

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2008;118;1535-1540; originally published online Sep 22, 2008;

DOI: 10.1161/CIRCULATIONAHA.108.784801

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Passive Smoking and Risk of Peripheral Arterial Disease and Ischemic Stroke in Chinese Women Who Never Smoked

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Background—The association between secondhand smoke (SHS) and risk of peripheral arterial disease (PAD) and stroke remains uncertain.

Methods and Results—We examined the relationship between SHS and cardiovascular diseases, particularly PAD and stroke, in Chinese women who never smoked from a population-based cross-sectional study in Beijing, China. SHS exposure was defined as exposure to another person's tobacco smoke at home or in the workplace. Cardiovascular disease events included coronary heart disease, stroke, and PAD. PAD was defined by signs of intermittent claudication as measured by the World Health Organization Rose questionnaire and an ankle-brachial index of <0.90 . Among 1209 women who never smoked, 39.5% were exposed to SHS at home or in workplaces. Those individuals who were exposed to SHS had a significantly higher risk of coronary heart disease (adjusted odds ratio [OR], 1.69; 95% CI, 1.31 to 2.18) and ischemic stroke (OR, 1.56; 95% CI, 1.03 to 2.35) than those never exposed to SHS after adjustment for 13 potential risk factors. The adjusted ORs of PAD defined by intermittent claudication, by ankle-brachial index <0.90 , and by either intermittent claudication or ankle-brachial index <0.90 were 1.87 (95% CI, 1.30 to 2.68), 1.47 (95% CI, 1.07 to 2.03), and 1.67 (95% CI, 1.23 to 2.16), respectively. Dose-response relationships were found between SHS exposure amount (cigarettes per day) and duration (minutes per day) and increasing prevalence of coronary heart disease, ischemic stroke, and PAD.

Conclusions—In China, SHS exposure in women is highly prevalent. In addition to being a risk factor for coronary heart disease, SHS should be considered an important risk factor for ischemic stroke and PAD in nonsmoking women. (*Circulation*. 2008;118:1535-1540.)

Key Words: peripheral arterial disease ■ smoking ■ stroke ■ tobacco smoke pollution ■ women

China is the largest producer and consumer of tobacco in the world; 30% of the world's cigarettes are consumed by China's 350 million smokers.¹ In 2002, the prevalence of current smoking in the population ≥ 15 years of age was 66.0% in men and 3.1% in women. Among female nonsmokers, 55% were exposed to passive smoking for >15 minutes a day.² There is strong evidence that passive smoking, also known as secondhand smoke (SHS), is causally associated with coronary heart disease (CHD).³⁻⁷ Several studies from Western countries⁸⁻¹³ and China¹⁴⁻¹⁶ suggest a positive association between SHS and stroke. To date, however, no study has reported on the association of SHS with peripheral arterial disease (PAD). We have recently reported estimates of the prevalence of PAD attributable to active smoking in a Chinese population.¹⁷ The aim of the present study was to examine the relationship between SHS in women who never smoked and the risk of CHD, stroke, and PAD in a population-based survey of older Chinese in Beijing, China.

Editorial p 1521
Clinical Perspective p 1540

Methods

Study Population

Details of data collection, physical examinations, and other tests for the present study have been reported elsewhere.¹⁷ Briefly, we carried out a population-based cross-sectional survey of older people living in the Wanshoulu community of the Haidian district, a metropolitan area representative of the geographic and economic characteristics in Beijing, China. A 2-stage stratified sampling method was used. First, 9 residential communities or streets (≈ 300 to 600 households) were randomly selected from a total of 94 residential communities in the Wanshoulu area. Second, all individuals were chosen from the selected streets, but only 1 participant was selected from each household. From April 2001 to March 2002, 2680 people ≥ 60 years of age were selected and invited for screening. A total of 2334 subjects (943 men, 1391 women) completed the survey, yielding a response rate of 87.1% (83.5% of men, 89.7% of women). The

Received April 7, 2008; accepted June 27, 2008.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.108.784801

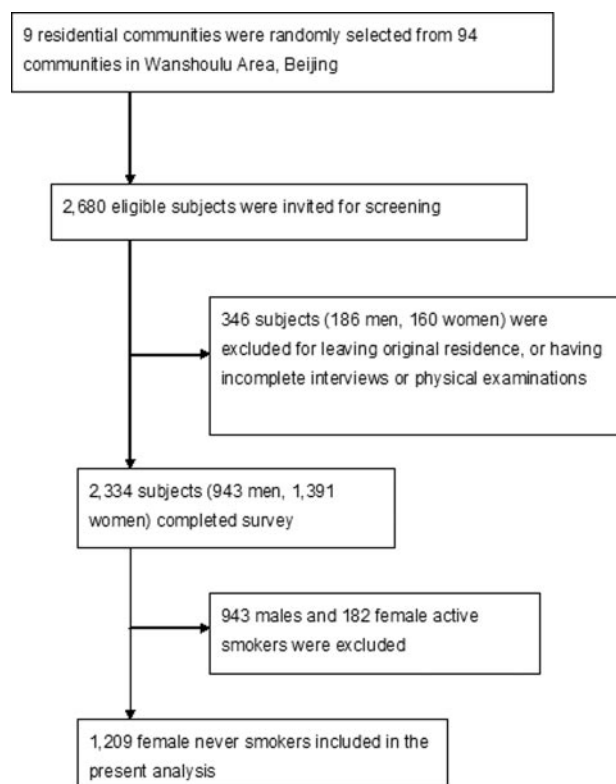


Figure. Flow diagram of participant entry and exclusion.

present study focused on 1209 female participants who were never-smokers, defined as individuals who reported not smoking currently and having smoked <100 cigarettes in their lifetime. Subject entry and exclusions are displayed in the flow chart in the Figure.

Measurement of Ankle and Arm Blood Pressures

The ratio of systolic blood pressure at the ankle (measured by an 8-MHz continuous-wave Doppler probe at the dorsal pedal artery or the posterior artery) and at the arm (measured by a standard mercury sphygmomanometer at the brachial tree) was calculated for each leg, creating an ankle-brachial index (ABI). The lowest value of the ABI was used in the analysis. Measurements in all subjects were carried out by a trained research nurse and a physician who were blinded to the history of smoking exposure in the subjects. The quality control procedures showed high concordance in ABI measurements between 2 observers and 2 measurements 20 days apart, with κ statistics of 0.78 and 0.82 ($P < 0.01$).¹⁷ ABI was not calculated for diabetic patients who had gangrene of the foot or leg because this condition can falsely elevate ABI; these patients ($n=4$) were considered positive PAD cases.

Definition of SHS Exposure

SHS exposure was defined as exposure to another person's tobacco smoke at home or in the workplace for at least 15 minutes daily for >1 day every week for at least 2 years during the past 10 years.¹ Each participant was asked about personal lifetime exposure to SHS in the home and workplace. For SHS exposure at home, we asked 3 questions: How many people living with you smoked cigarettes and/or pipes? How many cigarettes per day were smoked by these smokers who live with you? And for how long per day were you exposed to these smokers? An estimation of workplace SHS exposure was based on 3 questions: Did you have coworkers who smoked cigarettes near you so that you frequently breathed in their smoke? If yes, how many cigarettes per day were you exposed to by these smokers? For how long per day were you exposed to these coworkers who smoked?

Table 1. General Characteristics by SHS Status in the 1209 Female Never-Smokers

Characteristic	Non-SHS (n=732)	SHS (n=477)	P
Age, y	66.8 (5.8)	66.3 (6.1)	0.20
Body mass index, kg/m ²	25.8 (3.6)	25.9 (3.5)	0.56
Systolic blood pressure, mm Hg	137.5 (21.6)	137.9 (21.5)	0.75
Diastolic blood pressure, mm Hg	76.9 (10.7)	77.7 (10.0)	0.20
Total cholesterol, mmol/L	5.5 (1.0)	5.5 (1.0)	0.58
Triglycerides, mmol/L	1.7 (1.1)	1.7 (1.3)	0.64
HDL cholesterol, mmol/L	1.5 (0.5)	1.4 (0.3)	0.30
LDL cholesterol, mmol/L	3.4 (0.9)	3.4 (1.5)	0.82
Fasting glucose, mmol/L	6.2 (2.1)	6.1 (2.0)	0.30
Waist circumference, cm	85.8 (9.0)	86.2 (8.9)	0.42
Education, n (%)			
0–6 y	329 (44.9)	237 (49.7)	0.18
7–12 y	278 (38.0)	174 (36.5)	
≥13 y	125 (17.1)	66 (13.8)	
Marital status, n (%)			
Married	563 (76.9)	407 (85.3)	0.002
Single or divorced	4 (0.5)	2 (0.4)	
Widowed	165 (22.5)	68 (14.3)	
Physical exercise, n (%)			
<1 h/d	194 (26.5)	135 (28.3)	0.78
1–3 h/d	274 (37.4)	176 (36.9)	
≥4 h/d	264 (36.1)	166 (34.8)	
Current alcohol drinking, n (%)	17 (2.3)	41 (8.6)	<0.001
Hypertension, n (%)	368 (50.3)	239 (50.1)	0.95
Diabetes mellitus, n (%)	123 (16.8)	64 (13.4)	0.11
CHD, n (%)	231 (31.6)	200 (41.9)	<0.001
Stroke, n (%)	89 (12.2)	83 (17.4)	0.007
PAD, n (%)	142 (19.4)	129 (27.0)	0.002
Family history of CHD or stroke, n (%)	266 (36.3)	185 (38.8)	0.39

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Values are mean (SD) when appropriate.

Diagnoses of Cardiovascular Diseases

Hypertension was defined as diastolic blood pressure ≥ 90 mm Hg, systolic blood pressure ≥ 140 mm Hg, or current use of medication for hypertension (as defined by World Health Organization [WHO] in 1999). CHD and stroke were defined using the WHO Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) criteria.¹⁸ Myocardial infarction was diagnosed by a representative set of ECG, cardiac enzyme values, and typical symptoms (including prolonged chest pain, a sensation of a heavy weight or squeezing in the chest, or a discomfort as constricting, crushing, oppressing, or compressing in the chest). Angina was defined as use of nitroglycerine, experience of typical chest pain, or ECG changes compatible with ischemic heart disease (58% of the cases were confirmed by exercise test or B ultrasound heart image). Strokes were defined as events requiring hospitalization; this information was verified from local hospital records, and 83% of the cases were confirmed by computed tomography and/or magnetic resonance imaging. PAD was defined as positive intermittent claudication (IC) by the WHO Rose questionnaire (ie, a pain in the calf while walking that disappeared when the patient was standing still and was not present when the patient was resting)¹⁹ or an ABI <0.9. Diabetic subjects with gangrene of the foot or leg ($n=4$) were considered PAD cases.

Table 2. ORs of IC, ABI <0.90, and PAD by SHS Status

	Non-IC (n=1056)	IC			Non-ABI (n=1008)	ABI <0.90			Non-PAD (n=938)	PAD		
		n=153	OR* (95% CI)	P		n=201	OR* (95% CI)	P		n=271	OR* (95% CI)	P
SHS												
No	656	76	1.00		622	110	1.00		590	142	1.00	
Yes	400	77	1.87 (1.30–2.68)	0.001	386	91	1.47 (1.07–2.03)	0.018	348	129	1.67 (1.23–2.16)	<0.001
SHS amount, cigarettes/d												
0	656	76	1.00		622	110	1.00		590	142	1.00	
1–9	115	21	1.81 (1.04–3.16)	0.04	116	20	1.10 (0.64–1.87)	0.74	104	32	1.40 (0.87–2.28)	0.12
10–19	152	28	1.79 (1.10–2.92)	0.02	141	37	1.55 (1.03–2.42)	0.03	129	50	1.76 (1.20–2.61)	0.005
≥20	133	28	2.01 (1.22–3.31)	0.006	129	34	1.63 (1.09–2.81)	0.01	115	47	1.90 (1.27–2.86)	0.002
P for linear trend			0.009				0.002				0.002	
SHS cumulative time, min/d												
0	656	76	1.00		622	110	1.00		590	142	1.00	
≤20	117	22	2.00 (1.16–3.46)	0.01	112	27	1.51 (0.92–2.46)	0.10	103	37	1.62 (1.04–2.58)	0.02
≤40	243	40	1.61 (1.04–2.48)	0.03	234	49	1.35 (0.92–1.99)	0.13	213	70	1.59 (1.11–2.30)	0.007
>40	40	15	2.79 (1.41–5.54)	0.003	40	15	1.97 (1.02–3.81)	0.04	32	22	2.68 (1.49–4.88)	0.001
P for linear trend			0.003				0.048				0.001	

*Adjusted for age (years), marital status, education (≤6, 7 to 12, ≥13 y), exercise (<1, 1 to 3, ≥4 h/d), alcohol consumption (current drinkers vs non-current drinkers), body mass index, systolic blood pressure (mm Hg), total cholesterol (mmol/L), triglycerides (mmol/L), history of hypertension and diabetes mellitus, and family history of CHD or stroke.

Cardiovascular disease (CVD) was defined by the presence of ≥1 of 3 outcomes: CHD, stroke, or PAD.

Statistical Analysis

Student’s *t* test and Wald’s χ^2 test were used to compare differences in continuous and categorical variables, respectively, between the SHS-exposed and -unexposed groups. Logistic regression was used to estimate the odds ratios (ORs) and their 95% CIs of CVD with adjustment for age, marital status, years of education, hours per day of physical exercise, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, triglyceride levels, history of hypertension and diabetes mellitus, and family history of CHD or stroke. The Hosmer-Lemeshow goodness-of-fit index was used to assess overall model fit. We used the statistical package SPSS (version 14.0, SPSS Inc, Chicago, Ill) for all analyses.

The Committee for Medical Ethics of the Chinese PLA General Hospital approved the study in 2001. Each participant signed an informed consent form before completing the questionnaire.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

We documented 431 prevalent cases of CHD (19 myocardial infarction, 412 stable angina), 172 cases of stroke (109 ischemic, 31 hemorrhagic, 32 others), and 271 cases of PAD. The prevalence of SHS exposure was 39.5% (477 subjects), with 414 (86.8%) exposed at home and 63 (13.2%) exposed in the workplace. There was no significant difference in most of the covariates according to SHS exposure status, but the prevalence of CHD, stroke, and PAD was significantly higher in the exposed than in the unexposed subjects (Table 1).

In this Chinese elderly population, the prevalence of PAD was 11.3% (8.0% for men, 13.6% for women) by IC, 15.3% (11.7% for men, 17.7% for women) by ABI, and 19.8% (14.7% for men, 23.2% for women) by both criteria.¹⁷ Those

individuals who were exposed to SHS had a significantly higher risk of PAD (Table 2) than those unexposed. The adjusted OR of PAD was 1.87 (95% CI, 1.30 to 2.68) for IC, 1.47 (95% CI, 1.07 to 2.03) for ABI <0.90, and 1.67 (95% CI, 1.23 to 2.16) for either IC or ABI <0.90. There was a significant dose-response relationship between the amount of SHS exposure (cigarettes per day) and cumulative SHS exposure time (minutes per day) and increasing risk of IC, ABI <0.90, or overall prevalence of PAD (*P* for linear trend=0.048 to 0.001) (Table 2).

The adjusted ORs of hemorrhagic stroke, ischemic stroke, and total stroke were 1.10 (95% CI, 0.52 to 2.34), 1.56 (95% CI, 1.03 to 2.35), and 1.65 (95% CI, 1.17 to 2.32), respectively, with significant trends for increasing exposure of SHS and prevalence of ischemic and total stroke (*P* for linear trend=0.02 to <0.001) (Table 3). SHS exposure was significantly associated with increased risk of CHD (OR, 1.69; 95% CI, 1.31 to 2.18) and total CVD (OR, 1.68; 95% CI, 1.30 to 2.16) (Table 4).

The tests of goodness of fit for the logistic regression models in Tables 2 through 4 showed that the overall model fits were good and that there were no statistically significant differences between the observed and expected values (*P*=0.24 to 0.95).

Discussion

In the 1996 National Prevalence Survey of Smoking Patterns in mainland China, the prevalence of smoking was 66.9% in men and 4.2% in women, and 53.5% of the respondents reported passive smoke exposure.¹ In addition, most Chinese adults were unaware of health hazards of either active or passive smoking, with only 32% knowing that SHS poses serious health hazards and 21% knowing that smoking can

Table 3. OR of Ischemic Stroke, Hemorrhagic Stroke, and Total Stroke by SHS Status

	Nonstroke (n=1178)	Hemorrhagic Stroke			Nonstroke (n=1100)	Ischemic Stroke			Nonstroke (n=1037)	Total Stroke		
		n=31	OR* (95% CI)	P		n=109	OR* (95% CI)	P		n=172	OR* (95% CI)	P
SHS												
No	713	19	1.00		674	58	1.00		643	89	1.00	
Yes	465	12	1.10 (0.52–2.34)	0.80	426	51	1.56 (1.03–2.35)	0.035	394	83	1.65 (1.17–2.32)	0.004
SHS amount, cigarettes/d												
0	713	19	1.00		674	58	1.00		643	89	1.00	
1–9	135	1	0.34 (0.05–2.60)	0.30	124	12	1.31 (0.66–2.57)	0.44	119	17	1.10 (0.62–1.96)	0.74
10–19	172	8	1.96 (0.82–4.73)	0.13	154	18	1.45 (0.84–2.86)	0.18	136	32	1.72 (1.08–2.77)	0.02
≥20	158	3	0.79 (0.22–2.75)	0.70	148	21	1.72 (1.09–3.04)	0.02	139	34	1.83 (1.15–3.37)	0.004
P for linear trend			0.25				0.002				<0.001	
SHS cumulative time, min/d												
0	713	19	1.00		674	58	1.00		643	89	1.00	
≤20	137	2	0.65 (0.15–2.88)	0.57	123	14	1.49 (0.75–2.96)	0.22	112	25	1.68 (1.06–2.57)	0.02
≤40	275	8	1.18 (0.49–2.82)	0.72	254	29	1.44 (0.88–2.35)	0.15	236	47	1.56 (1.05–2.34)	0.03
>40	53	2	1.98 (0.42–9.33)	0.39	49	8	1.98 (0.96–4.36)	0.07	46	11	1.74 (0.90–3.86)	0.09
P for linear trend			0.73				0.02				0.004	

*Adjusted for age (years), marital status, education (≤6, 7 to 12, ≥13 y), exercise (<1, 1 to 3, ≥4 h/d), alcohol consumption (current drinkers vs non-current drinkers), body mass index, systolic blood pressure (mm Hg), total cholesterol (mmol/L), triglycerides (mmol/L), history of hypertension and diabetes mellitus, and family history of CHD or stroke.

cause CVD.² In our study, because the vast majority of women were never-smokers (87%), we had a unique opportunity to evaluate the association of SHS with risk of CVD, particularly PAD. PAD is an underdiagnosed and undertreated condition in China; ≈43% of PAD patients were asymptomatic, and most of them were unaware of their condition.^{17,20} It is difficult to examine the association between SHS and risk of PAD in a cohort study because

comprehensive ascertainment of PAD incidence is challenging.

To the best of our knowledge, this is the first study showing an increased risk of PAD with increasing SHS exposure. We found significant ORs of 1.87 and 1.47 for IC and PAD by ABI <0.90, respectively, in never-smoking older Chinese women exposed to SHS, with significant dose-response relationships for both the number of cigarettes

Table 4. OR of CHD and CVD by SHS Status

	Non-CHD (n=778)	CHD			Non-CVD (n=548)	CVD		
		n=431	OR* (95% CI)	P		n=661	OR* (95% CI)	P
SHS								
No	501	231	1.00		361	372	1.00	
Yes	277	200	1.69 (1.31–2.18)	<0.001	187	289	1.68 (1.30–2.16)	<0.001
SHS amount, cigarettes/d								
0	501	232	1.00		361	372	1.00	
1–9	84	52	1.41 (0.94–2.11)	0.09	60	75	1.35 (0.89–2.02)	0.12
10–19	102	78	1.85 (1.31–2.63)	0.001	63	116	1.98 (1.39–2.85)	<0.001
≥20	91	70	1.77 (1.23–2.55)	0.002	64	98	1.65 (1.13–2.38)	0.007
P for linear trend			<0.001				0.001	
SHS cumulative time, min/d								
0	501	231	1.00		361	372	1.00	
≤20	87	52	1.46 (0.98–2.18)	0.07	56	83	1.66 (1.11–2.47)	0.01
≤40	162	121	1.78 (1.32–2.40)	<0.001	116	166	1.60 (1.18–2.13)	0.003
>40	28	27	1.86 (1.05–3.31)	0.04	15	40	2.36 (1.26–4.52)	0.006
P for linear trend			0.001				<0.001	

*Adjusted for age (years), marital status, education (≤6, 7 to 12, ≥13 y), exercise (<1, 1 to 3, ≥4 h/d), alcohol consumption (current drinkers vs non-current drinkers), body mass index, systolic blood pressure (mm Hg), total cholesterol (mmol/L), triglycerides (mmol/L), history of hypertension and diabetes mellitus, and family history of CHD or stroke.

and duration of exposure after adjustment for 13 potential confounders. We focused on never-smoking women ≥ 60 years of age because they were at high risk of developing CVD and most of them were lifelong never-smokers. Our sample was randomly selected from a representative sample of residential communities in Beijing, and the response rate was quite high. Hence, the observed association between SHS and risk of PAD and other CVDs should be generalizable to similar populations in China.

Several previous studies have shown an association between SHS and stroke,^{8–16} a leading cause of death and disability in China.^{14,15} However, 3 reports from Shanghai and Hong Kong did not investigate subtypes of stroke.^{14–16} This population-based study is the first to report a positive association of SHS exposure with ischemic stroke but not with hemorrhagic stroke among Chinese female nonsmokers. The likelihood of having an ischemic stroke was 1.5 times higher in women who were exposed to SHS than in those who were not exposed. This association was independent of socioeconomic, lifestyle, and other established risk factors for stroke. Our finding of a dose-dependent association of SHS with CHD is consistent with the literature.^{3–7,15,16}

An important advantage of our study is that PAD was diagnosed by the ABI measurement.^{20–22} Although this study was cross-sectional, our data on SHS status should not have been affected by differential reporting bias in CVD cases versus noncases because the SHS questions were asked before physical examination and disease end-point ascertainment. Moreover, most Chinese women were unaware of the health hazard caused by passive smoking; thus, bias resulting from overreporting of exposure in CVD patients was unlikely. The bias resulting from misclassification of current and ex-smokers as lifelong never-smokers should be small because the prevalence of female smokers in China was very low. Misclassification of SHS exposure is inevitable, which may have biased the results toward null. In this retired elderly sample, the relatively low (39.5%) prevalence of SHS exposure in never-smokers may be attributable to 2 factors. First, the prevalence of current smoking in elderly men in our study was much lower (24.7%) than that in the general population.¹⁷ Second, exposure to SHS was restricted to passive smoking in the past 10 years to minimize recall error, and there were fewer opportunities for exposure to SHS at work than among women in the general population. Because some people may have died from smoking-related diseases before the present survey, our participants were survivors, which may have led to a conservative estimate of the effects of SHS exposure. The lack of detailed information about SHS exposure in public settings and the duration (years) of SHS were other limitations in this study. Thus, the observed associations between SHS and CVD, including CHD, stroke, and PAD, are likely to be underestimated. Because of the low prevalence of SHS exposure in the workplace (13.2%) in this sample, we did not examine SHS exposure at home and in the workplace separately.

Conclusions

SHS exposure in women is highly prevalent in China. The present study is the first to show a positive association

between SHS exposure and prevalence of PAD in Chinese female never-smokers. Our results also add to the evidence that SHS is associated with CHD and ischemic stroke. In China, $\approx 4\%$ women are current smokers, but $>50\%$ of women are exposed to SHS either at home or at work.² Most people in China are unaware of the serious health hazards of passive smoking. Thus, urgent public health measures are warranted to protect women from exposure to SHS.

Acknowledgments

We thank Drs Y. Jiang, Q. Chang, and K. Feng for research assistance. We also thank L. Wu for clerical assistance.

Sources of Funding

This study is supported by research grants from the National Natural Science Foundation of China (30671809, 30771859), Beijing Natural Science Foundation (7062063), and the Health Service in the Health Ministry of China (06H050). Dr Hu was partly supported by an American Heart Association Established Investigator Award. Dr He was partly supported by the Gordon Wu and Cheng YuTung Exchange Professorships in the Faculty of Medicine at the University of Hong Kong.

Disclosures

None.

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CLINICAL PERSPECTIVE

We conducted a population-based cross-sectional study in an urban Beijing sample of women who had never smoked to assess the association between secondhand smoke (SHS) and risk of peripheral arterial disease (PAD), stroke, and coronary heart disease in China. SHS exposure was defined as exposure to another person's tobacco smoke at home or at work. PAD was defined by symptoms of intermittent claudication and an ankle-brachial index of <0.90. Among 1209 Chinese women who never smoked, 39.5% were exposed to SHS. We found that compared with women who were not exposed to SHS, among women who were exposed to SHS, risk of intermittent claudication was increased by 87% and risk of PAD assessed by ankle-brachial index <0.90 was increased by 47%, with significant dose-response relationships for both number of cigarettes exposed to and duration of exposure after adjustment for established cardiovascular risk factors. PAD is an underdiagnosed and undertreated condition in China; ≈43% of PAD patients were asymptomatic, and most of them were unaware of their condition and did not know the risk factors for PAD. Our results add to the evidence that SHS exposure is associated with increased risk of coronary heart disease by 69% and ischemic stroke by 56% in Chinese nonsmoking women. In China, ≈4% women are current smokers, but >50% of women are exposed to SHS, and most people are unaware of the serious health hazards of SHS. Thus, urgent public health measures are warranted to protect individuals from exposure to SHS.