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The Association of Secondhand Tobacco Smoke and CT Angiography-Verified Coronary Atherosclerosis

David F. Yankelevitz, MD,[a] Matthew D. Cham, MD,[a] Harvey Hecht, MD,[b] Rowena Yip, MPH,[a] Joseph Shemesh, MD,[c] Jagat Narula, MD,[b] Claudia I. Henschke, PhD, MD[a]

ABSTRACT

OBJECTIVES The aim of this study was to assess the relationship of the extent of atherosclerosis on coronary computed tomographic angiography to the extent of secondhand tobacco smoke (SHTS) exposure in asymptomatic never smokers.

BACKGROUND A dose-related association between SHTS and coronary artery calcium has been reported, but the total extent of atherosclerosis has not been investigated.

METHODS A total of 268 never smokers, ages 40 to 80 years, completed a questionnaire assessing risk factors and extent of lifetime SHTS exposure, providing a total SHTS exposure score. Ordinal coronary artery calcium scores were derived from low-dose nongated computed tomographic scans, followed by computed tomographic angiography. Analyses of the prevalence, extent, and plaque characteristics of atherosclerosis were performed, and the independent contribution of SHTS, adjusted for other documented risk factors, was determined.

RESULTS Coronary atherosclerosis was noted in 48% and was more frequent with low to moderate and high versus minimal SHTS exposure (48% and 69% vs. 25%; $p < 0.0001$). Adjusted odds ratios for any atherosclerosis were 2.1 (95% confidence interval: 1.0 to 4.4; $p = 0.05$) for low to moderate and 3.5 (95% confidence interval: 1.4 to 8.5; $p = 0.01$) for high exposure versus minimal SHTS exposure and were not significant for standard risk factors of diabetes ($p = 0.56$), hyperlipidemia ($p = 0.11$), hypertension ($p = 0.65$), and renal disease ($p = 0.24$). With increasing SHTS exposure, the percentage of major vessel (14%, 41%, and 45%; $p = 0.0013$) with any plaque or stenosis increased, as did the number with 5 or more involved segments (0%, 39%, and 61%; $p = 0.0001$). Also the average number of involved segments increased (0.82, 1.98, and 3.49; $p < 0.0001$), with calcified plaques alone (0.25, 0.77, and 1.52; $p < 0.0001$), with calcified and partially calcified plaques (0.28, 0.82, and 1.58; $p < 0.001$), but not with noncalcified plaques alone ($p = 0.11$).

CONCLUSIONS The presence and extent of atherosclerosis were associated with the extent of SHTS exposure even when adjusted for other risk factors, further demonstrating the causal relationship of SHTS exposure and coronary disease. (J Am Coll Cardiol Img 2017;10:652–9) © 2017 by the American College of Cardiology Foundation.

From the [a]Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; and the [c]Department of Cardiology, The Grace Ballas Cardiac Research Unit, Sheba Medical Center, Tel Hashomer, Tel-Aviv University Sackler Faculty of Medicine, Tel-Aviv, Israel. This study was supported in part by the Flight Attendants Medical Research Institute. Dr. Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest, including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are nonexclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation CRF may receive from its commercialization of these patents; and he is an equity owner in Accumetra, a privately held technology company committed to improving the science and practice of image-based decision making. Dr. Henschke is also an inventor of the patents and pending patents owned by CRF, but as of April 2009, she has divested herself of all royalties and other interests arising from these. Dr. Hecht is a consultant to Philips Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Jonathon Leipsic, MD, served as the Guest Editor for this paper.

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The global cardiovascular ravages of smoking are much better appreciated than the damage inflicted by secondhand tobacco smoke (SHTS). It was not until Hirayama (1,2) first reported the association of SHTS exposure and coronary artery disease (CAD) that investigations began, culminating in the 2006 surgeon general's report (3) supporting a causal association between SHTS and CAD mortality and morbidity independent of standard cardiac risk factors (4–8). Similar to the well-documented effects of smoking on subclinical atherosclerosis, coronary artery calcification (CAC) has been found to be significantly more prevalent in people who never smoked but were exposed to SHTS than in nonexposed never smokers (9). Subsequently, we demonstrated a significant quantitative dose-response relationship between the extent of SHTS exposure and the extent of CAC that was independent of standard CAD risk factors (10). However, there are no studies investigating the association of SHTS with the total extent of atherosclerosis in the asymptomatic population.

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In this report, we extend our evaluation of atherosclerosis associated with SHTS exposure to a cohort of asymptomatic people who never smoked and who underwent coronary computed tomographic angiography (CTA).

METHODS

COHORT. All asymptomatic men and women without established CAD enrolled in FAMRI-I-ELCAP (Flight Attendant Medical Research Institute-International Early Lung Cancer Action Program) from 2005 to 2014 who volunteered to undergo coronary CTA were evaluated (11) (112 men and 156 women). Any person with known iodine contrast allergy or renal impairment (serum creatinine >1.5 mg/dl) was not eligible for CTA. All were never smokers, defined by the accepted convention as having smoked <100 cigarettes in their lifetimes. Consent was obtained from all participants according to a Health Insurance Portability and Accountability Act-compliant Institutional Review Board-approved protocol. All had completed a background form that included questions about diabetes, hypertension, hypercholesterolemia, and renal disease at the time of initial enrollment into FAMRI-I-ELCAP.

LOW-DOSE BASELINE COMPUTED TOMOGRAPHIC SCAN. At the time of enrollment, a low-dose, nongated, noncontrast computed tomographic (CT) scan was performed on each subject at 120 kVp and 60 mAs or less and collimation of 1.25 mm or less. Images were obtained from the lung apices to the bases in a single breath at maximum inspiration. The CT readings used in this report were performed at the coordinating center on high-resolution monitors. CAC assessment was done using standard mediastinal settings (width 350 Hounsfield units, level 50 Hounsfield units). The presence of CAC in the left main, left anterior descending, left circumflex, and right coronary arteries was categorized as absent, mild, moderate, or severe and given a score of 0, 1, 2, or 3, respectively (10,12). CAC was classified as mild calcification if less than one-third of the length of the entire artery contained calcification (CAC = 1), moderate if one-third to two-thirds (CAC = 2), and severe if more than two-thirds of the artery showed calcification (CAC = 3). Each participant received a total ordinal CAC score, defined as the sum of the CAC score for each of the coronary arteries, ranging from 0 to 12. The ordinal CAC scores were divided into 3 categories of increasing severity: 0, 1 to 3, and 4 to 12 (12).

CORONARY CTA. Volunteers underwent coronary CTA at the Icahn School of Medicine at Mount Sinai using a routine clinical protocol. CTA was performed using a 256-detector CT scanner (Philips Brilliance iCT, Philips Healthcare, Best, the Netherlands), with tube parameters set at 100 to 120 kV and 100 to 360 mAs depending on body habitus. Unless contraindicated, all patients received 0.4 mg of sublingual nitroglycerin and up to 30 mg of intravenous metoprolol to achieve a heart rate of 65 beats/min or less. Prospective electrocardiographic triggering was

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification
CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
CTA = computed tomography angiography
OR = odds ratio
SHTS = secondhand tobacco smoke

TABLE 1 Characteristics by Secondhand Tobacco Smoke Exposure in Never Smokers by Sex, Age, Risk Factors, and Coronary Artery Calcification Score

	Minimal (n = 60)	Low to Moderate (n = 141)	High (n = 67)	p Value
Sex				
Male	25 (42)	62 (44)	25 (37)	0.66
Female	35 (58)	79 (56)	42 (63)	
Age, yrs	49 (43-55)	53 (48-59)	60 (53-65)	<0.0001
Risk factors				
Diabetes	1 (2)	7 (5)	6 (9)	0.20
Hypercholesterolemia	8 (13)	45 (32)	25 (37)	0.007
Hypertension	10 (17)	36 (26)	19 (28)	0.27
Renal disease	1 (2)	1 (1)	0 (0)	0.46
CAC score				
None	51 (85)	102 (72)	39 (58)	0.009
1-3	9 (15)	37 (26)	25 (37)	
4-12	0 (0)	2 (1)	3 (4)	

Values are n (%) or median (interquartile range).
CAC = coronary artery calcification.

used unless the heart rate could not be reduced to <66 beats/min, which then led to retrospective electrocardiographic gating. Contrast was administered using 65 ml of Isovue 370 (Bracco, Milan, Italy) injected intravenously at a rate of 4.5 ml/s and was followed using standard bolus tracking. Iterative reconstruction was used for all studies.

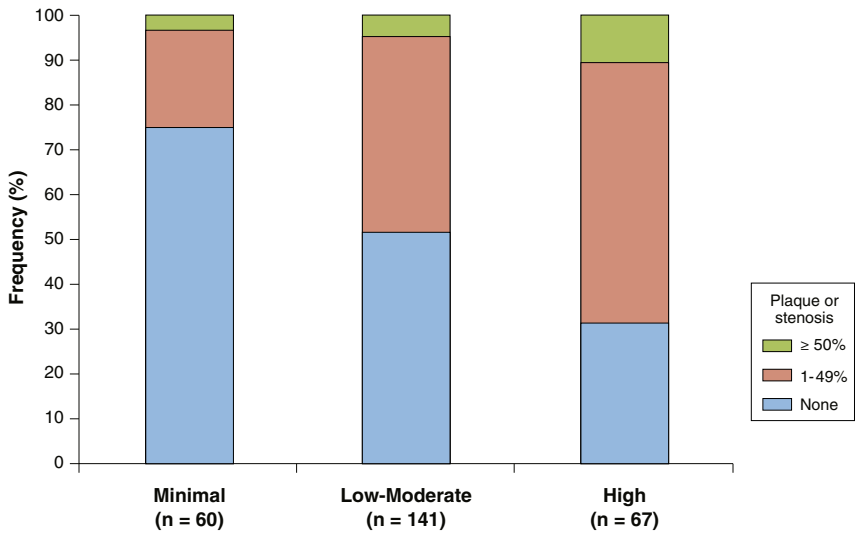
EXTENT OF ATHEROSCLEROSIS. Each CT angiogram was independently reviewed on a 3-dimensional workstation by a board-certified radiologist and cardiologist (M.D.C. and H.H., each with at least 10 years of experience in performing clinical coronary CTA). Readers were blinded to SHTS exposure history. Any interpretive discrepancy between the 2 readers was settled by consensus.

The extent of atherosclerosis was assessed as follows. For each coronary artery, the severity of atherosclerosis was visually classified into 1 of 3 categories: no plaque, plaque with 1% to 49% stenosis in at least 1 coronary artery, and any plaque with >50% stenosis in at least 1 coronary artery. For participants with any plaque with >50% stenosis, the responsible physician was immediately informed of the findings. Each plaque identified on the CTA was classified as noncalcified, partially calcified, or calcified.

The major vessel involvement score was obtained by determining the number of major vessels with any plaque or stenosis. Similarly, the segmental involvement score was obtained by determining the number of individual coronary artery segments with any plaque or stenosis (13). The segments were determined by dividing the coronary artery tree into 15 separate segments (left main artery, left anterior descending artery [proximal, mid, and distal], right coronary artery [proximal, mid, and distal], left circumflex [proximal, mid, and distal], posterior descending artery, obtuse marginal branch [OM1, OM2], and diagonal/intermediate branch [D1, D2]). These segments are the same as those used in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) algorithm (13), except that the diagonal/intermediate branch and obtuse marginal branch were divided into 2 rather than 3 segments, and the posterior descending artery was not subdivided. Thus the segmental involvement score for each never smoker could range from 0 to 15.

SHTS EXPOSURE SCORE. Upon entry into the FAMRI-I-ELCAP study, all participants completed a background questionnaire about SHTS exposure before age 18 as a child and after age 18 as an adult at home and at work, which is detailed in the prior publication (10). The answers determined the permission status, duration of SHTS exposure (years), and daily intensity of SHTS exposure (packs per day) for each of 3 life exposures, as a child and as an adult at home and at work (10). The product of permission status, exposure duration, and daily exposure intensity was calculated and the total SHTS exposure score was obtained. SHTS exposure was categorized as minimal,

FIGURE 1 Severity of Atherosclerosis by Secondhand Tobacco Smoke Exposure



The percentages of coronary artery plaque or stenosis in the 3 secondhand tobacco smoke exposure categories.

low, moderate, or high according to the classification performed (10), and the individual SHTS score for each volunteer was also used in this analysis.

STATISTICAL ANALYSIS. All statistical analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina). Frequencies and descriptive statistics were obtained for all variables. Univariate analysis of CAC, CTA, SHTS exposure score, and other variables was performed using Kruskal-Wallis, chi-square, and Fisher exact tests. Logistic regression analysis was used to address the relationship of CAC to SHTS exposure categories while adjusting for other risk factors of CAC and coronary artery stenosis, including age, sex, diabetes, hypercholesterolemia, hypertension, and renal disease, as reported on the background questionnaire.

RESULTS

BASELINE CHARACTERISTICS AND SHTS EXPOSURE. Sex, diabetes, hypertension, and renal disease were not significantly different among SHTS exposure groups. However, SHTS exposure was associated with increasing age ($p < 0.0001$), hypercholesterolemia ($p = 0.007$), and presence of CAC ($p = 0.009$) (Table 1).

EXTENT OF ATHEROSCLEROSIS. Any stenosis ($p < 0.0001$), extent of plaque or stenosis ($p < 0.0001$) (Figure 1), and any calcified plaques ($p < 0.0001$) were significantly associated with SHTS exposure (Table 2). Calcified, partially calcified, and noncalcified plaques were present in 34%, 4%, and 22% of the subjects (Table 2). There was a significant increase in the number of major coronary vessels with plaque or stenosis (vessel involvement score) with increasing SHTS exposure ($p = 0.0013$) (Table 3). For those with no major vessel involvement, 16% (25 of 153) had high SHTS exposure, which increased with 1, 2, and 3 major vessels involved to 30% (18 of 60), 42% (14 of 33), and 45% (10 of 22) (Table 3). Similarly, the segmental involvement score increased significantly with increasing SHTS exposure ($p < 0.0001$). For those with no involved segments, 17% (25 of 149) had high SHTS scores, which increased with the number of involved segments to 29% (28 of 96) and 61% (14 of 23) for 1 to 4 and 5 or more involved segments (Table 3). Finally, there was a significant increase in the mean number of segments per patient with any plaque or stenosis (0.82 ± 1.65 to 1.98 ± 2.78 to 3.49 ± 3.63; $p < 0.0001$) as SHTS exposure increased from minimal to low or moderate to high (Table 4). There was a significant increase in the mean number of segments with calcified ($p < 0.0001$) and with calcified or partially calcified ($p < 0.0001$) plaque with increasing SHTS exposure but not for exclusively noncalcified plaque ($p = 0.11$) or exclusively partially calcified plaque ($p = 0.94$) (Table 4).

TABLE 2 Secondhand Tobacco Smoke Exposure Score by Extent of Atherosclerosis as Measured by Percentage Plaque or Stenosis

Atherosclerosis	Minimal (n = 60)	Low to Moderate (n = 141)	High (n = 67)	Total (n = 268)	p Value
Any plaque	15 (25)	68 (48)	46 (69)	129 (48)	<0.0001
No plaque	45 (75)	73 (52)	21 (31)	139 (52)	<0.0001
Plaque with stenosis 1%–49%	13 (22)	61 (43)	39 (58)	113 (42)	
Plaque with stenosis >50%	2 (3)	7 (5)	7 (10)	16 (6)	
Calcified	9 (15)	46 (33)	36 (54)	91 (34)	<0.0001
Partially calcified	2 (3)	6 (4)	3 (4)	11 (4)	1.00
Noncalcified	10 (17)	28 (20)	20 (30)	58 (22)	0.15

Values are n (%).

BASELINE CHARACTERISTICS AND STENOSIS ON CTA. Of the 268 never smokers, 129 (48.1%) had plaque or stenosis in 1 or more coronary arteries. Men (64 of 129 [50%] vs. 48 of 139 [35%]; $p = 0.01$), older age (56 vs. 50 years; $p < 0.0001$), hyperlipidemia (40% vs. 19%; $p = 0.0003$), and hypertension (32% vs. 17%; $p = 0.01$) more frequently had any coronary artery stenosis on CTA (Table 5). Compared with those with no atherosclerosis, those with any atherosclerosis more frequently had high CAC ordinal scores of 4 to 12 (5 of 129 [4%] vs. 0%; $p < 0.0001$) and higher SHTS exposure scores (46 of 129 [36%] vs. 21 of 139 [15%]; $p < 0.0001$). An example of severe coronary artery stenosis is presented in Figure 2.

RELATIONSHIP OF CORONARY STENOSIS AND SHTS EXPOSURE AFTER ADJUSTING FOR OTHER RISK FACTORS. Multivariate logistic regression analysis of the contributors to any stenosis, adjusted for documented risk factors, demonstrated a higher odds ratio

TABLE 3 Secondhand Tobacco Smoke Exposure Score by Extent of Atherosclerosis as Measured by Vessel Involvement and Segmental Involvement Scores

	Secondhand Tobacco Smoke Exposure				
	Minimal	Low to Moderate	High	Total	p Value
Number of involved arteries					0.0013
0	45 (29)	83 (54)	25 (16)	153 (100)	
1	9 (15)	33 (55)	18 (30)	60 (100)	
2	3 (9)	16 (48)	14 (42)	33 (100)	
3	3 (14)	9 (41)	10 (45)	22 (100)	
Number of involved segments					<0.0001
0	45 (30)	79 (53)	25 (17)	149 (100)	
1–4	15 (16)	53 (55)	28 (29)	96 (100)	
≥5	0 (0)	9 (39)	14 (61)	23 (100)	
Total	60 (22)	141 (53)	67 (25)	268 (100)	

Values are n (%).

TABLE 4 Plaque Characterization by Secondhand Tobacco Smoke Exposure in 4,020 Segments in 268 Patients

	Minimal (n = 60)	Low to Moderate (n = 141)	High (n = 67)	Kruskal-Wallis p Value
Number of segments with any plaque or stenosis	0.82 (0; 0-6)	1.98 (0; 0-13)	3.52 (3; 0-13)	<0.0001
Number of segments with stenosis >50%	0.03 (0; 0-1)	0.09 (0; 0-2)	0.19 (0; 0-3)	0.14
Number of segments with noncalcified plaques	0.25 (0; 0-4)	0.35 (0; 0-5)	0.7 (0; 0-9)	0.11
Number of segments with partially calcified plaques	0.03 (0; 0-1)	0.05 (0; 0-2)	0.06 (0; 0-2)	0.94
Number of segments with calcified plaques	0.25 (0; 0-3)	0.77 (0; 0-8)	1.52 (1; 0-9)	<0.0001
Number of segments with calcified or mixed plaques	0.28 (0; 0-3)	0.82 (0; 0-8)	1.58 (1; 0-9)	<0.0001

Values are mean (median; range).

(OR) (OR: 2.1; 95% confidence interval [CI]: 1.0 to 4.4; p = 0.05) for low to moderate versus minimal SHTS and an even higher OR (OR: 3.5; 95% CI: 1.4 to 8.5; p = 0.01) for high versus minimal SHTS score. Other contributors were male sex (OR: 3.7; 95% CI: 2.0 to 6.8) and age in decades (OR: 2.8; 95% CI: 1.8 to 4.2). The ORs were not statistically significant for the other risk factors of diabetes, hyperlipidemia, hypertension, and renal disease. After further adjustment for CAC, the p value for low to moderate SHTS became borderline significant (p = 0.06), and high SHTS remained significant (p = 0.006) (Table 6).

TABLE 5 Distribution of Risk Factors, Ordinal CAC Score and Secondhand Tobacco Smoke Exposure Score in Never Smokers Without and With Coronary Artery Stenosis on Coronary Computed Tomographic Angiography

	No Plaque (n = 139)	Plaque With 1%–49% and >50% Stenosis (n = 129)	p Value
Sex			
Male	48 (35)	64 (50)	0.01
Female	91 (65)	65 (50)	
Age, yrs	50 (44–57)	56 (52–62)	<0.0001
Risk factors			
Diabetes	4 (3)	10 (8)	0.07
Hypercholesterolemia	27 (19)	51 (40)	0.0003
Hypertension	24 (17)	41 (32)	0.01
Renal disease	1 (1)	1 (1)	1.00
CAC score			
None	136 (98)	56 (43)	<0.0001
1–3	3 (2)	68 (53)	
4–12	0 (0)	5 (4)	
SHTS score			
Minimal	45 (32)	15 (12)	<0.0001
Low to moderate	73 (53)	68 (53)	
High	21 (15)	46 (36)	

Values are n (%) or median (interquartile range).
CAC = coronary artery calcification; SHTS = secondhand tobacco smoke.

ATHEROSCLEROSIS BY INDIVIDUAL ARTERY CALCIFICATION

The frequency and severity of stenosis increased with increasing CAC score (p < 0.0001). Zero CAC was present in 89% of individual coronary arteries (951 of 1,072), and among them, 88% (841 of 951) had no stenosis, 11% (103 of 951) had 1% to 49% stenosis, and 1% (7 of 951) had >50% stenosis due to noncalcified plaque on CTA. The frequency of stenosis >50% was 9%, 18%, and 50% when the CAC score was 1, 2, and 3 for a single coronary artery, respectively (Table 7).

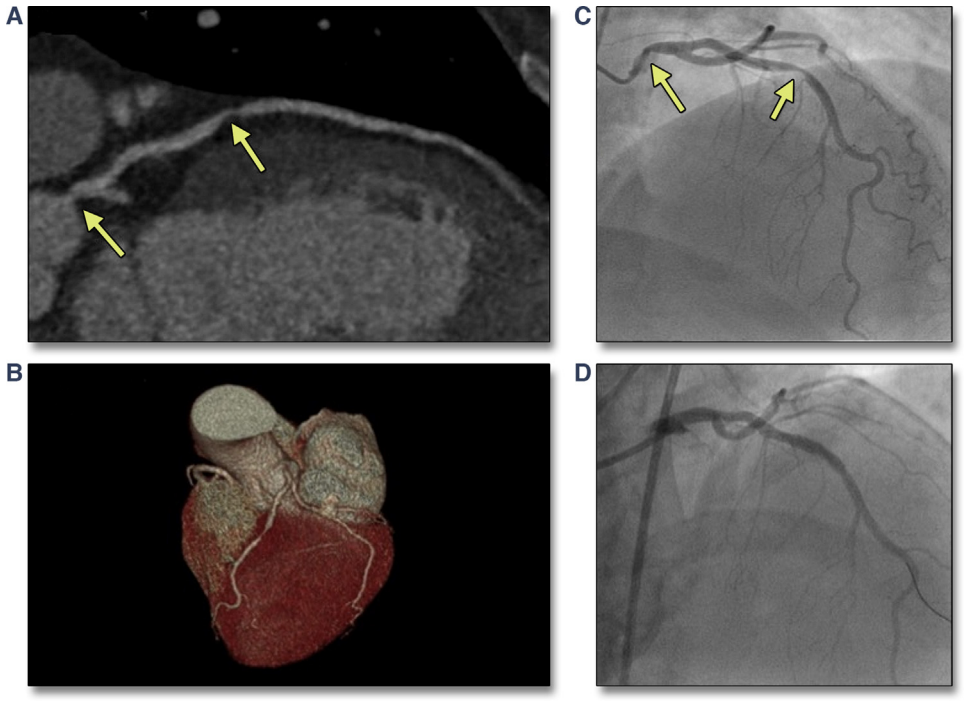
DISCUSSION

This study is the first to document a significant quantitative dose-response relationship in never smokers between the extent of SHTS exposure and the total extent of atherosclerosis manifested by CTA, independent of conventional risk factors. There were significant relationships between the extent of SHTS exposure and the number of major vessels involved as well as segmental involvement with plaque or stenosis, the coronary calcium score, and the percentage of segments with calcified, partially calcified, and noncalcified plaque. These results extend the findings of prior work that had demonstrated an increased prevalence (9) and extent (10) of CAC associated with the extent of SHTS exposure.

SHTS EXPOSURE. The extent and importance of SHTS exposure as a major global health issue (14-16) cannot be overestimated. One-third of both male and female never smokers and 40% of children are exposed to SHTS, and estimated deaths exceed 600,000 annually; the majority (63%) are secondary to CAD, 33% are from respiratory diseases, and 4% are from lung cancer. Increasing awareness of the heavy toll exacted by SHTS exposure, particularly cardiovascular, has resulted in more intensive investigation of the accompanying atherosclerosis, particularly that detectable in early stages by noninvasive imaging modalities. The potential responsible factors are numerous and encompass increased white blood cells, C-reactive protein, homocysteine, oxidative stress, insulin resistance, progenitor cell abnormalities, endothelial dysfunction, arterial stiffness, platelet activation, and increased infarct size (3-8,16,17). These and others are comprehensively and elegantly discussed in a recent review (18).

SHTS EXPOSURE AND THE EXTENT OF ATHEROSCLEROSIS. There are no prior reports documenting the dose-response relationship between the extent of

FIGURE 2 A 48-Year-Old Asymptomatic Woman With High Secondhand Tobacco Smoke Exposure



The coronary artery calcium score was 0. **(A)** Curved multiplanar reconstruction of the left anterior descending coronary artery revealing 70% ostial left main stenosis and 80% proximal left anterior descending stenosis **(arrows)** secondary to noncalcified plaque. **(B)** Volumetric rendering. **(C)** Invasive coronary angiogram confirming the stenoses **(arrows)**. **(D)** Invasive coronary angiography following stenting of both lesions.

atherosclerosis and increasing SHTS exposure. The results remarkably parallel those of Kim et al. (19) in a study of 1,784 asymptomatic current smokers who underwent CTA, consistent with a similar causality of tobacco smoke, whether direct as in smokers or indirect as in those exposed to SHTS.

TABLE 6 Multivariate Logistic Regression Analysis of the Prevalence of Coronary Artery Plaque on Coronary Computed Tomographic Angiography by Secondhand Tobacco Smoke Exposure Score Categories

	OR	95% CI	p Value
SHTS score			
Minimal	Reference		
Low to moderate	2.1	(1.0–4.4)	0.05
High	3.5	(1.4–8.5)	0.01
Age (in decade)	2.8	(1.8–4.2)	<0.0001
Male	3.7	(2.0–6.8)	<0.0001
Diabetes	1.5	(0.4–6.3)	0.56
Hyperlipidemia	1.7	(0.9–3.1)	0.11
Hypertension	1.2	(0.6–2.3)	0.65
Renal disease	6.1	(0.3–124.8)	0.24

CI = confidence interval; OR = odds ratio; SHTS = secondhand tobacco smoke.

They demonstrated a dose-response relationship between the extent of smoking and subclinical atherosclerosis, with a higher prevalence of any plaque, stenosis >50%, noncalcified plaque, and higher calcium scores compared with never smokers. The prevalence of any plaque was 37.2%, >50% stenosis was noted in 6.0%, and noncalcified plaque in 15.4%, compared with 45.5%, 5.6%, and 17.0% in the present SHTS study. An increased incidence of noncalcified plaque was noted in 2 smaller studies of current smokers (20,21).

The results of the present study are most appropriately viewed in the context of the increasing appreciation of the prognostic importance of nonobstructive CAD and the extent of atherosclerosis as demonstrated by CTA. Hadamitzky et al. (22) included 17,793 symptomatic patients in the CONFIRM registry and reported the greatest prognostic value for the prediction of all-cause mortality to be the number of proximal segments with mixed or calcified plaques (C-index = 0.64; $p < 0.0001$), followed by the number of proximal segments with stenosis >50% (C-index = 0.56; $p = 0.002$). Interestingly, in the

TABLE 7 Distribution of Individual Artery CAC Score by Severity of Coronary Artery Stenosis on Coronary Artery Computed Tomographic Angiography for 1,072 Coronary Arteries in 268 Asymptomatic Never Smokers

Individual Artery CAC Score	Extent of Coronary Artery Stenosis			
	None	1%–49%	≥50%	Total
>0	16 (13)	91 (75)	14 (12)	121 (100)
0	841 (88)	103 (11)	7 (1)	951 (100)
1	14 (14)	77 (77)	9 (9)	100 (100)
2	2 (12)	12 (71)	3 (18)	17 (100)
3	0 (0)	2 (50)	2 (50)	4 (100)
Total	857 (80)	194 (18)	21 (2)	1,072 (100)

Values are n (%). The frequency and severity of stenosis increased with increasing CAC score ($p < 0.0001$).

CAC = coronary artery calcification.

study by Hadamitzky et al. (22), noncalcified plaque was the only characteristic that did not contribute to prognosis. Bittencourt et al. (23), in a study of 3,242 symptomatic patients, reported hazard ratios of 3.1 for extensive (>4 segments) nonobstructive disease, 3.0 for nonextensive obstructive CAD, and 3.9% for extensive obstructive disease. In the CONFIRM study of 7,590 asymptomatic patients (24), like the participants in the present study, 37% had 1% to 49% stenosis, with a hazard ratio of 2.04 for all-cause mortality compared with normal arteries and hazard ratios of 2.77, 4.61, and 7.91 for obstructive single-, double-, and triple-vessel disease, respectively. Thus, despite the low incidence of >50% stenosis (5.6%) in the present study, the 42.5% incidence of nonobstructive disease that increases with increasing SHTS exposure strongly suggests that these patients are at increased risk.

The importance of SHTS exposure compared with conventional risk factors of diabetes, hyperlipidemia, hypertension, and renal disease (**Table 5**) was even more striking than for CAC in our prior report of 3,098 never smokers (11). The higher incidence of calcified but not noncalcified plaque with increasing SHTS exposure differs from the findings in smokers who have been noted to have a significant association with noncalcified plaque (19–21). Of interest is the CONFIRM report (22), which demonstrated no contribution of noncalcified plaque to prognosis.

STUDY LIMITATIONS. The volunteer cohort was a subset recruited from a previously reported much larger group of 3,098 never smokers 40 to 80 years of age, enrolled in the FAMRI-I-ELCAP screening program and may therefore be subject to selection bias. In addition, SHTS exposure was self-reported without validation of the exposure and, therefore, subject to potential bias. However, because this was a prospective cohort study and SHTS exposure was collected using a standardized, well-structured questionnaire before the occurrence of study outcomes, we expect that such bias, if present, would be nondifferential and biased toward the null. This was not an outcome study. Nonetheless, the striking results support the strong dose-response association of SHTS exposure with coronary artery stenosis; confirmation in a large outcome study would be valuable. There was no clinical indication for performing CTA in this asymptomatic population, and this study was performed solely for research purposes. Outcome studies are needed to determine the prognostic significance of the nonobstructive plaque, although there is no reason to assume it would be different from that previously reported in asymptomatic patients.

CONCLUSIONS

On the basis of the cumulative evidence linking SHTS exposure to CAD, we have previously recommended that SHTS exposure should be officially recognized as an important risk factor and that standard medical history taking be broadened to include SHTS exposure (10). The present study lends strength to this recommendation by demonstrating the association of SHTS exposure with the extent of atherosclerosis to a greater degree than the traditional risk factors. Although SHTS avoidance is essential and beneficial, as evidenced by the reduction in acute myocardial infarction after implementation of smoke-free laws (25–27), without increased recognition on a global level, the risk is likely to persist.

ADDRESS FOR CORRESPONDENCE: Dr. Claudia I. Henschke, Icahn School of Medicine at Mount Sinai, Department of Radiology, One Gustave L. Levy Place, Box 1234, New York, New York 10029. E-mail: claudia.henschke@mountsinai.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence and extent of atherosclerosis evaluated by coronary CTA is associated with the extent of SHTS exposure, even when adjusted for other risk factors, further demonstrating the causal relationship of SHTS exposure and coronary disease.

TRANSLATIONAL OUTLOOK: Additional studies are needed to correlate the atherosclerosis associated with the degree of SHTS with a corresponding increase in major adverse clinical events.

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