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Incense Use and the Risk of Chronic Limb-Threatening Ischemia Among Middle-Aged and Older Adults in the Singapore Chinese Health Study

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Background: Epidemiologic studies have shown that daily exposure to incense smoke is associated with greater risk of cardiovascular mortality, which suggests that chronic exposure to incense could be linked to atherosclerosis. We studied the association between home incense use and the risk of chronic limb-threatening ischemia (CLTI), the most severe outcome of peripheral arterial disease.

Methods: We used data from the Singapore Chinese Health Study, which recruited 63,257 Chinese participants 45–74 years old from 1993–1998. Data were collected via in-person interviews conducted at the participants' homes by trained interviewers. Linkage to the nationwide hospital discharge database was used to determine incident cases, defined as participants who underwent revascularization or lower extremity amputation for CLTI. Association between use of incense and risk of CLTI was examined using multivariable Cox proportional hazards regression models, adjusted for demographics and cardiovascular risk factors.

Results: In this cohort, 76.9% were current users of incense at recruitment, and 92.6% of those used incense daily at home. During a mean 18.8 years of follow-up, 1,097 participants developed CLTI. Compared to never or former users, current users had a 22% higher risk of CLTI [hazard ratio (HR) = 1.22; 95% confidence interval (CI): 1.04, 1.43]. The risk was greater with chronicity of use, and the HR was highest and statistically significant in participants who had used incense daily for >40 years [HR = 1.25 (95% CI: 1.06, 1.46)]. The results did not differ by sex, history of diabetes, or smoking status.

Conclusions: Daily exposure to incense in the home environment for more than 40 years was associated with a greater risk of developing CLTI. https://doi.org/10.1289/EHP14674

Introduction

Peripheral arterial disease (PAD) is a result of progressive atherosclerosis affecting the arteries of the lower limbs, and the most severe manifestation is chronic limb-threatening ischemia (CLTI), which presents clinically as ischemic rest pain, nonhealing ulcers, and/or gangrene.[1] Patients with CLTI usually require surgical intervention of either revascularization or lower limb amputation (LEA) and are at high risk of morbidity and mortality. In fact, the five-year mortality for CLTI is over 50%, which is higher than the mortality for many cancers.[2]

The prevalence of PAD is rising worldwide, thus necessitating the need to identify potential risk factors of PAD, and particularly of the severe disease that progresses to CLTI.[3] As expected, the classical risk factors of atherosclerosis are also associated with risk of PAD, and these are diabetes, hypertension, hyperlipidemia, and cigarette smoking.[4] In addition, studies have shown that ambient air pollution, from the release of particulate matter, carbon monoxide, sulfur dioxide, and volatile organic compounds into the air due to the burning of various products such as cigarettes, solid fuels, or incense in the home environment, is also a risk factor for atherosclerotic disease.[5,6] While cigarette smoke and biomass combustion have been well-studied in the context of atherosclerosis, relatively fewer studies have examined the impact of incense smoke on risk of atherosclerotic diseases, especially PAD.

As part of religious practice, daily exposure to incense smoke, whether due to active use or passive exposure, is common in many Asian and Middle Eastern countries.[7] Epidemiology studies, including our previous study in the Singapore Chinese Health Study cohort, have examined associations between long-term exposure to incense smoke in the home environment and risk of atherosclerotic diseases and reported that users of incense at home were at higher risk of coronary artery disease and stroke, the two most common and potentially fatal presentations of cardiovascular diseases.[8–10] However, to the best of our knowledge, no study has examined the impact of incense smoke on the development of PAD.

Hence, in this large prospective population-based cohort, we aimed to examine the association between long-term exposure to incense smoke at home and the risk of CLTI as the most severe form of PAD, widely recognized as the third most common cardiovascular disease after coronary artery disease and stroke.[11] Specifically, we hypothesized that the long-term use of incense in the home setting could increase the risk of severe PAD.

Research Design and Methods

Study Population

The Singapore Chinese Health Study was a large, prospective population-based cohort that recruited 27,959 men and 35,298 women 45–74 years old at baseline from 1993 to 1998. Study participants were recruited from Singapore citizens and permanent residents who resided in government purpose-built housing estates, which comprised 86% of the population at the time of recruitment.[12] The study was approved by the institutional review board at the National University of Singapore (NUS-IRB) (reference code LH-17-058), and informed consent was obtained from all participants.

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Assessment of Covariates

Trained interviewers used structured questionnaires to interview study participants in their homes. Information collected included age, weight, height, education level, physical activity per week, smoking status, alcohol consumption, history of hypertension, history of diabetes, history of coronary artery disease, and history of stroke. Incense use was assessed via questions that explored whether the participant had never used incense at home (never user) or was a former user or a current user of incense in the home setting during the baseline interview. For ever users (former and current users), we also asked about the total number of years incense was used, the frequency of incense use, whether they had been using incense at age 10, and the location of the incense altar in the house.

Surviving participants were recontacted for the follow-up 1 interviews, which were conducted via telephone calls from 1999 to 2004, approximately 6 years after enrollment. A total of 52,322 participants were contacted successfully, during which they were again asked about their weight, height, smoking status, history of hypertension, history of diabetes, history of coronary artery disease, and history of stroke.

Ascertainment of CLTI and Follow-Up

The cohort database was linked to the Singapore MediClaim System, a nationwide database that has been established to collect data related to hospitalization from all public and private hospitals in Singapore since 1990. We used surgical codes for lower extremity amputation (LEA) and surgical revascularization procedures listed in the Table of Surgical Procedures to identify incident cases of CLTI after enrollment into the cohort (Table S1).[13] LEAs performed for nonvascular causes, such as trauma, malignancy, peripheral neuropathy, necrotizing fasciitis, osteomyelitis, and osteonecrosis, were identified via the International Classification of Disease version 9 (ICD-9) and version 10 (ICD-10) codes for diagnosis, and these were excluded as cases in the study.[14]

Record linkage to the nationwide Registry of Births and Deaths database was also performed to obtain dates of death for deceased participants during follow-up. As of 31 December 2017, which was the censored date for record linkages with the MediClaim System and death databases, only 41 participants (0.06%) in this cohort were known to be lost to follow-up due to reasons such as emigration, which was reported by their family members during subsequent follow-up interviews conducted within this cohort. As such, data capture was virtually complete.

Statistical Analysis

From the cohort, we excluded 123 subjects who had undergone a surgical procedure for CLTI prior to recruitment (Figure 1). For the 63,134 subjects remaining, person-years were calculated from the date of enrollment to the date of CLTI procedure, date of death, or 31 December 2017, whichever came first.

Multivariable Cox proportional hazards models were used to examine the associations between incense use and risk of CLTI, with adjustment for potential confounders. Status of incense use was analyzed as a categorical variable (never, former, current). Among current incense users, data on duration and frequency were combined and analyzed as a categorical variable (nondaily, daily for $\leq$40 years, and daily for >40 years). Participants who were not current users of incense at home during baseline interviews were used as the reference group, and the strength of a given association was measured by the hazard ratio (HR), its corresponding 95% confidence interval (CI), and the two-sided p-value. The confounders in the model were established risk factors of CLTI in the literature and from our previous publication.[14] Model 1 was adjusted for age at recruitment (year), period of study enrollment (1993–1995, 1996–1998) as a proxy for consistency of data quality through the 5 years of recruitment, educational level (no formal education, primary school, secondary school or higher) as a proxy for socioeconomic status, weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, $\geq$4 hours/week) as weekly physical activity has been associated with CLTI progression, sex (men, women), and alcohol consumption (never/monthly, weekly/daily). Model 2 was additionally adjusted for six cardiovascular risk factors as time-varying covariates using data from both baseline and follow-up 1 interviews, namely body mass index (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, $\geq$27.5 kg/m^2), smoking (never, former,

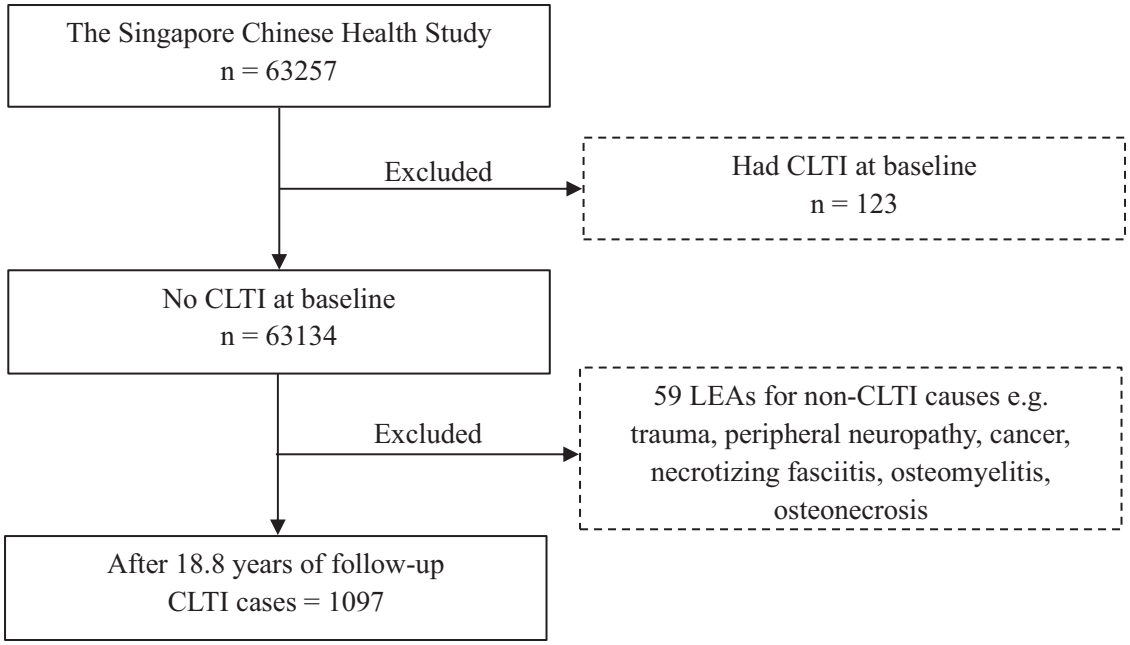

Figure 1. Flow diagram of the Singapore Chinese Health Study and the exclusion criteria of this study. Note: CLTI, chronic limb-threatening ischemia; LEA, lower extremity amputation.

Table 1. Baseline characteristics of participants according to status of incense use, the Singapore Chinese Health Study, 1993–1998.

	Current users	Never/former users
Number of subjects	48,519 (76.9%)	14,615 (23.1%)
Number of CLTI cases	898 (1.9%)	199 (1.4%)
Age at interview in years (mean ± SD)	56.5 (8.0)	56.4 (8.2)
BMI in kg/m^2 (mean ± SD)	23.2 (3.3)	22.9 (3.2)
Sex		
Men	21,587 (44.5%)	6,293 (43.1%)
Women	26,932 (55.5%)	8,322 (56.9%)
Level of education		
No formal education	14,967 (30.9%)	2,328 (15.9%)
Primary school	22,927 (47.2%)	5,057 (34.6%)
Secondary or higher	10,625 (21.9%)	7,230 (49.5%)
Weekly physical activity		
<0.5 hours/week	33,238 (68.5%)	9,138 (62.5%)
0.5 to <4 hours/week	9,249 (19.1%)	3,503 (24.0%)
≥4 hours/week	6,032 (12.4%)	1,974 (13.5%)
Smoking		
Never	32,929 (67.9%)	10,942 (74.9%)
Former	5,322 (11.0%)	1,641 (11.2%)
Current	10,268 (21.1%)	2,032 (13.9%)
Alcohol drinking		
Never/monthly	42,828 (88.3%)	13,000 (89.0%)
Weekly/daily	5,691 (11.7%)	1,615 (11.0%)
Medical history		
Diabetes	4,419 (9.1%)	1,197 (8.2%)
Hypertension	11,442 (23.6%)	3,565 (24.4%)
Coronary artery disease	1,926 (4.0%)	655 (4.5%)
Stroke	701 (1.4%)	239 (1.6%)
Duration of incense usage		
≤20 years	1,476 (3.0%)	—
21–40 years	6,326 (13.0%)	—
>40 years	40,717 (84.0%)	—
Frequency of current incense usage		
Less than daily	3,569 (7.4%)	—
Daily	44,950 (92.6%)	—

Note: —, not applicable; BMI, body mass index; CLTI, chronic limb-threatening ischemia; SD, standard deviation.

current), history of hypertension (no, yes), history of diabetes (no, yes), history of coronary artery disease (no, yes), and history of stroke (no, yes).

The Schoenfeld residuals method was used to test the proportionality assumption of the Cox models, and no violation was observed. The *p* for trends were calculated by treating categories of incense use as an ordinal variable to represent increasing dose of use in a single model. Stratified analyses by sex, history of diabetes, history of hypertension, and smoking status were performed. Mediation analyses for all confounders were also performed to assess their potential mediation effects.

All statistical analyses were performed using SAS (version 3.81; SAS Institute, Inc.). All *p*-values presented are two-sided, and a *p*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the 63,134 subjects, accounting for 1,188,257 person-years included in this study, are presented in Table 1. Incense use was common in this cohort, with current users accounting for 76.9% of the cohort (77.4% of all men and 76.4% of all women), while former users who had stopped for at least 1 year accounted for 13.0% of the cohort, and only 10.1% had never used incense before. Almost all (92.6%) of the current users burned incense at home daily, and 84.0% of them had been doing so for more than 40 years. Compared to never/former users, current users were more likely to have lower education levels and to be less physically active. In terms of vascular risk factors, current incense users were much more likely to be current smokers and to have diabetes but less likely to have a history of hypertension and coronary artery disease than never/former users.

After a mean follow-up of 18.8 years, 1,097 incident cases of CLTI were identified. Table 2 shows the associations between incense use status and frequency and CLTI risk. Compared to never users, former incense users did not experience a statistically significant greater CLTI risk, and thus in subsequent analyses, never and former users were grouped together as the reference group. After adjusting for potential confounders, current users of incense had a 22% higher chance of developing CLTI (HR = 1.22; 95% CI: 1.04, 1.43; $p = 0.02$) compared to never/former users. Detailed analysis by frequency and duration of incense use showed that this increased risk was only statistically significant in subjects who had used incense daily for more than 40 years (HR compared to never/former users = 1.25; 95% CI: 1.06, 1.46). However, in subjects who had used incense daily but for <40 years, there was also a greater risk estimate (HR compared to never/former users = 1.19; 95% CI: 0.94, 1.51), albeit this did not reach statistical significance.

Mediation analyses were performed on all confounders described in the model (Table S2). Only history of diabetes had a statistically significant indirect effect on CLTI risk (indirect effect HR = 1.05; 95% CI: 1.03, 1.07). Nonetheless, despite being statistically significant in terms of *p*-value, the actual mediation effect was very small. In addition, the direct effect of incense use and CLTI risk remained statistically significant (direct effect HR = 1.20; 95% CI: 1.05, 1.35)

Table 2. Association between incense use and the risk of developing CLTI by status, frequency, and duration of incense use among participants in the Singapore Chinese Health Study.

Exposure	Person-years	CLTI cases	Model 1[a] [HR (95% CI)]	Model 2[b] [HR (95% CI)]
Status of incense use				
Never user	122,934	90	1.00	1.00
Former user	156,547	109	1.01 (0.76, 1.34)	1.00 (0.76, 1.33)
Current user	908,775	898	1.25 (1.00, 1.56)	1.22 (0.98, 1.53)
Never/former user	279,481	199	1.00	1.00
Current user	908,775	898	1.25 (1.07, 1.47)	1.22 (1.04, 1.43)
Frequency and duration of incense use				
Never/former user	279,481	199	1.00	1.00
Current user, nondaily	67,341	56	1.06 (0.79, 1.43)	1.02 (0.76, 1.37)
Current user, daily for ≤40 years	142,940	120	1.18 (0.93, 1.49)	1.19 (0.94, 1.51)
Current user, daily for >40 years	698,495	772	1.29 (1.09, 1.51)	1.25 (1.06, 1.46)
p for trend	—	—	0.02	0.04

Note: Data presented as hazard ratio (HR) [95% confidence interval (CI)]. —, not applicable; BMI, body mass index; CLTI, chronic limb-threatening ischemia.
[a]Model 1: Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrollment (1993–1995, 1996–1998), educational level (no formal education, primary school, secondary school or higher), weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, ≥4 hours/week), sex (men, women), and alcohol consumption (never/monthly, weekly/daily).
[b]Model 2: Model 1 plus body mass index (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, ≥27.5 kg/m^2), smoking (never, former, current), hypertension (no, yes), diabetes (no, yes), coronary artery disease (no, yes), and stroke (no, yes).

Table 3. Association between incense use and the risk of developing CLTI, stratified by sex, diabetes, and hypertension among participants in the Singapore Chinese Health Study.

Exposure	CLTI cases	HR (95% CI)	CLTI cases	HR (95% CI)	*p* for interaction
Stratified by sex[a]	Men		Women		0.37
Never/former user	100	1.00	99	1.00	—
Current user, nondaily	32	1.13 (0.76, 1.68)	24	0.90 (0.58, 1.42)	—
Current user, daily for ≤40 years	51	0.97 (0.68, 1.37)	69	1.44 (1.05, 1.98)	—
Current user, daily for >40 years	351	1.23 (0.98, 1.55)	371	1.25 (0.99, 1.57)	—
p for trend	—	0.17	—	0.05	—
Stratified by diabetes[b]	No diabetes		Has diabetes		0.25
Never/former user	103	1.00	96	1.00	—
Current user, nondaily	36	1.26 (0.86, 1.85)	20	0.81 (0.50, 1.32)	—
Current user, daily for ≤40 years	66	1.15 (0.83, 1.58)	54	1.24 (0.88, 1.76)	—
Current user, daily for >40 years	386	1.31 (1.05, 1.64)	336	1.15 (0.91, 1.46)	—
p for trend	—	0.12	—	0.27	—
Stratified by hypertension[c]	No hypertension		Has hypertension		0.67
Never/former user	121	1.00	78	1.00	—
Current user, nondaily	30	0.88 (0.59, 1.32)	26	1.25 (0.80, 1.96)	—
Current user, daily for ≤40 years	80	1.24 (0.93, 1.66)	40	1.12 (0.75, 1.65)	—
Current user, daily for >40 years	430	1.21 (0.99, 1.49)	292	1.31 (1.01, 1.70)	—
p for trend	—	0.12	—	0.20	—

Note: Data presented as hazard ratio (HR) [95% confidence interval (CI)]. —, not applicable; BMI, body mass index; CLTI, chronic limb-threatening ischemia.
[a]Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrollment (1993–1995, 1996–1998), educational level (no formal education, primary school, secondary school or higher), weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, ≥4 hours/week), alcohol consumption (never/monthly, weekly/daily), BMI (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, ≥27.5 kg/m^2), hypertension (no, yes), diabetes (no, yes), coronary artery disease (no, yes), stroke (no, yes), and smoking status (never, former, current).
[b]Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrollment (1993–1995, 1996–1998), educational level (no formal education, primary school, secondary school or higher), weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, ≥4 hours/week), alcohol consumption (never/monthly, weekly/daily), BMI (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, ≥27.5 kg/m^2), hypertension (no, yes), coronary artery disease (no, yes), stroke (no, yes), and smoking status (never, former, current).
[c]Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrollment (1993–1995, 1996–1998), educational level (no formal education, primary school, secondary school or higher), weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, ≥4 hours/week), alcohol consumption (never/monthly, weekly/daily), BMI (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, ≥27.5 kg/m^2), diabetes (no, yes), coronary artery disease (no, yes), stroke (no, yes), and smoking status (never, former, current).

and was close to the total effect (total effect HR = 1.26; 95% CI: 1.10, 1.42).

Stratified analyses by sex, diabetes, and hypertension at baseline are shown in Table 3, while stratified analysis by smoking status at baseline is shown in Table 4. The risk estimates between men and women, between those with and without history of diabetes at baseline, and between those with and without history of hypertension at baseline were comparable (*p* for interaction ≥0.25). For smoking status at baseline, sample sizes were considerably small, and there was no suggestion of a difference in the results among never, former, or current smokers at baseline (*p* for interaction ≥0.45).

Discussion

In this large prospective population-based cohort of middle aged and older Singaporean Chinese, we found that daily exposure to incense in the home environment for more than 40 years was associated with a greater risk of developing CLTI and that this association was independent of other risk factors such as sex, cigarette smoking, hypertension, and diabetes.

Preclinical studies have proposed biological mechanisms underlying incense exposure and atherosclerosis. Studies on rats have reported that chronic exposure to incense smoke induced systemic levels of oxidative stress and inflammation as well as endothelial dysfunction.[15,16] Another study on flow-mediated dilation in pigs observed that exposure to incense smoke, as compared to exposure to candle smoke or tobacco smoke, caused significantly greater suppression of endothelial function.[17] Similar results were observed in human cell cultures, where exposure to particulate matter collected from an incense-burning temple in Taiwan was found to directly induce cytokine production in human coronary artery endothelial cells.[18]

Despite rising public awareness that incense smoke is harmful to health, the burning of incense at home is still a part of common practice in many parts of the world, not only for religious purposes but also for air freshening or therapeutic purposes.[9,19] Recently published studies estimating the prevalence of incense use at home have reported anywhere from 20% in Hong Kong[20] to 49.2% in the United States[21] to 60.8% in Portugal[22] to 70.6% in Taiwan,[23] although studies on indoor air pollution conducted outside Asia did not differentiate between incense and candle use. This is important

Table 4. Association between incense use and the risk of developing CLTI, stratified by smoking habits among participants in the Singapore Chinese Health Study.

Exposure	CLTI cases	HR (95% CI)	CLTI cases	HR (95% CI)	CLTI cases	HR (95% CI)
Stratified by smoking status[a]	Never smoker		Former smoker		Current smoker	
Never/former user	132	1.00	26	1.00	41	1.00
Current user, nondaily	26	0.76 (0.50, 1.16)	12	1.82 (0.91, 3.62)	18	1.23 (0.70, 2.14)
Current user, daily for ≤40 years	80	1.23 (0.93, 1.64)	6	0.71 (0.29, 1.76)	34	1.26 (0.79, 2.01)
Current user, daily for >40 years	436	1.24 (1.02, 1.53)	102	1.32 (0.84, 2.06)	184	1.19 (0.84, 1.68)
p for trend	—	0.02	—	0.17	—	0.75

Note: Data presented as hazard ratio (HR) [95% confidence interval (CI)]. *p* for interaction between incense use and smoking status (never versus former smokers) = 0.95. *p* for interaction between incense use and smoking status (never versus current smokers) = 0.45. —, not applicable; BMI, body mass index; CLTI, chronic limb-threatening ischemia.
[a]Hazard ratio (HR) adjusted for age at recruitment (year), year of study enrollment (1993–1995, 1996–1998), educational level (no formal education, primary school, secondary school or higher), weekly physical activity (<0.5 hours/week, 0.5 to <4 hours/week, ≥4 hours/week), alcohol consumption (never/monthly, weekly/daily), BMI (<18.5 kg/m^2, 18.5 kg/m^2 to <23 kg/m^2, 23 kg/m^2 to <27.5 kg/m^2, ≥27.5 kg/m^2), hypertension (no, yes), diabetes (no, yes), coronary artery disease (no, yes), and stroke (no, yes).

as the components of incense smoke include fine and ultrafine particulate matter, gases such as carbon monoxide, nitrogen and sulfur oxides, volatile organic compounds such as formaldehyde, and polycyclic aromatic hydrocarbons, many of which have been linked to cardiovascular diseases.[19,24]

To the best of our knowledge, although two prospective cohort studies have recently examined associations between indoor air pollution and PAD risk,[25] no other prospective cohorts have studied the specific effects of incense exposure on PAD. The Korean National Health Insurance Service–National Sample Cohort reported that exposure to SO_2 and NO_2 were independently associated with PAD risk in their cohort (multivariable-adjusted HR per 0.01 ppm for $SO_2 = 1.69$; 95% CI: 1.11, 2.57; HR for $NO_2 = 1.20$; 95% CI: 1.10, 1.34).[25] Conversely, the German Epidemiological Trial on Ankle Brachial Index did not find any association between air pollutants [particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}), NO_2, or proximity of the home to a major road] and PAD risk in their cohort.[26] This discrepancy may be due to the fact that the Korean cohort used air pollutant data as measured by monitoring facilities in the area, while the German cohort used prediction models to generate air pollutant data.

Although no prospective studies have examined the effects of incense exposure on PAD risk, several of them have reported associations between incense exposure and risk of other cardiovascular diseases. The Singapore Chinese Health Study has previously found that daily exposure to incense in the home environment for at least 20 years increased the risk of cardiovascular mortality (multivariable-adjusted HR compared to never/former incense users = 1.12; 95% CI: 1.06, 1.53), and this was true for both coronary artery disease and stroke.[10] Another Thai–Vietnamese study found that adults with daily exposure to incense had significantly greater carotid intima media thickness compared to those without long-term household incense use, suggesting that they could be at higher risk of cerebrovascular disease.[8] Finally, a randomized controlled trial that exposed individuals to either clean air or concentrated ambient ultrafine particles for two hours found that exposure to particulate matter, even for such a short duration, could cause electrocardiographic changes, decreases in blood plasminogen and thrombomodulin, and increases in C-reactive protein and serum amyloid A.[27]

The main strengths of the present study include the prospective population-based cohort design, the usage of semi-structured questionnaires by trained interviewers, the long follow-up period, the high prevalence and long duration of incense use in this cohort, the clinically significant end point, and the detailed information on medical history and potential vascular risk factors obtained well before the development of disease. As such, observer bias and temporal bias have been minimized. In addition, due to the relatively low prevalence of cigarette smoking (especially among women) and minimal sources of other indoor air pollution such as solid fuel use,[28] we could assume that the main source of indoor ambient air pollution in this cohort was incense smoke. Surgical outcomes were captured comprehensively via linkage to a nationwide database and those who had undergone these procedures due to nonvascular causes were excluded, thus minimizing the risk of outcome misclassification. Important cardiovascular risk factors, such as body mass index (BMI), smoking habits, diabetes status, and hypertension status were also updated in follow-up 1 interviews conducted about 6 years after baseline interviews; thus, analyses that included these confounders as time-varying covariates could be performed.

We acknowledge the limitations to the study. First, incense exposure was only examined at baseline recruitment, and therefore it was possible that a small number of participants could have stopped using incense over the follow-up period. However, given that 84.0% of the incense users had been doing so for over 40 years, and mainly for religious reasons, it was unlikely for many of them to have quit using incense during follow-up and thus any effect on the risk estimate should be minimal. Next, the medical conditions were self-reported, but as the accuracy of the self-reported diabetes and hypertension were subsequently validated in this cohort to be 97% and 88%, respectively, any misclassification should be minimal and nondifferential.[29,30] In addition to this, as we did not collect detailed information on the type and adequacy of treatment for diabetes and hypertension, we were unable to comment on the adequacy of medical treatment. Finally, as the present study was focused on CLTI necessitating surgical intervention, we did not have baseline information about ankle–brachial index or other forms of measurement for less severe forms of PAD, and hence would not be able to confidently extrapolate these findings to stable or asymptomatic PAD.

In conclusion, daily exposure to incense in the home setting for over 40 years was associated with a greater risk of CLTI among Chinese living in Singapore. Given the prevalence of incense use worldwide and the high risk of morbidity and mortality for CLTI, it would be important to increase public awareness regarding the potential harmful effects of long-term incense exposure in order to reduce the risk of CLTI.

Acknowledgments

W.-P.K. designed the research; W.-P.K. and A.F.Y. conducted the research, analyzed the data, and interpreted the statistical analysis; A.F.Y. wrote the paper with critical input from W.-P.K. and D.J.H., and all authors read and approved the manuscript. W.-P.K. has primary responsibility for final content.

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