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Epidemiological Studies on Long Distance Cross-Country Skiers

Participants in the Vasaloppet 1955-2010

ULF HÅLLMARKER



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Abstract

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The overall aim of this thesis was to study the influence of physical activity on health. Risks and benefits of physical activity is of particular interest since there is a global trend of less physical activity among youths and adults.

In order to investigate this aim we used a database from a large cross country ski race, Vasaloppet, with participants with a wide age range, and with both elite athletes and ordinary people who exercise and promote their health. The most serious risk of strenuous exercise is sudden death and it is challenging to identify preventive effects of major endemic diseases.

Using epidemiological methodology we studied 200 000 Vasaloppet skiers and compared them with the general population. Based on personal identification numbers we added data from Swedish national personal and health registers, clinical registers as the cancer register, Swedeheart, or Swedish stroke register, and socioeconomic information from Statistics Sweden. In the Vasaloppet database we collected data on age, gender, finish time and number of races during the period 1989 to 2010.

We evaluated risk of death during the race in two papers (I,II). During 90 years of annual races, cardiac arrest occurred in 20 skiers, of which five survived. The death rate is in average two per 100 000 skiers.

We also studied the association with cancer incidence (paper III). The overall reduction of cancer was modest among skiers compared with the general population, but for cancers related to lifestyle the risks were markedly lower.

We investigated the risk for recurrent myocardial infarction and found a 30% reduction among skiers (paper IV). In paper V we showed that skiers with a first stroke have a lower incidence of all-cause death. The skiers had a higher frequency of atrial fibrillation but had less severe stroke and no increased risk of recurrent stroke. Thus our data suggest that a lifestyle with a high level of physical activity may work as a protection after a cardiovascular event.

Summary: The short excess mortality in endurance physical activity is by far outweighed by the long term protective effect of exercise in cardiovascular diseases and cancer.

Keywords: Epidemiology, Cohort study, Physical activity, Lifestyle, Prevention, Sports medicine, Cancer, Cardiovascular disease, Mortality, Cardiac arrest, Atrial fibrillation, Myocardial infarction, Stroke, Cross-Country skiing, Vasaloppet, Sweden

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Gustav Vasa 1520

En flykting. A fugitive.

Anders Zorn 1907

**“In the footsteps of our forefathers for
the victories of tomorrow.”**

In 1520, the first steps were taken towards creating a Swedish nation. An early part of that process was Gustav Eriksson Vasa’s 90 km long cross-country ski escape from the Danes. Two of the area’s best skiers, Lars and Engelbrekt, were sent after Gustav and history was changed. Gustav Vasa was king of Sweden from 1523 to 1560.

400 years later, in 1922, Gustav’s flight gave the Mora-born newspaperman Anders Pers the idea of starting a ski competition. Gustaf Ankarcrona formulated the slogan that inspired the people in Mora and which, year after year, has developed the Vasaloppet into the health-promoting activity it is for thousands today.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Farahmand B, Hållmarker U, Brobert GP, Ahlbom A Acute mortality during long-distance ski races (Vasaloppet). *Scand J Med Sci Sports*, 2007. 17(4): p. 356-61.
- II Hållmarker U, Michaësson K, Ärnlov J, James S Cardiac Arrest in a Long-Distance Ski Race (Vasaloppet) in Sweden. *Journal of the American College of Cardiology*, 2012. 60(15): p. 1431-1432.
- III Hållmarker U, James S, Michaësson K, Ärnlov J, Sandin F, Holmberg L Cancer incidence in participants in a long-distance ski race (Vasaloppet, Sweden) compared to the background population. *European Journal of Cancer*, 2015; 51: p.558-568.
- IV Hållmarker U, Michaësson K, Ärnlov J, Hellberg D, Lagerqvist B, Lindbäck J, James S Risk of recurrent ischemic events after myocardial infarction in long-distance ski race participants. *European Journal of Heart Prevention*. [doi: 10.1177/2047487315578664] Accepted for publication 2015-03-01.
- V Hållmarker U, Åsberg S, Michaësson K, Ärnlov J, Hellberg D, Lindbäck J, Wester P, James S Risk of recurrent stroke and death after first stroke in long-distance ski race participants. *Journal of American Heart Association*. [doi: 10.1161/JAHA.115.002469] Accepted for publication 2015-08-28.

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Published papers not included in the present thesis:

Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. Farahmand BY, Ahlbom A, Ekblom O, Ekblom B, Hållmarker U, Aronson D, Brobert GP. *J Intern Med.* 2003;253(3):276-83¹.

Heart arrest in our fathers' tracks. Three successfully treated cases during the Vasa Ski Race 2010. Hållmarker U, Aronson D, Jansson A, Hambræus K, Sjögren I. *Läkartidningen.* 2010 Nov 3-9;107(44):2720-2. Swedish. No abstract available².

Skiers in the long-distance ski race invest in their health. Carlsson S, Olsson L, Farahmand BY, Hållmarker U, Ahlbom A. *Läkartidningen.* 2007 Feb 28-Mar 6;104(9):670-1. Swedish. No abstract available³.

Amyotrophic lateral sclerosis among cross-country skiers in Sweden. Fang F, Hållmarker U, James S, Ingre C, Michaëlsson K, Ahlbom A, Feychting M. *Eur J Epidemiol.* 2015 Jul 29. [Epub ahead of print]⁴.

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Abbreviations

| | |
|--|---|
| AC | After Christ |
| BC, AD | Before Christ |
| CA | Cardiac arrest |
| CI | Confidence interval |
| CDR | Causes of Death Register |
| CHADS ₂ | Congestive heart failure, Hypertension, Age \geq 75 years, Diabetes, previous Stroke |
| CHA ₂ DS ₂ -VASc | Vascular disease, Age 65-74 years, Sex category |
| Bystander-CRP | Cardiopulmonary Resuscitation, without breathing |
| A-CPR | Advanced (Medical staff) Cardiopulmonary Resuscitation, with breathing and defibrillation |
| ECG | Electrocardiogram |
| HDL | High density lipoprotein |
| HIT | Hyper intensity interval training |
| HR | Hazard ratio |
| LBBB | Left bundle branch block |
| MI | Myocardial infarction |
| NPR | National Registration Register |
| NCR | National Cancer Register |
| PA | Physical activity |
| Re-MI | Recurrent myocardial infarction |
| Re-stroke | Recurrent stroke |
| SCB | Statistiska centralbyrån (Statistics Sweden) |
| SMR | Standardized mortality ratio |
| T@VO ₂ -max | Period of time above 90% of VO ₂ -max |
| VO ₂ -max | Maximal oxygen uptake |

Definitions

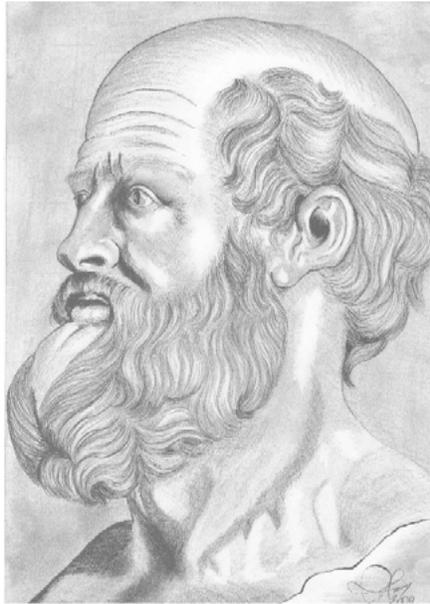
| | | |
|---|--|---|
| Atrial fibrillation (AF) | AF is a common supra-ventricular arrhythmia that is characterized by chaotic contraction of the atrium. An electrocardio-gram (ECG) recording is necessary to diagnose AF | Consensus statement 2012 ⁵ |
| Cancer | Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body's cells begin to divide without stopping and spread into surrounding tissues. | Natioanal Cancer Institute USA ⁶ |
| Cardiac arrest, see also sudden cardiac death | Numerous definitions of sudden cardiac death has been proposed over the past twenty-five years. However, such deaths can be caused by many mechanisms and no all-purpose definition can be applied to every situation. | WHO Scientific report 726, Geneva 1985 |
| Energy expenditure | Reported in kJ or Kcal over a specific time, often per week. An alternative is to report MET-h or MET-min per week. | Byrne 2005 ⁷ |
| Exercise (training) | A subcategory of leisure-time physical activity in which planned, structured, and repetitive bodily movements are performed to improve or maintain one or more components of physical fitness. | Howley 2001 ⁸ |

| | | |
|--|--|--|
| Health-related fitness components | <ul style="list-style-type: none"> a) Cardiorespiratory endurance b) Muscular endurance c) Muscular strength d) Body composition e) Flexibility | Caspersen 1985 ⁹ |
| High intensity interval training (HIT) | Optimal stimulus in intervals to spend at least several minutes where athletes reach at least 90% of their maximal oxygen uptake. | Buchheit ^{10, 11} |
| Performance-related fitness components | <ul style="list-style-type: none"> a) Muscular power b) Speed c) Agility d) Balance e) Reaction time | US Department of Health and Human Service 1996 ¹² |
| Physical activity | Any bodily movement produced by contraction skeletal muscles that substantially increases energy expenditure. | Howley 2001 ⁸ |
| Physical fitness | A set of attributes that people have or achieve that relates to the ability to perform physical activity. | Caspersen 1985 ⁹ |
| MET | <p>Metabolic equivalent.</p> <p>Used as an index of the intensity of activities.</p> <p>One MET is the estimated resting energy expenditure measured as oxygen uptake in average with 3.5 ml O₂ kg⁻¹ min⁻¹.</p> <p>This is equivalent to 1 kcal kg⁻¹ min⁻¹ or 4.2 kJ kg⁻¹ min⁻¹. E.g. 4 METs = four times the resting rate.</p> | Mc Ardle 2006 ¹³ Kenney 2012 ¹⁴ |
| Moderate intensity physical activity | For young adults, activity requiring approximately 3-6 times as much energy as rest. Equivalent to brisk walking (3-6 MET). | Sallis, Owen 1999 ¹⁵ |

| | | |
|--|--|--|
| Myocardial infarction | Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: Symptoms of ischaemia; New or presumably new significant ST-T changes or new LBBB; Development of pathological Q waves in the ECG; Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality; Identification of an intracoronary thrombus by angiography or autopsy. | Steget et al ¹⁶ European guidelines 2012 |
| Stroke | Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous-system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and sub-arachnoid hemorrhage (SAH), and is a major cause of disability and death worldwide. Despite its global impact, the term “stroke” is not consistently defined in clinical practice, in clinical research, or in assessments of the public health. | Sacco et al 2013 ¹⁷ Statement from American Heart Association and American Stroke Association. |
| Sudden cardiac death from cardiac arrest | Sudden cardiac death (SCD)/sudden cardiac arrest (SCA) refers to an unexpected death or arrest from a cardiovascular cause that occurs rapidly outside of the hospital or in the emergency room. | Hayashi 2015 ¹⁸ |
| Vigorous intensity physical activity | For young adults, activity requiring 7 times as much energy as rest, or greater. Equivalent to jogging (7 MET). | Sallis, Owen 1999 ¹⁵ |

Introduction

“All parts of the body which have a function,
if used in moderation
and exercised in labors to which each is accustomed,
become healthy and well developed, and age slowly,
but if unused and left to idle,
they become liable to disease,
defective in growth, and age quickly”¹⁹.



Hippocrates 460-370 BC

The body was built for movement

“All of the body’s tissues and our genetic material generally look like they did in our ancestors 10 000 years ago. The human body was built for movement. Body and mind benefit from physical activity. Regular physical activity significantly reduces the risk of premature death.” These four sentences are from the introduction to a textbook from the Swedish National Institute of Public Health from 2010 ²⁰.

Global problems with lack of physical activity

Our understanding of the benefits of physical activity is not new. But interest has been growing in the medical community as society has become more and more inactive. Modern transportation by car, more sedentary means of communication and less physical work leads to earlier problem with overweight, obesity, diabetes, cardiovascular diseases, joint problems, cancer and mental disturbances. These problems are global and statistically well-known even in young people ²¹.

Physical activity in prevention of disease

A common challenge everywhere is to create motivation and persistence so that people follow the medical community’s recommendations ²²⁻²⁴. Many studies show that physical activity in primary and secondary prevention improves therapy and can be added to pharmaceutical or other health protocols.

In recent decades, exercise training has been more common among some groups. In addition to the elite sport competitions, a movement of exercise training races has evolved. Many marathon races gather thousands of participants in big cities around the world. In places with snow, wintertime cross-country ski races have also been big and popular as well as biking, orienteering and endurance sports. These events motivate the participants to exercise training all year round. With this training follows a healthier lifestyle including non-smoking, better food and being less overweight.

New epidemiological methods have become available as, over the last twenty years, more and more clinical registers have come into use. Sweden is a pioneer in working with such registers, and the personal identity number provides good opportunities to do studies between, for example, the Vasaloppet cohort, national health registers and clinical registers. This thesis provides and shares new information about the risks and benefits of physical activity.

Background

Physical activity and physical fitness

Physical activity and physical fitness seems to act similarly in their relationship to morbidity and mortality. Physical fitness appears more strongly predictive of health outcome. Many studies shows at least a 50% reduction in mortality among highly fit people compared with less fit people. Laboratory observations such as ergometer cycle tests with oxygen consumption or doubly labeled water techniques can be used to estimate standards for measuring energy expenditure. More indirect and practical methods are heart rate monitors and motion sensors like pedometers or accelerometers. Assessment of physical fitness is often neither feasible nor practical in large population-based investigations. Self- reported physical activity has been used in many studies. It is a common critique that these include overestimation, sometimes underestimation.

Participants in the Vasaloppet

The participants in the Vasaloppet have already proven that they have a fitness level that enables them to cross-county ski 30, 45 or 90 kilometers. A study in 2003 showed that this group had a lower risk of dying compared with standardized mortality rate data. Thus the Vasaloppet participants can be used as a group representative for fit people. Through surveys it is also known that, physical activity is closely linked to a healthy life style in general. Therefore, participants also have a lifestyle that differs from the general population. They are seldom smokers, and they have a lower body weight and they consume more fruit and vegetables. They are also more highly educated. The risk factors for cardiovascular diseases are less represented. When we study physical activity we necessarily study this lifestyle.

Major disease groups

The major disease groups causing high mortality in the population are cardiovascular diseases²⁵ represented by coronary heart disease²⁶ and stroke²⁷. Together with cancer²⁸ they account for about 75 % of all deaths in the developed countries and these diseases are growing globally.

Medical registers

The use of register studies that cover many participants would be a technique for confirming the value of physical activity and physical fitness for health in primary and secondary prevention. In Sweden, one basis for register studies is the *National Registration Number* (NRN), unique to every citizen. This identity number had been used for participants in the Vasaloppet since 1989 (covering more than 200 000 men and women). This cohort provides the opportunity to study a cohort with a high level of fitness. With ethical approval, a number of Swedish health registers and clinical registers can be used for epidemiological studies where the NPR (National Patient Register) is the base. In this thesis national registers are used; all hospital admissions in the *NPR*²⁹, cancer incidence in the *National Cancer Register (NCR)*³⁰ and death and causes of death in the *Causes of Death Register (CDR)*³¹. These registers are held at the National Board of Health and Welfare. The cohorts were also linked to *Statistics Sweden* adding information about educational level, occupational and civil status. Of the many existing national clinical registries, the *Cardiac Arrest Register*³², *Swedeheart*³³ and *Swedish Stroke Register (Riksstroke)*³⁴ have been used in this thesis. *Statistics Sweden* data were included as a frequency matched group of the same age (five-year-intervals), gender and county of residence in Sweden for the same years as the Vasaloppet skiers. Physical activity can be undertaken in many different ways, in daily life or in sport situations.

Risks associated with physical activity

There are risks associated with the practice of physical activity and exercise training. It is therefore in this case also reasonable to highlight the risks associated with physical activity.

Lifestyle/Health

Health depends on lifestyle

“An individual's health depends a lot on lifestyle. Maintaining physical and mental health is crucial to an individual's longevity. The more time spent on hygiene, physical fitness and diet regulation, the healthier the lifestyle. Those who choose to participate in any kind of physical activity on a daily basis are generally healthier than those who do not.” This introduction from Wikipedia³⁵ adds some other aspects. Mental illness is also involved. Poor habits may eventually lead to a poor or even dangerous lifestyle. The discussion in this thesis has its base in the western industrialized countries, but the subject is global.

The search term “lifestyle” results in 112 205 hits in the scientific data base Pubmed. In combination with cancer, this represents 4% of 3.1 million hits, for diabetes it is 3% of 0.4 million hits and for cardiovascular disease it is 10% of 2 million hits. This shows that lifestyle is of great interest in the medical research community and much work is being done in the field that this thesis includes.

Lifestyle transmitted across generations

A healthy or unhealthy lifestyle will likely be transmitted across the generations. There is evident that it is 27% more likely that a child will become healthy and adopt the same lifestyle as its parents³⁶. Parents with high income are more likely to eat organic food, have time to exercise, and provide the best living conditions. Low income parents are more likely to participate in unhealthy activities such as smoking to help them release poverty-related stress and depression. Parents are the first teachers for every child. Everything that parents do will very likely be transferred to their children through the learning process³⁷. In sociological terms it is easier to transmit an unhealthy lifestyle. The degree of parental altruism, socialization and mortality patterns play a role in the resulting long-term impact on lifestyle. There is also an interaction with government policy³⁸.

Smoking, poor diet, physical inactivity

Three behaviors; smoking, poor diet and physical inactivity, are the most important causative factors of about one-third of deaths in developed countries.

These risk factors are often causing today's chronic disease killers: heart disease, cancer, stroke and diabetes. Three modern trends are increasing the incidence of these diseases: the epidemic of obesity, inactivity in children and the increasing age of the population ³⁹.

The HALE (Healthy Ageing: A Longitudinal Study in Europe) project in 2004 ⁴⁰ showed that those who used a Mediterranean diet and a healthy lifestyle (non-smoking, physically active and moderate alcohol intake) had more than a 50% lower rate of all-cause and cause-specific mortality.

One other study from 2008 combined the effects of behavioral factors and mortality, this time with a four-fold difference in total mortality, with an estimated impact equivalent to 14 years in chronological age. A score was built up of non-smoking, physical activity, moderate alcohol-, fruit and vegetable intake ⁴¹. In another study from 2013 olive oil and nuts were added to the Mediterranean diet that resulted in a prevention on cardiovascular diseases ⁴².

Nine behavioral and environmental risk factors

Background data from Comparative Risk assessment project and WHO shows ²⁸ that nine behavioral and environmental risk factors can decrease the risk of cancer by up to 35%. Along with smoking, obesity, low fruit/vegetable intake, alcohol use, physical inactivity, the following are also among the risk factors: unsafe sex, air pollution, indoor smoke and contaminated injections.

In a study about primary prevention in women there was decreased risk for myocardial infarction by consuming a healthy diet, moderate amounts of alcohol, regular physical activity, non-smoking and maintaining a healthy weight ⁴³. In a large group of men with cardiovascular risks the total risk for stroke and other stroke types decreased with the increasing number of healthy lifestyle factors ⁴⁴.

Ability to change lifestyle

It is well known that the ability to change lifestyle in secondary prevention presents difficulties in the long run. For patients with diabetes type 2, intervention resulting in modest weight lacked preventative effect on cardiovascular diseases ⁴⁵.

In a recent review of the effectiveness of secondary prevention lifestyle interventions following stroke, the changes in life style were positive. However, the authors found insufficient evidence on the incidence of stroke recurrence ⁴⁶.

In 1985, Persson et al published a study of lifestyle and biological risk markers over a 26-year period in all men in Habo ⁴⁷. They allocated risk points depending on lifestyle (smoking, physical activity and alcohol consumption) and biological markers (BMI, blood pressure and serum cholesterol). Men

with the lowest summarized risk points had a significantly lower risk for cardiovascular diseases and cancer. Those with the lowest risks in lifestyle had the lowest risk for cardiovascular diseases. Those with the lowest biological risk points had both fewer cardiovascular diseases and lower cancer risk. Smoking and serum cholesterol level had the greatest impact. The age and follow-up time in this Swedish study are close to our Vasaloppet studies.

Besides medical recommendations in different lifestyle areas, the challenge for the medical community is to amend lifestyles and change habits in the population to promote a healthier life. Families, schools, universities, politicians, food markets, sport clubs, working places, media and health care systems must all be involved in this work.

“The Vasaloppet life style”

Vasaloppet lifestyle was studied about average living conditions from a questionnaire performed in 2006 that covered more than 12 000 skiers³, published in 2007. The skiers were compared with a population survey⁴⁸.

Table 1. Survey of participants in the Vasaloppet in 2006 and comparison with the national population surveys of 2005 and 2006. All results are age standardized. *Figures in percent.*

| | Vasaloppet skiers | | Population survey | |
|----------------------------------|-------------------|------------------|-------------------|-------------------|
| | Men n=7 061 | Women n=5 180 | Men n=18 558 | Women n=21 444 |
| Poor or very poor health | 0.4 | 0.2 | 7 | 8 |
| Diabetes | 0.9 | 0.8 | 6 | 4 |
| Hypertension | 6 | 5 | 18 | 17 |
| Allergy | 20 | 17 | 24 | 27 |
| High level of physical activity* | 64 | 56 | 17 | 18 |
| BMI >25 | 31 | 16 | 52 | 39 |
| Smoking daily | 1 | 2 | 13 | 15 |
| Snuff daily | 11 | 2 | 21 | 4 |
| Fruit/vegetables > 5 times week | 12 | 33 | 6 | 14 |
| High school or university | 56 | 70 | 15 | 18 |
| Occupation, white collar | 60 | 67 | 34 | 33 |

*Vasaloppet participants >4 h per week. National survey > 1.5 h per week

Physical activity

“Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that requires energy expenditure”⁸. Physical inactivity has been identified as the fourth leading risk factor for global mortality causing an estimated 3.2 million deaths globally per year^{49,50}.

A breakthrough work is “Physical activity, all-cause mortality, and longevity of college alumni”. In a study of Paffenberger et al 1986⁵¹ was shown a decrease in mortality with higher weekly periods of PA during the period 1962 to 1978. PA was measured by means of a questionnaire. A direct measurement of the energy consumption with doubly labeled water in the Health Ageing and Body Composition Study⁵² have verified the results even if there were fewer participants in that study.

Today the health benefits of PA are well established^{49, 53, 54}. Physical activity on a regularly basis is inversely associated with different diseases and death, e. g. ischemic heart disease, cerebrovascular disease, breast cancer, colorectal cancer, and diabetes mellitus^{53,55-57}. Physical activity is also associated with psychological wellbeing, and it is an important factor for preventing obesity. Moreover, adequate levels of PA will decrease the risk of a hip or vertebral fracture and help control weight. Despite this, a large part of the population remains sedentary, making physical inactivity a health risk of epidemic proportions. In a global perspective, one in five is not active enough to preserve their health⁵⁰.

Genetic factors are known to account for a considerable part of the variance in physical activity within populations, but previous studies show variation in the degree of its heritability. In young adults estimates a heritability of 54%⁵⁸. A twin study in seven European countries reports heritability in 48-71%, with no differences between men and women and just modest geographical variation⁵⁹.

PA trends in adolescents in Europe and the USA have been studied and differences mapped between 2002 and 2010⁶⁰. Fourteen percent of girls and 23.1% of boys reported at least 60 minutes of moderate to vigorous physical activity daily. A decrease over time was reported among boys from nine of the 25 countries over these years. Girls from ten countries showed an increase but a decrease in PA from eight countries over time.

Recommendations of level of physical activity

The following are the WHO ²⁴ recommendations 2015 for adults:

- Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.
- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.
- Muscle-strengthening activities should be done involving major muscle groups on two or more days a week.

Lee recommends 5-10 minutes daily running ⁵⁷, which is lower than the current minimum in the global recommendations 2007 for adults ²² or adolescents ⁶⁰.

The aim is to preserve health effects, but higher- intensity activity is important to improve fitness.

General effects of physical activity

The effects of exercise take some weeks to be seen if a person has not previously trained. The effects are considerably greater if training / physical activity is continuous for months and years. Acute exertion impacts most of the body's organ systems and metabolism. Other effects are seen over the long term. Many mechanisms are known but not in full detail.

Cardiovascular system

PA decreases the risk of developing the *metabolic syndrome*, sometimes called the *insulin resistance syndrome*. A number of risk factors for cardiovascular diseases cluster together: dyslipidemia, diabetes, obesity and hypertension. They coexist more than would be expected by chance. These risk factors may have a common etiology. PA has a preventive effect on all of these risk factors. The prevalence of the metabolic syndrome is age dependent, 7 % among the 20-29 age group in the USA, and 44% in the 60-69 age group ⁶¹. The primary causative component is abdominal obesity. Often the metabolic syndrome is also accompanied with endothelial dysfunction in vessels and

prothrombotic factors. PA acts as prevention when it involves energy expenditure on many days during the week.

Many studies report that higher levels of PA are associated with a lower prevalence of the metabolic syndrome with a dose-response relationship^{62, 63}. Muscle strength as well as fitness may protect against the metabolic syndrome⁶⁴.

Skeletal muscles

Skeletal muscle is the largest insulin sensitive tissue in the body, and the energy expenditure during PA is located in the muscles. In low intense exertion, motor units with slow-twitch muscle fibers (type I) are recruited. In more intense exertion fibers in fast-twitch motor units (types IIa and IIx) are also recruited. Sources for energy are carbohydrates (stored as glycogen) and fatty acids (stored in fat tissue). A well-trained person uses more fat for energy extraction and saves carbohydrates. This makes it possible to maintain a higher intensity for a longer period. In hypothermia or hotter temperatures, more carbohydrates are used. When oxygen is limited, carbohydrates are used to a greater extent. Muscle fatigue is experienced with lack of glycogen and dehydration in a longer session of PA⁶⁵⁻⁶⁷.

Muscle size changes only a little in endurance training compared with strength training. Type IIa fibers increase after training, as do mitochondria and small vessels. Glucose transporters (GLUT-4) in the cell membrane increases when exercise starts. This increases sensitivity to insulin. Fatty acid binding proteins also increases in the capillaries and muscle cells to improve transport of fatty acids into the cells and also to increase the transport of lactic acid from the cells. In a few days, ATPase activity of the sodium-potassium pumps increases⁶⁶. Glycogen and triglycerides develop a larger storage capacity as an effect of training. Another mechanism is that hormones and growth factors e. g. vascular endothelial growth factor (VEGF) supports new formation of blood vessels. The changes only affect the muscles that have been used in training⁶⁸. The activation of some genes also supports to control of the adjustment to exercise training.

Biological mechanisms – physical activity and cancer

Cancer develops in an interplay between genetic predisposition, environment and lifestyle. An overview⁶⁹ of factors in the mechanisms follows:

Energy metabolism – Fat deposits and weight gain are risk factors for some cancer diseases. PA reduces fat and carcinogen deposits.

Blood flow – With increased flow, carcinogens are reduced.

Transit time in stomach-intestine - PA gives a shortened transit time, with the consequence of reduced time under carcinogenic influence.

Respiration- PA produces a higher respiration and more particles in the lung can be reduced.

Heat – PA give higher temperature and cell regeneration can increase.

Sex hormones – PA reduces the level and affects the cell growth of cells in breast, prostate and uterus.

Insulin – PA reduces the insulin level and the influence on cell growth diminishes.

Inflammation and immune reactions increase the cancer risk. The role of PA is unclear.

DNA and cell repair – PA affects the cells so that they grow normally.

Measuring Energy Expenditure

Calorimetry

Direct calorimetry (measuring heat) ¹⁴ is the basic unit calorie. With calorimetry the heat generated from the body, is the person's metabolic rate. The method is expensive and slow.

Oxygen consumption and carbon dioxide production

In indirect calorimetry, the oxidative metabolism of glucose and fat, substrate for aerobic exercise utilizes oxygen and produces carbon dioxide. Total body energy expenditure can be estimated from the rate of exchange of these two gases. The relationship between O₂ and CO₂, called the respiratory exchange ratio, gives information about the source of “fuel”. Fat, carbohydrates and amino acids produce different levels of energy (calories). Stationary or mobile equipment for measuring of gases is available ¹⁴.

To simplify the method, a standardized ergometer cycle or tread mill test are used and give approximate figures of VO₂-max when the performance of energy and pulse rate are measured. The increase in oxygen uptake with increasing power was originally proposed by Åstrand and Rodahl ⁷⁰.

Examples related to the subject of this thesis: The maximal oxygen uptake (fitness), VO₂-max, for skiers is 45-80 ml kg⁻¹ min⁻¹ compared with the general population's VO₂-max 35 ml kg⁻¹ min⁻¹ ⁷¹.

Doubly labeled water

Isotopic methods can measure energy metabolism but they are slow, and will take weeks. Doubly labeled water is the most significant technical method.

Metabolic equivalent (MET)

Under resting conditions an average person consumes about 0.3 L O₂ per minute. One metabolic equivalent (MET) is the unit when it is assumed that the body consumes 3.5 ml of oxygen per kilogram of body weight per minute at

rest, which is 1 kilocalorie per kg and minute. The intensity of physical activity is often translated into MET units, per day or per week. In tables different activities give information of presumed MET, e.g. brisk walking 3 MET, jogging 6 MET, hard running 12 MET. These figures are approximate and vary between different individuals and ages. Very often the MET system is simplified, and information from questionnaires is transformed to MET units. Frequently, the weekly amount over time is measured. The PA is sometimes categorized into working time PA, leisure time PA and total PA.

Pedometers, accelerometers

In recent years, a truer image of PA can be measured with pedometers, but it does not cover all kinds of PA, e.g. non-safe measures during bicycling. Accelerometers can be used over long periods, and will also give figures for sedentary time. These tools will help in future research to find optimal levels of PA, e.g. in prevention. Using this technique in a study with 948 participants, the Swedish School of Sport and Health has recently found that only 7.1% reach the national recommendation of PA for middle-aged Swedes ⁷².

Sciences in sports and physiology

Much of knowledge about PA has its roots from interests to study the human body and the limits in sport activities.

Last year's questions of optimizing the physical training has been important for athletes and physiologists. Laursen put 2010 the question: "Training for intense exercise: high-intensity or high-volume training?" ⁷³

Together with Buchheit he wrote two review articles 2013 about the current status of knowledge ^{10, 11}. High-intensity interval training (HIT) is today one of the most effective means of improving the cardiorespiratory and metabolic function and the physical performance of athletes. HIT involves an optimal stimulus to spend at least several minutes where athletes reach at least 90% of their maximal oxygen uptake. Measured as $T@VO_2\text{-max}$.

Prescription for HIT use up to nine variables; work interval intensity and duration, relief interval intensity and duration, exercise modality, number of repetitions, number of series, as well as the between-series recovery duration and intensity. Any manipulation of these variables affect the responses to HIT. Additional programming and periodization will be discussed. The programming process for each athlete can enable to reach $VO_2\text{-max}$. The most efficient way of accumulating a given $T@VO_2\text{-max}$ is still to be determined.

Much about PA in this theses is PA measured by MET units, fitness and sedentary time. The outcome has been measured to find incidence of different diseases related to PA. More and more studies has now been presented where different HIT technics has been used with patients in prevention. In two cases they could not draw any conclusions if HIT had any advantages ^{74, 75}. In a third case they reached the same result but with shorter training ⁷⁶.

Cross country skiing

The ethnic groups living north of the Arctic Polar Circle have used skiing for transportation for millennia. To date, the first evidence of skis is found in cave engravings that date back to 8000 BC in Dundebulake in Altay City, Xinjiang, China ⁷⁷. The rock drawings are of hunter skiers, some with one pole (Figure 1). The Altay declaration stated in 2005 that Altay is the birthplace of origin of skiing. There are different opinions on the early documentations ^{78,79}. In the Sapporo Winter Sports Museum, Japan, a map describes how skiing migrated from its beginnings in western China. The Encyclopedia Britannica describes ancient skis from Sweden and Finland dating back some 4 000 – 5 000 years. In northern Norway petroglyphs were engraved in rocks about 4 500 years ago (Figure 2). Russian archeological sources tell of the remains of skis from Vis made in 6 000 BC.

Old preserved Swedish skis have been found in different places; In Kalvträsk were two skis and one pole from 3 400 BC found 1924 in a wet area. The skis are placed in Västerbottens Museum. In Hoting, Ångermanland skis from 2 500 BC was found in trenching 1921, they were 111 cm long. Close to Färnäs in Mora skis were found 1932 in a wet-area on a deep of 125 cm. They are dated from 350 AC ⁸⁰.



Figure 1. Rock paintings in Dundebulake, Altay city. Skiers in China 8 000 BC.



Figure 2. A skiing petroglyph in Norway from 2000 BC.

In the arctic area, skis were a tool used in hunting, herding and foraging during the long, freezing winters. Written references⁷⁸ to skiing date from the 6th century when a Gothic monk, Jordanes, and a Byzantine historian, Procopius, mentioned gliding Finns. In 1168, Saxo Grammaticus described “slippery boards” used in fighting. In the mid-1500s, Olaus Magnus, a Swedish archbishop, wrote about the high speed that inhabitants in northern Norway used on planks with a bow-like front fixed on their feet. Women also skied “with great dexterity”. For a long time, skis were made from one piece of wood: pine, ash, spruce, birch or hickory. Some were of equal length and some had a long gliding ski together with a shorter one for kicking. For kicking, the ski’s underside was covered by some skin. In the 1880s, the demand for skis was great enough that ski manufacturing factories appeared. By the 1970s, wood laminates were replaced by synthetic materials. In the early days, there were no poles, then a single long pole was used. At the end of the 19th century, two poles were considered faster for competitions. The history of skis has also been published in the National Geographic⁷⁹.

The Scandinavian tradition of using skiing in sports became more international after Greenland was crossed on skis in 1888. After this, cross-country skiing developed as a sport and became an Olympic competition at Chamonix in 1924.

Human locomotion on snow

The Royal Society published a paper in 2005 about speed and energy costs in experiments with skis from different eras⁸¹. Skis were found and used in experiments from periods from year 542 to 2004. Skis were traditionally made by wood. Since 2004 they have in this test been made of synthetic materials like carbon fiber. The variation in mass for skis and poles ranged from 6.7 to 2 kg.

The results showed that skiing has been associated with a progressive decrease in the metabolic cost of transport. In a nomadic lifestyle the inhabitants tried to minimize energy waste.

Today, it is possible to travel at twice the speed of ancient times using the same power. The cost of transport is speed-independent for each ski model as for running. The historical famous ski races connected to Nordic kings were also calculated as *curiosa*, (Norwegian race Birkebeinerrennet in 1206 and the Swedish Vasaloppet in 1520). A prediction of the maximum skiing speed according to the distance is also provided for past epochs.

The experiment was performed in an air-conditioned ski tunnel in Finland. Participants skied in a standardized way and used copies of the different types of skis. Lower limb kinematics were recorded and bioenergetics measurements were done with a portable metabograph (heart rate, carbon dioxide output and oxygen uptake).

For each new ski there was a benefit of less fuel needed to cover the distance. Migration speed corresponds to 7 W/kg, hunting to 9 W/kg and skating to 10-11 W/kg. With the help of Figure 4, it is possible to predict maximum sustainable performance in terms of speed and distance. If Lars and Engelbrekt (see page 30) had had the same capacity as the winners of Vasaloppet today, their time in 1520 with equipment from that time would have been eight hours and ten minutes. That is close to the median time for the Vasaloppet skiers today.

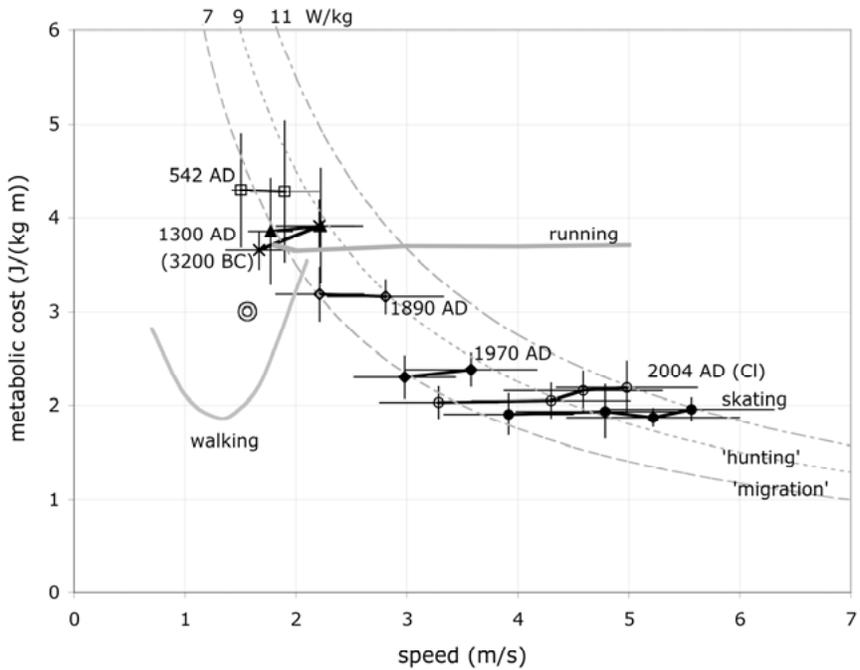


Figure 3 and text from reference ⁸¹

The metabolic cost of transport (means with standard deviations) is plotted against the speed for all the skis investigated (the one marked 3200 BC refers to the replica of ‘Salla’, a controversial ski-like specimen under which no fur was found in the archaeological site). The units have been changed from ml O₂ to J according to the breath-by-breath measured respiratory exchange ratio measured breath by breath. Walking and running costs on firm terrain (grey curves) are reported for the sake of comparison ⁸². The double circle symbol refers to walking on snow in the tunnel. The slowest point for each ski relates to the ‘migration’ speed. The three hyperbolae represent different iso-metabolic power curves (cost × speed=constant). While the metabolic cost is the analogous to fuel consumption (per unit distance travelled), the hyperbolae show the cost/speed combination at which the effort (approximately proportional to the heart rate) is the same. Bars show s.d.

*UH: W/kg can be converted to MET. 1 W=1 J/s. Converting factor from W to MET is 1.162. s.d. = standard deviation

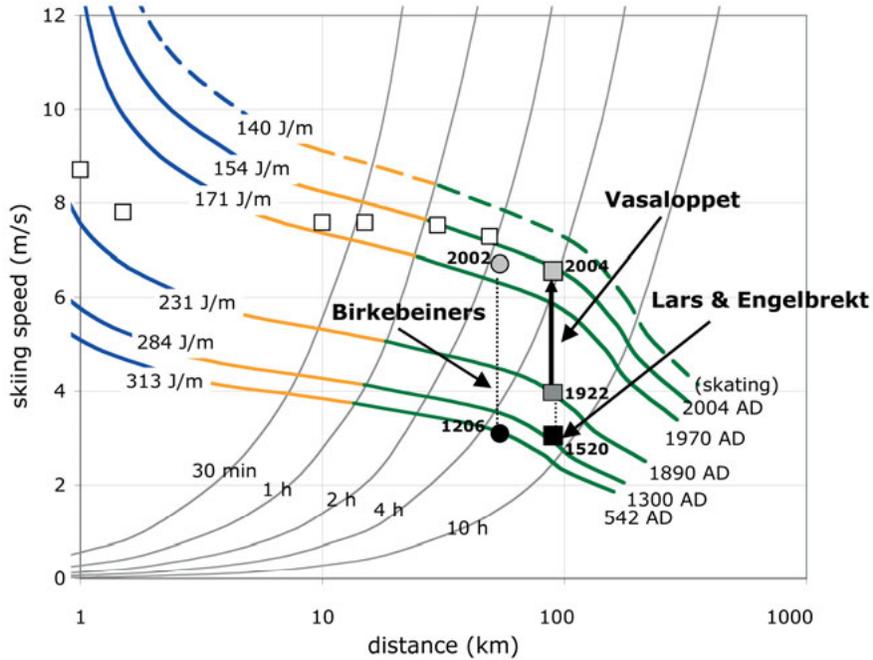


Figure 4. From reference ⁸¹.

The three-color curves represent the maximum speed/distance relationships for constant metabolic cost, each of which refers to a different ski. They were obtained by combining the relationships between the time to exhaustion and the available fraction of the metabolic power used, as suggested by Wilkie, Saltin and Davies for different exercise duration ranges (blue: 40s–10min; light orange: 10min–1h; green: 1–24h, respectively). In this computational frame, 20.3 W kg^{-1} has been assumed as the maximum metabolic power available. In the graph, the grey curves show iso-duration speed/distance pairs and the open square symbols represent recent records in cross-country skiing, from sprint events to endurance races.

Vasaloppet

History

The history of the Vasaloppet⁸³ dates from 1520. At that time, Sweden was in a union with Denmark. Discontent with the Danish king Christian was great, in part because Gustav Eriksson (later the first King of Sweden, Gustav Vasa) had been jailed in Denmark for resistance. The 24 year-old Gustav managed to escape. He urged the peasants to revolt. The hope was to flee to the county of Dalarna (Dalecarlia), where the people are known to be tough and rarely support the authorities' and king's decisions. Gustav was chased to Dalarna by Danish pursuers, but the people protected him from King Christian's soldiers.

After a month on the run through Dalarna, Gustav stood outside Mora church and spoke to the masses. Weeks before, his father and brother had been beheaded in the Stockholm Bloodbath along with 80 other magnates. Gustav wondered how long people could endure such cruelties and urged them to take up arms. But the congregation wanted to first consult with their neighboring villagers before it became a question of war. Pursuers approached Gustav before he got the answer he wanted. Therefore, he was forced to flee westward toward Norway.

A few days later the news of King Christian's brutal rampage in Sweden reached Mora. Then the people repented that no-one had directly endorsed Gustav. Mora's two best skiers, Lars and Engelbrekt, were therefore sent off to locate the fleeing Gustav. They caught up with Gustav in the region of Sälen. He was persuaded to return to Mora to lead the fight against the Danes.

In 1521 Gustav began his assault with Dalecarlians in the lead. It took two and a half years before the war was over and Sweden was a free country. On June 6, 1523, Gustav Vasa was elected king of Sweden during a parliamentary session in Strängnäs. Today he is a symbol of the world's biggest ski race – the Vasaloppet!

The Mora-born newspaper editor, Anders Pers, took the initiative in 1922 to start a cross-country ski competition from Sälen to Mora (90 km). The first race attracted 119 participants. Before starting, they had to undergo a medical examination. The second race one of the participants was a woman. Given the historical background and the rising interest in cross-country skiing, the race has continued to develop.

The Vasaloppet has three sister races, in Mora, Minnesota, USA, in Asahikawa, Japan, and in Changchun, China. The Vasaloppet is also a part of the Worldloppet, sixteen long-distance ski races in different countries around the world. The Vasaloppet is a member of the Swedish and International Ski Federations.

The classic 90 Km race takes place on the first Sunday in March every year. Other distances and races have been added to the classic race, arranged during the Vasaloppet Winter week. One week in summer, MTB (mountain bike) races are arranged together with a 90 Km running relay with ten athletes in each team. Established in 2014, Ultra Vasa is a competition for runners with a total distance of 90 Km.

All events in the Vasaloppet combine an elite competition with many leisure skiers who see the race as a goal for their physical training. The Vasaloppet plays an important role as a health promoting event. The winner is crowned with a laurel wreath by a “Kranskulla” or “Kransmas”, the Swedish names of the girl and the boy who has been honored for this task. They wear the traditional folk costumes.



Figure 5. Every skier has a national identification number (but not on the bib), which is the same in Swedish health care and clinical registries.

Development of the ski race Vasaloppet

The growing number of participants

Several hundred cross-country skiers participated in the first competitions. By 1950 there were more than one thousand and in 1976, more than 10 000. Since then, the race has grown to more than 50 000 in 2013. Figure 6 shows the number of participants.

The number races has also been various, races has been adding over time. There have been more than one million starts. This probably makes this Vasaloppet winter week the largest cross-county ski event in the world. Table 2 presents the numbers in each individual race during the Vasaloppet winter week. To allow for more skiers, the 90 Km race was duplicated under the name Öppet Spår (open track). A shorter race just for women, Tjejvasan, was added in 1988. Halvvasan (half vasa) and Kortvasan (short vasa) were new shorter alternative races from 1997 on. Free style (skating) needs more space and a separate day was added to the program from 2002 to 2012, in Swedish called “Skejtvasan”

Table 2. Number of starts and drop-outs in the various races over the years.

| Race | Km | Years | To start | Dropped out | To finish |
|-------------------|--------|--|------------------|----------------------|------------------|
| Vasaloppet | 90 | 1922-2015 (cancelled 1932, 1936, 1990) | 578 756 | 43 955 (7.6%) | 534 801 |
| Öppet Spår | 90 | 1979-2015 (cancelled 1989, 1990) | 312 631 | 21 856 (7.0%) | 290 749 |
| Tjejvasan | 30 | 1988-2015 | 159 077 | 1 814 (1.1%) | 157 256 |
| Halvvasan | 45 | 1997-2015 | 47 741 | 1 023 (2.1%) | 47 711 |
| Kortvasan | 30 | 1997-2015 | 90 470 | 2 131 (2.4%) | 75 234 |
| Skejtvasan | 30, 45 | 2002-2012 | 5 096 | 107 (2.1%) | 4 989 |
| Totals | | | 1 193 771 | 70 886 (5.9%) | 1 110 740 |

For the 90 Km Vasaloppet the lower age limit is 19 years; for the Kortvasan it is 12. The other races are open for everyone over 17 years of age.

Vasaloppet (90 K) 1922-2015, Öppet spår (90 K) 1979-2015,
 Tjejvasan (30 K) 1988-2015, Kortvasan (30 K) and Halvvasan (45 K) 1997-2015,
 Skejtvasan (30,45 K) 2002-2012

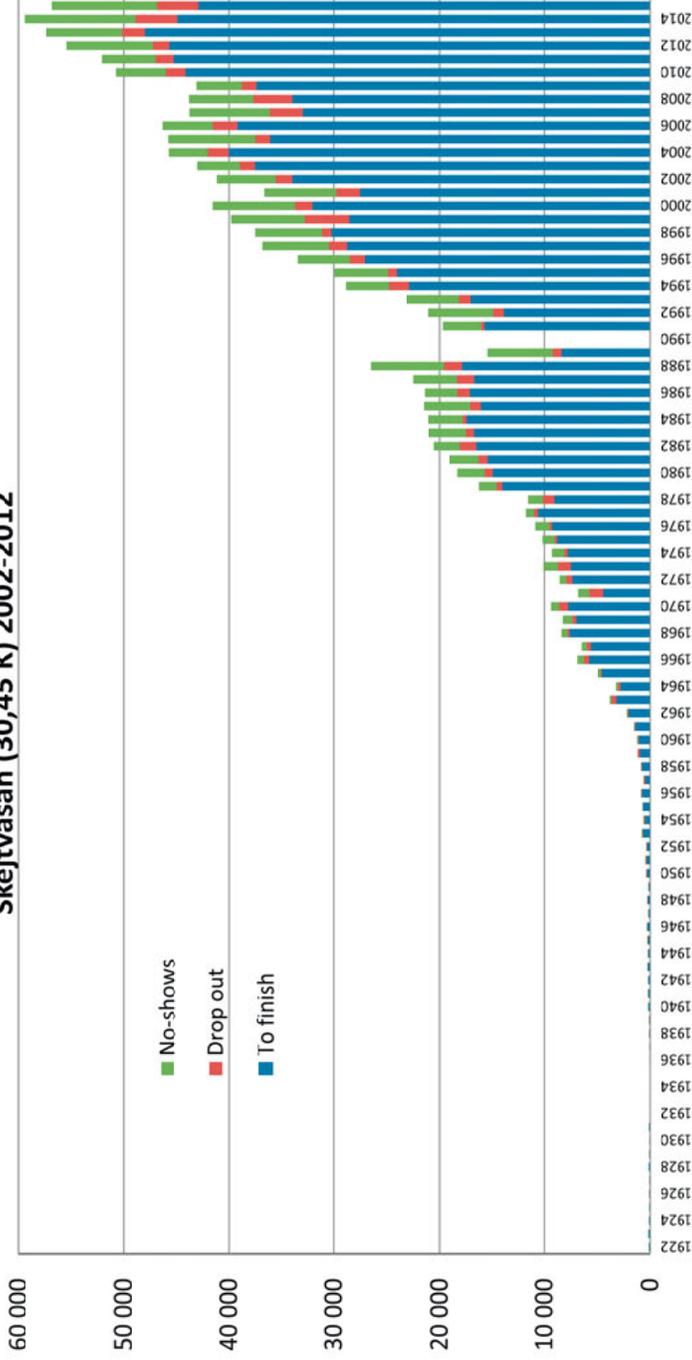


Figure 6. The number of starts in the different ski races in the Vasaloppet from its beginning in 1922 to 2015. Some of the registered participants were no-shows (green), others did not complete the distance (orange). In 1934, 1936, 1989 and 1990 some of the races were cancelled.

The changing of participants gender

One woman participated in the second race in 1923. Later on the competition was not open to women until 1981. It was considered too dangerous for them and the regulations in the Ski Federations did not allow female participants in such long courses. The number of female participants has increased, especially after the introduction of the women's race, Tjejvasan, in 1988. In Figure 7 the ongoing increase in female participants is shown with 10 year intervals.

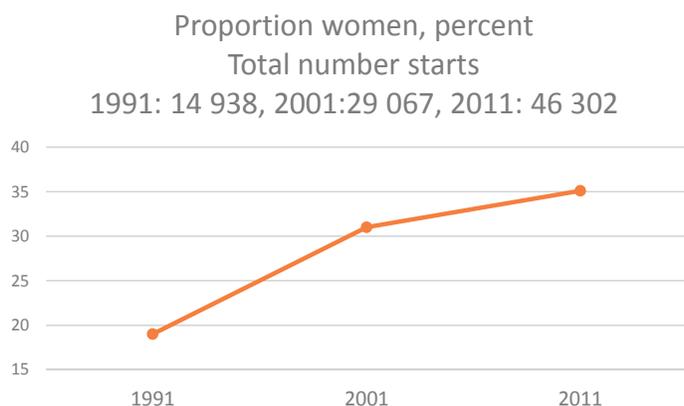


Figure 7 Proportion of women participants in the various races in the Vasaloppet winter ski week. Participants from 1991, 2001 and 2011. Y-axis is broken.

The changing of participants age

The mean age was investigated in a study using data from 1955-57 Vasaloppet. At that time only men participated and the distance was 90 Km. The mean age of the racers at that time was 32.8 years, median 32, Standard Deviation (SD) 6.5 and range 21-61. From 1989 on, the Swedish identification number was available for all participants, which made it possible to follow the mean age for every year. On average the participants in 2011 were about 40-42 years old (Figure 8) which shows that the skiers have become older compared with the race in 1955-57.

Table 3 Gender and age in the races 2013

| Gender | Number | Mean age | Median age | SD | Range |
|--------|--------|----------|------------|------|-------|
| Male | 39 515 | 43.6 | 43 | 13.4 | 14-87 |
| Female | 18 250 | 40.4 | 41 | 12.7 | 14-85 |

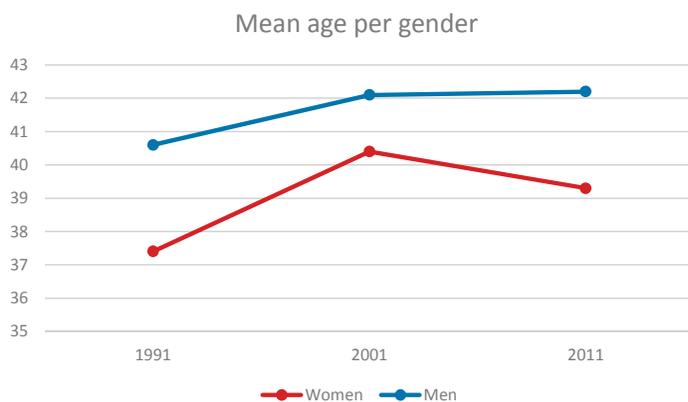


Figure 8. Mean age for participants in all races (30-90 Km) during Vasaloppet Winter Week in 1991, 2001 and 2011.

The growing number of foreigners

The Vasaloppet has become more and more well-known abroad and the number of participants from foreign counties has increased. See Figure 9.

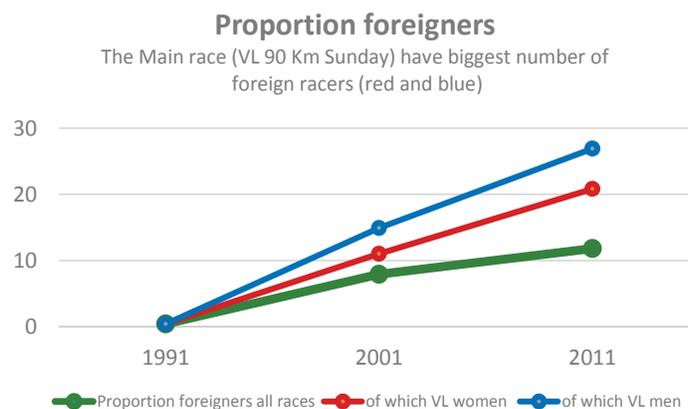


Figure 9. Percentage of foreign skiers in Vasaloppet Winter Week. Increasing trends from 1991 to 2011.

Social differences the last 50 years

Some variables are known from 6 301 surveys. These give the impression of differences between 1955-57 and 2010 among the participants. 1955-57 were all male. About one third of the participants in 2010 were female. Their ages are mentioned above. Approximate comparisons can be done. Answers are available from 90% of participants 1955-57 (n=1 171) and 10% from 2010 (n=5 130).

Table 4. Comparisons of attitudes and social differences between participants in the Vasaloppet races between 1955-57 and 2010. Figures in percent (%).

| | 1955-57 | 2010 |
|--|---------|------|
| Sport merits (national and international level) | 40 | 20 |
| Physical activity > 10 h/week from 20 years old and up | 25 | 10 |
| Years with more than 50 km cross country skiing | 40 | 15 |
| Good knowledge about physical activity and health | 80 | 90 |
| Motive for participation; competition | 30 | 10 |
| “ inspiration for exercise training | 20 | 40 |
| Single | 12 | 7 |
| Living in the countryside | 50 | 30 |
| Family situation; no children | 15 | 20 |
| Sedentary work | 15 | 60 |
| Blue collar work | 60 | 10 |

Acute medical risks in the Vasaloppet ski competitions

Emergency unit at Mora Hospital

From 1979 to 2013 the number of skiers that were admitted to the emergency unit at Mora Hospital, the only hospital serving the area close to the Vasaloppet arena, was 912 out of a total number of 979 795 skiers.

Skiers to emergency unit, orthopedics and surgery over 34 years, 1979-2013, n=590

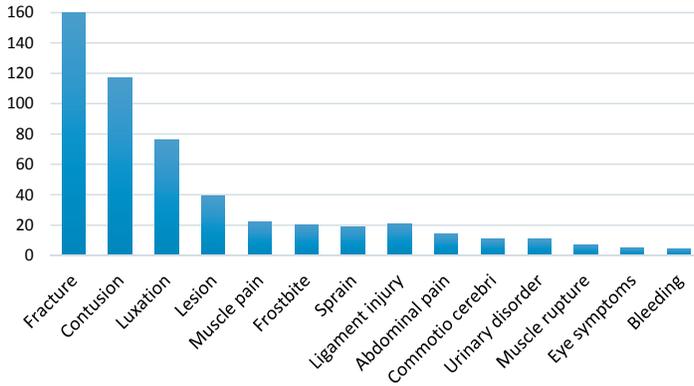


Figure 10. Diagnoses for 590 skiers that visited orthopedics and surgery in emergency unit, Mora hospital, 89% were able to leave the hospital the same day.

Skiers to emergency unit, internal medicine over 34 years, 1979-2013, n=322

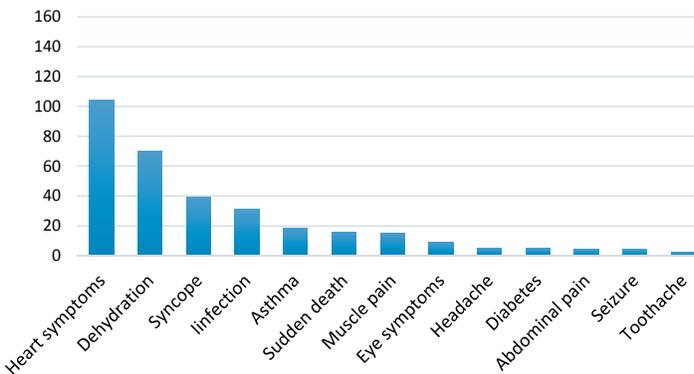


Figure 11. Diagnoses for 322 skiers that visited the emergency unit, internal medicine, Mora Hospital, over 34 years. 67% were able to leave the hospital the same day.

In Figures 10 and 11 the patients are divided into those who attended the surgical department and those who attended the internal medicine department. On average one per thousand starting the race will receive care at the emergency unit.

Rescue and health stations in the arena

The cross-country skiers can ask for support with all kind of problems at the rescue and health stations at the starting point, at the seven food stations and at the finish. They can also drop out of the race to take a bus to the finish⁸⁴. The medical staff registers the “diagnosis” and treatments and sends those who need it to hospital. In Figure 12, the visits from 1983 to 2013 make it obvious that blisters are the most common condition⁸⁵. Good treatment exists. The next largest problem is muscle pain, most commonly the legs, which is more difficult to treat. The number of accidents and injuries is small, ten on average per year. In Figure 13 the circle graph give the reasons per thousand skiers.

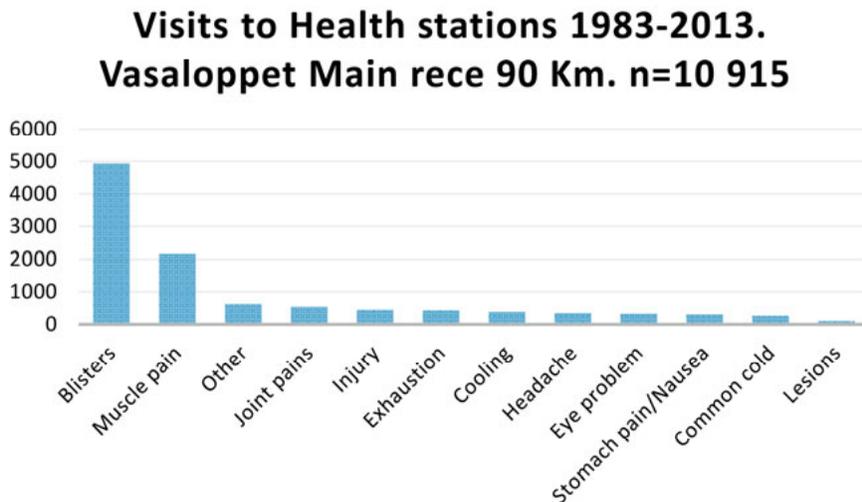


Figure 12. Health services are available at the starting point, food stations and finish. From 1983 to 2013, some 375 073 started the 90 km main race, the Vasaloppet. Medical help was requested by 10 915.

Cardiopulmonary resuscitation (CPR) is the most serious activity along the track, with 30% successful cases^{2, 86, 87}.

**Reasons to visits to Health stations Vasaloppet
Main race 90 Km 1983-2013.
Total 10 915 visits, 29 per 1 000 skiers.**

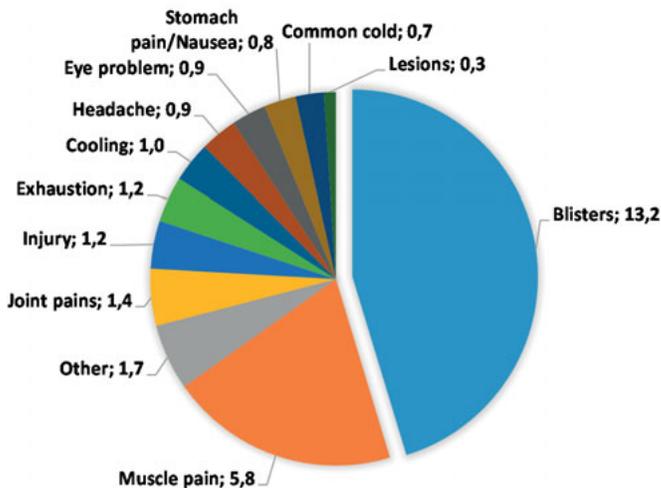


Figure 13. Reasons for visits to the Vasaloppet health stations along the track per 1 000 skiers. There were 10 915 health service visits out of 375 073 skiers starting the race. All reasons together are totally 29 visits per 1 000 skiers (3%).

Mortality in the Vasaloppet

Mortality and longevity of Vasaloppet participants have been described in the literature before the series of papers published as part of the present thesis. All sudden death during the race is of interest and often results in media reactions.

Mortality among participants from the races 1955-1957 ⁸⁸

Fifty-six years after the races, year 2011, 463 out of 1 171 participants were still alive. The average age among them was 84 years. Seven hundred and seven had died.

The number of deaths among controls was estimated to 867 in the general population 2011 in persons born the same year as the skiers (and alive 1960). Median death year was 1999 and the median death age was 76 years.

Thus, survival was longer than expected for 160 of the skiers. We concluded that the Vasaloppet ski population had an 18% longer longevity. Standardized mortality rate (SMR) was 0.82 (95% CI 0.76 – 0.88).

Cause of death is known for 665 of the 707 that had died. Figure 14.

Cause of death Vasaloppet skiers 1955-57

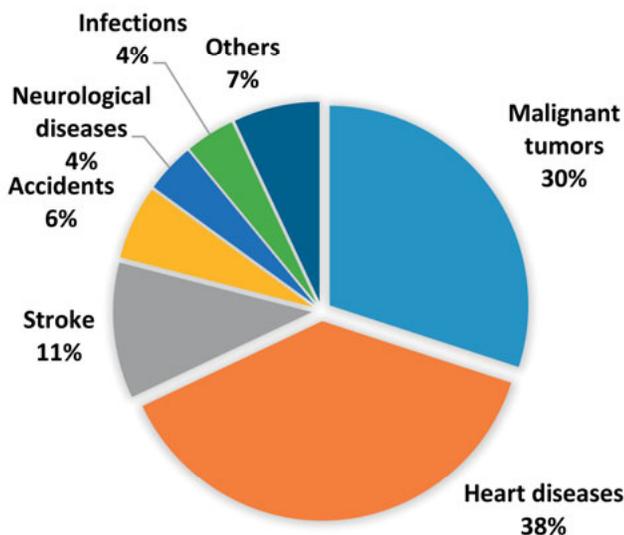


Figure 14. Cause of death for Vasaloppet skiers, 1955-57. Seven hundred and seven skiers died between 1963 and 2011 (median year 1999). In 1999, the causes of death for men in Sweden were 47% from cardiovascular diseases (the figure for skiers was 49%), 23% from malignant tumors (skiers 30%) and 4.5% from injuries (6% among skiers).

In 2011, the causes of death in the three big groups were 38% (cardiovascular), 27% (malignancies) and 6.5% (injuries) respectively.

Mortality amongst Vasaloppet participants 1989-1998. ¹

The aim of a study from 2003 was to assess mortality in a group that had practiced regular physical training over long periods. The cohort of 49 219 men and 24 403 women participated in the Vasaloppet from 1989 to 1998. They were followed until 1999 in the National Cause of Death Register in Sweden. The standardized mortality ratios (SMR) were calculated adjusted for age and calendar year. Four hundred and ten deaths occurred, compared with 850.6 expected, yielding an SMR of 0.48 (95% CI 0.44-0.53).

A lower mortality was observed in all major diagnostics groups. Some differences were seen in subgroup analyses. Skiers that participated in more races had lower risk of death, see Table 5.

Table 5. Standardized mortality rate (SMR) for all causes of death and in some sub-groups, with 95% confidence intervals in brackets. Women in the 90 km race have few cases.

| | Men 90 Km | Women 90 Km | Women 30 Km |
|--|----------------------|------------------------|------------------------|
| All causes of death | 0.49 (0.44-0.54) | 0.39 (0.19-0.70) | 0.46 (0.35-0.59) |
| All cancers | 0.62 (0.52-0.74) | 0.44 (0.16-0.96) | 0.60 (0.43-0.83) |
| Coronary heart disease | 0.46 (0.36-0.54) | | 0.18 (0.02-0.67) |
| Cerebrovascular disease | 0.30 (0.16-0.53) | 1.34 (0.17-5.0) | 0.58 (0.16-1.49) |
| Injury and poisoning | 0.76 (0.61-0.94) | 0.50 (0.06-1.82) | 0.56 (0.26-1.06) |
| Number of races completed; men 6+, women 4+ | 0.32 (0.20-0.48) | | 0.43 (0.14-1.01) |

A survey was done in this study with answers from about 500 individuals from the general population and skiers. Strenuous and regular strenuous exercise was much more common among skiers than others. Fewer skiers smoked and they had a lower level of chronic and mental diseases. The question is, how much of the apparent low mortality in the cohort that can be attributed to physical activity and fitness? Low mortality is at least due to some confounding from other lifestyle factors. Confounding factors such as socioeconomic status (SES), genetics and selection could explain some part of the low SMR. More studies are needed.

Sudden death among Vasaloppet cross-country skiers during the races 1922-2014.^{89, 90}(Paper I and II)

Over a long period 1 131 214 skiers have started the competition in races from 30 to 90 km. Nineteen have died during the races, 15 in the 90 km race and four in the 30 km race. This risk, in average two per 100 000, is discussed in papers I and II in this thesis.

However, in this cross-country race medical risks are few. Three percent had problems handled at the race health stations (Figure 12). One per thousand was sent to the emergency unit at hospital with very often temporary problems (Figures 10 and 11).

Cardiac arrest

Factors influencing survival

There are many components that influence survival after cardiac arrest (CA). In Europe, the number of acute and unexpected cardiac arrests has been reported to be 37 persons per 100 000 per year and in the USA, 52 per 100 000 per year^{91,92}. If the event occurs in hospital, the patient has a 30% chance of surviving the coming 30 days. If it happens outside the hospital, the chance is 10%⁹³.

Five types of prognostic factors are: 1) Patient characteristics. Patients between 10 and 35 years old have a better prognosis.⁹⁴⁻⁹⁶ A prior history of diabetes and heart failure is associated with a worse prognosis⁹⁷. 2) Chances improve if the patient can inform medical personnel about their symptoms as early as possible. This is dependent on the alarm situation. 3) Circumstances around the cardiac arrest. If the initial rhythm is ventricle fibrillation, the chance of surviving is dramatically higher⁹⁸. If the CA happens in the patient's home without a bystander, chances of survival decrease⁹³. 4) Different time factors play an important role: time from cardiac arrest to raising the alarm⁹⁹, time from cardiac arrest to cardiopulmonary resuscitation (CPR)⁹⁹ and time from raising the alarm to ambulance arrival¹⁰⁰. 5) Other factors include the quality of the CPR, namely whether the CPR is started by competent personnel or not. It is also possible that the attitudes of health staff play a role¹⁰¹.

Out-of-hospital cardiac arrest surveillance is described for 1905 - 2000 in the United States, where 92% of the 300 000 annual events end in death¹⁰². Non-cardiac cases are trauma, drowning, overdose, asphyxia, electrocution, primary respiratory arrests. The majority of events (70% - 85%) have a cardiac cause (myocardial infarction and arrhythmia). Only 33.3% of all patients received bystander cardiopulmonary resuscitation (CPR), and only 3.7% were treated by bystanders with an automated external defibrillator¹⁰². Improvements in logistics can increase survival, even if the situation is different in the countryside compared with in cities. The organizers of mass sports events have to be prepared for cardiac arrests^{2, 103, 104}.

In Sweden there are 35 000 defibrillators placed in official places across the community. Police, ambulance and volunteers are recruited to come early to places where an alarm is raised. The goal is to save 1 200 lives every year, which increases the percentage from 10% to about 20%. That goal has been reached in Holland, Norway and Seattle in the United States. In this thesis we

deal with the questions that can increase the survival. In which way can the ongoing research evaluate the guidelines of today and here are three areas named where we expect changes? 1. Hypothermia therapy ¹⁰⁵⁻¹⁰⁸. 2) Are drugs given in CPR situations useful or not? ¹⁰⁹. 3) Chest compressions with or without rescue breathing is basic.

New techniques have emerged to simplify CPR performed by lay people. Rescue breathing is taken away from some guidelines (bystander-CRP). There are also discussions about manual mechanical chest compressions in advanced CPR (A-CPR) performed by medical professionals.

A cardiac output of 20 to 30% can be established with chest compressions with a frequency of about 100 to 120 per minute when the thorax is compressed by about 5 to 6 centimeters.

Cardiac arrest during physical activity and sports

Sudden death among young athletes

Sudden death among young competitive athletes is a very visible and well-described group. The term sudden cardiac death seems more often used for these events than cardiac arrest. Over a 27-year period from 1980 to 2006 in the USA, 1 866 cases were registered in the age group 19 +/- 6 years. The most common cardiovascular causes were hypertrophic cardiomyopathy (36%) and congenital coronary artery anomalies (17%). Incidence in the USA was less than 100 per year ¹¹⁰.

In a broader international review in 2009 ¹¹¹, which included Europe, incidence is calculated as 1-3 per 100 000 person years. There is a debate whether there is a geographical difference in incidence. Coverage of registration can also play a role. Preventive pre-participation programs are also different. The higher incidence in athletes compared with non-athletes causes may be of a combination of underlying cardiovascular disease and intense exercise that can trigger arrhythmias leading to cardiac arrest. It is likely that the high level of cardiovascular work is a risk in sports.

Cardiomyopathies and coronary anomalies are a more common cause of sudden death in athletes. Coronary atherosclerotic disease is seldom a disease in this group of young athletes. There is a higher incidence among males as compared to females ¹¹¹.

Middle-aged and older physically active people and sudden death during exercise

The increase of participants in long-distance races in running or cross-country skiing has been accompanied with reports of event-related cardiac arrest ^{112, 113}. Media attention has led to discussions regarding the health risks of these sports activities. Participants in these long races are an older population with

different cardiovascular risks and underlying medical conditions ¹¹⁴. The incidence of cardiac arrest of marathon runners is described as 0.54 per 100 000 participants. The average age in long distant races is approximately 40 years and the rate of cardiac arrest was calculated in marathon runners per 100 000 running hours, it was 0.2 cardiac arrests compared with 0.14 sudden deaths. This is lower than in other athletic populations, for example in triathlons it is 1.5 per 100 000 participants ^{115, 116}. The Vasaloppet has 0.3 cardiac arrests per 100 000 skiing hours ⁹⁰.

Prevention

Many groups have tried to discover the best ways to prevent sudden death in relation to sports. The European Association for Cardiovascular Prevention and Rehabilitation, Sports Cardiology section, has published a report for guiding sports associations, sports clubs and the medical profession. It is probably more difficult to standardize prevention for people who are somewhat older and who practice physical activity in mass events. Their exercise is often private and less in sport clubs. ¹¹⁷

Cancer

Cancer is a leading cause of morbidity and mortality, accounting for about one quarter of all deaths. Lifetime risk is around one in three in developed countries. WHO estimates that the number of new cases annually will rise from one million in 2000 to 15 million by 2020³⁹. The role of environmental factors in cancer causation is illustrated by the big geographical differences in incidence world-wide. Some risk factors for cancer can be changed and some cancers prevented. Danaei et al.²⁸ have estimated that 35% of cancers world-wide are associated with nine modifiable risk factors (e.g. smoking, alcohol use, being overweight, low fruit and vegetable intake and physical inactivity).

Physical activity and lifestyle in cancer prevention

In 2007, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) issued eight recommendations on diet, physical activity and weight management for cancer prevention¹¹⁸. Project director Wiseman states that these recommendations represent the most authoritative review of the topic¹¹⁹. The role of physical activity, food and nutrition in different cancers is presented in this review¹²⁰ and research activities are high¹²¹. Other recommendations are also available in the literature^{122, 123} and the European Code against Cancer has "11 commandments" for cancer prevention issued by the European Partnership in Action against Cancer. The first six are about lifestyle¹²⁴.

The risk reduction of dying from cancer in individuals with lifestyle factors has been shown to be about ten percent. The hazard ratio for death from cancer and high lifestyle score was, for example, 0.93 for body fatness and 0.90 for physical activity¹²⁵. The European Prospective Investigation into Cancer and Nutrition (EPIC) study from ten European countries investigated how different diets can increase cancer prevention¹²⁶. In the EPIC material is a¹²⁷ summary that a high score based on WCRF/AICR recommendations was associated with a reduced risk for all cancers. A one point increment in the score was associated with 5% (95% CI 3-7%) lower risk; 12% (95% CI 9-16%) for colorectal cancer, and 16% (95% CI 9-22%) for stomach cancer. Significant associations were also observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver and esophagus but not for prostate, ovarian, pancreatic and bladder cancers. It is obvious that different cancers

have different levels of sensitivity to different preventive factors. The results in the various studies are not coherent.

In real life the compliance of the various recommendations are not easy to separate from each other. In diet studies from 2002 and 2004^{128 129} discuss how physical activity and lack of body fatness have an important protective effect. Physical activity has been associated with lower cancer risk in many studies^{20, 39}

In 2011, Courneya and Friedenreich in Alberta, Canada¹³⁰ state that there is convincing evidence that physical activity has a beneficial effect on the risk of colon cancer; that there is probably evidence for an effect on breast and endometrial cancers; possible evidence for a beneficial effect on cancers of the prostate, lung and ovary, and insufficient or no evidence for remaining cancer sites. The issue that physically active people also have a lifestyle with a more healthy diet, and are less prone to being overweight etc., was studied by Giovannucci¹³¹. He found that physical activity had an independent protective effect against colon cancer.

Physical activity or body fatness has no protective effect in bladder cancer. In esophageal cancer, body fatness is a risk. There are no comments about physical activity for cancers of the esophagus, stomach, mouth, pharynx and larynx¹¹⁸.

Cancers related to tobacco smoking

Non-smoking as part of the lifestyle has a preventive effect on cancer. For a long time now, cigarette smoking has been clearly and unambiguously identified as a direct cause of cancers of the oral cavity, esophagus, stomach, pancreas, larynx, lung, bladder, kidney and leukemia (especially acute myeloid leukemia)¹³². The evidence of the association between lung cancer and smoking is strong, evident for all lung cancer types, dose-related and insensitive to covariate adjustments. It is a causal relationship shown in a broad meta-analysis in 2012¹³³.

Tobacco also has an additive effect together with alcohol for developing esophageal cancer and cancer in the ear, nose and throat region.

Overview of cancers of major interest in this thesis

Prostate cancer is the second most common cancer worldwide. Five-year survival probabilities are about 60%. Incidence increased dramatically between 1988 and 2002, largely because of screening with prostate specific antigen (PSA) in men without symptoms. The test leads to the detection of many prostate cancers that are small and would otherwise remain unrecognized. Screening is increasingly popular in many high-income countries¹¹⁸. PSA testing is a possible source of detection bias in epidemiological studies¹³⁴. Tests are still not recommended on a population basis in Sweden, but everyone who wants

the test can have one done. Growth factors, particularly IGF as well as androgens, have been implicated in the development of prostate cancer. Declining levels of testosterone in older age can contribute to this cancer. In a review¹³⁵ of the literature was a weak inverse association found between physical activity and prostate cancer. Stronger effects were seen when fatal prostate cancer was an outcome. Further research will investigate more deeply and reveal more answers about prostate cancer and physical activity.

Breast cancer is the most common cancer in women worldwide, representing 23% of all cancers in women. Breast cancer incidences increased with industrialization and urbanization, and also in situations where screening contributes to early detection. In western countries the rate is 75-100 per 100 000 compared with about 20 per 100 000 in Asia and Africa. Four to nine percent of cases have a hereditary element. Five-year survival in developed countries is high, approaching 90 %¹³⁶. Breast cancer is hormone related, but in a different way for cancers diagnosed in premenopausal women compared to postmenopausal, the latter form being more common. Early life events are of importance, including diet and hormone status. Late menarche, early pregnancy and number of pregnancies, and early menopause are protective factors. Lactation diminishes the cancer risk while drinking alcohol and height attained as an adult increase the risk in both forms. Body fatness decreases the risk in the premenopausal form and increases the risk in the postmenopausal form. Greater birth weight increases the risk in the premenopausal form and physical activity decreases the risk in postmenopausal breast cancer¹¹⁸.

Lynch et al¹³⁶ present epidemiological evidence between physical activity and breast cancer from 73 studies conducted around the world. They found a 25% risk reduction when comparing the most physically active women with the least active. Activity levels after menopause appeared to have the greatest impact on the risk of breast cancer.

Lung cancer is the most common cancer in the world (12%). The majority of cases, 75%, are among males. Lung cancer is most common in high-income countries. The incidence is 5% in Africa and 60% in Eastern Europe. The main cause is tobacco smoking. It has taken 35 years of changing smoking habits to see results in the number of patients with lung cancers. Fruit and carotenoids may have a protective effect. Five-year survival is 5%. There is limited evidence suggesting that physical activity protects against lung cancer¹¹⁸. On the other hand, Emaus and Thune talk about physical activity having a 20-50% preventive effect. The crucial caveat to this data is that those who have never smoked do not benefit from physical activity in lung cancer prevention¹³⁷. Hypothetical, plausible biological mechanisms exist^{137 3}.

Colorectal cancers are the third most common cancer. Rates are increasing with industrialization and urbanization. Incidence is about 40 per 100 000 in

industrialized countries and about 5 per 100 000 in Africa. Five-year survival globally is about 50%, with a wide range depending on stage etc. Five to ten percent of cases have a hereditary component. It is fatal in just under half of all cases. Food and nutrition play a highly important role in prevention and causation. The evidence that physical activity protects against colorectal cancers is convincing, evidence that is stronger for colon cancer than rectal cancer. Risk factors of this cancer are red and processed meats, alcoholic drinks, body fatness, abdominal fatness and height as an adult. There is probably a protective benefit from dietary fiber, garlic, milk and calcium ¹¹⁸.

Many studies show that physical activity has been associated with a lower risk for colon cancer: the indication is a 30% reduction in risk ³⁹. There is also some evidence of a relationship between the amount of physical activity and colon cancer risk, for example in the US Nurse Health Study ¹³⁸. Wolin and Tuchman ¹³⁹ report a reduction in colon cancer with higher physical activity levels, with an average reduction of 25%, but they found no association with rectal cancer.

Cancers related to outdoor activities present a higher risk because of exposure to sunlight. Ninety-five percent of all skin cancers are non-melanoma. They are more common in high-income countries and among light-skinned people. Non-melanoma skin cancer is almost never fatal. Melanoma has 80-90% five-year survival rates.

Some potential mechanisms for developing cancer

Several mechanisms have been proposed to explain that physical inactivity (see page 24) is a causal factor in the development of cancer. Some of these are systemic mechanisms while others are site-specific mechanisms. The three most important are: a) the roles of metabolic hormones, b) changes of body fat and c) influences on immune functions.

Hyperinsulinemia and IGF are reduced by physical activity. Weight regulation can be done more easily through physical activity. The immune system may be most active in persons with moderate exercise and will thus reduce the risk for cancer. Sex hormones with powerful mitogenic and proliferative effects will be involved more specifically in cancer of the breast, prostate, testes and endometrium. Exercise lowers the levels ³⁹.

It should be noted that cancers are many diseases. The cancer burden cannot be reduced by a few factors. It is not true that 35% all cancers can be prevented by lifestyle in a group such as participants in leisure-time physical training. But in some cancer sites, namely those groups of cancer influenced by lifestyle, this goal can be reached. To study all cancers as one group is misleading because of the big differences between cancer sites and different possible etiologies.

Cancer diseases have a complex etiology and often need a long time to become established. Many of the participants in the study in this thesis have not yet reached the age when cancer is most common in their lives.

One question of interest to discuss is the role of oxygen consumption. The oxygen uptake (fitness), VO_2 -max, for cross-country skiers is 45-80 ml kg^{-1} min^{-1} compared with the general population's VO_2 -max of 35 ml kg^{-1} min^{-1} ⁷¹. This corresponds approximately to a mean value of oxygen consumption among Vasaloppet skiers of about 20 MET-h $week^{-1}$. The difference may have a high impact on the risk for cancers in the esophagus, colon, endometrium and kidney¹¹⁸. Whether it is VO_2 -max itself or fruit and vegetable consumption impacting the risk for cancer is not very clear.

Myocardial infarction

Acute coronary syndrome is the acute phase of coronary artery disease that includes the clinical manifestations of unstable angina pectoris, acute myocardial infarction and sudden coronary arrest. Cardiac arrest has been discussed above. Acute myocardial infarction (MI) is the disease that is characterized by retrosternal pains or a strangling sensation together with an abnormal electrocardiogram (ECG) appearance and a rise in cardiac biomarkers reflecting myocardial damage^{16, 140}.

Clinical approach

The clinical approach differs to some degree depending whether it is an ST-elevation MI or a non-ST-elevation MI. The ST-elevation MIs are often more acute but have a better in-hospital prognosis. Non-ST-elevation MIs has a worse long term prognosis. Mortality rates have significantly improved in recent years due to treatment strategies together with treatment of risk factors for coronary artery disease. Nevertheless, one in three patients dies before arrival at the hospital.

Atherosclerotic plaque is formed in the coronary arteries throughout life. For long periods there may be no symptoms but the plaque can slowly increase and give the patient chest pains, angina pectoris, correlated to stress or strenuous physical exercise. A rupture or erosion of a plaque is a potential danger and can be a trigger to thrombus formation.

Incidence change and Swedish register

The incidence rate for MI has changed during recent decades in the western part of the world. In some populations there has been a 25% decrease since the year 2000¹⁴¹. This trend shows the value of prevention and treatment of risk factors. About 35 000 individuals are affected by MI annually in Sweden, making this the most common cause of death among the cardiovascular diseases. Moreover, in Sweden the decrease in mortality is obvious. Since 1991 the Swedish Clinical Registry Riks-HIA (part of the Swedeheart) has registered most cases of MI treated in coronary units in all Swedish hospitals. The Swedeheart clinical registry follows the development and mortality across the different counties.

The risk of dying within 28 days in MI, case fatality, is an international accepted figure for comparison. About 1990 this figure was more than 40%. The percentage in Sweden, age standardized was close to 30% in the period 2004-2006. The variation between counties was from 24.5 to 38.1 %. About 20% die out-of-hospital. The hospital mortality in MI within 28 days hospital care was for the years 2005-2007 in average 14,4% and 15.5% for respectively women and men (age standardized). E.g. 1993 this proportion was 27% ¹⁴².

Swedeheart's coverage of patients with MI has been improving continuously. Swedeheart data 1989-2010 from patients among skiers and non-skiers have been used in this thesis (paper IV).

The decrease in mortality has many causes. From around year 2000 the reperfusion treatment has been generally more introduced; thrombolysis and later on Percutaneous Coronary Intervention (PCI) with stent implantations and in some cases CABG (Coronary Artery Bypass Grafting). The quality of prehospital and hospital care and secondary prevention has increased.

Prevention

Data support the hypothesis that the growing trend in increased physical activity can be one reason to lower incidence in MI. Physical fitness and activity as a risk factor is described in a meta-analyze ¹⁴³. Both decrease the incidence.

All-cause mortality is twice as high in unfit individuals with the metabolic syndrome than in fit individuals with the syndrome ^{63 56 144}.

Stroke

The global burden of stroke has decreased in high-income countries over the last twenty years, but has increased in low- and middle-income countries.

Estimates from the Global Burden of Disease Study in 2010¹⁴⁵ show that stroke was the second most common cause of death and the third most common cause of disability-adjusted life years worldwide in 2010. This was based on 119 studies from 58 high-income countries and 61 from low- and middle-income countries between 1990 and 2010. Mortality has decreased over the past two decades but the absolute number has grown. In 2010 the incidence in absolute numbers of people suffering a first stroke was 16.9 million. The number of stroke survivors was 33 million and stroke-related deaths was 5.9 million. The global burden is great and increasing.

In 2007 information was published from the Framingham study¹⁴⁶ indicating that the lifetime risk of stroke for persons who were stroke-free at 55 years age was one of six among men and one of five among women.

The Swedish Stroke Register

Hospitalized patients with stroke are annually reported in the Swedish National Quality Register for Stroke Care (Riks-stroke)^{147, 148} and can also be followed over time. The registers give important knowledge and possibility to compare with other countries. The value of e.g. stroke units¹⁴⁹ and thrombolysis¹⁵⁰ as well as to follow the secondary preventions was important. The register increase the possibility to implement guidelines.

Reports from hospital wards about stroke incidence in Sweden are given in regional comparisons¹⁴². Stroke takes up a large proportion of hospital beds compared with other diseases. The hospital mortality rate in Sweden 2013 four weeks after stroke was 14.4% for men and 13.8% for women. Within 90 days, the mortality is about 18%. When those who died out of hospital are included, the mortality figure is about 27%. Stroke is the third most common cause of death after myocardial infarction and cancer and the most common cause of physical disability in adults. Thrombolytic treatment has increased and is given in five to 22% of cases in the different counties in Sweden, 12% on average. Eighty-one percent of the survivors were ADL-independent three months after discharge. The figures are adjusted for age and consciousness at admission¹⁴². Nine percent experience recurrent stroke in the year following the first stroke.

This thesis has used information from the Swedish Stroke Register 1994-2010 to follow up recurrent stroke and compare between skiers and non-skiers.

Risk factors

Guidelines from the American Heart Association and American Stroke Council have described the modifiable risk factors for ischemic stroke: hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, obesity and non-normal body fat distribution¹⁵¹.

One of the problems with the stroke diagnosis is that it includes different etiological background mechanisms. The most common is cerebral thrombosis, which is a part of a disseminated atherosclerotic vessel disease. The ischemic strokes dominates and are about 85% and the core include prevention; statins, antihypertensive, anticoagulation and antiplatelet therapies. In case of atrial fibrillation anticoagulant therapy is often important as secondary prophylaxis, see next paragraph.

In smaller groups of patients with an acute ischemic stroke, early reperfusion of ischemic brain areas can possibly diminish the brain damage. The sooner one can treat the stroke, within a window of 4.5 hours, the more favorable the outcome.

The most positive outcome occurs if there is treatment within the first 90 minutes. Patients with transitory ischemic attacks have different choices of antiplatelet regimens to reduce the risk of recurrent stroke.

For patients with recent carotid territory ischemic events, carotid endarterectomy is an effective addition to best medical treatment. Carotid stenting is a newer, less invasive revascularization strategy¹⁵².

Intra cerebral bleeding is less frequent, and may have other causes. It constitutes about 10 - 15% of all stroke cases and is of course a clinical problem found in combination with antiplatelet or anticoagulation therapy. The 30-day mortality for these events is very high (25-50%). Hypertension is the most common background to intra cerebral bleeding. Unfortunately, surgery has not proven helpful except in certain exceptions such as in large cerebellar hemorrhage¹⁵³.

Prevention

Higher physical activity together with a healthy lifestyle has been shown to reduce the risk for cardiovascular diseases^{44, 151} including stroke. If older people as physical training walk they have a lower incidence for stroke than those that not are physical active¹⁵⁴⁻¹⁵⁶. The protective effect of physical activity may be partly mediated through its role in reducing blood pressure and controlling other risk factors for cardiovascular disease, diabetes and increased

body weight. Other biological mechanisms have also been associated with physical activity, including reductions in plasma fibrinogen and platelet activity and elevations in plasma tissue plasminogen activator activity and HDL concentrations.

Efforts to motivate people to exercise is done in primary care. In a British study single interventions had modest effect. The most intense intervention, exercise prescription and relevant counselling can probably increase physical activity ¹⁵⁷.

In one inter-stroke pilot study ¹⁵⁸, the most important way of preventing a first stroke was by blood pressure reduction.

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in elderly people and a potent risk for stroke. Stroke prevention is an increasing challenge amongst the more elderly in the population. An investigation from California¹⁵⁹ from 2001 presented a prevalence study showing that atrial fibrillation ranged from 0.1% among persons less than 55 years old; 3.8% in those above 60 and 9% among patients of 80 years or older. It is difficult to estimate whether paroxysmal atrial fibrillation influences prevalence statistics. Atrial flutter is included in the discussion.

The number of patients with atrial fibrillation in the USA is estimated to increase 2.5 times over the next 50 years because of the growing proportion of elderly individuals. It is a challenge in the USA and worldwide to respond to this increasing threat with optimal stroke prevention and risk management. A community study from Olmsted, Minnesota, states that atrial fibrillation and survival have remained constant over recent decades. An excess risk of mortality was observed 90 days after diagnosis. Comorbidity is an important explanation. It is essential to gain a better understanding of how to optimize the management of AF and prevent strokes¹⁶⁰.

Endurance training and atrial fibrillation

Two Italian assessments have been done. In one the left ventricular cavity was examined 1999 in 1 329 highly trained athletes. The other 2005 in 1 777 also competitive athletes when the left atrium size was investigated. To the echocardiographic examination was added a clinical evaluation. Fourteen percent of the left ventricular cavities were enlarged and of the left atrium 20% were enlarged. The only clinical deviation was 0.8 % with atrium fibrillation or supraventricular tachycardia found in those with enlarged atrium. That is the same frequency as among the general population. The conclusion in both studies was that the larger sizes and dilatation are physiologic consequences of endurance conditioning, remodeling of the “athletes heart”^{161, 162}.

In a study from 2008¹⁶³, marathon runners were compared with a population-based sample of sedentary men. During follow-up with these two groups, there was a higher incidence of lone atrial fibrillation among the marathon runners with a hazard ratio of 8.8 (95% confidence interval 1.26–61.29). In contrast to the Italian study this study showed an association between a larger

left atrium (inferior-superior diameter and volume) and physically active subjects along with higher incidence of atrial fibrillation.

There is evidence to suggest that sports practice is associated with a higher risk of lone atrial fibrillation in men. One must suspect that it is long term, intense training that causes this and further studies can perhaps clarify a threshold limit for intensity and duration of physical activity and the risk for atrial fibrillation.

In 2013, Andersen ¹⁶⁴ published a study based on the 1989-1998 Vasaloppet cohort, where he 2005 in a follow up found 681 cases with atrial fibrillation. He looked only at 90 Km-racers. Those who competed in the highest number of races had a higher risk of arrhythmias. Also skiers with shorter finishing times had more arrhythmias compared with the less fit skiers. The incidence rate was 49 (95% CI 43-51) per 10 000 person years among men 55-64 years old, which could indicate a higher rate atrial fibrillation in skiers than in the general population.

In paper V in this thesis we involved studying the frequency of atrial fibrillation but in our case we had also possibility to compare with the non-skiers matched for age, gender and residence county.

Atrial fibrillation and risk for stroke

A question of interest is whether atrial fibrillation with a background in endurance training has the same risk for stroke as others ¹⁶⁵. With different scores, the higher risk for stroke is clear for patients with an earlier TIA/stroke, diabetes, greater age ¹⁶⁶. Higher CHADS₂ (Congestive heart failure, Hypertension, Age \geq 75 years, Diabetes, previous Stroke) score is associated with stroke risk ¹⁶⁷. In studies about low risk for stroke in atrial fibrillation patients CHADS₂ and even more CHA₂DS₂-VASc (Vascular disease, Age 65-74 years, Sex category) score was able to identify "lone atrial fibrillation" with low risk (score=0) ¹⁶⁸⁻¹⁷⁰.

Prevention

The need for studies that may find ways to prevent the risk for atrial fibrillation without limiting the cardiovascular benefits of exercise is being discussed in the literature ^{171, 172}.

The population with atrial fibrillation will grow because more people are practicing endurance training and a proportion of them will experience atrial fibrillation.

Aims

Papar I: 1) To study acute mortality during the cross-country ski race, the Vasaloppet, with distances of 30, 45 and 90 km from 1970 to 2005. 2) To map the reasons for sudden death while racing. 3) To compare the mortality rate with the mortality risk in the general population.

Papar II: 1) To study the absolute and relative risk for cardiac arrest during the various distances in the Vasaloppet from 1922 to 2010. 2) To map the reasons for cardiac arrest while on the course. 3) To compare the risks with data from marathon running.

Papar III: 1) To compare the total incidence of cancer and incidence of groups of different cancer types in a large cohort of cross-country skiers from 1989 to 2009 (the Vasaloppet) with an unexposed matched group in the population. 2) To study the pattern of cancers in relation to gender and performance in the races.

Papar IV: To compare recurrent myocardial infarction (re-MI) and death after a first myocardial infarction in a large cohort of cross-country skiers (the Vasaloppet) from 1989 to 2010 with re-MI and death in an unexposed matched group in the population.

Papar V: 1) To compare recurrent stroke (re-stroke) and death after a first stroke in a large cohort of cross-country-skiers from 1989 to 2010 (the Vasaloppet) with an unexposed matched group in the population. 2) To relate atrial fibrillation to the cohorts we studied.

Methods

Study populations

The basic cohort consisted of all men and women who started in any of the distances in the Vasaloppet ski races from 1922 to 2010 (n=926 350).

Paper I about acute mortality was restricted to participants from 1970 to 2005 (n=13 cases out of 698 102 skiers).

Information about the deaths was collected. Medical team reports and other documentation from the health service were available for the years in question and because of that all severe medical incidents that happened during the races from start to finish were identified. Death certificates with cause of death were received. Autopsies were performed in eleven of the thirteen cases. Relatives of all who died were contacted for interviews. They provided answers about frequency of physical activity, smoking habits, height, weight, presence of acute or chronic diseases before the race, and also family history of cardiovascular diseases. We also collected information about the previous number of races participated in and the point in the race where the death occurred.

Paper II analyzed 20 skiers with cardiac arrests between 1922 and 2010. The Vasaloppet medical team had all the information about the deaths. Thirteen of the fifteen who died are described in Paper I. Medical records were available for the five survivors (mean age 47 years). The point in the race where the cardiac arrest occurred was identified. The comparison of risk was done with the normal out-of-hospital cardiac arrest rate in Swedish registries. Comparisons were also done with available information about cardiac arrest in marathon runners.

Paper III-V used the cohort of skiers 19 and older from Sweden identified by their National Registration Number between 1989 and 2010 (n=204 038 individuals, 62% males and 38% females). On average each skier participated in 2.46 races. Fifty-five percent of the skiers participated in the classic 90 km race and the rest participated in the 30 or 45 km races.

Men and women from the general population were randomly matched to the skiers by Statistics Sweden from the National Population Registry by age (by 5-year categories), sex, county of residence and year of the ski race. For each race of those exposed, one matched person was selected and denoted as

unexposed. The unexposed has also been named controls or non-skiers. They are not exposed to any Vasaloppet race.

In Paper III, each individual in the exposed and unexposed groups was frequency matched and selected so that the date of their first race and their age corresponded. In this cancer incidence study we only studied cancers occurring at least one year after inclusion. The number for analysis was 370 029: 185 412 exposed and 184 617 unexposed.

Flowchart figures in the papers show the total study population including the exposed and unexposed study subjects and exclusions.

Paper III-V are based on a comparison between cross-county skiers exposed to the Vasaloppet and unexposed non-participants (also denoted non-skiers) from a matched cohort from the population, but in three different common diseases: cancer (III), myocardial infarction (IV) and stroke (V). To avoid a selection of healthier individuals among the Vasaloppet skiers, we also excluded from both the skiers and non-skiers those with hospitalizations because of severe diseases. Individuals with a diagnosis that made skiing in a Vasaloppet race unlikely were excluded. Diagnoses that excluded study persons were as follows (number of exposed in brackets). One individual could be included in more than one disease-group. Heart diseases including myocardial infarction 7 154 (527), lung diseases 1 360 (59), serious psychiatric diseases 3 934 (181), stroke 2 743 (173), osteoarthritis-prosthesis surgery 1 750 (177), chronic neurologic disease 790 (37), invasive cancer 7 278 (1 598), sickness from all causes registered for more than 120 days in the year before the race 13 699 (926). This gave a total of 38 669 (3 678).

The Charlson co-morbidity index¹⁷³ was used to evaluate how successful the exclusions had been when we removed the sickest persons. The index was also used to check for the level of remaining co-morbidity. The Charlson index was calculated based on hospital admission data in the National Patient Register from 1964 onward.

Paper III: The individuals among the Vasaloppet skiers and the controls with any cancer diagnosis before the first race or the selection date for the controls were excluded. Cancers were studied in eight groups: 1. *All cases of invasive cancer.* 2. *Prostate cancer.* 3. *Breast cancer.* 4. *Colo-rectal cancer.* 5. *Lung cancer.* 6. Cancers with *tobacco smoking* as a probable etiological factor. 7. Cancers where *physical activity, overweight, diet with fruits and vegetables* play an important role in the etiology. 8. Cancers where *exposure to sunlight* plays an important role in the etiology. In all groups there were 12 822 cases.

Paper IV The number available to study the incidence of first myocardial infarction in order to find cases of recurrent myocardial infarction (re-MI) was 7 092 (1 039 exposed and 6 053 unexposed).

Paper V: The same procedures were used as in Paper IV. The number of first strokes to study in order to find recurrent stroke (re-stroke) was 5 964 (1 083 in the exposed group and 4 881 unexposed).

Registers

Using the unique Swedish National Registration Numbers (NRN), the Vasaloppet skiers and the control cohorts were linked to information about all hospital admissions in the *National Patient Register (NPR)*, about incidence of cancers in the *National Cancer Register (NCR)* and about death and causes of death in the *Causes of Death Register (CDR)*, all held at the *National Board of Health and Welfare*. The cohorts were also linked by the NRN to *Statistics Sweden* adding information about educational, occupational and civil status. *Swedeheart* is a national clinical registry that has been introduced successively to all hospitals that have taken care of patients with myocardial infarction in Sweden since 1991. *Swedeheart* includes data about risk factors such as smoking, use of moist snuff, hypertension, diabetes, stroke, body mass index and laboratory tests. It also contains data on reperfusion treatment, recurrent myocardial infarction, classification of myocardial infarction and drugs prescribed. *The Swedish Stroke Register (Riks-stroke)* is another clinical registry used in all Swedish hospitals to follow a number of quality variables from the time spent in hospital by stroke patients and over a three-month follow-up period. Information is available about previous stroke, atrial fibrillation, hypertension, diabetes mellitus, level of consciousness at attendance, medications before and after the stroke together with quality of life, smoking habits, information about activities of daily life (ADL) and thrombolysis treatment.

Since 1989, the *Vasaloppet registry* has held information about the year and distance for each race, name, Swedish citizen's identification number, address, number of races and finish time, also presented as a percent of the winner's time.

Statistical analyses

Paper I: Information registered from a cohort of 698 102 starters in Vasaloppet ski races from 1970 to 2005 was used. The skiers represented 581 person-years of skiing. For some years, 1970 to 1988, the ages of the racers were not known. The age distribution in our calculation of the standardized mortality rate (SMR) was used from those years after 1988. The large number of participants was after that year. We therefore estimated the age distributions based on data from the more recent years. The SMR was calculated with a 95% confidence interval (CI) for all causes of death and deaths due to cardiovascular diseases, obtained from the national Cause of Death Register. The average

skiing times for each race was used: 8 hours for 90 km, 5 hours for 45 km and 4 hours for 30 km. Calendar year, gender and age in 5-year increments were taken into account in the analyses.

Paper II: We assessed the incidence of cardiac arrest in the Vasaloppet between 1922 and 2010 among 926 350 participants. The twenty cases were all men. We calculated the incidence proportion per 100 000 skiers, but also the incidence rate per 100 000 skiing hours to make it possible to compare this with information from marathon runners. Fatality was also calculated for comparison.

Paper III: In the analyses of the probability of cancer diagnosis, follow-up started one year after inclusion and ended on the date of diagnosis of the cancer of interest, death, emigration, or December 31, 2010, whichever came first.

The net probability of cancer was estimated with the Kaplan-Meier method by treating the cancer diagnosis as the event of interest, while censoring for death from any cause. This approach resulted in estimates of the probability of cancer in a hypothetical world where being diagnosed with cancer is the only event that is allowed to occur. Differences in net probability were univariately tested using the log rank test, and hazard ratios with corresponding 95% confidence intervals were estimated with Cox proportional hazard models.

We verified the results from the analysis of net probability by comparing them to an analysis of the crude probability of cancer, which was estimated by treating cancer diagnosis and death from any cause as competing events. This approach resulted in estimates of the probability of a cancer diagnosis in a real world setting where it is possible for the individuals to die before being diagnosed with cancer. The results from the two different analyses were very similar for all cancer groups.

All statistical analyses were performed with the R statistical software package.

Paper IV: The subjects were followed from the diagnosis of myocardial infarction to the time of an event or to a maximum follow-up time of ten years for the first myocardial infarction included. The subjects were followed from the first race to the time of an event or a maximum follow-up time of twenty years from the first myocardial infarction included. Incidence rates were estimated as the number of events divided by the total follow-up time. Cox regression models were used to compare the event-free survival probability between the exposed and unexposed groups. To adjust for potential confounding we included age, gender and socioeconomic variables (educational, family and occupational status) in the model. As the exposed group is representing “healthy lifestyle” we did not include comorbidities in the model as these are not really confounders but rather indicators of health.

All analyses were done using the R environment for statistical computing (version 3.0) ¹⁷⁴.

Paper V: The subjects were followed from the diagnosis of stroke either to the date of an event or the end of follow-up (Dec 31, 2010), maximum ten years with median 2.3 years. Incidence rates were estimated as the number of events divided by the total follow-up time. Cox regression models were used to compare the event-free survival probability between those exposed to the Vasaloppet (skiers) and those not exposed (non-skiers). The proportional hazard assumptions were confirmed graphically. We used the directed acyclic graph approach ¹⁷⁵ to select suitable covariates for the multivariable model.

The model included age (continuous), race year (1994-2000, 2001-2005, 2006-2010), gender, smoking habits (never, ex-smoker, current), education (primary school, high school, university), family (single) and occupation status (employed, unemployed, retired). We did not include hypertension, diabetes and type of discharge medication in the primary model as we regard these as a consequential part of the lifestyle rather than true confounding factors. They were, however, included in an additional model. Atrial fibrillation was registered on admission, which made it possible to perform stratified analyses by atrial fibrillation status. Finally, we included data on the Activity of Daily Living (ADL) - situation, health assessment and discharge medication to attempt to estimate the severity of the stroke for skiers and non-skiers.

Ethical approval

Ethics committee approval was granted for the study (Uppsala Dnr 2010/305, 2012/067, Stockholm Dnr 2011/Ö30).

Results

Acute Mortality during Long-distance Ski Races (Vasaloppet). (Paper I)

Characteristics of the deceased

Overall, 13 deaths occurred (Table 6). Almost all deaths were caused by cardiovascular disease ($n=12$) and occurred among men 30–72 years of age. The causes were coronary heart diseases ($n=9$), hypertrophic cardiomyopathy ($n=2$), myocarditis ($n=1$), and stroke ($n=1$). The deaths were scattered across the years. Five of the deaths occurred at, or immediately after, the start. Four took place within 50 km of the start, while another four occurred after 60 km or more of skiing. Those who died early mostly had done races before. Four cases had a family history of coronary heart disease and one reported diabetes mellitus in the family. Chronic disease was reported in four: two were treated for arterial hypertension but with no other symptoms of cardiovascular disease. One suffered from angina pectoris, hypertension, and renal insufficiency, and one had been rehabilitated after a myocardial infarction eight years earlier. We found three cases with anamnestic viral infections during the final days before the race.

Mortality comparisons with the general population

The mortality rate while skiing was 2.6 deaths per million person-hours, i.e., one death per 53 700 starters in the races. The expected number of deaths was 1.68, yielding an SMR of 7.7 (95% CI 4.1–13.2) (Table 7). Correspondingly, we observed 12 deaths due to cardiovascular disease vs 0.54 expected, resulting in an SMR of 22.1 (95% CI 11.4–38.6). Increased SMRs were observed for long as well as short races. The expected number of deaths in women was 0.34, partly reflecting the facts that the women were fewer in numbers, too small for reliable analysis.

Table 6. Characteristics of subjects who died during the race in Vasaloppet week competitions during the period 1970-2005

| CM/CA | Age | Race/ order | BMI (kg/m ²) | Tobacco use | Degree of exercise | Skied until collapsed | Known chronic diseases or acute sickness before the race (medication) | Heridity for CVD | Cause of death (identified by autopsy) |
|-------------|-----|--------------------|-----------------------------|--|---|--------------------------|--|---|--|
| -3.0/-1.7 | 54 | VL 1st | 23.2 | Smoked pipe and cigar daily | Jogging every week | 2 km | No signs of CVD (no medication) | Mother (75) died heart disease, son (40) treated with PCI. Daughter treated for high cholesterol value | CHD gravis (Yes) |
| -3.0/-1.7 | 52 | VL 10th | 27.9 | Non-smoker | Jogging and cycling every week | At start | Hypertension (Yes) | Son (49) treated for hypertension and with PCI | Stroke (typical clinical picture) (No) |
| -18.2/-9.1 | 59 | VL 9th | 25.3 | Non-smoker | Exercised several times a week | 62 km | No signs of CVD. Upper respiratory infection the week before the race (No) | Not known | MI, CHD (Yes) |
| -21.8/-7.1 | 54 | VL 4th | 26.1 | Non-smoker | Exercised 2-3 times a week | 2 km | Hypertension (Yes) | Fathers diabetes and heart attack, mother (75) stroke | MI, CHD (Yes) |
| -1.0/0.8 | 63 | VL 10th | 23.6 | Former-smoker (Quit at age 50) | Exercised almost every day | 300 m | Had cold but felt hale days before the race. Underwent cardiovascular examination the day before the race (No) | No history of CVD among parents. Uncle (60) MI | CHD and myocardfibrosis (Yes) |
| -16.4/-9.6 | 72 | ÖS 10th | 25.3 | Smoker, had been decreased number of cigar | Exercised regularly | At start | Angina Pectoris, hypertension and renal insufficiency (Yes) | No history of CVD among parents | MI, CHD (No) |
| -21.8/-11.9 | 48 | ÖS 6th | 22.6 | Smoker, daily | Jogging every week | 74 km | Common cold close to the race. (No) | No | Myocarditis + ulcer in coronary artery (Yes) |
| /1.6 | 58 | KV 1st | 24.9 | Former smoker (Quit at age 40) | Exercised two times a week | 15 km | Intensive MI 8 years earlier (Yes) | Mother (35-40) died caused by probably CVD | MI, CHD (Yes) |
| -5.8/-5.8 | 40 | VL 1st | 23.1 | Non-smoker | Physical exercise and jogging every week | 26 km | Working-ECG previous to race showed no abnormalities (No) | No | Hyperthrophic cardiomyopathy (Yes) |
| /-12.6 | 66 | KV 12th (VL 11) | 31.0 | Non-smoker | Very active during a long period, but less active last years | 24 km | Healthy, but had experienced chest pain for 6-8 years before decease (No) | No | Hyperthrophy and fibrosis caused by an old MI, CHD (Yes) |
| -21.0/-7.4 | 61 | VL 1st | 20.9 | Non-smoker | Exercised once a week and was well prepared to the race | 62 km | Somewhat high cholesterol value treated by diet. (No) | No | Fibrosis caused by previous MI, CHD. (Yes) |
| -16.8/-5.6 | 67 | VL 6th | 24.2 | Smoker | Exercised many times a week | 48 km | Healthy. (No) | No | Hyperthrophic cardiomyopathy and emphysema (Yes) |
| -16.8/-5.6 | 30 | VL 1st | 23.9 | Non-smoker | Exercised 5 days a week | 70 km | Healthy (No) | No | CHD, old and new MI (Yes) |

VL, Vasaloppet 50 km; ÖS, Öppet spår 90; KV, Kort/Vasan 30 km. CVD, cardiovascular disease; MI, myocardial infarction; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CM/CA, morning and average temperature during the race. The mean of the temperature measured as daily averages was -4.8 °C and the mean of the morning temperatures was -9.6 °C.

Table 7. Standardized mortality ratio (SMR) and 95% confidence intervals (CI) of death during the race among participants in Vasaloppet week during the period 1970-2005.

| | All causes | | | | | Cardiovascular diseases | | | | |
|---------------------------|-------------------|-----|------|------|----------|--------------------------------|------|------|-----------|--|
| | Py | Obs | Exp | SMR | 95% CI | Obs | Exp | SMR | 95% CI | |
| All | 581 | 13 | 1.68 | 7.7 | 4.1–13.2 | 12 | 0.54 | 22.1 | 11.4–38.6 | |
| Age (years) | | | | | | | | | | |
| –40 | 341 | 1 | 0.29 | 3.5 | 0.1–19.5 | 1 | 0.03 | 28.7 | 0.7–159.9 | |
| 41–50 | 143 | 2 | 0.39 | 5.2 | 0.6–18.6 | 2 | 0.10 | 20.5 | 2.5–74.2 | |
| 51–60 | 75 | 5 | 0.48 | 10.5 | 3.4–24.5 | 4 | 0.16 | 24.5 | 6.7–62.7 | |
| 61–70 | 19 | 4 | 0.37 | 10.9 | 3.0–28.0 | 4 | 0.16 | 24.5 | 6.7–62.7 | |
| >70 | 3 | 1 | 0.16 | 6.1 | 0.2–34.1 | 1 | 0.08 | 11.9 | 0.3–66.3 | |
| Gender | | | | | | | | | | |
| Male | 465 | 13 | 1.34 | 9.7 | 5.2–16.5 | 12 | 0.43 | 27.9 | 14.4–48.7 | |
| Female | 116 | 0 | 0.34 | | 0.0–10.9 | 0 | 0.11 | | 0.0–33.5 | |
| Race distance (km) | | | | | | | | | | |
| 90 | 521 | 11 | 1.51 | 7.3 | 3.2–12.2 | 10 | 0.49 | 22.6 | 9.8–37.7 | |
| 30 and 45 | 60 | 2 | 0.17 | 11.5 | 1.4–41.4 | 2 | 0.06 | 35.4 | 4.3–127.9 | |

Py=Personyears Obs=Observed Exp=Expected

Cardiac Arrest in a Long-Distance Ski Race (Vasaloppet) in Sweden. (Paper II)

Over 90 years of racing, 20 cases (mean age 55 years) of cardiac arrest (CA) occurred, five of whom survived the acute event (mean age 47 years). All cases were men, and had the support of bystander cardiopulmonary resuscitation (CPR). Coronary heart disease was the cause for 16 skiers, two had hypertrophic cardiomyopathy, one had myocarditis and one had ventricular fibrillation of unknown cause.

The incidence proportion of CA was 2.16 per 100 000 skiers. The incidence rate was 0.31 per 100 000 skiing hours. The incidence rate was 0.46 per 100 000 racing hours in the past decade compared with 0.22 per 100 000 hours of skiing from 1922 to 2000.

The mean distance until CA occurred was 25.7 +/- 15.8 km (95% CI: 6 - 45) for the survivors, and the distance for non-survivors was 33.6 +/- 29.8 km (95% CI 17-50).

The absolute risk of CA during the ski race is low. Nevertheless, the relative risk seems to be much higher than expected, considering the incidence in the race (4 030 per 100 000 person-years of skiing) compared with the normal out-of-hospital CA rate (range 13-52 by region per 100 000 person-years) in the general Swedish population.

Comparison between marathon runners and Vasaloppet skiers:

The risk for CA with vigorous physical activity was very similar per 100 000 hours, 0.20 for long-distance runners and 0.31 for long-distance skiers. However, the timing of the occurrence was different. Although CA occurred mainly during the last quarter for runners, it occurred mainly in the first third of the ski race. That may indicate different types of athletes, different age, different trigger mechanisms for the induction of CA in different sports and perhaps different temperatures.

A striking similarity between the running and the ski races was that the fatality rates were 75% and 71% respectively, despite the 10-year higher mean age of the skiers.

Cancer incidence in participants in a long-distance ski race (Vasaloppet, Sweden) compared to the background population. (Paper III)

The relative reduction of invasive cancers associated with participation in the Vasaloppet was six percent (HR 0.94 (95%CI 0.91-0.98)) rising to 14% when prostate cancer was excluded. Prostate cancer was more common among Vasaloppet skiers, as was skin cancer and malignant melanomas. There was an 18 % relative reduction of cancers related to physical activity, diet and bodyweight and a marked reduction in cancers related to smoking, e.g. 70% relative reduction in the incidence of lung cancer. When cancers related to smoking and other lifestyle factors were combined, there was a 32% relative risk reduction (HR 0.68 (95%CI 0.63-0.72)).

Table 8 shows events of cancer per 1000 person years and hazard ratios (HR) for Vasaloppet skiers compared to non-participants derived from Cox proportional hazards models at a median of 9.8 years follow up. The table give first the picture of risk for all invasive cancer and after that the four large groups of cancer (prostate, breast, colon and lung). Last is cancers related to lifestyle.

Table 8

| Cancer site and cancer groups | No. of cancers per 1000 person-years | | Univariate Cox model | | |
|--|--------------------------------------|------------|----------------------|-------------|----------|
| | Skiers | Non-skiers | HR | (95% CI) | <i>p</i> |
| All invasive cancers | 3.31 | 3.48 | 0.94 | (0.91-0.98) | 0.001 |
| All invasive cancers (excluding prostate cancer) | 2.35 | 2.73 | 0.86 | (0.82–0.89) | <0.001 |
| Prostate cancer | 1.51 | 1.22 | 1.22 | (1.13–1.30) | <0.001 |
| Premenopausal breast cancer | 0.82 | 0.80 | 1.02 | (0.88–1.19) | 0.774 |
| Postmenopausal breast cancer | 2.57 | 2.64 | 0.97 | (0.86–1.11) | 0.688 |
| Colon cancer | 0.16 | 0.20 | 0.81 | (0.69–0.94) | 0.007 |
| Lung cancer | 0.07 | 0.23 | 0.30 | (0.24–0.36) | <0.001 |
| Cancers related to tobacco smoking | 0.22 | 0.50 | 0.44 | (0.39–0.50) | <0.001 |

| Cancer site and cancer groups | No. of cancers per 1000 person-years | | Univariate Cox model | | |
|--|--------------------------------------|------------|----------------------|-------------|----------|
| | Skiers | Non-skiers | HR | (95% CI) | <i>p</i> |
| Cancer with relation to lifestyle with physical activity, normal weight, diet with fruits and vegetables | 0.60 | 0.72 | 0.82 | (0.76–0.89) | <0.001 |
| Cancers related to tobacco smoking or cancer with relation to lifestyle with physical activity, normal weight, diet with fruits and vegetables | 0.81 | 1.18 | 0.68 | (0.63–0.72) | <0.001 |
| Cancers where exposure to sunlight is important (out-door activities) | 0.43 | 0.31 | 1.38 | (1.24–1.54) | <0.001 |

Exposed: Vasaloppet skier. Unexposed: Non-participants, matched individuals from the Swedish population of same gender, age and county of residence. 95% CI: 95% confidence interval

Net probability of death and invasive cancer, figure 15-19

We estimated net probability for death and for invasive cancer to illustrate the absolute risks and the pattern over time. The probability of death from any cause, even after 20 years, was low but about twice as high among the controls during the follow-up. The net probability of any invasive cancer event was also low, but similar among Vasaloppet skiers and controls. Due to the difference in death rates, we also compared the results of net probability against those of crude probability the results were virtually equal, which was true for all cancer groups.

We showed graphically the net probabilities by etiology group. As expected, for cancers related to tobacco smoking (Fig 15) the pattern is similar to that of lung cancer. For cancers related to diet, being overweight and physical activity, the net probability begins to differ early between Vasaloppet skiers and controls, but increases modestly over time to 1.6 and 1.8% respectively at 20

years (Fig 16). When this analysis was repeated by finishing time, dividing the skiers into three performance groups (from very high performance with 100-150% of the winner's finishing time to performance groups of 151-200% and more than 200% of the winner's finishing time), a dose-response pattern was seen. The net probability for the lowest performance group was similar to that of the controls. (Fig 17). Cancers in colon showed a distinct difference between skiers and controls that was increasing over years (Fig 18). Cancers related to outdoor activities had a higher net probability of occurring among the Vasaloppet skiers (Fig 19).

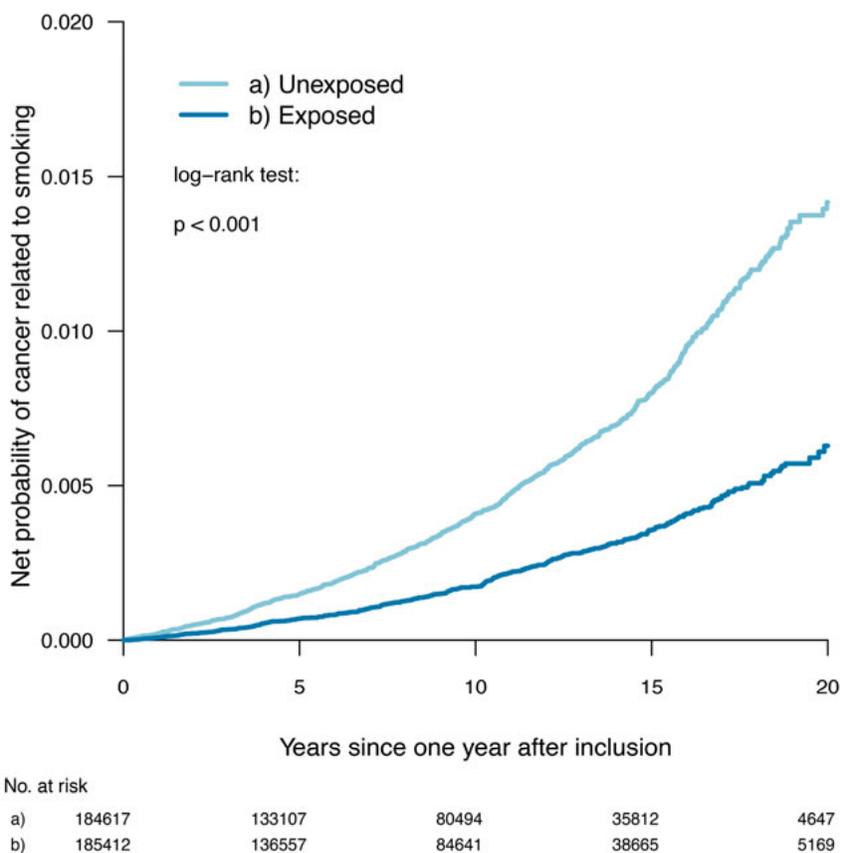


Figure 15. Net probability of cancers related to smoking.

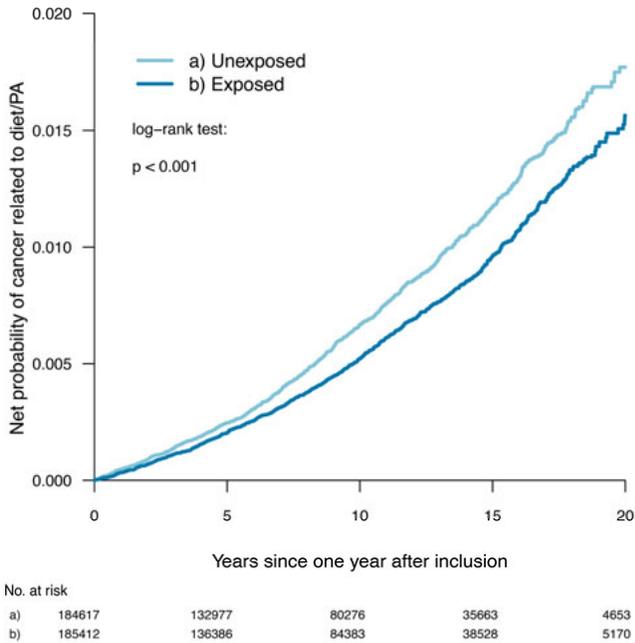


Figure 16. Net probability of cancers related to diet, weight and physical activity.

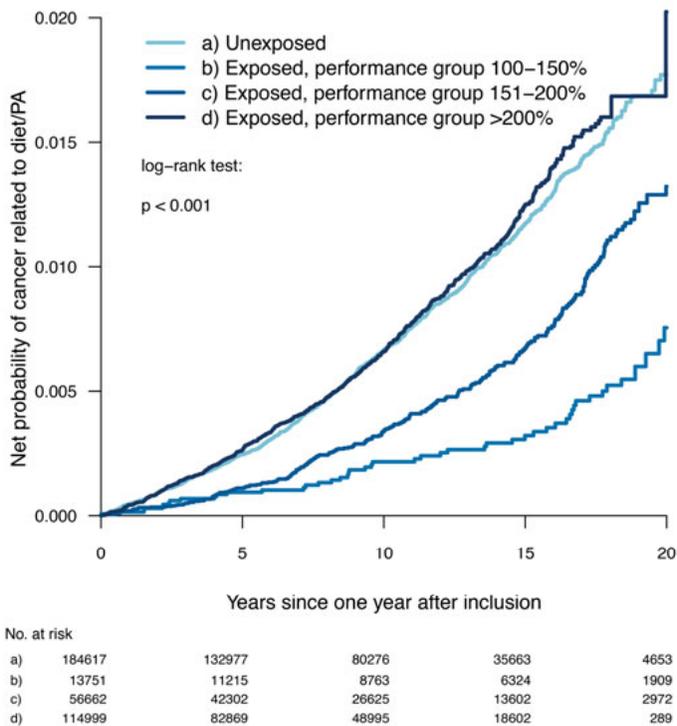


Figure 17. Net probability of cancers related to diet, weight and physical activity, divided into three performance groups.

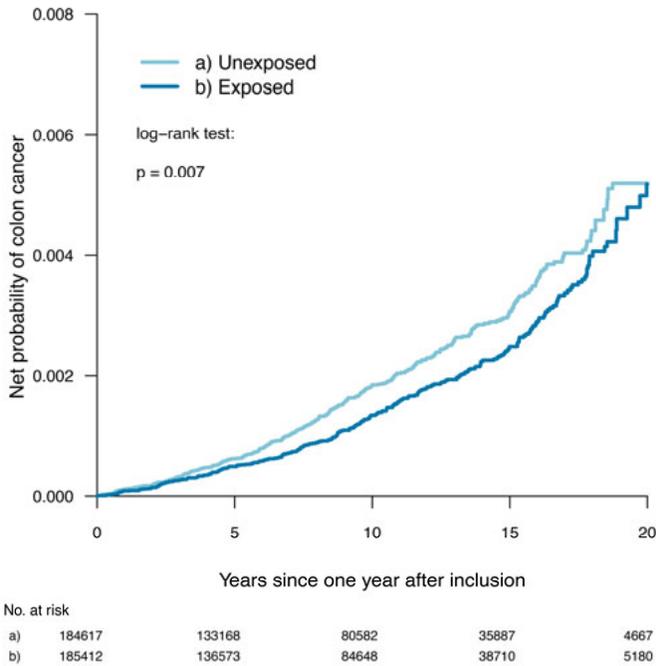


Figure 18. Net probability Colon cancer

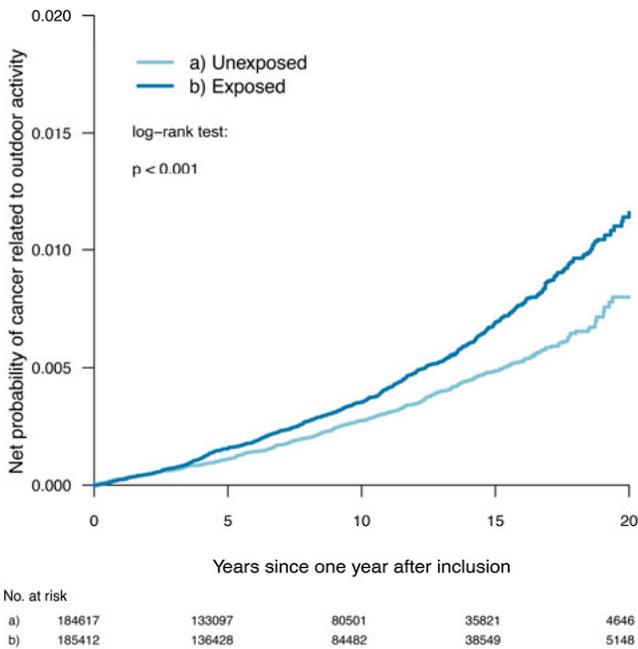


Figure 19. Net probability to cancers related to out-door activity

Different cancer risk between men and women? Stratified analysis.

We explored whether the association between Vasaloppet participation and cancer risk was modified by year of first participation, gender, age at first participation, educational level, employment status or Charlson comorbidity index. The only indication of an interaction that was not random was for gender in cancers related to physical activity and weight/diet: Hazard ratio (HR) for women was 0.92 and for men 0.70, which was significant, $P=0.002$. . After exclusion of breast cancer, the HR was lowered to 0.80 for women and a test of interaction was no longer statistically significant ($p=0.218$).

Risk of Recurrent Ischemic Events after Myocardial Infarction in Long-Distance Ski Race Participants. (Paper IV)

The incidence rate of all cause deaths or myocardial infarction (MI) was 3.9% among skiers and 5.6% among non-skiers. Total number of these events was 1 515. Hazard ratio (HR) for recurrent MI (re-MI) or death between the two groups was 0.70 (95% CI 0.59-0.82) (Table 9). After adjustment for smoking and socioeconomic factors, the HR was 0.73 (95%, CI 0.61-0.87). After adjustment for clinical risk factors for MI and discharge treatment, the HR was 0.80 (95%, CI 0.67-0.97). The result was consistent in subgroups.

The incidence rate for re-MI of 2.0% for skiers and 3.0% for non-skiers. Unadjusted HR between groups for re-MI was 0.66 (95%, CI 0.52-0.82) and with adjustment for possible confounders, the HR rose to 0.76 (95%, CI 0.59-0.98) (Table 9).

We studied the dose-response relationship the hazard ratio was the same for both groups when adjustments were made for age and gender.

Table 9. Events (incidence rates) and unadjusted and adjusted hazard ratios

| | Non-skiers | Skiers | HR | Adj HR** | Adj HR*** |
|----------------------------|------------------|---------------|----------------------|----------------------|----------------------|
| | Events py*(%) | Events py*(%) | [95% C.I.] | [95% C.I.] | [95% C.I.] |
| Death /re- MI | 1352 (5.6) | 163 (3.9) | 0.70 [0.59,0.82] | 0.73 [0.61, 0.87] | 0.80 [0.67, 0.97] |
| CV death /re-MI | 951 (3.9) | 116 (2.8) | 0.71 [0.58, 0.86] | 0.73 [0.59, 0.90] | 0.78 [0.62, 0.97] |
| CV death | 801 (3.0) | 98 (2.2) | 0.73 [0.59, 0.90] | 0.74 [0.58, 0.94] | 0.87 [0.68, 1.11] |
| Re-MI | 300 (1.1) | 40 (0.9) | 0.79 [0.57, 1.09] | 0.78 [0.53, 1.15] | 0.79 [0.51, 1.21] |
| | 722 (3.0) | 82 (2.0) | 0.66 [0.52, 0.82] | 0.68 [0.53, 0.87] | 0.76 [0.59, 0.98] |

* Incidence rate per 100 person-years. ** Adjusted for age, gender, year of MI, educational, family and occupational status and smoking. *** Adjusted for age, gender, year of MI, educational, family and occupational status, smoking, hypertension, diabetes, discharge beta blockers and discharge diuretics.

Skiers: the participants in the Vasaloppet. Non-skiers: population-based controls with the same age, gender and county of residence. MI = myocardial infarction. Re-MI = Recurrent MI. CV = cardiovascular.

Risk of Recurrent Stroke and Death after First Stroke in Long Distance Ski Race Participants. (Paper V)

Among the baseline data we noticed that non-skiers in first stroke experienced worse health, more depression, had worse ADL functions and were taking more pharmaceutical agents for prevention of cardiovascular diseases. However, warfarin was prescribed more frequently to the skiers, who also had more atrial fibrillation.

The incidence rate for of all-cause deaths or re-stroke was 8.3 per 100 person-years among skiers and 11.1 among non-skiers. Total number of these events was 2 047. The hazard ratio (HR) for re-stroke or death between the two groups was 0.76 (95% CI: 0.67-0.86). The result was consistent in subgroups. The HR for death was 0.66 (95% CI: 0.56-0.78) and for re-stroke 0.82 (95% CI: 0.70-0.96) (Table 10). After adjustment for smoking and socioeconomic factors, the HR for death was consistently 0.70 (95% CI: 0.56- 0.87) while the risk for re-stroke was not significant, 1.02 (95% CI: 0.84- 1.24).

Table 10 Events (incidence rates) and unadjusted and adjusted hazard ratios with corresponding 95% confidence intervals. Analysis is based on 4 614 cases with non-missing data.

| | Non-skiers | Skiers | HR | Adj HR** | Adj HR*** |
|---------------------------|--------------------------|--------------------------|----------------------|----------------------|----------------------|
| | Events py*(%) | Events py*(%) | [95% C.I.] | [95% C.I.] | [95% C.I.] |
| Death | 1 089 (5.8) | 163 (3.8) | 0.66 [0.56, 0.78] | 0.71 [0.57, 0.88] | 0.70 [0.56, 0.87] |
| Death/Re-stroke | 1 744 (11.1) | 303 (8.3) | 0.76 [0.67, 0.86] | 0.86 [0.74, 1.00] | 0.88 [0.75, 1.03] |
| Death/Re-stroke/MI | 1 825 (11.9) | 323 (9.0) | 0.77 [0.69, 0.87] | 0.88 [0.76, 1.02] | 0.91 [0.78, 1.05] |
| Re-stroke | 941 (6.0) | 177 (4.8) | 0.82 [0.70, 0.96] | 0.96 [0.79, 1.17] | 1.02 [0.84, 1.24] |
| MI | 261 (1.4) | 203 (1.0) | 0.69 [0.50, 0.96] | 0.74 [0.47, 1.15] | 0.85 [0.54, 1.33] |
| Re-Stroke/MI | 1 086 (7.1) | 177 (5.6) | 0.81 [0.70, 0.94] | 0.95 [0.79, 1.14] | 1.02 [0.85, 1.23] |

* Incidence rate per 100 person-years. ** Adjusted for age, gender, education, family and occupation status, and smoking. *** Adjusted for age, gender, education, family and occupation status, smoking, hypertension, and diabetes. Skiers: the participants in the Vasaloppet. Non-skiers: population-based controls with the same age, gender and same county of residence. Re-stroke: recurrent stroke. MI: Myocardial Infarction.

Atrial fibrillation

Atrial fibrillation (AF) was more common among skiers compared with non-skiers, 20.4% and 14.7% respectively, $p < 0.0011$. However skiers still had a lower incidence rate of re-stroke compared with the age-matched population. Skiers, with and without AF, had a lower risk of the composite of death or recurrent stroke compared with non-skiers. (Figure 20)

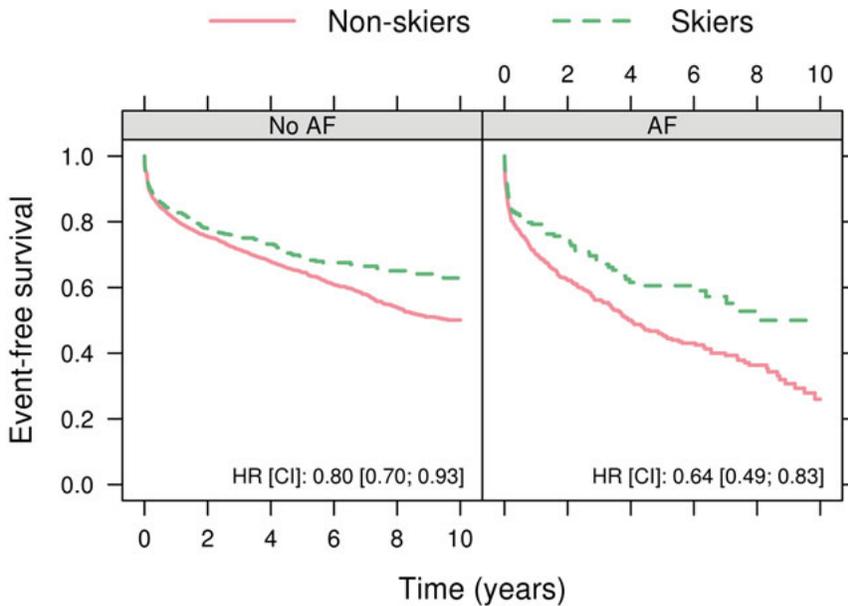


Figure 20. Stroke-free survival with unadjusted hazard ratios (HR) and corresponding 95% confidence interval (CI) for subjects with and without atrial fibrillation (AF).

Skiers: Participants of Vasaloppet. Non-skiers: Population based controls with the same age, gender och same county residence.

Dose-response

We also studied the dose-response relationship with the finish time in relation to the winner's time, as a proxy measure of physical fitness and training intensity in a separate model shown in Figure 21. Overall there was an association showing a lower risk for death and re-stroke for skiers with better performance. However, there appeared to be a gender difference with a more obvious association between race time and outcome for women.

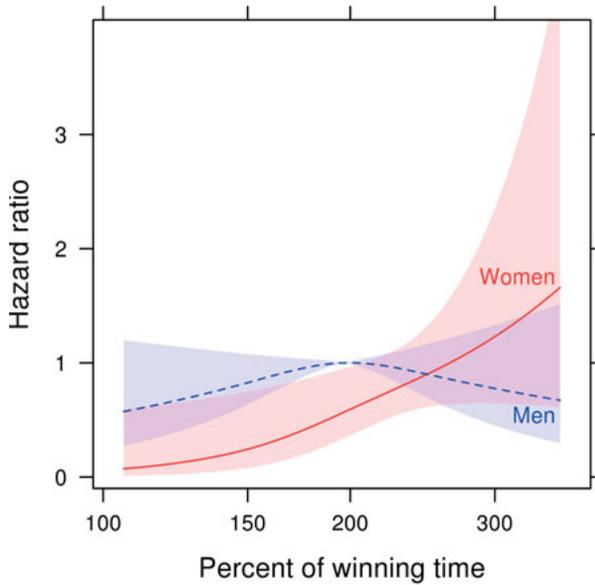


Figure 21. Estimated hazard of death or Stroke vs. race time adjusted for age. The overall median relative race time (197%) and male gender is set at the reference. Note the log scale.

Discussion

Main findings

Risks for Cardiac Arrest and Sudden Death (Papers I and II)

We observed a marked increase in acute mortality during the long-distance ski races during the Vasaloppet week from 1922 to 2010: thirteen deaths in the study in 2007 and twenty cardiac arrests in the study 2010 of which five survived. The women seem to have a lower risk. Had the risk been the same, we would have expected three to four women among the deaths. Acute mortality during sports activity is reported, but not often compared with reference populations^{176,177}. Death rates during sports events are higher than at other times^{178,179}. The comparison in our sudden death study yields an SMR of 7.7. When we compare with data from marathon running¹¹⁵, cardiac arrests are close to the Vasaloppet figures per 100 000 competition hours: 0.3 in skiing and 0.2 in running. The absolute risk is very low, occurring in about one per 50 000 starters in ski races. All deaths occurred in men and most were among those between 51 and 70 years of age. Cardiovascular disease was almost exclusively the cause of the deaths and all but one (stroke) were due either to myocarditis, hypertrophic cardiomyopathy, or myocardial infarction. The marathon runners¹¹⁵ are ten years younger on average and often have hypertrophic cardiomyopathies as the cause. In marathons, most of the events happened in the last quarter of the race, while in skiing most deaths occur during the first third of the track.

Incidence of Cancer (Paper III)

In our 350 000 study subjects with more than 12 800 cancers during the median ten-year follow-up, we found a small overall reduction of cancer incidence following participation in a challenging long-distance cross-country ski race. However, the relative reduction of cancer incidence was 32% for cancers where lifestyle is presumed to have a protective effect, which includes 29% of all cancer events in the cohort. Interestingly, we found a dose-response relationship: skiers with higher performance had a lower cancer incidence than skiers with lower fitness. Male skiers had a clearer inverse association with the occurrence of lifestyle cancers than women, a difference that was not as clear when breast cancer as an event was excluded.

The overall cancer reduction is also hampered by the increased incidence of cancers related to sunlight exposure among Vasaloppet skiers, probably due to the fact that the most physically active groups are more often engaged in outdoor activities.

Risk of Recurrent Ischemic Events after Myocardial Infarction (Paper IV)

The main finding was that MI patients who had been physically active (as evidenced by their participation in a long distance cross-country ski race) were associated with a 30% lower relative risk reduction of re-MI and all-cause death compared with non-skiers, less physically active patients. This difference was not explained by the severity of the first MI. After adjustment for confounders like socioeconomic data and smoking, the correlation remained essentially unchanged.

Risk of Recurrent Stroke and Death after First Stroke (Paper V)

The main result was that the risk for recurrent stroke was the same among skiers as among non-skiers. However we found that skiers seemed to have a less severe stroke than non-skiers. However it was obvious that there was an association with lower risk for death among the skiers, this despite the skiers had an increased number of atrial fibrillation.

Specific items in relation to papers I-V

Sudden death and cardiac arrest

The excess risks that we observed in the current study based on a group of predominantly well-trained subjects are well in agreement with what others have reported and clearly confirm the existence of an increased mortality in connection with intense physical activity¹⁷⁶⁻¹⁸⁰. Corresponding results in joggers in the United States and runners of various distances in Switzerland were reported to be 7- and 50-fold respectively. In a study of long-distance skiing, a fivefold increased risk of death was found compared with the general population in Finland. Previous studies indicate an increased risk during high physical activity that is even higher in less fit people. Myocardial infarction can be triggered by physical exertion and particularly so among the less fit¹⁸¹. One could speculate that the first minutes of skiing imply a strong stress-related impact both psychologically and physiologically, especially in those starting without warming up.

Cancer incidence

The result that a reduction of just 6% in relative terms of *all invasive cancers* was associated with Vasaloppet participation was disappointing in the light of expectations of the preventive effects of lifestyle changes²⁸. For example, lifestyle was estimated to account for 26% of all cancers in a European study (skin cancer and melanoma excluded)¹²⁷.

Our data indicate that abstaining from smoking is an important component of the preventive effect of a lifestyle associated with high degree of physical activity.

The evidence that physical activity is protective is convincing for colon but less for rectal cancer. Physical activity has been associated with up to a 30% reduction in risk^{39, 138, 139} with a dose-response relationship¹³⁸. Our data show a temporal pattern for colorectal cancer that differs from the overall pattern. The explanation is not clear and may be an interesting field for further exploration. Alcohol intake and diet is of interest to take into account.

Access to health care and participation in screening may also contribute to a low overall estimate of cancer risk reduction. A healthier lifestyle is associated with higher participation in prostate specific antigen (PSA) testing¹³⁴ and mammography screening¹⁸² where long lead times and over-diagnosis - especially for prostate cancer introduce a diagnostic bias. Prostate cancer increased dramatically between 1988 and 2002 in Sweden largely because of screening with PSA in men without symptoms. A review¹³⁵ suggests only a weak inverse association between physical activity and prostate cancer which is not likely to annihilate the increased incidence by screening. For breast cancer the call is closer: current estimates of over-diagnosis in overview of all breast cancer screening trials suggest 10-15%¹⁸², which may partly cancel out the effects of physical activity, e.g. a 25% risk reduction comparing the most physically active to the least active women in a review¹³⁶. The Swedish population-based and nation-wide mammography program and a higher participation rate among the health conscious may be the explanation why our results for breast cancer differ from other studies. This is further supported by the disappearance of the interaction for gender and the similar result in men and women when breast cancer was excluded.

Genetics and heritability

One alternative explanation for the results is that the Vasaloppet skiers have a genetic predisposition, an inherited lower risk for cancer, myocardial infarction and stroke, and that consequently our material is selective. Physical activity itself can have a background in genetic disposition⁵⁹. Parent-offspring studies have confirmed a significant familial influence on physical activity. Twin studies conclude that genetic factors are important^{59, 183 58}. On the other hand, another author believes that the environment has a greater influence¹⁸⁴.

However, persistent participation in leisure-time physical activity is associated with a clinically significant decreased rate of weight gain and a smaller waist circumference even after partially controlling for genetic liability and childhood influences. A large proportion of the participants have not reached the age when cancer is common. Cancer heritability that may override cancer prevention by lifestyle modifications is probably more common in younger cohorts, which in this study may mask some of the potentially protective effects of physical activity.

The biological age, that is probably genetic, may also be involved in discussing physical activity and health.

Comparison with the literature

Recurrent myocardial infarction

Few have studied physical activity prior to an MI in relation to the risk of suffering a re-MI. Gerber et al.¹⁸⁵ did not show a lower risk for re-MI in more physically active persons but the study was limited by the absence of other lifestyle components. Our results are supported by a study by Apullan et al.¹⁸⁶ with coronary heart disease material and a study by Pitsavos et al.¹⁸⁷ with its cross-sectional design comparing active and less active coronary patients.

Recurrent stroke

Physically fit or active people have a lower incidence of stroke and stroke-related deaths¹⁸⁸. However, to our knowledge there are no prior reports regarding the benefits of physical activity prior to a stroke in relation to the risk of suffering a recurrent stroke. Nor are we aware of any studies reporting that individuals with a high level of physical activity suffer a less severe stroke than less physically active individuals. Our finding that 15% of stroke events are due to atrial fibrillation is similar to the estimates from a previous study¹⁵⁹.

Potential mechanisms

Physical activity

The level of physical activity, for the majority of Vasaloppet skiers, is at least 20 MET-h weekly. Earlier studies related to Vasaloppet skiers support physically active people have a lower incidence of death, myocardial infarction and stroke¹⁸⁹⁻¹⁹⁴. Many cohort studies have supported those findings both in primary prevention^{190, 192, 195-197} and other studies^{1, 3, 164, 198}. A more detailed study from 2014 can show a differentiated picture with a J-shaped association, where the most fit were worse set¹⁹⁹.

It is known that physical activity after Myocardial Infarction, secondary prevention lowers the risk for recurrent myocardial infarction ^{185,200}. Physical activity results in a similar level of risk reduction as secondary prevention with pharmaceutical agents ²⁰¹.

Fitness

The level of fitness for a majority of skiers may be VO₂ max more than 40. A higher fitness level may according the literature lead to a protective effect against developing atherosclerosis, better in cerebral vessels compared with coronary arteries ¹⁴³. We did not find a positive relationship between better performance (shorter finish times) and better outcome to reduce risk for recurrent myocardial infarction or death (Paper IV) ²⁰², which we found for recurrent stroke or death (Paper V). Our experience can contribute to the results and discussion in William's ¹⁴³ meta-analyses that concludes that increased fitness was better to decrease risk for events than physical activity.

Possible mediating factors

We know that various cardiovascular risk factors have a different impact on the different cardiovascular outcomes and it is likely that the benefits of physical activity are also different. The potential mediating mechanisms for physical activity and a lower risk for cardiovascular events have been studied in a large cohort study ²⁰³. Inflammatory/hemostatic biomarkers made the largest contribution to lower risk followed by blood pressure, lipids, body mass index and hemoglobin A1c/diabetes. The cause is probably a lower incidence of the metabolic syndrome. This mechanism makes hypertension and diabetes a part of the myocardial infarction or ischemic stroke, and thus they should not be considered as confounders.

Even if adjustment in our studies are done it is important to complain the big difference in education och socioeconomic factors that are different among skiers and non-skiers in the cohort. We can not only see this factors belonging to a positive lifestyle. However a good education can also contribute to stress and e.g. lack of influence on the working place and therefore be a negative lifestyle factor and increase risk for cardiovascular disease.

Atrial fibrillation

In our cohort, the non-skiers had a 14.7% incidence of AF, while skiers had 20.4% ($p < 0.0011$), regardless of age correlation. The prevalence of AF as a risk factor for stroke has been highlighted in a study in which AF increased the risk of stroke five-fold and caused 15% of all strokes ¹⁵⁹. There was a strong relationship between age and AF in stroke as shown in the Swedish

Stroke Register where rates range from 10% in stroke patients below the age of 65 years to 40% in those above the age of 80 ²⁰⁴.

There is evidence from other publications that people who practice strenuous sports ²⁰⁵ have a higher proportion of AF than is found in the general population. However in our fit population we found less severe strokes among skiers with AF. Thus, physically active people appear to suffer fewer strokes despite more AF. The explanation for this finding can only be speculated. In the Swedish context we do not think it results from differences in the quality of anticoagulant therapy ²⁰⁶. There might be a lower incidence of concomitant diseases or structural cardiac changes among skiers, factors that reduce their risk for thromboembolic stroke. People with a high level of physical activity are likely to have a low CHADS₂ (Congestive heart failure, Hypertension, Age \geq 75 years, Diabetes, previous Stroke)/CHA₂DS₂-VASc (Vascular disease, Age 65-74 years, Sex category) score, with a low stroke risk. CHA₂DS₂-VASc grade 0 in a patient with AF is associated with less than one percent annual risk for stroke ²⁰⁷. This fact, in addition to a generally lower risk of cardiovascular events, may explain the trend in our study (Figure 20) that skiers have fewer strokes, even if they have a higher frequency of AF. One question is whether recommendations can be made that minimize risk of AF? Can further research find identifiable limits in endurance training depending on age, gender and other factors? Can it be a difference between groups of young athletes compared to leisure time middle-aged older people practicing physical training?

The question is also whether the prognosis for stroke in athletes with “lone” AF is better than for others. Perhaps the indications for anticoagulant therapy have to be different in this group?

Strengths and limitations

The strengths of our studies were the large number of participants and the complete record of follow-up with information on all severe medical incidents. Our study included a larger population of physically active people than most previous studies and a matched population not exposed to the long-distance ski race, the Vasaloppet. This was possible thanks to the individual personal identification number of each ski race participant and the national registries in Sweden.

We were unable to differentiate whether the lifestyle associated with skiing rather than physical exercise, physical fitness or other mechanisms may be a reason for the results.

We have defined three kinds of stroke as one group; ischemic, hemorrhagic and non-specific stroke. The consequences of ischemic strokes may therefore be diluted. We are unaware of the physical activity of each study participant among the skiers and non-skiers. Therefore we cannot isolate the physical activity factor and sedentary time from other factors related to a healthy lifestyle.

Conclusions

Paper I:

There is a clearly increased risk of acute mortality during long-distance skiing as in other endurance sports. However, as physically active people spend only a minority of their time in races, in that population the short-term excess mortality during these periods is by far outweighed by the long-term protective effects on mortality. The extent to which this protection is due to physical activity, related lifestyle factors, genetics or selection bias is yet to be assessed.

Paper II:

The incidence of cardiac arrest during skiing has increased slightly in recent years but was very similar to long-distance running and is very low. Although cardiac arrest occurred mainly during the last quarter of the race for runners, it occurred mainly in the first third of the ski race. This may indicate different trigger mechanisms for the induction of cardiac arrest. Importantly, skiers have overall lower mortality compared to the general population and the overall benefit of regular physical activity to public health is larger than the risk.

Paper III:

Even though the risk of several severe forms of cancers was substantially lower in participants of long distance skiing races, the overall reduction of cancer incidence was modest. Of interest is that cancers incidence related to life style factors, including a high degree of physical activity, will markedly reduce the cancer incidence compared with the general population.

Paper IV:

Participants in long distance skiing races that suffer a myocardial infarction have a lower incidence of recurrent myocardial infarction compared to non-skiers despite similar severity of the initial myocardial infarction. Thus, our data suggest that a lifestyle with an increased physical activity may work as a protection against recurrent cardiovascular events.

Paper V:

Among patients with a first stroke, participants in long distance skiing races have a lower incidence of all-cause death but a similar incidence of recurrent stroke as non-skiers. Even though the skiers had a higher frequency of atrial fibrillation, they appeared to suffer less severe stroke and had no increased risk of recurrent stroke.

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Nils "Mora-Nisse" Karlsson (1917-2012) won Gold medal 50 km in Olympics 1948. He was a nine-fold winner of the Vasaloppet between 1943 and 1953. He was many years a leader and coach in sports. He wrote one part of a book about his life 1983 among other things: *"What I long have seen as the largest value of Vasaloppet is the big carrot to get people to keep going and keep themselves in good physical shape"*.²⁰⁸

Reflections and suggestions

Risks awareness

Despite cardiopulmonary resuscitation (CPR), the fatality rate is similar in marathons and the Vasaloppet, 75 and 71% respectively. Out-of-hospital fatality rates are often 90%. This shows the importance of bystander CPR and resources in the medical rescue team in mass sports events with heart starters (defibrillators) available.

Even if the mortality risk is higher during the races, the excess mortality is far outweighed by the long-term protective effect of exercise. Exercise training in itself acts as a preventive method.

Pre-event counselling for young athletes in schools and sport clubs can use international guidelines from sports cardiologists in an attempt to minimize sudden death among athletes.

It is also important to inform middle-aged and older exercise trainers to be aware of early cardiopulmonary symptoms and to make good preparations before competitive events. If they take cardiovascular medication or have any kind of symptoms, they should follow the event organizers' recommendations and consult their doctor before registering.

Research about endurance training and atrial fibrillation should be promoted to develop recommendations on how to train safely and prevent the complications of atrial fibrillation.

Possible further research of the Vasaloppet cohort

One planned project together with Lunds university is to study the most common neuropsychiatric disorders; Dementia, Parkinson's disease, Epilepsy, Meningitis/Encephalitis, Mental and behavioral disorders due to use of alcohol, Schizophrenia, Manic episodes, Bipolar disorder, Depressive episodes, Anxiety disorders in relation to Vasaloppet life style including physical activity.

The Vasaloppet cohort and relation to health registers gives possibility to study the use of antibiotic drugs the weeks after the races in comparison with the non-skiers. The question is if there is an increased sensibility to infections the weeks after 90 Km skiing.

Another activity is studies of exercise-induced asthma together with Umeå University.

The result in the cancer incidence study can be followed of a comparison of mortality between skiers and non-skiers in the cancer diseases.

Prevention

It is important globally for society to diminish the burden of diseases that are preventable. There is a vast body of knowledge suggesting that a healthy lifestyle can prevent many of the diseases that are included in this thesis: cancer, myocardial infarction and stroke. The goals for families, schools, universities, sport clubs, working places, businesses, sports organizations, the medical community, media and politicians should be:

- - to establish good food habits, avoid being overweight and eat enough fruits and vegetables
- - to follow the age-related recommendations for levels of physical activity among the young, middle-aged and elderly
- - to promote research so that we can understand more deeply the mechanisms behind the activities we need to reach to get a healthy lifestyle for all.

Summary in Swedish

Syftet med avhandlingen har varit att belysa risker och hälso nytta med en hög grad av fysisk aktivitet. För att göra detta använde vi en fysiskt aktiv grupp, i detta fall vasaloppsåkare som vi jämförde med normalbefolkningen. Vasalöparna är fysiskt mycket aktiva men har därtill en högre grad av en hälsosam livsstil. De skiljer sig också mot andra genom en högre utbildningsnivå, lägre arbetslöshet och lägre andel som lever ensamma.

Vasaloppsåkarna har som grupp betraktat en hög konditionsnivå och en hälsa som gör det möjligt att genomföra ett skidlopp på 30, 45 eller 90 km. Men givetvis skiljer sig Vasaloppsåkarna i jämförelse med varandra både vad gäller prestation och övrigt. Eftersom åkarna är en stor grupp blir statistiska jämförelser med normalbefolkningen säkrare.

Utgångsmaterialet är mer än 200 000 åkare som vi matchade för ålder, kön och bostadsort mot 500 000 personer som ej genomfört något Vasalopp. För att undersöka sjukdomar och risker har vi använt patientregistret och kliniska kvalitetsregister i Sverige.

Avhandlingen har inledande avsnitt om forskningsläget inom de områden som berörs, utförliga uppgifter om metodik och register samt en övergripande beskrivning av Vasaloppet ur allmän och medicinsk synpunkt.

Epidemiologiska studier

Epidemiologiska studier innebär att studera och beskriva förekomst av sjukdomar och att göra observationer kring skillnader mellan olika grupper av människor. Metodiken innebär sällan möjligheter att med någon större säkerhet ge förklaringar till skillnader som man upptäcker. Däremot kan resultaten ge stöd till annan forskning och till fördjupande studier inom området. I denna avhandling har stora folksjukdomar behandlats; cancer, hjärtinfarkt och stroke. Cirka 75% av alla människor i västvärlden avlider till följd av dessa sjukdomar. Hälsförbättrande åtgärder inom dessa områden kan därför få ett genomslag i folkhälsan.

Hjärtstopp under tävlingen

Givetvis är riskerna med fysisk aktivitet och träning av vikt att väga in i relation till nyttan. I två delarbeten har dödligheten under genomförandet av loppet behandlats. I genomsnitt avlider två av 100 000 startande. En risk som

även kan anges som 0,3 dödsfall per 100 000 skidtimmar. I vasaloppsspåren har det under 90 år skett 20 fall av hjärtstopp, varav 15 avlidit. Orsaken är hjärtsjukdom, vanligen kranskärlssjukdom. Genom en beredskap för hjärt-lungräddning under tävlingen har en av fyra kunnat räddas. Medelåldern för de drabbade är 55 år.

Slutsats: Det innebär alltså en ökad risk för hjärtstopp i samband med fysisk ansträngning, men den risken är mycket liten jämfört med det långsiktiga skydd som träning medför för dödligheten.

Insjuknande i cancer

Under en genomsnittlig observationstid på 10 år har vi fångat upp insjuknanden i cancer. Vi identifierade 12 800 cancerfall hos skidåkarna och kontrollpersonerna. Vi valde att studera cancer inom fyra stora cancertyper dvs prostata, bröst, tjocktarm och lungor. Vi undersökte också cancer som annan forskning har ansetts ha samband med livsstil. De faktorer som då vägts in har varit tobaksrökning, fysisk aktivitet, kroppsvikt och intag av frukt och grönsaker. Positiva livsstilsfaktorer finns i högre grad hos Vasaloppsåkarna. Förmodad ökad utomhusvistelse hos vasalöparna ligger troligen bakom ökad förekomst av hudcancer.

Ett slående fynd var att cancer som påverkas av livsstil är 32% lägre i skidåkargruppen än i den allmänna befolkningen. Totalt sett är dock insjuknandet i cancer hos vasalöparna endast lätt sänkt. Vasaloppsåkare med bättre åktider visade sig ha lägre cancerrisk.

Slutsats: Dessa fynd innebär att allmänna rekommendation om fysisk aktivitet i viss grad skulle sänka den totala cancerrisken i samhället. För varje individ kan risken att insjukna i några av de vanliga cancertyperna minska genom träning, till exempel tjocktarmscancer.

Insjuknande i hjärt-kärlsjukdomar

Det är känt från många andra studier att fysiskt aktiva med ofta tillhörande positiv livsstil har ett lägre antal av hjärtinfarkter (blodpropp i hjärtats kranskärl) och stroke (blodpropp i hjärnans kärl eller hjärnblödning). Kunde de resultaten bekräftas av våra studier?

En viktig fråga när två grupper jämförs är om Vasaloppsgruppen är friskare pga. träning eller om det beror på att de som är kontroller i befolkningen inte kan åka Vasaloppet pga. sjukdom. För att försöka undvika att sjukdom påverkar resultatet tog vi bort alla med svåra sjukdomar.

En första hjärtinfarkt fann vi hos 1 039 personer i Vasaloppsmaterialet, vilket är ungefär hälften av motsvarande antal i befolkningen vid samma ålder och kön. Hjärtinfarkterna bland skidåkarna hade samma storlek och allvarlighetsgrad som de som inte var vasaloppsåkare.

Vår studie tog sikte på att i tio år följa upp den andel som fick ett återfall med en andra hjärtinfarkt. På det sättet kom frågan om urval delvis bort. Vi följde upp åkarna som fick en andra hjärtinfarkt. Resultatet blev att de som fick en andra hjärtinfarkt var en tredjedel färre bland skidåkarna än i befolkningen.

När det gäller stroke fanns 1 083 förstagsstroke bland skidåkarna i materialet, vilket var en tredjedel färre än motsvarande i befolkningen. Men för stroke noterade vi att de var lindrigare hos skidåkarna än hos de som inte var vasaloppsåkare.

När sedan statistiska beräkningar gjordes efter 10 års uppföljning för att se hur många som avlidit eller fått nytt stroke visade det sig att dödfallen var en tredjedel färre i Vasaloppsgruppen än i befolkningen, medan andelen med återfall i stroke var densamma bland skidåkarna och icke-skidåkarna. De tränade skidåkarna hade alltså en minskad andel som dog men de fick återfall i stroke i samma omfattning som den övriga befolkningen

Vi noterade att skidåkarna i samband med sin första stroke oftare hade förmaksflimmer. Förmaksflimmer är en av orsakerna till stroke, så man hade därför kunnat tänka sig fler andragångsinsjuknanden i stroke skulle ske hos skidåkarna.

Slutsats: Vår tolkning är att livsstilen och träningen som genomförts tidigare i livet utgör ett skydd mot en ny hjärtinfarkt efter den första. När det gäller stroke hade skidåkarna ett lindrigare första stroke, men inget skydd mot återfall i nytt stroke. En tredjedel av skidåkarna levde längre än de som ej var skidåkare.

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Two very important co-authors did a great job in the reports and discussions concerning the biostatistics and epidemiology that are behind all the figures and tables: Johan Lindbäck, Center for Clinical Research and Fredrik Sandin, Regional Cancer Center, both Uppsala.

From the beginning, much of the inspiration and help with the first paper came from Professor Anders Ahlbom and his team at the Institute of Environmental Medicine, Karolinska Institute, Stockholm. Professor Michail Tonkonogi and the Head of CKF Marianne Omne-Pontén, both Falun gave advice in starting the PhD studies.

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My thanks and thoughts go back to my forefathers who lived for hundreds of years along the Vasaloppet ski track in the villages of Sjurby, Oxberg and Gopshus. My grandfather Oscar and wife Christina arranged the soup station close to their shop in Oxberg from 1924 to 1930. My father Carl and uncles Holger and Albin, and aunts Selma and Barbro, had the track passing their garden. One other uncle, Rune, was the first employee in the Vasaloppet organization from 1967 to 1983. My grandmother Lovisa with my mother Ebba, her brother Carl-Fredrik and her sister Marianne also lived alongside the track close to their farm north in Oxberg. My brother Owe has been an enthusiastic Vasaloppet skier and fan. When Owe and I (six and eight years old) tried to ski to Oxberg from Mora, our mother Ebba went after us on skis and did her "Tjejvasa" (Ladies' Vasa) in about 1952.

As a school-boy, I started to do some volunteer work for the Vasaloppet and that has continued. I have raced fifteen 90 Km, nine 45 Km and three 30 Km races. My beloved family has followed in my footsteps. My wife, Marianne, has done some 90 Km races as have our daughters Lena-Stina, Maria, Sofia and our son Ola. The grandchildren; Erik, Ellen, Stella, Albin, Klara, Assar, Alfred, Alva, Noel and Matteo have started to do shorter trips along the tracks. I want to thank them all for the inspiration they have given me and the patience they have shown during my work on this thesis.

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