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A population based study on cardiovascular diseases in Northwest Russia. The Arkhangelsk study 2000.

Maria Averina

Tromsø 2005

Institute of Community Medicine
Faculty of Medicine
University of Tromsø,
9037 Tromsø, Norway

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A POPULATION BASED STUDY ON CARDIOVASCULAR DISEASES IN NORTHWEST RUSSIA.

The Arkhangelsk study 2000.

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Institute of Community Medicine
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CONTENTS

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This doctoral thesis is based on data from the Arkhangelsk study 2000 and its first follow-up in 2003-2004. The Arkhangelsk study is a result of a long-term cooperation between the Northern State Medical University in Arkhangelsk and the University of Tromsø. The Norwegian Research Council provided financial support for the Arkhangelsk study 2000, while the Norwegian Health- and Care Department provided funding for the follow-up study.

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LIST OF PAPERS

The thesis is based on the following papers:

I. Averina M, Nilssen O, Brenn T, Brox J, Kalinin AG, Arkhipovsky VL. High cardiovascular mortality in Russia cannot be explained by the classical risk factors. The Arkhangelsk study 2000. European Journal of Epidemiology 2003; 18: 871-8.

II. Averina M, Nilssen O, Brenn T, Brox J, Arkhipovsky VL, Kalinin AG. Factors behind the increase in cardiovascular mortality in Russia: apolipoprotein AI and B distribution in the Arkhangelsk study 2000. Clinical Chemistry 2004; 50: 346-54.

III. Averina M, Nilssen O, Brenn T, Brox J, Arkhipovsky VL, Kalinin AG. Social and lifestyle determinants of depression, anxiety, sleeping disorders and self-evaluated quality of life in Russia: a population-based study in Arkhangelsk. Social Psychiatry and Psychiatric Epidemiology 2005; 40: 511-8.

IV. Averina M, Nilssen O, Arkhipovsky VL, Kalinin AG, Brox J. C-reactive protein and alcohol consumption: is there an U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study. Submitted.

V. Nilssen O, Averina M, Brenn T, Brox J, Kalinin AG, Archipovski VL. Alcohol consumption and its relation to risk factors for cardiovascular disease in the north-west of Russia: the Arkhangelsk study. International Journal of Epidemiology 2005; 34: 781-8.

1. GENERAL BACKGROUND

1.1 Public health crisis in Russia.

The main reason for the Arkhangelsk study and for this thesis was the alarming public health situation in post-soviet Russia. Since the collapse of the Soviet Union in 1991, Russian population has experienced a rapid increase in mortality and a dramatic fall in life expectancy. In 1992 the difference between life expectancy in Norway and Russia was 12.1 years for men and 6.5 years for women, in 2002 the gap increased to 18.1 and 9.4 years, respectively (Fig. 1-2) [1, 2].

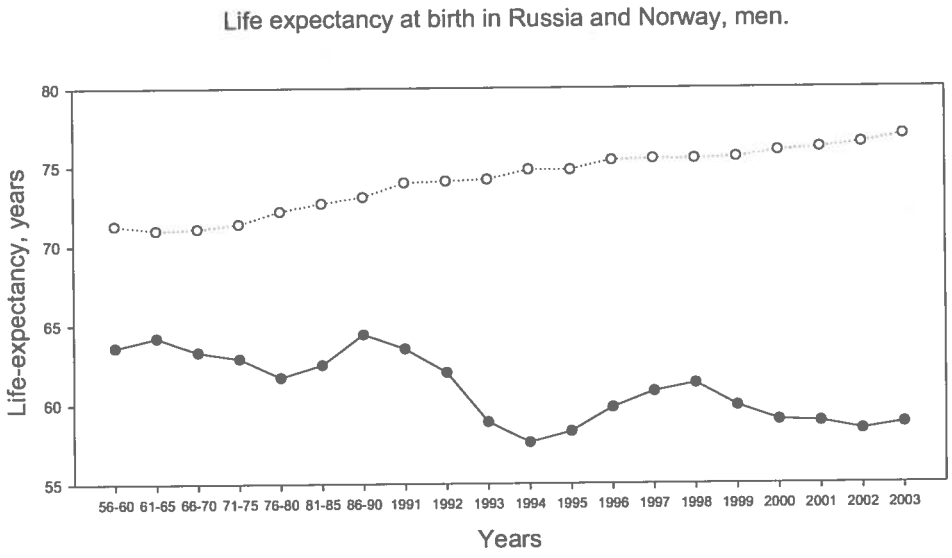
In the mid-60s the gap between Russia and Western countries was not so large as in the 90s. In 1965 life expectancy was 64.3, 67.5 and 66.8 years for men and 73.4, 74.7, 73.7 years for women in Russia, France and USA, respectively. In the 80s the gap between Russia and Western countries increased to about 10 years for men and 6 years for women [3]. In the period of Gorbachev's anti-alcohol campaign there was a short rise in life expectancy over a period of three years (from 1984 to 1987). However, by 1987 the anti-alcohol campaign was abolished, and life expectancy began gradually to fall.

After the collapse of the USSR, life expectancy fell abruptly: from 63.8 years in 1990 to 57.6 years in 1994 in men, and from 74.4 years in 1990 to 71.2 years in 1994 in women (Fig. 1-2). Mortality rates have risen rapidly for both sexes and for all ages, except infants. There was a slight increase in life expectancy in 1995-1998, but from 1999 life expectancy has been decreasing. In 2002, life expectancy in Russia was 58.4 years for men and 72.1 years for women (the gap between the genders was 13.7 years, which was the highest in Europe) [1].

Since 1991 Russia has been experiencing a natural population loss due to an excess number of deaths over the number of births. In the recent years the population loss was 700-800.000 citizens per year (about 0.5 % of the general Russian population).

According to the prognosis of the Goskomstat (Central Statistics Agency of Russia) [1], if the population loss tempo remains the same, during next 50 years Russia may lose about 1/3 of its population. Entire regions of Russia are under the threat of depopulation, especially in the North, Siberia and in the Far East. The considerable annual decline in the population size has become a matter of great concern in Russia, as it may have serious socioeconomic and geopolitical consequences. One of the main reasons for the population decline is high premature mortality of working-age population from cardiovascular/cerebrovascular diseases and from external reasons (injuries, accidents, poisonings and suicides).

Fig 1.


Life expectancy at birth in Russia and Norway, men.
Life-expectancy, years
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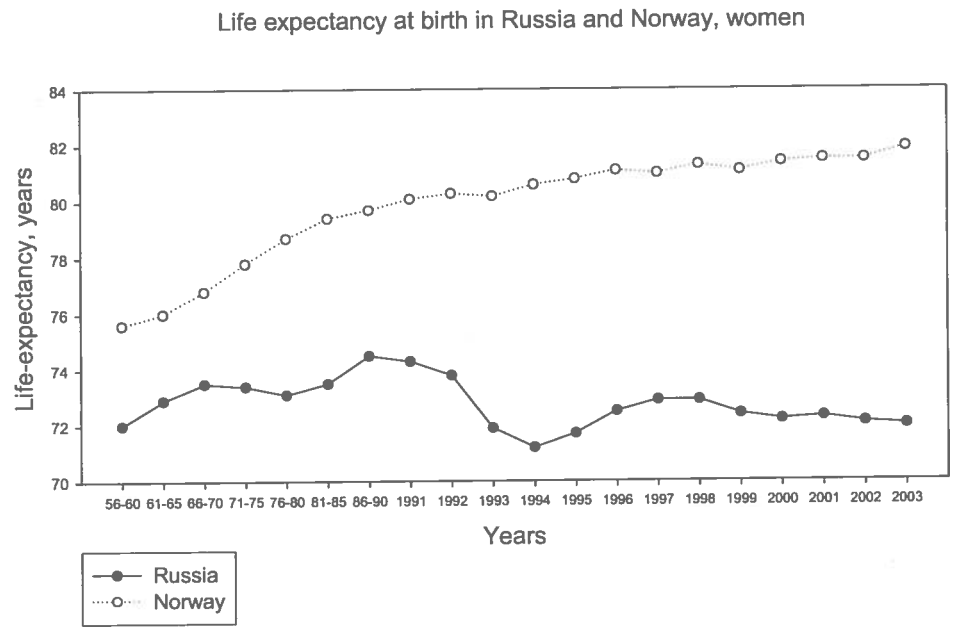
Years

Fig 2.


Life expectancy at birth in Russia and Norway, women
Life-expectancy, years
84
82
80
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76
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72
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56-60 61-65 66-70 71-75 76-80 81-85 86-90 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Years
Russia
Norway

1.2 Mortality rates

Russia has one of the highest all-cause mortality rates in Europe that is often called "unprecedented for a country not at war". Mortality rates increased abruptly in the beginning of the 90s when the Soviet Union went into decay and the post-soviet period of political and economical instability started. After a slight decrease in mortality in 1995-98, Russia has experienced the second rise in mortality from 1999 (Table 1). Mortality in 2003 was almost 1.5 times higher than in 1990 (16.5 and 11.2 per 1000, respectively) [1]. The leading cause of death was cardiovascular/cerebrovascular diseases (CVD) (Table 1). CVD mortality in Russia is now more than twice as high as in Norway.

Table 1. Total mortality and mortality from CVD in Russia and Norway (per 1000 citizens) [1, 2].

	Russia		**Norway**	
Year	Total mortality	CVD mortality	Total mortality	CVD mortality
1997	13.8	7.5	10.1	4.4
1998	13.6	7.5	10.0	4.4
1999	14.7	8.1	10.1	4.3
2000	15.4	8.5	9.8	4.1
2001	15.6	8.7	9.7	4.0
2002	16.3	9.1	9.8	3.9
2003	16.5	9.3	9.3	3.6

Although all-cause mortality has increased in Russia in all ages, it is mainly deaths in working ages (16-59 years) that contributed most to the mortality rise [1]. From 1990 to 1995 mortality in men and women in working ages increased by approximately 60% and 50%, respectively (Table 2). The largest increase in mortality was seen in men aged 40-44 years (by 86%).

Table 2. Total mortality in Russia in 1990, 1995 by age- and sex groups (per 1000 citizens) [1].

	1990		1995	
Age, years	Men	Women	Men	Women
15-19	1.6	0.6	2.4	0.9
20-24	2.6	0.7	4.3	1.0
25-19	3.3	0.8	5.4	1.3
30-34	4.3	1.1	7.4	1.8
35-39	5.6	1.5	10.0	2.5
40-44	7.6	2.4	14.1	3.9
45-49	11.7	3.8	19.3	5.8
50-54	16.1	5.4	27.3	8.5
55-59	23.4	8.6	34.0	11.4
60-64	34.1	13.5	46.1	17.2
65-69	46.5	22.0	60.0	25.9

An enormous increase in CVD mortality happened in Russia in the 90s, especially in men and women of working ages (Tables 3 and 4). Meanwhile in Norway the same age groups have experienced a substantial decrease in CVD mortality.

Table 3. CVD mortality in the beginning of 90s in Russia and Norway per 1000 citizens, all ages [2, 4].

	Russia		Norway	
	Men	Women	Men	Women
1987 year	10.8	7.5	5.4	4.8
1994 year	13.9	8.9	4.6	4.5
Difference 1994/1987	+29%	+19%	-15%	-6%

Table 4. CVD mortality in the beginning of 90s by sex in Russia and Norway per 1000 citizens, ages 40-44 years for Russia and 40-49 years for Norway [2, 4].

	Russia		Norway	
	Men	Women	Men	Women
1987 year	1.92	0.49	0.93	0.23
1994 year	4.23	1.07	0.67.	0.21
Difference 1994/1987	+120%	+118%	-28%	-9%

Trends in CVD mortality in Russia are more of a puzzle for epidemiologists. CVD mortality has been changing dramatically from one year to another. CVD deaths tend to be sudden and occur at younger ages than in western countries. The classical CVD risk factors, such as serum lipids, identified in the western epidemiological studies appeared to have little predictive value in Russia [5-9]. Another specific feature of the Russian mortality crisis is a big gender difference in mortality rates. In 1995, all-cause mortality of men in working ages was four times higher than that of women, while CVD mortality was almost five times higher in men than in women [1].

CVD mortality has increased simultaneously with mortality from external causes (injuries, suicides, alcohol poisonings, homicides and accidents), which is the second most important cause of death and is five times higher in Russia than in Norway (228,9 and 50.4 per 100.000, respectively in 2003, 2002) [1, 2]. There is a large sex gap in mortality from external causes with four times higher mortality in men than in women [3]. According to the Russian reports on public health many of these deaths are alcohol-related.

1.3 Epidemiological studies in Russia

A few epidemiological studies on CVD risk factors were conducted in Russia in this period. In the 70s the Russian Lipid Research Clinics study (LRC-study) was started in Moscow and St-Petersburg. It included participants 40-59 years old at baseline and had 12 years of follow-up [6, 7]. The LRC-study in Russia was carried out under a government-to-government agreement between USA and Soviet Union in a joint program on CVD.

The MONICA study (Monitoring of Trends and Determinants in Cardiovascular disease) started in 1984-85 in Moscow and Novosibirsk and included participants of both sexes aged 35-64 at baseline [8, 9]. Three MONICA surveys were conducted in Russia in three periods,

namely 1984-86, 1988-89 and 1992-95. In 1998 the MONICA follow-up study was started in Novosibirsk with a median follow-up duration of 9.5 years.

The Russian Longitudinal Monitoring Survey (RLM-study) was conducted in 1992-2000. The survey was based on interviews of a national sample of households and included questions on income, unemployment, alcohol consumption and nutrition [10]. There have also been some publications based on the Goskomstat data and from the Moscow Center of Demography and Human Ecology [4, 11-14].

The LRC- and MONICA studies could not explain the excessive cardiovascular mortality only by the classical risk factors (serum lipids, smoking, blood pressure) [6-9]. The classical risk factors identified in long-term epidemiological studies in the western countries [15-18] appeared to be relatively low in the Russian population. Several other explanations for high CVD mortality in Russia have been suggested. A hypothesis of high alcohol consumption has been discussed by several authors as one of the main reasons for CVD epidemic in Russia [11, 19-23]. The RLM-study found that alcohol consumption had increased rapidly since the collapse of the Soviet Union [10]. According to the official data, alcohol consumption in the mid-90s was 14.5 liters per person per year with 7.5-8.5 liters of this coming from illegal alcohol production [3]. The peak of alcohol consumption occurred in 1994-95, the years with the lowest life expectancy in Russia.

Other authors have emphasised the role of psychosocial distress in the society undergoing transition to marked economy [10, 12, 13, 24]. The public health crisis in Russia took place in a period with devastating economic decline and enormous growth of individual poverty. According to the Goskomstat data (Central Statistics Bureau of Russia), in the beginning of 2000 about 41% of the Russian population lived in poverty with incomes less than subsistence minimum calculated by the Russian government [1]. In 2001, about 28% of the population and in the beginning of 2003 about 26% of the population had income below the subsistence minimum [1]. Also unhealthy lifestyle (lack of exercise, poor nutrition, smoking, alcohol drinking) and decay of health care system have been suggested as possible reasons for high CVD mortality in Russia [12, 25]. However, although these hypotheses were widely discussed, there were actually very few attempts to test them in population-based studies.

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1.4 CVD risk factors

Although humanity has learned a lot about the causes of CVD, half of all CVD patients in the world do not have any of the established classical risk factors (hypercholesterolemia, smoking, hypertension, obesity, and diabetes mellitus) [26]. The epidemic of CVD in Russia is of special interest for epidemiologists, as the classical CVD risk factors have little predictive value in Russian population [5-9].

In our study we decided to investigate both the classical and other CVD risk factors in a sample of Russian population. On the basis of what is known about CVD mortality in Russia, we decided to pay special attention to alcohol consumption and psychosocial factors. Experience from other studies have raised questions about reliability of Russian laboratories [27], therefore all the laboratory analyses were performed at the Department of Clinical Chemistry, University Hospital of Tromsø, Norway. It gave us the opportunity to assess serum markers of cardiovascular risk in Russia by internationally standardized methods with several levels of quality control. To our knowledge, some of the CVD risk markers that we investigated have never been measured in population studies in Russia before (apolipoproteins AI and B; C-reactive protein measured by a highly sensitive method).

Apolipoproteins AI and B100

Apolipoprotein AI (apo AI) is a major protein component of high density lipoprotein particles (HDL). HDL take up free cholesterol from cell membranes and other lipoproteins and esterify it through an action of lecithin cholesterol acyltransferase (LCAT) enzyme. Apo AI is important for the activation of the LCAT enzyme, and thus plays an essential role in the removal of excess cholesterol from cells [28, 29].

Apolipoprotein B100 (apo B) is a protein component of low density lipoprotein particles (LDL). Although apo B is also a component of chylomicrons, very low density lipoprotein particles (VLDL), lipoprotein (a), and metabolic remnants of chylomicrons and VLDL, most of the circulating apo B is associated with LDL [28, 29]. LDL is major cholesterol-carrying lipoproteins that transport cholesterol to peripheral cells. Apo B mediates the uptake of LDL by cells through a specific interaction with the LDL receptor.

Several studies have reported that low apo AI and high apo B levels were better indicators of atherosclerotic risk than other serum lipids [30-32]. The prospective AMORIS study showed that apo B and apo B/apo AI ratio were strongly positively associated with increased risk of fatal myocardial infarction in both sexes [33]. These findings have been supported by other studies [32, 34]. The INTERHEART study in 52 countries showed an increased risk for myocardial infarction in persons with raised apoB/apo AI ratio [35]. Some authors have emphasized the importance of investigating apo AI in populations with low classical risk profiles [36].

Markers of inflammation

There is a compelling evidence from epidemiological and clinical studies that atherosclerosis is an inflammatory process. Increased levels of systemic markers of inflammation have been

shown to predict coronary heart disease, stroke, peripheral vascular disease and sudden cardiac death [37-42].

Among the systemic markers of inflammation, C-reactive protein (CRP) has been most extensively described. The main source of CRP production is the liver, but also arterial tissue produces CRP [38]. CRP has been found directly within atheromatous plaques [43]. CRP is an endogenous activator of complement and it has been shown to mediate monocyte recruitment and LDL uptake by macrophages in the atheromatous lesion [28, 43, 44]. High sensitivity method allows to measure CRP at levels below 10 mg/l (hsCRP) and to reveal low-grade inflammation during chronic inflammatory process of atherosclerosis [28]. Later, hsCRP was described as an independent CVD risk factor in the MONICA Augsburg Cohort study, in the MRFIT study, the Atherosclerosis Risk in Communities study, the Women's Health study, the Physician's Health study, the Cardiovascular Health study and the Rural Health Promotion project [39, 45-49]. These studies have concluded that hsCRP had an independent predictive value for CVD along with the classical CVD risk factors such as sex, age, smoking, blood pressure, diabetes, and dyslipidemia. Some authors even suggested that hsCRP is better predictor of cardiovascular events than the classical risk factors [49, 50].

Serum albumin is another marker of inflammation that predicts CVD events in healthy subjects and patients with subclinical atherosclerosis. The Framingham offspring study has reported that low serum albumin was associated with an increased risk of myocardial infarction in both sexes [51]. An Austrian study has found that low serum albumin was associated with cardiovascular outcome and was particularly useful for risk prediction in patients with few classical risk factors [52].

Socioeconomic and psychosocial factors

Socioeconomic inequalities in health and mortality have been reported in many studies [53-69]. In these studies low socioeconomic status has been defined as low education, low income and/or low employment status (unemployment, low-skilled work). In the Whitehall study CVD mortality was 3.6 times higher in men in the lowest social grade compared with the top social grade [61]. Difference in the classical risk factors failed to explain the social gradient. Low income was reported as a substantial predictor of mortality in a study from Canada [63]. An inverse socioeconomic gradient in coronary heart disease morbidity was described in the Framingham study and the British Regional Heart study [65, 66]. In a Norwegian study, high income level was negatively correlated with all-cause and CVD mortality rates in Oslo [70]. The Russia LRC-study and the MONICA study found an inverse association between educational level and all-cause/CVD mortality [71-73].

Low social status is known to be associated with depression and anxiety and the adoption of unhealthy lifestyles (smoking, alcohol drinking, poor diet and lack of physical activity). In the INTERHEART study in 52 countries, the psychosocial factors (depression, perceived stress, stressful life events) were associated with significantly higher risk of myocardial infarction in both sexes [35, 74]. A positive association between depression, anxiety, sleep disturbances and nonfatal/fatal CVD have been reported in several prospective studies [Reviews: 75, 76]. Also life dissatisfaction was found to be positively associated with disease- and injury mortality [77].

Psychosocial distress is a factor that is difficult to measure. In our study we decided to concentrate on self-reported low quality of life and symptoms of psychosocial distress such as self-reported depression, anxiety, and sleeping disorders.

Poverty in childhood

Prof. Forsdahl was the first to suggest that poverty in childhood was a risk factor for CVD in adult life [78, 79]. Later, Kaplan & Salonen have supported the same hypothesis [80]. Barker has reported that reduced fetal and infant growth was an important determinant of CVD risk in adulthood [81]. Russian population has experienced a devastating situation in 1914-40s (first world war, the October Revolution, civil war, famine, second world war, repressions of the Stalin's regime). Many in the generation of 60-80 years old have probably experienced poverty and malnutrition in childhood, thus having a possible increased vulnerability for CVD according to Forsdahl-Barker hypothesis. However, this hypothesis cannot be tested directly in our study, as no information on living conditions in childhood was collected.

Alcohol consumption

Many epidemiological studies have shown a J- or U- shaped association between amount/ frequency of alcohol intake and all-cause mortality [82-84]. A recent meta-analysis of data from 29 cohort studies confirmed the J-shaped association [85]. Another meta-analysis has shown a decreased risk of CVD in moderate drinkers, and increased risk in heavy drinkers [86].

However, some studies have reported rather different results. For example, a study of White et al. reported a direct dose-response relation between alcohol consumption and risk of death in women aged 16-44 and in men aged 16-34, and an U-shaped relation at older ages [87]. Also the NHANES I study reported a significant linear association between alcohol consumption and all-cause mortality for women and men less than 60 years of age, and a non-significant U-shaped association for the older ones [88]. The US National Alcohol Survey demonstrated the well-known J-shaped association between all-cause mortality and amount of

alcohol consumption [89]. But at the same time, light and moderate drinkers in this study had higher mortality risks if they reported heavy drinking occasions (8 drinks on one occasion or getting drunk at least monthly). The results of these studies have brought criticism about the U-shaped association between alcohol intake and mortality.

There is emerging evidence that the pattern of alcohol drinking may have a profound influence on mortality risk. Cohort studies from Sweden and Norway have shown an increased risk of death from cardiovascular diseases in heavy drinkers with especially increased risk of sudden coronary death [90, 91]. A study from Canada has demonstrated an increased risk of CVD in binge drinkers of both sexes [92]. The MONICA study in Finland has also shown that binge alcohol drinking (6 or more drinks at one occasion) was associated with higher all-cause mortality and higher mortality from ischemic heart disease [93]. The Kuopio Ischemic Heart Disease Risk Factor study found the highest atherosclerosis progression in men who consumed a whole bottle of vodka or more in one session [94]. The same study demonstrated that binge beer drinking was associated with progression of atherosclerosis and increased risk of fatal myocardial infarction [94, 95].

Binge alcohol drinking is the pattern of alcohol consumption historically common in Russia, especially among men [22, 96, 97]. A study in Moscow found increased number of CVD deaths on Saturdays, Sundays and Mondays compared with others weekdays. Such daily variations in CVD mortality could not be explained by the classical risk factors, more likely they reflected the consequences of binge drinking at weekends [98].

However, the debate on the role of alcohol in the Russian mortality crisis continues. Some researchers point out the absence of direct evidence that alcohol is the main reason for high CVD mortality in Russia [99]. Results of the MONICA study in Novosibirsk did not entirely support the hypothesis about the major contribution of binge alcohol drinking to the CVD mortality fluctuations [97]. No significant association between binge drinking and CVD mortality was found in this study; only a small group of frequent heavy drinkers had significantly raised risks of CVD death [100].

In our study we decided to investigate biological and social effects of alcohol intake in a sample of Russian population taking into account drinking pattern. Our data include not only self-reported alcohol intake, but also the Alcohol Use Disorders Identification Test (AUDIT) and measurement of gamma-glutamyltransferase (GGT) - a serum marker of alcohol consumption.

2. AIMS OF THE THESIS

- To investigate the distribution of the classical cardiovascular risk factors (blood lipids, smoking, blood pressure) in a sample of Russian population. To evaluate CVD risk using different risk scores.

- To study the distribution of other than classical CVD risk factors (markers of inflammation, apolipoproteins) and their association with alcohol variables and lifestyle factors.

- To investigate psychosocial factors and their associations with socioeconomic and lifestyle variables

- To assess the level of alcohol consumption, the prevalence of alcohol use disorders and their association with health variables

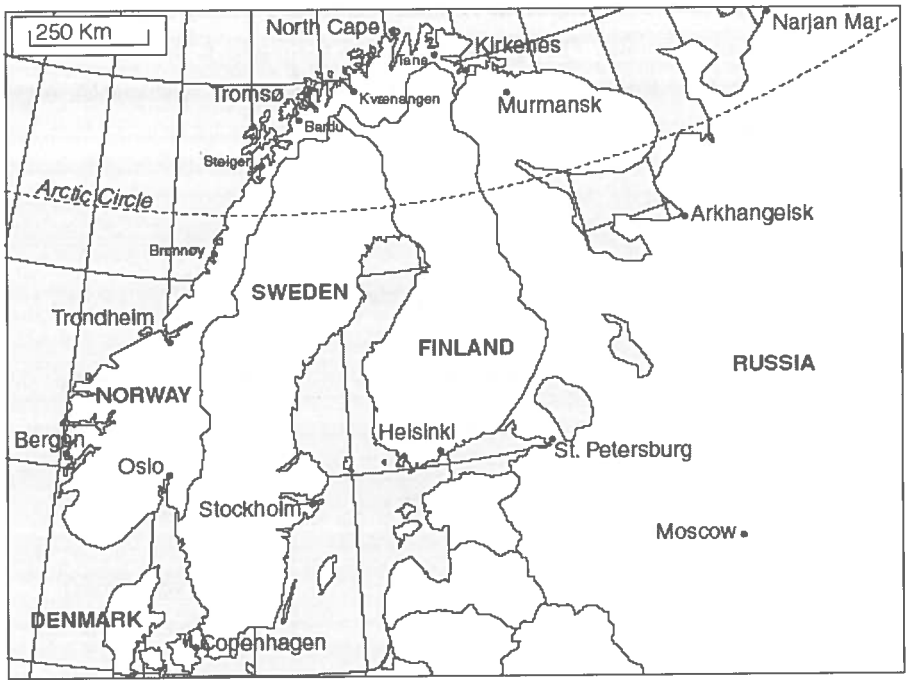
- To conduct a follow-up study and to analyze the results.

3. METHODS

3.1 Study area and background population

The study was carried out in Arkhangelsk - the capital of the Arkhangelsk region, which is the largest region in the European part of Russia. The White Sea and the Barents Sea border the region in the North. The climate is subarctic with long and cold winters that last up to 250 days a year. Average temperature ranges from about +15 °C in July to –17 °C in January. Because of difficult climate conditions and long distances, the population is settled mainly along rivers, railways and on the seashore. The most important industries in the region are fishing and forestry. The total population of the region was 1.44 million in 2000. Over one million lived in cities and towns. The main city, Arkhangelsk has a history dating back almost 400 years. In 1999 the population of Arkhangelsk city was 170,000 men and 197,000 women (0.3 percent of the general Russian population in 1999) [101].

Fig 3. Map of Arkhangelsk and the Barents area.



The whole Russian Federation has more than 100 European and Asiatic nationalities. The population of the Arkhangelsk region (as well as the population of the whole Russia) is mainly of Russian nationality. Many small nationalities are not represented in the Arkhangelsk region (Table 5).

Table 5. Ethnic distribution in Russia and in the Arkhangelsk region [1].

Ethnic distribution, %:	**Russia**	**Arkhangelsk region**
Russians	81.5	92.1
Ukrainians	3.0	3.4
Tatars	3.8	0.3
Other nationalities	11.7	4.2

However, we believe that the population of the Arkhangelsk region is fairly representative for at least the European part of Russia. The age distribution in the region is the same as in the entire Russia (Paper III, IV). Total mortality and CVD mortality in the Arkhangelsk region population are almost similar to that of the entire Russia (Table 6).

Table 6. Total and cardiovascular mortality and life expectancy at birth [1].

	Russia	**Arkhangelsk region**
Total mortality in 2000	15.4 per 1,000	15.1 per 1,000
CVD mortality in 2000	8.5 per 1,000	8.3 per 1,000
Life expectancy in 1999	59.9 (men) 72.4 (women)	60.0 years (men) 73.0 years (women)
	Arkhangelsk city: 60.0 years (men) and 72 years (women)	

3.2 Recruitment of participants

No population register was available for medical research in Arkhangelsk; therefore we had to find other methods of establishing the study population. Primary medicine, as it is in western countries, are non-existent in Russia. All types of patients get their medical service at outpatient clinics (polyclinics). The polyclinics are responsible for two types of patients: 1) those who are ill and need to see a doctor, and 2) those who have to see a doctor for their "compulsory annual medical examination". The polyclinics provide medical aid to the general Russian population according to territorial and occupational principles: each clinic is responsible for a defined numbers of companies, industrial units, etc. (occupational principles), and a certain region of the town (territorial principles). The outpatient clinics have a kind of register for the population they are serving.

We established our study centre at one of the largest polyclinics in Arkhangelsk (Semashko polyclinic). It made it possible to provide a certain quality of investigation with minimum of missing data. Altogether four nurses and two doctors were responsible for the daily registration, examination and blood testing.

Participants were consecutively recruited from the group of citizens who came for their "annual compulsory medical examination". This group had no fixed appointment at the clinic. They might attend between 08.00 and 12.00 at certain days during the week, and within a year since last examination. The daily number of attendees fluctuated between 2-4 and 30 subjects. As a part of a routine, they reported at a certain office where they were registered. At this situation they were informed about the project and asked to participate in the study. At the end of the project we established that about 1% of those invited (n=40) had refused to participate, the main reason for this was lack of time.

From the beginning of the study we decided to recruit about 4000 persons and to have age and sex groups approximately of the same size. During the study we had a constant control over the number of participants in each age group. We stopped to recruit participants in age groups when they were "filled up", and continued with the other age groups.

Some of the working entities and study places were actively contacted at the end of the study and told that their staff/employees could attend for the annual medical examination within the next weeks or months. Those "invited" subjects were not informed about our project until they attended the clinic.

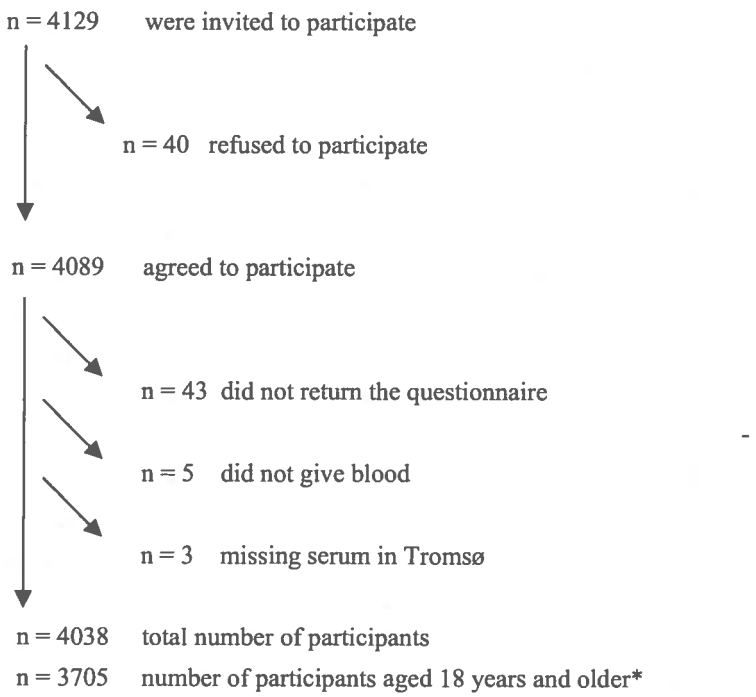
3.3 Ethics

At the time of the study there was no Centralized Ethical Committee in Russia and no Ethical Committee in the Arkhangelsk region. The Regional Ethical Committee, Norway, approved the study. Informed consent of all participants was verbally obtained.

3.4 Study population

Altogether 1968 men and 1737 women aged 18 years and older took part in the study. The mean age was 41.8 years for men and 44.2 years for women.

Fig 4. Participants in the Arkhangelsk study 2000.



*Participants younger than 18 years were excluded from further analysis

3.5 Examination

Survey procedures

The same four-stage survey procedure was followed for each participant. At the first stage, participants were informed about the study and invited to participate. Those who agreed to participate were registered as study participants (in a special journal) and given their personal participant number. A trained nurse performed anthropometrical measurements: height, weight, waist-hips circumference. Weight was measured by an electronic device with participant without clothes and shoes.

Questionnaire

At the second stage, each participant was followed to a separate room, where he/she filled in a questionnaire (Appendix I). The questionnaire was in Russian language and consisted of 111 questions (six pages). Questionnaires from the Tromsø study, the Finnmark and Svalbard studies had been used for the development of the questionnaire. An English version of the questionnaire had been first developed, then translated to Russian and re-translated again to English by two different translators for quality control purpose. A trained nurse was present in the room where participants filled in the questionnaire. She assisted participants if there were some difficulties in understanding the questions. At the end, each participant returned the questionnaire to her, and she checked if all questions were completed.

Blood pressure, heart rate

At the third stage, each participant was invited to another room, where blood pressure and heart rate were measured. There were no other activities in the room during the measurement. Blood pressure and heart rate were measured three times at intervals of two minutes on the right upper arm in a sitting position using an electronic automatic device (DINAMAP-R, Criticon, Tampa, Florida). A trained nurse performed all the measurements and registered blood pressure and heart rate.

Blood samples

At the fourth stage, each participant was invited to a special room for venepuncture. We did not demand to obtain only fasting blood samples, however the majority of participants was probably fasting, as it is required for annual medical examination. Blood samples (25ml) were obtained from the cubital vein and centrifuged within 15-25 minutes at the Semashko polyclinic laboratory. Specially trained nurses were responsible for venepuncture. GGT and lipids were analyzed at the Semashko clinic laboratory the same day. The rest of serum (four

glasses of serum for each patient) and one glass of full blood were frozen down to -20 °C. Serum was stored at -20°C for 3-4 weeks and then transported to Tromsø in boxes containing freezing elements by a 5-hour flight.

All laboratory measurements that were used for this thesis were performed at the Department of Clinical Chemistry, University hospital in Tromsø. The results from the laboratory in Arkhangelsk were used for quick answers to the participants.

Laboratory analyses

Serum total cholesterol was determined by an enzymatic colorimetric method (cholesterol esterase, cholesterol oxidase). Analytic coefficient of variation (CV) was 5%. HDL cholesterol was determined by an enzymatic colorimetric test (PEG cholesterol esterase, PEG cholesterol oxidase). CV was 3%. Triglycerides were measured by an enzymatic colorimetric test (lipoprotein lipase, glycerokinase, glycerolfosfat oxidase). CV was 2%. Analyses of total cholesterol, HDL cholesterol and triglycerides were performed in a Hitachi 917 device. If serum triglycerides were <4 mmol/l, the Friedwald's formula was used for LDL cholesterol (LDL cholesterol = total cholesterol - HDL cholesterol - (triglycerides × 0.46)). If serum triglycerides were higher, LDL cholesterol was measured directly by an enzymatic colorimetric test in a Hitachi 737 device (Roche, selective inhibition of VLDL-, chylomicron-, HDL-cholesterol). CV was 3%. Apo AI and apo B were determined by an immunoturbidimetric assay with polyclonal sheep anti-human apolipoprotein antibodies (Roche), which was standardized against WHO and International Federation of Clinical Chemistry (IFCC) SP-07 standard. CV for both tests was <3%.

Gamma-glutamyltransferase was determined by an enzymatic colorimetric assay (standardized method that corresponds to IFCC recommendations, Roche): the formation of free 5-amino-2-nitrobenzoate was proportional with GGT activity and it was measured photometrically in a Hitachi 917 device. CV was 2.5%. Serum C-reactive protein was measured by a highly sensitive particle-enhanced immunoturbidimetric method (hsCRP) in a Roche Modular P analyzer with lower detection limit 0.03 mg/l. CV was 3%. Serum albumin was determined by a colorimetric assay with bromcresol green in a Roche modular P analyzer. The lower detection limit was 2 g/l; CV was 1.7%.

Assessment of cardiovascular risk

Several risk scores based on the classical CVD risk factors have been developed in the world: the Framingham risk score, the European Coronary risk chart, the New Zealand Cardiovascular risk prediction chart, the Sheffield Risk Table, the PROCAM risk score [28, 102-106].

To assess CVD risk in our study population, we used the Framingham risk score, as it is best known and has been validated in northern European populations [107]. The score has also shown an acceptable risk prediction in white Australian and UK populations [28, 108]. The Framingham risk score specifies absolute risk for fatal and non-fatal coronary events over the next 10-years [102, 103]. Absolute risk is defined as the probability that an individual will experience a specified event during a specified period [28]. Synonyms to absolute risk are crude probability and cumulative incidence [109]. Framingham risk score predicts total coronary heart disease, which includes angina pectoris, clinical myocardial infarction, silent myocardial infarction (defined by electrocardiography), coronary insufficiency (unstable angina), and coronary death. The Framingham risk score includes age, total cholesterol, smoking status (smoker, non-smoker), HDL cholesterol and systolic blood pressure. Family history is not included in the Framingham risk score.

We have also used the Norwegian risk score for myocardial infarction and compared our data with Norwegian studies. The Norwegian risk score is based on five risk factors: sex, total cholesterol, systolic blood pressure, mean number of cigarettes per day, and family history of CVD [110, 111]. Different level of each risk factor has its own index. The total infarction risk is a result of multiplication of indexes of the five risk factors. An index for male sex is 5. A woman with minimum values for the other four risk factors has an infarct risk 1.0. A nonsmoking man with minimum values for total cholesterol, systolic blood pressure and without family history of CVD has an infarct risk 5.0. It gives an approximate relative risk for this man to have myocardial infarction compared with a woman that has the infarct risk 1.0.

3.6 Preliminary follow-up

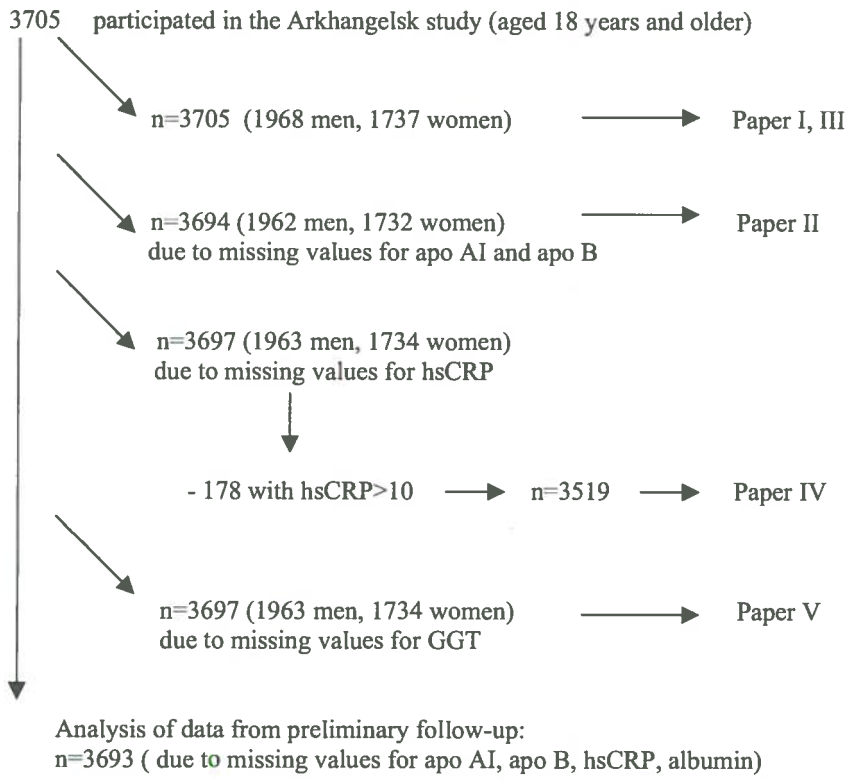
Altogether 4089 persons that agreed to participate in the first study in Arkhangelsk were included in the preliminary follow-up study in June 2003 - June 2004. Information on diseases and treatment was obtained from participants' medical records at the polyclinic. These medical records include not only information on diagnosis and treatment at the polyclinic, but also information from hospitals if such treatment had taken place. A specially trained medical expert evaluated each medical record. All the diagnoses were registered according to the International Classification of Diseases (ICD-10). Information on deaths was obtained from death records at the polyclinic and the database of the Arkhangelsk Health Care Department.

Altogether 2851 medical records were found (70% of the study participants). Medical records for about 30% of participants (n=1238) were not found. For 19 subjects we got death records from the Health Care Department. The reasons for absent medical records might be: persons were healthy and therefore no medical documentation was found; persons might have moved from the city and have taken their medical records. A follow-up questionnaire was sent

to participants whose medical records were not found (Appendix II); 229 of them completed the questionnaire.

Altogether 3099 subjects were found during this first follow-up, i.e. about 76% of the Arkhangelsk study population. In further survival analyses, those without medical- or death records were censored as healthy/alive. Results from the preliminary follow-up have not been published.

Fig 5. Creation of the study population in papers I-V.



4. MAIN RESULTS

The classical cardiovascular risk factors and the CVD risk score in the Russian population (Paper I).

Altogether 1968 men and 1737 women aged 18 years and older participated in the Arkhangelsk study in 1999-2000. The classical cardiovascular risk factors were assessed: smoking, blood pressure, serum lipids, and family history of CVD. The classical CVD risk factors were relatively favorable in the Russian population, especially lipid profile. Total cholesterol and triglycerides were lower than in studies from Northern Norway. The prevalence of smoking was higher in men, but lower in women in Arkhangelsk compared with the Finnmark and Tromsø studies. Mean diastolic blood pressure was lower in Arkhangelsk than in Northern Norway, while mean BMI and systolic blood pressure were almost the same in these populations. About 16% of men and 34% of women reported family history of cardiovascular diseases, the prevalence of self-reported positive family history was lower than in populations from Northern Norway.

The classical CVD risk factors in the Arkhangelsk population were not very different from two other samples of Russian population in the MONICA study.

The Framingham risk score and the Norwegian myocardial infarction risk score were used to evaluate CVD risk. Although cardiovascular mortality is three times higher in Russia compared to Norway, the myocardial infarction risk score was lower in all age groups of men and women from Arkhangelsk compared with the Tromsø study and the Finnmark study. For all age groups of men and women the Framingham risk score was the same or lower than the 'average risk' in the Framingham study. The Framingham risk score for the whole study population was 4.9 (SD 3.8) points for men and 3.7 (SD 8.1) points for women, that corresponds to 8% and 4% 10-year CVD risk respectively.

Apolipoproteins AI and B (apo AI, apo B) distributions in the Russian population, associations with alcohol and other variables (Paper II).

Among 3705 participants aged 18 years and older that participated in the study in 1999-2000, 1962 men and 1732 women had their apo AI and B serum levels measured. Apo AI and B profiles appeared to be favorable in the study participants compared with similar studies from Western Europe an USA. The results are consistent with those published in Paper I, indicating

that lipid profile was relatively favorable in the examined Russian population compared with other populations. The pattern of apo AI distribution was different in our study compared with studies from other countries. There was an abrupt increase in apo AI values in the young Russian men aged 18-30 years, while other studies did not observe such increase. In all age groups of men and women, except the youngest age group of men, apo AI values were markedly higher than in two studies from USA. Multiple linear regression analysis was used to estimate influence of different lifestyle variables on apo AI and B levels. Apo AI levels were significantly positively associated with age, physical activity, volume and frequency of alcohol consumption, with serum albumin and total cholesterol. Apo AI was negatively associated with BMI, self-reported myocardial infarction, smoking and triglycerides. The abrupt increase in apo AI values in young men seemed to be lifestyle, rather than age-related. Physical activity decreased gradually with age, but self-reported vodka consumption doubled from 3.3 AU/week in men aged 18-19 years to 6.3 AU/week in men 30-39 years of age. GGT, which is a marker of alcohol consumption, was also positively associated with apo AI in both sexes. GGT concentrations in Russian men were twice as high as in Norway indicating high alcohol consumption. High apo AI levels in this population are probably due to high alcohol consumption.

Psychosocial factors: depression, anxiety, sleeping disorders and low self-evaluated quality of life (Paper III).

All the participants in the Health study 2000 in Arkhangelsk (1968 men and 1737 women) answered the part of the questionnaire exploring depression, anxiety, sleeping disorders and quality of life. About 32% of the men and 70% of the women reported depression and/or anxiety and/or sleeping disorder (age-standardized to the general Russian population in 2000). About 20% of men and 33% of women reported low quality of life. In a logistic regression analysis, depression, anxiety, sleeping disorders and low life quality were positively associated self-evaluation of nutrition as poor and with low consumption of fruits/vegetables, meat/meat products, fish /fish products (low consumption was defined as "once a week or less"). About 40% of men and 36% of women reported low consumption of fruits and vegetables. Self-evaluation of nutrition as poor was significantly positively associated with low consumption of fruits/vegetables, fish and meat. These food items are easily found at shops in Arkhangelsk, but they are relatively expensive and might be unavailable to the general population to the extent they would have preferred. Poor nutrition might be an important indicator of low socioeconomic status in our data. Depression, anxiety and sleeping disorders were also

positively associated with another indicator of low socioeconomic status: low-paid job. Depression and sleeping disorders were positively associated with alcohol dependence (AUDIT score 13 or more), hazardous level of alcohol drinking (AUDIT = 8-12) and with smoking. Anxiety and low self-evaluated quality of life were positively associated with alcohol dependence. Depression, anxiety, sleeping disorders and low quality of life showed a strong positive association with CVD. This association remained significant after adjustment for smoking, poor nutrition, low-paid professional status and alcohol variables.

Markers of inflammation in the Russian population: C-reactive protein and its association with alcohol consumption (Paper IV).

C-reactive protein was measured by a highly sensitive method (hsCRP) in 1963 men and 1734 women that participated in the Arkhangelsk study 2000. Altogether 4.8% of the study population with hsCRP values over 10 mg/l was excluded from the analyses, because they might have had an active infection. About 16.7% of participants had hsCRP values of 3-10 mg/l. Before the adjustment for other factors, hsCRP had an U-shaped association with alcohol consumption in both sexes, with the highest hsCRP levels in ex-drinkers. Ex-drinkers were older, had higher body mass index (BMI) and waist-hip ratio, and reported more CVD than non-abstainers. After adjustment for age, BMI and smoking, the U-shaped association became non-significant in both sexes. When abstainers were excluded from the analyses, a positive linear association between hsCRP and vodka consumption was revealed in non-abstainers of both sexes. Other alcohol beverages showed no association with hsCRP levels in multiple regression analyses. Total alcohol consumption was positively linearly associated with hsCRP in male non-abstainers. The majority of male non-abstainers were binge drinkers (6 AU or more on one occasion at least once a month).

GGT had a positive association with hsCRP levels in non-abstainers of both sexes. In abstainers, there was no association between hsCRP and GGT, which means that the association in non-abstainers was probably alcohol-mediated. The study shows the pro-inflammatory effect of vodka consumption and suggests that the higher hsCRP levels in ex-drinkers than in non-abstainers might be explained by factors other than alcohol.

Alcohol consumption. Association with health variables (Paper V).

Altogether 1963 men and 1734 women that participated in the Arkhangelsk study 2000 had their GGT values measured. AUDIT and its sections were used to reveal alcohol use disorders.

Mean GGT in total population was 43.8 U/l in men and 28.3 U/l in women. GGT levels in both sexes were more than twice as high as found in comparable studies from other countries. Elevated GGT-levels were 4-5 times more frequent than found in the 3rd Tromsø study. In men the highest mean GGT-level was found in the group of seamen, while industrial workers displayed highest GGT values in women.

Mean AUDIT score was 7.5 and 3.9 for men and women, respectively. Corresponding figures for mean weekly alcohol intake were 8.6 AU and 3.3 AU. We assume that alcohol intake was substantially underreported in this study. Almost 2/3 of male industrial workers who reported any intake of alcohol scored 8 or more on AUDIT and 3/4 scored 5 or higher on section-1 of AUDIT (indicating hazardous or harmful alcohol consumption). Between 1/2 and 2/3 of male civil employees and "others" (unemployed and self-employed) had hazardous or harmful alcohol consumption. Females displayed figures lower than men. However, about 44% of female industrial workers and 47% of housewives scored positively on the AUDIT section-I.

Vodka/liquor consumption showed a strong positive association with logarithmically transformed GGT (logGGT) in multiple regression analyses in both sexes. Intake of table wine and beer displayed a significant positive association with logGGT in men, while in women intake of strong wine and frequency of binge drinking were positively associated with logGGT.

After adjustment for age, men and women with elevated GGT displayed significantly higher values for systolic and diastolic blood pressure, total cholesterol, triglycerides, LDL cholesterol, apo AI, apo B, and the Framingham risk score compared with those who had GGT under 50 U/l (men) or 45 U/l (women).

Results of the preliminary follow-up study

Cox proportional hazards survival regression analysis was performed to test hypotheses about the role of the classical- and other risk factors for CVD death, first non-fatal myocardial infarction and first non-fatal stroke. The analytic possibilities were reduced as we had relatively few incident cases.

Total number 3693, age 18 years and more

Table 7. Risk factors for CVD death.

Case identification: Cardiovascular death (ICD-10 codes: I 10-I 13, I 20-I 25, I 42, I 44-I 51, I 60-I 67, I 69-I 72, I 74)

Variables	Men and women (44 cases)		
	Model 1	Model 2	Model 3
	Hazard ratio (CI)	Hazard ratio (CI)	Hazard ratio (CI)
Sex (female vs. male)	0.47 (0.24-0.92)*	0.44 (0.23-0.85)*	0.33 (0.15-0.72)**
Age, 1 year	1.11 (1.09-1.14)‡	1.11 (1.09-1.14)‡	1.09 (1.06-1.12)‡
Smoking (yes vs. no)	0.77 (0.36-1.67)	0.71 (0.33-1.53)	0.61 (0.27-1.36)
Systolic BP, 1 mmHg	1.00 (0.98-1.01)	0.99 (0.98-1.01)	1.00 (0.98-1.02)
Total cholesterol, 1 mmol/l	0.91 (0.71-1.17)	–	–
Ratio LDL/HDL	–	1.26 (1.05-1.52)*	–
Ratio apo B/apo AI	–	–	8.57 (2.83-25.99)†
Albumin, 1 g/l	–	–	0.89 (0.83-0.95)†
Log10 (hsCRP)	–	–	1.10 (0.60-2.03)
Body Mass Index, 1 kg/m^2	–	–	0.91 (0.84-0.99)*
Alcohol ≤ 4 times/month [a]	–	–	1.24 (0.57-2.70)
Alcohol ≥ 2-3 times/week [a]	–	–	1.95 (0.49-7.83)
Low fruit/vegetable consumption [b]	–	–	2.41 (1.23-4.70)*
Depression [c]	–	–	1.26 (0.62-2.54)

* p<0.05; **p<0.01; † p<0.001; ‡ p<0.0001; – not included in the model;

[a] vs. abstainers; [b] once a week or less (yes vs. no); [c] yes vs. no

CVD death

The classical CVD risk factors (smoking, systolic blood pressure and total cholesterol) showed no association with CVD death (Model 1, Table 7). In Model 2 total cholesterol was

substituted by the ratio LDL-cholesterol/HDL-cholesterol, which appeared to be positively associated with CVD death. In Model 3 the ratio LDL/HDL was substituted by the ratio apo B/apo AI, which turned out to be the strongest predictor of CVD death in this analysis. Low fruits/vegetables consumption showed a positive significant association with CVD death. Serum albumin levels were significantly negatively associated with CVD death, while log-transformed hsCRP levels showed no significant association. Rather unexpected was a significant negative association between BMI and CVD death.

Table 8. Risk factors for first non-fatal myocardial infarction.
Case identification: ICD-10 code: I 21

Variables	Men and women (20 cases)		
	Model 1	Model 2	Model 3
	Hazard ratio (CI)	Hazard ratio (CI)	Hazard ratio (CI)
Sex (female vs. male)	0.20 (0.05-0.74)*	0.19 (0.05-0.71)*	0.16 (0.04-0.64)**
Age, 1 year	1.06 (1.02-1.09)**	1.05 (1.02-1.09)**	1.04 (1.00-1.09)*
Smoking (yes vs. no)	1.71 (0.66-4.46)	1.68 (0.64-4.40)	1.66 (0.60-4.55)
Systolic BP, 1 mmHg	1.03 (1.01-1.05)**	1.03 (1.01-1.05)**	1.03 (1.01-1.05)*
Total cholesterol, 1 mmol/l	1.09 (0.75-1.57)	–	–
Ratio LDL/HDL	–	1.27 (0.93-1.71)	–
Ratio apo B/apo AI	–	–	7.94 (1.78-35.41)**
Albumin, 1 g/l	–	–	0.99 (0.86-1.14)
Log10 (hsCRP)	–	–	1.94 (0.80-4.74)
Body Mass Index, 1 kg/m^2	–	–	0.99 (0.89-1.11)
Frequency of alcohol intake [a]	–	–	0.85 (0.49-1.45)
Low fruit/vegetable consumption [b]	–	–	0.77 (0.18-3.40)
Depression [c]	–	–	1.43 (0.49-4.13)

* $p<0.05$; **$p<0.01$; – not included in the model;

[a] categorized as: 1-never, 2- once a month or less, 3- two-four times a month, 4- two-three times a week, 5- four or more times per week; [b]once a week or less (yes vs. no); [c] yes vs. no

Non-fatal first myocardial infarction and stroke

The classical CVD risk factors showed stronger predictive value for first non-fatal myocardial infarction and stroke than for CVD death (Tables 8, 9). Systolic blood pressure showed a positive association with first non-fatal myocardial infarction and stroke (Model 1). Smoking was positively associated with first non-fatal stroke. Those who smoked had 3.3 times higher

risk for stroke than non-smokers. An increase in systolic blood pressure by one mmHg was associated with 5% higher risk for stroke and 3% higher risk for myocardial infarction (Models 2-3). Total cholesterol and LDL/HDL-ratio showed no association with non-fatal myocardial infarction or stroke. The ratio apo B/apo AI was significantly positively associated with first non-fatal myocardial infarction, while frequency of alcohol consumption showed significant positive association with first non-fatal stroke (Model 3).

Table 9. Risk factors for first non-fatal stroke.
Case identification: ICD-10 code: I 60-64.

Variables	Men and women (16 cases)		
	Model 1	Model 2	Model 3
	Hazard ratio (CI)	Hazard ratio (CI)	Hazard ratio (CI)
Sex (female vs. male)	0.64 (0.18-2.26)	0.66 (0.19-2.28)	1.02 (0.27-3.90)
Age, 1 year	1.06 (1.02-1.10)**	1.06 (1.01-1.10)*	1.09 (1.03-1.14)**
Smoking (yes vs. no)	3.30 (1.01-10.80)*	3.35 (1.03-10.97)*	3.27 (1.01-10.61)*
Systolic BP, 1 mmHg	1.04 (1.02-1.07)‡	1.05 (1.02-1.07)‡	1.05 (1.02-1.07)‡
Total cholesterol, 1 mmol/l	1.25 (0.85-1.84)	–	–
Ratio LDL/HDL	–	1.28 (0.94-1.76)	–
Ratio apo B/apo AI	–	–	4.32 (0.51-36.27)
Albumin, 1 g/l	–	–	0.99 (0.84-1.18)
Log10 (hsCRP)	–	–	1.24 (0.38-4.02)
Body Mass Index, 1 kg/m^2	–	–	1.04 (0.98-1.10)
Frequency of alcohol intake [a]	–	–	2.03 (1.13-3.64)*
Low fruit/vegetable consumption [b]	–	–	0.90 (0.19-4.28)
Depression [c]	–	–	0.75 (0.20-2.86)

* p<0.05; **p<0.01; ‡ p<0.0001; – not included in the model;
[a] categorized as: 1-never, 2 - once a month or less, 3 - two-four times a month, 4 - two-three times a week, 5 - four or more times a week; [b] once a week or less (yes vs. no); [c] yes vs. no.

5. DISCUSSION

5.1 Representativity of the study population.

Representativity of the study sample has to be considered, as the method we used to recruit participants was not ideal. It was not possible to select a randomized sample from a centralized register of the general population, as such population register was not available in Arkhangelsk. Recruitment of participants during obligatory annual medical examination was an attempt to reach the general population. These obligatory annual medical examinations are the remnants of a soviet system of prophylactic medical check-ups of the entire general population [3]. Although in the post-soviet period this system went gradually into decay because of the lack of finance and medical personnel, some of its elements preserve until now (medical examination of the working and studying population, as well as of some categories of pensioners).

People who attend annual medical examination are obliged to do so through their place of work or study. Therefore they don't represent the group with particular health problems, but the general studying and working population.

Selection bias

Selection bias is "a distortion in the estimate of effect resulting from the manner in which subjects are selected for the study population" [109]. To avoid a "healthy volunteer effect" (selective self-recruitment of healthy volunteers), we have recruited participants consecutively as they came to the annual medical examination. Although the outpatient clinic has actively contacted some work and study places about the possibility to have the annual medical examination, the participants were not informed about the study until they came to the polyclinic to attend the regular medical examination. Then they were informed about the possibility to take part in the study, and each of them had a chance to refuse to participate. Most of those who refused to participate explained the refusal by lack of time.

Healthy worker effect

However, unemployed and socially marginalized people (homeless, alcoholised, without job) had little chance to be recruited during annual medical examinations at the polyclinics. This group is extremely difficult to recruit: they may have no definite place to live (homeless), they may be unable to go to the polyclinic because of the absent medical insurance, or they may be not interested to attend medical examination. As described in Paper I, this group was underrepresented in the study, especially in men. On the other hand, this group is probably underrepresented in most epidemiological studies. As a consequence, it may result in underestimation of health problems because the most marginalized members of the society with high risk for diseases and death are underrepresented in the study sample.

To what extend is our population sample representative for the general population?

To answer this question we compared the study population with the Arkhangelsk region population and the entire Russian population in 2000 (Table 10, 11). The data for the whole Russian population were obtained from the Goskomstat [1]. The census in 2002 was carried out in the whole Russia and gave more exact information about the country population. It showed that the data from the Goskomstat before 2002 were not very precise.

Table 10. Age groups in 2000 according to the Goskomstat of Russia (%).

	Men			**Women**		
Age	Russia	Arkhangelsk region	Study population	Russia	Arkhangelsk region	Study population
Number	54.59×10^6	56.99×10^4	1968	64.37×10^6	62.09×10^4	1737
15-19*	10.9	11.4	11.8	9.0	10.1	4.2
20-29	19.5	19.6	14.7	16.0	16.8	17.3
30-39	19.6	20.4	18.0	16.6	16.3	18.2
40-49	21.1	23.0	22.7	19.1	20.4	24.2
50-59	11.8	11.7	15.7	12.0	11.9	17.6
60+	17.1	13.9	16.9	27.3	24.5	18.5
	100%	100%	100%	100%	100%	100%

*The first age group for the whole Russian population and the Arkhangelsk region population includes participants younger than 18 years that were not included in our study.

In Papers III-IV we used the Goskomstat data before 2002 for comparisons. The reason for this was that the data from the 2002-census have not been published at the time when the papers were submitted. Below we present the comparison with the recent census data.

Table 11. Comparison of the study population with the population of the entire Russia (more precise data for Russia from census in 2002):

	Men		Women	
Age	Russia	Study population	Russia	Study population
Number	55.41 x10^6	1968	65.89 x10^6	1737
15-19*	11.7	11.8	9.6	4.2
20-29	20.0	14.7	16.7	17.3
30-39	17.9	18.0	15.3	18.2
40-49	20.9	22.7	19.1	24.2
50-59	12.6	15.7	12.8	17.6
60+	16.8	16.9	26.6	18.5
	100%	100%	100%	100%

*The first age group for the whole Russian population and the Arkhangelsk region population includes participants younger than 18 years that were not included in our study.

We assume that there was no big difference in age-distribution between the study population and the general Russian population. All the age groups were represented in the study population. However, in our papers we have presented sex- and age-specific data, age-adjusted data or age-standardized data (standardized to the general population of Russia in 2000 according to the Goskomstat).

Working status

Proportions of pensioners of both sexes were similar in the study sample to that in the Arkhangelsk region population (Paper I). Proportions of employed women, female students and women out of work (housewives and unemployed) were also similar (Paper I). The study population contained more male students and employed men than the general population of the Arkhangelsk region. Those unemployed who were in search for work and attended annual medical examinations were also recruited in the study. The group of unemployed was underrepresented in the study population, which is a limitation of this study.

Working status and age

Participants younger than 25 years were mainly students (72 percent of men and 61 percent of women). The majority of 25-59 years old men were seamen and industry workers (86 percent), while women of this age were mainly civil employees and factory workers (73 percent). Civil employees were predominantly occupied in educational and health care systems. About 84 percent of all examined civil employees were women and only 16 percent were men. The official statistical data for the entire Arkhangelsk region in 1999 showed the same skewed sex-distribution in these professions (84-85 percent women and 15-16 percent men) [101]. In the age groups over 60 years there were mostly pensioners (80 percent of men and 88 percent of women).

Educational status

The study population was generally more educated than the Arkhangelsk region population (Paper I). This difference may be partially interpreted as an urban-rural difference (when children in villages graduate from secondary school they either begin to work at farms or move to the city to continue education). The city-village difference may also be partly responsible for the lower percentage of unemployed in the study population compared to the general Russian population, as unemployment is higher in Russian villages compared with cities.

Family status

Marital status of the study sample was similar to that as in the general Arkhangelsk region population (Paper I).

Disease status

The age-standardised prevalence of self-reported circulatory diseases in our study population was close to the official figures for the general population of Northwest Russia (Paper I).

With few exceptions, the major demographic characteristics of the study population were close to those of the general Arkhangelsk region population. The study population sample seems to be fairly representative for the general working population, students and pensioners in Arkhangelsk.

5.2 Information bias or data collection bias

Information bias can occur from errors in obtaining the information, whenever there are errors in the measurement of subjects [112]. Bias in data collection can arise from errors of the observer, errors of the measuring instruments, errors of the subjects and errors during data handling [109].

Instrument and observer bias

These biases can occur due to inaccurate measuring instruments and due to difference among observers (interobserver variation) [109]. In order to avoid this type of bias all the participants in our study were examined by specially trained medical personnel according to the same routine at the same place of examination. Each medical nurse was responsible for her particular part of examination. It allowed us to avoid the interobserver variation in examination of subjects. The same routine and place of examination allowed to avoid the instrument bias. For example, blood pressure measurement by the DINAMAP is very sensitive to any changes in circumstances of the measurement: high level of noise or presence of many people in the room may affect the result. To avoid this, we had a special room for this measurement. No other activities took place in this room. A medical nurse was trained to use DINAMAP and to perform the measurement.

The laboratory results used for analyses were performed at the Department of Clinical Chemistry, University hospital of Tromsø, Norway. This laboratory is highly reliable and it routinely uses both external and internal methods of quality control.

Subject bias

By definition, subject bias refers to the inaccuracy of the data provided by the subjects [109].
One type of subject bias is "unacceptable exposure bias", which means that socially unacceptable exposures tend to be underreported. We concluded in Paper V that alcohol consumption was substantially underreported. It is known from other studies that participants tend to underreport their actual alcohol consumption [113]. Although all the participants were informed that the study was strictly confidential, some professional groups might have underreported alcohol consumption because they feared to loose job or because it was socially undesirable to report the actual alcohol intake.

Another type of subject bias is a cultural bias, which means that subjects' responses may differ because of cultural reasons [109]. As we have discussed in Paper III, cultural differences may apply when a "western" questionnaire is translated into Russian. To avoid incorrect or unclear formulations of the questions, a double back-translation of the questions by two independent translators was used. A specially trained nurse was also present in the room where

participants filled inn the questionnaire. She was instructed to help participants if there were some difficulties in understanding the questions. However, cultural bias could not be completely excluded. For example, lower prevalence of self-reported family history of CVD in Russians compared with Norwegians might be due to different attitude towards the diseases and less information about them in Russian families.

5.3 Confounding

Confounding occurs when effects of exposure of interest is mixed with effects of extraneous factors (confounders). Confounding factor is associated both with the exposure and the health outcome of interest. Confounding factor must not intermediate in exposure/outcome pathway [109]. The strength of association between exposure and outcome may be under- or overestimated because of confounding; in some cases confounding may even change the direction of the association. We tried to control for possible confounding through adjustment for age and other factors in multivariable models (Paper II, III, IV, V) and through stratification by age and sex (Paper I, V). However, residual confounding may be still present, as data on some potential confounders were not obtained (for example, we had no direct measurement of exposure to poverty).

5.4 Discussion of the main results

Our results indicate that the CVD epidemic in Russia could not be explained only by the classical CVD risk factors (Paper I). Levels of the classical CVD risk factors were lower than expected for a population with high CVD mortality and morbidity. Serum lipid profile was especially favorable in this population. These findings are in accordance with results from other studies in Russia [6-9]. Despite the high CVD incidence in the general population, the CVD risks predicted by the Framingham risk score and the Norwegian Myocardial infarction risk score were not especially high. Since these risk scores represents a cumulative score of only classical risk factors (age, blood pressure, blood lipids, smoking), it is likely that other factors (not included in the risk equation) are responsible for the excess incidence of CVD.

High alcohol consumption turned out to be a powerful factor in our study. Paper V concluded that a considerable part of the study population had high level of alcohol consumption. Some professional groups were especially alcoholised, for example seamen and industrial workers. High GGT levels together with responses to the AUDIT-questionnaire suggest that the real alcohol consumption was much higher than reported.

All factors investigated in this population (classical CVD risk factors, apolipoproteins, hsCRP, psychosocial factors, life quality) were strongly associated with the alcohol variables (Papers II, III, IV, V). In Paper II we described the unusually high levels of apo AI in men and

women compared with population studies in other countries. Apo AI was especially high in groups with high alcohol intake, and was strongly positively associated with alcohol consumption and GGT levels. We suggest that the unusually high apo AI levels in middle-aged men are alcohol-related. Alcohol is known to increase HDL-cholesterol and apo AI levels [114, 115], however acute ingestion of alcohol also increases blood pressure and other serum lipids. In Paper V we have shown that the group with high GGT had higher triglycerides, apo B and LDL cholesterol, higher blood pressure and higher Framingham risk score than those with low GGT. Although this group had higher apo AI than the group with low GGT, the effect of high alcohol consumption might be more damaging than the positive effect of apo AI.

Clearly, high alcohol consumption not only affects the level of the classical CVD risk factors, it also increases the risk of CVD through other mechanisms. One mechanism might be a pro-inflammatory effect of alcohol described in Paper IV. We found no protective (anti-inflammatory) effect of light/moderate alcohol consumption in our study, which is rather different from other studies. This may be due to the fact that alcohol consumption was substantially underreported, and to a special drinking pattern. The prevailing pattern of alcohol consumption was binge drinking of vodka (Paper IV, V). Consumption of wine, which has antioxidant/anti-inflammatory properties, was relatively low in our study.

The drinking pattern seems to play a major role in alcohol's effect on health variables. The well-known "French paradox" (low cardiovascular mortality in wine-drinking countries) may be the result of a more favorable drinking pattern with regular moderate wine intake. There is evidence that binge drinking has different physiological effects than regular moderate alcohol consumption. Binge drinking may increase the probability of arrhythmias and cause adverse changes in lipid profile, blood pressure and haemostatic system [116-118]. A pro-inflammatory effect of alcohol revealed in our study adds to the knowledge about damaging mechanisms of binge drinking.

Our assumptions on the important role of alcohol for the CVD epidemic in Russia were partly confirmed by the results of Cox regression analysis of the preliminary follow-up data. Frequency of alcohol consumption was a significant predictor for first non-fatal stroke. There was also a tendency towards positive association between CVD death and alcohol consumption, but the association was not statistically significant. Further analysis should be considered when information on more CVD cases is obtained.

Another important feature in this population was psychosocial distress (depression, anxiety, sleeping disorders). As reported in Paper III, a substantial part of the study population (especially women) displayed psychosocial distress and low quality of life. The level of psychosocial distress was higher than in comparable studies from Northern Norway. Psychosocial distress was positively associated with self-reported CVD and gastrointestinal

diseases. These associations remained significant after adjustment for possible confounders. Although the cross-sectional design of our study does not allow conclusions about causality, these results are consistent with findings of several prospective studies, which have described the positive association between psychosocial factors and CVD [75, 76]. Psychosocial distress may affect cardiovascular system directly through neurophysiological mechanisms. There is evidence that through its effect on central and autonomic nervous system, psychosocial distress produces a cascade of physiological responses that may result in coronary thrombosis, plaque rupture, myocardial ischemia, ventricular fibrillation, and promote a hypercoagulation state in patients with atherosclerosis [119-121]. Psychosocial distress was strongly positively associated with smoking and alcohol use disorders in our study. It confirms the hypothesis that psychosocial distress may have a direct effect on the initiation and continuance of risk behaviors such as smoking and excessive alcohol consumption. At the same time the symptoms of psychosocial distress were associated with poor nutrition (low consumption of food items and dissatisfaction with own nutrition). It is possible that deficiency of vitamins and other essential nutrients may contribute to the development of depression and insomnia. However, it is more likely that psychosocial distress and poor nutrition in this population are consequences of socioeconomic difficulties.

Poor nutrition appeared to be an essential risk factor for CVD in this population, especially nutrition with low consumption of fresh fruits/vegetables. About 40% of men and 36% of women reported low consumption of fruits and vegetables (once a week or less). This finding is consistent with official Goskomstat data and shows that a substantial part of the Russian population is likely to have nutritional deficiencies and particularly shortage of fruits and vegetables. Nutrition with low fruits/vegetables intake was significantly positively associated with CVD death in our study. Poor nutrition may reduce resistance to diseases due to vitamin and antioxidant deficiency, insufficient intake of fiber, proteins and minerals. Insufficient dietary intake of vitamin B12 and folate may result in higher concentrations of homocysteine, which has been reported as an independent risk factor for CVD [122, 123].

Vitamin deficiency may influence the effect of alcohol consumption. There is evidence that cardioprotective effect of moderate drinking may be partially reduced unless drinkers have high folate intake, because products of ethanol metabolism inactivate folate and influence homocysteine metabolism [124, 125]. Several studies have shown an increased CVD risk in drinkers outside meals compared with drinkers with meals [126, 127]. The unfavourable combination of binge drinking pattern and poor nutrition may be the reason why alcohol has different effect on health in Russia compared with Mediterranean countries where frequent moderate wine consumption is combined with meals rich in fruits and vegetables.

Malnourished people have low levels of total cholesterol and other serum lipids [128]. The absence of the classical positive linear association between total cholesterol and CVD death in Russian population may represent the effect of poor nutrition. In Cox regression analysis we found a significant negative association between BMI and CVD mortality. This controversial finding fits well with results from the MONICA study in Russia. In one of their publications, the MONICA research group had to exclude the data from former USSR from the general analysis in order to reveal the usual positive association between BMI and CVD [9]. In the former USSR populations from the MONICA study, the association between BMI and CVD events was negative [9]. We believe that the absence of the positive association between BMI and CVD death in Russian population may represent the effect of poor nutrition.

In paper III we postulated that poor nutrition probably was a marker of low socioeconomic status. According to a study of nutritional status, weight loss among elderly in Russia was strongly associated with lack of money to buy food [129]. The Goskomstat data on nutrition show that about 70% of the population in the mid-90s had insufficient protein consumption. The lowest protein intake was observed in groups with the lowest income [130]. Low serum albumin is known as a marker of inflammation, but it might be also a marker of low protein intake. In Cox regression analysis in our study levels of serum albumin were inversely associated with CVD death. In linear regression analysis (Appendix III, Table 12), low serum albumin was significantly associated with low education, alcohol consumption, depression and smoking. Low fruit/vegetable consumption was also associated with the same factors and low quality of life (Appendix III, Table 13).

Low fruit/vegetable consumption and low albumin may identify a vulnerable group with poor nutrition, low socio-economic status, psychosocial distress and unfavorable lifestyle (smoking, alcohol consumption). As alcohol is relatively inexpensive in Russia compared with food, it is plausible that this group buys alcohol as a cheap pleasure that "helps to forget everyday cares and difficulties" [131]. This group may be particularly vulnerable to diseases, as effect of poor nutrition is combined with high alcohol intake, smoking and psychosocial distress.

Strong positive associations between psychosocial distress, poor nutrition, high alcohol consumption and low self-reported quality of life in our study indicate that these factors tend to cluster and may interact. Aggregation of these factors is characteristic for the poorest part of the population. The long-term socioeconomic crisis after the collapse of the Soviet Union has led to a high level of individual poverty. According to the official data about 1/4-1/3 of the Russian population live in extreme poverty, e.g. have income below a subsistence level. At the same time a large proportion of the population lives on income close to the subsistence level.

Some independent sources report that about 65% of the Russian population consider themselves poor [132].

Poverty in Russia is a particular socioeconomic phenomenon as there is an enormous gap between the rich and poor without established middle class. This change took place in the last 15 years implying a rapid growth of social inequality. In the 90s, privatization of state property at low prices by a small group of people produced a monstrously corrupt economy [133]. Today, 80% of national wealth is controlled by less than 5% of the population, while entire social groups are sunk into poverty [134]. Increased income inequality is at least in part responsible for high level of frustration and psychosocial distress in this population.

Millions of poor fulltime workers (low salaries) and pensioners (low retirement pensions) is another particular feature of the Russian poverty. Hyperinflation of the 90s has devaluated personal savings leaving the majority of the elderly with retirement pension lower than the subsistence minimum. In the 90s, there were delays of salaries and pensions for several months. The situation has improved in the recent years, but salaries are still low and paid with delays in some sectors of Russian economy. Persistent socioeconomic deprivation implies poor nutrition due to lack of money to buy food, chronic psychosocial distress and frustration, and severely reduced access to leisure and health services. High level of suicides in the post-soviet Russia reflects the devastating psychosocial atmosphere. High alcohol consumption is probably the consequence of the socioeconomic deprivation in the country with highly available cheap alcohol and social tolerance towards drinking. A relatively large proportion of the population has become marginalized: homeless, unemployed, alcohol- and drug abusers [1]. According to rough estimations, about 1000 homeless people were living in the center of Arkhangelsk city in 2004.

Unfortunately, we had no direct measure of poverty in our data. The most marginalized part of the population was probably underrepresented in the study population. However even in the sample of working and studying population we found high prevalence of poor nutrition, psychosocial distress, alcohol use disorders and low self-perceived quality of life. We consider these factors to be consequences of the devastating socioeconomic situation. The results of our study indicate that the combination of these factors is probably a keystone of the public health crisis and CVD epidemic in the post-soviet Russia. The problem of socioeconomic deprivation and its unfavorable consequences for public health in Russia should be investigated further. In future research it will be important to obtain more detailed information on socioeconomic factors like level of personal income and household income, as well as on one's relative ranking in society.

5.5 Other possible explanations

Case fatality

Case-fatality is expressed as a proportion of patients dying in the follow-up interval out of all patients under observation [109]. Case-fatality may markedly influence cardiovascular mortality. CVD case-fatality is affected by availability of effective treatment in the acute stage of the disease (thrombolysis, heparin, percutaneous transluminal coronary angioplasty (PTCA)). The problem of treatment availability is closely related to the problem of poverty and lack of finance in the Russian health care system. The MONICA study estimated that the age-standardized case-fatality in Russia was one of the highest among the 37 examined populations [135]. A study from St-Petersburg described that thrombolysis, heparin-therapy and PTCA were used much less at Russian hospitals than at hospitals in USA [136]. From personal communications with Russian cardiologists we know that thrombolysis and PTCA are not available at some hospitals in the Arkhangelsk region due to lack of finance [137]. In the Arkhangelsk study 2000, we had no data about hospital treatment of CVD, and thus were not able to investigate whether effective methods of treatment were available to the population. At a later follow-up study we have planned to collect information on treatment of CVD. This will be the topic for further research.

Misclassification of CVD death

The results of Cox regression analysis were somewhat different for fatal and non-fatal events. The classical CVD risk factors had more predictive value for non-fatal myocardial infarction and stroke than for CVD death. The discrepancy might be the result of better diagnostic practice for non-fatal events and/or misclassification of conditions other than CVD under the official diagnosis of CVD death.

There is also some evidence that acute alcohol poisonings might be misclassified as cardiovascular deaths in Russia. A study from Kursk showed that many people with cardiovascular death diagnoses had lethal or nearly lethal alcohol levels in blood [138]. Another study from Izhevsk found that many of those recorded as dying from cardiovascular diseases had high blood alcohol level, however, the levels were not sufficient to cause death from acute alcohol poisoning [139]. In the mid-80s an autopsy-based study of death diagnoses was also conducted in Arkhangelsk [140]. The results were published, but only in Russian. The study reported that among those who died in Arkhangelsk in 1983-85 from sudden coronary death, about 87% of men and 47% of women had been drinking alcohol prior to death.

Medical diagnostic practices might be different in different regions of Russia. In Arkhangelsk region, the number of autopsies has decreased substantially in the 90s due to lack

of finance. It is often young doctors from emergency service that write death diagnosis, which is often based mainly on clinical history described by relatives of the dead. In many situations it might be socially unacceptable to reflect the fact of alcohol intake or malnutrition in death diagnosis. Validation studies of death diagnoses are necessary to reveal possible misclassification of death causes in Russia.

6. SUMMARY AND IMPLICATIONS

This study was designed and carried out in Arkhangelsk to investigate reasons for high CVD mortality/morbidity in Northwest of Russia. It revealed that the high CVD morbidity and mortality in this population could not be explained only by the classical CVD risk factors (blood pressure, serum lipids, smoking). Lipid profile was especially favorable. These results from the Arkhangelsk study are consistent with findings from other studies in Russia.

High alcohol consumption, psychosocial distress and poor nutrition with low intake of fresh fruits/vegetables emerged as more important factors than the classical CVD risk factors. A substantial part of this population had hazardous or harmful level of alcohol consumption, mainly in the form of binge vodka drinking. Vodka consumption showed a linear positive association with marker of inflammation – hsCRP, which is a known indicator of CVD risk. The study population had also high levels of GGT – a serum marker of high alcohol consumption. GGT levels in both sexes were more than twice as high as found in comparable studies from other countries. Participants with high GGT levels had higher risk score for CVD. Alcohol consumption was an important risk determinant for non-fatal stroke, and showed a non-significant tendency for positive association with CVD-death.

A large part of the study population reported psychosocial distress (depression, anxiety and sleeping problems) and poor nutrition with low consumption of fruits/vegetables. Psychosocial distress was strongly associated with low socioeconomic status, poor nutrition and high alcohol consumption, as well as with CVD. Low fruits/vegetables consumption was independently associated with CVD death. These findings underline the importance of psychosocial and nutritional variables for CVD epidemiology in Russia.

High prevalence of psychosocial distress, poor nutrition and high alcohol consumption probably reflects the high level of individual poverty in this population. In a society experiencing large socioeconomic problems these factors probably act in chain. Our results indicate that the combination of these factors may play a major role in the CVD epidemic in post-soviet Russia.

7. FURTHER RESEARCH:

Our research group is planning to continue the follow-up registration of deaths and diseases. A major challenge is to find information about participants that have moved, because no centralized population register is available for medical research in Russia. We shall use alternative sources to reduce missing to follow-up: data from insurance company, telephone catalog, data from the Arkhangelsk Health Care Department. It will be important to develop a closer collaboration with Russian researchers in order to maintain the continuing registration of disease/death cases. We are also discussing with our Russian colleagues the possibility of a verification study for death/disease diagnoses. Another topic that will be investigated is availability of effective treatment and case-fatality of CVD events in Russia compared with Western countries.

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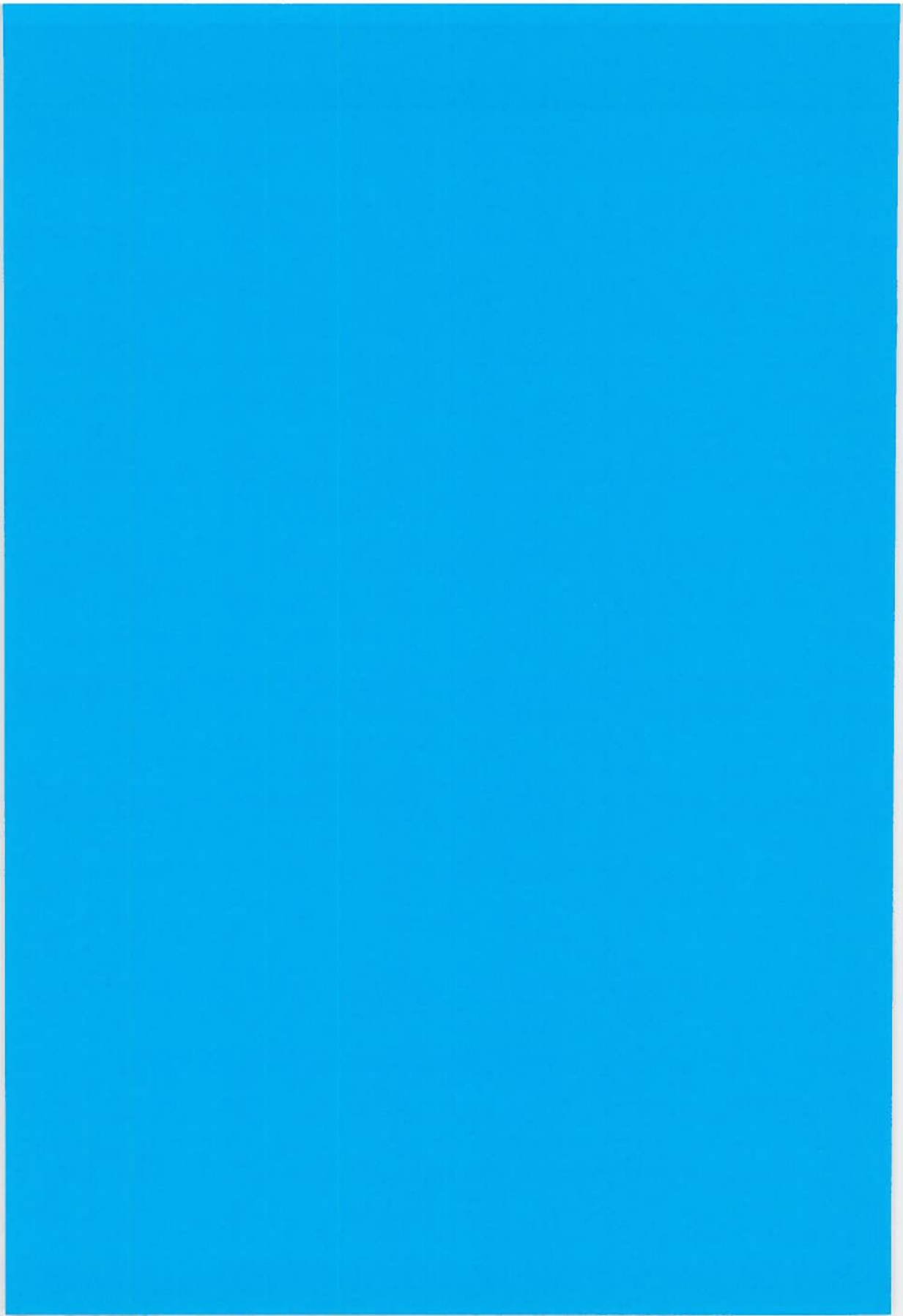
Paper I



Errata in Paper I

Page 871 in abbreviations: CV = analytic coefficient of variation

Page 874, line 9 from the top: the 10-year risk for women is 4%, not 7%.

These printed mistakes do not influence the conclusions of the paper.

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MORTALITY

High cardiovascular mortality in Russia cannot be explained by the classical risk factors. The Arkhangelsk study 2000

Maria Averina[1,*], Odd Nilssen[1], Tormod Brenn[1], Jan Brox[2], Alexei G. Kalinin[3] & Vadim L. Arkhipovsky[4]

[1]*Institute of Community Medicine, Medical Faculty, University of Tromsø;* [2]*Department of Clinical Chemistry, University Hospital of Tromsø, Tromsø, Norway;* [3]*Northern State Medical University, Arkhangelsk, Russia;* [4]*Semashko Clinic, Arkhangelsk, Russia*

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Abstract. Since the beginning of the 1990s the public health situation in Russia has been characterized by an extremely high mortality and a significant reduction in life expectancy. Cardiovascular diseases remained the major cause of death. Only a few large population studies were conducted in Russia during this period. A total of 1968 men and 1737 women aged 18–75 years participated in a health survey in Arkhangelsk, Russia, over the period 1999–2000. Investigation included assessment of classic cardiovascular risk factors (family history, smoking, blood pressure, and blood lipids) along with general health variables. The paper presents sex specific data on risk factors for coronary heart disease. Though the cardiovascular mortality is high in Russia, the calculated risk for coronary heart disease (the Framingham risk score and the Norwegian risk score) was lower in all age groups of men and women in Arkhangelsk compared with studies from the Western Europe and USA. Our data suggest that high cardiovascular mortality in Russia may be driven not only by the classic risk factors for coronary heart disease.

Key words: Coronary heart disease, Risk score, Russia

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CV = analytic

Introduction

The size of Russian population has been rapidly declining since the beginning of 1990s. Life expectancy at birth remained low during the last 15 years [1–11]. Cardiovascular diseases were the major cause of death [1, 10]. The ratio of cardiovascular mortality in the former Soviet Union to the mortality in the Western Europe was highest in the age group 35–44 years, especially in men [12]. Premature death of middle-aged men resulted in a large sex gap in life expectancy. In the year 2000 life expectancy in Russia was 59.0 and 72.2 years for men and women, respectively [11]. The gap in healthy life expectancy (HALE) between Russia and Western Europe countries was 18–20 years for men and 10–13 years for women [13].

Despite the crisis in public health, only a few epidemiological studies were carried out in Russia during the post-soviet period [14–18]. The Lipid Research Prevalence Study (LRPS) was conducted in Moscow and St-Petersburg (1978–1982), the MONICA study was carried out in Moscow and Novosibirsk (1984–1995), and the population study in Karelia was accomplished in 1992 [15–18]. In addition to these studies there were some publications based on the information from the Goskomstat (the Russian Central Statistics Agency) and from the Moscow Centre for Demography and Human Ecology [1, 2, 5, 10].

Lack of epidemiological studies results in absence of reliable and comparable information about the public health. The few previous studies were conducted mostly in Moscow or St-Petersburg in the 1980s.

According to the official statistics the largest decrease in life expectancy was observed in the North of Russia [5, 6]. Therefore, after a pilot study in 1996, we decided to carry out a population study in the Arkhangelsk region – the largest region in the North of European Russia. So far, no population studies have been published from this area. The health survey was a co-project between the Northern State Medical University, Arkhangelsk, Russia and the Institute of Community Medicine, University of Tromsø, Norway. The aim of the survey was to study risk factors for coronary heart disease (CHD) together with alcohol consumption, social stress, nutrition, and quality of life, and to explore the potential impact of alcohol on the population health. This paper presents the data about risk factors for CHD.

Materials and methods

Study population

Arkhangelsk region is the largest region of the European Russia; it accounts 3.4% of the whole territory [19]. In 1999 the town of Arkhangelsk had a population of 170,000 men and 197,000 women [20]. As a population register in Russia was not available for medical research, we had to find other ways to recruit participants. Outpatient clinics in Russia provide primary medical care for the general population according to territorial and occupational principles. From November 1999 to November 2000 we investigated the population registered at the Semashko outpatient clinic in Arkhangelsk. From the beginning of the study it was decided to have similarly sized age and sex groups. To avoid a 'healthy volunteer effect', participants were recruited consecutively during the obligatory annual medical examination at the outpatient clinic or through their work/study place. Of those who were invited, 40 persons refused to participate (1.1%). Altogether 1968 men and 1737 women aged 18 years and more participated in the study (1.0% of the city population, 0.3% of the region population). People with different occupational status were recruited: seamen, workers, teachers, doctors, domestic services, office and trade employees, students and pensioners.

Examination

Each participant completed a questionnaire covering education, marital status, profession, previous, present and family diseases, self-estimation of health, complaints, diet habits, physical activity at work and leisure time, active physical training, smoking, coffee-, alcohol- and drug consumption. Weight, height, waist and hip circumference were measured. Blood pressure was measured three times at intervals of two minutes on the right arm in a sitting position using DINAMAP R (Criticon, Tampa, Florida). Non-fasting venous blood samples were drawn and centrifuged within 15–25 min of venepuncture at the outpatient clinics' laboratory. The serum samples were kept at −20 °C and transported to Tromsø in boxes with freezing elements by a 5-h flight. As the results of a Norwegian–Russian co-project on Svalbard [21] had shown both systematical and arbitrary differences between laboratories in Norway and Russia, we decided to perform parallel laboratory analyses at the Department of Clinical Chemistry, University Hospital of Tromsø and at the laboratory in Arkhangelsk. This paper presents the results from the laboratory in Tromsø.

Analyses

Total serum cholesterol was measured by the enzymatic colorimetric test (cholesterolesterase, cholesteroloxidase). Analytic coefficient of variation (CV) was 5%. Triglycerides were assayed by the enzymatic colorimetric test (lipoproteinlipase, glycerokinase, and glycerophosfat oxidase), CV was 2%. High-density lipoprotein cholesterol (HDL-cholesterol) was measured by the homogeneous enzymatic colorimetric test (PEG cholesterolesterase, PEG peroxidase), CV was 3%. Results of the study were compared with two studies from Northern Norway: the Finnmark study (1987–1988) [22, 23] and the Tromsø study (1994–1995) [24, 25]. Populations examined in our study and in the two Norwegian studies, were relatively similar concerning occupation and climate conditions: many of participants were involved in fishing industry, they lived in northern climate conditions with lack of sunlight and low temperatures in wintertime. Our study had the same design as the Norwegian studies (similar questionnaire, measurement of blood pressure and pulse by DINAMAP and the same laboratory in Tromsø for serum analysis). In fact, the Arkhangelsk study was designed using the experience from the population studies in Tromsø and Finnmark.

The risk for CHD was calculated using two types of risk scores: the *Framingham risk score* [26, 27] and the Norwegian *Myocardial infarction risk score* [28]. The *Framingham risk score* includes subjects' age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, smoking (yes/no) and presence of diabetes mellitus. Self-reported information about diabetes mellitus was used: Do you have diabetes mellitus (yes, no). The *Framingham risk score* estimates the 10-year risk for CHD (%). The *Myocardial infarction risk score* includes subjects' sex, total cholesterol, systolic blood pressure, family history of CHD and number of cigarettes smoked daily. The *Myocardial infarction risk score* presents the 10-year relative risk for myocardial infarction (women with no increase in any of the risk factors have RR = 1.0). Risk score $\geqslant 58 + 2x(\text{age}-39)$ indicates a very high risk for myocardial infarction. Risk factor levels and the *Myocardial infarction risk score* for the Tromsø study were calculated using the database of this study that belongs to the Institute of Community Medicine, University in Tromsø. A written permission to use the database was obtained.

The data for 35–60 years old men and women in Arkhangelsk were age standardized using the same method as in the MONICA study [15]: the sample was stratified by the three 10-year age groups and the sample means were standardized with weights 12, 11 and 8, respectively. SAS software package was used for statistical analysis (SAS Institute Inc, Cary, NC) [29].

Ethics

The study was approved by the Regional Ethical Committee, Norway.

Results

Table 1 shows general characteristics of the study population compared with the Arkhangelsk region population (aged 15–72 years) in 1999 [20].

Marital status, proportion of pensioners, employed women and female students was almost similar in the two populations, whereas educational status, numbers of male students and unemployed men were different. The proportion of women out of work (housewives or unemployed) was similar in the study population to that in the Arkhangelsk region population.

Table 2 presents age-adjusted data on the classic risk factors for CHD in Arkhangelsk compared with the Finnmark study [22, 23] and the Tromsø study [24].

Mean total cholesterol was lower in men and women in Arkhangelsk compared with Finnmark and Tromsø. Mean triglycerides were lower in Russian men than in both studies from Norway. In Russian women, mean triglycerides were lower than in Finnmark, but the same as in Tromsø. Mean HDL-cholesterol was the same in men, but lower in women in Arkhangelsk compared with the Norwegian populations [22]. Mean systolic blood pressure and body mass index were almost similar in these populations, whereas diastolic blood pressure was lower in Arkhangelsk than in Norway. Mean number of cigarettes per day was lower in men and women in Arkhangelsk than in Finnmark and Tromsø.

Table 3 presents prevalence of smoking and mean *Myocardial infarction risk score* in the Arkhangelsk study compared with the figures from Finnmark and Tromsø.

The prevalence of smoking was higher in men, but much lower in women in Arkhangelsk compared with Finnmark and Tromsø. In Arkhangelsk there was an evident sex difference in the prevalence of smoking: the prevalence in men was almost three times greater than in women. The highest prevalence of smoking was found in the young age groups. In women there was a continuous decrease in smoking with age to 1% in the oldest age group, whereas in men the prevalence of smoking decreased after the age of 60 years.

About 16% men and 34% women reported positive family history of angina pectoris and/or myocardial infarction (data not shown). The prevalence of positive family history for CHD was lower in the Arkhangelsk population compared with the studies in Finnmark and Tromsø: about 45% of men and 40% of women in Finnmark, and 41% of men and 45% of women in Tromsø have reported presence of angina pectoris and/or myocardial infarction in parents [23].

The *Myocardial infarction risk score* was lower in all age groups of men and women from Arkhangelsk compared with the Finnmark and Tromsø studies.

Table 1. General characteristics (%) of the study population compared with the population of the Arkhangelsk region

	The study population		Arkhangelsk region[a]	
	Men	Women	Men	Women
Working status				
Student	14.3	8.7	9.0	10.0
Employed	69.1	57.9	62.0	55.0
Housewife	–	6.0	–	2.0
Pensioner	15.4	23.5	15.0	24.0
Unemployed	1.2	3.9	14.0	9.0
Marital status				
Not married[b]	25.8	21.9	25.0	20.2
Married	66.7	53.6	66.4	56.4
Divorced	4.2	11.0	4.4	8.0
Widower/widow	3.3	13.5	4.1	15.3
Education				
Primary	5.8	8.6	13.3	10.8
Secondary	16.8	17.4	55.5	48.2
Professional[c]	56.5	41.5	19.1	29.2
Higher[d]	20.8	32.5	12.1	11.8

[a] The population of the Arkhangelsk region in 1999 (aged 15–72 years), according to the official statistics [20].
[b] Including not registered marriage.
[c] Secondary professional.
[d] Complete and incomplete higher education.

Table 2. Age adjusted means (SD) of blood pressure (BP), serum lipids and body mass index (BMI) in men and women from the Arkhangelsk study compared with the Finnmark study[a,b] and the Tromsø study[c]

	Men			Women		
	Arkhangelsk N = 1968	Finnmark[a] N = 9012	Tromsø[c] N = 12736	Arkhangelsk N = 1737	Finnmark[a] N = 8797	Tromsø[c] N = 14153
Mean age, years	41.8 (16.3)	43.4 (5.3)	46.7 (14.5)	44.2 (15.9)	43.4 (5.3)	47.2 (15.5)
Total cholesterol, mmol/l	5.0 (1.2)	6.6 (1.3)	6.1 (1.2)	5.1 (1.2)	6.6 (1.4)	6.1 (1.4)
Triglycerides, mmol/l	1.4 (0.9)	2.1 (1.5)	1.8 (1.1)	1.3 (0.9)	1.6 (1.0)	1.3 (0.9)
HDL-cholesterol, mmol/l[b]	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	1.5 (0.4)	1.6 (0.4)
Systolic BP, mmHg[d]	133.5 (19.0)	135.1 (17.0)	137.5 (17.4)	128.1 (22.4)	129.5 (19.3)	131.9 (22.6)
Diastolic BP, mmHg[d]	75.7 (14.6)	81.2 (11.2)	79.9 (11.8)	73.0 (13.3)	77.7 (10.9)	76.1 (12.7)
BMI, kg/m^2	25.3 (4.0)	26.0 (3.4)	25.6 (3.3)	26.0 (5.7)	25.7 (4.5)	24.8 (4.2)
Cigarettes per day[e]	13.0 (7.3)	15.8 (7.7)	14.0 (7.1)	6.4 (5.1)	12.6 (6.0)	11.1 (5.4)

[a] Westlund et al. [23].
[b] DAta for Finnmark: Njølstad et al. [22].
[c] The database of the Tromsø study (1994–1995).
[d] In Arkhangelsk and Tromsø: mean of the 2nd and the 3rd of Dinamap measurements; in Finnmark: the lowest of three Dinamap measurements (systolic BP about 2.1 mmHg and diastloic BP 1.3 mmHg lower than the mean of the 2nd and 3rd Dianamap measurements).
[e] Smokers only.

Table 4 presents the 10-year CHD risk (*Framingham risk score*) calculated for the Arkhangelsk study participants aged 30–74 years [26].

The CHD risk in Arkhangelsk was the same or lower than the 'average risk' in the Framingham study for all age groups of men and women [26]. The *Framingham risk score* for the whole study population was 4.9 (3.8) and 3.7 (8.1) for men and women, respectively, that corresponded to 8% and 7% 10-year CHD risk.

Discussion

It is difficult to draw a representative sample of the whole Russian population because of the vast territory, ethnical, religious and cultural heterogeneity (more than 100 European and Asiatic nationalities) and the unavailability of a population register for medical research. We conducted the study in the capital of the largest region in the European Russia and limited our study to the working population, students and pensioners. As data about the general population of Arkhangelsk town were not available, we compared the study population with the Arkhangelsk region population aged 15–72 years. The study population was older (from 18 years), that may partly explain its higher educational level. Marital status, proportions of pensioners, female students, employed women and women out of work (unemployed or housewives) were almost similar to that in the region population, but unemployed men were underrepresented in the study. The educational and occupational differences between the study population and the Arkhangelsk region population may be interpreted as an urban–rural difference, with more opportunities for education and work in the city. Nevertheless, with these exceptions the study population seems fairly representative for the Arkhangelsk region population.

Our findings were similar to other studies in Russia, even though these studies differed somewhat in design, population samples, methods of data collection and laboratory measurements. Table 5 presents the data for 35–64 years old participants age standardized using the same method as in the MONICA study [16].

BMI and total cholesterol in men and women were not very different in Arkhangelsk than in the MONICA study. Smoking pattern in men and women from Arkhangelsk was similar to the average smoking pattern in the MONICA study in Moscow and Novosibirsk. Systolic blood pressure was almost the same in women and 4–6 mmHg higher in men from Arkhangelsk than in the MONICA study. It is of importance that while the MONICA study used a mercury sphygmomanometer for blood pressure measurement, we used the oscillometric blood pressure device DINAMAP. This device tends to overestimate SBP and underestimate DBP compared with sphygmomanometers [30, 31]. With this consideration we conclude that the classical risk factors for CHD in the Arkhangelsk population were not very different from the final MONICA study in Moscow and Novosibirsk, supporting our suggestion about representativity of the Arkhangelsk study.

The CHD risk pattern in our study was less favorable in men than in women, mainly due to differences in smoking habits. The prevalence of daily smoking has traditionally been high in Russian men in all age groups [32]. The vast difference in smoking between younger and elder women could be ex-

Table 3. Mean risk score (SD) for myocardial infarction and prevalence of smoking (%) in the Arkhangelsk study compared with the Finnmark (1987–1988) and Tromsø (1994–1995) studies in Northern Norway

	Age, years								
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	⩾60	Total
Number, men/women									
Arkhangelsk study	140/138	181/130	176/187	217/190	230/230	221/204	87/101	332/320	1584/1500
Finnmark study[a]	138/176	438/480	815/845	2116/1932	1562/1491	1405/1363	1517/1474	882/863	8873/8624
Tromsø study[b]	1432/1777	1488/1782	1553/1791	1585/1664	1505/1615	1212/1197	848/864	2433/3073	12056/13763
Risk score[c], men									
Arkhangelsk study	19.1 (25.5)	18.0 (12.4)	25.8 (31.7)	27.0 (33.0)	35.9 (49.0)	37.9 (40.3)	62.9 (79.7)	56.8 (64.5)	33.8 (46.4)
Finnmark study[a]	25.1 (42.4)	32.5 (44.5)	38.5 (70.0)	48.4 (70.2)	55.8 (77.0)	62.6 (81.4)	69.6 (96.1)	72.5 (90.2)	55.3 (79.4)
Tromsø study[b]	21.0 (35.3)	24.7 (31.2)	31.5 (48.2)	39.2 (58.2)	48.4 (64.6)	56.2 (86.9)	65.3 (87.8)	74.2 (99.9)	45.9 (71.9)
Risk score[c], women									
Arkhangelsk study	1.7 (1.0)	1.7 (1.2)	2.0 (1.3)	2.8 (3.4)	3.8 (5.8)	5.1 (9.2)	5.6 (6.1)	7.9 (10.2)	3.9 (6.6)
Finnmark study[a]	3.3 (4.9)	3.8 (4.1)	4.3 (5.0)	5.7 (7.6)	8.1 (10.7)	12.6 (19.3)	15.6 (19.2)	16.6 (22.1)	9.6 (15.0)
Tromsø study[b]	2.8 (2.7)	3.3 (3.7)	4.0 (4.4)	5.5 (7.6)	7.6 (11.2)	11.8 (17.1)	15.6 (22.1)	22.1 (25.6)	9.8 (16.9)
Smoking, men, %									
Arkhangelsk study	67.9	59.7	60.8	60.4	48.3	61.5	55.2	39.8	56.7
Finnmark study[a]	58.1	57.9	55.1	54.2	51.9	52.6	50.0	48.0	52.6
Tromsø study[b]	38.4	39.3	38.8	40.8	40.0	38.3	36.2	30.8	37.4
Smoking, women, %									
Arkhangelsk study	37.7	31.5	31.0	31.6	17.8	9.3	7.9	1.3	21.3
Finnmark study[a]	51.9	58.4	53.4	49.9	45.5	43.8	39.2	32.2	45.7
Tromsø study[b]	38.7	39.6	42.4	45.2	40.2	37.7	35.3	23.0	36.3

[a] Westlund K et al. [23].
[b] The database of the Tromsø study (1994–1995).
[c] Risk score presents the risk of having myocardial infarction in the next 10 years.

Table 4. The 10-year risk for CHD (%) in men and women in Arkhangelsk together with the 'average' and 'low risk' (%) according to the Framingham score

	Age, years								
	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74
Men									
Arkhangelsk study	2	4	5	8	10	13	18	25	28
Average risk[a]	3	5	7	11	14	16	21	25	30
Low risk[b]	2	3	4	4	6	7	9	11	14
Women									
Arkhangelsk study	<1	<1	2	4	8	10	13	13	13
Average risk[a]	<1	<1	2	5	8	12	12	13	14
Low risk[b]	<1	<1	2	3	5	7	8	8	8

[a] The 10-year risk for CHD reported as 'average' in the Framingham study [26].
[b] The idealized 'low risk' for CHD from the Framingham study based on the optimal blood pressure, optimal blood lipids, no diabetes and no smoking [26].

Table 5. Age-standardized prevalence of daily smoking, means of BMI, systolic blood pressure and total cholesterol in 35–64 years old men and women from the Arkhangelsk study compared with the final MONICA study in Moscow and Novosibirsk

	N	Daily smoking, %	BMI, kg/m^2	SBP, mmHg	Total cholesterol[c]
Men					
Arkhangelsk study[a]	1064	51	26.3	136	5.3
MONICA Moscow[b]	1873	47	25.2	130	5.3
MONICA Novosibirsk[b]	1088	60	25.9	132	5.0
Women					
Arkhangelsk study[a]	1032	10	27.3	132	5.5
MONICA Moscow[b]	1648	14	26.5	133	5.6
MONICA Novosibirsk[b]	1089	6	28.5	131	5.3

[a] Arkhangelsk data for participants aged 35–64 years standardized to the MONICA study.
[b] The final MONICA study in Moscow and Novosibirsk [16].
[c] In mmol/l.

plained by the changed attitude to women's smoking. Social changes in Russia have led to implementation of the western smoking pattern characterized by younger women smoking as much as men.

However, despite the high prevalence of smoking in men, the 10-year risk for CHD, calculated according to the *Framingham risk score* (including prevalence of smoking), was the same or lower than the CHD risk estimated as 'average' in the Framingham study in all age groups of men and women [26].

The 10-year CHD risk provides an estimate of the probability that individuals will develop a disease during a 10-year period, and corresponds to the 10-year cumulative incidence of CHD. The 10-year CHD risk in the study population was 7–8%, which estimates the annual CHD incidence of 7–8 per 1000 adults. According to the official data for the Arkhangelsk region, the annual incidence in the time of the study was 16.9 per 1000 adults [33], which is twice as high as that estimated by the Framingham risk score. It could be argued that a smaller population at highest risk might have been missed since this population sample represents mainly working participants. However, the prevalence of self-reported cardiovascular diseases in the study population was 130.7 per 1000 participants (age-standardized to the total Russian population), which agrees well with the official data for the adult population in the Northwest of Russia in 1998 (132.9 per 1000) [34]. Although the 'healthy worker effect' cannot completely be excluded, the gap between the estimated aggregate risk and the vital statistics data is too large to be explained by a possible selection bias.

The classic risk factors for CHD were in general more favourable in the Arkhangelsk population than in Norway (Finnmark and Tromsø) except for prevalence of smoking in men and HDL cholesterol in women. However, mean number of cigarettes/day in smokers was lower in Arkhangelsk than in the Norwegian studies. The *Myocardial infarction risk score* was lower in the Arkhangelsk population than in the populations in Finnmark and Tromsø. Unlike the *Framingham score*, the *Myocardial infarction risk score* includes numbers of cigarettes/day (not prevalence of smoking). However, both scores displayed a

more favourable risk profile in the Arkhangelsk population compared with other studies.

According to official Russian data the age standardized cardiovascular mortality in Arkhangelsk region in 1999 was 805 and 860 per 100,000 men and women, respectively [20]. In 1995 (the time of the Tromsø IV study) and in 1988 (the time of the Finnmark study) the age standardized cardiovascular mortality was 598 and 316 per 100,000 men and women in Tromsø and 737 and 424 per 100,000 men and women in Finnmark, respectively [35]. Cardiovascular mortality is steadily rising in Russia and gradually decreasing in Norway.

The prevalence of positive family history for CHD was lower in the Arkhangelsk population compared with Finnmark and Tromsø. Unless awareness of family diseases is low in Russia, the reasons for the high cardiovascular mortality do not seem to lie in the genes either.

Our study did not confirm the importance of the classic risk factors in relation to the high cardiovascular mortality in Russia. In fact the MONICA study also pointed in the same direction, although they did not focus on that item [15, 16]. If the 'power' of the classic risk factors in Russia is the same as in the Western Europe and USA, we certainly have to search for other factors to explain the high cardiovascular mortality in Russia.

Further investigations are therefore necessary to explain the Russian mortality paradox, 'unprecedented in the history of the recorded mortality in the world' [36].

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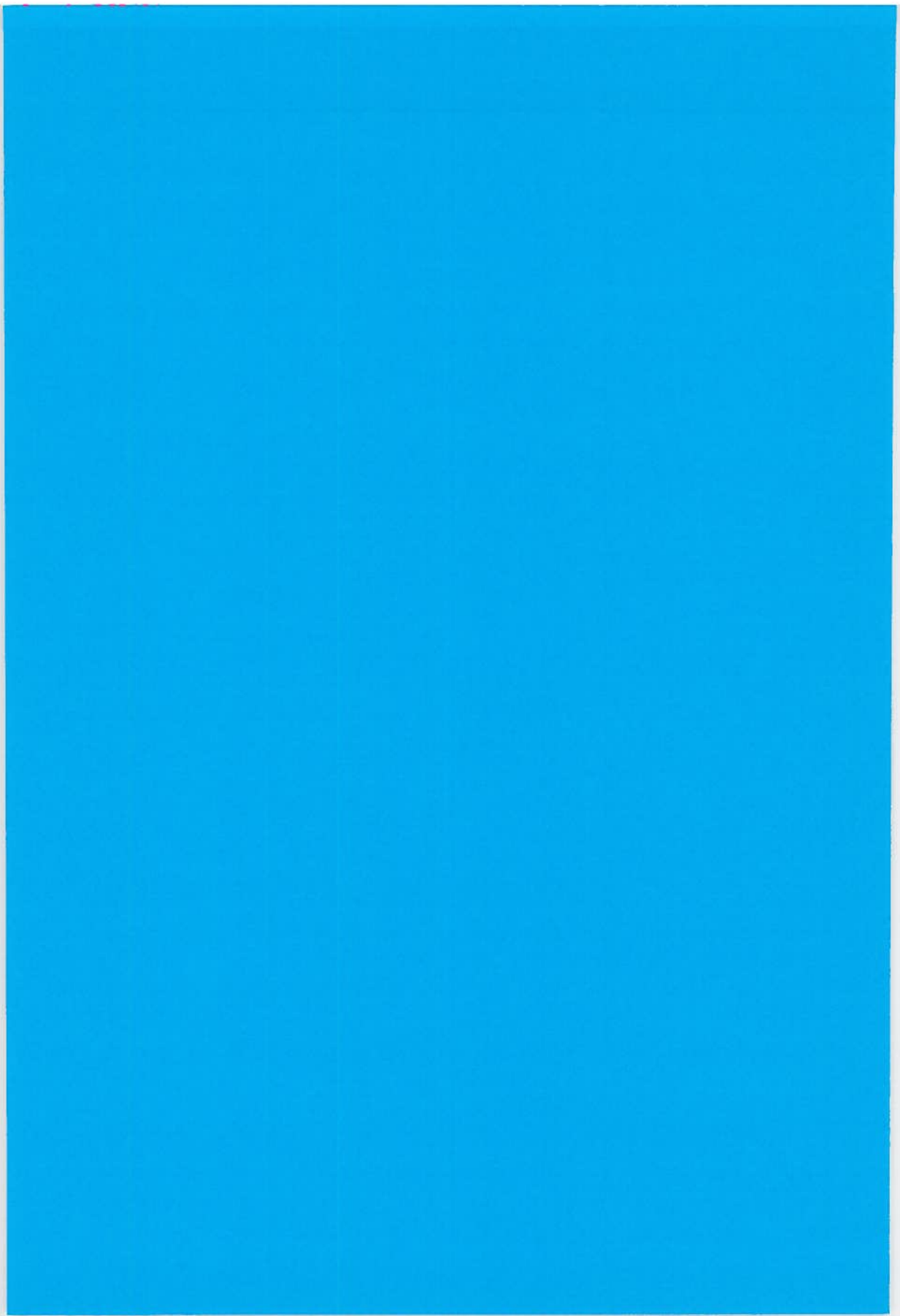
Address for correspondence: M. Averina, Institute of Community Medicine, Medical Faculty, University of Tromsø, N-9037 Tromsø, Norway
Phone: +47-776-44811; Fax: +47-776-44831
E-mail: Maria.Averina@ism.uit.no

Paper II



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Factors behind the Increase in Cardiovascular Mortality in Russia: Apolipoprotein AI and B Distribution in the Arkhangelsk Study 2000

MARIA AVERINA,[1*] ODD NILSSEN,[1] TORMOD BRENN,[1] JAN BROX,[2] VADIM L. ARKHIPOVSKY,[3] and ALEXEI G. KALININ[4]

Background: **Cardiovascular mortality is markedly higher in Russia than in Western Europe and the US. Little is known about indicators of atherosclerotic risk in the Russian population. To our knowledge, this is the first study of apolipoprotein (apo) AI and B in Russia based on the WHO-IFCC standard.**

Methods: **We measured apo AI and B by immunoturbidimetric assay in 3694 men and women from Arkhangelsk, Russia, in 1999–2000.**

Results: **The age-related distribution of apo B was similar to that in other countries, whereas the apo AI profile was different. For men ≥20 years, apo AI was considerably higher than in studies from other countries. Women had also relatively high apo AI concentrations, although the difference was not as pronounced as in men. The apo AI concentration was positively associated with age and lifestyle variables such as alcohol consumption and physical activity, and negatively associated with body mass index and self-reported myocardial infarction. γ-Glutamyltransferase was positively associated with apo AI in both sexes.**

Conclusions: **The apparently favorable apolipoprotein profiles contrast with official death statistics indicating high cardiovascular mortality in Russia. High apo AI might indicate excessive alcohol consumption.**

[1] Institute of Community Medicine, Medical Faculty, University of Tromsø, N-9037 Tromsø, Norway.
[2] Department of Clinical Chemistry, University Hospital of Tromsø, Tromsø, Norway.
[3] Semashko Clinic, Arkhangelsk, Russia.
[4] Northern State Medical University, Arkhangelsk, Russia.
*Author for correspondence. Fax 47-776-44831; e-mail Maria.Averina@ism.uit.no.

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Mortality from cardiovascular disease (CVD)[5] is markedly higher in Russia than in Western Europe and the US. Dramatic increases in mortality rates on an epidemic scale took place in post-Soviet Russia after 1991 *(1)*. In the mid-1990s the cardiovascular mortality rate was double that of the US *(1)*. After a temporary decrease in the late 1990s, cardiovascular mortality in Russia continues to increase *(2)*. In an earlier report *(3)* we showed that such factors as total cholesterol concentrations, blood pressure, and smoking had little predictive value. These findings supported the results of former studies in Russia *(4–6)*. High cardiovascular mortality and its significant fluctuations in post-Soviet Russia seemed to be only partially associated with the "classic" risk factors identified in epidemiologic studies in Western Europe and the US.

Little is known, however, about other indicators of atherosclerotic risk in the Russian population. Low serum concentrations of apolipoprotein (apo) AI, the main protein component of HDL, and increased concentrations of apo B100, the main protein component of LDL, have been reported as CVD risk factors in case–control studies, studies of patients undergoing angiography, and in prospective studies *(7–16)*. Some authors have concluded that apo AI and B were better indicators of atherosclerotic risk than other serum lipids *(9, 10, 13)*. A study of patients with angiographically confirmed coronary heart disease and without apparent risk factors has emphasized the importance of investigating apo AI in populations with low classic risk profiles *(12)*. Significant differences in lipid and apolipoprotein profiles have been found between Estonian and Russian men living in Estonia *(17)*. These results have emphasized the need for obtaining data to establish apolipoprotein reference values in Rus-

[5] Nonstandard abbreviations: CVD, cardiovascular disease; apo, apolipoprotein; AU, alcohol unit(s); BMI, body mass index; GGT, γ-glutamyltransferase; and NHANES, National Health and Nutrition Examination Survey.

sia. The aims of the present study were to determine the distribution of apo AI and B and to identify their determinants in an adult Russian population.

Materials and Methods

STUDY POPULATION

The town Arkhangelsk is the center of the Arkhangelsk region, the largest northern region of the European Russia. In 1999, the population of the Arkhangelsk town was 170 000 men and 197 000 women (0.3% of the general Russian population in 1999) *(18)*.

No population register was available for medical research in Arkhangelsk. Outpatient clinics in Russia provide primary medical care to the general population according to territorial and occupational principles. We therefore decided to consecutively recruit residents registered at one of the outpatient clinics in Arkhangelsk. Pensioners were recruited through the clinic's register. Working people and students were consecutively invited either through obligatory annual medical examinations or through their places of work or study. Inclusion criteria were being a Russian resident and age >17 years. Altogether 1962 men and 1732 women ≥18 years of age participated in the study in 1999–2000 and had their apolipoprotein concentrations measured. The age distribution of the study population was close to that of the total Russian adult population in 2000, and marital status was similar to that the general population of the Arkhangelsk region *(3)*. Participants younger than 25 years were mainly students (72% of men and 61% of women). The majority of men 25–59 years of age were seamen and harbor workers (86%), whereas women of this age were mainly civil employees and factory workers (73%). Civil employees were predominantly occupied in educational and healthcare systems. Approximately 84% of all examined civil employees were women, and only 16% were men. The official statistical data for the entire Arkhangelsk region in 1999 *(18)* showed the same skewed sex distribution in these professions (84–85% women and 15–16% men). In the age groups over 60 years there were mostly pensioners (80% of men and 88% of women). The proportion of pensioners in the study population was the same as in the Arkhangelsk region *(3)*.

ETHICS APPROVAL

The study was approved by the Regional Ethical Committee, Norway. Verbal informed consent was obtained from all participants.

QUESTIONNAIRE, PHYSICAL EXAMINATION, AND LABORATORY ANALYSES

All participants answered a 6-page questionnaire (111 items) covering education, marital status, occupation, family diseases, smoking, and physical activity at work and leisure. Participants answered questions on their frequency of alcohol consumption (categories: never, once a month, two to four times per month, two or more times per week) and on their weekly consumption of beer, wine, and vodka in alcohol units (1 AU = 13.8 g of pure alcohol). Physical activity was assessed at work and at leisure. Three categories were used for analysis: sedentary, moderate, and high physical activity. A sedentary job and sedentary leisure lifestyle were defined as sedentary physical activity. Walking, cycling at least 4 h per week during leisure time, or a job requiring considerable walking were defined as moderate physical activity. High physical activity included amateur sport activities at least 4 h per week, regular physical training several times per week with participation in sport competitions, or a job requiring considerable walking, lifting, and physical strain.

Dietary habits were estimated by four questions concerning how often participants ate fresh fruits and vegetables, fish, meat and meat products, and milk and milk products (never or very rarely, once a week, two to three times per week, four to five times per week, or almost daily). Bread consumption was assessed by a separate question that asked how many pieces of bread (all bread types) participants ate daily (<2, 2–4, 5–6, 7–12, ≥13).

Self-reported information about coronary heart disease (angina pectoris, myocardial infarction), stroke, and diabetes mellitus was obtained. Participants reported use of cardiovascular medicines without specification of the types of medicines. Body height, weight, and blood pressure were measured, the latter with a DINAMAP-R automatic device.

Nonfasting venous blood samples were drawn and centrifuged within 15–25 min at the laboratory servicing outpatient clinics in Arkhangelsk. Serum was stored at −20 °C for 3–4 weeks and then transported to Norway in boxes containing freezing elements by a 5-h flight. Serum was kept at −80 °C before analyses. All laboratory measurements were performed in Norway at the Laboratory of the Department of Clinical Chemistry, University Hospital in Tromsø.

Apo AI and B were assayed by an immunoturbidimetric method with polyclonal sheep anti-human apolipoprotein antibodies (Roche). Methods for measurement of apolipoprotein were standardized against the WHO/IFCC SP-07 standard *(19, 20)*. The laboratory used both internal and external methods of quality control. The analytic CV was <3% for both apo AI and apo B measurements. External quality control showed apolipoprotein values within the established control limits.

HDL-cholesterol was measured by the homogeneous enzymatic colorimetric test (polyethylene glycol-cholesterol esterase, peroxidase) with a CV of 3%. This method meets the goals of the 1998 NIH National Cholesterol Education Program for acceptable performance. The results of the method correlate well with those obtained by precipitation-based methods *(21)*. All analyses were performed in a Hitachi 917 analyzer.

STATISTICAL METHODS

The two-sample *t*-test was used to compare the results for men and women. Pearson correlation coefficients and forward stepwise linear regression analyses were performed separately for each sex with use of SAS statistical software package 8e (*22*) to study the relationships between the apolipoproteins and other variables. A 5% significance level was used for reminding or removal from the final regression model.

The independent variables introduced in the initial regression model comprised demographic characteristics (age, civil status, occupation), education (categories: 1, incomplete and complete secondary education; 2, secondary professional education; 3, unfinished university; 4, high education; i.e., complete university education), previous and present diseases (myocardial infarction, angina pectoris, stroke, diabetes), diseases in parents and siblings (myocardial infarction, angina pectoris, stroke), cardiovascular medication (no/yes), lifestyle variables (active and passive smoking, physical activity), alcohol consumption (in general and separate for each type of beverage), and physical measurements [body mass index (BMI), serum γ-glutamyltransferase (GGT), albumin, and serum lipids].

Results of the regression analysis were presented as β-coefficients. The formula $\beta \times 100$ was introduced to make the presentation of the results easier. These coefficients show the change in apolipoprotein concentrations (in g/L, multiplied by 100) if the independent variables change by one unit. The following independent variables remained in the final regression models for apo AI in one or both of sexes: age (years), BMI (kg/m^2), physical activity (sedentary, moderate, high physical activity), self-reported myocardial infarction (no/yes), smoking (no/yes), high education (vs secondary education), serum albumin (g/L), GGT (U/L), total cholesterol (mmol/L), and triglycerides (mmol/L). Alcohol variables that remained in the final analysis were frequency of alcohol intake (see previous categorization of the variable), weekly consumption of vodka (in AU), and weekly consumption of beer (in AU).

The final regression model for apo B contained the following independent variables: daily bread consumption (see previous categorization of the variable), weekly beer intake (in AU), meat and meat products consumption (see previous categorization of the variable), age (years), BMI (kg/m^2), high education (vs secondary education), smoking (no/yes), GGT (U/L), serum albumin (g/L), and triglycerides (mmol/L).

Results

The baseline characteristics of the participants are listed in Table 1. The age-standardized prevalence of self-reported CVD and stroke in the study population was 130.7 per 1000 participants (age-standardized to the general Russian population in 1998). This number agrees well with the official data on prevalence of circulatory diseases in the northwestern regions of European Russia in 1998 (132.9 per 1000 citizens) (*23*).

Table 1. Baseline characteristics of participants in the Arkhangelsk Study 2000.

	Men (n = 1962)	Women (n = 1732)
Mean (SD) age, years	41.9 (16.3)	44.3 (15.9)
Mean (SD) BMI, kg/m^2	25.2 (4.0)	26.1 (5.7)
Mean (SD) SBP,[a] mmHg	132.7 (19.0)	129.1 (22.4)
Mean (SD) DBP, mmHg	75.2 (14.6)	73.6 (13.3)
Mean (SD) total cholesterol,[b] mmol/L	5.0 (1.2)	5.2 (1.2)
Mean (SD) HDL-cholesterol,[b] mmol/L	1.3 (0.4)	1.4 (0.4)
Mean (SD) triglycerides,[c] mmol/L	1.4 (0.9)	1.3 (0.8)
Mean (SD) alcohol intake/week,[d] AU		
Vodka	5.1 (7.2)	1.0 (3.2)
Beer	2.1 (3.2)	0.6 (1.2)
Wine	0.3 (1.4)	0.7 (1.5)
Frequency of alcohol intake, %		
Never	12.2	27.1
Once a month or less	22.5	33.5
2–4 times per month	51.0	34.4
2 times per week or more	14.3	5.0
Physical activity, %		
Sedentary	14.3	31.7
Moderate	27.6	45.5
High	58.1	22.8
Smoking, %	56.6	21.3
Self-reported CVD[e] and stroke, %	9.4	12.6
Self-reported diabetes, %	1.5	3.0
BMI ≥30 kg/m^2, %	11.7	20.9
Total cholesterol >6 mmol/L, %	18.8	22.8
Triglycerides >2 mmol/L, %	15.0	12.7
Use of medicines,[f] %	6.6	14.3

[a] SBP, systolic blood pressure; DBP, diastolic blood pressure.
[b] Nonfasting blood.
[c] One missing value for triglycerides in women.
[d] 1 AU = 13.8 g of pure alcohol.
[e] CVD includes myocardial infarction and angina pectoris.
[f] All cardiovascular medicines.

Approximately 10% of the study population reported use of cardiovascular medicines. Exclusion of those who took medicines did not change the apo AI and B distributions substantially. Thus, we decided to present the final results from all of the participants.

Apo AI and B distributions were close to gaussian (Table 2). Apo AI concentrations were significantly lower in all age groups of men than in women ($P < 0.0001$). In men, apo AI concentrations increased steeply between 18 and 29 years, plateaued at 30–59 years, and decreased gradually after 60 years. In women, apo AI concentrations plateaued at the age of 20 years. As in men, apo AI decreased in the oldest age group of women.

Apo B concentrations increased in men from the age of 18 to 59 years and tended to decrease in the older age groups. In women, there was a continuous increase in apo B concentrations with age. Men had higher apo B concentrations than women in all age groups from 20 to 49 years

Table 2. Apo A-I and B (g/L) serum concentrations in men and women: The Arkhangelsk Study 2000.

		Men									Women							
				Percentile									Percentile					
	Age, years	n	Mean (SD)	5th	10th	25th	50th	75th	90th	95th	n	Mean (SD)	5th	10th	25th	50th	75th	90th	95th
Apo AI																			
	18–19	233	1.27 (0.20)	0.94	1.01	1.11	1.27	1.39	1.52	1.61	73	1.51 (0.21)	1.13	1.23	1.36	1.53	1.65	1.77	1.85
	20–29	289	1.45 (0.25)	1.07	1.12	1.28	1.43	1.61	1.79	1.86	299	1.57 (0.22)	1.24	1.31	1.42	1.57	1.70	1.85	1.98
	30–39	354	1.52 (0.23)	1.17	1.23	1.38	1.52	1.66	1.80	1.92	316	1.59 (0.23)	1.23	1.31	1.43	1.58	1.75	1.89	1.98
	40–49	446	1.52 (0.26)	1.13	1.21	1.34	1.50	1.67	1.86	1.98	419	1.60 (0.24)	1.21	1.30	1.44	1.59	1.74	1.88	2.00
	50–59	308	1.52 (0.24)	1.17	1.25	1.34	1.50	1.71	1.84	1.92	305	1.61 (0.25)	1.18	1.32	1.46	1.60	1.75	1.90	1.97
	>60	332	1.48 (0.27)	1.08	1.18	1.30	1.45	1.65	1.81	1.93	320	1.56 (0.24)	1.21	1.30	1.41	1.55	1.67	1.87	1.99
	Total	1962	1.47 (0.26)	1.07	1.16	1.30	1.46	1.63	1.80	1.92	1732	1.58 (0.23)	1.22	1.30	1.43	1.57	1.73	1.87	1.98
Apo B																			
	18–19	233	0.69 (0.16)	0.47	0.52	0.59	0.67	0.77	0.87	0.99	73	0.68 (0.16)	0.46	0.51	0.57	0.66	0.76	0.88	1.02
	20–29	289	0.83 (0.24)	0.49	0.56	0.68	0.81	0.95	1.14	1.22	300	0.75 (0.16)	0.50	0.53	0.64	0.74	0.84	0.95	1.03
	30–39	354	0.98 (0.23)	0.64	0.71	0.82	0.96	1.14	1.28	1.40	317	0.85 (0.20)	0.56	0.60	0.72	0.84	0.96	1.11	1.23
	40–49	446	1.07 (0.24)	0.70	0.78	0.88	1.06	1.23	1.40	1.47	419	0.98 (0.22)	0.64	0.72	0.84	0.96	1.10	1.26	1.34
	50–59	308	1.10 (0.25)	0.71	0.76	0.93	1.11	1.25	1.42	1.50	305	1.11 (0.24)	0.75	0.83	0.94	1.09	1.27	1.41	1.54
	>60	332	1.07 (0.24)	0.67	0.76	0.92	1.06	1.21	1.38	1.47	320	1.17 (0.27)	0.75	0.85	1.01	1.15	1.34	1.56	1.62
	Total	1962	0.98 (0.27)	0.57	0.64	0.78	0.96	1.16	1.33	1.43	1734	0.96 (0.27)	0.57	0.63	0.76	0.93	1.13	1.32	1.44

(P <0.0001), but there was a reverse relationship in the oldest age group (P <0.0001).

We have presented the regression analysis of apo AI as two models (Table 3): the first model is without serum lipids, the second model includes total cholesterol and triglycerides.

The first regression model included two different types of alcohol variables: frequency of alcohol intake (without consideration for volume and type of beverage), and volume of vodka and beer consumed per week. Volume of wine consumed per week showed no significant association with apo AI and was not included in the model (only 9% of men reported any intake of wine).

Model 1 (without alcohol variables) explained 10.4% and 10.3% of the apo AI variance in men and women, respectively. When the alcohol frequency variables were added, r^2 increased to 12.4% in men and 12.6% in women. When the frequency variables were substituted by the alcohol volume variables, r^2 was 12.9% and 11.3%, respectively. When both types of alcohol variables were added, the model explained 13.5% of apo AI variance in men and 12.8% in women (Table 3).

A frequency of alcohol intake of "2–4 times per month" was associated with increases in apo AI of 0.060 and 0.077 g/L in men and women, respectively. An alcohol intake of "2 times per week or more" was associated with increases in apo AI concentrations of 0.064 g/L in men and 0.129 g/L in women (vs abstainers).

Serum GGT was significantly associated with apo AI in both sexes. However, when the analysis was done separately only for lifetime abstainers, we found no association between GGT and apo AI (data not shown).

In men with self-reported myocardial infarction, apo AI was 0.111 g/L lower than in healthy men (model 1). In women the association between apo AI and myocardial infarction was also negative, but not significant. Moderate physical activity showed a positive association with apo AI in both sexes. Men with high physical activity had apo AI concentrations 0.072 g/L higher than those with a sedentary lifestyle. In women this association was not significant (relatively few women reported high physical activity).

Inclusion of serum lipids in the analysis (model 2) increased r^2 substantially in both sexes. Apo AI was strongly positively associated with total cholesterol and negatively associated with triglycerides.

The correlation coefficients between apo AI and HDL were 0.75 in men and 0.81 in women, respectively, and those between apo B and total cholesterol were 0.91 in men and 0.90 in women. Because of the high correlation coefficients, HDL- and total cholesterol were not included in the regression analyses for apo AI and B, respectively.

Apo B was positively associated with meat consumption and negatively associated with bread consumption in both sexes (Table 4). Consumption of vegetables, fruits, fish, milk, and coffee was not associated with apo B concentrations. In men, apo B was positively associated with smoking and beer consumption. Apo B concentrations were positively associated with GGT in both sexes; however, we found no significant association between GGT and apo B when the analysis was done separately for lifetime abstainers.

COMPARISON WITH OTHER STUDIES

The results of our study were compared only with population studies that used the WHO-IFCC standard for

Table 3. Multiple linear regression analysis of apo AI (g/L) in the Arkhangelsk Study 2000.

	β × 100			
	Men (n = 1962)		Women (n = 1731)[a]	
	Model 1	Model 2	Model 1	Model 2
Age, years	0.6[b]	0.3[b]	0.3[b]	0.08
BMI, kg/m^2	−0.8[b]	−0.8[b]	−0.3[c]	−0.2[d]
Moderate physical activity[f]	4.4[d]	3.0	4.0[c]	2.4
High physical activity[f]	7.2[b]	4.9[c]	2.9	2.3
Alcohol intake once a month[g]	2.3	0.7	3.1[d]	2.5
Alcohol intake 2–4 times/month[g]	6.0[c]	3.8[d]	7.7[b]	6.3[b]
Alcohol intake ≥2 times/week[g]	6.4[d]	5.0[d]	12.9[b]	10.9[e]
Volume of vodka/week, AU	0.4[b]	0.3[b]	0.4[d]	0.5[c]
Volume of beer/week, AU	0.4[d]	0.3	0.1	0.6
Myocardial infarction, no/yes	−11.1[c]	−11.5[e]	−7.8	−3.5
Smoking, no/yes	−1.9	−2.4[d]	−3.4[d]	−2.2
High education, no/yes	2.6	1.2	2.6[d]	1.6
GGT, U/L	0.04[b]	0.03[e]	0.05[e]	0.02
Albumin, g/L	1.9[b]	1.1[b]	2.3[b]	1.6[b]
Total cholesterol, mmol/L	–[h]	8.0[b]	–[h]	7.8[b]
Triglycerides, mmol/L	–[h]	−5.1[b]	–[h]	−8.6[b]
R^2, %	13.5	22.2	12.8	23.9

[a] The number of women is lower than in Table 2 because of one missing value for triglycerides.
[b–e] Significance: [b]P <0.0001; [c]P <0.01; [d]P <0.05; [e]P <0.001.
[f] Compared with sedentary life style.
[g] Compared with abstainers.
[h] Not included in the model.

Table 4. Multiple regression analysis of apo B (g/L) in the Arkhangelsk Study 2000.

	β × 100			
	Men (n = 1962)		Women (n = 1733)[a]	
	Model 1	Model 2	Model 1	Model 2
Age, years	0.6[b]	0.6[b]	0.9[b]	0.7[b]
BMI, kg/m^2	1.7[b]	1.1[b]	1.0[b]	0.5[b]
Bread/day,[f] categories	−3.1[b]	−3.4[b]	−1.5[c]	−1.5[c]
High education[g]	4.9[d]	3.6[e]	1.5	1.7
Smoking, no/yes	3.6[d]	3.1[e]	0.2	−0.8
Volume of beer/week, AU	0.4[c]	0.4[c]	−0.8	−0.9
Meat/week,[h] categories	1.0[c]	1.1[c]	0.6	0.9[c]
GGT, U/L	0.04[b]	0.02[e]	0.06[b]	0.04[e]
Albumin, g/L	1.4[b]	1.2[b]	1.3[b]	1.1[b]
Triglycerides, mmol/L	–[i]	8.3[b]	–[i]	12.0[b]
R^2, %	29.9	36.7	37.5	45.9

[a] The number of women is lower than in Table 2 because of one missing value for triglycerides.
[b–e] Significance: [b]P <0.0001; [c]P <0.05; [d]P <0.001; [e]P <0.01.
[f] Pieces of bread per day (all bread types).
[g] Compared with secondary education.
[h] Meat/meat product consumption from never to daily.
[i] Not included in the model.

apolipoprotein measurements. Only studies with means for total cholesterol and BMI similar to our population were selected: the National Health and Nutrition Examination Survey (NHANES) III Study *(24)* and the Framingham Offspring Study in the US *(25, 26)*. A Finnish study *(27)* reported HDL-cholesterol values similar to those in our study, but the participants had higher total and LDL-cholesterol. Despite this, we used this study for comparison.

The pattern of apo AI distribution was different in our study compared with those reported in other studies (Fig. 1). In men, there was an abrupt increase in apo AI at the age of 18–30 years, whereas in other studies there was a relatively gradual increase or no age-dependent increase. Furthermore, actual apo AI concentrations were markedly higher in all age groups of men in Arkhangelsk compared with other studies. For the youngest men (<20 years) the results were similar to those in the NHANES III Study *(24)*. Women 20–29 and 40–59 years of age had apo AI concentrations similar to the values in the Finnish study *(27)*, but markedly higher than those reported in the two studies from the US *(24, 25)*.

The pattern of apo B distribution in men was almost equal to that in the Framingham Offspring Study and in the NHANES III Study *(24, 25)*, i.e., increasing with age, slightly decreasing in the oldest age groups, higher apo B concentrations in young men compared with women of the same age, and the reverse relationship after the age of 60 years. Women >30 years of age had the same concentrations and pattern of apo B distribution as in the NHANES III Study, whereas those under 30 years had lower values *(24)*.

Discussion

STUDY ADVANTAGES

To our knowledge, this is the first report of apo AI and B distributions in Russia based on the WHO-IFCC Reference Materials. The study was carried out in a region with total mortality (15.1 per 1000 citizens) and cardiovascular mortality (8.3 per 1000 citizens) rates similar to those in Russia as a whole in 2000 (15.4 and 8.5 per 1000 citizens, respectively) *(18, 28)*. The age-standardized prevalence of self-reported CVD in the study population corresponds well with the official data for the northwest of Russia.

METHODOLOGIC ISSUES

To avoid "between-laboratory differences" we compared our data only with reports based on the WHO-IFCC Reference Standard. Storage of serum at −80 °C does not affect apo AI and B values *(25, 26, 29)*. Blood samples in our study were nonfasting. The NHANES III Study showed no significant difference in apo AI and B concentrations between fasting and nonfasting individuals stratified by age and sex *(24)*.

Taking into consideration the large difference in apo AI concentrations between our sample and other studies, we

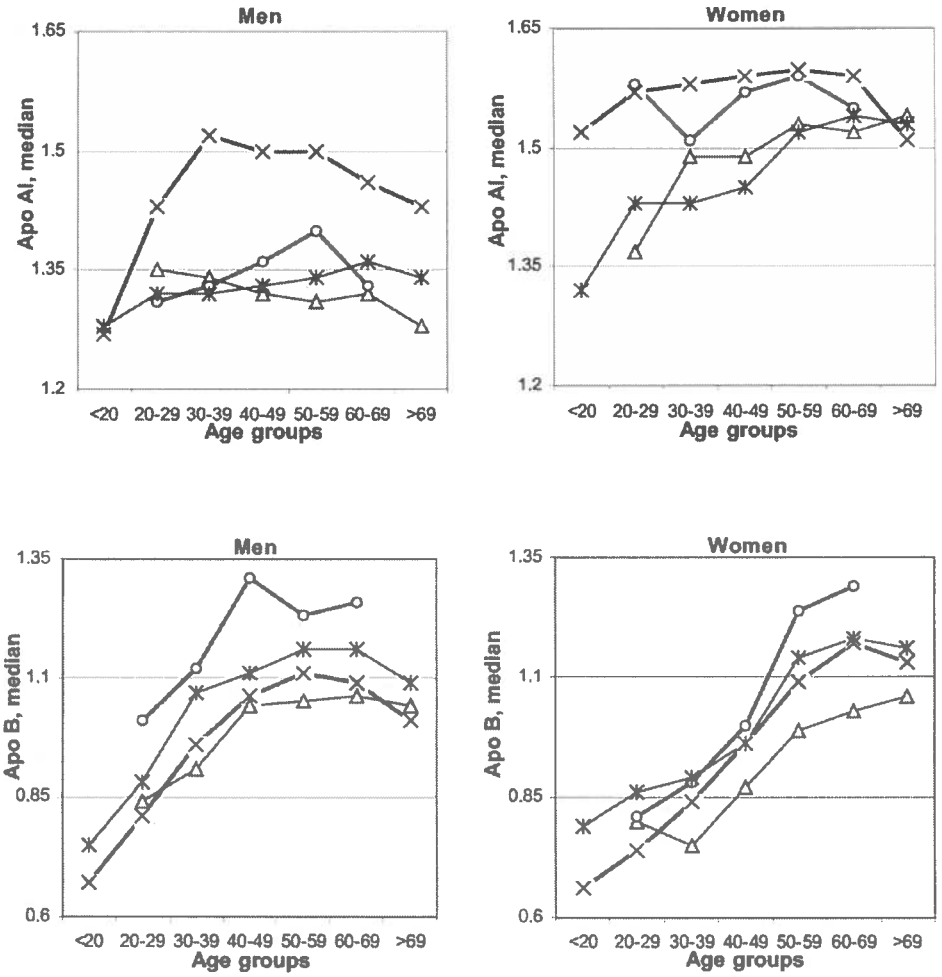

Fig. 1. Distribution of apo AI and B median values (g/L) by age in men and women in Arkhangelsk compared with other studies.
×, the Arkhangelsk Study; △, the Framingham Study *(24, 25)*; •, the NHANES III Study *(23)*; ○, the Finnish study *(26)*.

investigated the possibility of a methodologic bias. External quality control at the laboratory showed that apo AI values were within the established control limits. We also believe that the abrupt increase in apo AI in young men could hardly be explained by a systematic laboratory difference.

STUDY LIMITATIONS

One limitation of the study is that the method used to establish a study population was not ideal. Because a population register was not available for medical research in Arkhangelsk, we had to recruit participants through the primary healthcare system. However, the demographic characteristics of the study population were close to those for the general Arkhangelsk region population. Furthermore, we compared the values for classic CVD risk factors in our population with the results from other population-based studies in Russia (the MONICA Study in Moscow and in Novosibirsk) *(3)* and found no substantial difference between these population samples. However, we cannot exclude the possibility of different distribution of CVD risk factors in some geographic regions of Russia, especially in small nationalities with mortality rates higher than the average for Russia. Our population was recruited from a region with a mortality rate similar to the average mortality rate for Russia as a whole.

Another limitation of the study is that recruitment of participants during the obligatory medical examination might have led to underreporting of alcohol consumption.

INTERPRETATION OF THE FINDINGS

The apo AI and B profiles appeared to be favorable in our study participants. These results are consistent with our previous work indicating that, regardless of the high cardiovascular mortality, the values for the classic cardiovascular risk factors are more favorable in the examined Russian population than in similar studies from Western Europe and the US *(3)*.

In addition, there was a different pattern of apo AI distribution in young Russian men compared with men in other studies. The abrupt increase in apo AI in young men seemed to be lifestyle- rather than age-dependent. There were considerable socioeconomic differences between the 18–19 and 20–39 age groups: the majority of men in the youngest age group were students (97%), whereas 73% and 90% of men in the age groups 20–29 and 30–39 years, respectively, were well-paid seamen and workers. Although reported physical activity decreased gradually with age, self-reported vodka consumption doubled from 3.3 AU/week in men 18–19 years to 6.3 AU/week in men 30–39-years of age. This increase is somewhat parallel to the increase in apo AI (Fig. 2).

Furthermore, the frequency of alcohol intake and the amount of alcohol consumed were important predictors of apo AI in both sexes. This supports the results from other studies, in which apo AI and HDL-cholesterol concentrations were positively associated with alcohol consumption *(30–33)*. Daily and weekend drinkers (males) in our study had apo AI concentrations similar to those of the same groups of male drinkers in a study from Australia *(34)*.

GGT was significantly positively associated with apo AI in both sexes. GGT is known as a biological marker for alcohol consumption, but it is also reported as a risk factor for stroke, hypertension, and diabetes *(35–37)*. GGT concentrations in Russian men and women were double those in similar studies in Norway, indicating high alcohol consumption (data not shown). Mean (SD) self-reported alcohol consumption in our study was 7.5 (8.7) AU/week for men and 2.3 (3.8) AU/week for women, which corresponds to 6.2 and 1.9 L of pure alcohol/year. The discrepancy between the self-reported moderate alcohol intake and the high GGT values indicates a possible underreporting of alcohol consumption. Previous studies of alcohol consumption showed that participants tended to underestimate alcohol intake, reporting only ~40% of actual consumption *(38)*. According to a WHO report, consumption of pure alcohol per adult (15 years and older) adjusted for the unrecorded production was much higher in Russia in the mid-1990s than in Finland and the US (14.5 L/year vs 9.8 and 9.0 L/year, respectively) *(39)*.

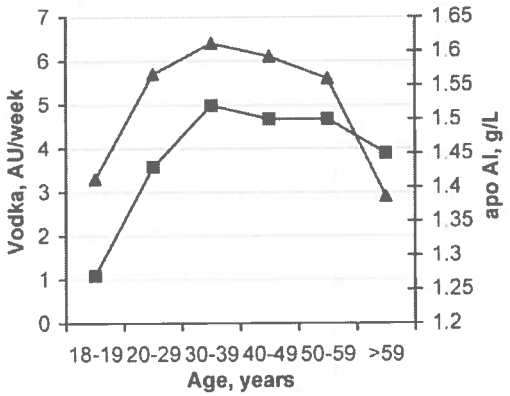

Fig. 2. Median apo AI concentrations and weekly vodka consumption in men: The Arkhangelsk Study 2000.
▲, vodka in AU/week (1 AU = 13.8 g of pure alcohol); ■, median apo AI (g/L).

Several prospective studies showed that heavy alcohol consumption was associated with higher risk of sudden cardiovascular death and fatal myocardial infarction *(40–43)*. It has been expressed that many deaths from arrhythmias and cardiomyopathies in middle-aged Russian men might have been classified as coronary heart disease *(44)*. The quality of cause-of-death reports in Russia has not been investigated since the late 1980s. The role of binge drinking as a possible risk factor for cardiovascular death from arrhythmias and cardiomyopathies was emphasized in a report about increased cardiovascular death on weekends in Moscow *(45)* and in a similar study in Lithuania *(46)*. In these cases the traditional CVD risk factors would have little predictive value.

The epidemic of CVD in Russia has another striking peculiarity. The considerable increase in cardiovascular mortality took place after the collapse of the Soviet Union in 1991 and paralleled increases in mortality rates from external causes of death, such as fatal alcohol poisonings, accidents, and violence. Increasing alcohol consumption in a situation with economic and social instability, rising poverty, and dissolution of social controls has apparently played a substantial role in the rising mortality from external causes.

At the same time results of population studies in Russia have shown little predictive value of the traditional risk factors in explaining the excess in CVD mortality rates *(3–6)*. The Lipid Research Clinics Study *(6)* also found higher HDL concentrations in Russian men compared with US men, and a positive association between high HDL and all-cause mortality in Russia. These findings indicate a strong influence of other powerful factors that are associated with increased risk of death as well as with high HDL and apo AI concentrations. It is possible that high apo AI and HDL-cholesterol concentrations serve more as markers of liver problems secondary to excessive alcohol use. We believe that further prospec-

tive studies are necessary to elucidate the set of risk factors responsible for the high mortality rate in Russia.

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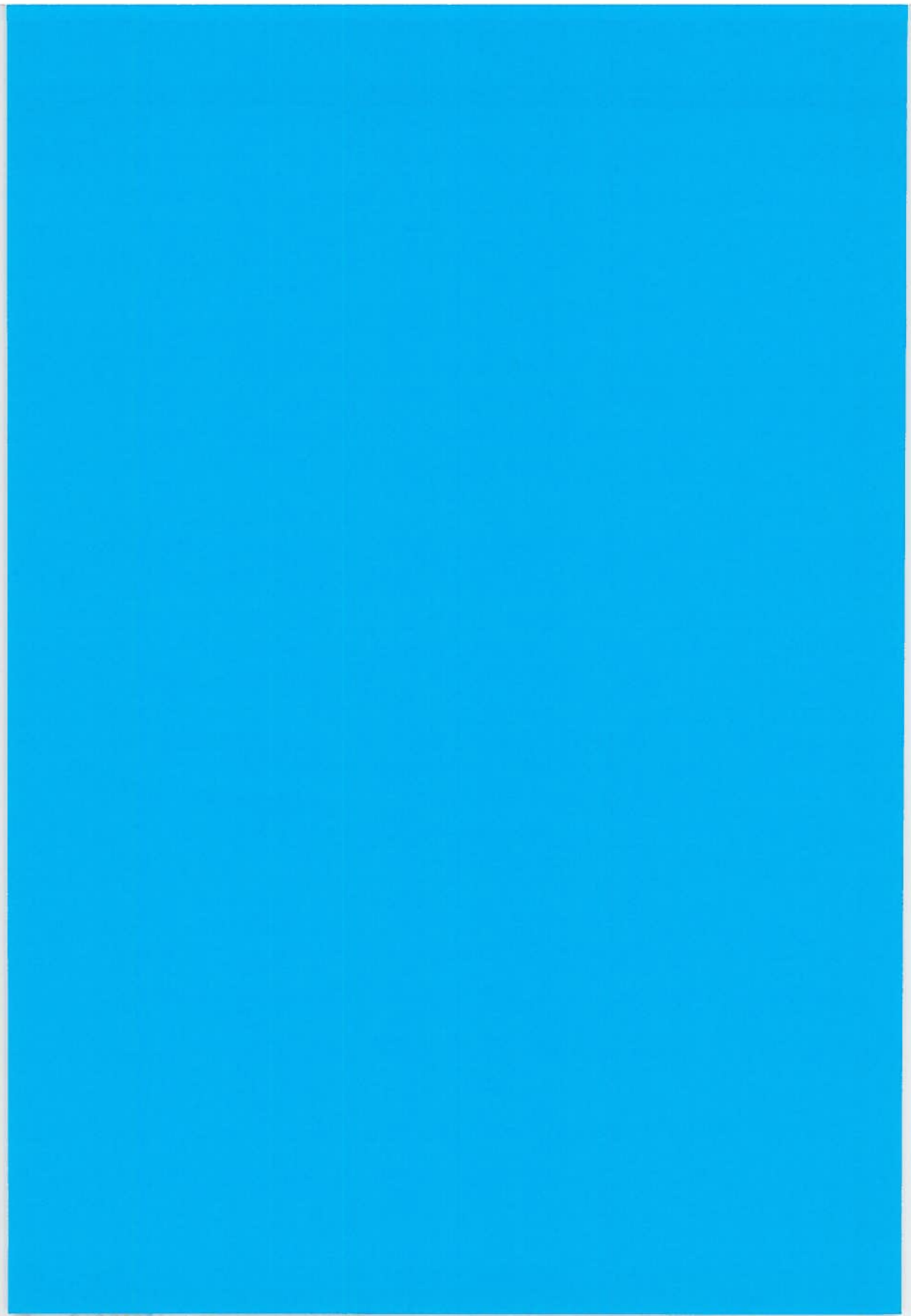
Paper III



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ORIGINAL PAPER

Maria Averina · Odd Nilssen · Tormod Brenn · Jan Brox · Vadim L. Arkhipovsky · Alexei G. Kalinin

Social and lifestyle determinants of depression, anxiety, sleeping disorders and self-evaluated quality of life in Russia

A population-based study in Arkhangelsk

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Abstract *Background* The paper investigates social and lifestyle determinants of depression, anxiety, sleeping disorders and self-evaluated low quality of life in a population sample from the northwest of Russia. *Methods* Altogether 1968 men and 1737 women aged 18–90 years participated in a population-based study in Arkhangelsk, Russia, in the period 1999–2000. Depression, anxiety, and sleeping disorders were evaluated by a questionnaire with the formulations that have been previously used in population studies in Northern Norway. Alcohol dependence was diagnosed by the Alcohol Use Disorders Identification Test (AUDIT). Quality of life was evaluated by a 10-score Cantril Ladder. A score lower than five was defined as low quality of life. Relations between depression, anxiety, and sleeping disorders and socioeconomic/lifestyle factors were tested by logistic regression analyses. *Results* Women reported significantly higher prevalence of depression, anxiety and/or sleeping disorders than men: 68.7% and 32.3%, respectively. Depression, anxiety, sleeping disorders and low quality of life were positively associated with self-evaluation of nutrition as "poor", low consumption of food, and with low-paid professional status. Depression and sleeping disorders were associated with smoking, hazardous level of alcohol drinking and alcohol dependence. Anxiety and low quality of life were associated with alcohol dependence. Depression, anxiety, sleeping disorders and low quality of life had a strong positive association with circulatory diseases and gastrointestinal diseases, the association remained significant after adjustment for smoking and alcohol variables. *Conclusions* A considerable part of the examined Russian population experienced depression, anxiety, and sleeping disorders that were strongly positively associated with poor nutrition, low socioeconomic status and adverse health behaviors (alcohol use disorders, smoking).

Key words depression – anxiety – sleeping disorders – quality of life – Russia

M. Averina (✉) · O. Nilssen · T. Brenn
Institute of Community Medicine (ISM)
University of Tromsø
9037 Tromsø, Norway
Tel.: +47/77644811
Fax: +47/77644831
E-Mail: Maria.Averina@ism.uit.no

J. Brox
Dept. of Clinical Chemistry
University Hospital of Tromsø
Tromsø, Norway

V. L. Arkhipovsky
Semashko Clinic
Arkhangelsk, Russia

A. G. Kalinin
Northern State Medical University
Arkhangelsk, Russia

Introduction

Russia has experienced dramatic economical, political and social changes since the collapse of the Soviet Union. These changes have been followed by a devastating decline in public health. Life expectancy has decreased, especially in middle-aged men, and the gap between Russia and Western Europe is now more than 10 years for both sexes. Mortality rates have increased considerably since 1990, and are still rising (Goskomstat of Russia 2004; Notzon et al. 1998). External reasons (trauma, accidents, suicide, homicide) remain one of the leading causes of death. According to WHO data (2003), Russia is emerging as a world leader in suicides.

Cardiovascular diseases (CVD) also represent a major cause of death in Russia. In contrast to West-European countries, CVD mortality in Russia continues to increase. Several studies have shown that high cardiovascular mortality and its recent fluctuations in Russia could not be explained by the classic risk factors (Ginter 1995; Kuulasmaa et al. 2000; Perova et al. 1995; Averina et al. 2003, 2004). This "Russian paradox" still remains without explanation, although several hypotheses have been suggested. Some researchers have suggested

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that heavy alcohol consumption might be responsible both for the increase in CVD mortality and deaths from external causes (Chenet et al. 1998; Nemtsov 2002; Shkolnikov et al. 2001). Others point to the importance of mental distress as a result of increasing poverty and unemployment, declining social and medical support, and considerable fall in living standards (Kennedy and Kawachi 1998; Notson et al. 1998; Shkolnikov et al. 1998; Walberg et al. 1998). The MONICA study in Novosibirsk found that CVD mortality was associated with high alcohol consumption (Malyutina et al. 2002), whereas CVD morbidity was associated with anxiety and sleeping problems (Gafarov et al. 2003). Carlson (2001) found that self-rated health was closely related to indicators of economic difficulties in Russia. Economic difficulties were postulated to give rise to stress, anxiety and depression that could lead to ill health. Studies from other countries have shown that mental distress, negative emotions and low socioeconomic status contribute to the development of cardiovascular diseases and stroke (Hallqvist et al. 1998; Ketterer et al. 2000; Smith 2001; Truelsen et al. 2003). Life dissatisfaction and low social participation have been reported as risk factors for mortality in prospective studies (Dalgard and Håheim 1998; Koivumaa-Honkanen et al. 2000).

The objective of this study was to evaluate the prevalence of depression, anxiety and sleeping disorders in a population-based study in Russia. Furthermore, the aim was to test how and to what degree depression, anxiety, sleeping disorders and low self-evaluated quality of life are associated with socioeconomic and lifestyle variables such as nutrition, alcohol consumption, smoking, education, occupational and civil status, and self-reported diseases.

Subjects and methods

Study population

The study was conducted in Arkhangelsk – the center of the largest region in the northwest of Russia. In 1999, the population of the Arkhangelsk town consisted of 367000 residents (0.3% of the general Russian population). Total mortality and cardiovascular mortality rates in the Arkhangelsk region were similar to the figures for the whole Russian population in 2000 (the Goskomstat of Russia 2004).

No population register was available for medical research in Arkhangelsk. Primary healthcare departments (polyclinics) provide medical aid to the general population according to territorial and occupational principles. For this purpose, outpatient clinics possess a kind of register over the general population. Citizens are registered at the clinics on a population basis according to their home address or place of work. Therefore, we decided to consecutively recruit residents registered at one of the outpatient clinics in Arkhangelsk. All the participants were investigated at the same outpatient clinic by specially trained medical personnel, which made it possible to provide the same quality of investigation with a minimum of missing data. To avoid the "healthy volunteer effect", participants were consecutively recruited. Prevalence of circulatory diseases in the study population was almost the same as in the general adult population in the northwest of Russia: 130.7 and 132.9 per 1000, respectively (Averina et al. 2003). From November 1999 to November 2000, altogether 1968 men and 1737 women aged 18 years and more participated in the study (1% of the town population, 0.3% of the Arkhangelsk region population). Of those who were invited, 40 persons refused to participate (1.1%). Working population and students were consecutively invited either through the obligatory annual medical examination or through their places of work or study. Pensioners were recruited through the clinic's register. Comparison of the study population with the general Arkhangelsk region population has been presented in our previous articles (Averina et al. 2003, 2004). The study population had higher level of education and lower number of unemployed men compared with the general Arkhangelsk region population. Other demographic characteristics of the study sample were close to those for the general Arkhangelsk region population, thus leaving us with a fairly representative sample.

Ethics

The Regional Ethical Committee, Norway, approved the study. No equivalent ethical committee existed in the Arkhangelsk region at the time of the study. Verbal informed consent was obtained from all participants.

Statistic analyses

A logistic regression analysis with dependent variables depression, anxiety, sleeping disorders and low life quality was performed using the SAS software package (DiIorio and Hardy 1996). Characteristics on diet, alcohol consumption, education, occupational and civil status were included in the regression models as independent variables. The forward stepwise selection of variables was used with a 5% significance level for reminding or removal from the final regression model. The final results were presented as mutually adjusted odds ratios with 95% confidence intervals (CI). For comparison with other studies the Chi^2 test and the two-sample t-test were used.

Dependent variables

A six-page questionnaire (111 questions) was used in this population-based study. A part of the questionnaire was devoted to psychosocial aspects. We included in the questionnaire the same type of questions that were previously used in population-based studies in Norway (Westlund et al. 1993; Nilssen et al. 1999). The questionnaire was administered at the outpatient department with assistance from a specially trained nurse.

The following question was used for depression: Do you have long periods (2 weeks or more) during which you feel sad, blue or depressed (yes; no)? Similar formulation was used for sleeping disorders: Do you have long periods (2 weeks or more) during which you have problems with sleep (yes; no)? Sleeping disorders were defined in the questionnaire as: difficult to fall asleep in the evening; falling asleep too early in the evening; waking up several times during the night; waking up too early in the morning; waking up not rested in the morning; sleeping too long in the morning. Anxiety was estimated by the question: Do you experience now or did you experience during the last year anxiety (yes; no)?

Quality of life was self-evaluated by the Cantril Ladder (Cantril 1965) that was illustrated as a scale with ten levels: "Imagine that the highest level represents the highest quality of life, while the lowest level represents the worst quality of life. Which level, in your opinion, is in agreement with your current life?". A score lower than five was defined as low life quality.

Independent variables

The following three questions on nutrition were used: How often do you eat fresh fruits or vegetables; fish or fish products; meat or meat products (rarely or never; once a week; 2–3 times a week; 4–5 times a week; almost daily)? These three variables were further dichotomized as "once a week or less" and "more than once a week". The participants were also asked to evaluate their nutrition: How do you evaluate your

nutrition (good; satisfactory; poor)? If the answer was "poor nutrition", the participant was defined as unsatisfied with nutrition.

Alcohol problems were examined by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders 1993a, 1993b). This ten-item questionnaire includes three questions on quantity and frequency of alcohol consumption, three questions on abnormal drinking behavior and four questions on alcohol-related problems. The maximum possible AUDIT score is 40. A score of 8–12 indicates hazardous level of alcohol drinking and a score of 13 or more indicates alcohol dependence.

The variable smoking was dichotomized: "yes" (occasional and daily smokers) or "no" (non-smokers and ex-smokers). Self-reported circulatory diseases were assessed by three questions: Do you have now or have you had myocardial infarction; angina pectoris; stroke (yes; no; I don't know)? Equal formulation was used for gastrointestinal diseases (stomach/duodenal ulcer, pancreatitis, hepatitis/cirrhosis, dyspepsia). The variables circulatory diseases and gastrointestinal diseases were further dichotomised: "yes" (if at least one of the diseases was reported) or "no" (if the answer was "no" or "I don't know" about all the diseases).

Education was categorized as secondary (unfinished or completed secondary school), secondary professional, or high (unfinished or completed university education). Civil status comprised categories: married (registered marriage or cohabitant), unmarried, divorced, or widow/widower.

The participants reported their professional status: students, pensioners, civil employees (white collars), industry workers, seamen/mariners, housewives, or other (unemployed). Income level was defined according to the official data on the average salary level in different professions (Goskomstat 2004): professions with high income (seamen), average income (industry workers), and low income (civil employees). According to the Goskomstat data for the year 2000, civil employees earned 40% of the average salary in industry; the mean retirement pension in Russia was below the officially established survival level and was lower than the average salary (Goskomstat 2004). Pensioners were included in the analyses as a separate group with low income. There were no definite data on average income in students, housewives and unemployed; therefore, these groups were included in the analysis as a group without known income.

Results

The age structure of the study population was close to the age distribution in the entire Russian adult population in 2000 (Table 1). Table 2 shows that one-third of

Table 1 Age distribution of the study population compared with the total Russian adult population in 2000 (%)

Age	Russia[a] n = 54.59 x 10^6	Study population n = 1968	Russia[a] n = 64.37 x 10^6	Study population n = 1737
15–19[b]	10.9	11.8	9.0	4.2
20–29	19.5	14.7	16.0	17.3
30–39	19.6	18.0	16.6	18.2
40–49	21.1	22.7	19.1	24.2
50–59	11.8	15.7	12.0	17.6
60+	17.1	16.9	27.3	18.5
Total	100.0	100.0	100.0	100.0

[a] Data of the Goskomstat for 2000 (the State Statistical Committee)
[b] The first age group for the whole Russian population includes participants younger than 18 years that were not included in our study

Table 2 Prevalence (%) of depression, anxiety, and sleeping disorders

Age, years	Number	Depression	Sleeping disorders	Anxiety	Total[a]
Men					
18–19	234	6.4	4.3	15.8	23.5
20–29	290	7.2	3.1	17.9	24.1
30–39	357	6.4	5.6	20.2	26.1
40–49	447	9.4	9.2	19.9	30.2
50–59	308	14.6	15.9	22.4	37.0
60+	332	19.9	28.3	31.6	50.6
All	1968	10.8	11.3	21.5	32.3
Age-standardized[b]		10.5	10.8	21.4	31.8
Women					
18–19	73	31.5	15.1	38.4	54.8
20–29	302	26.5	15.9	41.4	56.0
30–39	317	35.0	30.9	51.4	66.6
40–49	420	33.1	29.5	53.6	67.4
50–59	305	32.8	41.0	58.4	71.8
60+	320	41.3	62.2	63.4	84.7
All	1737	33.7	34.8	53.1	68.7
Age-standardized[b]		34.4	35.6	53.2	69.6

[a] "Yes" on at least one of the three other variables
[b] Age-standardized to the general Russian population in 2000

men and more than half of women reported depression, sleeping disorders and/or anxiety. About 20 % of men and 30 % of women reported low quality of life (Table 3). The results were age-standardized using the direct method (the entire Russian adult population in 2000 was chosen as a standard population). Age standardization did not substantially change the results.

Table 4 shows that a considerable part of the study population reported low consumption of fruits/vegetables, fish, and meat. These nutritional variables were significantly associated with self-evaluation of nutrition as "poor". Age- and sex-adjusted Pearson correlation coefficients between self-evaluated "poor nutrition" and low consumption of food items were 0.26 ($p < 0.0001$) for low fruit/vegetable consumption, 0.23 ($p < 0.0001$) for low fish consumption and 0.22 ($p < 0.0001$) for low meat consumption.

More than one-third of the men met the criteria for alcohol use disorders. The prevalence of hazardous level of alcohol drinking and alcohol dependence was 4–5 times higher in men than in women. Prevalence of smoking was twice as high in men compared with women.

Tables 5 and 6 present the results of logistic regression analyses with depression, anxiety, sleeping disorders and low quality of life as dependent variables. Women had significantly higher odds for depression, anxiety and sleeping disorders compared with men. Low consumption of food items was positively associated with depression, anxiety, sleeping disorders and low quality of life. Thus, the odds for sleeping disorders were 60 % higher for those who ate few fruits or vegetables compared with those who consumed fruits or vegetables more than once per week. Participants who evaluated their nutrition as poor also had significantly higher odds for depression, anxiety, sleeping disorders and low quality of life.

Three categories were considered for alcohol use disorders (no alcohol use disorder, hazardous level of alcohol drinking and alcohol dependence). The first category was chosen as a reference group and the two others were included in the model as indicator variables. Alcohol dependence was strongly positively associated with depression, sleeping disorders, anxiety and low quality of life. Smoking and hazardous level of alcohol drinking were positively associated with depression and sleeping disorders.

The odds for depression, sleeping disorders and anxiety were significantly higher for participants with circulatory and gastrointestinal diseases compared with those without such diseases. This association remained significant after adjustment for smoking and alcohol use disorders. There was also a strong positive association between low life quality and circulatory/gastrointestinal diseases.

The variables "income", "education" and "civil status" had three or more categories, one of them was chosen as a reference group and the others were included in the model as indicator variables. Professions with low income and pensioners had higher odds for depression, anxiety and sleeping disorders compared with the high-income group. The group of pensioners had especially high odds for low quality of life.

Education and civil status had no association with low quality of life. Persons with secondary professional

Table 3 The Cantril Ladder and prevalence of low self-evaluated quality of life (Cantril Ladder < 5)

Age, years	Cantril Ladder Mean (SD)		Low life quality, %	
	Men	Women	Men	Women
18–19	6.0 (1.6)	6.0 (1.7)	16.2	15.1
20–29	6.4 (1.7)	6.1 (1.6)	10.3	15.9
30–39	5.9 (1.8)	5.5 (1.8)	17.7	27.8
40–49	5.9 (1.6)	5.4 (1.8)	15.0	26.2
50–59	5.6 (1.8)	5.0 (1.6)	23.1	31.8
60+	4.9 (1.7)	4.3 (1.8)	40.7	55.9
All	5.8 (1.8)	5.3 (1.8)	20.5	30.7
Age-standardized[a]	5.8	5.2	20.1	32.6

[a] Age-standardized to the general Russian population in 2000

Table 4 Several characteristics of the study population

	Men n = 1968	Women n = 1737
Age, mean (SD)	41.8 (16.3)	44.2 (15.9)
Consumption once a week or less, %:		
Fruits or vegetables	40.3	36.0
Fish or fish product	33.8	49.0
Meat or meat product	15.0	24.4
Unsatisfied with nutrition, %	10.8	21.9
Alcohol use disorders[a], %		
Hazardous level of alcohol drinking	26.1	7.2
Alcohol dependence	12.5	2.4
Smoking, %	56.6	21.3
Circulatory diseases[b], %	9.4	12.6
Gastrointestinal diseases[c], %	23.1	50.7
Education, %:		
High	21.0	32.5
Secondary professional	56.4	41.5
Secondary	22.6	26.0
Income, %:		
High salary	54.4	2.1
Average salary	7.4	11.2
Low salary	7.3	44.7
Retirement pension	15.4	23.5
Other[d] (unknown income)	15.5	18.5
Civil status, %:		
Married/co-habitant	71.3	58.3
Unmarried	21.2	17.2
Divorced	4.2	11.0
Widow/widower	3.3	13.5

[a] Based on the AUDIT
[b] Angina pectoris, myocardial infarction and/or stroke
[c] Stomach/duodenal ulcer, pancreatitis, hepatitis/cirrhosis, and/or dyspepsia
[d] Student, housewife, unemployed

Table 5 Logistic regression analysis of depression, anxiety and sleeping disorder with mutually adjusted odds ratios (OR) and 95% confidence intervals (CI)

Variables	Depression OR (95% CI)	Sleeping disorders OR (95% CI)	Anxiety OR (95% CI)
Gender: women vs. men	3.6 (2.8–4.7)****	3.9 (3.0–5.0)****	3.3 (2.7–4.0)****
Age, 10 years	1.1 (0.9–1.2)	1.3 (1.2–1.5)****	1.0 (0.9–1.1)
Low consumption of:			
Fruits or vegetables[a]:	1.4 (1.2–1.7)***	1.6 (1.3–1.9)****	1.1 (0.9–1.3)
Fish or fish products[a]:	1.4 (1.2–1.7)***	1.2 (1.0–1.4)	1.2 (1.03–1.4)*
Meat or meat products[a]:	1.2 (1.0–1.5)	1.0 (0.8–1.3)	1.3 (1.03–1.5)*
Unsatisfied with nutrition: yes vs. no	2.1 (1.7–2.7)****	1.9 (1.5–2.4)****	1.7 (1.4–2.1)****
Alcohol use disorders[b]:			
Hazardous level of alcohol drinking[c]	1.4 (1.1–1.8)*	1.3 (1.01–1.8)*	1.2 (0.9–1.5)
Alcohol dependence[d]	1.8 (1.3–2.6)***	2.0 (1.4–2.9)***	1.6 (1.2–2.1)**
Smoking (yes vs. no)	1.6 (1.3–2.0)****	1.4 (1.1–1.8)**	1.1 (0.9–1.3)
Circulatory diseases (yes vs. no)	2.0 (1.5–2.6)****	2.1 (1.6–2.8)****	2.2 (1.7–2.9)****
Gastrointestinal diseases (yes vs. no)	1.7 (1.4–2.0)****	1.4 (1.2–1.7)***	1.4 (1.2–1.6)****
Education (secondary is a reference):			
Secondary professional	0.8 (0.7–1.0)	0.7 (0.6–0.9)**	0.8 (0.7–1.0)
High	0.9 (0.7–1.1)	1.0 (0.8–1.3)	0.8 (0.7–1.1)
Income[e] (high salary is a reference):			
Average salary	1.5 (1.02–2.2)*	1.4 (0.9–2.0)	1.3 (0.9–1.7)
Low salary	1.5 (1.04–2.0)*	1.8 (1.3–2.6)***	1.4 (1.1–1.8)*
Retirement pension	1.5 (1.02–2.3)*	1.8 (1.2–2.7)**	1.4 (1.03–2.0)*
Other (unknown income)	1.3 (0.9–2.0)	1.2 (0.8–1.8)	1.2 (0.9–1.6)
Civil status (married is a reference):			
Unmarried	1.0 (0.7–1.3)	1.0 (0.7–1.4)	0.7 (0.5–0.9)**
Divorced	1.2 (0.9–1.6)	0.9 (0.7–1.3)	0.9 (0.7–1.1)
Widow/widower	1.4 (1.0–1.9)	1.3 (1.0–1.8)	1.0 (0.8–1.4)

[a] Once a week or less (yes vs. no)
[b] Reference group is AUDIT-score ≤ 7
[c] AUDIT-score 8–12
[d] AUDIT-score ≥ 13
[e] High salary (seamen), average income (industry workers), low salary (civil employees), retirement pension (pensioners), other (students, housewives and unemployed)
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

education had lower odds for sleeping disorders than those who had only secondary school education. Odds for anxiety were lower in unmarried persons compared with married ones.

Comparison with other studies

Our results were compared with two population-based studies from Northern Norway that used the same formulations of questions for depression and quality of life. Before the comparison, the results from Arkhangelsk were age-standardized to these Norwegian population samples (data not shown). Women in our study had significantly higher prevalence of self-reported depression ($p < 0.0001$) compared with Norwegian women in the Finnmark study (11.3%) and the Svalbard study (15.6%) (Westlund et al. 1993; Nilssen et al. 1999). In men, the prevalence of depression was the same as on Svalbard (10.7%), but higher than in Finnmark (6.3%, $p < 0.0001$). The average score of life quality was significantly lower ($p < 0.0001$) in our study population compared with the Norwegians on Svalbard (7.6 and 7.0 for women and men, respectively).

Discussion

Study limitations

It is difficult to draw a population sample representative for the whole of Russia (about 144 million citizens, more than 100 nationalities and 11 time zones). The present study was conducted in the northwest of Russia, in the region where mortality rates were similar to the figures for the entire area of Russia. The study was limited to the working population, students, housewives and pensioners. The unemployed were underrepresented in this study.

The main limitation of the study was that findings were based on self-reports of depression, anxiety and sleeping disorders. Study subjects may understand questions and report their condition differently. A different pattern of results might have been obtained if diagnostic interviews had been utilized. However, it is time- and resource-consuming to incorporate such interviews in a large-scale population study. Therefore, we included in the questionnaire the formulations that were used in other population studies and compared our results only with reports from these studies.

Table 6 Logistic regression analysis of low life quality (Cantril Ladder < 5) with mutually adjusted odds ratios (OR) and 95% confidence intervals (CI)

Variables	Low life quality OR (95% CI)
Gender: women vs. men	1.2 (0.9–1.5)
Age, 10 years	1.2 (1.1–1.3)**
Low consumption of:	
Fruits or vegetables[a]:	1.6 (1.4–2.0)****
Fish or fish products[a]:	1.4 (1.2–2.7)****
Meat or meat products[a]:	1.3 (1.02–1.5)*
Unsatisfied with nutrition: yes vs. no	3.8 (3.1–4.7)****
Alcohol use disorders[b]:	
Hazardous level of alcohol drinking[c]	0.9 (0.7–1.2)
Alcohol dependence[d]	1.7 (1.3–2.3)***
Smoking (yes vs. no)	1.0 (0.8–1.2)
Circulatory diseases (yes vs. no)	1.7 (1.3–2.2)***
Gastrointestinal diseases (yes vs. no)	1.3 (1.1–1.5)**
Education (secondary is a reference):	
Secondary professional	1.1 (0.9–1.4)
High	1.1 (0.8–1.4)
Income[e] (high salary is a reference):	
Average salary	1.6 (1.2–2.3)**
Low salary	1.1 (0.8–1.5)
Retirement pension	2.0 (1.4–2.8)***
Other (unknown income)	1.2 (0.9–1.7)
Civil status (married is a reference):	
Unmarried	0.9 (0.6–1.2)
Divorced	1.3 (1.0–1.8)
Widow/widower	1.3 (0.9–1.8)

[a] Once a week or less (yes vs. no)
[b] Reference group is AUDIT-score ≤ 7
[c] AUDIT-score 8–12
[d] AUDIT-score ≥ 13
[e] High salary (seamen), average salary (industry workers), low salary (civil employees), other (students, housewives and unemployed)
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Language and cultural differences in the perception of questions may apply when a "western" questionnaire is translated into Russian. However, when comparing answers on other questions (diet, use of medicines), no evidence of misunderstanding or "eager to please" response pattern was found. The standard back-translation procedure by the two independent translators was applied to assure the accuracy of the translation.

Interpretation of the main results

The gender difference in prevalence of depression and sleeping problems was higher in Russia than in the Norwegian population in Finnmark and on Svalbard. This finding may reflect the weak position of women in the Russian society. Although Russian laws guarantee gender equality, in real life, women are the first to be fired and usually receive a lower salary than men even if they are more educated and skilled (Human Rights Watch 1995). The majority of unemployed people in Russia are women (WHO 2002). Women are also concentrated in low-paid sectors of the economy. The same situation is seen in other countries from the ex-Soviet Union (Alyanak 1999).

Depression, anxiety and sleeping disorders were strongly associated with nutrition variables (unsatisfied with own nutrition; low consumption of fruits and vegetables, fish, meat). This probably means that some food types are not available to the general population to the extent they would have preferred. Although fresh fruits, vegetables, fish and meat are easily accessible in Arkhangelsk, they are expensive, at least for all those with low salaries and retirement pensions. Nutrition may be an important indicator of socioeconomic status in our data. Other potential indicators of socioeconomic status are level of education and occupational status. The low odds for sleeping disorders among people with secondary professional education may suggest that they cope better with the difficult economic situation. Surprisingly, higher education showed no negative association with depression, anxiety and sleeping disorders. This might be explained by the fact that nowadays many people with high education in Russia are employed in low-paid sectors of the economy where salaries are substantially lower than in industry. Among the working population in this study, 67% of those with secondary professional education were seamen or industry workers, while the majority with high education were low-paid civil employees (65%). Civil employees and pensioners had the highest odds for depression, sleeping disorders and anxiety. Poor economy and health problems may be the reason for the decrease in life quality with age. In the 1990s, the high inflation in Russia substantially depreciated the level of retirement pensions. At the beginning of 2000, the mean monthly pension in Russia was one-half of the established poverty level (Goskomstat of Russia 2004). According to the study of the elderly in the 1990s (Rush and Welch 1996), 57% of Russian pensioners complained about lack of money to buy food, 50% consumed less than half a kilogram of fruit per week, and 40% consumed less than half a kilogram of meat per week.

Depression and sleeping disorders were positively associated with alcohol dependence, hazardous level of alcohol drinking and smoking. Anxiety was positively associated with alcohol dependence. The comorbidity of depression and anxiety with alcohol use disorders has been shown in other studies (Sloan et al. 2003; Grant et al. 2004). This cross-sectional study does not determine the casual mechanisms underlying the relationship between alcohol use disorders and depression, anxiety and sleeping disorders. Psychosocial factors may have an adverse effect on health-related behaviors and result in increased smoking and alcohol drinking. When alcohol dependence develops, the positive AUDIT reveals substantial problems with job, family relationships, and with health. The cluster of social problems associated with alcohol dependence might contribute to further depression and anxiety.

Low self-evaluated quality of life was positively asso-

ciated with alcohol dependence, but showed no association with hazardous level of alcohol drinking. In fact, the frequency of alcohol consumption alone (the first question of AUDIT) was negatively associated with low life quality (data not shown). The possibility to buy and drink alcohol is obviously judged as a marker of a good life standard and, thus, is not associated with lower quality of life, at least before any manifestation of alcohol-related problems.

Even though our study points to a strong association between mental distress/low life quality and self-reported circulatory and gastrointestinal diseases, the cross-sectional design does not allow us to draw any conclusions about causality. Disease itself can be a reason for depression, anxiety, sleeping problems and lower quality of life. On the other hand, mental distress and life dissatisfaction have been reported as risk factors for diseases and predictors for mortality (Ketterer et al. 2000; Koivumaa-Honkanen et al. 2000; Smith 2001; Truelsen et al. 2003). The most striking rises in Russian mortality occurred after the collapse of the Soviet Union and after the crisis in the Russian economy in 1998, which were both followed by a significant increase in individual poverty and mental distress. Leon & Shkolnikov (1998) wrote in their paper about the mortality crisis in Russia that "social stresses... appear to have played such a central part in the recent crisis". Further prospective studies are required to test this hypothesis.

Conclusions

Our study provides evidence that a considerable part of the Russian population suffers from depression, anxiety and sleeping disorders that are strongly associated with low socioeconomic status, poor nutrition, smoking, alcohol use disorders and history of circulatory and gastrointestinal diseases.

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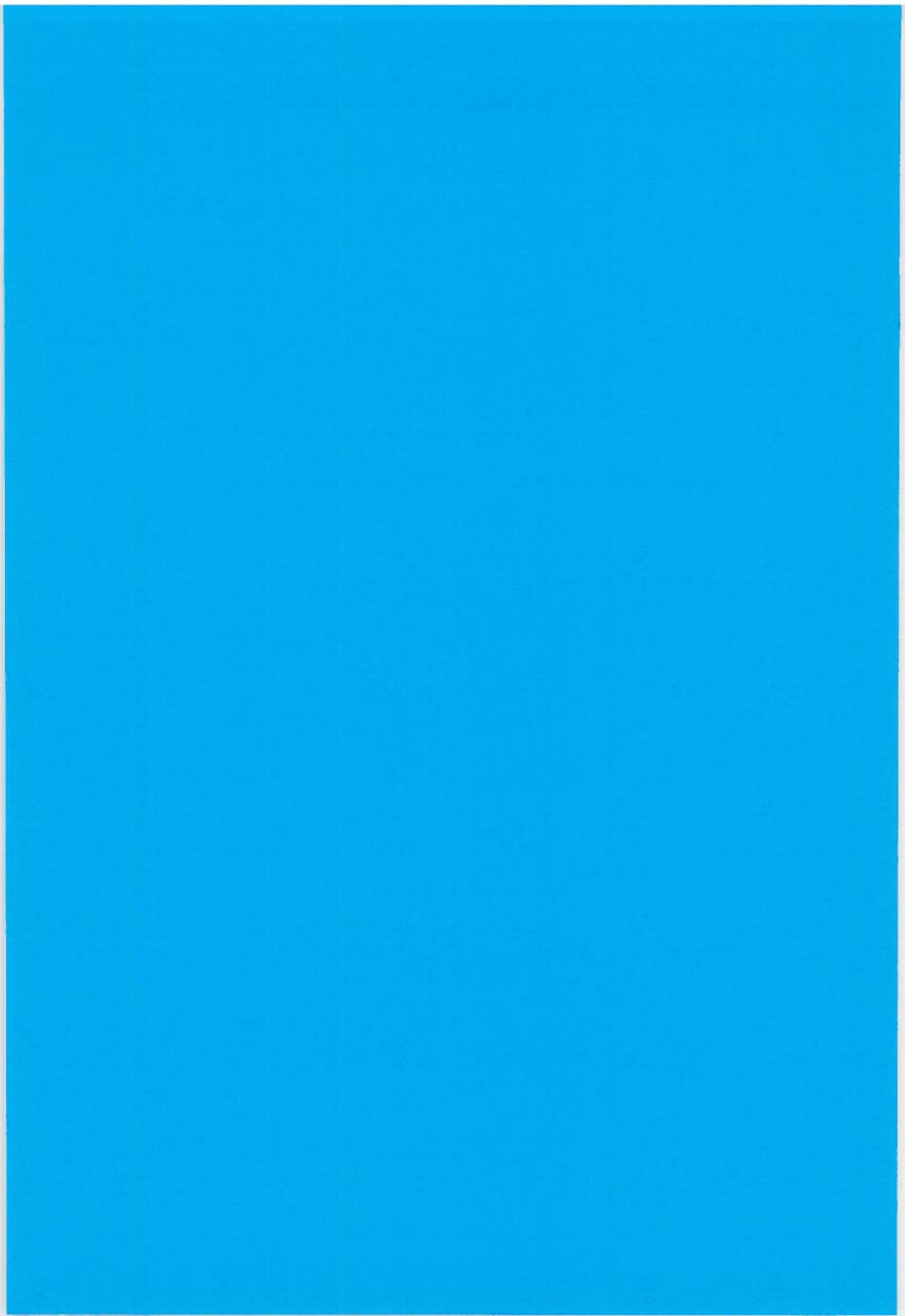
Paper IV



Title: C-reactive protein and alcohol consumption: is there an U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study.

Maria Averina[1], Odd Nilssen[1], Arkhipovsky VL[2], Kalinin AG[3], Jan Brox[4].

1. Institute of Community Medicine, Medical Faculty, University of Tromsø, N-9037, Tromsø, Norway (address for correspondence); fax +47 77 64 48 31; tel. +47 77 64 48 11; e-mail: Maria.Averina@ism.uit.no
2. Semashko clinic, Arkhangelsk, Russia
3. Northern State Medical University, Arkhangelsk, Russia
4. Department of Clinical Chemistry, University Hospital of Tromsø, Norway

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Key words: C-reactive protein, binge alcohol drinking.

ABSTRACT.

Background: Little is known about association between markers of inflammation and alcohol consumption in Russian population where binge drinking pattern is prevalent.

Methods and Results: C-reactive protein was measured by a highly sensitive particle-enhanced immunoturbidimetric assay (hsCRP) in 1963 men and 1734 women, aged 18-90 years, in a population-based cross-sectional study. Total alcohol consumption consisted mainly of binge vodka intake. An U-shaped association between hsCRP and total alcohol intake in both sexes disappeared when ex-drinkers were excluded from the analysis. Ex-drinkers of both sexes were older and reported more diseases than non-abstainers. In non-abstainers, hsCRP was positively linearly associated with vodka intake in both sexes and with total alcohol consumption in men. A biological marker for alcohol consumption – gamma-glutamyltransferase – showed a positive linear association with hsCRP in non-abstainers, and no association with hsCRP in abstainers.

Conclusions: The U-shaped association between hsCRP and weekly alcohol consumption was due to higher hsCRP levels in ex-drinkers than in non-abstainers. Factors other than the current level of alcohol consumption might be responsible for high hsCRP levels in ex-drinkers. When abstainers were excluded from analyses, the results indicated a pro-inflammatory effect of binge vodka consumption in non-abstainers.

INTRODUCTION.

C-reactive protein measured by highly sensitive methods (hsCRP) is considered to be a valuable predictor for cardiovascular diseases (CVD). Several studies have reported a positive association between hsCRP and fatal/ nonfatal coronary heart disease, sudden cardiac death and ischemic stroke [1-5]. Furthermore, in some studies, hsCRP showed higher predictive value for CVD than total cholesterol, LDL cholesterol, apolipoprotein B, homocysteine and lipoprotein (a) [4, 5].

Some authors have reported a J- or U-shaped relationship between CRP and alcohol consumption, postulating an anti-inflammatory effect of light and moderate alcohol intake [6-10]. However, the majority of these studies have not distinguished between lifetime abstainers and ex-drinkers. Ex-drinkers may have quitted drinking because of various diseases and may suffer from consequences of previous alcohol intake. Lifetime abstainers may have diseases prohibiting alcohol intake or they may initially have healthier lifestyle. To avoid bias, it is necessary to distinguish between lifetime abstainers, ex-drinkers and non-abstainers, and to adjust results of analysis for possible confounders like lifestyle and socioeconomic factors. Adjustment for smoking is especially important, as smoking is known to be associated with both alcohol intake and CRP levels.

The aim of the present study was to examine possible association between hsCRP levels and alcohol consumption distinguishing between non-abstainers, ex-drinkers and lifetime abstainers and taking into account type of beverage, smoking and socioeconomic status.

The study was conducted in a sample of a general Russian adult population. CVD is a leading cause of death in Russia. CVD mortality in Russia is almost three times higher than in Western Europe and US. Epidemiological studies have shown that the high CVD mortality in Russia could not be explained only by the classical risk factors for the disease (dyslipidemia, hypertension, smoking, diabetes) [11-13]. At the same time Russia is a world leader in alcohol consumption. To our knowledge, no studies have examined the association between the systemic markers of inflammation and alcohol consumption in a Russian population. In a population based cross-sectional study in Arkhangelsk, Russia, we had the opportunity to carry through this type of analysis.

MATERIALS AND METHODS.

Arkhangelsk region is one of the largest regions in the Northwest of Russia. At the time of the study mortality and morbidity rates in the Arkhangelsk region was almost similar to the average rates in the entire Russia [13]. No population register was available for medical research in Arkhangelsk. The study population was recruited through the primary health care system. Primary health care in Russia is provided at outpatient clinics (polyclinics) according to territorial and occupational principles. Residents are registered at polyclinics on a population basis according to their home address or place of work. Through this system we came close to an analog of a population register. Polyclinics provide services for two groups of citizens: 1) sick persons who need to see a doctor; 2) persons, who need to have compulsory medical examination. For the second group, the compulsory medical examination is usually required at work or study place. Therefore they represent not a group with health problems, but the general working or studying population. This group has no fixed appointment at the polyclinic, they may report at a special office between 08.00 and 12.00 at certain days during the week.

Our study participants were invited *consecutively* as they came to the obligatory medical examination at the polyclinic. Of those invited, 40 refused to participate in the study (approximately 1% of the study sample). The process of recruitment has been described in detail elsewhere [13].

Altogether, 1963 men and 1734 women aged 18-90 years took part in the study in 1999-2000 and had their CRP values measured. Socio-demographic characteristics of the study population (educational, occupational and family status) were similar to that of the general Arkhangelsk region population with two exceptions: unemployed men were underrepresented in our study; the percentage of people with university education and secondary professional education was higher in the study population compared with the general population of the Arkhangelsk region [13].

The subjects completed a 6-page questionnaire, which covered education, occupational and marital status, medical history, family diseases, dietary habits, smoking, physical activity, alcohol consumption, and use of medicines. The formulations of questions were previously used and validated in population-based studies in Northern Norway (the Tromsø study, the Svalbard study). The standard back-translation procedure by two independent translators was used.

Abstainers and non-abstainers were defined by the question: Do you drink alcohol beverages (yes, no). The group of abstainers was further subdivided into ex-drinkers and lifetime abstainers. Non-abstainers were asked about actual alcohol consumption: How many alcohol units did you drink during the last week. The question had five answer categories for beer, table wine, strong wine, vodka and total alcohol intake. One alcohol unit (AU) was defined as 40 ml of vodka; 80 ml of strong wine; 120 ml of table wine; 1 bottle (0.33 l) of strong beer or 2 bottles (0.33 l x 2) of light beer. One AU corresponds approximately 13.8 gr of pure alcohol. Further, the variable *alcohol consumption* was stratified for analyses as 1-3 AU/week; 4-6 AU/week and 7 or more AU/week. Participants were also asked about the pattern of alcohol consumption: How often do you drink 6 AU or more at one occasion (never; less than once per month; once per month; once per week; daily or almost daily). *Binge drinking* was defined as 6 AU or more at one occasion at least once a month.

Circulatory diseases were defined as self-reported myocardial infarction, angina pectoris, and stroke (at least one of the diseases). Smoking status had three categories: current smokers, non-smokers and ex-smokers. A sedentary physical activity was defined as sedentary job (e.g. office work, etc.) and sedentary lifestyle at leisure time (reading, watching TV, mostly sitting activity). Routine physical examination included weight, height, and waist-hip ratio measurements. Systolic and diastolic blood pressure was assessed three times at intervals of two minutes by an electronic device DINAMAP R with participants in a sitting position. The mean of the second and third measurement was used for analyses.

Ethics

The study was approved by the Regional ethical committee for Health Region V in Norway. No equivalent ethical committee existed in the Arkhangelsk region at the time of the study. Verbal informed consent was obtained from all the participants.

Laboratory procedures

Nonfasting blood samples were obtained from all subjects. The serum was stored at –20 °C and transported to Norway in boxes with freezing elements by a 5-h flight. All the laboratory analyses were done at the Department of Clinical Chemistry, University Hospital of Tromsø, Norway.

High-density lipoprotein cholesterol (HDL-cholesterol) was measured by a homogeneous enzymatic colorimetric test (PEG cholesterolesterase, PEG peroxidase) in the Hitachi 917 analyzer. Analytic coefficient of variation (CV) was 3%. Low density lipoprotein cholesterol (LDL-cholesterol) was calculated according to Friedwald's formula. For samples with triglycerides more than 4 mmol/l (354 mg/dl) LDL-cholesterol was determined directly using the homogeneous enzymatic colorimetric test (Roche, selective inhibition of VLDL-, chylomicron-, HDL-cholesterol), CV was 3%. Triglycerides were assayed by an enzymatic colorimetric test (lipoproteinlipase, glycerokinase, and glycerophosfat oxidase), CV was 2%. Gamma-glutamyltransferase (GGT) was measured by a standard enzymatic colorimetric test in accordance with recommendations of the International Federation of Clinical Chemistry, CV was 2.5%.

Measurement of CRP

Serum concentrations of CRP were measured by a highly sensitive particle-enhanced immunoturbidimetric assay (hsCRP) [14, 15] in the Roche Modular P analyzer (Roche Diagnostics GmbH, D-68298 Mannheim). CV was 3%. The lower detection limit was 0.03 mg/l.

The distribution of hsCRP in the study population was right skewed with mean values of 3.2 mg/l (SD 9.0) in men and 2.7 mg/l (SD 5.8) in women, and median values of 1.17 and 1.19 mg/l, respectively. The level of 3 mg/l corresponded approximately 75th percentile of hsCRP distribution. As in other studies [10], we considered values above 3 mg/l as elevated hsCRP. Altogether 617 of 3697 participants (16.7 %) had hsCRP values in the range 3-10 mg/l. About 4.8% of the study population (178 participants) had hsCRP higher than 10 mg/l, which might indicate an active infection. Participants with hsCRP above 10 mg/l were excluded from the further analyses. The number of participants in the analyzed sample was 3519 (1860 men and 1659 women).

Statistical analyses

SAS statistical package was used for the analyses (SAS Institute Inc., USA). Chi^2 test and t-test were used to assess differences in health-related variables between ex-drinkers, lifetime abstainers and non-abstainers. Proc GLM procedure in SAS was used to test differences in hsCRP levels between categories of total weekly alcohol consumption. A forward stepwise multivariate linear regression analysis with log-transformed hsCRP as a dependent variable was performed to test associations between hsCRP and other variables among abstainers and non-abstainers. A 5% significance level was used for reminding or removal from the regression model.

RESULTS

Age- and sex distribution in the study population was close to that in the general population of the Arkhangelsk region and entire Russia (table 1). Age-standardized prevalence of self-reported circulatory diseases in the study population (standardized to the total Russian population) was 130.7 per 1000 participants, which agrees well with the official data for the adult population in the Northwest of Russia in 1998 (132.9 per 1000) [13].

Self-reported total alcohol consumption in the study sample was 5.9 AU (SD 10.0) and 2.3 AU (SD 4.6) per week in men and women, respectively. About 61% of the total alcohol consumption was vodka/liquor and 29% was beer. Intake of wine was relatively low (10% of the total alcohol intake per week). Among all non-abstainers, 52.3% of men and 16.9% of women were regular binge drinkers. About 58% of men and 40% of women with weekly alcohol consumption 4-6 AU and 79% of men and 71% of women with weekly alcohol consumption $\geq$ 7 AU were binge drinkers.

Table 2 shows hsCRP levels stratified by categories of weekly alcohol consumption. Before adjustment for other factors, the association between hsCRP and total weekly alcohol consumption was U-shaped in both sexes due to significantly higher hsCRP levels in ex-drinkers compared with lifetime abstainers and non-abstainers. In both sexes there was no statistically significant difference in hsCRP levels between lifetime abstainers and light or moderate drinkers (1-3 and 4-6 AU/week). The U-shaped association between hsCRP and alcohol consumption became non-significant in both sexes after adjustment for age, BMI, smoking status (current smoker, non-smoker, ex-smoker), diabetes

mellitus and cardiovascular medication. When ex-drinkers were excluded from the analysis, the U-shaped trend disappeared in both sexes (data not shown).

Beverage-specific analysis was performed for men and women together because of small numbers in groups that consumed only one type of alcohol beverage (table 2). Before adjustment, vodka consumption showed an U-shaped association with hsCRP, while beer consumption had a negative linear association with hsCRP. These associations became non-significant after adjustment for possible confounders. Wine consumption showed a negative linear association with hsCRP, the association remained significant after the adjustment. However, when ex-drinkers were excluded from the analysis, the negative linear association between hsCRP and wine intake became non-significant (data not shown).

Table 3 presents the characteristics of abstainers (lifetime abstainers and ex-drinkers) compared with non-abstainers. Ex-drinkers of both sexes were older, had higher BMI and waist-hip ratio, reported more circulatory diseases and evaluated their health as "poor" more often than lifetime abstainers and non-abstainers. Lifetime abstainers also appeared to be a special group. Male lifetime abstainers were younger and smoked less than non-abstainers. Female lifetime abstainers were older, smoked less, but reported worse health than non-abstainers.

As ex-drinkers and lifetime abstainers appeared to be different from non-abstainers, we performed multiple regression analysis with log-transformed CRP as the dependent variable separately for non-abstainers and abstainers (tables 4, 5). β-coefficients show the change in log-transformed CRP values if independent variables change by one unit. Model 1 includes total alcohol consumption during the last week (all beverages). In Model 2 total alcohol consumption is substituted by weekly vodka consumption. Log-transformed CRP was positively associated with total weekly alcohol consumption in men and with weekly vodka consumption in both sexes. Age, BMI, waist-hip ratio, LDL cholesterol, GGT were positively associated with hsCRP, whereas HDL cholesterol was negatively associated with hsCRP in male and female non-abstainers (Table 4). HsCRP was positively associated with current smoking in male non-abstainers and with systolic blood pressure and triglycerides in female non-abstainers. There were no significant associations between hsCRP and self-reported diabetes mellitus, cardiovascular diseases and use of cardiovascular medicines. Inclusion of these

variables in the regressions models did not substantially change the results presented in the table 4 (data not shown). Socioeconomic status (educational level, professional status), sedentary physical activity, consumption of fruits or vegetables, meat, fish, and milk showed no significant associations with hsCRP levels. No significant interactions between total alcohol intake/vodka intake and systolic blood pressure or HDL-cholesterol were found. Beer and wine intake (table wine and/or strong wine) showed no significant association with hsCRP in multiple regression analysis (data not shown). However, this result could be due to relatively low consumption of these beverages in the study population.

In non-abstainers of both sexes hsCRP levels were positively associated with GGT (Table 4), while in abstainers there was no significant association between hsCRP and GGT (Table 5). Furthermore, a positive association between hsCRP and total alcohol intake/vodka intake per week, as well as between hsCRP and GGT remained significant in male non-abstainers with CRP levels higher than 10 mg/l (data not shown).

DISCUSSION

STUDY LIMITATIONS

The method of participant's recruitment was not ideal. As the population register was not available for medical research in Russia, we used the population registration system in the primary health care. To avoid "healthy volunteer effect" we recruited participants consecutively as they came to the obligatory medical examination at the polyclinic. However, the "healthy worker effect" could not completely be ruled out, as the most marginalized part of the population (jobless, homeless, alcohol and drug abusers) is less likely to attend such medical examination. The group of unemployed was underrepresented in this study. Other demographic characteristics of the study population were close to that of the general population in the Arkhangelsk region [13]. Another limitation of the study is that data on diseases were self-reported. However, age-standardized prevalence of circulatory diseases in the study population was almost the same as in the Northwest of Russia [13].

Alcohol consumption probably was underreported in our study, especially among those professional groups who were afraid of loosing their job if alcohol consumption proved to be too high.

Though the study was anonymous and all the participants were informed that the data would not affect their professional status, some participants may have taken their own precautions and reported lower alcohol intake.

INTERPRETATION OF THE MAIN FINDINGS

Before adjustment for possible confounders, hsCRP showed an U-shaped association with total alcohol consumption in both sexes with the highest hsCRP levels in ex-drinkers. Test for the U-shaped association showed a non-significant result after the adjustment. The U-shaped association disappeared in both sexes when ex-drinkers were excluded from the analysis. These findings are somewhat different from other studies that reported a significant U- or J-shaped association between hsCRP and alcohol [6-10]. However, the majority of these studies have not distinguished between lifetime abstainers and ex-drinkers. Distinguishing between the two groups of abstainers seems to be a crucial point in investigation of alcohol effects on health variables. In our study the U-shaped association between hsCRP and total alcohol intake was due to high hsCRP levels in ex-drinkers. Ex-drinkers in our study comprised a special group of participants that were older than non-abstainers and had more health problems. It is possible that ex-drinkers suffer from consequences of previous alcohol consumption. Lifetime abstainers also appeared to be a special group with somewhat healthier lifestyle (less smoking). Female lifetime abstainers reported more diseases than non-abstainers. We assume that the difference in hsCRP levels between abstainers and non-abstainers may be related to factors other than their current level of alcohol consumption.

Drinking pattern and preferred alcohol beverage in our study were substantially different from other studies that investigated the relation between alcohol intake and markers of inflammation. A considerable part of the study population was binge drinkers of strong alcohol beverages (vodka). This finding corresponds well with results of other studies that also have reported high prevalence of binge drinking in Russia [16].

It is known that high ethanol consumption may directly and indirectly contribute to oxidative stress and inflammation [17, 18]. Pro-oxidant effects of ethanol have been considered an important

mechanism responsible for increased cardiovascular risk in patients with chronic excessive alcohol use [17]. In our study, multiple regression analysis in non-abstainers showed a pro-inflammatory effect of weekly vodka consumption in both sexes and of total alcohol consumption in men. This finding is in agreement with a study from Finland, which also showed increased CRP and LDL oxidation in persons with excessive alcohol consumption [19].

Nevertheless, rather different results were reported from studies that investigated effect of wine- and beer intake in populations with another drinking pattern. For example, a study from Italy reported a negative association between moderate daily wine intake and serum LDL oxidation [20]. The British Regional Heart study found no association between total alcohol consumption and hsCRP, and a significant inverse association between wine consumption and hsCRP [21]. A Spanish intervention study has demonstrated that intake of red wine resulted in significant decrease of hsCRP levels, while intake of gin did not show significant effect on hsCRP [22]. It is known that some polyphenolic substances in wine have antioxidant properties, which might explain anti-inflammatory benefits of moderate wine drinking [23]. In our study there was a tendency to negative association between hsCRP and wine consumption in the group of wine drinkers. However, the number of wine drinkers was relatively small, which might be the reason for insignificant effect of wine intake on the population level. Total alcohol consumption consisted mainly of binge vodka intake.

GGT is a well-known marker of alcohol consumption. We assume that GGT level is a more objective marker of alcohol consumption than self-reported intake in our study. A strong positive association between hsCRP and GGT emerged in non-abstainers of both sexes, while in abstainers there was no such association. We suppose that the positive association between hsCRP and GGT in non-abstainers was alcohol-mediated. Some authors consider GGT to be a marker of oxidative stress [24]. Increased GGT levels may be the indicator of oxidative stress associated with high ethanol consumption. GGT is also known as a risk marker for hypertension, stroke, CVD and cardiac death [25, 26]. A positive linear association between hsCRP levels and weekly vodka consumption, as well as between hsCRP and GGT in non-abstainers may reflect the pro-inflammatory effect of binge alcohol consumption in this population. Russian population has one of the highest alcohol consumption per capita in the world (15.4 litres per capita in 1998) [27]. There is growing evidence

that excessive alcohol drinking is implicated in the increase in CVD mortality in Russia [28]. Although many studies from other countries have reported a cardio-protective effect of moderate alcohol consumption, several prospective studies have reported increased CVD mortality in binge and heavy alcohol drinkers [29-31]. HsCRP is a known predictor of CVD events and sudden cardiac death in healthy people and in patients with CVD. Although the cross-sectional design of the study does not allow conclusions about causality, the findings indicate that the pro-inflammatory effect of binge vodka/liquor consumption might be one of the possible mechanisms explaining the increased CVD risk in populations with high ethanol intake.

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Table 1. Age distribution (%) of the study population in comparison with the general population of the Arkhangelsk region and the whole Russian population.

	Men			Women		
Age Number	Russia 54.59×10^6	Arkhangelsk region 56.99×10^4	Study population 1963	Russia 64.37×10^6	Arkhangelsk region 62.09×10^4	Study population 1734
15-19*	10.9	11.4	11.9	9.0	10.1	4.2
20-29	19.5	19.6	14.7	16.0	16.8	17.3
30-39	19.6	20.4	18.1	16.6	16.3	18.2
40-49	21.1	23.0	22.7	19.1	20.4	24.2
50-59	11.8	11.7	15.7	12.0	11.9	17.6
60+	17.1	13.9	16.9	27.3	24.5	18.5
Total	100.0	100.0	100.0	100.0	100.0	100.0

* the age group 15-19 years in the study population comprises only subjects 18-19 years old.

Table 2. Means and geometric means of CRP according to drinking status.

	Ex-drinkers	Lifetime abstainers	1-3 AU/week	4-6 AU/week[#]	≥7 AU/week	p-value
All alcohol beverages:						
Men						
Total number	142	78	1013	178	449	
Unadjusted mean	2.27	1.39	1.68	1.73	1.74	<0.01*
Unadjusted geometric mean	1.61	0.91	1.12	1.16	1.14	<0.001*
Adjusted geometric mean‡	1.22	1.10	1.12	1.16	1.18	0.20*
Women						
Total number	246	200	990	131	92	
Unadjusted mean	2.83	1.76	1.64	1.42	1.51	<0.0001*
Unadjusted geometric mean	2.01	1.17	1.04	0.93	0.97	<0.0001*
Adjusted geometric mean‡	1.30	1.17	1.11	1.08	1.20	0.06*
Only vodka, both sexes:						
Total number	388	278	204	74	147	
Geometric mean†	1.83	1.07	1.35	1.25	1.46	<0.05*
Adjusted geometric mean‡	1.47	1.30	1.38	1.39	1.64	0.11*
Only beer, both sexes:						
Total number	388	278	488	107	-	
Geometric mean†	1.85	1.09	0.87	0.90	-	<0.0001**
Adjusted geometric mean‡	1.24	1.15	1.11	1.10	-	0.23**
Only wine, both sexes:						
Total number	388	278	144	58	-	
Geometric mean†	1.88	1.09	0.98	0.98	-	<0.0001**
Adjusted geometric mean‡	1.49	1.35	1.16	1.16	-	<0.05**

*p for U-shaped trend; **p for linear trend; † adjusted for sex; ‡adjusted for age, BMI, smoking status (current smoker, non-smoker, ex-smoker), diabetes mellitus, cardiovascular medication;

[#] the category is ≥ 4 AU/week for drinkers who consume only beer or wine.

Table 3. Characteristics (mean, SD) of ex-drinkers, lifetime abstainers and non-abstainers.

	Ex-Drinkers	Lifetime abstainers	Non-abstainers
Men			
Number	142	78	1640
Age, years	59.0 (15.4)†	33.1 (15.7)‡	40.3 (15.0)
BMI, kg/m^2	26.3 (3.7)†	24.4 (3.9)	25.1 (4.0)
Waist-hip ratio	0.88 (0.1)†	0.84 (0.1)	0.86 (0.1)
Smoking, %	37.3‡	44.9‡	58.6
Poor self-rated health, %	16.2†	0.0	1.7
Circulatory diseases *, %	43.0†	2.6	6.0
Women			
Number	246	200	1213
Age, years	63.2 (12.9)†	45.5 (16.4)‡	39.9 (13.2)
BMI, kg/m^2	27.8 (4.7)†	25.4 (4.9)	25.7 (6.0)
Waist-hip ratio	0.81 (0.1)†	0.78 (0.1)	0.77 (0.1)
Smoking, %	3.7†	10.5‡	26.2
Poor self-rated health, %	32.1†	11.0‡	6.0
Circulatory diseases*, %	40.2†	14.0	6.3

*myocardial infarction, angina pectoris, stroke; † significantly different from lifetime abstainers and non-abstainers ($p<0.05$); ‡ significantly different from non-abstainers ($p<0.05$).

Table 4. Multiple linear regression analysis with hsCRP (log10-transformed) as a dependent variable in non-abstainers.

	Men (n=1640)				Women (n=1212)[#]			
	Model 1		Model 2		Model 1		Model 2	
Variables	β	t-value	β	t-value	β	t-value	β	t-value
Age, years	0.004	5.2‡	0.004	5.1‡	0.003	3.1**	0.003	3.1**
Body mass index, kg/m^2	0.014	4.7‡	0.014	4.7‡	0.014	6.4‡	0.014	6.4‡
Waist-hip ratio	0.557	3.2**	0.561	3.2**	0.534	2.9**	0.518	2.8**
HDL, mmol/l	-0.124	-4.5‡	-0.121	-4.4‡	-0.074	-2.3*	-0.076	-2.3*
LDL, mmol/l	0.041	4.2‡	0.041	4.2‡	0.022	1.9*	0.023	1.9
Triglycerides, mmol/l	-0.007	-0.6	-0.006	-0.6	0.037	2.0*	0.036	1.9
Current smoker (yes, no)	0.116	5.4‡	0.117	5.5‡	-0.021	-0.8	-0.021	-0.8
Ex-smoker (yes, no)	0.040	1.4	0.041	1.5	-0.046	-1.1	-0.049	-1.1
Systolic BP, mmHg	0.0004	0.6	0.0004	0.6	0.002	3.6†	0.002	3.6†
GGT, U/l	0.001	6.6‡	0.001	6.6‡	0.001	2.0*	0.001	2.0*
Weekly total alcohol intake[§]	0.002	2.3*	-	-	0.004	1.7	-	-
Weekly vodka intake[§]	-	-	0.002	2.0*	-	-	0.006	2.2*
Adjusted r^2, %	21.7		21.6		25.5		25.6	

* p<0.05, ** p<0.01, † p<0.001, ‡ p<0.0001;

[§] Model 1: total alcohol intake (all beverages), alcohol units per last week; Model 2: vodka/liquor intake, alcohol units per last week (1 AU = 13.8 gr pure alcohol);

[#] the number is lower than in the table 3 because of one missing value for waist-hip ratio;

To convert β-coefficients for HDL and LDL to mg/dl, divide by 0.0259. To convert β-coefficients for triglycerides to mg/dl, divide by 0.0113.

Table 5. Multiple linear regression analysis with hsCRP (log10-transformed) as a dependent variable in abstainers.

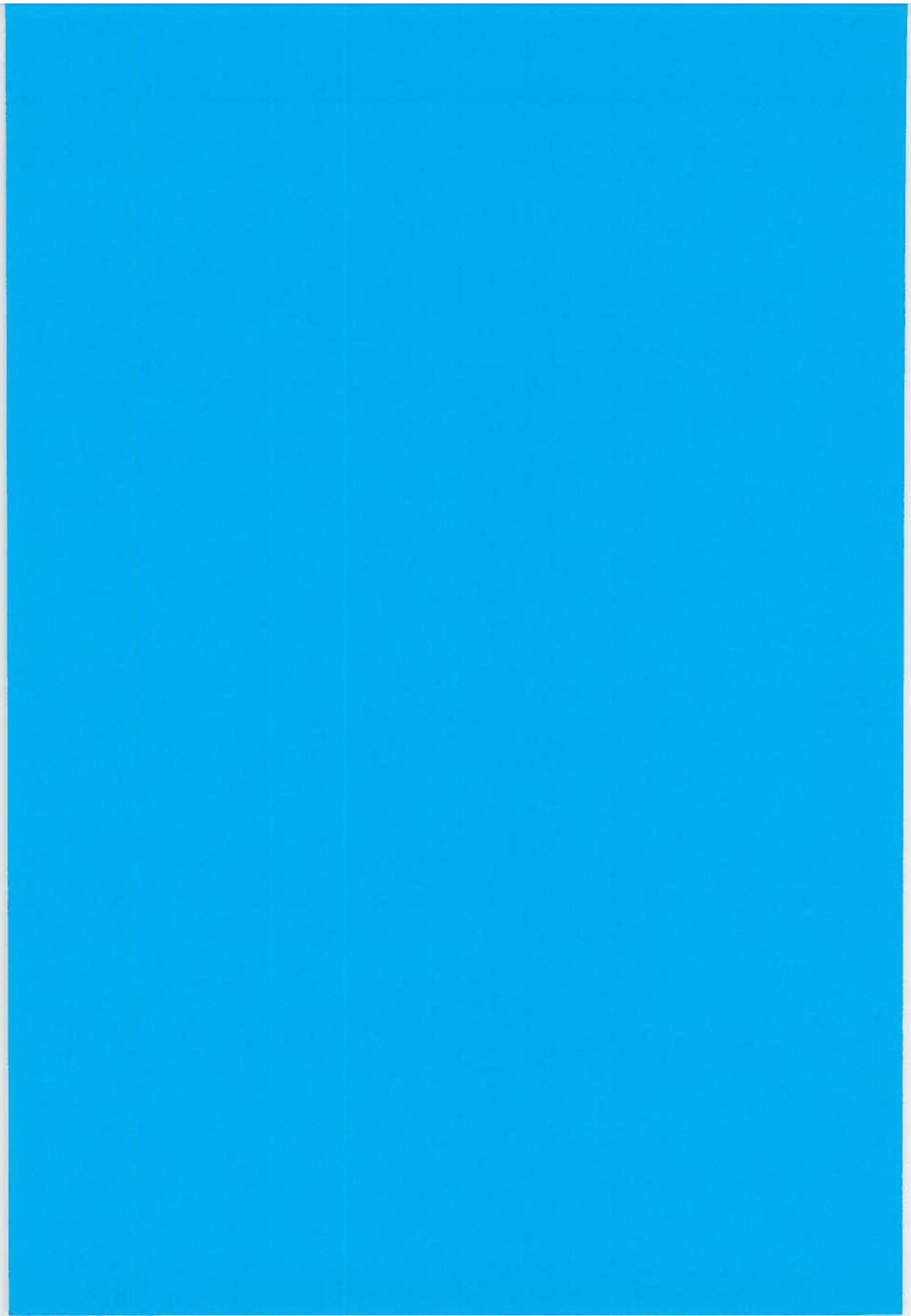
	Men (n=220)		**Women (n=445)** [§]	
Variables	β	t-value	β	t-value
Age, years	0.004	2.4*	0.005	4.0‡
BMI, kg/m^2	0.005	0.6	0.017	4.0‡
Waist-hip ratio	0.117	0.3	0.314	1.2
HDL, mmol/l	-0.306	-3.2**	-0.161	-3.0**
LDL, mmol/l	0.059	2.4*	0.030	1.9
Triglycerides, mmol/l	0.006	0.2	0.035	1.5
Current smoker (yes, no)	0.153	2.6*	-0.073	-1.1
Ex-smoker (yes, no)	0.109	1.7	0.061	0.8
Systolic BP, mmHg	0.003	2.2*	0.002	2.6*
GGT, U/l	0.0006	1.1	0.0009	1.9
Adjusted r^2, %	23.1		33.9	

* p<0.05, ** p<0.01; † p<0.001, ‡ p<0.0001,

[§] the number is lower than in the table 3 because of one missing value for HDL cholesterol;

To convert β-coefficients for HDL and LDL to mg/dl, divide by 0.0259. To convert β-coefficients for triglycerides to mg/dl, divide by 0.0113.

Paper V



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Alcohol consumption and its relation to risk factors for cardiovascular disease in the north-west of Russia: the Arkhangelsk study

Odd Nilssen,[1]* Maria Averina,[1] Tormod Brenn,[1] Jan Brox,[2] Alexei Kalinin[3] and Vadim Archipovski[4]

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Background To explore indicators and levels of alcohol consumption in a Russian population, and to elaborate these in relation to risk factors for cardiovascular disease.

Methods A total of 1963 men and 1734 women, aged 18–75 years, consecutively recruited at their compulsory annual medical check-up at the Semashko outpatient clinic, Arkhangelsk, participated in a cross-sectional health survey. The survey comprised a physical examination, a six-page questionnaire on health and lifestyle, and blood tests.

Results Gamma-glutamyltransferase (GGT) levels in both sexes were more than twice as high as found in comparable studies. Elevated GGT-levels were 4–5 times more frequent than found in Norwegian studies. Alcohol Use Disorder Identification Test (AUDIT) identified up to 75% of male workers and 47% of female workers as hazardous or harmful alcohol drinkers. The traditional risk factors for cardiovascular disease were significantly higher in subjects with a high level of GGT.

Conclusion The findings indicate an extremely high level of alcohol consumption in this population. Elevation in GGT was significantly associated with increased risk for cardiovascular disease.

Keywords Alcohol, audit, gamma-glutamyltransferase, cardiovascular disease

Public health in Russia appears to have undergone a dramatic change for the worse since the collapse of the Soviet Union.[1] During the last decade, significant increases in cardiovascular disease (CVD), infectious disease, suicide, and fatal injuries have been observed.[2] In contrast to west European countries CVD mortality has increased and continues to rise.[3] The increase from 2002 to 2003 was 2.5% (Goskomstat of Russia; www.gks.ru). As a consequence, life expectancy has decreased sharply and is significantly lower than in other European countries,[4] being 57 years in males and 70 years in females. Life expectancy in the northern regions of Russia was found to be even worse[5] in the range of 52–57 years for men and 64–70 years for women (Arkhangelsk, Comi, Karel).

[1] Institute of Community Medicine, University of Tromsö, Norway.
[2] University Teaching Hospital, Tromsö, Norway.
[3] Northern State Medical University, Arkhangelsk, Russia.
[4] Semashko Outpatient Clinic, Arkhangelsk, Russia.
* Corresponding author. Institute of Community Medicine, University of Tromsö, 9037 Tromsö, Norway. E-mail: Odd.Nilssen@ism.uit.no

Against this background a Norwegian–Russian cross-sectional population study was carried out in Arkhangelsk, Russia, in 1999–2000. The results showed that traditional risk factors for CVD were lower than expected.[6,7] Adjusted values for apolipoprotein-AI (APO-AI), high-density lipoprotein (HDL) and physical activity were significantly higher, whereas blood pressure, total cholesterol, low-density lipoprotein (LDL), APO-B, BMI and the Framingham Risk Scores[8] were significantly lower than in comparable studies from Europe. Thus other factors need to be considered.

While some health professionals have underlined the importance of poverty and socioeconomic distress as the main reason for the setback in population health and increase in CVD mortality,[9,10] others have called attention to the effect of the heavy alcohol consumption in Russia.[11–15] For example, data from the Russian Central Statistic Agency (Goskomstat) shows that even if deaths from natural causes account for a large proportion of the increase in death rates, deaths caused by alcohol, may be the largest proportion of the increase seen during the last decade (Goskomstat of Russia; www.gks.ru).

Such an inference must take into account that official figures for alcohol consumption in Russia are uncertain and figures for unregistered sources of alcohol are still more uncertain.[15,16] However, it appears that after the abolition of the State alcohol monopoly in 1992, the Russian populace has become one of the world leaders in alcohol consumption.[14,17–20] As alcohol consumption could be a decisive factor, both directly and indirectly, for the high mortality rate in Russia, this study was designed to more carefully evaluate this role.

Materials and methods

Arkhangelsk is located near the White Sea in the north-west of Russia. In this region there are ~1.5 million inhabitants of whom 370 000 live in Arkhangelsk itself. The majority of the population are employed in fishery or fishery-related work, but woodworking, military, and public service also employ significant sections of the population.

No population register for Arkhangelsk town was available to us. To overcome this problem we established our study centre at one of the outpatient clinics in the town. As this clinic (like all the other clinics in Arkhangelsk) was responsible for a certain number of specific factories and places of work and for a certain area of the town (according to occupational and territorial principles), they also had a kind of overview of the subjects they were responsible for. Their patients were of two categories; those who were ill and needed to see a doctor and those employed people who had to go through a 'compulsory annual medical examination' because of the particular industry or sector they worked in. In accordance with the clinic's leadership we decided to focus on the last group. This group had no fixed appointment at the clinic, but could attend the clinic between 8 a.m. and 12 noon on certain weekdays. Once they reported at the clinic, they were consecutively informed about the project and asked to participate. All of them were told that the study was anonymous and that the data would not affect their working status. As we aimed to get at an approximately equal number of participants of each sex and age group, some of the work places were contacted at the end of the study and informed that their staff/employees could report for the annual examination within the coming weeks or months, thus allowing us to reach an approximately equal number in each group. These 'invited' subjects were not informed about our project until they attended the clinic. All the subjects who refused to participate were registered, and the reason for this was recorded. At the end of the study period <1% of those asked had refused to participate, mainly due to lack of time. The regional ethical committee, Tromsö, Norway approved the study protocol.

Altogether 3697 subjects, 1963 men and 1734 women, aged 18–70 years were examined. Height, weight, waist and hip measurements were recorded and body mass index (BMI) and waist-hip ratio were calculated. Blood pressure and heart rate were measured with an automatic device (Dinamap-R, Criticon, Tampa, Florida) and measured three times at intervals of two minutes on the right upper arm in a sitting position. Blood lipid determinations and the calculation of the Framingham risk scores are described elsewhere (6). Each participant completed a questionnaire on demographical data, previous and present diseases, familiar disease, education, dietary habits, physical activity, smoking, drug and alcohol use, quality of life together with mental and sleeping problems. When used in the analyses, education was categorized as 1; primary (primary and incomplete secondary), 2; secondary (complete secondary), 3; professional secondary; 4; higher (incomplete and complete higher education or university).

Venous non-fasting blood samples were collected from all participants. The serum samples were kept at −20°C and transported to Tromsö once a month in special freezing boxes with freezing elements. All laboratory analyses were done by the Department of Clinical Chemistry, University Teaching Hospital, Tromsö, Norway.

Information on alcohol use was obtained through the use of the Alcohol Use Disorder Identification Test (AUDIT). The AUDIT[21] consists of 10 items on alcohol drinking and has a maximum score of 40. A score of ⩾8 indicates hazardous or harmful alcohol consumption, whereas ⩾13 scores are likely to reflect alcohol dependence. In addition, AUDIT consists of three sections; a score of ⩾5 (⩾4 in women) on the first three questions (section-1) indicates a hazardous drinking level, a score of ⩾4 on questions 4–6 (section-2) suggests psychological or physical dependence, and a score of ⩾4 on questions 7–10 (section-3) suggests significant alcohol problems. The participants were also asked about frequency of alcohol intake (beer, wine, strong wine and liquor, categorized as, 1; seldom or a few times per year, 2; once a month, 3; 2–4 times per month, 4; 2–3 times per week, 5; about daily) and average weekly intake of liquor, beer, and wine (in alcohol units, 1 AU ≈ 13.8 gram pure alcohol).

Gamma-glutamyltransferase (GGT) was measured in all participants and used as a biological marker for alcohol intake.[22] The measurements of GGT were done using a standard enzymatic colorimetric test (Roche, Mannheim, Germany) and performed at 37°C according to recommendations from the International Federation of Clinical Chemistry.[23] The rise of free 5-amino-2-nitrobenzoate, proportional with the GGT activity, was determined photometrically with a Hitachi 917. The coefficient of variation (CV) was <2.5% for a commercial control serum. Study data were analysed using the SAS software package.[24]

Results

Mean age was 41.8 and 44.2 years for men and women, respectively. Among men 71.3% were married or lived with a partner, 56.5% had professional education, and 21% had education from university or high school. Corresponding figures for women were 58.4%, 41.5%, and 32.5%. Altogether 12.1% of men and 29.9% of women reported to be teetotallers.

Table 1 gives mean GGT-values with standard deviations and medians for all participants, and mean GGT, AUDIT scores, and weekly intake (in AU) for non-abstainers according to age groups and sex. On average, males displayed 65% higher GGT values than females did. Mean GGT was 43.8 U/litre in males and 28.3 U/litre in females and increased with age (except for the highest age groups in males). Highest AUDIT scores were found in the age group 30–39 years in both sexes. Overall means were 7.5 and 3.9 for males and females, respectively. Corresponding figures for average weekly alcohol intake were 8.6 AU and 3.3 AU.

Highest mean GGT-level among males was found in the group of seamen (Table 2), but also employees (white collars), industrial

Table 1 Numbers, mean values with standard deviation (SD) and medians of GGT (U/L) for the total population, together with percentages non-abstainers, mean GGT, AUDIT (scores) and weekly alcohol intake (in AU) for non-abstainers

		GGT total				GGT[a]		AUDIT[a]		Intake[a]	
Age	Number	x	(SD)	median	Non-abstainers (%)	x	(SD)	x	(SD)	x	(SD)
Males											
18–19	233	21.7	(9.2)	19	89.3	22.1	(9.5)	6.7	(4.6)	6.9	(7.0)
20–29	289	32.2	(32.3)	24	92.4	32.7	(33.4)	7.8	(5.2)	10.1	(9.8)
30–39	355	43.9	(38.3)	31	94.4	44.4	(39.1)	8.3	(5.3)	10.5	(9.3)
40–49	446	51.5	(77.0)	34	89.5	52.3	(80.0)	7.6	(4.7)	9.7	(9.5)
50–59	308	57.5	(78.9)	38	90.6	58.2	(77.0)	8.0	(4.8)	8.0	(8.7)
60+	332	45.9	(68.7)	30	71.7	48.0	(75.2)	6.1	(4.4)	4.8	(6.0)
Total	1963	43.8	(60.5)	28	87.9	44.5	(61.8)	7.5	(4.9)	8.6	(8.9)
Females											
18–19	73	15.1	(5.6)	14	79.5	15.3	(6.2)	4.3	(4.2)	2.9	(2.6)
20–29	300	18.7	(13.3)	16	90.7	18.9	(13.9)	4.6	(3.8)	3.9	(4.7)
30–39	317	23.8	(22.4)	18	84.4	24.1	(21.7)	5.0	(4.1)	4.3	(4.1)
40–49	419	32.9	(58.4)	20	82.3	33.8	(62.6)	3.6	(3.3)	2.6	(2.3)
50–59	305	31.3	(32.3)	23	71.8	32.2	(36.4)	3.0	(2.2)	2.8	(5.7)
60+	320	35.9	(43.0)	24	31.6	32.3	(24.4)	2.2	(1.5)	2.1	(3.2)
Total	1734	28.3	(38.9)	19	70.1	27.3	(39.0)	3.9	(3.5)	3.3	(4.1)

[a] Only for non-abstainers.

Table 2 Means with standard deviation (SD) for age, GGT, alcohol intake per week (units) and AUDIT scores for non-abstainers (numbers and % non-abstainers) for different working groups and gender

	Males											
	Students $n = 252$ (89.7%)		Industrial workers $n = 134$ (92.4%)		Employees $n = 134$ (93.1%)		Seamen $n = 987$ (91.9%)		Pensioners $n = 205$ (67.7%)		Others $n = 22$ (91.7%)	
	x	SD	x	SD	x	SD	x	SD	x	SD	x	SD
Age (years)	18.9	(1.5)	42.8	(13.3)	45.4	(12.8)	40.1	(10.1)	65.0	(6.2)	41.7	(12.9)
GGT (U/litre)	22.8	(9.8)	42.8	(42.0)	45.5	(39.3)	49.6	(70.1)	46.4	(73.9)	47.7	(47.6)
Weekly intake (AU)	7.0	(7.6)	11.4	(12.9)	9.2	(9.0)	9.3	(8.7)	4.5	(5.1)	12.7	(13.7)
AUDIT scores	6.8	(4.8)	10.0	(6.1)	8.4	(5.4)	7.5	(4.5)	6.2	(4.5)	9.0	(6.7)
	Females											
	Students $n = 127$ (84.1%)		Industrial workers $n = 152$ (78.0%)		Employees $n = 645$ (83.2%)		Housewives $n = 89$ (85.5%)		Pensioners $n = 163$ (40.0%)		Others $n = 93$ (90.3%)	
	x	SD	x	SD	x	SD	x	SD	x	SD	x	SD
Age (years)	20.5	(3.0)	39.7	(10.6)	40.5	(10.0)	33.9	(8.2)	59.2	(8.0)	36.2	(8.2)
GGT (U/litre)	16.0	(10.4)	35.2	(87.5)	27.4	(29.1)	22.9	(17.4)	29.7	(22.5)	28.0	(26.9)
Weekly intake (AU)	2.7	(2.0)	3.7	(4.0)	3.1	(3.1)	3.3	(2.4)	2.7	(6.7)	5.2	(5.9)
AUDIT scores	3.9	(3.3)	5.2	(4.4)	3.8	(3.2)	4.2	(3.2)	2.5	(2.1)	5.4	(5.0)

workers, pensioners, and 'others' (private business and unemployed) showed mean GGT-values >40 U/litre. Industrial workers and 'others' scored highest on AUDIT and they also reported highest intake of alcohol. Among females, pensioners and industrial workers displayed highest GGT values, whereas 'others' reported highest alcohol intake and scored highest on AUDIT.

Almost two-thirds of the male industrial workers who reported any intake of alcohol (non-abstainers) scored ⩾8 on AUDIT (Table 3), and three-fourths scored ⩾5 on section-1 on AUDIT (indicating hazardous or harmful alcohol consumption). Between one half and two-thirds of the employees and 'others' reported hazardous or harmful levels of alcohol consumption. The same three groups also showed the highest percentage of subjects with GGT-levels above 50 U/litre and an alcohol intake >14 AU per week. In general, females displayed lower figures than males even though almost 50% of female industrial workers, housewives, and 'others' revealed scores on AUDIT section-1 corresponding to harmful drinking.

Table 3 Specific characteristics (in %) in non-abstainers (numbers and % non-abstainers) for different working groups and gender

	Males					
	Students $n = 252$ (89.7%)	Industrial workers $n = 134$ (92.4%)	Employees $n = 134$ (93.1%)	Seamen $n = 987$ (91.9%)	Pensioned $n = 205$ (67.7%)	Others $n = 22$ (91.7%)
AUDIT ≥8 (%)	36.9	61.9	50.0	44.8	31.2	50.0
Section 1 AUDIT ≥5 (%)	46.8	74.6	66.4	63.8	48.3	63.6
GGT ≥50 U/litre (%)	2.4	26.1	31.3	25.8	20.0	28.6
Intake ≥14 AU/week (%)	16.3	32.1	26.1	25.3	8.8	36.4
	Females					
	Students $n = 127$ (84.1%)	Industrial workers $n = 152$ (78.0%)	Employees $n = 645$ (83.2%)	Housewives $n = 89$ (85.5%)	Pensioned $n = 163$ (40.0%)	Others $n = 93$ (90.3%)
AUDIT ≥8 (%)	10.2	25.7	11.8	14.6	3.1	23.4
Section 1 AUDIT ≥4 (%)	33.1	44.1	36.1	47.2	17.2	46.3
GGT ≥45 U/litre (%)	0.8	13.2	12.1	9.0	15.3	13.1
Intake ≥7 AU/week (%)	7.9	17.1	9.5	9.0	5.5	25.3

Table 4 Subjects (in %) in different categories for AUDIT and GGT, and mean weekly intake of alcohol according to levels of education

	Levels of education							
	Primary		Secondary		Professional		Higher	
	M ($n = 114$)	F ($n = 149$)	M ($n = 330$)	F ($n = 302$)	M ($n = 1111$)	F ($n = 721$)	M ($n = 413$)	F ($n = 565$)
Full AUDIT (>8 scores)	40.3	21.1	40.5	16.9	45.7	13.9	42.2	9.5
AUDIT section-1 (≥5/≥4 scores)[a] (%)	58.6	40.4	55.1	35.3	62.3	39.1	61.0	31.6
AUDIT question 1 (category 4–5)[b] (%)	11.0	7.1	12.8	6.0	16.2	6.5	20.6	7.9
AUDIT question 1 (category 3–5)[b] (%)	58.4	47.4	71.9	54.7	76.0	53.0	74.6	56.2
AUDIT question 2 (category 4–5)[c] (%)	41.5	17.5	37.2	11.4	42.7	12.2	35.7	7.7
AUDIT question 2 (category 3–5)[c] (%)	57.3	29.8	49.3	20.4	56.5	23.3	50.8	15.8
AUDIT question 3 (category 4–5)[d] (%)	30.5	14.1	32.1	9.0	34.6	8.1	30.3	7.2
AUDIT question 3 (category 3–5)[d] (%)	46.3	22.8	48.5	18.4	54.8	19.7	49.5	13.1
GGT (>50/45 U/litre)[e] (%)	22.0	26.3	23.6	10.5	20.4	12.4	29.1	8.6
Mean weekly intake of alcohol (g)	98.0	56.6	120.1	45.6	121.5	46.9	114.5	40.0

[a] ≥5 scores in males, ≥4 scores in females.

[b] How often do you drink alcohol (5 = ≥4 times a week; 4 = 2–3 times a week; 3 = 2–4 times a month).

[c] How many alcohol units do you normally drink at one occasion (5 = ≥10; 4 = 7–9; 3 = 5–6).

[d] How often do you drink ≥6 units at one occasion (5 = almost daily; 4 = once a week; 3 = once a month).

[e] Cutoffs for males and females, respectively.

Table 4 gives the percentages for some drinking characteristics according to educational levels. Among males, AUDIT section-1 (≥5 scores) identified 50% more hazardous or harmful drinkers than did the full AUDIT (≥8 scores), among females even 100% more. Both sexes with education from high school or university reported highest intake frequency, but they drank less alcohol each time. Intake above 6 drinks per occasion among males was most frequent for those with professional education (mainly seamen). They also showed highest weekly intake. In males, 52.3% consumed ≥6 AU/occasion at least monthly, and 31.1% at least weekly. Almost 55% reported intake of ≥5–6 units per occasion, and 40.3% ≥7–9 units, whereas 74.2% reported intake of any alcohol ≥2–4 times a month, and 16.4% at least 2–3 times a week (data not shown). The highest mean GGT scores were among males with the most years of education. Females at all educational levels displayed substantially lower figures for all variables compared with males.

A cross-tabulation of weekly intake (AU) and mean GGT with the first three questions (Q1–Q3) in AUDIT (frequency and volume) is shown in Table 5. Both numbers of AU per week and GGT increased with higher categories for all three questions except for GGT in the highest categories on Q1 and Q3.

In age adjusted multiple regression analyses of logarithmically transformed GGT intake of liquor was significantly associated with GGT for both sexes. Among males, also intake of table wine, beer and numbers of alcohol units per drinking occasion

Table 5 Weekly intake of alcohol (AU) with numbers and mean GGT according to questions on frequency and volume (AUDIT 1–3) in non-abstainers

	Males			Females		
	n	AU	GGT	*n*	AU	GGT
How often do you have a drink containing alcohol?[1]						
Never	4	–	27.0	2	–	17.0
Monthly or less	446	3.6	41.4	582	1.8	27.0
2–4 times a month	1002	8.6	45.4	599	3.9	27.5
2–3 times a week	232	14.4	47.1	85	8.2	27.4
4 or more a week	51	25.5	41.6	3	8.7	23.0
How many drinks on a typical drinking day?[2]						
1–2 drinks	392	3.5	39.0	611	1.8	24.6
3–4 drinks	401	5.6	38.5	398	2.9	27.0
5–6 drinks	241	9.6	48.5	124	5.5	32.5
7–9 drinks	310	8.5	45.4	94	6.4	38.7
10 or more	387	16.4	53.1	42	13.2	27.5
How often do you have ⩾6 AU at one occasion?[3]						
Never	358	3.1	37.3	694	1.8	25.3
Less than monthly	468	4.9	42.9	355	3.5	24.2
Monthly	332	7.4	44.9	116	4.7	33.6
Weekly	538	14.5	50.3	97	9.2	44.4
Daily or almost daily	35	34.8	46.4	7	25.3	24.6

[1,2,3]: Q1, Q2 and Q3—section 1 of AUDIT.

displayed significant associations with GGT; among females increasing intake of strong wine and increasing frequency of intake >6 AU per drinking occasion increased the GGT-levels significantly (data not shown).

Table 6 displays age adjusted, sex-specific comparisons of risk factors for CVD and the Framingham risk score between groups with 'high' and 'low' GGT values in ANOVA analysis. The group 'high GGT-level' displayed significantly higher values for all variables in both sexes (except for cigarette smoking in females and HDL cholesterol in both sexes). As the Framingham risk score is only calculated for subjects >30 years, the sex-specific numbers for this variable are reduced. The Framingham risk scores are not adjusted for age, as mean age was almost equal for males and females.

Discussion

The study population

The study population differed slightly from the Arkhangelsk region population[6,7] as both levels of employment and education were higher in the current study. This may be seen as a rural–urban difference with better opportunities for work and education in the city. Age, marital status, rates of pensioners, female students, employed females, and females out of work were almost similar in the two populations. Thus, with these exceptions, the study population was found fairly representative for the Arkhangelsk region population.[25]

Alcohol consumption and drinking pattern

A potential weakness in the study is a possible underreporting of alcohol consumption. Study indicators of alcohol consumption (AUDIT, GGT) reveal a relatively high intake of alcohol among the participants. Corresponding figures from self-reported intake (Table 1) were not consistent with these findings. This may be owing to study context; workers might be worried that revealing a high alcohol intake at the annual medical check-up would put them at risk of losing their jobs. Even though they were assured that their questionnaire responses were confidential, the participants could have reported defensively on this type of request. It could be argued that asking for 'an average week's intake' could cause recall bias, as infrequent heavy users are more prone to underreport their intake when this method is used.[20] However, asking participants about one week's intake is one of the most commonly used methods, and gives better estimates for frequent drinkers.[20] Another possible explanation may be found in the drinking pattern: binge drinking (⩾80 g at least once a month) was found for 52.3% of males and for 17.3% of females. These figures are slightly higher than those found among males in Novosibirsk,[14] but much higher than the figures found in a study from Russia, Czech, and Poland.[19] The figures for females were considerable higher in our study. Average intake at each drinking occasion was between 65–80 g and 150 g for 54.2% of males (20.5% of females), and ~75% of males (55% of females) consumed any alcohol between 2–4 times a month and daily. At the same time ~55% of males reported an average intake of ⩾5–6 drinks each time they drank, but self-reported weekly intake was only 10 AU per week. Both quantity and frequency indicate a pattern of binge drinking. The magnitude of reported weekly intake does not reflect the high rate of binge drinking or the frequency and volume of intake on the AUDIT questions. It is also considerably less (annual 5.2 litres pure alcohol/capita) than official statistics (13.3 litres/capita) would indicate for total consumption in Russia.[16] When the group 'others' reported highest weekly intake of alcohol in both sexes (Table 2 and 3), the explanation may be found in the composition of the group; it contains the unemployed and the self-employed workers, none of which were subject to possible sanctions in case of evident misuse of alcohol. We therefore believe that the discrepancy between self-reported alcohol consumption and GGT/AUDIT is likely to be due to underreporting.

GGT

One of the most striking features in this study was the high GGT-level (Table 1). Both sexes revealed a mean level up to 100% higher than found in comparable studies. In a prospective study from England[26] mean level of GGT was 15.6 U/litre in a sample of 7613 middle-aged men, and in the Third Tromsö Study (1986–87, with 20 782 participants), mean GGT was 22.4 U/litre in men and 13.8 U/litre in women.[27] In Tromsö altogether 3.7% of the examined population had elevated GGT-values (⩾50 U/litre in men, ⩾45 U/litre in women) compared with 16.8% in this study (i.e. 4–5 times higher). Age may represent a confounding factor at least for GGT levels. The observed increase in GGT for the highest age groups in women thus proved to be mainly an effect of increased age and BMI (data not shown). Other possible reasons for the elevated

Table 6 ANOVA analyses of low and high GGT with age-adjusted mean serum lipids and blood pressure (BP) and the Framingham risk score in non-abstainers

		GGT < 50 IU/litre (<45 in women)		GGT ⩾ 50 IU/litre (⩾45 in women)		Age-adjusted	
	Sex	*n*	Mean	*n*	Mean	difference	*P*-value
Systolic BP	M	1346	130.9	381	134.7	3.8	<0.0001
	F	1122	124.9	144	128.8	3.9	0.0083
Diastolic BP	M	1346	73.8	381	79.0	5.8	<0.0001
	F	1122	71.7	144	74.9	3.2	0.0007
Cigarettes	M	1346	9.7	381	12.1	2.4	<0.0001
	F	1122	2.1	144	2.2	0.1	NS
Total cholesterol	M	1346	4.8	381	5.5	0.7	<0.0001
	F	1122	5.0	144	5.4	0.4	<0.0001
Triglycerides	M	1346	1.2	381	1.8	0.6	<0.0001
	F	1122	1.2	144	1.5	0.3	<0.0001
HDL cholesterol	M	1346	1.27	381	1.30	0.03	NS
	F	1122	1.41	144	1.40	−0.01	NS
LDL cholesterol	M	1346	3.0	381	3.4	0.4	<0.0001
	F	1122	3.0	144	3.3	0.3	0.0005
APO-AI	M	1345	1.46	381	1.54	0.8	<0.0001
	F	1120	1.59	144	1.65	0.06	0.0028
APO-B	M	1345	0.95	381	1.08	0.13	<0.0001
	F	1122	0.91	144	0.99	0.08	<0.0001
Framingham Score[a]	M	902	4.6	350	5.5	0.9	<0.0001
	F	802	1.3	134	4.7	3.4	<0.0001

[a] Unadjusted, only subjects >29 years.

NS, not significant.

GGT-levels in this study were evaluated, but complicating factors, such as use of drugs, dietary habits, and medical diseases (especially of the hepatobiliary type), gave no support to explanations of this kind.

GGT is well known as a marker of alcohol intake. Thus, the associations between GGT and alcohol intake in linear regression analyses was not unexpected. Less known is GGT as an indicator of oxidative stress and inflammation.[28] There is also evidence that high alcohol consumption directly and indirectly contributes to oxidative stress and inflammation, and that the pro-oxidative effect plays an important role for the increased cardiovascular risk in subjects with high alcohol intake.[29] GGT is also considered an independent predictor for hypertension, diabetes, and stroke.[26,30,31] With the extremely high—probably alcohol-mediated—GGT-level found in our population, it is tempting to suggest that alcohol may be a major contributor to the setback in public health in the region, especially regarding CVDs.

AUDIT

An analysis of non-abstainers in different working groups (Table 2) revealed low coherence between AUDIT scores and GGT-levels on one hand, and separately reported alcohol intake for men in all groups except for students. Hazardous or harmful drinking is diagnosed when a subject scores ⩾8 on the AUDIT, the same applies if a person drinks >40 g pure alcohol/day. Average AUDIT scores were close to 8 or above for all professional workers (i.e. industrial workers, employees, and seamen). Self-reported intake on the other hand, was only between 1 and 1.5 AU/day (corresponding to 14–21 g/day) and thus significantly below a hazardous drinking level.[32] The entire AUDIT identified significantly fewer hazardous drinkers than did the section-1 in AUDIT. In a publication from Seattle[33] the 3-items AUDIT (labelled 'AUDIT-C') was tested in a group of male problem drinkers (heavy drinking, active alcohol abuse, or dependence). They concluded that the 3-items (AUDIT section-1 or AUDIT-C) performed better in identifying problem drinkers than did the entire AUDIT. Using ⩾5 as cut-off, they found that AUDIT-C displayed higher sensitivity but slightly lower specificity than the entire AUDIT. Even though we are unable to give estimates for sensitivity and specificity, our data confirm the differences in performance between the two instruments. Between two-thirds and three-quarters of active male workers (industrial workers, employees, seamen, and others) were identified as hazardous or harmful drinkers according to the criteria in AUDIT section-1, whereas only ~50% of the subjects in these groups were labelled as hazardous drinkers when the entire AUDIT were used (Table 3). The same differences were observed in women, but the absolute figures were smaller.

No substantial differences were seen in AUDIT, GGT, and weekly intake when these variables were analysed separately for the different educational levels, although both males and females with higher education displayed somewhat higher figures for intake frequency. On the other hand, they drank less each time, and few reported binge drinking (⩾6 drinks at one occasion). Nevertheless, well-educated males had slightly

higher mean GGT-level (not in females), which may indicate that drinking frequency is of importance for elevated GGT.

Alcohol drinking and CVD

As reported in a previous paper, the classical risk factors for CVD (except for smoking) were more favourable in our Russian sample than in comparable studies from Western Europe and USA.[6] At the same time the rates for CVD deaths is higher than elsewhere, and is still increasing.[3] This apparent paradox is not easy to explain. One hypothesis is that predispositions for CVD may result from exposure to poverty and malnutrition in childhood and adolescence (the Forsdahl/Barker-hypothesis), leaving subjects with increased vulnerability for CVD.[34,35] Subjects with increased vulnerability and a total cholesterol level of e.g. 5 mmol/litre might therefore carry a higher risk for CVD than do the un-exposed with the same cholesterol level. The devastating situation in Russia in the interwar period, during the war, and in the post-war period, might therefore be more important for the increase in death rates seen in the last decades rather than the absolute level of the classical risk factors.

In a study from England Wannamethee *et al.*[26] found that GGT was strongly associated with CVD, all causes mortality and with the risk factors for CVD. Also studies from Russia have pointed to alcohol consumption (especially heavy and binge drinking) as a risk factor for increased CVD mortality.[14,15,36] Our study did not include variables to directly analyse the effect of alcohol on CVD mortality. We found high levels of problem drinkers and high levels of GGT, which were associated with risk factors for CVD (Table 5). On the other hand, the risk factors were in general low in our study population. A possible explanation is that alcohol may not be the cause of high CVD because of its effect on the risk factors alone, but may (in addition) have a direct effect on CVD. Further investigations are needed, and a follow-up based on information from a newly established disease- and death-registers for our study population is under way.

Conclusions

Mean GGT level was extremely high in this population, and AUDIT section-1 indicated that up to 75% of the subjects in some working groups met the criteria for hazardous or harmful alcohol drinking. Classical risk factors for CVD were significantly more favourable in subjects with low GGT than in those with high GGT.

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KEY MESSAGES

- Altogether, 1963 males and 1734 females were examined in a health survey in Arkhangelsk in northwest Russia.
- Mean levels of gamma-glutamyltransferase (GGT) were more than twice as high as those found in comparable western studies, and considerably higher than found in Russian studies.
- Hazardous or harmful drinkers were between 4 and 5 times higher than in studies from Norway.
- High GGT was significantly associated with risk factors for coronary heart disease.

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Commentary: Pattern of drinking and the Russian heart

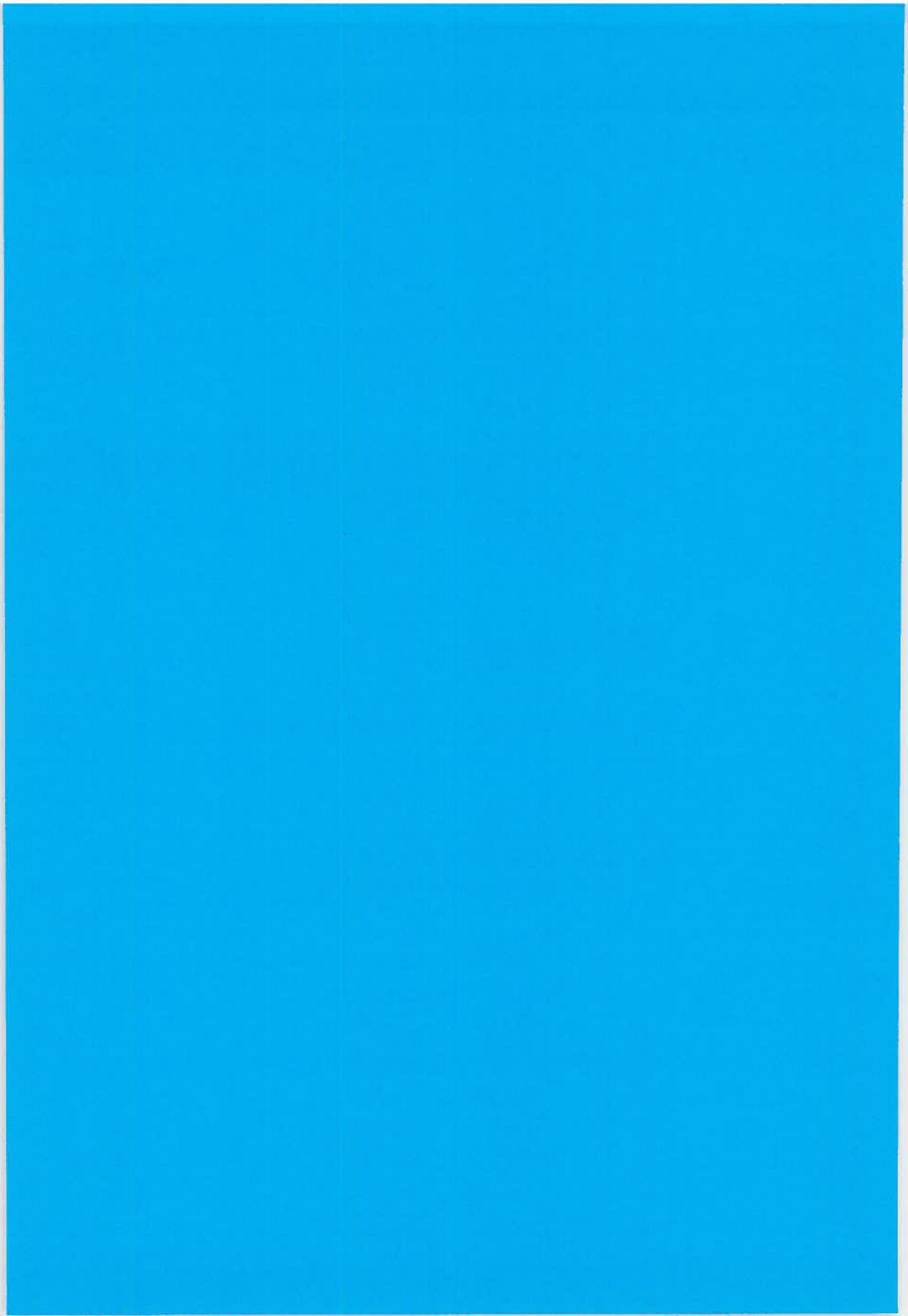
Robin Room

Our knowledge about alcohol consumption levels and drinking patterns in Russia is steadily increasing and the paper by Nilssen and colleagues in this issue of the IJE[1] makes a valuable addition to the developing store of literature. As discussed in the paper, a better understanding of the patterns and the trends of alcohol consumption is important for understanding the determinants of trends in cardiovascular disease (CVD); but the significance extends beyond this. Our best gauge of the effects of alcohol on the health of Russians in general is what happened in 1985–1988, during the period of a major anti-alcohol campaign in the former Soviet Union. During that period, the Soviet Union was still intact, and there was little of the massive and complex social and economic changes that make it so difficult to sort out causes of the rise in death rates since 1990. According to the best estimates,[2] consumption in 1987 was 25% lower than it had been in 1984, before the anti-alcohol campaign was instituted, even when estimated illicit (and thus unrecorded) alcohol supplies were included. There

Centre for Social Research on Alcohol and Drugs (SoRAD), Stockholm University, Sveaplan, 106 91 Stockholm, Sweden.
E-mail: robin.room@sorad.su.se

Appendix I

Questionnaire used in the Arkhangelsk study in 1999-2000. Original questionnaire in Russian, English translation.



Карта анонимного обследования

Здоровье человека 2000 года

Главной целью проводимого анонимного обследования является установление вероятности возникновения различных заболеваний.

Недостаток информации о факторах, влияющих на развитие многих серьезных заболеваний, в частности, сердечно-сосудистых, поставил нас перед необходимостью задать Вам несколько вопросов, касающихся Вашего здоровья и образа жизни.

Мы будем признательны, если Вы ответите на них в нашей анкете.

Обращаем Ваше внимание, что все сведения, полученные в результате данного обследования, абсолютно конфиденциальны, а медицинский персонал, принимающий участие в обработке и анализе этих сведений, предупрежден об ответственности за сохранение врачебной тайны.

Пожалуйста, если Вы не уверены ни в одном из предложенных вариантов ответа - отметьте тот, который, все же наиболее близок Вам.

Заранее благодарим Вас.

1.1. **ВАШ ПОЛ:** мужской женский

1.2. **ВАШ ВОЗРАСТ:** лет

1.3. **МЕСТО РОЖДЕНИЯ:** на Севере не на Севере

1.4. **СРОК ПРЕБЫВАНИЯ НА СЕВЕРЕ:** лет

1.5. **СЕМЕЙНОЕ ПОЛОЖЕНИЕ:**

- холост/незамужем
- женат/замужем
- разведен/разведена
- вдовец/вдова
- гражданский брак

2.1. **ОБРАЗОВАНИЕ:**

- неполное среднее
- среднее
- среднее специальное
- неполное высшее
- высшее

2.2. **СООТВЕТСТВУЕТ ЛИ СЕЙЧАС ВАША РАБОТА ПОЛУЧЕННОМУ ОБРАЗОВАНИЮ:**

да нет

2.3. **ПРОФЕССИЯ/РОД ЗАНЯТИЙ:**

- студент
- рабочий
- служащий
- плавсостав
- летный состав
- пенсионер
- домохозяйка
- другое

3.1. ПЕРЕНЕСЛИ КТО-ЛИБО ИЗ ВАШИХ РОДИТЕЛЕЙ, СЕСТЕР ИЛИ БРАТЬЕВ:

	да	нет	не знаю
инфаркт миокарда			
стенокардию			
кровоизлияние в мозг (инсульт)			
психические заболевания			
злоупотребляли алкоголем			
умерли в возрасте до 45 лет			

3.2. У ВАС ЕСТЬ ИЛИ БЫЛИ В ПРОШЛОМ:

	да	нет	не знаю
инфаркт миокарда			
стенокардия			
кровоизлияние в мозг (инсульт)			
сахарный диабет			
высокое артериальное давление (гипертоническая болезнь)			
панкреатит			
гепатит или цирроз печени			
невриты			
желудочное кровотечение			
диспепсия (нарушение пищеварения)			
язвенная болезнь желудка, 12-п кишки			
сотрясение мозга			
травмы конечностей, позвоночника			

4.1. ЕСТЬ ЛИ У ВАС ЖАЛОБЫ НА СОСТОЯНИЕ ЗДОРОВЬЯ:

да нет

4.2. ОТМЕЧАЕТЕ ЛИ ВЫ У СЕБЯ СЕЙЧАС ИЛИ В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА:

	да	нет
грипп		
диарею (частый жидкий стул)		
тошноту		
головные боли		
расстройства сна		
невозможность сосредоточить внимание		
ухудшение памяти		
боли в спине, пояснице		
мышечные боли		
понижение настроения, печаль		
раздражительность		
повышенную утомляемость		
тревогу		
беспокойство		
наличие стресса		

4.3. СОСТОЯНИЕ ВАШЕГО ЗДОРОВЬЯ СЕЙЧАС:

плохое
удовлетворительное
хорошее
отличное

4.4. ПРИНИМАЕТЕ ЛИ ВЫ СЛЕДУЮЩИЕ ЛЕКАРСТВА:

	иногда	часто	постоянно, регулярно
болеутоляющие			
жаропонижающие			
мазь от экземы			
лекарства от давления			
сердечные лекарства			
инсулин			
лекарства от аллергии			
лекарства от астмы			
снотворные			
успокоительные			
лекарства от эпилепсии			
лекарства от головной боли			
витамины			
лекарства от анемии			

5.1. ОЦЕНИТЕ СТЕПЕНЬ ВАШЕЙ ФИЗИЧЕСКОЙ АКТИВНОСТИ В СВОБОДНОЕ ВРЕМЯ:

ЕСЛИ АКТИВНОСТЬ РАЗНАЯ (НАПРИМЕР, ЛЕТОМ И ЗИМОЙ) ВОЗЬМИТЕ СРЕДНИЕ ДАННЫЕ ЗА ПОСЛЕДНИЙ ГОД

читаете, смотрите телевизор (в основном, сидячий образ жизни)
ходите, катаетесь на велосипеде или двигаетесь другим образом не менее 4-х часов в неделю (вкл. ходьбу на работу, прогулки в выходные и т.п.)
занимаетесь спортом для здоровья, работой на даче (не менее 4-х часов в неделю)
тренируетесь регулярно, по несколько раз в неделю, участвуете в соревнованиях

5.2. ОЦЕНИТЕ СТЕПЕНЬ ВАШЕЙ ФИЗИЧЕСКОЙ АКТИВНОСТИ НА РАБОТЕ:

В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА У ВАС БЫЛА:

в основном, сидячая работа (например, за письменным столом и т.п.)
работа, требующая много ходьбы (например, продавец, официант и т.п.)
работа, требующая много ходьбы и подъемов (например, почтальон, строитель и т.п.)
работа, требующая большой физической нагрузки (например, сельское хозяйство, лесная промышленность и т.п.)

5.3. **КАК ЧАСТО ВЫ ЗАНИМАЕТЕСЬ ФИЗИЧЕСКИМИ НАГРУЗКАМИ,** (НЕ МЕНЕЕ 20 МИНУТ) **КОТОРЫЕ ВЫЗЫВАЮТ ПОТООТДЕЛЕНИЕ И УЧАЩЕНИЕ ДЫХАНИЯ:**

	по осени	на даче
редко или никогда		
раз в неделю		
несколько раз в неделю		
почти ежедневно		

6.1. **КАК ЧАСТО ВЫ ЕДИТЕ:**

	редко или никогда	от 1 раза в неделю	2-3 раза в неделю	4-5 раза в неделю	почти ежедневно
свежие фрукты или овощи					
рыбу или рыбные блюда (обед, ужин)					
мясо или мясные блюда (обед, ужин)					
молоко или молочные продукты					

6.2. **СКОЛЬКО ХЛЕБА ВЫ СЪЕДАЕТЕ ЕЖЕДНЕВНО:**

- меньше двух кусков
- 2-4
- 5-6
- 7-12
- 13 или больше кусков

6.3. **КАК СЕЙЧАС ВЫ ОЦЕНИВАЕТЕ СВОЕ ПИТАНИЕ:**

- хорошее
- достаточное
- недостаточное

6.4. **СКОЛЬКО КОФЕ ВЫ ОБЫЧНО ПЬЕТЕ В ДЕНЬ:**

- не пью или меньше чашки в день
- 1-4
- 5-8
- 9 или более чашек в день

7.1. **КУРИЛ ЛИ КТО-НИБУДЬ ИЗ ВЗРОСЛЫХ ДОМА, КОГДА ВЫ БЫЛИ РЕБЕНКОМ:**

да нет

7.2. **ЖИВЕТЕ ЛИ ВЫ СЕЙЧАС ВМЕСТЕ С ЗАЯДЛЫМИ КУРИЛЬЩИКАМИ ИЛИ ЖИЛИ ЛИ ВЫ С ТАКИМИ ЛЮДЬМИ ПОСЛЕ 20 ЛЕТ:**

да нет

ЕСЛИ ДА, ТО СКОЛЬКО ЛЕТ ВЫ ЖИЛИ ВМЕСТЕ:

лет

7.3. **СКОЛЬКО ЧАСОВ В ДЕНЬ ВЫ ОБЫЧНО ПРОВОДИТЕ В НАПОЛНЕННОМ ТАБАЧНЫМ ДЫМОМ ПОМЕЩЕНИИ:**

ПОСТАВЬТЕ НОЛЬ, ЕСЛИ ВЫ НЕ БЫВАЕТЕ В ЗАДЫМЛЕННЫХ ПОМЕЩЕНИЯХ

часов

7.4. **КУРИТЕ ЛИ ВЫ:**

- да, каждый день
- иногда
- нет, никогда не курил (а)
- курил (а) до этого

7.5. **ЕСЛИ ДА, ТО ЧТО ВЫ КУРИТЕ:**

- самокрутки
- сигареты
- сигары
- папиросы
- трубку

7.6. **ЕСЛИ ВЫ ПРЕЖДЕ КУРИЛИ КАЖДЫЙ ДЕНЬ, ТО КАК ДАВНО ВЫ БРОСИЛИ:**

лет

7.7. **ОЩУЩАЕТЕ ЛИ ВЫ ДИСКОМФОРТ, КОГДА НАХОДИТЕСЬ В НАПОЛНЕННОМ ТАБАЧНЫМ ДЫМОМ ПОМЕЩЕНИИ:**

да нет

НА СЛЕДУЮЩИЕ ВОПРОСЫ МЫ ПРОСИМ ОТВЕТИТЬ ТЕХ, КТО КУРИТ ИЛИ КУРИЛ ПРЕЖДЕ. ОСТАЛЬНЫЕ МОГУТ ПЕРЕЙТИ К РАЗДЕЛУ 8.

7.8. **ЕСЛИ ВЫ КУРИТЕ ИЛИ КУРИЛИ ЕЖЕДНЕВНО:**

- сколько сигарет в день?
- сколько сигарет вы выкуриваете/выкуривали в рабочее время
- сколько вам было лет, когда вы начали курить каждый день?
- сколько лет в целом Вы курили каждый день?

7.9. **ЕСЛИ ВЫ БРОСИЛИ КУРИТЬ, ТО КАКАЯ ИЗ ПРИЧИН БЫЛА ДЛЯ ВАС НАИБОЛЕ ЗНАЧИМОЙ:**

- улучшение собственного здоровья
- улучшение здоровья детей/семьи
- улучшение здоровья коллег по работе
- в целях экономии
- чтобы показать, что я контролирую себя
- беременность
- здоровый внешний вид
- другие

7.10. **КАКАЯ ОСНОВНАЯ ПРИЧИНА, ЧТО ВЫ ПРОДОЛЖАЕТЕ КУРИТЬ:**

- я боюсь набрать лишний вес
- я чувствую больше энергии после курения
- я курю, когда хорошо провожу время
- я чувствую потребность в никотине
- я курю по привычке
- я курю, чтобы успокоиться

7.11. **СКОЛЬКО РАЗ ВЫ ПЫТАЛИСЬ БРОСИТЬ КУРИТЬ:**

раз

7.12. **НАСКОЛЬКО ВЫ ЗАИНТЕРЕСОВАНЫ В ТОМ, ЧТОБЫ БРОСИТЬ КУРИТЬ:**

- не заинтересован
- немного заинтересован
- очень заинтересован

8.1. **УПОТРЕБЛЯЕТЕ ЛИ ВЫ СПИРТНЫЕ НАПИТКИ:**

да нет

Мы приводим объяснение понятия АЛКОГОЛЬНАЯ ЕДИНИЦА. Одна алкогольная единица это:

Таким образом, это означает, что, например, 0.5 л крепкого пива или 1 л легкого пива = 1.5 алк. единицы; 1 бутылка столового вина = 5 алк. единиц, 1 бутылка крепленого вина = 8 алк. единиц; 1 бутылка водки = 15 алк. единиц

1 бутылка (0.33 л) крепкого пива или 2 бутылки (0.33 л) легкого пива

1 обыкновенный бокал столового вина (120 мл)

1 бокал крепленого вина (80 мл)

1 рюмка водки (40%, 40 мл)

8.2. **СКОЛЬКО АЛК. ЕДИНИЦ ВЫ ВЫПИВАЕТЕ ЗА НЕДЕЛЮ:**

- пива
- столового вина
- крепленого вина
- водки
- всего

8.3. **СКОЛЬКО ЛЕТ ВЫ УПОТРЕБЛЯЕТЕ АЛКОГОЛЬ В ТАКИХ КОЛИЧЕСТВАХ:**

лет

Попробуйте вычислить, сколько таких алкогольных единиц вы выпивали в течение последней недели (за семь последних дней до заполнения анкеты)

8.4. **ЗА ПОСЛЕДНЮЮ НЕДЕЛЮ Я ВЫПИЛ:** (АЛК. ЕД.)

- пива
- столового вина
- крепленого вина
- водки
- всего

8.5. **НЕ ВОЗНИКАЕТ ЛИ У ВАС МЫСЛЬ О НЕОБХОДИМОСТИ ОТКАЗАТЬСЯ ОТ УПОТРЕБЛЕНИЯ АЛКОГОЛЯ:**

да нет

8.6. **НЕ НАДОЕДАЕТ ЛИ ВАМ КРИТИКА ОКРУЖАЮЩИХ ПО ПОВОДУ ВАШИХ ВЫПИВОК:**

да нет

8.7. **НЕ ВОЗНИКАЕТ ЛИ У ВАС ПЕРЕЖИВАНИЙ ИЛИ ЧУВСТВА ВИНЫ В СВЯЗИ С ВАШИМИ ВЫПИВКАМ**

да нет

8.8. **НЕ БЫВАЕТ ЛИ ТАК, ЧТО ВЫ ПО УТРАМ В ПЕРВУЮ ОЧЕРЕДЬ ПРИНИМАЕТЕСЬ ЗА ВЫПИВКУ ДЛЯ УСПОКОЕНИЯ НЕРВОВ ИЛИ УСТРАНЕНИЯ ЯВЛЕНИЙ ПОХМЕЛЬЯ:**

да нет

8.9. **КАК ЧАСТО ВЫ УПОТРЕБЛЯЕТЕ НАПИТКИ,СОДЕРЖАЩИЕ АЛКОГОЛЬ:**

- никогда
- 1 раз в месяц или реже
- 2-4 раза в месяц
- 2-3 раза в неделю
- 4 или более раз в неделю

8.10. **СКОЛЬКО АЛК. ЕД. ВЫ ОБЫЧНО ВЫПИВАЕТЕ В ТЕЧЕНИЕ ОДНОГО РАЗА (ВЫПИВКИ):**

- 1-2
- 3-4
- 5-6
- 7-9
- 10 или более алк. единиц

8.11. **КАК ЧАСТО ВЫ УПОТРЕБЛЯЕТЕ 6 И БОЛЕЕ АЛК. Е В ТЕЧЕНИЕ ОДНОГО РАЗА (ВЫПИВКИ):**

- никогда
- реже 1 раза в месяц
- 1 раз в месяц
- 1 раз в неделю
- ежедневно или почти ежедневно

8.12. **КАК ЧАСТО В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА ВЫ ОЩУЩАЕТЕ, ЧТО НЕ МОЖЕТЕ ОСТАНОВИТЬСЯ НАЧАВ ПИТЬ:**

- никогда
- реже 1 раза в месяц
- 1 раз в месяц
- 1 раз в неделю
- ежедневно или почти ежедневно

8.13. КАК ЧАСТО В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА ВЫ ДОЛЖНЫ БЫЛИ ЧТО-ТО ВЫПОЛНИТЬ ИЛИ СДЕЛАТЬ, НО НЕ СМОГЛИ ИЗ-ЗА УПОТРЕБЛЕНИЯ АЛКОГОЛЯ:

никогда

реже 1 раза в месяц

1 раз в месяц

1 раз в неделю

ежедневно или почти ежедневно

8.14. КАК ЧАСТО В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА ВАМ НЕОБХОДИМО БЫЛО ОПОХМЕЛИТЬСЯ УТРОМ, ЧТОБЫ ПРИЙТИ В СЕБЯ ПОСЛЕ ОБИЛЬНОГО УПОТРЕБЛЕНИЯ АЛКОГОЛЯ НАКАНУНЕ:

никогда

реже 1 раза в месяц

1 раз в месяц

1 раз в неделю

ежедневно или почти ежедневно

8.15. КАК ЧАСТО В ТЕЧЕНИЕ ПОСЛЕДНЕГО ГОДА ВЫ НЕ МОГЛИ ВСПОМНИТЬ ТО, ЧТО БЫЛО ПРЕДЫДУЩИМ ВЕЧЕРОМ ПО ПРИЧИНЕ УПОТРЕБЛЕНИЯ АЛКОГОЛЯ:

никогда

реже 1 раза в месяц

1 раз в месяц

1 раз в неделю

ежедневно или почти ежедневно

8.16. ПОЛУЧАЛИ ЛИ ВЫ ИЛИ КТО-ЛИБО ДРУГОЙ ТРАВМУ В РЕЗУЛЬТАТЕ ВАШЕГО УПОТРЕБЛЕНИЯ АЛКОГОЛЯ:

нет

да, но не в этом году

да, в этом году

8.17. ВЫСКАЗЫВАЛ ЛИ КТО-ЛИБО ИЗ ВАШИХ РОДСТВЕННИКОВ, ДРУЗЕЙ ИЛИ МЕДРАБОТНИКОВ БЕСПОКОЙСТВО ПО ПОВОДУ ВАШЕГО ПЬЯНСТВА И ПРЕДЛАГАЛ ВАМ ОГРАНИЧИТЬ УПОТРЕБЛЕНИЕ АЛКОГОЛЯ:

нет

да, но не в этом году

да, в этом году

8.18. Как часто в течение последнего года Вы испытывали чувство вины или сожаления после употребления алкоголя?

Никогда
Реже 1 раза в месяц
1 раз в месяц
1 раз в неделю
Ежедневно или почти ежедневно

9.1. СПРАВА ШКАЛА С 10 СТУПЕНЯМИ. ПРЕДСТАВЬТЕ СЕБЕ, ЧТО ВЫСШАЯ СТЕПЕНЬ ПРЕДСТАВЛЯЕТ НАИЛУЧШУЮ ЖИЗНЬ, КОТОРУЮ ВЫ СЕБЕ МОЖЕТЕ ВООБРАЗИТЬ, А НИЗШАЯ СТУПЕНЬ - ХУДШУЮ ВООБРАЖАЕМУЮ ЖИЗНЬ. КАКАЯ СТУПЕНЬ, ПО-ВАШЕМУ, ЛУЧШЕ ПОДХОДИТ К ВАШЕЙ ТЕПЕРЕШНЕЙ ЖИЗНИ.

10 НАИЛУЧ
9
8
7
6
5
4
3
2
ваш выбор
1 НАИХУД

9.2. ИЗМЕНЯЕТСЯ ЛИ У ВАС В ЗАВИСИМОСТИ ОТ ВРЕМЕНИ ГОДА:

	НЕТ	НЕЗНАЧИТЕЛЬНО	УМЕРЕННО	ЗНАЧИТЕЛЬНО	ОЧЕНЬ
продолжительность сна					
общественная деятельность					
настроение					
вес					
аппетит					
работоспособность, желание деятельности					

9.3. ЕСЛИ ВЫ ОТВЕТИЛИ, ЧТО ЕСТЬ ИЗМЕНЕНИЯ, СВЯЗАННЫЕ С ВРЕМЕНАМИ ГОДА, КАЖЕТСЯ ЛИ ВАМ, ЧТО ЭТО ПРОБЛЕМА ДЛЯ ВАС:

да нет

9.4. ЕСЛИ ДА, ТО ЭТО ПРОБЛЕМА:

небольшая

умеренная

значительная

серьезная

нарушает жизнедеятельность

9.5. КОГДА ЭТИ ИЗМЕНЕНИЯ ОБЫЧНО ПРОИСХОДЯ

зимой

летом

весной

осенью

9.6. БЫВАЮТ ЛИ У ВАС ДЛИТЕЛЬНЫЕ ПЕРИОДЫ (2 НЕДЕЛИ И БОЛЕЕ), КОГДА ВАМ ГРУСТНО, ВЫ В ПОДАВЛЕННОМ ИЛИ УДРУЧЕННОМ СОСТОЯНИИ:

да нет

9.7. ЕСЛИ ДА, В КАКОЕ ВРЕМЯ ГОДА ВЫ БОЛЬШЕ СТРАДАЕТЕ:

зимой

летом

весной

осенью

9.8. **БЫВАЮТ ЛИ У ВАС ДЛИТЕЛЬНЫЕ ПЕРИОДЫ (2 НЕДЕЛИ И БОЛЕЕ), КОГДА ВОЗНИКАЮТ ПРОБЛЕМЫ СНА:**

да нет

9.9. **ЕСЛИ ДА, В КАКОЕ ВРЕМЯ ГОДА ВЫ БОЛЬШЕ СТРАДАЕТЕ:**

зимой

летом

весной

осенью

9.10. **В ЧЕМ ЗАКЛЮЧАЮТСЯ ВАШИ ПРОБЛЕМЫ СНА?**
МОЖНО ОТМЕТИТЬ НЕСКОЛЬКО ПОЗИЦИЙ.
РАБОТАЮЩИМ ПОСМЕННО НУЖНО ОТВЕЧАТЬ, ИСХОДЯ ИЗ РАБОТЫ В ДНЕВНУЮ СМЕНУ:

трудно заснуть вечером

слишком рано засыпаю вечером

плохо спится, несколько раз просыпаюсь

просыпаюсь слишком рано утром

просыпаюсь не отдохнувшим утром

сплю слишком долго по утрам

ДАННЫЙ РАЗДЕЛ ЗАПОЛНЯЕТСЯ МЕД. ПЕРСОНАЛОМ

10. Антропометрические данные

10.1. **ВЕС:** кг

10.2. **РОСТ:** см

10.3. **ОКРУЖНОСТЬ ТАЛИИ:** см

10.4. **ОКРУЖНОСТЬ БЕДЕР:** см

10.5. **СИСТОЛИЧЕСКОЕ ДАВЛЕНИЕ:**
1 2 3

10.6. **ДИАСТОЛИЧЕСКОЕ ДАВЛЕНИЕ:**
1 2 3

10.7. **ЧАСТОТА ПУЛЬСА:**
1 2 3

10.8. **ДАТА И ВРЕМЯ ОБСЛЕДОВАНИЯ:**

10.9. **КОД МЕДРАБОТНИКА:**

11. Лабораторные показатели

11.1. **ТРИГЛИЦЕРИДЫ**

11.2. **ХОЛЕСТЕРИН**

11.3. **ЛИПОПРОТЕИДЫ ВЫСОКОЙ ПЛОТНОСТИ**

11.4. **ЛИПОПРОТЕИДЫ НИЗКОЙ ПЛОТНОСТИ**

11.5. **АРО ЛИПОПРОТЕИДЫ**

11.6. **АЛЬБУМИНЫ**

11.7. **ГГТ**

11.8. **АЛТ**

11.9. **АСТ**

11.10. **АМИЛАЗА**

11.11. **ТИАМИН**

11.12. **КАК**

11.13. **ИНТЕРЛЕЙКИН 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 ○ female ○

1.2. **AGE:** ○○ years

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

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

1.5. **MARITAL STATUS:**

single	○
married	○
divorced	○
widowed	○
common law married	○

2. Occupational activity and social conditions

2.1. **EDUCATION:**

primary school	○
secondary school	○
secondary professional school	○
some college	○
graduated from college	○

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

2.3. **CURRENT POSITION:**

student	○
technical worker	○
clerk	○
ship crew	○
aircraft crew	○
pensioner	○
homemaker	○
other	○

3. Heredity and disease history

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

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

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

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

4. Health conditions

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

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

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

4.3. **YOUR CURRENT HEALTH:**

poor	O
fair	O
good	O
excellent	O

4.4. **DO YOU TAKE ANY OF THE FOLLOWING MEDICATIONS:**

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

5. Physical activity

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

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

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

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

During the last year you have had:

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

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

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

6. Diet

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

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

6.2. **HOW MUCH BREAD DO YOU EAT PER DAY:**

less than two slices	O
2-4	O
5-6	O
7-12	O
13 or more slices	O

6.3. **HOW WOULD YOU RATE YOUR CURRENT DIET:**

good	O
sufficient	O
insufficient	O

6.4. **HOW MUCH COFFEE DO YOU USUALLY DRINK PER DAY:**

do not drink coffee or less than one cup a day	O
1-4	O
5-8	O
9 or more cups a day	O

7. Smoking

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

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

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

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

7.4. **DO YOU SMOKE:**

yes, every day	O
sometimes	O
no, never smoked	O
smoked previously	O

7.5. **IF YES, WHAT DO YOU SMOKE:**

hand-rolled	O
filter cigarettes	O
cigars	O
papyrosy	O
pipe	O

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

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

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

7.8. **IF YOU CURRENTLY SMOKE OR PREVIOUSLY SMOKED EVERY DAY:**

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

7.9. **IF YOU HAVE STOPPED SMOKING, WHICH ONE WAS THE MOST IMPORTANT REASON FOR YOU:**

promote my own health	O
promote the children's/family's health	O
promote the health of colleagues at work	O
for economic purposes	O
in order to show that I am in control of myself	O
pregnancy	O
healthy look	O
other	O

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

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

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

OO times

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

not interested O
somewhat interested O
very interested O

8. Alcohol

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

yes O no O

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

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

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

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

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

OO years

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

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

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

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

yes O no O

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

yes O no O

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

yes O no O

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

yes O no O

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

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

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

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

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

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

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

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

8.13. **HOW OFTEN DURING THE LAST YEAR SHOULD YOU HAVE FULFILLED OR DONE SOMETHING, WHICH YOU WERE NOT ABLE TO DO BECAUSE OF ALCOHOLCONSUMPTION:**

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

8.14. **HOW OFTEN DURING THE LAST YEAR DID YOU HAVE TO DRINK ALCOHOL IN THE MORNING IN ORDER TO COME ROUND AFTER HEAVY ALCOHOL INTAKE THE DAY BEFORE:**

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

8.15. **HOW OFTEN DURING THE LAST YEAR WERE YOU UNABLE TO RECALL WHAT HAPPENED IN THE EVENING OF THE DAY BEFORE BECAUSE OF ALCOHOL CONSUMPTION:**

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

8.16. **HAVE YOU OR ANYBODY ELSE EVER HAD TRAUMA AS A RESULT OF YOUR ALCOHOL CONSUMPTION:**

no O
yes, but not in this year O
yes, in this year O

8.17. **HAVE ANY OF YOUR RELATIVES, FRIENDS OR PERSONS IN THE HEALTH SERVICE EVER EXPRESSED ANXIETY REGARDING YOUR HARD DRINKING AND SUGGESTED THAT YOU BETTER CUT DOWN THE ALCOHOL CONSUMPTION:**

no O
yes, but not in this year O
yes, in this year O

8.18. **HOW OFTEN DURING THE LAST YEAR HAVE YOU FELT GUILT BECAUSE OF YOUR DRINKING:**

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

9. Quality of life

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

O your choice

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

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

9.3. **IF YOU ANSWERED THAT THERE ARE CHANGES DEPENDING ON THE SEASONS, DO YOU THINK THIS IS A PROBLEM FOR YOU:**

yes O no O

9.4. **IF YES, THIS PROBLEM IS:**

small O
moderate O
considerable O
serious O
interferes with activities of daily life O

9.5. **WHEN DO THESE CHANGES USUALLY OCCUR:**

in winter O
in summer O
in spring O
in autumn O

9.6. **DO YOU EVER HAVE LONG PERIODS (2 WEEKS OR MORE), DURING WHICH YOU FEEL SAD, BLUE OR DEPRESSED:**

yes O no O

9.7. **IF YES, IN WHICH SEASON ARE YOU MOST BOTHERED:**

in winter O
in summer O
in spring O
in autumn O

9.8. **DO YOU EVER HAVE LONG PERIODS (2 WEEKS OR MORE), DURING WHICH YOU HAVE TROUBLE SLEEPING:**
yes ○ 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 ○

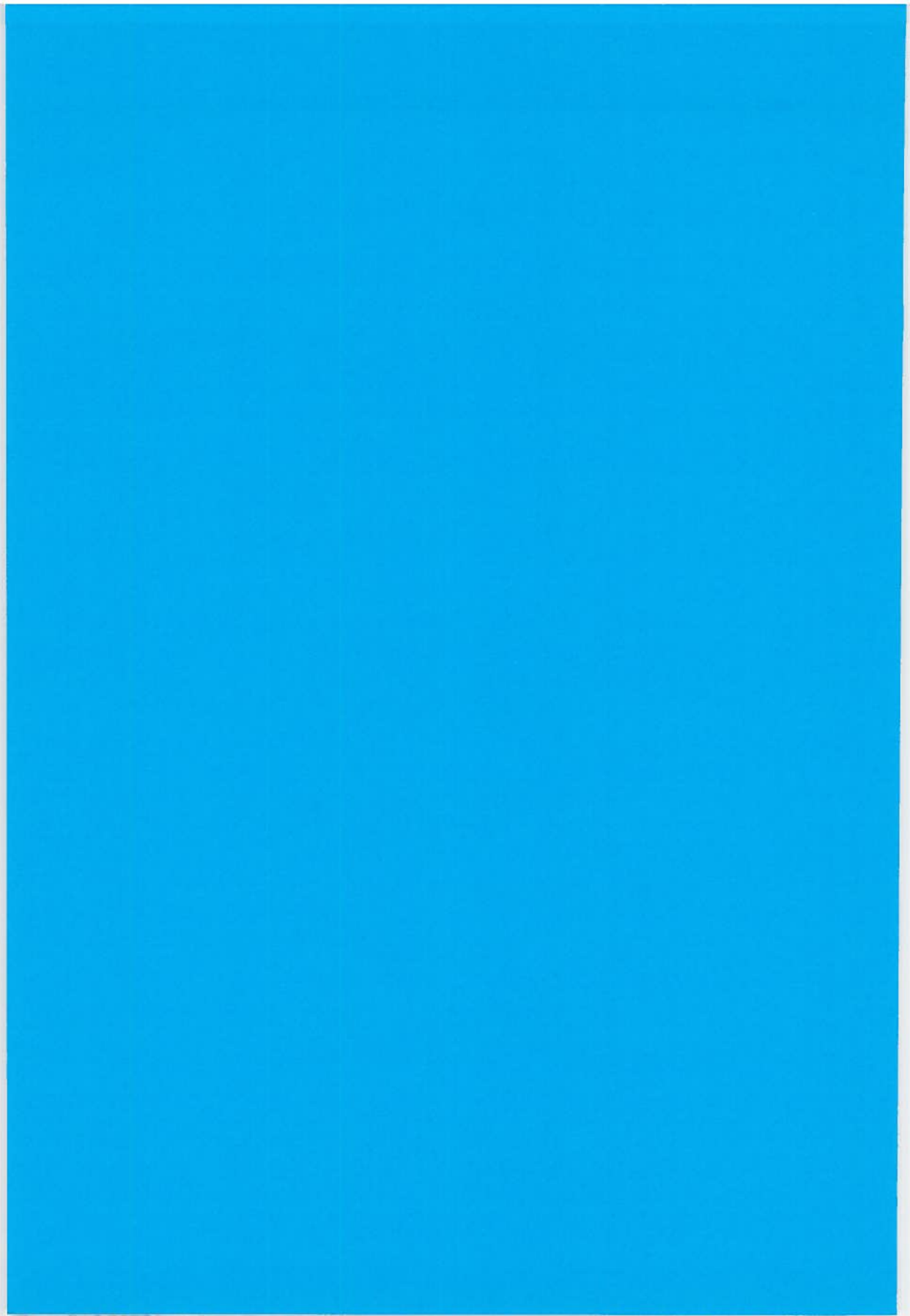
THIS PART WILL BE FILLED IN BY MED. PERSONELL

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

Questionnaire used in the follow-up study in 2003-2004. Original questionnaire in Russian, English translation.



Северный Государственный Медицинский Университет N

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 получили 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 письма 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 её нам в этом конверте.

Если Вам в 1999-2004 гг. не был поставлен диагноз заболеваний сердца, инсульта, сахарного диабета, рака, серьезной 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 или 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 повышенного давления	☐	☐	☐
Сердечные лекарства	☐	☐	☐
Инсулин	☐	☐	☐
Таблетки от сахарного диабета	☐	☐	☐

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

.....

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

Благодарим Вас за сотрудничество.

The Northern State Medical University
University of Tromsø, Norway

Number of participant

Dear, *name of the participant*

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

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

Now, 4 years after the study, we are sending letters 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 inn a questionnaire on the back of this page and to send the answer to us in the return envelope.

If you in 1999-2004 did not get diagnosis of heart diseases, stroke, diabetes mellitus, cancer or trauma that requires treatment, than you don't need to fill inn 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 you 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. Do 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 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

Additional tables.

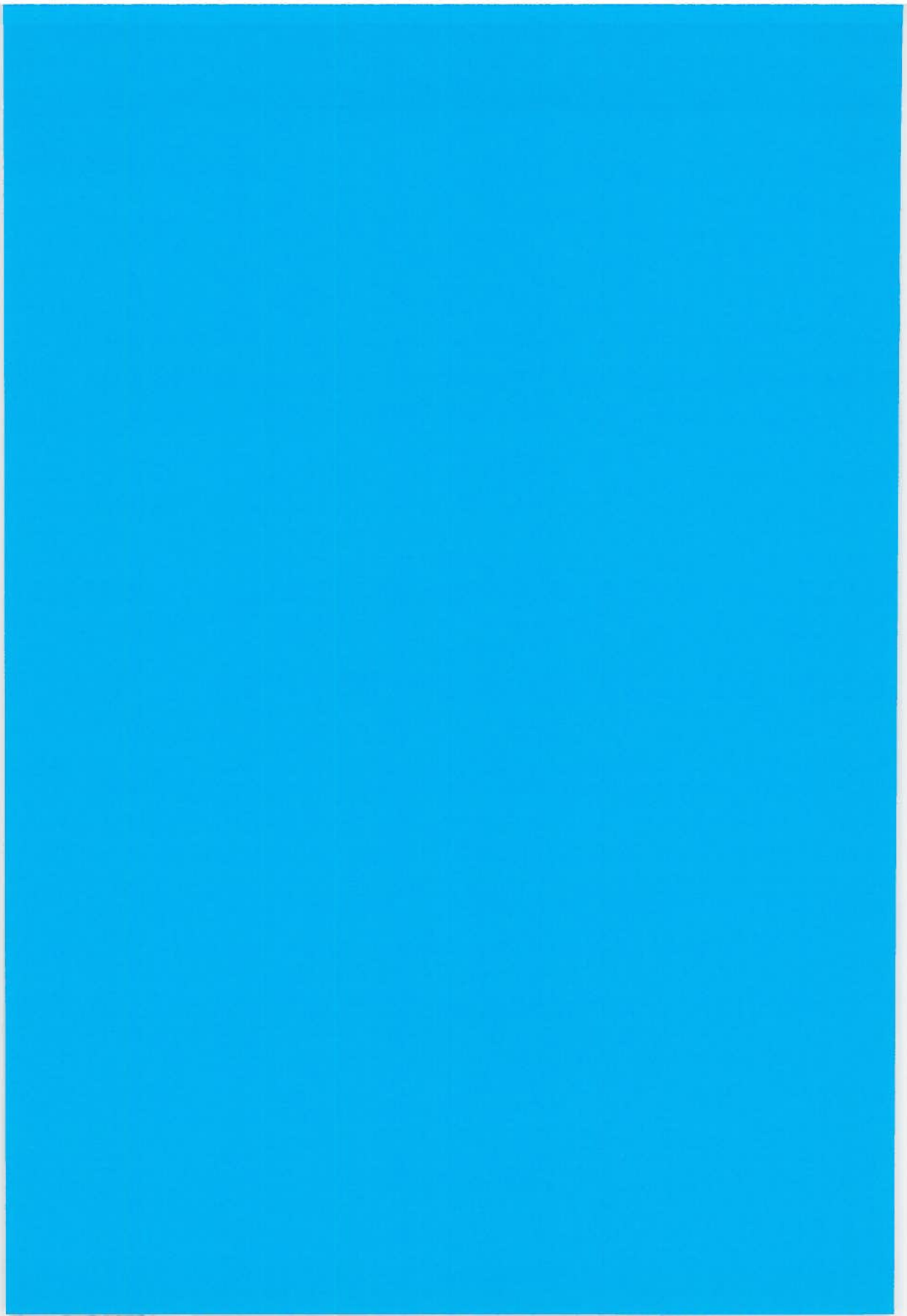


Table 12. Result of multiple linear regression analysis with serum albumin as dependent variable (men and women, n=3697).

Variables	β-coefficient	t-value	p-value
Sex (male vs. female)	1.72	16.8	<0.0001
Age, years	-0.08	-25.8	<0.0001
Secondary professional education [a]	-0.29	-2.6	0.0098
Secondary school [a]	-0.35	-2.7	0.0067
Depression (yes vs. no)	-0.24	-2.1	0.0369
Smoking (yes vs. no)	-0.23	-2.2	0.0266
Alcohol intake/last week, AU	-0.02	-2.7	0.0080

[a] vs. higher education (unfinished or completed university education).

Level of serum albumin was negatively associated with weekly alcohol consumption, depression and smoking. People with secondary professional and secondary school education had lower serum albumin levels than those with university education.

Table 13. Results of logistic regression analysis with low fruit/vegetable consumption (intake of fresh fruits and vegetables once a week or less) as dependent variable (men and women, n = 3705).

Variables	OR (Confidence interval)	p-value
Sex (male vs. female)	1.44 (1.22-1.69)	<0.0001
Age, 1 year	0.99 (0.98-0.99)	0.0078
Secondary professional education [a]	1.52 (1.28-1.82)	<0.0001
Secondary school [a]	2.22 (1.81-2.72)	<0.0001
Depression (yes vs. no)	1.45 (1.21-1.74)	<0.0001
Frequency of intake ≥ 6 AU [b]	1.08 (1.0-1.16)	0.0171
Low life quality [c]	1.77 (1.49-2.10)	<0.0001
Self-evaluation of nutrition as poor	3.09 (2.52-3.78)	<0.0001

[a] vs. higher education (unfinished or completed university education); [b] on one occasion, categorized as 1-never; 2-less than once a month; 3-once a month; 4-once a week; 5-daily or almost daily; [c] Cantril Ladder < 5.

Low fruit consumption was positively associated with frequency of drinking ≥ 6 AU on one occasion, depression, education lower than university, low life quality and self-evaluation of nutrition as poor.

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. D. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. D. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

7.* Blodtrykksovervåkning og blodtrykksmåling.
Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
Av Toralf Hasvold, 1984.

10. D. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
Av Georg Høyer, 1986.

11. D. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
Av Bjarne Koster Jacobsen, 1988.

12.* Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

13. D. Health education and self-care in dentistry - surveys and interventions.
Av Anne Johanne Søgaard, 1989.

14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. D. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. D. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. D. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. D. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. D. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
Av Vinjar Fønnebø, 1992.

22. D. Aspects of breast and cervical cancer screening.
Av Inger Torhild Gram, 1992.

23. D. Population studies on dyspepsia and peptic ulcer disease: Occurrence, aetiology, and diagnosis. From The Tromsø Heart Study and The Sørreisa Gastrointestinal Disorder Studie.
Av Roar Johnsen, 1992.

24. D. Diagnosis of pneumonia in adults in general practice.
Av Hasse Melbye, 1992.

25. D. Relationship between hemodynamics and blood lipids in population surveys, and effects of n-3 fatty acids.
Av Kaare Bønaa, 1992.

26. D. Risk factors for, and 13-year mortality from cardiovascular disease by socioeconomic status. A study of 44690 men and 17540 women, ages 40-49.
Av Hanne Thürmer, 1993.

27. Utdrag av medisinalberetninger fra Sulitjelma 1891-1990.
Av Anders Forsdahl, 1993.

28. Helse, livsstil og levekår i Finnmark. Resultater fra Hjerte-karundersøkelsen i 1987-88. Finnmark III.
Av Knut Westlund og Anne Johanne Søgaard, 1993.

29. D. Patterns and predictors of drug use.
A pharmacoepidemiologic study, linking the analgesic drug prescriptions to a population health survey in Tromsø, Norway.
Av Anne Elise Eggen, 1994.

30. D. ECG in health and disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972.
Av Per G. Lund-Larsen, 1994.

31. D. Arrhythmia, electrocardiographic signs, and physical activity in relation to coronary heart risk factors and disease. The Tromsø Study.
Av Maja-Lisa Løchen, 1995.

32. D. The Military service: mental distress and changes in health behaviours among Norwegian army conscript.
Av Edvin Schei, 1995.

33. D. The Harstad injury prevention study: Hospital-based injury recording and community-based intervention.
Av Børge Ytterstad, 1995.

34.* D. Vilkår for begrepsdannelse og praksis i psykiatri. En filosofisk undersøkelse.
Av Åge Wifstad, 1996. (utgitt Tano Aschehoug forlag 1997)

35. Dialog og refleksjon. Festskrift til professor Tom Andersen på hans 60-års dag, 1996.

36. D. Factors affecting doctors´ decision making.
Av Ivar Sønbø Kristiansen, 1996.

37. D. The Sørreisa gastrointestinal disorder study. Dyspepsia, peptic ulcer and endoscopic findings in a population.
Av Bjørn Bernersen, 1996.

38. D. Headache and neck or shoulder pain. An analysis of musculoskeletal problems in three comprehensive population studies in Northern Norway.
Av Toralf Hasvold, 1996.

39. Senfølger av kjernefysiske prøvespreninger på øygruppen Novaya Semlya i perioden 1955 til 1962. Rapport etter programmet "Liv". Arkangelsk 1994.
Av A.V. Tkatchev, L.K. Dobrodeeva, A.I. Isaev, T.S. Podjakova, 1996.

40. Helse og livskvalitet på 78 grader nord. Rapport fra en befolkningsstudie på Svalbard høsten 1988. **Av Helge Schirmer, Georg Høyer, Odd Nilssen, Tormod Brenn og Siri Steine, 1997.**

41.* D. Physical activity and risk of cancer. A population based cohort study including prostate, testicular, colorectal, lung and breast cancer.
Av Inger Thune, 1997.

42. The Norwegian - Russian Health Study 1994/95. A cross-sectional study of pollution and health in the border area.
Av Tone Smith-Sivertsen, Valeri Tchachtchine, Eiliv Lund, Tor Norseth, Vladimir Bykov, 1997.

43. D. Use of alternative medicine by Norwegian cancer patients
Av Terje Risberg, 1998.

44 D. Incidence of and risk factors for myocardial infarction, stroke, and diabetes mellitus in a general population. The Finnmark Study 1974-1989.
Av Inger Njølstad, 1998.

45. D. General practitioner hospitals: Use and usefulness. A study from Finnmark County in North Norway.
Av Ivar Aaraas, 1998.

45B Sykestuer i Finnmark. En studie av bruk og nytteverdi.
Av Ivar Aaraas, 1998.

46. D. No går det på helsa laus. Helse, sykdom og risiko for sykdom i to nord-norske kystsamfunn.
Av Jorid Andersen, 1998.

47. D. The Tromsø Study: Risk factors for non-vertebral fractures in a middle-aged population.
Av Ragnar Martin Joakimsen, 1999.

48. D. The potential for reducing inappropriate hospital admissions: A study of health benefits and costs in a department of internal medicine.
Av Bjørn Odvar Eriksen, 1999.

49. D. Echocardiographic screening in a general population. Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease. The Tromsø Study.
Av **Henrik Schirmer, 2000.**

50. D. Environmental and occupational exposure, life-style factors and pregnancy outcome in artic and subartic populations of Norway and Russia.
Av Jon Øyvind Odland, 2000.

50B Окружающая и профессиональная экспозиция, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России
Юн Ойвин Удлан 2000

51. D. A population based study on coronary heart disease in families. The Finnmark Study 1974-1989.
Av Tormod Brenn, 2000.

52 D. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study.
Av Oddmund Joakimsen, 2000.

53. D. Risk factors for carotid intima-media thickness in a general population. The Tromsø Study 1979-1994.
Av Eva Stensland-Bugge, 2000.

54. D. The South Asian cataract management study.
Av Torkel Snellingen, 2000.

55. D. Air pollution and health in the Norwegian-Russian border area.
Av Tone Smith-Sivertsen, 2000.

56. D. Interpretation of forearm bone mineral density. The Tromsø Study.
Av Gro K. Rosvold Berntsen, 2000.

57. D. Individual fatty acids and cardiovascular risk factors.
Av Sameline Grimsgaard, 2001.

58. Finnmarkundersøkelsene
Av Anders Forsdahl, Fylkesnes K, Hermansen R, Lund E, Lupton B, Selmer R, Straume E, 2001.

59. D. Dietary data in the Norwegian women and cancer study. Validation and analyses of health related aspects.
Av Anette Hjartåker, 2001.

60. D. The stenotic carotid artery plaque. Prevalence, risk factors and relations to clinical disease. The Tromsø Study.
Av Ellisiv B. Mathiesen, 2001.

61. D. Studies in perinatal care from a sparsely populated area.
Av Jan Holt, 2001.

62. D. Fragile bones in patients with stroke? Bone mineral density in acute stroke patients and changes during one year of follow up.
Av Lone Jørgensen, 2001.

63. D. Psychiatric morbidity and mortality in northern Norway in the era of deinstitutionalisation. A psyhiatric case register study.
Av Vidje Hansen, 2001.

64. D. Ill health in two contrasting countries.
Av Tom Andersen, 1978/2002.

65. D. Longitudinal analyses of cardiovascular risk factors.
Av Tom Wilsgaard, 2002.

66. Helseundersøkelsen i Arkangelsk 2000.
Av Odd Nilssen, Alexei Kalinin, Tormod Brenn, Maria Averina et al.,2003.

67. D. Bio-psycho-social aspects of severe multiple trauma.
Av Audny G. W. Anke, 2003.

68. D. Persistent organic pollutants in human plasma from inhabitants of the artic.
Av Torkjel Manning Sandanger, 2003.

69. D. Aspects of women's health in relation to use of hormonal contraceptives and pattern of child bearing.
Av Merethe Kunmle, 2003.

70. Pasienterfaringer i primærlegetjenesten før og etter fastlegereformen.
Av Olaug Lian, 2003.

71. D. Vitamin D security in northern Norway in relation to marine food traditions.
Av Magritt Brustad, 2004.

72. D. Intervensjonsstudien i Finnmark. Evaluering av lokalsamfunns basert hjerte- og kar forebygging i kystkommunene Båtsfjord og Nordkapp.
Av Beate Lupton, 2004.

73. D. Environmental factors, metabolic profile, hormones and breast and endiometrial cancer risk.
Av Anne-Sofie Furberg, 2004.

74. D. Det skapende mellomrommet i møtet mellom pasient og lege.
Av Eli Berg, 2004.

75. Kreftregisteret i Arkhangelsk oblast i nordvest Russland. Med en sammenligning av kreftforekomst i Arkhangelsk oblast og Norge 1993 - 2001.
Av Vaktskjold Arild, Lebedintseva Jelena, Korotov Dmitrij, Tkatsjov Anatolij, Podjakova Tatjana, Lund Eiliv, 2004

76. D. Characteristics and prognosis of long-term stroke survivors. The Tromsø Study.
Av Torgeir Engstad, 2004

77. D. Withdrawal and exclusion. A study of the spoken word as means of understanding schizophrenic patients.
Av Geir Fagerjord Lorem, 2005.

78. "Søkelys på safunnsmedisinene." Evaluering av kommunal samfunnsmedisinsk legetjeneste, offentlig legearbeid og de forebyggende oppgaver i Fastlegeordningen.
Av Betty Pettersen og Roar Johnsen, 2005.

79. **Prosjekt egenmelding Kristiansand kommune.** Evaluering av kontrollert intervensjonsforsøk i stor skala, med utvidet rett til egenmelding i kombinasjon med økt og formalisert samhandling mellom arbeidstaker og arbeidsplassen ved sykefravær.
Av Nils Fleten og Roar Johnsen, 2005.

80. D. Abdominal aortic aneurysms:Diagnosis and epidemiology. The Tromsø study.
Av Kulbir Singh, 2005.

De som er merket med D er doktorgradsarbeid.
De som er merket med * har vi dessverre ikke flere eksemplar av.