# A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences

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***Objective:*** **A population-based point-prevalence study was conducted to determine the prevalence of peripheral arterial disease (PAD) in Sweden, with special attention to critical limb ischemia and sex differences.**
***Methods:*** **An age-standardized randomly selected population sample of 8000 women and men, aged 60 to 90 years, from four different regions in Sweden was invited to participate. The sample had the same age and gender distribution as the Swedish population in this age group. Participating subjects completed questionnaires on medical history, present medication, and symptoms, and their ankle-brachial index (ABI) was measured. Subjects were analyzed for presence of PAD according to reported symptoms and an ABI <0.9.**
***Results:*** **A total of 5080 subjects were included, giving a participation rate of 64%. The prevalence of any PAD, asymptomatic PAD, intermittent claudication, and severe limb ischemia was, respectively, 18% (95% confidence interval [CI], 16% to 20%) 11% (9% to 13%), 7% (6.5 to 7%) and 1.2% (1% to 1.5%). Women had a higher prevalence than men when PAD was diagnosed with ABI only; that is, asymptomatic PAD (12.6% vs 9.4%, $P = .03$) and severe limb ischemia (1.5% vs 0.8%, $P < .008$). The prevalence of any PAD was 7.9% in the age group 60 to 65 years and increased to 47.2% among the age group 85 to 90 years. Severe limb ischemia occurred in 0.3% in the youngest age group, was highest in the age group 80 to 84 years at 3.3%, and declined to 2.5% among the oldest. The prevalence of PAD differed between regions ($P < .0001$).**
***Conclusions:*** **PAD is common in Sweden, and almost a fifth of all elderly individuals have some stage of this disease. Women are more often afflicted than men. The prevalence of severe ischemia, as a measure of critical limb ischemia, is about 1% the population. (J Vasc Surg 2007;45:1185-91.)**

Peripheral arterial disease (PAD) is defined as atherosclerosis in the arteries distal to the aortic bifurcation, with or without symptoms in the legs. It is diagnosed by ankle-brachial pressure index (ABI) measurements and symptoms, and a confirmed diagnosis is associated with an increased cardiovascular mortality reaching the same levels as in patients with symptomatic coronary disease.[1] To reduce this risk, advice on lifestyle changes and exercise as well as pharmacologic treatment, including antiplatelet and statin therapy, should be offered to patients.[2-4] Symptomatic treatment is indicated for PAD patients with significant symptoms, but its use is highly variable between different parts of the world and even within countries.

Previous populations-based prevalence estimations indicate that a large proportion of Western populations has PAD, but most studies were performed more than a decade ago. [5-7] Since then, changes in PAD prevalence may have occurred because of the aging population, increased awareness of this disease in the health care community, and improved risk factor management, including smoking cessation.[8-10] Such positive developments may differ among regions depending on implementations of health care programs. Moreover, little information is available in the literature about sex differences in PAD prevalence, and data on severe symptomatic forms of PAD are entirely missing.[11-13]

Accurate and up-to-date information on PAD prevalence is important to enable identification of groups in the population where risk reduction and symptomatic treatment are needed. This could facilitate better projection of the resources needed and their allocation. The purpose of this study was to determine the PAD prevalence in Sweden. In particular, we aimed for identification of differences in prevalence between genders. A secondary goal was to establish a population-based prevalence of severe ischemia, as a measure of critical limb ischemia (CLI), for the first time in the literature.

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This study was supported by an independent research grant from Sanofi-Synthelabo AB, Eric Wahlberg's grants from the Swedish Heart and Lung Foundation and Konung Gustav V:s och Drottning Victorias Stiftelse. Birgitta Sigvant receives salary support from Värmland's County Research Council and Eric Wahlberg from the Swedish Heart and Lung Foundation.

Competition of interest: Eric Wahlberg is on the speakers' bureau for Pfizer, Sanofi-Aventis, and Schering-Plough. He receives funding from Pfizer as an IRG for a different study.

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0741-5214/$32.00



doi:10.1016/j.jvs.2007.02.004

## MATERIAL AND METHODS

**Pilot study.** A pilot study was performed in February 2004 to determine logistic factors influencing the final protocol and to estimate the sample size needed for the main study. The goal set was to identify at least 400 subjects with symptomatic PAD for later follow-up studies. The pilot study included 53 subjects, aged 59 to 89 years, who were selected at random from a population register. Of these, 33 (62%) accepted the first invitation, and five (9%) were examined in their homes, giving a participation rate of 72%. The mean age ± standard deviation the group was 72.3 ± 7.8 years. Twelve subjects (32%) with an ABI <0.9 were identified, and three (8%) had symptomatic PAD. Time management studies from this pilot study were then used to calculate the resources needed for the main study, and a cohort size of 8000 subjects was chosen.

**Population.** The population of Sweden in 2004 was 9.2 million. Seventeen percent were >65 years old, and 10% were born outside the country or had parents who were immigrants.[14] To cover demographic and geographic distributions in the Swedish population, four separate regions in the country were selected for the study. A random sample from these regions with the same age and gender distribution as the Swedish population in this age group, consisting of 2000 subjects from each region, was extracted from the government's tax register in June 2004. The age interval used was 60 to 90 years. The subjects were selected by residence and, thereby, use of health care centers (HCs). Seven HCs were involved to cover the population. In Malmö, representing a southern and urban community, Rosengard HC was enrolled. This HC covers a population with 59% immigrants, mainly from Yugoslavia and Iraq. The other HCs were Karlstad, a western urban community; Skutskär, an eastern rural and industrial community; and Skellefteå region covering a northern rural and agriculture district. Very few immigrants lived in the latter three regions. In the southern region, two HCs were used for logistic and practical reasons. In the northern region, three HCs were included because each covered only small populations.

**Ethical approval.** The study was approved by the local ethics committees in Stockholm (KI 03-538), Umeå University (Dnr 03-459), Lunds University (Dnr 832-0), Uppsala University (Dnr 03-564), and Örebro (Dnr 374- 03). Informed consent was obtained from each participant.

**Data collection.** The subjects were invited to participate in the study by a letter. Enclosed with the invitation were three self-administered questionnaires, which were translated into languages other than Swedish when needed. One questionnaire assessed the presence of risk factors, such as diabetes mellitus, hypertension, coronary heart disease, cerebrovascular disease, and renal failure and included current and former smoking habits. It also covered the Rose's World Health Organization (WHO) questionnaire questions and leg symptoms.[15] Another covered present use and duration of any pharmacologic treatment, and the third was a validated walking impairment questionnaire.[16,17] Analyses of questionnaire data for risk factors, pharmacologic treatment, and walking impairment have not yet been performed and therefore are not presented in this report.

The participants were invited to the HC, and house calls were made when requested. Specially trained nurses performed ABI measurements, checked the quality of the questionnaire answers, and assisted if they were incomplete. The study lasted about 8 weeks at each site, and for the entire study, 12 nurses were trained and employed. Before starting the trial, each nurse was required to pass a theoretical and practical test evaluating PAD knowledge and the ABI measurement technique. A coordinating research nurse visited each HC at least twice during the assessment period to monitor and validate the examination procedure and data recording.

ABI was determined by measuring the blood pressure at the right arm using a 12-cm-wide BP cuff with the patient in a sitting position. The ankle blood pressure was measured using a pocket CW-Doppler (8-MHz Doppler-probe, Hadeco, Sweden) and the same blood pressure cuff. These measurements were performed twice in each leg with the subject in supine position by insonating both the posterior tibial and dorsal pedal arteries. One specific nurse in each region entered the recorded data into an Access database (Microsoft Inc, Redmond, Wash).

Subjects who were considered at risk for severe ischemia or who had a high blood pressure (>180 mm Hg) were referred to their general practitioners, but no other interventions were made during the assessment period.

**Diagnosis criteria and definitions.** ABI was defined as the ratio of the lowest systolic blood pressure in the ankle divided by systolic blood pressure in the arm, as suggested in the literature.[18] The rationale for using the lowest ankle blood pressure was to make sure that subjects with generalized arteriosclerosis were included in the definition of asymptomatic PAD because this group is associated with a high risk for cardiovascular events. The definitions used for analysis of the data collected are listed in Table I. Severe ischemia-2 (SI-2) was used to improve prevalence estimation of CLI and to complement SI-1 by covering the most common definitions of CLI—having an ankle pressure <70 mm Hg *and* rest pain.[13] The second part of the CLI definition concerning ulcer and gangrene manifestation was not included in the questionnaires or examinations in this study. We also used a third CLI criteria (SI-3) that constituted all subjects with an ankle pressure <50 mm Hg. Incompressible vessels, as a sign of PAD, was defined as an ABI >1.4.[13]

**Statistical analysis.** Because the distribution of age was skewed, the Mann-Whitney *U* test was used for comparison of the median between participants and nonparticipants. For analyses of frequencies, the Fisher exact test and $\chi^2$ test were used. The $\chi^2$ test was also used for comparison of prevalence between regions. Adjustment for age, sex, and participation rate was performed for this analysis and had no influence in prevalence. The test of equal proportions was used to analyze gender differences in prevalence, accounting for sample design and participating rate.

**Table I.** Definitions of peripheral arterial disease used for analysis of the collected data

| *Nomenclature* | *Definition* |
|---|---|
| 1. Peripheral arterial disease (PAD) | All subjects with an ABI <0.9 with or without symptoms. |
| 2. Asymptomatic PAD (APAD) | Subjects with an ABI <0.9 without qualifying answers in the questionnaire (ie, no pain in the calf or thigh when walking). |
| 3. Intermittent claudication (IC) | Subjects with an ABI <0.9 and qualifying answers in questionnaire (ie, pain in calf or thigh when walking). |
| 4. Severe ischemia-1 (SI-1) | All subjects with an ankle pressure <70 mm Hg. |
| 5. Severe ischemia 2 (SI-2) | All subjects with ankle pressure <70 mm Hg and a qualifying answer in the questionnaire. This was defined as pain in the leg at rest. |

*ABI,* Ankle-brachial index.

**Table II.** Reasons given in response to the invitation letter for not participating in the study.

| *Reason* | *N (%)* |
|---|---|
| Dead | 51 (4) |
| Moved out of the area | 17 (1) |
| Alzheimer's disease | 98 (7) |
| Terminal disease | 115 (8) |
| Perceived themselves as healthy | 26 (2) |
| Do not want to | 809 (54) |
| No contact | 79 (4) |
| Other reasons* | 292 (20) |
| Total | 1488 (100) |

*Other reasons include: gone on holiday, busy working, do not have the time, too tired, taking care of a sick relative.

**Table III.** Reasons given by randomly selected nonparticipators at telephone interviews for not participating in the study.

| *Reason* | *N (%)* |
|---|---|
| Dead | 18 (7) |
| Moved out of the area | 3 (1) |
| Alzheimer's disease | 14 (5) |
| Terminal disease | 18 (7) |
| Perceived themselves as healthy | 11 (4) |
| Do not want to | 55 (21) |
| No contact | 29 (11) |
| Other reasons* | 114 (44) |
| Total | 262 (100) |

*Other reasons include: gone on holiday, busy working, do not have the time, too tired, taking care of a sick relative.

A comparison for SI-2 was not performed because this cohort of patients was small and therefore results were considered unreliable.

All statistical analyses were performed using SPSS 12.0 software (SPSS Inc, Chicago, Ill). Values of $P < .05$ were considered statistically significant, and data were presented as median and interquartile range (IQR) for age and percentages with 95% confidence intervals (CI) for prevalence.

## RESULTS

**Study population.** Of the 8000 invited persons, 5080 agreed to participate. This gave a response rate of 64%. There were 2779 women (55%) and 2301 men (45%), with a median age of 71 (IQR, 13 years). The participation rate differed with age. It was lowest (40%) in the oldest age group of 80 to 90 years and highest (70%) among those aged 60 to 70 years.

**Characteristics of nonparticipators.** There were significantly fewer participating subjects in Malmö (44%; $P < .001$) compared with the other regions: Älvkarleby had 65%, Skellefteå region had 74%, and Karlstad had 70%. Those choosing not to participate were a median age of 74 years (IQR, 16 years), which was significantly higher than in the study group ($P < .001$). Significantly more women than men decided not to participate (1702 vs 1213, $P = .001$). The reason for not participating given by 1488 subjects in response to the study invitation letter is given in Table II.

For further characterization, 262 subjects were randomly selected from the entire group of nonparticipators and were interviewed by telephone. The results are given in Table III. These subjects were also asked to respond to the questions in Rose's WHO questionnaire, and 18 (7%) gave a positive answer according to the intermittent claudication (IC) definition; 92 (35%) did not. Most of this group, 152 (58%), preferred to not answer this question.

**Prevalence.** According to definition 1, 18% (95% CI, 16.0 to 19.9) of the study population had any type of PAD, and 566 subjects were asymptomatic as established by definition 2 (Table IV). IC according to definition 3 was present in 340 subjects, whereas 61 had SI-1 according to definition 4. According to definition 5, 20 subjects (0.4%) had SI-2, and the prevalence for SI-3 was 0.33% in the total population (0.54% among women, 0.07% among men). The ABI was >1.4 in 12 subjects (7 men, 5 women).

**Sex differences.** Fig 1 displays the prevalence figures in relation to the age of the participants by sex. Asymptomatic PAD was more frequent among women ($P = .03$) than men. SI-1 ($P = .008$) and SI-2 (no statical analysis performed) were also more common among women. This pattern was consistent for all age groups. IC prevalence tended ($P = .09$) to be more common among men overall. For the oldest age group and for subjects aged 75 to 79 years, IC had a higher prevalence among men.

**Regional differences.** Regional prevalence is presented in Fig 2. The prevalence of PAD was 22% in Karlstad, which was significantly ($P < .0001$) higher than in other regions, as was the prevalence of asymptomatic PAD (15%, *P*

**Table IV.** Peripheral arterial disease prevalence by gender and stage of disease*

| *Stage of PAD* | *Total* | *Women* | *Men* | *P*† |
|---|---|---|---|---|
| Peripheral arterial disease (all with ABI <0.9) | 18.0 (16.0-19.9) | 19.2 (15.9-22.4) | 16.5 (15.8-18.4) | .112 |
| Asymptomatic PAD (all with ABI <0.9 without symptoms) | 11.1 (9.5-12.8) | 12.6 (9.7-15.4) | 9.4 (8.8-9.9) | .03 |
| Intermittent claudication (all with ABI <0.9 and positive Rose Q) | 6.8 (6.5-7.1) | 6.6 (6.1-7.1) | 7.1 (6.9-7.3) | .092 |
| Severe ischemia 1 (all with ankle BP <70 mm Hg) | 1.2 (1.0-1.4) | 1.5 (1.1-1.9) | 0.83 (0.6-1.1) | .001 |
| Severe ischemia 2‡ (all with ankle BP <70 mm Hg and rest pain) | 0.4 | 0.6 | 0.1 | |

*PAD,* Peripheral arterial disease; *ABI,* ankle-brachial index.
*Data presented as percentage (95% confidence interval).
†Comparing prevalences among women and men with test of equals proportions.
‡No comparisons performed for severe ischemia-2 due to a small cohort.

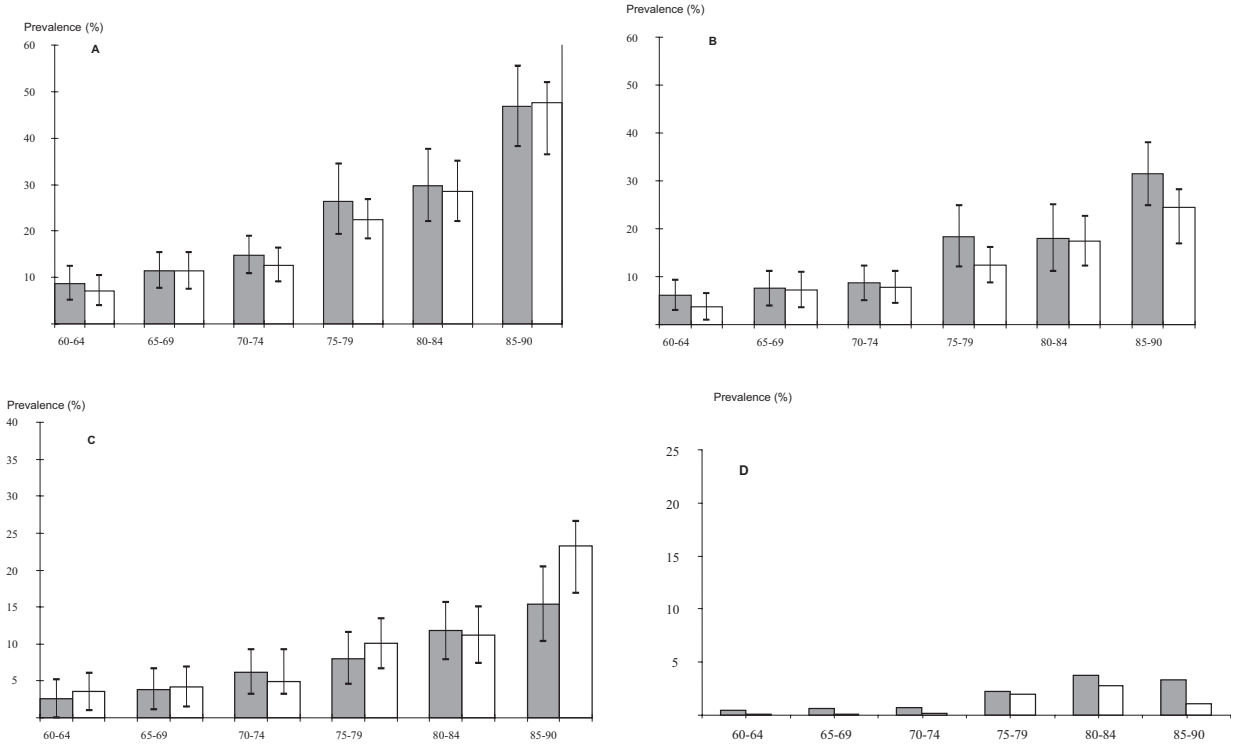


**Fig 1.** Prevalence of peripheral arterial disease (PAD) specific to age and sex (women, *filled bars*; men, *open bars*) presented with 95% confidence intervals (CIs). **A,** All PAD stages. **B,** Asymptomatic PAD. **C,** Intermittent claudication. **D,** Severe ischemia based on ankle pressure only (the CI is not displayed because of small cohorts).

< .0001). The prevalence of IC tended ($P = .08$) to be higher in Malmö. This region demonstrated a slight dominance for IC compared with asymptomatic PAD (8.4% vs 7.8%). The highest prevalence of SI-1, 2.2%, was found in Älvkarleby, were it was more common ($P = .008$) than in the other regions.

## DISCUSSION

Two findings in this study support the previous literature on the subject. PAD is very common in older age groups and most subjects with this disease are asymptomatic. The present study also reveals some more unique observations. The first is that women dominate among those with PAD when the definition is based only on ABI, the second is that the prevalence differs between geographic regions, and finally, that the prevalence of severe ischemia, as measure of CLI, seems to be present in almost 1% of the population over 60 years old.

The overall prevalence of PAD of 18% in our study is in the same range as in other population-based point-prevalence studies, especially when compared with data that are based on similar age groups and study design.[5-7] Although the assessment periods for these three studies are dispersed over a 10-year period, the prevalence figures reported were very similar to the present study. For instance, almost identical overall prevalences were found in the Rotterdam study,[7] suggesting a rather constant occurrence of PAD over time. Accordingly, the PAD prevalence remains the same despite a

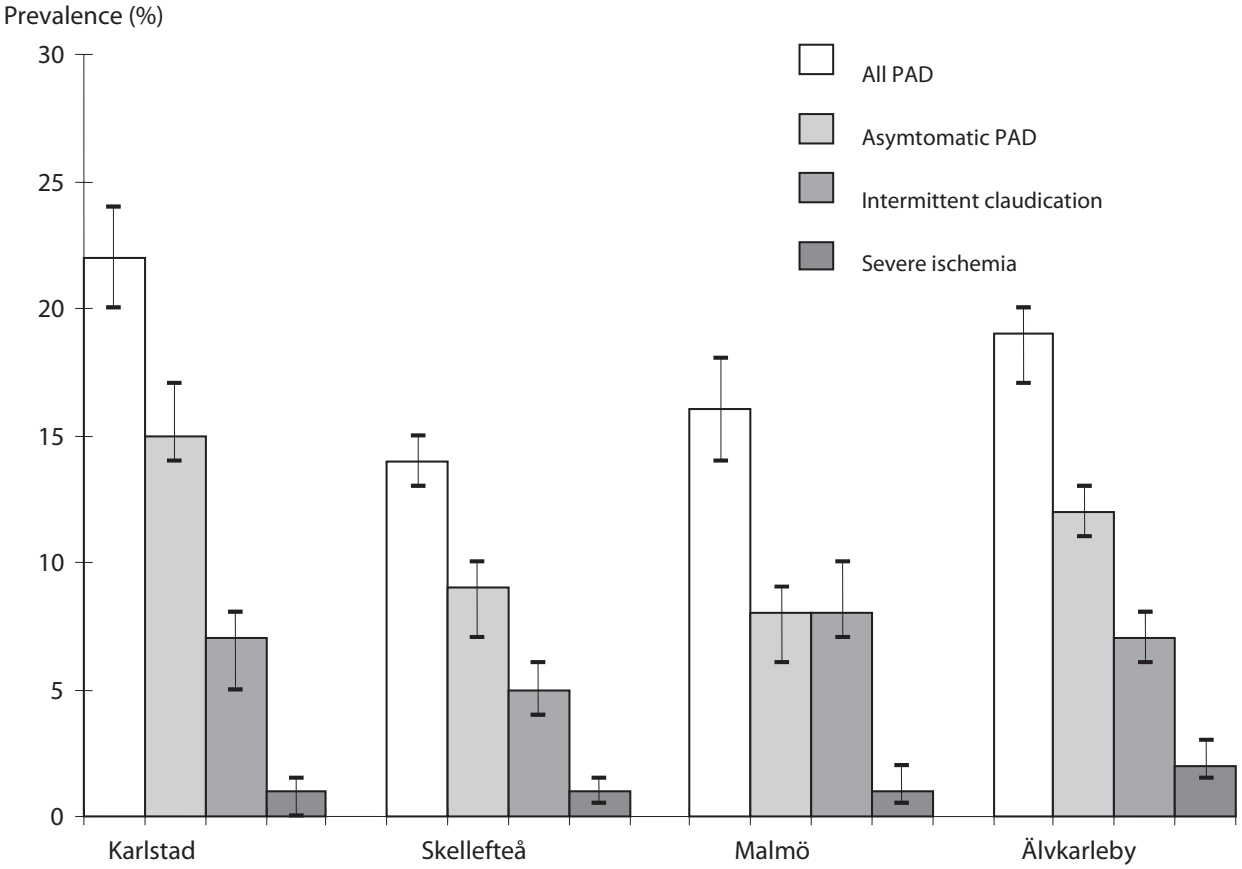


**Fig 2.** Prevalence of peripheral arterial disease *(PAD)* stages separated by geographic regions is presented in percentages and 95% confidence intervals.

decline in smoking habits and more aggressive risk-factor management for atherosclerosis during this time period.[19,20]

This observation is contradicted by the data from Fowkes et al[5] published in 1991, who determined the prevalence for PAD, asymptomatic PAD, and IC to 16.6%, 8%, and 4.5%, respectively. Although also presenting similar data, the investigated population was substantially younger (55 to 74 years) in that study. Comparing our data for this age group with the findings by Fowkes et al findings indicates a decline in PAD prevalence over time. Variations in risk factor burden, study design, and dissimilarities between countries or between ethnic groups could be other plausible explanations for this difference.[21] The overall prevalence found in this study was also similar to more recent data that did not use a population-based selection of study participators.[22,23]

Previous prevalence data on IC vary greatly in the literature and range from 1% to 14 %.[24-27] It is noteworthy that no IC prevalence studies have been performed in the last decade to our knowledge, and only a few of the previous ones included women. The variation in IC prevalence is likely to be an effect of problems using subjective symptoms for diagnosis in addition to differences in study design. Our IC prevalence of 7% is higher, in particular among women, than in the comparable Rotterdam study, which also used questionnaire data and an ABI <0.9 to establish the diagnosis.[7] It is also much higher than in a study from North America.[28] Because of the similarities in study design, these discrepancies probably reflect a true high IC prevalence among Swedish women.

Our prevalence data on SI are, to our knowledge, the first to be recorded using population-based identification of cohorts. The prevalence of 1.2% when based on <70 mm Hg in ankle blood pressure and 0.5% when adding symptoms is in the vicinity of data extrapolated from registers of vascular interventions for CLI.[13,29] Basing the presence of SI on an ankle blood pressure <50 mm Hg also indicated a prevalence of about 0.5%.

It can be argued that our SI definitions are not equivalent to the definitions of CLI used in the TransAtlantic Inter-Society Consensus (TASC) document. As discussed subsequently, we encountered several problems when trying to estimate this prevalence and decided to use two definitions to cover as much of it as possible. It is possible, however, that the SI prevalence is underestimated in this study. We may have identified more subjects with SI with a higher participation rate in the group ≥80 years, where SI was most prevalent. This is suggested by the decline in SI prevalence in the oldest age group, 85 to 90 years, which had the highest nonparticipation rate. The most common reasons given for nonpartici-

pation in this group—being too tired or ill to participate—further support this interpretation.

Estimating the number of patients with SI in Sweden from our data suggests that up to 15,000 subjects had CLI in 2004 (1% of the Swedish population over 60 years old). Comparing this figure with 1700 interventions for CLI in the Swedish Vascular Registry the same year suggests that too few patients underwent vascular reconstruction for symptomatic relief. Using our prevalence data and the estimated number of persons over 60 years old from the United States Census Bureau data from 1999 (50 million), we conclude that about 500,000 persons in the United States may have CLI.

Determining PAD prevalence is associated with problems with ABI measurements and the reporting of symptoms. ABI is generally accepted as valid tool to diagnose PAD,[30] and an ABI <0.9 has a 95% to 98% specificity and 90% sensitivity in detecting the symptomatic forms of PAD when angiography findings are used as the gold standard.[31,32] The interobserver variability is reported to be 11%.[33] In this study, we tried to minimize this variability by having workshops in measurement techniques, including skill tests, for the nurses performing the measurements. We also used closed monitoring throughout the study period. Accordingly, we believe that the prevalence figures based on ABI are valid and comparable with data in other reports.

Determining the prevalence of IC and SI-2 requires an addition of symptoms to the ABI and thus the diagnosis is more uncertain. Walking problems are difficult to assess in questionnaires, and separating IC from other walking disabilities is almost impossible. In most previous studies Rose's WHO questionnaire has been used, with a specificity of 80% to 90% but a sensitivity of only 50% for detecting PAD diagnosed by a treadmill test.[27] Also for SI, the reported symptoms are difficult to interpret.

According to the CLI definitions by the TASC group, manifest rest pain or ulcers should be added to the objective assessment of ankle blood pressure.[13] Unfortunately, rest pain symptoms depend on pain perception, which in turn is influenced by neuropathy. They could also be influenced by analgesics.

In addition, arterial ulcers can be of venous or inflammatory etiology and they can be located in the distal calf.[34] Whether such ulcers should be included when defining and assessing SI can be questioned, and we found it almost impossible to define ulcers with a predominately arterial etiology in a standardized way. The problems with this assessment were the reason for using the nomenclature SI instead of CLI in this study.

Women dominated both types of PAD determined by ABI in our study as they did in the National Health and Nutrition Examination Survey.[23] Constitutionally higher ABI in women, smoking habits, postmenopausal hormonal effects, lower prescription rates of drugs to reduce risk factors, and smaller vessels could be possible explanations for this difference between men and women.[35-37] As mentioned, studies focusing on IC have often reported a higher prevalence among men.[27,38] The reason for the discrepancy between these studies and ours may be differences in study design such as diagnostic criteria or an increase in female IC prevalence over time. Questionnaire data may also underreport IC in women because women experience walking problems differently from men.[39] They are also less likely to report symptoms owing to a lower level of physical activity.[11] Of interest in our study was that the PAD prevalence figures differed most among the genders in the oldest age group. This difference in absolute points in our study was 8% higher in men for IC, who in turn had 3% lower SI prevalence. This may be a consequence of the mentioned difference in walking habits and a general higher morbidity in women.

The overall prevalence of PAD was significantly higher in the Karlstad region compared with the other areas. Cardiovascular mortality has previously been studied in the counties of Sweden and an east-western regional gradient of cardiovascular mortality was found, with Karlstad in the area with the highest mortality.[40] Nerbrand et al[40] could not identify variations in risk factors alone as an explanation for this; instead, they suggested drinking water hardness was an important factor influencing mortality.[40] SI was prominent in the Älvkarleby region. This area has a large proportion of second-generation immigrants from eastern Finland with a high cardiovascular morbidity, and it is probable that the smoking rate in this area also is high. The inhabitants in Rosengård displayed a slightly higher prevalence of IC compared with the other regions, but PAD occurrence in general was similar. Ethnic and cultural differences in walking impairment perception may be an explanation for this.[41,42]

## CONCLUSION

PAD is very common among elderly individuals, and the prevalence differs between regions. Women more often have asymptomatic PAD and SI than men. The explanation of why women have a similar prevalence of IC as men may be a consequence of the need for using the subjective perception of walking problems to obtain the diagnosis. The prevalence of SI is likely to be in the area of 0.5% to 1.2 %, but may be underestimated in this study owing to a large proportion of nonparticipators in the oldest age group, where SI was most common.

We thank Maritha Johansson, head research nurse at the Department of Vascular Surgery, Karolinska University Hospital, Stockholm, for her great contributions to this study.

## AUTHOR CONTRIBUTIONS

Conception and design: BS, EW
Analysis and interpretation: BS, KWH, EW
Data collection: BS, OR, BA, EP
Writing the article: BS
Critical revision of the article: EW, DB, OR
Final approval of the article: EW
Statistical analysis: KWH
Obtained funding: EW
Overall responsibility: EW
EW and BS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Submitted Oct 31, 2006; accepted Feb 5, 2007.