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# Coronary Artery Calcium Scoring in Low Risk Patients with Family History of Coronary Heart Disease: Validation of the SCCT Guideline Approach in the Coronary Artery Calcium Consortium

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## Abstract

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**Background:** The Society of Cardiovascular Computed Tomography (SCCT) recommends consideration of coronary artery calcium (CAC) scoring among individuals with a family history (FH) of coronary heart disease (CHD) and atherosclerotic cardiovascular disease (ASCVD) risk <5%. No dedicated study has examined the prognostic significance of CAC scoring among this population.

**Methods:** The CAC Consortium is a multi-center observational cohort study from four clinical centers linked to long-term follow-up for cause-specific mortality. All CAC scans were physician referred and performed in patients without a history of CHD. Our analysis includes 14,169 patients with ASCVD scores <5% and self-reported FH of CHD.

**Results:** This cohort had a mean age of 48.1 (SD 7.4), was 91.3% white, 47.4% female, had an average ASCVD score of 2.3% (SD 1.3), and 59.4% had a CAC=0. The event rate for all-cause mortality was 1.2 per 1,000 person-years, 0.3 per 1,000 person-years for CVD-specific mortality, and 0.2 per 1,000 person-years for CHD-specific mortality. In multivariable Cox proportional hazard models, those with CAC>100 had a 2.2 (95% CI 1.5–3.3) higher risk of all-cause mortality, 4.3 (95% CI 1.9–9.5) times higher risk of CVD-specific mortality, and a 10.4 (95% CI 3.2–33.7) times higher risk of CHD-specific mortality compared to individuals with CAC=0. The NNS to detect CAC >100 in this sample was 9.

**Conclusion:** In otherwise low risk patients with FH of CHD, CAC>100 were associated with increased risk of all-cause and CHD mortality with event rates in a range that may benefit with preventive pharmacotherapy. These data strongly support new SCCT recommendations regarding testing of patients with a family history of CHD.

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## 1. INTRODUCTION

Coronary Artery Calcium (CAC) scoring is an inexpensive, sensitive tool for coronary artery disease and is routinely used for risk stratification.[1] Elevated CAC scoring is associated with higher risk of all-cause mortality[2–4], coronary heart disease (CHD)[5–8], and cardiovascular disease (CVD)[5,7], even among those at low risk based on traditional risk factors[2]. Similarly, a CAC score of 0 has been associated with low risk of CHD[9,10], even in the presence of traditional CVD risk factors.[10] As a result, the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on treatment of blood cholesterol recommended utilizing CAC scoring in patients at borderline to intermediate risk (5–20% 10-year ASCVD risk) in whom statin therapy decisions are uncertain. In these patients, CAC scoring leads to marked risk reclassification across different levels of ASCVD risk.[11] More recent data has suggested that in those at low risk, those with any CAC have higher rates of ASCVD than those with CAC scores of 0.[12] Additionally, CAC scoring when combined with family history (FH) portends an increase in the event rates of ASCVD and coronary heart disease (CHD) compared to those without FH in those with CAC=1–399.[13] The recent ACC/AHA cholesterol guidelines reflect this suggesting that CAC scoring should be considered for intermediate risk patients with family history (FH) or other newly labeled

"risk enhancers" when the decision for pharmacologic therapy is uncertain.[14] Given these data, we sought to critically assess the unique 2017 Society of Cardiovascular Computed Tomography (SCCT) recommendation of considering CAC scoring in low risk individuals (<5%) with a FH of CHD[15] using the largest multi-center observational cohort study of CAC scoring yet assembled, the CAC Consortium.[16]

## 2. METHODS

### 2.1 Study Design

The Coronary Artery Calcium Consortium is a multi-center (Los Angeles, CA; Columbus, OH; Torrance, CA; and Minneapolis, MN) observational cohort study in the United States.[16] The full details of the cohort design, rationale, and inclusion and exclusion criteria have been published elsewhere.[16] Briefly, the CAC Consortium is a retrospective cohort of asymptomatic patients ≥ 18 years without known history of CHD who were referred for CAC scoring by a physician.[16] History of CHD was defined as prior history of myocardial infarction, obstructive coronary artery disease, percutaneous coronary intervention, or coronary artery bypass surgery.[16]

In this study, we included participants with a self-reported FH of CHD and ASCVD risk <5% as defined using the 2013 ACC/AHA Pooled Cohort Equation[17] (N=14,169). In the CAC Consortium, FH of CHD was reported as the presence of a first-degree relative with a history of CHD, with exception of the Columbus, OH site which reported the presence of a first-degree relative with a premature FH of CHD (<55 years in old in a male relative and <65 years old in a female relative).[16] Hypertension, dyslipidemia, and diabetes were considered present if a patient reported a prior diagnosis and/or was on therapy with anti-hypertensives, lipid-lowering medications, or oral hypoglycemics or insulin.[16] Smoking status was characterized as "never, former, or current smoker"[16].

### 2.2 Risk factor data

Risk factor data was complete in 91.7% of this cohort. The remaining 8.3% had partially missing information on at least one data element. For patients with missing risk factor data, we imputed values using a multivariable model adjusting for age, sex, race, CAC score, and the remaining non-missing traditional risk factors from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, as previously described.[16] 10-year ASCVD risk scores were then calculated for all patients with imputed means and medians being almost identical to calculated ones (9.3% vs. 9.4% and 5.0% vs. 4.9%, respectively).[16] Validation of this approach yielded a correlation coefficient of 0.952 between the two approaches for calculating scores.[16]

### 2.3 Coronary Artery Calcium Score Scans

CAC scans were physician referred for "cardiovascular risk stratification" and were conducted between 1991–2010[16] and were scored according to the Agatston method[18]. The majority of scans (93%) were conducted using electron beam tomography with the remainder utilizing multi-detector CT (7%).[16] The details regarding specific types of CT scanners are as follows: 13% of patients were scanned with the Imatron C-100 scanner, 38%

with the C-150, 38% with the C-300, and 3.5% with the e-Speed scanner (GE-Imatron). The remaining scans (7%) were performed on a 4-slice MDCT scanner (Somatom Volume Zoom, Siemens Medical Solutions) and the General Electric LightSpeed VCT 64-slice platform (GE Healthcare).[16]

### 2.4  Mortality Outcomes

Data on cause-specific mortality was gathered from the Social Security Death Index Death Master File[16] and linked to patients through a previously validated algorithm[19] that uses multiple different patient identifiers. Specific causes were coded as, "CVD, cancer, pulmonary disease, gastrointestinal disease, nervous system disorders, endocrine and metabolic disease, injury and poisoning, or other" using ICD-9 and ICD 10 codes.[16] Cardiovascular disease includes CHD, stroke, other circulatory disorders, and congestive heart failure.

### 2.5  Statistical Analysis

For the analysis, baseline characteristics are presented for the total study sample, with continuous data presented as mean (standard deviation) and categorical data as total number (percentage). The absolute event rates of all-cause and cause-specific deaths are presented for each CAC strata (0, 1–99, 100–399,   400) and expressed per 1,000 patient-years.

Kaplan-Meier plots were used to plot the proportion free of mortality over time by CAC group. Multivariable-adjusted Cox proportional hazards regression was then used to estimate the hazard ratio of all-cause and cause specific death by CAC score strata, with CAC 0 as the reference. Hazard ratios were first calculated for the whole sample and then repeated after stratification by sex. Models presented are adjusted for age, sex, race, hypertension, hyperlipidemia, smoking status, and diabetes mellitus. Receiver-operating-characteristic (ROC) curves for all-cause, CVD-specific, and CHD-specific mortality were performed comparing models with traditional risk factors to those with traditional risk factors plus CAC scores. The resultant areas under the curve were compared for all persons after stratification by sex and in sub-group analysis limited to individuals aged 40–75 years old (the age range recommended for risk assessment in the 2013 ACC/AHA guidelines). All data was analyzed using STATA/SE 15.1. A p-value of <0.05 was considered statistically significant.

## 3.1  RESULTS

A total of 14,169 individuals were followed for an average of 11.6 years (SD 2.7). The mean age of this cohort was 48.1 years (SD 7.4), 47.4% women, 91% white, and the average ASCVD score was 2.3% (SD 1.3%) (Table 1). Approximately 11% of participants had a CAC score >100. There were significant differences in the CAC distribution between men and women (P=<0.001). Women were more likely to have CAC scores of 0 (68.4% vs 51.3%) and men were more likely to have CAC scores of 400+ (4.3% vs. 1.9%) (Figure 1).

The absolute event rates in the study population were 1.2 (95% CI 1.1–1.4) per 1,000 patients-years for all-cause mortality, 0.3 (95% CI 0.2–0.4) per 1,000 patient-years for CVD-specific mortality, and 0.2 (95% CI 0.13–0.26) per 1,000 patient-years for CHD-specific mortality. The number needed to screen (NNS) to detect CAC >100 in this sample was 9.

For those with CAC scores >100 compared to those with CAC=0, there was a 3.0 times higher event rate of all-cause mortality, a 4.7 times higher event rate of CVD-specific mortality, and an 11.4 times higher event rate of CHD-specific mortality (Table 2).

Cumulative all-cause mortality occurred more frequently in those with CAC>100 compared to those with CAC=0 (3.1% vs. 1.0%, $P$=<0.001), as was the case with CVD-specific mortality (1.1% vs. 0.2%, $P$=<0.001), and CHD-specific mortality (0.8% vs. 0.1%, $P$=<0.001). In multivariable Cox proportional hazard models, those with higher CAC scores were at higher risk of all outcomes of interest. Specifically, those with CAC scores >100 had a 2.2 (95% CI 1.5–3.3) times higher risk of all-cause mortality, 4.3 (95% CI 1.9–9.5) times higher risk of CVD-specific mortality, and a 10.4 (95% CI 3.2–33.7) times higher risk of CHD-specific mortality than patients with CAC=0 (Table 3). Similarly, we found consistent results when stratifying by sex—namely, that higher CAC scores remained associated with all outcomes of interest (Table 3).

Comparison of the area under the ROC curves demonstrated improvement with the addition of the CAC score to models that included only traditional risk factors with significant improvement in the prediction for CVD mortality (0.66 to 0.76, $P$=0.02) and CHD mortality (0.72 to 0.82, $P$=0.03). Additionally, there were improvements in each of the sex-stratified models, and in sub-analysis of those age 40–75 (Table 4).

## 4.1 DISCUSSION

Our study examined the prognostic significance of CAC scoring in low-risk individuals with a FH of CHD, a group identified for potential CAC scoring in the new SCCT guidelines[15]. Our findings demonstrate a significantly higher risk of all-cause, CVD-specific, and CHD-specific mortality with an increasing CAC score. It also shows a substantial increase in the AUC, which demonstrates that CAC maintains its discriminatory ability in these low-risk individuals. When stratified by sex, this improvement in AUC is only significant for men. We believe this to be related to the higher proportion of men in this sample, their higher CAC burden, and the fact that their event rates are higher, thus providing more power to see a difference. In our sample, two-thirds of women had CAC=0, whereas half of men had CAC=0. This distribution is consistent with previous studies.[8]

The absolute event rates of CHD-specific mortality in those in the highest CAC strata (>100) are consistent with rates commonly accepted as translating to net benefit with preventive pharmacotherapy.[14] These findings strongly support the new SCCT guideline approach and may guide clinicians in earlier identification of higher risk patients with FH, leading to earlier pharmacotherapy interventions.

Recently, Nasir et al. assessed ASCVD and CVD events in the MESA cohort stratified by both statin candidacy based on the then current ACC/AHA cholesterol management guidelines[21] and CAC scores. The authors found that the presence of CAC in patients whom statins were recommended ( 7.5–20%) or considered (ASCVD 5 to <7.5%) had higher risks of ASCVD and CHD events, respectively, compared to those with CAC scores of 0 (statin recommended group: HR 2.15, 95% CI 1.53–3.04 and HR 2.9, 95% CI 1.8–4.6,

respectively; statin considered group: HR 5.11, 95% CI 1.8–14.1 and HR 7.7, 95% CI 1.7–35.9, respectively).[11] Furthermore, in the broad group of patients with 10-year ASCVD risk between 5% to 20%, a CAC score of 0 reclassified almost 50% of patients as their actual event rate was below the generally recommended treatment threshold.[11] These results helped to inform the primary recommendation of the SCCT[15], which is to consider CAC scoring in the context of shared decision making in those with 10-year ASCVD risk 5–20%, a recommendation recently adopted by the ACC and AHA[14].

However, the study by Nasir et al. concluded that general screening with CAC in people with 10-year ASCVD risk <5% was not likely to lead to efficient risk stratification. More recent studies have focused on low risk populations and have shown promising results for selective use of CAC.[12,22] Kavousi et al. in their meta-analysis of CAC screening in women with ASCVD <7.5% found an increase in incident ASCVD for those with any CAC score compared to those with a score of 0 (4.33 events per 1,000 person-years vs. 1.41 events per 1,000 person-years; HR 2.04, 95% CI 1.44–2.90).[12] Patel et al., using data from the MESA study, which includes asymptomatic individuals without known ASCVD, describe a gradual increase in hard event rates of ASCVD and CHD based on CAC score and FH status.[13] Interestingly, though, they found that those in the highest CAC strata ( 400) did not have any significantly different risk based on their FH status (HRs of 2.80 (95% CI, 1.44–5.43) in those with FH compared to 3.22 (95% CI, 2.15–4.84) in those without).[13] As such, CAC scores may be particularly useful in further stratifying patients with reported FH, as there is uncertainty in how much risk is attributable to FH.

The current belief that CAC scoring should be used in certain low risk population, and the data cited above, helped encourage the SCCT to recommend CAC screening in these low risk patients with a positive FH of CHD. As the new ACC/AHA guidelines demonstrate the importance of "risk enhancers" in identifying those most likely to benefit from statin therapy in an intermediate risk group, these data favor the utility of risk enhancers in certain low risk groups, as well.

Our study is not without limitations. First, our study is an observational, retrospective cohort study of patients referred for clinical CAC scanning, and as such, our results may not be generalizable to all patients with FH of CHD because of potential referral bias. Second, our population is predominantly white (91.3%), which limits its generalizability to other ethnic groups. Additionally, the effect of our study is likely to be underestimated as both patients and clinicians were informed about the results of the CAC scan[16], which may have led to altered treatment decisions and risk factor modification in those with the highest CAC scores.

Finally, although the SCCT guidelines specify those with premature FH of CHD would benefit most, our study includes participants with both premature and any FH of CHD. FH, in and of itself, can be heterogeneous with the risk of CHD imparted by FH alone varying due to incomplete penetrance and the diversity of subsequent environmental risk exposures.[13] For example, Nasir et al. illustrated this complexity in showing that the number and age of family members with history of premature CHD confers different gradations of risk—those with a FH of sibling and parent with premature CHD were at highest risk, followed by a

sibling alone, and then parent alone.[23] Others have shown that a single question on presence of FH among first-degree family members performs as well as more complicated assessments emphasizing on the role of other cardiovascular risk factors for those with FH.[24]

Our study also has a number of strengths—the CAC Consortium represents the largest database of CAC scans linked to long-term cause-specific mortality, which allows for new granularity in understanding the clinical importance of CAC. Additionally, each CAC scan was physician referred for the purpose of cardiovascular risk stratification, which increases the internal validity.

In conclusion, our study demonstrates that in a large retrospective cohort of low risk patients with a FH of CHD, CAC scoring was a reliable predictor of all-cause, CVD, and CHD mortality. Our findings are the first to validate the new SCCT guidelines which recommend CAC screening for those low risk patients with FH of CHD.

## Grant Support:

## ABBREVIATIONS

| | |
|---|---|
| **ACC** | American College of Cardiology |
| **AHA** | American Heart Association |
| **ASCVD** | Atherosclerotic Cardiovascular Disease |
| **AUC** | Area under the curve |
| **CAC** | Coronary Artery Calcium |
| **CHD** | Coronary Heart Disease |
| **CI** | Confidence Interval |
| **CVD** | Cardiovascular Disease |
| **FH** | Family History |
| **MESA** | Multi-Ethnic Study of Atherosclerosis |
| **ROC** | Receiver-operating-characteristic |
| **SCCT** | Society of Cardiovascular Computed Tomography |
| **SD** | Standard Deviation |

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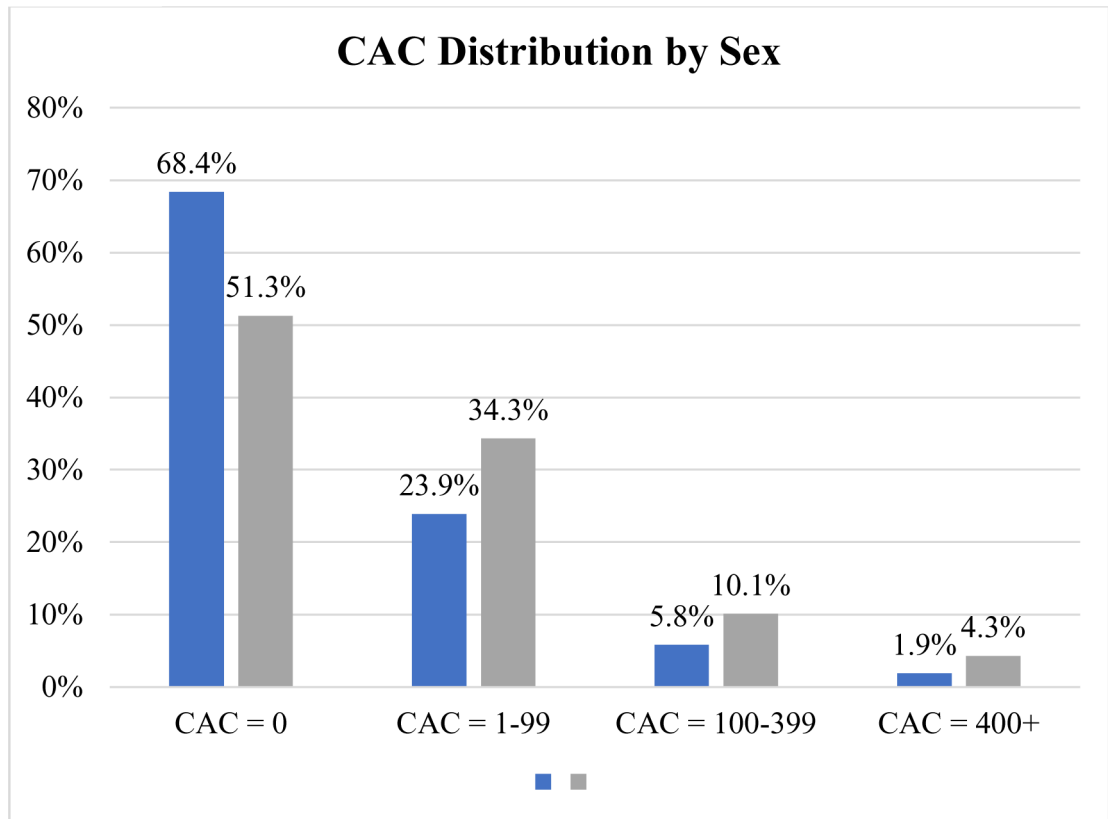
**Figure 1.**
CAC Distribution by Sex

**Table 1.**

Baseline Characteristics of Study Cohort[*].

| Characteristic | N=14,169 |
|---|---|
| Age, mean (SD) | 48.1 (7.4) |
| Sex | |
| Female | 6,727 (47.4) |
| Male | 7,462 (52.6) |
| Race (N=1 1,741) | |
| Black | 114(1.0) |
| White | 10,724(91.3) |
| All Others | 903 (7.7) |
| 10-year ASCVD Risk, mean (SD) | 2.3% (1.3%) |
| 10-year Framingham Risk Score, mean (SD) | 6.6% (3.9%) |
| Hypertension | 2,635 (18.6) |
| Hyperlipidemia | 7,178(50.6) |
| Diabetes | 285 (2.0) |
| Active Smoking | 780 (5.5) |
| CAC = 0 | 8,428 (59.4) |
| CAC = 1–99 | 4,167(29.4) |
| CAC = 100–399 | 1,144(8.1) |
| CAC = 400+ | 450 (3.2) |

[*]
Data are presented as No. (%) unless otherwise indicated

**Table 2.**

Absolute Event Rates per 1000 patient-years by CAC score group

| | CAC Score Groups | | | |
| --- | --- | --- | --- | --- |
| | **0** | **1–99** | **100–399** | **400+** |
| **All-cause Mortality** | 0.9 (0.7–1.1) | 1.3 (1.04–1.7) | 2.1 (1.4–3.0) | 4.2 (2.7–6.3) |
| **CVD*Mortality** | 0.2 (0.1–0.3) | 0.3 (0.2–0.5) | 0.7 (0.4–1.3) | 1.5 (0.8–3.0) |
| **CHD Mortality** | 0.06 (0.03–0.14) | 0.2 (0.1–0.4) | 0.5 (0.3–1.1) | 1.1 (0.5–2.5) |

*
CVD mortality includes the following: other circulatory disorder, CHD, stroke, and congestive heart failure.

**Table 3.**

Hazard Ratios for all-cause and cause-specific mortality by CAC score, stratified by sex

| | | CAC Score Strata | | |
|---|---|---|---|---|
| | 0 | 1–99 | 100–399 | 400+ |
| **All-cause Mortality** | 1 (ref) | 1.3 (0.9–1.9) | 1.7 (1.0–2.8) | 3.6 (2.1–6.1) |
| Female | 1 (ref) | 1.3 (0.8–2.1) | 1.0 (0.4–2.3) | 3.1 (1.4–7.1) |
| Male | 1 (ref) | 1.5 (0.9–2.5) | 2.7 (1.4–5.2) | 4.4 (2.1–9.2) |
| **CVD*Mortality** | 1 (ref) | 1.1 (0.5–2.6) | 3.4 (1.4–8.2) | 6.5 (2.3–18.5) |
| Female | 1 (ref) | 0.7 (0.1–3.7) | 4.4 (1.1–17.0) | 10.2 (2.1–50.2) |
| Male | 1 (ref) | 1.3 (0.5–3.6) | 3.2 (1.0–9.9) | 5.2 (1.3–20.4) |
| **CHD Mortality** | 1 (ref) | 3.1 (1.0–9.4) | 8.5 (2.5–29.4) | 15.8 (3.7–67.1) |
| Female | 1 (ref) | 1.3 (0.1–15.7) | 8.4 (1.2–58.5) | 12.3 (0.8–181.3) |
| Male | 1 (ref) | 4.2 (1.1–16.3) | 9.4 (2.0–43.3) | 19.9 (3.6–108.8) |

Model includes age (as a continuous variable), sex, race, hypertension, hyperlipidemia, smoking status, diabetes mellitus.

*
CVD mortality includes the following: other circulatory disorder, CHD, stroke, and congestive heart failure.

**Table 4.**

Comparison of Models with Traditional Risk Factors to Models of Traditional Risk Factors with CAC Scores for All-cause mortality, CVD-specific mortality, and CHD-specific mortality

| | All-cause Mortality | | | CVD-specific Mortality | | | CHD-specific Mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | Traditional RF[*],[†] | Traditional RF + CAC Score | P-Value | Traditional RF | Traditional RF + CAC Score | P-Value | Traditional RF | Traditional RF + CAC Score | P-Value |
| **All** | 0.66 | 0.68 | .06 | 0.66 | 0.76 | .02 | 0.72 | 0.82 | .03 |
| **Female** | 0.66 | 0.68 | .16 | 0.79 | 0.82 | .31 | 0.85 | 0.93 | .41 |
| **Male** | 0.68 | 0.71 | .04 | 0.62 | 0.71 | .12 | 0.59 | 0.78 | .007 |
| **Age 40–75** | 0.65 | 0.66 | .05 | 0.67 | 0.72 | .02 | 0.74 | 0.76 | .02 |
| **Female** | 0.65 | 0.65 | .33 | 0.78 | 0.81 | .15 | 0.84 | 0.86 | .36 |
| **Male** | 0.68 | 0.69 | .03 | 0.64 | 0.68 | .04 | 0.62 | 0.66 | .02 |

[*] RF = Risk Factor

[†] Includes Age, Sex, Race, Hypertension, Hyperlipidemia, Diabetes Mellitus, and Smoking status