Influence of smoking on incidence and prevalence of peripheral arterial disease

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Objective: Many studies have been published regarding the influence of smoking on the incidence and prevalence of peripheral arterial disease (PAD). A systematic review was performed to establish the magnitude of the effect of smoking on the development of PAD, and a possible dose-response relationship.
Methods: English-language articles were reviewed by 2 observers using a standardized form, and were summarized in tabular form. Data were extracted by 2 independent observers. Where possible, outcome data, expressed in terms of prevalence or incidence, were recalculated as odds ratio or relative risk, with never-smokers as the reference group, or if this was not available the nonsmoker group. Most studies did not provide primary data. Therefore the weighted means were reported as a summary estimate, provided that a funnel plot between sample size and observed effect size made publication bias unlikely.
Results: Sixteen articles describing 17 studies were included in the analysis. Four of the studies were prospective, and 13 were cross-sectional. The prevalence of symptomatic PAD was increased 2.3-fold in current smokers. Even in former smokers the prevalence was substantially increased by a factor of 2.6. A clear dose-response relationship, with a strong increase in risk for PAD in heavy smokers was observed. In countries where approximately 30% of the population are smokers, 50% of PAD can be attributed to smoking.
Conclusions: Smoking is a potent risk factor for symptomatic PAD, with an important and consistent dose-response relationship. With the persistence of high risk for PAD in former smokers, tobacco control programs should continue to advocate smoking cessation, but focus even more on preventing future generations from ever starting to smoke. (J Vasc Surg 2004;40:1158-65.)

According to World Health Organization (WHO) estimates, there are currently 1.1 billion tobacco smokers worldwide. This is about a third of the world population aged 15 years and older. Recently, smoking-related death has been upwardly adjusted to 4.9 million persons per year.[1]

Tobacco use is considered the most important preventable vascular risk factor for peripheral arterial disease (PAD) in men and women.[2] The association between smoking and PAD is even stronger than that between smoking and coronary heart disease.[3] The diagnosis of PAD is made a decade earlier in smokers than in nonsmokers.[3] In addition, the amputation rate in patients with PAD who smoke is twice that in persons who have never smoked.[3]

The relationship between smoking and PAD has been recognized since 1911, when Erb reported that intermittent claudication was 3 times more common in smokers and 6 times more common in heavy smokers, compared with nonsmokers.[4] Since then numerous studies have been performed on the relationship between smoking and the incidence and prevalence of PAD. We performed a systematic review to establish the so far unknown magnitude of the effect of smoking on development of symptomatic PAD, and if possible to determine a dose-response relationship.

METHODS

Search strategy and selection criteria. A search of English, French, Dutch, and German medical articles and reviews related to the influence of smoking on the incidence and prevalence of symptomatic PAD was made with MEDLINE, SUMsearch, Cochrane Library, and Pubmed for the period from 1970 to the end of 2002. In addition, a manual search of reference lists for relevant articles was conducted. Search terms, using MeSH and free text, included peripheral arterial disease, peripheral vascular disease, claudication, smoking, smoking cessation, nicotine, incidence, prevalence, and risk factors.

Studies considered for inclusion met the following criteria: (1) they evaluated the influence of smoking on the incidence and prevalence of symptomatic PAD; (2) the diagnosis of PAD was made with the ankle-brachial index, Rose questionnaire or the WHO questionnaire, or at iliofemoral angiography. The Rose and WHO questionnaires have been widely used in epidemiologic surveys to determine the presence of PAD. The questionnaires consist of short questions on pain location and duration, and

Table I. Characteristics of 17 included studies

	No. of subjects	Contr	Sex	Age (y)	Method of diagnosis	Smoking status	Smoking intensity	Means of smoking	Smoking assessment
Prospective studies									
Ingolfsson et al[11]	8045		M	34-80	Questionnaire	Current, former, never	Light : 1-14 Moderate:15-24 Heavy : >25	Cigarettes, pipe, cigars	Questionnaire
Price et al[19]	1592		M/F	55-74	Questionnaire	Current, never	Moderate: <25 pack-years; Heavy: >25 pack-years	Cigarettes	Questionnaire, thiocyanate
Hooi et al[10]	2327		M/F	>39	ABI, questionnaire	Current, former, never	Current, former, never	Cigarettes	Questionnaire
Murabito et al[15]	5209		M/F	28-62	Questionnaire	Current, nonsmoker	Cigarettes/day	Cigarettes	Questionnaire
Cross-sectional studies									
Cole et al[5]	102	99	M	—	ABI, angiography	Current, former, never	Light: 1-20 Moderate: 20-40 Heavy: >40	Cigarettes	Questionnaire, plasma cotinine
Drexel et al[6]	102	100	M/F	51-73	Angiography	Current, nonsmoker	Pack-years	Cigarettes	Questionnaire
Fowkes et al[7]	418	1080	M/F	55-74	ABI, questionnaire	Current, former, never	Current, former, never	Cigarettes, pipe, cigars	Questionnaire
Fowkes et al[8]	167	1369	M/F	55-74	ABI, questionnaire	Current, former, never	Current, former, never	Cigarettes	Questionnaire
Fowler et al[9]	744	3726	M	65-83	ABI, questionnaire	Current, former, never	Light: 1-14 Moderate: 15-24 Heavy: >25	Cigarettes	Questionnaire
Ingolfsson et al[11]	96	9045	M	34-80	Questionnaire	Current, former, never	Light: 1-14 Moderate: 15-24 Heavy: >25	Cigarettes, pipe, cigars	Questionnaire
Lee et al[12]	617	722	M/F	55-74	Questionnaire, ABI	Current, former, never	Pack-years	Cigarettes	Questionnaire
Leng et al[13]	131	722	M/F	55-74	Questionnaire	Current, former, never	Pack-years	Cigarettes	Questionnaire, thiocyanate
Lowe et al[14]	45	1096	M/F	55-74	ABI, questionnaire	Current, former, never	Pack-years	Cigarettes	Questionnaire, thiocyanate
Ness et al[16]	184	1727	M/F	72-89	ABI	Current, nonsmoker	Current, nonsmoker	Cigarettes	Questionnaire
Planas[17]	61	512	M	55-74	ABI	Current, nonsmoker	Pack-years	Cigarettes	Questionnaire
Powell[18]	291	828	M/F	56-71	ABI, questionnaire	Current	Pack-years, Cigarettes/day	Cigarettes, pipe, cigars	Questionnaire, thiocyanate, CHb, plasma cotinine
Smith[20]	147	18066	M	40-64	Questionnaire	Current, former, never	Cigarettes/day	Cigarettes, pipe, cigars	Questionnaire

ABI, Ankle-brachial index; *CHb,* Carboxyhemoglobin.

provocative factors. The sensitivity of these questionnaires in low in comparison with noninvasive tests for PAD, which is to be expected because in most patients PAD is asymptomatic. In epidemiologic surveys the large amount of included patients often leave no other option than use of these surveys, with known underestimation of the presence of PAD.

Studies were excluded on the basis of the following criteria: (1) the data on PAD in smokers and nonsmokers had not been separated; (2) the data on symptomatic and asymptomatic PAD had not been separated; (3) additional medication had been added to the study protocol.

Data extraction. The identification of studies was performed by 1 reviewer (E.M.W.), and was checked for

Table II. Effect of current smoking on prevalence of PAD in prospective studies

Reference	Smoking description	Symptomatic PAD	P
Hooi et al[10]	Current smoker, PAD	OR, 4.3; 95% CI, 1.9-10.1	NP
	Former smoker, PAD	OR, 1.4; 95% CI, 0.5-3.7	NS
Ingolfsson et al[11]	1-14 cigarettes/day	RR, 2.6	<.001
	15-24 cigarettes/day	RR, 7.7	<.001
	>25 cigarettes/day	RR, 10.2	<.01
	Pipe or cigars	RR, 3.6	<.001
	Former smoker	RR, 2.3	NS
Murabito et al[15]	Per 10 cigarettes/day	OR, 1.4; 95% CI, 1.3-1.5	.0001
Price et al[19]	<25 pack-years	RR, 1.87; 95% CI, 0.9-3.9	≤.001
	>25 pack-years	RR, 3.94; 95% CI, 2.0-7.6	≤.001
	√pack-years	Mean ± SD, 4.46 ± 0.35	≤.001

PAD, Peripheral artery disease; *NP,* value not provided; *NS,* not significant; *OR,* odds ratio; *CI,* confidence interval; *RR,* relative risk.

eligibility for inclusion in the review by another of the authors (M.H.P.). Data from the studies included in the survey were extracted by 2 independent observers (E.M.W., M.H.P.) using a standardized form, and were summarized in tabular format. Disagreements were resolved by discussion, and the final results were included in the review. Since the objective was to obtain a quantitative estimate of the effect size and dose-response relationship for the influence of smoking on symptomatic PAD, results adjusted for the effects of other risk factors for PAD were included in the final summary. This summary was on the difference in incidence or prevalence of PAD between current smokers, former smokers, never-smokers, and nonsmokers (where no differentiation was made between never-smokers and former smokers), and smoking intensity.

Data analysis. When possible, outcome data, expressed in terms of prevalence or incidence, were recalculated as odds ratio or relative risk, with never-smokers as the reference group, or if this was not available the nonsmokers group. Odds ratios are used in cross-sectional studies, and describe the ratio of the probability of PAD in smokers divided by the probability of PAD in nonsmokers. Relative risk is used in prospective studies to describe the ratio of the risk for development of PAD in smokers divided by the risk for development of PAD in nonsmokers. Inasmuch as, retrospectively, most studies did not provide the primary data (number exposed, years of exposure, number of outcome events) or confidence intervals, an alternative method was sought to provide summary estimates. To this end, an assessment was made if a publication bias was present, using a standard funnel plot. The performed funnel plots are scatter plots of the effect of smoking on the development of PAD on the x-axis against the study sample size on the y-axis. The effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of a publication bias the plot should resemble a symmetric inverted funnel. In the absence of bias, the weighted mean was calculated with the number of patients as the weight factor.

RESULTS

The literature search resulted in identification of 20 potentially eligible articles.[5-24] Of these, 4 articles had to be excluded, either because no incidence or prevalence data were available or because no differentiation had been made between symptomatic and asymptomatic PAD and other atherosclerotic diseases.[21-24] Of the remaining articles, 3 described prospective data and 12 others described cross-sectional data.[5-10,12-20] One other article described both prospective and cross-sectional data.[11] One prospective and 4 cross-sectional articles referred to the Edinburgh Artery Study, but described in the majority of cases different (sub)populations or outcomes.[7,8,13,14,19] In case of multiple results of the Edinburgh Artery Study on a single outcome, the study with the largest number of patients was included in the relevant analysis.

Sixteen articles describing 17 studies satisfied the inclusion and exclusion criteria, and therefore were included in the analysis.[5-20] No systematic reviews were identified. Details of the articles included are summarized in the Table I.

Definitions. Most studies included in the survey confirmed the PAD diagnosis on the basis of the ankle-brachial index, whereas 6 studies used either the Rose claudication questionnaire or the WHO claudication questionnaire, and another 2 studies used (additional) angiography (Table I). All studies evaluated the effects of cigarette smoking; pipe and cigar smoking was added to the analysis in 1 prospective and 4 cross-sectional studies. Duration of smoking was reported as never-smoker, former smoker, nonsmoker, and current smoker. For former smokers the duration of cessation was registered in 1 study. The intensity of smoking was predominantly recorded in terms of pack-years (number of cigarette packs a day multiplied by number of smoking years) or in different classes. Classes varied from number of cigarettes a day to never-smoker, former smoker, or current smoker.

Incidence of PAD in current smokers. The 4 prospective studies describing the incidence of PAD are summarized in Table II. Two prospective studies provided odds ratios rather than hazard ratios.[10,15] One provided odds ratios for the incidence of PAD in smokers, and the second

Table III. Effect of current smoking on prevalence of PAD in cross-sectional studies

Reference	Smoking description	Symptomatic PAD		
		OR	95% CI	P
Drexel et al[6]	Overall (30 pack-years)	1.7	1.2-2.5	NP
Fowkes et al[7]	Overall	3.7	1.7-8.0	<.001
Fowkes et al[8]*	Overall	2.7		NP
Fowler et al[9]	Overall	3.9	2.9-5.1	NP
Ingolfssen et al[11]	Pipe or cigars	7.4		NP
Lee et al[12]	Overall	2		NP
Lowe et al[14]*	Overall	2.4	1.3-4.4	NP
Ness et al[16]	Male smokers	2.6		NP
	Female smokers	4.6		NP
Smith et al[20]	Overall	1.8		.009
Planas et al[17]	Start at age <17 years	3.3		NP

PAD, Peripheral artery disease; *OR,* odds ratio; *CI,* confidence interval; *NP,* value not provided.
*Edinburgh Artery Study; not included in weighted mean calculation.

described a dose-response odds ratio.[10,15] One study described the increasing incidence of PAD in smokers as a function of pack-years without discriminating between current smokers and former smokers.[19] All studies showed that the risk for development of symptomatic PAD increased in smokers. Since all 4 studies used different categories to define current smoking, the data could not be used for an overall effect size of smoking on the incidence of PAD.

Prevalence of PAD in current smokers. The studies all showed a significant increase in PAD in current smokers (Table III). Three studies of the Edinburgh Artery Study reported on this subject, and therefore only 1 study has been used for the summary analysis.[7] The funnel plot gave no indication for the presence of a publication bias (Fig 1). The weighted mean for the overall odds ratios for symptomatic PAD in current smokers was 2.3. One study determined the risk for male and female subjects, and showed a higher prevalence in female smokers.[18] In 1 study the age at onset of smoking was taken into account, with a significant increase in risk when a person started smoking at age 16 years or younger.[17] Powell et al[18] analyzed the effect of low-tar cigarettes in reducing risk for PAD development, but found no evidence that these cigarettes are less harmful. And finally, 4 prospective studies analyzed the influence of pipe and cigar smoking. One of these studies found comparable odds ratios between cigarettes and pipe or cigar smoking, and the remaining studies did not present separate data on pipe and cigar smoking in their analysis.[7,11,18,20]

PAD in relation to smoking exposure. The smoking dose-response relationship was evaluated in 2 prospective studies (Table II) and 8 cross-sectional studies (Table IV). The prospective studies that assessed the relationship between smoking dose response and PAD found a statistically significant exposure associated with an increase in PAD incidence.[11,15,19] One study determined the incidence of symptomatic PAD in relation to smoking exposure, with an increase from 2.6% in never-smokers to 9.8% in heavy smokers.[19]
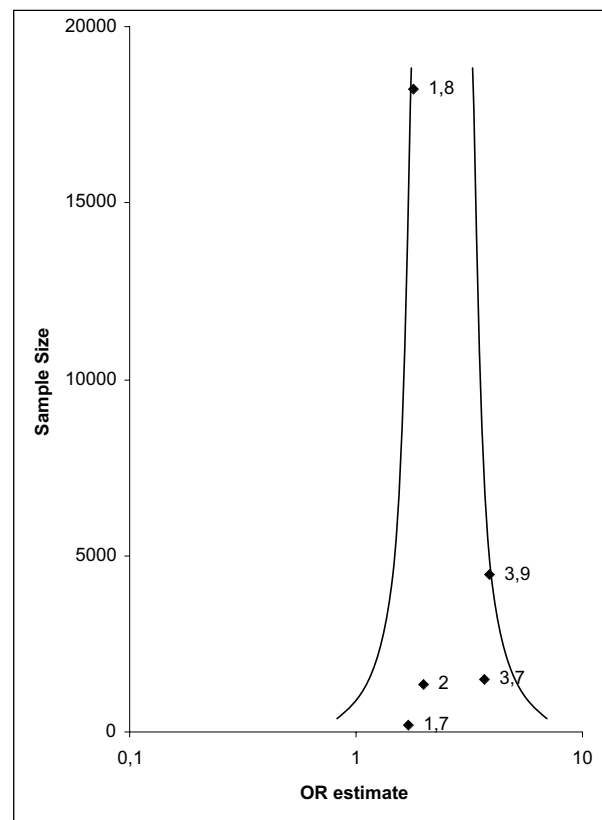
Fig 1. Funnel plot of cross-sectional studies of smokers versus nonsmokers. Effect of smoking on development of peripheral artery disease is represented on the x-axis; study sample size is represented on the y-axis. Funnel-shaped lines represent 95% confidence interval around estimated effect size. *OR,* Odds ratio.

In six of the 8 cross-sectional studies a clear dose-response relationship was observed.[5,7,9,13,14,18] In the remaining 2 studies an identical picture of increasing odds ratios with number of cigarettes smoked per day was seen,

Table IV. Presence of smoking dose-response relationship for prevalence of PAD

Reference	Smoking description	Symptomatic PAD		
		OR	95% CI	P
Cole et al[5]	1-20 cigarettes/day	8.3		NP
	+41 cigarettes/day	15.0		NP
Fowler et al[9]	1-14 cigarettes/day	3.9	2.7-5.6	NP
	15-24 cigarettes/day	6.6	4.2-10.5	NP
	>25 cigarettes/day	7.3	4.2-12.8	NP
Ingolofsen et al[11]	1-14 cigarettes/day	10.7		NP
	15-24 cigarettes/day	13.9		NP
	>25 cigarettes/day	8.1		NP
Powell et al[18]	1-14 cigarettes/day	1.0		.522
	15-24 cigarettes/day	1.4	1.0-2.1	.522
	>25 cigarettes/day	1.1	0.7-1.6	.522
Leng et al[13]	<25 pack-years	3.6		NP
	>25 pack-years	5.9		NP
Lowe et al[14]	$\sqrt{\text{Pack-years}} + 1$	1.3	1.2-1.5	NP
Fowkes et al[7]	Pack-years	1.1	1.0-1.3	<.001
Cole et al[5]	11 pack-years	2.3		NP
	22 pack-years	4.1		NP
	33 pack-years	8.8		NP
	44 pack-years	10.8		NP
	>44 pack-years	12.9		NP
Powell et al[18]	<31 pack-years	1.0		0.011
	31-49 pack-years	1.23	0.84-1.79	0.011
	>49 pack-years	1.63	1.11-2.39	0.011

PAD, Peripheral artery disease; *OR,* odds ratio; *CI,* confidence interval; *NP,* value not provided.

Table V. Difference between development of PAD in former smokers and never-smokers in prospective and cross-sectional studies

Reference	Smoking description	Symptomatic PAD		
		OR	95% CI	P
Cole et al[5]	Overall	2.3		NP
Fowler et al[9]	Overall	2.1	1.6-2.6	NP
Fowkes et al[7]	Cessation <5 years	3.0	1.5-6.3	NP
Fowkes et al[8]*	Overall	2.1		NP
Ingolofsen et al[11]	Overall	3.5		NP
Lee et al[12]	Overall	1.9		NP
Leng et al[13]	<25 pack-years before cessation	3.6		NP
	>25 pack-years before cessation	4.8		NP
Lowe[14]*	Cessation < 5 years	4.3	2.0-9.2	NP
Cessation duration (y)				
Fowler et al[9]	<1	5.4	2.4-11.9	NP
	1-4	3.8	2.5-5.7	NP
	5-9	3.7	2.5-5.7	NP
	10-19	2.7	2.0-3.6	NP
	>20	1.3	1.0-1.7	NP

OR, Odds ratio; *CI,* confidence interval; *NP,* value not provided.
*Edinburgh Artery Study; not included in weighted mean calculation.

but with a decrease in the heavy-smoker group (>25 cigarettes per day).[11,18]

PAD in former smokers. Two prospective studies (Table II) and 9 cross-sectional studies (Table V) divided the nonsmoker group into never-smokers and former smokers. In the prospective studies an increase in risk for PAD in former smokers was present, but was not significant in either study.[10,11]

In 1 cross-sectional study the odds ratios correlated with the severity of PAD.[7] A dose-response relationship

before cessation was seen, with an odds ratio of 3.6 in subjects who smoked for less than 25 pack-years, and 4.8 in those who smoked 25 or more pack-years.[13] One study took the duration of cessation into account, with odds ratios ranging from 5.4 in subjects who had stopped smoking less than 1 year previously, down to 1.3 in those who stopped smoking more than 20 years before.[9]

The overall relative risks and odds ratios for symptomatic PAD in former smokers are summarized in Fig 2. The funnel plot gave no indication of the presence of a publica-

tion bias (Fig 2). The weighted mean for the overall odd ratios for symptomatic PAD in former smokers was 2.6.

The prevalence of symptomatic PAD in former smokers decreased in every study when compared with current smokers, but nevertheless was still closer to the status of current smokers than to never-smokers.

Additional observations. Three cross-sectional studies showed that smokers in whom PAD develops have a higher pack-year level than do smokers in whom PAD does not develop, with an average number of pack-years of 37.7 for PAD versus 17.9 for smokers without PAD.[6,12,17] Consistent with these findings, a dose-response relationship was observed, with 23 pack-years for smokers without PAD compared with 25 pack-years for patients with minor asymptomatic PAD, 32 pack-years for those with major asymptomatic PAD, and 36 pack-years for those with symptomatic PAD.[7]

The reported relative risks for cigarette smoking were higher for PAD than for coronary artery disease.[19] Age-adjusted and sex-adjusted relative risk for PAD associated with smoking was 1.9 for moderate smokers and 3.9 for heavy smokers. Similarly adjusted risk for coronary artery disease was 1.6 and 1.7, respectively.[19]

DISCUSSION

PAD in smokers. All studies that qualified for our review showed an increase in risk for symptomatic PAD in current and former smokers. The increase observed in the prevalence of symptomatic PAD in smokers was 2.2. This indicates that in countries where approximately 30% of the population smokes, 50% of PAD can be attributed to smoking. This population attributable risk is substantially higher than for smoking on coronary heart disease deaths (30%).[25] There was continued increase in risk in former smokers. Of interest, a clear dose-response relationship between smoking and risk for PAD was observed.

Limitations of this review. The inability of some older studies to comply with the applied inclusion criteria with respect to PAD diagnosis resulted in exclusion of these studies. In the remaining studies a large variety of outcome measurements showed little similarity in the definitions used for PAD diagnosis, duration of smoking, and intensity of smoking.

Most articles provided cross-sectional data, which is a serious source of bias, especially with respect to assessment of tobacco exposure. However, if the number of cigarettes smoked per day was substantially underestimated, this would imply that the actual dose-response relationship was more pronounced. Furthermore, the decrease in dose-response relationship in the heavy smoker group could imply that those patients died from other smoking-related diseases.

The Edinburgh Artery Study, with 1 prospective study and 4 cross-sectional studies included, was overrepresented. Therefore multiple studies of the same analysis have been excluded, taking only 1 study into account.

Most studies evaluated the influence of smoking as an item among many different risk factors. However, crude
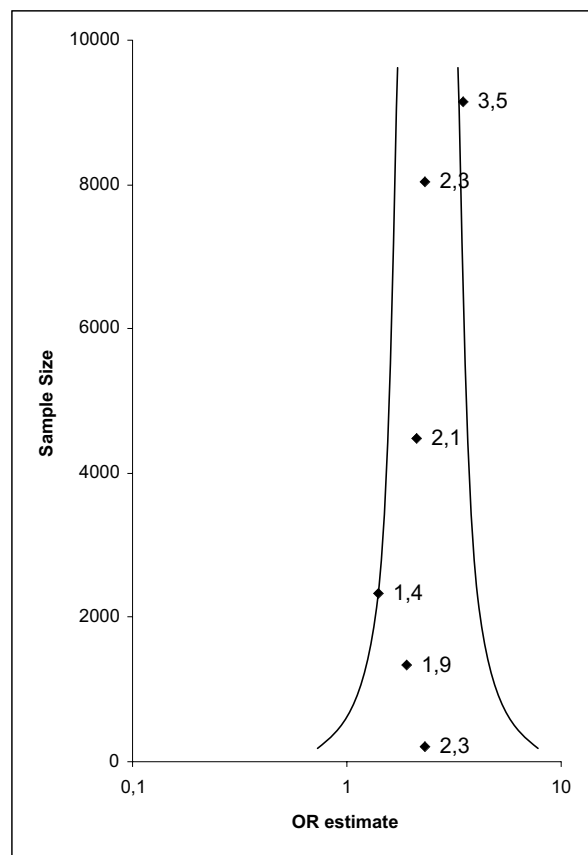

Fig 2. Funnel plot of prospective and cross-sectional studies of former smokers versus nonsmokers. Effect of former smoking on development of peripheral artery disease is represented on the x-axis; study sample size is represented on the y-axis. Funnel-shaped lines represent 95% confidence interval around estimated effect size. *OR*, Odds ratio.

and adjusted effected size of smoking was similar. Raw data were often not available, which resulted in inability to perform a classic meta-analysis. Although confidence intervals could not be calculated, most individual studies indicated that their results were already statistically significant. Hence we believe that our summary effect estimates will have confidence intervals that are highly significant. To provide an alternative best estimate of effect size, the weighted mean was calculated. Despite the limitations of the individual studies, the data represented gave a consistent description of the influence of smoking.

Implications. Without doubt, the best method for limiting the risk for development of atherosclerotic and other smoking-related diseases is to not start smoking in the first place. The prevalence of smoking has decreased considerably over the last decades, from approximately 50% in the mid-1960s to 30% at the present time.[26] On the down side, however, is the increase in smoking in young adults, on whom anti-smoking campaigns seem to have little effect.[27] When taking into account that the prevalence

of PAD is higher in smokers who started before age 16 years, the limited effect of anti-smoking campaigns for teenagers is a serious cause for concern.[17]

The gender gap between male and female smokers has narrowed considerably over the last 3 decades, but despite women still smoking less, they are at higher risk for PAD than their male counterparts. This higher susceptibility to the effects of smoking is analogous with the risk for lung cancer, and evidence is growing for increased risk for myocardial infarction.[28,29]

The rapid reduction in risk after smoking cessation, as has been shown in the development of coronary heart disease and stroke, seems deficient with respect to PAD.[30,31] Furthermore, patients with PAD seem to be less successful in smoking cessation than patients after myocardial infarction, with success rates of only 11% for PAD compared with 50% in patients after myocardial infarction.[32,33] Only after a substantial period of smoking cessation, which is correlated with smoking exposure, was a reduction in risk for development of symptomatic PAD apparent.

Smokers who do not to stop often replace normal cigarettes with low-tar cigarettes or cigars. However, a reduction in risk as a result of smoking low-tar cigarettes has not been provided. In 2 studies the effect of cigar smoking was comparable to that of cigarette smoking, but in general the data on the risk-reducing influence of cigars, pipes, and low-tar cigarettes are too few to draw firm conclusions.[11] In addition to this replacement strategy, reduction (ie, cutting down on the number of cigarettes smoked per day) is a common strategy used by smokers to reduce harm. Although a dose-response relationship for smoking in PAD was present and has been reported in other atherosclerotic diseases, such as stroke and coronary heart disease, no evidence exits that major health risks are reduced with this stategy.[20,33]The presence of a dose-response relationship, that is, persons who smoke less are at reduced excess risk, does not imply that heavy smokers who reduce the number of cigarettes smoked acquire the same reduced risk. Furthermore, smoking is primarily a nicotine-seeking behavior, and smokers who reduce the number of cigarettes smoked tend to compensate by taking more and deeper puffs from each cigarette and smoking more of it.[34] This results in a much smaller proportional reduction in intake of nicotine, and associated tar and other toxins, than the reduction in number of cigarettes suggests.[34]

CONCLUSION

This review shows a considerable increased risk for symptomatic PAD due to smoking. This risk was substantial and consistent, with a clear dose-response relationship. Adverse effects were even more pronounced in female smokers and persons who started smoking before age 16 years. Many adverse health effects of smoking are reversible, but the risk for developing PAD seems to persist, in contrast to the rapidly decreasing risk for myocardial infarction and stroke. With the persistence of high risk in former smokers, tobacco control programs should continue to advocate smoking cessation. However, even more effort should be put into preventing new generations from starting to smoke.

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