8/19=0.4211	10/16=0.6250	30/42=0.7143
Specificity	2773/3340=0.8302	3135/3737=0.8389	3040/4002=0.7596
LR+ (sensitivity/1-specificity)	42.11/16.98=2.48	62.50/16.11=3.88	71.43/24.04=2.97
LR- ((1-sensitivity)/specificity)	57.89/83.02=0.70	37.50/83.89=0.45	28.57/75.96=0.38
PPV	8/575=0.0139	10/612=0.0163	30/992=0.0302
NPV	2773/2784=0.9961	3135/3141=0.9981	3040/3052=0.9961
AUROC (95% CI)	0.63 (0.51-0.74)	0.73 (0.61-0.86)	0.74 (0.67-0.81)
Harrell's C	0.6267	0.7413	0.7356

In male HAPIEE samples, the proportion of the outcome variation explained by the dichotomous high-risk SCORE was maximal in the Czech Republic (R^2=0.31) and minimal in Poland (0.08) (**Table 6.4.4**). Compared to respective male samples, the proportion of explained variation was smaller in Czech women (0.18), but higher in Polish and Russian women (0.53 and 0.47, respectively). Since the dichotomisation of SCORE might have resulted in the loss of predictive information, R^2 values for continuous SCORE were typically higher than those for the traditional, dichotomous instrument, and reached 0.42 in Czech men and 0.69 in Polish women.

Table 6.4.4. Discrimination of high-risk SCORE estimated by Royston's R^2 in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men			
Dichotomous SCORE	0.3075 (0.1593, 0.4873)	0.0838 (0.0000, 0.2957)*	0.2304 (0.1376, 0.3370)
Continuous SCORE	0.4216 (0.1977, 0.6531)	0.3501 (0.1004, 0.6291)	0.3154 (0.1950, 0.4561)
Women			
Dichotomous SCORE	0.1747 (0.0000, 0.5294)*	0.5263 (0.0729, 0.8626)	0.4729 (0.2419, 0.7022)
Continuous SCORE	0.1708 (0.0000, 0.4592)*	0.6910 (0.2503, 0.9375)	0.6003 (0.3603, 0.7928)

* Lower confidence limits calculated as negative were regarded as 0.

Similar results were obtained for low-risk SCORE, with a larger proportion of explained variation typically observed for continuous vs. dichotomous scale, and maximal R^2 values registered in Czech men and Polish women (0.42 and 0.72, respectively, for the continuous instrument) (***Appendix II***, **Table A6.4.4**).

A direct comparison of the SCORE discrimination in MONICA vs. HAPIEE samples was not possible, due to the current difference in the follow-up length between these two studies. However, SCORE sensitivity appeared to be higher, and specificity lower in most HAPIEE samples, compared to the MONICA samples. The proportion of explained variation was more or less similar in respective MONICA and HAPIEE samples. Overall, the MONICA and HAPIEE data have demonstrated satisfactory SCORE discrimination, as assessed by traditional discrimination measures. Together with the findings presented in ***Sections 6.2-6.3***, these results have addressed the third research objective (the examination of SCORE performance in MONICA and HAPIEE) and supported the second research hypothesis of satisfactory SCORE discrimination but varying calibration, with risk under-estimation in Russian samples.

Chapter 7. Education, marital status, and SCORE performance

Although the discrimination of the dichotomised high-risk SCORE, as assessed by traditional parameters, was more or less satisfactory in MONICA and HAPIEE, this SCORE version typically did not explain more than 50% of the outcome variation. These findings suggest that SCORE performance may benefit from adding other cardiovascular risk predictors to the model. Therefore, it has been explored whether extending the predictive model by socioeconomic parameters or alcohol consumption measures improves its calibration and discrimination, in accordance with the third and fourth research hypotheses.

For MONICA, additional risk factors included education (all samples) and marital status (Czech, Lithuanian, and Russian samples; no data on marital status were available for Poland). For HAPIEE, these parameters included education, marital status, alcohol consumption frequency, binge drinking, and CAGE score. In order to obtain stable effect estimates, most additional risk predictors were dichotomised. In particular, education was defined as "higher" (university, secondary, or vocational) or "lower" (primary or less), while marital status categories included "married" (married/cohabiting) and "non-married" (single, divorced/separated, or widowed).

Before including additional risk factors into the SCORE-based predictive model, calibration and discrimination of the original SCORE instrument were evaluated in the stratified data (for example, in higher vs. lower-educated people, and married vs. non-married participants, separately for men and women), to investigate whether the risk might be over-predicted in more advantaged subjects and under-predicted in their less advantaged peers. The analyses of SCORE performance by education and marital status in MONICA and HAPIEE failed to demonstrate any substantial difference in calibration or discrimination for participants with higher vs. lower education, or for married vs. non-married subjects (results available on request). The original SCORE performance was similar across socioeconomic strata, which suggested that there is no interaction between SCORE and education or marital status. However, this did not yet mean that socioeconomic characteristics would be irrelevant for extension of the SCORE model.

7.1. SCORE, education, and marital status as predictors of atherosclerotic CVD mortality

The next step of the analysis was to combine SCORE and education or marital status in prognostic models and to assess their role as predictors of atherosclerotic CVD mortality in MONICA and HAPIEE men and women. The baseline Model 1, which only included SCORE, was compared to Model 2 (SCORE and education), Model 3 (SCORE and marital status), and Model 4 (SCORE, education, and marital status). The mutual adjustment of SCORE and socioeconomic effects was possible, since no statistical interaction has been found between SCORE (both dichotomous and continuous high and low-risk versions) and either education or marital status in LR tests (all *p* values for interaction terms >0.1). In addition, as there was no marked collinearity between education and marital status across MONICA and HAPIEE samples (all phi correlation coefficient values <0.1, as shown in **Tables 7.1.1-7.1.2**), it was possible to simultaneously include these two parameters in the extended SCORE model (Model 4).

Table 7.1.1. Phi correlation coefficients for education and marital status in MONICA men and women

	Czech Republic	Poland (Warsaw)*	Poland (Tarnobrzeg)*	Lithuania	Russia
Men	0.0463	N/A	N/A	0.0038	-0.0031
Women	0.0065	N/A	N/A	0.0324	0.0764

* For Polish samples, data on marital status were unavailable.

Table 7.1.2. Phi correlation coefficients for education and marital status in HAPIEE men and women

	Czech Republic	Poland	Russia
Men	0.0841	0.0402	0.0487
Women	0.0199	0.0280	0.0722

7.1.1. SCORE, education, and marital status as predictors of atherosclerotic CVD mortality in MONICA

In most MONICA samples, high-risk SCORE ≥5% remained a significant predictor of 10-year CVD mortality after controlling for education, marital status, or both (**Table 7.1.3**). This adjustment slightly changed HR values for SCORE (reduced or increased, depending on the sample), but overall, it did not substantially affect the strength of the association between SCORE and fatal CVD. The only exceptions were Lithuanian and Russian female samples, where adjustment for education resulted in a slightly more pronounced reduction in SCORE HR (from 5.1 to 3.8 in Lithuania and from 6.3 to 5.4

in Russia). It suggests that the association of interest could be partly explained by educational differences in these samples; however, due to fewer outcomes and wider 95% CI in women vs. men, these findings should be interpreted with caution.

Across all samples, with the exception of Polish women from Tarnobrzeg, lower education was linked to a higher risk of 10-year CVD mortality. After adjustment for SCORE, this association reached statistical significance in men from Warsaw and Novosibirsk (HR 1.6 and 1.7, respectively), as well as in women from Warsaw, Kaunas, and Novosibirsk (HR 4.5, 4.4, and 1.7, respectively). In Warsaw and Kaunas, the detrimental effect of lower education seemed to be more pronounced in women than in men, while in Novosibirsk, no gender difference was observed for the association between lower education and fatal CVD risk.

Not being married was linked to a higher 10-year risk of atherosclerotic CVD in all male and female MONICA samples (data on marital status were unavailable for Polish subjects). After controlling for SCORE, this association was statistically significant in Czech and Russian men (HR 5.1 and 1.7, respectively), but not in women, suggesting that the protective effect of marriage may be more important for men. On the other hand, the absence of statistical significance for the marital status-fatal CVD association in women could be due to lower outcome numbers.

Overall, these findings seem to support the use of education (Warsaw men and women, Lithuanian women, Russian women), marital status (Czech men), or both education and marital status (Russian men) as additional independent predictors of atherosclerotic CVD mortality. Similar results were obtained for continuous high-risk SCORE (***Appendix III***, **Table A7.1.1**), as well as for dichotomous and continuous low-risk SCORE (**Tables A7.1.2-A7.1.3**), confirming the existence of positive, albeit heterogeneous, links between socioeconomic disadvantage and fatal CVD in MONICA samples.

Table 7.1.3. Dichotomous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	5.32 (2.30-12.30)	4.50 (2.68-7.56)	3.06 (1.77-5.29)	3.99 (2.24-7.10)	2.66 (1.96-3.62)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	5.35 (2.31-12.38)	4.32 (2.56-7.27)	2.90 (1.67-5.05)	3.75 (2.08-6.76)	2.43 (1.78-3.33)
Lower education (vs. higher)	1.20 (0.58-2.49)	1.56 (1.02-2.41)	1.44 (0.76-2.73)	1.30 (0.77-2.20)	1.70 (1.25-2.30)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	5.73 (2.46-13.33)	N/A	N/A	4.05 (2.28-7.21)	2.70 (1.99-3.68)
Non-married (vs. married)	5.13 (2.51-10.50)			1.93 (0.88-4.26)	1.73 (1.12-2.68)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	5.77 (2.47-13.43)	N/A	N/A	3.82 (2.12-6.88)	2.48 (1.81-3.40)
Lower education (vs. higher)	1.16 (0.56-2.42)			1.29 (0.76-2.18)	1.66 (1.23-2.25)
Non-married (vs. married)	5.14 (2.51-10.52)			1.92 (0.87-4.23)	1.76 (1.13-2.72)
Women					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	5.02 (1.64-15.36)	1.70 (0.57-5.06)	4.15 (1.49-11.52)	5.07 (2.20-11.66)	6.32 (4.08-9.79)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	4.72 (1.53-14.58)	1.62 (0.54-4.80)	4.26 (1.52-11.96)	3.78 (1.60-8.90)	5.44 (3.44-8.60)
Lower education (vs. higher)	1.55 (0.42-5.69)	4.48 (1.64-12.23)	0.82 (0.27-2.49)	4.35 (1.70-11.09)	1.70 (1.09-2.66)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	4.96 (1.62-15.17)	N/A	N/A	4.98 (2.16-11.49)	6.22 (3.98-9.71)
Non-married (vs. married)	2.15 (0.70-6.58)			1.26 (0.50-3.15)	1.22 (0.77-1.91)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	4.67 (1.51-14.43)	N/A	N/A	3.77 (1.60-8.91)	5.44 (3.42-8.66)
Lower education (vs. higher)	1.54 (0.42-5.67)			4.35 (1.70-11.09)	1.64 (1.05-2.58)
Non-married (vs. married)	2.16 (0.71-6.60)			1.03 (0.39-2.75)	1.22 (0.77-1.91)

7.1.2. SCORE, education, and marital status as predictors of atherosclerotic CVD mortality in HAPIEE

After accounting for education and marital status, the association between high-risk SCORE ≥5% and atherosclerotic CVD mortality remained significant in all HAPIEE samples (**Table 7.1.4**). This adjustment slightly changed SCORE HR values, to a greater extent for education than for marital status, in both men (unadjusted vs. education-adjusted HR 10.5 vs. 9.6 in the Czech Republic, 2.6 vs. 2.4 in Poland, and 7.6 vs. 7.1 in Russia) and women (3.6 vs. 3.4, 8.8 vs. 7.7, and 7.4 vs. 6.7, respectively). These findings, suggesting a more important role of education vs. marital status as a partial explanation of the SCORE-fatal CVD link, should be interpreted carefully, due to a relatively short follow-up of HAPIEE subjects, hence fewer outcomes and wider 95% CI.

Across all samples, the fatal CVD risk was higher among lower-educated subjects than in their higher-educated peers. After controlling for SCORE, lower education was a significant predictor of cardiovascular mortality in all male samples (HR 3.3, 2.6, and 1.8 for Czech, Polish, and Russian men, respectively). In all female samples, lower education was linked to a two-fold increase in fatal CVD risk; however, this association did not reach statistical significance, probably due to lower outcome numbers among women. Higher risk of atherosclerotic CVD death among non-married participants was observed across all samples, with HR ranging from 1.3 in Polish women to 2.6 in Polish men. After adjustment for SCORE, this association was statistically significant in Polish men (HR 2.6), Russian men (2.3), and Russian women (2.6).

These results are consistent with the possible addition of education (Czech men), marital status (Russian women), or both (Polish and Russian men), as independent predictors of CVD mortality, to the SCORE model. Similar findings, showing positive, although heterogeneous across samples, associations between SCORE, education, marital status, and fatal CVD in HAPIEE were obtained for continuous high-risk SCORE (***Appendix III***, **Table A7.1.4**) and dichotomous and continuous low-risk SCORE (**Tables A7.1.5-A7.1.6**).

Table 7.1.4. Dichotomous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	Poland	Russia
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	10.51 (2.53-43.71)	2.56 (1.11-5.87)	7.63 (3.35-17.40)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	9.61 (2.30-40.06)	2.39 (1.04-5.51)	7.06 (3.08-16.14)
Lower education (vs. higher)	3.25 (1.35-7.83)	2.61 (1.13-6.02)	1.84 (1.15-2.95)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	10.70 (2.57-44.50)	2.49 (1.09-5.73)	7.65 (3.35-17.44)
Non-married (vs. married)	1.70 (0.78-3.72)	2.57 (1.20-5.50)	2.32 (1.47-3.66)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	9.74 (2.34-40.66)	2.35 (1.02-5.42)	7.12 (3.11-16.29)
Lower education (vs. higher)	3.04 (1.24-7.41)	2.50 (1.08-5.77)	1.77 (1.10-2.84)
Non-married (vs. married)	1.57 (0.71-3.48)	2.48 (1.16-5.32)	2.26 (1.43-3.56)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	3.59 (1.44-8.91)	8.79 (3.19-24.18)	7.36 (3.77-14.38)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	3.36 (1.34-8.43)	7.71 (2.75-21.68)	6.68 (3.37-13.24)
Lower education (vs. higher)	1.97 (0.74-5.24)	2.27 (0.77-6.68)	1.87 (0.90-3.85)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	3.47 (1.40-8.65)	8.48 (3.06-23.53)	6.74 (3.44-13.19)
Non-married (vs. married)	1.91 (0.78-4.71)	1.32 (0.49-3.56)	2.55 (1.34-4.86)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	3.25 (1.29-8.17)	7.48 (2.64-21.21)	6.20 (3.13-12.30)
Lower education (vs. higher)	1.91 (0.72-5.09)	2.23 (0.76-6.59)	1.74 (0.84-3.59)
Non-married (vs. married)	1.88 (0.76-4.64)	1.27 (0.47-3.46)	2.49 (1.31-4.74)

To summarise ***Section 7.1***, significant associations between SCORE and cardiovascular mortality were observed in both MONICA and HAPIEE even after adjustment for socioeconomic parameters, which addressed Research Objective 4a. The link between SCORE and fatal atherosclerotic CVD appeared to be influenced, to a varying extent, by education and marital status, as demonstrated by the changes in SCORE HR values after controlling for these additional risk determinants. This concurs with the suggestion of differential impact of extra risk factors on the magnitude of the SCORE-fatal CVD association across populations and over time. However, this impact was relatively modest for all MONICA and HAPIEE samples, and did not result in the loss of statistical significance for the main association of interest, which supports the first research hypothesis of SCORE as a significant predictor of cardiovascular risk.

Most MONICA and HAPIEE samples demonstrated positive associations between socioeconomic parameters and cardiovascular mortality, after accounting for the effects of SCORE. These associations were statistically significant in some, but not all samples, which could be due to limited outcome numbers and reduced power of multiply adjusted analyses. Statistical significance of the SCORE-adjusted associations between additional risk determinants and fatal CVD supports the rationale for extending SCORE by these factors, but does not automatically mean that the extended models will have better calibration and discrimination. Therefore, prior to recommending specific socioeconomic parameters (if any) to be added to SCORE, as the third research hypothesis suggests, the predictive performance of such extended models needs to be investigated, which is the focus of the next section.

7.2. Calibration and discrimination of the SCORE model extended by education and marital status

To investigate whether enriching SCORE with additional risk determinants, such as education and marital status, improves its prognostic performance in MONICA and HAPIEE samples, various measures of calibration and discrimination were compared for the baseline Model 1 (SCORE only) vs. Model 2 (SCORE and education), Model 3 (SCORE and marital status), and Model 4 (SCORE, education, and marital status). Specifically, the values of Hosmer-Lemeshow χ^2, Harrell's C-statistic, and Royston's R^2 index were compared across these models. Additional prognostic information, provided by extra risk predictors, was also assessed by LR test *p* values and by integrated

discrimination improvement (IDI). To enable these cross-model comparisons, the present analyses included only subjects with known education and marital status.

7.2.1. Calibration and discrimination of the SCORE model extended by education and marital status in MONICA

Since the comparison of the predicted to observed CVD deaths by both education and marital status would not be informative, due to very low outcome numbers across individual strata, SCORE calibration of extended models in MONICA and HAPIEE was assessed with the Hosmer-Lemeshow goodness-of-fit test. This test quantifies the agreement between predicted and observed events across risk deciles (***Methods***, ***Section 4.5.3***), and was, therefore, applied to the continuous high and low-risk versions of SCORE.

The results of the Hosmer-Lemeshow analyses for MONICA samples are presented in **Table 7.2.1**. In most male samples, χ^2 values were under 20 for high-risk SCORE predictions across all four models, which denoted satisfactory calibration. However, in Lithuanian men, most χ^2 values exceeded 20, which points to imperfect fit of both original and extended SCORE models. Adding education to the SCORE model reduced Hosmer-Lemeshow χ^2 values (and, therefore, improved calibration) in Czech men (from 17.2 to 9.4), Polish men from Warsaw (from 13.9 to 10.7), and, to a lesser extent, in Lithuanian men (from 20.6 to 18.0). By contrast, in men from Tarnobrzeg and Novosibirsk, the original SCORE model fitted somewhat better than the education-extended one (χ^2 values 4.6 vs. 9.2, and 4.4 vs. 4.5, respectively). Analysing the calibration of the SCORE model extended by marital status produced mixed results: compared to the original instrument, this model was better calibrated in Czech men (respective χ^2 values 17.2 vs. 13.8), but not in their peers from Lithuania (20.6 vs. 28.4) or Russia (4.4 vs. 5.7, respectively). For Polish samples, data on marital status were unavailable (***Methods***, ***Section 4.3.3***), hence, the calibration analyses could only be performed for Models 1 and 2.

In women, almost all Hosmer-Lemeshow χ^2 values were under 20, and extending the baseline SCORE model by education and/or marital status would generally result in improved calibration (**Table 7.2.1**). Thus, adding education to the original SCORE scale decreased χ^2 values in women from the Czech Republic (from 7.9 to 5.8), Warsaw (from 8.4 to 7.1), Lithuania (from 19.2 to 9.1), and Russia (from 14.9 to 11.2), but not in their peers from Tarnobrzeg, who showed a slight increase in χ^2 (from 11.2 to 13.9).

Compared to the baseline model, marital status-extended instrument demonstrated worse calibration in Czech women (χ^2 values 7.9 vs. 12.1, respectively) and Novosibirsk females (14.9 vs. 21.3), but not in women from Kaunas (19.2 vs. 12.1, respectively).

Table 7.2.1. Continuous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
HL χ^2 (*p*)					
Men					
Model 1 (SCORE only)	17.15 (0.0164)	13.89 (0.0533)	4.62 (0.7059)	20.55 (0.0022)	4.41 (0.7313)
Model 2 (SCORE and education)	9.38 (0.2264)	10.69 (0.2201)	9.16 (0.3291)	18.01 (0.0212)	4.52 (0.8079)
Model 3 (SCORE and marital status)	13.84 (0.0542)	N/A	N/A	28.40 (0.0002)	5.74 (0.5709)
Model 4 (SCORE, education, and marital status)	17.86 (0.0126)	N/A	N/A	20.62 (0.0082)	6.47 (0.5944)
Women					
Model 1 (SCORE only)	7.89 (0.0959)	8.42 (0.0772)	11.19 (0.0245)	19.17 (0.0007)	14.92 (0.0049)
Model 2 (SCORE and education)	5.80 (0.4454)	7.09 (0.3123)	13.93 (0.0304)	9.10 (0.1051)	11.75 (0.0383)
Model 3 (SCORE and marital status)	12.07 (0.0338)	N/A	N/A	12.12 (0.0165)	21.25 (0.0007)
Model 4 (SCORE, education, and marital status)	7.74 (0.2575)	N/A	N/A	9.21 (0.2380)	11.54 (0.1169)

Therefore, among the four models of interest, the best calibration for men from Tarnobrzeg and Novosibirsk and for women from Tarnobrzeg was shown by Model 1; for Czech, Polish (Warsaw), and Lithuanian men and women by Model 2; and for Russian women by Model 4.

In the analysis of the low-risk SCORE calibration in MONICA, the Hosmer-Lemeshow test typically produced lower χ^2 values than the high-risk SCORE calibration assessment (***Appendix III***, **Table A7.2.1**). However, the patterns of calibration change after extending the original SCORE model by education and/or marital status were heterogeneous and generally similar to those patterns for the high-risk version of SCORE. Thus, the results of the calibration assessment in MONICA samples were

inconclusive and could not identify a single best-performing instrument among the four analysed models. Since discrimination is considered an intrinsically more important characteristic of prognostic performance than calibration (for details, see ***Methods***, ***Section 4.5.3***), the next step of the analysis was to explore various discrimination measures for Models 1-4.

Among MONICA men, the values of Harrell's C-statistic slightly increased when education and/or marital status were added to the original high-risk SCORE instrument (**Table 7.2.2**). Such a modest discrimination improvement could be due to the low sensitivity of C-statistic to the model extension, even when additional risk determinants are highly significant independent risk predictors (for details, see ***Background***, ***Section 2.1.1***). The best discrimination, as denoted by the highest C-statistic, among Polish men from Warsaw and Tarnobrzeg was observed for Model 2 (SCORE and education; respective C values 0.69 and 0.65); among Czech men for Model 3 (SCORE and marital status; 0.76); and among Lithuanian and Russian men for Model 4 (SCORE, education, and marital status; 0.70 and 0.66, respectively). In women, adding education and/or marital status to the original high-risk SCORE also resulted in increased values of Harrell's C-statistic (**Table 7.2.3**). Among Polish women from Warsaw and Tarnobrzeg, these values were the highest for Model 2 (0.69 and 0.60, respectively), and among Czech, Lithuanian, and Russian women for Model 4 (0.75, 0.74, and 0.71).

In addition, discrimination of Models 1-4 was assessed with Royston's R^2 index. This parameter was adjusted by model dimension, and 95% CI were calculated, using the minimal recommended bootstrap replication number of 1,000. Among MONICA men, extending the dichotomous high-risk SCORE by socioeconomic parameters would typically result in some R^2 increase, even though the 95% CI for all extended instruments were overlapping with the 95% CI for the baseline model (**Table 7.2.2**). The best discrimination, as denoted by the highest R^2, in Polish men from Warsaw and Tarnobrzeg was observed for Model 2 (respective R^2 values 0.28 and 0.16); in Czech and Lithuanian men for Model 3 (0.53 and 0.25, respectively); and in Russian men for Model 4 (0.19). In women, the results were generally similar, even though most R^2 values were lower than in men from respective samples (**Table 7.2.3**). The proportion of explained variation among women from Tarnobrzeg was the highest for Model 1 (R^2=0.15); among women from Warsaw, Kaunas, and Novosibirsk for Model 2 (0.25, 0.45, and 0.37, respectively); and among Czech women for Model 3 (0.27).

The difference in discrimination ability of original vs. extended SCORE models was also assessed by likelihood ratio tests (LRT), where lower *p* values indicate a larger difference in predictive performance between two nested models (***Methods***, ***Section 4.5.3***). According to the LRT results for male samples (**Table 7.2.2**), the extended instruments which performed better than the original SCORE were Model 2 (SCORE and education) in Warsaw and Novosibirsk men (p=0.04 and <0.01, respectively); Model 3 (SCORE and marital status) in Czech and Russian men (p<0.01 and 0.02); and Model 4 (SCORE, education, and marital status) in Czech and Russian men (p<0.01 for both samples). Across female samples (**Table 7.2.3**), the only extended scales performing better than the baseline instrument were Model 2 in women from Warsaw, Kaunas, and Novosibirsk (p<0.01, <0.01, and 0.03, respectively), and Model 4 for women from Kaunas (p<0.01).

Finally, the improvement in the SCORE-based model discrimination was quantified via a recently introduced integrated discrimination improvement (IDI), which measures the separation between the subjects who develop an outcome and those who do not, in terms of the average predicted risks for these two groups (***Methods***, ***Section 4.5.3***). In men, adding education and/or marital status to the original SCORE improved model discrimination very slightly (**Table 7.2.2**). For Model 2, the highest IDI value reached 0.36% in Novosibirsk men, while for Models 3 and 4, the highest IDI values were observed in Czech men (4.11% and 4.07%). In women, the discrimination improvement for extended SCORE models was even more modest (**Table 7.2.3**). The highest IDI values for Model 2 were observed in Warsaw women (0.91%); for Model 3, in Czech women (0.13%); and for Model 4, in Lithuanian women (0.70%).

Table 7.2.2. Dichotomous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men: Harrell's C, Royston's R^2, LRT *p* value, and integrated discrimination improvement (IDI)

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.6867	0.6665	0.6319	0.6644	0.6220
R^2	0.3057 (0.0764, 0.5502)	0.2605 (0.1405, 0.4076)	0.1593 (0.0398, 0.3211)	0.2419 (0.0941, 0.4343)	0.1408 (0.0676, 0.2322)
Model 2 (SCORE and education)					
Harrell's C	0.7011	0.6931	0.6457	0.6854	0.6525
R^2	0.2914 (0.0945, 0.5731)	0.2799 (0.1532, 0.4389)	0.1625 (0.0500, 0.3481)	0.2414 (0.1037, 0.4318)	0.1719 (0.1024, 0.2701)
LRT *p* value	0.7154	0.0405	0.2437	0.3304	0.0010
IDI (*p* value)	-0.00014 (0.77817)	0.00326 (0.12816)	0.00129 (0.16621)	<0.00001 (0.99941)	0.00363 (0.01292)
Model 3 (SCORE and marital status)					
Harrell's C	0.7587	N/A	N/A	0.6767	0.6356
R^2	0.5332 (0.2588, 0.7796)			0.2537 (0.0989, 0.4548)	0.1550 (0.0851, 0.2538)
LRT *p* value	<0.0001			0.1302	0.0193
IDI (*p* value)	0.04106 (0.00711)			0.00192 (0.26219)	0.00196 (0.12433)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7402	N/A	N/A	0.6991	0.6630
R^2	0.5228 (0.2551, 0.8036)			0.2525 (0.1222, 0.4630)	0.1860 (0.1141, 0.2824)
LRT *p* value	0.0002			0.2060	0.0003
IDI (*p* value)	0.04068 (0.00693)			0.00168 (0.31093)	0.00547 (0.00564)

Table 7.2.3. Dichotomous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.6372	0.5354	0.5922	0.6200	0.6471
R^2	0.2443 (0.0000, 0.7478)*	0.0052 (0.0000, 0.2194)*	0.1475 (0.0000, 0.5697)*	0.2505 (0.0000, 0.6090)*	0.3518 (0.1810, 0.5236)
Model 2 (SCORE and education)					
Harrell's C	0.7000	0.6885	0.5946	0.7408	0.6962
R^2	0.2220 (0.0000, 0.7182)*	0.2495 (0.0160, 0.6008)	0.1212 (0.0000, 0.5580)*	0.4466 (0.2001, 0.7260)	0.3735 (0.2084, 0.5513)
LRT *p* value	0.4971	0.0013	0.7249	0.0008	0.0285
IDI (*p* value)	-0.00079 (0.72702)	0.00911 (0.00048)	0.00022 (0.60651)	0.00695 (0.03391)	0.00169 (0.35834)
Model 3 (SCORE and marital status)					
Harrell's C	0.7138	N/A	N/A	0.6388	0.6738
R^2	0.2721 (0.0000, 0.7617)*			0.2296 (0.0000, 0.5757)*	0.3507 (0.1991, 0.5520)
LRT *p* value	0.1939			0.8921	0.3687
IDI (*p* value)	0.00129 (0.75402)			-0.00006 (0.47351)	-0.00009 (0.91470)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7532	N/A	N/A	0.7427	0.7061
R^2	0.2500 (0.0000, 0.7944)*			0.4291 (0.1702, 0.7671)	0.3717 (0.2158, 0.5752)
LRT *p* value	0.3428			0.0038	0.0641
IDI (*p* value)	0.00112 (0.83336)			0.00695 (0.03370)	0.00185 (0.38298)

* Lower confidence limits calculated as negative were regarded as 0.

In most MONICA samples, discrimination analysis of the models based on continuous high-risk SCORE demonstrated slightly higher values of Harrell's C-statistic and R^2, compared to the dichotomous SCORE-based models, which could be explained by the dichotomisation-related loss of prognostic power (***Appendix III***, **Tables A7.2.2-A7.2.3**). Nonetheless, LRT *p* values and IDI values were more or less similar for dichotomous and continuous high-risk SCORE, as original and extended models. Similarly, LRT *p* values and IDI values were relatively close for high and low-risk dichotomous SCORE-based instruments, although the latter SCORE version typically demonstrated slightly lower values of Harrell's C-statistic and Royston's R^2 (**Tables A7.2.4-A7.2.5**). Analysing discrimination of Models 1-4 based on low-risk dichotomous vs. continuous SCORE, or high vs. low-risk continuous SCORE (**Tables A7.2.6-A7.2.7**), provided similar results, showing slightly better discrimination parameters of extended SCORE scales.

To summarise, in MONICA samples, the inclusion of education and/or marital status in the original SCORE model resulted in some discrimination improvement. However, the magnitude of this improvement, as quantified by IDI, varied across samples and, overall, was relatively modest.

7.2.2. Calibration and discrimination of the SCORE model extended by education and marital status in HAPIEE

To check whether the MONICA results could be replicated in more recent data, calibration and discrimination of the four models of interest were assessed in HAPIEE participants. Calibration of the high-risk SCORE, both as the original instrument and its education and/or marital status-extended variants, was satisfactory in male samples from the Czech Republic and Poland, as denoted by Hosmer-Lemeshow χ^2 values under 20 (**Table 7.2.4**). Russian men, however, demonstrated a worse model fit, with χ^2 values ranging from 18.9 to 29.8. The latter could be explained by the Hosmer-Lemeshow test sensitivity to small deviations in fit for larger samples, as well as for samples where at least two subjects have the same levels of predicted risk, especially when these levels are relatively low (***Methods***, ***Section 4.5.3***). Adding education and/or marital status to the original SCORE model reduced χ^2 values, denoting better model fit, across all male HAPIEE samples. The best calibration was observed in Russian men for Model 2 (SCORE and education; χ^2 18.9) and in Czech or Polish men, for Model 3 (SCORE and marital status; χ^2 6.7 and 13.1, respectively).

In women, all Hosmer-Lemeshow χ^2 values were under 20, but adding education and/or marital status to the original SCORE model did not result in better calibration (**Table 7.2.4**). The best calibration was observed in Polish and Russian women for Model 1 (SCORE only; respective χ^2 2.0 and 5.4), and in Czech women for Model 2 (SCORE and education; 5.7). This lack of calibration improvement for extended models could be partly explained by the already low χ^2 values for the original SCORE, as well as by the same, relatively low levels of predicted risk in a substantial proportion of HAPIEE women.

Table 7.2.4. Continuous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland**	**Russia**
HL χ^2 (*p*)			
Men			
Model 1 (SCORE only)	10.72 (0.2178)	16.28 (0.0386)	29.83 (0.0002)
Model 2 (SCORE and education)	8.87 (0.3532)	14.12 (0.0786)	18.88 (0.0155)
Model 3 (SCORE and marital status)	6.70 (0.5698)	13.06 (0.1096)	26.90 (0.0003)
Model 4 (SCORE, education, and marital status)	9.64 (0.2916)	13.68 (0.0905)	23.23 (0.0031)
Women			
Model 1 (SCORE only)	7.28 (0.2009)	2.03 (0.7306)	5.36 (0.3738)
Model 2 (SCORE and education)	5.69 (0.3375)	3.29 (0.5106)	7.96 (0.1586)
Model 3 (SCORE and marital status)	10.06 (0.1221)	2.20 (0.8206)	7.41 (0.2848)
Model 4 (SCORE, education, and marital status)	18.27 (0.0108)	3.70 (0.7166)	7.23 (0.2997)

The results of the calibration assessment for the low-risk SCORE in HAPIEE men and women were more or less similar to those for the high-risk SCORE version (***Appendix III***, **Table A7.2.8**), with no single model demonstrating the best fit across all samples.

The next step was to study various discrimination parameters for Models 1-4 in HAPIEE samples. In men, a slight increase in Harrell's C-statistic was observed for the education and/or marital status-extended SCORE models, compared to the original, dichotomous high-risk SCORE instrument (**Table 7.2.5**). The highest C values (0.68-0.71) were observed for Model 4 (SCORE, education, and marital status) in men from

all three countries of interest. In women from the Czech Republic, Harrell's C values for Models 1-4 were lower than in Czech men, while for Polish and Russian women, they were higher than in men from the respective samples (**Table 7.2.6**). Nonetheless, the same pattern of higher Harrell's C for extended SCORE scales was observed across all female samples, with Model 4 demonstrating the best discrimination (C-statistic 0.68-0.78).

The analysis based on the R^2 measure of explained variation confirmed that, in general, the model discrimination in HAPIEE men and women was better for extended SCORE instruments, compared to the original risk scale (**Tables 7.2.5-7.2.6**). However, across all samples, 95% CI for extended models were overlapping with those for the baseline model and were relatively wide. The highest proportion of explained variation was observed for Model 4 in men from the Czech Republic (0.37), Poland (0.20), and Russia (0.30), as well as in Czech and Russian women (0.22 and 0.56, respectively). Although in Polish women, the absolute value of R^2 statistic was marginally higher for Model 2 (0.55) than for Model 4 (0.53), these results should be interpreted with caution, due to relatively few outcomes in this sample.

The comparison of the baseline vs. extended SCORE models in LR tests suggested that in men, most extended instruments performed better than the original SCORE (**Table 7.2.5**). The lowest LRT *p* values in Czech men were observed for Model 2 (SCORE and education; p=0.02), while in Polish and Russian men, the lowest *p* values were obtained for Model 4 (SCORE, education, and marital status; p=0.01 and <0.01, respectively). In women, however, most extended models failed to demonstrate a better performance, according to the LRT results, which could be explained by fewer outcomes among female HAPIEE subjects (**Table 7.2.6**). The only exception was the female Russian sample, which had the highest outcome number, despite the shortest follow-up time. Specifically, in Russian women, Models 3 and 4 seemed to perform better than the baseline Model 1 (LRT *p* values <0.01 for both comparisons).

Table 7.2.5. Dichotomous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.6589	0.5962	0.6290
R^2	0.3042 (0.1351, 0.4863)	0.0835 (0.0000, 0.2934)*	0.2304 (0.1464, 0.3385)
Model 2 (SCORE and education)			
Harrell's C	0.6889	0.6361	0.6535
R^2	0.3643 (0.1626, 0.6048)	0.1372 (0.0000, 0.4121)*	0.2542 (0.1610, 0.3825)
LRT *p* value	0.0202	0.0415	0.0171
IDI (*p* value)	0.00412 (0.08328)	0.00181 (0.11383)	0.00243 (0.04203)
Model 3 (SCORE and marital status)			
Harrell's C	0.6839	0.6349	0.6638
R^2	0.3158 (0.1628, 0.5137)	0.1508 (0.0054, 0.4463)	0.2812 (0.1815, 0.4056)
LRT *p* value	0.1767	0.0258	0.0009
IDI (*p* value)	0.00075 (0.36530)	0.00209 (0.06535)	0.00468 (0.01082)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7068	0.6771	0.6824
R^2	0.3659 (0.1848, 0.6199)	0.1974 (0.0223, 0.4971)	0.3007 (0.1978, 0.4370)
LRT *p* value	0.0385	0.0123	0.0003
IDI (*p* value)	0.00453 (0.07561)	0.00346 (0.02612)	0.00681 (0.00233)

* Lower confidence limits calculated as negative were regarded as 0.

Table 7.2.6. Dichotomous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.6277	0.7412	0.7356
R^2	0.1788 (0.0000, 0.5546)*	0.5255 (0.1329, 0.8382)	0.4729 (0.2458, 0.6985)
Model 2 (SCORE and education)			
Harrell's C	0.6445	0.7464	0.7497
R^2	0.1985 (0.0000, 0.6424)*	0.5486 (0.0997, 0.9059)	0.4882 (0.2560, 0.7117)
LRT *p* value	0.1954	0.1601	0.1096
IDI (*p* value)	0.00079 (0.34764)	0.00187 (0.25032)	0.00186 (0.16387)
Model 3 (SCORE and marital status)			
Harrell's C	0.6688	0.7552	0.7675
R^2	0.2065 (0.0000, 0.6299)*	0.5081 (0.0839, 0.8586)	0.5458 (0.2931, 0.7684)
LRT *p* value	0.1619	0.5909	0.0031
IDI (*p* value)	0.00089 (0.26968)	0.00021 (0.63073)	0.00510 (0.00168)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.6745	0.7641	0.7754
R^2	0.2222 (0.0000, 0.6993)*	0.5302 (0.1209, 0.8904)	0.5548 (0.3333, 0.7760)
LRT *p* value	0.1735	0.3338	0.0046
IDI (*p* value)	0.00179 (0.20254)	0.00180 (0.22343)	0.00690 (0.00296)

* Lower confidence limits calculated as negative were regarded as 0.

In addition, the changes in discrimination for the extended vs. original SCORE models in HAPIEE samples were quantified using the IDI parameter. In men, the inclusion of education and/or marital status in the SCORE risk scale resulted in a very modest discrimination improvement (**Table 7.2.5**). For Model 2, the highest IDI value reached 0.41% in Czech men, while for Models 3 and 4, the respective maximal values were 0.47% and 0.68% in Russian men. The findings for women confirmed that the discrimination improvement for extended vs. baseline SCORE models was not substantial (**Table 7.2.6**). The highest IDI values for Models 2, 3, and 4 reached only 0.19% (Polish women), 0.51% (Russian women), and 0.69% (Russian women), respectively.

For most HAPIEE samples, the discrimination analysis of continuous high-risk SCORE-based Models 1-4 produced slightly higher values of Harrell's C-statistic and Royston's R^2, compared to their dichotomous high-risk SCORE equivalents, since dichotomisation is likely to result in the loss of prognostic power of the model (***Appendix III***, **Tables A7.2.9-A7.2.10**). Nonetheless, the LRT *p* values and IDI values were relatively close for dichotomous and continuous high-risk SCORE, as original and extended instruments. These values were also similar for high and low-risk dichotomous SCORE-based models, even though for the latter, Harrell's C and Royston's R^2 parameters were slightly higher in men and slightly lower in women (**Tables A7.2.11-A7.2.12**). Comparing various discrimination measures for the models based on low-risk dichotomous vs. continuous SCORE, or on high vs. low-risk continuous SCORE, provided similar results, which confirmed a modest, sample-specific improvement in discrimination for the prognostic instruments extended by education and/or marital status (**Tables A7.2.13-A7.2.14**). The degree of this improvement did not exceed 1% in both HAPIEE men and women, regardless of the SCORE version used as a baseline model (high vs. low-risk, or dichotomous vs. continuous).

To conclude ***Section 7.2***, the investigation of the education and/or marital status-extended SCORE performance in MONICA and HAPIEE (Research Objective 4b) failed to identify the best performing instrument out of the four models examined. The extension of the original SCORE scale by adding socioeconomic parameters was accompanied by an improvement in some, but not all, calibration and discrimination indices. Trying to consider the dynamics of all studied performance measures, since to my knowledge, no hierarchy currently exists for calibration and discrimination

characteristics[39;76;326;358], the following "better-performing" models were identified for male MONICA samples: Model 2 (SCORE and education) in Poland (both Warsaw and Tarnobrzeg); Model 3 (SCORE and marital status) in the Czech Republic and Lithuania; and Model 4 (SCORE, education, and marital status) in Russia. For female MONICA samples, the "better-performing" SCORE versions were Model 2 in Warsaw, Tarnobrzeg, and Kaunas; Model 3 in the Czech Republic; and Model 4 in Novosibirsk. Among HAPIEE men, the "better-performing" risk assessment instrument was Model 4 for the Czech Republic, Poland, and Russia, while in HAPIEE women, it was Model 2 for Poland, and Model 4 for the Czech Republic and Russia. It should be noted, though, that the results for HAPIEE samples could change when the 10-year follow-up data become available.

Importantly, better statistical characteristics of the extended models do not always mean better clinical performance. Integrated discrimination improvement (IDI) appears to be the most clinically relevant performance measure, since it quantifies the change in the ability of the extended risk model to distinguish between individuals with and without the future outcome, compared to the baseline model. Across all MONICA and HAPIEE samples, IDI values were under 5% in men and under 1% in women, which suggests a very modest improvement in SCORE performance after adding education and/or marital status to the model. Therefore, the available data for MONICA and HAPIEE disagree with the third research hypothesis and justify the use of the original SCORE in CEE/FSU populations, as its prognostic performance appeared to be only marginally worse, compared to education and/or marital status-extended SCORE modifications.

Chapter 8. Alcohol consumption and SCORE performance in HAPIEE

As reviewed in ***Section 2.3.3*** (***Background***), various alcohol consumption characteristics could significantly predict fatal CVD, independently of traditional cardiovascular risk factors. Since in CEE/FSU populations, high levels of CVD mortality are combined with a relatively high prevalence of hazardous drinking, it was important to investigate whether adding alcohol consumption parameters to cardiovascular risk prediction models, such as SCORE, might improve their predictive performance. As a preliminary step of this investigation, SCORE calibration and discrimination were assessed across alcohol consumption strata (for example, in binge drinkers vs. non-bingers, and in those with CAGE score <2 vs. ≥2), separately for HAPIEE men and women (for MONICA samples, compatible alcohol consumption data were unavailable). Currently, the follow-up of HAPIEE subjects is under 10 years, and the observed levels of fatal CVD are lower than the high-risk SCORE predictions across all samples. It might be the case that the extent of this risk over-estimation is lower, and the discrimination between the subjects who develop or do not develop an outcome is less accurate in hazardous drinkers, compared to their peers who did not report hazardous alcohol consumption at baseline.

The stratified analyses of the HAPIEE data (results available on request) demonstrated that the categorical variable of alcohol consumption frequency could not be dichotomised, as its association with fatal CVD seemed to be J or U-shaped. Observed mortality tended to be higher, and predicted to observed mortality ratio appeared lower in self-reported "never-drinkers" and/or people consuming alcohol at least once a week, compared to those who reported drinking ≤3 times a month. To some extent, higher CVD rates in "never-drinkers" could be explained by the "sick quitter" effect (e.g.[280;285;363]). The specifics of HAPIEE data collection did not allow the differentiation between true never-drinkers and ex-drinkers across all samples. Excluding all "never-drinkers" from the analyses would dramatically reduce the sample size, especially for HAPIEE women. Therefore, the analyses were focused on binge drinking and CAGE score, as the main alcohol consumption parameters of interest. Across HAPIEE samples, SCORE showed similar prognostic performance among binge drinkers vs. non-bingers, or in people with CAGE score <2 vs. ≥2. Calibration and discrimination of the original SCORE did not substantially differ between the hazardous drinking strata,

but these results did not yet reject the possibility that adding bingeing and/or CAGE to the SCORE model could improve its performance.

8.1. SCORE and alcohol consumption parameters as predictors of atherosclerotic CVD mortality

In order to assess the role of hazardous drinking parameters as potential independent predictors of fatal atherosclerotic CVD, the next step of the analysis was to combine SCORE, binge drinking, and CAGE in prognostic models. The baseline Model 1 (SCORE only) was compared to Model 2 (SCORE and binge drinking), Model 3 (SCORE and CAGE), and Model 4 (SCORE, binge drinking, and CAGE). Since LR tests demonstrated no statistical interaction between various SCORE versions (dichotomous and continuous high and low-risk scale) and either binge drinking or CAGE (all *p* values for interaction terms >0.3), the mutual adjustment of SCORE and drinking parameters was appropriate.

While phi correlation coefficient values did not demonstrate marked collinearity between the two measures of hazardous alcohol consumption (all values <0.4; see **Table 8.1.1**), OR for the association between binge drinking and CAGE were relatively high, particularly in women (results available on request). However, considering the distribution of hazardous drinking parameters in the samples, when the majority of subjects reported no bingeing and were CAGE-negative, and the number of so-called discordant observations (binge drinking without positive CAGE, or positive CAGE in the absence of bingeing) was low, assessing the strength of the bingeing-CAGE association via OR might be problematic. Moreover, as the aim of this research is to investigate the prognostic performance of extended SCORE models, rather than compare the impact of different alcohol consumption measures as cardiovascular risk predictors, it was decided to include both binge drinking and CAGE in the extended SCORE (Model 4).

Table 8.1.1 Phi correlation coefficients for binge drinking and CAGE score in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men	0.2269	0.3396	0.3745
Women	0.2079	0.1995	0.2655

In all HAPIEE samples, high-risk SCORE ≥5% significantly predicted the currently observed CVD mortality, both before and after adjustment for binge drinking and/or

CAGE (**Table 8.1.2**). This adjustment resulted in modest, sample-specific changes of SCORE HR values. Czech men demonstrated some SCORE HR reduction after controlling for binge drinking or CAGE (unadjusted HR 10.5 vs. respective adjusted HR 10.3 and 10.0). At the same time, accounting for either hazardous drinking parameter barely changed the SCORE HR for Polish and Russian men. Among Czech and Russian women, adjustment for hazardous drinking slightly increased the SCORE HR values, and to a greater extent for CAGE than for binge drinking (respective unadjusted HR 3.6 and 7.4, vs. CAGE-adjusted HR 4.2 and 7.7). In Polish women, however, controlling for binge drinking did not affect the SCORE HR, while accounting for CAGE resulted in a minimal HR reduction (unadjusted HR 8.8 vs. CAGE-adjusted HR 8.7).

Thus, the impact of hazardous drinking measures on the SCORE-fatal CVD association was modest, without substantial changes in the strength of this link, or loss of statistical significance. After controlling for the effects of both binge drinking and positive CAGE (Model 4), SCORE ≥5% was linked to a marked increase in cardiovascular death risk (HR 9.7, 2.6, and 7.6 in Czech, Polish, and Russian men and 4.2, 8.7, and 7.8 in women from the respective countries). Nonetheless, due to the current HAPIEE follow-up being under 10 years, the outcome numbers were relatively low, and 95% CI were quite wide, especially for women, which warrants a cautious interpretation of these high HR values.

For all male samples, there was no evidence that binge drinking was a significant predictor of atherosclerotic CVD death after controlling for the dichotomous high-risk SCORE, since all adjusted HR values approached 1.0 (from 0.9 for Poland to 1.2 for Russia) (**Table 8.1.2**). Among Czech and Russian women, binge drinking was linked to an increased risk of cardiovascular mortality, but this association was significant only in the latter sample, with respective SCORE-adjusted HR of 2.0 and 5.8. In Polish women, the numbers of observations and outcomes were too low to calculate HR for binge drinking. In most HAPIEE samples, additional adjustment for CAGE (Model 4) only slightly affected HR for binge drinking, but in Russian women, it resulted in the loss of statistical significance (HR 3.3).

CAGE score ≥2 was linked to a higher risk of fatal CVD in men from the Czech Republic, Poland, and Russia when adjusted for SCORE only (Model 3: HR 1.2, 1.7, and 1.1, respectively), or for SCORE and binge drinking (Model 4: respective HR 1.3, 1.9, and 1.1). Nonetheless, CAGE could not be regarded as an independent, significant

predictor of cardiovascular risk, since all 95% CI in Models 3 and 4 included 1.0 (**Table 8.1.2**). While in Polish women, HR values for CAGE, adjusted for SCORE (Model 3) or for SCORE and binge drinking (Model 4), could not be calculated due to the low numbers of observations and outcomes, Czech and Russian women demonstrated a link between CAGE ≥2 and elevated risk of CVD mortality. Among Czech females, 95% CI of CAGE HR included 1.0 for Model 3 and Model 4. In Russian women, this association lost statistical significance after additional controlling for binge drinking (HR 5.6 for Model 3 vs. 3.2 for Model 4).

Table 8.1.2. Dichotomous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	10.51 (2.53-43.71)	2.56 (1.11-5.87)	7.63 (3.35-17.40)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	10.26 (2.46-42.71)	2.56 (1.12-5.89)	7.62 (3.34-17.38)
Binge drinking (vs. no binge drinking)	0.96 (0.40-2.30)	0.87 (0.27-2.84)	1.18 (0.79-1.75)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	10.00 (2.40-41.66)	2.58 (1.12-5.93)	7.63 (3.35-17.40)
CAGE ≥2 (vs. <2)	1.19 (0.42-3.37)	1.67 (0.65-4.31)	1.13 (0.72-1.78)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	9.67 (2.32-40.36)	2.60 (1.13-5.96)	7.63 (3.35-17.39)
Binge drinking (vs. no binge drinking)	0.78 (0.29-2.10)	0.69 (0.20-2.45)	1.16 (0.76-1.77)
CAGE ≥2 (vs. <2)	1.32 (0.44-3.94)	1.89 (0.69-5.20)	1.06 (0.65-1.73)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	3.59 (1.44-8.91)	8.79 (3.19-24.18)	7.36 (3.77-14.38)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	4.08 (1.61-10.35)	8.78 (3.19-24.16)	7.72 (3.93-15.15)
Binge drinking (vs. no binge drinking)	2.01 (0.27-15.17)	too few observations	5.75 (1.38-24.02)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	4.19 (1.64-10.67)	8.69 (3.16-23.92)	7.74 (3.94-15.20)
CAGE ≥2 (vs. <2)	3.85 (0.51-29.23)	too few observations	5.64 (1.35-23.59)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	4.21 (1.65-10.70)	8.65 (3.14-23.79)	7.78 (3.97-15.24)
Binge drinking (vs. no binge drinking)	1.49 (0.17-13.25)	too few observations	3.29 (0.54-20.03)
CAGE ≥2 (vs. <2)	3.36 (0.38-30.11)	too few observations	3.19 (0.52-19.42)

Similarly, the analysis of binge drinking, CAGE, and continuous high-risk SCORE (***Appendix IV***, **Table A8.1.1**), or dichotomous and continuous low-risk SCORE (**Tables A8.1.2-A8.1.3**) demonstrated that in HAPIEE men, there was no clear link between binge drinking and CVD mortality, while CAGE ≥2 was related to a higher risk of cardiovascular death, but not significantly. In women, these links were not statistically significant after adjustment for SCORE, or for SCORE and another parameter of hazardous drinking.

To summarise ***Section 8.1***, the assessment of the associations between SCORE, drinking measures, and fatal CVD across HAPIEE samples (Research Objective 5a) has demonstrated that positive SCORE (≥5%) was a statistically significant predictor of the currently observed cardiovascular mortality in men and women, after accounting for the effects of hazardous alcohol consumption. The strength of the link between SCORE and fatal CVD seemed to be affected, to a varying extent, by binge drinking (Czech men) and CAGE (Czech men; Czech, Polish, and Russian women), as shown by heterogeneous changes in the SCORE HR values after adjustment for these extra risk determinants. This suggests differential influence of additional risk factors on the magnitude of the SCORE-fatal CVD association across populations. However, the impact of hazardous drinking was modest for all samples, and did not result in the loss of statistical significance for the link between SCORE and currently observed cardiovascular mortality. These findings agree with the first research hypothesis of SCORE as a significant determinant of fatal CVD.

By contrast, the HAPIEE data did not provide strong support for the fourth research hypothesis which suggests inclusion of binge drinking and/or CAGE in the SCORE-based prognostic algorithm. One of the possible explanations could be the present follow-up length, which limited outcome numbers and reduced the analysis power, especially in women. The next section investigates whether the absence of statistically significant associations between hazardous drinking and CVD mortality manifested in the lack of SCORE performance improvement after adding binge drinking and/or CAGE to the model.

8.2. Calibration and discrimination of the SCORE model extended by alcohol consumption parameters

To assess the SCORE performance improvement, if any, after adding binge drinking and CAGE to the original SCORE scale, various measures of calibration and discrimination were compared for the baseline Model 1 (SCORE only) vs. Model 2 (SCORE and binge drinking), Model 3 (SCORE and CAGE), and Model 4 (SCORE, binge drinking, and CAGE). In particular, the values of Hosmer-Lemeshow χ^2, Harrell's C-statistic, and Royston's R^2 were compared across these four models, separately for HAPIEE men and women. The additional prognostic information provided by hazardous drinking parameters was assessed via LR test *p* values and integrated discrimination improvement (IDI). These analyses included only participants with available data on binge drinking and CAGE, in order to enable the cross-model comparisons.

The comparison of the predicted to observed CVD death ratios by both binge drinking and CAGE would not be informative, due to relatively few outcomes in each individual stratum, especially in women. Therefore, the calibration of extended SCORE models was assessed with the Hosmer-Lemeshow test, applied to continuous high and low-risk SCORE versions. In Czech and Polish men, χ^2 values were under 20 for high-risk SCORE predictions across all four models of interest, denoting satisfactory calibration (**Table 8.2.1**). Among Russian men, however, all χ^2 values exceeded 20, which signifies an imperfect fit of both original and alcohol-extended SCORE models and could be partly explained by the Hosmer-Lemeshow test sensitivity to small deviations in fit for larger samples, and for samples where at least two subjects have identical levels of predicted risk, or these levels are relatively low (***Methods***, ***Section 4.5.3***). Including binge drinking in the SCORE model resulted in slightly increased Hosmer-Lemeshow χ^2 values (and, therefore, deteriorated calibration) among Czech men (from 7.2 to 8.1) and Polish men (from 9.17 to 11.2). Russian men demonstrated a somewhat better fit for the model extended by binge drinking than for the original SCORE (respective χ^2 values 27.0 vs. 29.8).

Compared to the original instrument (Model 1), the calibration of the CAGE-extended SCORE (Model 3) appeared to be slightly better in Czech men (respective χ^2 values 7.2 vs. 6.6) and Russian men (29.8 vs. 28.6), but not among their Polish peers (9.1 vs. 12.9). The instrument with the best calibration was Model 3 (SCORE and CAGE) for Czech

men and Model 4 (SCORE, binge drinking, and CAGE) for Russian men, even though the calibration improvement in both cases was minimal. Among Polish men, adding hazardous drinking parameters to SCORE did not result in better calibration.

In women, Hosmer-Lemeshow χ^2 values were under 20 for all four models, but extending SCORE by binge drinking and/or CAGE typically did not result in improved calibration (**Table 8.2.1**). Adding binge drinking to the original SCORE scale increased χ^2 values in Czech women (from 8.8 to 9.3) and Russian women (from 5.4 to 8.6), while not affecting SCORE calibration in Polish females (2.0). Compared to the baseline Model 1, the fit of the CAGE-extended instrument (Model 3) appeared to be slightly better among Czech women (respective χ^2 values 8.8 vs. 8.1), the same among Polish women (2.0), and somewhat worse in Russian women (5.4 vs. 8.9). Out of the four models explored, the best calibration among HAPIEE women was observed for Models 1 and 3 in the Czech Republic and for Model 1 in Poland and Russia (in the Polish sample, χ^2 values were identical across all models, but Model 1 was the most parsimonious). The absence of the marked calibration improvement for the extended models could be due to the already low χ^2 values for the original SCORE instrument, and also due to a large proportion of women with the same, relatively low predicted risk levels (***Methods***, ***Section 4.5.3***).

Table 8.2.1. Continuous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland**	**Russia**
HL χ^2 (*p*)			
Men			
Model 1 (SCORE only)	7.24 (0.5113)	9.07 (0.2477)	29.83 (0.0002)
Model 2 (SCORE and binge drinking)	8.11 (0.4226)	11.16 (0.1926)	26.99 (0.0007)
Model 3 (SCORE and CAGE)	6.58 (0.5828)	12.88 (0.1161)	28.62 (0.0004)
Model 4 (SCORE, binge drinking, and CAGE)	7.01 (0.5359)	14.50 (0.0696)	26.18 (0.0010)
Women			
Model 1 (SCORE only)	8.76 (0.1190)	2.04 (0.7282)	5.36 (0.3738)
Model 2 (SCORE and binge drinking)	9.26 (0.0548)	2.04 (0.7277)	8.63 (0.1246)
Model 3 (SCORE and CAGE)	8.08 (0.0885)	2.04 (0.7282)	8.91 (0.1126)
Model 4 (SCORE, binge drinking, and CAGE)	13.00 (0.0113)	2.04 (0.7281)	11.19 (0.0478)

The calibration assessment of the original and extended low-risk SCORE typically produced lower χ^2 values than the high-risk SCORE calibration analysis (***Appendix IV***, **Table A8.2.1**). It could be explained by the fact that in most samples, the currently observed CVD mortality is closer to the low-risk SCORE predictions, due to the follow-up length presently being under 10 years. Nonetheless, the pattern of calibration changes, after extending the low-risk SCORE by binge drinking and/or CAGE, was similar to that observed for the high-risk SCORE. The low-risk SCORE-based instruments with the best fit were Model 2 for Czech men (χ^2 6.9) and Polish men (5.2) and Model 4 for Russian men (35.1). In women, the best-calibrated scales were Model 3 for the Czech Republic (χ^2 value 4.3); Models 1 and 2 for Poland (2.6 for both models); and Models 1 and 3 for Russia (3.0 and 2.9, respectively).

Overall, the results of the calibration assessment in HAPIEE were inconclusive and did not identify a single model which would demonstrate the best performance across all samples. Moreover, the extent of calibration improvement, observed for the hazardous drinking-extended SCORE models, was rather modest. The next step of the analysis was to explore various measures of discrimination, another important characteristic of prognostic performance, for Models 1-4 in HAPIEE men and women.

Across all male samples, the values of Harrell's C slightly increased when binge drinking and/or positive CAGE were added to the dichotomous high-risk SCORE (**Table 8.2.2**). Such a minimal improvement is consistent with relatively low sensitivity of C-statistic to the model extension, and also with the absence of statistically significant, SCORE-independent associations between the measures of hazardous drinking and current CVD mortality (***Section 8.1***). The highest Harrell's C values, denoting the best discrimination, were observed in Russian men for Model 2 (SCORE and binge drinking; 0.64); in Czech men for Model 3 (SCORE and CAGE; 0.66); and in Polish men for Model 4 (SCORE, binge drinking, and CAGE; 0.63). In women, the inclusion of binge drinking and/or positive CAGE in the original SCORE also resulted in a minimal increase in Harrell's C (**Table 8.2.3**). The highest values were registered in Czech females for Model 2 (0.66), and in their Polish and Russian peers for Model 4 (0.74 and 0.77, respectively).

The values of Royston's R^2, a measure of explained variation for survival models, did not change substantially in HAPIEE men after the addition of binge drinking and/or positive CAGE to the dichotomous high-risk SCORE (**Table 8.2.2**). The highest R^2

values were observed in Czech and Russian men for Model 1 (SCORE only; 0.30 and 0.22, respectively), and in Polish men for Model 3 (SCORE and CAGE; 0.09). In the Czech Republic, the proportion of the explained outcome variation tended to be slightly lower for women than for men, while in Poland and Russia, it appeared to be higher in females than in males. However, due to lower outcome numbers in women, 95% CI for Royston's R^2 were typically wider (**Table 8.2.3**). Therefore, high R^2 values in female samples should be interpreted cautiously. Regardless of gender differences in R^2 values, HAPIEE women also demonstrated the lack of marked discrimination improvement after adding hazardous drinking parameters to the dichotomous high-risk SCORE. In Polish women, the highest R^2 index (0.53) was observed for the baseline Model 1. Among Czech and Russian women, R^2 values were the highest for Models 3 and 4, respectively, but they did not substantially differ from the Model 1 values (0.22 for Czech females and 0.47-0.50 for their Russian peers).

The difference in the discrimination ability of original vs. alcohol-extended SCORE models was also assessed in likelihood ratio tests (LRT). In each male sample, no extended instrument performed better than the original SCORE, with all *p* values exceeding 0.3 (**Table 8.2.2**). A similar result was observed for Czech women (all LRT *p* values >0.2), while in Polish women, the low numbers of observations and outcomes prevented the acquisition of meaningful LRT findings (**Table 8.2.3**). In Russian women (a female sample with the highest outcome number, despite the shortest follow-up), both Model 2 (SCORE and binge drinking) and Model 3 (SCORE and positive CAGE) were performing marginally better than Model 1 (both *p* values 0.06). The magnitude of this improvement decreased after the SCORE adjustment for both binge drinking and CAGE, as denoted by *p* value of 0.09 for Model 4.

In addition, the potential change in SCORE discrimination, after extending the original model by hazardous drinking parameters, was assessed using integrated discrimination improvement (IDI). In men, including binge drinking and/or positive CAGE in the original SCORE scale resulted in a very modest discrimination improvement (**Table 8.2.2**). The highest IDI values, registered for Model 4 (SCORE, binge drinking, and CAGE) across all male samples, did not exceed 0.05%. In women, the improvement in the discrimination of alcohol-extended models was also minimal, with the highest IDI values reaching only 0.18% in the Czech Republic (Model 3), 0.002% in Poland (Model 3), and 0.05% in Russia (Model 4) (**Table 8.2.3**).

Table 8.2.2. Dichotomous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.6582	0.5971	0.6290
R^2	0.2986 (0.1181, 0.4881)	0.0851 (0.0000, 0.2858)*	0.2304 (0.1432, 0.3403)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.6605	0.6001	0.6443
R^2	0.2859 (0.1317, 0.4994)	0.0686 (0.0000, 0.3088)*	0.2286 (0.1427, 0.3450)
LRT *p* value	0.6960	0.8335	0.4193
IDI (*p* value)	0.00005 (0.82256)	0.00002 (0.70365)	0.00034 (0.37348)
Model 3 (SCORE and CAGE)			
Harrell's C	0.6638	0.6148	0.6317
R^2	0.2854 (0.1380, 0.4912)	0.0855 (0.0000, 0.3506)*	0.2266 (0.1461, 0.3424)
LRT *p* value	0.7248	0.3118	0.6050
IDI (*p* value)	-0.00001 (0.97562)	0.00043 (0.37518)	0.00007 (0.72787)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.6613	0.6286	0.6432
R^2	0.2743 (0.1513, 0.5064)	0.0743 (0.0000, 0.3455)*	0.2238 (0.1444, 0.3373)
LRT *p* value	0.8233	0.5032	0.7001
IDI (*p* value)	0.00008 (0.84499)	0.00050 (0.29915)	0.00034 (0.38090)

* Lower confidence limits calculated as negative were regarded as 0.

Table 8.2.3. Dichotomous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.6415	0.7411	0.7356
R^2	0.2153 (0.0000, 0.6199)*	0.5254 (0.1021, 0.8701)	0.4729 (0.2484, 0.6918)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.6585	0.7425	0.7555
R^2	0.1970 (0.0000, 0.6023)*	0.5042 (0.0835, 0.8277)	0.4984 (0.2941, 0.6948)
LRT *p* value	0.5285	too few observations	0.0576
IDI (*p* value)	<0.00001 (0.99603)	0.00001 (0.00022)	0.00023 (0.70817)
Model 3 (SCORE and CAGE)			
Harrell's C	0.6415	0.7431	0.7507
R^2	0.2207 (0.0000, 0.6967)*	0.5060 (0.0814, 0.8404)	0.4977 (0.2935, 0.7083)
LRT *p* value	0.2777	too few observations	0.0600
IDI (*p* value)	0.00181 (0.38049)	0.00002 (0.00022)	0.00021 (0.72203)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.6576	0.7441	0.7653
R^2	0.1939 (0.0000, 0.7103)*	0.4826 (0.0625, 0.8380)	0.5016 (0.2813, 0.7260)
LRT *p* value	0.5235	too few observations	0.0845
IDI (*p* value)	0.00145 (0.39110)	0.00001 (0.00022)	0.00050 (0.60983)

* Lower confidence limits calculated as negative were regarded as 0.

In most HAPIEE samples, the continuous vs. dichotomous high-risk SCORE, using both the original and extended models, demonstrated slightly higher values of such discrimination parameters as Harrell's C and Royston's R^2, which could be due to the dichotomisation-related loss of prognostic power (***Appendix IV***, **Tables A8.2.2-A8.2.3**). At the same time, LRT *p* values and IDI values were more or less similar for the instruments based on dichotomous and continuous high-risk SCORE. In addition, LRT *p* values and IDI values were relatively close for high and low-risk dichotomous SCORE-derived models, despite the fact that the values of Harrell's C and Royston's R^2 for the latter vs. former SCORE version were slightly higher in men and slightly lower in women (**Tables A8.2.4-A8.2.5**). Comparing discrimination parameters of the instruments based on low-risk dichotomous vs. continuous SCORE, or high vs. low-risk continuous SCORE (**Tables A8.2.6-A8.2.7**), provided similar results. Most importantly, the findings for continuous high-risk, dichotomous low-risk, and continuous low-risk SCORE versions were consistent with the evidence obtained for the officially recommended SCORE algorithm (dichotomous high-risk scale): the inclusion of binge drinking and/or positive CAGE in the original SCORE either did not affect or only marginally improved the model discrimination.

In summary, the investigation of the hazardous drinking-extended SCORE performance in HAPIEE samples (Research Objective 5b) has shown that adding binge drinking and positive CAGE to the original instrument did not result in a marked improvement of calibration and/or discrimination of the prognostic model. Alcohol-extended models, based on the dichotomous high-risk SCORE, explained only 7-29% and 19-51% of the outcome variation in HAPIEE men and women, respectively. The degree of discrimination improvement for these extended models, quantified by IDI, was under 1% in all samples. The failure of binge drinking and CAGE to add prognostic value to the SCORE instrument could be, at least partly, explained by the relatively short follow-up time and limited outcome numbers in the samples. In women, the prevalence of self-reported hazardous drinking was low, which also restricted the analysis power.

It is possible that the 10-year follow-up data will demonstrate the additional value of hazardous drinking characteristics in predicting the risk of CVD mortality among HAPIEE participants. However, the current evidence disagrees with the fourth research hypothesis and is instead consistent that SCORE performance in HAPIEE does not improve, or improves only marginally, after the inclusion of binge drinking and/or

positive CAGE in the original instrument. Together with the data which demonstrated a modest improvement in calibration and discrimination for the education and/or marital status-extended models (***Section 7.2***), these findings support the use of the original SCORE in CEE/FSU populations. To investigate whether this conclusion is still relevant when the effect estimates from different MONICA and HAPIEE samples are pooled, the overall strength of the association between SCORE and fatal CVD was assessed before and after the adjustment for socioeconomic and alcohol consumption parameters, using the random effects meta-analysis technique. The results of these combined analyses are presented in ***Chapter 9***.

Chapter 9. SCORE as a predictor of atherosclerotic CVD mortality in pooled analyses

As demonstrated in ***Chapters 6-8***, SCORE was a significant predictor of fatal atherosclerotic CVD in most MONICA and HAPIEE samples, both before and after adjustment for various measures of socioeconomic position or hazardous drinking. However, this association was less consistent for lower education and/or non-married status, which were linked to CVD mortality in some, but not all, MONICA and HAPIEE samples. There was no evidence of independent associations between binge drinking or CAGE score and the current risk of cardiovascular death in HAPIEE samples. Moreover, the magnitude of the impact of socioeconomic parameters and hazardous drinking characteristics on the main association of interest varied considerably across individual samples.

One of the possible explanations for this inconsistency could be the limited sample sizes and outcome numbers in the study-, country-, and gender-specific analyses. The pooling of the individual-level observations into one dataset was not possible, due to the inability to gain direct access to the Russian MONICA data, as well as due to marked cross-sample differences in the strength of the associations between CVD mortality, SCORE, socioeconomic parameters, and alcohol consumption characteristics. Producing combined estimates of calibration and discrimination for the original and extended SCORE models did not appear feasible without pooling the individual-level data. However, it was possible to pool the SCORE effect estimates (HR and 95% CI) from MONICA and HAPIEE samples, using the random effects meta-analysis technique which provides more conservative results than the fixed effects approach (***Methods***, ***Section 4.5.4***).

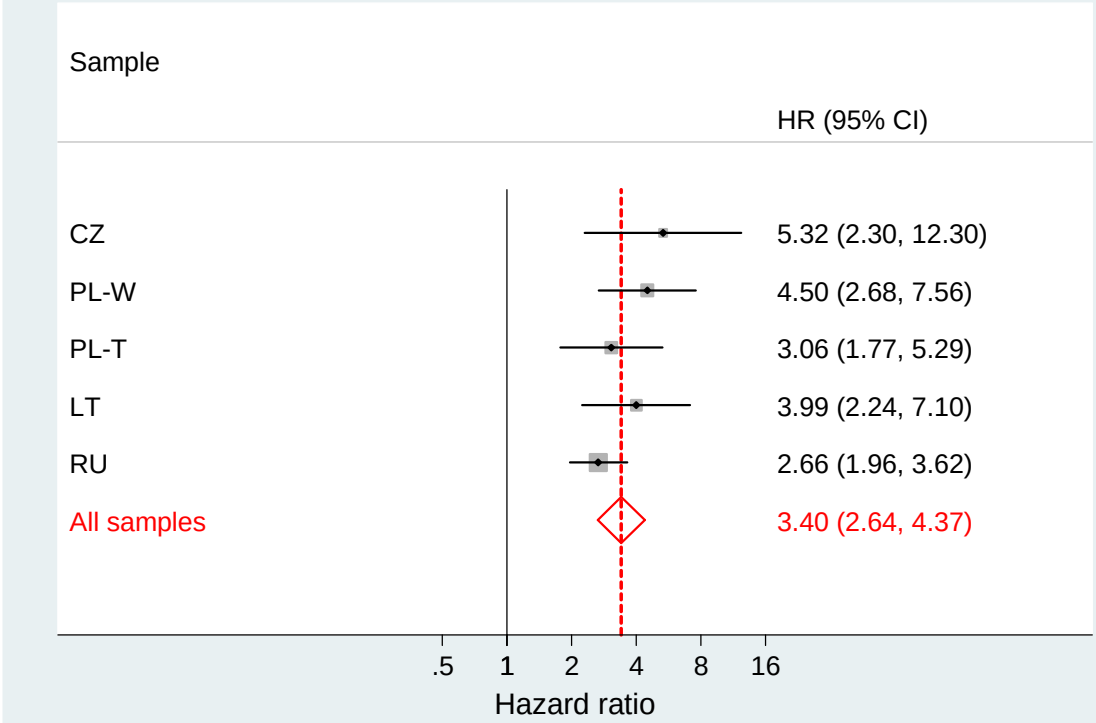
9.1. SCORE as a predictor of atherosclerotic CVD mortality in pooled unadjusted analyses

The first step of the combined analyses was to assess the role of positive SCORE (≥5%) as a predictor of fatal atherosclerotic CVD in all MONICA and all HAPIEE samples, separately for men and women (Research Objective 6). Pooled analyses were focused on the dichotomous high-risk SCORE, which is the instrument officially recommended for use in CEE/FSU populations.

9.1.1. SCORE in pooled unadjusted analyses: combining effect estimates from individual MONICA samples

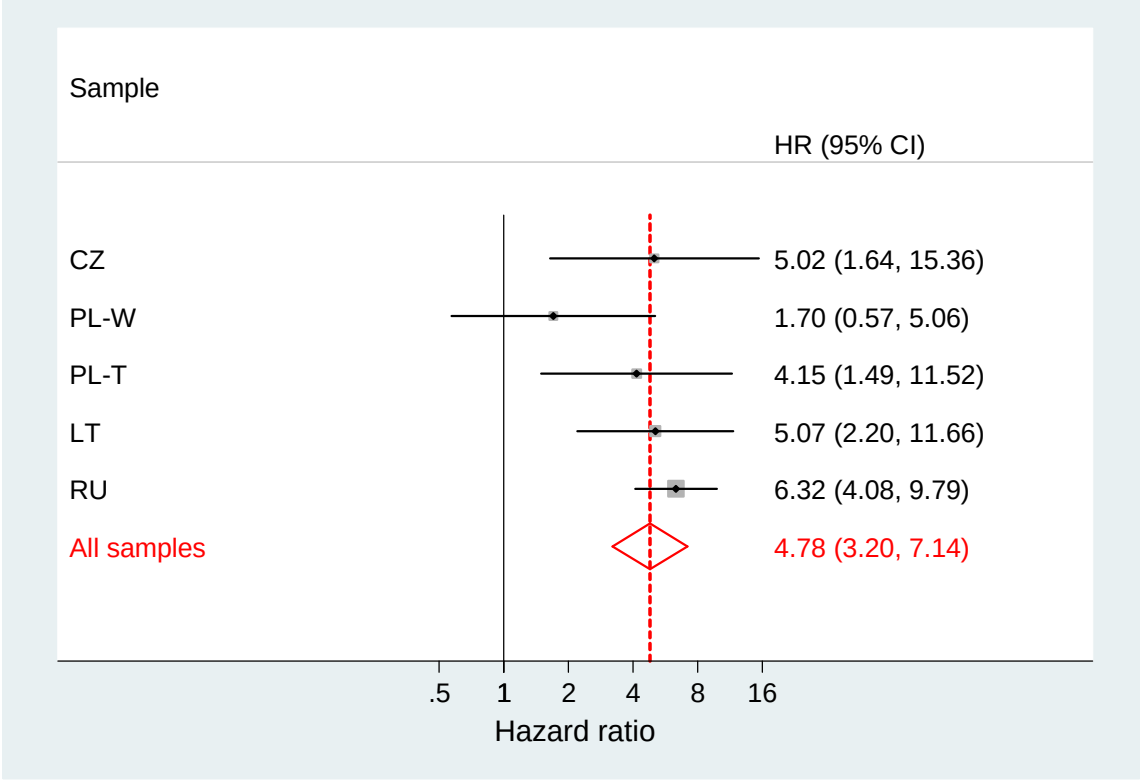
In most MONICA samples, the high-risk SCORE ≥5% was significantly associated with fatal atherosclerotic CVD (***Section 6.1.1***). The data on sample-specific effect estimates, as well as the combined HR and 95% CI, are presented in **Figures 9.1.1-9.1.2**. While among men, sample-specific HR values varied from 2.7 in Russia to 5.3 in the Czech Republic, none of the 95% CI included 1.0 (**Figure 9.1.1**). In accordance with these findings, the combined analysis demonstrated that positive SCORE was significantly associated with an increased 10-year risk of cardiovascular mortality, with a pooled HR of 3.4 and a relatively narrow 95% CI.

Figure 9.1.1. Dichotomous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men: sample-specific and combined hazard ratios and 95% confidence intervals



In all female MONICA samples, the high-risk SCORE ≥5% was linked to a higher risk of atherosclerotic CVD death. However, due to lower outcome numbers in women than in men, 95% CI were relatively wide and, for Warsaw females, even included 1.0 (**Figure 9.1.2**). The pooling of the sample-specific effect estimates produced a narrower 95% CI and a combined HR of 4.8.

Figure 9.1.2. Dichotomous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA women: sample-specific and combined hazard ratios and 95% confidence intervals

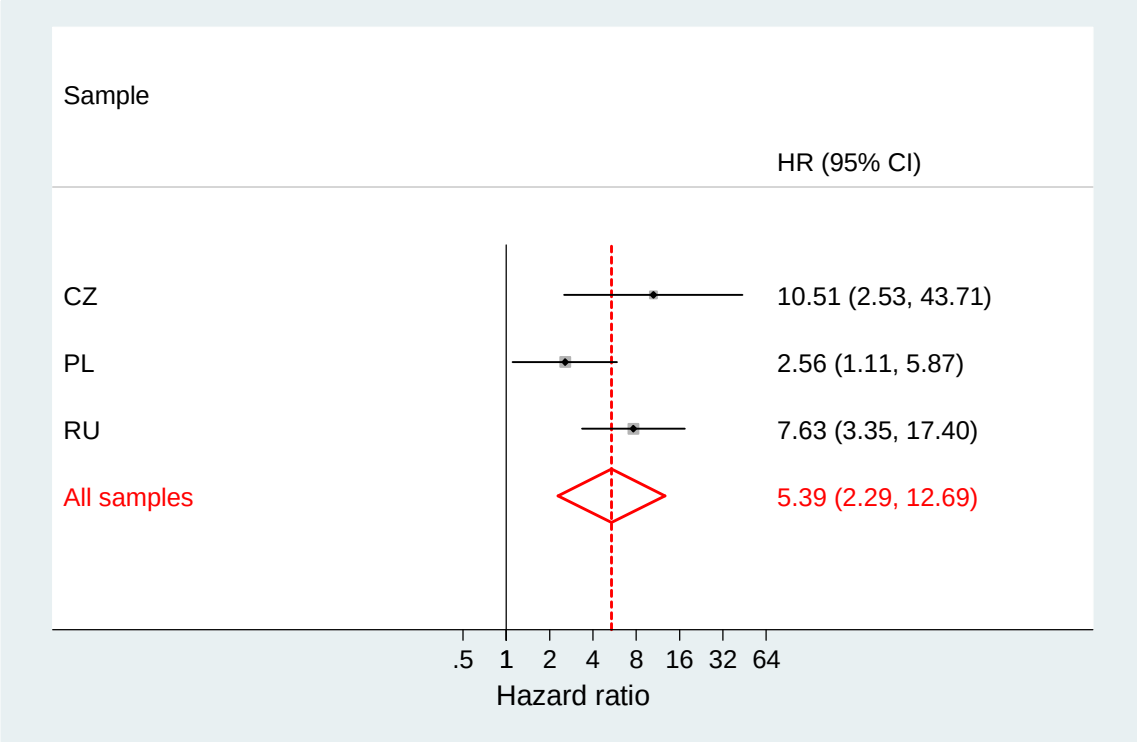


It might appear that positive SCORE was associated with a higher CVD risk in MONICA women, compared to MONICA men (respective HR 4.8 vs. 3.4). Nevertheless, this difference should be interpreted with caution, since the respective 95% CI overlapped. The next section investigates the magnitude and statistical significance of the pooled unadjusted association between SCORE and fatal CVD in contemporary HAPIEE samples.

9.1.2. SCORE in pooled unadjusted analyses: combining effect estimates from individual HAPIEE samples

Among HAPIEE men, positive SCORE was a significant predictor of fatal atherosclerotic CVD, but the sample-specific HR varied considerably, from 2.6 in Poland to 10.5 in the Czech Republic (**Figure 9.1.3**). The combined 95% CI was still relatively wide, due to the current HAPIEE follow-up being under 10 years, and, hence, the limited number of outcomes. The overall HR was 5.4, somewhat higher than the combined effect estimate for MONICA men (3.4).

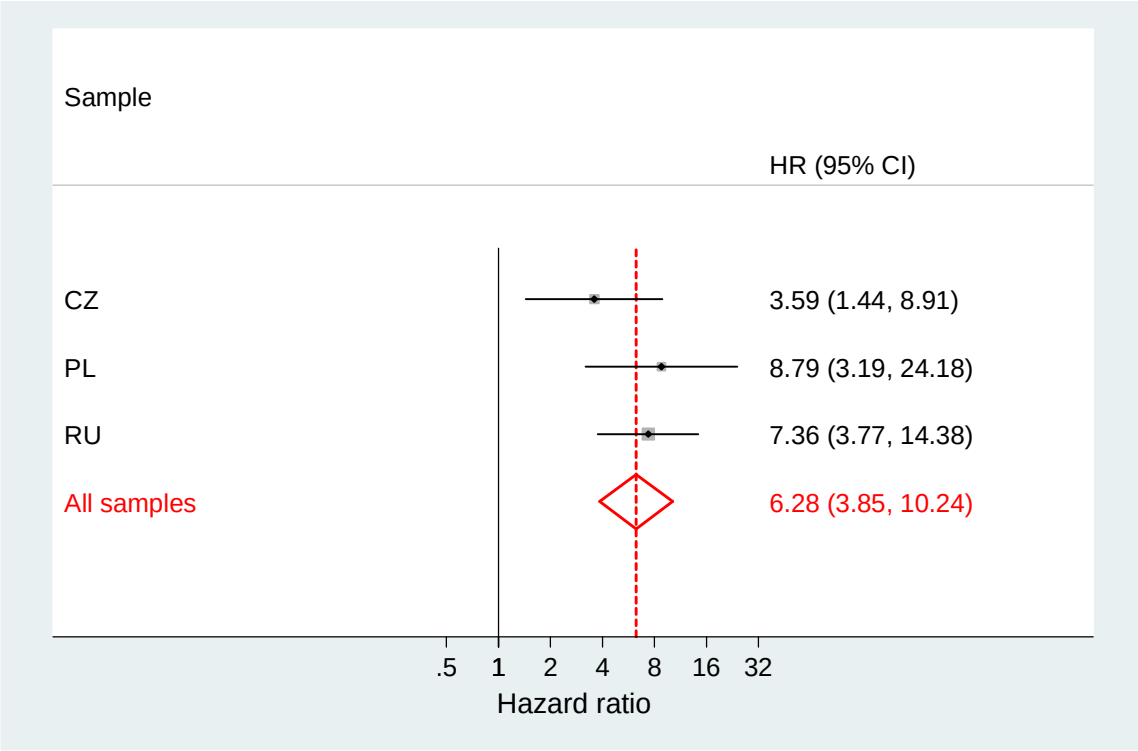
Figure 9.1.3. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE men: sample-specific and combined hazard ratios and 95% confidence intervals



One of the possible explanations could be the follow-up difference for HAPIEE vs. MONICA. When the 10-year data are available for HAPIEE samples, the combined HR could become closer to the MONICA value. This scenario is supported by the current overlap of the respective 95% CI. Additional explanation of the difference between MONICA vs. HAPIEE SCORE HR could be potential residual confounding by multiple extra risk determinants not included in SCORE. The effects of these measured (socioeconomic parameters or hazardous drinking characteristics) and non-measured factors could vary across populations and over time and, therefore, affect the magnitude of the SCORE-fatal CVD association to a different extent.

Among HAPIEE women, relatively low outcome numbers resulted in wide sample-specific 95% CI, as well as in the substantially varying HR values (**Figure 9.1.4**). The combined HR (6.3) was somewhat higher than the respective values for HAPIEE men (5.4) or MONICA women (4.8), probably due to chance. All pooled 95% CI for these three HR considerably overlapped, and it is possible that after 10 years of HAPIEE follow-up, the respective combined effect estimates will be relatively close to one another. The currently observed SCORE HR discrepancies could also be due to the differential effect of multiple potential confounders on the association of interest.

Figure 9.1.4. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE women: sample-specific and combined hazard ratios and 95% confidence intervals



Thus, the combination of the sample-specific results by study and gender in the random effects meta-analyses confirmed the significant association between the high-risk SCORE ≥5% and cardiovascular mortality in MONICA and HAPIEE men and women, which supports the first research hypothesis. The overall increase in the risk of fatal CVD was at least three-fold in MONICA and at least five-fold in HAPIEE. The difference between gender-specific pooled estimates for MONICA vs. HAPIEE could be partly explained by a shorter follow-up, fewer outcomes, and limited analysis power for HAPIEE samples. Moreover, while the SCORE model is based on the proportional hazards assumption (satisfied by both MONICA and HAPIEE data; ***Methods***, ***Section 4.5.4***) and, hence, suggests relative stability of SCORE HR values, there is still room for potential residual confounding by manifold non-classical risk factors. In this thesis, additional risk determinants included socioeconomic parameters and hazardous drinking characteristics. ***Sections 9.2-9.3*** evaluate the changes in strength and statistical significance of the pooled association between positive SCORE and atherosclerotic CVD mortality after adjustment for these risk factors.

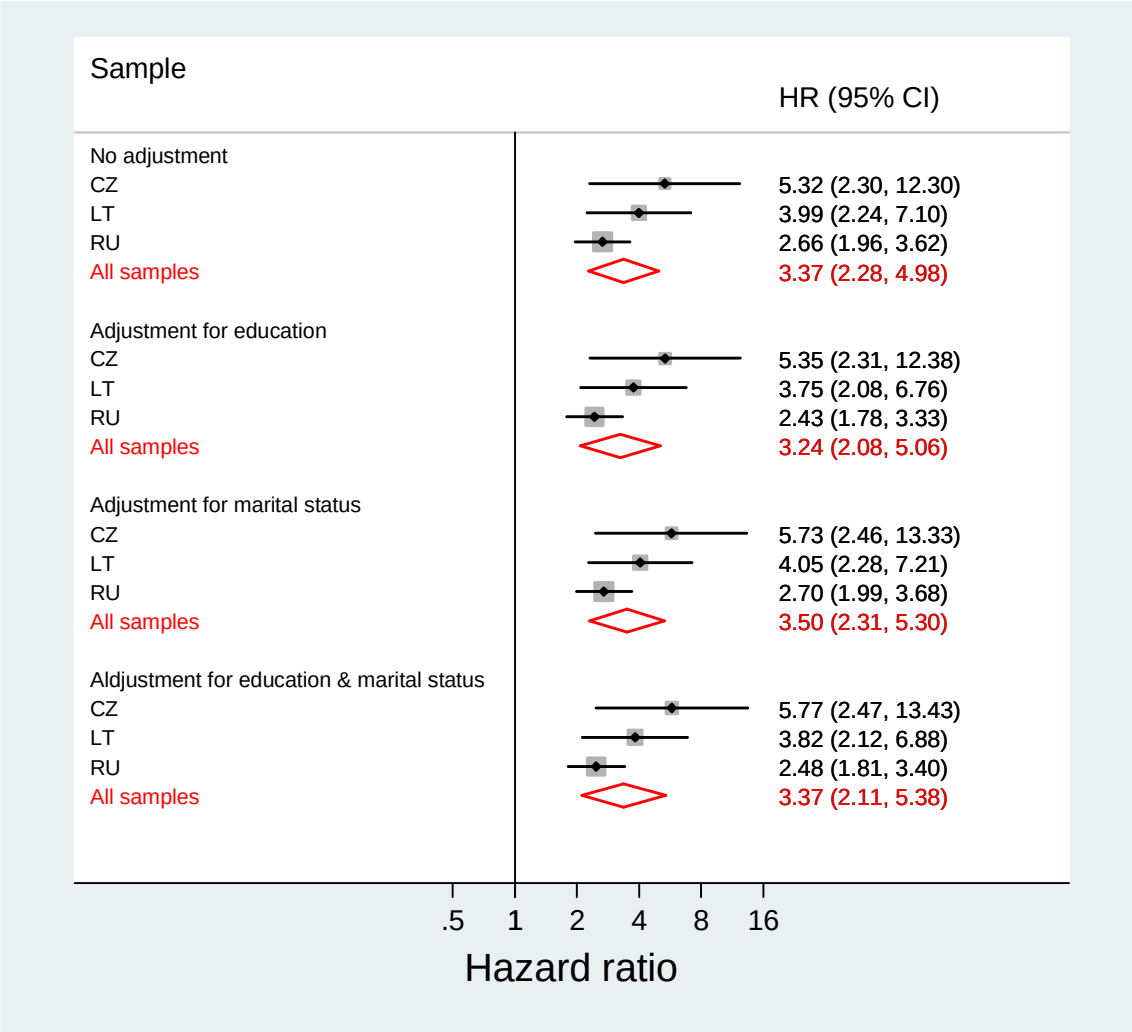
9.2. SCORE as a predictor of atherosclerotic CVD mortality in pooled analyses adjusted for education and marital status

Across individual MONICA and HAPIEE samples, positive SCORE was shown to predict cardiovascular risk even after adjustment for education and marital status (***Section 7.1***), and the combined unadjusted effect of SCORE on fatal CVD risk was significant in the random effects meta-analyses (***Section 9.1***). To check whether this pooled effect changed after controlling for socioeconomic measures of interest, the respective adjusted sample-specific HR were combined, separately for men and women. Since for MONICA participants from Warsaw and Tarnobrzeg, the association between SCORE and fatal CVD could not be controlled for marital status (these data were unavailable for Polish MONICA samples), the present analysis of MONICA data included only samples from the Czech Republic, Lithuania, and Russia.

9.2.1. SCORE in pooled analyses adjusted for socioeconomic parameters: combining effect estimates from individual MONICA samples

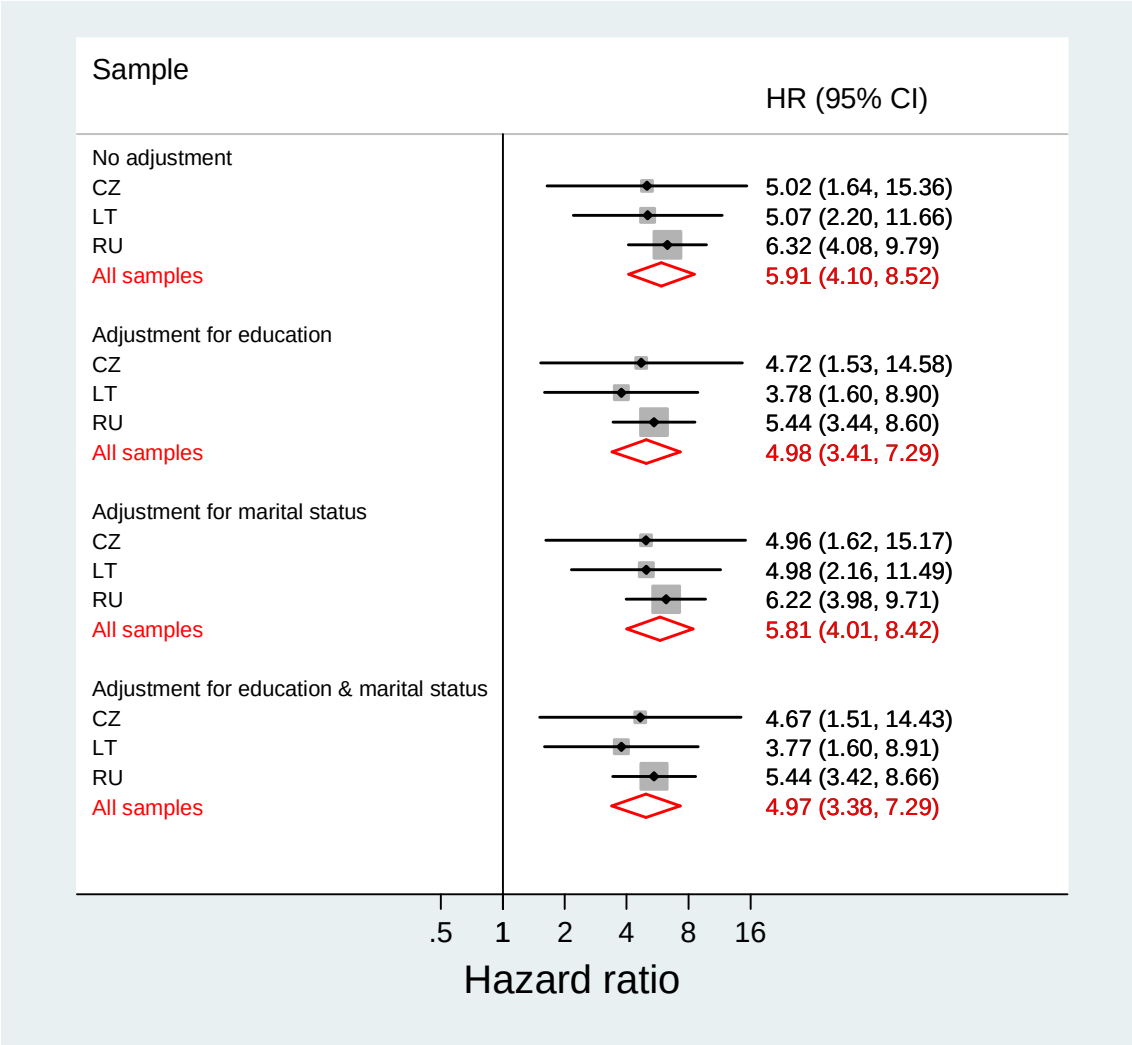
In MONICA men, the adjustment for education marginally weakened the overall association between SCORE and 10-year atherosclerotic CVD mortality (unadjusted vs. adjusted HR 3.4 vs. 3.2) and did not result in the loss of statistical significance (**Figure 9.2.1**, top and upper middle panels). Controlling for marital status slightly increased the combined HR to 3.5 (**Figure 9.2.1**, lower middle panel). The SCORE-CVD association did not change its magnitude substantially when the effects of both socioeconomic parameters were taken into account, as demonstrated by the education and marital status-adjusted HR of 3.4 (**Figure 9.2.1**, bottom panel). These findings suggest only a modest impact of education and/or marital status on the association of interest and also confirm the existence of the significant, education and marital status-independent link between the high-risk SCORE ≥5% and the 10-year atherosclerotic CVD mortality among MONICA men.

Figure 9.2.1. Dichotomous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for education (*upper middle panel*), marital status (*lower middle panel*), and education and marital status (*bottom panel*)



Similar to men, controlling for education slightly reduced HR for the overall SCORE-fatal CVD association among MONICA women from the Czech Republic, Lithuania, and Russia (unadjusted vs. adjusted combined HR 5.9 vs. 5.0), without affecting its statistical significance (**Figure 9.2.2**, top and upper middle panels). However, in contrast to their male peers, MONICA women demonstrated a modest HR reduction (HR 5.8) after accounting for marital status (**Figure 9.2.2**, lower middle panel). As a result, taking into consideration the impact of both socioeconomic characteristics weakened the association of interest to some extent, as demonstrated by the difference between the unadjusted HR of 5.9 and the education and marital status-adjusted HR of 5.0 (**Figure 9.2.2**, bottom panel).

Figure 9.2.2. Dichotomous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA women: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for education (*upper middle panel*), marital status (*lower middle panel*), and education and marital status (*bottom panel*)



While the changes in HR were more pronounced for women than for men, these findings might be partly explained by lower outcome numbers in female participants. In addition, although marital status and, to a greater extent, education appeared to affect the association between SCORE and cardiovascular atherosclerotic mortality in women, the magnitude of this impact was relatively modest. The closeness of the non-adjusted and the education and marital status-adjusted HR and 95% CI supports the role of positive SCORE as a statistically significant, independent predictor of fatal CVD among Czech, Lithuanian, and Russian females.

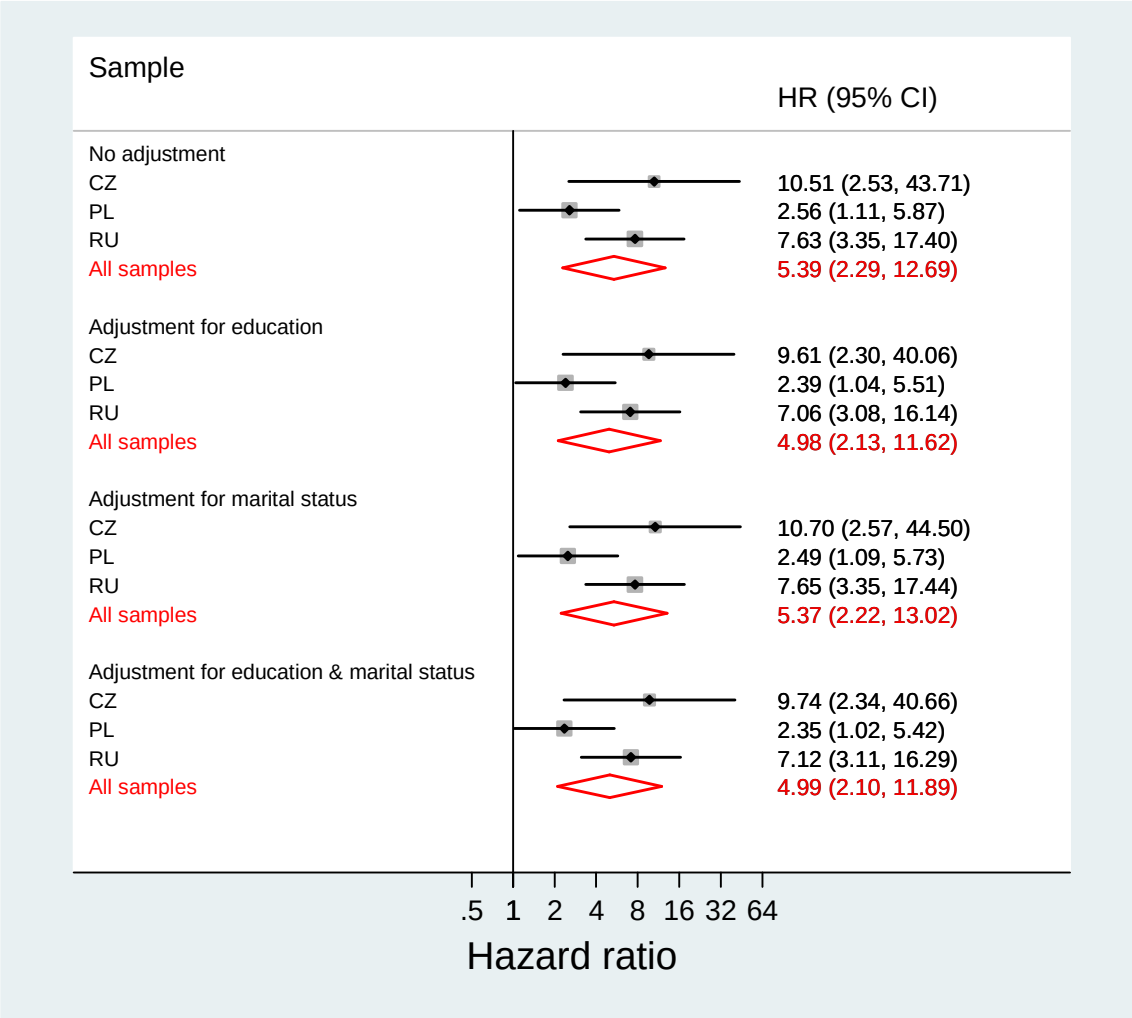
Therefore, according to the results of the random effects meta-analyses, the high-risk SCORE ≥5% significantly predicted 10-year atherosclerotic CVD mortality among

MONICA men and women, even after controlling for the socioeconomic parameters of interest. To compare these findings with the results obtained in contemporary CEE/FSU settings, the next step was to perform similar meta-analyses for male and female HAPIEE samples.

9.2.2. SCORE in pooled analyses adjusted for socioeconomic parameters: combining effect estimates from individual HAPIEE samples

Among HAPIEE men, the strength of the pooled association between positive SCORE and fatal CVD somewhat decreased after controlling for education (unadjusted vs. adjusted HR 5.4 vs. 5.0) (**Figure 9.2.3**, top and upper middle panels). Once accounted for marital status, the combined effect estimate barely changed (HR 5.4), which suggests that the association of interest could be affected more by education than by marital status (**Figure 9.2.3**, lower middle panel). Finally, when the combined association between positive SCORE and the currently observed atherosclerotic CVD mortality was adjusted for both education and marital status, its strength slightly reduced, as denoted by the HR of 5.0 (**Figure 9.2.3**, bottom panel). However, the high-risk SCORE ≥5% remained a statistically significant predictor of cardiovascular death in HAPIEE men, even after accounting for both socioeconomic parameters of interest.

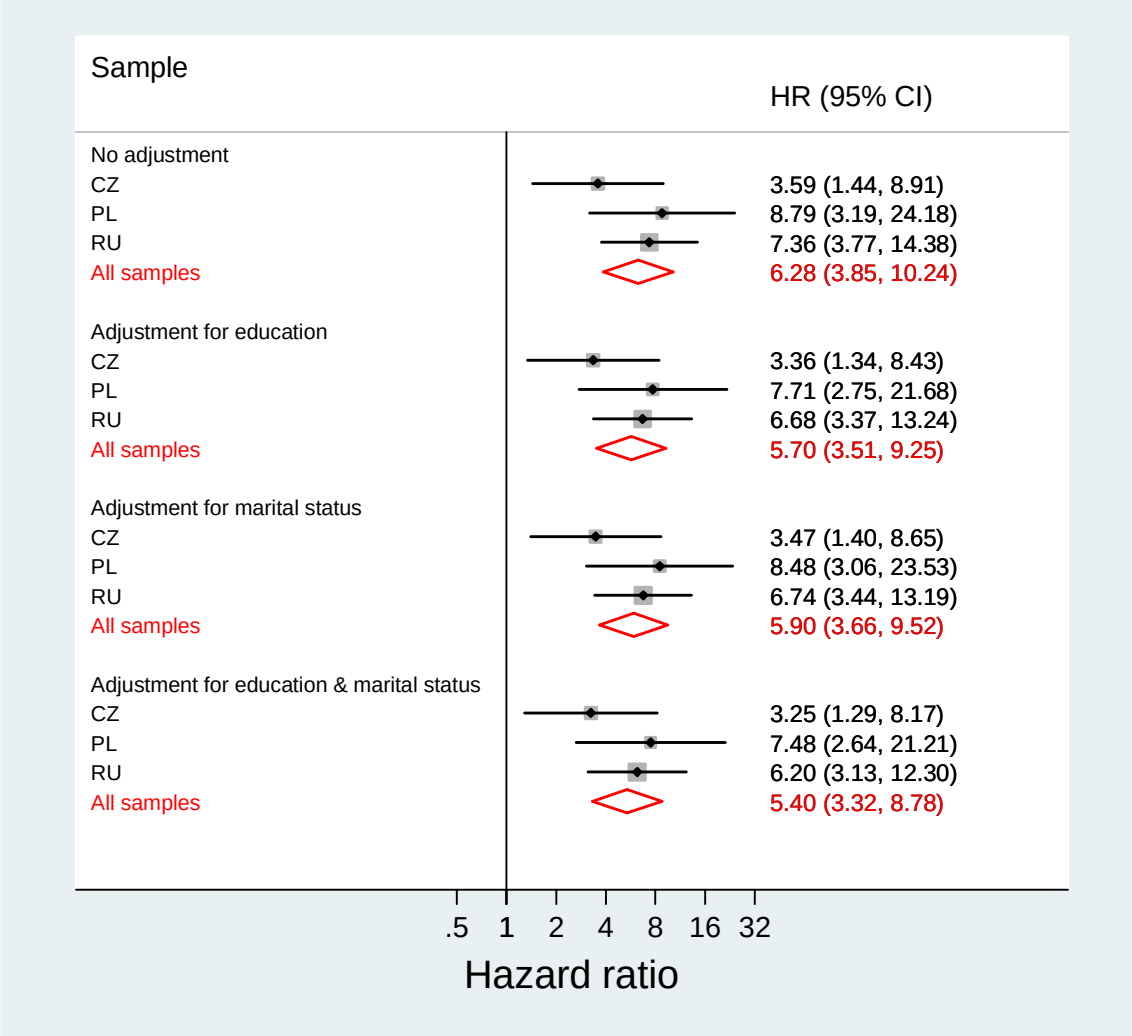
Figure 9.2.3. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE men: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for education (*upper middle panel*), marital status (*lower middle panel*), and education and marital status (*bottom panel*)



The combined analysis of the significant SCORE-fatal CVD association in HAPIEE women demonstrated some reduction in HR values (from 6.3 to 5.7) after adjustment for education (**Figure 9.2.4**, top and upper middle panel). Accounting for the effect of marital status also reduced the strength of this association, but the impact of marital status appeared to be slightly smaller than that for education, as suggested by adjusted HR of 5.9 (**Figure 9.2.4**, lower middle panel). The education and marital status-adjusted link between SCORE ≥5% and atherosclerotic CVD death was slightly weaker than the unadjusted association (pooled adjusted HR 5.4), but still statistically significant (**Figure 9.2.4**, bottom panel). Therefore, although the effect of SCORE as a cardiovascular risk predictor in women could be, to some extent, explained by the impact of education and marital status, the overall magnitude of the risk increase among

females with SCORE ≥5% was at least five-fold, even after adjustment for these socioeconomic characteristics.

Figure 9.2.4. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE women: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for education (*upper middle panel*), marital status (*lower middle panel*), and education and marital status (*bottom panel*)



To summarise ***Section 9.2***, the results of the random effects meta-analyses demonstrated that in MONICA and HAPIEE men and women, the high-risk SCORE ≥5% predicted the risk of atherosclerotic CVD mortality, independently of the impact of education and marital status. This is consistent with the first research hypothesis of SCORE as a significant determinant of cardiovascular risk. Moreover, these findings, together with the absence of marked improvement in the SCORE model performance after adding

education and/or marital status (***Section 7.2***), support the use of the original SCORE instrument in CEE/FSU populations.

Overall adjusted effects of positive SCORE on the fatal CVD risk were comparable for MONICA and HAPIEE women (pooled HR 5.0 and 5.4, respectively), but somewhat lower for MONICA men than for their HAPIEE peers (respective HR 3.4 vs. 5.0), which could partly be due to the current HAPIEE follow-up being under 10 years and, therefore, restricted outcome numbers and larger random errors. When the 10-year HAPIEE data become available, they may demonstrate that the strength of the SCORE-fatal CVD association is similar to that in MONICA men. This possibility is indirectly supported by the currently observed overlap between the pooled adjusted 95% CI for MONICA and HAPIEE men, as well as by the closeness of the SCORE effect estimates for MONICA and HAPIEE women. In addition, the impact of measured and non-measured non-classical risk factors on the association between SCORE and cardiovascular mortality could vary across populations and over time, and, hence, might affect the magnitude of this association both in individual samples and in combined analyses.

In this thesis, additional risk predictors included not only socioeconomic parameters, but also measures of hazardous alcohol consumption. The overall strength of the hazardous drinking-adjusted associations between SCORE and fatal CVD will be addressed in the following section.

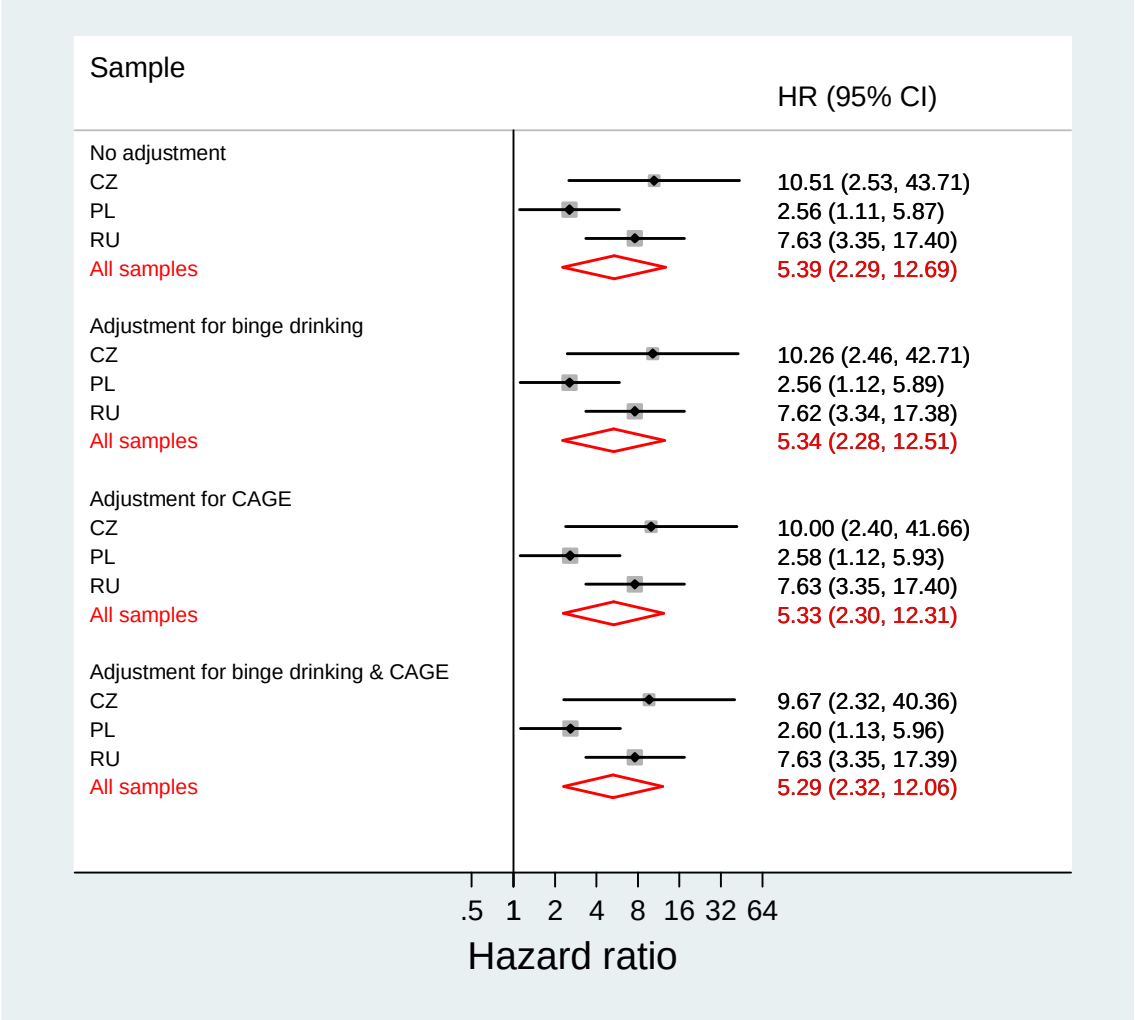
9.3. SCORE as a predictor of atherosclerotic CVD mortality in pooled analyses adjusted for binge drinking and CAGE

Positive SCORE appeared to be a hazardous drinking-independent determinant of fatal CVD risk across individual HAPIEE samples (see ***Section 8.1***). Moreover, the combined unadjusted effect of SCORE on cardiovascular risk was significant for both HAPIEE men and women (***Section 9.1.2***). Therefore, the next step was to check whether this pooled effect remained statistically significant after controlling for hazardous alcohol consumption, by combining the respective adjusted effect estimates in the gender-specific meta-analytic models.

Adjustment for binge drinking barely affected the strength of the link between SCORE and the risk of atherosclerotic CVD mortality in HAPIEE men, as demonstrated by unadjusted vs. adjusted HR of 5.4 vs. 5.3 (**Figure 9.3.1**, top and upper middle panels).

Similarly, controlling for another measure of hazardous drinking – CAGE score ≥2 – did not substantially weaken the significant link (adjusted HR 5.3) between positive SCORE and cardiovascular risk (**Figure 9.3.1**, lower middle panel). When the SCORE-fatal CVD association was adjusted for both bingeing and CAGE, the reduction in its magnitude was minimal (adjusted HR 5.3) (**Figure 9.3.1**, bottom panel). These findings support the independent role of SCORE ≥5% as a predictor of cardiovascular mortality in HAPIEE men.

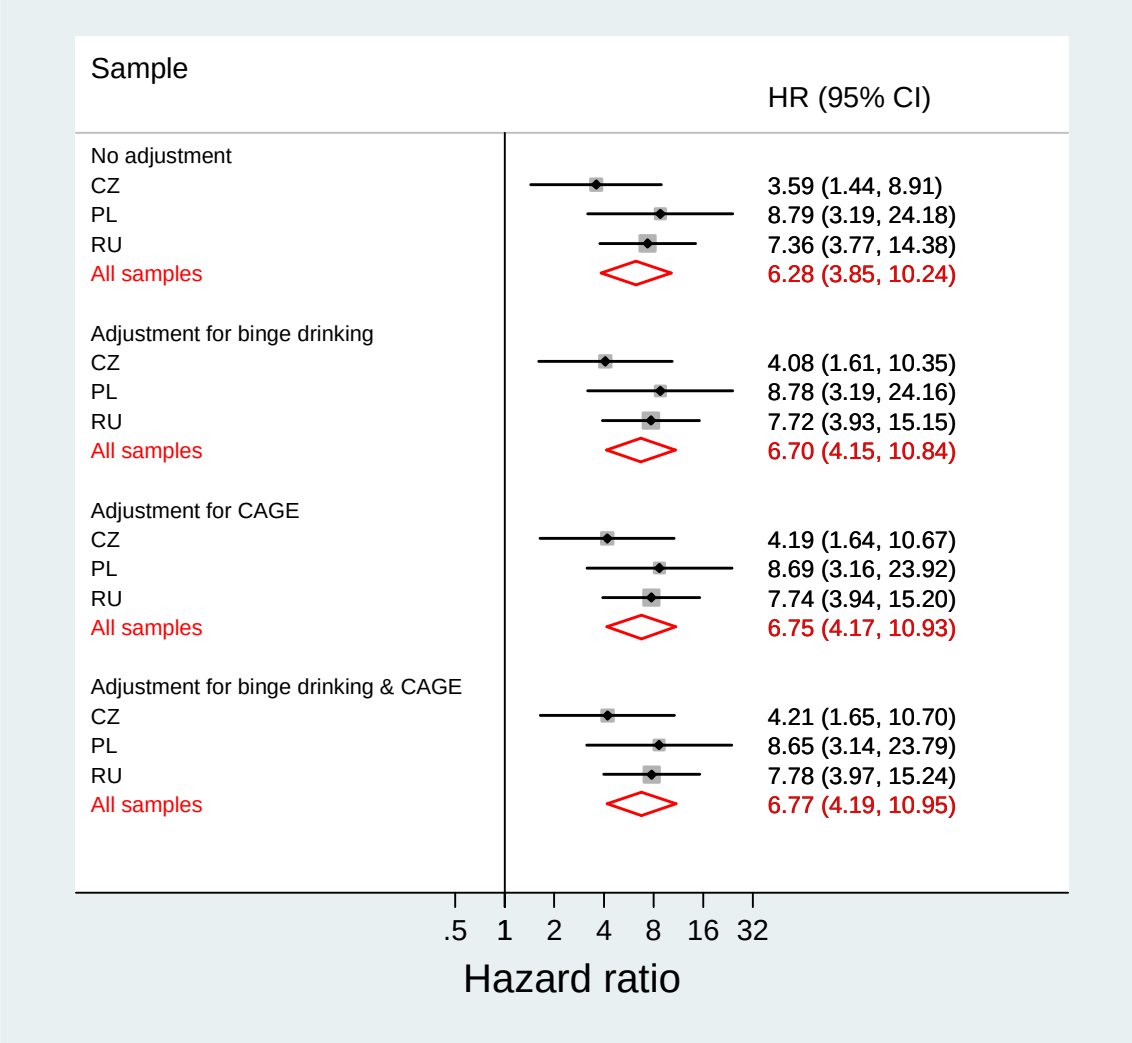
Figure 9.3.1. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE men: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for binge drinking (*upper middle panel*), CAGE (*lower middle panel*), and binge drinking and CAGE (*bottom panel*)



In contrast to men, HAPIEE women showed some increase in the combined effect estimate after controlling for binge drinking, from 6.3 to 6.7, respectively (**Figure 9.3.2**, top and upper middle panels). The significant association between the high-risk SCORE

≥5% and the currently observed CVD mortality also became somewhat stronger, once the impact of CAGE was taken into account (pooled adjusted HR 6.8) (**Figure 9.3.2**, lower middle panel). Similarly, controlling for the detrimental effects of both hazardous drinking measures slightly increased the pooled HR to 6.8 (**Figure 9.3.2**, bottom panel).

Figure 9.3.2. Dichotomous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE women: sample-specific and combined hazard ratios and 95% confidence intervals before adjustment (*top panel*) and after adjustment for binge drinking (*upper middle panel*), CAGE (*lower middle panel*), and binge drinking and CAGE (*bottom panel*)



The magnitude of the association between positive SCORE and fatal CVD appeared to be larger in HAPIEE females, compared to their male peers, as demonstrated by the respective binge drinking and CAGE-adjusted HR of 6.8 vs. 5.3. However, these results require a cautious interpretation. First, both 95% CI were not only wide, possibly due to the current follow-up being under 10 years, but also overlapped considerably. Second,

for HAPIEE women, the self-reported prevalence of binge drinking and/or CAGE ≥2 was low, especially in Poland, which resulted in limited outcome numbers among female bingers or CAGE-positives. Third, since in CEE/FSU populations, drinking remains less culturally acceptable for women than for men[298;301;364], the gender-specific misreporting of hazardous alcohol consumption could partly affect the magnitude of the adjusted SCORE-fatal CVD association. Overall, a very modest change in the strength of the main association of interest after adjustment for hazardous drinking, together with the absence of prognostic performance improvement for the SCORE model extended by binge drinking and/or CAGE (see ***Section 8.2***), supports the use of the original SCORE in CEE/FSU.

The meta-analysis findings were consistent with the sample-specific results and, in agreement with the first research hypothesis, confirmed that among HAPIEE men and women, the high-risk SCORE ≥5% was a statistically significant and hazardous drinking-independent determinant of atherosclerotic cardiovascular death. Among men, the overall strength of the association of interest was comparable after adjustment for binge drinking and CAGE (HR 5.3) and after controlling for education and marital status (HR 5.0). However, in women, accounting for both hazardous drinking parameters increased the combined HR to 6.8, while adjustment for both socioeconomic measures reduced it to 5.4. This discrepancy should be interpreted with caution, due to the very low outcome numbers across the small-sized subgroups of female bingers and/or CAGE-positives. Only when the 10-year follow-up data become available, will it be seen whether the strength of the link between SCORE and fatal CVD in HAPIEE women increases after controlling for hazardous drinking, or whether it does not change substantially, similar to the results for HAPIEE men.

To conclude ***Chapter 9***, positive SCORE has been shown to predict CVD mortality significantly and independently of either socioeconomic characteristics or hazardous drinking parameters, not only across individual MONICA and HAPIEE male and female samples, but also in the random effects meta-analyses, which additionally supports the first research hypothesis.

Therefore, in ***Chapters 5-9***, various aspects of SCORE performance in MONICA and HAPIEE samples were studied, comparing predicted, observed, and estimated levels of atherosclerotic CVD mortality, and investigating not only the two versions of the original SCORE scale, but also the models extended by socioeconomic parameters or by

measures of hazardous alcohol consumption. The main findings of the thesis will be summarised in the first section of the next chapter.

Chapter 10. Discussion

This chapter summarises the results of the thesis and then discusses its methodological limitations and strengths. A critical analysis of the findings, placed in a broader context of the evidence available from the existing literature, is also presented. The future directions of CVD risk assessment and reduction are debated. The chapter closes with research and policy implications and overall conclusions of the thesis.

10.1. Summary of the findings

The main findings of the thesis can be summarised as follows. First, the positive SCORE (≥5% as assessed by the high-risk version of this scale, recommended by the European Society of Cardiology) was a significant predictor of atherosclerotic CVD mortality across MONICA and HAPIEE samples and in both genders, which confirmed the first research hypothesis.

Second, the calibration of the non-extended high-risk SCORE was good in most MONICA samples, with the exception of Russia where the observed risk was substantially higher than the SCORE predictions. Comparing the estimated 10-year CVD mortality in HAPIEE samples with the predictions by high and low-risk SCORE versions showed that better calibration could be achieved by the high-risk SCORE in Russian samples and by the low-risk SCORE in Czech and Polish samples. Most discrimination parameters of the high-risk SCORE were satisfactory in the majority of MONICA and HAPIEE samples. These findings were consistent with the second hypothesis of varying SCORE calibration, despite its satisfactory discrimination, across the CEE/FSU populations of interest.

Third, education and marital status were significantly and independently from SCORE associated with atherosclerotic CVD mortality in some, but not all, MONICA and HAPIEE samples. However, the inclusion of these additional risk determinants in the prognostic model did not substantially improve its calibration and discrimination parameters, which does not support third research hypothesis and justifies the use of the original SCORE scale.

Fourth, the inclusion of binge drinking or positive CAGE in the SCORE model either did not change or only marginally improved its calibration and discrimination

parameters. These findings fail to support the fourth research hypothesis and to warrant the extension of SCORE by hazardous drinking characteristics.

Finally, the question of the strength and independence of the associations between SCORE and fatal CVD was revisited in the meta-analyses of sample-specific effect estimates. The pooled associations between the high-risk SCORE ≥5% and atherosclerotic cardiovascular death remained statistically significant and independent of socioeconomic measures, or hazardous drinking characteristics.

10.2. Methodological limitations and strengths of the present study

Before discussing the results of the present study in the context of the external evidence, it is important to highlight some methodological aspects of this thesis. In particular, the use of data from two separate studies, MONICA and HAPIEE, is discussed in this section, as well as representativeness of the samples, response rates, and data comparability. The issues of random error, study power, data missingness, and systematic error are also debated, followed by the analysis of the limitations and strengths of the SCORE model and additional risk factors. The last part of the section outlines other methodological issues, such as the evolving nature of the presently available measures of prognostic performance.

10.2.1. Use of the data from two separate studies

The major feature of the thesis was the employment of several datasets from two separate studies, MONICA and HAPIEE. These studies were conducted during two different historical periods: the MONICA follow-up typically lasted from the mid-1980s to the mid-1990s, while HAPIEE started in 2002-2004 and is ongoing. These two studies included different samples, rather than the same re-examined and followed-up subjects. For the region of interest, MONICA and HAPIEE data are the best available approximations of the national levels of cardiovascular risk factors and fatal CVD, respectively, for the 1980-1990s (the period characterized by the divergence of CVD rates in CEE/FSU) and the 2000s (the period of continuing decline in fatal CVD across CEE vs. fluctuating, but still high CVD levels in FSU).

While at present, MONICA data might appear to possess mostly historical interest, their strength is the availability of the 10-year follow-up information, which is required to adequately assess SCORE calibration and discrimination. As the HAPIEE study started in the early 2000s, the 10-year follow-up results will be unavailable for the next few

years. Nonetheless, the HAPIEE data better reflect the current levels of CVD and its determinants in the region of interest, and also provide additional information on novel risk factors (for example, alcohol consumption). Moreover, the 10-year levels of atherosclerotic cardiovascular mortality in HAPIEE samples, as well as the 10-year SCORE calibration, could be estimated, based on the MONICA mortality patterns or the exponential survival model.

10.2.2. Sample representativeness

In both MONICA and HAPIEE studies, the subjects were randomly selected from the population registers in the Czech Republic, Poland, and Lithuania, and electoral lists in Russia. The characteristics of six districts in the Czech Republic, two Warsaw districts and the towns and rural communities of the Tarnobrzeg province in Poland, Kaunas in Lithuania, and three Novosibirsk districts in Russia are generally considered as satisfactory approximations of the national levels of CVD, cardiovascular risk factors, and additional risk determinants.[42;159;160;323] Although predominantly urban HAPIEE samples are not entirely representative of the populations of whole countries, it can be assumed that overall, cardiovascular risk profiles, socioeconomic characteristics, drinking patterns, and CVD mortality in Czech towns, Krakow, and Novosibirsk satisfactorily approximate those in urban populations of the Czech Republic, Poland, and Russia, respectively.[297;300;301;365]

10.2.3. Response rates

Another factor, restricting generalizability of the MONICA and HAPIEE results, was non-response to the baseline survey. Although within specific countries, MONICA response rates somewhat declined over time (***Methods***, ***Section 4.1.1***), the lowest rates were 60% or higher. Similarly, the percentage of HAPIEE responders (approximately 60%) reflects the general trend of declining response rates in population studies.[43] Although these figures are similar to the response rates observed in other contemporary studies in CEE/FSU or elsewhere (e.g.[366-368]), it is likely that MONICA and HAPIEE participants were healthier and more affluent, compared to the non-responders. For example, the HAPIEE non-responders from Poland had substantially higher all-cause mortality than their peers who participated in the study (Professor A. Pajak, personal communication).

As baseline SCORE levels could not be measured in MONICA and HAPIEE non-responders, the strength of the SCORE-fatal CVD link also could not be assessed in

these individuals. The extent of the "healthy volunteer" effect, when the study non-responders tend to be less healthy than responders (e.g.[369-371]), could vary across populations and especially over time, which might affect the between-sample comparisons of the main association of interest. Although the "healthy volunteer" phenomenon could weaken the strength of this association, the real sample-specific effects were unlikely to be lower than the ones observed.

An additional problem was non-response to clinical examination, which is particularly relevant to the Czech and Lithuanian MONICA samples and Czech and Polish HAPIEE samples (for example, approximately 20% of Czech HAPIEE participants did not attend the clinic). The resulting missingness of the baseline SCORE data appeared to be non-random, as suggested by the typically higher levels of total and CVD mortality across study and country-specific subgroups with missing vs. available SCORE (for details, see ***Methods, Section 4.5.1***). The potential implications and solutions for the problem of SCORE data missingness are discussed in more detail in ***Section 10.2.6.***

Therefore, the MONICA and HAPIEE samples were not entirely representative of the respective national populations, and their estimates of cardiovascular mortality and risk factors were, to some extent, affected by non-response. However, no better individual-level datasets are presently available for the assessment of cardiovascular risk factors and CVD mortality in CEE/FSU populations. The present investigation of SCORE prognostic performance could be regarded as a useful step in the complex process of SCORE recalibration for CEE/FSU (see ***Section 10.4.1***).

10.2.4. Data comparability

Although this thesis used data from four countries for MONICA and three countries for HAPIEE, the comparability of the international baseline and prospective data could be regarded as high. Within each study, the same methods were used for all centres, and the protocols of the cardiovascular part of both MONICA and HAPIEE were very close. In MONICA and HAPIEE, the baseline survey and physical examination were performed by trained study personnel, according to standardized methods, with internal and external quality control. The individual-level data on cause-specific mortality were also obtained similarly for both studies, via the same national or local mortality registers.

10.2.5. Random error and study power

In order to assess the role of chance as a possible explanation of MONICA and HAPIEE findings and to represent the most likely effect estimates in the study populations, 95% CI were calculated for all HR. As the number of statistical tests was relatively large, some "statistically significant" results might be due to chance. However, the main association of interest (SCORE-fatal CVD) was consistently positive and significant at the different analysis steps, for both genders, across countries, and over time, which makes chance an unlikely explanation. All research hypotheses were formulated *a priori*, before performing statistical analyses. The results of this thesis appear to be plausible and consistent with the extensive external evidence base, confirming that SCORE is a reliable predictor of cardiovascular mortality.

As described in ***Methods*** (***Section 4.4***), the study power, based on the confidence level of 95% and the minimal increase of 25% in the risk of fatal CVD among the participants with SCORE ≥5% vs. <5%, was at least 80% across all MONICA and HAPIEE samples. Multiple regression analyses, adjusting the association of interest for socioeconomic characteristics and alcohol consumption parameters, would inevitably reduce the study power. This was, to some extent, addressed by assessing the magnitude of the pooled association in the random effects meta-analyses (***Chapter 9***).

The statistical power of a risk assessment study depends not only on the sample size and prognostic ability of the predictors, but also on the number of events or, more specifically, the number of "events per variable" (EPV) which is calculated as the outcome number divided by the number of predictors in the model.[69;327;372;373] According to the current consensus, advised EPV values are ≥10, in order to provide stable coefficient estimates for individual predictors[69;327;372;373], although recently, a more relaxed approach has been introduced, with EPV of 5-9 considered acceptable.[374]

Since MONICA and HAPIEE studies were not designed specifically for the assessment of prognostic performance of extended risk models, EPV values were reasonably high for some, but not all, country- and gender-specific samples (**Table 10.2.1**). For the original, non-extended SCORE model (one predictor), EPV exceeded 10 for all samples. For the models extended by one additional risk factor (either education, or marital status, or binge drinking, or CAGE, in addition to SCORE; two predictors in total), EPV values were maximal in Russian MONICA men (90.5) and minimal in Czech MONICA women (6.5). Finally, for the SCORE instrument extended either by

two socioeconomic parameters, or by two hazardous drinking characteristics (three predictors in total), EPV were expectedly lower and ranged from 60.3 in Russian MONICA men to 4.3 in Czech MONICA women.

Table 10.2.1. Number of events per variable (EPV) for original and extended SCORE models: MONICA and HAPIEE samples

	EPV	
	Men	*Women*
MONICA		
Czech Republic		
SCORE	32	13
SCORE + one extra predictor	16	6.5
SCORE + two extra predictors	10.7	4.3
Poland (Warsaw)		
SCORE	86	21
SCORE + one extra predictor	43	10.5
SCORE + two extra predictors	28.7	7
Poland (Tarnobrzeg)		
SCORE	62	19
SCORE + one extra predictor	31	9.5
SCORE + two extra predictors	20.7	6.3
Lithuania		
SCORE	58	26
SCORE + one extra predictor	29	13
SCORE + two extra predictors	19.3	8.7
Russia		
SCORE	181	86
SCORE + one extra predictor	90.5	43
SCORE + two extra predictors	60.3	28.7
HAPIEE		
Czech Republic		
SCORE	37	19
SCORE + one extra predictor	18.5	9.5
SCORE + two extra predictors	12.3	6.3
Poland		
SCORE	34	16
SCORE + one extra predictor	17	8
SCORE + two extra predictors	11.3	5.3
Russia		
SCORE	105	42
SCORE + one extra predictor	52.5	21
SCORE + two extra predictors	35	14

Thus, the thesis findings require cautious interpretation for the samples with lower EPV, such as Czech MONICA men and women, or Polish HAPIEE women. The results for these samples should be regarded as lacking clear evidence of prognostic performance improvement for the extended SCORE, rather than definitely proving the absence of such an improvement.

10.2.6. Missing data

Another important factor limiting the study power was the missingness of baseline SCORE values, due to non-attendance or incompleteness of the clinical examination in some MONICA (the Czech Republic and Lithuania) and HAPIEE samples (the Czech Republic and Poland) (see ***Chapter 5***). Participants with missing baseline values of TCH and/or SBP were excluded from survival analyses and analyses of SCORE prognostic performance. This analytical strategy is in agreement with the so-called complete case approach, which has been extensively used in the area of cardiovascular risk assessment (e.g.[33;99;235;261;328-330]).

However, the complete case approach reduces the sample size and outcome numbers and decreases the study precision and power.[335;339;375;376] An alternative would be multiple imputation, which allows for missing data uncertainty, by creating numerous different imputed datasets and combining their results, and produces valid interferences, due to averaging the missing data distribution based on observed data (e.g.[334;336;338-340;375;377]). The available multiple imputation methods are typically based on the assumption of data missing at random, or completely at random.[23;332-337] Baseline SCORE values in MONICA and HAPIEE appeared to be missing not at random, and the missingness patterns varied across samples (***Methods***, ***Section 4.5.1***). Since using the imputation techniques which are based on the random missingness assumption for the analysis of MONICA and HAPIEE data could produce biased results[338-341], the present study employed the compete case approach.

As excluding the observations with non-randomly missing values cannot be entirely bias-free (for example[334;337-339]), the complete case approach could have, to some extent, affected the strength of the SCORE-fatal CVD association in MONICA and HAPIEE samples. Nonetheless, it has previously been demonstrated that among the second-stage non-responders (people who participated in the initial health interview survey, but failed to take part in the following health examination), the predicted levels of major CVD risk factors, such as TCH or SBP, were within 95% CI of the respective values in the participants who attended the examination.[378] Moreover, the relationships between selected interview variables and several health outcomes (e.g., poor self-rated health and longstanding illness) were not affected substantially when the analyses were confined only to the health examination participants.[378] As the second-stage non-response rate in the above-cited study (49%) was higher than in Czech and Lithuanian MONICA

samples (<30%) or Czech and Polish HAPIEE samples (<22%), these findings support the validity of MONICA and HAPIEE estimates. In another study, the associations between baseline cardiovascular risk factors and subsequent CVD mortality were shown to be unaffected by the resurvey non-response.[331]

The absence of a marked non-responder bias, as reported by Boshuizen and colleagues[378], could be explained by the fact that second-stage non-responders comprise a mixture of groups with different reasons for not participating, different connections between these reasons and health outcomes, and, hence, potential partial cancellation of the non-response influences. This explanation is consistent with the findings of the present research (results available on request) which suggested that in HAPIEE, some examination non-responders were "too ill", as denoted, for example, by worse self-rated health, while others were "too healthy", reporting no previous CVD diagnosis, hospitalisation, or treatment (in MONICA, similar analyses of second-stage non-response were not feasible, due to limited availability of covariate data). Therefore, it is not possible to predict the magnitude, or even the direction, of the difference in the SCORE-fatal CVD association between participants with complete examination data vs. those with missing TCH and/or SBP values.

Finally, the strength of the association between the high-risk dichotomous SCORE and atherosclerotic fatal CVD was assessed in the Cox regression analyses using not only complete, but also multiply imputed data for the samples with the highest proportion of missing baseline SCORE values – Czech and Lithuanian MONICA and Czech and Polish HAPIEE (for the description of the imputation model, see ***Section 4.5.1***). Across these samples, the HR values were very close for both approaches (***Sections 6.1.1-6.1.2***), which suggested that the results of the complete case MONICA and HAPIEE analyses were unlikely to be markedly biased.

10.2.7. Misclassification

As some of the variables assessed in this thesis were self-reported (such as prevalent CVD at baseline, smoking, education, marital status, binge drinking, and CAGE), both non-differential and differential misclassification might have taken place. Non-differential misclassification would reduce the strength of the associations between exposure variables and the outcome of interest, while differential misclassification could lead to both under- and over-estimation of these associations.

While the probability of exposure misclassification during the baseline interviews and examinations in MONICA and HAPIEE could not be excluded completely, it was minimized via the use of standard questionnaires, protocols, and procedures by well-qualified local research personnel. Due to the prospective nature of the study, the assessment of baseline exposures and covariates took place before the outcome data were available. Participants whose higher cardiovascular risk levels were known to their relatives, general practitioners, and other health professionals might have been more likely to be assigned an atherosclerotic CVD cause of death, compared to their peers without known elevation of cardiovascular risk. However, the ascertainment of the outcome was performed by the local mortality register personnel, who were not aware of the clinical characteristics of the MONICA or HAPIEE subjects.

The present study excluded people with self-reported pre-existing CVD, such as earlier diagnosed CHD or stroke (***Methods***, ***Section 4.1***). These prevalent CVD cases were not verified against medical records in MONICA or HAPIEE samples.[42;43] There is a possibility that some subjects without valid CHD or stroke diagnosis could be wrongly excluded from the present analyses. Since non-fatal CVD tends to be over-reported across populations, mostly due to poor discrimination between different types of cardiovascular events[379-381], this scenario was more likely than the opposite situation, when participants with earlier diagnosed CVD did not report it at baseline and, hence, were erroneously included in the analyses. Excluding participants who wrongly reported prevalent CVD could potentially reduce the outcome numbers, affect the study power, and dilute the main association of interest, between baseline SCORE levels in CVD-free people and subsequent cardiovascular mortality.

The estimates of self-reported smoking status in epidemiological surveys have been shown to be reasonably accurate and only slightly different from the data obtained by the so-called gold standard methods, such as carbon monoxide or cotinine measurements.[382-384] Due to lower cultural acceptability of female smoking in Russia[385;386], some under-reporting was possible among women from Novosibirsk. Similarly, smoking could be under-reported by Lithuanian women, although there are no published studies confirming this possibility. The risk of misclassification of baseline SBP and TCH levels was likely to be similar in participants who subsequently did or did not develop fatal atherosclerotic CVD. In HAPIEE, TCH measurements were performed by local laboratories, and, hence, systematic between-country differences

could not be excluded. However, it is not possible to speculate on the direction and magnitude of the potential impact of these differences on the SCORE performance across countries. Moreover, the findings of country-specific analyses were unlikely to be affected. The potential problem of SBP and TCH regression to the mean is discussed in ***Section 10.2.8(b)***.

The possibility that education and marital status categories were misreported was low. Even if there was some misclassification across their full scales, it should not have substantially affected the results, as both socioeconomic parameters were dichotomised (lower vs. higher education, and married vs. non-married status; for further discussion on dichotomisation of additional risk factors, see ***Section 10.2.9(b)***).

All data of alcohol consumption were self-reported by HAPIEE participants. This could result in over- or, more likely, under-estimation of drinking patterns. However, first, it is known that the GF method, employed in HAPIEE, under-estimates alcohol consumption to a lesser extent than other techniques.[311;320] Second, the degree of drinking under-reporting is expected to have a lower magnitude than in Western populations, since alcohol does not seem to be associated with social stigma in male CEE/FSU populations.[297;300;301;387-389] Third, it was demonstrated earlier that self-reported drinking correlated with serum gamma-glutamiltransferase (GGT) concentrations in a subsample of Russian MONICA men.[297;300] In other words, self-reported drinking measures, despite under-estimating the actual consumption, still satisfactorily reflect the ranking of participants in terms of their drinking behaviour. Accordingly, in the HAPIEE participants who would later develop or not develop fatal atherosclerotic CVD, the degree of hazardous drinking under-reporting was likely to be similar. Such a non-differential misclassification would weaken the association between alcohol and CVD mortality and, hence, undermine the prognostic value of hazardous drinking measures as cardiovascular risk determinants. This should also be the case for the Polish HAPIEE sample, where a wrongly imposed filter question in the health questionnaire resulted in additional, albeit non-differential, under-reporting of alcohol consumption frequency.

A possibility for differential misclassification of drinking measures would, however, arise if HAPIEE subjects with more hazardous drinking patterns and at a higher CVD risk under-reported their alcohol consumption to a greater extent than non-hazardous drinkers. This is particularly relevant to HAPIEE women, since traditionally, female

drinking is socially stigmatized in the CEE/FSU populations.[298;301;364;390] In addition, non-conventional measures of hazardous drinking, such as surrogate/non-beverage alcohol consumption, *zapoi*, or frequent hangovers[391;392], which can be more strongly related to cardiovascular risk, were not measured in HAPIEE samples at baseline. This could lead to under-estimation of the link between alcohol and fatal CVD, due to both selection bias (subjects with positive non-conventional measures of hazardous drinking less likely to participate) and information bias (incomplete drinking information obtained from the participants). The above-mentioned factors might, to some extent, explain the lack of an independent association between hazardous drinking and CVD mortality observed across HAPIEE samples (***Section 10.3.4***).

Differential misclassification of the outcome could happen if the registration of fatal atherosclerotic CVD was less likely in disadvantaged people (those with lower education and/or non-married status) or hazardous drinkers (bingers and CAGE-positives). However, for all MONICA and HAPIEE samples, mortality registers covered the whole population of the respective district, city, region, or country, and combined various sources of mortality data. The outcomes of interest could still be missed, if the participant moved out of the coverage area, but the likelihood of moving out was expected to be lower for people experiencing socioeconomic disadvantage or hazardous drinking.

Another possibility for differential outcome misclassification would occur if fatalities of other aetiology among those with additional risk exposures (namely, adverse socioeconomic circumstances or hazardous alcohol consumption) were coded as atherosclerotic CVD deaths. It has been suggested that a substantial proportion of "coronary deaths" in Russians is presented by alcohol-related deaths, such as alcohol poisoning or alcoholic cardiomyopathy.[169;200;201;310;393] If that was true for HAPIEE participants, fatal CVD would be over-diagnosed in hazardous drinkers, compared to their peers who did not report hazardous drinking at baseline. This would result in a stronger and more consistent association between alcohol and cardiovascular mortality than was observed. Neither bingeing nor CAGE were significant predictors of CVD death in any of the HAPIEE samples (***Section 8.1***), and therefore, it is unlikely that baseline hazardous drinking was linked to a higher chance of misclassifying the cause of death as atherosclerotic fatal CVD.

10.2.8. Limitations and strengths of SCORE as a prognostic model

The primary methodological tool of this thesis was the SCORE model of cardiovascular risk. The intrinsic limitations and strengths of SCORE have been reflected in the analyses of MONICA and HAPIEE data, as discussed in this section.

a) Probability approach

The key limitation that SCORE shares with most other risk prediction instruments is related to the considerable non-reducible variability of the binary outcome data. While a model can successfully predict the proportion of people with/without an outcome at a pre-specified time point, it is still uncertain for individual participants whether they survive or not, and what is their individual survival time with a relatively narrow confidence interval.[40;394] This limitation is the major explanation of the fact that discrimination parameters did not reach "ideal" values (such as AUROC/C-statistic of 1.0) in MONICA and HAPIEE data analyses, as well as in many other studies.

Despite the innate uncertainty of the assessment of fatal CVD risk over the next 10 years, SCORE provides point estimates of the predicted risk without any CI. Ignoring this uncertainty, which arises from variability of regression coefficients in the statistical model, the population-level distribution of risk predictors, and "behaviour" of individual atherosclerotic plaques[58;73;395], can create a false sense of precision in both clinicians and patients, when SCORE is used for the prediction of individual cardiovascular risk levels. At the same time, all evidence-based practice currently employs the application of average population effects to individuals. A single-estimate approach also makes SCORE more user-friendly, more interpretable, and more applicable to the time-constrained clinical practice settings.[9;10]

b) Broad categorisation and cross-sectional assessment of SCORE components

Although some SCORE components, such as SPB and TCH, are essentially continuous variables, the SCORE chart presents them as rather arbitrary categories. While considering smoking status as a dichotomous parameter (presence vs. absence of current smoking) appears straightforward, it ignores such important characteristics of smoking-related behaviour as, for example, the number of cigarettes smoked daily, the specific quit date in ex-smokers, or passive smoking exposure. Categorization of continuous risk predictors leads to a loss of statistical power and residual confounding[59;76;78;82;325-327] (see ***Methods***, ***Section 4.3.2***). This SCORE limitation could not be completely resolved in the thesis; however, it was partly addressed by investigating the performance of

continuous vs. dichotomous SCORE instruments in MONICA and HAPIEE samples (***Section 10.2.8(c)***).

Due to potential regression to the mean, the levels of such risk factors as SBP and TCH could undergo systematic change over time, which may dilute the strength of their associations with cardiovascular outcomes.[132;177;244;396-399] It is also known that CVD treatment decreases the true effect of risk factors on the outcomes by up to 50%.[58;134] As the SCORE model does not account for these effects, it might over-predict the risk in people who start treatment after the initial examination. Since repeated measurements of major cardiovascular risk factors were not performed for most MONICA and HAPIEE samples, and the data on CVD treatment uptake were unavailable for both MONICA and HAPIEE, the present study focused on baseline levels of risk determinants. Ultimately, this approach agrees with the general concept of the SCORE instrument – assessment of the *10-year* risk based on *current* levels of risk factors.

c) Dichotomised risk threshold

SCORE not only categorises continuous risk factors, but also dichotomises the well-known phenomenon of cardiovascular risk continuum into lower vs. higher-risk, and establishes this threshold as a basis for withholding vs. starting therapeutic interventions. This has several implications. First, it has been shown that for most CVD risk assessment instruments, the risk cut-offs, or intervention thresholds, lack balance between sensitivity and specificity, which reflects the stochastic nature of any risk scale and, hence, the implicit limitations of any threshold.[100] Second, apart from the above-mentioned dangers of categorisation, dichotomisation of the continuous explanatory variables, as an "extreme form of rounding", could affect the overall predictive ability of the model.[325] In order to address this limitation, the performance of dichotomous vs. continuous SCORE instrument was evaluated across MONICA and HAPIEE samples; as expected, the continuous SCORE version demonstrated slightly better calibration and discrimination (***Sections 6.2*** and ***6.4***). Third, as age is the major determinant of risk level in any cardiovascular scale, including SCORE, the predicted mortality levels were relatively high in MONICA and HAPIEE participants, who were at least 40 years old at baseline. Subsequently, a considerable proportion of people at increased risk remained outcome-free, as demonstrated by low PPV values. Such an approach could potentially lead to unnecessary medicalization of otherwise healthy middle-aged and older

individuals[135;136], and needs to be counterbalanced by taking into account other traditional and novel factors influencing total cardiovascular risk.

Indeed, the current ESC guidelines on cardiovascular prevention explain that clinicians should consider numerous additional factors before deciding on the necessity of intervention[17], rather than be confined to the "black-and-white" thinking that risk 4% automatically means no intervention, and risk 6% means intervention. In the present analysis of MONICA and HAPIEE data, socioeconomic characteristics and hazardous drinking parameters were selected as extra predictors of interest which could affect the risk of atherosclerotic cardiovascular mortality in addition to, and independently from, SCORE-comprising factors. The strengths and limitations of these selected characteristics will be discussed in ***Section 10.2.9***.

d) Fatal atherosclerotic CVD as an outcome

SCORE estimates the 10-year risk of fatal atherosclerotic cardiac events and, hence, does not take into account the burden of CVD morbidity, which remains high, both in Europe as a whole and in CEE/FSU countries. On the other hand, the HAPIEE data on incident non-fatal CHD and stroke (results not presented) clearly demonstrate that CEE/FSU countries vary considerably in terms of the availability of information needed to validate and harmonise non-fatal CVD diagnoses. The cause-specific mortality data are much more comparable, both across the countries and over time. Although some context-specific systematic misclassification of outcomes within the broad category of atherosclerotic CVD deaths might occur, it was unlikely to affect the main association of interest, between SCORE and atherosclerotic cardiovascular mortality, in CEE/FSU populations.

e) Applicability of the high-risk SCORE version to CEE/FSU context

SCORE is the only cardiovascular risk scale which exists in two versions (high and low-risk) and, therefore, reflects Europe's heterogeneity in terms of the background risk. However, the high-risk version of SCORE, currently recommended for the CEE/FSU region, was, in fact, developed without using local data. As reported in ***Section 2.2.3***, the estimates based on the 30-year-old findings from Scandinavian cohorts could over-predict CVD mortality in some CEE/FSU countries and under-predict it elsewhere. Accordingly, across the contemporary HAPIEE samples, high-risk SCORE could substantially over-estimate the 10-year risk of fatal CVD in the Czech Republic and Poland, but not in Russia (see ***Section 6.3*** for the estimates of 10-year

SCORE calibration in HAPIEE). Adjusting, or recalibrating, the original SCORE instrument for specific CEE/FSU countries should improve the prognostic performance of this scale in the region of interest, as discussed in more detail in ***Section 10.4.1***.

10.2.9. Limitations and strengths of additional risk factors

When assessing such a multifaceted concept as cardiovascular risk as a whole, or even investigating only two of its determinants, namely socioeconomic disadvantage and hazardous drinking, residual confounding is hardly avoidable. Even a wide array of measures may not capture all the relevant aspects of socioeconomic milieu and alcohol consumption profile which may directly or indirectly influence the risk of cardiovascular pathology. In addition, a broader categorisation, such as dichotomisation, of additional risk parameters increases the risk of residual confounding. The limitations and strengths of the socioeconomic characteristics and drinking parameters employed in this thesis are discussed below.

a) Selection of socioeconomic parameters and alcohol consumption measures of interest

As outlined in ***Section 2.3.2*** (***Background***), no single "ideal" socioeconomic characteristic has been identified thus far for the CEE/FSU context (or elsewhere). When assessing socioeconomic CVD gradient in this region, it is advisable to consider several parameters reflecting different mechanisms of socioeconomic influences on CVD. Education and marital status refer to different pathways between socioeconomic/sociodemographic circumstances and cardiovascular health and disease (such as the acquisition of beneficial skills and assets for the former and familial and social connections for the latter; for details, see ***Section 2.3.2(d)***), and they both have been shown to independently predict CVD across Western and CEE/FSU populations. These routinely measured parameters were available for both MONICA and HAPIEE samples (with the exception of marital status data unavailability for Polish MONICA participants). They also did not demonstrate any marked statistical collinearity, which allowed their inclusion in the extended SCORE model not only separately, but also in combination (***Section 6.1***). In addition, the potential differences in the contextual meaning of lower education or non-married status across countries and over time, specifically in terms of their influence on cardiovascular risk, should not substantially affect the magnitude of the associations between socioeconomic parameters, SCORE,

and fatal CVD, as the performed analyses were study- (MONICA vs. HAPIEE) and country-specific.

In HAPIEE, additional socioeconomic parameters were measured, which included various characteristics of absolute and relative deprivation. However, the generalizability and clinical applicability of these results would be limited, since respective data are not routinely collected in epidemiological studies on CVD risk (hence, they were not available for MONICA samples) and are problematic to obtain in clinical practice settings. These extra socioeconomic measures also did not provide sufficient outcome numbers across original categories, and lacked pre-existing, accepted cut-off points for potential dichotomisation. Arbitrary dichotomisation of these measures would undermine the comparability of HAPIEE findings with external evidence. Therefore, although focusing on only two parameters, such as education and marital status, does not capture the complex phenomenon of socioeconomic and sociodemographic position of individuals[263;265], this restriction ensured data comparability not only across MONICA and HAPIEE samples, but also with other existing and future studies.

Currently, no single standardized, universally accepted measure of drinking patterns or hazardous drinking exists.[274;276] However, in this thesis, there were several reasons for concentrating on binge drinking and CAGE score as the selected characteristics of alcohol consumption, a multicomponent health behaviour. First, these parameters are relatively easy to measure and comparable across HAPIEE samples and with findings from other studies. Their validity and reliability in the HAPIEE population were previously demonstrated.[365] Second, there is a lack of universally accepted cut-off points for drinking amount measures as cardiovascular risk predictors.[276;288] In HAPIEE samples, alcohol consumption frequency could not be dichotomised, due to the J or U-shaped association with fatal CVD (***Section 8.1***). This non-linear association could be partly due to the well-known "sick quitter" effect.[273;274;276;280;285;363;400] The available data did not permit the differentiation between never-drinkers and ex-drinkers. Since excluding all self-reported "never-drinkers" from the analyses would result in a substantial sample size reduction, especially for HAPIEE women, it was decided to consider bingeing and CAGE as the main alcohol consumption parameters of interest. Although binge drinking and positive CAGE were more correlated than education and marital status (***Section 8.1***), the aim of this thesis was to explore the prognostic

performance of extended SCORE, rather than quantify the relative impact of hazardous drinking parameters as CVD risk predictors. Therefore, it was decided to simultaneously include bingeing and CAGE in the extended SCORE model.

Education, marital status, binge drinking, and CAGE are only few parameters out of the wide range of socioeconomic characteristics and alcohol consumption measures which potentially influence cardiovascular risk. Other components of these two important groups of CVD risk determinants will be further discussed in ***Section 10.4.3***.

b) Dichotomisation and cross-sectional assessment of additional risk factors

The limitations of categorising or dichotomising risk predictors, mentioned in ***Section 10.2.8(b)***, also apply to the socioeconomic parameters and hazardous drinking measures employed in this thesis. While the original categories of extra risk predictors were used in descriptive analyses, the estimation of prognostic performance of the extended SCORE models required dichotomisation, as the outcome numbers across original non-dichotomised categories were insufficient for performing analyses of adequate power (***Methods***, ***Section 4.3.3***). Broader categories of educational attainment or marital status were also more comparable across MONICA and HAPIEE samples. Moreover, bingeing and CAGE were originally constructed as dichotomous measures of hazardous drinking.

This thesis analysed only the baseline measures of socioeconomic circumstances and alcohol consumption. While educational attainment was expected to be relatively stable in the selected age groups, the other three parameters of interest (marital status, binge drinking, and CAGE) could change over the study time and possibly modify the level of CVD risk predicted at baseline. In addition, across HAPIEE samples, it was not feasible to differentiate not only between never- and ex-drinkers, but also between the subjects who could never be considered as binge drinkers and/or CAGE-positives from the people with previous history of hazardous drinking and, hence, higher "residual" cardiovascular risk.[311;398;401] These limitations might have affected the strength of the association between current hazardous alcohol consumption and fatal CVD in HAPIEE participants. At the same time, the evidence from the subsample of Russian MONICA men suggested that their drinking patterns were sufficiently stable over a six-year period.[300] Finally, focusing on the *current* levels of risk factors, whether classical or novel, such as socioeconomic disadvantage or hazardous drinking, in order to estimate

the *future* risk of cardiovascular outcomes, agrees with the general concept of total risk prediction (***Section 10.2.8(b)***).

c) Residual confounding

Socioeconomic disadvantage and hazardous drinking are only two groups of variables out of the wide array of additional, non-conventional risk determinants which might influence cardiovascular risk. Given the assumption of relatively stable and, hence, generalizable risk coefficients for SCORE[20], one of the possible explanations of slightly different SCORE HR across MONICA and HAPIEE samples could be the so-called "case-mix" phenomenon, which denotes dissimilarity in the distribution of predictors (both included and not included in the model) and outcomes between the participants in different centres or populations.[98;346;350;394;402]

Specifically, MONICA and HAPIEE samples could differ by the distribution of potential residual confounders – so-called "omitted predictors", which may still affect, to a varying extent, the strength of the main association of interest, as well as the performance of prognostic models. However, increasing the number of non-omitted predictors would reduce the power and precision of the analyses, via decreasing EPV values (***Section 10.2.5***). The justification, benefits, and limitations of extending cardiovascular risk models, such as SCORE, with new risk predictors will be discussed in ***Section 10.4.4***.

10.2.10. Other methodological issues

The results of MONICA and HAPIEE data analyses, presented in this thesis, could be partly explained by the employed statistical measures of model calibration and discrimination. Currently, no single parameter of prognostic performance can capture all the different aspects of risk prediction, and therefore, the use of multiple measures is recommended.[76] There is no "hierarchy" for different indices of prognostic performance, although discrimination is typically considered as a core, intrinsic property of the model, which, unlike calibration, cannot be adjusted in external populations. The discrimination measures which reflect the risk reclassification in the extended model are regarded as more sensitive to the positive changes in the model's performance, and also as more clinically relevant, with the potential to influence clinical decisions and outcomes (for details, see ***Methods***, ***Section 4.5.3***). Therefore, while several measures of calibration and discrimination of the original and extended SCORE models were assessed for MONICA and HAPIEE samples, the main focus was on the

practically relevant indices of reclassification, such as IDI. Relatively low IDI values, obtained for SCORE models after adding socioeconomic parameters or hazardous drinking characteristics, are in agreement with current external evidence: in attainable studies, the majority of extended risk models have demonstrated a very modest reclassification improvement.

In particular, in some studies, a model based on traditional cardiovascular risk factors was extended by a single additional risk predictor, for example, HDL-CH[71], glycated haemoglobin[35], fibrinogen[37], carotid-femoral pulse wave velocity[403], ankle-brachial index[184], or coronary artery calcification score.[36] In other studies, the model was expanded by different combinations of novel biomarkers, such as troponin I, N-terminal pro-brain natriuretic peptide, midregional proadrenomedullin, midregional proatrial natriuretic peptide, cystatin C, high-sensitivity C-reactive protein (hsCRP), fibrinogen, interleukin (IL) 6, IL-8, tumour necrosis factor (TNF) alpha, lipoprotein-associated phospholipase 2, glycated haemoglobin, or insulin-like growth factor-1 (e.g.[32-34;38;186]). A statistically significant improvement in AUROC/Harrell's C-statistic and/or significant NRI or IDI values for extended risk models have been demonstrated in some of these studies[32;33;36;38;71;186;403], but not in others.[34;35;37;184] Even when the discrimination improvement for the extended model was statistically significant, it was still modest in absolute terms: the maximal increase in AUROC/C-statistic was 0.10[33], while the highest IDI value was 12%.[38] Similarly, the extension of SCORE scale with HDL-CH[192], resting heart rate[193], or biochemical and instrumental markers of subclinical organ damage[194] increased AUROC/C-statistic values by 0.01-0.02, and NRI did not exceed 9%.

While the limited improvement in prognostic performance, observed across MONICA and HAPIEE samples, might be primarily related to the nature of extended models *per se* (***Section 10.2.9***), it could also be affected by the choice of statistical parameters. The recently introduced measures of prognostic performance, such as reclassification indices, are considered "work in progress", as, for example, the exact interpretation of IDI magnitude remains a challenge.[79;85;354;404] However, MONICA and HAPIEE results were generally consistent across all performance indices, which supported their validity.

To summarise ***Section 10.2***, this thesis has several limitations, such as the use of data from two separate studies, relatively low outcome numbers in some subgroup analyses, and limited follow-up length in HAPIEE. On the other hand, it also has some important

strengths, for instance, comparison of generally compatible prospective data across several CEE/FSU populations and over time; examination of several versions of the original SCORE instrument, as well as of the SCORE models extended by a range of additional risk factors; evaluation of sample-specific and combined effect estimates; and the assessment of numerous statistical measures of calibration and discrimination. These strengths support the validity of the results and enable the comparison of MONICA and HAPIEE findings with the results of other studies.

10.3. Consistency of the results with the evidence from other studies

In this section, the thesis findings are compared and contrasted with the data from other studies, performed both inside and outside the region of interest. The following issues are addressed: the prevalence of classical and additional cardiovascular risk factors and the levels of atherosclerotic CVD mortality (***Section 10.3.1***); performance of the original SCORE scale (***Section 10.3.2***); socioeconomic parameters and SCORE (***Section 10.3.3***); and alcohol consumption characteristics and SCORE (***Section 10.3.4***).

10.3.1. Distribution of cardiovascular risk factors and fatal CVD levels

The performance of cardiovascular risk scales, including SCORE, depends on the levels of the major risk factors, such as smoking, SBP, and TCH, and the levels of the baseline risk, i.e. population levels of CVD mortality. Therefore, it is important to compare these parameters in MONICA and HAPIEE samples not only between these two studies, but also to respective national levels, despite the limited representativeness of the former in regard to entire populations of the Czech Republic, Poland, Lithuania, and Russia. Similar comparison also needs to be performed for the additional cardiovascular risk determinants of interest, such as socioeconomic characteristics (namely, education and marital status) and alcohol consumption measures (binge drinking and CAGE). The rationale for these comparisons is to confirm that MONICA and HAPIEE levels of risk factors and CVD mortality adequately reflect the respective national cross-sectional estimates and trends and, hence, could be used for the investigation of SCORE performance in CEE/FSU settings.

Smoking: As outlined in ***Chapter 5***, both MONICA and HAPIEE samples demonstrated a relatively high, although not uniform, baseline prevalence of classical cardiovascular risk factors. In particular, smoking prevalence was over 30% in men from all MONICA samples, and exceeded 20% in Czech women and Polish women from Warsaw. By contrast, the proportion of smokers in Polish women from Tarnobrzeg

and their Lithuanian and Russian peers was under 10%. These findings generally agree with the relevant national data, collected independently from MONICA surveys and collated in the WHO Global InfoBase.[173] Thus, in the Czech Republic, the smoking prevalence in 35-64-year-old men and women, who participated in the 1993 Survey of the Health Status of the Czech Population, was 36.7% and 24.7%, respectively. In the urban Polish population, 53.9% of men and 48.2% of women aged over 16 years were current smokers (1986), while for the rural population, the respective figures were 35.5% and 14.7% (1985). In Lithuania, the national prevalence of current smoking in 1994 was 39.7% in 35-64-year-old men and 5.0% in women of the same age. According to the national data for 1996, as the year closest to the period of interest, smoking prevalence was 61.3% in Russian men aged 35-64 years, and 10.3% in their female peers.

In HAPIEE samples, compared to MONICA samples from the respective countries, smoking prevalence was lower among Czech and Polish men, relatively stable in Czech and Polish women or Russian men, and higher among Russian women. These patterns agree with the dynamics demonstrated by the data from the WHO Global InfoBase and other sources, obtained in the early to mid-2000s. Thus, among 45-74-year-old Czech men and women – participants of the 2002 Survey of the Health Status of the Czech Population, the proportion of current smokers was 25.8% and 17.4%, respectively.[173] The analysis of Czech MONICA and post-MONICA data by Cifkova and colleagues demonstrated that smoking prevalence in 25-64-year-old Czech men declined from 39.7% in 1992 to 35.4% in 2000-2001, while in Czech women, the respective figures were quite stable (approximately 23%).[160] In Polish general population aged over 40 years, smoking prevalence was 37.0% and 24.7% among men and women, respectively, in 2007, as the database year closest to the period of interest.[173] These estimates were similar to the 2005 smoking prevalence reported for 25-74-old Polish men and women (40.1% and 25.1%, respectively).[158] Among Russian LLH study participants, aged 40 years or older in 2001, the respective figures were 56.9% and 9.5%.[173] In Russian men and women from Arkhangelsk, examined in 1999-2000 at the age of ≥18 years, smoking prevalence was 56.7% and 21.3%, respectively, which was slightly higher than in male and female Russian HAPIEE samples and could be due to the younger mean age of the Arkhangelsk cohort.[256] The difference in the age distribution might also explain higher smoking prevalence in 25-64-year-old Russian men (66%) and women (15-21%) from Pitkäranta and Aunus districts of Karelia, examined in 2002-2003.[405]

Therefore, the higher mean age of HAPIEE vs. MONICA participants could, to some extent, explain certain dynamics (such as lower smoking prevalence in HAPIEE men from the Czech Republic and Poland), but not all the changes in smoking levels (such as higher rates in HAPIEE women from Russia). In addition, population-level data confirm the existing trends of decreasing smoking prevalence in Czech and Polish men and increasing smoking rates in Russian women, which reflects the transition of the respective populations via different stages of tobacco epidemic.[254]

Total cholesterol: In all MONICA samples, mean TCH levels were close to 6 mmol/l, which agrees with the WHO data for the respective period.[173] However, it should be noted that, for the countries of interest, the respective WHO estimates of TCH levels were sourced from MONICA samples. In Czech male and female MONICA-3 participants, mean TCH levels reported in the WHO Global InfoBase were 6.0 and 5.9 mmol/l, respectively. Among Polish men and women from MONICA-Warsaw, mean levels of TCH were 5.6 and 5.7 mmol/l, respectively, while in MONICA-Tarnobrzeg, they were 5.4 and 5.6 mmol/l. In men and women from MONICA-Kaunas, mean TCH levels were 6.0 and 6.2 mmol/l. Among MONICA-Novosibirsk participants, these levels were 5.6 mmol/l in men and 5.8 mmol/l in women.[173] Therefore, due to limited data availability, an adequate comparison between MONICA findings from the present study and independent national estimates is not feasible.

In HAPIEE samples, mean levels of TCH were slightly lower in Czech males and females, compared to their MONICA peers, while in Russian men and women, these levels were somewhat higher than in MONICA. The latter, but not the former could be partly explained by the higher mean age of HAPIEE subjects. In Polish men and women, mean TCH levels did not differ substantially for HAPIEE vs. MONICA. These findings generally concur with the dynamics demonstrated by the national/subnational data from WHO or other sources. However, the systematic WHO analysis of worldwide TCH trends among adults aged 25 years or older[406] mostly, although not exclusively, employed CEE/FSU data from MONICA surveys and, hence, has limited potential for external comparison of the thesis findings. According to the WHO analysis, mean levels of TCH in both Czech men and women decreased from 5.8 mmol/l to 5.1 mmol/l in 2008.[406] Similarly, among Czech adults from MONICA and post-MONICA samples, mean TCH levels decreased from 6.0 mmol/l (1992) to 5.3 mmol/l (2007-2008).[160] A minimal TCH decline was observed for Polish women (5.3 mmol/l in 1990 and 5.2

mmol/l in 2008), while TCH concentrations remained stable (5.3 mmol/l) in their male peers.[406]

The WHO analysis also demonstrated some TCH decline for Russia, from 5.3 mmol/l (1990) to 4.9 mmol/l (2008) for men, and from 5.6 to 5.1 mmol/l, respectively, for women. By contrast, the comparison of the Russian MONICA and HAPIEE data did not show any reduction in TCH levels, which could be due to the difference in sample selection and sample characteristics between this thesis and the analysis by Farzadfar and colleagues.[406] Moreover, mean TCH levels among adult men and women from Arkhangelsk examined in 1999-2000 (5.0 and 5.2 mmol/l, respectively)[256], as well as in Karelian men and women examined in 2002-2003 (5.3 and 5.1-5.5 mmol/l, respectively)[405], were somewhat lower than in male and female HAPIEE participants from Novosibirsk. This is most likely explained by the younger mean age of the subjects in these two studies from Northwest Russia.

Systolic blood pressure: In MONICA samples, mean SBP levels were relatively high and close to 140 mm Hg in both genders. The consistency of these results with the WHO Global InfoBase estimates[173] is not surprising, as the respective Global InfoBase data were MONICA-derived, which prohibited an adequate external comparison of the findings from the present study. In particular, mean SBP levels reported by WHO for Czech MONICA-3 men and women were 134.4 and 129.9 mm Hg, respectively.[173] Among Polish men and women participating in MONICA-Warsaw, mean SBP levels reached 142.3 and 135.1 mm Hg, respectively. In MONICA-Tarnobrzeg participants, the respective levels were 135.1 and 137.7 mm Hg. In male and female Lithuanian MONICA subjects, they were 136.7 and 135.2 mm Hg, respectively. Among Russian MONICA participants from Novosibirsk, mean SBP was 133.6 mm Hg in men and 134.1 mm Hg in women.[173] As expected, these figures are very close to the results obtained from descriptive analyses of MONICA samples in this thesis.

Mean SBP levels generally followed the same pattern as TCH concentrations, being similar or lower in male and female HAPIEE subjects from the Czech Republic and Poland, compared to their MONICA peers. By contrast, men and women from Russian HAPIEE samples had slightly higher SBP levels than Russian MONICA participants. These patterns largely agree with the WHO findings and the data from other sources. According to the WHO systematic analysis, which included CEE/FSU data not only from MONICA, but also from other, independent studies, mean levels of SBP in Czech

men aged 25 years or older decreased from 136.1 mm Hg in 1990 to 133.7 mm Hg in 2008; in Czech women, respective figures were 132.5 and 125.7 mm Hg.[407] A slightly less pronounced reduction was observed in the Czech MONICA and post-MONICA population, aged 25-64 years: mean SBP levels changed from 134.2 mm Hg (1993) to 132.5 mm Hg (2007-2008) for men, and from 130.2 to 126.7 mm Hg for women.[159;160] In Polish men, SBP levels remained relatively stable (135.9 mm Hg in 1990 and 135.0 mm Hg in 2008), while their female peers demonstrated some SBP reduction (from 133.0 to 129.7 mm Hg, respectively).[407]

In Russia, the overall decline in SBP was relatively modest: from 133.7 mm Hg (1990) to 132.3 mm Hg (2008) for men and from 132.3 to 128.5 mm Hg for women.[407] For Russian HAPIEE vs. MONICA data analysed in this thesis, no SBP reduction was detected, which might be explained by the difference in selection and characteristics of the samples in the present study vs. the WHO analysis. Of note, mean SBP levels among Karelian men and women (140-146 and 136-140 mm Hg, respectively; 2002-2003)[405] were similar to those in male and female HAPIEE samples from Novosibirsk, despite the younger mean age of the subjects in the former study.

Education: In MONICA samples, the prevalence of lower education was relatively high, approximately 40% or higher. The percentage of men and women with university education was the highest in Lithuania (over 20%), followed by Russia, Warsaw, the Czech Republic, and Tarnobrzeg. These data mostly agree with the national statistics from the WHO Health for All database.[21] Specifically, in the Czech Republic, the overall percentage of people aged over 25 years with higher than secondary education was 8.5% (1991); in Poland, 7.9% (1988); in Lithuania, 12.6% (1989); and in Russia, 14.1% (1989) (no gender-specific levels were reported).

In all HAPIEE samples, the proportion of lower-educated participants was substantially smaller than in the respective MONICA samples, which might reflect improved access to further education in people born later in the 20th century, whose educational attainment potential was less affected by World War II and its aftermath.[146;227] In the CEE/FSU region, the progressive decline in the proportion of lower-educated people over time has been confirmed, for example, in the adult Polish population, where the prevalence of lower educational attainment (primary or lower secondary education) decreased from 66.4% in 1990-1991 to 52.9% in 2002.[155] Across the waves of the Novosibirsk MONICA study, from 1985-1986 to 1994-1995, the percentage of people

with primary education decreased from 31% to 26% in men and from 26% to 19% in women.[387] Similarly, this proportion declined from 42% in the late 1970s to 27% in the late 1980s among St. Petersburg men.[224] A comparable decline, from 38% in 1980 to 17% in 2000, was reported by Murphy and colleagues for a Russian national sample.[225]

Marital status: As expected for the age groups involved in MONICA and HAPIEE studies, the majority of the participants (>65% and >60%, respectively) were married/cohabiting (data on marital status were unavailable for Polish MONICA). According to the United Nations statistics from the late 1980s or the early 1990s (for the age group 40-64 years, to compare the results with MONICA) and from the early 2000s (for 45-69-year-olds, to enable the comparison with HAPIEE), the proportion of married/cohabiting Czech men and women was 82.7% and 74.2% in 1991 and 78.2% and 68.2% in 2001, respectively. In 1988, 87.7% and 75.4% of Polish men and women were married; in 2001, the respective figures were 82.9% and 69.5%. Among Lithuanian men and women, 85.8% and 69.9% were married in 1989, while in 2001, this proportion was 78.9% and 60.5%, respectively. In Russia, the percentage of married men and women was 86.2% and 67.0%, respectively, in 1989, compared to 80.9% and 59.6% in 2002.[408] Therefore, it can be concluded that marriage rates in MONICA and HAPIEE participants were generally close to those in respective national populations for the relevant time periods.

Alcohol consumption: The patterns of alcohol consumption were assessed only in HAPIEE samples (***Methods, Section 4.3.3***), and the prevalence of self-reported alcohol abstinence in the last year (ranging among men from 5.5% in the Czech Republic to 19.5% in Poland, and among women, from 14.7% in Russia to 43.1% in Poland) was the only parameter that could be compared with the national data from respective countries. Typically, the national estimates were considerably higher. For example, in 45-74-year-old participants of the 2002 Survey of the Health Status of the Czech Population, the proportion of non-drinkers was 30.8% in men and 68.1% in women.[173] According to the recent WHO report, the percentage of non-drinkers was 10.7% and 23.0% in Czech men and women aged over 15 years (2003); 16.4% and 34.3% in Polish men and women (2007); and 29.0% and 50.6% in Russian men and women (2003).[287] The most likely explanation of this discrepancy is a more thorough data collection and a lesser degree of under-reporting in HAPIEE samples, especially in Russia. On the other hand, in the secondary analysis of the 2002 WHO data, the proportion of non-drinkers

or “very light drinkers” (0-24 g/day) was 9.0%, 16.4%, and 13.8% among Czech, Polish, and Russian men, and 19.9%, 34.3%, and 27.5% in women from the respective countries[296], which is somewhat closer to the HAPIEE findings.

The rates of non-drinking in individual-level CEE/FSU studies were also close to the HAPIEE estimates. Among male and female Russian participants of the LLH study (2001), the prevalence of non-drinking was 11% and 27%, respectively.[298] In a relatively young cohort from Arkhangelsk, examined in 1999-2000, it was 12.2% and 27.1% in men and women, respectively.[256] As expected, the proportion of non-drinkers across male HAPIEE samples from the Czech Republic, Poland, and Russia (5.5%, 19.5%, and 12.4%, respectively) was close to that among Czech, Polish, and Russian men from the pilot HAPIEE study (6%, 14%, and 11% in 1999-2000).[297] The percentages of female non-drinkers from the respective countries were also relatively similar for the main HAPIEE study (16.3%, 43.1%, and 14.7%) and the pilot HAPIEE project (17%, 24%, and 16%). In addition, the percentage of Russian male non-drinkers in HAPIEE was very close to the average estimate (13.7%) among MONICA-Novosibirsk men examined in 1984-1985, 1988-1989, and 1994-1995.[300] Although in 1994-1995, the proportion of non-drinkers in MONICA-Novosibirsk samples (approximately 8% for both men and women)[301] was somewhat lower than the HAPIEE estimates, it could be partly explained by the slightly lower mean age of the participants in the former study.

The prevalence of binge drinking in Czech, Polish, and Russian HAPIEE men (18.3%, 10.1%, and 32.9%, respectively) was similar to that in the male participants of the pilot HAPIEE study (16%, 7%, and 26%, respectively)[409], confirming the most hazardous drinking pattern in Russian men. Binge drinking prevalence in female participants of the pilot HAPIEE was low (percentages not reported), which also agreed with the findings from the main study (1-3%). Moreover, the Russian estimates from the main HAPIEE study were somewhat lower than those obtained for the latest survey (1994-1995) of binge drinking prevalence in MONICA-Novosibirsk men and women (51% and 5%, respectively).[301] This could be due to not only the lower mean age of the participants, but also the lower cut-off for bingeing in the latter vs. former study (≥80 g vs. ≥100 g of pure alcohol at least once a month, respectively). For a higher threshold (≥120 g at least once a month), respective MONICA figures were 36% in men and 2% in women, which is very similar to HAPIEE values, as well as to the estimates from a national Russian

sample examined in 1996 (31% of men and 3% of women reported consuming ≥78.5 g of ethanol on one occasion at least once a month).[299]

Despite some difference in the definitions of binge drinking for HAPIEE vs. LLH (for the latter study, ≥80 g of alcohol from beer, ≥90 g from wine, or ≥86 g from spirits on one occasion at least once every two-three weeks), the prevalence of bingeing was relatively similar in Russian HAPIEE men and women (32.9% and 1.4%) and male and female LLH participants (30% and 4%, respectively).[410] However, HAPIEE estimates of binge drinking were somewhat lower than the 2003 findings from the recent WHO report: 34.4% and 6.0% in Czech men and women, respectively; 22.1% and 5.8% in Russian men and women; no compatible data were available for Poland.[287] This could be explained by a different definition of "heavy episodic drinking" by WHO (consumption of ≥60 g of pure alcohol on at least one occasion weekly).

The prevalence of positive CAGE score in male Czech, Polish, and Russian HAPIEE samples (9.1%, 9.6%, and 20.9%, respectively) was relatively close to that in their peers from the pilot HAPIEE (18.5%, 13.7%, and 34.8%). In women, positive CAGE was substantially less prevalent than in men, both in the main study (1.9%, 1.0%, and 1.5%) and across pilot HAPIEE samples (3.5%, 0.7%, and 2.6%, respectively).[297] No external data on the positive CAGE prevalence across the populations of interest were attainable. However, HAPIEE estimates of hazardous drinking in Novosibirsk men were more or less comparable to the prevalence of problematic beverage drinking and non-beverage alcohol consumption (13.3%) among working-age Izhevsk men.[392]

Cardiovascular mortality: Among MONICA men, the percentage of participants who died from atherosclerotic CVD over a 10-year period was the highest in Novosibirsk (7.0%), lower in Warsaw (6.7%), the Czech Republic (5.0%) and Tarnobrzeg (4.9%), and the lowest in Kaunas (3.5%). Among MONICA women, the highest cardiovascular mortality levels were registered in Novosibirsk (3.2%), followed by the Czech Republic (1.9%), Warsaw (1.8%), Kaunas (1.6%), and Tarnobrzeg (1.3%). Similar ranking of cardiovascular mortality was shown by the national data from the WHO Health for All database, which were reported for both genders, all ages, and 2005 as the latest follow-up year for MONICA samples included in the thesis. Specifically, the national fatal CVD rates (per 100,000) were substantially higher for Russia (837.3) than for the Czech Republic (419.0), Poland (384.2), or Lithuania (562.8).[21]

In HAPIEE, the percentage of atherosclerotic CVD deaths registered during the current follow-up period was also higher among Russian men than in their Czech and Polish peers (3.2% vs. 1.4% and 1.0%, respectively). The same ranking was observed for female HAPIEE samples, with Russian levels of cardiovascular mortality (1.0%) being higher than Czech (0.6%) or Polish ones (0.4%). This gap between Russia vs. the Czech Republic or Poland was confirmed by the WHO data for 2008 (the latest follow-up year for HAPIEE samples from Poland and Russia): Russian levels of fatal CVD were 724.2 per 100,000, while Czech and Polish levels were, respectively, 355.6 and 356.9 per 100,000.[21]

Therefore, the levels of cardiovascular risk factors and CVD mortality reported in this thesis were consistent with the respective national/subnational levels, despite the limited representativeness of MONICA and HAPIEE samples. This supports the validity of MONICA and HAPIEE findings on SCORE performance, which are discussed below.

10.3.2. Performance of the original SCORE

The investigation of the SCORE prognostic performance in MONICA and HAPIEE samples involved evaluating the strength of the SCORE-fatal CVD association and measuring calibration and discrimination of the original SCORE instrument. The results of each of these analysis steps are summarised below and discussed in the context of attainable external evidence.

a) Strength of the SCORE-fatal CVD association

The main association of interest, between baseline SCORE and fatal atherosclerotic CVD, was statistically significant across individual MONICA and HAPIEE samples and in the combined analyses (***Sections 6.1*** and ***9.1***). Thus, in MONICA men, sample-specific HR values varied from 2.7 in Russia to 5.3 in the Czech Republic, while the random effects meta-analysis produced a pooled HR of 3.4. Among MONICA women, HR for the SCORE-fatal CVD association ranged from 1.7 in Warsaw to 6.3 in Novosibirsk, and the combined HR (4.8) was slightly higher than in men. However, this gender difference should be interpreted cautiously, due to the 95% CI overlap. In HAPIEE men, sample-specific HR varied considerably, from 2.6 in Poland to 10.5 in the Czech Republic; the pooled HR reached 5.4, with a relatively wide 95% CI due to the current follow-up being under 10 years. Among HAPIEE women, sample-specific HR ranged from 3.6 in the Czech Republic to 8.8 in Poland. Although the pooled HR (6.3) was somewhat higher than the respective values in HAPIEE men or MONICA

women, the respective combined 95% CI overlapped. Some gender- and study-specific difference in the SCORE HR values could be partly explained by the limited follow-up length in HAPIEE, as well as by the "case-mix" phenomenon (varying influence of measured and unmeasured covariates on the association of interest; see ***Section 10.2.9(c)***). The analysis of the currently available data is not adequately powered to distinguish between the presence of genuine HR differences vs. chance.

To my knowledge, only two other studies have previously reported the magnitude of the SCORE-CVD association. Among middle-aged Austrian men and women, the strength of a significant link between baseline SCORE (as a continuous variable, assessed with the non-calibrated low-risk scale) and 10-year CVD mortality was reported only after adjustment for several physiological and socioeconomic parameters, such as obesity, hyperglycaemia, triglycerides, GGT, and job status.[123] Since no unadjusted HR were presented, and the set of covariates differed from that used in the present study, these results were not directly comparable. However, the HR values presented by Ulmer and colleagues (1.1 for men and 1.2 for women)[123] were still very close to the findings for the high-risk continuous SCORE in MONICA men and women (1.1 and 1.2-1.3, respectively), or in HAPIEE men and women (1.1 and 1.2-1.3, respectively).

Among adult participants of the Greek ATTICA study, HellenicSCORE levels, derived from age, gender, smoking, TCH, and SBP, were significantly associated with the five-year risk of incident CVD, as demonstrated by the OR of 1.2 per 1% increase in HellenicSCORE.[411] Despite the difference in the analysed SCORE versions and outcomes (any incident CVD event in ATTICA vs. atherosclerotic fatal CVD in MONICA and HAPIEE) or employed statistical analysis methods (logistic regression vs. Cox regression, respectively), the strength of the SCORE-CVD association observed in the study by Vlismas and colleagues[411] and across MONICA and HAPIEE samples was very similar. Therefore, the present study and the evidence from Austrian and Greek samples confirm the important role of SCORE as a cardiovascular risk predictor, which agrees with the first research hypothesis.

In the thesis, estimates of the association between baseline SCORE (both dichotomous and continuous versions of the high and low-risk instrument) and fatal CVD were very close for the standard Cox, competing-risk, and Weibull regression analyses (***Section 6.1***). This agrees with the results obtained earlier for the SCORE Project dataset[20] and the Framingham Study data[412], and also demonstrates that the impact of competing risk

(mortality from causes other than atherosclerotic CVD) on the main association of interest was minimal. The latter could be due to the relatively high levels of mortality from CVD, compared to mortality from other causes, in MONICA and HAPIEE samples of middle-aged CEE/FSU populations.

b) SCORE calibration

The high-risk SCORE demonstrated good calibration in most MONICA samples, as confirmed by the relative closeness of P/O ratio to 1.0 and the low Hosmer-Lemeshow χ^2 values. This SCORE version, however, under-predicted risk in Russian men and women. Across HAPIEE samples, followed for less than 10 years, the actual P/O ratios were understandably over 1.0 (see ***Section 6.2***). The MONICA-based and the exponential model-based 10-year projections of CVD mortality in HAPIEE (***Section 6.3***) suggested that high-risk SCORE is likely to over-estimate the risk of fatal CVD in contemporary Czech and Polish samples, while in Russia, the risk might be either not over-estimated or even under-estimated. The use of the low-risk SCORE improved the estimated calibration in Czech and Polish participants, but at a price of markedly under-predicting the fatal CVD risk in Russia. In agreement with the second research hypothesis, these findings suggest that the low-risk SCORE might be better suited for the use in contemporary Czech and Polish populations, while the high-risk instrument may be preferred for Russia.

It is difficult to compare the SCORE calibration estimates from this thesis to other data from CEE/FSU populations, due to the lack of studies on SCORE prognostic performance in this region. For example, among 40-70-year-old male participants of the Polish WOBASZ study (2003-2005), the prevalence of high-risk SCORE levels ≥5% was somewhat lower than in Polish HAPIEE subjects (46% vs. 61%), possibly due to the lower mean age of WOBASZ participants. For women, these figures were similar in WOBASZ and HAPIEE (21% and 16%, respectively).[413] However, in WOBASZ, mean SCORE levels were not reported; moreover, predicted risk was not linked to observed CVD mortality, which made the assessment of SCORE performance impossible.

The findings from Western studies suggest that the high-risk SCORE tends to over-predict cardiovascular risk in populations with declining rates of CVD mortality, which agrees with the estimates of the expected 10-year SCORE calibration in Czech and Polish HAPIEE samples (P/E ratios of 2.1-3.8). For example, although the high-risk SCORE is officially recommended for Iceland and Norway, these populations

demonstrated worse calibration for high vs. low-risk instrument. Among middle-aged Icelanders, P/O ratios for high and low-risk SCORE were 1.6 and 0.8 in men, and 2.1 and 1.2 in women.[63] In middle-aged Norwegians, the high-risk SCORE substantially over-predicted the risk of fatal CVD: P/O ratios ranged from 1.9 to 2.2 for men and from 1.7 to 2.7 for women. However, for the low-risk SCORE, respective P/O ratios were closer to 1.0 (1.1-1.3 and 1.1-1.8).[125] Although Austria is also considered a "high-risk SCORE" country, even the low-risk SCORE version was shown to over-predict the 10-year CVD risk in middle-aged Austrian men (P/O ratio 1.2) and, to a greater extent, women (P/O ratio 1.9).[123]

These examples suggest that the SCORE calibration may be improved by the adjustment of the risk scale to local settings (so-called recalibration). Indeed, local SCORE versions typically show better calibration than the original, non-calibrated SCORE. For instance, in middle-aged Belgian men and women, the calibration of the locally adapted SCORE was excellent, as demonstrated by the overall P/O ratio of 1.0 and the Hosmer-Lemeshow χ^2 value of 8.3.[66] Among middle-aged Australians, the local SCORE model demonstrated lower Hosmer-Lemeshow χ^2 values (and, hence, better calibration) than the non-calibrated high and low-risk scales: 2.3 vs. 32.8 and 4.4 for men, and 7.4 vs. 27.3 and 12.9 for women, respectively.[67] However, even recalibrated SCORE might become poorly calibrated. Among middle-aged people from North Sweden, the local SCORE over-estimated the risk of fatal CVD, as shown by P/O ratios of 1.6 for both men and women.[143] In Dutch adults, the local SCORE version demonstrated poor calibration, with the Hosmer-Lemeshow χ^2 value of 35[141]. In another, partly overlapping Dutch population sample, the local SCORE and the original high-risk instrument over-estimated the fatal CVD risk, while the low-risk SCORE showed relatively good calibration: respective P/O values were 1.3, 1.9, and 0.9 in men, and 1.8, 1.8, and 1.1 in women.[142]

As demonstrated by the above-cited studies and MONICA and HAPIEE results for the Czech Republic and Poland, even if original or recalibrated SCORE versions previously showed good calibration, it does not exclude the possibility that calibration ability will decline over time. On the other hand, if SCORE calibration was initially not ideal, it might improve later, as suggested by the comparison of Russian MONICA and HAPIEE data. These findings emphasize the need for the ongoing update and adjustment of all

CVD risk scales, including the original and recalibrated SCORE instruments, to contemporary settings (for details, see ***Section 10.4.1***).

c) SCORE discrimination

The high-risk SCORE generally demonstrated satisfactory discrimination in both MONICA and HAPIEE samples, as shown in ***Section 6.4***. In HAPIEE, the assessment of SCORE discrimination was based on the available mortality data for the current follow-up covering less than 10 years, hence, the results obtained should be interpreted cautiously. Due to the previously mentioned lack of the attainable CEE/FSU studies on SCORE prognostic performance, MONICA and HAPIEE findings need to be compared with the evidence from the Western populations. In the latter, SCORE has typically shown good discrimination ability, regardless of the specific version assessed (the original high or low-risk instrument or the local, recalibrated scale). However, the fact that published Western studies have mostly focused on only one or two measures of SCORE discrimination further complicates any comparison with the MONICA and HAPIEE estimates.

Sensitivity of the high-risk SCORE was higher than its specificity both in MONICA men (0.7-0.8 vs. 0.5-0.6) and HAPIEE men (0.8-0.9 vs. 0.3-0.4, respectively). However, the opposite was true for MONICA women (specificity 0.9 vs. sensitivity 0.2-0.4) and HAPIEE women (0.8 vs. 0.4-0.7, respectively). This gender difference may be partly explained by the considerably higher number of outcomes in male participants of both studies, compared to females. Similar to the findings for MONICA and HAPIEE men, SCORE sensitivity was higher than its specificity in some Western studies. The original SCORE publication reported that across high-risk cohorts, the high-risk instrument showed sensitivity of 0.6-0.8 and specificity of 0.5-0.7 (no gender-specific estimates were presented).[20] The recalibrated SCORE showed high sensitivity (0.8) and slightly lower specificity (0.7) in middle-aged Belgians.[66]

Other Western studies demonstrated limited sensitivity and better specificity of SCORE across various middle-aged populations, which is consistent with the results obtained for MONICA and HAPIEE women. The specificity of the low-risk scale across low-risk SCORE Project cohorts (0.9) was higher than its sensitivity (0.2-0.4).[20] In the FINRISK study participants, the sensitivity of the non-calibrated high-risk SCORE reached 0.6 in men and 0.2 in women; for specificity, respective values were 0.7 and 0.9.[328] Among Icelandic adults, sensitivity and specificity were 0.7 and 0.8 for the high-risk SCORE

version, and 0.4 and 0.9 for the low-risk instrument.[63] In a Spanish population, specificity of the low-risk SCORE (0.9) was considerably higher than its sensitivity (0.3).[122] Among Austrian men and women, the low-risk SCORE sensitivity was relatively low (0.6 and 0.1, respectively), while SCORE specificity was high for both genders (0.9).[123] Therefore, these findings suggest that in the populations where the levels of atherosclerotic CVD mortality are declining (most Western populations), or are relatively low (MONICA and HAPIEE women), SCORE is less effective for identifying the people who will die from CVD during the follow-up than for selecting the individuals who will not develop the outcome of interest.

The positive predictive values (PPV) were low in all MONICA and HAPIEE samples (approximately 0.1), in contrast to high negative predictive values (NPV), which exceeded 0.9. To the best of my knowledge, SCORE PPV were assessed in only two studies, neither of which also reported NPV. Specifically, in the middle-aged Spanish population, the non-calibrated low-risk SCORE demonstrated PPV of 0.1.[122] Among middle-aged Austrians, PPV was only 0.1 in men and <0.1 in women for the low-risk SCORE.[123] These results agree with the MONICA and HAPIEE findings and suggest that only a small proportion of individuals with positive (≥5%) SCORE will die from atherosclerotic CVD within the next decade. However, since PPV is always low for relatively rare outcomes, in this case it cannot be regarded as the most appropriate discrimination measure.

The AUROC and Harrell's C-statistic values exceeded 0.5 (the value denoting overall discrimination no better than chance) across all male MONICA samples (0.6-0.7), being somewhat lower (0.5-0.6) in MONICA women. Among HAPIEE men and women, these values reached 0.6-0.7. The values of summary discrimination measures in MONICA and HAPIEE were only slightly lower than the estimates from the studies of middle-aged Western populations. For example, the original SCORE publication reported AUROC values of 0.7 and 0.7-0.8 for high and low-risk cohorts, respectively.[20] In a Norwegian population sample, AUROC reached 0.7 for the non-calibrated high-risk SCORE[125], while in Icelandic men and women, AUROC for both high and low-risk SCORE was 0.8.[63] Among Austrian men and women, AUROC values for the non-calibrated low-risk SCORE approached 0.8.[123] The recalibrated SCORE produced similar or higher values of AUROC/C-statistic, compared to non-calibrated versions. Thus, in Australian men and women, discrimination of the locally adjusted SCORE, as

well as the original high and low-risk versions, was good, as demonstrated by C-statistic values of 0.8 for men and 0.7 for women.[67] Among Dutch and Belgian adults, the local SCORE versions produced AUROC/C-statistic values over 0.8.[66;141]

The maximal proportion of outcome variation explained by dichotomous high-risk SCORE reached 32% and 34% in MONICA men and women, respectively. SCORE also explained a relatively modest proportion of the outcome variation in male and female HAPIEE samples (up to 31% and 53%, respectively). These results are consistent with the findings of the ecological analysis of cross-sectional MONICA data, which demonstrated that smoking, high BP, and high TCH explained up to 21% of CVD mortality in men and 35% in women.[126] Similarly, a later analysis of the MONICA data from the early 1990s showed that contemporary levels of traditional cardiovascular risk factors accounted for 30% and 45% of coronary mortality variation in men and women, respectively.[149] It might not be appropriate to compare the individual-level R^2 estimates obtained in this thesis to the results of the ecological analyses. However, to the best of my knowledge, no attainable prospective CEE/FSU or Western studies have assessed the magnitude of the outcome variation explained specifically by SCORE, using individual-level data.

To summarise ***Section 10.3.2***, while SCORE was a significant predictor of atherosclerotic fatal CVD across MONICA and HAPIEE samples, it failed to explain more than 50% of the variation in cardiovascular mortality risk. One possibility to improve SCORE discriminatory potential might be extending the risk model by extra predictors, such as socioeconomic characteristics and alcohol consumption parameters, which is discussed in the next two sections.

10.3.3. Education, marital status, and SCORE performance

This section debates the role of SCORE, education, and marital status as cardiovascular mortality predictors. It also discusses SCORE calibration and discrimination after the model has been extended by socioeconomic parameters.

a) Strength of the SCORE-fatal CVD association, adjusted for education and marital status

Across individual MONICA and HAPIEE samples, the association between SCORE risk levels and 10-year atherosclerotic CVD mortality remained statistically significant and did not change its strength substantially after controlling for education and/or

marital status (***Section 7.1***). In the random effects meta-analyses (***Section 9.2***), the adjustment for socioeconomic parameters only slightly reduced the strength of the main association of interest, which was relatively similar in MONICA and HAPIEE women (respective pooled HR 5.0 and 5.4), and slightly lower in MONICA vs. HAPIEE men (HR 3.4 vs. 5.0, respectively). The difference in MONICA vs. HAPIEE HR for men should be regarded with care, since the respective pooled 95% CI overlapped. The possible explanations of this difference could include limited outcome numbers over the current HAPIEE follow-up and the varying extent of residual confounding influences on the magnitude of the SCORE-CVD mortality association (so-called "case-mix"; see ***Section 10.2.9(c)***). Moreover, this HR discrepancy is less important than the fact that in both MONICA and HAPIEE, positive SCORE was a significant predictor of cardiovascular death, independent of such risk factors as lower education and/or non-married status.

To compare these findings with the external evidence is not possible, as, to the best of my knowledge, no published studies thus far have investigated the changes in the strength of the link between SCORE and fatal CVD before and after adjustment for socioeconomic parameters. However, an Austrian study reported HR for the continuous low-risk SCORE after controlling for multiple covariates, including job status.[123] These HR values (1.1 in men and 1.2 in women) were similar to those for the continuous high-risk SCORE in MONICA and HAPIEE men (1.1) and women (1.2-1.3), after adjustment for both education and marital status. Similar effect estimates were obtained in an adult Greek population for a continuous HellenicSCORE (OR 1.1) after adjustment for numerous extra risk determinants, including the socioeconomic index based on education and family income.[411] These findings support the first research hypothesis of SCORE as a significant cardiovascular risk predictor, independent of socioeconomic characteristics.

Although the links between additional risk factors, such as socioeconomic parameters or hazardous drinking measures, and cardiovascular mortality were not the primary focus of the thesis, it is still important to compare the observed magnitude of these associations with the relevant external evidence. First, if the direction and strength of the links between additional risk determinants and fatal CVD are consistent between this and other studies, it will indirectly justify the validity of MONICA and HAPIEE data on the association between SCORE and cardiovascular mortality, after adjustment

for extra risk factors. Second, if both the MONICA and HAPIEE data and the results from other studies demonstrate that education and marital status independently predict fatal CVD, it will support the extension of the SCORE model by these socioeconomic parameters.

In almost all MONICA and HAPIEE samples, lower education and non-married status were linked to a significant or non-significant increase in CVD risk, even after controlling for SCORE (***Section 7.1***). Only in MONICA women from Tarnobrzeg, did lower-educated participants appear to be at a lower risk (HR 0.8), although this association did not reach statistical significance. It might be explained by the fact that Tarnobrzeg sample was predominantly rural, and slightly "behind" the rest of the samples in the process of socioeconomic and epidemiological transition, characterised by the well-described phenomenon of inverse social gradient in cardiovascular risk factors and CVD mortality (e.g.[146;202-204]). Specifically, for Poland, it was shown that fatal CVD rates were higher in higher-educated Krakow residents in the late 1960s and 1970s[218], while in the 1980-1990s, higher cardiovascular mortality was observed in lower-educated Warsaw adults.[146]

Once the effects of SCORE and both socioeconomic parameters on cardiovascular mortality risk were simultaneously taken into account (not possible for Polish MONICA, due to the unavailability of marital status data), selected study samples demonstrated a statistically significant positive association between fatal CVD and lower education (Lithuanian MONICA women, Russian MONICA men and women, and Czech, Polish, and Russian HAPIEE men) or non-married status (Czech and Russian MONICA men, Polish HAPIEE men, and Russian HAPIEE men and women). While no external attainable studies, to my knowledge, have adjusted the impact of lower education or non-married status by the baseline SCORE level, such an adjustment was performed by a varying set of classical risk determinants (for details, see ***Background***, ***Section 2.3.2***). In some CEE/FSU studies, socioeconomic characteristics were significant, independent predictors of CVD mortality. For example, among male participants of the Russian LRC Study[227], adjusted RR for lower vs. higher education (1.9) agreed with the findings for Russian men from MONICA (SCORE-adjusted HR 1.7) and HAPIEE (1.8), despite some differences in end-points, covariates, and education categories between the LRC Study and this thesis. It was also demonstrated earlier for male MONICA-Novosibirsk participants[230] that divorced status is related to a

significantly increased risk of CVD death (adjusted RR 1.8). This effect size is very close to that obtained in the thesis for non-married MONICA men from Novosibirsk (adjusted HR 1.8).

Many Western studies have also shown an independent, statistically significant link between lower educational attainment and higher CVD risk, similar to the findings for Russian MONICA men and women (adjusted HR 1.7 and 1.6, respectively), Lithuanian MONICA women (4.4), and Czech, Polish, and Russian HAPIEE men (3.0, 2.5, and 1.8, respectively). Lower education was a significant predictor of fatal CVD among American participants of the NHANES I study (adjusted RR ranged from 1.5 to 2.3)[238;239] and Finnish men and women (adjusted HR 1.2 and 1.9, respectively).[240] Moreover, increased risk of cardiovascular death, which was not explained by classical risk factors, has been observed not only for non-married men from Czech MONICA (adjusted HR 5.1), Russian MONICA (1.8), Polish HAPIEE (2.5), and Russian HAPIEE (2.3), but also for non-married middle-aged Dutch men (adjusted RR 2.2)[210], widowed male Whitehall civil servants (adjusted mortality rate 1.3)[211], single male BRHS participants (adjusted RR 1.5)[212], and single, widowed, or separated/divorced middle-aged Scottish men and women (adjusted RR varied from 2.1 to 2.6).[214]

By contrast, in other study samples (Czech MONICA men and women, Lithuanian MONICA men, and Czech, Polish, and Russian HAPIEE women), an association between lower education and higher risk of fatal CVD failed to achieve statistical significance after accounting for conventional risk factors. This is in agreement with several CEE/FSU studies, performed in Udmurt men of working age[255], Novosibirsk men and women[230], and Arkhangelsk men[256], as well as with some Western studies of Norwegian men and women[231], middle-aged men from France and Northern Ireland who participated in the PRIME study[232;233], and middle-aged participants of the Melbourne Collaborative Cohort Study.[234] After taking classical risk determinants into account, the increase in cardiovascular mortality risk associated with non-married status was non-significant not only in Lithuanian MONICA men and women, Czech MONICA women, Russian MONICA women, and Czech HAPIEE men and women, but also among men and women from Novosibirsk[230] or Arkhangelsk[256], male and female Framingham Offspring Study participants[235], and French and Northern Irish men who took part in the PRIME study.[233]

The lack of statistically significant, independent associations between socioeconomic parameters and fatal CVD in most MONICA and HAPIEE samples, or in some of the above-cited CEE/FSU and Western research projects, might be partly explained by limited outcome numbers in some studies, but could also be due to the fact that multiple mechanisms of adverse effects of lower education and non-married status on cardiovascular health involve classical risk factors, such as smoking. Controlling for these conventional risk determinants, captured by SCORE, might result in over-adjustment and attenuate a positive link between socioeconomic factors and CVD mortality.[211;255;414]

Therefore, both the results of this thesis and the evidence from other studies generally support the role of not only SCORE, but also socioeconomic disadvantage as important predictors of cardiovascular risk. This was the rationale behind extending the original SCORE model by socioeconomic characteristics, such as education and marital status. Such an extension was expected to improve SCORE calibration and discrimination, in agreement with the third research hypothesis. In the next section, the prognostic performance of extended SCORE in MONICA and HAPIEE samples is compared with the findings available in the literature.

b) Calibration and discrimination of the SCORE model extended by education and/or marital status

In most MONICA and HAPIEE samples, the extension of the SCORE instrument by education and/or marital status failed to substantially improve the model calibration, probably because Hosmer-Lemeshow χ^2 values were relatively low even before the model extension (***Section 7.1***). The changes in discrimination were more promising for extended SCORE models, as demonstrated by increased values of Harrell's C-statistic and Royston's R^2 index, as well as by low *p* values in LR tests. However, it was not possible to identify a single extended model which would produce universally better discrimination measures across all study-, country-, and gender-specific samples. The overall change in the discrimination of extended models, operationalized via integrated discrimination improvement (IDI), was modest, <5% for MONICA men and <1% for MONICA women, HAPIEE men, or HAPIEE women. Therefore, the MONICA and HAPIEE results support the use of the original SCORE for cardiovascular risk prediction in CEE/FSU populations, as its performance was very similar to that for the education and marital status-extended models.

To my knowledge, no studies have assessed the changes in calibration or discrimination of SCORE (or other cardiovascular risk scales) extended by socioeconomic parameters in CEE/FSU populations. However, several Western studies investigated the changes in selected calibration and/or discrimination indices for the extended Framingham risk scale, with mixed results. Adding either current or lifetime social class, or the area deprivation (operationalized via the Carstairs-Morris index) to the Framingham model did not improve its discrimination in middle-aged Scottish men.[415] Among middle-aged participants of ARIC and NHANES III studies, adding lower socioeconomic position (<12 years of education or low income) improved the Framingham scale calibration without substantially affecting its discrimination.[261] One study[259] assessed the overall discrimination improvement for the Framingham scale extended by socioeconomic parameters. In particular, adding occupational social class to the Framingham model slightly improved risk reclassification in middle-aged BRHS participants, as reflected by low NRI and IDI values (0.2% and 0.1%, respectively). Indirectly, these findings are consistent with the results for MONICA and HAPIEE samples, where the addition of education and/or marital status marginally improved the overall SCORE discrimination.

The absence of a marked performance improvement for the models extended by socioeconomic parameters might appear contradictory to the evidence of better performance of the cardiovascular risk scales which incorporate socioeconomic characteristics, such as ASSIGN and QRISK/QRISK2, compared to traditional instruments, such as Framingham scale (***Background, Section 2.3.2***). ASSIGN, which includes the area-based SIMD (Scottish Index of Multiple Deprivation), demonstrated better discrimination[104] and a steeper, closer to the observed, deprivation gradient in CVD risk[262] than the Framingham score. QRISK/QRISK2, which included a different area-based deprivation index (Townsend deprivation score), showed better calibration and discrimination than the Framingham instrument.[105-108] However, these studies compared different risk scales, rather than nested models, and, hence, they did not address directly the issue of incremental prognostic value of socioeconomic parameters when added to classical risk factors.

Therefore, MONICA and HAPIEE findings, as well as the current evidence from other studies, support the use of the original SCORE instrument. It remains to be seen whether future research identifies suitable ways of extending cardiovascular risk models

by socioeconomic characteristics, in order to improve the prognostic performance in specific populations (***Section 10.4.3***).

10.3.4 Alcohol consumption and SCORE performance

Another important predictor of CVD risk in CEE/FSU is alcohol consumption. This section, structured in a similar way to ***Section 10.3.3***, puts the HAPIEE findings on SCORE and alcohol in the context of external evidence.

a) Strength of the SCORE-fatal CVD association, adjusted for alcohol consumption parameters

Across all HAPIEE samples, baseline high-risk SCORE ≥5% remained a significant predictor of atherosclerotic cardiovascular death after accounting for binge drinking and/or CAGE. This adjustment barely affected the strength of the main association of interest (***Section 8.1***). Similarly, in the random effects meta-analyses (***Section 9.3***), the overall association did not change substantially after taking both measures of hazardous drinking into account. While the alcohol-adjusted overall association between SCORE and fatal CVD appeared to be stronger in HAPIEE women (adjusted HR 6.8) than in their male peers (HR 5.3), these findings should be interpreted with care. Not only did 95% CI for these values overlap, but also the outcome numbers across small subgroups of female bingers or CAGE-positives were relatively low, possibly due to limited cultural acceptability and, hence, under-reporting of hazardous drinking in CEE/FSU women.[298;301;364]

To my knowledge, no published CEE/FSU or Western studies have compared the potential of SCORE, or any other risk scale, as a cardiovascular mortality predictor before and after adjustment for alcohol consumption parameters. At the same time, smoking, one of the classical risk factors, appeared a significant, or close to significant, predictor of fatal CVD, even after controlling for alcohol and other risk determinants, among male and female LRC Study participants[308], or in working-age Udmurt men.[255]

While SCORE remained a significant determinant of atherosclerotic cardiovascular mortality in all HAPIEE samples after accounting for hazardous drinking, the SCORE-adjusted associations between fatal CVD and either bingeing or positive CAGE were substantially weaker (***Section 8.1***). After controlling for SCORE and CAGE, the link between bingeing and CVD mortality failed to reach statistical significance in all samples, and was even negative in Czech and Polish men. Positive CAGE did not

significantly predict fatal CVD in HAPIEE men and women, once the effects of SCORE and binge drinking were taken into account.

The absence of significant associations between hazardous drinking and fatal CVD across HAPIEE samples could be, to some extent, explained by the current follow-up being less than 10 years and the limited outcome numbers, particularly in women. When the 10-year data are available for HAPIEE, it might be that bingeing and/or CAGE will become more reliable predictors of cardiovascular death, independent of SCORE and each other. This would agree with the evidence of the important role of various drinking measures as significant predictors of fatal CVD risk, even after controlling for conventional and novel risk determinants, which has been obtained in numerous Western studies[273;274;280-282;284;285;289-291] and several CEE/FSU studies performed in working-age Udmurt men[201;255;309], men and women from Tomsk, Barnaul, and Biysk[310], middle-aged Novosibirsk men[300], and Arkhangelsk women[256] (for details, see ***Background***, ***Section 2.3.3***).

However, currently, the findings from most HAPIEE samples demonstrate a positive, albeit not significant after adjustment, association between atherosclerotic CVD mortality and binge drinking (Russian men, Czech and Russian women; adjusted HR 1.2-3.3) or positive CAGE (men from all three countries, Czech and Russian women; adjusted HR 1.2-3.4). Similarly, in Novosibirsk men, followed for 9.5 years, binge drinking was linked to a non-significant adjusted increase in CHD mortality (RR 1.3).[300] Despite the difference in binge drinking definitions between the study by Malyutina and colleagues (≥160 g of alcohol on a typical occasion at least once a month)[300] and this thesis, as well as some difference in study outcomes and covariates, these earlier obtained results are relatively close to the findings for HAPIEE men from Novosibirsk (adjusted HR 1.2).

The absence of a clear association between binge drinking and CVD risk among Czech and Polish HAPIEE men (adjusted HR 0.8 and 0.7, respectively, with both 95% CI including 1.0) was consistent with the results of some CEE/FSU studies which also failed to establish a link between hazardous drinking and cardiovascular mortality. For example, in two St. Petersburg cohorts, followed throughout the 1980s and 1990s, the 10-year fatal CVD rates were similar in men with low and high alcohol consumption.[224] The 13-year follow-up of the LRC Study participants also did not show any marked difference in adjusted cardiovascular mortality hazards between male and female

drinkers vs. non-drinkers.[308] Bingeing did not appear to be associated with fatal CVD risk among middle-aged Novosibirsk men (adjusted RR 0.9)[300] or men from Arkhangelsk (RR 0.9).[256]

The lack of a consistent, independent association between hazardous drinking and fatal CVD across HAPIEE samples and in some of the above-cited external studies could be due to several reasons. First, outcome numbers in bingers and/or CAGE-positives were relatively low (especially in women), which did not allow the performance of adequately powered analyses. Second, classical risk factors, such as SBP and TCH, could partly explain the elevated CVD risk in hazardous drinkers. Adjusting for these conventional risk determinants could have decreased the magnitude of the association between drinking and fatal CVD.[272;280;290;400] Third, differential misclassification[317], when participants with more hazardous drinking patterns and at a higher cardiovascular risk would under-report their alcohol consumption to a greater extent than non-hazardous drinkers, might also have weakened the link between drinking and atherosclerotic CVD mortality. Finally, the magnitude of the alcohol effect on cardiovascular risk could be, to a considerable extent, influenced by the recent episodes of hazardous drinking, and, hence, be larger in case-control vs. cohort studies.[392;416]

In summary, the adjusted positive link to cardiovascular mortality was significant for SCORE in all HAPIEE samples, although it did not reach statistical significance for hazardous drinking, which agrees with the evidence from some, but not all, CEE/FSU studies. In this thesis, the assessment of the associations between SCORE, hazardous drinking, and cardiovascular mortality was a preliminary step towards investigating the prognostic performance of SCORE extended by bingeing and/or positive CAGE, in order to address the fourth research hypothesis. However, the absence of a clear link between alcohol and fatal CVD risk suggested that such an extension was unlikely to result in improved SCORE performance.

b) Calibration and discrimination of the SCORE model extended by alcohol consumption parameters

The evaluation of the alcohol-extended SCORE performance across male and female HAPIEE samples demonstrated that adding either binge drinking, or positive CAGE, or both, to the high-risk SCORE did not markedly affect Hosmer-Lemeshow χ^2 values, as a measure of model calibration (S***ection 8.2***). Moreover, it was impossible to identify a single model, original or extended, that would demonstrate better calibration across all

HAPIEE samples. SCORE extension by hazardous drinking parameters also failed to show a substantial improvement in the model discrimination, as assessed by Harrell's C-statistic, Royston's R^2, and LRT *p*-values. Alcohol-extended SCORE could explain up to 50% of the outcome variation, and the overall discrimination improvement, denoted by IDI, was <1%. These results disagreed with the fourth research hypothesis, although they did not reject it completely. The current HAPIEE follow-up is less than 10 years, which limited the outcome numbers. Moreover, the self-reported prevalence of hazardous drinking in HAPIEE women (particularly in Poland) was low, which restricted the power of the alcohol-extended analyses. On the other hand, the current absence of considerable improvement in SCORE performance after the model extension by hazardous drinking parameters was similar to the results for the SCORE instrument enriched by socioeconomic characteristics (***Section 7.2***). These findings suggest that, at the moment, the original SCORE could be the algorithm of choice for cardiovascular risk assessment in CEE/FSU populations.

Despite the wealth of data on alcohol as a cardiovascular risk factor (***Background***, ***Section 2.3.3***), no studies in CEE/FSU or Western populations, to the best of my knowledge, have investigated the prognostic performance of SCORE, or any other cardiovascular risk instrument, after extending it by alcohol consumption measures. Moreover, no cardiovascular risk scale developed thus far includes any drinking parameters. This lack of evidence not only complicates the comparison of HAPIEE findings with other data, but also points to the important knowledge gap, which should be addressed in future studies (***Section 10.4.3***).

To summarise ***Section 10.3***, SCORE demonstrated a significant association with atherosclerotic CVD mortality, as well as satisfactory discrimination, across most MONICA and HAPIEE samples, which agreed with the existing external evidence. At the same time, SCORE markedly under-predicted the fatal CVD risk in Russian MONICA. The estimated 10-year SCORE calibration in HAPIEE suggested that in contemporary CEE/FSU populations, different versions of this instrument could be used (low-risk for the Czech Republic and Poland, and high-risk for Russia). These results, as well as the data from numerous Western studies, emphasize the importance of a regular reassessment of SCORE performance across populations and over time and, if necessary, its recalibration. Despite some evidence of the association between CVD mortality and socioeconomic parameters or hazardous drinking characteristics in

selected MONICA and HAPIEE samples, which agrees with the findings of other studies, the improvement in calibration and discrimination of the extended SCORE was modest. A marginal improvement in the prognostic performance of extended cardiovascular risk models has also been shown in other studies. While these results suggest that the original SCORE instrument could be used as effectively as its extended versions, they do not deny the possibility of further improvement of the SCORE-based cardiovascular risk prediction.

10.4. Future directions of CVD risk assessment and reduction

This section discusses the areas for optimisation of cardiovascular risk prediction and reduction and debates such topics as SCORE recalibration and "evolution" as a prognostic model, the potential of socioeconomic parameters and alcohol consumption characteristics as CVD risk determinants, the extension of cardiovascular risk models with novel risk predictors, and the importance of targeting lifestyle risk factors in cardiovascular prevention.

In the field of CVD risk prediction and reduction, research and practice are closely related. For example, the development of effective risk assessment instruments requires routine collection of local data on cardiovascular risk factors and outcomes, while the CVD burden reduction involves accurate risk evaluation and identification of the individuals, groups, and populations at the highest risk, i.e. those most likely to benefit. Therefore, the research and policy-related aspects of further development of CVD risk prediction and management are presented together.

10.4.1. SCORE recalibration

Recalibrated, or locally adjusted, cardiovascular risk scales, such as SCORE, typically demonstrate better prognostic performance in local populations than original, non-calibrated instruments; however, even recalibrated scales might become less accurate over time (e.g.[141-143]). This emphasises the need for continuous revision, update, and readjustment of risk assessment instruments, particularly in populations with rapidly changing levels of cardiovascular risk factors and fatal CVD, such as CEE/FSU. Country-specific SCORE models, which were introduced in the Czech Republic[175] and Poland[176] in the mid-2000s, are very close to the original high-risk SCORE. Presently, these scales lack a description of recalibration procedure and/or comparison of their predictive performance with the original instrument, and it is possible that they over-estimate the risk in contemporary Czech and Polish populations. The analysis of the

estimated 10-year SCORE calibration in HAPIEE samples (***Section 6.3***) demonstrated that the low-risk SCORE might predict CVD mortality in Czech and Polish participants more accurately than the high-risk SCORE.

In this thesis, it was not possible to recalibrate SCORE to the contemporary Czech, Polish, or Russian settings, as HAPIEE samples represented selected urban communities, rather than populations of the whole countries. This, together with non-response, affected the generalizability of the observed levels of risk factors and CVD mortality. The information on background risk levels, which were assessed in 2002-2004, was somewhat out-dated; and the current follow-up length was under 10 years. Nonetheless, this study is an important first step towards SCORE recalibration and, hence, the improvement of its prognostic accuracy in the CEE/FSU context.

Essentially, SCORE recalibration requires two local sources of updated information: the current national statistics on cardiovascular mortality and representative surveys of conventional risk factor levels in the population.[9;13] While fatal CVD rates are available for CEE/FSU, albeit with varying time lags, obtaining the local representative data on risk factors is a more challenging task, due to the lack of extensive epidemiological research expertise and preventive infrastructure in these countries.[24;146;417] An obvious option is to use local prospective individual-level studies as a source of information on CVD mortality and risk factors, required for SCORE recalibration. However, due to such issues as limited sample representativeness and/or follow-up time, these studies are unlikely to be an adequate substitute for a national system of health and disease surveillance. If the enormous burden of CVD in CEE/FSU is to be reduced, the current focus of healthcare systems, health research communities, and policy-makers needs to be gradually extended from treatment of the patients with already developed circulatory pathology to primordial and primary prevention and, hence, to routine monitoring and management of cardiovascular risk factors.

One of the possible mid-term solutions to the problem of data availability for the recalibration of cardiovascular risk scales, such as SCORE, is to use the data routinely collected in general practice. Probably the best-known example of this strategy is the UK QRISK/QRISK2 Project (for details, see ***Section 2.1.2***). In large cohorts of British general practice patients, the eponymous prognostic algorithm has been shown to predict CVD risk more accurately than the Framingham model.[105;107;108] Another example is PREDICT-CVD, a web-based clinical decision support programme,

operating in the Auckland region, New Zealand.[418-420] This programme provides cardiovascular risk assessment and management advice to primary care patients with or without manifested CVD. Since its implementation in 2002, it has generated comprehensive data on individual cardiovascular risk for large numbers of patients. Such data could also be linked to national hospital discharge database and mortality registers, providing a unique opportunity to study the CVD risk continuum in a large community cohort. In some CEE/FSU countries, the general practice data on conventional cardiovascular risk factors and outcomes are also routinely collected and typically computerised. These data can potentially be analysed on the national or regional level and used for the development and validation of relevant, context-specific SCORE versions. However, the major obstacle is the issue of data confidentiality, as the possibility of individual-level data linkage is restricted by local legislation.

Importantly, not only will the research on CVD risk prediction benefit from using clinically derived data, but also the routine use of reliable cardiovascular risk instruments will provide numerous benefits in clinical practice settings. It will increase physicians' trust in risk scales, stimulate doctors' compliance with cardiovascular prevention guidelines and risk assessment implementation, enhance the accuracy of risk prediction, and, ultimately, improve clinical outcomes.[16;55;189;346;421] Cardiovascular risk prediction provides clinicians with an opportunity to discuss with their patients the potential impact of lifestyle changes and treatment on both short and long-term risk. Such a discussion might help the patients better understand their risk at earlier disease stages and, hence, improve their motivation for early, prolonged risk reduction.[7;17;53;54;422;423] The repeated provision of information on total CVD risk to patients appears to reduce predicted risk levels slightly but significantly (by up to 2% over 10 years in the studies using the Framingham scale).[424] This highlights the importance of a routine, consistent, sustainable, and repeated cardiovascular risk assessment, which should be incorporated into the healthcare structure and function, as a part of the general framework for surveillance, monitoring, prevention, and treatment of chronic non-communicable disease.[2;24;44;417]

10.4.2. Post-recalibration SCORE "evolution"

Recalibration is an important step in the risk model "evolution", which reflects the process of statistical validation – measuring calibration and discrimination of the model (ideally, in external populations, as addressed in this thesis) and updating the risk

prediction algorithm, if necessary. While this first step is particularly important for CEE/FSU countries, due to their high but heterogeneous CVD rates, these populations also require clinical validation of cardiovascular risk instruments, such as SCORE. Clinical validation of the risk model involves assessing its uptake by physicians and the subsequent effects on clinical decisions, outcomes, and treatment cost-effectiveness, in datasets of adequate size.[39;76;350;394;423;425] The clinical impact of "upgrading" SCORE from a prediction rule to a decision rule should be evaluated in terms of both efficacy and effectiveness, or, respectively, potential and actual impact.[426] As these parameters can differ substantially across clinical settings even within one country, not to mention the potential discrepancies between European populations, they need to be thoroughly investigated in future studies.

Since the SCORE model is expected to guide clinical decisions on the initiation of the pharmacological primary CVD prevention, it is necessary to investigate its decision analytic measures, such as the net benefit-plotting decision curves.[83;427;428] The relatively inexpensive and time-saving method of decision-analysis modelling could be used to simulate both health outcomes (comparative effectiveness modelling) and economic outcomes (cost-effectiveness modelling), to systematically compare the efficiency and effectiveness of all preventive strategies across all relevant subgroups, and to generate actionable information for clinicians and policy-makers. As the quality of its results depends on how well a simplified model captures the relevant trade-offs, and how much data are available to base the key model assumptions on[422], decision-analysis modelling also identifies the main areas of uncertainty, which require more clinical evidence from randomised controlled trials (RCTs) and other studies.[86;346;422]

Although RCTs are considered the best approach to directly evaluate the health impact of cardiovascular risk measurement[39;348;422;429], thus far they have not demonstrated that assessing CVD risk substantially changes clinical management, reduces the levels of individual risk factors and/or total risk, or improves the outcomes.[9;31;54;424] This is an important area for further research, which should first define a conceptual framework for the impact of total risk assessment and explicitly measure the potential mediators of outcome improvement. Relevant to both Western and CEE/FSU populations, the key points to address are: whether clinicians and patients accurately interpret and use risk scores; how exactly doctors calculate risk levels in clinical practice settings; whether the presentation of additional information, for example, about specific risk factors, can

affect the outcomes; and what are the acceptable measures of success in the total CVD risk assessment.[54;350]

Preliminary information could be obtained from observational studies, and one such example is the international collaborative project EURIKA (European Study on Cardiovascular Risk Prevention and Management in Daily Practice).[430-432] It is aimed at determining the degree of cardiovascular risk factor control in the current clinical practice across 12 European countries, assessing physicians' knowledge of and attitudes towards CVD prevention, and identifying barriers for the implementation of the ESC guidelines on cardiovascular prevention. EURIKA results are not completely representative for Europe (e.g., Russia is the only CEE/FSU country included), or even for the participating countries, and no analysis of the outcome impact is possible due to cross-sectional design. Nonetheless, it is an important step towards the ambitious goal of evaluating the risk factor control across the whole spectrum of primary CVD prevention settings.

10.4.3. Socioeconomic characteristics and hazardous drinking parameters as cardiovascular risk predictors

Although this thesis did not demonstrate any substantial improvement in SCORE performance after adding socioeconomic measures or alcohol consumption parameters to the model, it does not mean that people experiencing socioeconomic disadvantage or hazardous drinking are not at increased CVD risk in CEE/FSU or elsewhere. As shown in ***Section 2.3.2*** (***Background***), the social gradient in cardiovascular risk is only partly explained by classical risk factors in both Western and CEE/FSU populations. Using SCORE, or any other scale which excludes socioeconomic characteristics, might potentially lead to the relative under-treatment of deprived individuals and over-treatment of their more privileged peers, exacerbating the existing inequalities in cardiovascular mortality and morbidity.[205;258-260;395;433]

The analysis of the 15-year follow-up data from the Whitehall Study demonstrated that when applied population-wide, the so-called best-practice interventions (reducing SBP by 10 mm Hg, TCH by 2 mmol/l, and blood glucose by 1 mmol/l; halving the prevalence of Type 2 DM; and achieving complete smoking cessation) could not only reduce CHD mortality by 57%, but also decrease the mortality difference between high and low employment grade groups by 69%. Achieving primordial (ideal) levels of risk factors could reduce coronary mortality and mortality difference by 73% and 86%,

respectively.[434] Of note, such an improvement requires equal implementation and similar effectiveness of the intervention across socioeconomic groups, which, in turn, entails comparable accuracy of CVD risk assessment. Therefore, new risk scales which include socioeconomic characteristics (such as the UK-oriented QRISK/QRISK2 and ASSIGN) may be more equitable, even if their statistical performance is only moderately better than that for traditional instruments.[106;395;435]

Education and marital status are only two of the multitude of socioeconomic parameters that independently affect cardiovascular risk levels. Adding other measures to the risk scales, such as SCORE, could, therefore, demonstrate an improvement in the model's prognostic performance. While these additional socioeconomic parameters could be problematic to assess in routine clinical settings, they deserve further investigation, as they might facilitate better identification of individuals and groups at higher risk, as well as implementation of complex, multilevel preventive interventions. For example, during the second wave of the HAPIEE study (2005-2006), a wide range of data on individual and household income and wealth was collected. In future, this information could be linked to the cause-specific mortality records and used for a more extensive modification of the SCORE instrument.

A link between area-level socioeconomic deprivation, operationalized via unemployment rate and overcrowding, and higher levels of selected cardiovascular risk factors was demonstrated for Czech HAPIEE participants.[436] Although area-level deprivation could potentially act as an independent predictor of atherosclerotic fatal CVD in both MONICA and HAPIEE, and its measures are relatively easy to obtain in some populations (and can potentially be used as a substitute for individual-level socioeconomic characteristics), it was not assessed in all MONICA samples and most HAPIEE samples. Moreover, it is known that the impact of the neighbourhood-level socioeconomic deprivation on cardiovascular risk is relatively small after adjustment for individual-level socioeconomic characteristics.[437-440] Presently, the contextual socioeconomic predictors of CVD mortality remain understudied for CEE/FSU. This issue should be addressed by future research, in order to provide the evidence base for more effective and efficient multilevel policies, practices, and interventions aimed at cardiovascular risk reduction.

Marital strain, or the level of stress associated with marital factors, appears to be linked to higher CVD morbidity and mortality, via such physiological mechanisms as

excessive cardiovascular reactivity, endocrine dysfunction, and immune disregulation.[267;269;271] If unhappy marriage was related to increased cardiovascular risk in MONICA and HAPIEE participants, it would have weakened the association between non-married status and CVD mortality. However, only the data on formal categories of marital status, rather than marital strain levels, were available for MONICA and HAPIEE. Future studies, employing more detailed assessment of not only marital status *per se*, but also its "quality", might provide a better estimation of the underlying link between marital status and fatal CVD.

It has been shown that cardiovascular care quality and psychosocial factors are important and socioeconomically patterned determinants of CVD mortality in CEE/FSU. Across international MONCA Project centres, coronary treatment scores partly explained the cross-sectional differences in case fatality and CHD mortality between CEE/FSU and Western Europe[149], as well as the 10-year trends in CHD event rates and mortality.[322] This could be due to the fact that treatment quality not only influences CVD rates directly, but also reflects a major underlying determinant of cardiovascular risk – socioeconomic circumstances of individuals and populations.[149;441] In addition, it has been demonstrated that psychosocial factors, such as depression, perceived control, job strain, and hopelessness, are distributed less favourably in CEE/FSU than in Western Europe, which might be linked to both adverse socioeconomic characteristics and increased CVD risk (e.g.[149;442-447]). Since the availability of the data on cardiovascular care quality and psychosocial factors was limited for MONICA and HAPIEE samples, these parameters were not analysed in the thesis. Nonetheless, future studies should also address the possible prognostic value of these factors as additional predictors in the cardiovascular risk models.

More research is also necessary on alcohol consumption, and hazardous drinking in particular, in relation to cardiovascular risk in CEE/FSU. Adequately powered future studies, focusing on the association between various, repeatedly measured characteristics of drinking amount and patterns (including surrogate/non-beverage alcohol intake and novel biomarkers[200;391;392;448;449]), and, possibly, involving CEE/FSU subpopulations with higher prevalence of hazardous alcohol consumption, might reveal the role of alcohol as an important component of cardiovascular risk assessment in specific populations or population groups.

In this thesis, the investigation of the simultaneous effects of socioeconomic factors and hazardous drinking on fatal CVD would not be informative. Such an analysis would be restricted to HAPIEE samples, since compatible data on alcohol consumption were not available for all MONICA samples. It would also result in very low outcome numbers across the subgroups defined by both socioeconomic measures and alcohol consumption characteristics (***Methods***, ***Section 4.5.4***). Moreover, the aim of the present study was to investigate the general possibility of extending SCORE in the CEE/FSU context, and it first required a separate assessment of selected extra risk determinants, before adding them to SCORE as a combination. Since neither socioeconomic disadvantage nor hazardous drinking markedly improved the prognostic performance of the SCORE model in MONICA and HAPIEE samples, it was highly unlikely that their combination could achieve this goal. Nevertheless, future studies of adequate power could demonstrate that SCORE-comprising classical risk factors, socioeconomic measures, and alcohol consumption parameters might each be significantly associated with CVD mortality and provide an incremental prognostic value to the cardiovascular risk assessment model.

Although in this thesis, socioeconomic factors or hazardous drinking did not substantially improve SCORE performance, it neither denotes their irrelevance for cardiovascular risk prediction, nor denies the important role of tackling socioeconomic disadvantage and hazardous alcohol consumption in decreasing the overall burden of disease and, specifically, CVD burden.[241;415] At the same time, socioeconomic disadvantage and hazardous drinking are important, but not exclusive additional determinants of total CVD risk. The issue of extending cardiovascular risk scales by other risk predictors is discussed below.

10.4.4. Other cardiovascular risk predictors

The already extensive and constantly growing panel of cardiovascular risk markers currently includes: laboratory markers of inflammation, endothelial dysfunction, or oxidative stress (such as hsCRP, homocysteine, folate, IL-6, vascular and cellular adhesion molecules, matrix metalloproteinase 1, E-selectin, leptin, and antibodies to infectious agents – e.g., cytomegalovirus and chlamydia), cardiac injury (troponins), neurohormonal activation (brain natriuretic peptide, aldosterone), renal injury (cystatin C, urinary albumin/creatinine ratio), procoagulation (for instance, fibrinogen, thromboxane A2, D-dimer, plasminogen activator inhibitor type 1), dyslipidaemia

(lipoprotein (a), apolipoprotein B/apolipoprotein A1 ratio, lipoprotein-associated phospholipase, small dense LDL, oxidised LDL), and hyperglycaemia (glycated haemoglobin); genetic biomarkers (such as single nucleotide polymorphisms from chromosomes 9p21.3, 1p13.3, 2q36.3, or 10q11.21); imaging biomarkers (for example, coronary calcification or carotid intima-media thickness); vascular function markers (such as aortic pulse wave velocity, ankle-brachial index, or brachial artery flow-mediated dilation); and various abnormalities at exercise stress electrocardiography, stress echocardiography, or stress myocardial perfusion (e.g.[26;28-32;40;86;177;450-454]).

There have been several attempts to extend the original SCORE model by adding HDL-CH (overall improvement in AUROC by 0.01; NRI 2%)[192], resting heart rate (AUROC improvement <0.01; NRI 0.3%)[193], or markers of subclinical organ damage, such as left ventricular mass index, atherosclerotic carotid plaques, carotid/femoral pulse wave velocity, and urine albumin/creatinine ratio (increase in C-statistic 0.02; NRI 9%).[194] These studies have demonstrated statistically significant, but modest from a clinical perspective, changes in the prognostic performance. It should be taken into account that the more predictors the model includes, the more expensive their measurement, and the less focused the quality control.[10;76;394] Presently, there is no evidence that reducing the levels of novel risk determinants could effectively reduce total cardiovascular risk.[32;33;180;185]

On the other hand, the continuous search for new cardiovascular risk predictors is justified by the fact that the share of additional risk determinants in the population-attributable risk of CVD and, hence, their preventive potential is unrestrictedly large. Given the unlimited number of possible combinations of component causes which would result in CVD development, the maximal sum of disease fractions attributable to all the component causes is infinite, as well as the potential number of risk determinants.[8;455] Adding several new predictors to the risk model appears to be more beneficial for the prognostic performance measures, compared to individual extra risk determinants. This so-called multiple biomarker, or multimarker, approach supports extending the model by a number of predictors which reflect different pathogenetic pathways and, hence, provide additional prognostic information.[32-34;41;86;186;456] The essential condition is that these novel risk markers provide incremental prognostic value beyond standard risk factors, and/or can assist in the treatment selection, and/or improve clinical outcomes via altered management.[8;31;39;40;75;86;180;188;457] Ultimately, the extended

instruments need to undergo all the steps of the complex risk scale "evolution" (***Section 10.4.2(b)***), which must also include test standardisation and validation of population norms; evaluation of observer bias and reliability; investigation of the model generalizability to external populations; and assessment of potential harms, costs, and benefits of additional testing.[31;86;346]

The most appropriate and cost-effective strategy for applying extended risk models could be their use for individuals at intermediate risk, since in the traditionally established low-risk group, even abnormal results of additional testing may not justify further investigation or treatment. At the same time, in the conventionally identified high-risk group, even normal results of extra tests could not lead to discontinuation of preventive treatment.[10;13;31;34;39-41;180;188;347] Introduction of an additional "intermediate risk" category, which has a particular need for collecting extra prognostic information, to the SCORE instrument could enable a better representation of the well-established concept of cardiovascular risk continuum, without sacrificing SCORE clarity and user-friendliness. Potentially, this "grey" category would benefit the most from extending the original SCORE instrument by additional risk determinants, and may demonstrate not only statistically, but also clinically significant improvement in the model performance.

The adequate assessment of extended cardiovascular risk models requires large outcome numbers, in order to achieve adequate EPV values (***Section 10.2.5***), and large samples drawn from diverse populations. One of the promising approaches might be the meta-analysis based on individual participant data (IPD).[458-461] Despite numerous logistic and methodological difficulties, it provides an opportunity to perform data analyses in a consistent, standardised way, including the data from both published and unpublished studies. Pooling the information across studies requires extensive data harmonisation, which is a challenging, but rewarding task, as demonstrated by the example of the collaborative multidisciplinary DataSHaPER (DataSchema and Harmonization Platform for Epidemiological Research) Project.[462;463] For CEE/FSU countries, it is particularly important to participate in such collaborations, since they produce valid, generalizable, and context-relevant results even if the sample sizes of individual studies are understandably limited.

10.4.5. Lifestyle-oriented CVD risk assessment and risk reduction

The area of cardiovascular risk assessment is currently developing in two opposite, but complementary directions: the search for more complex models, extended by novel risk

determinants (see previous section) vs. the simplification of risk scales and minimisation of risk predictors. Recently, it has been demonstrated that the number of variables in CVD risk models can be successfully reduced to the core, easily measurable risk factors, such as age, gender, TCH, SBP, and smoking. For instance, this so-called low-information approach was proven successful in contemporary Chinese populations.[23] After recalibration, based on the data from non-Chinese Asian cohorts, discrimination and calibration of the "low-information" Framingham model were adequate.

The low-information approach can be simplified even further, involving only the assessment of demographic characteristics (age and gender) and non-laboratory parameters (such as smoking status, SBP, BMI, waist-to-hip ratio, self-reported DM, AH, current antihypertensive treatment, or family history). For example, non-laboratory models have shown satisfactory calibration and discrimination among middle-aged participants of the Framingham Heart Study and Framingham Offspring Study[48], American men and women participating in the NHANES Follow-up Study[464], middle-aged Finnish men and women[465], EPIC-Norfolk Study subjects[466], and participants of the well-known case-control INTERHEART study.[467] Moreover, the performance of the CVD risk algorithms that were derived exclusively from questionnaire data is only slightly worse than that for the models including data from questionnaires, physical examination, and blood tests, as demonstrated, for example, for middle-aged participants of the Norwegian Tromsø Study[330], or members of the nine European cohorts participating in the MORGAM Project.[468]

These findings are particularly promising for transitional, developing, low and middle-income countries, including CEE/FSU populations, due to the limited resources of their healthcare systems.[24;52] In all settings, evaluating CVD risk with laboratory-based scales means the individuals have to return for a fasting blood test, which compromises their compliance and the potential for risk reduction, while non-laboratory risk assessment can be performed during the same clinical visit, in 5-10 minutes, using non-invasive routine procedures.[12;156;464] In addition, simplified, non-laboratory CVD risk scales could be used as a pre-stratification test in the stepwise population screening, prior to visiting the clinic[466;469], and potentially even be self-administered.[13]

As a clinical reflection of this non-laboratory paradigm, the updated version of HeartScore, an interactive tool calculating individual SCORE risk levels, features the

"fast track" calculator which replaces BP and TCH inputs with BMI values. While this approach might be useful when instrumental measures are not available, it is recommended only for preliminary risk assessment.[139] The comparative prognostic performance of this simplified algorithm across Western and CEE/FSU populations deserves to be addressed in future studies, since the relationship between BMI and SBP, or between BMI and TCH, was demonstrated to be rather different in Russia and Western Europe.[470]

The important role of conventional risk factors not only for CVD risk assessment, but also for risk reduction has been re-emphasized by the INTERHEART study. Across 52 participating countries, only nine potentially modifiable and largely lifestyle-determined factors (smoking, dyslipidaemia, AH, DM, abdominal obesity, physical activity, diet, alcohol, and psychosocial stress) explained over 90% of population-attributable risk (PAR) of the first MI, while four of them – smoking, dyslipidaemia, AH, and DM – accounted for 76% of PAR.[49] Since classical risk factors explain the vast majority of cardiovascular events across populations, even modest downward shifts in the population levels of BP, TCH, and smoking prevalence could result in a substantial reduction of total cardiovascular risk and CVD rates, without additional costs or increased risk of adverse effects associated with pharmacological risk management.[237;396;471-480]

Although pharmacological treatments are important for managing some classical risk determinants, such as AH, dyslipidaemia, or DM, there is also a need for addressing lifestyle as the underlying cause, via rebalancing the current research, clinical care, and health policy priorities. Specifically, more research is needed on the "upstream" lifestyle risk factors (smoking, obesity, physical inactivity, and unhealthy diet), their personal and environmental determinants, and effective, early interventions to control these factors.[7;44;475;481-485] The importance of the so-called primordial prevention, or prevention of risk factors, is highlighted by the fact that patients receiving antihypertensive, lipid-lowering, and glucose-lowering drugs are still at a higher cardiovascular risk than people without AH, dyslipidaemia, or DM; moreover, in the real-world clinical practice, even treated CVD patients often have uncontrolled lifestyle risk determinants.[329;432;472;481;486;487] While lifestyle changes are the cornerstone of primary prevention, due to their population-wide benefits and minimization of adverse drug effects, they also provide similar relative impacts in secondary prevention and,

hence, result in an even greater reduction of absolute risk. In addition, the preventive programmes promoting healthy lifestyle are able to lower the costs to individuals, healthcare systems, and societies as a whole.[44;471;473;475;480;481;487-490]

Targeting classical risk factors in order to reduce CVD risk levels is particularly important for the CEE/FSU populations, which currently demonstrate the lowest control rates even among individuals with already developed cardiovascular pathology. For example, among treated middle-aged outpatients from 12 European countries, examined in 2009 as a part of the international EURIKA study, Russia had a lower than average prevalence of achieving target levels of BP (36%), TCH and LDL-CH (24%), glycated haemoglobin (4%), and BMI (1%).[430;431] Therefore, lifestyle interventions in CEE/FSU populations, such as more effective smoking cessation strategies and advice on healthy diet, weight reduction, and physical activity, may result in substantially improved control of total cardiovascular risk.

This thesis has focused on the SCORE risk assessment and identification of individuals and groups at higher risk. However, this strategy alone is unlikely to substantially reduce the overall CVD prevalence, since the "low-risk" population, due to its larger size, will comprise more events.[7;40;47;53;197;471;491] At the same time, a substantial proportion of cardiovascular events occur in patients with established CVD, who should be the highest priority for comprehensive, aggressive risk management.[6;14;418;492;493] Therefore, in order to curb the worldwide CVD epidemic and, in particular, to reduce the high burden of disease in CEE/FSU populations, a combination of population-level and high-risk approaches is necessary. The first strategy is targeted at reducing the CVD incidence, by shifting the distribution of risk factors in the entire population through community-based interventions. The second strategy aims to identify and treat the individuals at the highest risk, who gain the most from aggressive risk factor modification, while low-risk individuals avoid unnecessary medicalization.[4;7;10;13;17;24;52;147;177;197;347;433;471;483;484;494;495]

As demonstrated by the widely used IMPACT model of coronary mortality, the recent CHD decline in developed countries is partly explained by the changes in major risk factors (approximately 60%), which mostly reflect the population-level risk reduction, and partly by specific cardiovascular treatments (approximately 40%), which typically represent the high-risk approach.[203;474;475;496;497] To my knowledge, the IMPACT model has only recently been applied to some CEE/FSU populations, and the preliminary data

suggest that the relative impact of risk factor reduction and treatment is similar to that in Western populations. For example, in the Polish adult population, aged 25-74 years, coronary mortality halved from 1991 to 2005 (over 26,000 fewer CHD deaths), which was explained by beneficial dynamics in risk factors (54%) and the increased uptake of cardiovascular treatments (37%).[158]

The recent modelling studies suggest that both population and high-risk approaches can be effective for Europe as a whole and for individual CEE/FSU countries. For instance, in the selected SCORE Project cohorts from the "high-risk" European countries, a 10-year reduction of TCH levels by 10%, SBP levels by 10%, and smoking prevalence by 10% could save 9,125 lives per million of adult population, while treating all high-risk individuals with statins, antihypertensive agents, and aspirin would save up to 7,452 lives per million.[471] Another modelling study showed that a sustained reduction in the mean SBP levels by 5 mm Hg, either pharmacological or non-pharmacological, could avert up to 69.4, 83.4, and 100.7 cardiovascular deaths per 100,000 person-years among 30-69-year-old people from the Czech Republic, Poland, and Lithuania, respectively, and that the higher the baseline CVD risk in the population, the greater the benefits of risk reduction.[498]

Therefore, to effectively reduce the high levels of CVD in CEE/FSU, as well as to avoid the reversal of declining CVD rates in other countries, the complementary population-level and high-risk strategies of cardiovascular prevention should be based on robust, accurate, up-to-date risk prediction instruments, together with the effective control of conventional, lifestyle-related risk factors and, possibly, novel risk determinants.

10.5. Study implications and conclusions

Cardiovascular risk prediction and reduction is an extensive, multidisciplinary, dynamic field, with numerous scientific and practical directions for further development. This section focuses on the research and policy implications of the thesis and outlines how the data on SCORE performance in CEE/FSU populations could be used for both the optimisation of cardiovascular risk assessment and the effective management of this risk, in order to reduce the CVD burden. The conclusion summarises how the key findings of this thesis help to address the existing gaps in knowledge and to expand the evidence base of cardiovascular risk assessment.

10.5.1. Research implications

This thesis has focused on the prognostic performance of the high-risk SCORE version, as the use of this scale is recommended for CEE/FSU countries.[17;20] It was shown that the high-risk SCORE was a significant predictor of fatal atherosclerotic CVD in all MONICA and HAPIEE samples, both before and after the adjustment for socioeconomic characteristics and hazardous drinking parameters. At the same time, the high-risk SCORE under-predicted the risk in Russian MONICA participants, and could over-estimate the risk in Czech and Polish HAPIEE samples. These findings have several research implications.

First, the high-risk SCORE could be effectively used for the populations of interest which still face high levels of cardiovascular mortality, such as Russia. However, in the countries which have experienced a decline in fatal CVD, such as the Czech Republic and Poland, the low-risk SCORE might be the instrument of choice. A longer-term solution for the task of further improvement of SCORE performance in the region of interest should be the recalibration of this scale for respective CEE/FSU populations, using local levels of cardiovascular mortality and risk factors.[139] The possible sources of information on CVD risk determinants are local epidemiological studies, clinical practice databases, and national systems of health and disease surveillance.

Second, the next step in the "evolution" of recalibrated SCORE versions should be their clinical validation, such as the investigation of the scale uptake by health professionals and the impact on clinical decisions, health outcomes, and healthcare costs. This research step is especially important for CEE/FSU populations, as they might face additional barriers to the implementation of cardiovascular risk assessment and its translation into effective risk reduction.

Third, this thesis did not demonstrate a marked improvement in SCORE performance after extending the model by socioeconomic parameters or hazardous drinking characteristics. However, this does not necessarily negate the need for further investigation of these additional cardiovascular risk factors, which are particularly relevant to CEE/FSU populations. Future studies may show that other measures of socioeconomic disadvantage (such as area-level deprivation or individual and household income and wealth), or hazardous alcohol consumption (for example, surrogate/non-beverage drinking), when added to SCORE separately or in combination, could be independently related to the fatal CVD risk and provide incremental prognostic value.

Fourth, the findings of the thesis stressed the importance of assessing the improvement in discrimination of extended models, as, for example, IDI values for the extended SCORE were under 1% across most MONICA and HAPIEE samples. In future, other novel predictors may provide a clinically significant improvement in the performance of the expanded SCORE instrument, most likely in people with intermediate risk levels. New SCORE versions, therefore, may progress from the current "dichotomous" approach (risk levels ≥5% have been regarded as "increased risk", which implies that levels <5% denote "non-increased risk") and introduce an intermediate risk category.

Fifth, in the CEE/FSU context, the data on novel risk factors are not routinely collected in epidemiological studies or in the clinical practice. An alternative is to employ the "low-information" approach, which uses non-laboratory measurements and self-reported characteristics for the assessment of cardiovascular risk. Future studies need to compare the prognostic performance and the cost-effectiveness of the original SCORE vs. the recently introduced modified SCORE instrument, in which SBP and TCH are substituted with BMI[139], across the CEE/FSU populations.

Finally, the findings of this thesis, consistently with the WHO data on cardiovascular mortality trends and the results of international and local studies, demonstrate that some CEE countries, such as the Czech Republic and Poland, have experienced a recent reduction in fatal CVD rates. The relative impact of the risk factor dynamics and cardiovascular treatments on this decline should be compared across populations of interest (for example, using the IMPACT model), in order to identify the context-specific priorities for both population-level and high-risk strategies of cardiovascular prevention.

10.5.2. Policy implications

The development of recalibrated local SCORE instruments in CEE/FSU is essential for improving the accuracy of cardiovascular risk prediction in these populations, characterised by high but heterogeneous risk levels. This task requires a major shift in health policy, as the priorities of healthcare systems need to expand from treatment to prevention. In particular, the adequate assessment and effective management of cardiovascular risk, which follows the current ESC recommendations[17], should be incorporated into routine clinical practice and supported by sufficient organisational, educational, and material resources.

The availability of an accurate, context-specific SCORE version could increase the physicians' uptake of this instrument and their compliance with the clinical guidelines on CVD prevention, and, hopefully, improve both the clinical effectiveness and the cost-effectiveness of cardiovascular risk reduction. The real-world performance of SCORE should be constantly monitored, and health policy decisions should take this evidence into account.

This thesis has re-emphasised the importance of classical risk factors, captured by SCORE, for the prediction of cardiovascular risk in CEE/FSU settings. Moreover, these conventional risk factors and their lifestyle determinants should be the main target of cardiovascular prevention. Controlling their levels both across whole populations and in higher-risk groups and individuals (identified with risk assessment instruments, such as SCORE) will help to reduce the burden of CVD in CEE/FSU.

10.5.3. Conclusions

The global burden of CVD, which remains one of the leading public health problems, is not evenly distributed. Some countries, such as CEE/FSU states, face particularly high albeit heterogeneous levels of cardiovascular mortality, morbidity, and disability. To address this problem, future CVD cases should be prevented via accurate assessment of cardiovascular risk and its effective management, with a specific focus on individuals and groups at higher risk. The risk scale which is officially recommended by the ESC for the use in CEE/FSU populations is the high-risk SCORE version. However, this instrument, which was developed without using any local data, has not been properly recalibrated to local settings, and thus far, its prognostic performance has not been investigated in the region of interest. Moreover, the SCORE-comprising classical risk factors are important, but not exclusive, determinants of cardiovascular risk. Previous attempts to expand the SCORE model did not employ socioeconomic parameters or hazardous drinking, as additional determinants of cardiovascular risk which might be particularly important in CEE/FSU settings.

In order to address these gaps, the thesis used prospective individual-level data from Czech, Polish, Lithuanian, and Russian samples of two large international studies, MONICA and HAPIEE. It was shown that the high-risk SCORE was a significant, independent predictor of fatal atherosclerotic CVD both across individual study-, country-, and gender-specific samples and in random-effects meta-analyses. While this

SCORE version demonstrated satisfactory discrimination in most MONICA and HAPIEE samples, it substantially under-predicted the 10-year risk of CVD death in Russian MONICA. In HAPIEE, 10-year calibration estimates suggested that the high-risk SCORE could adequately reflect the risk in contemporary Russian settings, although the low-risk SCORE might be better fitted for Czech and Polish populations. SCORE extension by socioeconomic characteristics or hazardous drinking parameters did not substantially improve the prognostic performance of the model in MONICA and HAPIEE.

These findings demonstrate that, in order to optimise cardiovascular risk prediction in CEE/FSU populations, SCORE should be recalibrated to local settings, which will better reflect recent heterogeneous trends in fatal CVD across the region of interest. Accurate cardiovascular risk assessment and effective risk management should be incorporated into routine clinical practice and established as one of the priorities of healthcare systems. While the search for novel risk predictors should continue, preventive measures need to be focused primarily on conventional, lifestyle-determined risk factors. As demonstrated by a steady decline in cardiovascular mortality rates across most Western populations over the last 50 years and, more recently, by the positive dynamic of CVD trends in the Czech Republic and Poland, the task of reducing CVD burden in CEE and particularly FSU is challenging but nonetheless feasible.

Addendum

As this thesis went to press (May 2012), the Fifth Joint Task Force of the European Society of Cardiology and other societies published the latest guidelines on CVD prevention in clinical practice.[499] The references to the current CVD prevention guidelines throughout the thesis reflect the information presented in the respective 2007 document by the Fourth Joint Task Force.[17]

The major updates in the newest guidelines[499] include modifications to the list of high and low-risk European countries. In particular, while the high-risk SCORE version is still recommended for the Czech Republic and Poland, it is now expected to under-estimate the risk in Russia and Lithuania, which have become "very-high-risk countries". However, no SCORE modification for the populations at very high risk is presented, and no evidence supporting this division of CEE and FSU countries is given, apart from the 2008 national rates of CVD and DM mortality. At the same time, the differentiation of CEE/FSU populations in terms of background risk levels (and, hence, the locally appropriate SCORE versions) agrees with the findings of this thesis.

The change in SCORE calibration over time, demonstrated for MONICA vs. HAPIEE samples, is consistent with the fact that the 2012 guidelines no longer consider countries such as Austria, Germany, Iceland, the Netherlands, or Norway as "high-risk". This also confirms that it is feasible to reduce the CVD burden in a relatively short period and across different populations.

Finally, one of the research implications of this thesis – the assessment of extra risk factors in the intermediate risk group – is mirrored in the new recommendations which suggest the measurement of novel biomarkers and the employment of cardiovascular imaging methods among asymptomatic adults at "moderate risk" (SCORE levels ≥1% and <5%).

Therefore, the results of the present research, obtained and summarised prior to May 2012, should be regarded as generally consistent with the latest European guidelines on CVD prevention.

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Appendix I. SCORE-predicted 10-year risk of fatal CVD in populations at high and low CVD risk

Table A4.3.1. SCORE-predicted 10-year risk of fatal CVD in populations at high CVD risk[17;20]

Age, years	SBP (mm Hg)	**Women**										**Men**									
		Non-smoker					Smoker					Non-smoker					Smoker				
		TCH (mmol/l)					TCH (mmol/l)					TCH (mmol/l)					TCH (mmol/l)				
		4	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*
65	180	7	8	9	10	12	13	15	17	19	22	14	16	19	22	26	26	30	35	41	47
	160	5	5	6	7	8	9	10	12	13	16	9	11	13	15	16	18	21	25	29	34
	140	3	3	4	5	6	6	7	8	9	11	6	8	9	11	13	13	15	17	20	24
	120	2	2	3	3	4	4	5	5	6	7	4	5	6	7	9	9	10	12	14	17
60	180	4	4	5	6	7	8	9	10	11	13	9	11	13	15	18	18	21	24	28	33
	160	3	3	3	4	5	5	6	7	8	9	6	7	9	10	12	12	14	17	20	24
	140	2	2	2	3	3	3	4	5	5	6	4	5	6	7	9	8	10	12	14	17
	120	1	1	2	2	2	2	3	3	4	4	3	3	4	5	6	6	7	8	10	12
55	180	2	2	3	3	4	4	5	5	6	7	6	7	8	10	12	12	13	16	19	22
	160	1	2	2	2	3	3	3	4	4	5	4	5	6	7	8	8	9	11	13	16
	140	1	1	1	1	2	2	2	2	3	3	3	3	4	5	6	5	6	8	9	11
	120	1	1	1	1	1	1	1	2	2	2	2	2	3	3	4	4	4	5	6	8
50	180	1	1	1	2	2	2	2	3	3	4	4	4	5	6	7	7	8	10	12	14
	160	1	1	1	1	1	1	2	2	2	3	2	3	3	4	5	5	6	7	8	10
	140	0	1	1	1	1	1	1	1	1	2	2	2	2	3	3	3	4	5	6	7
	120	0	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	3	3	4	5
40	180	0	0	0	0	0	0	0	0	1	1	1	1	1	2	2	2	2	3	3	4
	160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	2	2	2	3
	140	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2
	120	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

Table A4.3.2. SCORE-predicted 10-year risk of fatal CVD in populations at low CVD risk[17;20]

Age, years	SBP (mm Hg)	**Women**										**Men**									
		Non-smoker					Smoker					Non-smoker					Smoker				
		TCH (mmol/l)					TCH (mmol/l)					TCH (mmol/l)					TCH (mmol/l)				
		4	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*	*4*	*5*	*6*	*7*	*8*
65	180	4	5	6	6	7	9	9	11	12	14	8	9	10	12	14	15	17	20	23	26
	160	3	3	4	4	5	6	6	7	8	10	5	6	7	8	10	10	12	14	16	19
	140	2	2	2	3	3	4	4	5	6	7	4	4	5	6	7	7	8	9	11	13
	120	1	1	2	2	2	3	3	3	4	4	2	3	3	4	5	5	5	6	8	9
60	180	3	3	3	4	4	5	5	6	7	8	5	6	7	8	9	10	11	13	15	18
	160	2	2	2	2	3	3	4	4	5	5	3	4	5	5	6	7	8	9	11	13
	140	1	1	1	2	2	2	2	3	3	4	2	3	3	4	4	5	5	6	7	9
	120	1	1	1	1	1	1	2	2	2	3	2	2	2	3	3	3	4	4	5	6
55	180	1	1	2	2	2	3	3	3	4	4	3	4	4	5	6	6	7	8	10	12
	160	1	1	1	1	1	2	2	2	3	3	2	2	3	3	4	4	5	6	7	8
	140	1	1	1	1	1	1	1	1	2	2	1	2	2	2	3	3	3	4	5	6
	120	0	0	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	3	3	4
50	180	1	1	1	1	1	1	1	2	2	2	2	2	3	3	4	4	4	5	6	7
	160	0	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	3	3	4	5
	140	0	0	0	0	0	1	1	1	1	1	1	1	1	1	2	2	2	2	3	3
	120	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	2	2	2
40	180	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2
	160	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1
	140	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1

APPENDIX II. SCORE performance in MONICA and HAPIEE: additional tables and figures

Table A6.1.1. Dichotomous and continuous low-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE (≥5% vs. <5%)	4.29 (2.13-8.63)	4.76 (3.12-7.27)	3.76 (2.28-6.20)	2.45 (1.42-4.24)	3.04 (2.25-4.10)
Continuous SCORE (per 1% increase)	1.16 (1.11-1.22)	1.18 (1.13-1.23)	1.20 (1.14-1.26)	1.15 (1.08-1.23)	1.20 (1.17-1.24)
Women					
Dichotomous SCORE (≥5% vs. <5%)	too few observations	5.19 (1.75-15.43)	too few observations	too few observations	6.30 (3.26-12.17)
Continuous SCORE (per 1% increase)	1.39 (1.09-1.76)	1.34 (1.15-1.55)	1.54 (1.24-1.93)	1.47 (1.28-1.69)	1.56 (1.44-1.70)

Table A6.1.2. Dichotomous and continuous high-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals obtained by standard Cox analysis (1st line), competing-risks Cox analysis (2nd line), and Weibull analysis (3rd line)

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE (≥5% vs. <5%)	5.32 (2.30-12.30) 5.00 (2.16-11.54) 5.33 (2.30-12.32)	4.50 (2.68-7.56) 4.24 (2.52-7.13) 4.50 (2.67-7.56)	3.06 (1.77-5.29) 3.00 (1.73-5.19) 3.06 (1.77-5.29)	3.99 (2.24-7.10) 3.79 (2.13-6.73) 3.97 (2.23-7.06)	2.66 (1.96-3.62) 2.54 (1.87-3.45) 2.66 (1.96-3.62)
Continuous SCORE (per 1% increase)	1.09 (1.06-1.12) 1.09 (1.06-1.12) 1.09 (1.06-1.12)	1.10 (1.07-1.12) 1.09 (1.07-1.12) 1.10 (1.07-1.12)	1.11 (1.08-1.14) 1.11 (1.07-1.14) 1.11 (1.08-1.14)	1.08 (1.05-1.12) 1.08 (1.05-1.11) 1.08 (1.05-1.12)	1.11 (1.09-1.13) 1.11 (1.09-1.12) 1.11 (1.09-1.13)
Women					
Dichotomous SCORE (≥5% vs. <5%)	5.02 (1.64-15.36) 4.98 (1.63-15.15) 5.06 (1.66-15.47)	1.70 (0.57-5.06) 1.65 (0.55-4.90) 1.71 (0.58-5.08)	4.15 (1.49-11.52) 3.97 (1.43-11.01) 4.15 (1.49-11.52)	5.07 (2.20-11.66) 4.94 (2.15-11.33) 5.02 (2.18-11.54)	6.32 (4.08-9.79) 6.14 (3.97-9.50) 6.30 (4.07-9.76)
Continuous SCORE (per 1% increase)	1.23 (1.06-1.43) 1.23 (1.11-1.36) 1.23 (1.06-1.43)	1.21 (1.10-1.33) 1.20 (1.10-1.32) 1.21 (1.10-1.33)	1.33 (1.16-1.53) 1.32 (1.21-1.45) 1.33 (1.16-1.53)	1.27 (1.16-1.39) 1.27 (1.19-1.37) 1.27 (1.16-1.39)	1.34 (1.27-1.41) 1.33 (1.27-1.41) 1.34 (1.27-1.41)

Table A6.1.3. Dichotomous and continuous low-risk SCORE and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals obtained by standard Cox analysis (1st line), competing-risks Cox analysis (2nd line), and Weibull analysis (3rd line)

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE (≥5% vs. <5%)	4.29 (2.13-8.63) 3.97 (1.98-7.97) 4.30 (2.14-8.64)	4.76 (3.12-7.27) 4.31 (2.82-6.57) 4.76 (3.12-7.27)	3.76 (2.28-6.20) 3.63 (2.20-5.98) 3.77 (2.28-6.21)	2.45 (1.42-4.24) 2.34 (1.35-4.05) 2.44 (1.41-4.21)	3.04 (2.25-4.10) 2.87 (2.13-3.87) 3.04 (2.26-4.10)
Continuous SCORE (per 1% increase)	1.16 (1.11-1.22) 1.16 (1.10-1.22) 1.16 (1.11-1.22)	1.18 (1.13-1.23) 1.17 (1.13-1.22) 1.18 (1.13-1.23)	1.20 (1.14-1.26) 1.20 (1.13-1.26) 1.20 (1.14-1.26)	1.15 (1.08-1.23) 1.14 (1.09-1.20) 1.15 (1.08-1.22)	1.20 (1.17-1.24) 1.20 (1.16-1.23) 1.20 (1.17-1.24)
Women					
Dichotomous SCORE (≥5% vs. <5%)	too few observations	5.19 (1.75-15.43) 5.06 (1.70-15.07) 5.22 (1.76-15.51)	too few observations	too few observations	6.30 (3.26-12.17) 6.16 (3.23-11.76) 6.29 (3.25-12.16)
Continuous SCORE (per 1% increase)	1.39 (1.09-1.76) 1.39 (1.19-1.62) 1.39 (1.09-1.76)	1.34 (1.15-1.55) 1.33 (1.15-1.53) 1.34 (1.15-1.55)	1.54 (1.24-1.93) 1.53 (1.33-1.76) 1.54 (1.24-1.93)	1.47 (1.28-1.69) 1.47 (1.31-1.65) 1.47 (1.28-1.69)	1.56 (1.44-1.70) 1.55 (1.42-1.69) 1.56 (1.44-1.70)

Table A6.1.4. Dichotomous and continuous low-risk SCORE and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	Poland	Russia
Men			
Dichotomous SCORE (≥5% vs. <5%)	6.55 (3.09-13.88)	3.24 (1.64-6.42)	5.52 (3.45-8.84)
Continuous SCORE (per 1% increase)	1.19 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
Women			
Dichotomous SCORE (≥5% vs. <5%)	2.39 (0.55-10.33)	9.15 (3.18-26.33)	6.91 (3.75-12.74)
Continuous SCORE (per 1% increase)	1.34 (1.11-1.62)	1.56 (1.38-1.76)	1.56 (1.40-1.73)

Table A6.1.5. Dichotomous and continuous high-risk SCORE and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals obtained by standard Cox analysis (1st line), competing-risks Cox analysis (2nd line), and Weibull analysis (3rd line)

	Czech Republic	Poland	Russia
Men			
Dichotomous SCORE (≥5% vs. <5%)	10.51 (2.53-43.71) 10.35 (2.49-43.09) 10.52 (2.53-43.73)	2.56 (1.11-5.87) 2.50 (1.09-5.74) 2.55 (1.11-5.86)	7.63 (3.35-17.40) 7.50 (3.30-17.08) 7.61 (3.34-17.34)
Continuous SCORE (per 1% increase)	1.10 (1.07-1.13) 1.10 (1.07-1.12) 1.10 (1.07-1.13)	1.10 (1.06-1.13) 1.10 (1.07-1.13) 1.10 (1.06-1.13)	1.08 (1.06-1.10) 1.08 (1.06-1.09) 1.08 (1.06-1.10)
Women			
Dichotomous SCORE (≥5% vs. <5%)	3.59 (1.44-8.91) 3.56 (1.44-8.84) 3.57 (1.44-8.88)	8.79 (3.19-24.18) 8.67 (3.15-23.83) 8.79 (3.20-24.19)	7.36 (3.77-14.38) 7.34 (3.75-14.35) 7.49 (3.83-14.62)
Continuous SCORE (per 1% increase)	1.20 (1.06-1.35) 1.20 (1.10-1.30) 1.20 (1.06-1.35)	1.32 (1.22-1.43) 1.32 (1.24-1.41) 1.32 (1.22-1.43)	1.32 (1.24-1.41) 1.32 (1.24-1.41) 1.32 (1.24-1.42)

Table A6.1.6. Dichotomous and continuous low-risk SCORE and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals obtained by standard Cox analysis (1st line), competing-risks Cox analysis (2nd line), and Weibull analysis (3rd line)

	Czech Republic	Poland	Russia
Men			
Dichotomous SCORE (≥5% vs. <5%)	6.55 (3.09-13.88) 6.43 (3.04-13.63) 6.56 (3.09-13.89)	3.24 (1.64-6.42) 3.16 (1.60-6.25) 3.24 (1.64-6.42)	5.52 (3.45-8.84) 5.41 (3.38-8.66) 5.50 (3.44-8.80)
Continuous SCORE (per 1% increase)	1.19 (1.13-1.25) 1.18 (1.14-1.23) 1.19 (1.13-1.25)	1.18 (1.12-1.25) 1.18 (1.12-1.24) 1.18 (1.12-1.25)	1.14 (1.11-1.18) 1.14 (1.11-1.17) 1.14 (1.11-1.18)
Women			
Dichotomous SCORE (≥5% vs. <5%)	2.39 (0.55-10.33) 2.36 (0.55-10.25) 2.36 (0.55-10.21)	9.15 (3.18-26.33) 8.97 (3.12-25.80) 9.19 (3.19-26.44)	6.91 (3.75-12.74) 6.90 (3.74-12.74) 6.99 (3.79-12.88)
Continuous SCORE (per 1% increase)	1.34 (1.11-1.62) 1.34 (1.17-1.53) 1.34 (1.11-1.62)	1.56 (1.38-1.76) 1.55 (1.41-1.71) 1.55 (1.38-1.75)	1.56 (1.40-1.73) 1.55 (1.40-1.72) 1.56 (1.41-1.74)

Table A6.2.1. Predicted (P) by low-risk SCORE and observed (O) 10-year atherosclerotic CVD mortality by age groups and SCORE level in MONICA men

	Czech Republic			Poland (Warsaw)			Poland (Tarnobrzeg)			Lithuania			Russia		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	2.71 (3.06) N=17.2	5.03 N=32	0.54	3.00 (3.04) N=37.6	6.68 N=86	0.45	2.82 (2.63) N=35.7	4.89 N=62	0.58	2.58 (2.69) N=42.6	3.51 N=58	0.74	2.78 (2.69) N=71.6	7.03 N=181	0.40
Age groups, years															
40-44.9	0.42 (0.51) N=0.7	1.16 N=2	0.36	0.39 (0.50) N=1.1	3.32 N=9	0.12	0.39 (0.51) N=0.9	2.71 N=6	0.14	0.30 (0.46) N=1.2	1.02 N=4	0.29	0.33 (0.47) N=1.5	3.96 N=18	0.08
45-49.9	1.94 (1.12) N=2.8	4.20 N=6	0.46	1.87 (1.00) N=4.9	3.85 N=10	0.49	1.74 (0.88) N=4.6	2.28 N=6	0.76	1.61 (0.96) N=5.1	1.57 N=5	1.03	1.68 (0.91) N=9.8	4.12 N=24	0.41
50-54.9	2.72 (1.74) N=3.7	5.22 N=7	0.52	2.56 (1.75) N=6.4	5.98 N=15	0.43	2.42 (1.60) N=6.6	5.47 N=15	0.44	2.10 (1.39) N=6.3	2.68 N=8	0.78	2.28 (1.45) N=12.2	6.92 N=37	0.33
55-59.9	4.19 (2.65) N=4.2	4.95 N=5	0.85	4.44 (2.52) N=12.5	9.57 N=27	0.46	3.83 (2.34) N=11.3	5.78 N=17	0.66	3.88 (2.49) N=14.7	6.08 N=23	0.64	3.94 (2.40) N=23.5	7.55 N=45	0.52
60-64.9	6.84 (4.79) N=5.9	13.95 N=12	0.49	6.73 (4.15) N=12.7	13.23 N=25	0.51	5.76 (3.31) N=12.4	8.37 N=18	0.69	5.83 (3.27) N=15.3	6.87 N=18	0.85	6.06 (3.40) N=24.7	14.00 N=57	0.43
SCORE level															
<5%	1.65 (1.23) N=8.7	3.42 N=18	0.48	1.74 (1.23) N=17.1	4.17 N=41	0.42	1.81 (1.19) N=18.6	3.31 N=34	0.55	1.59 (1.23) N=21.7	2.86 N=39	0.56	1.73 (1.17) N=36.1	2.86 N=39	0.61
≥5%	7.84 (3.95) N=8.6	12.84 N=14	0.61	7.59 (3.25) N=20.4	16.73 N=45	0.45	7.12 (2.72) N=17.2	11.62 N=28	0.61	7.24 (2.81) N=20.9	6.62 N=19	1.09	7.24 (2.72) N=35.6	6.62 N=19	1.09

Table A6.2.2. Predicted (P) by low-risk SCORE and observed (O) 10-year atherosclerotic CVD mortality by age groups and SCORE level in MONICA women

	Czech Republic			**Poland (Warsaw)**			**Poland (Tarnobrzeg)**			**Lithuania**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	0.99 (1.34) N=7.0	1.85 N=13	0.54	1.13 (1.58) N=13.0	1.82 N=21	0.62	0.97 (1.26) N=14.2	1.30 N=19	0.75	0.88 (1.25) N=14.5	1.58 N=26	0.56	0.92 (1.29) N=24.6	3.21 N=86	0.29
Age groups, years															
40-44.9	0.00 (0.00) N=0.0	0.59 N=1	N/A	0.00 (0.00) N=0.0	0.00 N=0	N/A	0.00 (0.00) N=0.0	0.37 N=1	N/A	0.00 (0.00) N=0.0	0.25 N=1	N/A	0.00 (0.00) N=0.0	0.38 N=2	N/A
45-49.9	0.33 (0.51) N=0.6	0.00 N=0	N/A	0.27 (0.47) N=0.7	2.01 N=5	0.13	0.25 (0.44) N=0.8	0.32 N=1	0.78	0.17 (0.39) N=0.6	0.29 N=1	0.59	0.12 (0.32) N=0.7	2.04 N=12	0.06
50-54.9	0.80 (0.61) N=1.0	2.42 N=3	0.33	0.83 (0.83) N=2.0	0.00 N=0	N/A	0.63 (0.56) N=2.0	0.32 N=1	1.97	0.64 (0.59) N=2.1	0.62 N=2	1.03	0.60 (0.56) N=3.4	1.61 N=9	0.37
55-59.9	1.61 (0.97) N=2.1	3.13 N=4	0.51	1.87 (1.21) N=4.5	3.33 N=8	0.56	1.51 (0.94) N=4.7	3.25 N=10	0.47	1.54 (0.87) N=4.9	2.82 N=9	0.55	1.43 (0.86) N=7.9	4.74 N=26	0.30
60-64.9	3.07 (1.66) N=3.3	4.63 N=5	0.66	3.31 (2.16) N=5.8	4.55 N=8	0.73	2.63 (1.57) N=6.8	2.33 N=6	1.13	2.73 (1.59) N=7.0	5.10 N=13	0.54	2.77 (1.63) N=12.8	8.01 N=37	0.35
SCORE level															
<5%	0.87 (1.08) N=6.0	1.89 N=13	0.46	0.88 (1.08) N=9.7	1.55 N=17	0.57	0.84 (1.00) N=12.0	1.33 N=19	0.63	0.79 (1.03) N=12.8	1.60 N=26	0.49	0.80 (1.03) N=20.9	2.90 N=76	0.28
≥5%	6.19 (1.28) N=1.0	0.00 N=0	N/A	6.25 (1.71) N=3.3	7.55 N=4	0.83	5.68 (0.58) N=2.2	0.00 N=0	N/A	6.14 (1.35) N=1.7	0.00 N=0	N/A	6.12 (0.97) N=3.6	16.95 N=10	0.36

Table A6.2.3. Predicted (P) by low-risk SCORE and observed (O) atherosclerotic CVD mortality by age groups and SCORE level in HAPIEE men

	Czech Republic			**Poland**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	4.00 (3.32) N=106.4	1.39 N=37	2.88	3.92 (3.26) N=135.5	0.98 N=34	4.00	4.84 (4.07) N=157.1	3.23 N=105	1.50
Age groups, years									
<50	1.56 (0.87) N=7.2	0.22 N=1	7.09	1.64 (0.97) N=11.6	0.28 N=2	5.86	1.78 (0.96) N=10.9	0.65 N=4	2.74
50-54.9	2.10 (1.36) N=11.0	0.38 N=2	5.53	2.16 (1.49) N=16.2	0.93 N=7	2.32	2.52 (1.66) N=17.4	1.59 N=11	1.59
55-59.9	3.41 (2.18) N=18.8	1.63 N=9	2.09	3.68 (2.23) N=27.2	0.81 N=6	4.54	4.38 (2.80) N=30.7	3.14 N=22	1.40
60-64.9	5.53 (3.48) N=31.7	2.09 N=12	2.65	5.68 (3.28) N=36.0	0.79 N=5	7.19	7.43 (4.35) N=43.9	4.06 N=24	1.83
≥65	6.82 (3.78) N=37.7	2.35 N=13	2.90	7.11 (3.91) N=44.7	2.23 N=14	3.19	8.31 (4.50) N=54.0	6.77 N=44	1.23
SCORE level									
<5%	2.21 (1.09) N=39.4	0.51 N=9	4.33	2.20 (1.08) N=52.2	0.59 N=14	3.73	2.26 (1.01) N=43.4	1.14 N=22	1.98
≥5%	7.64 (3.35) N=67.0	3.19 N=28	2.40	7.71 (3.25) N=83.5	1.85 N=20	4.17	8.58 (3.93) N=113.6	6.27 N=83	1.37

Table A6.2.4. Predicted (P) by low-risk SCORE and observed (O) atherosclerotic CVD mortality by age groups and SCORE level in HAPIEE women

	Czech Republic			**Poland**			**Russia**		
	P	*O*	*P/O*	*P*	*O*	*P/O*	*P*	*O*	*P/O*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Whole sample	1.46 (1.54) N=49.0	0.57 N=19	2.56	1.39 (1.56) N=52.2	0.43 N=16	3.23	1.77 (1.83) N=71.6	1.04 N=42	1.70
Age groups, years									
<50	0.17 (0.39) N=1.1	0.00 N=0	N/A	0.17 (0.39) N=1.5	0.23 N=2	0.74	0.20 (0.41) N=1.7	0.12 N=1	1.67
50-54.9	0.55 (0.58) N=3.9	0.28 N=2	1.96	0.56 (0.61) N=4.9	0.11 N=1	5.09	0.66 (0.62) N=5.6	0.36 N=3	1.83
55-59.9	1.27 (0.87) N=7.8	0.33 N=2	3.85	1.34 (0.87) N=10.4	0.26 N=2	5.15	1.45 (0.88) N=12.8	0.23 N=2	6.30
60-64.9	2.28 (1.50) N=18.2	0.75 N=6	3.04	2.47 (1.48) N=16.4	0.30 N=2	8.23	3.11 (1.77) N=21.6	1.44 N=10	2.16
≥65	3.09 (1.66) N=18.0	1.55 N=9	1.99	3.28 (1.84) N=19.1	1.55 N=9	2.12	3.76 (1.81) N=29.9	3.27 N=26	1.15
SCORE level									
<5%	1.22 (1.13) N=39.0	0.53 N=17	2.30	1.15 (1.12) N=41.1	0.31 N=11	3.71	1.31 (1.20) N=47.9	0.66 N=24	1.99
≥5%	6.09 (1.25) N=9.9	1.23 N=2	4.95	6.12 (1.44) N=11.2	2.73 N=5	2.24	6.05 (0.96) N=23.4	4.65 N=18	1.30

Table A6.3.1. Estimation of 10-year atherosclerotic CVD mortality in HAPIEE men and women, based on the exponential survival model

	Czech Republic		**Poland**		**Russia**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Observed HAPIEE deaths, N (%)	37 (1.39)	19 (0.57)	34 (0.98)	16 (0.43)	105 (3.23)	42 (1.04)
Current mean HAPIEE follow-up, complete years	6		5		4	
Estimated HAPIEE deaths in 10 years, N (%)	61.4 (2.31)	31.9 (0.95)	67.4 (1.95)	32.3 (0.86)	255.8 (7.88)	104.3 (2.58)

Table A6.3.2. Predicted (P) by high-risk SCORE and exponentially estimated (E) atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic			**Poland**			**Russia**		
	P	*E*	*P/E*	*P*	*E*	*P/E*	*P*	*E*	*P/E*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Men	7.51 (5.99) N=199.7	2.31 N=61.4	3.25	7.37 (5.89) N=254.7	1.95 N=67.4	3.78	9.07 (7.27) N=294.4	7.88 N=255.8	1.15
Women	2.53 (2.39) N=85.0	0.95 N=31.9	2.66	2.45 (2.41) N=92.0	0.86 N=32.3	2.85	3.08 (2.90) N=124.6	2.58 N=104.3	1.19

Table A6.3.3. Predicted (P) by low-risk SCORE and exponentially estimated (E) atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic			**Poland**			**Russia**		
	P	*E*	*P/E*	*P*	*E*	*P/E*	*P*	*E*	*P/E*
	%(SD),N	*%,N*		*%(SD),N*	*%,N*		*%(SD),N*	*%,N*	
Men	4.00 (3.32) N=106.4	2.31 N=61.4	1.73	3.92 (3.26) N=135.5	1.95 N=67.4	2.01	4.84 (4.07) N=157.1	7.88 N=255.8	0.61
Women	1.46 (1.54) N=49.0	0.95 N=31.9	1.54	1.39 (1.56) N=52.2	0.86 N=32.3	1.62	1.77 (1.83) N=71.6	2.58 N=104.3	0.69

Table A6.4.1. Discrimination characteristics of the 5% cut-off for low-risk SCORE predicting 10-year atherosclerotic CVD mortality in MONICA men and women

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Sensitivity	14/32=0.4375	45/86=0.5233	28/62=0.4516	19/58=0.3276	71/181=0.3923
Specificity	509/604=0.8427	943/1167=0.8081	992/1205=0.8232	1324/1593=0.8311	1974/2395=0.8242
LR+ (sensitivity/ 1-specificity)	43.75/15.73=2.78	52.33/19.19=2.73	45.16/17.68=2.55	32.76/16.89=1.94	39.23/17.58=2.23
LR- ((1-sensitivity)/ specificity)	56.25/84.27=0.67	47.67/80.81=0.59	54.84/82.32=0.67	67.24/83.11=0.81	60.77/82.42=0.74
PPV	14/109=0.1284	45/269=0.1673	28/241=0.1162	19/288=0.0660	71/492=0.1443
NPV	509/527=0.9658	943/984=0.9583	992/1026=0.9669	1324/1363=0.9714	1974/2084=0.9472
AUROC (95% CI)	0.64 (0.55-0.73)	0.67 (0.61-0.72)	0.64 (0.57-0.70)	0.58 (0.52-0.64)	0.61 (0.57-0.65)
Harrell's C	0.6429	0.6680	0.6341	0.5797	0.6084
Women					
Sensitivity	0/13=0	4/21=0.1905	0/19=0	0/26=0	10/86=0.1163
Specificity	675/691=0.9769	1081/1130=0.9566	1405/1443=0.9737	1596/1624=0.9828	2542/2591=0.9811
LR+ (sensitivity/ 1-specificity)	0/2.31=0	19.05/4.34=4.39	0/2.63=0	0/1.72=0	11.63/1.89=6.15
LR- ((1-sensitivity)/ specificity)	100.00/97.69=1.02	80.95/95.66=0.85	100.00/97.37=1.03	100.00/98.28=1.02	88.37/98.11=0.90
PPV	0/16=0	4/53=0.0755	0/38=0	0/28=0	10/59=0.1695
NPV	675/688=0.9811	1081/1098=0.9845	1405/1424=0.9867	1596/1622=0.9840	2542/2618=0.9710
AUROC (95% CI)	0.49 (0.48-0.49)	0.57 (0.49-0.66)	0.49 (0.48-0.49)	0.49 (0.49-0.50)	0.55 (0.52-0.58)
Harrell's C	0.5115	0.5745	0.5122	0.5086	0.5474

Table A6.4.2. Discrimination of low-risk SCORE estimated by Royston's R^2 in MONICA men and women

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Dichotomous SCORE	0.2432 (0.0319, 0.5382)	0.3100 (0.1513, 0.4812)	0.2163 (0.0650, 0.4120)	0.0830 (0.0000, 0.2606)*	0.1503 (0.0716, 0.2504)
Continuous SCORE	0.3442 (0.1148, 0.6315)	0.2896 (0.1562, 0.4498)	0.2777 (0.1289, 0.4794)	0.1382 (0.0403, 0.2805)	0.2666 (0.1638, 0.3850)
Women					
Dichotomous SCORE	0.0185 (0.0000, 0.0057)*	0.1448 (0.0000, 0.5332)*	0.0021 (0.0000, 0.0132)*	0.0023 (0.0000, 0.0074)*	0.1246 (0.0179, 0.2905)
Continuous SCORE	0.1858 (0.0000, 0.4919)*	0.2407 (0.0000, 0.6219)*	0.2988 (0.0835, 0.5617)	0.3393 (0.1672, 0.5511)	0.4339 (0.2809, 0.5914)

* Lower confidence limits calculated as negative were regarded as 0.

Table A6.4.3. Discrimination characteristics of the 5% cut-off for low-risk SCORE predicting atherosclerotic CVD mortality in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men			
Sensitivity	28/37=0.7568	20/34=0.5882	83/105=0.7905
Specificity	1773/2622=0.6762	2359/3422=0.6894	1900/3141=0.6049
LR+ (sensitivity/1-specificity)	75.68/32.38=2.34	58.82/31.06=1.89	79.05/39.51=2.00
LR- ((1-sensitivity)/specificity)	24.32/67.62=0.36	41.18/68.94=0.60	20.95/60.49=0.35
PPV	28/877=0.0319	20/1083=0.0185	83/1324=0.0627
NPV	1773/1782=0.9950	2359/2373=0.9941	1900/1922=0.9886
AUROC (95% CI)	0.72 (0.65-0.79)	0.64 (0.56-0.72)	0.70 (0.66-0.74)
Harrell's C	0.7178	0.6446	0.6925
Women			
Sensitivity	2/19=0.1053	5/16=0.3125	18/42=0.4286
Specificity	3180/3340=0.9521	3559/3737=0.9524	3633/4002=0.9078
LR+ (sensitivity/1-specificity)	10.53/4.79=2.20	31.25/4.76=6.57	42.86/9.22=4.65
LR- ((1-sensitivity)/specificity)	89.47/95.21=0.94	68.75/95.24=0.72	57.14/90.78=0.63
PPV	2/162=0.0124	5/183=0.0273	18/387=0.0465
NPV	3180/3197=0.9947	3559/3570=0.9969	3633/3657=0.9934
AUROC (95% CI)	0.53 (0.46-0.60)	0.63 (0.52-0.75)	0.67 (0.59-0.74)
Harrell's C	0.5192	0.6415	0.6656

Table A6.4.4. Discrimination of low-risk SCORE estimated by Royston's R^2 in HAPIEE men and women

	Czech Republic	**Poland**	**Russia**
Men			
Dichotomous SCORE	0.4122 (0.1888, 0.6380)	0.1810 (0.0114, 0.4313)	0.3364 (0.1965, 0.4790)
Continuous SCORE	0.4201 (0.2079, 0.6432)	0.3509 (0.1033, 0.6172)	0.3143 (0.1916, 0.4658)
Women			
Dichotomous SCORE	0.00260 (0.0000, 0.3033)*	0.3664 (0.0000, 0.7914)*	0.3905 (0.1493, 0.6438)
Continuous SCORE	0.1813 (0.0000, 0.4760)*	0.7197 (0.2618, 0.9449)	0.5904 (0.3606, 0.7862)

* Lower confidence limits calculated as negative were regarded as 0.

APPENDIX III. Education, marital status, and SCORE performance in MONICA and HAPIEE: additional tables

Table A7.1.1. Continuous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Men					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	1.09 (1.06-1.12)	1.10 (1.07-1.12)	1.11 (1.08-1.14)	1.08 (1.05-1.12)	1.11 (1.09-1.13)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	1.09 (1.06-1.13)	1.10 (1.07-1.12)	1.10 (1.07-1.14)	1.08 (1.04-1.12)	1.10 (1.08-1.12)
Lower education (vs. higher)	1.44 (0.68-3.06)	1.63 (1.06-2.51)	1.28 (0.67-2.45)	1.39 (0.82-2.38)	1.58 (1.16-2.14)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.14)	N/A	N/A	1.08 (1.05-1.12)	1.11 (1.09-1.13)
Non-married (vs. married)	5.80 (2.74-12.29)			1.84 (0.83-4.05)	1.72 (1.11-2.67)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	1.11 (1.07-1.14)	N/A	N/A	1.08 (1.04-0.12)	1.10 (1.08-1.13)
Lower education (vs. higher)	1.34 (0.63-2.88)			1.38 (0.81-2.36)	1.54 (1.14-2.10)
Non-married (vs. married)	5.77 (2.72-12.20)			1.81 (0.82-4.00)	1.74 (1.12-2.69)
Women					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	1.23 (1.06-1.43)	1.21 (1.10-1.33)	1.33 (1.16-1.53)	1.27 (1.16-1.39)	1.34 (1.27-1.41)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	1.23 (1.05-1.43)	1.21 (1.10-1.34)	1.34 (1.16-1.54)	1.22 (1.10-1.34)	1.33 (1.26-1.40)
Lower education (vs. higher)	1.65 (0.46-6.01)	4.39 (1.61-12.00)	0.68 (0.22-2.10)	3.92 (1.52-10.12)	1.48 (0.94-2.31)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	1.23 (1.05-1.43)	N/A	N/A	1.28 (1.16-1.40)	1.34 (1.27-1.41)
Non-married (vs. married)	2.07 (0.68-6.33)			1.37 (0.55-3.42)	1.18 (0.75-1.84)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	1.22 (1.04-1.43)	N/A	N/A	1.22 (1.10-1.34)	1.33 (1.26-1.40)
Lower education (vs. higher)	1.63 (0.45-5.95)			3.91 (1.52-1.10)	1.43 (0.91-2.24)
Non-married (vs. married)	2.07 (0.68-6.33)			1.09 (0.41-2.91)	1.18 (0.75-1.85)

Table A7.1.2. Dichotomous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	Poland (Warsaw)	Poland (Tarnobrzeg)	Lithuania	Russia
Men					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	4.29 (2.13-8.63)	4.76 (3.12-7.27)	3.76 (2.28-6.20)	2.45 (1.42-4.24)	3.04 (2.25-4.10)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	4.31 (2.14-8.67)	4.54 (2.97-6.96)	3.57 (2.15-5.93)	2.21 (1.26-3.88)	2.75 (2.03-3.73)
Lower education (vs. higher)	1.17 (0.57-2.43)	1.53 (0.99-2.36)	1.41 (0.75-2.68)	1.51 (0.89-2.56)	1.72 (1.27-2.34)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	4.09 (2.00-8.37)	N/A	N/A	2.46 (1.42-4.26)	3.08 (2.28-4.16)
Non-married (vs. married)	4.53 (2.22-9.26)			1.81 (0.82-3.99)	1.63 (1.05-2.53)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	4.10 (2.00-8.38)	N/A	N/A	2.22 (1.26-3.90)	2.80 (2.06-3.81)
Lower education (vs. higher)	1.09 (0.52-2.27)			1.49 (0.88-2.54)	1.69 (1.25-2.30)
Non-married (vs. married)	4.52 (2.21-9.24)			1.79 (0.81-3.94)	1.66 (1.07-2.58)
Women					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	too few observations	5.19 (1.75-15.43)	too few observations	too few observations	6.30 (3.26-12.17)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	too few observations	4.40 (1.47-13.12)	too few observations	too few observations	5.02 (2.57-9.83)
Lower education (vs. higher)	1.86 (0.51-6.77)	4.24 (1.55-11.60)	too few observations	5.46 (2.18-13.68)	2.13 (1.38-3.29)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	too few observations	N/A	N/A	too few observations	5.95 (3.06-11.59)
Non-married (vs. married)	2.24 (0.73-6.83)			1.40 (0.56-3.49)	1.39 (0.89-2.17)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	too few observations	N/A	N/A	too few observations	4.86 (2.47-9.58)
Lower education (vs. higher)	1.84 (0.51-6.70)			5.45 (2.18-13.65)	2.04 (1.31-3.17)
Non-married (vs. married)	2.24 (0.73-6.83)			1.11 (0.42-2.95)	1.34 (0.85-2.10)

Table A7.1.3. Continuous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: hazard ratios and 95% confidence intervals

	Czech Republic	Poland (Warsaw)	Poland (Tarnobrzeg)	Lithuania	Russia
Men					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	1.16 (1.11-1.22)	1.18 (1.13-1.23)	1.20 (1.14-1.26)	1.15 (1.08-1.23)	1.20 (1.17-1.24)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	1.17 (1.11-1.23)	1.18 (1.13-1.23)	1.19 (1.13-1.26)	1.14 (1.07-1.22)	1.19 (1.15-1.23)
Lower education (vs. higher)	1.43 (0.67-3.03)	1.65 (1.07-2.53)	1.28 (0.67-2.45)	1.41 (0.82-2.40)	1.58 (1.16-2.14)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.26)	N/A	N/A	1.15 (1.08-1.23)	1.21 (1.17-1.25)
Non-married (vs. married)	5.87 (2.77-12.47)			1.84 (0.84-4.06)	1.72 (1.11-2.66)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	1.20 (1.14-1.27)	N/A	N/A	1.14 (1.07-1.22)	1.20 (1.15-1.24)
Lower education (vs. higher)	1.34 (0.63-2.88)			1.39 (0.81-2.38)	1.55 (1.14-2.10)
Non-married (vs. married)	5.85 (2.76-12.41)			1.82 (0.82-4.00)	1.74 (1.12-1.69)
Women					
Model 1 (SCORE only)					
SCORE ≥5% (vs. <5%)	1.39 (1.09-1.76)	1.34 (1.15-1.55)	1.54 (1.24-1.93)	1.47 (1.28-1.69)	1.56 (1.44-1.70)
Model 2 (SCORE and education)					
SCORE ≥5% (vs. <5%)	1.38 (1.08-1.77)	1.34 (1.15-1.57)	1.56 (1.25-1.96)	1.37 (1.17-1.60)	1.53 (1.40-1.67)
Lower education (vs. higher)	1.66 (0.46-6.03)	4.36 (1.60-11.91)	0.70 (0.23-2.14)	3.89 (1.51-10.04)	1.47 (0.93-2.30)
Model 3 (SCORE and marital status)					
SCORE ≥5% (vs. <5%)	1.38 (1.08-1.76)	N/A	N/A	1.48 (1.28-1.70)	1.56 (1.43-1.70)
Non-married (vs. married)	2.05 (0.67-6.28)			1.40 (0.56-3.49)	1.17 (0.75-1.84)
Model 4 (SCORE, education, and marital status)					
SCORE ≥5% (vs. <5%)	1.37 (1.07-1.77)	N/A	N/A	1.37 (1.17-1.60)	1.53 (1.40-1.68)
Lower education (vs. higher)	1.64 (0.45-5.96)			3.88 (1.50-10.02)	1.42 (0.90-2.23)
Non-married (vs. married)	2.05 (0.67-6.29)			1.11 (0.41-2.95)	1.17 (0.75-1.84)

Table A7.1.4. Continuous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.09)
Lower education (vs. higher)	2.69 (1.10-6.59)	2.29 (0.99-5.29)	1.67 (1.03-2.69)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.14)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
Non-married (vs. married)	1.89 (0.86-4.17)	2.60 (1.21-5.58)	2.26 (1.43-3.56)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
Lower education (vs. higher)	2.54 (1.04-6.23)	2.19 (0.95-5.07)	1.62 (1.00-2.61)
Non-married (vs. married)	1.86 (0.84-4.15)	2.52 (1.18-5.41)	2.22 (1.40-3.50)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.20 (1.06-1.35)	1.32 (1.22-1.43)	1.32 (1.24-1.41)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	1.19 (1.05-1.35)	1.32 (1.21-1.44)	1.31 (1.22-1.40)
Lower education (vs. higher)	2.00 (0.76-5.29)	2.57 (0.89-7.40)	1.60 (0.77-3.32)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	1.19 (1.06-1.34)	1.32 (1.21-1.44)	1.32 (1.23-1.41)
Non-married (vs. married)	1.87 (0.76-4.62)	1.03 (0.36-2.99)	2.61 (1.38-4.97)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	1.18 (1.05-1.34)	1.32 (1.21-1.44)	1.31 (1.22-1.40)
Lower education (vs. higher)	1.96 (0.74-5.19)	2.57 (0.89-7.39)	1.45 (0.70-3.03)
Non-married (vs. married)	1.85 (0.75-4.57)	1.03 (0.36-2.95)	2.55 (1.34-4.86)

Table A7.1.5. Dichotomous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	6.55 (3.09-13.88)	3.24 (1.64-6.42)	5.52 (3.45-8.84)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	7.05 (3.21-15.51)	3.03 (1.52-6.03)	5.20 (3.23-8.35)
Lower education (vs. higher)	3.16 (1.31-7.62)	2.44 (1.05-5.63)	1.68 (1.05-2.70)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	6.65 (3.14-14.10)	3.14 (1.59-6.23)	5.49 (3.43-8.78)
Non-married (vs. married)	1.73 (0.79-3.78)	2.50 (1.17-5.36)	2.26 (1.43-3.57)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	7.14 (3.24-15.70)	2.96 (1.49-5.89)	5.19 (3.23-8.35)
Lower education (vs. higher)	2.93 (1.19-7.20)	2.35 (1.02-5.42)	1.63 (1.02-2.63)
Non-married (vs. married)	1.57 (0.70-3.51)	2.43 (1.13-5.21)	2.22 (1.41-3.51)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	2.39 (0.55-10.33)	9.15 (3.18-26.33)	6.91 (3.75-12.74)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	2.24 (0.52-9.72)	7.89 (2.69-23.09)	6.07 (3.23-11.42)
Lower education (vs. higher)	2.23 (0.85-5.89)	2.83 (0.97-8.27)	2.09 (1.00-4.35)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	2.31 (0.53-10.02)	8.65 (2.97-25.18)	6.38 (3.46-11.79)
Non-married (vs. married)	2.01 (0.82-4.94)	1.43 (0.53-3.87)	2.74 (1.44-5.21)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	2.17 (0.50-9.43)	7.50 (2.53-22.21)	5.73 (3.05-10.76)
Lower education (vs. higher)	2.19 (0.83-5.77)	2.77 (0.95-8.14)	1.92 (0.92-3.99)
Non-married (vs. married)	1.98 (0.80-4.87)	1.38 (0.51-3.74)	2.65 (1.39-5.05)

Table A7.1.6. Continuous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	1.18 (1.12-1.24)	1.17 (1.11-1.24)	1.14 (1.10-1.17)
Lower education (vs. higher)	2.70 (1.10-6.61)	2.28 (0.99-5.27)	1.66 (1.03-2.69)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
Non-married (vs. married)	1.90 (0.86-4.20)	2.62 (1.22-5.61)	2.23 (1.42-3.53)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.17 (1.11-1.25)	1.14 (1.10-1.17)
Lower education (vs. higher)	2.55 (1.04-6.25)	2.18 (0.94-5.04)	1.62 (1.00-2.61)
Non-married (vs. married)	1.88 (0.84-4.18)	2.54 (1.18-5.44)	2.20 (1.39-3.47)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.34 (1.11-1.62)	1.56 (1.38-1.76)	1.56 (1.40-1.73)
Model 2 (SCORE and education)			
SCORE ≥5% (vs. <5%)	1.33 (1.09-1.61)	1.56 (1.37-1.77)	1.53 (1.37-1.71)
Lower education (vs. higher)	2.00 (0.76-5.29)	2.56 (0.89-7.37)	1.61 (0.78-3.35)
Model 3 (SCORE and marital status)			
SCORE ≥5% (vs. <5%)	1.32 (1.10-1.60)	1.56 (1.36-1.78)	1.54 (1.38-1.72)
Non-married (vs. married)	1.86 (0.75-4.59)	0.99 (0.34-2.90)	2.57 (1.35-4.89)
Model 4 (SCORE, education, and marital status)			
SCORE ≥5% (vs. <5%)	1.31 (1.08-1.59)	1.56 (1.36-1.79)	1.52 (1.36-1.70)
Lower education (vs. higher)	1.96 (0.74-5.19)	2.56 (0.89-7.36)	1.46 (0.70-3.05)
Non-married (vs. married)	1.83 (0.74-4.53)	0.99 (0.34-2.85)	2.51 (1.32-4.78)

Table A7.2.1. Continuous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
HL χ^2 (*p*)					
Men					
Model 1 (SCORE only)	10.92 (0.0530)	9.26 (0.0991)	4.33 (0.5025)	14.93 (0.0106)	3.83 (0.5753)
Model 2 (SCORE and education)	13.02 (0.1110)	10.94 (0.1412)	14.95 (0.0207)	14.92 (0.0371)	6.05 (0.5344)
Model 3 (SCORE and marital status)	10.45 (0.1070)	N/A	N/A	9.96 (0.1264)	4.43 (0.6190)
Model 4 (SCORE, education, and marital status)	16.68 (0.0336)	N/A	N/A	10.00 (0.1885)	8.37 (0.3011)
Women					
Model 1 (SCORE only)	6.19 (0.1028)	8.25 (0.0411)	6.61 (0.0367)	17.46 (0.0002)	12.38 (0.0062)
Model 2 (SCORE and education)	5.13 (0.2739)	8.41 (0.1350)	7.66 (0.1047)	16.01 (0.0068)	7.33 (0.1974)
Model 3 (SCORE and marital status)	10.92 (0.0275)	N/A	N/A	19.84 (0.0005)	12.74 (0.0259)
Model 4 (SCORE, education, and marital status)	13.59 (0.0589)	N/A	N/A	4.75 (0.4466)	13.35 (0.0203)

Table A7.2.2. Continuous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.7597	0.7245	0.7114	0.6981	0.6789
R^2	0.3540 (0.1214, 0.6471)	0.2878 (0.1533, 0.4374)	0.2802 (0.1267, 0.4681)	0.1421 (0.0353, 0.3008)	0.2813 (0.1751, 0.3995)
Model 2 (SCORE and education)					
Harrell's C	0.7464	0.7289	0.7112	0.6892	0.6896
R^2	0.3491 (0.1187, 0.6572)	0.3119 (0.1825, 0.4808)	0.2768 (0.1238, 0.4815)	0.1467 (0.0536, 0.3184)	0.3007 (0.1993, 0.4234)
LRT *p* value	0.4078	0.0239	0.2437	0.2253	0.0053
IDI (*p* value)	0.00030 (0.86057)	0.00311 (0.27529)	0.00006 (0.93754)	0.00059 (0.50166)	0.00149 (0.34840)
Model 3 (SCORE and marital status)					
Harrell's C	0.8085	N/A	N/A	0.6957	0.6907
R^2	0.5856 (0.3140, 0.8391)			0.1518 (0.0480, 0.3298)	0.2936 (0.1826, 0.4152)
LRT *p* value	<0.0001			0.1587	0.0218
IDI (*p* value)	0.03975 (0.01224)			0.00092 (0.43458)	0.00290 (0.10363)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7892	N/A	N/A	0.6949	0.6989
R^2	0.5809 (0.2885, 0.8261)			0.1553 (0.0589, 0.3346)	0.3015 (0.1201, 0.4350)
LRT *p* value	0.0001			0.1877	0.0014
IDI (*p* value)	0.04051 (0.01247)			0.00132 (0.32030)	0.00423 (0.07949)

Table A7.2.3. Continuous high-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.7465	0.7244	0.7848	0.8101	0.7898
R^2	0.1843 (0.0000, 0.5052)*	0.2526 (0.0000, 0.6580)*	0.3248 (0.0865, 0.5771)	0.3314 (0.1646, 0.5435)	0.4872 (0.3230, 0.6548)
Model 2 (SCORE and education)					
Harrell's C	0.7487	0.7830	0.7877	0.8085	0.7861
R^2	0.1686 (0.0000, 0.5614)*	0.4589 (0.1204, 0.7802)	0.3094 (0.0713, 0.6148)	0.4809 (0.2508, 0.7251)	0.4947 (0.3293, 0.6490)
LRT *p* value	0.4259	0.0015	0.7249	0.0024	0.1117
IDI (*p* value)	0.00028 (0.87199)	0.00776 (0.33194)	0.00066 (0.00108)	0.00773 (0.00133)	-0.00037 (0.84053)
Model 3 (SCORE and marital status)					
Harrell's C	0.7662	N/A	N/A	0.8065	0.7935
R^2	0.2073 (0.0000, 0.6274)*			0.3133 (0.1576, 0.5582)	0.4851 (0.3279, 0.6513)
LRT *p* value	0.2142			0.7652	0.4492
IDI (*p* value)	0.00234 (0.45472)			0.00005 (0.82733)	-0.00088 (0.19522)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7685	N/A	N/A	0.8064	0.7909
R^2	0.1905 (0.0000, 0.6560)*			0.4647 (0.2392, 0.7313)	0.4923 (0.3395, 0.6638)
LRT *p* value	0.3421			0.0097	0.2194
IDI (*p* value)	0.00304 (0.46620)			0.00780 (0.00132)	-0.00103 (0.63172)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.4. Dichotomous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.6341	0.6680	0.6341	0.5796	0.6124
R^2	0.2168 (0.0189, 0.4942)	0.3100 (0.1695, 0.4852)	0.2163 (0.0730, 0.4034)	0.0825 (0.0000, 0.2527)*	0.1604 (0.0787, 0.2648)
Model 2 (SCORE and education)					
Harrell's C	0.6344	0.6970	0.6654	0.6197	0.6523
R^2	0.2008 (0.0031, 0.5017)	0.3261 (0.1760, 0.5083)	0.2180 (0.0863, 0.4226)	0.0958 (0.0012, 0.2801)	0.1933 (0.1046, 0.3039)
LRT *p* value	0.7626	0.0521	0.2747	0.1286	0.0007
IDI (*p* value)	0.00005 (0.79410)	0.00319 (0.17150)	0.00012 (0.92540)	0.00099 (0.35148)	0.00401 (0.01099)
Model 3 (SCORE and marital status)					
Harrell's C	0.7118	N/A	N/A	0.6018	0.6266
R^2	0.4350 (0.1241, 0.7490)			0.0917 (0.0018, 0.2579)	0.1710 (0.0902, 0.2729)
LRT *p* value	0.0001			0.1670	0.0372
IDI (*p* value)	0.03700 (0.00729)			0.00080 (0.47051)	0.00208 (0.11622)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.6817	N/A	N/A	0.6396	0.6600
R^2	0.4214 (0.1520, 0.7521)			0.1036 (0.0188, 0.2876)	0.2042 (0.1200, 0.3243)
LRT *p* value	0.0006	N/A	N/A	0.1291	0.0003
IDI (*p* value)	0.03603 (0.00713)			0.00156 (0.24537)	0.00599 (0.00388)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.5. Dichotomous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.5116	0.5745	0.5122	0.5086	0.5488
R^2	0.0184 (0.0000, 0.0042)*	0.1448 (0.0000, 0.5264)*	0.0021 (0.0000, 0.0130)*	0.0031 (0.0000, 0.0078)*	0.1297 (0.0206, 0.2972)
Model 2 (SCORE and education)					
Harrell's C	0.5725	0.7126	0.5148	0.7024	0.6435
R^2	0.0190 (0.0000, 0.3819)*	0.3571 (0.0893, 0.7183)	0.0342 (0.0000, 0.1637)*	0.3311 (0.0894, 0.6212)	0.1949 (0.0795, 0.3752)
LRT *p* value	0.3206	0.0021	0.9521	0.0001	0.0010
IDI (*p* value)	0.00137 (0.28955)	0.00962 (0.02027)	<0.00001 (0.96014)	0.01005 (0.00001)	0.00257 (0.25090)
Model 3 (SCORE and marital status)					
Harrell's C	0.5940	N/A	N/A	0.5206	0.6054
R^2	0.0218 (0.0000, 0.4170)*			0.0250 (0.0000, 0.1275)*	0.1375 (0.0295, 0.2969)
LRT *p* value	0.1726			0.7434	0.1431
IDI (*p* value)	0.00304 (0.23549)			0.00006 (0.77713)	-0.00088 (0.37901)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.6253	N/A	N/A	0.6998	0.6635
R^2	0.0197 (0.0000, 0.5173)*			0.3120 (0.0800, 0.6326)	0.1985 (0.0838, 0.3634)
LRT *p* value	0.0933			0.0001	0.0022
IDI (*p* value)	0.00469 (0.14434)			0.01016 (0.00001)	0.00227 (0.37337)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.6. Continuous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.7648	0.7254	0.7116	0.6943	0.6763
R^2	0.3483 (0.0872, 0.6393)	0.2896 (0.1503, 0.4441)	0.2777 (0.1197, 0.4718)	0.1376 (0.0419, 0.2938)	0.2780 (0.1626, 0.3971)
Model 2 (SCORE and education)					
Harrell's C	0.7521	0.7268	0.7113	0.6854	0.6877
R^2	0.3420 (0.1082, 0.6433)	0.3147 (0.1913, 0.4807)	0.2741 (0.1268, 0.4628)	0.1430 (0.0447, 0.3039)	0.2977 (0.2002, 0.4123)
LRT *p* value	0.4159	0.0218	0.4473	0.2137	0.0051
IDI (*p* value)	0.00042 (0.80506)	0.00326 (0.26091)	-0.0003 (0.96810)	0.00068 (0.44709)	0.00151 (0.34182)
Model 3 (SCORE and marital status)					
Harrell's C	0.8059	N/A	N/A	0.6949	0.6875
R^2	0.5835 (0.2789, 0.8350)			0.1474 (0.0434, 0.3165)	0.2903 (0.1903, 0.4111)
LRT *p* value	<0.0001			0.1577	0.0220
IDI (*p* value)	0.04096 (0.00911)			0.00085 (0.45800)	0.00294 (0.09707)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7819	N/A	N/A	0.6938	0.6962
R^2	0.5790 (0.2868, 0.8529)			0.1516 (0.0593, 0.3208)	0.3100 (0.2043, 0.4320)
LRT *p* value	0.0001			0.1803	0.0014
IDI (*p* value)	0.04187 (0.00927)			0.00133 (0.31031)	0.00430 (0.07373)

Table A7.2.7. Continuous low-risk SCORE, education, marital status, and 10-year atherosclerotic CVD mortality in MONICA women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland (Warsaw)**	**Poland (Tarnobrzeg)**	**Lithuania**	**Russia**
Model 1 (SCORE only)					
Harrell's C	0.7465	0.7066	0.7755	0.8092	0.7661
R^2	0.1859 (0.0000, 0.4538)*	0.2407 (0.0000, 0.6000)*	0.2988 (0.0700, 0.5702)	0.3419 (0.1604, 0.5709)	0.4500 (0.2848, 0.6064)
Model 2 (SCORE and education)					
Harrell's C	0.7507	0.7796	0.7822	0.8088	0.7729
R^2	0.1706 (0.0000, 0.5491)*	0.4475 (0.1441, 0.7525)	0.2819 (0.0558, 0.5874)	0.4871 (0.2542, 0.7346)	0.4571 (0.3063, 0.5425)
LRT *p* value	0.4227	0.0016	0.5410	0.0026	0.1233
IDI (*p* value)	0.00042 (0.79908)	0.00699 (0.37111)	0.00053 (0.54904)	0.00744 (0.00290)	-0.00019 (0.91063)
Model 3 (SCORE and marital status)					
Harrell's C	0.7622	N/A	N/A	0.8057	0.7742
R^2	0.2074 (0.0000, 0.5719)*			0.3243 (0.1512, 0.5665)	0.4478 (0.2974, 0.6051)
LRT *p* value	0.2195			0.7402	0.4522
IDI (*p* value)	0.00215 (0.46860)			0.00006 (0.81194)	-0.00079 (0.18946)
Model 4 (SCORE, education, and marital status)					
Harrell's C	0.7739	N/A	N/A	0.8069	0.7754
R^2	0.1910 (0.0000, 0.6671)*			0.4711 (0.2310, 0.7349)	0.4544 (0.3024, 0.6247)
LRT *p* value	0.3466			0.0105	0.2395
IDI (*p* value)	0.00298 (0.45103)			0.00752 (0.00289)	-0.00076 (0.69457)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.8. Continuous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland**	**Russia**
HL χ^2 (p)			
Men			
Model 1 (SCORE only)	6.61 (0.3581)	7.18 (0.3042)	36.52 (<0.0001)
Model 2 (SCORE and education)	6.40 (0.3802)	9.09 (0.1688)	20.94 (0.0039)
Model 3 (SCORE and marital status)	7.54 (0.3747)	6.58 (0.3616)	27.83 (0.0002)
Model 4 (SCORE, education, and marital status)	8.01 (0.3315)	13.43 (0.0622)	22.98 (0.0017)
Women			
Model 1 (SCORE only)	3.79 (0.2847)	2.55 (0.4658)	3.00 (0.5586)
Model 2 (SCORE and education)	2.05 (0.7268)	3.18 (0.5281)	4.08 (0.3955)
Model 3 (SCORE and marital status)	4.59 (0.5971)	2.71 (0.8442)	6.94 (0.3260)
Model 4 (SCORE, education, and marital status)	7.56 (0.3726)	1.87 (0.9310)	6.56 (0.3630)

Table A7.2.9. Continuous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7848	0.7181	0.7387
R^2	0.4385 (0.2015, 0.6691)	0.3497 (0.1010, 0.6470)	0.3154 (0.1885, 0.4645)
Model 2 (SCORE and education)			
Harrell's C	0.7891	0.7338	0.7423
R^2	0.4725 (0.2549, 0.7037)	0.3804 (0.1163, 0.6805)	0.3295 (0.2057, 0.4678)
LRT *p* value	0.0497	0.0415	0.0460
IDI (*p* value)	0.00198 (0.50455)	0.00292 (0.27913)	-0.00044 (0.73991)
Model 3 (SCORE and marital status)			
Harrell's C	0.7827	0.7144	0.7497
R^2	0.4566 (0.2469, 0.7074)	0.4064 (0.1401, 0.7320)	0.3595 (0.2355, 0.4994)
LRT *p* value	0.1135	0.0258	0.0012
IDI (*p* value)	0.00192 (0.32185)	0.00739 (0.08068)	0.00404 (0.10852)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7888	0.7324	0.7539
R^2	0.4848 (0.2587, 0.7428)	0.4313 (0.1392, 0.7652)	0.3711 (0.2547, 0.5191)
LRT *p* value	0.0518	0.0123	0.0009
IDI (*p* value)	0.00362 (0.25584)	0.00898 (0.01096)	0.00353 (0.20136)

Table A7.2.10. Continuous high-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.6946	0.8034	0.7983
R^2	0.1727 (0.0000, 0.4388)*	0.6903 (0.2143, 0.9431)	0.6003 (0.3511, 0.8113)
Model 2 (SCORE and education)			
Harrell's C	0.7020	0.8007	0.8006
R^2	0.1947 (0.0000, 0.5262)*	0.7173 (0.2711, 0.9455)	0.6041 (0.3613, 0.8048)
LRT *p* value	0.1852	0.1601	0.2251
IDI (*p* value)	0.00054 (0.43688)	-0.00362 (0.43566)	0.00114 (0.55238)
Model 3 (SCORE and marital status)			
Harrell's C	0.7025	0.8083	0.8047
R^2	0.1963 (0.0000, 0.5471)*	0.6729 (0.1753, 0.9337)	0.6620 (0.4231, 0.8414)
LRT *p* value	0.1784	0.5909	0.0024
IDI (*p* value)	0.00096 (0.16772)	0.00019 (0.23286)	0.00716 (0.03613)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7040	0.8058	0.8090
R^2	0.2156 (0.0053, 0.6000)	0.7013 (0.2737, 0.9500)	0.6615 (0.4377, 0.8483)
LRT *p* value	0.1756	0.3338	0.0062
IDI (*p* value)	0.00162 (0.15442)	-0.00347 (0.43917)	0.00811 (0.03843)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.11. Dichotomous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7307	0.6444	0.6925
R^2	0.4498 (0.2003, 0.6723)	0.1804 (0.0176, 0.4305)	0.3364 (0.2093, 0.4662)
Model 2 (SCORE and education)			
Harrell's C	0.7470	0.6755	0.7074
R^2	0.4988 (0.2615, 0.7402)	0.2227 (0.0514, 0.5069)	0.3510 (0.2303, 0.4956)
LRT *p* value	0.0222	0.0569	0.0417
IDI (*p* value)	0.00511 (0.11836)	0.00151 (0.21992)	0.00141 (0.24670)
Model 3 (SCORE and marital status)			
Harrell's C	0.7438	0.6712	0.7182
R^2	0.4612 (0.2173, 0.7243)	0.2399 (0.0389, 0.5555)	0.3799 (0.2553, 0.5275)
LRT *p* value	0.1618	0.0300	0.0012
IDI (*p* value)	0.00180 (0.18280)	0.00273 (0.05785)	0.00406 (0.05477)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7569	0.6973	0.7300
R^2	0.5002 (0.2717, 0.7584)	0.2763 (0.0714, 0.5977)	0.3920 (0.2674, 0.5283)
LRT *p* value	0.0418	0.0177	0.0008
IDI (*p* value)	0.00629 (0.08426)	0.00381 (0.04394)	0.00537 (0.03235)

Table A7.2.12. Dichotomous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.5193	0.6414	0.6656
R^2	0.0028 (0.0000, 0.3073)*	0.3654 (0.0000, 0.7954)*	0.3905 (0.1417, 0.6600)
Model 2 (SCORE and education)			
Harrell's C	0.5822	0.7048	0.7025
R^2	0.0453 (0.0000, 0.4027)*	0.4256 (0.0560, 0.8218)	0.4168 (0.1648, 0.6880)
LRT *p* value	0.1262	0.0789	0.0644
IDI (*p* value)	0.00062 (0.33274)	0.00061 (0.76520)	0.00160 (0.38632)
Model 3 (SCORE and marital status)			
Harrell's C	0.5666	0.6611	0.7228
R^2	0.0422 (0.0000, 0.4890)*	0.3498 (0.0000, 0.8130)*	0.4854 (0.2363, 0.7376)
LRT *p* value	0.1345	0.4883	0.0015
IDI (*p* value)	0.00106 (0.08709)	0.00048 (0.49403)	0.00567 (0.00868)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.6079	0.7287	0.7380
R^2	0.0807 (0.0000, 0.5240)*	0.4082 (0.0348, 0.8257)	0.5021 (0.2558, 0.7507)
LRT *p* value	0.1067	0.1764	0.0016
IDI (*p* value)	0.00334 (0.02211)	0.00059 (0.69555)	0.00669 (0.01593)

* Lower confidence limits calculated as negative were regarded as 0.

Table A7.2.13. Continuous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7938	0.7215	0.7406
R^2	0.4359 (0.2134, 0.6457)	0.3505 (0.0997, 0.6307)	0.3143 (0.1794, 0.4571)
Model 2 (SCORE and education)			
Harrell's C	0.7962	0.7376	0.7440
R^2	0.4702 (0.2456, 0.7030)	0.3805 (0.1226, 0.6775)	0.3282 (0.2068, 0.4672)
LRT *p* value	0.0491	0.0765	0.0476
IDI (*p* value)	0.00196 (0.49770)	0.00297 (0.28428)	-0.00049 (0.71332)
Model 3 (SCORE and marital status)			
Harrell's C	0.7905	0.7178	0.7491
R^2	0.4545 (0.2325, 0.6859)	0.4080 (0.1151, 0.7139)	0.3575 (0.2247, 0.5054)
LRT *p* value	0.1107	0.0231	0.0014
IDI (*p* value)	0.00209 (0.30298)	0.00736 (0.08661)	0.00406 (0.10660)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7960	0.7364	0.7532
R^2	0.4831 (0.2655, 0.7183)	0.4321 (0.1548, 0.7650)	0.3690 (0.2499, 0.5133)
LRT *p* value	0.0500	0.0184	0.0010
IDI (*p* value)	0.00378 (0.230580)	0.00893 (0.01099)	0.00351 (0.20257)

Table A7.2.14. Continuous low-risk SCORE, education, marital status, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7052	0.8236	0.7953
R^2	0.1833 (0.0000, 0.4544)*	0.7191 (0.2575, 0.9348)	0.5904 (0.3482, 0.7756)
Model 2 (SCORE and education)			
Harrell's C	0.7017	0.8193	0.7966
R^2	0.2054 (0.0000, 0.5513)*	0.7436 (0.3369, 0.9528)	0.5947 (0.3750, 0.8025)
LRT *p* value	0.1845	0.1048	0.2166
IDI (*p* value)	0.00049 (0.47953)	-0.00351 (0.45686)	0.00105 (0.57809)
Model 3 (SCORE and marital status)			
Harrell's C	0.6993	0.8226	0.8006
R^2	0.2055 (0.0000, 0.5528)*	0.7031 (0.2312, 0.9432)	0.6512 (0.4251, 0.8323)
LRT *p* value	0.1841	0.9883	0.0028
IDI (*p* value)	0.00104 (0.15199)	0.00003 (0.27314)	0.00687 (0.03072)
Model 4 (SCORE, education, and marital status)			
Harrell's C	0.7022	0.8170	0.8042
R^2	0.2247 (0.0119, 0.6192)	0.7289 (0.2671, 0.9571)	0.6508 (0.4313, 0.8376)
LRT *p* value	0.1793	0.2682	0.0072
IDI (*p* value)	0.00159 (0.13932)	-0.00349 (0.45704)	0.00773 (0.03433)

* Lower confidence limits calculated as negative were regarded as 0.

APPENDIX IV. Alcohol consumption parameters and SCORE performance in HAPIEE: additional tables

Table A8.1.1. Continuous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.14)	1.10 (1.07-1.14)	1.08 (1.06-1.10)
Binge drinking (vs. no binge drinking)	1.00 (0.41-2.39)	0.75 (0.23-2.48)	1.08 (0.73-1.61)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.13)	1.10 (1.06-1.13)	1.08 (1.06-1.10)
CAGE ≥2 (vs. <2)	1.03 (0.36-2.94)	1.74 (0.67-4.49)	1.06 (0.67-1.68)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	1.10 (1.07-1.14)	1.10 (1.07-1.14)	1.08 (1.06-1.10)
Binge drinking (vs. no binge drinking)	0.83 (0.31-2.22)	0.59 (0.17-2.08)	1.07 (0.70-1.64)
CAGE ≥2 (vs. <2)	1.17 (0.39-3.44)	2.05 (0.75-5.62)	1.03 (0.64-1.68)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.20 (1.06-1.35)	1.32 (1.22-1.43)	1.32 (1.24-1.41)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	1.22 (1.09-1.37)	1.32 (1.22-1.43)	1.33 (1.24-1.42)
Binge drinking (vs. no binge drinking)	1.89 (0.25-14.23)	too few observations	6.75 (1.60-28.53)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	1.22 (1.08-1.37)	1.32 (1.22-1.43)	1.33 (1.24-1.43)
CAGE ≥2 (vs. <2)	3.27 (0.44-24.57)	too few observations	6.84 (1.61-29.08)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	1.22 (1.08-1.37)	1.32 (1.22-1.43)	1.33 (1.25-1.43)
Binge drinking (vs. no binge drinking)	1.37 (0.15-12.72)	too few observations	3.62 (0.57-22.89)
CAGE ≥2 (vs. <2)	2.89 (0.31-26.76)	too few observations	3.67 (0.58-23.33)

Table A8.1.2. Dichotomous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	6.55 (3.09-13.88)	3.24 (1.64-6.42)	5.52 (3.45-8.84)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	6.38 (3.00-13.58)	3.24 (1.64-6.42)	5.52 (3.45-8.83)
Binge drinking (vs. no binge drinking)	0.98 (0.41-2.35)	0.92 (0.28-3.00)	1.18 (0.80-1.76)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	7.27 (3.30-16.02)	3.30 (1.66-6.53)	5.53 (3.46-8.85)
CAGE ≥2 (vs. <2)	1.31 (0.46-3.71)	1.78 (0.69-4.61)	1.16 (0.74-1.83)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	7.02 (3.18-15.53)	3.30 (1.66-6.54)	5.53 (3.45-8.85)
Binge drinking (vs. no binge drinking)	0.79 (0.29-2.13)	0.73 (0.21-2.56)	1.15 (0.76-1.76)
CAGE ≥2 (vs. <2)	1.44 (0.49-4.29)	1.98 (0.72-5.45)	1.10 (0.68-1.79)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	2.39 (0.55-10.33)	9.15 (3.18-26.33)	6.91 (3.75-12.74)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	2.51 (0.58-10.95)	9.20 (3.20-26.49)	7.26 (3.92-13.46)
Binge drinking (vs. no binge drinking)	1.72 (0.23-12.96)	too few observations	5.23 (1.25-21.93)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	2.51 (0.58-10.93)	9.11 (3.16-26.21)	7.29 (3.93-13.54)
CAGE ≥2 (vs. <2)	3.05 (0.41-22.91)	too few observations	5.17 (1.23-21.74)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	2.48 (0.57-10.81)	9.08 (3.15-26.13)	7.48 (4.02-13.94)
Binge drinking (vs. no binge drinking)	1.34 (0.16-11.54)	too few observations	3.37 (0.65-17.66)
CAGE ≥2 (vs. <2)	2.79 (0.33-23.97)	too few observations	3.32 (0.63-17.41)

Table A8.1.3. Continuous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: hazard ratios and 95% confidence intervals

	Czech Republic	**Poland**	**Russia**
Men			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
Binge drinking (vs. no binge drinking)	0.99 (0.41-2.39)	0.76 (0.23-2.50)	1.09 (0.73-1.62)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	1.18 (1.13-1.25)	1.18 (1.12-1.25)	1.14 (1.11-1.18)
CAGE ≥2 (vs. <2)	1.04 (0.36-2.97)	1.76 (0.68-4.54)	1.07 (0.68-1.68)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	1.19 (1.13-1.25)	1.19 (1.12-1.26)	1.14 (1.10-1.18)
Binge drinking (vs. no binge drinking)	0.83 (0.31-2.21)	0.59 (0.17-2.09)	1.07 (0.70-1.64)
CAGE ≥2 (vs. <2)	1.18 (0.40-3.48)	2.07 (0.76-5.68)	1.04 (0.64-1.69)
Women			
Model 1 (SCORE only)			
SCORE ≥5% (vs. <5%)	1.34 (1.11-1.62)	1.56 (1.38-1.76)	1.56 (1.40-1.73)
Model 2 (SCORE and binge drinking)			
SCORE ≥5% (vs. <5%)	1.37 (1.14-1.65)	1.56 (1.38-1.76)	1.57 (1.41-1.75)
Binge drinking (vs. no binge drinking)	1.89 (0.25-14.18)	too few observations	6.47 (1.54-27.18)
Model 3 (SCORE and CAGE)			
SCORE ≥5% (vs. <5%)	1.37 (1.14-1.65)	1.55 (1.37-1.76)	1.57 (1.41-1.75)
CAGE ≥2 (vs. <2)	3.28 (0.44-24.69)	too few observations	6.48 (1.53-27.44)
Model 4 (SCORE, binge drinking, and CAGE)			
SCORE ≥5% (vs. <5%)	1.37 (1.14-1.64)	1.55 (1.37-1.75)	1.58 (1.42-1.76)
Binge drinking (vs. no binge drinking)	1.36 (0.15-12.70)	too few observations	3.54 (0.57-22.08)
CAGE ≥2 (vs. <2)	2.91 (0.31-27.21)	too few observations	3.53 (0.56-22.14)

Table A8.2.1. Continuous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men and women: Hosmer-Lemeshow (HL) test results

	Czech Republic	**Poland**	**Russia**
HL χ^2 *(p)*			
Men			
Model 1 (SCORE only)	6.92 (0.3286)	7.13 (0.3089)	36.52 (<0.0001)
Model 2 (SCORE and binge drinking)	6.88 (0.3318)	5.15 (0.5250)	36.28 (<0.0001)
Model 3 (SCORE and CAGE)	7.46 (0.4874)	9.51 (0.1470)	36.29 (<0.0001)
Model 4 (SCORE, binge drinking, and CAGE)	12.97 (0.0435)	9.85 (0.1311)	35.06 (<0.0001)
Women			
Model 1 (SCORE only)	5.90 (0.1168)	2.56 (0.4643)	3.00 (0.5586)
Model 2 (SCORE and binge drinking)	6.61 (0.0856)	2.58 (0.4615)	5.45 (0.2443)
Model 3 (SCORE and CAGE)	4.32 (0.2293)	3.42 (0.3315)	2.87 (0.5792)
Model 4 (SCORE, binge drinking, and CAGE)	6.97 (0.1375)	3.42 (0.3316)	6.87 (0.1432)

Table A8.2.2. Continuous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7818	0.7187	0.7387
R^2	0.4249 (0.1950, 0.6748)	0.3511 (0.1053, 0.6352)	0.3154 (0.1865, 0.4558)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.7877	0.7143	0.7399
R^2	0.4130 (0.1950, 0.6628)	0.3399 (0.1023, 0.6456)	0.3113 (0.1905, 0.4549)
LRT *p* value	0.7497	0.6379	0.7000
IDI (*p* value)	-0.00002 (0.94580)	0.00044 (0.11387)	0.00032 (0.36090)
Model 3 (SCORE and CAGE)			
Harrell's C	0.7844	0.7225	0.7387
R^2	0.4121 (0.2146, 0.6543)	0.3532 (0.1146, 0.6749)	0.3109 (0.1823, 0.4711)
LRT *p* value	0.8543	0.2838	0.7992
IDI (*p* value)	-0.00015 (0.50627)	0.00047 (0.60970)	0.00007 (0.68504)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.7915	0.7246	0.7395
R^2	0.4006 (0.1896, 0.6728)	0.3599 (0.1220, 0.6564)	0.3066 (0.1939, 0.4706)
LRT *p* value	0.9159	0.3838	0.9207
IDI (*p* value)	-0.00023 (0.46984)	0.00134 (0.22561)	0.00032 (0.36797)

Table A8.2.3. Continuous high-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7348	0.8032	0.7983
R^2	0.2192 (0.0140, 0.4860)	0.6890 (0.1618, 0.9412)	0.6003 (0.3665, 0.8008)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.7428	0.8041	0.8229
R^2	0.1989 (0.0169, 0.4910)	0.6742 (0.1923, 0.9298)	0.6246 (0.4362, 0.8149)
LRT *p* value	0.5658	too few observations	0.0425
IDI (*p* value)	0.00001 (0.96040)	-0.00002 (0.58128)	0.00068 (0.36079)
Model 3 (SCORE and CAGE)			
Harrell's C	0.7298	0.8046	0.8158
R^2	0.2178 (0.0000, 0.5649)*	0.6752 (0.1657, 0.9353)	0.6249 (0.3973, 0.8126)
LRT *p* value	0.3293	0.6497	0.0417
IDI (*p* value)	0.00063 (0.49880)	-0.00004 (0.47808)	0.00100 (0.26596)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.7406	0.8051	0.8263
R^2	0.1895 (0.1451, 0.5896)	0.6587 (0.1123, 0.9299)	0.6292 (0.4373, 0.8258)
LRT *p* value	0.5993	0.8633	0.0574
IDI (*p* value)	0.00049 (0.52914)	-0.00011 (0.37014)	0.00121 (0.26346)

* Lower confidence limits calculated as negative were regarded as 0.

Table A8.2.4. Dichotomous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7266	0.6445	0.6925
R^2	0.4340 (0.1907, 0.6771)	0.1808 (0.0111, 0.4400)	0.3364 (0.2142, 0.4794)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.7358	0.6469	0.7044
R^2	0.4223 (0.2038, 0.6780)	0.1646 (0.0000, 0.4480)*	0.3350 (0.2139, 0.4762)
LRT *p* value	0.7536	0.9085	0.4082
IDI (*p* value)	-0.00008 (0.76183)	-0.00001 (0.96207)	0.00027 (0.59758)
Model 3 (SCORE and CAGE)			
Harrell's C	0.7338	0.6589	0.6967
R^2	0.4246 (0.1836, 0.6728)	0.1855 (0.0126, 0.4832)	0.3336 (0.2124, 0.4707)
LRT *p* value	0.6006	0.2573	0.5252
IDI (*p* value)	0.00025 (0.62409)	0.00067 (0.33253)	0.00022 (0.52834)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.7380	0.6701	0.7045
R^2	0.4144 (0.1946, 0.6848)	0.1734 (0.0016, 0.4611)	0.3309 (0.2160, 0.4879)
LRT *p* value	0.7791	0.4610	0.6618
IDI (*p* value)	0.00022 (0.76092)	0.00062 (0.30812)	0.00035 (0.51307)

* Lower confidence limits calculated as negative were regarded as 0.

Table A8.2.5. Dichotomous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.5216	0.6415	0.6656
R^2	0.0063 (0.000, 0.2928)*	0.3668 (0.0000, 0.7891)*	0.3905 (0.1370, 0.6363)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.5372	0.6440	0.6883
R^2	0.0193 (0.0000, 0.3396)*	0.3434 (0.0000, 0.7822)*	0.4154 (0.1707, 0.6778)
LRT *p* value	0.6213	0.6365	0.0696
IDI (*p* value)	0.00006 (0.77643)	0.00004 (0.02697)	0.00086 (0.32862)
Model 3 (SCORE and CAGE)			
Harrell's C	0.5438	0.6449	0.6826
R^2	0.0017 (0.0000, 0.3952)*	0.3453 (0.0000, 0.7789)*	0.4150 (0.1832, 0.6873)
LRT *p* value	0.3525	0.5940	0.0714
IDI (*p* value)	0.00033 (0.55147)	0.00003 (0.02704)	0.00078 (0.33912)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.5617	0.6467	0.6946
R^2	0.0300 (0.0000, 0.3824)*	0.3183 (0.0000, 0.7674)*	0.4220 (0.1844, 0.6857)
LRT *p* value	0.6281	too few observations	0.0816
IDI (*p* value)	0.00029 (0.55086)	0.00003 (0.02718)	0.00155 (0.28912)

* Lower confidence limits calculated as negative were regarded as 0.

Table A8.2.6. Continuous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE men: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7891	0.7220	0.7406
R^2	0.4217 (0.2193, 0.6617)	0.3520 (0.0951, 0.6170)	0.3143 (0.1855, 0.4521)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.7930	0.7173	0.7424
R^2	0.4098 (0.1873, 0.6617)	0.3407 (0.0998, 0.6539)	0.3103 (0.1861, 0.4564)
LRT *p* value	0.7508	0.6479	0.6855
IDI (*p* value)	0.00002 (0.94933)	0.00043 (0.10636)	0.00035 (0.34028)
Model 3 (SCORE and CAGE)			
Harrell's C	0.7919	0.7260	0.7408
R^2	0.4090 (0.2117, 0.6690)	0.3547 (0.1084, 0.6473)	0.3099 (0.1812, 0.4691)
LRT *p* value	0.8380	0.2749	0.7853
IDI (*p* value)	-0.00016 (0.47032)	0.00045 (0.62326)	0.00009 (0.63340)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.7974	0.7298	0.7423
R^2	0.3975 (0.2010, 0.6528)	0.3512 (0.0975, 0.6903)	0.3056 (0.1926, 0.4575)
LRT *p* value	0.9108	0.3786	0.9121
IDI (*p* value)	-0.00020 (0.50788)	0.00130 (0.22622)	0.00036 (0.34481)

Table A8.2.7. Continuous low-risk SCORE, binge drinking, CAGE, and atherosclerotic CVD mortality in HAPIEE women: Harrell's C, Royston's R^2, LRT *p* value, and IDI

	Czech Republic	**Poland**	**Russia**
Model 1 (SCORE only)			
Harrell's C	0.7406	0.8233	0.7953
R^2	0.2281 (0.0259, 0.4985)	0.7177 (0.2813, 0.9482)	0.5904 (0.3361, 0.7859)
Model 2 (SCORE and binge drinking)			
Harrell's C	0.7512	0.8241	0.8178
R^2	0.2078 (0.0235, 0.5271)	0.7039 (0.2120, 0.9457)	0.6142 (0.3938, 0.8063)
LRT *p* value	0.5667	0.7071	0.0460
IDI (*p* value)	-0.00001 (0.98969)	-0.00004 (0.41919)	0.00065 (0.40645)
Model 3 (SCORE and CAGE)			
Harrell's C	0.7465	0.8245	0.8080
R^2	0.2269 (0.0124, 0.5710)	0.7048 (0.1697, 0.9356)	0.6142 (0.4070, 0.8021)
LRT *p* value	0.3267	0.6566	0.0462
IDI (*p* value)	0.00063 (0.50396)	-0.00006 (0.40785)	0.00112 (0.26535)
Model 4 (SCORE, binge drinking, and CAGE)			
Harrell's C	0.7446	0.8250	0.8202
R^2	0.1988 (0.0247, 0.6160)	0.6896 (0.1800, 0.9367)	0.6184 (0.4224, 0.8250)
LRT *p* value	0.5977	0.8684	0.0635
IDI (*p* value)	0.00048 (0.54117)	-0.00014 (0.34798)	0.00137 (0.28866)