Smoking intensity (pack/day) is a better measure than pack-years or smoking status for modeling cardiovascular disease outcomes

Robin Nance[a],*, Joseph Delaney[b], John W. McEvoy[c], Michael J. Blaha[d], Gregory L. Burke[e], Ana Navas-Acien[f], Joel D. Kaufman[g], Elizabeth C. Oelsner[h], Robyn L. McClelland[a]

[a]*Department of Biostatistics, Collaborative Health Studies Coordinating Center, University of Washington, Building 29, Suite 210, 6200 NE 74th Street, Box 354922, Seattle, WA 98115, USA*
[b]*Department of Epidemiology, Collaborative Health Studies Coordinating Center, University of Washington, Box 354922, Building 29, Suite 310, 6200 NE 74th Street, Seattle, WA 98115-8160, USA*
[c]*Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA*
[d]*Department of Medicine, Johns Hopkins Hospital, Johns Hopkins University, 600 N. Wolfe Street, Blalock 524C, Baltimore, MD 21287, USA*
[e]*Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157-1063, USA*
[f]*Department of Environmental Health Sciences, Columbia University, 722 168th W St, Office 1105, New York, NY 10032, USA*
[g]*Departments of Environmental & Occupational Health Sciences, Medicine, and Epidemiology, University of Washington, 4225 Roosevelt Way NE, Suite 100, Seattle, WA 98105, USA*
[h]*Department of Medicine, Division of General Medicine, Presbyterian Hospital, Columbia University, 630 West 168th Street, 9-105E, New York, NY 10032, USA*

Abstract

Objectives: Smoking as an epidemiological exposure can be quantified in many ways including duration, intensity, pack-years, recency, and age at initiation. However, it is not clear which of these are most important for cardiovascular disease (CVD) and how they should be modeled.

Study Design and Setting: Using the Multi-Ethnic Study of Atherosclerosis, Cox models for time to incident CVD adjusted for age, sex, race/ethnicity, education category, and income category were compared which included various characterizations of smoking history.

Results: Duration, age at starting, time since quitting, and noncigarette forms of smoking were not independently associated with CVD, whereas baseline current intensity was associated with CVD [e.g., hard CVD hazard ratio 1 pack/d of 1.85 95% confidence interval (1.33, 2.57)]. Former smokers, regardless of duration, intensity, or recency, were not at increased risk, suggesting that risk may risk may drop precipitously from the time of quitting. For CVD events, representing smoking exposure as baseline smoking intensity produced better model fit as measured by Akaike information criterion than models using smoking status or pack-years.

Conclusion: The association of smoking with incident CVD events was well captured by including a simple term for baseline smoking intensity. © 2016 Elsevier Inc. All rights reserved.

Keywords: Smoking; Intensity; Cardiovascular disease; Multi-Ethnic Study of Atherosclerosis; Cohort; Pack-years

1. Introduction

In 2012, there were 17.5 million deaths from cardiovascular disease (CVD), and tobacco use is a modifiable cause of many of these deaths [1]. Smoking increases CVD risk, consequently it is of interest to know which components of smoking are most associated with CVD outcomes. Even if a study is not investigating smoking as an exposure directly, smoking is so strongly related to CVD that it is also important to adjust for this exposure to control confounding. However, there are many different ways to quantify

* Corresponding author. Tel.: 1-206-897-1906; fax: 206-616-4075.

E-mail address: rmnance@uw.edu (R. Nance).

What is new?

Key findings

- This paper demonstrates that smoking intensity is the primary risk factor for associations between cardiovascular disease (CVD) events and tobacco cigarette use and provides the best fit for statistical models.

- Duration of smoking was not associated with increased risk among former smokers, who showed a rapid (within a few years at most) return to baseline CVD risk.

- Deep vein thrombosis and death follow different patterns, and the association between smoking and events for these outcomes remains elevated much longer than for CVD events.

What this adds to what was known?

- Adjusting for smoking intensity is preferable to adjusting for pack-years of smoking or smoking status (never/former/current) in models with CVD outcomes.

- Time since quitting and duration of smoking, to the precision we could measure these parameters, were not associated with increased risk of CVD for former smokers.

What is the implication and what should change now?

- The optimal adjustment for the association of smoking in CVD studies, smoking intensity, should be used instead of the more commonly used pack-years.

- Smoking cessation programs aimed at CVD prevention may be encouraged by a relatively quick drop in this particular association.

smoking, including whether the person is currently smoking, how long the person has smoked, what type of tobacco product is used, how much the person smokes each day, and the period of life during which the tobacco exposure occurred. Consequently, how smoking should be modeled is not clear. That is, which components of smoking are associated with CVD outcomes, how these components should be modeled to increase our understanding of smoking-CVD relationships, and what may be the best way to adjust for smoking as a potential confounder.

One of the most common ways to model smoking is by dividing subjects into never, former, and current smoking categories. Compared to never smokers, current smoking was associated with increased CVD risk, whereas the

evidence was not as strong for past smoking [2–4]. However, one way that heterogeneity can enter into smoking status categories is via smoking intensity, specifically cigarettes/d. Previous studies suggest that there is increased risk of coronary heart disease (CHD) death with increased intensity [2,3,5,6]. Pope et al. studied the functional form of how CVD death risk varies over a range of intensities and concluded that a nonlinear model of tobacco smoke intensity fits the data best [7].

Pack-years is a cumulative measurement of smoking and is generally calculated by multiplying average packs smoked per day by the duration of smoking, in years [8]. However, with no definitive evidence that duration, in isolation, is significantly associated with CVD risk, the question of the utility of using pack-years is a valid one, especially because this is a common way of adjusting for smoking in studies [8–11].

Forms of tobacco exposure other than active cigarette smoking, including secondhand smoke exposure, cigar use, and pipe use, were also associated with CVD [12–15]. There was, however, conflicting evidence about whether age at starting smoking affected heart disease risk [2,6]. Higher time since quitting is a widely acknowledged protective factor for CVD [16,17]. In addition, age, age at starting, duration, and time since quitting are often additive combinations of the other variables and so care must be taken not to adjust for all of these in the same model [8].

In part due to the problem of collinear aspects of smoking and to reduce the number of adjustment covariates, single smoking indices have been proposed [9,18,19]. Two indices were discussed in Leffondré et al. [19]. which both incorporated nonlinear forms of time since quitting, duration, and intensity, and two parameters that can be based either on features of the data set in use or on earlier scientific findings/hypotheses. In this paper, we evaluate which of the above quantitative aspects of smoking behavior are most associated with incident cardiovascular events. Our aim is to inform the future modeling of smoking behavior in the context of CVD research.

2. Methods

2.1. Study population

MESA is a cohort of 6,814 participants initially free of clinical heart disease at baseline in 2000–2002 [20]. MESA participants were recruited at six sites across the United States, had an age range of 45–84 years, and were 47% male [20]. The ethnic proportions were 38% Caucasian, 12% Chinese-American, 28% African-American, and 22% Hispanic. MESA collected questionnaire data on smoking status, and participants were considered to be smokers if they reported smoking at least 100 cigarettes in their lifetimes and then further classified into current or former smokers at baseline by whether they "smoked