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The prevalence of symptomatic arterial disease of the lower limb

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The HUNT Study
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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.

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.

III. Jensen SA, Vatten LJ, Nilsen TIL, Romundstad PR, Myhre HO. Serum lipids and anthropometric factors related to the prevalence of intermittent claudication.

IV. Jensen SA, Vatten LJ, Nilsen TIL, Romundstad P, Myhre HO. The association between smoking and the prevalence of intermittent claudication.

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.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABPI</td>
<td>Ankle brachial pressure index</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>c.i.</td>
<td>Confidence interval</td>
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<tr>
<td>CLI</td>
<td>Critical limb ischemia</td>
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<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
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<tr>
<td>IC</td>
<td>Intermittent claudication</td>
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<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>PAOD</td>
<td>Peripheral arterial occlusive disease</td>
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<tr>
<td>TC</td>
<td>Total cholesterol</td>
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<td>TG</td>
<td>Triglycerides</td>
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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., 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.,
The first properly organized field survey was conducted early in the 1960s (Rose, 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 wheelchair 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 \( (P \text{ trend} = .032), \) waist
circumference \((P \text{ trend} = .021)\), and hip circumference \((P \text{ trend} = .020)\) 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 \((\text{age-adjusted OR}=0.91, 95 \text{ per cent c.i.}=0.52–1.58)\), 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 characterized 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 ischemic pain may become apparent in the thigh or calf depending on the anatomical localization of the arterial obstruction.
Intermittent claudication is therefore 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, ischemic 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
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, fluctuations in the ischemic state is common, and failure of surgical treatment may not necessary result in amputation. A strict definition is therefore warranted, and recommendations 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 ischaemia. 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 susceptibility of arterial diseases (Collins,

**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 (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.
References


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

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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 measure-
ments of height, weight, blood pressure and a blood sample was collected. A second questionnaire includ-
ing 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 question-
naires covered more than 200 health related questions.

¹ Please address all correspondence to: H. O. Myhre, Department of
Surgery, St Olavs Hospital, University Hospital of Trondheim,
N-7006 Trondheim, Norway.
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). 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.

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.](image)

<table>
<thead>
<tr>
<th>Table 1. The questionnaire on intermittent claudication (IC) in the HUNT study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you experienced pain in one or both legs during walking?</td>
</tr>
<tr>
<td>Where is the pain localized?</td>
</tr>
<tr>
<td>Does the pain regress after a period of rest?</td>
</tr>
<tr>
<td>Is the pain present at rest?</td>
</tr>
<tr>
<td>Can you walk further than 50 meters?</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 2. The prevalence of intermittent claudication (IC) by self reporting of symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
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<tr>
<td>---</td>
</tr>
<tr>
<td>40–44</td>
</tr>
<tr>
<td>45–49</td>
</tr>
<tr>
<td>50–54</td>
</tr>
<tr>
<td>55–59</td>
</tr>
<tr>
<td>60–64</td>
</tr>
<tr>
<td>65–69</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Age standardized prevalence by direct age-standardization.
Table 3. Prevalence ratio between men and women.

<table>
<thead>
<tr>
<th>Age group</th>
<th>PR*</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–44</td>
<td>0.8</td>
<td>(0.3–2.1)</td>
</tr>
<tr>
<td>45–49</td>
<td>1.0</td>
<td>(0.4–2.2)</td>
</tr>
<tr>
<td>50–54</td>
<td>1.9</td>
<td>(0.9–3.8)</td>
</tr>
<tr>
<td>55–59</td>
<td>1.4</td>
<td>(0.7–2.7)</td>
</tr>
<tr>
<td>60–64</td>
<td>0.7</td>
<td>(0.4–1.2)</td>
</tr>
<tr>
<td>65–69</td>
<td>1.1</td>
<td>(0.7–1.6)</td>
</tr>
<tr>
<td>Total</td>
<td>1.0</td>
<td>(0.8–1.3)</td>
</tr>
</tbody>
</table>

*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. 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 arthritis 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. The population over 67 years of age in Norway is expected to nearly double, reaching 0.9 to 1.2 million persons in 2050. Also, the incidence of diabetes is increasing in the western world. 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. These prognoses must be taken into careful consideration for future health care planning.

Previous reports from the 1950’s and the 1960’s indicated that the male prevalence of IC was higher than for females. 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. The previously reported sex difference has been attributed to the effect of sex hormones on lipoproteins. The prevalence of IC in men over 60 years of age has been relatively stable since the 1950’s. 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.

Prevalence estimates for IC in previous studies vary from 0.4–14.4%. 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. 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.

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.
References


Accepted 14 November 2002
Paper II
Paper II is not included due to copyright.
Paper III
Serum Lipids and Anthropometric Factors Related to the Prevalence of Intermittent Claudication

S.A. Jensen, L.J. Vatten, T.I.L. Nilsen, P.R. Romundstad and H.O. Myhre

Departments of 1Community Medicine and General Practice, and 2Surgery, 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 trendmen < .023; P trendwomen < .001) and triglycerides (P trendmen < .029; P trendwomen < .002) were positively associated with the prevalence of IC. HDL cholesterol was negatively (P trendmen < .131; P trendwomen < .001) associated, whereas BMI (P trendwomen < .032), waist circumference (P trendwomen < .021), and hip circumference (P trendwomen < .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.8

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...
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. 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%.

**Serum lipids and anthropometric factors**

Total serum cholesterol concentrations were measured by the Liebermann–Buchard method, and triglycerides by a fluorimetric method. HDL cholesterol concentrations were determined in frozen sera with a heparin-manganese method. The ratio of total cholesterol to HDL cholesterol was finally calculated and this ratio will be referred to as TC/HDL cholesterol. 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. 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 = .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 = 0.029) 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 2). 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 cholesterol and the prevalence of IC in both genders, which is in line with previous studies.

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

<table>
<thead>
<tr>
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<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Non-cases</td>
<td>Cases</td>
<td>Non-cases</td>
</tr>
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<td>n = 122</td>
<td>n = 10,122</td>
<td>n = 108</td>
<td>n = 9,297</td>
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<td>Age</td>
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<td>52.6 ± 8.5</td>
<td>59.1 ± 8.3</td>
<td>52.9 ± 8.5</td>
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<td>Total cholesterol level (mmol/L)</td>
<td>6.64 ± 1.31</td>
<td>6.12 ± 1.22</td>
<td>6.35 ± 1.32</td>
<td>6.06 ± 1.13</td>
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<tr>
<td>HDL-Cholesterol level (mmol/L)</td>
<td>1.43 ± 0.42</td>
<td>1.55 ± 0.40</td>
<td>1.24 ± 0.51</td>
<td>1.34 ± 0.42</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.12 ± 1.21</td>
<td>1.68 ± 1.02</td>
<td>2.46 ± 1.83</td>
<td>2.15 ± 1.29</td>
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<td>Height (m)</td>
<td>1.64 ± 0.06</td>
<td>1.63 ± 0.07</td>
<td>1.77 ± 0.06</td>
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<td>Weight (kg)</td>
<td>71.5 ± 12.5</td>
<td>74.1 ± 13.3</td>
<td>84.6 ± 11.9</td>
<td>83.9 ± 12.6</td>
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<td>Body mass index (kg/m²)</td>
<td>26.5 ± 4.4</td>
<td>28.0 ± 5.0</td>
<td>26.9 ± 3.4</td>
<td>27.2 ± 3.8</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>85.9 ± 11.1</td>
<td>82.2 ± 11.1</td>
<td>94.9 ± 10.4</td>
<td>93.0 ± 8.8</td>
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<tr>
<td>Hip circumference (cm)</td>
<td>105.4 ± 9.2</td>
<td>102.8 ± 9.0</td>
<td>102.5 ± 6.2</td>
<td>102.7 ± 5.9</td>
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<td>Waist to hip ratio</td>
<td>0.81 ± 0.06</td>
<td>0.79 ± 0.06</td>
<td>0.92 ± 0.07</td>
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<td>Former smokers (n)</td>
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<tr>
<td>Current smokers (n)</td>
<td>50</td>
<td>5270</td>
<td>54</td>
<td>2706</td>
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</tbody>
</table>

Values are given as mean ± standard deviation.

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*Eur J Vasc Endovasc Surg* Vol 30, 12 2005
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>
<thead>
<tr>
<th>Variables</th>
<th>Women</th>
<th>Men</th>
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<td></td>
<td>Cases</td>
<td>Non-cases</td>
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<td>Total cholesterol (mmol/L)$^1$</td>
<td></td>
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</tr>
<tr>
<td>T1 31 3410 1.0 Reference</td>
<td>27 3130 1.0 Reference</td>
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<tr>
<td>T2 26 3340 0.6 (0.4–1.0)</td>
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<td>T3 64 3462 1.1 (0.7–1.7) .461</td>
<td>47 3102 1.6 (1.0–2.6) .055</td>
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<td>HDL cholesterol (mmol/L)$^2$</td>
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<td>T1 67 3502 1.0 Reference</td>
<td>40 2702 1.0 Reference</td>
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<tr>
<td>T2 32 3124 0.6 (0.4–0.9)</td>
<td>33 3420 0.6 (0.4–1.0)</td>
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<td>T3 22 3586 0.3 (0.2–0.5) &lt;.001</td>
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<td>Total-/HDL-cholesterol§</td>
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<td>27 3116 1.0 Reference</td>
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<td>T2 33 3409 1.5 (0.8–2.7)</td>
<td>34 3078 1.3 (0.8–2.1)</td>
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<td>T3 70 3370 2.8 (1.6–4.7) &lt;.001</td>
<td>47 3087 1.7 (1.1–2.8) .023</td>
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<tr>
<td>Triglycerides (mmol/L)$^5$</td>
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<tr>
<td>T1 19 3411 1.0 Reference</td>
<td>30 3113 1.0 Reference</td>
<td></td>
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<tr>
<td>T2 40 3423 1.6 (0.9–2.8)</td>
<td>30 3087 1.0 (0.6–1.6)</td>
<td></td>
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<tr>
<td>T3 62 3378 2.2 (1.3–3.8) .022</td>
<td>48 3084 1.6 (1.0–2.6) .029</td>
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</tr>
</tbody>
</table>

* $P$ 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Non-cases</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)$^1$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 26 3416 1.0 Reference</td>
<td>32 3094 1.0 Reference</td>
<td></td>
</tr>
<tr>
<td>T2 38 3403 1.2 (0.8–2.1)</td>
<td>38 3099 1.2 (0.7–1.9)</td>
<td></td>
</tr>
<tr>
<td>T3 57 3380 1.7 (1.0–2.7) .032</td>
<td>37 3090 1.1 (0.7–1.8) .658</td>
<td></td>
</tr>
<tr>
<td>Waist (cm)$^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 26 3465 1.0 Reference</td>
<td>33 3265 1.0 Reference</td>
<td></td>
</tr>
<tr>
<td>T2 36 3321 1.2 (0.7–2.0)</td>
<td>28 2801 0.9 (0.5–1.5)</td>
<td></td>
</tr>
<tr>
<td>T3 60 3408 1.2 (1.1–2.8) .021</td>
<td>47 3214 1.2 (0.8–1.9) .392</td>
<td></td>
</tr>
<tr>
<td>Hip (cm)$^5$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 29 3459 1.0 Reference</td>
<td>39 3424 1.0 Reference</td>
<td></td>
</tr>
<tr>
<td>T2 35 3410 1.1 (0.7–1.8)</td>
<td>34 2624 1.2 (0.7–1.8)</td>
<td></td>
</tr>
<tr>
<td>T3 58 3326 1.7 (1.1–2.6) .020</td>
<td>35 3232 1.0 (0.6–1.5) .921</td>
<td></td>
</tr>
<tr>
<td>Waist/hip-ratio$^4$</td>
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</tr>
<tr>
<td>T1 26 3391 1.0 Reference</td>
<td>27 3125 1.0 Reference</td>
<td></td>
</tr>
<tr>
<td>T2 47 3380 1.6 (1.0–2.6)</td>
<td>29 3085 1.0 (0.6–1.6)</td>
<td></td>
</tr>
<tr>
<td>T3 49 3423 1.4 (0.9–2.4) .179</td>
<td>52 3070 1.5 (0.9–2.4) .076</td>
<td></td>
</tr>
</tbody>
</table>

* $P$ 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 1.02 for men, and 0.77 and 0.82 for women.
selected group of subjects. 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%). 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. Thus, our questionnaire had test properties similar to those of the WHO/Rose questionnaire and the Edinburgh claudication questionnaire.

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. 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. 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. Nevertheless, findings now indicate that most patients with a high risk of vascular events could benefit from such treatment. 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. Further, TC/HDL cholesterol is the best predictor both for outcome and treatment benefit in obese people. Weight reduction lowers plasma lipids, and may therefore slow down the development of vascular occlusive diseases. Both large waist circumference and high waist-to-hip ratio (‘apple-shape’) are suggested to predispose to coronary heart disease. 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. However, there is little evidence in the literature for such associations. 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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Paper IV
Paper IV is not included due to copyright.
Paper V
The Prevalence of Chronic Critical Lower Limb Ischaemia in a Population of 20,000 Subjects 40–69 Years of Age

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

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 9,640 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

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/m² 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).

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 age.

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLI Participants</td>
<td>Prevalence (%)</td>
<td>CLI Participants</td>
</tr>
<tr>
<td>40–49</td>
<td>8</td>
<td>0.21</td>
<td>4</td>
</tr>
<tr>
<td>50–59</td>
<td>8</td>
<td>0.25</td>
<td>10</td>
</tr>
<tr>
<td>60–69</td>
<td>9</td>
<td>0.36</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>0.26</td>
<td>25</td>
</tr>
</tbody>
</table>

* Age adjusted prevalence.

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

<table>
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<tr>
<th>Variables</th>
<th>Women and men</th>
<th>CLI</th>
<th>Not CLI</th>
<th>OR</th>
<th>95% CI</th>
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<td>Smoking habit</td>
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<tr>
<td>Former and never smokers</td>
<td>32</td>
<td>13,288</td>
<td>1.0</td>
<td>Reference</td>
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<td>Current smokers</td>
<td>18</td>
<td>6394</td>
<td>1.2</td>
<td>0.6–2.2</td>
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<tr>
<td>Never smokers</td>
<td>12</td>
<td>6957</td>
<td>1.0</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Former and current smokers</td>
<td>38</td>
<td>12,436</td>
<td>2.3</td>
<td>1.1–4.6</td>
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<td>Diabetes mellitus</td>
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<td>Not diabetes mellitus</td>
<td>44</td>
<td>19,684</td>
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<td>Current diabetes mellitus</td>
<td>6</td>
<td>500</td>
<td>4.4</td>
<td>1.9–10.5</td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never myocardial infarction</td>
<td>45</td>
<td>19,473</td>
<td>1.0</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Previous myocardial infarction</td>
<td>4</td>
<td>696</td>
<td>1.8</td>
<td>0.6–5.2</td>
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<tr>
<td>Angina pectoris</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not angina pectoris</td>
<td>46</td>
<td>19,699</td>
<td>1.0</td>
<td>Reference</td>
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<tr>
<td>Previous or current angina pectoris</td>
<td>4</td>
<td>483</td>
<td>2.7</td>
<td>1.0–7.6</td>
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</tr>
</tbody>
</table>

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),
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. 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. Compared to previous reports from Norway our data indicate a relatively high prevalence of CLI in a rather young population. 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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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
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