UNIVERSITY OF TROMSØ UIT

FACULTY OF HEALTH SCIENCES
DEPARTMENT OF COMMUNITY MEDICINE

Factors behind high cardiovascular disease mortality in Northwest Russia

The Arkhangelsk study

Oleg Sidorenkov

A dissertation for the degree of Philosophiae Doctor
April 2011

TABLE OF CONTENTS

1. ACKNOWLEDGEMENTS

This work would have never been possible without my first supervisor Professor Odd Nilssen who introduced me to the world of epidemiology and public health. I would like to thank Odd for his academic support, availability, readiness to share his knowledge and experience, for his constant willingness to help and support me.

I am very grateful to my co-supervisor Professor Andrei Grjibovski for his thoroughness, guidance and constructive criticism.

I want to express my deep gratitude to Professor Evert Nieboer for his valuable comments and help with the language

My sincere thanks to my Russian advisor Professor Sergey I. Martiushov for the helpful and interesting discussions, and an essential contribution to the data collection for the fourth article. I am grateful to my co-supervisor Tormod Brenn for his encouragement and optimism.

I am indebted to the chief forensic pathologist Yuri Ivanovich Kapralov for his valuable help with the collection and interpretation of data used in the fourth article

I wish to convey my thanks to Mari Ann Sæthre, Mona Ingebrigtsen and Gerd Furumo for their advices and administrative help with the project in Arkhangelsk.

Finally, my greatest thanks to my family: my grandmother, parents, sister and my wonderful wife and daughter, for the encouragement, support and patience.

2. LIST OF PAPERS

I. Oleg Sidorenkov, Odd Nilssen, Tormod Brenn, Sergey Martiushov, Vadim L. Arkhipovsky, Andrej M Grjibovski. Prevalence of the metabolic syndrome and its components in Northwest Russia: the Arkhangelsk study. BMC Public Health. 2010 Jan 19;10:23.

II. Oleg Sidorenkov, Odd Nilssen, Andrej M Grjibovski. Metabolic syndrome in Russian adults: associated factors and mortality from cardiovascular diseases and all causes. BMC Public Health. 2010 Sep 29;10:582.

III. Oleg Sidorenkov, Odd Nilssen, Andrej M Grjibovski. Determinants of cardiovascular and all-cause mortality in Northwest Russia: a 10-years follow-up study. Submitted to the Annals of Epidemiology 03.02.2011.

IV. Oleg Sidorenkov, Odd Nilssen, Evert Nieboer, Nikolay Kleshchinov, Andrej M Grjibovski. Premature cardiovascular mortality and alcohol consumption before death in Arkhangelsk: an analysis of consecutive series of forensic autopsies. Submitted to the International Journal of Epidemiology 14.11.2010

3. LIST OF ABBREVIATIONS

AMI - acute myocardial infarction

AP - angina pectoris

AU - alcohol unit

AHA - American Heart Association

AUDIT - the Alcohol Use Disorder Identification Test

BAC - blood alcohol concentration

BMI - body mass index

CDT - carbohydrate-deficient transferrin

CVD - cardiovascular disease

CHD - Coronary Heart Disease

CRP – C-reactive protein

CI – confidence interval

EtG - ethyl glucuronide

GGT - gamma-glutamyltransferase

HDL-C – high density lipoprotein cholesterol

ICD-10 - International Classification of Diseases and Related Health Problems, 10th Revision

IDF - International Diabetes Federation

IHD - Ischemic Heart Disease

LDL-C – low density lipoprotein cholesterol

MetS - metabolic syndrome

MONICA - WHO’s Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Project

MRR - mortality rate ratio

NCEP ATPIII - National Cholesterol Education Program Adult Treatment Panel III

SDR – standardized death rate

TC - total cholesterol

TG - triglycerides

4. INTRODUCTION

4.1. General overview

4.1.1 Global burden of cardiovascular diseases

At the end of the XIXth century infectious diseases, injuries and malnutrition were the most common causes of death worldwide. Diseases of cardiovascular system were responsible for less than 10% of all deaths. Following the age of epidemiological transition, to the beginning of the 21st century cardiovascular diseases have become the most common cause of death worldwide, accounting for about 30% of all deaths, including approximately 40% in developed industrial countries (1). Coronary Heart Disease (CHD) and cerebrovascular diseases became the most common causes of death throughout the world, accounting for 12.2 and 9.7 % of total death toll or, respectively, 7.2 and 5.7 million deaths per year. Men die more often from cardiovascular diseases (31.5%) than women (26.8%) (2).

4.1.2 Mortality from cardiovascular diseases in Russia

Deaths due to cardiovascular diseases (CVD) constituted about 55% of all-cause mortality in 2003 (age-standardized to the world standard population mortality rate of 871 cases per 100.000 inhabitants). CHD (ICD-10 codes I20-I25) and cerebrovascular diseases (ICD-10 codes I60-I69) constituted 26.4% and 20.2% of total mortality (3). The age-standardized mortality rates for CHD and cerebrovascular diseases were 414.6 and 316.5 per 100.000.

The CVD mortality is high in both genders. The crude rates for men (815.8 per 100.000) are even lower than for women (852.4 per 100.000) (4). However, the age-standardized to the European standard population rates in men are much higher than in women, respectively, 913.3 and 441.0 per 100.000 (5) due to high CVD mortality rate in young and middle age (3). Vaguely defined diagnostic subcategories; “Chronic Ischemic Heart Disease” (ICD-10 codes I25.0-25.9) and “Other (than acute myocardial infarction) forms of acute or sub-acute ischemia” (ICD-10 codes I24.0-24.9) constitute about 80% of mortality from CHD(6). Acute myocardial infarction (AMI) composes, respectively, only 7.7% and 5.9% in the overall burden of cardiovascular mortality in the middle aged men and women (Table 1). Whereas the group of cardiovascular nosologies with vaguely defined diagnostic criteria such as “Other forms of acute or sub-acute ischemia” and “Chronic Ischemic Heart Disease” constitute, respectively, 30.6% and 16.2% in men, and 22.2% and 16.2% in women of overall CVD mortality. The use of term Coronary Heart Disease in medical literature often implies angina pectoris and acute myocardial infarction (nosologies with definite clinical signs and symptoms, laboratory and ECG-findings) as its main compound. In the Russian routine mortality statistics AMI constitutes only 14% of all fatal CHD-outcomes (Table 1).

Table 1 Age-standardized[1] mortality rate from cardiovascular diseases[2] among young (15-34 years) and middle aged (35-69) Russians by gender in 2006, per 100.000 persons

Death diagnoses	Men		Women	
	15-34	35-69	15-34	35-69
All cardiovascular diseases (I00-99)	48.6	1054	13.8	368
-Coronary Heart Disease (I20-25)				
-Myocardial infarction (I21-23)	1.33	81.2	0.19	21.7
-Other forms of acute and chronic ischemia[3] (I24)	10.4	322	2.06	81.6
-Atherosclerotic heart disease (I25)	1.13	171	0.27	59.7
-Cerebrovascular diseases (I60-69)	5.41	261	2.54	125

[1]Age-standardized to the world standard population
[2]In brackets included corresponding ICD-10 codes
[3]Is often reflected in death certificates as acute coronary insufficiency and acute heart failure

In contrast, of 735 CHD deaths of males aged 35-69 years in Norway in 2008 (7), 472 (64%) were classified as AMI and only 168 (34.1%) deaths were attributed to “Chronic Ischemic Heart Disease”. Corresponding figures for women were: 187 (100%) CHD deaths, 137 (73.3%) and 46 (24.6%). Myocardial infarction composed 35.7% of all CVD deaths in men and 30.0% in women. No deaths were allocated into the category “Other acute or sub-acute ischemic heart diseases” in the age-group 35-69 years!

It is difficult to explain the high proportion of vague CVD diagnoses because about 40-50% of all death certificates issued in Russia are based on the results of a postmortem pathological examination (autopsy). In the Arkhangelsk region in 2009, 64% of all diagnoses in death certificates were made by either hospital pathologist or forensic pathologist. In the city of Arkhangelsk, 92% of all death diagnoses were based on autopsy in 2009 (8)!

4.1.3 Comparison of CVD mortality in Russia with other European countries

The annual absolute number of deaths from CHD and stroke in Russia is comparable with such demographic giants as China and India, having the highest absolute number of deaths from these diseases in the world. However, the Russian population is about 8-9 times smaller than the Indian or the Chinese ones (9).

Although Siberia or the Asian part, situated to the east from Urals, constitutes about ¾ of Russia’s territory, it accounts for only ¼ of the population. According to the census performed in 2002, ethnic Russians constituted over 80% of the population (10). These facts call for comparison of Russian mortality data with the corresponding figures from Europe. Age-standardized mortality rates in 2003 according to the WHO (3) are shown in Table 2.

Table 2 Mortality from all causes and cardiovascular diseases in Russia (2003), countries of Central and Eastern Europe[1] (Eur-B+C; 2003), countries of Western Europe[2] (Eur-A; 2002) and Russia-to-Eur-A ratio by age and gender: SDR per 100.000 population

Age groups and causes of death	Males				Females			
	Russia	Eur-B+C	Eur-A	Rus/Eur-A	Russia	Eur-B+C	Eur-A	Rus/Eur-A
0-14								
All causes	166.4	170.5	55.3	3.0	122.5	131.9	43.3	2.8
CVD	1.9	3.3	1.4	1.4	1.5	2.6	1.3	1.2
15-29								
All causes	381.4	241.7	82.0	4.7	108.1	79.0	29.3	3.7
CVD	26.2	17.6	4.1	6.4	8.4	7.3	2.3	3.7
30-44								
All causes	1060.8	700.0	161.6	6.6	293.4	215.6	78.5	3.7
CVD	243.8	158.6	26.1	9.3	64.0	45.3	10.4	6.2
-CHD	111.0	73.7	11.8	9.4	20.3	14.4	2.4	8.5
-Cerebrovascular diseases	34.2	24.6	4.4	7.8	13.7	10.6	3.6	3.8
45-59								
All causes	2702.4	1981.7	580.1	4.7	864.8	698.9	293.3	2.9
CVD	1112.8	793.1	156.4	7.1	350.8	271.7	50.9	6.9
-CHD	623.8	435.3	86.2	7.2	144.0	111.1	17.8	8.1
-Cerebrovascular diseases	233.2	168.6	23.7	9.8	113.9	88.4	14.5	7.9
60-74								
All causes	6131.6	4996.4	2156.9	2.8	2601.9	2339.0	1069.2	2.4
CVD	3661.1	2903.0	744.9	4.9	1728.1	1507.8	335.7	5.1
-CHD	1960.9	1582.2	381.3	5.1	791.7	731.4	133.5	5.9
-Cerebrovascular diseases	1218.0	833.7	143.3	8.5	712.3	528.9	86.7	8.2
75+								
All causes	17258.3	14838.0	9832.0	1.8	12137.2	11421.7	7112.5	1.7
CVD	11617.8	10221.2	4356.2	2.7	9510.1	8805.6	3577.9	2.7
-CHD	5674.0	4925.6	1708.0	3.3	4136.3	4028.6	1150.0	3.6
-Cerebrovascular diseases	4465.8	3004.4	1119.8	4.0	4135.0	2967.6	1026.9	4.0

[1]Eur-B+C comprises Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Poland, Republic of Moldova, Romania, Russia, Serbia and Montenegro, Slovakia, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan
[2]Eur-A comprises Andorra, Austria, Belgium, Croatia, Cyprus, the Czech Republic, Denmark, Germany, Greece, Finland, France, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom

Some important conclusions can be drawn from the data in the table:

1. The cardiovascular and CHD disease mortality rates in Russian adults are higher in all age-groups, except for the youngest age-group (Table 2), than the average rates in the countries of Central and Eastern Europe. The gap in CVD mortality rates markedly increases when age- and sex-specific rates in Russia are compared to the corresponding figures from the Western Europe (Eur-A). The ratio of the CVD mortality in Russia to the average CVD mortality in the Eur-A countries varied from 1.4 to 9.3 in men and from 1.2 to 6.9 in women, being highest in the middle-aged. The incidence of fatal cardiovascular events among 30-44 and 45-59 year old Russian men in 2003 was, respectively, 9.3 and 7.1 times higher than the corresponding average estimates for the Eur-A countries. If the cardiovascular mortality rate in Russia had been the same

as in Western Europe (the age and gender distribution of the Russian population in 2002(11) is applied), the total number of cardiovascular deaths in 2003 would have been reduced by app. 1 million! It would spare about half a million lives of men and women, with ⅓ of men's and 10% of women's lives in the active working ages (30-59 years). It leads us to the third important feature of CVD mortality in Russia;

2. The all-cause and cardiovascular mortality rate in men in all age groups is considerably higher than the mortality rate in women in Russia. The difference is largest among the middle-aged and is the most obvious for CHD-deaths. The male-to-female CHD mortality rate ratio (MRR) in age-groups 30-44 and 45-59 years in 2003 was 5.5 and 4.3. Corresponding MRR for CVD in general, was 3.8 and 3.2. The absolute difference in mortality between men and women is more evident than the relative one (MRR). If such large male-to-female difference in all-cause mortality might be explained by a four times higher mortality from external causes (accidents, poisonings, suicides, violence) among men (4), the underlying reasons for differences between genders in CVD mortality, and particularly, CHD mortality are less evident.

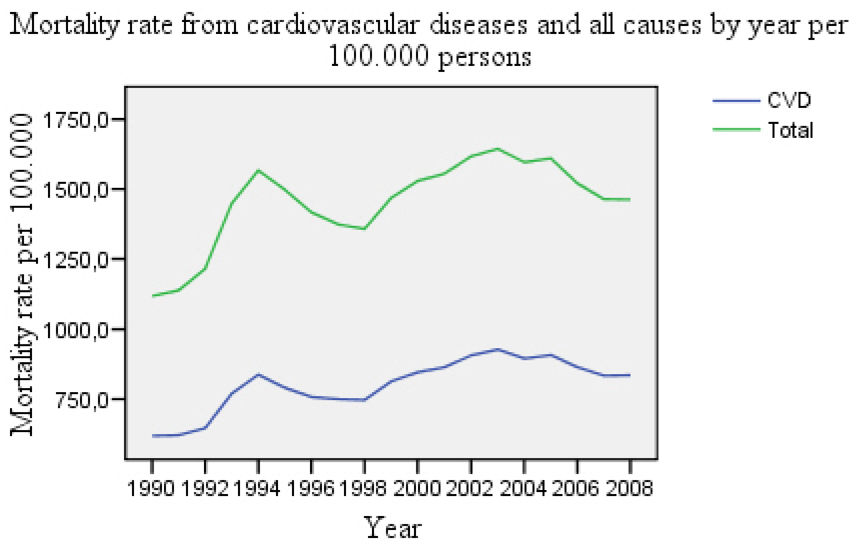
3. Cardiovascular death in Russian men occurs, in average, much earlier than in women. A very high CVD mortality in middle-aged men is an important cause of the low life expectancy among Russian men, which results to the largest in Europe gap in life expectancy between men and women. The life expectancy at birth in 2003 was 58.6 years for men and 71.8 years for women, corresponding figures in 2008 were 61.8 and 74.2 years(12).

4.1.4 Historical aspects of mortality from cardiovascular diseases in Russia

The Russian mortality crisis at the end of the XXth century

After the collapse of the Soviet Union in 1991, Russia has experienced an abrupt reduction in life expectancy at birth due to increasing mortality. The increasing number of cardiovascular deaths was its main driving force (Figure 1) (13). During just three years, CVD mortality rate has increased by 35% (from 621 in 1991 to 837.5 deaths per 100.000 in 1994). It was followed by 37.5% increase in total mortality (from 1139.3 to 1566.5 deaths per 100.000 during the same period). This dramatic increment was characterized as "beyond the peacetime experience of industrialized countries"(14) or "unprecedented in a modern industrialized country in peacetime"(15). In Russia it became known as "Yeltsin's genocide" and coincided with the collapse of the Soviet Union and the initiation of a profound societal transformation, liberalization of the economy, including the alcohol market, and the abolishment of the state's monopoly on alcohol production and sales.

Figure 1



Since the beginning of the 1990s a wave-shaped pattern persists in CVD and all-cause mortality (Figure 1) with no obvious trends for improvement until now. Thus, the highest ever registered cardiovascular mortality in Russia (927.5 deaths per 100.000 inhabitants) was observed in 2003.

Cardiovascular and all-cause mortality in the Soviet Union

The Russian mortality crisis of the 1990s has attracted worldwide attention. The leading biomedical journals have published expert opinions, analyses of national mortality statistics and results of a few epidemiological studies. However, the mortality in the period before the collapse of the USSR attracted less attention. Therefore, it may give a misleading impression of that Russia has encountered the problem of increasing CVD mortality for the first time in 1991 and before the mortality was decreasing.

The author could not find a detailed cause-specific mortality statistics for the first half of the XXth century. It is possible that it simply does not exist for this period, which can be described as a period of demographic disaster or the period of intermittent social catastrophes. Three such demographic crises may be clearly defined: 1914-1922, (World War I, followed by the October revolution, Civil War and famine), 1930-1936, (Stalin's "collectivization" with arrests and executions of millions of the better-off peasants and their families and followed by famine), 1941-1948, (the Great Patriotic War and famine of 1946-47). Only the number of direct "excessive" losses of human lives during the period from 1927 to 1947 is 35 millions! There is however no agreement about this number. It is likely that the real estimates are even higher(16). During these years, deaths from violence, malnutrition and infectious diseases determined the mortality.

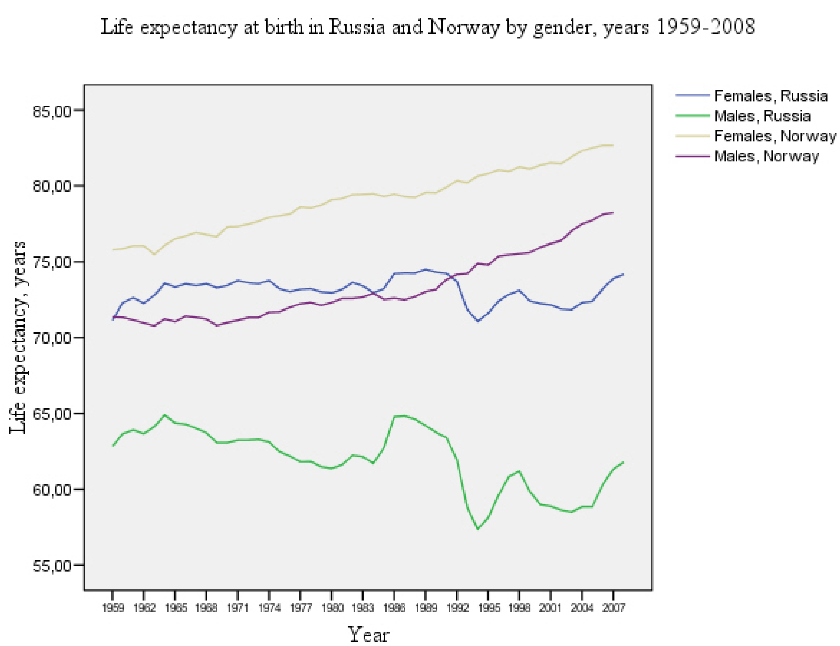
One may only suggest that deaths from a cardiovascular disease at the first half of the XXth century in Russia were not as common as in our days.

The first reliable sex-, age- and cause-specific mortality data from the Soviet Union are available from 1965. They were openly published first only in the 1980s and were not available to the public before the Gorbachev's "perestroika". There were substantial reasons for this, since during the period of ideological opposition they could be used as a weapon in the Cold War.

Following the end of the World War II and the famine in 1946-47 the life-expectancy has abruptly increased during the following 15 years. Russia entered the second phase of epidemiologic transition, characterized by improvements in nutrition and public health, an abrupt decline of mortality from infectious diseases, malnutrition and violence, as well as a low mortality of infants and children. The delay time from the western European countries constituted about 35-40 years.

The health gains were impressive, and the West-East differences in life-expectancy quickly and dramatically decreased. In 1964, the highest ever recorded life-expectancy among men (64.9 years) was registered; the corresponding one for women was 73.6 years (Figure 2).These estimates were lower than in western Europe (for comparison provided sex-specific data for Norway), but they were higher than the Russian national estimates in 2008(12;17).

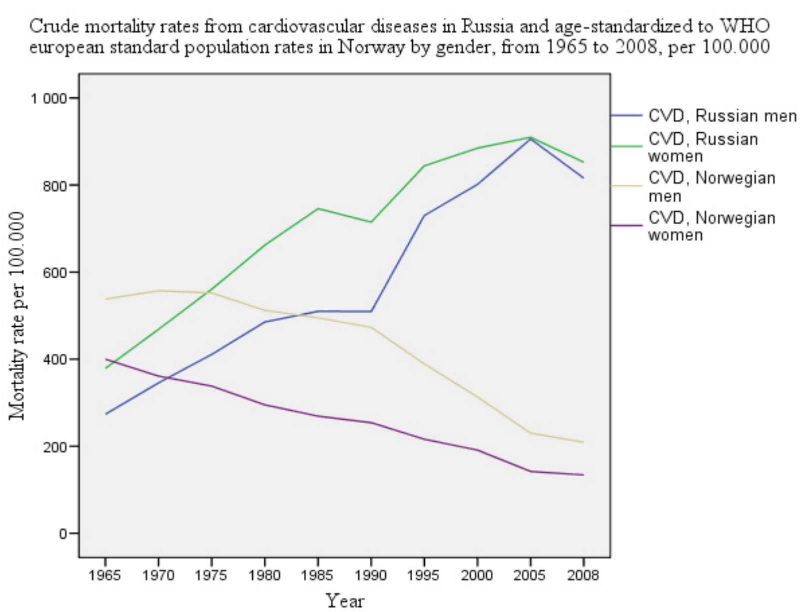
Figure 2



In 1964, the life-expectancy for both sexes was 69.9 years, which was almost identical to the one in the U.S. (70.3 years) and close to the one in Norway (73.6 years). These results, although important and impressive, were broadly used for propaganda of the Soviet regime's achievements. However, since 1964 the life expectancy has either stagnated or fallen in Russia, whereas it has been slowly increasing in Western Europe (Figure 2) and the U.S. As one of the main factors behind the reduction in life-expectancy, Russian experts blame the state's alcohol policy. The government urgently lacking money for the expensive nuclear arm race and space program, having the monopoly on alcohol production and sales, reduced prices at the beginning of 1960s, which stimulated alcohol consumption and filled the budget with "drunk money"(18). Since that time sale of alcohol has been an important source of income for the state's budget.

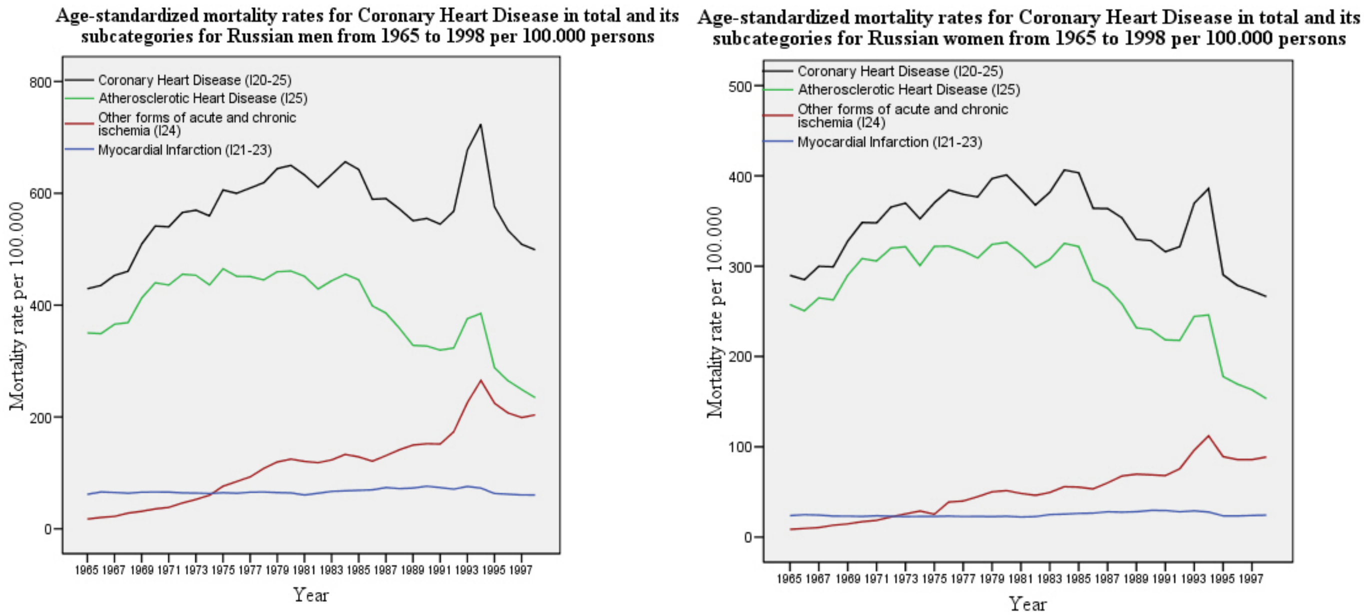
Two main groups of causes of death have dominated Russian mortality statistics since 1965 (4): cardiovascular diseases and external causes. The crude CVD mortality rate has tripled (Figure 3) in men and doubled in women from 1965 to 2008 (4). On the contrary, in the Western European countries, the mortality trends have been the opposite. In Norway, the age-standardized cardiovascular mortality rate has been reduced by 2.5 and 3.0 times, respectively, in men and women (19) during the same period.

Figure 3



Notably, the mortality rate from AMI in Russia remained constant at a relatively low level in both genders since 1965(6;20). However, the weight of the group with vaguely defined diagnostic criteria "other forms of acute or sub-acute ischemia" in CHD mortality has increased constantly (Figure 4). This increment particularly accelerated at the beginning of 1990s after the collapse of the Soviet Union and coincided with the abrupt increase in CVD mortality. The mortality from this cause of death has almost doubled among the middle-aged men and women from 1991 to 2006(6).

Figure 4



4.1.5 The importance of the problem

The high cardiovascular disease mortality may be characterized as an epidemic in Russia. Associated demographic and socio-economic detriment translated this problem from the rank of a common public health issue into the category of high priority national security challenges. Cardiovascular diseases are the leading cause of premature death and disability in the country, particularly among men of working age. Since the beginning of 1990s when cardiovascular and all-cause mortality has abruptly increased and the birth rate has fallen dramatically, the population of the Russian Federation is shrinking. In 2006, the Russian population might have been reduced by 687.100, but due to positive migration, it only decreased by 532.600 individuals (21). From 2002 to 2010 the population of Russia has shrunk by 2.2 million (1.6%) despite of annual migration of hundreds of thousands into the country (22).

The scale of the problem was recognized by the Russian government as one of the "most acute" and "fundamental" challenges for the development of the state and the civil society. In 2005, president Putin addressed the demographic problem in his speech to the nation (23) where he particularly stressed the significance of alcohol abuse as an important cause of the high mortality in the country.

High mortality in young and middle aged men causes gender imbalance, which is one of the largest in the world. There are 0.872 males to one female (11). The gap becomes evident at the age of 40 years and then continuously increases. The number of men aged 60 years or more in the Arkhangelsk region in 2006 was 63244; the corresponding number of women was 133492. The male-to-female ratio was 0.47 (24). The corresponding male-to-female ratio at the same year in Norway was 0.80 (25).

The population of Russia is an "aging population" with a low proportion of individuals in the age under 15 years, a high proportion of people older than 60, a high median age, a low total fertility rate, neonatal mortality rate and a maternal mortality rate (Table 3). Sharing these common features with other "old" European populations, the Russian population is marked by high adult mortality rate resulting in low life expectancy (26).

Table 3 Socio-demographic indicators for Russia and Norway in 2002-2006.

Indicator	Russia	Norway	Year	Rus/Nor ratio[1]
Population proportion under 15 years (%)	15.0	19.0	2006	-
Population proportion over 60 years (%)	17.0	20.0	2006	-
Total fertility rate (per woman), N	1.3	1.8	2006	0.72
Population median age, years	37.0	38.0	2006	-
Adult mortality rate, men[2]	432.0	86.0	2006	5.02
Adult mortality rate, women	158.0	53.0	2006	2.98
CVD mortality rate[3]	688.0	181.0	2002	**3.8**
Mortality from injuries[3]	217.0	35.0	2002	6.2
Life expectancy at birth (years), women	73.0	83.0	2006	-
Life expectancy at birth (years), men	60.0	78.0	2006	-
Maternal mortality ratio (per 100.000 live births)	28.0	7.0	2005	4.0
Neonatal mortality rate (per 1000 live births)	7.0	2.0	2004	3.5

[1] Ratio of an indicator for Russia to the corresponding one for Norway
[2] Probability of dying between 15 to 60 years per 1000 of population
[3] Age-standardized rate per 100.000 of population

4.2. Possible explanations for high CVD mortality in Russia

4.2.1. Established major risk factors for CVD

A high prevalence of conventional cardiovascular risk factors (smoking, dyslipidemia, arterial hypertension, overweight and obesity, diabetes mellitus) in Russia would be the simplest and the expected explanation of high CVD mortality rates. WHO's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project provided the largest and the reliable source of data on CVD mortality and risk factors to test this hypothesis. The study was performed in Moscow and Novosibirsk (a large industrial and scientific center in West Siberia with a population of about 1.5 million people). Three surveys based on independent probability samples were carried out in Moscow (in 1984-86, 1988-89 and 1992-95) and two surveys in Novosibirsk (at the beginning and at the end of the 10-year study period in 1985-86 and 1994-1995). Altogether 5678 men and 5939 women aged 35-64 years participated (27;28). The population distribution of current cigarette smoking, systolic blood pressure, total cholesterol and BMI were assessed individually and summarized in a risk score. The MONICA study established an effective standardized mechanism for registration of CHD and stroke events, which have been monitored during a 10-year period. The trends in the abovementioned risk factors and CHD mortality were compared within 34 populations from 20 countries. The study failed to explain high CHD mortality in the Russian cohorts with high levels of the "classic" risk factors, assessed neither separately nor jointly as a risk score. Moreover, the average population risk score levels were lower in Russians (27), than in some western European populations with lower cardiovascular mortality rates (Finland, Sweden, the United Kingdom and some other). Notably, the pattern of association in trends for these four risk factors with the trends in coronary (27) and stroke event rates (29) in multiple-regression analyses in the four Russian and the Lithuanian MONICA populations, was totally different from the other populations in the study. While CHD and stroke event rates were increasing in these former Soviet Union countries, a favorable trend in the CVD risk factors has been observed. These five populations poorly fit the regression model and therefore were excluded from the analyses. A strong negative association between the trends in coronary events and BMI was found in men in all four Russian populations. As a plausible explanation for the discrepant results it was suggested that the increase in coronary event rates in Russia was driven by other factors, such as hazardous alcohol consumption and misattribution of deaths from other causes to CHD-deaths (27).

Another important finding of the MONICA study was the low diagnostic precision for fatal coronary events in the Russian populations. About one fifth of all deaths, certified as deaths due to CHD, has not been confirmed by the well organized and standardized between the study populations validation procedure (28). This proportion was the highest among all participating populations. A case fatality rate for CHD patients of 57% in men and 60% in women reported for both Moscow populations was among the highest of all MONICA populations. It is necessary to mention that the quality of healthcare services in Moscow is, in general, remarkably higher than in other Russian territories, since the city concentrates the country's financial, intellectual and technical resources.

The distribution of the major cardiovascular risk factors in Russia was further compared with three Scandinavian populations: a Finnish(30), a Swedish(31) and a Norwegian (Tromsø)(32). Findings from these studies were generally in line with those reported in the MONICA study (Table 4). The cardiovascular risk scores based on the major conventional cardiovascular risk factors in Russian populations were either lower or equal to the scores reported for the Nordic populations. Only prevalence of smoking was considerably higher among Russian men than among men in the Western populations. It was concluded that classical risk factors do not provide a complete explanation for the high mortality in the former Soviet Union countries (33). The authors have also suggested that psychosocial, nutritional, socio-economic factors and hazardous alcohol consumption play an essential role in the mortality crisis.

Table 4 Age-adjusted means of cardiovascular risk factors in men and women from the Russian population-based samples and the corresponding samples of Western populations. P-values are given for difference between the Russian and Finnish estimates.

	Russian vs. Swedish		Russian vs. Finnish		p-value	Russian vs. Norwegian		Russian vs. MONICA	
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)		Mean(SD)	Mean(SD)	Mean[4]	Mean[4]
MEN	Russian	Swedish	Russian	Finnish		Russian	Norwegian	Russian	MONICA
TC, mmol/l, mean ± SD[1]	5.23±0.06	6.29±0.10	5.19±0.93	5.84±1.12	<0.001	5.0±1.2	6.1±1.2	5.3 (-0.021)	5.8 (-0.008)
HDL-C, mmol/l, mean± SD	1.36±0.02	1.23±0.25	1.38±0.36	1.28±0.33	<0.001	1.3±0.4	1.3±0.4	-	-
TG, mmol/l, mean ± SD	1.24±0.04	1.66±0.11	1.20±0.72	1.86±1.21	<0.001	1.4±0.9	1.8±1.1	-	-
SBP, mmHg, mean ± SD	134.9±1.24	130.8±1.49	142±23	140±19	ns	133.5±19.0	137.5±17.4	130 (-0.39)	133 (-0.21)
DBP, mmHg, mean ± SD	87.6±0.67	83.0±0.96	83±13	83±13	ns	75.7±14.6	79.9±11.8	-	-
BMI, kg/m², mean ± SD	26.11±0.20	26.44±0.30	25.2±4.0	27.0±4.0	<0.001	25.3±4.0	25.6±3.3	25.2 (-0.07)	26.6 (0.05)
Smoking, %	56.3±2.80	20.6±3.41	65	31	<0.001	56.7	37.4	47	36
TC ≥6.5 mmol/l,%	12.2±1.82	44.4±4.00	9	27	<0.001		-	-	-
Diabetes prevalence, %	4.0±1.10	4.9±1.75	-	-	-	-	-	-	-
Risk Score	6.9[2]	7.1[2]	-	-	-	33.8±46.4[3]	45.9±71.9[3]	6.8 (-2.15)[2]	7.1 (-1.08)[2]
WOMEN									
TC, mmol/l, mean ± SD[1]	5.44±0.07	6.16±0.11	5.32±1.14	5.62±1.12	<0.001	5.1±1.2	6.1±1.4	5.6 (-0.000)	5.8 (-0.015)
HDL-C, mmol/l, mean± SD	1.48±0.02	1.52±0.03	1.44±0.34	1.53±0.33	<0.001	1.4±0.4	1.6±0.4	-	-
TG, mmol/l, mean ± SD	1.28±0.04	1.36±0.07	1.22±0.73	1.37±1.0	ns	1.3±0.9	1.3±0.9	-	-
SBP, mmHg, mean ± SD	136.2±1.33	126.7±1.62	144±29	132±21	<0.001	128.1±22.4	131.9±22.6	133 (-0.89)	129 (-0.38)
DBP, mmHg, mean ± SD	86.5±0.68	78.5±0.87	82±14	78±11	<0.001	73.0±13.3	76.1±12.7	-	-
BMI, kg/m², mean ± SD	29.25±0.39	25.77±0.36	28.0±5.8	26.5±5.1	<0.001	26.0±5.7	24.8±4.2	26.5 (-0.26)	26.5 (0.01)
Daily smoking, %	5.9±1.30	27.6±3.54	11	16	<0.003	21.3	36.3	14 (-0.11)	21 (-0.14)
TC ≥6.5 mmol/l,%	16.3±2.09	37.5±3.84	15	20	<0.01	-	-	-	-
Diabetes prevalence, %	6.6±1.40	5.6±1.82	-	-	-	-	-	-	-
Risk Score	6.0[2]	6.3[2]	-	-	-	3.9±6.6[3]	9.8±16.9[3]	6.2 (-2.99)[2]	6.2 (-1.87)[2]

[1]TC-total cholesterol, HDL-C -high-density lipoprotein cholesterol, TG-triglycerides, SBP-systolic blood pressure, DBP-diastolic blood pressure, BMI-body mass index
[2]Risk score defined as a linear combination of the following factors: daily smoking, SBP, TC and BMI
[3]Risk score presents a 10-year risk of getting the myocardial infarction
[4]Mean with the average annual change of the factor during follow-up

4.2.2 Other CVD risk factors in Russia

1. **Psychosocial factors**

A large case-control study (INTERHEART) performed in 52 countries and based on 11119 cases of first AMI and 13648 age- and sex-matched controls found that the psychosocial factors were associated with the risk of AMI (34). A presence of depression increased the risk by 55% (OR 1.55; 99% CI: 1.42-1.69), permanent general stress (work, home or both) and stressful life events in the past year were associated with an OR of, respectively, 2.17 (1.84-2.55) and 1.48 (1.33-1.64) (35). These results were consistent within different regions, ethnic groups and for both genders.

A cross-sectional population-based study in Arkhangelsk (the Arkhangelsk 2000 study) found that 32% of men and 70% of women reported depression and/or anxiety and/or sleeping disorders. These percentages were higher than the ones found in Northern Norway (36). In the Arkhangelsk 2000 study these factors have shown a strong positive association with self-reported cardiovascular disease (AMI, stroke and AP). A positive association between depression and CVD mortality has also been demonstrated in several cohort studies (37-40). Presence of anxiety and distress was found to be associated with higher cardiovascular mortality (40;41). Nevertheless direct evidence of the association between psychosocial factors and cardiovascular risk in Russia is still limited.

2. **Socio-economic factors** (education, marital status and income) are important determinants of cardiovascular mortality in western populations (42-45). Low educational and single marital status are also factors positively associated with risk of cardiovascular death in Russia (46-50). Some studies have concluded that this association was of a similar magnitude as in the west (48).

3. A**lcohol consumption**

Results from numerous studies on association between alcohol intake and cardiovascular mortality in the west are consistent in that the association follows a U- or L-shaped curve. The lowest cardiovascular risk (including both CHD and stroke) was found among moderate drinkers (51-56). The US Cancer Prevention Study has examined the longitudinal association (9-year follow-up) between alcohol intake and risk of cardiovascular death in nearly half a million old- and middle-aged US inhabitants (53). The study found that the risk of CVD death in both genders was lower in all drinking categories than in abstainers. The CHD mortality started to increase when a daily consumption of alcohol in men without pre-existing CVD exceeded 28-42g (2-3 drinks). The corresponding threshold in women was 14g per day (one drink).

The current guidelines of American Heart Association state that a daily consumption of 28g of alcohol in men and 14g in women is not accompanied with excessive cardiovascular risk (57). A meta-analysis of 28 cohort studies found that the CHD risk was lowest at a daily consumption of 20g alcohol. There were evidences of a protective effect at a consumption level up to 72g/day and cardiovascular risk exceeded that of in abstainers when daily consumption was ≥89g (54). The study underlined the importance of the drinking pattern in assessment of alcohol-related CHD risk.

The vast majority of studies have used only “average alcohol consumption” per day, week month, etc. as a measure of alcohol consumption. However, the number of drinking episodes may be, probably, more important than “the average alcohol consumption” in a country with the drinking culture found in Russia. A bottle of vodka taken at one occasion may have different health effects than the same volume evenly spread during a week (58). Data on cardiovascular risk associated with alcohol binge drinking are limited. Also little is known about how this association is affected by the type of alcoholic beverage: wine, spirits or beer. Comparison between studies is difficult because authors use different criteria to define binge drinking. Two recently published meta-analyses have concluded that episodes of irregular heavy drinking may modify favorable effects of moderate drinking on CHD risk in such way, that the cardioprotective effect of moderate drinking disappears (59;60).

Consumption of large amounts of spirits at one drinking session is a pattern of drinking, which is widely spread in Russia, particularly among men (61-63). A study from Arkhangelsk found that among all non-abstainers, 52% of men and 17% of women were regular binge drinkers, who consumed 6 Alcohol Units (1AU=14g of pure alcohol) or more at least once a month. Vodka/liquor and beer constituted, respectively, 60% and 30% of the total consumption (64). This pattern of alcohol drinking may be associated with higher cardiovascular risk via several biologically plausible mechanisms (58;65). Recent epidemiological studies from Russia provided evidence that hazardous alcohol consumption is associated with higher cardiovascular risk (66-68). This finding was supported by the results of earlier published studies based on aggregated data (69-71).

4. **Societal transition and cardiovascular and all-cause mortality**

The break-up of the Soviet Union in December 1991 was followed by the unprecedented 40% increase in mortality during the next three years. The break-up has initially been followed by small increase in CVD mortality in former socialist countries of Central and Eastern Europe. However, this was quickly followed by declining mortality (26). The pattern was different in Russia were the rates continued to increase until 2005 (Figure 1). The main factors behind these dramatic changes in mortality might be grouped into three broad categories: socioeconomic deprivation, psychosocial stress and increased alcohol consumption, which might also partly mediate the effect of the first two factors (72). These three groups of factors correlate and have a tendency to clustering.

Poverty was quickly increasing after the break-up of the Soviet Union and the collapse of the Soviet ruble. In 1992 more than 1/3 of the population lived under the official minimum level of subsistence. The true estimate is likely to be higher. The level of inflation has reached an astronomical number of more than 13.000% from 1992 to 1995 (73). Tens of millions have lost all savings.

In Soviet Union, many cities have been built up by large industrial (often military) facilities where the majority of population was employed (mono-cities). Such cities as Chelyabinsk (1.100.000 inhabitants), Krasnoyarsk (930.000), Izhevsk (600.000), and Severodvinsk (250.000) are only few examples of large mono-cities. Tens of millions have become unemployed due to the collapse of industry and economy in the whole country. Cities with a predominantly unemployed adult population appeared. During several months unemployment reached threatening levels. Crimes and violence skyrocketed. The situation in rural areas was as catastrophic as in the cities.

The levels of alcohol consumption were increasing in parallel with the alcohol-related mortality. From 1990 to 1994 the proportion of all-cause deaths (both genders) with any Blood Alcohol Concentration (BAC) revealed by forensic autopsy has increased from 52.3 to 62.7%. The proportion of fatal alcohol poisonings among all deaths from external causes has increased from 9.5 to 18.7% (74). The increase in annual per capita alcohol consumption (for age 15+) from 16.2 l in 1991 to 18.5 l in 1994 was followed by increase in all-cause mortality (75).

To summarize; both poverty, stress, and alcohol were involved simultaneously as factors explaining the mortality increase in Russia during the 1990s. It seems difficult to separate the impact of one single factor due to the complex interplay between them and the limited data on this issue.

5. **Dietary factors**

The two main dietary factors associated with an increased CVD risk are **high saturated fat intake** and **low consumption of fresh fruits and vegetables**.

A high consumption of animal fat is associated with an unfavorable lipid status and, primarily, high serum total cholesterol (TC) levels, which is a major cardiovascular risk factor (76;77). If dietary intake of saturated fats was higher in Russia than in the West, this would mean that the mean serum levels of TC, triglycerides and LDL-cholesterol would also be higher. However, the results of epidemiological studies show that they were, in fact, lower or equal in Russian men and women (Table 4). It is also reasonable to suggest that the intake of animal fats was low in Russia where a system of distribution, based on food cards was introduced already in mid-80s. Strict quotas of consumption existed for virtually everything; from matches to salt and sugar. At the beginning of 90s, a considerable part of the population existed on the border of starvation (73).

Low dietary intake of antioxidant vitamins (A,C,E) is associated with an increased CVD risk (78-84). A strong inverse association between serum levels of vitamin E and A and CHD mortality was documented (85). Fresh fruits and vegetables are the main source of vitamins, possessing a protective antioxidant activity. The fruits and vegetables also contain many other valuable biologically active substances such as bioflavonoids, glutathione, ferulic acid etc. A large number of studies have documented beneficial effect of high consumption of fresh fruits and vegetables (86;87).

There is a lack of epidemiological studies on the prevalence of vitamin deficiency in Russia. In a study of 1.000 Finnish and 500 Russian men living in neighbor areas of the Russo-Finnish border, plasma ascorbic acid concentrations were compared within the populations. The study showed that 93% of Russian men had severe vitamin C deficiency and only less than 5% of Finnish men did so (88). It is likely that the severe vitamin C deficiency was a marker for low levels of other vitamins and antioxidants as well.

Vitamin deficiency in Russian men is likely worsened by high prevalence of smoking. A study comparing the distribution of major risk factors in Russian and Finnish population carried out in the same area three years earlier (30) found that the prevalence of smoking in Russian men was much higher than in their Finnish counterparts (65 vs. 31%). This proportion is consistent with the findings of other comparative studies (Table 4). A combination of low dietary vitamin intake and smoking is unfavorable, since both factors increase levels of oxidative stress (81). Hence, exposure to oxidative stress may be a possible risk factor for the high cardiovascular mortality in Russia (89).

5. AIMS OF THE THESIS

- To assess the prevalence of high levels of major cardiovascular risk factors taken individually and within the concept of the metabolic syndrome (MetS) in a sample of Russian adults

- To study the associations of MetS and its individual components with socio-demographic and lifestyle characteristics

- To study the associations between the MetS and mortality from cardiovascular diseases and all causes in the Arkhangelsk cohort

- To estimate gender-specific effects of the conventional and novel cardiovascular risk factors on CVD and all-cause mortality after a 10-year follow-up

- To study associations between alcohol consumption in the hours before death and premature cardiovascular mortality in Arkhangelsk

- To assess potential misclassifications of deaths from alcohol poisoning as cardiovascular deaths in Arkhangelsk

6. MATERIAL AND METHODS

6.1 Study design

Data used in papers I, II and III were collected in population based cohort study. The data on exposure were collected in 1999-2000 and the follow-up continued to the 1st of October 2010. Paper IV was based on cross-sectional design.

6.2 Background population

The study was performed in the city of Arkhangelsk, the capital of the Arkhangelsk region in Northwest Russia. The population of Arkhangelsk consisted of 154.285 men and 191.359 women in 2005 (90) and was decreasing. The population which is ethnically homogeneous, consists of 95% of Russians and 3% of Ukrainians and Byelorussians and, in general, is representative for Northwestern region of Russia (91). The mortality by gender, age and cause of death in the Arkhangelsk region is close to the national estimates (92;93).

6.3 Study population (papers I, II, III)

There was no population register available for medical research in Arkhangelsk in 1999. The study participants were recruited from the attendees of one of the largest out-patient clinics in Arkhangelsk, the Seamen or “Semashko” clinic. The out-patient clinics provide primary health care to the general population by occupational (subjects having a particular occupation) and territorial principles (population of a certain district), or both. The out-patient clinics also provide an obligatory annual medical examinations of the working and studying population at the age of 18 years or more (“dispensarization”).

From the beginning it was decided to recruit about 4.000 individuals, distributed in age and sex groups of a similar size. Participants were consecutively recruited as they came for the annual medical examination to the Seamen clinic. They attended the clinic between 8.00 and 12.00 and were asked at the registration board to participate in the study. Of those who were invited only 40 subjects (1.1%) refused to participate. At the end of the data collection, in 2000 schools and shoe factory were contacted and their employees (mainly females) were invited to participate in the study.

Altogether, 1968 men and 1737 women aged 18 years or more were enrolled. About 90% of men and 70% of women were recruited through an annual medical examination. Other participants were invited. Workers constituted about 66%, students 12%, pensioners 19% and unemployed 3% of the study population.

6.4 Data collection (Paper I-III)

Individuals who agreed to participate were followed to the study office and registered in the journal with individual number. Data were collected by specially trained nurses. At first, anthropological measurements were made: height, weight, waist and hip circumference. Height and weight were measured in subjects wearing light clothing and without shoes.

Then each participant went to a separate room were a questionnaire was filled (Appendix I). A nurse was present in the room to assist if there were difficulties in understanding the questions.

At the third stage the participants were guided to another room where blood pressure and heart rate were measured. Measurements were made three times with intervals of two minutes, in a sitting position, using an electronic automatic device (DINAMAP-R, Criticon, Tampa, Florida).

Finally the participants were followed to another room where blood samples were drawn. We assume that the majority of the participants were fasting, since the annual medical examinations we used to recruit the study sample, included screening on diabetes. However, none of the participants was directly asked to fast before the medical examination. Venous blood samples were centrifuged within 15-25 minutes. The serum samples were stored at -20°C and then transported frozen to Norway where they were kept at -80°C pending analysis. All laboratory analyses were carried out at the Department of Clinical Chemistry of the University Hospital in Northern Norway, using internationally standardized procedures.

Measurement of exposure to alcohol (Papers I, II and III)

Alcohol intake was described in terms of the drinking frequency and volume of alcohol consumption at one drinking episode:

-The frequency of alcohol consumption was classified into 4 groups: abstainers, ≤1 time a month, 2-4 times a month, ≥5 times a month.

-The number of alcohol units (AU) normally consumed on one occasion was categorized as abstainers, 1-4 AU and ≥5 AU. One AU was equal to 13.8 g of pure alcohol.

-Data on alcohol consumption by type of drink were collected asking the question: “During the last week I drank” (number of AUs) of beer, wine, liquor, in total.

In paper III several additional estimates of alcohol consumption were used:

-Frequency of 6 or more AU consumption (6 AU was equivalent to about 250 ml of vodka) at one drinking session was presented as never (included abstainers), less than once a month and ≥1 time a month

-the Alcohol Use Disorder Identification Test (AUDIT)(94;95) and the CAGE test(96), respectively, consisting of 10 (giving a maximum score of 40) and 4 items (a maximum score of four) were used to assess the alcohol intake.

Assessment of anxiety and psycho-social distress (Paper III)

Three indicators were used: presence of depression, sleeping problems and low self-evaluated quality of life. The examinees who answered “yes” to the question “Do you have periods of 2 weeks or more during which you feel sad, blue or depressed?” were classified as having depression. As having sleeping disorders were defined those who answered “yes” to the question “Do you have periods of 2 weeks or more during which you have problems with sleep?” Quality of life was self-evaluated according to a scale from one to ten (Cantril Ladder), where “1” represents the worst quality of life. Those subjects who had scored less than 5 were considered as having low quality of life.

Laboratory analyses

Enzymatic colorimetric tests were used to measure total cholesterol (cholesterol esterase, cholesterol oxidase) and triglycerides (lipoprotein lipase, glycerokinase, and glycerophosphate oxidase). HDL-C was measured by a homogenous enzymatic colorimetric test (PEG cholesterol esterase, and PEG peroxidase). If the serum triglycerides (TG) level was less than 4mmol/l, the Friedewald equation was used to calculate the LDL-C concentration(97). If the TG concentration was higher than 4mmol/l LDL-C was measured directly by an enzymatic colorimetric test. All biochemical analyses of serum lipids were performed using a Hitachi 737 analyzer. Serum glucose (SG) was measured by the hexokinase method using a Hitachi 917 analyzer. Glycohemoglobin (HBA1c) was determined using the Bio-Rad Variant II HPLC system with reagents from Bio-Rad Laboratories (Inc., Hercules, CA 94547, USA). Apolipoproteins A1and B were assayed by an immunoturbidimetric method with polyclonal sheep anti-human apolipoprotein antibodies (Roche). Gamma-glutamyltransferase (GGT) was measured by an enzymatic colorimetric test (standardized method, Roche). Aspartate-aminotransferase (AST) and alanin-aminotransferase (ALT) were measured photometrically by Hitachi 917 analyzer. Serum C-reactive protein (CRP) was measured by particle-enhanced immunoturbidimetric assay in a Roche Modular P analyzer (Roche Diagnostics GmbH, D-68298 Mannheim). Serum albumin was measured colorimetrically by an automated method using bromcresol green as the indicator on Hitachii-917 analyzer. The analytic coefficient of variation was $\leq$3% for all laboratory measurements except TC (5%).

Measurement of cardiovascular risk

As an indicator of cardiovascular risk in Papers I and II we used Metabolic Syndrome (MetS); a cluster of four major cardiovascular risk factors such as dyslipidemia, arterial hypertension, hyperglycemia and central adiposity (98). Almost all main components constituting the MetS concept, are strongly related to atherosclerosis. The presence of the MetS is associated with a predilection for atherosclerotic vascular disease (99) and higher cardiovascular mortality and morbidity in western countries (100-102).

There is no uniform internationally accepted definition of the MetS. Six main sets of diagnostic criteria have been elaborated by different expert groups. Although they are based on the same metabolic components, these definitions interpret weight of individual metabolic abnormalities differently. This results in low diagnostic agreement between some definitions. The main difference is that some sets of criteria consider central obesity and insulin resistance as the key or obligatory element in the MetS's pathology, whereas the other definitions consider it equal to the other components (103).

The MetS was defined according to criteria commonly used in scientific literature: by the National Cholesterol Education Program Adult Treatment Panel III (NCEP) (104), its modified version of the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) (105) and International Diabetes Federation (IDF) (106). The prevalence of the MetS was age-standardized according to the world standard population and compared with the estimates from western countries.

Follow-up study (Paper II and III)

All subjects who participated in the baseline examination 1999-2000 were included in the follow-up study. The end-point was death coded according to the ICD-10. Only deaths of the participants who were 18 or more years of age at baseline were included in the analyses. The first follow-up was performed in 2003-04 and was based on the following sources of data:

1. The participants' medical records at the out-patient clinics of Arkhangelsk. Altogether 2851 (70%) medical records were found at the first follow-up.
2. The mortality database of the Arkhangelsk Regional Healthcare Department.
3. Contact by mail of those participants whose medical records were not found (n=1238 or 30.5%). They received a letter containing a small questionnaire (Appendix II) about their health status and use of medications. Only 229 (18.5%) subjects completed the questionnaire. Because of the low response rate contact by mail has not been used since.

The vital status was determined for 3099 subjects (76% of the study sample) at the first follow-up. The same procedure was followed in 2005-06. At this time only approximately 60 % of the initial study population was found. The vital status for the participants whose medical records were not found was checked through the mortality database of the Arkhangelsk Regional Healthcare Department. This is a computerized registry which is based on the official death certificates (Appendix III) issued in the Arkhangelsk region. It contains information about the name/surname, date of birth, date and cause of death, the address where the deceased was registered and the medical specialist who certified the death. The registry was used in 2007 to determine the vital status for all participants during the period from 1999 to 2007. Since then an annual repeated follow-up based on the registry data was launched. The latest data on mortality were available to the 1st October 2010 making the mean duration of follow-up 10.2 years.

Validation of cardiovascular deaths

In 2007 we searched the out-patient records for 142 deaths known to August 2006. The records were found for 70 (50%) subjects; among whom 42 (60%) died from a CVD (ICD-10 codes I00-99). We validated only 32 deaths from CHD (ICD-10 codes I20-25) and stroke (I60-64). Hospital records were found for 7 CHD deaths and 6 stroke deaths and the validation of 19 CHD deaths was only based on out-patient records. We assessed the validity of CHD diagnoses based on the criteria proposed by the American Heart Association (107). Validation of deaths from stroke was based on the criteria used in the MONICA study (108).

We concluded that the in-hospital diagnostic accuracy for CHD and stroke deaths was high. A broad range of diagnostic procedures was applied to make a correct diagnosis. For example, either CT or/and MRI scan were performed in all 6 cases of fatal strokes. Accuracy was less for out-of-hospital CHD deaths (mainly because of limited data provided in the records), however, we, in principle, agreed with all 19 diagnoses.

Autopsy data on exposure to alcohol before death (paper III)

When the death certificate was issued by forensic pathologist the Arkhangelsk Regional Centre of Forensic Expertise was contacted. Then data on presence of alcohol or surrogates were retrieved from the autopsy records.

Ethics

The study was approved by the Regional Ethics Committee, Tromsø, Norway. All participants provided verbal informed consent.

6.5 Data collection (Paper IV)

The mortality database of the Arkhangelsk Regional Healthcare Department was used to examine death certificates of all men (n=5065) and women (n=4489) who died in Arkhangelsk from 01.01.08 to 31.12.09 (Figure 5). Men (n=1334) and women (n=629) who died from a cardiovascular disease (ICD-10 codes I00-99) at the age of 30 to 70 years, were selected. Then death certificates issued by a forensic pathologist were selected for 964 men and 390 women.

The Arkhangelsk Regional Centre of Forensic Expertise where all forensic autopsies in Arkhangelsk are performed was contacted and the access to the archive of autopsy reports was granted. The data on presence of alcohol at autopsy were retrieved from the autopsy reports for 795 men and 324 women who died from 01.01.08 to 31.08.2009. A measurement of alcohol concentration in body fluids and tissues is a routine part of a forensic examination in case of all premature deaths (under 70 years). As a standard, alcohol is measured in blood and urine. In some cases it is also detected in specimens of gastric mucosa or the thigh muscle. The alcohol concentration is measured by gas chromatography(109) in g/l with a detection limit of 0.0001g/l.

The ethical approval of the study was obtained from the Ethical Committee of the Northern State Medical University in Arkhangelsk.

Figure 5. Selection of the study population (paper IV)

5065 men and 4489 women who died from 01.01.08 to 31.12.09 in Arkhangelsk

↓

2113 men and 2510 women who died from a CVD (ICD 10 code I00-99)

↓

1334 men and 629 women who died from CVD at the age of 30-70 years

↓

964 men and 390 women; the death certificate issued by a forensic pathologist

↓

796 men and 324 women who died from 01.01.08 to 31.08.09

6.6 Statistical analyses

The differences between genders in the studied characteristics were assessed by unpaired t-tests and Pearson's chi-squared tests, respectively, for continuous and categorical variables (Papers I-III).

Sex-specific cut-offs for waist circumference corresponding to BMIs of $\geq$25 kg/m² and $\geq$30 kg/m² were calculated using a receiver operating characteristic (ROC) analysis. Agreement between the MetS definitions was assessed by Cohen's kappa statistic (paper I). Sex-specific MetS prevalence rates (Paper I) and mortality rates (paper IV) were age-standardized to the world standard population.

Adjusted sex-specific risk estimates for cardiovascular and all-cause death with 95% confidence intervals (CI) were assessed using Poisson regression with robust variance estimates (paper II) and Cox regression (paper III).

Odds Ratios (OR) with 95% CI and p-values for probability of being identified with any alcohol concentration at autopsy by gender and death diagnosis were calculated using Mantel-Haenszel methods (Paper IV).

7. RESULTS

Paper I

The prevalence of atherosclerotic vascular disease determinants: MetS and its individual components in the Russian population

We found a large difference in prevalence of MetS between men and women. The prevalence rate of MetS defined according to the NCEP criteria was 11.5% (95% CI: 10.1-12.9) in men. This was 50% lower than in women (19.8%; 95% CI: 18.1-21.5). The MetS prevalence was similar in the youngest age-groups (18-29 and 30-39 years). The difference in MetS prevalence increased dramatically in the age-group 40-49 years (11.6% in men vs. 19.8% in women) and was almost 2-fold in the age-groups 50-59 (18.8% vs. 37.2%) and 60+ years (24.4% vs. 44.8%).

The age distribution of the individual metabolic abnormalities had similar pattern. Low prevalence of the two metabolic components mainly contributed to a lower MetS rates in men than in women: central obesity and low serum HDL-C levels. The prevalence of these metabolic abnormalities in men was lower in all age-groups compared to women. In the age-groups 50-59 and 60+ years the difference was almost 5-fold for central obesity and 1.5-fold for the low HDL-C.

Paper II

Socio-economic and life-style factors associated with MetS and individual metabolic abnormalities, and the association of MetS with cardiovascular and all-cause mortality

The pattern of alcohol drinking was an important correlate of the MetS in the Arkhangelsk adults. Both the frequency of alcohol intake and amount of alcohol consumed at one drinking episode were independently associated with MetS and individual metabolic abnormalities. In men, consumption of ≥5 AU (≥75g of alcohol) at one drinking episode (binge drinking) was independently related to 50% lower prevalence of the MetS, and, respectively, 27%, 21% and 50% lower prevalence of high TG levels, low-HDL-C levels and hyperglycemia compared to abstainers. No association with binge drinking was found in women in whom, however, a statistically significant inverse association was found between the frequency of alcohol intake and MetS. A frequency of alcohol consumption ≥5 times a month was associated with 60% lower MetS prevalence, a 50% lower prevalence of low HDL-C levels compared to non-drinkers. The probability of hyperglycemia linearly decreased with the frequency of consumption ($p=0.03$).

The pattern of alcohol drinking was different in men and women: men consumed alcohol more frequently and reported a higher prevalence of binge drinking than women did (47.5% vs. 15.1%). About 70% of AUs consumed by men were from liquor (mainly vodka) whereas only 30% was so in women. It was concluded that differences in alcohol consumption between men and women might explain the differences in the MetS prevalence. To test the validity of our findings we included several biomarkers in the regression analyses: GGT, CRP and AST-to-ALT ratio. All three factors were independently associated with MetS in line with previous research.

No statistically significant association of MetS with all-cause and cardiovascular mortality (I00-99) was found during a 9-year follow-up. The association was only present in a selected group of cerebral strokes (I60-64) and myocardial infarctions (I21-23), and only in men. MetS strongly and significantly predicted death from stroke, RR 3.76 (95% CI: 1.35-10.46) and death from either stroke or myocardial infarction, RR 2.87 (95% CI: 1.32-6.23) in men. Notably, in a fully adjusted model, men with MetS had 27% lower risk of CHD death (I20-25), RR 0.73 (95% CI: 0.30-1.76) than men without MetS. Although this finding could be due to chance.

Paper III

Predictors of cardiovascular and all-cause mortality in Russian adults: a 10-year follow-up Arkhangelsk study

The article presents the results of 10-year follow up study of 1966 men and 1738 women, who were examined in 1999-00 in Arkhangelsk and followed-up to the October 2010. To our knowledge, this study provided the first longitudinal evidence of the association between hazardous alcohol consumption and the risk of cardiovascular death in Russian women. A consumption of 6 AU (80g alcohol) or more at least monthly was associated with a 5-fold increased risk: RR 5.05 (95% CI: 1.54-16.7) and binge drinking was associated with a 3-fold risk: RR 3.21 (95% CI: 1.07-9.58) of cardiovascular death compared to abstainers. The risk of cardiovascular death increased with the frequency of binge drinking (p for trend 0.005). A positive answer on 1 item of the AUDIT and the CAGE questionnaires, respectively, increased the risk of cardiovascular death by 1.26 (95% CI: 1.14-1.40) and 2.45 (95%: 1.44-4.19) times in women.

In men, the self-reported frequency of alcohol intake of once a month or less and a consumption of 1-4 AU (14-56g alcohol) at one drinking episode were associated with a 2-fold increase in risk of cardiovascular death. University education and obesity (BMI$\geq$30 kg/m^2**)** were associated with a 40% lower risk of all-cause death in men. Low serum albumin was associated with high CVD and all-cause mortality in both genders. Higher ApoB/ApoA1-ratio was strongly and directly related to cardiovascular mortality in men (RR 7.62 (95% CI: 3.15-18.4) and women (RR 3.12 (95% CI: 1.08-8.98), and an all-cause mortality in men (RR 4.39 (95% CI: 2.22-8.68).

Paper IV

Premature cardiovascular mortality and alcohol consumption before death in Arkhangelsk: an analysis of consecutive series of forensic autopsies

Firstly, age-specific mortality by the cause of death in Arkhangelsk in 2008-09 was compared between men and women. The largest male-to-female MRR was found for cardiovascular mortality (MRR of 4.3) and mortality from external causes (MRR 4.6) in the age group 50-59 years. Notably, the absolute number of cardiovascular deaths in men was higher in the age 50-59 years (N=525) than in the age 60-69 years (N=468).

Secondly, cardiovascular mortality by cause and age was analyzed in men and women who died at the age of 30-70 years. The proportion of deaths certified by a forensic pathologist on the base of autopsy increased from 37% in 2006 to 69% in 2008-09. Measurement of alcohol concentration in body fluids and tissues is a routine part of the autopsy. We used this favorable opportunity to study cardiovascular mortality by postmortem data on alcohol concentration.

Cardiomyopathies constituted a high proportion of cardiovascular deaths. At the age of 30-59 years, it constituted 24% and 30% of all cardiovascular deaths, respectively, in men and women. About 1/3 of men and women, who died from a CVD at the age of 30-59 years, consumed alcohol in the hours before dying. Alcohol was more likely to be found at the autopsy of men than that of women who died from all cardiovascular causes (OR 1.55; 95% CI: 1.14-2.10), Ischemic Heart Disease (OR 2.04; 95% CI: 1.36-3.05) and Chronic Ischemic Heart Disease (OR 2.02; 95% CI: 1.23-3.31). No difference was found for deaths from cerebrovascular diseases (I60-69), myocardial infarction (I21-23) and cardiomyopathy (I42.0-42.9).

The study did not support the hypothesis of a substantial misclassification of alcohol poisonings as cardiovascular deaths, since less than 1% of the deceased had blood alcohol concentration 4g/l or higher.

8. DISCUSSION

8.1 The validity of the results. Bias and confounding

1. Selection bias (papers I-III)

No centralized register of general population of Arkhangelsk was available for research, and it was not possible to select a random sample of the town's population. Thus, it was difficult to select a representative sample in this situation. The decision to use the obligatory annual medical examination at the "Seamen" out-patient clinic to recruit the participants had several limitations. Firstly, the main target population for this examination was working seamen and port workers. The vast majority of these subjects were men. Arkhangelsk is a large sea-port and has a large fishing and trade fleet; therefore seamen and port workers constitute a large proportion of its working male population. However, this proportion is smaller than in the study. Some seamen participating in the study (about 20%) were not residents of the Arkhangelsk region. They lived and had registration in other regions of Russia. The latter also had implications for the follow-up.

Secondly, the obligatory examination in the "Seamen" out-patient clinic had a limited value for the recruitment of female participants. To reach the female population the managements at schools, universities and some factories (where employees are mainly women) in Arkhangelsk were contacted and their workers were invited to participate in the study. The proportion of the invited women who agreed to participate was not assessed. However, presumably, the majority of women who had come to the examination offices in the "Seamen" clinic filled in the questionnaire and gave blood for analyses.

Thereby, the utilized recruitment methods were not ideal. However, they opened up for a recruitment of people with different occupational status, broadly representing general studying and working population, and ensured a high participation rate. Age and sex distribution of the study population was similar to the general population of Russia (110). A higher proportion of women than men in the sample had university education (26.7% vs. 16.3%), which was in line with the national estimates for the Russian urban population(111).

However, unemployed, handicapped, homeless, alcohol abusers and other socially isolated individuals were likely to be underrepresented in the study. This problem is common in general to all population-based studies, also from Russia; the problem drinkers were also likely to be underrepresented in the other large Russian population-based cohorts (the Lipid Research Clinics and the Novosibirsk cohorts)(112).

On the other hand, samples of working age population recruited about the same time in Novosibirsk and Izhevsk, and based on the population registers had response rate of, respectively, 61%(113) and 57%(114). The response rate was relatively low despite of a well-elaborated, methodologically strong, adequate and expensive recruitment procedure.

2. Selection bias (paper IV)

The eligible population for analyses of autopsy series was all men (N=1099) and women (N=519) who died in Arkhangelsk from a CVD at the age of 30-70 years from 01.01.2008 to 31.08.2009. Only forensic pathologists routinely measure alcohol concentration. Therefore, we included into analyses only 1119 (69.2%) cases where death was certified by a forensic pathologist.

The high proportion of individuals included in the study from the target population limits the potential for selection bias. However, "average" individuals who were more likely to die from a CVD in a hospital and, therefore, to be autopsied by a hospital pathologist, might be slightly underrepresented in the study. On the contrary, homeless, alcoholics, drug abusers more often die outside a hospital and are more likely to be autopsied by a forensic pathologist. Thus, the association between premature cardiovascular mortality in Arkhangelsk and alcohol could be slightly overestimated.

3. Information bias

Information bias occurs with the misclassification of exposure either due to incorrect information provided by the study subjects, or due to errors in the measurements (115).

Measurement bias

To minimize the probability of this type of bias, physical examination was performed by the experienced and specially trained nurses according to the standard procedure in the same office and using the same facility. To avoid interobserver variability, each nurse was responsible for a definite part of the examination and followed the protocol strictly.

All laboratory analyses were performed in the laboratory of the University Hospital of Northern Norway using internationally standardized methods. The laboratory routinely participates in external and internal formal quality assurance exercises.

Measurement of alcohol concentration (paper IV) was performed according to the national standardized methods (116). The results of these measurements should be reliable, because forensic autopsy protocols are also used in legal practice.

Subject and social desirability bias

This type of bias occurs when the study subjects either consciously or unconsciously provide incorrect information. Analyses in the papers II and III were largely based on self-reported data on pattern of alcohol consumption and smoking. Subjects tend to underreport the level of exposure to these socially unacceptable factors(117;118), leading to social desirability bias, which is a subtype of the subject bias. An earlier article based on the data collected in 2000 in Arkhangelsk concluded that alcohol consumption was substantially underreported in the sample (62).

The use of obligatory medical examination organized by employer might affect the validity of answers. The majority of male participants were seamen with a relatively high salary. These people were recruited through the obligatory medical examination organized by their employer. It is possible that some of them distrusted our reassurances that the collected data will be unavailable to the employer. They might have underreported alcohol consumption to avoid a possible conflict with the employer, thus, some hazardous drinkers could be falsely classified as light or moderate drinkers. This suggestion is supported by the data; a higher proportion of men than women (14.3% vs. 6.3%) had positive result on alcohol at autopsy. It may also explain higher risk of cardiovascular death in moderate drinkers (but not in hazardous drinkers) in men. Our finding that the association of frequent and binge drinking with cardiovascular mortality was found only in women allowed us to conclude that women were more honest than men reporting their drinking habits.

8.1.2 Confounding

Confounding is the confusion of two supposedly causal variables, so that part of all of the purported effect of one variable is actually due to the other(119). The analyses were stratified by gender and the multivariate regression was used to control for possible confounding in papers II and III. In paper III we controlled the studied associations for gender (using stratified analyses), age, socio-economic status (education), life-style factors (alcohol consumption, smoking, physical activity), major cardiovascular risk factors (blood pressure, lipid status and BMI) and the history of cardiovascular disease (myocardial infarction or stroke). However, as some of the covariates included into the regression models were based on self-reported data, we can not exclude residual confounding due to imprecise measurement of exposure to these factors (mainly due to underreport).

Stratification by age, gender and cardiovascular diagnosis was used to present data on postmortem alcohol concentration in paper IV.

8.2 Follow-up

The Arkhangelsk study was initially planned as a cross-sectional study and the reliable follow-up mechanism was not initially built-in the data collection. From the beginning it was decided to recruit similarly sized age and sex groups(32). The sample size of 3705 adults aged 18 years or more was relatively small for a cohort study of mortality. The cohort was also relatively young. Only 638 (32.5%) men and 626 (36%) women were older than 50 years at baseline. It resulted in a relatively small number of deaths and, hence, loss of statistical power. Regular contacts with the participants were not established from the beginning. The first attempt to initiate follow-up was undertaken in 2003 but it was already difficult to establish direct contact with the participants at that time. An attempt to contact 1238 subjects by mail in 2003-04 resulted in a response rate of 18.5% and this method was abandoned as impractical.

The possibility to use a telephone book was considered as we had participants' home address. However, it was not possible due to several reasons, including legal restrictions.

The effectiveness of the originally chosen primary source of mortality data (out-patient clinical records) has rapidly decreased. The records were found for 70% of the participants in 2004, whereas this proportion was only 50% in 2006.

Thus, the only available effective source of mortality data was the database of the Arkhangelsk Regional Healthcare Department. However, it had several limitations. Firstly, the database covers only the Arkhangelsk Region, and those participants who moved from the region during a 10-year follow-up period and died "outside", could not be traced. Secondly, this source of data did not provide us the information necessary for censoring people lost to follow-up, which led to underestimation of mortality.

To get access to the personal-sensitive data on migration, we have tried to get access to the population registries of the Arkhangelsk regional police department and the Arkhangelsk regional office of the Pension Fund of the Russian Federation. Official letters have been sent to the heads of these two institutions. Both denied access to their registry explaining the denial by the legal restrictions in the national body of lows for delivering access to the personal data.

However, the effect of migration on mortality was, likely, relatively small. It was calculated that if the rate of out-migration from the cohort has been the same as from the Arkhangelsk region (120) the loss to follow-up would be about 17.5% during the 10-year observation period. The probability of migration was higher in young subjects (under 30-40 years), i.e. in the age groups with the lowest mortality.

The expected number of deaths for male and female participants during a 10-year follow-up has been calculated. These calculations were based on the official data on cause-specific mortality by sex and age in the Arkhangelsk region (92;121). If the all-cause mortality rate in the cohort had been the same as in the Arkhangelsk region, we would expect about 366 male and 108 female deaths during a 10-year follow-up. The ratio of actual/expected number of deaths was 0.4 (147/366) for men and 0.88 (95/108) for women. To summarize, the difference between the actual and expected mortality is likely explained by three groups of factors: 1. selection of healthier individuals at baseline (healthy worker effect); 2. loss to follow-up due to migration and 3. the baseline inclusion of the subjects who had a permanent residence in a territory, other than the Arkhangelsk region. The latter was more likely among men and might contribute to the explanation of the higher difference between the actual and expected number of deaths among them.

However, these limitations are not unique for the Arkhangelsk study. The latest published large cohort study of associations between alcohol intake and mortality in men of Novosibirsk likely had somewhat similar limitations (68). The study reported that 91% of the participants were married. But this proportion was higher than the proportion, which could be expected if the Russian national estimates (122) were applied to the age and sex composition of the study population (70%). The same authors reported that the unmarried men had higher mortality from all-cause and cardiovascular diseases than married ones (48). This study used, in principle, the same source of data on mortality as we did. The used database of the civil registration office (ZAGS) is also based on the information from the official death certificates and these data were likely also restricted to the Novosibirsk region. We also calculated the number of all-cause deaths expected in this cohort during the median 9.5-year follow-up (from 1989 to 1998). The mean of the national age-specific mortality rates for men in 1990 and 1995 were used(93). The ratio of actual to expected mortality was 0.81 (836/1028), which was lower than that for women in our study (0.88). However, the study from Novosibirsk is a valuable and reliable one, despite of the aforementioned limitations, which are rather common to all few population-based cohort studies from Russia.

8.3 Discussion of the main results

According to the modern concept of Ischemic Heart Disease etiology and pathology widely accepted in clinical medicine, the most common cause of IHD is systemic atherosclerosis resulting in the atherosclerotic lesions in coronary arteries. The main driving mechanism in IHD's pathophysiology is an imbalance between blood supply and demand in the myocardium. The logical sequence of a natural course of an advanced IHD is myocardial infarction (necrosis of the myocardium) (123).

The main life-style risk factors associated with the severity of atherosclerosis are high-fat and energy-rich diet, smoking and sedentary lifestyle. The effect of these factors is mediated by the dyslipidemia (high plasma LDL-C and triglycerides and low plasma HDL-C), obesity, diabetes mellitus (mainly type 2 diabetes that occurs due to insulin resistance in older ages) and hypertension. All aforementioned factors strongly correlate with each other and constitute the concept of the metabolic syndrome.

Dyslipidemia, which is often seen together with obesity and insulin resistance, results in subintimal collection of fat and occurrence of atherosclerotic plaques, which gradually grow and narrow the lumen of coronary arteries. If the diameter is reduced by more than 80%, myocardial ischemia at rest occurs. However, the cap of a plaque may rupture at any stage of plaque maturation, which is followed by occurrence of thrombus, which blocks coronary blood flow and causes myocardial ischemia. The ischemia, in turn, causes biochemical, electrical and mechanical dysfunction of the myocardium, thereby reducing myocardial pump function. An ischemia that lasts more than 20 min (for total occlusion of the artery in the absence of collaterals) causes irreversible damage (myocardial necrosis). Electrical instability that often occurs in the ischemic area of the heart may cause different types of ventricular arrhythmias (from solitary extrasystole to ventricular fibrillation). An individual dies from either extensive myocardial necrosis (infarction) resulting in a dramatic reduction of the ejection fraction, or from disturbances of the heart rhythm caused by acute ischemia. This clear and logically coherent mechanism is currently widely accepted among the clinicians and underlies the majority of IHD deaths (123).

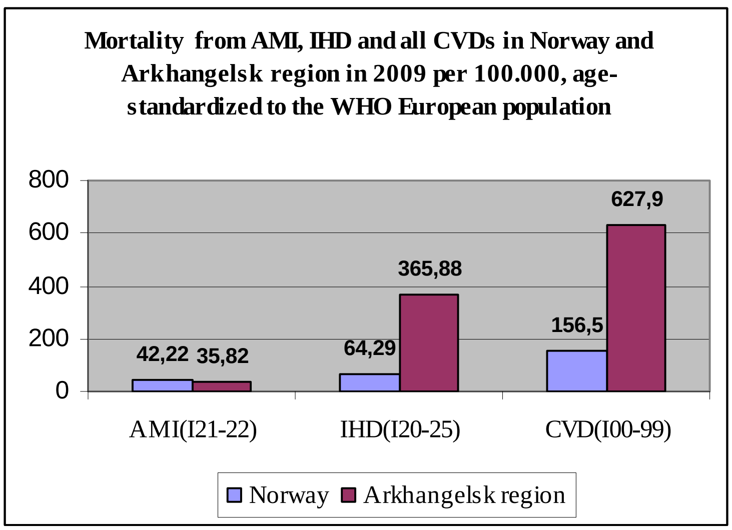
According to the current understanding, systemic atherosclerosis is also the main cause of ischemic stroke. This type accounts for approximately 85-90% of all stroke types. The pathophysiology of IHD is, in principle, similar to the one of the ischemic stroke(124).

IHD is the leading single cause of cardiovascular and all-cause death in Russia (3). Deaths from IHD (I20-25) constituted 59.1% of all CVD deaths in Arkhangelsk in 2009, whereas AMI (I21-22) made up only 10% of all IHD deaths and 5.5% of all CVD deaths (92). A similarly low proportion of AMI has also been reported in earlier studies from other regions of Russia (6;66). The validity of estimates for the low AMI rates, reported in the official mortality statistics in Arkhangelsk region, was confirmed in Paper IV. The unusually high proportion of autopsy-verified diagnoses (97%) gives credibility to this assessment. AMI constituted only 11% (men) and 20% (women) of deaths from IHD at age 30-70 in 2008-09. By contrast, in Norway in 2008; 472 (64%) male and 137 (73.3%) female deaths from IHD at age 35-69 were classified as AMI (125).

The results of the autopsy study led us to conclude that at autopsy there was no evidence of clots in a coronary artery, ruptured plaques, or areas of myocardial necrosis in the majority of deaths classified as an IHD (126). The immediate cause of about 90% of IHD deaths other than AMI in men and 80% in women was defined as acute heart failure. However, its pathophysiological mechanism was likely different than that one would expect to find for a typical IHD death (acute thrombus or area of myocardial necrosis). In the majority of these cases, the underlying cause of death was defined as *chronic ischemic heart disease* (ICD-10 I25). Thus the pathologists found atherosclerotic lesions, which are typically seen in an aging heart (stable atherosclerotic plaques and, possibly, scarring after myocardial infarction), and accordingly defined the acute heart failure to be due to chronic IHD (I25).

The IHD mortality in Arkhangelsk (and, likely, generally in Russia) could be divided in two groups: 1) caused by atherosclerotic heart disease (AMIs); and 2) caused by other factors (likely with hazardous alcohol consumption as a major contributor, possibly by aggravating the existing stable atherosclerotic lesions). As indicated, the relative weight of the first group is small. The mortality from AMI (I21-22) in Russia is comparable to or somewhat lower than that in Western Europe. The age-standardized for the European standard population mortality rate from AMI (for both genders) in the Arkhangelsk region in 2009 was 35.82 per 100.000 (92); by comparison, in Norway (Figure 5) it was 42.22 per 100.000(127).

Figure 6



The mortality in the Arkhangelsk region is similar to the national estimates (93). Hence, the large difference in IHD mortality between Western Europe and Russia (Table 2) is likely due to the IHD deaths assigned to the second group (caused by nonatherosclerotic factors).

The low mortality from AMI in Russia is in agreement with the low prevalence of abnormally high levels of conventional cardiovascular risk factors associated with systemic atherosclerosis such as dyslipidemia, diabetes and obesity (Table 4). The prevalence of these factors was either comparable to or lower than in Western populations. The only exception was the prevalence of smoking among Russian men, which was about 1.5-fold higher than among their Western counterparts. The particular feature of all studies (Table 4) is the considerably more favorable lipid profile in Russian men than for men in Western populations. Although a similar difference was also found for Russian women, its magnitude was remarkably smaller than for men. This could also contribute to the explanation of the 2-fold higher proportion of AMIs within the group of IHD deaths in women than in men.

To test our hypothesis on this dichotomy of IHD mortality we assessed the atherosclerotic risk in the Arkhangelsk study. As a measure of atherosclerotic risk, we used the prevalence of metabolic syndrome (98), a cluster of atherogenic cardiovascular risk factors with obesity (particularly abdominal obesity) as the core element (106). Atherosclerosis is the primary pathological consequence of MetS (128).

It was found that the age-standardized MetS prevalence rates were either lower (in men) or comparable (in women) to rates reported for Western Europe and North America (Paper I). These results suggested that MetS (and systemic atherosclerosis) is unlikely to be a major contributor to the high CVD mortality in Russian men. The pattern of alcohol consumption was strongly and inversely associated with MetS (Paper II). Both high frequency of alcohol drinking and large amount of alcohol consumed at one drinking episode were strongly and inversely associated with MetS. The effect of alcohol consumption on the metabolic risk reduction was mediated by the improvements in lipid profile and insulin sensitivity. It was suggested (Paper II) that the different pattern of alcohol consumption in men and women might explain the discrepancy in MetS rates between genders.

The results of longitudinal analyses were somewhat unexpected and contradictory. No statistically significant association of MetS with CHD (I20-25) and cardiovascular (I00-99) mortality was found during a 9-year follow-up. Moreover, in the fully adjusted sex-specific regression analyses men with MetS unexpectedly had a 27% lower 10-year risk of CHD-death, whereas the corresponding risk was 45% higher in women with MetS. Although these results were not statistically significant (likely due to low statistical power), this difference is important. Interestingly, MetS appeared to be a strong predictor of death in men in the selected group of cerebral strokes and myocardial infarctions, supporting the hypothesis of duality of CVD mortality.

The major cardiovascular risk factors: smoking, high serum TC and TG levels, high BMI were not predictive for the risk of cardiovascular death neither in men nor in women after 10-year follow-up (Paper III). On the contrary, hazardous alcohol consumption (binge drinking and higher CAGE and AUDIT scores) were strongly associated with the risk of CVD death in women. No corresponding statistically significant association was revealed in men. However, it is likely that the association with hazardous drinking in men was even stronger than in women. Substantial underreporting of alcohol consumption by men (62) is likely the reason this was not observed. This hypothesis is supported by the following data: (i) men who reported light and moderate alcohol consumption had a 2-fold risk of

CVD death compared with abstainers; (ii) higher proportion of men than women (14.3% vs. 6.3%) were alcohol-positive at forensic autopsy; (iii) during a 10-year follow-up 7 deaths due to alcohol poisoning were registered in the cohort (all in men), representing 1/3 (7/21) of all external-cause deaths among men (Paper III); and (iv), alcohol was 55% more likely to be found at forensic autopsy in men than in women who died from a CVD (Paper IV).

The data have shown that alcohol consumption is a factor which is associated with a large proportion of CVD deaths in Arkhangelsk. About 30% of men and 22% of women who died from a CVD at the age of 30-70 in 2008-09 consumed alcohol in the hours before death according to forensic autopsy reports (Paper IV). About 85% of all alcohol-positive deaths in both genders were allocated within the two “narrow” diagnostic groups: *chronic ischemic heart disease* (ICD-10 codes I25.0-I25.9) and *cardiomyopathies* (I42-I42.9). Interestingly, the relative weight of the group *cardiomyopathies* was twice as high in women (44%) than in men (22%), whereas the *chronic ischemic heart disease* accounted for 39% and 63% of the alcohol-positive deaths, respectively. Only 5% (men) and 7% (women) of alcohol-positive CVD deaths were allocated within the diagnostic groups: *myocardial infarction* (I21-22) and *cerebrovascular diseases* (I60-69).

Public health implications

The currently prevailing concept of CVD risk reduction is based on the elimination or attenuation of effects of the atherosclerotic risk factors. The CVD risk factors recognized by the current NCEP ATP III (104) are: hypertension, low HDL-C, diabetes, family history of premature CHD, age, obesity, smoking, physical inactivity, atherogenic diet and some emerging risk factors. Alcohol consumption is not included into this concept as a risk factor. It is often viewed as a factor reducing CVD risk mainly *via* improvement of the lipid profile and insulin sensitivity, and, thereby, retarding the development of atherosclerosis (light-to-moderate drinking). It is probably true in the Western populations where light and moderate drinking habits prevail.

However, the cardiovascular disease risk profile in Russia may be appreciably different to that in the US and Western Europe due to high burden of alcohol-related non-atherosclerotic cardiac pathologies. The pattern of hazardous alcohol intake (a consumption of large amounts of spirits at one drinking episode), which is highly prevalent in Russian men, may dramatically modify the protective effect of light-to-moderate alcohol consumption. Therefore, the scope of primary prevention needs to extend beyond the standard “Western” approach with its primary focus on diet, smoking and physical activity. It is likely that reduction of hazardous drinking through taxation, legislation and effective treatment programs will be followed by the substantial reduction of CVD mortality, primarily among men. A large experience accumulated in the Scandinavian countries within the field of alcohol policy should be utilized. Cardiovascular risk screening in primary care also needs to consider hazardous drinking.

Implications for further research

There is an urgent need to conduct a large study (10.000-15.000 individuals) based on a representative sample of the Russian adult population aged 35-70 to assess the proportion of CVD mortality attributable to hazardous alcohol consumption and to clarify the aetiology of CVD deaths. It is desirable to recruit the participants in two or three centers to enhance generalizability of the results. Particular attention should be paid to the validity of data on exposure to alcohol. It would be practical to combine self-reported data together with biomarkers of recent alcohol consumption, such as: carbohydrate-deficient transferrin (CDT), ethyl glucuronide (EtG), EtS, PEth (129), and markers of liver inflammation including GGT and Cytokeratin-18 (CK 18) (130). The outcome variable (heart disease) should be carefully measured either at baseline (using echocardiography, Holter monitoring and/or biomarkers of heart failure, such as beta-natriuretic peptide (131) and high-sensitivity troponin) This study should include follow-up based on effective procedure of death registration and validation. To avoid severe methodological deviations at the stages of sample selection and collection of data it would be desirable to utilize the experience of implementation of the few population-based studies already ongoing in Russia.

Reference List

(1) Thomas A, Gaziano J, Michael Gaziano. Epidemiology of Cardiovascular Disease. Harrison's Principles of Internal Medicine. 17 ed. 2008. p. 1375-9.

(2) Mathers CD, Boerma T, Ma FD. Global and regional causes of death. Br Med Bull 2009;92:7-32.

(3) Highlights on health in the Russian Federation 2005. World Health Organisation 2010 [cited 2010 Apr 14];Available from: URL: http://www.euro.who.int/document/E88405.pdf

(4) Mortality rate by cause [Russian]. Russian Federal State Statistics Service (Goskomstat) 2010 [cited 2010 Apr 19];Available from: URL: http://www.gks.ru/free_doc/new_site/population/demo/demo25.htm

(5) Medico-demographic indicators of Arkhangelsk region in 2009 [Russian]. Arkhangelsk, Russia: The Arkhangelsk Regional Healthcare Department; 2010.

(6) Zaridze D, Maximovitch D, Lazarev A, Igitov V, Boroda A, Boreham J, et al. Alcohol poisoning is a main determinant of recent mortality trends in Russia: evidence from a detailed analysis of mortality statistics and autopsies. Int J Epidemiol 2009 Feb;38(1):143-53.

(7) Diseases of circulatory system (I00-99). 2008 [Norwegian]. Statistics Norway 2010 [cited 2010 May 13];Available from: URL: http://www.ssb.no/dodsarsak/arkiv/2008/kap-ix-i00-i99.html

(8) Medico-demographic indicators of Arkhangelsk region in 2009 [Russian]. Arkhangelsk, Russia: The Arkhangelsk Regional Healthcare Department; 2010.

(9) The Atlas of Heart Disease and Stroke. World Health Organisation 2010 [cited 2010 Apr 15];Available from: URL: http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html

(10) National composition of the population [Russian]. The official site of Russian 2002 census 2010 [cited 2010 Apr 16];Available from: URL: http://perepis2002.ru/ct/doc/TOM_04_01.xls

(11) The whole population by age and gender [Russian]. The official site of Russian 2002 census 2010 [cited 2010 Apr 19];Available from: URL: http://perepis2002.ru/ct/doc/_02-01_new.xls

(12) Life expectancy at birth (number of years) [Russian]. Federal State Statistics Service of Russia (Goskomstat) 2010 [cited 2010 Apr 12];Available from: URL: http://www.gks.ru/free_doc/new_site/population/demo/demo26.htm

(13) Deaths by main classes and causes per 100.000 per year [Russian]. Federal State Statistics Service of Russia (Goskomstat) 2010 [cited 2010 Apr 23];Available from: URL: http://www.gks.ru/dbscripts/Cbsd/DBInet.cgi?pl=2415011

(14) Notzon FC, Komarov YM, Ermakov SP, Sempos CT, Marks JS, Sempos EV. Causes of declining life expectancy in Russia. JAMA 1998 Mar 11;279(10):793-800.

(15) Men T, Brennan P, Boffetta P, Zaridze D. Russian mortality trends for 1991-2001: analysis by cause and region. BMJ 2003 Oct 25;327(7421):964.

(16) Vishnevsky A. Demographics of Stalin's epoch [Russian]. Population and society 2003;70.

(17) The Human Mortality Database. Max Planck Institute for Demographic Research and University of California 2010 [cited 2010 Apr 20];Available from: URL: http://www.mortality.org/

(18) Alcohol abuse in the Russian Federation: the socio-economic consequences and measures of counteraction [Russian]. Report of the Civic Chamber of the Russian Federation 2010 [cited 2010 May 7];44. Available from: URL: http://www.oprf.ru/files/dokladalko.pdf

(19) Mortality from cardiovascular diseases by gender and age [Norwegian]. Statistics Norway 2010 [cited 2010 Jun 10];Available from: URL: http://www.ssb.no/dodsarsak/tab-2010-02-19-06.html

(20) Standardized mortality coefficients from 1965 to 1998 by gender and cause of death [Russian]. Demoscope Weekly, electronic bulletin 2010 [cited 2010 May 19];Available from: URL: http://demoscope.ru/weekly/app/appbd01.php

(21) Table 1: Indicators of natural movement in the population [Russian]. Federal State Statistics Service of Russia (Goskomstat) 2010 [cited 2010 May 10];Available from: URL: http://www.gks.ru/bgd/free/b08_00/IssWWW.exe/Stg/d01/7-0.htm

(22) Population has decreased [Russian]. The official site of the national 2010 census 2011 [cited 2011 Apr 8];Available from: URL: http://www.perepis-2010.ru/smi/detail.php?ID=6377

(23) Putin V. Annual Address to the Federal Assembly of the Russian Federation. 2005.

(24) Medico-demographic indicators of Arkhangelsk region in 2006 [Russian]. Arkhangelsk, Russia: The Arkhangelsk Regional Healthcare Department; 2007.

(25) Population by gender and one-year age. The 1st of January 1986 - 2010 [Norwegian]. Statistics Norway 2010 [cited 2010 May 11];Available from: URL: http://www.ssb.no/folkemengde/

(26) Statistical Information System (WHOSIS) . WHO 2010 [cited 2010 May 10];Available from: URL: http://apps.who.int/whosis/data/Search.jsp

(27) Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet 2000 Feb 26;355(9205):675-87.

(28) Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation 1994 Jul;90(1):583-612.

(29) Tolonen H, Mahonen M, Asplund K, Rastenyte D, Kuulasmaa K, Vanuzzo D, et al. Do trends in population levels of blood pressure and other cardiovascular risk factors explain trends in stroke event rates? Comparisons of 15 populations in 9 countries within the WHO MONICA Stroke Project. World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease. Stroke 2002 Oct;33(10):2367-75.

(30) Puska P, Matilainen T, Jousilahti P, Korhonen H, Vartiainen E, Pokusajeva S, et al. Cardiovascular risk factors in the Republic of Karelia, Russia, and in North Karelia, Finland. Int J Epidemiol 1993 Dec;22(6):1048-55.

(31) Stegmayr B, Vinogradova T, Malyutina S, Peltonen M, Nikitin Y, Asplund K. Widening gap of stroke between east and west. Eight-year trends in occurrence and risk factors in Russia and Sweden. Stroke 2000 Jan;31(1):2-8.

(32) Averina M, Nilssen O, Brenn T, Brox J, Kalinin AG, Arkhipovsky VL. High cardiovascular mortality in Russia cannot be explained by the classical risk factors. The Arkhangelsk Study 2000. Eur J Epidemiol 2003;18(9):871-8.

(33) M Bobak, M Marmot. Coronary heart disease in Central and Eastern Europe and the former Soviet Union. In: Michael Marmot, Paul Elliott, editors. Coronary Heart Disease Epidemiology From aetiology to public health. Second edition ed. Oxford University press; 2005. p. 83-101.

(34) Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004 Sep 11;364(9438):937-52.

(35) Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004 Sep 11;364(9438):953-62.

(36) M Averina. A population based study on cardiovascular diseases in Northwest Russia. The Arkhangelsk study 2000. Tromsø: ISM skriftserie; 2005.

(37) Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 2000 Jan;108(1):2-8.

(38) Cole SR, Kawachi I, Sesso HD, Paffenbarger RS, Lee IM. Sense of exhaustion and coronary heart disease among college alumni. Am J Cardiol 1999 Dec 15;84(12):1401-5.

(39) Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, et al. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001 Mar;58(3):221-7.

(40) Herrmann C, Brand-Driehorst S, Buss U, Ruger U. Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. J Psychosom Res 2000 Apr;48(4-5):455-62.

(41) Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994 May;89(5):1992-7.

(42) Marmot MG. Socio-economic factors in cardiovascular disease. J Hypertens Suppl 1996 Dec;14(5):S201-S205.

(43) Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993 Oct;88(4 Pt 1):1973-98.

(44) Rose G, Marmot MG. Social class and coronary heart disease. Br Heart J 1981 Jan;45(1):13-9.

(45) Pocock SJ, Shaper AG, Cook DG, Phillips AN, Walker M. Social class differences in ischaemic heart disease in British men. Lancet 1987 Jul 25;2(8552):197-201.

(46) Shkolnikov VM, Leon DA, Adamets S, Andreev E, Deev A. Educational level and adult mortality in Russia: an analysis of routine data 1979 to 1994. Soc Sci Med 1998 Aug;47(3):357-69.

(47) Pridemore WA, Tomkins S, Eckhardt K, Kiryanov N, Saburova L. A case-control analysis of socio-economic and marital status differentials in alcohol- and non-alcohol-related mortality among working-age Russian males. Eur J Public Health 2010 Oct;20(5):569-75.

(48) Malyutina S, Bobak M, Simonova G, Gafarov V, Nikitin Y, Marmot M. Education, marital status, and total and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. Ann Epidemiol 2004 Apr;14(4):244-9.

(49) Perlman F, Bobak M. Socioeconomic and behavioral determinants of mortality in posttransition Russia: a prospective population study. Ann Epidemiol 2008 Feb;18(2):92-100.

(50) Dennis BH, Zhukovsky GS, Shestov DB, Davis CE, Deev AD, Kim H, et al. The association of education with coronary heart disease mortality in the USSR Lipid Research Clinics Study. Int J Epidemiol 1993 Jun;22(3):420-7.

(51) Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. JAMA 2003 Feb 5;289(5):579-88.

(52) Costanzo S, Di CA, Donati MB, Iacoviello L, de GG. Alcohol consumption and mortality in patients with cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2010 Mar 30;55(13):1339-47.

(53) Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW, Jr., et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997 Dec 11;337(24):1705-14.

(54) Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. Addiction 2000 Oct;95(10):1505-23.

(55) Marmot MG. Alcohol and coronary heart disease. Int J Epidemiol 1984 Jun;13(2):160-7.

(56) Fagrell B, De FU, Bondy S, Criqui M, Gaziano M, Gronbaek M, et al. The effects of light to moderate drinking on cardiovascular diseases. J Intern Med 1999 Oct;246(4):331-40.

(57) International Drinking Guidelines. International Center for Alcohol Policies 2011 [cited 2011 Feb 19];Available from: URL: http://www.icap.org/PolicyIssues/DrinkingGuidelines/GuidelinesTable/tabid/204/Default.aspx

(58) McKee M, Britton A. The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. J R Soc Med 1998 Aug;91(8):402-7.

(59) Bagnardi V, Zatonski W, Scotti L, La VC, Corrao G. Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. J Epidemiol Community Health 2008 Jul;62(7):615-9.

(60) Roerecke M, Rehm J. Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. Am J Epidemiol 2010 Mar 15;171(6):633-44.

(61) Popova S, Rehm J, Patra J, Zatonski W. Comparing alcohol consumption in central and eastern Europe to other European countries. Alcohol Alcohol 2007 Sep;42(5):465-73.

(62) Nilssen O, Averina M, Brenn T, Brox J, Kalinin A, Archipovski V. Alcohol consumption and its relation to risk factors for cardiovascular disease in the north-west of Russia: the Arkhangelsk study. Int J Epidemiol 2005 Aug;34(4):781-8.

(63) Pomerleau J, McKee M, Rose R, Haerpfer CW, Rotman D, Tumanov S. Hazardous alcohol drinking in the former Soviet Union: a cross-sectional study of eight countries. Alcohol Alcohol 2008 May;43(3):351-9.

(64) Averina M, Nilssen O, Arkhipovsky VL, Kalinin AG, Brox J. C-reactive protein and alcohol consumption: Is there a U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study. Atherosclerosis 2006 Oct;188(2):309-15.

(65) Bing RJ. Cardiac metabolsim: its contributions to alcoholic heart disease and myocardial failure. Circulation 1978 Dec;58(6):965-70.

(66) Leon DA, Shkolnikov VM, McKee M, Kiryanov N, Andreev E. Alcohol increases circulatory disease mortality in Russia: acute and chronic effects or misattribution of cause? Int J Epidemiol 2010 Jun 30.

(67) Zaridze D, Brennan P, Boreham J, Boroda A, Karpov R, Lazarev A, et al. Alcohol and cause-specific mortality in Russia: a retrospective case-control study of 48,557 adult deaths. Lancet 2009 Jun 27;373(9682):2201-14.

(68) Malyutina S, Bobak M, Kurilovitch S, Gafarov V, Simonova G, Nikitin Y, et al. Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. Lancet 2002 Nov 9;360(9344):1448-54.

(69) Leon DA, Chenet L, Shkolnikov VM, Zakharov S, Shapiro J, Rakhmanova G, et al. Huge variation in Russian mortality rates 1984-94: artefact, alcohol, or what? Lancet 1997 Aug 9;350(9075):383-8.

(70) McKee M, Shkolnikov V, Leon DA. Alcohol is implicated in the fluctuations in cardiovascular disease in Russia since the 1980s. Ann Epidemiol 2001 Jan;11(1):1-6.

(71) Chenet L, McKee M, Leon D, Shkolnikov V, Vassin S. Alcohol and cardiovascular mortality in Moscow; new evidence of a causal association. J Epidemiol Community Health 1998 Dec;52(12):772-4.

(72) Bobak M, Marmot M. Alcohol and mortality in Russia: is it different than elsewhere? Ann Epidemiol 1999 Aug;9(6):335-8.

(73) Main socio-economic indicators of living standard of population. Federal State Statistics Service of Russia (Goskomstat) 2011 [cited 2011 Feb 21];Available from: URL: http://www.gks.ru/bgd/regl/b10_12/IssWWW.exe/stg/d01/07-01.htm

(74) Nemtsov AV. Estimates of total alcohol consumption in Russia, 1980-1994. Drug Alcohol Depend 2000 Feb 1;58(1-2):133-42.

(75) Nemtsov AV. Alcohol-related human losses in Russia in the 1980s and 1990s. Addiction 2002 Nov;97(11):1413-25.

(76) Neaton JD, Kuller LH, Wentworth D, Borhani NO. Total and cardiovascular mortality in relation to cigarette smoking, serum cholesterol concentration, and diastolic blood pressure among black and white males followed up for five years. Am Heart J 1984 Sep;108(3 Pt 2):759-69.

(77) Daviglus ML, Stamler J, Pirzada A, Yan LL, Garside DB, Liu K, et al. Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. JAMA 2004 Oct 6;292(13):1588-92.

(78) Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 1994 Jun 15;139(12):1180-9.

(79) Knekt P, Ritz J, Pereira MA, O'Reilly EJ, Augustsson K, Fraser GE, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr 2004 Dec;80(6):1508-20.

(80) Pocobelli G, Peters U, Kristal AR, White E. Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. Am J Epidemiol 2009 Aug 15;170(4):472-83.

(81) Honarbakhsh S, Schachter M. Vitamins and cardiovascular disease. Br J Nutr 2009 Apr;101(8):1113-31.

(82) Riccioni G, Bucciarelli T, Mancini B, Di IC, Capra V, D'Orazio N. The role of the antioxidant vitamin supplementation in the prevention of cardiovascular diseases. Expert Opin Investig Drugs 2007 Jan;16(1):25-32.

(83) Gaziano JM. Vitamin E and cardiovascular disease: observational studies. Ann N Y Acad Sci 2004 Dec;1031:280-91.

(84) Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 1996 May 2;334(18):1156-62.

(85) Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. Am J Clin Nutr 1991 Jan;53(1 Suppl):326S-34S.

(86) He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. Lancet 2006 Jan 28;367(9507):320-6.

(87) Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. Int J Epidemiol 1997 Feb;26(1):1-13.

(88) Matilainen T, Vartiainen E, Puska P, Alfthan G, Pokusajeva S, Moisejeva N, et al. Plasma ascorbic acid concentrations in the Republic of Karelia, Russia and in North Karelia, Finland. Eur J Clin Nutr 1996 Feb;50(2):115-20.

(89) Ginter E. High cardiovascular mortality in postcommunist countries: participation of oxidative stress? Int J Vitam Nutr Res 1996;66(3):183-9.

(90) Population distribution by age and gender in Arkhangelsk region per 01.01.2006 [Russian]. The Arkhangelsk Regional Healthcare Department; 2006.

(91) Official site of the National Census 2002 **Volume 4.3: "Distribution of the population by nationalities in federal subjects of the Russian Federation" [Russian]**. Official site of the National Census 2002 2009Available from: URL: http://www.perepis2002.ru/ct/doc/TOM_04_03.xls

(92) Medico-demographic indicators of Arkhangelsk region in 2009 [Russian]. Arkhangelsk, Russia: The Arkhangelsk Regional Healthcare Department; 2010.

(93) Table: Mortality rate by age groups per 1000 individuals [Russian]. Federal State Statistics Service of Russia (Goskomstat) 2010 [cited 2010 Jun 8];Available from: URL: http://www.gks.ru/free_doc/2008/demo/osn/04-26.htm

(94) Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med 1998 Sep 14;158(16):1789-95.

(95) Saunders JB, Aasland OG, Babor TF, de lF, Jr., Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993 Jun;88(6):791-804.

(96) Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984 Oct 12;252(14):1905-7.

(97) Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin Chem 1990 Jan;36(1):15-9.

(98) Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. Nutrition 1997 Jan;13(1):65.

(99) Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. Am Heart J 2005 Jan;149(1):33-45.

(100) Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007 Apr;28(7):857-64.

(101) Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007 Jan 30;49(4):403-14.

(102) Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006 Oct;119(10):812-9.

(103) Day C. Metabolic syndrome, or What you will: definitions and epidemiology. Diab Vasc Dis Res 2007 Mar;4(1):32-8.

(104) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001 May 16;285(19):2486-97.

(105) Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. Cardiol Rev 2005 Nov;13(6):322-7.

(106) Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. Lancet 2005 Sep 24;366(9491):1059-62.

(107) Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003 Nov 18;108(20):2543-9.

(108) Section 2: Stroke event registration data component. MONICA Manual 2011 [cited 2011 Mar 7];Available from: URL: http://www.ktl.fi/publications/monica/manual/part4/iv-2.htm#s2-2

(109) Lavreshin A.N. "Measurement of ethanol in organs of a human corpse by gas chromatography" [Russian]. Sudebnaja Medicina (Forensic Medicine) 1982;2:45.

(110) Averina M, Nilssen O, Brenn T, Brox J, Arkhipovsky VL, Kalinin AG. Social and lifestyle determinants of depression, anxiety, sleeping disorders and self-evaluated quality of life in Russia--a population-based study in Arkhangelsk. Soc Psychiatry Psychiatr Epidemiol 2005 Jul;40(7):511-8.

(111) Population distribution by the level of education, age and sex. Urban, rural and total population. Official cite of the National 2002 Census 2010 [cited 2010 Aug 26];Available from: URL: http://perepis2002.ru/ct/doc/TOM_03_01.xls

(112) Tomkins S, Shkolnikov V, Andreev E, Kiryanov N, Leon DA, McKee M, et al. Identifying the determinants of premature mortality in Russia: overcoming a methodological challenge. BMC Public Health 2007;7:343.

(113) Peasey A, Bobak M, Kubinova R, Malyutina S, Pajak A, Tamosiunas A, et al. Determinants of cardiovascular disease and other non-communicable diseases in Central and Eastern Europe: rationale and design of the HAPIEE study. BMC Public Health 2006;6:255.

(114) Leon DA, Saburova L, Tomkins S, Andreev E, Kiryanov N, McKee M, et al. Hazardous alcohol drinking and premature mortality in Russia: a population based case-control study. Lancet 2007 Jun 16;369(9578):2001-9.

(115) Laake P, Hjartaker A, Thelle DS, Veierod MB. Epidemiologiske og kliniske forskningsmetoder. Oslo, Norway: Gyldendal Norsk Forlag AS; 2007.

(116) Shaev AI, Barinskaya TO, Solomatin EM, Morozov YE, Smirnov AV. Assessment of the correlation between the alcohol concentration in blood, urine and exhaled air. Guidelines for forensic experts. [Russian]. 2005. Moscow, Russia, Ministry of Healthcare and Social development of the Russian Federation.
Ref Type: Serial (Book,Monograph)

(117) Hoyer G, Nilssen O, Brenn T, Schirmer H. The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 1995 Apr;90(4):539-44.

(118) Midanik LT. Validity of self-reported alcohol use: a literature review and assessment. Br J Addict 1988 Sep;83(9):1019-30.

(119) Jekel JF, Katz DL, Elmore JG. Epidemiology, biostatistics, and preventive medicine. 2nd ed. Philadelphia, USA: W.B. Saunders company; 2001.

(120) Migration of population in the Arkhangelsk region in 1998-2009 [Russian]. Arkhangelsk Regional Center of the Federal State Statistics Service (Arkhangelskstat) 2010 [cited 2010 Dec 19];Available from: URL: http://www.arhangelskstat.ru/digital/DocLib7/%D0%9C%D0%B8%D0%B3%D1%80%D0%B0%D1%86%D0%B8%D1%8F%20%D0%BD%D0%B0%D1%81%D0%B5%D0%BB%D0%B5%D0%BD%D0%B8%D1%8F/%D0%9C%D0%B8%D0%B3%D1%80%D0%BD%D0%B0%D1%811.htm

(121) Medico-demographic indicators of Arkhangelsk region in 2006 [Russian]. Arkhangelsk, Russia: The Arkhangelsk Regional Healthcare Department; 2007.

(122) Population of Russia by age, gender and marital status [Russian]. Official site of the National Census 2002 2011 [cited 2011 Mar 21];Available from: URL: http://www.perepis2002.ru/ct/doc/_02-03_.xls

(123) EM Antman, AP Selwyn, E Braunwald, J Loscalzo. Ischemic Heart Disease. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, et al., editors. Harrison's Principles of Internal Medicine. 17th ed. USA: The McGraw-Hill Companies, Inc; 2008. p. 1514-27.

(124) WS Smith, JD English, SC Johnston. Cerebrovascular Diseases. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, et al., editors. Harrison's Principles of Internal Medicine. 17th ed. USA: The McGraw-Hill Companies, Inc; 2008. p. 2513-36.

(125) Diseases of circulatory system (I00-99). 2008 [Norwegian]. Statistics Norway 2010 [cited 2010 May 13];Available from: URL: http://www.ssb.no/dodsarsak/arkiv/2008/kap-ix-i00-i99.html

(126) Personal communication to the chief forensic pathologist Y.I. Kapralov. 2011. 12-6-2010. Ref Type: Personal Communication

(127) Diseases of circulatory system (I00-99). 2009 [Norwegian]. Statistics Norway 2011 [cited 2011 Mar 28];Available from: URL: http://www.ssb.no/dodsarsak/kap-ix-i00-i99.html

(128) Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: evaluation of pathological and therapeutic outcomes. Am Heart J 2005 Jan;149(1):20-32.

(129) Helander A. Biological markers in alcoholism. J Neural Transm Suppl 2003;(66):15-32.

(130) Feldstein AE, Wieckowska A, Lopez AR, Liu YC, Zein NN, McCullough AJ. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. Hepatology 2009 Oct;50(4):1072-8.

(131) Di AE, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009 Dec 1;120(22):2177-87.

Paper I

Paper II

Paper III

Paper IV

Appendix I

Questionnaire Archangelsk 2000

The Archangelsk Medical Academy/Russia
The Institute of Community Medicine/Tromsø, Norway
The Northern Central Clinical Hospital in the name of N. A. Semashko/Russia

Questionnaire of the anonymous investigation

Human
Health in Year 2000

The main purpose of this anonymous investigation is to assess the risk of getting different diseases.

The insufficient knowledge about factors influencing the development of many serious diseases, in particular cardiovascular diseases, makes it compelling for us to ask you some questions regarding your health and lifestyle.

We would be grateful if you would answer them in our questionnaire.

Please note, that all the information obtained during the course of this survey, is completely confidential and that the medical personnel taking part in processing and analysis of this information, is bound to observe professional secrecy.

Please, if you are not sure about any of the suggested alternative answers, mark the one which fits you most.

Thank you in advance.

1. Personal information

1.1. **SEX:** male O female O

1.2. **AGE:** OO years

1.3. **BIRTHPLACE:** in the North O not in the North O

1.4. **LENGTH OF TIME LIVING IN THE NORTH:** OO years

1.5. **MARITAL STATUS:**
- single O
- married O
- divorced O
- widowed O
- common law married O

2. Occupational activity and social conditions

2.1. **EDUCATION:**
- primary school O
- secondary school O
- secondary professional school O
- some college O
- graduated from college O

2.2. **DOES YOUR CURRENT OCCUPATION CORRESPOND TO YOUR EDUCATION:**
yes O no O

2.3. **CURRENT POSITION:**
- student O
- technical worker O
- clerk O
- ship crew O
- aircraft crew O
- pensioner O
- homemaker O
- other O

3. Heredity and disease history

3.1. HAVE ANY OF YOUR PARENTS, SISTERS, OR BROTHERS HAD:

	Yes	No	Don't know
myocardial infarction	O	O	O
angina pectoris	O	O	O
cerebral stroke or brain haemorrhage (insult)	O	O	O
mental disorders	O	O	O
alcohol abuse	O	O	O
died before the age of 45 years	O	O	O

3.2. DO YOU NOW HAVE OR HAVE YOU EVER HAD:

	Yes	No	Don't know
myocardial infarction	O	O	O
angina pectoris	O	O	O
cerebral stroke or brain haemorrhage (insult)	O	O	O
sugar diabetes	O	O	O
high blood pressure (hypertensive disease)	O	O	O
pancreatitis	O	O	O
hepatitis or cirrhosis of the liver	O	O	O
nephritis	O	O	O
stomach bleeding	O	O	O
dyspepsia (digestive trouble)	O	O	O
stomach or duodenal ulcer	O	O	O
brain concussion	O	O	O
trauma to the extremities or to the spine	O	O	O

4. Health conditions

4.1. HAVE YOU ANY COMPLAINTS ABOUT YOUR HEALTH: yes O no O

4.2. DO YOU NOW EXPERIENCE OR DID YOU DURING THE LAST YEAR EXPERIENCE:

	Yes	No
flu	O	O
diarrhoea (frequent watery stool)	O	O
nausea	O	O
headache	O	O
trouble sleeping	O	O
difficulty concentration	O	O
memory loss	O	O
back pain or low back pain	O	O
muscular pain	O	O
depression, sadness	O	O
short-tempered	O	O
exhausted	O	O
restlessness	O	O
anxiety	O	O
mental stress	O	O

4.3. YOUR CURRENT HEALTH:

poor	O
fair	O
good	O
excellent	O

4.4. DO YOU TAKE ANY OF THE FOLLOWING MEDICATIONS:

	Never	Some times	Almost daily
painkillers	O	O	O
antipyretics	O	O	O
eczema ointment	O	O	O
blood pressure medication	O	O	O
heart medication	O	O	O
insulin	O	O	O
allergy medication	O	O	O
asthma medication	O	O	O
sleeping tablets	O	O	O
nerve tablets	O	O	O
epilepsy medication	O	O	O
headache tablets	O	O	O
vitamins	O	O	O
iron tablets	O	O	O

5. Physical activity

5.1. PLEASE ESTIMATE YOUR LEVEL OF PHYSICAL ACTIVITY IN LEISURE TIME:

If the activity varies (for example in summer and winter), then give an average for the last year

reading, watching TV (mostly sitting activity)	O
walking, bicycling or other forms of exercise at least 4 hours per week (including walking to place of work, Sunday walking, etc.)	O
participation in recreational sports, gardening (at least 4 hours per week)	O
training regularly several times a week, participation in sports competitions	O

5.2. PLEASE ESTIMATE YOUR LEVEL OF PHYSICAL ACTIVITY IN THE WORK PLACE:

During the last year you have had:

mostly sedentary work (e.g. office work, etc.)	O
work that requires a lot of walking (e.g. shop-assistant, waiter, etc.)	O
work that requires a lot of walking and lifting (e.g. postman, construction, etc.)	O
heavy manual work (e.g. farmer, forestry, etc.)	O

5.3. **HOW OFTEN DO YOU TAKE PART IN PHYSICAL ACTIVITY** (AT LEAST 20 MINUTES) **WHICH MAKES YOU PERSPIRE OR GET SHORT OF BREATH:**

	Leisure	Work
rarely or never	O	O
once a week	O	O
several times a week	O	O
almost daily	O	O

6. Diet

6.1. **HOW OFTEN DO YOU EAT:**

	Rarely or never	About once a week	2-3 times a week	4-5 times a week	Almost daily
fresh fruit or vegetables	O	O	O	O	O
fish or fish dishes (lunch, dinner)	O	O	O	O	O
meat or meat dishes (lunch, dinner)	O	O	O	O	O
milk or milk products	O	O	O	O	O

6.2. **HOW MUCH BREAD DO YOU EAT PER DAY:**
- less than two slices O
- 2-4 O
- 5-6 O
- 7-12 O
- 13 or more slices O

6.3. **HOW WOULD YOU RATE YOUR CURRENT DIET:**
- good O
- sufficient O
- insufficient O

6.4. **HOW MUCH COFFEE DO YOU USUALLY DRINK PER DAY:**
- do not drink coffee or less than one cup a day O
- 1-4 O
- 5-8 O
- 9 or more cups a day O

7. Smoking

7.1. **DID ANY OF THE ADULTS IN YOUR HOME SMOKE WHEN YOU WERE A CHILD:**
yes O no O

7.2. **DO YOU CURRENTLY LIVE TOGETHER WITH HEAVY SMOKERS OR HAVE YOU LIVED TOGETHER WITH SUCH PEOPLE AFTER THE AGE OF 20 YEARS:**
yes O no O

IF YES, FOR HOW MANY YEARS HAVE YOU LIVED TOGETHER:
OO years

7.3. **HOW MANY HOURS A DAY DO YOU USUALLY SPEND IN A LOCALITY FILLED UP WITH TOBACCO SMOKE:**
WRITE ZERO, IF YOU NEVER HAPPEN TO BE IN SMOKY LOCALITIES
OO hours

7.4. **DO YOU SMOKE:**
- yes, every day O
- sometimes O
- no, never smoked O
- smoked previously O

7.5. **IF YES, WHAT DO YOU SMOKE:**
- hand-rolled O
- filter cigarettes O
- cigars O
- papyrosy O
- pipe O

7.6. **IF YOU PREVIOUSLY SMOKED EVERY DAY, HOW LONG IS IT SINCE YOU QUIT:**
OO years

7.7. **DO YOU FEEL UNCOMFORTABLE WHEN YOU ARE IN A VERY SMOKY LOCALITY:**
yes O no O

WE ASK THOSE WHO SMOKE CURRENTLY OR WHO HAVE SMOKED PREVIOUSLY TO ANSWER THE FOLLOWING QUESTIONS. THE OTHERS CAN SKIP TO PART 8.

7.8. **IF YOU CURRENTLY SMOKE OR PREVIOUSLY SMOKED EVERY DAY:**
- how many cigarettes per day? O O
- how many cigarettes do/did you smoke during working hours O O
- how old were you when you started smoking daily? O O
- for how many years in total did you smoke daily? O O

7.9. **IF YOU HAVE STOPPED SMOKING, WHICH ONE WAS THE MOST IMPORTANT REASON FOR YOU:**
- promote my own health O
- promote the children's/family's health O
- promote the health of colleagues at work O
- for economic purposes O
- in order to show that I am in control of myself O
- pregnancy O
- healthy look O
- other O

7.10. **WHAT IS THE MAIN REASON WHY YOU CONTINUE SMOKING:**

I am afraid of gaining weight O
I feel more energetic after smoking O
I smoke when I am relaxing O
I feel the need for nicotine O
I smoke out of habit O
I smoke to calm down O

7.11. **HOW MANY TIMES HAVE YOU TRIED TO STOP SMOKING:**

OO times

7.12. **HOW INTERESTED ARE YOU IN TRYING TO STOP SMOKING:**

not interested O
somewhat interested O
very interested O

8. Alcohol

8.1. **DO YOU DRINK ALCOHOLIC BEVERAGES:**

yes O no O

We provide an explanation of the term ALCOHOL UNIT. One alcohol unit corresponds to *(illustration in Russian questionnaire)*:
1 bottle (0.33 l) of strong beer or 2 bottles (0.33 l) of light beer
1 ordinary glass of table wine (120 ml)
1 glass fortified wine (80 ml)
1 shot of liquor (40%, 40 ml)

This means that for instance, 0.5 l strong beer or 1 l light beer = 1.5 alc. units; 1 bottle of table wine = 5 alc. units; 1 bottle of fortified wine = 8 alc. units; 1 bottle of liquor = 15 alc. units.

8.2. **HOW MANY ALC. UNITS DO YOU DRINK PER WEEK:**

beer OO
table wine OO
fortified wine OO
liquor OO
in total OO

8.3. **FOR HOW MANY YEARS DID YOU DRINK ALCOHOL IN SUCH AMOUNTS:**

OO years

Try to calculate how many such alcohol units you drank during the last week (during the last seven days before answering the questionnaire)

8.4. **DURING THE LAST WEEK I DRANK:**

(ALC. UN.)
beer OO
table wine OO
fortified wine OO
liquor OO
in total OO

8.5. **DO YOU EVER HAVE THOUGHTS ABOUT THE NECESSITY TO GIVE UP DRINKING ALCOHOL:**

yes O no O

8.6. **DOES CRITICISM OF YOUR DRINKING FROM THE SURROUNDINGS EVER BOTHER YOU:**

yes O no O

8.7. **DO YOU EVER HAVE WORRIES OR A SENSE OF GUILT REGARDING YOUR DRINKING:**

yes O no O

8.8. **DOES IT EVER HAPPEN IN THE MORNINGS THAT YOU FIRST OF ALL START DRINKING IN ORDER TO CALM DOWN OR GET RID OF A HANGOVER:**

yes O no O

8.9. **HOW OFTEN DO YOU DRINK ALCOHOLIC BEVERAGES:**

never O
once a month or less O
2-4 times a month O
2-3 times a week O
4 or more times a week O

8.10. **HOW MANY ALC. UN. DO YOU USUALLY DRINK ON ONE OCCASION:**

1-2 O
3-4 O
5-6 O
7-9 O
10 or more alc. units O

8.11. **HOW OFTEN DO YOU DRINK 6 OR MORE ALC. UN. ON ONE OCCASION:**

never O
less than once a month O
once a month O
once a week O
daily or almost daily O

8.12. **HOW OFTEN DURING THE LAST YEAR DID YOU FEEL THAT YOU COULD NOT STOP DRINKING ONCE YOU HAVE STARTED:**

never O
less than once a month O
once a month O
once a week O
daily or almost daily O

8.13. **HOW OFTEN DURING THE LAST YEAR SHOULD YOU HAVE FULFILLED OR DONE SOMETHING, WHICH YOU WERE NOT ABLE TO DO BECAUSE OF ALCOHOLCONSUMPTION:**
never O
less than once a month O
once a month O
once a week O
daily or almost daily O

8.14. **HOW OFTEN DURING THE LAST YEAR DID YOU HAVE TO DRINK ALCOHOL IN THE MORNING IN ORDER TO COME ROUND AFTER HEAVY ALCOHOL INTAKE THE DAY BEFORE:**
never O
less than once a month O
once a month O
once a week O
daily or almost daily O

8.15. **HOW OFTEN DURING THE LAST YEAR WERE YOU UNABLE TO RECALL WHAT HAPPENED IN THE EVENING OF THE DAY BEFORE BECAUSE OF ALCOHOL CONSUMPTION:**
never O
less than once a month O
once a month O
once a week O
daily or almost daily O

8.16. **HAVE YOU OR ANYBODY ELSE EVER HAD TRAUMA AS A RESULT OF YOUR ALCOHOL CONSUMPTION:**
no O
yes, but not in this year O
yes, in this year O

8.17. **HAVE ANY OF YOUR RELATIVES, FRIENDS OR PERSONS IN THE HEALTH SERVICE EVER EXPRESSED ANXIETY REGARDING YOUR HARD DRINKING AND SUGGESTED THAT YOU BETTER CUT DOWN THE ALCOHOL CONSUMPTION:**
no O
yes, but not in this year O
yes, in this year O

8.18. **HOW OFTEN DURING THE LAST YEAR HAVE YOU FELT GUILT BECAUSE OF YOUR DRINKING:**
never O
less than once a month O
once a month O
once a week O
daily or almost daily O

9. Quality of life

9.1. **TO THE RIGHT IS A SCALE WITH 10 LEVELS. (*See Russian questionnaire for illustration of scale from 10 (best) to 1 (worst).*) IMAGINE, THAT THE HIGHEST LEVEL REPRESENTS THE BEST WAY OF LIFE, THAT YOU CAN ENVISION FOR YOURSELF, WHILE THE LOWEST LEVEL – THE WORST WAY OF LIFE. WHICH LEVEL, IN YOUR OPINION, IS IN BEST AGREEMENT WITH YOUR CURRENT LIFE.**

O your choice

9.2. **DO YOU EXPERIENCE ANY CHANGES DEPENDING ON THE SEASON OF THE YEAR:**

	None	Little	Moderate	Some	Much
length of sleep	O	O	O	O	O
social activities	O	O	O	O	O
mood	O	O	O	O	O
weight	O	O	O	O	O
appetite	O	O	O	O	O
working capacity, mood for work	O	O	O	O	O

9.3. **IF YOU ANSWERED THAT THERE ARE CHANGES DEPENDING ON THE SEASONS, DO YOU THINK THIS IS A PROBLEM FOR YOU:**
yes O no O

9.4. **IF YES, THIS PROBLEM IS:**
small O
moderate O
considerable O
serious O
interferes with activities of daily life O

9.5. **WHEN DO THESE CHANGES USUALLY OCCUR:**
in winter O
in summer O
in spring O
in autumn O

9.6. **DO YOU EVER HAVE LONG PERIODS (2 WEEKS OR MORE), DURING WHICH YOU FEEL SAD, BLUE OR DEPRESSED:**
yes O no O

9.7. **IF YES, IN WHICH SEASON ARE YOU MOST BOTHERED:**
in winter O
in summer O
in spring O
in autumn O

9.8. **DO YOU EVER HAVE LONG PERIODS (2 WEEKS OR MORE), DURING WHICH YOU HAVE TROUBLE SLEEPING:**
yes O no O

9.9. **IF YES, IN WHICH SEASON ARE YOU MOST BOTHERED:**
in winter O
in summer O
in spring O
in autumn O

9.10. **WHAT KIND OF SLEEP DISTURBANCES DO YOU HAVE?**
YOU MAY MARK SEVERAL LINES. FOR THOSE WHO WORK SHIFTS THE ANSWER HAS TO BE BASED ON WORK ON THE DAY SHIFT.
trouble falling asleep O
falling asleep too early in the evening O
bad sleep, waking up several times O
waking up too early in the morning O
waking up not rested in the morning O
sleeping too long in the morning O

THIS PART WILL BE FILLED IN BY MED. PERSONELL

10. Anthropometry

10.1. **WEIGHT:** ☐☐☐ kg
10.2. **HEIGHT:** ☐☐☐ cm
10.3. **WAIST CIRCUMFERENCE:** ☐☐☐ cm
10.4. **HIP CIRCUMFERENCE:** ☐☐☐ cm
10.5. **SYSTOLIC BLOOD PRESSURE:**
☐ 1 ☐ 2 ☐ 3
10.6. **DIASTOLIC BLOOD PRESSURE:**
☐ 1 ☐ 2 ☐ 3
10.7. **PULSE RATE:**
☐ 1 ☐ 2 ☐ 3
10.8. **DATE AND TIME OF THE EXAMINATION:**
☐☐ ☐☐ ☐☐ ☐☐ ☐☐
10.9. **CODE OF MEDICAL PERSONNEL:** ☐☐

11. Laboratory parameters

11.1. **TRIGLYCERIDE** ☐
11.2. **CHOLESTEROL** ☐
11.3. **HIGH-DENSITY LIPOPROTEIN** ☐
11.4. **LOW-DENSITY LIPOPROTEIN** ☐
11.5. **APO LIPOPROTEIN** ☐
11.6. **ALBUMIN** ☐
11.7. **GGT** ☐
11.8. **ALAT** ☐
11.9. **ASAT** ☐
11.10. **AMYLASE** ☐
11.11. **THIAMINE** ☐
11.12. **KAK** ☐
11.13. **INTERLEUKIN-1** ☐

Appendix II

Северный Государственный Медицинский Университет
Университет в г.Трумсё,Норвегия

Уважаемый (-ая), Фамилия Имя Отчество

В 1999-2000 гг. Вы проходили медицинское обследование в рамках совместного российско-норвежского проекта "Здоровье человека 2000" на базе поликлиники СЦБКБ им.Семашко. Целью проводимого обследования было установление вероятности возникновения различных заболеваний.

Группа лиц, у которых был выявлен повышенный риск заболеваний, была проинформирована об этом по телефону или письмом в течение первого года после обследования. Если Вы не получали такое письмо, то это значит, что результаты Ваших анализов на момент обследования не указывали на повышенный риск возникновения заболеваний.

Сейчас, по истечении 4 лет с момента обследования, мы посылаем письмо всем его участникам и просим ответить на несколько вопросов о состоянии здоровья и приеме лекарств. Эта информация необходима для комплексной оценки состояния здоровья и лекарственного обеспечения.

Все сведения, полученные в результате этого обследования, конфиденциальны, а медицинский персонал, принимающий участие в разработке и анализе этих сведений предупрежден о сохранении врачебной тайны.

В письме Вы найдете вложенный конверт с обратным адресом и оплаченной почтовой маркой. Мы просим заполнить небольшую анкету на обратной стороне этого листа и отправить ее нам в этом конверте.
Если Вам в 1999-2004гг. не был поставлен диагноз заболеваний сердца, инсульта, сахарного диабета, рака, серьёзной травмы, требующей лечения, то Вам не нужно заполнять анкету, отметьте, пожалуйста, здесь , и пошлите незаполненную анкету нам обратно.

Заранее благодарим за сотрудничество,

Северный Государственный Медицинский Университет
Университет в г. Трумсё, Норвегия

P.S.Если адресат письма переехал, то мы просим Вас отправить письмо нам обратно с пометкой: Адресат письма переехал и, если вы знаете, то укажите, пожалуйста, адрес и телефон переехавшего
....
Если Ваш адрес изменился, то укажите, пожалуйста, правильный адрес
....

Анкета:

1. Отметьте, пожалуйста, если Вам в 1999-2004 гг. был поставлен диагноз:

	Да	когда Месяц	 год
Инфаркт миокарда			
Стенокардия			
Инсульт (кровоизлияние в мозг)			
Аритмия			
Сахарный диабет			
Рак			
Травма (любая)			

....

2.Принимаете ли Вы следующие лекарства:

	Нет	Иногда	Каждый день
Лекарства от повышенногодавления			
Сердечные лекарства			
Инсулин			
Таблетки от сахарного диабета			

Для того,чтобы оценить, насколько современные лекарства Вы получаете,напишите,пожалуйста, названия сердечных лекарств или лекарств от давления, которые Вы принимаете (если Вы не помните названия лекарств, то на этот вопрос можно не отвечать):

....

3.Укажите номер поликлиники города, в которой Вы наблюдаетесь:
....

Благодарим Вас за сотрудничество!

The Northern State Medical University
University of Tromsø, Norway

Number of participant

Dear, *name of the participant*

In 1999-2000 you have participated in a medical study in frames of the Russian-Norwegian project “Human health in year 2000” at the Semashko polyclinic. The aim of the study was to assess the risk of getting different diseases.

The group of participants that had high risk of diseases was contacted by telephone or letter during the first year after the study. If you have not received such letter, it means that the results of your analyses at the moment of the study did not reveal high risk of diseases.

Now, 4 years after the study, we are sending letter to all the participants and ask them to answer several questions about health status and use of medicines. This information is needed for complete evaluation of health status and availability of medicines.

All the information obtained during this study is confidential, and the medical personnel taking part in processing and analysis of this information, is bound to preserve professional secrecy.

In this letter you will find an envelope with return address and paid postal fee. We ask you to fill in a questionnaire on the back of this page and to send the answer to us in the return envelope.

If you in 1999-2000 did not get diagnosis of heart diseases, stroke, diabetes mellitus, cancer or trauma that requires treatment, than you don’t need to fill the questionnaire. Please note here and send the questionnaire back to us.

Thank you in advance for your cooperation,

The Northern State Medical University
University of Tromsø, Norway

P.S. If the addressee of this letter has moved, please send this letter back to us with a note: addressee has moved and, if you know, please write the new address or telephone number of the recipient…………………………………………………………………….

If your address has changed, please write your new address

…………………………………………………………………………………………

1. Please, note if you in 1999-2004 got the diagnosis of:

	Yes	When	
		Month	Year
Myocardial infarction			
Angina pectoris			
Stroke			
Arrhythmia			
Diabetes mellitus			
Cancer			
Trauma (any)			

…………………………………………………………………………………………….

2. Du you take the following medicines.

	No	Sometimes	Every day
Medicines against high blood pressure			
Medicines against heart diseases			
Insulin			
Tablets against diabetes mellitus			

To evaluate if you get the up-to-date treatment, please write the names of medicines that you are taking against heart diseases or high blood pressure (if you don't remember the names of the medicines, then you may not answer on this question)

……………………………………………………………………………………………

3. Please write the number of polyclinic where you are registered:……………………….

Thank you for cooperation.

Appendix III

Приложение № 2
к приказу Минздравсоцразвития России
от 26 декабря 2008 г. № 782н

КОРЕШОК МЕДИЦИНСКОГО СВИДЕТЕЛЬСТВА О СМЕРТИ К УЧЕТНОЙ ФОРМЕ № 106/у-08

СЕРИЯ №

Дата выдачи «_____» __________________ 20 __ г.

(окончательного, предварительного, взамен предварительного, взамен окончательного)

(подчеркнуть)

серия _______ № _________ «_____» ___________________ 20 __ г.

1. Фамилия, имя, отчество умершего(ей) ____
2. Пол: мужской [1], женский [2]
3. Дата рождения: число _______, месяц _____________________, год ___________
4. Дата смерти: число _______, месяц _____________________, год ___________, время ___________
5. Место постоянного жительства (регистрации) умершего(ей): республика, край, область __________________
район _______________________ город ________________________ населенный пункт ________________________
улица _______________________________________ дом ________________________ кв. ________________________
6. Смерть наступила: на месте происшествия [1], в машине скорой помощи [2], в стационаре [3], дома [4], в другом месте [5]

Для детей, умерших в возрасте до 1 года:

7. Дата рождения: число ______, месяц __________________, год __________, число месяцев _______, дней жизни _______
8. Место рождения ____
9. Фамилия, имя, отчество матери ____

--**Линия отреза**--

Министерство здравоохранения и социального развития Российской Федерации Наименование медицинской организации ____ адрес ____________________________________ Код по ОКПО _______________________________ Для врача, занимающегося частной практикой: номер лицензии на медицинскую деятельность, адрес ______________	Код формы по ОКУД ______________________ Медицинская документация Учетная форма № 106/у-08 Утверждена приказом Минздравсоцразвития России от 26 декабря 2008 г. № 782н

МЕДИЦИНСКОЕ СВИДЕТЕЛЬСТВО О СМЕРТИ

СЕРИЯ №

Дата выдачи «_____» __________________ 20 __ г.

(окончательное, предварительное, взамен предварительного, взамен окончательного *(подчеркнуть)*

серия _______ № _________ «_____» ___________________ 20 __ г.

1. Фамилия, имя, отчество умершего(ей) ____
2. *Пол: мужской* [1], *женский* [2]
3. Дата рождения: число _______, месяц _____________________, год ___________
4. Дата смерти: число _______, месяц _____________________, год ___________, время ___________
5. Место постоянного жительства (регистрации) умершего(ей): республика, край, область __________________
район _______________________ город ________________________ населенный пункт ________________________
улица _______________________________________ дом ________________________ кв. ________________________
6. Местность: городская [1], сельская [2]
7. Место смерти: республика, край, область ____
район _______________________ город ________________________ населенный пункт ________________________
улица _______________________________________ дом ________________________ кв. ________________________
8. Местность: городская [1], сельская [2]
9. Смерть наступила: на месте происшествия [1], в машине скорой помощи [2], в стационаре [3], дома [4], в другом месте [5]
10. Для детей, умерших в возрасте от 168 час. до 1 месяца: доношенный (37-41 недель) [1], недоношенный (менее 37 недель) [2], переношенный (42 недель и более) [3].
11. Для детей, умерших в возрасте от 168 час. до 1 года:
масса тела ребенка при рождении ______________ грамм [1], каким по счету был ребенок у матери (считая умерших и не считая мертворожденных) _____ [2], дата рождения матери ________ [3], возраст матери (полных лет) _____ [4], фамилия матери __________________________________ [5], имя ________________________________ [6], отчество ________________________________ [7].
12. *Семейное положение: состоял(а) в зарегистрированном браке [1], не состоял(а) в зарегистрированном браке [2], неизвестно [3].
13. *Образование: *профессиональное*: высшее [1], неполное высшее [2], среднее [3], начальное [4]; *общее*: среднее (полное) [5], основное [6], начальное [7]; не имеет начального образования [8]; неизвестно [9].
14. *Занятость: *был(а) занят(а) в экономике*: руководители и специалисты высшего уровня квалификации [1], прочие специалисты [2], квалифицированные рабочие [3], неквалифицированные рабочие [4], занятые на военной службе [5]; *не был(а) занят(а) в экономике*: пенсионеры [6], студенты и учащиеся [7], работавшие в личном подсобном хозяйстве [8], безработные [9], прочие [10].
15. Смерть произошла: от заболевания [1]; *несчастного случая*: не связанного с производством [2], связанного с производством [3], убийства [4]; самоубийства [5]; *в ходе действий*: военных [6], террористических [7]; род смерти не установлен [8].

*В случае смерти детей, возраст которых указан в пунктах 10-11, пункты 12-14 заполняются в отношении их матерей.

10. Причины смерти:

	Приблизительный период времени между началом патологического процесса и смертью	Код по МКБ-10
I. а) ______ (болезнь или состояние, непосредственно приведшее к смерти)	______	☐☐☐.☐
б) ______ (патологическое состояние, которое привело к возникновению вышеуказанной причины)	______	☐☐☐.☐
в) ______ (первоначальная причина смерти указывается последней)	______	☐☐☐.☐
г) ______ (внешняя причина при травмах и отравлениях)	______	☐☐☐.☐
II. Прочие важные состояния, способствовавшие смерти, но не связанные с болезнью или патологическим состоянием, приведшим к ней, включая употребление алкоголя, наркотических средств, психотропных и других токсических веществ, содержание их в крови, а также операции (название, дата) ______	______	☐☐☐.☐

11. В случае смерти в результате ДТП: смерть наступила – в течение 30 суток [1], из них в течение 7 суток [2].
12. В случае смерти беременной (независимо от срока и локализации) [1], в процессе родов (аборта) [2], в течение 42 дней после окончания беременности, родов (аборта) [3]; кроме того в течение 43-365 дней после окончания беременности, родов [4].
13. Фамилия, имя, отчество врача (фельдшера, акушерки), заполнившего Медицинское свидетельство о смерти ______ Подпись ______
14. Фамилия, имя, отчество получателя ______
Документ, удостоверяющий личность получателя (серия, номер, кем выдан) ______
«___» ______ 20___ г. *Подпись получателя* ______

---------- Линия отреза ----------

16. В случае смерти от несчастного случая, убийства, самоубийства, от военных и террористических действий, при неустановленном роде смерти – указать дату травмы (отравления): число ___, месяц ______, год ____, время ____, а также место и обстоятельства, при которых произошла травма (отравление) ______

17. Причины смерти установлены: врачом, только установившим смерть [1], лечащим врачом [2], фельдшером (акушеркой) [3], патологоанатомом [4], судебно-медицинским экспертом [5].
18. Я, врач (фельдшер, акушерка) ______,
(фамилия, имя, отчество)

должность ______,
удостоверяю, что на основании: осмотра трупа [1], записей в медицинской документации [2], предшествующего наблюдения за больным(ой) [3], вскрытия [4] мною определена последовательность патологических процессов (состояний), приведших к смерти, и установлены причины смерти.

19. Причины смерти:

	Приблизительный период времени между началом патологического процесса и смертью	Код по МКБ-10
I. а) ______ (болезнь или состояние, непосредственно приведшее к смерти)	______	☐☐☐.☐
б) ______ (патологическое состояние, которое привело к возникновению вышеуказанной причины)	______	☐☐☐.☐
в) ______ (первоначальная причина смерти указывается последней)	______	☐☐☐.☐
г) ______ (внешняя причина при травмах и отравлениях)	______	☐☐☐.☐
II. Прочие важные состояния, способствовавшие смерти, но не связанные с болезнью или патологическим состоянием, приведшим к ней, включая употребление алкоголя, наркотических средств, психотропных и других токсических веществ, содержание их в крови, а также операции (название, дата) ______	______	☐☐☐.☐

20. В случае смерти в результате ДТП: смерть наступила – в течение 30 суток [1], из них в течение 7 суток [2].
21. В случае смерти беременной (независимо от срока и локализации) [1], в процессе родов (аборта) [2], в течение 42 дней после окончания беременности, родов (аборта) [3]; кроме того в течение 43-365 дней после окончания беременности, родов [4].
22. Фамилия, имя, отчество врача (фельдшера, акушерки), заполнившего Медицинское свидетельство о смерти ______ Подпись ______

Руководитель медицинской организации,
частнопрактикующий врач (подчеркнуть) ______ ______
(подпись) (фамилия, имя, отчество)

Печать

23. Свидетельство проверено врачом, ответственным за правильность заполнения медицинских свидетельств.

«___» ______ 20___ г. ______ ______
(подпись) (фамилия, имя, отчество)

MEDICAL DEATH CERTIFICATE

SERIAL NUMBER

Date of issue ”…” …………….. 20..

(final, preliminary, issued instead of preliminary, issued instead of final (*underline)*

Serial number ”…” …………….. 20..

1. Surname, Name, Patronymic of the deceased
2. Sex: *male 1; female 2*
3. Date of birth: date, month, year
4. Date of death: date, month, year, time
5. Registration address of the deceased: republic, region, oblast……………………

District…………………… Town…………………. Community…………………..

Street……………………… House……………….. Apartment…………………...

6. Area: urban 1, rural 2
7. Place of death: republic, region, oblast……………………

District…………………… Town…………………. Community…………………..

Street……………………… House……………….. Apartment…………………...

8. Area: urban 1, rural 2
9. The death has occurred: at the place of accident 1, in the ambulance car 2, in the hospital 3, at home 4, at another place 5
10. For infants who died at the age of 168 hours to 1 month:
11. For infants who died at the age 168 hours to 1 year
12. Family status: married 1, unmarried 2, unknown 3
13. Education; *professional:* high 1, incomplete high 2, secondary school 3, primary school 4; *general:* secondary school (complete) 5, primary school 6, basic 7, do not have basic education 8, unknown 9.
14. Working status: *has been working in economy*: highly qualified managers and specialists 1, other specialists 2, qualified workers 3, non qualified workers 4, military

personnel 5, *has not been working in economy:* pensioners 6, students 7, worked at home 8, unemployed 9, other 10

15. Death has occurred: due to a disease 1, *accident:* not associated with an industrial production 2, associated with an industrial production 3, murder 4, suicide 5; *during:* military operations 6, terrorist attack 7, type of death was not established 8

16. In case of death due to accident, murder, suicide, death during military actions and terrorist attacks, when type of death has not been established-point the date of trauma (intoxication) day……, month………, year…………, time……….., as well as the place and the circumstances……………………………………………………………………….
…………………………………………………………………………………………

17. Causes of death were defined by: the medical doctor who has only confirmed the death 1, treating doctor 2, feldsher 3, pathologist 4, forensic expert 5.

18. I, doctor (feldsher, midwife) surname, name, patronymic…………………………...
working position…………………………………………………………………………
confirm that based on: examination of the body 1, medical documents 2, observations proceeding to death 3, autopsy 4, I have defined the following sequence of the pathological process (conditions) which caused the death.

19. Causes of death:

	Approximate period of time from the beginning of the pathological process and death	ICD-10 code
I. a) The disease or condition which was an immediate cause of death		□□□ □
□b) The pathological condition which was the cause of the aforementioned disease (condition)		□□□ □
c) The underlying cause of death		□□□ □
d) external cause in cases of trauma or intoxication		□□□ □
II. Other important conditions, contributing to death, which, however, are not associated with the cause of death, including: alcohol consumption, use of narcotics, use of psychotropic and other toxic substances, their concentration in the blood, and also surgeries (type and date of the surgery)		□□□ □

20. In case of death due to road accident:

21. In case of death of the pregnant (irrespectively the term and the localization)

22. Surname, name, patronymic of the doctor (feldsher, midwife) who has filled-in the medical death certificate……………………………………………Signature…………….

Chief of the medical organization,
private physician (underline)…………..Signature…………Surname, name, patronymic

<u>Stemple</u>

23. The death certificate was checked by the medical doctor who is responsible for the correctness of filling-in the medical certificates.

Date, moth, year   Signature……………… Surname, name, patronymic

ISBN xxx-xx-xxxx-xxx-x