Svein Arthur Jensen

The prevalence of symptomatic arterial disease of the lower limb

Doctoral thesis
for the degree of philosophiae doctor

Trondheim, June 2006

Norwegian University of Science and Technology
Faculty of Medicine
Department of Circulation and Medical Imaging

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Norwegian University of Science and Technology

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ISBN 82-471-7988-1 (printed version)
ISBN 82-471-7987-3 (electronic version)
ISSN 1503-8181

Doctoral theses at NTNU, 2006:115

Printed by NTNU-trykk

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Svein Arthur Jensen

Department of Surgery

St. Olavs Hospital

University Hospital of Trondheim

Department of Public Health

Faculty of medicine

Norwegian University of Science and Technology

Department of Circulation and Medical Imaging

Faculty of medicine

Norwegian University of Science and Technology

The HUNT Study

Contents

Acknowledgements

The present work was carried out at the Department of Surgery, St.Olavs Hospital, University Hospital of Trondheim, the Department of Public Health and the Department of Circulation and Medical Imaging, Faculty of Medicine, the Norwegian University of Science and Technology. The study was initiated by Professor Lars Vatten and Professor Hans Olav Myhre and was part of the Nord-Trøndelag Health Survey 1995-97 (the HUNT Study).

I would like to express my most sincere gratitude to my supervisor Professor Hans Olav Myhre whose scientific approach, kind and gentle personality, and constant encouragement have been of utmost importance for me in carrying out the studies, and to stimulate the interest for further research projects.

I am sincerely grateful to my supervisor Professor Lars Johan Vatten who introduced me to the field of epidemiology, and whose excellent writing skills and scientific standards in epidemiological research have been of invaluable importance for the completion of this thesis.

Sincere thanks to my co-authors, research colleagues and instructors in epidemiological research, Pål Romundstad, PhD, and Tom Ivar Lund Nielsen, PhD, for valuable comments.

My warmest thanks to Ann Mari Østraat for helping with the data, and accurate typing of manuscripts.

Thanks to Mr. Arild Skaug Hansen for supporting my work and organizing scholarships during my years as a student at the Norwegian University of Science and technology.

Special thanks to my mother Arnhild, father Magn Arne and brother Øystein for giving me the opportunity and encouragement to study medicine, and for supporting me throughout this work.

The work received support by grants of the Norwegian Research Council and the Norwegian University of Science and Technology.

List of papers

This thesis consists of the following publications, which will be referred to by their roman numerals.

I. Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of intermittent claudication. Sex-related differences have been eliminated.
Eur J Vasc Endovasc Surg. 2003;25:209-12.

II. Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of asymptomatic arterial obstruction in the lower extremities among men and women 60 to 69 years of age.
Int Angiol. 2003;22:340-3.

III. Jensen SA, Vatten LJ, Nilsen TIL, Romundstad PR, Myhre HO. Serum lipids and anthropometric factors related to the prevalence of intermittent claudication.
Eur J Vasc Endovasc Surg. 2005;30:582-7.

IV. Jensen SA, Vatten LJ, Nilsen TIL, Romundstad P, Myhre HO. The association between smoking and the prevalence of intermittent claudication.
Vasc Med. 2005;10:257-263.

V. Jensen SA, Vatten LJ, Myhre HO. The prevalence of chronic critical lower limb ischaemia in a population of 20,000 subjects 40–69 years of age.
Eur J Vasc Endovasc Surg. 2006; 32: 60-65.

Abbrevations

ABPI	Ankle brachial pressure index
BMI	Body mass index
CHD	Coronary heart disease
c.i.	Confidence interval
CLI	Critical limb ischemia
HDL	High density lipoprotein
IC	Intermittent claudication
LDL	Low density lipoprotein
MI	Myocardial infarction
PAD	Peripheral arterial disease
PAOD	Peripheral arterial occlusive disease
TC	Total cholesterol
TG	Triglycerides

Introduction

Intermittent claudication, IC, is the term used to describe symptoms of ischemic pain in the lower limbs during exercise, but with subsequent relief of the discomfort when at rest (Cimminiello, 2002;Tierney et al., 2000). The condition is no threat to life or limb in itself. However, IC is associated with an increased risk of coronary heart disease or stroke, conditions that carry a high risk of morbidity and death (Criqui et al., 1998;Criqui et al., 1997;de Vries et al., 1998;De Backer et al., 1979;Diehm et al., 2004;Widmer, 1967).

Patients suffering from chronic critical lower limb ischemia have constant pain in the lower extremities, and often ulcerations or tissue loss due to inadequate blood supply. Most of these subjects will eventually require surgical interventions (Tierney et al., 2000;Bouchier-Hayes, 2001). Nevertheless, although reconstructive surgery both improves limb salvage and is cost-effective, the mortality of CLI patients remains high (Dormandy et al., 1999;Luther et al., 2000;Myhre et al., 1995;Myhre et al., 1996;Pell JP et al., 1997;Rutherford et al., 1997).

Given the natural history of these two conditions, it would be convenient to think of intermittent claudication as a relatively mild form of arterial disease that eventually develops into CLI (Laing et al., 1983). However, some researchers conclude otherwise, and this may indicate a more complex disease etiology (Dormandy et al., 1999;Dormandy et al., 1999;Dormandy et al., 1991;McGrath et al., 1983;Mätzke et al., 2001).

The epidemiology of lower limb arterial diseases has changed markedly during the last decades, and though large variations in frequency have been reported, IC is becoming more common in the developed countries (Bothig et al., 1976;Fowkes et al., 1991;Hughson et al., 1978). The first properly organized field survey was conducted early in the 1960s (Rose, 1962;Widmer, 1967;Da Silva et al., 2000;Hallet, 2001). The main objectives of these pioneering population studies were to investigate disease frequency, to screen for risk factors, and to detect markers predicting deterioration of the condition. The intention was to plan treatment regimens for lower limb arterial disease that were in accordance with these epidemiological findings. Thus, a prerequisite became to make data comparable over time and between populations. Consequently the construction of uniform definitions was stressed (Belcher, 1994;Bell et al., 1982;Carter, 1997;Criqui et al., 1997;Cimminiello, 2002). Nevertheless, definitions of IC and CLI that are feasible for population surveys are still debated (Rutherford, 1986;European consensus on critical limb ischaemia, 1989;Second European Consensus Document on Chronic Critical Leg Ischaemia, 1991;Dormandy et al., 2000;Greenland et al., 2000;Bertelé V et al, 1996)

Most physicians use anamnestic information in addition to measuring the ankle brachial pressure index, ABPI, when identifying those needing further testing to diagnose PAD (Scholl et al., 1981;Carter et al., 1968;Newman et al., 1993;Hooi, 2002; Khan et al., 2006). ABPI is only slightly less sensitive in detecting arterial occlusion compared to the gold standard angiography and also predicts mortality well (Vogt et al., 1993;Ögren et al., 1993;Kornitzer et al., 1995;Jonsson et al., 2002). However, the test is not easily applied to large populations, and for screening purposes diseased subjects must be identified by symptomatic outcome measures. The Edinburg Claudication questionnaire was constructed for the identification of IC in large surveys, and the present thesis is partly based on this questionnaire (Leng et al., 1992). However, to our knowledge, a questionnaire for chronic critical lower limb ischemia has not previously been investigated in a large unselected population.

This thesis is concerned with the epidemiology of symptomatic lower limb arterial occlusive disease. The main objectives were to assess the prevalence of intermittent claudication, IC, and chronic critical lower limb ischemia, CLI, in a large unselected population of both men and women 40 to 69 years of age. For this purpose, we constructed questionnaires intended to identify diseased subjects. Furthermore, we investigated several possible risk factors for vascular disease in relation to the prevalence of IC and CLI.

Study objectives

Paper I

The objective was to estimate the prevalence of intermittent claudication using simple anamnestic questions in an unselected population of nearly 20,000 men and women 40 to 69 years of age.

Paper II

The purpose was to estimate the prevalence of asymptomatic arterial obstruction in the lower limb arteries in a sub-sample of the population investigated in Paper I during the same time period.

Paper III

The main aim was to assess the association between blood lipids, body mass index and the prevalence of intermittent claudication in nearly 20,000 men and women 40 to 69 years of age.

Paper IV

We used logistic regression analyses to estimate prevalence odds ratios for the association between active and passive smoking and the prevalence of intermittent claudication in an unselected population of nearly 20,000 men and women 40 to 69 years of age.

measurements of height, weight, and brachial blood pressure were conducted, and a sample of venous blood was collected. At this examination, participants 20 to 69 years of age received a second questionnaire that included questions designed to identify individuals with intermittent claudication and chronic critical lower limb ischemia. This second questionnaire was to be filled in at home and returned by mail. Since both IC and CLI are very rare at a young age, we restricted the analysis to participants 40 to 69 years of age. Unfortunately, participants older than 70 years of age did not receive the second questionnaire.

Patients were included in the CLI and the IC studies if they had accepted the invitation and attended the examination. In addition, for inclusion in the IC study, participants had to answer yes or no to the following questions: (1) Do you have pain in one or both lower limbs when walking? (2) Do you have ulcers on toes, foot or ankle that have failed to heal? For inclusion in the CLI study, however, only question number 2 was compulsory to answer since we considered the first question not to be applicable for participants using a wheel chair or who otherwise were walking disabled. This inclusion procedure ensured that the subjects had read and considered symptoms related to arterial disease in the lower limbs. The questions for IC were completed by 9,405 men and 10,343 women. For CLI, the corresponding study population consisted of 9,640 men and 10,651 women 40 to 69 years of age.

Definition of intermittent claudication

Subjects with IC should indicate (1) pain in one or both legs during walking;(2) the pain should be located to the calf;(3) it should disappear when the subject stopped walking, and (4) be absent at rest.

Definition of chronic critical lower limb ischemia

Subjects suspected of having CLI should answer yes to one or both of the following questions: (1) Do you have ulcers on toes, foot or ankle that have failed to heal? (2) Do you have persistent pain in the forefoot while in the supine position, but with relief of the pain when standing up?

Study factors

Information about the study factors both for the IC population and the CLI population were collected from the second questionnaire that was handed out at the examination. Most variables were treated as categorical variables in the regression model to produce prevalence odds ratios, and further as ordinal variables for trend analyses.

Individuals who had never smoked cigarettes daily were considered never smokers, and those who reported previous or current daily smoking were classified as former or current smokers, respectively. History of diabetes mellitus (both insulin-dependent and non-insulin-dependent), previous myocardial infarction, and current or previous angina pectoris were obtained from the questionnaire.

Blood pressure measurements were always preceded by rest in a quiet room for at least 10 minutes. Brachial blood pressure was recorded with the patient in the sitting position and with the blood pressure cuff on the right upper arm. Ankle systolic blood pressure was recorded in both lower extremities with the cuff placed proximal to the malleoles and with the subject in the supine position (II). The Doppler probe (Doppler modell 841-A, Parks medical electronics, Inc., USA) was placed over the posterior tibial artery in the first measurement, and over the dorsalis pedis artery in the second measurement. The highest of the two measurements was denoted systolic ankle blood pressure. Subsequently, with the patient still in the supine position, brachial blood pressure was measured. All blood pressure recordings were based on the mean value of the second and third measurement and rounded off to the nearest 2 mm Hg (Bernstein et al., 1982;Holmen et al., 2003).

In article III concentrations of total serum cholesterol (TC) were measured by the Liebermann-Buchard method, and triglyceride concentrations by a fluorimetric method (National Institute of Health and National Heart and Lung Institute, 1975). High density lipoprotein (HDL) was determined with a heparin-manganese method (National Institute of Health and National Heart and Lung Institute, 1975).

Recordings of height (in cm), hip- and waist circumference (in cm) and weight (in kg) were standardized and performed by trained personnel (III). Body mass index (BMI) was computed as weight (in kg) divided by the height (in meters) squared.

Statistical analyses

Age adjustments for the total prevalence of both IC and CLI were calculated using the direct method and with the total HUNT 2 study population between 40 to 69 years of age as the reference standard (I and IV). Gender differences in prevalence estimates were investigated by age-adjusted prevalence ratios, and the precision of these ratios was estimated with 95 per cent confidence intervals (c.i.)(I and V).

Logistic regression analyses were used to investigate the associations between the different study factors and the prevalence of disease. Age was included in the regression model, divided into 5-year categories, to produce age-adjusted prevalence odds ratios (OR) with 95 per cent confidence intervals (95 per cent c.i.). The effect of potential confounding by other study factors was assessed in subsequent multivariate analyses by comparing age-adjusted and multivariate adjusted estimates.

All statistical analyses were performed using the statistical software package SPSS for Microsoft Windows (Release 10.07 - 13.00, Copyright SPSS Inc., Chicago, USA, 1989-2005).

Summary of results

Paper I

9,405 men and 10,343 women were eligible for investigation. 1.2 per cent of the women and 1.1 per cent of the men had intermittent claudication; yielding a total crude prevalence of 1.2 per cent. The prevalence increased steadily by age and was similar between the genders.

Paper II

333 randomly selected participants between 60 and 69 years of age were offered a more comprehensive examination including ankle blood pressure measurements. Subjects with IC were identified by the anamnestic questions similar to those used in I. Further, ankle brachial blood pressure index lower than 0.9 (ABPI<0.9) was used as indicator of arterial occlusive disease. Of all 333 participants 7.8 per cent had ABPI measurements below the threshold value, and 1.5 per cent had IC according to our questionnaire. Thus, 6.3 per cent had asymptomatic lower limb arterial disease. The prevalence of asymptomatic arterial obstruction of the lower limb arteries was nearly identical for men (6.2 per cent) and women (6.4 per cent).

Paper III

IC was certified according to the questions used in I, and measurements of height, weight and a venous blood sample were obtained at the examination. In both genders the ratio of total cholesterol to HDL cholesterol (TC/HDL cholesterol) (P $\text{trend}_{\text{men}} = .023$, P $\text{trend}_{\text{women}} < .001$) and triglycerides ($P$ $\text{trend}_{\text{men}} = .029$, P $\text{trend}_{\text{women}} = .002$) were both positively associated with the prevalence of intermittent claudication. HDL cholesterol was negatively (P $\text{trend}_{\text{men}} = .131$, P $\text{trend}_{\text{women}} < .001$) associated with the prevalence of IC. BMI (P trend = .032), waist circumference (*P* trend = .021), and hip circumference (*P* trend = .020) were all positively associated with IC in women, but not among men. Adjustment for smoking, diabetes, and systolic or diastolic blood pressure in multivariate analyses did not substantially change these results.

Paper IV

The questions presented in I identified subjects with intermittent claudication, and history of smoking was obtained from the questionnaire. Both current and former smokers were more likely to have IC compared to never smokers ($P\ \text{trend}_{\text{men}} < 0.001$, $P\ \text{trend}_{\text{women}} < 0.001$). Individuals who had stopped smoking more than 20 years ago had a substantially lower prevalence of IC ($P\ \text{trend}_{\text{men}} < 0.001$, $P\ \text{trend}_{\text{women}} < 0.001$) compared to those who were current smokers. We found no association between passive smoking and IC. The effect of potential confounding was assessed in subsequent multivariable analyses but none of the results changed substantially after adjustment for diabetes, blood lipids, and diastolic or systolic blood pressure.

Paper V

The prevalence of chronic critical lower limb ischemia was investigated by simple anamnestic questions, and 0.26 per cent of the men and 0.24 per cent of the women had CLI; yielding a total age-adjusted prevalence of 0.24 per cent. We observed no gender difference in any age group (age-adjusted OR=0.91, 95 per cent c.i.=0.52–1.58), and there was an increase in the prevalence with increasing age. The presence of smoking, diabetes mellitus, angina pectoris, high triglyceride levels, and high BMI were all independently associated with the prevalence of CLI. Thus, risk factors usually seen in relation to atherosclerotic disease were common among the suspected CLI subjects.

Discussion

In this thesis we have investigated the epidemiology of intermittent claudication and chronic critical lower limb ischemia in an unselected population of people 40 to 69 years of age. Subjects suspected to have IC or CLI were identified by simple anamnestic questions. The total age-adjusted prevalence of intermittent claudication was 1.2 per cent, and 0.24 per cent of the population had chronic critical lower limb ischemia.

The estimated prevalence of IC was somewhat low compared to most previous reports. However, frequency data for IC have been shown to vary considerably between populations and cultures (Kannel, 1970;Hughson et al., 1978;De Backer et al., 1979;Reunanen et al., 1982;Stoffers et al., 1991;Fowkes et al., 1991;Smith et al., 1991;Novo et al., 1992). We found sparse evidence for any population studies of CLI. However, the estimated prevalence of CLI was somewhat higher than in the few studies that have addressed this question (Catalano, 1993;Dormandy et al., 2000). The result may indicate that our questionnaire identified some more false positive cases of CLI. Nevertheless, it should be noted that the prevalence of CLI is in general low. Therefore, even a small number of incorrectly identified subjects would bias the results considerably.

Definition of intermittent claudication in population surveys

Intermittent claudication is symptoms of limited blood and oxygen supply to the muscles in the lower limbs. IC is characerized as a cramping discomfort in one or both legs that is present during exercise and relieved by rest (Balkau, 1994;Cimminiello, 2002;Dormandy et al., 2000;Fowkes, 1988;Rutherford et al., 1997). This ichaemic pain may become apparent in the thigh or calf depending on the anatomical localization of the arterial obstruction.

Intermittent claudication is therfore only a symptom of peripheral arterial occlusive disease, PAOD. Consequently, screening for IC is difficult as a patient with quite severe PAOD may not have symptoms of IC because some other condition limits exercise. Likewise, patients with very mild PAD may have symptoms of IC only if they are very active. Further, ichaemic pain in the thigh and gaiter area may often be interchangeable with other medical conditions, and consequently, previous surveys concerning the epidemiology of IC have mainly aimed at identifying calf claudication (Dormandy et al., 2000).

Several questionnaires have been developed for use in epidemiological investigations. The WHO/Rose questionnaire has been the most widely used questionnaire for the identification of IC in large population cohorts (Rose, 1962). The questionnaire has proven very specific in excluding healthy individuals, but only moderately sensitive in detecting subjects with arterial disease (Criqui et al., 1985). In order to improve the test's sensitivity the WHO/Rose questionnaire has been modified and in 1985 the questionnaire was extended to include "possible claudicants" (Criqui et al., 1985). Later, self administered questionnaires became warranted as larger field surveys were conducted. Thus, the WHO/Rose questionnaire was reformulated once again and presented as the Edinburgh Claudication Questionnaire (Leng et al., 1992). Nevertheless, the principal problem with these questionnaires is that they have a low sensitivity (Dormandy et al., 1999). Thus, the prevalence of IC in population surveys may be underestimated.

In this work, responses to twelve anamnestic questions from the second questionnaire were the basis for the identification of subjects with IC. Different combinations of the questions were tested in 333 randomly selected individuals using ankle brachial pressure index (ABPI) less than 0.9 as the reference standard of arterial occlusive disease in the lower limbs (symptomatic and asymptomatic subjects)(II)(De Backer et al., 1979;Criqui et al., 1997;de Vries et al., 1998;Ogren et al., 1993;Widmer, 1967). The four questions that were used were feasible for self administration and had comparable test properties to previous questionnaires on intermittent claudication (Criqui et al., 1985;Fowkes et al., 1991;Leng et al., 1992). The questions had a specificity of 98.0% and a positive predictive value of 45.5%.

Defining chronic critical lower limb ischemia in a population study

Critical lower limb ischemia is a condition that endangers the leg or part of the leg. A definition may have been simple if all patients with CLI and whose blood flow could not be significantly improved required amputation. However, fluctations in the ischemic state is common, and failure of surgical treatment may not necessary result in amputation. A strict definition is therefore warranted, and recommodations have been presented (Dormandy et al., 2000).

The Second European Consensus Document on Chronic Critical Leg Ischaemia defined CLI by two criteria: Persistently recurring ischemic rest pain requiring regular adequate analgesia for more than two weeks, with an ankle systolic pressure ≤50 mm Hg and/or a toe systolic pressure ≤30 mm Hg;or ulceration or gangrene of the foot or toes, with an ankle systolic pressure of ≤50 mm Hg or a toe systolic pressure ≤30 mm Hg (Second European Consensus Document on Chronic Critical Leg Ischaemia, 1991). This definition may, however, not be suitable for population screening purposes due to the cost and time consumption required for the toe and ankle blood pressure measurements. The Fontaine stages grade the severity of lower limb ischaemia into four stages by symptomatic outcome measures;asymptomatic individuals (stage I), intermittent claudication (stages IIa and IIb), rest pain (stage III), and trophic lesions (stage IV)(Fontaine et al., 1954). Patients in stage III and IV may be regarded as having critical ichaemia. However, for stage III (rest pain), the definition may not distinguish well between claudicants (IC) with occasional nocturnal pain and CLI patients. The Rutherford classification is intended for administration by trained personnel, and though Grade II (ischaemic rest pain) is more clearly defined compared to the Fontaine stage III, the definition is based on ABPI measurements or pulse palpation (Rutherford et al., 1997). Thus, both symptom scores rely on administration by trained personnel and the general population would most likely fail to understand the terms included in the definitions. Further, very few attempts have been made to validate the definitions. Thus, a properly validated definition of CLI that is suitable for population screening purposes is warranted (Belcher, 1994;Carter, 1997;Thompson et al., 1993). Our objective was to investigate the prevalence of CLI in the population by using a simple screening tool (V). Thus, a challenge became to test the validity of the questionnaire.

The questions used to detect symptoms and signs related to CLI were constructed based on clinical knowledge. Most questions were extracted from the work carried out by previous consensus documents (Second European Consensus Document on Chronic Critical Leg Ischaemia, 1991;Dormandy et al., 2000;Fontaine et al., 1954;Rutherford et al., 1997). CLI was suspected in subjects with any form of chronic ischemic pain or ulcers on the foot, and the level of physical activity was not taken into consideration. Nevertheless, subjects that have sensory neuropathy, but are without ulcers on foot or toes may have escaped detection. Patients with ulcers of other origins than occlusive arteries may also have been included. Thus, one cannot exclude the possibility that some patients with venous ulcers in the gaiter area might have been included in our data. Further, discomfort from other medical conditions, such as orthopaedic disorders, may be interchangeable with ischemic pain even though the questions seek to exclude these patients by adding the aspect of pain relief while the foot was dependent. Finally, some subjects with acute limb ischaemia may have been included.

We attempted to test different combinations of the questions regarding CLI by comparing the results to ABPI measurements in 333 randomly selected participants. The occurrence of disease was, however, too low to produce reasonable test statistics. Furthermore, due to patient confidentiality reasons, we were unable to contact the suspected CLI subjects after the completion of the study. One major disadvantage of the currently used questionnaire was therefore that the questions could not be validated against a ‘gold standard’. Thus, to compensate for this we investigated the relation between suspected CLI subjects and risk factors that are known to be present in subjects with arterial diseases (Fowkes FG et al., 1992;MacGregor et al., 1999; Kannel, 1992;Powell et al., 1997;Trayer et al., 1980). Subjects who smoked, had high values of triglycerides and total cholesterol and had diabetes were more likely to have CLI compared to the non-smokers, the ones with low serum lipids and people without diabetes. Thus, the results of this risk factor evaluation may indicate that the questions identified subjects with high susceptability of arterial diseases (Collins, 2002;Kannel, 1973, Liedberg, 1983).

General methodological considerations

The Nord-Trøndelag Health Study 1995-97 (HUNT 2) is a large population based study. It was approved by the Norwegian Data Inspectorate and recommended by the Regional Committee for Medical Research Ethics.

The prevalence of symptomatic atherosclerosis in the lower extremities is low in subjects younger than 70 years of age. The cross sectional design used in this study may therefore be a cost-effective method to study the epidemiology of this condition. Although the number of CLI cases was too low for gender specific analyses, the results are strengthened by the large number of controls. Further, available information from two comprehensive questionnaires, clinical measurements and blood samples, enables control of confounding, using multivariable analyses. This adds further credibility to the results.

Bias

The first HUNT Study (HUNT 1) was performed in the same geographical area in 1984-86, and 88.1 per cent of those invited attended. In comparison, 71.2 per cent participated in the HUNT 2 Study ten years later. The decline in participation was most apparent among males and in younger age groups (Holmen et al., 2003). The strongest decline was among participants 20 to 40 years of age, a segment that was not included in our study. Nevertheless, the decline in participation could have influenced our results. It is, however, reassuring that the reason for non-attendance was lack of time, or that the person was too busy at work (Langhammer et al., 2000;Holmen et al., 2003). Among those who could not participate, 9.6 per cent were immobilized due to disease. Only 8.6 per cent reported that the survey was unnecessary, and declined to attend for that reason (Holmen et al., 2003;Langhammer et al., 2000).

In Nord-Trøndelag County, both income, distribution of higher education, and the proportion of current smokers are slightly lower than the average for Norwegian counties. The population is mainly rural, with four townships no larger than 20,000 inhabitants. In many respects, the county is fairly representative for Norway as a whole.

Misclassification of exposure

Except for questions on smoking, nearly all participants answered the questions that were used in this study. Although a dose-risk relation between smoking and peripheral arterial disease has been observed previously, this was confirmed only for men in our study (IV)(Smith et al., 1996;Quick et al., 1982;Wiggers et al., 2003). In some studies, it appears that women have tended to underreport their smoking. (Wells et al., 1998;Rebagliato, 2002;Willigendael et al., 2004). In our study, 83 percent of smoking women reported how many cigarettes they usually smoked, whereas 94% of smoking men reported their amount of smoking (IV).

Confounding

Confounding may arise when an outcome has at least two determinants that are themselves associated. Of course, not all possible determinants are considered in this study. However, the large number of relevant factors available from the HUNT 2 study gave us the opportunity to check for potential confounding. Age, for example, is related to the prevalence of lower limb arterial disease, but is also associated with most risk factors for cardiovascular disease. Thus, adjustment for age was necessary to avoid confounding, as demonstrated in the age-adjusted estimates of effect, presented as age-adjusted odds ratios.

We further addressed the issue of potential confounding by comparing age-adjusted and multivariate adjusted results. Factors thought to be associated with the disease and simultaneously with the exposure under study were included. Only for passive smoking the multivariate adjusted results differed substantially from the age-adjusted results, and current smoking appeared to be a confounding factor for this association (IV)(Glantz et al., 1991;Werner et al., 1998). Thus, the initial observation that passive smoking was positively associated with intermittent claudication disappeared after adjustment for current smoking.

Precision

Although HUNT 2 is a large study, IC and especially CLI are diseases with low prevalence, and this in itself could represent a threat to the precision of the results. However, in the IC studies the large number of controls produced reasonable confidence intervals for the odds ratios and the *p*-values for linear trend across exposure categories. For CLI, however, the number of cases was too low, and gender specific analyses could not be performed.

Causality

In cross-sectional studies, exposures and outcomes are measured at the same time. Since cause must precede outcome, no causal effect can be firmly established in cross-sectional studies. Exposures may only be causally interpreted if it can be assumed as plausible that the exposure was present before the disease occurred. This assumption may be made for most study factors in this investigation. For example, most current smokers had a history of at least 20 years of smoking, and further, the prevalence of IC increased steadily with age (IV). That smoking is a cause, and not an effect of IC, is therefore highly plausible. Similar effects are likely to be present for blood lipids, diabetes mellitus and body size (Dormandy et al., 1999;Dormandy et al., 2000;Fowkes, 1988;Harris, 1995;Cimminiello, 2002).

Conclusions

The age-standardized prevalence of intermittent claudication, IC, was 1.1 per cent among men and 1.2 per cent among women; yielding a total crude prevalence of 1.2 per cent for men and women 40 to 69 years of age. Disease frequency increased gradually by age, and we observed no difference by gender.

Arterial obstruction in the lower limbs indicated by ankle brachial pressure index lower than 0.9 (ABPI<0.9) in one or both legs was observed in 7.8 per cent of participants 60 to 69 years of age. However, only one in five persons who had objectively verified arterial obstruction indicated symptoms of intermittent claudication.

High levels of triglycerides and of the ratio of total to HDL cholesterol were more common among subjects with IC compared to subjects without disease. Thus, blood lipids showed strong associations with the prevalence of IC, and we observed no differences among the genders.

Women with high body mass index, and large waist and hip circumference, were more likely to have intermittent claudication than females with low BMI, and smaller waist and hip circumferences. In men, however, we failed to observe similar associations between body shape and the prevalence of IC.

Both current and previous smoking was strongly associated to the prevalence of intermittent claudication, and the results showed no gender difference. The associations became stronger with duration of smoking, and showed a gradual reduction after smoking cessation. Passive smoking was not associated with the prevalence of IC.

The total crude prevalence of chronic critical lower limb ischemia was 0.24 per cent. We observed no gender difference and, similar to intermittent claudication, the prevalence of CLI increased with age.

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Paper I

Eur J Vasc Endovasc Surg 25, 209–212 (2003)
doi:10.1053/ejvs.2002.1836, available online at http://www.sciencedirect.com on SCIENCE DIRECT

The Prevalence of Intermittent Claudication. Sex-related Differences have been Eliminated

S. A. Jensen[1], L. J. Vatten[1], P. R. Romundstad[1] and H. O. Myhre*[2]

Departments of [1]Community Medicine and General Practice and [2]Surgery, Norwegian University of Science and Technology, University Medical Center, N-7489 Trondheim, Norway

Objectives: *to investigate the prevalence of intermittent claudication (IC) in an unselected population of nearly 20 000 individuals between 40 and 69 years of age.*
Design: *epidemiologic investigation of residents in Nord-Trøndelag County, Norway.*
Material and Methods: *between 1995 and 1997, all residents 20 years of age or older in Nord-Trøndelag County, Norway, were invited to attend the HUNT Study. A total of 19 748 participants between 40 and 69 years of age responded to questions related to the symptoms of intermittent claudication. We estimated the prevalence of IC based on these questions.*
Results: *the age-adjusted prevalence of intermittent claudication in the total population was 1.1% for men and 1.2% for women. We found an increase in the prevalence of IC by age, however, no sex differences were observed.*
Conclusion: *the prevalence of intermittent claudication increased gradually by age. However, in contrast to previous reports, there was no difference by sex.*

Key Words: Epidemiology; Prevalence; Intermittent claudication.

Introduction

Intermittent claudication (IC) is a manifestation of generalized atherosclerosis often associated with life threatening cardiac- and cerebro-vascular disease. Intermittent claudication may not be fatal, but the disease represents a heavy burden of disability and discomfort.[1] In western societies, the aging of the population will result in an increasing number of patients with IC. The increasing prevalence of type II diabetes will also contribute to increase the impact of this disease.[1–3]

The history of IC is usually characterized by leg pain during exercise which is relieved by rest. Although several questionnaires have been developed for epidemiological studies, the TASC Consensus document concluded that for self reporting of symptoms the Edinburgh Claudication Questionnaire has shown reasonable predictive capability.[1] The questions used to identify suspected cases of IC in this study were therefore made in accordance with these recommendations. Our objective was to estimate the prevalence of IC in a population of nearly 20 000 individuals between 40 and 69 years of age.[4]

Material and Methods

Between 1995 and 1997, the Nord-Trøndelag Health Survey (the HUNT Study) in Norway was conducted as a collaboration between the National Health Screening Service, the National Institute of Public Health, and the Norwegian University of Science and Technology. All residents aged 20 years or more were invited to participate. The participants were asked to fill in a questionnaire which was mailed together with the invitation, and to attend a physical examination. The examination included measurements of height, weight, blood pressure and a blood sample was collected. A second questionnaire including the questions regarding IC was handed out at the examination and the participants were asked to fill in this questionnaire at home and return it in the included pre-stamped envelope. The two questionnaires covered more than 200 health related questions,

* Please address all correspondence to: H. O. Myhre, Department of Surgery, St Olavs Hospital, University Hospital of Trondheim, N-7006 Trondheim, Norway.

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including five specific questions on intermittent claudication (Table 1).

A total of 66 140 individuals attended the study, yielding 71.2% of all those invited. All participants in the age group 40–69 years who completed the questions on IC were included in this study, yielding 9405 men and 10 343 women. Persons older than 69 years of age were not included in the investigation because of practical problems for this group to fill in a relatively complicated questionnaire and to attend the physical examination.

To identify cases of IC we used four questions in conformity with the consensus criteria formulated during the work with the Trans Atlantic Inter-Society Consensus on management of peripheral arterial disease (TASC).[1] Briefly, by using these questions, the participants were suspected of having IC if they (1) indicated pain in one or both legs during walking; (2) the pain was located to the calf; (3) the pain disappeared after a period of rest; and (4) the pain was absent at rest.

Age adjustment for the prevalence of IC in the study population was done using the direct age standardizing method with the corresponding total population of the HUNT study, 40–69 years of age as the reference standard.[5]

To investigate the differences in prevalence between men and women, we also constructed a simple prevalence ratio (PR) between men and women, and estimated an age-adjusted precision of this ratio by 95% confidence intervals (C.I.).[5]

All statistical analyses were performed using SPSS for Windows (Release 10.07, Copyright © SPSS Inc., 1989–2002). The investigation was approved by the local ethics committee.

Table 1. The questionnaire on intermittent claudication (IC) in the HUNT-study.

Have you experienced pain in one or both legs during walking?	Yes ☐	No ☐		
Where is the pain localized?	Foot ☐	Calf ☐	Thigh ☐	Hip ☐
Does the pain regress after a period of rest?	Yes ☐	No ☐		
Is the pain present at rest?	Yes ☐	No ☐		
Can you walk further than 50 meters?	Yes ☐	No ☐		

Results

The age-adjusted prevalence of intermittent claudication in the total study population was 1.2% for women and 1.1% for men (Table 2); yielding a total crude prevalence of 1.2%. We observed a gradual increase of the prevalence of IC with age in both men and women (Fig. 1). Between the age group 40–44 years to 65–69 years the prevalence difference was nearly 8-fold, and this pattern was similar for men and women. The prevalence ratios (Table 3) showed no substantial sex difference in any age group, and the total prevalence sex ratio was 1.0 (95% C.I. 0.8–1.3).

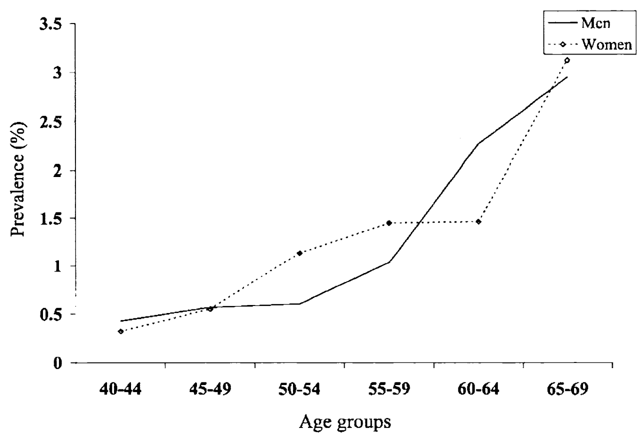

Fig. 1. The prevalence of intermittent claudication (IC) in the different age groups of a population including 9.405 men and 10 343 women between 40 and 69 years of age.

Table 2. The prevalence of intermittent claudication (IC) by self reporting of symptoms.

Age	Men			Women		
	Intermittent claudication	Participants	Prevalence (%)	Intermittent claudication	Participants	Prevalence (%)
40–44	8	1858	0.4	7	2158	0.3
45–49	11	1935	0.6	12	2178	0.6
50–54	11	1819	0.6	23	2020	1.1
55–59	14	1351	1.0	21	1447	1.5
60–64	27	1188	2.3	18	1227	1.5
65–69	37	1254	3.0	41	1313	3.1
Total	108	9405	1.1[a]	122	10343	1.2[a]

[a] Age standardized prevalence by direct age-standardization.

Table 3. Prevalence ratio between men and women.

Age group	PR[a]	95% C.I.
40–44	0.8	(0.3–2.1)
45–49	1.0	(0.4–2.2)
50–54	1.9	(0.9–3.8)
55–59	1.4	(0.7–2.7)
60–64	0.7	(0.4–1.2)
65–69	1.1	(0.7–1.6)
Total	1.0	(0.8–1.3)

[a] Prevalence ratio with 95% confidence interval (C.I.).

Discussion

The prevalence of diseases related to atherosclerosis may vary significantly from one country to another. We therefore wanted to investigate the prevalence of intermittent claudication in Nord-Trøndelag county including a part of the population of nearly 20 000 individuals. We constructed a set of questions in conformity with guidelines forming the basis for the TASC document to ascertain cases of IC. This questionnaire is highly specific in excluding normal individuals, but only moderately sensitive in detecting those with IC compared with a physician's assessment of signs and symptoms.[1] However, the questionnaire is convenient for epidemiologic investigations on IC in a large population. We found an age-adjusted prevalence of 1.1% in men and 1.2% in women among individuals 40–69 years of age. Since the questions on IC were handed out at the physical examination, this might have excluded some subjects unable to attend because of leg pain. Therefore the prevalence of IC could have been underestimated. The questionnaire also included pain in the thigh and hip as well as the calf. Objects indicating hip and thigh pain only were however excluded. First of all individuals with ischaemic hip and thigh pain represent a minority of patients with IC. Further, those with ischaemic hip and thigh pain usually also have leg pain. Finally, including objects with hip and thigh pain only would have included diseases like low back pain, hip athrosis etc. decreasing the specificity and the positive predictive value of the test.

In Norway, as in most other western countries, the elderly population is expected to increase over the next 30 years due to the "baby boom" generation born between 1945 and 1955 following the second World War.[2] The population over 67 years of age in Norway is expected to nearly double, reaching 0.9 to 1.2 million persons in 2050.[2] Also, the incidence of diabetes is increasing in the western world.[1] The aging of the population combined with an increased incidence of diabetes will most likely result in an increased number of persons with IC as well as more serious leg ischaemia leading to an increased need for vascular procedures. Without proper planning and resource allocation, the consequences could be that the patients will not receive appropriate treatment due to lack of financial resources.[1,3] These prognoses must be taken into careful consideration for future health care planning.[3]

Previous reports from the 1950's and the 1960's indicated that the male prevalence of IC was higher than for females.[6–9] In the present study, however, the prevalence in women did not differ from that in men (Prevalence ratio = 1.0, 95% C.I. 0.8–1.3). This result is in accordance with recent findings, indicating that a real change has taken place over this time period.[1,10] The previously reported sex difference has been attributed to the effect of sex hormones on lipoproteins.[1] The prevalence of IC in men over 60 years of age has been relatively stable since the 1950's.[8,11–14] There has, however, been a marked increase in smoking among women. Taking the positive association between smoking and IC into consideration, smoking is likely to be an important cause of the increased prevalence of IC in women.[1,6,9,10]

Prevalence estimates for IC in previous studies vary from 0.4–14.4%.[1] Compared to most previous reports, we observed low prevalence estimates for men in all age groups under the age of 60. However, among women in the same age groups, we found a higher prevalence than in most other studies.[1,7,8,11–14] In age groups over 60 years, the prevalence among men was in accordance with other studies, but for women, the prevalence in our study was substantially higher than in previous reports.[1]

In summary, the age-adjusted prevalence of intermittent claudication was 1.1% among men and 1.2% among women between 40 and 69 years of age. We observed a gradual increase in prevalence by age, but in contrast to previous findings in the 1950's and 1960's there were no differences in prevalence by sex. The expected increase in the number of patients with intermittent claudication in the years to come will represent a major challenge to the health care system in most western countries, and there will most likely be an increased need for treatment of vascular diseases.

Acknowledgement

This investigation was supported by a grant from the Norwegian Research Council. Financial support from Schering AG, Germany, is also appreciated.

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Accepted 14 November 2002

Paper II

Paper II is not included due to copyright.

Paper III

Eur J Vasc Endovasc Surg **30**, 582–587 (2005)
doi:10.1016/j.ejvs.2005.06.008, available online at http://www.sciencedirect.com on SCIENCE DIRECT

Serum Lipids and Anthropometric Factors Related to the Prevalence of Intermittent Claudication

S.A. Jensen,[1,2] L.J. Vatten,[1] T.I.L. Nilsen,[1] P.R. Romundstad[1] and H.O. Myhre[2*]

Departments of [1]Community Medicine and General Practice, and [2]Surgery, University Medical Center, Norwegian University of Science and Technology, N-7489 Trondheim, Norway

***Purpose**. To study serum lipids, body mass index (BMI), and body shape in relation to intermittent claudication (IC) in 19,748 men and women 40–69 years of age.*
***Method**. All residents (1995–1997) in Nord-Trøndelag County, Norway, were invited to attend the cross sectional study and received a Norwegian translation of the WHO/Rose questionnaire on intermittent claudication and the Edinburgh claudication questionnaire. Blood lipids and anthropometric data were measured at a consecutive examination. Odds ratios (OR) were estimated for associations with IC by multiple regression analysis.*
***Results**. The ratio of total cholesterol to HDL cholesterol (TC/HDL cholesterol) (P $trend_{men}=.023$; P $trend_{women}<.001$) and triglycerides (P $trend_{men}=.029$; P $trend_{women}=.002$) were positively associated with the prevalence of IC. HDL cholesterol was negatively (P $trend_{men}=.131$; P $trend_{women}<.001$) associated, whereas BMI (P $trend_{women}=.032$), waist circumference (P $trend_{women}=.021$), and hip circumference (P $trend_{women}=.020$) were positively associated with IC in women, but not in men. Adjustment for smoking, diabetes, and systolic or diastolic blood pressure did not change the results.*
***Conclusion**. TC/HDL cholesterol and triglycerides were positively, and HDL cholesterol negatively associated with IC in both genders. In women, but not in men, BMI, waist and hip circumference were positively associated with IC.*

Keywords: Serum lipids; Anthropometric factors; Intermittent claudication.

Introduction

Lower limb arterial disease is common in the population, but for most patients the condition runs a benign course and will only require medical or surgical intervention in about one third of the patients.[1–4] For patients with intermittent claudication (IC), 5 and 10 year mortality are about 30 and 50% higher, respectively, than the general population.[4,5] In order to improve the survival of patients with peripheral vascular disease co-ordinated modification of identifiable risk factors is of major importance. Such measures include increased physical activity, smoking cessation, and optimal treatment of hypertension, dyslipidemia, and diabetes.[6,7]

Most population studies investigating the epidemiology of intermittent claudication (IC) were carried out 20–30 years ago.[8–10] The aim of this study was to examine the relation between serum concentrations of lipids, body mass, body shape, and the prevalence of IC in an unselected population of nearly 20,000 individuals between 40 and 69 years of age.[2]

*Corresponding author. Prof Hans O. Myhre, MD, PhD, Department of Surgery, Norwegian University of Science and Technology, N-7006 Trondheim, Norway.
E-mail address: hans.myhre@medisin.ntnu.no

Patients and Methods

The study population

Between 1995 and 1997 all residents 20 years or older in Nord-Trøndelag County, Norway, were invited to participate in a health study (HUNT 2).[11] In total, 71.2% (66,140) attended and responded to a brief questionnaire enclosed with the invitation. The study also included a physical examination, with measurements of height, weight, waist and hip circumference, brachial blood pressure, and a sample of venous blood was collected. At the examination, participants 20–69 years of age received another questionnaire including questions specifically aimed at identifying individuals with IC. This second questionnaire was to be filled in at home and returned in a pre-stamped envelope. Together, answers to the questions in the first and second questionnaire provided information on a

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variety of health related issues. Since, IC is very rare at a young age, we restricted the analysis to participants 40–69 years of age, yielding a study population of 9405 men and 10,343 women.

Diagnosing intermittent claudication—validation of the questions

Twelve questions were constructed to identify individuals with intermittent claudication and included Norwegian translations of the questions used in the WHO/Rose questionnaire on intermittent claudication and the Edinburgh claudication questionnaire. Different combinations of the questions were validated in 333 randomly selected participants using ankle brachial pressure index <0.9 as the gold standard of arterial occlusive disease (symptomatic and asymptomatic subjects). Four simple questions eligible for self-administration had test properties similar to the WHO/Rose questionnaire and the Edinburgh claudication questionnaire.[12–14] IC subjects should have pain (1) in one or both legs during walking; (2) located to the calf; (3) that disappears after a period of rest; and (4) which is absent at rest. These questions had a specificity of 98.0% and a positive predictive value of 45.5%.[15,16]

Serum lipids and anthropometric factors

Total serum cholesterol concentrations were measured by the Liebermann–Buchard method, and triglycerides by a fluorimetric method.[17] HDL cholesterol concentrations were determined in frozen sera with a heparin-manganese method.[17] The ratio of total cholesterol to HDL cholesterol was finally calculated and this ratio will be referred to as TC/HDL cholesterol.[18] Each variable (total cholesterol, HDL cholesterol, triglycerides, and TC/HDL cholesterol) was categorized into three approximately equal groups (tertiles).

Recordings of height (in cm), weight (in kg), and waist and hip circumference (in cm) were standardized and performed by trained personnel. Body mass index (BMI) was computed as weight (in kg) divided by the squared value of height (in m), and body shape was calculated as waist circumference (in cm) divided by hip circumference (in cm). All variables were categorized into tertiles for the statistical analyses.

The presence of diabetes was ascertained by one simple question in the questionnaire and used as a dichotomized variable in the regression model. In addition, non-fasting blood glucose levels (mmol/L) and HbA1c levels (mg%) were measured in sera obtained at the examination. We used these measures, treated as ordinal variables, in the multivariate analyses.

Individuals who had never smoked cigarettes daily were considered non-smokers, and those who reported previous or current daily smoking were classified as former and current smokers, respectively. Both current and former smokers were asked to report how many cigarettes they currently usually smoked, or previously used to smoke. A pack-year was defined as smoking 20 cigarettes daily for one year, and the number of pack years each individual had smoked was calculated on the basis of the information provided by current or former smokers. Information on duration of smoking, age when starting smoking, and time since cessation of smoking was collected from the questionnaire, and the response to each variable was divided into tertiles for the statistical analyses.

Brachial blood pressure was recorded in the sitting position with the cuff placed on the right upper arm. The registered systolic and diastolic blood pressures were based on the mean value of the second and third out of three consecutive measurements. For statistical analyses both systolic and diastolic brachial blood pressure were treated as ordinal variables.

Statistical analyses

Logistic regression analysis was used to examine the association between serum lipids, BMI, body shape, and the prevalence of IC.[19] Age was included in 5-year categories to produce age-adjusted prevalence odds ratios (OR) with 95% confidence intervals (95% CI). All analyses were performed separately for men and women, and *P* values were computed to assess trend across categories (tertiles) by treating each exposure variable as a continuous variable in the regression model. In subsequent multivariate analyses we assessed the effect of potentially confounding variables such as smoking habits, diabetes and diastolic or systolic brachial blood pressure, by comparing age-adjusted and multivariable adjusted estimates. All statistical analyses were performed using the statistical software SPSS for Windows (Release 11.07, Copyright SPSS Inc., 1989–2003).

Results

The prevalence of IC was similar for men (1.1%) and women (1.2%), and IC subjects were approximately 6 years older than individuals without IC (Table 1). The prevalence was much higher among those who were 65 years or older (3.0% for men and 3.1% for women) compared to those under the age of 45 (0.4% for men and 0.3% for women). We observed no gender differences for any of the 5 years age groups.[16]

For women, total cholesterol was not associated with the prevalence of IC (*P* trend = .461, Table 2). However, for men there was a weak positive association (*P* trend = .055) between total cholesterol and the prevalence of IC. Moreover, in men with total serum cholesterol 6.6 mmol/L or higher the prevalence of IC was 60% higher (OR = 1.6; 95% CI = 1.0–2.6) than men whose total cholesterol was lower than 5.5 mmol/L.

HDL cholesterol was strongly and negatively associated with the prevalence of IC in women (*P* trend < .001, Table 2) but not in men (*P* trend = 0.131). The OR for women in the highest (≥1.7 mmol/L) compared with the lowest tertile (<1.3 mmol/L) of HDL cholesterol was 0.3 (95% CI = 0.2–0.5). Comparing women in the highest and lowest tertile of TC/HDL cholesterol, the OR was 2.8 (95% CI = 1.6–4.7; *P* trend < .001, Table 2). Among men, there was a positive trend in prevalence related to tertiles of TC/HDL cholesterol (OR of 1.7; 95% CI = 1.1–2.8; *P* trend = 0.023).

There was a positive association between serum concentrations of triglycerides and the prevalence of IC in both genders (Table 2). In women, the association displayed a strong trend across tertiles (*P* trend = .002). Women in the highest triglyceride category (≥1.40 mmol/L) were more than twice (OR = 2.2; 95% CI = 1.3–3.8) as likely to have IC compared to women in the lowest tertile (<1.10 mmol/L). For men, the strength of the association was weaker (*P* trend = .029) than for women, and the OR comparing the highest with the lowest category of serum levels of triglycerides was 1.6 (95% CI = 1.0–2.6).

Women with body mass index (BMI) in the highest tertile (≥27.7) were more likely to have IC compared to women whose BMI was in the lowest tertile (<24.2) (OR = 1.7; 95% CI = 1.0–2.7, *P* trend = .032), but in men, we observed no such association (*P* trend = .658, Table 3). Women in the highest tertile of waist (≥86 cm) (OR = 1.7; 95% CI = 1.1–2.8, *P* trend = .021) and hip circumference (≥105 cm) (OR = 1.7; 95% CI = 1.1–2.6, *P* trend = .020) were more likely to have IC compared with women in the lowest tertile (Table 3). In men, however, the measurements of waist (*P* trend = .392) and hip circumference (*P* trend = .921) were not related to the prevalence of IC. We observed no association with IC for the ratio between waist and hip circumference (body shape) in either gender.

In supplementary analyses, we assessed whether any of these associations could be due to confounding by current or previous smoking, number of cigarettes smoked, time since smoking cessation, duration of smoking, and number of pack years. Adjustment for these factors, however, did not substantially influence any of the results. Additional adjustments were made for systolic and diastolic blood pressure, BMI, blood levels of HbA1c, blood glucose levels, and previously diagnosed diabetes mellitus, but the estimates remained nearly identical.

Discussion

We found a strong positive association between serum concentrations of TC/HDL cholesterol and triglycerides and the prevalence of intermittent claudication. We observed a negative association between HDL

Table 1. Baseline characteristics of the cross sectional data stratified by gender

	Women		Men	
	Cases *n* = 122	Non-cases *n* = 10,122	Cases *n* = 108	Non-cases *n* = 9297
Age	58.6 ± 8.1	52.6 ± 8.5	59.1 ± 8.3	52.9 ± 8.5
Total cholesterol level (mmol/L)	6.64 ± 1.31	6.12 ± 1.22	6.35 ± 1.32	6.06 ± 1.13
HDL-Cholesterol level (mmol/L)	1.43 ± 0.42	1.55 ± 0.40	1.24 ± 0.51	1.34 ± 0.42
Triglycerides (mmol/L)	2.12 ± 1.21	1.68 ± 1.02	2.46 ± 1.83	2.15 ± 1.29
Height (m)	1.64 ± 0.06	1.63 ± 0.07	1.77 ± 0.06	1.75 ± 0.06
Weight (kg)	71.5 ± 12.5	74.1 ± 13.3	84.6 ± 11.9	83.9 ± 12.6
Body mass index (kg/m^2)	26.5 ± 4.4	28.0 ± 5.0	26.9 ± 3.4	27.2 ± 3.8
Waist circumference (cm)	85.9 ± 11.1	82.2 ± 11.1	94.9 ± 10.4	93.0 ± 8.8
Hip circumference (cm)	105.4 ± 9.2	102.8 ± 9.0	102.5 ± 6.2	102.7 ± 5.9
Waist to hip ratio	0.81 ± 0.06	0.79 ± 0.06	0.92 ± 0.07	0.89 ± 0.06
Never smokers (n)	39	4722	19	3577
Former smokers (n)	33	2229	35	3014
Current smokers (n)	50	3270	54	2706

Values are given as mean ± standard deviation.

Table 2. Age-adjusted odds ratio (OR) and 95% confidence interval (CI) for the prevalence of IC associated with blood lipid measurements

Variables	Women					Men				
	Cases	Non-cases	OR	95% CI	*P* trend*	Cases	Non-cases	OR	95% CI	*P* trend*
Total cholesterol (mmol/L)†										
T1	31	3410	1.0	Reference		27	3130	1.0	Reference	
T2	26	3340	0.6	(0.4–1.0)		34	3052	1.2	(0.7–2.0)	
T3	64	3462	1.1	(0.7–1.7)	.461	47	3102	1.6	(1.0–2.6)	.055
HDL cholesterol (mmol/L)‡										
T1	67	3502	1.0	Reference		40	2702	1.0	Reference	
T2	32	3124	0.6	(0.4–0.9)		33	3420	0.6	(0.4–1.0)	
T3	22	3586	0.3	(0.2–0.5)	<.001	35	3159	0.7	(0.5–1.1)	.131
Total-/HDL-cholesterol§										
T1	18	3433	1.0	Reference		27	3116	1.0	Reference	
T2	33	3409	1.5	(0.8–2.7)		34	3078	1.3	(0.8–2.1)	
T3	70	3370	2.8	(1.6–4.7)	<.001	47	3087	1.7	(1.1–2.8)	.023
Triglycerides (mmol/L)¶										
T1	19	3411	1.0	Reference		30	3113	1.0	Reference	
T2	40	3423	1.6	(0.9–2.8)		30	3087	1.0	(0.6–1.6)	
T3	62	3378	2.2	(1.3–3.8)	.002	48	3084	1.6	(1.0–2.6)	.029

* *P* values for test of trend by logistic regression model when variables as ordinal variables.
† Cut points for tertiles of total cholesterol were 5.6 and 6.6 for men, and 5.5 and 6.5 for women.
‡ Cut points for tertiles of HDL-cholesterol were 1.1 and 1.4 for men, and 1.3 and 1.7 for women.
§ Cut points for tertiles of the ratio of total cholesterol to HDL-cholesterol were 3.5 and 4.6 for men, and 4.3 and 5.6 for women.
¶ Cut points for tertiles of triglycerides were 1.1 and 1.7 for men, and 1.1 and 1.4 for women.

cholesterol and the prevalence of intermittent claudication, especially in women. In agreement with our findings, most previous studies have shown positive associations between TC/HDL cholesterol, triglycerides, and IC. However, for total serum cholesterol and HDL cholesterol results have varied between studies and no consistent pattern has emerged.[8,18,20–23] Most previous population surveys addressing lower limb arterial disease were designed to study coronary heart disease, few studies included a large number of women, and very few have investigated an unselected population with a large number of male and female smokers.

We have tested the validity of the questions by adding the ankle brachial pressure index <0.9 as a gold standard of peripheral occlusive disease in a

Table 3. Age-adjusted odds ratio (OR) and 95% confidence interval (CI) for the prevalence of IC associated with BMI, waist, hip and waist to hip-ratio

Variables	Women					Men				
	Cases	Non-cases	OR	95% CI	*P* trend*	Cases	Non-cases	OR	95% CI	*P* trend*
BMI (kg/m^2)†										
T1	26	3416	1.0	Reference		32	3094	1.0	Reference	
T2	38	3403	1.2	(0.8–2.1)		38	3099	1.2	(0.7–1.9)	
T3	57	3380	1.7	(1.0–2.7)	.032	37	3090	1.1	(0.7–1.8)	.658
Waist (cm)‡										
T1	26	3465	1.0	Reference		33	3265	1.0	Reference	
T2	36	3321	1.2	(0.7–2.0)		28	2801	0.9	(0.5–1.5)	
T3	60	3408	1.7	(1.1–2.8)	.021	47	3214	1.2	(0.8–1.9)	.392
Hip (cm)§										
T1	29	3459	1.0	Reference		39	3424	1.0	Reference	
T2	35	3410	1.1	(0.7–1.8)		34	2624	1.2	(0.7–1.8)	
T3	58	3326	1.7	(1.1–2.6)	.020	35	3232	1.0	(0.6–1.5)	.921
Waist/hip-ratio¶										
T1	26	3391	1.0	Reference		27	3125	1.0	Reference	
T2	47	3380	1.6	(1.0–2.6)		29	3085	1.0	(0.6–1.6)	
T3	49	3423	1.4	(0.9–2.4)	.179	52	3070	1.5	(0.9–2.4)	.076

* *P* values for test of trend by logistic regression model when variables as ordinal variables.
† Cut points for tertiles of BMI were 25.3 and 27.9 for men, and 24.2 and 27.7 for women.
‡ Cut points for tertiles of waist circumference were 89.1 and 96.2 for men, and 76.3 and 86.0 for women.
§ Cut points for tertiles of hip circumference were 100.1 and 105.2 for men, and 98.0 and 105.2 for women.
¶ Cut points for tertiles of the ratio of waist to hip circumference were 0.88 and 0.92 for men, and 0.77 and 0.82 for women.

selected group of subjects.[24] The results showed that only about 20% of those with ABPI <0.9 were likely to be detected by our questions (sensitivity of 19.2%).[15,16] Symptoms of IC may be interchangeable with other diseases, and such misclassification is likely even in symptomatic subjects. We estimated the positive predictive value of our IC questionnaire to be 45.5% compared to the gold standard of ABPI <0.9.[15,16] Thus, our questionnaire had test properties similar to those of the WHO/Rose questionnaire and the Edinburgh claudication questionnaire.[12–14]

In the analysis of each lipid we did not simultaneously adjust for other lipids, because of their close biological relation, which may result in statistical colinearity. In supplementary analyses, however, we explored whether the results related to serum lipids could be confounded by different smoking habits, diabetes, body mass, and systolic or diastolic blood pressure. Adjustment for these factors, however, did not substantially change the results.

The prevalence of previously diagnosed diabetes in this population was 2.8% for men and 2.1% for women. Diabetes mellitus is associated with hypertriglyceridemia, thus low levels of HDL cholesterol, and consequently progression of lower limb arterial disease.[7] Adjustment for the presence of diabetes, blood levels of glucose or HbA1c did not substantially influence any of the results. The association between hypertriglyceridemia, low serum concentrations of HDL cholesterol, and IC are, therefore, not influenced by diabetes, and thus these factors must be considered independent risk factors for IC even in otherwise healthy subjects.

Statins protect against coronary events and stroke, and recent clinical trials comparing standard regimens with more intensive statin therapy have shown that the latter reduces the risk of disease even further.[25,26] Thus, lipid lowering treatment for indigent coronary and stroke patients appears to be an area of high priority. In relation to patients with IC but without coronary heart disease, however, lipid lowering treatment has not yet become a standard regimen.[27] Nevertheless, findings now indicate that most patients with a high risk of vascular events could benefit from such treatment.[28–31] Our results suggest that serum levels of TC/HDL cholesterol and triglycerides are positively associated with IC both for men and women, and thus, the results may support lipid lowering treatment for IC patients.

Obese people have a relatively high serum concentration of TC/HDL cholesterol and triglycerides, and are thus at increased risk of hypertension, diabetes, and cardiovascular events.[32,33] Further, TC/HDL cholesterol is the best predictor both for outcome and treatment benefit in obese people.[18] Weight reduction lowers plasma lipids, and may therefore slow down the development of vascular occlusive diseases.[34] Both large waist circumference and high waist-to-hip ratio ('apple-shape') are suggested to predispose to coronary heart disease.[35,36] In women, we found high BMI to be associated with higher prevalence of IC, but there was no clear association between body shape and the prevalence of IC in either women or men.

It has been hypothesized that elevated levels of estrogens may reduce the risk of peripheral arterial disease in women by lowering TC/HDL and increasing HDL cholesterol.[37] However, there is little evidence in the literature for such associations.[37] We observed no gender differences for the association between IC, TC/HDL and HDL cholesterol, and our findings therefore support previous reports suggesting that there is no association between endogenous sex hormones and the development of peripheral arterial disease.

In summary, TC/HDL cholesterol and triglycerides were positively, and HDL cholesterol was negatively associated with the prevalence of intermittent claudication both in men and women, but the associations were generally stronger for women than for men. High BMI and wide waist and hip circumference were positively associated with the prevalence of IC in women, but not in men.

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Accepted 4 June 2005
Available online 14 July 2005

Paper IV

Paper IV is not included due to copyright.

Paper V

Eur J Vasc Endovasc Surg **32**, 60–65 (2006)
doi:10.1016/j.ejvs.2005.12.022, available online at http://www.sciencedirect.com on SCIENCE DIRECT

The Prevalence of Chronic Critical Lower Limb Ischaemia in a Population of 20,000 Subjects 40–69 Years of Age

S.A. Jensen,[1,2] L.J. Vatten[3] and H.O. Myhre[1,2*]

Departments of [1]Circulation and Medical Imaging, Faculty of Medicine, University Medical Center, Norwegian University of Science and Technology, N-7489 Trondheim, [2]Surgery, St Olavs Hospital, University Hospital of Trondheim, Olav Kyrres Gate 17, N-7006 Trondheim, and [3]Public Health, University Medical Center, Norwegian University of Science and Technology, N-7489 Trondheim, Norway

***Objective**. To study the prevalence and possible risk factors for chronic critical lower limb ischaemia (CLI) in an unselected population of 20,291 Norwegian men and women 40–69 years of age.*
***Methods**. Between 1995 and 1997, all residents 20 years or older in Nord-Trøndelag County, Norway, were invited to participate in a population study (the HUNT 2 Study). Among the 71.2% who attended, 20,291 participants 40–69 years of age responded to questions specifically aimed at identifying CLI. Chronic critical ischaemia was suspected if participants indicated: (1) ulcers on toes, foot or ankle that had failed to heal and/or; (2) persistent pain in the forefoot while in the supine position, but with relief of this pain when standing up. Using logistic regression analyses, we estimated the association between the prevalence of CLI and smoking, diabetes mellitus, previous cardiovascular events, blood lipids and glucose levels, and body mass index (BMI).*
***Results**. The age-adjusted prevalence of CLI was 0.26% among men and 0.24% among women, and there was no gender difference in any age group (age-adjusted OR = 0.91, 95% CI = 0.52–1.58). The presence of increased age, diabetes mellitus, angina pectoris, high triglyceride levels, and high BMI were all independently associated with higher prevalence of CLI.*
***Conclusion**. The prevalence of CLI was 0.24%, similar for both genders, and increased with age. Risk factors usually seen in atherosclerotic patients were associated with suspected CLI.*

Keywords: Peripheral arterial disease; Epidemiology; Population study; Prevalence; Association.

Introduction

Chronic critical lower limb ischaemia (CLI) is a serious condition if left untreated. Over 25% of CLI patients will require major amputation, but reconstructive arterial surgery improves limb salvage.[1–4] Although surgical interventions are costly, they have proven cost-effective compared to conservative treatment.[5–8] Nevertheless, mortality is expected to be 20% within the first year of presentation, and 40–75% are likely to die within 5 years.[3,9,10] The occurrence of CLI has been studied by inference made from major amputations and CLI hospitalization rates. Others have studied the progression to CLI in patients with intermittent claudication.[3,4,11–17] Although these estimates are approximations, different approaches within comparable populations have yielded fairly similar estimates of the disease frequency.[12,17] Thus, reports on incidence of CLI have ranged from 500 to 1000 per million inhabitants per year, and the prevalence has been estimated to be 1 per 2500 inhabitants.[12,13,17] However, some CLI patients may never be hospitalized, and the true prevalence may only be obtained in population based studies.[18]

Critical lower limb ischaemia is recognized in patients with persistent ischaemic pain of more than 14 days duration requiring analgesia and/or characterized by tissue loss due to ischaemia.[8,13,15] The Fontaine and the Rutherford classifications seek to identify patients with lower limb ischaemia including CLI.[5,8] However, these classifications do not include a clear definition of CLI, rely on trained personnel for the diagnosis, and require the use of ankle brachial pressure index, ABPI, as an objective outcome

*Corresponding author. Professor Hans O. Myhre, MD, PhD, Department of Surgery, St Olavs Hospital, University Hospital of Trondheim, Olav Kyrres Gate 17, N-7006 Trondheim, Norway.
E-mail address: hans.myhre@ntnu.no

measure.[14,15,19] Such objective diagnostic tests are costly and in larger population surveys simple screening tests are easier to use.[13–15,19,20]

The aim of this study was to use a questionnaire to estimate the prevalence of CLI in an unselected population of 20,291 Norwegian men and women between 40 and 69 years of age. Further, we studied the association between risk factors for atherosclerotic disease in relation to the prevalence of suspected CLI.

Patients and Methods

The study population

Between 1995 and 1997 all residents 20 years or older in Nord-Trøndelag County, Norway, were invited to participate in a health study called HUNT 2 (Helseundersøkelsen i Nord-Trøndelag: HUNT 2).[21] 71.2% (66,140) of those invited attended and all participants responded to a brief questionnaire enclosed with the invitation. They also underwent a physical examination and received a second questionnaire that was to be completed at home and returned by mail. The clinical examination included measurements of height, weight, brachial blood pressure, and a sample of venous blood was collected. The second questionnaire was handed to participants aged 20–69 years of age and included questions designed to identify individuals with CLI. Participants 70 years of age and older did not receive the second questionnaire. Since, CLI is very rare at a young age, we restricted the analysis to participants 40–69 years of age and thus, the study population consisted of 9640 men and 10,651 women.

The diagnosis of CLI

We constructed a simple questionnaire that was based only on symptoms or signs of the disease, and to fulfill the criteria of suspected CLI, participants should answer yes to one or both of the following questions: (1) Do you have ulcers on toes, foot or ankle that have failed to heal?; (2) Do you have persistent pain in the forefoot while in the supine position, but with relief of the pain when standing up?

Study factors

Individuals who had never smoked cigarettes daily were considered never smokers, and those who reported previous or current daily smoking were classified as former or current smokers, respectively. For the regression analyses, smoking was categorized into current, former, or never smokers. History of diabetes mellitus (both insulin-dependent and non-insulin-dependent), previous myocardial infarction (MI), and current or previous angina pectoris were obtained from the questionnaire. The variables were dichotomized for the regression analyses. Non-fasting blood glucose levels (millimole per litre) were measured in sera obtained at the examination.[21] Further, in diabetic patients, analyses of HbA1c levels (milligram percentage) were performed. These two variables were divided at the median for the statistical analyses. Concentrations of total serum cholesterol (TC) were measured by the Liebermann–Buchard method, and triglyceride concentrations by a fluorimetric method.[22] High density lipoprotein (HDL) was determined with a heparin–manganese method.[22] Each variable (total cholesterol, HDL–cholesterol and triglycerides) was categorized into two approximately equal groups using the median as cut point and included in the regression model as a categorical variable. Recordings of height (in centimetre) and weight (in kilogram) were standardized and performed by trained personnel. Body mass index (BMI) was computed as weight (in kilogram) divided by the height (in metre) squared. The variable was categorized into two approximately equal groups before inclusion in the regression model.

Statistical analyses

Age adjustment for the total prevalence of CLI among men and women was calculated using the direct method with the total HUNT 2 study population between 40 and 69 years of age as the reference standard. Gender differences in the prevalence of CLI were investigated by age-adjusted prevalence ratios, and precision of the ratios was estimated with 95% confidence interval (CI). Associations between the prevalence of CLI and smoking, diabetes mellitus, blood lipids and glucose levels, previous cardiovascular events and BMI were investigated using logistic regression analyses. Age was included in the regression model and the variable divided into 5-year categories to produce age-adjusted prevalence odds ratios (OR) with 95% confidence intervals (95% CI). The effect of potential confounding by smoking, diabetes and blood lipids was assessed in subsequent multivariate analyses by comparing age-adjusted and multivariate adjusted estimates. All statistical analyses were performed using the

Table 1. The prevalence of chronic critical lower limb ischaemia in men and women 40–69 years of age

Age	Men			Women			Total		
	CLI	Participants	Prevalence (%)	CLI	Participants	Prevalence (%)	CLI	Participants	Prevalence (%)
40–49	8	3860	0.21	4	4420	0.09	12	8280	0.14
50–59	8	3264	0.25	10	3575	0.28	18	6839	0.26
60–69	9	2516	0.36	11	2656	0.41	20	5172	0.39
Total	25	9640	0.26*	25	10,651	0.24*	50	20,291	0.24*

* Age adjusted prevalence.

statistical software package SPSS for Windows (Release 13.00, Copyright SPSS, Inc., 1989–2005).

Results

The age-adjusted prevalence of CLI in the total population was 0.24% (Table 1), 0.26% for men and 0.24% for women. We observed no gender differences in any age group. The ratio between women and men was 0.91 (95% CI, 0.52–1.58), and the prevalence increased with age in both genders (Fig. 1).

Current smoking showed no association with the prevalence of CLI when compared to former and never smokers (OR = 1.2; 95% CI = 0.6–2.2, Table 2). However, the prevalence of CLI was substantially higher in former and current smokers compared to the occurrence of disease among never smokers (OR = 2.3; 95% CI = 1.1–4.6).

CLI was 4.4 times more common among people with diabetes compared to the general population (OR = 4.4; 95% CI = 1.9–10.5). There was also a tendency that previous cardiovascular events were more common among the CLI subjects: they were nearly twice as likely to have suffered from myocardial infarction (OR = 1.8; 95% CI = 0.6–5.2), and nearly three times more likely to have angina pectoris (OR = 2.7; 95% CI = 1.0–7.6), compared to the general population.

Subjects with serum total cholesterol concentrations higher than 6.0 mmol/L had an OR of 1.6 (95% CI = 0.9–3.0) compared to subjects with TC concentrations less than 6.0 mmol/L. Further, CLI was more likely in subjects with serum triglyceride concentrations higher than 1.50 mmol/L compared to lower TG levels (OR = 2.1; 95% CI = 1.2–4.0). Symptoms of CLI were almost 2.6 times as common for subjects with BMI higher than 26.3 kg/m^2 compared to subjects with lower recordings (OR = 2.6; 95% CI = 1.4–4.9). However, serum concentrations of HDL–cholesterol (OR = 0.9; 95% CI = 0.5–1.5), blood glucose (OR = 1.1; 95% CI = 0.6–1.9), and HbA1c (OR = 1.0; 95% CI = 0.2–4.9) were not associated with the prevalence of CLI (Table 3).

Potential confounding by smoking, diabetes and blood factors of the association between the prevalence of CLI and the different study variables was assessed in multivariate analyses. However, adjustment for these variables, either individually or in combination, did not substantially change any of the results (data not shown).

Discussion

In this cross-sectional study of an unselected population of over 20,000 individuals an attempt was made to estimate the prevalence of CLI and assess the association between the occurrence of disease and possible risk factors. Two thousand and five hundred per million inhabitants had CLI, the prevalence was similar among men and women, and increased by age in both genders. We observed positive associations between the prevalence of CLI and smoking, diabetes mellitus, angina pectoris, serum triglyceride levels and body mass index.

The annual case fatality rate for CLI seems fairly stable at 15–20%.[1–3,9,12,23–25] In Norway, the incidence of CLI has previously been computed to 600–800 per million per year.[16] Thus, our prevalence estimate appears to correspond well with these numbers provided the life expectancy on average is about 5 years for patients with CLI. However, a higher prevalence of CLI among subjects over 70 years of

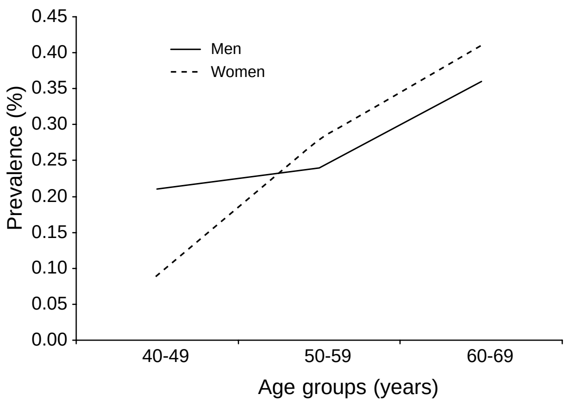

Fig. 1. The prevalence of chronic critical lower limb ischaemia in men and women 40–69 years of age increased by age.

Table 2. Age-adjusted odds ratio (OR) and 95% confidence interval (CI) for the prevalence of CLI associated with smoking, diabetes mellitus, previous myocardial infarction and previous or current angina pectoris

Variables	Women and men			
	CLI	Not CLI	OR	95% CI
Smoking habit				
Former and never smokers	32	13,288	1.0	Reference
Current smokers	18	6034	1.2	0.6–2.2
Smoking habit				
Never smokers	12	6957	1.0	Reference
Former and current smokers	38	12,436	2.3	1.1–4.6
Diabetes mellitus				
Not diabetes mellitus	44	19,684	1.0	Reference
Current diabetes mellitus	6	500	4.4	1.9–10.5
Myocardial infarction				
Never myocardial infarction	45	19,473	1.0	Reference
Previous myocardial infarction	4	696	1.8	0.6–5.2
Angina pectoris				
Not angina pectoris	46	19,699	1.0	Reference
Previous or current angina pectoris	4	483	2.7	1.0–7.6

age is likely, and inclusion of these subjects would most likely have contributed to an even higher frequency of the disease. Thus, the occurrence of CLI in the present investigation may seem relatively high. In conformity with previous reports, our findings support that the prevalence of CLI increases with age.[25–27]

Smoking is an important risk factor for peripheral arterial disease. The risk increases with the number of cigarettes smoked, and becomes weaker with time after smoking cessation.[28] Furthermore, amputations are more common in IC patients who have been heavy smokers.[28,29] The presence of CLI before the age of 70 was in our data, however, not significantly higher among current smokers compared to never and former smokers. Nevertheless, current and former smokers combined had a substantially higher prevalence of CLI compared to never smokers. Our results may, therefore, indicate that a large proportion of suspected CLI subjects had stopped smoking prior to participation in our study when realizing that they were severely diseased.[17]

Diabetes is an independent risk factor for peripheral arterial occlusive disease, and smoking appears to have an additive effect on this risk.[26,30–32] In diabetics, major amputations are up to eleven times more frequent, and surgical procedures are performed at an earlier age than in CLI subjects without diabetes.[13,33–36] In this study, CLI were more than four times more likely in diabetics compared to the general population. Diabetes showed the strongest association with the prevalence of CLI among the investigated risk factors. However, due to the relatively small number of patients who had the combination of CLI and diabetes, our data do not allow firm conclusions on this point.

We found no association with non-fasting blood glucose and the prevalence of CLI. Non-fasting glucose levels may not distinguish well between diabetics and non-diabetics, and the glucose lowering treatment in known diabetics will prevent any association from becoming apparent. HbA1c is the concentration of glycosylated red blood cells, and the recording is a good indicator for blood glucose levels during the last few weeks. Among diabetics, however, levels of HbA1c were not associated with the prevalence of CLI. Thus, well regulated diabetics may share the same risk of developing CLI as diabetics with poorly regulated glucose concentrations.

For blood lipids there is evidence that peripheral arterial disease is associated with high levels of total cholesterol and triglycerides, and our data supports such findings for CLI.[36] Since patients with CLI in the present study may be regarded as relatively young, they might have a different lipid profile, compared to older subjects with this disease. Recent studies have even shown that high concentrations of HDL–cholesterol are negatively associated with the prevalence of IC.[13] However, this association was not apparent from our results.

In cross sectional data the exposure and outcome variables are measured at the same time, and thus, a temporal cause and effect relation cannot be firmly established. Nevertheless, it seems more plausible to interpret high serum lipids, high BMI, previous or current angina pectoris, and diabetes mellitus as elements in the causal pathway of CLI, rather than the opposite. Thus, one could interpret the presented associations as possible risk factors for the disease.

A uniform definition of CLI is important for epidemiological analyses to be comparable over time. According to the European consensus document chronic critical leg ischaemia is defined by clinical criteria like pain and use of analgesics in addition to objective measurements of ankle (ABPI) or toe systolic blood pressure.[5,8,13,15] Although, measurement of ABPI may give important information in addition to the medical history, this test is not easily used in large epidemiological investigations due to costs and time consumption. Furthermore, the reproducibility of blood pressure measurements have proven highly influenced by the experience of the examiners, and furthermore, the measurements of ABPI may be unreliable in diabetics.[14,15,19,37] Thus, in large population studies, it may be easier to identify CLI on information about symptoms and clinical signs.

The Fontaine stages grade the severity of lower limb ischaemia; asymptomatic individuals (stage I),

Table 3. Age-adjusted odds ratio (OR) and 95% confidence interval (CI) for the prevalence of CLI associated with lipids, glucose and HbA1c levels, and body mass index (BMI)

Variables	Women and men			
	CLI	Not CLI	OR	95% CI
Total cholesterol (mmol/L)*				
Low	16	9600	1.0	Reference
High	34	10,597	1.6	0.9–3.0
HDL–cholesterol (mmol/L)†				
Low	26	9979	1.0	Reference
High	24	10,215	0.9	0.5–1.5
Triglycerides (mmol/L)‡				
Low	15	10,027	1.0	Reference
High	35	10,170	2.1	1.2–4.0
Glucose (mmol/L)§				
Low	20	9030	1.0	Reference
High	30	11,155	1.1	0.6–1.9
HbA1c (%)¶				
Low	3	241	1.0	Reference
High	3	245	1.0	0.2–4.9
Body mass index (kg/m^2)‖				
Low	13	10,107	1.0	Reference
High	37	10,073	2.6	1.4–4.9

* Cut-points for high and low values of total cholesterol was 6. 00 mmol/L.
† Cut-points for high and low values of HDL–cholesterol was 1. 40 mmol/L.
‡ Cut-points for high and low values of triglycerides was 1. 51 mmol/L.
§ Cut-points for high and low values of glucose was 5.2 mmol/L.
¶ Cut-points for high and low values of HbA1c was 7.8%.
‖ Cut-points for high and low values of body mass index was 26.3 kg/m^2.

intermittent claudication (stages IIa and IIb), rest pain (stage III), and trophic lesions (stage IV). For stage III (rest pain), however, the definition is rather wide, and may not distinguish well between claudicants (IC) with occasional nocturnal pain and CLI patients. The Rutherford classification was primarily constructed to detect clinical improvement after treatment and intended for administration by trained personnel.[8,16] Grade II (ischaemic rest pain) is more clearly defined compared to the Fontaine stage III, however, based on ABPI measurements or pulse palpation. Thus, as both symptom scores rely on administration by trained personnel, the general population would most likely fail to understand the terms included in these definitions. Further, the additional objective tests used to verify the diagnosis are not easily used in large population screenings. We, therefore, decided to construct a combination of simple questions intended for self administration.

The currently presented questionnaire was based only on symptoms and signs of CLI. Subjects with any form of chronic ischemic pain or trophic ulcers on the foot were regarded as having CLI. The level of physical activity was not taken into consideration. Nevertheless, subjects with sensory neuropathy without ulcers on foot or toes may have escaped detection. Further, ulcers of other origins than atherosclerosis may have been included. Thus, one cannot exclude the possibility that some patients with venous ulcers in the gaiter area might have been included in our data. Finally, discomfort from orthopaedic conditions may be interchangeable with ischemic pain, but the questions were designed in an attempt to exclude these patients by adding the aspect of pain relief while the foot was dependent. Other disadvantages of the present study are that the questions had not been validated against a 'gold standard' including history, a thorough physical examination and measurement of ABPI. Further, it was impossible to call back subjects with CLI for a second evaluation due to patient confidentiality. To compensate for this we investigated the relation between suspected CLI subjects and risk factors, which are known to be associated with the condition. Finally, one cannot exclude the possibility that subjects with acute limb ischaemia have been included.

Compared to previous reports from Norway our data indicate a relatively high prevalence of CLI in a rather young population.[16,38] Thus, with the general aging of the Norwegian population the number of patients presenting with CLI may be expected to increase in the future.

In conclusion, the prevalence of CLI was 0.24%, similar between the genders, and increased with age. Risk factors commonly observed in atherosclerotic patients were found among the suspected CLI subjects we identified.

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Accepted 23 December 2005
Available online 02 March 2006

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
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86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
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98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
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103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139.Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140.Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.
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141.Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142.Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143.Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144.Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145.Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146.Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147.Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148.Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149.Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150.Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151.Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152.Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153.Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154.Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155.Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156.Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157.Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES
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158.Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160.Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161.Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162.Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163.Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164.Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165.Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166.John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167.Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198.Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199.Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200.Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES
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201.Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202.Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203.Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204.Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205.Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206.Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207.Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208.Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209.Pål Klepstad: MORPHINE FOR CANCER PAIN
210.Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211.Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212.Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
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214.Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215.Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS
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216.Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217.Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218.Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219.Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220.Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221.Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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223.Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS

251.Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252.Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253.Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254.Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255.Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256.Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257.Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258.Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259.Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260.Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
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