ARIC Manuscript Proposal #1575

PC Reviewed: 11/10/ 09	**Status: A**	**Priority: 2**
SC Reviewed:_____	**Status:_____**	**Priority:_____**

1 **a. Full Title**: Risks of incident cardiovascular disease among users of smokeless tobacco in the ARIC study

b. Abbreviated Title: Smokeless tobacco and incident CVD

2 **Writing Group**:

Writing group members:

Hiroshi Yatsuya, Aaron Folsom, and others

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. HY

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3 **Timeline**: Analysis will begin immediately, once the proposal is accepted, using surveillance data files through 2005 or the latest available. A draft will be prepared within four months and will be submitted to the Publications committee by 6 months.

4 Rationale:

A recent meta-analysis that included five cohort studies, mostly on fatal myocardial infarction (MI) and stroke, reported a positive association between smokeless tobacco use and cardiovascular diseases mortality among never smokers.[1] Nevertheless, the association of smokeless tobacco with incidence of cardiovascular disease (CVD) remains largely unknown. In addition, the recent meta-analysis was not consistent with another recent meta-analysis.[2] Smokeless tobacco use has been associated with hypertension,[3] metabolic syndrome,[4], or periodontal diseases,[5] forming biological rationale for its association with the development of cardiovascular diseases; however, such associations were not found by others.[6] While the health effects of smokeless tobacco remain inconclusive,[2] some advocated the substitution of smokeless tobacco, particularly snuff, to help reduce cigarette smoking rates, under the claim of a smaller risk to health.[7] Thus, it is necessary to examine the association between cardiovascular disease incidence, not mortality, and smokeless tobacco use since mortality does not necessarily represent the burden of the disease due to the exposure. Since smokeless tobacco use is reportedly associated with the presence, initiation, or quitting of cigarette smoking,[8, 9] the association with CVD incidence should be assessed in never and past cigarette smokers separately. It seems also important to consider other tobacco product use, and second hand smoke, for which no previous studies adjusted. Since the physiological effects of smokeless tobacco have been thought to be rather short-lasting,[10]and quitting or initiating of the habit is possibly associated with change in the use of other tobacco product or in lifestyle, such variables may need to be adjusted for as time-varying covariates.

5 Main Hypothesis/Study Questions:

Current use of smokeless tobacco is associated with increased incidence of CVD in never as well as past cigarette smokers. The association is independent of age, sex, race, center, educational level, usual ethanol intake, physical activity, other tobacco products use (pipe, cigar, and chewing tobacco), second hand smoke, and pack-years of cigarette smoking (only in past smokers). Further adjustment for waist circumference, total and HDL cholesterol, triglyceride, systolic blood pressure, antihypertensive medication, diabetes status will not eliminate the association.

6 Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Study design: A prospective cohort study

Inclusion/Exclusion:

Inclusion: From all black (enrolled in Jackson and Forsyth) and white ARIC visit 1 participants (n=15,689), the following subjects are excluded from the analyses: (1) those with missing values on cigarette smoking status and other tobacco product use (snuff, chewing tobacco, pipe, and cigar) at baseline (n=56); (2) those with missing values on education level, usual ethanol consumption, physical activity (n=169); (3) those with a self-reported history of coronary heart disease (CHD) or stroke at visit 1 (n=966); (4) and current smokers at visit 1, those who had declared at visit 1 to be a never smoker but reported ever smoking at visit 2, visit 3 or visit 4, or those who had declared at visit 1 to be a past smoker but identified themselves as a current smokers at visit 2, visit 3 or visit 4, leaving 5,318 never smokers and 4,262 past smokers for the analysis.

Dependent variables: Incident CVD measured through 2005 or the latest available. Separate analysis will be conducted for incident CHD (hospitalized MI, fatal CHD, ECG confirmed MI, cardiac procedure), and for incident stroke.

Independent variable: current or past smokeless tobacco (chewing tobacco or snuff) use at visit 1. (Chewing tobacco and snuff use will be examined separately.) Information on smokeless tobacco use at visit 2 and visit 3 will also be incorporated in time-dependent Cox regression analysis.

Modeling and covariates:

1. Hazard ratios for CVD (CHD and stroke) for current or past use of smokeless tobacco (chewing tobacco and snuff), with never users as the reference. A time-dependent Cox model will also be applied with the use of time-varying smokeless tobacco (chewing tobacco and snuff) use (up to visit 3) as well as pipe and cigar use (up to visit 2) and second hand smoke (visit 1 through 4).
2. Model 1 adjusts for age, sex, race-center, education level, usual alcohol consumption, physical activity, and pack-years (only in past smoker analysis) at visit 1.

   Model 2 adjusts for variables in the model 1 and current or past pipe and cigar use, second hand smoke (hours/week). In the analyses for chewing tobacco and snuff, these variables will be entered into the model simultaneously.

   Model 3 adjusts for variables in the model 2 and systolic blood pressure, use of antihypertensive medication, prevalent diabetes, waist circumference, blood levels of total and HDL cholesterol and triglyceride.

Analysis plan:

Assumption of the hazards proportionality will be assessed by examining the parallelness of the ln (-ln) survival curves for groups defined by current/past smokeless tobacco use. A formal test will be carried out by including an interaction term between smokeless tobacco use and time (continuous or dichotomous at median (10-year)) in the Cox model.

7 **Will the data be used for non-CVD analysis in this manuscript?**

_____Yes ___x___No

8 a. Will the DNA data be used in this manuscript?

_____Yes ___x___No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA=”No use/storage DNA”?

c. If yes, is the author aware that the participants with RES_DNA =”not for profit” restriction must be excluded if the data used by a for profit group?

9 The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

___x____Yes _____No

10 What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

N/A

11 Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

_____Yes ___x___No

12 Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

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8. Hergens MP, Ahlbom A, Andersson T, Pershagen G. Swedish moist snuff and myocardial infarction among men. Epidemiology 2005;16:12-6.
9. International Agency for Research of Cancer. Smokeless tobacco products. In: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: IARC; 2008.
10. Fant RV, Henningfield JE, Nelson RA, Pickworth WB. Pharmacokinetics and pharmacodynamics of moist snuff in humans. Tob Control 1999;8:387-92.