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

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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.

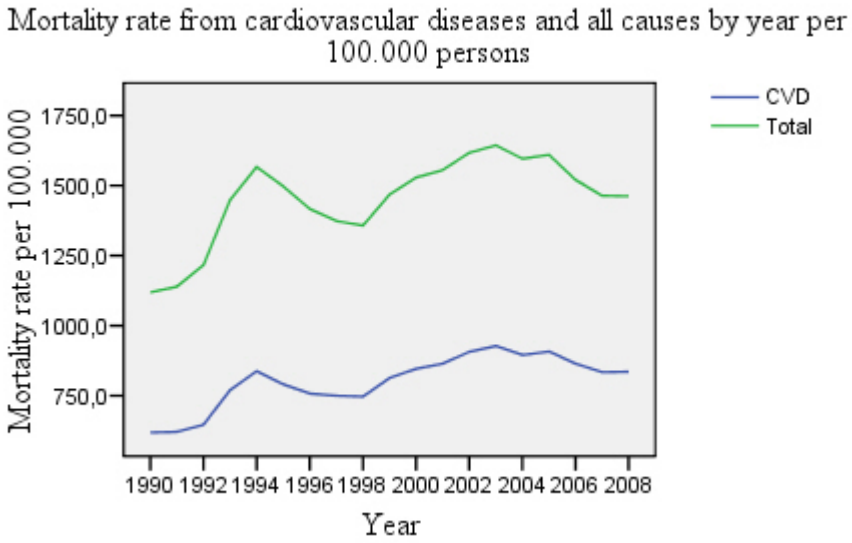
3. Cardiovascular death in Russian men occurs, in average, much earlier than in women. A very high CVD mortality in middle-aged men is an important cause of the low life expectancy among Russian men, which results to the largest in Europe gap in life expectancy between men and women. The life expectancy 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.

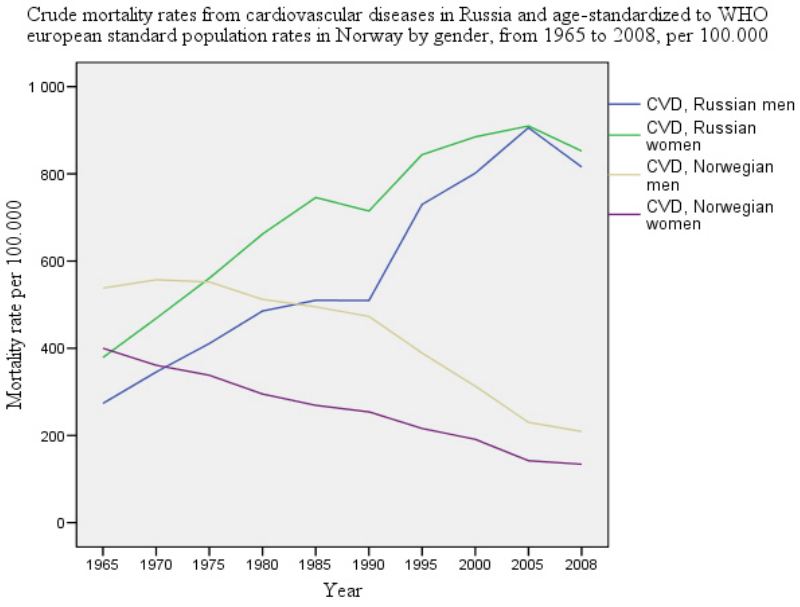
The health gains were impressive, and the West-East differences in life-expectancy quickly and dramatically decreased. In 1964, the highest ever recorded life-expectancy among men (64.9 years) was registered; the corresponding one for women was 73.6 years (Figure 2).These estimates were lower than in 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.

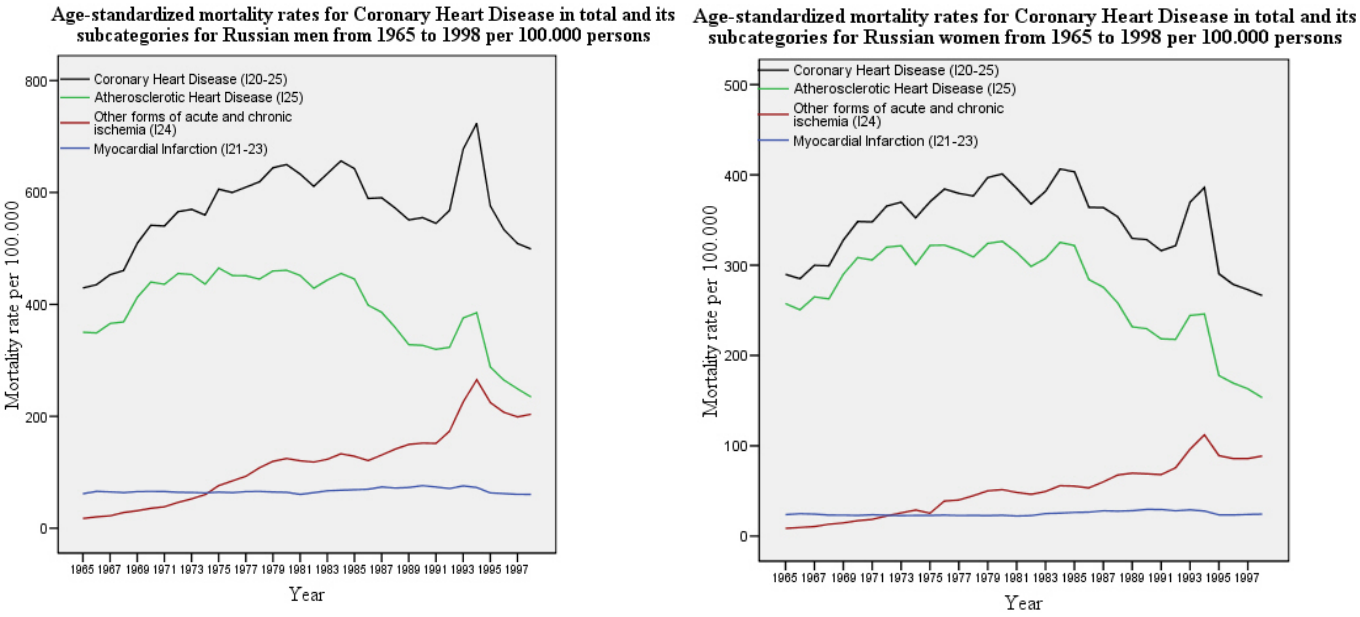
Figure 3



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.

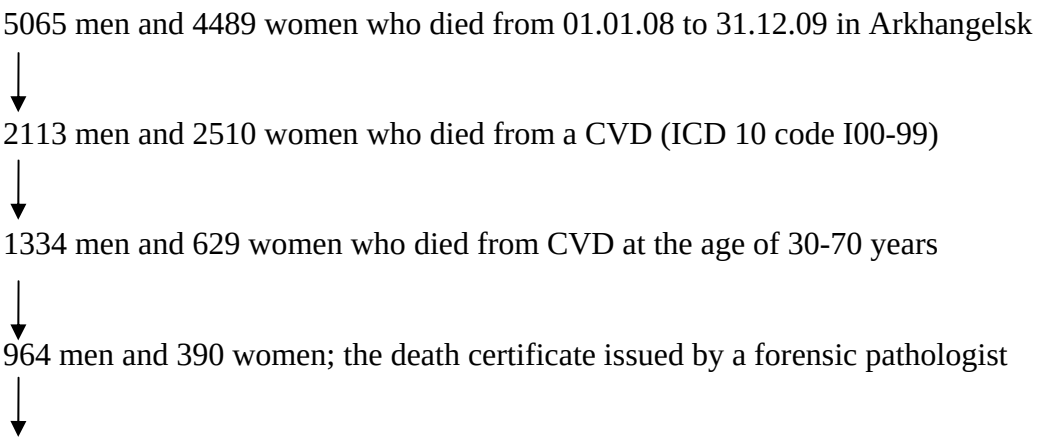
6.5 Data collection (Paper IV)

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)



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 ≥25 kg/m² and ≥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).

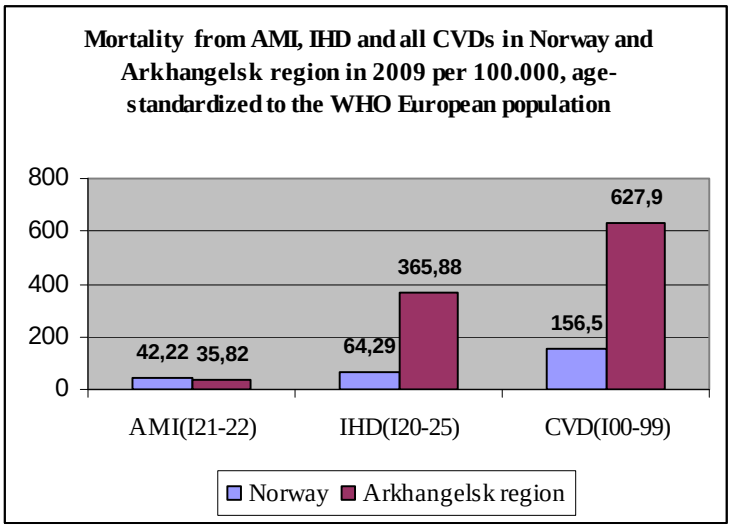
IHD is the leading single cause of cardiovascular and all-cause death in Russia (3). Deaths from IHD (I20-25) constituted 59.1% of all CVD deaths in Arkhangelsk in 2009, whereas AMI (I21-22) made up only 10% of all IHD deaths and 5.5% of all CVD deaths (92). A similarly low proportion of AMI has also 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.

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Paper I

BMC Public Health

RESEARCH ARTICLE Open Access

Prevalence of the metabolic syndrome and its components in Northwest Russia: the Arkhangelsk study

Oleg Sidorenkov[1,5*], Odd Nilssen[1,5], Tormod Brenn[1,5], Sergey Martiushov[2], Vadim L Arkhipovsky[3], Andrej M Grjibovski[1,4,5]

Abstract

Background: The metabolic syndrome (MetS) is a cluster of risk factors associated with morbidity from cardiovascular disease (CVD) and associated mortality. Russia has one of the highest CVD mortality rates in the world. However, the prevalence of MetS in Russia remains largely unknown. The aim of this study is to estimate the prevalence of MetS and its components in an urban Russian setting.

Methods: Altogether, 3705 Russian adults aged 18-90 years were enrolled in a cross-sectional study in Arkhangelsk (Northwest Russia). All subjects completed a questionnaire and underwent a physical examination. Blood samples were taken and analyzed in TromsØ, Norway. Three separate modified definitions of MetS were used, namely, the National Education Cholesterol Education Program Adult Treatment Panel III (NCEP), the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF). To ensure comparability of the findings, the prevalence data were standardized using world and European standard populations and Russian population.

Results: The age-standardized (Segi's world standard population) prevalence rates of the MetS among women were 19.8% (95% CI: 18.1-21.5), 20.6% (95% CI: 18.9-22.3) and 23.1% (95% CI: 21.3-24.9) by the NCEP, AHA/NHLBI and IDF criteria, respectively. The corresponding rates for men were 11.5% (95% CI: 10.1-12.9), 13.7% (95% CI: 12.2-15.2) and 11.0% (95% CI: 9.7-12.4). Among subjects with MetS, central obesity was more common among women, while elevated triglycerides and blood glucose were more common among men. Almost perfect agreement was found between the NCEP and AHA/NHLBI criteria (κ = 0.94). There was less agreement between the used definitions of MetS in men than in women.

Conclusions: While the prevalence of MetS among Russian women is comparable to the data for Europe and the U.S., the prevalence among Russian men is considerably lower than among their European and North-American counterparts. Our results suggest that MetS is unlikely to be a major contributor to the high cardiovascular mortality among Russian men. Further studies of MetS determinants and associated cardiovascular risk are needed for a better understanding of the mechanisms leading to the exceptionally high cardiovascular mortality in Russia.

Background

MetS is an unfavourable cluster of factors that increases the risk of CVD and type-2 diabetes [1-3]. MetS is associated with more than 50% increased risk of cardiovascular mortality and an almost 30% enhanced risk of mortality from all causes [4-6]. It is a considerable public health issue in both developed and developing countries. In general, its prevalence in Europe and among Americans of European descent varies between 20% and 30%, with approximately equal distribution by gender [7-11]. Although genetic predisposition has been suggested as an important determinant of MetS [12], genetic factors alone cannot explain the recent increase in prevalence in both Europe and the U.S.

* Correspondence: Oleg.Sidorenkov@ism.uit.no
[1]Institute of Community Medicine, University of Tromsø, postbox 9037 Tromsø, Norway

Internationally, there is no uniform accepted definition of MetS. Altogether, six sets of diagnostic criteria have been proposed by different expert groups. Despite considerable similarity among the definitions, the prevalence of the MetS in the same population may vary dramatically depending on the specific diagnostic criteria considered [13]. This complicates international comparisons and may challenge estimates of the global burden of the syndrome.

While cardiovascular mortality in Western Europe and the U.S. has decreased during recent decades, the opposite trend has been observed in Russia where it has increased from 412 per 100,000 in 1970 to 927 per 100,000 in 2003. Mortality from cardiovascular diseases in Russia is currently the highest in Europe. In 2003, CVDs accounted for about 56% of all deaths [14]. Coronary heart disease and cerebrovascular diseases alone, respectively, constituted 26 % and 20% of the total mortality. The highest increase in CVD has occurred among 30-60 year-olds, particularly among men [15].

Given that MetS is a strong predictor of cardiovascular mortality and morbidity [4-6], one may suspect a high prevalence of this syndrome in contemporary Russia. Few studies have described the prevalence of dyslipidemia, hypertension and obesity among Russians [16,17]. The actual rates reported were either comparable to or lower than those in Europe [18]. These studies, however, focused only on the distribution of major cardiovascular risk factors. To the best of our knowledge, no large Russian population-based studies on cluster of the major cardiovascular risk factors, such as the MetS, have been published.

The aim of the present study is to estimate the prevalence of MetS and its components in an urban Russian setting using several international definitions and reference populations to ensure comparability of the findings.

Methods

Sample characteristics

The survey was conducted in 2000 in Arkhangelsk, the capital of the Arkhangelsk Region of Russia. The population of Arkhangelsk prior to the study's initiation was approximately 170,000 men and 197,000 women. The city is ethnically homogenous: 95% of inhabitants are registered as Russians and most of the reminder are ethnically and culturally close to Russians (e.g. 2% of the population are registered as Ukrainians and 1% as Byelorussians).

No population register for medical research exists in Arkhangelsk. Primary health care departments provide medical services to the general population within the regional general health and occupational health network. People are registered at polyclinics according to their home address and/or place of work. All study participants when registered at the same out-patient clinic in Arkhangelsk. Of those who were invited, only 40 persons (1.1 %) refused to participate with "lack of time" as the primary reason given. Individuals coming for their annual medical check-up at the out-patient clinic were recruited consecutively to avoid the "healthy volunteer effect". Workers and students were similarly invited either through the obligatory annual medical examination or through their places of work or study. Pensioners were recruited through the clinic's register. About 90% of males and 70% of females were recruited through an annual medical examination consisting mainly of working people but also students, pensioners and unemployed individuals. Other subjects were invited to the study. Students constituted approximately 12%, pensioners 19%, unemployed 3% and working subjects 66 % of the study population.

Altogether, 1968 men and 1737 women aged 18-90 years participated in the study. It involved a physical examination, completion of a comprehensive questionnaire and donating blood for tests. Data were collected by trained medical personnel. The study was approved by the Regional Ethics Committee, TromsØ, Norway. Verbal informed consent was obtained from all participants.

Data collection

Anthropometric measurements included weight, height, waist and hip circumference. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Blood pressure and heart rate were measured (upper right arm) in a sitting position three times at two minute intervals using a semiautomatic electronic device (DINAMAP-R, Criticon, Tampa, Florida). Averages of the second and third systolic and diastolic blood pressure readings were used in the analysis. In addition, all subjects completed a six-page questionnaire on socio-demographic characteristics, medicines used (including regular intake of antihypertensive and anti-diabetic medications), smoking habit, alcohol consumption, diet and level of physical activity during leisure time and at work. History of cardiovascular diseases and diabetes were assessed by additional questions preceded by "do you now have or have you ever had" angina pectoris (AP), myocardial infarction (MI), stroke or diabetes mellitus (DM). Only basic socio-demographic data and self-reported diseases are presented for descriptive purposes in this paper. Age was categorized into five groups: 18-29, 30-39, 40-49, 50-59 and 60+ years. Education was classified as secondary or lower, vocational, incomplete higher, or higher. Income level was very difficult to determine during the year 2000 owing to high inflation and a collapsing economy, with about 30% of the

population (official data) having incomes below the survival minimum[19]. Consequently, we used self-reported occupational status data as a surrogate measure of income. Assigned income levels were based on the official year-2000 average salary levels recorded for different sectors of the economy [20], and were categorized as very low, low, medium or high. The income of groups for whom there were no official salary data (for example, students, the unemployed and housewives) was classified as unknown. Cigarette smoking was categorized as "yes" (occasional or daily smokers) or "no" (non-smokers or ex-smokers). Data on frequency of alcohol consumption were obtained by asking "How often do you drink alcoholic beverages?". More details about the study, recruitment details, sample and data collection protocols are presented elsewhere [21,22].

Laboratory measurements

Venous blood samples were drawn in the morning and centrifuged within 15-25 minutes in the laboratory at the study site in Arkhangelsk. Because subjects generally fast in preparation for these annual medical check-ups, since screening for diabetes and impaired glucose tolerance is part of the examination, we assume that most of the study participants indeed fasted. Nevertheless, none of them was directly asked by the study team to fast prior to the medical examination. The serum samples were stored at -20°C and then transported frozen to Norway where they were kept at -80°C pending analysis. Total serum cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), serum glucose (SG) and glycosylated hemoglobin (HBA1c) were measured. All laboratory analyses were carried out at the Department of Clinical Chemistry, University Hospital of Northern Norway (UNN) in Tromsø.

Enzymatic colorimetric tests were used to measure TC (cholesterol esterase, cholesterol oxidase) and TG (lipoprotein lipase, glycerokinase, and glycerophosphate oxidase). HDL-C was measured by a homogenous enzymatic colorimetric test (PEG cholesterol esterase, and PEG peroxidase). The coefficients of variation (CV) were, respectively, 5%, 2% and 3% for the TC, TG and HDL-C determinations. All biochemical analyses of serum lipids were performed using a Hitachi 737 analyzer. SG was measured by the hexokinase method using a Hitachi 917 analyzer (CV = 2%). HBA1c concentration was determined using the Bio-Rad Variant II HPLC system with reagents from Bio-Rad Laboratories (Inc., Hercules, CA 94547, USA), with CV <5%. The laboratory routinely participates in formal quality assurance exercises.

Definition of the metabolic syndrome

MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP) [23], the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) version [24] and the International Diabetes Federation (IDF) [25].

Statistical analysis

The prevalence estimates were standardized by age using Segi's world standard population, European standard population and Russian population (based on data from the National Census in 2002) [26]. The following age-strata were used: 20-29, 30-39, 40-49, 50-59 and 60 + years. Ninety-five percent confidence intervals (CI) were calculated for all prevalence estimates. Gender differences in socio-demographic and some life-style characteristics were compared using Pearson's chi-squared tests and unpaired t-tests for categorical and numerical data, respectively. To identify sex-specific cut-offs for waist circumference values corresponding to BMIs of ≥25 kg/m^2 and ≥30 kg/m^2, a receiver operating characteristic (ROC) analysis was carried out. Agreement between different diagnostic criteria for MetS was assessed by Cohen's kappa statistic. All analyses were performed using SPSS version 14 (SPSS Inc, Chicago, IL).

Results

Description of the study sample

Among the 3705 study participants, 150 (4.0%) had missing data on one or more variables and were therefore excluded. The final study group included 1918 men and 1637 women, corresponding to 95% of all those invited.

The women were slightly older and were better educated, but had much lower income and a higher prevalence of self-reported diseases than men. The men smoked more and took alcohol more frequently (Table 1).

The prevalence of abnormally high components of MetS as well as BMI and WHR increased with age in both genders (Table 2), as did the overall prevalence of MetS (Figure 1). This increase was more pronounced among women. The prevalence of MetS was similar in men and women in the youngest age group (2.5% vs. 2.9%), but was almost twice as high in women as compared to men in the oldest age group (44.8% vs. 24.4%).

The prevalence of obesity (Table 2) varied strikingly depending on the definition employed (WC, BMI or WHR). We performed a ROC analysis to evaluate the applicability of the given WC cut-offs in our study sample. The WC cut-off ≥94 cm identified men with BMI ≥25 kg/m^2 with sensitivity (Se) of 0.35 and specificity (Sp) of 0.99. The WC cut-off ≥102 cm identified men having BMI ≥30 kg/m^2 with a Se of 0.41 and Sp of 0.99. In men of our study setting, the BMI cut-offs of ≥25 kg/m^2 and ≥30 kg/m^2 corresponded best to WC of ≥84 cm

Table 1 Baseline characteristics of the sample

Sample characteristic	Men		Women		P[1]
	N	%	N	%	
Age, years					0.002
18-29	515	26.8	347	21.2	
30-39	352	18.4	303	18.5	
40-49	441	23.0	400	24.4	
50-59	298	15.5	290	17.7	
60+	312	16.3	297	18.1	
Marital status					<0.001
Single	409	21.3	278	17.0	
Married	1276	66.5	878	53.6	
Divorced	82	4.3	182	11.1	
Widow(er)	60	3.1	219	13.4	
Cohabiting	91	4.7	80	4.9	
Education					<0.001
Secondary	435	22.7	426	26.0	
Vocational	1083	56.5	669	40.9	
Incomplete higher	87	4.5	105	6.4	
Higher	303	16.3	437	26.7	
Income					<0.001
Very low	283	14.8	379	23.2	
Low	136	7.1	740	45.2	
Medium	144	7.5	189	11.5	
High	1058	55.2	34	2.1	
Unknown	297	15.5	295	18.0	
Frequency of alcohol intake, %					<0.001
Never	230	12.0	445	27.2	
Once a month or less	434	22.6	542	33.1	
2-4 times a month	979	51.0	571	34.9	
2 times a week or more	275	14.3	79	4.8	
Current smoking, %	1085	56.6	348	21.3	<0.001
Self-reported diseases					
Diabetes mellitus	28	1.5	48	2.9	0.002
Coronary heart disease	176	9.2	195	11.9	0.008
Stroke	9	0.5	30	1.8	<0.001
Total	1918	100.0	1637	100.0	

[1] Calculated by Pearson's chi-squared test

[2] One Alcohol Unit (AU) is equivalent to 13.8 grams of pure ethanol

(Se, 0.82; Sp, 0.85) and 92 cm (Se, 0.88; Sp, 0.86), respectively. The standard WC cut-offs of ≥80 cm and ≥88 cm applied in women, which corresponded respectively to BMIs of ≥25 kg/m^2 and ≥30 kg/m^2, were originally characterized by good test properties (respectively, Se of 0.79 and 0.87, and Sp of 0.91 and 0.88).

Prevalence of the metabolic syndrome

The overall prevalence of the MetS varied with the definition and reference population used (Table 3). Standardization by Segi's world population gave consistently lower prevalence estimates than standardization by the Russian population. The estimates standardized by the European standard population were almost identical to the latter and are therefore not presented. There was almost perfect agreement between the estimates of MetS in both men and women using the NCEP and AHA/NHLBI diagnostic criteria (Table 4). There was less agreement when the NCEP and IDF criteria were compared, especially among men. A comparable disparity was observed between the AHA/NHLBI and IDF estimates.

Prevalence of individual metabolic abnormalities

Using the NCEP definition of MetS, hypertension was the most frequent element in both sexes, followed by dyslipidemia (Table 5). The prevalence of central obesity was more than two times higher in women than in men (82.4 vs. 37.1%). Hyperglycemia was the least frequent MetS component in both men and women, regardless its definition.

Almost three quarters of the men and more than two thirds of the women in the total study sample had at least one MetS component (Table 6). Altogether, 17.3% had three or more metabolic abnormalities, of these, 60.7% had three, 33.0% had four, and 6.3% had all five.

Discussion

To our knowledge, this is the first relatively large study addressing the prevalence of MetS and its components in Russia. While the prevalence of MetS among Russian women is comparable to the European and the USA data, the prevalence among Russian men is considerably lower than among their European and North-American counterparts. The low prevalence rates of MetS combined with the high cardiovascular mortality among Russian men need to be explored in further studies.

Assessment of the MetS' burden is the first step towards monitoring the occurrence of the syndrome and developing effective preventive measures for this condition in Russia. The use of different internationally accepted diagnostic criteria and different standardization procedures provide a unique opportunity for comparison with both international and Russian studies. However, the results should be interpreted with caution, taking into account several limitations of the study.

The method used to recruit the study population might to a certain degree have resulted in a residual "healthy worker effect". Unemployed and marginalized subsets of the population such as alcohol or drug abusers and the homeless were underrepresented. Exclusion of 150 individuals from the sample because of missing values might represent another weakness. However, the prevalence of individual metabolic components in this

Table 2 Proportion of abnormal values (%)[1] for the components of the metabolic syndrome as well as body mass index (BMI) and waist to hip ratio (WHR) by age group and gender.

	Age-groups											
	18-29 years		30-39 years		40-49 years		50-59 years		60 and over		Total	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
						Women						
TG	6.1	3.9-9.2	9.9	6.9-14.0	21.3	17.4-25.7	29.7	24.5-35.3	37.4	31.9-43.2	20.3	18.4-22.4
HDL-C	36.3	31.3-41.6	36.3	30.9-42.0	38.0	33.3-43.0	49.3	43.4-55.2	54.5	48.7-60.3	42.3	39.9-44.8
DBP	0.3	0.02-1.9	5.6	3.4-9.0	17.3	13.8-21.4	32.8	27.5-38.5	43.4	37.8-49.3	19.0	17.1-21.0
SBP	7.5	5.0-10.9	13.9	10.3-18.4	35.8	31.1-40.7	62.1	56.2-67.6	75.8	70.4-80.4	37.6	35.3-40.0
Glucose	0.6	0.1-2.3	2.6	1.2-5.3	4.3	2.6-6.9	10.7	7.5-15.0	16.5	12.6-21.3	6.5	5.4-7.9
HBA1c	0.3	0.02-1.9	0.3	0.02-2.1	1.8	0.8-3.7	8.3	5.5-12.2	12.5	9.0-16.9	4.3	3.4-5.4
WC	4.3	2.5-7.2	14.5	10.9-19.1	32.5	28.0-37.4	47.6	41.7-53.5	49.8	44.0-55.7	29.0	26.8-31.3
BMI	3.5	1.9-6.1	13.2	9.7-17.7	21.5	17.6-25.9	35.9	30.4-41.7	33.3	28.1-39.1	20.8	18.9-22.9
WHR	3.2	1.7-5.8	7.3	4.7-10.9	18.8	15.1-23.0	31.0	25.8-36.8	33.3	28.1-39.1	18.1	16.3-20.1
						Men						
TG	12.0	9.5-15.1	21.3	17.2-26.0	25.4	21.5-29.8	32.2	27.0-37.9	28.2	23.4-33.6	22.6	20.7-24.5
HDL-C	27.2	23.4-31.3	17.1	13.4-21.5	24.5	20.6-28.8	32.9	27.6-38.6	38.1	32.8-43.8	27.4	25.4-29.4
DBP	1.4	0.6-2.9	17.6	13.9-22.1	33.6	29.2-38.2	39.3	33.7-45.1	42.9	37.4-48.7	24.4	22.5-26.4
SBP	22.3	18.9-26.2	39.2	34.1-44.5	52.8	48.1-57.6	68.5	62.8-73.6	78.5	73.5-82.9	48.8	46.5-51.0
Glucose	0.8	0.3-2.1	1.7	0.7-3.9	6.1	4.2-8.9	12.1	8.7-16.5	20.8	16.6-25.9	7.2	6.1-8.5
HBA1c	0.2	0.01-1.2	0	0-1.4	1.1	0.4-2.8	4.4	2.4-7.5	12.5	9.1-16.8	3.0	2.3-3.9
WC	0.8	0.3-2.1	4.3	2.5-7.1	7.5	5.3-10.5	12.1	8.7-16.5	10.6	7.5-14.7	6.3	5.3-7.5
BMI	3.3	2.0-5.3	9.1	6.4-12.7	14.7	11.6-18.5	20.1	15.8-25.2	15.4	11.7-20.0	11.6	10.2-13.1
WHR	4.9	3.2-7.2	25.0	20.6-29.9	30.2	26.0-34.7	37.9	32.4-43.7	46.8	41.2-52.5	26.3	24.4-28.4

[1] Proportions of abnormal values (%) with 95 % CI. BMI, body mass index in kg/m^2 >30; TG, triglycerides ≥1,7 mmol/l; HDL-C, high-density lipoprotein cholesterol <1,29 mmol/l (women) and <1,04 mmol/l (men); WC, waist circumference ≥88 cm (women) and ≥102 cm (men); DBP, diastolic blood pressure ≥ 85 mmHg; SBP, systolic blood pressure ≥ 130 mmHg; Glucose, serum glucose ≥ 6,1 mmol/l or self-reported DM, or Rt for hyperglycemia; HBA1c, glycosylated haemoglobin ≥ 6,1% or self-reported DM, or Rt for hyperglycemia; WHR, waist-to-hip ratio > 0,85 (women) and >0,9 (men).

group did not differ significantly from the group included into analyses.

There was a potential for clinical-chemical measurement errors in the study. Glucose was measured in serum, not in plasma. Because serum has a higher content of water, the cut-off point for defining hyperglycemia should be slightly higher. Moreover, we assumed that all blood samples were fasting but this was not ensured. Thus, the estimate of the prevalence of MetS may be inaccurate. To address these methodological problems, we also calculated the prevalence of MetS using two alternative criteria for hyperglycemia. The first criterion involved accepting one of the following: HBA1c ≥ 6.1 %, or self-reported DM, or receiving treatment for high blood sugar. The HBA1c marker reflects the average level of glycemia over the preceding 2'3 months and does not depend on fasting. In this study, HBA1c was measured using a precise and reliable method certified by the US National Glycohemoglobin Standardization Program [27]. An earlier published meta-analysis [28] and a recent systematic literature review showed that the performance of HBA1c in detecting type 2 diabetes was comparable with that of fasting plasma glucose, and a cut-off point of ≥6.1 %. was recommended [29]. The MetS rates based on the HBA1c were the most conservative, since for the chosen cut-off point of ≥6.1 % the test identifies subjects with Impaired Fasting Glucose (IFG) with lower sensitivity than those with the diabetes. Thus, some participants having IFG were falsely labelled as having normoglycemia. The second criterion involved raising the cut-offs

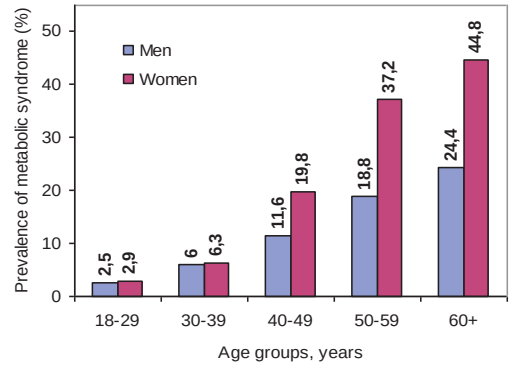

Figure 1 Sex-specific prevalence of the metabolic syndrome across age-groups according to NCEP definition.

Table 3 Age-standardized[1] prevalence of the metabolic syndrome according to the AHA/NHLBI, NCEP and IDF definitions

	Prevalence, % (95% CI)					
	AHA/NHLBI		NCEP		IDF	
	World	Russian	World	Russian	World	Russian
Men	13.7 (12.2-15.2)	15.3 (13.6-17.0)	11.5 (10.1-12.9)	12.9 (11.3-14.5)	11.0 (9.7-12.4)	12.3 (10.7-13.8)
Women	20.6 (18.9-22.3)	23.4 (21.5-25.4)	19.8 (18.1-21.5)	22.5 (20.6-24.5)	23.1 (21.3-24.9)	26.0 (24.0-28.0)
Total	17.0 (15.9-18.2)	19.3 (18.0-20.1)	15.5 (11.4-16.6)	17.6 (16.3-18.8)	16.8 (15.7-18.0)	18.9 (17.6-20.2)

[1] Standardized to the Segi's World standard population and the Russian population in 2002 by the following age-strata 20-29, 30-39, 40-49, 50-59, 60+ years.

for serum glucose from 5.6 to 5.8 mmol/l (IDF and AHA/NHLBI), and from 6.1 to 6.3 mmol/l (NCEP), according to the local standards at the UNN laboratory. Agreement between these two *ad hoc* definitions of hyperglycemia was relatively fair (kappa = 0.68). However when comparing the MetS rates defined by the NCEP criteria based on these two *ad hoc* definitions of hyperglycemia, corresponding agreement was very good (kappa = 0.97). Similar results were seen for other definitions (IDF, AHA/NHLBI). This might be rationalized by the cluster nature of MetS and by the fact that hyperglycemia was the least prevalent metabolic abnormality in both genders. The impact of the latter on the probability of having MetS was minimal.

The new estimates obtained by applying these modified criteria were slightly lower than previously described (data not shown), but the agreements between all three estimates were ≥0.95, suggesting that the degree to which the prevalence of MetS was overestimated in this study is small.

Our findings on the prevalence of MetS among Russian women are comparable to corresponding studies from Europe [9-11] and the USA [7,8]. However while in these studies the prevalence among men was equal to or even higher than that among women, our study shows that among men it is almost half that among women. This remarkable disparity might be explained by lifestyle and socio-economic differences between the genders. Females were slightly older, better educated and primarily employed in jobs where the level of physical activity at work was low, e.g. school teachers, office workers, sewing-factory workers. There was a higher proportion of pensioners among the women than the men (23 vs. 15%, respectively). Men had higher levels of physical activity at work and consumed more alcohol, with vodka binge drinking as a prevailing pattern. Men also smoked substantially more. The prevalence rates of visceral adiposity (as defined by both the NCEP and IDF criteria), which is the core element in metabolic syndrome's pathogenesis and the proxy-indicator of insulin-resistance, was also much lower among men than women in our study. A detailed analysis of the relationships among MetS, its components, and life-style and socio-demographic determinants among Russian adults is beyond the scope of this paper.

Only one research publication was found that examined the prevalence of MetS among Russians [30]. It was carried out in the Kuzmolovsky district (close to St. Petersburg) and reported a much higher prevalence rate (54% vs. 18.9% in our study). However, that study had severe limitations: small sample size (146 participants), questionable selection procedure (i.e. shifted gender and age distribution; 91% were women with a mean age of 68 years), prevalence was reported without gender- and age-standardization, and a high prevalence of co-morbidity occurred (90% reported heart disease). Nevertheless, if we compare the results of that study with ours for women in the age group 60+, the difference in MetS' prevalence is reduced considerably (54% vs. 45%).

A population-based study of men living in Kuopio in Eastern Finland [31] reported a prevalence of MetS (using the NCEP definition) similar to ours (13.7% vs.

Table 4 Kappa statistics (κ) with standard errors (SE) for the agreement between the prevalence of metabolic syndrome estimates obtained by three different diagnostic criteria

Agreement between the diagnostic criteria:	κ (SE)		
	Men (N = 1918)	Women (N = 1637)	Total(N = 3555)
NCEP and AHA/NHLBI	0.90 (0.02)	0.97 (0.01)	0.94 (0.01)M
NCEP and IDF	0.53 (0.03)	0.80 (0.02)	0.70 (0.02)
AHA/NHLBI and IDF	0.55 (0.03)	0.82 (0.02)	0.71 (0.02)

Table 5 Sex-specific prevalence of individual metabolic abnormalities[1] among study participants with NCEP diagnosed metabolic syndrome

Metabolic abnormality	Prevalence					
	Men (N = 210)		Women (N = 347)		Total (N = 557)	
	%	95 % CI	%	95 % CI	%	95 % CI
Central obesity	37.1	30.6-43.7	82.4	78.4-86.5	65.4	61.4-69.3
High TG	83.8	78.8-88.8	71.2	66.4-76.0	76.7	73.1-80.2
Low HDL-C	85.7	80.9-90.5	88.8	85.4-92.1	87.6	84.9-90.4
AH	93.8	90.5-97.1	89.1	85.8-92.4	90.8	88.4-93.3
Elevated SG	33.3	26.9-39.8	18.4	14.3-22.5	24.1	20.5-27.6
Elevated HBA1c	17.1	12.0-22.3	14.4	10.7-18.1	15.4	12.4-18.5

[1] Central obesity: WC ≥88 cm (women) and ≥102 cm (men); High TG: triglycerides ≥1,7 mmol/l; Low HDL-C, high-density lipoprotein cholesterol <1,29 mmol/l (women) and <1,04 mmol/l (men); Arterial hypertension (AH): SBP ≥ 130 mmHg, or DBP ≥ 85 mmHg, or Rt for hypertension ; Elevated SG: serum glucose ≥6.1 mmol/l or self-reported DM, or Rt for hyperglycemia; Elevated HBA1c: glycated haemoglobin ≥6.1% or self-reported DM, or Rt for hyperglycemia

12.4% in our study). The population in that study was older (mean age 52 years vs. 41.6 years in our study), which might at least partly explain the higher prevalence in the Finnish sample. However, the Finnish study was performed in the late 1980s and more recent data from Finland suggest that the current prevalence of the MetS is higher. The results of a 2001 cross-sectional study in Slovakia [32] were comparable to ours, with a similar highly significant difference between men and women in the prevalence of NCEP-defined MetS (15.9% vs. 23.9%). However, there was no significant difference in IDF-defined MetS between genders in the Slovakian study. One may speculate about a specific distribution of the MetS by gender in Eastern European countries, but more data from this region are needed before definite conclusions are drawn.

The prevalence of MetS in the Arkhangelsk study increased progressively with age. This has also been observed in other studies, but to a lesser extent [7-11]. In our study, there was a fifteen-fold increase among women and a nine-fold increase among men when the 18-29 and 60+ age groups were compared. In the sub-sample of individuals with MetS, the most frequent metabolic abnormalities were arterial hypertension and low HDL-C. Only one-third of men diagnosed with MetS (NCEP) had central obesity, whereas more than 80% of women with MetS were obese. Interestingly, although the prevalence of central obesity was higher among women, the mean WC was higher among males in all age groups.

The method used to define obesity (BMI, WC or WHR) strikingly affected the reported prevalence of this condition in both genders. The variation was particularly striking among men, ranging from 6% to 26% using the WC and WHR definitions, respectively. By contrast, among women, the frequency was highest when obesity was defined by the WC-criteria. The original sex-specific thresholds for WC were originally (at least partly) established in cross-sectional studies from Holland and the UK [33,34], using correlation between WC and BMI in subjects with BMI ≥25 kg/m^2 and 30 kg/m^2. The cut-offs for obesity using WC depend on ethnicity [25]. According to the ROC analysis, the optimal cut-offs for WCs corresponding to BMIs of ≥25 kg/m^2 and ≥30 kg/m^2 were about 10 cm lower (≥84 cm and ≥92 cm, respectively) than the original one (≥94 cm and ≥102 cm, respectively) suggesting a lower tendency for central adiposity at a given BMI among the men in our study setting. Similar results were reported from a study of middle-aged eastern Finnish men in the late 1980th [31]. On the contrary, the standard cut-offs of WC for

Table 6 Age-standardized[1] prevalence of one or more metabolic abnormalities among those who were diagnosed with metabolic syndrome according to NCEP definition

Number of abnormalities	Prevalence					
	Men (N = 1918)		Women (N = 1637)		Total (N = 3555)	
	%	95 % CI	%	95 % CI	%	95 % CI
≥1	72.5	70.7-74.3	68.7	66.7-70.7	70.8	69.5-72.2
≥2	31.4	29.3-33.5	39.5	37.4-41.6	35.4	33.9-36.9
≥3	12.4	10.9-14.0	22.4	20.5-24.3	17.3	16.0-18.5
≥4	4.0	3.0-4.9	9.9	8.4-11.3	6.8	5.9-7.7
5	0.55	0.2-0.9	1.7	1.0-2.3	1.1	0.7-1.5

[1] Standardized to the Russian population in 2002 by the following age-strata 20-29, 30-39, 40-49, 50-59, 60+ years.

women (≥80 cm and ≥88 cm) originally corresponded well to BMIs of 25 kg/m^2 and 30 kg/m^2. Therefore, the original cut-offs used for WC in NCEP and IDF definitions of MetS may be inappropriate for men living in Northwest Russia. This is an important finding that might largely explain the unequal distribution of MetS by sex. The finding needs further verification.

The most reasonable explanation for our main findings is the difference in life-style between Russian men and women: women smoked less, had lower alcohol consumption and, what is more important, lower levels of physical activity. In general, Russian women have occupations involving low levels of physical activity at work (service sector, office personnel, workers in the sewing industry), whereas men have higher levels of work-related physical activity.

Our study did not support the hypothesis that the high burden of cardiovascular morbidity and mortality among Russian men could be attributed to a high prevalence of MetS. A high prevalence of smoking and lifestyle associated with excessive alcohol consumption and specific drinking patterns may be other contributors to the high cardiovascular morbidity and mortality among Russian men. Alcohol consumption was high in our study population [35], especially among men. It might have had a "protective" effect on the development of the metabolic syndrome, but an opposite effect on the risk of fatal cardiovascular events. An alcohol-related increase in insulin sensitivity has been reported, involving a linearly-associated lower risk for MetS [36]. Nevertheless, alcohol consumption is an established risk factor for CVD mortality in Russia [37]. Analyses of associations between MetS and socio-demographic characteristics, smoking, alcohol and other factors, as well as cardiovascular risk attributable to MetS, are beyond the scope of this paper and will be pursued in future studies.

Differences in life expectancy between Russian men and women (59.0 and 72.3 years in 2000, respectively) may contribute to an explanation of the observed differences between genders in the prevalence of MetS [38], suggesting that Russian men do not reach the age when MetS becomes highly prevalent. Age-standardization, however, leveled out this difference only partially, suggesting that the difference in life expectancy is not the only contributor to the gender difference in the prevalence of MetS in Russia.

Conclusion

While the prevalence of MetS among Russian women is comparable to the data for Europe and the USA, the prevalence among Russian men is considerably lower than among their European and North-American counterparts. Our results suggest that MetS is unlikely to be a major contributor to high mortality from cardiovascular diseases among Russian men. Further studies of determinants for MetS and its components, and MetS and cardiovascular risk are needed for a better understanding of the mechanisms leading to the exceptionally high cardiovascular mortality in Russia.

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Author details

[1]Institute of Community Medicine, University of Tromsø, postbox 9037 Tromsø, Norway. [2]Department of Internal Medicine-II, Northern State Medical University, Troitsky Ave, 51, Arkhangelsk 163001, Russia. [3]Semashko Clinic, Arkhangelsk, Russia. [4]Norwegian Institute of Public Health, Postbox 4404 Nydalen, 0403 Oslo, Norway. [5]International School of Public Health, Northern State Medical University, Troitsky Ave, 51, Arkhangelsk 163001, Russia.

Authors' contributions

OS, AMG and ON drafted the manuscript. ON, TB, VA and SM planned the study and collected the data. OS and TB analyzed the data. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Paper II

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RESEARCH ARTICLE Open Access

Metabolic syndrome in Russian adults: associated factors and mortality from cardiovascular diseases and all causes

Oleg Sidorenkov[1*], Odd Nilssen[1], Andrej M Grjibovski[1,2,3]

Abstract

Background: Metabolic syndrome (MetS) is a cluster of four major obesity-related risk factors for cardiovascular disease (CVD). Russia has one of the highest CVD mortality in the world, but its association with MetS remains unknown. Also little is known about factors associated with MetS and its components in Russia.

Methods: Data on 3555 adults aged 18-90 years were collected in a cross-sectional study in 2000. MetS was defined by the International Diabetes Federation (IDF) and National Cholesterol Education Program (NCEP) criteria. Sex-specific associations between the IDF-defined MetS, its components, and life-style, socio-economic factors and laboratory indicators, were analysed using multivariable Poisson regression. Vital status of the study participants was identified by July 2009. Sex-specific associations between MetS and stroke, Coronary Heart Disease (CHD), CVD and all-cause death, were studied by Poisson regression adjusted for age, smoking, alcohol and history of CVDs.

Results: After adjustment for all studied factors except BMI, age, serum GGT, C-reactive protein and AST-to-ALT ratio were associated with MetS in both genders. Additionally, MetS was associated with sedentary lifestyle in women and with smoking in men. In the same regression model drinking alcohol 2-4 times a month and consumption of five or more alcohol units at one occasion in men, and drinking alcohol 5 times or more a month in women were inversely associated with MetS. After a 9-year follow-up, MetS was associated with higher risk of death from stroke (RR = 3.76, 95% CI:1.35-10.46) and from either stroke or myocardial infarction (MI, RR = 2.87, 95% CI:1.32-6.23) in men. No associations between MetS and any of the studied causes of death were observed in women.

Conclusion: Factors associated with MetS in both genders were age, GGT, C-reactive protein, and AST-to-ALT ratio. Moderate frequency of alcohol consumption and binge drinking in men and higher leisure time physical activity in women, were inversely associated with MetS.
Positive associations between MetS and mortality were only observed for deaths from stroke and either stroke or MI in men.

Background

The metabolic syndrome (MetS) is a cluster of four major cardiovascular disease (CVD) risk factors; obesity, insulin resistance (hyperglycemia), arterial hypertension and dyslipidemia where obesity and insulin resistance are the core elements [1]. Other important characteristics of MetS include low-grade inflammation, endothelial dysfunction, plasma hypercoagulability and atherosclerosis [2].

MetS is associated with increased CVD and all-cause mortality [3,4]. Moreover, it may be used as an alternative to the classic coronary heart disease (CHD) risk assessment scale such as the Framingham Risk Score [5]. The prevalence of MetS varies greatly between countries and ethnic groups [6]. Among Europeans and white Americans it varies between 20% and 30% with similar gender distribution [7,8]. Due to its high prevalence, MetS is considered as the major public health problem in Europe, and, particularly in the USA, where obesity and overweight are the second leading cause of preventable death accounting for 300.000 deaths per year [9].

* Correspondence: oleg.sidorenkov@uit.no
[1]Institute of Community Medicine, University of Tromsø, Tromsø, Norway
Full list of author information is available at the end of the article

The prevalence of MetS is associated with life-style, demographic, socio-economic, and genetic factors. Age, body mass index, postmenopausal status, diet rich in saturated fats, carbohydrates, and smoking have been positively associated with MetS, while inverse associations have been shown for physical activity, education, income, and alcohol intake [7,10-12].

Cardiovascular mortality in Russia is about four times higher than in Western Europe and the gap is the largest among middle aged men [13]. Although there is evidence for a high contribution of hazardous level of alcohol consumption to high death rates in Russia [14-16], other factors also need to be investigated. As MetS represents a cluster of the four of six major cardiovascular risk factors strongly associated with CVD mortality, one might expect similar high rates of MetS or its components in Russia.

Despite the fact that determinants of MetS and its contribution to mortality in Europe and North America receive much attention by the research community, it remains one of the least studied factors in Russia. In an earlier study we showed that while the prevalence of MetS among Russian women in 2000 was comparable with findings from other European countries, among men it was a half of that [17].

The aim of this study was to further explore the data collected in 2000 by studying socio-demographic and lifestyle correlates of MetS and associations between the MetS and CVD-and all-cause mortality after 9 years of follow-up.

Methods

Study sample

The data were obtained from a cross-sectional population-based study conducted in 2000 in Arkhangelsk, Northwest Russia. Detailed information on study design, sampling procedure and data collection is presented elsewhere [17-19]. In brief, we invited 3745 subjects aged ≥18 years from the patient register at the Semashko outpatient clinic in Arkhangelsk. Most of the participants were consecutively recruited when they came for their obligatory annual medical examinations. Others, particularly pensioners from the area served by the Semashko clinic, were specifically invited to participate in this study. Only 40 individuals refused to participate (response rate 98.9%).

Data collection

Data on education, occupational status, use of medications, history of myocardial infarction (MI), diabetes mellitus, and stroke as well as typical patterns of leisure time physical activity, smoking, frequency and amount of alcohol consumption, frequency of fresh fruits and vegetables intake with no specified time-frames were collected using a 6-page comprehensive questionnaire. Blood pressure (BP) was measured three times. The average of the two last readings was used in the study. Waist circumference (WC) was measured at the umbilical level. Weight and height were measured with subjects in light clothing and without shoes. Venous blood samples were drawn and centrifuged within 15-25 min. Most of the participants fasted prior to testing.

Laboratory analyses

Enzymatic colorimetric tests were used to measure TC (cholesterol esterase, cholesterol oxidase) and TG (lipoprotein lipase, glycerokinase, and glycerophosphate oxidase). HDL-C was measured by a homogenous enzymatic colorimetric test (PEG cholesterol esterase, and PEG peroxidase). All biochemical analyses of serum lipids were performed using a Hitachi 737 analyzer. 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). Glycated hemoglobin (HBA1c), which reflects the mean glucose level over the preceding 2-3 months, was assessed by Bio-Rad Variant II HPLC system with reagents from Bio-Rad Laboratories (Inc., Hercules, CA 94547, USA).

The inter-assay and intra-assay coefficients of variation for all laboratory tests were under 3%.

Definition of the metabolic syndrome

MetS was defined according to the International Diabetes Federation (IDF) [6] and National Cholesterol Education Program (NCEP) [20]criteria. We applied cut-offs for WC as it was recommended for europids (men ≥94 cm, women ≥80 cm) and (men ≥102 cm, women ≥88 cm), respectively, for IDF and NCEP. We used HBA1c as the measurement of hyperglycemia (defined as HBA1c ≥6.1%, and/or self-reported diabetes, and/or receiving treatment for diabetes).

Description of the variables

Education was divided into 3 categories: low (primary or secondary school), average (vocational school or incomplete university education) and high (complete university education). As income level was difficult to determine due to high inflation and collapsing economy due to the crisis and default in 1998-99, we used data on self-reported occupational status as a "surrogate" measure for income. Income level was defined according to official data on average salary levels in different sectors of the economy for year 2000 [21]. Five categories were

generated: very low, low, medium, high and unknown. Occasional and daily smokers comprised the group of smokers, while non-smokers and ex-smokers comprised the non-smoking group. Leisure-time physical activity was dichotomized as "inactive" or "sedentary lifestyle" (predominantly sitting activity like reading, watching TV) and "active" (walking or bicycling or yard working at least 4 hours per week, regular training and professional sport). Intake of fresh fruits or vegetables was dichotomized as "low" (once a week or less) and "high" (2 times a week or more). Alcohol consumption was presented by two variables: frequency of alcohol intake, and number of alcohol units (AU) consumed on one occasion. One AU was equal to 13.8 g of pure alcohol. The frequency of alcohol consumption was divided into 4 groups: abstainers, ≤1 times a month, 2-4 times a month, ≥5 times a month. The number of AU consumed at one drinking session was divided into 3 categories: abstainers, 1-4 AU and ≥5 AU (later referred to as binge drinking). Normal weight, overweight and obesity were defined as a BMI <25, 25-29.9, and ≥30 kg/m^2, respectively. As the distribution of the liver enzymes and CRP was right-skewed, we used logarithmically transformed values in the regression models.

Altogether 150 individuals had missing data on one or more variables and were excluded from the analyses. The final sample consisted of 3555 individuals (1918 men and 1637 women) aged 18-90 years or 96% of the initial sample.

Statistical analyses

Differences in the distribution of the studied characteristics between genders were studied by Pearson's chi-squared tests and unpaired t-tests for categorical and continuous data, respectively. Gender-specific associations between MetS defined by the IDF criteria, its individual components and socio-demographic, lifestyle and metabolic factors were calculated using Poisson regression with robust variance estimates as recommended by Barros and Hirakata [22], and are presented as crude and adjusted prevalence ratios (PR) with 95% confidence intervals (CI).

Follow-up study

In July 2009 we collected data on the vital status of all study participants, using the mortality register of the Arkhangelsk Regional Healthcare Department which is based on data from medical death certificates. Causes of death were coded using the International Classification of Diseases, 10th Revision (ICD-10). The study endpoints were: death from coronary heart disease (CHD) (I20-25); death from stroke (I60-64); death from either myocardial infarction (MI) or stroke (I21-23; I60-64); CVD death (I00-99); and all-cause death. By July 2009, 200 subjects of the 3555 participants had died and in 97 of the cases (48%) the diagnosis was verified by autopsy. To study associations between MetS in 2000 and mortality by 2009, we used both IDF and NCEP definitions of MetS to increase comparability of the findings with other studies. Gender-specific risk ratios (RR) were calculated by Poisson regression.

All analyses were performed using STATA 10 (STATA Corp, TX, USA). The study was approved by the Regional Ethical Committee in Norway.

Results

Sample characteristics

Participants' background characteristics and the prevalence of MetS are presented in Table 1. Men were younger, had higher income, but lower education than women. They were more physically active, smoked more, drank alcohol more often and had higher levels of alcohol intake at one drinking session. About 50% of the men reported binge drinking, by contrast to 15% among women. Vodka/liquor constituted about 66% and 45% of the total consumption in men and women, respectively (data not shown). Men also had higher levels of liver enzymes and CRP. The prevalence of MetS in men was half of that in women (Table 1).

Correlates of the metabolic syndrome

Among men, MetS was positively associated with age, BMI, sedentary lifestyle, GGT and CRP; and inversely associated with income, smoking, frequency and amount of alcohol intake as well as the AST-to-ALT ratio in the crude analysis. After adjustment for all studied factors except BMI, the associations between MetS and income disappeared. Additional adjustment for BMI attenuated most of the associations except the positive association with age, and inverse associations with the AST-to-ALT ratio, frequency and amount of alcohol consumption (Table 2).

In women, MetS was positively associated with BMI, age, very low income, sedentary lifestyle, GGT and CRP, and inversely associated with education, unknown income category, smoking, frequency and amount of alcohol consumption as well as AST-to-ALT ratio in crude analysis. After adjustment for all study factors except BMI, the associations between MetS and income, education, smoking and alcohol disappeared. After further adjustment for BMI, only age, sedentary lifestyle, GGT and CRP remained associated with MetS.

Correlates of the individual metabolic components

In the multivariable analysis of the MetS components (Table 3), frequency and volume of alcohol intake were inversely associated with prevalence of hypertriglyceridemia (high-TG), low levels of high density lipoproteins (low-HDL-C) and hyperglycemia in men. Similar

Table 1 Prevalence of the metabolic syndrome stratified by gender, age, BMI, laboratory tests, socio-demographic and the life-style characteristics

Socio-demographic and the life-style characteristics	Men		Women		P-value[2]
	N (%)	MetS, % with (95% CI)[1]	N (%)	MetS, % with (95% CI)[1]	
Age, years					0.002
18-29	515 (26.9)	1.75 (0.9-3.4)	347 (21.2)	3.8 (2.1-6.5)	
30-39	352 (18.4)	6.25 (4.1-9.5)	303 (18.5)	8.6 (5.8-12.5)	
40-49	441 (23.0)	11.3 (8.6-14.8)	400 (24.4)	22.8 (18.8-27.2)	
50-59	298 (15.5)	14.8 (11.0-19.4)	290 (17.7)	41.4 (35.7-47.3)	
60+	312 (16.3)	18.3 (14.2-23.1)	297 (18.1)	45.5 (39.7-51.3)	
BMI, kg/m^2					< 0.001
< 25.0	989 (51.5)	0.3 (0.1-1.0)	781 (47.7)	4.0 (2.8-5.7)	
25.0-29.9	707 (36.9)	9.3 (7.4-11.8)	515 (31.5)	28.9 (25.1-33.1)	
≥30.0	222 (11.6)	50.9 (44.1-57.6)	341 (20.8)	60.1 (54.7-65.3)	
Education					< 0.001
Secondary school	435 (22.7)	10.3 (7.7-13.7)	426 (26.0)	31.9 (27.6-36.6)	
College	1170(61.0)	7.9 (6.4-9.6)	774 (47.3)	21.3 (18.5-24.4)	
University	313 (16.3)	14.4 (10.8-18.9)	437 (26.7)	19.2 (15.7-23.3)	
Income					< 0.001
Very low	283 (14.8)	17.0 (12.9-22.0)	379 (23.2)	43.8 (38.8-49.0)	
Low	136 (7.1)	14.7 (9.4-22.0)	740 (45.2)	20 (17.2-23.1)	
Medium	144 (7.5)	6.9 (3.6-12.7)	189 (11.5)	23.8 (18.1-30.7)	
High	1058(55.2)	9.3 (7.6-11.2)	34 (2.1)	17.7 (7.4-35.2)	
Unknown	297 (15.5)	2.0 (0.8-4.6)	295 (18.0)	6.8 (4.3-10.4)	
Sedentary lifestyle					< 0.001
Yes	437 (22.8)	14.0 (10.9-17.7)	656 (40.1)	32.2 (28.6-35.9)	
No	1481(77.2)	8.2 (6.9-9.7)	981 (59.9)	17.7 (15.4-20.3)	
Current smoking					< 0.001
Yes	1085(56.6)	7.5 (6.0-9.2)	348 (21.3)	13.2 (9.9-17.3)	
No	833 (43.4)	12.1 (10.0-14.6)	1289(78.7)	26.3 (23.9.28.8)	
Low fresh fruits/vegetables intake					0.01
Yes	779 (40.6)	8.2 (6.4-10.4)	599(36.6)	25.5 (22.1-29.3)	
No	1139(59.4)	10.4 (8.7-12.3)	1038(63.4)	22.4 (19.9-25.0)	
Frequency of alcohol intake					< 0.001
Abstainers	230 (12.0)	15.2 (11.0-20.7)	445 (27.2)	34.2 (29.8-38.8)	
≤ 1 times a month	434 (22.6)	12.4 (9.6-16.0)	542 (33.1)	25.3 (21.7-29.2)	
2-4 times a month	979 (51.0)	7.2 (5.7-9.0)	571 (34.9)	15.9 (13.1-19.3)	
≥5 times a month	275 (14.3)	8.4 (5.5-12.4)	79 (4.8)	6.3 (2.4-14.8)	
Number of AU on occasion					< 0.001
Abstainers	230 (12.0)	15.2 (11.0-20.7)	445 (27.2)	34.2 (29.8-38.8)	
1-4 AU	780 (40.5)	9.5 (7.6-11.8)	946 (57.7)	20.0 (17.5-22.7)	
≥ 5 AU	912 (47.5)	8.0 (6.4-10.0)	248 (15.1)	17.7 (13.3-23.2)	
Self-reported MI or stroke	56 (2.9)		51 (3.1)		0.768
GGT, U/l, mean (SD)	43.7 (60.8)		28.4 (39.8)		< 0.001
AST, U/l, mean (SD)	29.5 (22.7)		23.6 (13.7)		< 0.001
ALT, U/l, mean (SD)	20.7 (20.8)		12.9 (12.8)		< 0.001
AST/ALT, mean (SD)	1.8 (0.9)		2.1 (0.8)		< 0.001
CRP, mg/l, mean (SD)	3.2 (9.1)		2.6 (5.6)		0.02
Metabolic syndrome[3]	182/1918	9.5 (8.2-10.9)	385/1637	23.5 (21.5-25.7)	< 0.001

[1] 95% CI for proportions calculated using Wilson procedure

[2] p-values for the differences between genders

[3] Metabolic syndrome defined according to the modified IDF criteria

Table 2 Sex-specific crude and multivariate adjusted PRs for metabolic syndrome[1]

Factor	Men			Women		
	Model 1[2]	Model 2	Model 3	Model 1[2]	Model 2	Model 3
Age						
18-29	Reference	Reference	Reference	Reference	Reference	Reference
30-39	3.58 (1.67-7.68)	2.24 (0.82-6.18)	1.4 (0.57-3.43)	2.29 (1.20-4.38)	1.55 (0.80-2.98)	1.42 (0.78-2.58)
40-49	6.49 (3.23-13.04)	3.75 (1.44-9.78)	2.03 (0.88-4.68)	6.07(3.46-10.67)	3.43 (1.90-6.19)	2.50 (1.45-4.33)
50-59	8.45 (4.18-17.06)	4.98 (1.89-13.14)	2.91 (1.25-6.75)	11.1(6.37-19.16)	5.39 (2.93-9.89)	3.76 (2.12-6.67)
60+	10.45 (5.25-20.82)	6.58 (2.34-18.49)	5.06 (2.09-12.21)	12.1(7.02-20.98)	5.09 (2.69-9.65)	3.97 (2.17-7.26)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Education						
Secondary school	Reference	Reference	Reference	Reference	Reference	Reference
College	0.76 (0.54-1.07)	1.03 (0.73-1.47)	1.23 (0.86-1.76)	0.67 (0.55-0.81)	0.96 (0.78-1.18)	0.89 (0.73-1.09)
University	1.39 (0.94-2.05)	1.10 (0.73-1.65)	1.18 (0.79-1.77)	0.60 (0.48-0.76)	0.80 (0.62-1.03)	0.89 (0.69-1.13)
P for trend	0.190	0.660	0.375	< 0.001	0.085	0.329
Income						
Very low	1.15 (0.71-1.86)	0.87 (0.48-1.59)	0.81 (0.46-1.44)	2.19 (1.82-2.63)	0.99 (0.77-1.26)	0.97 (0.76-1.23)
Low	Reference	Reference	Reference	Reference	Reference	Reference
Medium	0.47 (0.23-0.97)	0.67 (0.32-1.40)	0.62 (0.28-1.33)	1.19 (0.89-1.60)	1.11 (0.82-1.50)	1.03 (0.75-1.41)
High	0.62 (0.40-0.98)	0.84 (0.52-1.33)	0.81 (0.50-1.31)	0.88 (0.42-1.85)	0.97 (0.47-1.98)	1.01 (0.53-1.92)
Unknown	0.14 (0.06-0.33)	0.83 (0.26-2.62)	1.22 (0.45-3.31)	0.34 (0.22-0.53)	0.69 (0.45-1.07)	0.79 (0.52-1.19)
Fresh fruits/vegetab. intake; high vs. low	1.26 (0.94-1.69)	1.21 (0.90-1.63)	1.17(0.85-1.58)	0.88 (0.73-1.05)	1.05 (0.88-1.25)	1.06 (0.90-1.25)
Current smoking	0.62 (0.47-0.81)	0.74 (0.56-0.97)	1.08 (0.81-1.45)	0.50 (0.38-0.67)	0.98 (0.74-1.30)	1.04 (0.80-1.35)
Sedentary lifestyle	1.7 (1.28-2.28)	1.33 (0.99-1.81)	1.13 (0.84-1.52)	1.81 (1.52-2.16)	1.31 (1.11-1.55)	1.19 (1.01-1.40)
Frequency of alcohol intake						
Abstainers	Reference	Reference	Reference	Reference	Reference	Reference
≤1 times a month	0.82 (0.55-1.21)	0.90 (0.60-1.35)	0.66 (0.45-0.98)	0.74 (0.61-0.90)	1.13 (0.92-1.39)	1.04 (0.85-1.27)
2-4 times a month	0.47 (0.32-0.67)	0.62 (0.42-0.93)	0.59 (0.41-0.85)	0.47 (0.37-0.59)	0.96 (0.75-1.22)	0.90 (0.71-1.14)
≥5 times a month	0.55 (0.33-0.90)	0.76 (0.46-1.26)	0.61 (0.37-1.00)	0.19 (0.08-0.44)	0.42 (0.19-0.97)	0.58 (0.26-1.30)
P for trend	< 0.001	0.045	0.030	< 0.001	0.202	0.190
Body Mass Index						
< 25	Reference	Reference	Reference	Reference	Reference	Reference
25.0-29.9	30.78 (9.71-97.51)	-	22.0 (6.61-73.24)	7.3 (5.0-10.6)	-	4.4 (3.0-6.5)
30.0-34.9	163.1(52.2-509.6)	-	105.0 (31.6-349.1)	14.5 (10.1-20.9)	-	7.0 (4.6-10.5)
≥35	195.7 (61.0-628.1)	-	132.9 (39.1-451.5)	16.8 (11.5-24.5)	-	7.3 (4.8-11.3)
Number of AU on one occasion[3]						
Abstainers	Reference	Reference	Reference	Reference	Reference	Reference
1-4 AU	0.61 (0.42-0.89)	0.78 (0.53-1.15)	0.69 (0.48-0.99)	0.58 (0.49-0.70)	1.04 (0.85-1.26)	0.96 (0.79-1.17)
≥ 5 AU	0.52 (0.36-0.75)	0.61 (0.40-0.93)	0.52 (0.35-0.76)	0.52 (0.38-0.70)	1.07 (0.79-1.46)	1.06 (0.78-1.43)
P for trend	0.003	0.017	0.001	< 0.001	0.631	0.893
Log GGT	4.3 (3.18-5.81)	1.83 (1.22-2.75)	1.28 (0.82-2.0)	4.08 (3.28-5.07)	1.69 (1.27-2.26)	1.62 (1.22-2.15)
Log AST/Log ALT	0.11 (0.05-0.27)	0.09 (0.04-0.22)	0.19 (0.08-0.46)	0.34 (0.21-0.56)	0.56 (0.33-0.94)	0.82 (0.51-1.32)
Log CRP	2.28 (1.9-2.73)	1.63 (1.28-2.09)	1.27 (0.93-1.72)	3.16 (2.73-3.65)	2.17 (1.82-2.59)	1.61 (1.09-1.12)

[1] Metabolic syndrome is defined according to modified IDF criteria.

[2] Model 1: crude PRs. Model 2 estimates for the MetS adjusted for age, education, income, frequency of fresh fruit and vegetable intake, smoking habits, physical activity and the frequency of alcohol consumption. Model 3: estimates for the MetS adjusted for all covariates in Model 2 plus BMI.

[3] The PRs for "Number of AU on one occasion" in Model 2 and Model 3 adjusted as before excluding variable "Frequency of alcohol consumption".

results were found for frequency of alcohol consumption in women. The volume of consumed alcohol increased HDL-C levels, but showed weaker association in women than in men. Current smoking in men and sedentary lifestyle in women, were related to unfavorable lipid status. It was associated with 40% lower rates of central adiposity in men, as compared to non-smokers.

Serum levels of GGT and CRP in women were positively related to all five metabolic components (Table 3). High serum levels of GGT were the strongest metabolic marker in men, in whom it was related to increased prevalence of

Table 3 Gender-specific multivariable adjusted PRs[1] for individual components of the metabolic syndrome defined according to modified IDF criteria by frequency and volume of alcohol consumption, other life-style factors, levels of GGT, AST-to-ALT ratio and C-reactive protein

	Metabolic abnormalities				
	High TG	Low HDL-C	Central obesity[2]	Hypertension	Hyperglycemia
Men (1918)					
Frequency of alcohol intake					
Never	Reference	Reference	Reference	Reference	Reference
1 time a month	0.85(0.65-1.12)	0.94(0.75-1.18)	1.11(0.83-1.49)	1.01(0.90-1.14)	0.52(0.26-1.02)
2-4 times a month	0.76(0.59-0.97)	0.80(0.65-0.98)	0.95(0.71-1.26)	0.96(0.86-1.08)	0.59(0.33-1.05)
≥5 times a month	1.02(0.76-1.36)	0.85(0.64-1.12)	0.89(0.62-1.29)	0.97(0.83-1.13)	0.42(0.13-1.37)
P for trend	0.743	0.059	0.243	0.410	0.090
Number of AU on one occasion[3]					
Abstainers	Reference	Reference	Reference	Reference	Reference
1-4 AU	0.90(0.71-1.16)	0.86(0.70-1.06)	1.00(0.76-1.33)	0.97(0.87-1.09)	0.56(0.30-1.02)
≥5 AU	0.73(0.57-0.95)	0.79(0.63-0.98)	0.96(0.71-1.29)	0.96(0.86-1.08)	0.50(0.27-0.95)
P for trend	0.005	0.034	0.682	0.603	0.053
Current smoking	1.12(0.95-1.33)	1.25(1.07-1.46)	0.61(0.50-0.74)	0.95(0.87-1.03)	0.87(0.52-1.46)
Sedentary lifestyle	0.98(0.82-1.19)	1.11(0.93-1.31)	1.17(0.96-1.44)	1.04(0.95-1.15)	1.14(0.69-1.90)
LogAST-to-LogALT	0.39(0.22-0.67)	0.90(0.62-1.32)	0.19(0.11-0.33)	1.14(0.95-1.37)	0.82(0.22-3.04)
Log GGT	2.32(1.80-2.98)	0.80(0.59-1.08)	1.78(1.32-2.40)	1.21(1.05-1.40)	1.45(0.68-3.07)
Log CRP	0.92(0.76-1.11)	1.52(1.33-1.75)	1.57(1.30-1.89)	1.00(0.91-1.10)	1.51(0.95-2.41)
Women (1637)					
Frequency of alcohol intake					
Never	Reference	Reference	Reference	Reference	Reference
1 time a month	0.96(0.76-1.22)	0.90(0.78-1.04)	1.12(1.00-1.26)	0.96(0.85-1.09)	1.0(0.57-1.75)
2-4 times a month	0.83(0.63-1.10)	0.75(0.64-0.88)	1.03(0.91-1.18)	0.96(0.82-1.12)	0.42(0.17-1.04)
≥5 times a month	0.52(0.25-1.09)	0.48(0.32-0.72)	0.75(0.52-1.08)	0.76(0.45-1.30)	-
P for trend	0.065	< 0.001	0.605	0.346	0.030
Number of AU on one occasion[3]					
Abstainers	Reference	Reference	Reference	Reference	Reference
1-4 AU	0.88(0.71.1.11)	0.82(0.71-0.94)	1.06(0.95-1.18)	0.94(0.84-1.06)	0.77(0.44-1.35)
≥5 AU	0.98(0.70-1.37)	0.84(0.69-1.02)	1.15(0.98-1.36)	1.03(0.84-1.27)	0.79(0.28-2.20)
P for trend	0.684	0.039	0.087	0.915	0.442
Current smoking	1.40(1.08-1.82)	1.16(1.0-1.35)	0.94(0.81-1.09)	0.87(0.71-1.08)	1.08(0.37-3.18)
Sedentary lifestyle	1.24(1.03-1.50)	1.11(0.99-1.25)	1.06(0.97-1.16)	0.96(0.87-1.06)	0.98(0.60-1.60)
LogAST-to-LogALT	0.55(0.31-0.99)	1.17(0.88-1.55)	0.51(0.37-0.68)	0.92(0.70-1.21)	0.78(0.21-2.96)
Log GGT	1.93(1.42-2.62)	1.25(1.01-1.55)	1.27(1.08-1.50)	1.19(0.98-1.44)	2.18(0.99-4.83)
Log CRP	1.49(1.21-1.82)	1.42(1.25-1.61)	1.68(1.51-1.86)	1.29(1.14-1.45)	1.98(1.27-3.07)

[1] The regression models are adjusted for: age, intake of fresh fruits or vegetables, level of leisure time physical activity, income, education, smoking, frequency of alcohol intake and body mass index (BMI).

[2] PRs for central obesity are given for the regression model excluding BMI.

[3] PRs for "Number of alcohol units (AU) on one occasion" are given for the regression model excluding "Frequency of alcohol intake".

hypertriglyceridemia, central obesity and hypertension. The AST-to-ALT ratio was inversely associated with hypertriglyceridemia and central obesity in both genders, although the strength of association was larger in men.

Metabolic syndrome and mortality

MetS as defined by the IDF criteria was associated with more than 6 times higher risk of death from stroke among men after 9 years of observation in (Table 4, Model 1). Adjustment for age, history of CVD, smoking and alcohol attenuated the association, but the risk of death from stroke was still more than 3 times higher for men with MetS. Death from either stroke or myocardial infarction occurred twice as common among the men with IDF-defined MetS (Model 3). In women, the association between MetS and death from the former causes was much less pronounced (Model 1) and disappeared after adjustment for other covariates.

The risk of cardiovascular death was almost 2.5 times higher both in men and women with MetS (Table 4,

Table 4 Risk ratios (RR) with 95% confidence intervals (CI) for death from CHD, stroke, myocardial infarction or stroke, CVD and all causes associated with metabolic syndrome during the 9-year follow-up

Models[1]	RR (95% CI)			
	Men (1918)		Women (1637)	
	IDF	NCEP	IDF	NCEP
N (%)	**182 (9.5)**	**191 (10.0)**	**385 (23.5)**	**343 (21.0)**
CHD death, N		44		18
Model 1	1.84(0.81-4.18)	1.74(0.76-3.95)	1.64(0.61-4.39)	3.07(1.20-7.83)
Model 2	0.97(0.41-2.26)	0.87(0.37-2.03)	0.99(0.34-2.94)	1.53(0.54-4.34)
Model 3	0.78(0.32-1.91)	0.73(0.30-1.76)	0.86(0.27-2.67)	1.45(0.49-4.33)
Stroke death, N		15	17	
Model 1	6.36(2.29-17.67)	7.91(2.90-21.58)	1.77(0.66-4.77)	2.64(1.01-6.89)
Model 2	3.32(1.25-8.83)	4.07(1.55-10.72)	0.95(0.36-2.53)	1.23(0.48-3.14)
Model 3	3.16(1.11-9.00)	3.76(1.35-10.46)	0.92(0.36-2.33)	1.18(0.48-2.90)
Stroke/MI death, N		25		23
Model 1	4.49 (1.96-10.26)	6.03 (2.75-13.23)	1.15 (0.46-2.89)	2.01 (0.86-4.71)
Model 2	2.40 (1.09-5.31)	3.12 (1.45-6.73)	0.63 (0.25-1.56)	0.92 (0.40-2.11)
Model 3	2.22 (1.02-4.94)	2.87 (1.32-6.23)	0.60 (0.25-1.43)	0.89 (0.40-1.97)
CVD death, N		66		42
Model 1	2.34(1.30-4.21)	2.66(1.53-4.64)	2.00(1.09-3.69)	3.43(1.89-6.21)
Model 2	1.25(0.73-2.15)	1.38(0.83-2.28)	1.11(0.63-1.96)	1.58(0.91-2.73)
Model 3	1.08(0.64-1.82)	1.23(0.76-2.00)	1.09(0.63-1.89)	1.54(0.91-2.61)
All-cause death, N		124		76
Model 1	1.41(0.86-2.34)	1.95(1.26-3.02)	2.12(1.36-3.31)	2.90(1.87-4.49)
Model 2	0.80(0.51-1.27)	1.07(0.71-1.59)	1.15(0.76-1.72)	1.40(0.94-2.09)
Model 3	0.76(0.48-1.18)	1.01(0.69-1.49)	1.13(0.76-1.68)	1.38(0.94-2.04)

[1]Model 1 presents crude estimates.

Model 2 presents data adjusted for age.

Model 3 presents data adjusted for age, history of cardiovascular diseases, smoking status and alcohol intake (number of AU taken on one occasion).

Model 1). However, in both genders these associations disappeared after adjustment for age, and reduced even further after adjustment for other factors. Similar associations were found between all-cause death and MetS in crude analysis, but were attenuated after adjustment for age. The adjusted risk ratio for women was about 40% higher, but did not reach the level of statistical significance (Model 3). No consistent associations between CHD death and MetS were found. Associations between mortality and MetS defined by the NCEP criteria were in the same direction.

Discussion

To the best of our knowledge this is the first study in Russia on determinants of MetS and its association with all-cause and cardiovascular mortality. The main findings suggest that frequency of alcohol consumption and amount of alcohol consumed at one drinking episode are important correlates of MetS in Northwest Russia. Age, sedentary lifestyle and liver enzymes were also associated with MetS independently of all other studied factors. Moreover, MetS was associated with increased risk of death from stroke and either stroke or myocardial infarction among men during the 9-year observation period. The study discloses sex-specific adjusted relationships between frequency and volume of alcohol consumption in Russia (where these factors are considered to be very important correlates [15,16,23] of cardiovascular death) and all other major cardiovascular risk factors (except smoking) taken both individually and in frames of the MetS concept. GGT, AST, ALT and, particularly, C-reactive protein and AST-to-ALT ratio were associated with MetS and its individual components as expected from the current knowledge [2,24-27].

However, the results should be interpreted cautiously taking into account several limitations of the study. Unemployed and marginalized subjects are likely to be underrepresented. There were 150 participants with missing data on one or several characteristics, although, they did not differ systematically from those included in the analyses by characteristics for which the data were available. Application of modified IDF and NCEP criteria where we used HBA1c serum levels instead of plasma glucose could result in some underestimation of the prevalence of MetS, since the HBA1c is less sensitive. Other limitations related to study design including

glycemia measurement have been discussed in details elsewhere [17-19]. Given that diabetes is a risk factor for CVD, the sample was re-analyzed without those who reported diabetes in 2000, but the results were virtually identical.

During the 9-year follow-up we were not able to differentiate those who died in other regions and those who migrated, but did not die. This problem can be attributed to virtually all large Russian longitudinal studies, since there is no national population and mortality registers available for medical research. As a result, the participants, who moved from the Arkhangelsk region during the period of observation, could not be traced and those who died outside the region couldn't be registered. The approximate estimates of loss due to migration during the 9-year period is estimated to be between 15 and 17.5% [28]. Young people (≤30 years) were more likely to migrate to other regions, presumably looking for better work or education. Cardiovascular mortality in this age-group was lowest, compared to the other age-groups, and deaths from external causes accounted for more than 75%. Therefore, it seems unlikely that this loss to follow-up strikingly affected the observed associations between MetS and CVD mortality.

Both frequency of alcohol drinking and amount of alcohol consumed on one occasion were inversely associated with MetS, particularly among men. Interestingly, the crude association between the amount of alcohol consumed on one occasion and MetS was similar for men and women. However, after adjustment, the association persisted only among men. This association seems to be mediated by favorable changes in the lipid profile, but also by improvements in insulin action and lower risk for hyperglycemia (Table 3). A consumption of five or more AU on occasion (about ≥75 g of ethanol) was independently related to 50% lower prevalence of MetS (Table 2, Model 3), and, respectively, 25, 20 and 50% lower prevalence of hypertriglyceridemia, low-HDL-C levels and hyperglycemia (Table 3) among men.

Moderate alcohol consumption is known to increase serum triglycerides level, mainly because of alcohol-stimulated lipolysis [29]. There is evidence that a large part of this TG increase is mediated by contemporary fat consumption [30]. In western communities alcohol intake is often moderate and followed by affluent ingestion of foods, rich in polyunsaturated fats, whereas Russian men still widely combine a pattern of vodka binge drinking with low food intake [15,31]. These cultural peculiarities may explain the decrease of the TG level in response to higher amounts of alcohol consumed among Russian men. Taking into account that more than 50% of men in the study sample reported that they drink at least 5 AU (about one 200 ml glass of vodka) on occasion, and two thirds reported intake of mainly vodka at least two times a month (much the same findings were reported in other studies [32,33] from Russia), we consider that the life-style associated with such a pattern of alcohol intake plays an important role in metabolic risk reduction among Russian men. Thus, gender-specific pattern of alcohol intake and the type of alcohol consumed (high single occasion consumption of strong alcohol by men) together with a confirmed effect of alcohol on serum lipids and insulin resistance might at least partly explain lower rates of MetS among men. It is also possible that this mechanism might also explain the lower metabolic risk in Russian men compared to their Western counterparts. Higher metabolic risk among subjects who abstained from alcohol relative to moderate drinkers, has also been described in longitudinal [34] and cross-sectional [10,35,36] studies. Our results are in line with these findings, suggesting that the pattern of alcohol consumption we found, improves the lipid spectrum by increasing the HDL-C concentration and lowering the low-density lipoprotein cholesterol (LDL-C). Similar results were obtained in another study from Russia where the levels of HDL-C and LDL-C were, respectively, directly and inversely associated with alcohol consumption[37]. Our finding that a consumption of ≥5 AU on occasion is associated with improved glycemic profile, possibly, due to reduction of the insulin resistance, agrees also well with the existing knowledge [29,38].

Low education and low income has been consistently associated with MetS in the US [7,34]. In our study we found no clear effect of these factors. In crude analysis we found slightly lower prevalence of MetS in women with university education and in men with high income. This association disappeared after adjustment. This discrepancy with the findings from other countries may be due to the fact that in Russia the distribution of health outcomes is less strongly linked to socio-economic status compared to the US or the UK. Higher education in Russia does not guarantee high socio-economic status. Moreover, subjects included in the high income category were relatively poor by international standards with an average monthly salary of about 500 USD.

Several studies have reported sedentary life-style as a risk factor for MetS [7,11,12]. We also observed that low leisure-time physical activity was associated with higher prevalence of MetS in both genders, independently of other studied factors.

We observed an inverse association between smoking and MetS (crude analysis), but this association disappeared after adjustment. However, smoking was positively associated with dyslipidemia in both genders and inversely with central adiposity in men. These findings are consistent with previous research suggesting that nicotine increases the energy expenditure, reduces the appetite and stimulates the lipolysis, thus decreasing the

risk for obesity [39]. On the other hand, smoking negatively affects the coronary heart system through elevation of blood pressure and development of arteriosclerosis.

Increased serum levels of GGT, CRP and low AST-to-ALT ratio turned out to be independently associated with high metabolic risk, similarly to what has been observed in previous research[2,24-26]. The association of GGT and CRP with MetS was stronger in women, whereas the effect of AST-to-ALT ratio was more pronounced in men (Model 3, Table 2). Several studies have reported that both GGT and CRP synergistically increase with the risk of both metabolic syndrome and obesity as well as with a high alcohol intake [24,25,40]. The pattern of association of the AST-to-ALT ratio is totally different; the ratio tends to be lower (often ≤1) in obese and subjects with the MetS, and higher (often ≥2) in those with high alcohol consumption [27]. One possible explanation of this gender difference is that the association of BMI with MetS in men was much stronger. Another explanation is that the adjusted effects of AST-to-ALT ratio constitute a proxy of the protective action of alcohol which was not fully reflected by self-report [19]. This effect is not evident for GGT and CRP since they are synergistically related to both MetS and alcohol consumption, but it is apparent for the AST-to-ALT ratio (antagonistic association). This suggests that the gender-dependent strength of association for GGT and CRP levels and the AST-to-ALT ratio with MetS and its individual components underlines the protective effect of alcohol intake on MetS we found in our study.

MetS was associated with an increased risk of stroke-, either stroke or MI-, CVD-and all-cause death during the 9 year follow-up. After adjustment for age and other potential confounders, the risk was still more than 3 times higher for a fatal stroke and more than 2 times higher for death from either stroke or MI among men with MetS. The lack of significant associations between MetS and, CVD-, and, particularly, CHD-death in the adjusted analyses, might be due to heterogeneity of these diagnostic groups. The CHD, for example, included not only diagnoses of fatal myocardial infarction (I21-23) which are clinically well-distinguishable, characterized by progressing atherosclerosis and pathogenetically close to relatively homogenous and clinically well-defined group of cerebral strokes (I60-I64), but also such vaguely defined conditions as "other forms of acute or sub-acute ischemia" (I24) and "chronic ischemic heart disease" (I25). The latest evidences from Russia suggest that alcohol is an important factor implicated in the pathophysiology of the former two causes of death, and that some deaths within these subgroups are actually caused by acute alcohol intoxication[16] or alcoholic cardiomyopathy due to chronic toxic effects of alcohol on the myocardium[41,42]. We suggest that these CHD-subcategories should be included in future longitudinal analyses as separate end-points. However, it will require more statistical power which we lacked in the study. We also emphasize the need for larger population-based studies from Russia to either replicate or refute our results.

Thus, as a cluster of four major CVD risk predictors, MetS represents one of the factors contributing to the high cardiovascular mortality in Russia, but it is unlikely that it plays a central role at present. Following the improvements of living conditions during the last decade, the latest state's anti-alcohol initiatives launched in 2006, and the recent increase in life-expectancy [43], the prevalence of MetS is likely to increase in the nearest future, thereby enhancing the proportion of MetS-mediated cardiovascular and all-cause deaths in Russia.

Conclusion

Age, GGT and C-reactive protein, and AST-to-ALT ratio were associated with MetS in both men and women. High leisure time physical activity in women and moderate frequency of alcohol consumption and binge drinking in men were inversely associated with MetS. Differences between men and women in alcohol consumption may explain gender variation in the MetS prevalence. MetS increased the risk of death from stroke and from either myocardial infarction or stroke during the 9-year follow-up period in men while no associations with mortality were found in women.

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Author details

[1]Institute of Community Medicine, University of Tromsø, Tromsø, Norway. [2]Norwegian Institute of Public Health, Oslo, Norway. [3]International School of Public Health, Northern State Medical University, Arkhangelsk, Russia.

Authors' contributions

OS and ON planned the study and were responsible for collection of data. OS and AG performed data analysis. OS drafted the manuscript, which was further elaborated by AG and ON. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Paper III

Determinants of cardiovascular and all-cause mortality in Northwest Russia: a 10-years follow-up study

Oleg Sidorenkov[1*], Odd Nilssen[1], Andrej M Grjibovski[1-3]

[1]Institute of Community Medicine, University of Tromsø, Tromsø, Norway

[2]Norwegian Institute of Public Health, Oslo, Norway

[3]International School of Public Health, Northern State Medical University, Arkhangelsk, Russia

Email addresses:

OS: Oleg.Sidorenkov@uit.no

ON: Odd.Nilssen@uit.no

AG: Andrei.Grjibovski@fhi.no

* Corresponding author: Institute of Community Medicine, University of Tromsø, postbox 9037, Tromsø, Norway. tel: +47 966 77157, fax +47 776 44831

List of abbreviations and acronyms: CHD-Coronary heart Disease; GGT-gamma gultamyltransferrase, HBA1c-glycohemoglobin, ApoA1 and ApoB-apolipoproteins A1 and B, respectively, BAC-Blood Alcohol Concentration, AUDIT-Alcohol Use Disorders Identification Test, CAGE- CAGE questionnaire

Abstract

PURPOSE: To study the factors associated with high cardiovascular (CVD) and all-cause mortality in Russia.

METHODS: A prospective cohort study of 1966 men and 1738 women aged 18 years or more was performed in Arkhangelsk. The baseline examination was in 1999-2000. An average follow-up was 10.2 years. Information on life-style, marital, educational and psycho-social status was self-reported in a questionnaire. Data on risk factors were collected in a medical examination which included blood sampling.

RESULTS: To the October 2010 a total of 147 male and 95 women deaths occurred. In 59 male and 20 female deaths where diagnosis was made by a forensic pathologist, the autopsy data were studied to extract information on post-mortem Blood Alcohol Concentration (BAC). A positive BAC was found in 21(36%) of male and 6(30%) of female deaths. Women reporting a consumption of 80g alcohol or more at least monthly and a consumption of 5 alcohol units or more on one drinking episode had higher risk of cardiovascular death than abstainers (RR was 5.06 (1.54-16.7) and 3.21 (1.07-9.58), respectively). ApoB/ApoA1-ratio was the strongest predictor of CVD and all-cause death in men (RR 7.62(3.15+18.4) and 4.39(2.22-8.68), respectively) and CVD death in women: RR 3.12 (1.08-8.98). Men with obesity and university education had 40% lower risk of all-cause death. Low serum albumin was associated with high mortality in both genders.

CONCLUSIONS: Hazardous alcohol consumption is an independent risk factor of CVD mortality also in women. The mechanisms behind its damaging effect are yet not clear. Nutritional factors such as serum albumin are important. Further studies are needed.

MeSH heading key words: Russia, mortality, cardiovascular death, alcohol intake, Blood Alcohol Concentration, apolipoproteins, serum albumin, gamma glutamyl tansferrase, C-reactive protein, Body Mass Index

Running title: Predictors of high mortality in Russia

Introduction

Cardiovascular and all-cause mortality in Russia is among the highest in Europe. The age-standardized cardiovascular death rates are higher in all age groups of Russian men and women than the corresponding average estimates for the 27 countries of Western Europe (Eur-A). The difference at working ages is particularly high: a 9-fold in men and a 6-fold in women aged 30-44 years, and 7-fold in men and women aged 45-59 years(1) and explains most of the difference in life expectancy between Russia and other industrialized countries. The total number of deaths exceeded the number of births by almost 1 million in 2000 and by 850.000 in 2005(2)!

There is also a large difference in mortality between men and women in Russia resulting in gender imbalance with a male-to-female ratio of 0.87 (3) which is among the lowest in the world's. The ratio rapidly decreases with age and at the age over 60 years it wa below 0.5 in 2006 (4) while the corresponding ratio for Norway was 0.80 the same year (5). High premature mortality from cardiovascular diseases and external causes among Russian men is the main cause of the large gap in life expectancy between men and women (6). In 2003, life expectancy at birth was 58.6 years for men and 71.8 for women, since then it has increased to, respectively, 62.8 and 74.7 years in 2009(7), although it is still much lower than in Europe.

Contrary to high cardiovascular mortality, population-based studies from Russia have failed to reveal high levels of conventional risk factors, taken either individually

(8;9) or combined as a risk score (10-12). Instead, hazardous alcohol consumption was suggested as the main determinant of high cardiovascular(13) and all-cause mortality(14;15) among Russian men. Other risk factors such as low socio-economic status (16;17), unhealthy lifestyle (18) and psycho-social distress have also been studied (19). It was also suggested that cardiovascular mortality is artificially inflated due to misattribution of alcohol poisonings to cardiovascular deaths(6). However, it was not supported by other studies (13).

Only two longitudinal studies on factors associated with cardiovascular and all-cause mortality had been performed in Russia. The first included only men aged 40-59 years and was performed during the 1980s in Moscow and St. Petersburg (17). The other study included men and women aged 25-64 years and collected data during the 1990s in Western Siberia. Taking into account vast distances, ethnical and cultural heterogeneity of Russia, there is still a need in such longitudinal studies in Russia.

The principal aim of this study is to assess the influence of both conventional and novel risk factors (apolipoproteins, C-reactive protein, GGT, serum albumin and alcohol intake) on cardiovascular and all-cause mortality by gender in a typical Northwestern Russian town.

Methods

This is a prospective cohort study conducted in Arkhangelsk, Northwest Russia. Altogether, 1966 men and 1738 women aged ≥18 years who attended one outpatient

clinic in 1999-2000 comprised the cohort. The response rate was 98.9%. The participants underwent a medical examination, filled in a 6-page questionnaire and had blood tests drawn for laboratory analyses. Extensive details about recruitment and data collection are given elsewhere(11;20).

Marital status was dichotomized as single or married. The former group included also divorced, widowed and cohabiting. Education was divided into 3 categories: secondary school or lower, college (vocational school or incomplete university education) and university. Occasional and daily smokers were classified as smokers, while non-smokers and ex-smokers were coded as non-smokers. By leisure-time physical activity the participants were dichotomized into active, who reported walking or bicycling or yard working at least 4 hours per week, regular training or professional sport and inactive (low physical activity).

Alcohol consumption was described both as a frequency of consumption and volume of alcohol consumed on 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) on one occasion was categorized as abstainers, 1-4 AU and ≥5 AU. One AU was equal to 13.8 g of pure alcohol or 40 ml of vodka, or one 120 ml glass of table wine. Frequency of 6 or more AU consumption (6 AU was equivalent to about 250 ml of vodka) on one drinking session was presented as never (included abstainers), less than once a month and ≥1 time a month. Furthermore, the Alcohol Use Disorder Identification Test (AUDIT) and the CAGE test, respectively,

consisting of 10 (giving a maximum score of 40) and 4 items (a maximum score of four) were used to assess alcohol intake.

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 one represents the worst quality of life; as having low quality of life were considered those subjects who had scored less than 5.

Weight and height were measured with subjects in light clothing and without shoes. A BMI of <25, 25-29.9, and ≥30 kg/m^2 corresponded to normal weight, overweight and obesity, respectively. Diastolic blood pressure (DBP) was measured three times on the right arm in a sitting position. The average of the two last readings was used in the analyses.

Details on measuring total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are described elsewhere (11), as well as for C-reactive protein (CRP), gamma-glutamyltransferase (GGT) and glycohemoglobin (HBA1c) (12). Serum albumin was measured colorimetrically by an automated method using bromcresol green as the indicator on Hitachii-917 analyzer. Apolipoproteins A1and B were assayed by an immunoturbidimetric method with polyclonal sheep anti-human apolipoprotein antibodies (Roche). Analytic coefficient of variation was ≤3% for all laboratory measurements except TC (5%).

The cohort was followed-up until 1 October 2010. The mean duration of follow-up was 10.2 years. The list of participants was annually checked against the regional mortality registry. The last check was performed in November 2010. Underlying cause of death coded according to the International Classification of Diseases, 10th Revision (ICD-10) was retrieved from death certificates. The study end-points were cardiovascular death (I00-99) and death from all causes. Moreover, in cases where diagnosis was made by forensic expert we applied to the Regional Centre of Forensic Expertise where all forensic autopsies in Arkhangelsk are performed. A testing on presence of alcohol and alcohol surrogates with measurement Blood Alcohol Concentration (BAC) is a standard procedure of the forensic autopsies in case of death due to cardiovascular diseases or external causes. The proportion of deceased subjected to forensic autopsy decreases with age. Data on presence of alcohol or alcohol surrogates were extracted from the autopsy records.

Differences between genders by the studied characteristics were studied by unpaired t-tests and Pearson's chi-squared tests for continuous and categorical variables, respectively. Gender-specific relative risks (RR) adjusted first by age (Model 1) and all studied variables (Model 2) for all-cause and cardiovascular death with 95% confidence intervals (CI) were estimated using Cox regression.

The study was approved by the Regional Ethics Committee in Tromsø, Norway, and verbal informed consent was obtained from all participants.

Results

Baseline characteristics of the cohort by gender are presented in Table 1. Men smoked more and had more hazardous pattern of alcohol consumption. Women scored less than men on the AUDIT and CAGE tests. The proportion of single and subjects with university education was higher in women.

The means of TC and glycohemoglobin and prevalence of obesity (BMI≥30) were higher among women.

Altogether, 242 subjects (147 men and 95 women) died during a 10-year follow-up by October 2010 (Table 2). Deaths from cardiovascular diseases constituted the majority in men (n=77(52.4%) and women (n=52(54.7%). Among all cardiovascular deaths Coronary Heart Disease (CHD; ICD-10 codes I20-25) accounted for 69% (53 deaths) in men and 48% (25 deaths) in women. Deaths from myocardial infarction (ICD-10: I21-23) constituted only 21% (11 deaths) and 28% (7 deaths), respectively, in men and women of all CHD-deaths. Fifteen men and women died from cerebral stroke, constituting, respectively, 19.5% and 28.8% of all cardiovascular deaths. The mean age of cardiovascular death was 63.4 years (SD 13.5) for men compared to 70.0 (12.2) for women.

Malignancies accounted for the next largest group of decedents. The most frequent cancer localizations in men were lung (9 deaths) and esophagus/stomach (8 deaths). The most frequent form in women was *cancer coli* (6 deaths). Mean age for men in this group was 58.5 (11.9) years, and for women 61.2 (12.3) years.

The group of “external causes” refers to accidents and suicides/homicides. Men-to-women ratio in this group was 3.5:1. The majority of deaths occurred at the age of less than 50 years. All four deaths in subcategory including suicides and homicides in men

were suicides, whereas two of three female deaths in this group were due to violence (homicide). The mean age of death was the lowest in the group of external causes for both genders when compared with other groups. It was 46.3 (13.2) and 30.0 (10.2) years, respectively, for men and women.

Cardiovascular mortality

Lower levels of serum albumin, HDL-cholesterol, higher CRP levels, LDL/HDL-and ApoB/ApoA1-ratios, DBP≥90 mmHg were associated with increased risk of cardiovascular death among men (Table 3). Self-reported consumption of 1-4 AU on one occasion and frequency of alcohol consumption of once a month or less were associated with almost double risk of death compared to abstainers among men.

The pattern of association for alcohol-related variables differed between genders. Women who reported consumption of 5 AU or more at one drinking session and taking 80g of alcohol once a month or more, had, respectively, 3 and 5 times the risk of cardiovascular death of abstainers. An average increase in one score on the scale of AUDIT increased risk of cardiovascular death by 26% ($p \leq 0.001$); the corresponding risk estimate for CAGE was higher (RR 2.46 per increase in one score, $p \leq 0.001$). An increase in ApoB/ApoA1-ratio by 1 was associated with a 3-fold increase in risk.

All-cause mortality

In men, university education was associated with 40% lower risk of all-cause death. High CRP levels, DBP≥90 mmHg, high LDL/HDL-and ApoB/ApoA1-ratio were associated with increased all-cause mortality in men (Table 4). A higher risk of death from all causes was found in men and women with low levels of albumin and HDL-C.

Among women, age-adjusted all-cause mortality was higher in women with high levels of GGT.

One of the major findings was that the risk of all-cause death in obese men was lower than in normal-weight men.

Forensic examinations

Of 242 death certificates 42 (17.4%) were filled-up by a hospital pathologist and 79 (32.6%) by a forensic pathologist. More men than women were subjected to forensic autopsy (ratio 3:1). Positive BAC or presence of surrogates (3 cases) was found in 27 cases (Table 5). Of 7 alcohol-positive cases among men who died from external causes 6 were due to fatal intoxication with alcohol or its surrogates. In 3 cases BAC ≥5.0‰ was found, in other 3 cases alcohol surrogates were revealed.

In the majority of alcohol-positive cardiovascular deaths BAC was less than 1‰ (11 deaths from CHD: I20-25). A BAC of 2.97‰ and 2.26‰ was recorded for two male deaths, respectively, from ruptured aortic aneurism (I71.1) and unspecified cardiomyopathy (I42.9). Of 4 BAC-positive deaths from "other diseases" two were alcohol-related; acute pancreatitis (K85) and alcoholic liver cirrhosis (K70.3). Other two were death from pneumonia (J18.1) and a case were cause wasn't identified (R98).

Discussion

Main findings

This was the first cohort study from Russia where a significant dose-response association between hazardous alcohol consumption and the risk of cardiovascular death was found in women. A consumption of 80g alcohol (250ml vodka) or more at least

monthly was associated with a 5-fold increased risk of cardiovascular death compared to the reference group. Binge drinking (a consumption of ≥5 AU on occasion) was associated with a 3-fold risk compared to abstainers. A positive answer on one item of the AUDIT and the CAGE questionnaires, in average, respectively, increased the risk of cardiovascular death by 1.26 and 2.45 times.

In men, university education and obesity (BMI≥30 kg/m^2) were associated with 40% lower risk of death from all causes. The presence of arterial hypertension was associated with a 1.75-fold risk of death from cardiovascular diseases and all causes in men. Low levels of serum albumin in both genders and the high LDL/HDL and ApoB/ApoA1 ratio in men strongly predicted the 10-year mortality from cardiovascular diseases and all causes. Low serum levels of HDL-C were associated with higher all-cause (both genders) and cardiovascular mortality (in men).

Limitations

The study had several limitations. The first one was the young age and relatively small size of the cohort. Only 638 (32.5%) men and 626 (36.0%) women were 50 years or more at the beginning of follow-up which resulted in loss of statistical power. Loss to follow-up is another weakness. We used the regional person-sensitive mortality statistics based on official death certificates for death registration to identify the deceased, since no national personalized mortality registry available for research exists in Russia. Therefore, we were unable to trace the participants who moved from the Arkhangelsk region during the follow-up. Hence, those who died outside the region were not registered as the "case". Although, this problem is likely common for all longitudinal studies from Russia using the same source of mortality data (16;21;22). If the rate of out-migration from the cohort

was the same as ifrom the Arkhangelsk region (4;23), estimated annual loss to follow-up would be between 2% in 1999, 1.2% in 2005 and 2009, constituting, in average, around 15-17.5% loss during the 10-year observation period. The probability of migration was higher among young people (≤30 years), in the age-groups were cardiovascular mortality was the lowest. The third limitation was that unemployed and marginalized individuals such as alcohol abusers and homeless were underrepresented in the cohort. All three limitations weakened the observed associations and resulted in underestimation of RR.

CVD-death and alcohol

The few epidemiological studies of alcohol and cardiovascular and all-cause death were mainly performed in middle-aged men(13;17;22). The only longitudinal study which included women was undertaken in 1980s. It studied effects of conventional risk factors and disregarded exposure to alcohol(24). The only large study where effects of alcohol consumption on mortality were assessed in women had obvious methodological limitations: a case-control design, the crude measurement of exposure to alcohol (in bottles of vodka consumed per week), a high probability of recall bias (data were collected 8-9 years after death from a proxy-respondent), low response rate of 25% and a questionable selection of the reference group(15). This study found a significant dose-dependent association of alcohol drinking with death from CHD and stroke. However, its results are not directly comparable with ours due to different measurement of alcohol consumption.

Why no significant effect of hazardous drinking was demonstrated among men in our study? The majority of male and only few female participants were active workers employed in wealthy sea-fishing industry with a relatively high salary. They were

recruited during the obligatory medical check-up organized in the see-men out-patient clinic. Although very few men were not willing to participate, it is likely that many of them distrusted our reassurances that the collected data will be confidential and unavailable to the employer. To avoid possible conflict with employer some of them could underreport estimates of alcohol consumption. This hypothesis finds its explanation in the data; men reporting frequency of alcohol consumption once a month or less and a consumption of 1-4 AU on one occasion had almost 2-fold and 1.5-fold increased risk of cardiovascular death and all-cause death, respectively, compared to abstainers. Higher proportion of men than women (14.3% vs. 6.3%) had positive result of alcohol test at forensic autopsy.

BMI and all-cause mortality in men

Our finding that obesity (BMI≥30) was inversely related to 10-year all-cause mortality among Russian men was unexpected. Only one study from Russia investigated the risks of cardiovascular and all-cause death associated with BMI (25). It included only men and found no association with all-cause mortality. The same cohort study unexpectedly found an increased risk of death from CHD among Russian middle-aged men with lowest levels of TC and LDL-C(26). This association was present only among men having the lowest educational level. The authors have also reported a higher age-adjusted cardiovascular and all-cause mortality (Visit2) among men with higher levels of HDL-C. Men with the lowest levels of TC and LDL-C had also higher HDL-C, consumed more alcohol and had lower mean BMI(21). The authors suggested that other factors (among them educational status) might modify association between serum lipids and mortality. In our study BMI was unequally distributed across the strata of education

and marital status in men. The lowest BMI was found among unmarried men and men with secondary professional education. In our study BMI was strongly associated with lipid status: the mean LDL/HDL- and ApoB/ApoA1-ratio significantly ($p<0.03$) increased across the BMI levels in both genders. Inclusion of ApoB/ApoA1- and, in less degree, LDL/HDL-ratio in the regression has strengthened the inverse association between BMI and mortality.

A strong positive association of ApoA1 concentration with frequency and volume of alcohol consumption has earlier been described in our study(27) and was in line with the results from studies on Western populations(28;29). It is possible that the ApoB/ApoA1-ratio being included into the regression might not only be a factor reflecting lipid status but also the factor revealing residual confounding effects of alcohol consumption underestimated by self-report. Hence, obesity and education are likely the markers of a social group having the life-style, which is inversely associated with the risk of all-cause death. The life-style characterized by higher ApoB/ApoA1-ratio and lower alcohol consumption.

Serum lipids and mortality

Of five variables describing lipid status: TC, HDL-C, TG, ApoB/ApoA1- and LDL/HDL-ratio only ApoB/ApoA1-ratio predicted cardiovascular death in both genders. Remarkably, the positive association of ApoB/ApoA1-ratio with cardiovascular and all-cause mortality was considerably stronger among men, in whom the ratio was the strongest predictor of 10-year risk of death among all other factors included in the regression. The lipid-transporting apolipoproteins: ApoB, transporting proatherogenic VLDL and LDL particles, and ApoA1, transporting antiatherogenic HDL particles are

relatively newly established risk factors for cardiovascular disease(30). The ApoB/ApoA1 ratio is a sensitive indicator of cholesterol balance directly related to cardiovascular risk, i.e. the lower the ratio, the lower the risk.

After inclusion of ApoB/ApoA1-ratio in the regression model together with total cholesterol in men the latter became negatively associated with 10-year risk of cardiovascular death. A positive association of low TC levels with risk of death from coronary heart disease has earlier been reported in a Russian cohort study undertaken in 1980s(26). Hence, one may conclude that same forces increasing cardiovascular mortality are still present and influent in the Russian population in our days.

Another sensitive marker of lipid status - LDL/HDL-ratio was also directly associated with the 10-risk of cardiovascular and all-cause death but only in men. This finding was is in line with the results of others(31). The strength of the association was lower than that for ApoB/ApoA1-ratio.

One may question why pattern of association of serum lipids with mortality was so different in men and women. One explanation may lay in an effect-modification by life-style, primarily, alcohol habits. Both ApoB/ApoA1- and LDL/HDL-ratio have in their denominators factors which levels increase with drinking(27-29). To answer these questions, a new large population-based study is needed since ours had limited power.

Nutritional status and mortality

Levels of serum albumin represent a sensitive indicator of nutritional status and morbidity. In our study lower albumin levels at baseline were associated with higher cardiovascular and all-cause mortality in men and women confirming thereby importance

of nutritional factors in the mortality epidemic in Russia. The direction and the strength of the association were comparable with those reported in the literature(32;33).

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Table 1 Baseline characteristics of men and women in the study cohort

Factors	Men	Women	P[1]
	Number,%	Number,%	
Age, years			<0.001
18-29	524 (26.7)	375 (21.6)	
30-39	357 (18.2)	317 (18.2)	
40-49	447 (22.7)	420 (24.2)	
50-59	308 (15.7)	305 (17.5)	
60+	330 (16.7)	321 (18.4)	
Marital status			<0.001
Single	655 (33.3)	807 (46.4)	
Married	1311 (66.7)	931 (53.6)	
Education			<0.001
Secondary school	443 (22.5)	452 (26.0)	
College	1201 (61.1)	834 (48.0)	
University	322 (16.4)	452 (26.0)	
Current smoking	1114 (56.7)	370 (21.3)	<0.001
Sedentary lifestyle	452 (23.0)	695 (40.0)	<0.001
Frequency of alcohol intake			<0.001
Abstainers	240 (12.2)	471 (27.1)	
Once a month or less	442 (22.5)	580 (33.4)	
2-4 times a month	1001 (50.9)	599 (34.5)	
≥5 times a month	283 (14.4)	88 (5.1)	
Number of AU[2] on one occasion			<0.001
Abstainers	236 (12.0)	469 (27.0)	
1-4 AU	792 (40.3)	1009(58.1)	
≥5 AU	938 (47.7)	260 (15.0)	
Take ≥80g alcohol on occasion			<0.001
Never	594 (30.2)	1163(66.9)	
Less than once/month	467 (23.8)	355 (20.4)	
≥1 times a month	905 (46.0)	220 (12.7)	
AUDIT score, mean (SD)	6.63 (5.19)	2.88 (3.47)	<0.001
CAGE score, mean (SD)	0.67 (0.99)	0.31 (0.68)	<0.001
Depression	210 (10.7)	586 (33.7)	<0.001
Sleeping problems	221 (11.2)	606 (34.9)	<0.001
Quality of life	5.78 (1.76)	5.28 (1.84)	<0.001
BMI			<0.001
<25	974 (49.5)	799 (46.0)	
25-29.9	725 (36.9)	544 (31.3)	
≥30	267 (13.6)	395 (22.7)	
DBP ≥90 mmHg, %	315 (16.0)	249 (14.3)	0.16
Self-reported MI/stroke,%	59 (3)	53 (3)	1.0
HBA1c, %, mean (SD)[3]	4.92 (0.53)	4.98 (0.61)	0.002
TC, mmol/l, mean (SD)	4.98 (1.18)	5.16 (1.24)	<0.001
HDL-C, mmol/l, mean (SD)	1.27 (0.36)	1.38 (0.35)	<0.001
TG, mmol/l, mean (SD)	1.38 (0.91)	1.28 (0.76)	<0.001
LDL/HDL ratio	2.62 (1.17)	2.52 (1.25)	0.007
ApoB/ApoA ratio	0.68 (0.21)	0.62 (0.21)	<0.001
GGT, U/L, mean (SD)	43.8 (60.6)	28.3 (38.9)	<0.001
CRP, mg/l, mean (SD)	3.20 (9.04)	2.72 (5.8)	0.06
Albumin, g/l, mean (SD)	44.2 (3.0)	42.4 (2.95)	<0.001
Total	1966	1738	

[1] Calculated by Pearson's chi-squared test and Independent sample T-test
[2] One Alcohol Unit (AU) is equivalent to 13.8 grams of pure ethanol
[3] HBA1c (glycohemoglobin) was measured in 1919 men and 1640 women

Table 2 Mortality in the cohort in absolute numbers by cause, gender and age during the 10-year follow-up

Cause of death (ICD-10 codes)	Age, years	Men (N)	Women (N)
All external causes	<50	12	5
V01-Y98	≥50	9	1
Suicides/ homicides	<50	2	2
X6n-Y3n	≥50	2	1
Cardiovascular diseases	<50	12	6
I00-I99	≥50	65	46
Malignancies	<50	6	4
C00-C97	≥50	28	20
Other causes[1]	<50	5	2(3)
	≥50	6 (10)	7 (10)
Total	All	147	95

[1] In brackets given together with deaths were cause is unknown

Table 3 Relative Risks of death from cardiovascular diseases by social, life-style, psycho-social stress indicators and other risk factors

	Men		Women	
	Model 1[1]	**Model 2**	**Model 1**[1]	**Model 2**
Married (yes vs. no)	0.90 (0.54-1.50)	0.75 (0.44-1.29)	0.53 (0.26-1.11)	0.57 (0.27-1.19)
Education				
Secondary school	Reference	Reference	Reference	Reference
College	1.07 (0.64-1.79)	1.23 (0.72-2.08)	1.03 (0.52-2.04)	1.19 (0.57-2.50)
University	0.75 (0.37-1.52)	0.78 (0.38-1.61)	1.01 (0.41-2.51)	1.34 (0.53-3.39)
Smoking (yes vs. no)	0.91 (0.57-1.46)	1.03 (0.62-1.71)	1.13 (0.26-5.01)	0.65 (0.14-2.96)
Low physical activity	1.29 (0.82-2.07)	1.17 (0.71-1.92)	1.82 (0.88-3.74)	1.65 (0.78-3.48)
Frequency of alcohol intake[3]				
Abstainers	Reference	Reference	Reference	Reference
≤1 times a month	1.64 (0.89-3.03)	2.04 (1.09-3.84)*	1.09 (0.48-2.50)	1.18 (0.52-2.71)
2-4 times a month	1.17 (0.61-2.24)	1.45 (0.75-2.80)	1.59 (0.63-4.02)	1.61 (0.64-4.08)
≥5 times a month	0.80 (0.26-2.46)	1.06 (0.34-3.30)	2.65 (0.33-20.96)	3.76 (0.42-33.5)
Number of AU on one occasion[3]				
Abstainers	Reference	Reference	Reference	Reference
1-4 AU	1.55 (0.86-2.82)	1.92 (1.04-3.55)*	1.07 (0.50-2.30)	1.12 (0.52-2.41)
≥ 5 AU	1.07 (0.55-2.09)	1.33 (0.67-2.63)	2.90 (1.01-8.35)*	3.21 (1.07-9.58)*
Take ≥80g alcohol on occasion				
Never	Reference	Reference	Reference	Reference
Less than once/month	0.91 (0.49-1.70)	1.10 (0.58-2.08)	2.67 (0.96-7.39)	3.33 (1.16-9.59)*
≥1 times a month	0.85 (0.48-1.50)	0.96 (0.53-1.75)	4.17 (1.35-12.9)§	5.06 (1.54-16.7)§
AUDIT score[3]	1.01 (0.96-1.06)	1.02 (0.98-1.08)	1.20 (1.10-1.30)‡	1.26 (1.14-1.40)‡
CAGE score[3]	1.21 (0.96-1.52)	1.24 (0.99-1.54)	2.28 (1.36-3.84)§	2.46 (1.44-4.19)‡
Depression	0.79 (0.42-1.50)	0.70 (0.36-1.37)	1.35 (0.78-2.34)	1.11 (0.62-1.97)
Sleeping problems	0.84 (0.48-1.47)	0.69 (0.37-1.30)	1.08 (0.60-1.95)	0.91 (0.49-1.69)
Low quality of life	1.41 (0.88-2.26)	1.29 (0.78-2.12)	1.90 (1.03-3.50)*	1.71 (0.87-3.35)
BMI				
<25	Reference	Reference	Reference	Reference
25-29.9	0.96 (0.58-1.59)	0.73 (0.44-1.21)	1.02 (0.51-2.03)	0.89 (0.44-1.80)
≥30	1.34 (0.72-2.51)	0.62 (0.30-1.26)	1.40 (0.72-2.74)	1.54 (0.74-3.21)
DBP ≥90 mmHg	1.45 (0.91-2.32)	1.75 (1.09-2.89)*	0.67 (0.34-1.30)	0.63 (0.32-1.28)
Log GGT	1.51 (0.74-3.10)	1.07 (0.50-2.29)	1.90 (0.90-4.01)	1.29 (0.58-2.87)
Log CRP	1.73 (1.14-2.62)§	1.51 (0.94-2.42)	1.27 (0.70-2.31)	1.22 (0.60-2.48)
Albumin	0.93 (0.88-0.99)*	0.93 (0.88-0.98)*	0.89 (0.83-0.95)‡	0.93 (0.86-1.01)
Total cholesterol[4]	1.03 (0.85-1.25)	0.98 (0.81-1.19)	1.05 (0.85-1.30)	1.07 (0.86-1.32)
HDL-C[4]	0.36 (0.17-0.75)§	0.37 (0.18-0.77)§	0.49 (0.20-1.16)	0.45 (0.17-1.17)
Triglycerides[4]	1.02 (0.81-1.29)	0.94 (0.73-1.23)	1.31 (0.99-1.91)	1.25 (0.92-1.71)
LDL/HDL[4]	1.29 (1.11-1.52)§	1.26 (1.06-1.49)§	1.10 (0.92-1.32)	1.16 (0.95-1.41)
ApoB/ApoA1	8.53 (3.79-19.2)‡	7.62 (3.15-18.4)‡	3.08 (1.06-8.93)*	3.12 (1.08-8.98)§

[1] Model 1 adjusted for age; Model 2 adjusted for age, education, smoking, frequency of taking ≥80g alcohol on occasion, physical activity, DBP, ApoB/ApoA1 ratio, BMI, history of CVD

[2] P-value corresponding to * p≤0.05; § p≤0.01; ‡ p≤0.001

[3] Adjusted for the same covariates as in Model 2, except frequency of taking ≥80g alcohol on occasion

[4] Adjusted for the same covariates as in Model 2, except ApoB/ApoA1 ratio

Table 4 Relative Risks of death from all causes by social, life-style, psycho-social stress indicators and other risk factors

Risk factors	Men		Women	
	Model 1[1]	Model 2	Model 1[1]	Model 2
Married (yes vs. no)	1.00 (0.69-1.46)	1.02 (0.68-1.52)	0.65 (0.41-1.04)	0.70 (0.44-1.14)
Education				
Secondary school	Reference	Reference	Reference	Reference
College	0.88 (0.61-1.28)	0.97 (0.66-1.42)	0.75 (0.45-1.26)	0.81 (0.47-1.38)
University	0.54 (0.32-0.92)*	0.58 (0.33-1.0)*	0.78 (0.42.1.44)	0.84 (0.45-1.58)
Smoking (yes vs. no)	1.25 (0.90-1.74)	1.28 (0.89-1.83)	0.80 (0.31-2.06)	0.62 (0.23-1.63)
Low physical activity	1.22 (0.86-1.72)	1.13 (0.79-1.62)	1.32 (0.84-2.11)	1.27 (0.79-2.05)
Frequency of alcohol intake[3]				
Abstainers	Reference	Reference	Reference	Reference
≤1 times a month	1.30 (0.81-2.08)	1.56 (0.96-2.54)	0.79 (0.44-1.41)	0.82 (0.46-1.47)
2-4 times a month	1.14 (0.71-1.82)	1.44 (0.89-2.34)	1.07 (0.56-2.06)	1.10 (0.57-2.18)
≥5 times a month	0.98 (0.49-1.97)	1.18 (0.57-2.45)	1.33 (0.31-5.80)	1.51 (0.33-6.78)
Number of AU on one occasion[3]				
Abstainers	Reference	Reference	Reference	Reference
1-4 AU	1.23 (0.78-1.94)	1.53 (0.96-2.45)	0.84 (0.49-1.42)	0.86 (0.50-1.46)
≥ 5 AU	1.12 (0.70-1.78)	1.35 (0.83-2.22)	1.28 (0.56-2.93)	1.35 (0.59-3.12)
Take ≥80g alcohol on occasion				
Never	Reference	Reference	Reference	Reference
Less than once/month	0.84 (0.53.1.33)	0.93 (0.58-1.49)	1.58 (0.80-3.15)	1.66 (0.83-3.35)
≥1 times a month	1.02 (0.69-1.51)	1.05 (0.70-1.57)	1.31 (0.51-3.40)	1.37 (0.52-3.60)
AUDIT score[3]	1.02 (0.99-1.06)	1.03 (0.99-1.06)	1.06 (0.98-1.15)	1.08 (0.98-1.18)
CAGE score[3]	1.14 (0.97-1.34)	1.16 (0.99-1.36)	1.39 (0.92-2.10)	1.42 (0.94-2.16)
Depression	0.87 (0.54-1.38)	0.77 (0.48-1.25)	1.14 (0.76-1.72)	1.01 (0.66-1.54)
Sleeping problems	1.00 (0.67-1.51)	0.86 (0.55-1.35)	1.07 (0.69-1.64)	0.95 (0.61-1.48)
Low quality of life	1.28 (0.90-1.82)	1.17 (0.81-1.70)	1.46 (0.95-2.25)	1.29 (0.82-2.04)
BMI				
<25	Reference	Reference	Reference	Reference
25-29.9	0.89 (0.63-1.26)	0.78 (0.54-1.12)	0.81 (0.50-1.31)	0.76 (0.46-1.24)
≥30	0.85 (0.52-1.40)	0.56 (0.32-0.96)*	0.96 (0.59-1.57)	1.01 (0.59-1.73)
DBP ≥90 mmHg	1.47 (1.04-2.08)*	1.75 (1.23-2.49)§	0.87 (0.55-1.39)	0.83 (0.51-1.35)
Log GGT	1.59 (0.95-2.51)	1.23 (0.72-2.09)	2.03 (1.13-3.67)*	1.67 (0.92-3.04)
Log CRP	1.54 (1.12-2.10)§	1.40 (1.0-1.97)*	1.38 (0.89-2.15)	1.57 (0.96-2.57)
Albumin	0.95 (0.91-1.0)	0.94 (0.90-0.99)*	0.90 (0.85-0.94)	0.91 (0.86-0.96)‡
Total cholesterol	1.02 (0.89-1.18)	1.02 (0.88-1.17)	0.93 (0.79-1.10)	0.96 (0.82-1.13)
HDL-C[4]	0.64 (0.40-1.04)	0.58 (0.35-0.95)*	0.54 (0.29-1.01)*	0.52 (0.27-1.00)*
Triglycerides[4]	1.02 (0.86-1.20)	1.02 (0.85-1.22)	1.12 (0.89-1.41)	1.11 (0.87-1.42)
LDL/HDL[4]	1.16 (1.02-1.31)*	1.18 (1.03-1.34)*	1.05 (0.91-1.21)	1.09 (0.94-1.26)
ApoB/ApoA1	4.17 (2.17-8.0)‡	4.39 (2.22-8.68)‡	1.52 (0.63-3.66)	1.98 (0.81-4.80)

[1] Model 1 adjusted for age; Model 2 adjusted for age, education, smoking, frequency of taking ≥80g alcohol on occasion, physical activity, DBP, ApoB/ApoA1 ratio, BMI, history of CVD

[2] P-value corresponding to * p≤0.05; § p≤0.01; ‡ p≤0.001

[3] Adjusted for the same covariates as in Model 2, except frequency of taking ≥80g alcohol on occasion

[4] Adjusted for the same covariates as in Model 2, except ApoB/ApoA1 ratio

Table 5 Distribution of 27 forensic autopsy cases were positive BAC or alcohol surrogates were identified by gender and diagnosis

Cause of death	Alcohol status	Gender	
		Men	Women
CVD	Nr autopsies	29	7
V01-Y98	N (%) with alcohol	10(34.5)	4 (57.1)
External causes	Nr autopsies	19	6
I00-I99	N (%) with alcohol	7 (36.8)	2 (33.3)
Cancer	Nr autopsies	6	6
C00-C97	N (%) with alcohol	0 (0)	0 (0)
Other diseases	Nr autopsies	5	1
	N (%) with alcohol	4 (80)	0 (0)
All deaths	Nr autopsies	59	20
	N (%) with alcohol	21(35.6)	6 (30.0)

Paper IV

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

Oleg Sidorenkov[1*], Odd Nilssen[1], Evert Nieboer [1,2], Nikolay Kleshchinov[3], Andrej M Grjibovski[1,4,5]

[1]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway

[2] Department of Biochemistry and Biomedical Sciences, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

[3] Medical Informational Analytic Center, Ministry of Health and Social Development of the Arkhangelsk Region, Arkhangelsk, Russia

[4] International School of Public Health, Northern State Medical University, Arkhangelsk, Russia

[5] Department of Infectious Diseases Epidemiology, Norwegian Institute of Public Health, Oslo, Norway

Corresponding author:

Oleg Sidorenkov
Department of Community Medicine,
Faculty of Health Sciences,
University of Tromsø,
Postbox 9037 Tromsø,
Norway

Abstract

Background: High CVD mortality among the middle-aged is a major cause of low life expectancy in Russia, especially among men. Hazardous alcohol consumption is suspected to be a powerful factor.

Methods: All men (1099) and women (519) who died between 01.01.08 and 31.08.09 from cardiovascular disease at ages of 30-70 years in the city of Arkhangelsk, Northwest Russia, were included. CVD mortality was stratified by age, gender and diagnosis. For the cases diagnosed by forensic pathologists, the blood alcohol concentration (BAC) was determined. The forensic autopsy rate was 72% for men and 62% for women.

Results: The age-standardized CVD mortality rate (all age groups) in men was higher than in women. The largest male-to-female ratio (4.3) was observed in the age-group 50-59. Alcoholic and unspecified cardiomyopathies were the most dominant CVD mortalities in women, and second in men under fifty; they accounted for 50% and 25% of deaths, respectively. About one third of men and women who died from CVD under 60 had consumed alcohol shortly before death. This occurred most frequently among the diagnostic groups: “other acute or subacute cardiac ischemia”, “atherosclerotic heart disease” and “cardiomyopathies”. Alcohol was more likely to be found at autopsy in men than women (OR 1.55; 95% CI 1.14-2.10). No such difference was found for those who died from myocardial infarction, cerebrovascular diseases and cardiomyopathies. Less than 1% of the deceased had a BAC of 4g/l or higher.

Conclusions:

Alcohol consumption before death is an important correlate of premature CVD mortality in Northwest Russia, particularly among 50-59 year-old men. The largest gender difference in mortality, highest absolute number of premature CVD deaths, and the highest proportion of alcohol-positive autopsies occurred among them. Associations with alcohol consumption considerably vary between the types of CVD diagnoses, and this should be taken into account when planning future research. Our study does not support the hypothesis that a substantial number of cardiovascular deaths are misclassified cases of acute alcohol poisoning.

Introduction

The mortality rate from cardiovascular diseases (CVD) in Russia is one of the highest in the world (1), and has been increasing since the late 1980s to 2005.(2) High levels of CVD mortality result from both high incidence of cardiovascular events and high case fatality.(3-5) However, the few population-based studies conducted in Russia have failed to demonstrate the concurrent presence of high levels of the major cardiovascular risk factors. (4;6-8) Indeed, population cardiovascular risk scores based on the conventional cardiovascular risk factors have been found repeatedly to be lower among Russians than in other European populations.(6;7). Moreover, mortality from coronary heart disease (CHD) and stroke appear to have increased in spite of a decrease in the prevalences of the major risk factor during the 1990s.(6;9) In our earlier study, we observed that hazardous alcohol consumption was associated with favorable lipid and glycemic profiles.(10) It has also been suggested that a substantial fraction of deaths attributed to cardiovascular disease could represent misclassified deaths from acute alcohol poisonings.(11)

Consumption of large amounts of spirits in a single drinking episode is widely prevalent in Russia, primarily among middle-aged men.(12-14) This drinking pattern has been shown to increase the risk of CHD(15) by way of underlying myocardial dysfunction with increased propensity to cardiac arrhythmias and diminished myocardial contractility, increased clotting tendency, and transient increase of blood pressure.(16;17) Most of the current evidence for the association between high cardiovascular mortality in Russia and hazardous alcohol consumption originates from research based on combined population-level data(18-21). Further research using a single cohort with information on the individual level is therefore warranted.

The only large individual-level longitudinal study conducted in Russia in the past 20 years was one from Novosibirsk, which failed to explain high cardiovascular mortality by hazardous alcohol consumption.(22) By contrast two large case-control studies, which were based on interviews of proxy respondents for those who died from CVD, have reported considerably higher prevalence estimates of hazardous drinking and associated

risks.(23;24) Methodological challenges in Russia (25) associated with epidemiological research on this issue, combined with a lack of individual-level data and inconsistencies between the few published studies on the topic, suggest a need for additional types of input data (e.g., autopsy reports).(11;26)

Based on autopsy reports, the study by Zaridze et al. from Barnaul in Russia (11) found high (4g/l or higher) postmortem blood alcohol concentrations (BACs) in a high proportion of deaths among several types of cardiovascular causes. The authors suggested that high cardiovascular mortality could be overinflated due to considerable misattribution of fatal alcohol poisonings to cardiovascular deaths. By contrast and based on a study in Izhevsk, Russia (26), Leon et al. argue that the observed correlation between alcohol and mortality from CVD at the population-level remains nearly unchanged even after elimination of the potentially misclassified deaths. In addition, the percentage of deaths from cardiovascular disease with high BACs in Izhevsk was considerably lower than in Barnaul.

Given the lack of agreement between the mentioned studies, a further autopsy-based evaluation in another part of Russia is warranted. Moreover, there have been no studies on this topic using post-2005 data that would reflect the established decrease in cardiovascular mortality in Russia.(2)

The primary aim of the study is to determine to what extent alcohol consumption before death contributes to premature cardiovascular mortality, and how this contribution varies by age, gender and the diagnosis of cardiovascular death. A secondary aim is to use data on postmortem forensic autopsy examinations in an evaluation of the potential of misclassifying alcohol poisoning as cardiovascular death in Arkhangelsk during 2008-09.

Material and methods

Setting

The data were collected in the city of Arkhangelsk, Northwest of Russia. The population of Arkhangelsk was 354,700 in 2009, with typical Russian age and gender distributions. The mortality by age, gender and cause of death in Arkhangelsk (Table 1) was also similar to the national data.(27;28)

Death certificate

When an individual dies, a medical death certificate containing data on immediate, intermediate and underlying cause of death with the corresponding ICD-10 codes is issued. The regional and national mortality statistics is based on the underlying causes. The diagnosis in the medical death certificate may come from three different sources: forensic pathologist, hospital pathologist and other physicians. Only forensic pathologists routinely measure alcohol concentration in fluids and tissues of the deceased.

The proportion of diagnoses reported on death certificates based on forensic autopsy reports is higher in Russia than in Western European countries. In Norway, it was about 8.3% in 2005 (29), compared to 37% in Arkhangelsk.(28) The latter is congruent with other Russian studies from the 1990s.(11;30) Since 2008, forensic autopsy has become routine for all out-of-hospital deaths in Arkhangelsk, and the proportion of death certificates issued by forensic pathologists reached 69% in 2009.

Study population

All men (1099) and women (519) who died from cardiovascular disease (ICD-10 codes I00-99) at and between ages 30 to 70 years in Arkhangelsk in the period 1.01.2008 to 31.08.2009 constituted the target population. The subjects were identified through the Arkhangelsk Regional mortality register of the Regional Ministry of Health. For 1120 (69.2%) of the cases, diagnosis was based on the results of autopsies performed by forensic pathologists, and 448 (27.7%) by hospital pathologists. Only the former group was included in the calculation of odds ratios. Data on causes of death and presence of alcohol

in blood and tissues were extracted from the reports of the Regional Centre of Forensic Expertise where all forensic autopsies in Arkhangelsk are performed.

Forensic examination and measurement of alcohol concentration

All sudden deaths, cases with an unclear diagnosis (includes virtually all premature out-of-hospital deaths), and those in which violence is suspected are routinely subjected to forensic examination. A summary for Arkhangelsk of all autopsies carried out during the study period are provided in Table 1. The proportion of forensic autopsies of cardiovascular deaths decreases with age and is higher for men. Measurement of alcohol concentrations in body fluids and tissues is a routine component of forensic examinations in cases of premature deaths (under age 70). Alcohol concentrations are measured by gas chromatography(31) in blood and urine and, if not detected there, in the stomach's contents and sometimes in tissue specimens (muscle, kidney, lung, liver or brain).(32) Concentrations are registered in g/l, with a detection limit of 0.0001g/l. Forensic autopsies in Arkhangelsk are in most cases preformed within 24-48 hours after death.

Absolute numbers and percentages of deaths in which alcohol was detected at forensic autopsies are reported as well as the BACs. Cases with a positive BAC and those for whom alcohol wasn't found in the blood but detected in other fluids and tissues (mostly in urine and stomach contents; a total of 40) were counted.

We stratified BACs as follows: <0.5g/l (insignificant intoxication); 0.5-2.49g/l (slight to moderate); 2.5-3.99g/l (severe); and ≥4.0g/l (potentially lethal)(33). These categories were also chosen to ensure comparability with the findings from other studies.(11;26;30)
In general, this stratification corresponds to the official one accepted in the Russian forensic system (34), which classifies a BAC of 0.5-2.5 g/l as slight to moderate intoxication, 2.5-3.0 as severe, 3.0-5.0 as heavy and potentially lethal and 5.0-6.0 as lethal poisoning.

Statistical analyses

The mortality rates by cause (Table 1) were age-standardized to the world standard population. Odds Ratios (OR) and p-values for the probability of being identified with any alcohol concentration at autopsy by gender and death diagnosis were calculated using Mantel-Haenszel methods.

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

Results

Cardiovascular diseases in Arkhangelsk were the main cause of death at ages under 70, and were responsible for about 35% of all deaths in men and women in this age-group (Table 1). Both the absolute number of cardiovascular deaths and the age-standardized rates in men were more than twice as high as in women. The largest gender ratio in cardiovascular mortality rate (4.3) was observed for the 50-59 age-group.

CHD, cerebrovascular diseases and cardiomyopathies were the three main causes of premature cardiovascular mortality across all three age strata comprising, respectively: 62.5%, 21.5% and 9.8% in men (Table 2); and 51.4%, 25.2% and 14.5% in women (Table 3).

Deaths from myocardial infarction in the total sample constituted only 11% of all CHD deaths in men and 20% in women. The rest of the CHD diagnoses included “other acute or subacute cardiac ischemia” (ICD-10 code I24) and “chronic ischemic heart disease”(ICD-10 code I25). None of the cardiovascular deaths was coded as “sudden cardiac death” (ICD-10 code I46.1).

For ages 30 to 49, cardiomyopathy constituted one-half of all cardiovascular deaths in women and one-fourth in men. The majority of cardiomyopathies were classified as

alcoholic cardiomyopathy (ACMP), specifically 90% in men and 65% in women. The etiology for other cardiomyopathies was unspecified.

For approximately one third of men and women under age 60 who died from CVD, there was evidence of alcohol consumption prior to death. This proportion was lower for older ages. Four of five cases of cardiovascular death with a BAC ≥4.0g/l were registered among men aged 50 to 59 (Table 2).

The highest proportion of deaths with detectable levels of alcohol in blood was seen among those who died from cardiomyopathies and the two CHD subgroups "other acute or subacute cardiac ischemia" and "atherosclerotic heart disease". Only 5% of male and 1% of female deaths classified as being due to cardiovascular disease had high BACs (2.5 to 3.99g/l). Among the five men with potentially lethal BACs (≥4.0g/l), three died from the CHD, one from the cerebrovascular disease, and another from essential hypertension. Only one cardiovascular female death with a BAC ≥4g/l was identified.

Alcohol was more likely to be found at autopsy in men than in women who died from all cardiovascular causes (OR 1.55; 95% CI 1.14-2.10), ischaemic heart disease (OR 2.04 (1.36-3.05) and chronic ischaemic heart disease (OR 2.02; 95% CI 1.23-3.31). No such difference was found for deaths from myocardial infarction, cerebrovascular diseases, cardiomyopathies and alcoholic cardiomyopathy (Table 4).

Discussion

This is the most recent study on the association between alcohol use before death and cardiovascular mortality in Russia. It highlights the situation in the Northern city of Arkhangelsk in 2008-9 after the rising trend of cardiovascular mortality in Russia has reversed. We have found that a high proportion of people under the age of 60 dying from cardiovascular diseases in Arkhangelsk consumed alcohol in the hours before death. This is particularly so among men aged 50 to 59 years. The largest proportion of men and women with any alcohol identified at autopsy was found for the following cardiovascular

death diagnoses: “other acute or subacute cardiac ischemia” (I24), atherosclerotic heart disease (I25.1) and cardiomyopathies (I42). Cardiomyopathies, in general, and alcoholic cardiomyopathy are the largest components of premature cardiovascular mortality in women and the second largest in men under 50. We found little evidence of misclassification of deaths from acute alcohol poisoning as cardiovascular deaths.

Only few Russian studies used autopsy data to examine association between alcohol consumption and mortality. Two of them were conducted in Izhevesk (Urals Region) and were entirely focused on deaths among men of working age(26;30). The third by Zaridze et al.(11), and by far the largest study, examined 24800 male and female deaths (with 8,232 cardiovascular deaths under the age of 70) in 1990-2004 in the city of Barnaul in South Siberia. The proportion of the deceased who were subjected to the forensic examination in the corresponding age- and sex-groups in these studies was lower (25-60% in Barnaul and 50% or less in Izhevsk) than in the present study.

Strengths and weaknesses

Apart from the highest forensic autopsy rate in comparison with other publications, our study has two important additional advantages: it captures a complete set of death-events in a single city during a short time period, and employed uniform diagnostics and coding practices that remained virtually unchanged. Other strengths include: performing a study in the Northern part of Russia where no similar studies have been done, inclusion of women, comparison with Western European estimates (Norway), and being the first study using the data after 2005 when cardiovascular mortality in Russia started to decrease.(2) However, unlike the Izhevsk study we did not have any additional information about individual alcohol drinking behavior. Instead, we have had to rely on exposure to alcohol before death as indicated by the presence of alcohol in blood or other tissues. However, BAC quickly decreases after cessation of drinking, and the speed of alcohol elimination from blood in heavy drinkers may be as high as 0.2-0.3‰ per hour.(33) This limitation is common for all the aforementioned autopsy studies.(11;26;30)

Alcohol consumption before death and cardiovascular mortality

About one third of the men and women who died from cardiovascular diseases before the age of 60 consumed alcohol before death. This proportion is high, but it is considerably lower than found in Barnaul 45-50%.(11) The study from Izhevsk by Leon at al.(26) did not publish the corresponding data. However, when comparing the proportion of men who died from a cardiovascular disease with a BAC of >2.5g/l in Izhevsk and Arkhangelsk (age-group 30-49), it was two times higher in Izhevsk (17% versus 8.4%). Perhaps, these differences between Arkhangelsk and the two other settings can be attributed to geographic variations, temporal changes, socio-economic status or a more effective anti-alcohol policy. The available data suggest the presence of an East-to-West gradient from Barnaul to Izhevsk and Arkhangelsk.

A large population-based study undertaken in Arkhangelsk in 2000 found that binge drinking (i.e. a consumption of ≥80g of pure alcohol on one occasion at least once a month) was reported by 52% of men and 17% of women.(13) Vodka or other hard liquor constituted 61% of the total alcohol consumed.(35) The same study also showed that the highest population levels of gamma-glutamyltransferase (58.2 U/L) and the highest means of scores taken on the Alcohol Use Disorders Identification Test (8.0; where a score of ≥8.0 indicates hazardous or harmful alcohol consumption) were found in males aged 50 to 59.(13) In view of this fact, our finding that the absolute number of cardiovascular deaths in the corresponding age-group of men was surprisingly higher than in the age-group of 60-70 years is important. The highest number of deaths with severe and potentially lethal BAC was also found among them.

Since the detrimental effect of binge drinking on the cardiovascular system is well known (15) and is mediated by plausible physiological mechanisms(16;17), we hypothesized that the hazardous pattern of alcohol intake may accelerate the natural course of cardiovascular disease and prematurely trigger fatal cardiovascular collapse. At age of 50-59, the heart of an average man is not in perfect condition due to natural aging. Its vascular system is affected by multiple atherosclerotic plaques and slight to moderate hypertrophy or dystrophy of the myocardium.(36;37) These may decrease the threshold

for acute pathological events. It is likely that for this age-group that inherent compensating mechanisms start to fail in chronic binge drinkers. This would explain the considerable increase in cardiovascular mortality which, interestingly, waned for ages 60-70 years (Table 2). By comparison the observed pattern of cardiovascular mortality is totally different in Arkhangelsk women, amongst whom the absolute number of cardiovascular deaths linearly increases with age (Table 3) as is observed in Norwegian men and women.(38)

Heterogeneity of CHD-mortality

Our findings that the proportion of deceased with any alcohol detected on autopsy was the highest among those whose cause of death was classified as "other acute or subacute cardiac ischemia" or "atherosclerotic heart disease" agree with previous findings.(11;26) A large proportion of premature cardiovascular deaths among individuals in these two groups results from acute cardiovascular events that were quickly followed by fatal outcome. The typical original clinical diagnosis reported on death certificates issued in Arkhangelsk, corresponding to the ICD-10 subcategory of "other acute or subacute cardiac ischemia" (I24) was acute heart failure, with acute cardiovascular failure for atherosclerotic heart disease (I25.1). Both point to the acuteness of the pathological process. These two large diagnostic subcategories composed about 60% of all CHD-deaths in men under seventy. Acute myocardial infarction (AMI) constituted only 11% and 20% of CHD deaths under 70, respectively in men and women; this is in line with other Russian studies.(11;26) By contrast, in Norway in 2008, of 735 male CHD-deaths at age 35-69, 472 (64%) were classified as AMI and 168 (34.1%) deaths were attributed to atherosclerotic heart disease (I25.1); the respective numbers for 187 women with CHD deaths were 137 (73.3%) and 46 (24.6%), while no deaths were classified as "other acute or subacute cardiac ischemia".(38;38)

However, the AMI proportion we found in men is lower than that reported in other studies from Russia.(11;26) This finding was somewhat unexpected, since more than

95% of the diagnoses in our sample were based on the results of either forensic or hospital autopsy.

From this, one may conclude that the autopsy in Arkhangelsk did not detect a clot in the coronary arteries or area of myocardial necrosis in the majority of deaths classified as caused by a CHD. One could postulate that the pathological mechanism for many CHD-deaths having the ICD-10 codes I24 and I25 may be different from the one for AMI (I21-22). The pathological mechanism (a coronary thrombosis followed by myocardial necrosis) and diagnostic criteria for the AMI are well known and internationally standardized, but seem less clear for such vague diagnoses as acute heart failure and acute cardiovascular failure. Acute effects of binge drinking could plausibly enhance the underlying developmental mechanisms of the two categories of premature acute cardiac death among men.(15;16)

A total absence of deaths coded as sudden cardiac death (I46.1) among the deaths during the study period is another peculiarity of cardiovascular mortality in Arkhangelsk. We suspect that such deaths are classified as other diagnostic subcategories, most likely, the "other acute or subacute cardiac ischemia", and "atherosclerotic heart disease".

Premature mortality and alcoholic cardiomyopathy

ACMP is a dilated cardiomyopathy resulting from chronic toxic effects of alcohol on the myocardium and is a part of a clinical picture of advanced alcoholic disease. There are more than 10 etiological types of dilated cardiomyopathy(39) comprising more than 40 nosologies. Diagnosis of the ACMP is difficult and based on assessment of the following: history of alcohol consumption, general inspection of the body, presence of macro- and microscopic signs of cardiomyopathy (none of these signs are specific to ACMP), measurement of alcohol concentration in urine and blood, biochemical analyses of myocardium's specimens. From the former, ACMP differs with relatively mild atherosclerotic changes and absence of coronary stenoses, advanced atrophy/hypertrophy of the cardiomyocites, the affection by alcohol of other organs (fatty liver, pancreatitis, gastritis), the urine-to-blood alcohol concentration ratio of ≥2 and the potassium/sodium

ratio in the myocardium of >1. Differentiation of the ACMP from acute alcohol poisoning is more difficult. The latter is characterized by high BAC of ≥4g/l, age of death less than 40 years and very high urine alcohol concentration with a urine/blood concentration ratio of much higher than 2. Overfilled urinary bladder with signs of uncontrolled urination and other evidences of coma preceding death, support the diagnosis of alcohol poisoning.

ACMP was responsible for one third and one fifth of all female and male cardiovascular deaths under the age of 50 years in Arkhangelsk, respectively. Although the etiology of the majority of other cardiomyopathies was unspecified (ICD-10 code I42.9), it is also possible that alcohol contributed to the development of a substantial proportion of them. For comparison, of 144 men who died from a cardiovascular disease in Norway in 2008 under the age of 50, only five (2.8%) had the diagnosis cardiomyopathy and only one (0.7%) died from alcoholic cardiomyopathy. Corresponding figures for women were: 1 (2.1%) and 0 of 47 deaths.(38)

No difference in mortality from cardiomyopathy and alcoholic cardiomyopathy by age between men and women was found, suggesting that women suffering from advanced alcoholic disease had at least the same probability to die prematurely from alcoholic cardiomyopathy as men. We conclude that alcoholic and unspecified cardiomyopathies cause a large proportion of cardiovascular deaths under the age of 50, thereby contributing to the low life expectancy. Interestingly, in our sample there were deaths from alcoholic cardiomyopathy in a man aged 26 and a woman of 31. Taking into account that a duration of hazardous drinking (a daily consumption of 90-200g of alcohol) of at least 5 years (average is 15 years) is needed to develop asymptomatic cardiomyopathy, the consumption of large quantities of alcohol must have started early in life for these two individuals.(40;41)

Misclassification of cardiovascular deaths

Contrary to the Barnaul(11) study, our results are not consistent with the hypothesis that large-scale artificial inflation of the number of cardiovascular deaths

results from a misclassification of acute alcohol poisonings. This conclusion concurs with the findings of both studies from Izhevsk.(26;30) This discrepancy may be due to the different coding practices between the forensic pathologists in Arkhangelsk and those in Barnaul, or reflect some real differences between regions of Russia. It seems, however, that the regional differences are unlikely to explain the entire mismatch in the high prevalence of lethal BACs in cardiovascular deaths in Barnaul, and the lower prevalences of such deaths in Arkhangelsk and Izhevsk. Data in Barnaul had been collected mostly during the 1990s, and it is possible that the phenomenon of misclassification took place at a time of the implementation of ICD-10 system. In addition, this period was characterized by severe socio-economic instability and abruptly increasing cardiovascular mortality that diminished later. Another plausible explanation is that the average forensic autopsy rate, which should be viewed as the proxy for representativeness of the sample in this type of study, in Barnaul was considerably lower than in Arkhangelsk.

One final issue. Socially isolated and marginalized individuals (homeless, alcoholics, drug abusers), who are underrepresented in virtually all large epidemiological studies from Russia, are more likely to be autopsied by forensic experts. By contrast, “average” individuals die more often in a hospital, and are thus subjected to a post-mortem examination by hospital pathologists, thereby circumventing a forensic examination. Consequently, they are likely to be somewhat underrepresented in this type of study.

Key messages

- Alcohol consumption in the hours before death is associated with a high proportion of premature cardiovascular deaths in Arkhangelsk, Russia.
- The proportion of men dying from a cardiovascular disease with identified alcohol is higher than for women.
- The difference in cardiovascular mortality and the proportion with identified alcohol is highest among 50-59 year old men.
- The proportion of men and women with identified alcohol is highest in the large group of vaguely defined CHD-deaths and in the group of cardiomyopathies.

- Alcoholic cardiomyopathy is an important component of premature cardiovascular mortality in Northwest Russia.
- We found little evidence to support the hypothesis of misclassification of fatal alcohol poisonings as cardiac deaths.

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Table 1 Mortality in Arkhangelsk by age and gender from 01.01.2008 to 31.12.2009 with a proportion of forensic examinations within the groups of diagnoses

Cause of death (ICD-10 code)	Age groups (years)	Men			Women		
		N (%)[2]	Rate per 100.000[1]	N(%) forensic autopsies	N (%)[2]	Rate per 100.000[1]	N(%) forensic autopsies
Cardiovascular diseases (I00-99)	0-49	298 (21.9)	127.2	237 (79.5)	92 (18.6)	32.6	66 (71.7)
	50-59	525 (41.7)	2524.2	393 (74.9)	175 (32.7)	591.8	120 (68.6)
	60-69	468 (48.1)	4607.7	308 (65.8)	313 (49.2)	1757.9	177 (56.5)
	≥ 70	822 (55.9)	6622.6	557 (67.8)	1930(68.4)	5345.7	1288 (66.7)
	All ages	2113(41.7)	633.3	1495 (70.7)	2510(55.9)	322.7	1651 (65.8)
Malignansies (C00-97)	0-49	86 (6.3)	36.7	30 (34.9)	80 (16.2)	31.8	44 (55.0)
	50-69	468 (21.0)	755.9	251 (53.6)	351 (30.0)	370.5	198 (56.4)
	≥ 70	364 (24.8)	2932.7	241 (66.2)	453 (16.1)	1254.7	302 (66.7)
	All ages	918 (18.1)	250.1	522 (56.9)	884 (19.7)	120.7	544 (61.5)
External causes (V01-Y98)	0-49	565 (41.5)	241.2	563 (99.6)	135 (27.3)	53.6	134 (99.3)
	50-69	371 (16.6)	599.2	368 (99.2)	123 (10.5)	129.8	122 (99.2)
	≥ 70	82 (5.6)	660.7	82 (100)	80 (2.8)	221.6	78 (97.5)
	All ages	1018(20.1)	283.0	1013 (99.5)	338 (7.5)	64.2	334 (98.8)
Alcohol poisoning (T51.0-T51.9)	0-49	97 (7.1)	41.4	97 (100)	31 (6.3)	12.3	31 (100)
	50-69	119 (5.3)	192.2	119 (100)	46 (3.9)	48.5	46 (100)
	≥ 70	11 (0.75)	88.6	11 (100)	8 (0.3)	22.2	8 (100)
	All ages	227 (4.5)	62.4	227 (100)	85 (1.9)	16.2	85 (100)
Other causes	0-49	413 (30.3)	176.3	148 (35.8)	188 (38.0)	74.6	60 (31.9)
	50-69	400 (17.9)	646.1	189 (47.3)	210 (17.9)	221.6	82 (39.0)
	≥ 70	203 (13.8)	1635.5	105 (51.7)	359 (12.7)	994.3	194 (54.0)
	All ages	1016(20.1)	315.5	442 (43.5)	757 (16.9)	144.8	336 (44.4)
All deaths	0-49	1362	581.4	978 (71.8)	495	196.5	304 (61.4)
	50-69	2232	3605.1	1509 (67.6)	1172	1236.9	699 (59.6)
	≥ 70	1471	11851.4	985 (67.0)	2822	7816.3	1862 (66.0)
	All ages	5065	1508.7	3472 (68.5)	4489	663.8	2865 (63.8)

[1]Annual mortality rates for the age groups are given as crude. The rates for "all ages" are age-standardized to the world standard population

[2]Number and percent from all deaths in the corresponding age-group

Table 2 Cardiovascular mortality among men in Arkhangelsk from 01.01.2008 to 31.08.2009 by age and postmortem data on alcohol use prior to death

Cause of death (ICD-10 code)	Age-groups (years)	N (%) of deaths[1]	N (%) of forensic autopsies[2]	Alcohol detected N (%)[3]	Blood alcohol concentration (g/l), N (%) from the number of forensic autopsies			
					<0.5	0.5-2.49	2.5-3.99	≥4.0
Cardiovascular diseases (I00-99)	30-49	238	191 (80.3)	65 (34.0)	16 (8.4)	23 (12.0)	16 (8.4)	0
	50-59	432	318 (73.6)	110 (34.6)	32 (10.1)	36 (11.3)	24 (7.6)	4 (1.3)
	60-70	429	287 (66.9)	66 (23.0)	22 (7.7)	22 (7.7)	15 (5.2)	1 (0.4)
Ischaemic Heart Disease (I20.0-25.9)	30-49	131 (55.0)	120 (91.6)	36 (30.0)	11 (9.2)	12 (10.0)	9 (7.5)	0
	50-59	282 (65.3)	244 (86.5)	84 (34.4)	26 (10.7)	26 (10.7)	20 (8.2)	3 (1.2)
	60-70	274 (63.9)	218 (79.6)	57 (26.2)	18 (8.3)	20 (9.2)	14 (6.4)	0
-Myocardial infarction (I21-22)	30-49	10 (4.2)	4 (40)	2 (50.0)	0	1 (25.0)	1 (25.0)	0
	50-59	23 (5.3)	5 (21.7)	1 (40.0)	0	1 (25.0)	0	0
	60-70	43 (10.0)	14 (32.6)	1 (14.3)	1 (7.1)	0	0	0
-Other acute/subacute IHD (I24)	30-49	24 (10.1)	24 (95.8)	9 (37.5)	1 (4.2)	3 (12.5)	3 (12.5)	0
	50-59	17 (3.9)	14 (82.4)	8 (57.1)	4 (28.6)	2 (14.3)	1 (7.1)	1 (7.1)
	60-70	9 (2.1)	5 (55.6)	3 (60.0)	2 (40.0)	0	1 (20.0)	0
-Chronic IHD (I25)	30-70	561 (51.0)	517 (92.2)	153 (29.6)	47 (9.1)	51 (9.9)	37 (7.2)	2 (0.4)
-Atherosclerotic heart disease (I25.1)	30-49	70 (29.4)	70 (100)	18 (25.7)	7 (10.0)	6 (8.6)	4 (5.7)	0
	50-59	154 (35.7)	145 (94.2)	58 (40.0)	16 (11.0)	18 (12.4)	14 (9.7)	1 (0.7)
	60-70	116 (27.0)	113 (97.4)	34 (30.1)	11 (9.7)	13 (11.5)	7 (6.2)	0
-Old myocardial infarction (I25.2)	30-49	26 (10.9)	23 (88.5)	7 (30.4)	3 (13.0)	2 (8.79)	1 (4.4)	0
	50-59	85 (19.7)	80 (94.1)	17 (21.3)	6 (7.5)	5 (6.3)	5 (6.3)	1 (1.3)
	60-70	97 (22.6)	86 (88.7)	19 (22.1)	4 (4.7)	7 (8.1)	6 (7.0)	0
Cerebrovascular diseases (I60-69)	30-49	35 (14.7)	11 (31.4)	1 (9.1)	0	1 (9.1)	0	0
	50-59	84 (19.4)	25 (29.8)	2 (18.0)	1 (4.0)	1 (4.0)	0	0
	60-70	117 (27.3)	49 (41.9)	5 (10.2)	3 (6.1)	1 (2.0)	0	1 (2.0)
Cardiomyopathies (I42.0-I42.9)	30-49	54 (22.7)	52 (96.3)	27 (51.9)	5 (9.6)	9 (17.3)	7 (13.5)	0
	50-59	42 (9.7)	39 (92.9)	21 (53.9)	5 (12.8)	7 (18.0)	4 (10.3)	0
	60-70	12 (2.8)	11 (91.7)	3 (25.0)	1 (9.1)	0	1 (9.1)	0
-Alcoholic cardiomyopathy (I42.6)	30-49	47 (19.7)	45 (95.8)	23 (51.1)	5 (11.1)	7 (15.6)	6 (13.3)	0
	50-59	35 (8.1)	34 (97.1)	18 (52.9)	3 (8.8)	7 (20.6)	4 (11.8)	0
	60-70	11 (2.6)	10 (90.9)	3 (30.0)	1 (10.0)	0	1 (10.0)	0

[1] Percent of the total number of cardiovascular deaths in the corresponding age stratum
[2] Percent of the number of deaths with the same coding in the corresponding age stratum
[3] Any alcohol detected in the blood or other tissues at forensic autopsy

Table 3 Cardiovascular mortality among women in Arkhangelsk from 01.01.2008 to 31.08.2009 by age and postmortem data on alcohol use prior to death

Cause of death (ICD-10 code)	Age-groups (years)	Number of deaths[1]	N (%) of forensic autopsies[2]	Alcohol detected N (%)[3]	Blood alcohol concentration (g/l), N (%) from the number of forensic autopsies			
					<0.5	0.5-2.5	2.5-4.0	>4.0
Cardiovascular diseases	30-49	77	56 (72.7)	21 (37.5)	6 (10.7)	10 (17.9)	2 (3.6)	0
(I00-99)	50-59	147	98 (66.7)	27 (27.6)	9 (9.2)	10 (10.2)	2 (2.0)	0
	60-70	295	170 (57.6)	23 (13.5)	10 (5.9)	7 (4.1)	3 (1.8)	1 (0.6)
Ischaemic Heart Disease	30-49	14 (18.2)	11 (78.6)	1 (9.1)	0	1 (9.1)	0	0
(I20.0-25.9)	50-59	74 (50.3)	58 (78.4)	16 (27.6)	9 (15.5)	5 (8.6)	1 (1.7)	0
	60-70	179 (60.7)	129 (72.1)	18 (14.0)	8 (6.2)	5 (3.9)	2 (1.6)	1 (0.8)
-Myocardial infarction	30-49	2 (2.6)	1 (50.0)	0	0	0	0	0
(I21-22)	50-59	13 (8.8)	3 (23.1)	0	0	0	0	0
	60-70	38 (12.9)	13 (34.2)	2 (15.4)	1 (7.7)	0	0	0
-Other acute/subacute IHD	30-49	4 (5.2)	3 (75.0)	0	0	0	0	0
(I24)	50-59	12 (8.2)	9 (75.0)	4 (44.4)	2 (22.2)	1 (11.1)	1 (11.1)	0
	60-70	11(3.7)	6 (54.5)	1 (16.7)	0	1 (16.7)	0	0
-Chronic IHD (I25)	30-70	187 (36.0)	163 (87.2)	28 (17.2)	14 (8.6)	9 (5.5)	2 (1.2)	1 (0.6)
-Atherosclerotic heart	30-49	6 (7.8)	6 (100.0)	1 (16.7)	0	1 (16.7)	0	0
disease (I25.1)	50-59	37 (25.2)	37 (100.0)	11 (29.7)	7 (18.9)	3 (8.1)	0	0
	60-70	90 (30.5)	82 (91.1)	13 (15.9)	6 (7.3)	4 (4.9)	2 (2.4)	0
-Old myocardial	30-49	2 (2.6)	1 (50.0)	0	0	0	0	0
infarction (I25.2)	50-59	9 (6.1)	8 (88.9)	0	0	0	0	0
	60-70	34 (11.5)	28 (82.4)	2 (7.1)	1 (3.6)	0	0	1 (3.6)
Cerebrovascular diseases	30-49	14 (18.2)	5 (35.7)	1 (20.0)	0	1 (20.0)	0	0
(I60-69)	50-59	34 (23.1)	9 (26.5)	1 (11.1)	0	0	0	0
	60-70	83 (28.1)	27 (32.5)	1 (3.7)	1 (3.7)	0	0	0
Cardiomyopathies	30-49	37 (48.1)	37 (100.0)	19 (51.4)	6 (16.2)	8 (21.6)	2 (5.4)	0
(I42.0-I42.9)	50-59	29 (19.7)	27 (93.1)	9 (33.3)	0	5 (18.5)	1 (3.7)	0
	60-70	9 (3.1)	9 (100.0)	3 (30.0)	0	2 (22.2)	1 (11.1)	0
-Alcoholic cardiomyopathy	30-49	24 (31.2)	24 (100.0)	13 (54.2)	6 (25.0)	8 (30.0)	2 (8.3)	0
(I42.6)	50-59	24 (16.3)	23 (95.8)	8 (34.8)	0	5 (21.7)	1 (4.4)	0
	60-70	7 (2.4)	7 (100.0)	3 (42.9)	0	2 (28.6)	1 (14.3)	0

[1]Percent of the total number of cardiovascular deaths in the corresponding age stratum
[2]Percent of the number of deaths with the same coding in the corresponding age stratum
[3]Any alcohol detected in the blood or other tissues at forensic autopsy

Table 4 Sex-specific distribution of alcohol positive and negative autopsies by death diagnosis, with OR for probability of alcohol-positive autopsy result (men vs. women)

Cause of death (ICD-10 code)	Men	Women	OR (95% CI)	P-value
Total number of autopsies	795	324		
Cardiovascular diseases (I00-99)				
Alcohol positive	241	71	1.55	0.004
Alcohol negative	554	253	(1.14-2.10)	
IHD (I20.0-25.9)				
Alcohol positive	177	35	2.04	0.001
Alcohol negative	405	163	(1.36-3.05)	
-*Myocardial infarction (I21-22)*				
Alcohol positive	4	2	1.58	0.62
Alcohol negative	19	15	(0.25-9.82)	
-*Other acute/subacute IHD (I24)*				
Alcohol positive	20	5	2.36	0.15
Alcohol negative	22	13	(0.72-7.82)	
-*Chronic IHD (I25)*				
Alcohol positive	110	25	2.02	0.005
Alcohol negative	218	100	(1.23-3.31)	
Cerebrovascular diseases (I60-69)				
Alcohol positive	8	3	1.32	0.70
Alcohol negative	77	38	(0.33-5.25)	
Cardiomyopathies (I42.0-I42.9)				
Alcohol positive	51	31	1.36	0.33
Alcohol negative	51	42	(0.74-2.48)	
-*Alcoholic cardiomyopathy (I42.6)*				
Alcohol positive	44	24	1.22	0.56
Alcohol negative	45	30	(0.62-2.41)	

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? OO
- how many cigarettes do/did you smoke during working hours OO
- how old were you when you started smoking daily? OO
- for how many years in total did you smoke daily? OO

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 ○ no ○

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

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 ○
falling asleep too early in the evening ○
bad sleep, waking up several times ○
waking up too early in the morning ○
waking up not rested in the morning ○
sleeping too long in the morning ○

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 Number of participant
University of Tromsø, Norway

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

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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

Stemple

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

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