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## Temporal Associations Between Smoking and Cardiovascular Disease, 1971 to 2006 (from the Framingham Heart Study)

Gordon M. Burke, MD<sup>a</sup>, Michael Genuardi, MD<sup>b</sup>, Heather Shappell, MA<sup>c</sup>, Ralph B. D'Agostino Sr, PhD<sup>c,d</sup>, and Jared W. Magnani, MD, MSc<sup>b,\*</sup>

<sup>a</sup>Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts;

<sup>b</sup>Department of Medicine, Division of Cardiology, UPMC Heart and Vascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania;

<sup>c</sup>Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts;

<sup>d</sup>National Heart, Lung, and Blood Institute's and Boston University's Framingham Heart Study, Framingham, Massachusetts

### Abstract

Smoking has consistently been related to cardiovascular risk. Public health efforts have yielded reduced smoking prevalence and gains in cardiovascular disease (CVD) prevention. We hypothesized that the contribution of tobacco to CVD risk would be attenuated over prospective decades (1971 to 2006) in a community-based cohort. We evaluated 5,041 Framingham Heart Study Offspring Cohort participants (mean age 36.1 years, 52% women) without prevalent CVD. We collected prospective data on smoking status, relevant CVD risk factors, and incident CVD events across prospective decades. We used multivariable-adjusted, Cox proportional hazard models to measure the effect of smoking on incident CVD over 3 prospective 12-year follow-up periods. Our results demonstrated a consistent twofold increased risk of CVD in men who smoke compared with nonsmokers for each 12-year time period spanning from 1971 to 2006. Women who smoked had a 1.5-fold increased CVD risk. Smoking remains an important risk factor despite substantial improvements in the prevention and treatment of CVD. Significant, contemporary improvements in CVD prevention—such as gains in hypertension and cholesterol treatment—have not attenuated the strong and persistent associations between smoking and CVD observed here. In conclusion, our results highlight the importance of continued public health efforts to address smoking as a modifiable exposure that strongly contributes toward CVD risk.

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Tobacco smoking has a well-established relation with increased risk of cardiovascular disease (CVD).<sup>1,2</sup> The last 30 years have seen a proliferation of public health strategies to curb smoking, yielding a significant decrease in the prevalence of tobacco use in the United States.<sup>3</sup> During the same time period, CVD incidence and deaths from CVD have declined, likely stemming from advancements in both medical therapies for CVD and treatment of its

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\*Corresponding author: Tel: 412 648 6920; fax: 412 802 6395., magnanij@pitt.edu (J.W. Magnani).

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risk factors.<sup>4</sup> Despite this, CVD remains the leading cause of mortality.<sup>5</sup> How the considerable improvements in primary and secondary preventions of CVD have affected the recognized association between smoking and CVD merits investigation. We conducted the present study to examine contemporary and prospective changes in the relation between smoking and CVD. We aimed to compare the effect of smoking on CVD incidence in serial, prospective Framingham Heart Study exams over 3 consecutive, 12-year periods (1971 to 2006). We hypothesized that the relation of smoking with CVD risk would be attenuated, as we expected that the significant changes in treatment for CVD risk factors would limit the effect of smoking on CVD risk.

## Methods

The Framingham Heart Study began in 1948 with the enrollment of the Original Cohort to study the epidemiology of CVD and its associated risk factors.<sup>6</sup> In 1971, 5,124 children of the Original Cohort and their spouses were enrolled in what was termed the Offspring Cohort. Offspring Cohort participants have had successive examinations with medical history updates and health assessments every 4 to 8 years.<sup>7</sup> The present analysis employs data from the enrollment (1971 to 1975) and from the third (1983 to 1987) and sixth (1995 to 1999) examinations. Health histories and medical records are routinely obtained for review in the interim between exams. The Boston University School of Medicine Institutional Review Board approved all examinations and participants provided informed consent.

Participants underwent a standardized physical examination for blood pressure, height, and weight to determine the body mass index (BMI, kg/m<sup>2</sup>) at each examination. Standardized laboratory testing was used to measure the ratio of total cholesterol to high-density lipoprotein and triglyceride levels from blood samples obtained in the fasting state.<sup>8</sup> Participants were categorized as having diabetes mellitus if they had fasting blood glucose levels of >125 mg/dl (7 mmol/L) or treatment with oral hypoglycemic agents or insulin. Smoking status was determined by self-report at each exam, and the participants were classified as being active smokers or nonsmokers. Those who smoked cigarettes during the year before the examination were defined as active smokers.

Framingham Heart Study participants are routinely monitored through medical histories, physical examinations, communications with personal physicians, and hospitalization records.<sup>9</sup> CVD was defined by a history of angina, coronary insufficiency, myocardial infarction, coronary death, transient ischemic attack, ischemic or hemorrhagic stroke, peripheral artery disease, or congestive heart failure. A panel of 3 Framingham Heart Study cardiologists adjudicated cardiovascular events, and a neurologist evaluated and classified cerebrovascular events.<sup>9</sup>

Descriptive statistics of continuous variables, including means and standard deviations, and the distributions of categorical variables were calculated. We used examinations 1, 3, and 6 of the Framingham Offspring Study as the baseline assessment to relate smoking to the 12-year, prospective risk of incidence of CVD over 3 consecutive 12-year study periods: 1971 to 1982, 1983 to 1994, and 1995 to 2006. We selected 12-year intervals to prevent an over-

representation of a single time period. We calculated 12-year, Kaplan-Meier incidence rates of CVD for each 12-year follow-up period. We stratified participants by decade of life (fifth, sixth, and seventh decades) and gender because of the well-established associations of age and gender to CVD risk. We used a multivariable-adjusted Cox proportional hazards models to evaluate the CVD risk associated with smoking in reference to nonsmoking participants. Our model adjusted for systolic blood pressure, diastolic blood pressure, total cholesterol-to-high-density lipoprotein ratio, BMI, log of triglyceride levels, diabetes, treatment for hypertension, and treatment for an elevated cholesterol level. All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, North Carolina). We defined statistical significance to be a 2-sided *P* value of <0.05.

## Results

After excluding participants with a history of prevalent CVD ( $n = 83$ ), the analysis consisted of 5,041 subjects participating in the enrollment examination (1971 to 1975). Descriptive data of participants from the 3 examinations are summarized in Table 1. At examination 1, the mean age was 36.1 years, 52% were women, and the mean BMI was 25.1 kg/m<sup>2</sup>. At this initial examination, 44.4% of the participants were classified as smokers, 1.8% had diabetes, and 3% were being treated for hypertension. At each subsequent examination, the prevalence of smoking consistently decreased from 44.5% at examination 1 to 28.7% at examination 3, and finally to 15.0% at examination 6. In contrast, the prevalence of diabetes, hypertension treatment, and cholesterol treatment increased consistently over prospective decades of observation.

Table 2 presents the incidence rates of CVD stratified by the fifth, sixth, and seventh decades of age for each prospective, 12-year follow-up period. CVD incidence was higher for the 12-year follow-up after examination 1 for each decade of age than after examinations 3 or 6. In Table 3, we present the risk of CVD in participants who smoked relative to those who did not in multivariable-adjusted models stratified by age and gender. We observed that smoking was consistently associated with a two- to threefold increased risk of CVD among younger women (age 40 to 49), compared with the 2 older decades (ages 50 to 59 and 60 to 69). Among men, we observed a consistent association between smoking and increased risk of CVD. Men aged 40 to 49 and 50 to 59 who smoked had an approximately twofold increased risk of CVD relative to those who did not smoke. This association remained consistent across the multiple, prospective decades of observation. The association between smoking and CVD in men aged 60 to 69 became significant only in the most contemporary time period (1995 to 1996). We further determined the risk of CVD associated with smoking in gender-stratified multivariable-adjusted models additionally including age decade (Table 4). Smoking was associated with a 1.5-fold increased risk of CVD in women across prospective decades of observation. In men, smoking was consistently associated with a twofold increased risk of CVD.

## Discussion

We found that the association between smoking and CVD incidence was consistent over the 3-decade observation period. The finding was contrary to our initial hypothesis, as we

expected that the vast improvements in primary prevention and risk factor modification over this period would attenuate the known relations of smoking with CVD. Our analysis, also accounting for hypertension and dyslipidemia treatment, found that smoking was consistently associated with an increased risk of CVD across contemporary decades.

Notably, the prevalence of smoking and hypertension has been decreasing, with a simultaneous increase in obesity and diabetes.<sup>10,11</sup> We identified that the prevalence of smoking decreased from approximately 44% at the time of the enrollment examination in 1971 to 1975 to 15% in the late 1990s. These decreases are approximately consistent with national trends.<sup>12</sup> Our investigation demonstrates that despite this change in the baseline characteristics of a cohort at risk of CVD, as well as the improvement in primary prevention, men who smoke have maintained up to twofold increased risk of CVD and women have maintained a 1.6-fold increased risk compared with those who do not smoke (Table 4). Addressing CVD risk factors, such as hypertension, dyslipidemia, and diabetes, is of profound importance. Yet our results suggest the continued, essential relevance of addressing smoking as a modifiable risk factor for CVD prevention. Our data suggest that the continued advances in CVD prevention may have limited the effect in patients who continue to smoke.

Previous authors, examining short periods within the final 3 decades of the 20th century, have found relative risk ratios of CVD death in patients who smoke versus patients who do not smoke to be approximately 2 to 3.<sup>13-15</sup> There has not been an apparent change in the risk ratio over the decades, although there is a significant variability in the various estimates across studies. Previous analyses have suggested a possible gender difference, with smoking in women having a slightly larger relative risk of incident CVD than in men.<sup>16</sup> Although our study finds that the overall hazard ratio (HR) for CVD incidence is larger in men than in women, our data do suggest a possible effect modification by age: the effect of smoking trended toward a higher HR in women in the youngest age range (40 to 49) (Table 3).

Multiple authors have used estimates of the population attributable risk of traditional CVD risk factors to model or explain trends in CVD incidence and mortality over time.<sup>17,18</sup> Several investigations have examined the last 2 decades of the 20th century and found that the decreasing prevalence of smoking accounts for 9% to 48% of the decrease in the total cardiovascular deaths, depending on the rate of smoking decrease in the study population.<sup>17-19</sup> For the calculations' decreasing attributable prevalence to be valid, however, the risk factor's HR for the measured outcome should be constant across the modeling period. A typical method uses a contemporary estimate of the odds ratio for the development of CVD and applies it retroactively,<sup>20</sup> which is not necessarily true a priori, especially in consideration of the myriad changes in demographics and population health and behavior in many countries worldwide over the past several decades. The present study, in finding a consistent relation between cigarette exposure and CVD incidence in the 1970s to the 2000s, validates a modeling approach that assumed consistent HRs across decades.

Contrary to our hypothesis, our results demonstrate that smoking was consistently associated with an increased risk of CVD despite a 40% decrease in cardiovascular events in the United States from 1980 to 2000.<sup>4</sup> Our initial hypothesis was made under consideration of the

significant advancements in the prevention and treatment of risk factors associated with CVD and a decrease in the number of daily cigarettes smoked per tobacco user, given the dose-dependent relation between smoking and CVD.<sup>21</sup>

There are several strengths to our study. The Framingham Heart Study is a community-based sample with extensive accounting of covariates and event adjudication and limited loss to follow-up. Our study also has notable limitations. First, the Framingham Offspring Study includes participants primarily of European descent in 1 chief geographic area of the United States, which may limit generalizability. Second, we did not quantify smoking by the number of cigarettes smoked over time. However, we note that the purpose of this analysis was not to describe trajectories of cigarette use. As a result, we are not able to calculate a dose-response effect between smoking and risk of incident CVD. In addition, our data do not account for changes in cigarette composition over multiple decades. Fourth, the present study did not evaluate associations between CVD and smoking cessation, and thus we did not provide information regarding the association between CVD and smoking cessation or length of cessation. Fifth, we did not include socioeconomic status in our analyses and are unable to examine the effect of social determinants on the association between tobacco and CVD. In summary, we identified a consistent twofold increased risk of CVD in men who smoke compared with men who do not smoke from 1971 to 2006, and a smaller consistent increased risk in women who smoke compared with women who do not smoke.

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Table 1

## Characteristics of Framingham Offspring Study participants

Variable	Examination			
	1 (1971–1975, n = 5041)	3 (1983–1987, n = 3617)	6 (1995–1999, n = 3119)	
Women	2621 (52%)	1918(53%)	1721 (55%)	
Age, years	36.1+/-10.4	47.9+/-10.1	58.0+/-9.6	
Systolic blood pressure (mm Hg)	121.7+/- 16.4	123.5 +/-16.8	127.8+/- 18.6	
Diastolic blood pressure (mm Hg)	78.5 +/- 10.9	79.0+/-9.6	75.7+/-9.4	
Total cholesterol (mg/dL)	195.7+/-39.4	210.8+/-40.9	206.7+/-39.8	
Low-density lipoprotein (mg/dL)	126.5 +/-35.8	136.0+/-36.8	127.8+/-33.6	
High-density lipoprotein (mg/dL)	50.6+/-14.7	51.4+/-14.8	51.8+/-16.1	
Body mass index (kg/m <sup>2</sup> )	25.1+/-4.4	26.1+/-4.7	27.8+/-5.2	
Triglyceride (mg/dL)	94.6+/-88.1	120.8+/-116.0	138.3+/-130.6	
Diabetes mellitus	1.8%	3.6%	8.9%	
Hypertension Treatment	3.0%	14.6%	24.4%	
Cholesterol Treatment	0.4%	0.7%	9.6%	
Smoking	44.4%	28.7%	15.0%	



Incidence of cardiovascular disease: stratified by decade of life and 12-year follow-up after examinations 1, 3, and 6 in Framingham Offspring Study participants

Table 2

Age, years	N	Examination 1 (1971–1982)		Examination 3 (1983–1994)		Examination 6 (1995–2006)			
		Number of cvd events	KM incidence rate	N	Number of CVD events	KM incidence rate	N	Number of CVD events	KM incidence rate
40–49	1405	148	10.7%	1236	84	6.9%	552	42	7.8%
50–59	501	88	18.0%	1060	139	13.6%	1168	121	10.9%
60–69	37	10	29.3%	481	99	21.7%	908	160	18.9%

Age grouped by decade at start of 12-year follow-up period following examinations 1, 3, and 6. CVD = cardiovascular disease; KM = Kaplan-Meier.



Multivariable-adjusted\* Cox model: risk of CVD onset in smokers compared to nonsmokers during 12-year follow-up after examinations 1, 3, and 6 stratified by decade of life in Framingham Offspring Study participants

**Table 3**

Age (years)	Sex	Examination 1 (1971–1982)				Examination 3 (1983–1994)				Examination 6 (1995–2006)			
		N	HR	CI	P-value	N	HR	CI	P-value	N	HR	CI	P-value
40–49	Women	677	2.8	1.5–5.1	0.001	618	1.8	0.8–4.1	0.177	308	3.3	1.2–9.1	0.021
50–59	Women	216	0.7	0.3–1.7	0.445	525	1.5	0.7–3.3	0.272	629	1.5	0.7–3.1	0.263
60–69	Women	9	†	†	†	232	1.3	0.6–2.9	0.509	495	1.2	0.6–2.4	0.627
40–49	Men	636	2.5	1.6–3.9	<.0001	564	2.6	1.4–4.6	0.002	236	1.9	0.8–4.9	0.167
50–59	Men	248	1.7	1.0–3.0	0.042	483	2.0	1.2–3.0	0.003	531	2.3	1.3–4.1	0.004
60–69	Men	23	0.7	0.1–9.6	0.822	226	1.7	0.9–3.0	0.085	394	2.3	1.3–4.3	0.006

Age grouped by decade at start of 12-year follow-up period following examinations 1, 3, and 6. CVD = cardiovascular disease; HR = hazard ratio; CI = 95% confidence interval.

\* Multivariable-adjusted Cox model adjusted for systolic blood pressure, diastolic blood pressure, total cholesterol to high-density lipoprotein ratio, body mass index, log of triglyceride levels, diabetes, treatment for hypertension, treatment for elevated cholesterol.

† Sample size too small to calculate corresponding values.

**Table 4**

Multivariable-adjusted\* Cox model adjusted for decade of life<sup>†</sup>: Risk of CVD onset in smokers compared to nonsmokers during 12-year follow-up after examinations 1, 3, and 6 in Framingham offspring study participants

Sex	Examination 1 (1971–1982)			Examination 3 (1983–1994)			Examination 6 (1995–2006)			
	N	HR	CI	N	HR	CI	N	HR	CI	P-value
Women	902	1.7	1.0–2.7	1375	1.5	0.9–2.3	1432	1.6	1.0–2.4	0.038
Men	907	2.1	1.5–2.9	1273	2.0	1.5–2.7	1161	2.1	1.4–3.0	<0.0001

CVD = cardiovascular disease; HR = hazard ratio; CI = 95% confidence interval.

\* Multivariable-adjusted Cox model adjusted for systolic blood pressure, diastolic blood pressure, total cholesterol to high-density lipoprotein ratio, body mass index, log of triglyceride levels, diabetes, treatment for hypertension, treatment for elevated cholesterol.

<sup>†</sup>Decade of life: age grouped by decade at start of 12-year follow-up period following examinations 1, 3, and 6 as categorical variable (40–49 years: reference group, 50–59 years, and 60–69 years).