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ORIGINAL RESEARCH

Cigarette Smoking and Competing Risks for Fatal and Nonfatal Cardiovascular Disease Subtypes Across the Life Course

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BACKGROUND: Cigarette smoking is significantly associated with premature death related and not related to cardiovascular disease (CVD). Whether risk associated with smoking is similar across CVD subtypes and how this translates into years of life lost is not known.

METHODS AND RESULTS: We pooled and harmonized individual-level data from 9 population-based cohorts in the United States. All participants were free of clinical CVD at baseline with available data on current smoking status, covariates, and CVD outcomes. We examined the association between smoking status and total CVD and CVD subtypes, including fatal and nonfatal coronary heart disease, stroke, congestive heart failure, and other CVD deaths. We performed (1) modified Kaplan–Meier analysis to estimate long-term risks, (2) adjusted competing Cox models to estimate joint cumulative risks for CVD or noncardiovascular death, and (3) Irwin's restricted mean to estimate years lived free from and with CVD. Of 106 165 adults, 50.4% were women. Overall long-term risks for CVD events were 46.0% (95% CI, 44.7–47.3) and 34.7% (95% CI, 33.3–36.0) in middle-aged men and women, respectively. In middle-aged men who reported smoking compared with those who did not smoke, competing hazard ratios (HRs) were higher for the first presentation being a fatal CVD event (HR, 1.79 [95% CI, 1.68–1.92]), with a similar pattern among women (HR,1.82 [95% CI, 1.68–1.98]). Smoking was associated with earlier CVD onset by 5.1 and 3.8 years in men and women. Similar patterns were observed in younger and older adults.

CONCLUSIONS: Current smoking was associated with a fatal event as the first manifestation of clinical CVD.

Key Words: cardiovascular disease ■ cardiovascular mortality ■ smoking

Despite increasing awareness and public health measures to reduce tobacco use, ≈34 million adults in the United States report that they smoke cigarettes.[1] Tobacco use is the leading cause of disability-adjusted life years and the second-leading risk factor for death in the United States based on the US Burden of Disease Collaborators.[1] Smoking-related illness is estimated to cost >$300 billion a year in direct medical care and lost productivity in the United States.[2]

Studies have consistently demonstrated a strong link between cigarette use and the development of overall cardiovascular disease (CVD), individual CVD subtypes (including myocardial infarction [MI], stroke, and heart failure [HF]),[3–5] and noncardiovascular outcomes, including cancer and lung disease. However, few studies have evaluated the long-term morbidity and mortality attributed to CVD subtypes while adjusting for competing risk of non-CVD deaths, which is necessary as smoking is associated with an increased risk of multiple outcomes simultaneously.[4,6–8] Furthermore, a competing-risk framework allows for better understanding of the comparative risk of the first

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CLINICAL PERSPECTIVE

What Is New?

- Although it is well established that smoking is associated with both cardiovascular and noncardiovascular morbidity and mortality, the present analysis reports the lifetime risk of smoking for each cardiovascular disease subtype adjusting for noncardiovascular deaths.
- Smoking was associated with a fatal event as the first manifestation of clinical cardiovascular disease.

What Are the Clinical Implications?

- Preventive efforts focused on smoking cessation at the individual and population levels should emphasize the increased risk of cardiovascular disease across the lifetime, particularly the higher risk of cardiovascular death as the first presentation among those who smoke.

Nonstandard Abbreviations and Acronyms

BioLINCC	Biologic Specimen and Data Repository Information Coordinating Center
LRPP	Lifetime Risk Pooling Project

presentation of CVD being a fatal or nonfatal event as well as elucidating which of the different CVD subtypes are more likely to occur first. This is important to guide public health policies and physician–patient interactions on population and individual levels.

Our primary objective was to calculate long-term rates of incident CVD (overall and by subtypes) in adults aged 20 to 79 years. We also estimated years lived with and without CVD, on average, by baseline smoking status. Finally, we determined the hazard ratios (HRs) for incident CVD, overall and by subtype, after taking into account the competing risk from non-CVD mortality.

METHODS

Study Design

All data and materials are made publicly available by the National Heart, Lung, and Blood Institute bioLINCC (Biologic Specimen and Data Repository Information Coordinating Center). The LRPP (Lifetime Risk Pooling Project) is an individual-level pooled and harmonized data set from 20 community-based or population-based cardiovascular disease (CVD) cohorts in the United States available in BioLINCC spanning the past 70 years with detailed methods of cohort development and harmonization previously published.[9] There is nearly 100% complete follow-up for vital status. For the current analysis, we included data from participants free of clinical CVD at baseline from the following 9 prospective cohorts in the LRPP: the Coronary Artery Risk Development in Young Adults, the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, the Framingham Heart Study, the Framingham Offspring Study, the Kaiser Permanente Study of the Oldest Old, the Chicago Heart Association Detection Project in Industry Study, and the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study. All data were deidentified, and all study protocols were approved by the institutional review board at Northwestern University. Requests to access the data set from qualified researchers may be submitted at https://biolincc.nhlbi.nih.gov/studies/.

Study Population

We included data from only 1 examination for each cohort from participants who had available responses for self-reported smoking status, available data on covariates, and at least 10 years of follow-up. Smoking status was defined as yes or no based on the participant response in each cohort to current smoking (asked in each cohort at the baseline examination for current smoking or smoking within the past 30 days). We excluded 3192 participants who did not report White or Black race, 3961 participants with prevalent CVD at baseline, and 7773 participants without exposure or covariate information for the final analytic sample of 106 165 (which represented a complete case analysis). Baseline demographics of age, sex, and race and ethnicity were self-reported. In each cohort, trained clinical staff measured blood pressure, weight, and height. Fasting glucose and lipid profile were directly measured. Diagnosis of diabetes and use of diabetes/hypertensive medications were self-reported. Fatal and nonfatal MI were adjudicated based on defined clinical criteria that included at least 2 of the following: electrocardiographic changes consistent with MI, biomarker elevations consistent with myocardial injury, and typical chest pain or *International Classification of Diseases, Eighth Revision* (*ICD-8*)/*International Classification of Diseases, Ninth Revision* (*ICD-9*) codes. Stroke was adjudicated using the clinical criteria of new neurological deficit persisting for >24 hours consistent with neurological injury and/or *ICD-8*/*ICD-9* codes. HF was determined by clinical criteria and/or *ICD-8*/*ICD-9* codes. Vital status was obtained through linkage with the National Death Index, and cause of

death was adjudicated by review of medical records and autopsy records, when available.

Statistical Analysis

The study included 1 949 658 person-years of follow-up, including observations from 1948 to 2017. The participants were stratified by sex, index age groups (20–39 years for young adults, 40–59 years for middle-aged adults, and 60–79 years for older adults), and smoking status at the index examination. Long-term risk was calculated using a modified Kaplan–Meier analysis, which accounts for non-CVD death as a competing risk. This model accounts for fatal non-CVD events as a separate end point rather than a censoring event. Long-term risk of total CVD was estimated for each index age group by calculating the rates of CVD death, MI, stroke, and HF. We calculated cumulative risk for CVD events and non-CVD death by smoking status in age-stratified and sex-stratified analyses. We determined the proportion of incident first events, in which the occurrence of 1 type of event (CVD event or non-CVD death) precluded consideration of another event. The Lunn and McNeil data augmentation method was used to fit Cox proportional hazard models to estimate HRs for all CVD events combined compared with non-CVD death as the first event in those who currently smoke, stratified by index age group and sex.[10,11] We also used the method described by Fine and Gray to estimate the joint and simultaneous competing hazards for each CVD event subtype and non-CVD death as the first event in those who smoke, stratified by index age group and sex. Similarly, we used the Fine and Gray method to estimate the competing hazards for fatal and nonfatal CVD and non-CVD death as the first event in those who smoke, stratified by index age group and sex.[11,12] The analyses were adjusted for age, race and ethnicity, body mass index, hypertension, hyperlipidemia (defined as total cholesterol ≥240 mg/dL or lipid-lowering therapy), and diabetes. Mean overall survival time, mean CVD-free survival time, and mean survival time with CVD were estimated using the Irwin restricted mean to compare compression of morbidity by smoking status. The restricted mean is mathematically equivalent to the area under the survival curve.[11,13] For each index age group, the restriction time point was set as 95 years of age. The survival times were then compared between individuals who do and do not currently smoke, stratified by the age groups and sex. We performed a sensitivity analysis for middle-aged participants with a baseline exam before and after 1985 to mitigate bias related to changing secular trends in smoking status. We used a P value of <0.05 for a 2-sided significance test. All statistical analyses were performed with SAS version 9.2 (SAS Institute) and R version 3.1.2 (The R Foundation).

RESULTS

Study Sample

A total of 106 165 people were included in the pooled cohort, including 17 205 (16.2%) Black participants and 53 527 (50.4%) women. Baseline characteristics stratified by smoking status and sex in middle-aged, young, and older adults are described in Table 1.

Long-Term Risks of CVD Events and Non-CVD Death by Smoking Status

In middle-aged adults (index age of 40–59 years), there were 7002 incident fatal or nonfatal coronary heart disease events, 3527 incident fatal or nonfatal strokes, and 4559 incident HF events during the duration of the study. In addition, there were a total of 6224 deaths from all CVD causes (coronary heart disease, stroke, HF, and other) and 11 578 non-CVD deaths in middle-aged adults. The median (interquartile range) of follow-up was 23 years (15–32 years). The unadjusted event rates for CVD and non-CVD death were higher in those who reported smoking compared with those who did not in all adults (men and women across all 3 age groups; Table 2). The competing cumulative risks for both non-CVD death and total CVD events were higher in those who reported smoking compared with those who did not in all adults (across all sex and age groups; Figure 1 and Figures S1 and S2). Similarly, the long-term risk of non-CVD death and CVD were higher in those individuals who reported smoking compared with those who did not (Table 3). Middle-aged men had the largest absolute difference in long-term risk for CVD between those who reported smoking (46%) and those who did not (36%). MI was the most common CVD subtype, with those who reported smoking having a higher long-term risk than those who did not. Young men had the most pronounced absolute difference in long-term risk for HF between those who reported smoking (12%) and those who did not (5%).

Years Lived Free of and With CVD

Total survival in follow-up is composed of years lived free of CVD and years lived with CVD and is shown in Figure 2 and Figures S3 and S4 for middle-aged, young, and older men and women, respectively. Across all sex and age groups, overall survival was significantly shorter in those participants who reported baseline smoking compared with those who reported not smoking, which was attributed to the significantly lower number of years lived free of CVD or health span. For example, among middle-aged men, overall survival was significantly higher in those who reported not smoking (32.6 years) compared with those who reported smoking (27.1 years) at baseline, leading to a significantly higher number of years lived free of CVD

Table 1. Baseline Characteristics for Young (Aged 20–39 Years), Middle-Aged (Aged 40–59 Years), and Older (Aged 60–79 Years) Adults Stratified By Sex and Smoking Status

	Young adults, aged 20–39 y				Middle-aged adults, aged 40–59 y				Older adults, aged 60–79 y			
	Men		Women		Men		Women		Men		Women	
	Smoking (n=7310)	Nonsmoking (n=8352)	Smoking (n=5624)	Nonsmoking (n=7594)	Smoking (n=8826)	Nonsmoking (n=13 555)	Smoking (n=7403)	Nonsmoking (n=16 175)	Smoking (n=3212)	Nonsmoking (n=11 023)	Smoking (n=3050)	Nonsmoking (n=14 041)
Mean age (SD), y	29.8 (5.3)	29.5 (5.3)	28.6 (5.7)	27.9 (5.5)	48.1 (5.6)	49.0 (5.7)	48.1 (5.5)	49.0 (5.6)	63.8 (4.4)	65.3 (5.3)	64.0 (4.4)	65.3 (5.3)
Black race, n (%)	1033 (14.1)	1062 (12.7)	1360 (24.2)	1911 (25.2)	1148 (13.0)	1840 (13.6)	1097 (14.8)	2899 (17.9)	526 (16.4)	1561 (14.2)	423 (13.9)	2345 (16.7)
Risk factors												
Diabetes, n (%)	90 (1.2)	79 (1.0)	57 (1.0)	60 (0.8)	386 (4.4)	803 (6.0)	268 (3.7)	832 (5.2)	278 (8.7)	1217 (11.1)	215 (7.1)	1331 (9.5)
Treatment for diabetes, n (%)	75 (1.0)	64 (0.8)	48 (0.9)	49 (0.7)	247 (2.9)	516 (4.0)	181 (2.5)	563 (3.6)	150 (5.0)	608 (5.9)	132 (4.5)	732 (5.5)
Mean systolic blood pressure (SD), mm Hg	131.0 (16.3)	129.2 (15.9)	119.1 (15.0)	117.4 (14.7)	133.9 (21.0)	130.6 (20.3)	126.6 (21.8)	126.9 (21.9)	137.3 (23.7)	134.7 (21.9)	134.0 (23.9)	135.3 (23.4)
Treatment for hypertension, n (%)	126 (1.9)	158 (2.0)	124 (2.5)	155 (2.2)	678 (9.1)	1864 (14.3)	836 (12.7)	2634 (17.7)	599 (20.8)	3149 (29.8)	751 (26.0)	4615 (34.3)
Mean total cholesterol (SD), mg/dL	193.0 (38.9)	187.7 (35.5)	184.4 (35.2)	182.5 (33.5)	213.7 (41.0)	208.8 (39.0)	216.4 (43.4)	211.0 (42.3)	211.0 (40.3)	206.3 (40.9)	229.1 (46.1)	225.4 (44.6)
Mean body mass index (SD), kg/m^2	24.1 (3.7)	24.6 (3.7)	24.8 (5.7)	24.5 (4.8)	26.9 (4.4)	28.2 (4.6)	26.6 (5.8)	28.4 (6.6)	26.5 (4.0)	27.8 (4.2)	26.4 (5.0)	28.0 (5.3)

CVD indicates cardiovascular disease.

Table 2. Crude Event Rates for Non-CVD Death, CVD Event, and CVD Subtypes Stratified by Age, Sex, and Smoking Status

Sex and index age	Age-specific crude event rates											
	Non-CVD death/1000 PY		CVD event/1000 PY		CVD death/1000 PY		Fatal/NFMI per 1000 PY		Fatal/nonfatal stroke per 1000 PY		Heart failure/1000 PY	
	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking
Men												
Aged 20–39 y	5.5	2.2	7.8	3.3	2.6	1.0	3.1	1.3	1.0	0.5	1.0	0.4
Aged 40–59 y	16.8	9.1	31.9	20.0	10.0	5.7	12.1	7.4	4.2	2.9	5.5	4.0
Aged 60–79 y	35.7	22.8	59.4	47.4	18.5	13.3	20.0	15.7	8.4	6.9	12.5	11.4
Women												
Aged 20–39 y	4.3	2.3	4.5	2.5	1.2	0.6	1.3	0.6	1.1	0.7	0.8	0.6
Aged 40–59 y	13.3	8.1	21.2	14.4	6.0	3.7	6.3	3.9	3.8	3.1	5.1	3.7
Aged 60–79 y	29.1	18.1	44.3	36.8	12.2	10.2	11.9	9.8	8.1	6.8	12.0	10.0

CVD indicates cardiovascular disease; NFMI, nonfatal myocardial infarction; and PY, person-years.

(29.1 versus 24.0 years), indicating a delay in CVD onset by 5.1 years.

Competing Risks for CVD Morbidity and Non-CVD Mortality by Smoking Status

The proportions of middle-aged men and women who had incident CVD or non-CVD death as the first event are shown in Table 4, stratified by sex and smoking status. Incident CVD event as the first event occurred in a larger proportion of middle-aged men and women who reported smoking (52.1% and 44.1%, respectively) compared with those who reported not smoking (49.5% and 41.2%, respectively). Similarly, non-CVD death as the first event was more common in middle-aged men and women who reported smoking (36.5% and 33.9%, respectively) compared with those who reported not smoking (28.6% and 27.9%, respectively) at baseline. Similar findings were observed in young men and women (Table 4). However, among older men and women, incident CVD event as the first event occurred in a larger proportion of those individuals who reported smoking (59.2% and 57.5%, respectively) than those who reported not smoking (54.7% and 52.1%, respectively). Non-CVD death continued to occur in a greater proportion of older men and women who smoked compared with those who did not smoke. Among all age groups, a majority of the first CVD events were fatal or nonfatal MI. Although fatal and nonfatal stroke was the next leading cause of first CVD event in the young age group, HF became the second-leading cause in the middle-aged and older age groups. Adjusted competing HRs as determined by the Lunn and McNeil method was higher for CVD compared with non-CVD death in both middle-aged and older adults who reported smoking and those who reported not smoking.

Adjusted competing HRs as determined by the Fine and Gray method for first CVD subtype or non-CVD death in men and women across all 3 age groups are shown in Table 5 and Table S1. Individuals who reported smoking had an increased risk of non-CVD death and overall CVD as the first event across all age and sex groups compared with those who did not report smoking at baseline. Those who reported smoking had an increased risk of both fatal and nonfatal CVD events compared with those who did not smoke across all age and sex groups. The risk of fatal CVD event was higher than the risk of nonfatal CVD event across all age and sex groups except in older women. Sensitivity analysis stratified by index year before and after 1985 demonstrated similar findings (Table S2).

DISCUSSION

This large, pooled cohort analysis from 9 population-based cohorts with 1.9 million person-years of

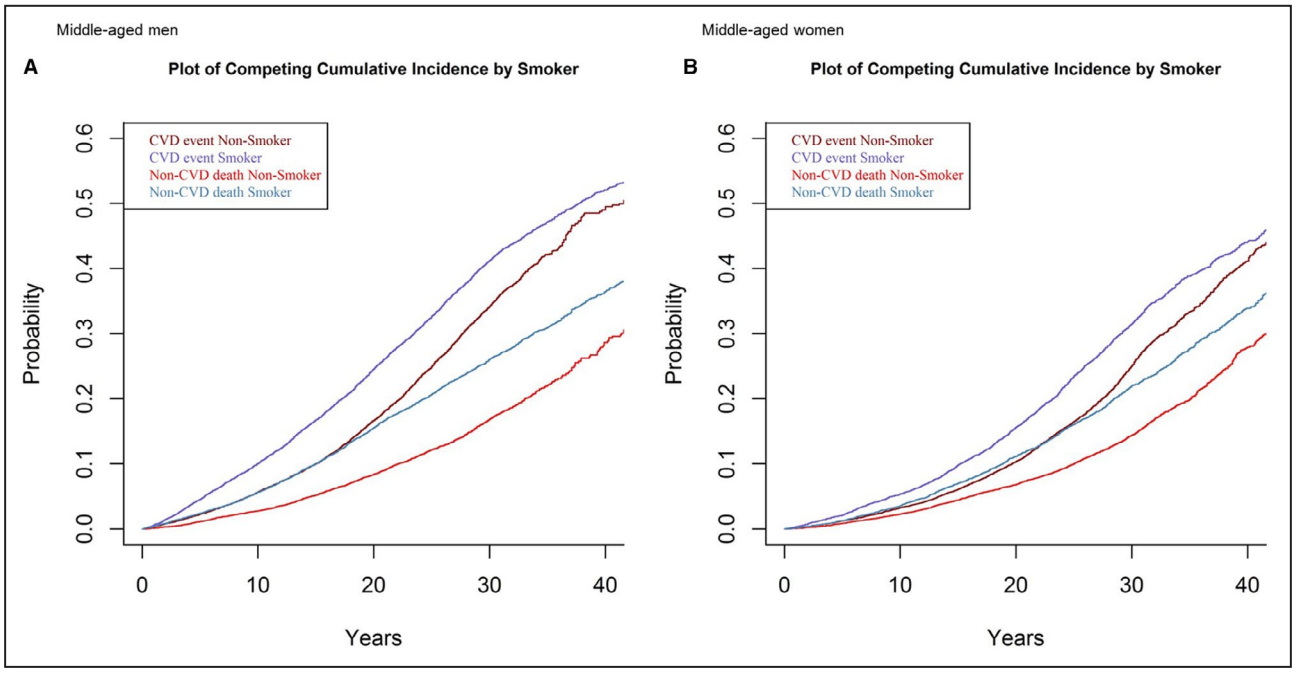

Figure 1. Cumulative incidence of cardiovascular disease (CVD) morbidity and mortality among middle-aged adults. Risk of cardiovascular disease in (**A**) men and (**B**) women aged 40 to 59 years based on smoking status and adjusted for competing risks of noncardiovascular death.

follow-up is the first to report the long-term risks of different CVD subtypes according to smoking status in the United States while accounting for competing risk of non-CVD deaths. In addition, the analytic approach highlights the greater burden of the first clinical manifestation of CVD as a fatal event in those who reported smoking compared with those who did not. This study leverages the unique LRPP data set, which allows for robust long-term risk estimates because of the substantial person-years follow-up, large sample size that is representative of the diverse population, and nearly 100% follow-up for vital status with ascertainment of CVD subtypes.

The current study expands on the available literature on long-term risks of CVD subtypes associated with smoking status. One prior analysis from England[4] only used diagnosis codes from electronic health records. The rate ratio of age-specific death rates from coronary artery disease in those who smoke compared with those who do not smoke has previously been shown to decline with age because of other smoking-related deaths and the significant age-related rise in background CVD risk.[14] Similarly, the relative risk of CVD subtypes, such as MI and HF, has also been shown to be lower with older age in those who smoke compared with those who do not smoke.[15,16] However, these studies did not show when the absolute CVD risk in those who smoke equals or is less than that of those who do not smoke with rising age. Given the size of this study and the extensive follow-up, this article demonstrates that the cumulative incidence of CVD in those older adults who smoked remained higher than those older adults who did not smoke during the 25 years of follow-up. The results herein emphasize the contribution of smoking on not only earlier onset of CVD overall but also the excess CVD risk well into the eighth decade of life for men and women even after adjusting for competing risk of non-CVD death.

We evaluated the risk of individual CVD subtypes, including fatal and nonfatal events. This study highlights the occurrence of fatal CVD as the first presentation of CVD, which is important in risk communication and smoking cessation counseling on a population level, which is increasingly important as the use of computed tomography screening for malignancy becomes more widespread among those who smoke.[17] Yet, guidance to use coronary artery calcification among those who smoke remains lacking, which is readily calculable from these computed tomography images. In addition, we identified the long-term risk of smoking on HF that adds to the available literature on the short-term risk of HF with smoking.[5,18–23] The long-term risk of HF was higher with older index age at baseline. The largest absolute difference in long-term risk of HF between those who reported smoking and those who did not was seen in young men (11.5% versus 5.0%). In addition, in older women, those who reported smoking had the highest risk of HF as the first event among the CVD subtypes. Thus, more attention needs to be placed on these subgroups with regard to

Table 3. Long-Term* Risks for Non-CVD Death, CVD Event, and CVD Subtypes With Adjustment for Competing Risk Stratified by Age, Sex, and Smoking Status

Sex and index age	Long-term risk percentage (95% CI), adjusted for competing risks											
	Non-CVD death		CVD event		CVD death		Fatal/NFMI		Fatal/nonfatal stroke		Heart failure	
	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking
Men												
Aged 20–39 y	40.8 (37.8–43.9)	27.0 (21.0–32.9)	38.2 (35.1–41.3)	32.7 (26.0–39.4)	20.8 (18.4–23.3)	12.3 (8.3–16.2)	24.0 (21.4–26.6)	19.6 (14.0–25.3)	12.4 (10.2–14.6)	9.9 (6.3–13.5)	11.5 (9.4–13.6)	5.0 (2.9–7.0)
Aged 40–59 y	39.9 (38.6–41.1)	24.5 (23.5–25.4)	46.0 (44.7–47.3)	35.8 (34.7–36.8)	24.4 (23.4–25.5)	15.6 (14.8–16.4)	29.6 (28.4–30.8)	20.8 (19.9–21.7)	10.4 (9.7–11.1)	8.5 (7.9–9.2)	13.2 (12.4–14.0)	11.2 (10.5–11.9)
Aged 60–79 y	37.1 (35.2–39.0)	21.8 (20.9–22.7)	42.0 (39.9–44.1)	31.4 (30.3–32.4)	19.8 (18.3–21.3)	12.0 (11.2–12.8)	24.7 (22.9–26.5)	18.0 (17.1–19.0)	10.3 (9.1–11.6)	8.1 (7.5–8.7)	13.9 (12.6–15.2)	11.2 (10.5–11.9)
Women												
Aged 20–39 y	33.2 (29.9–36.5)	23.1 (19.7–26.5)	24.7 (21.8–27.6)	22.1 (18.7–25.6)	11.3 (9.0–13.6)	6.8 (4.7–8.8)	11.1 (9.1–13.2)	8.7 (6.4–11.0)	10.8 (8.6–12.9)	10.0 (7.5–12.4)	7.2 (5.4–9.1)	8.7 (6.3–11.0)
Aged 40–59 y	32.6 (31.3–33.9)	20.4 (19.6–21.3)	34.7 (33.3–36.0)	24.8 (23.9–25.6)	15.2 (14.2–16.2)	8.4 (7.8–9.0)	16.5 (15.5–17.5)	10.2 (9.6–10.8)	9.8 (8.9–10.6)	8.6 (8.0–9.1)	13.2 (12.3–14.2)	9.9 (9.2–10.5)
Aged 60–79 y	28.8 (26.9–30.7)	15.2 (14.5–15.9)	31.7 (29.8–33.6)	22.6 (21.7–23.4)	12.6 (11.3–13.9)	7.5 (7.0–8.0)	13.9 (12.5–15.3)	9.8 (9.2–10.4)	9.9 (8.7–11.2)	7.1 (6.6–7.6)	13.2 (11.9–14.6)	9.8 (9.2–10.3)

CVD indicates cardiovascular disease; and NFMI, nonfatal myocardial infarction.

*To 70 years of age for the baseline 20 to 39 years of age and to 90 years of age for the baseline 40 to 79 years of age.

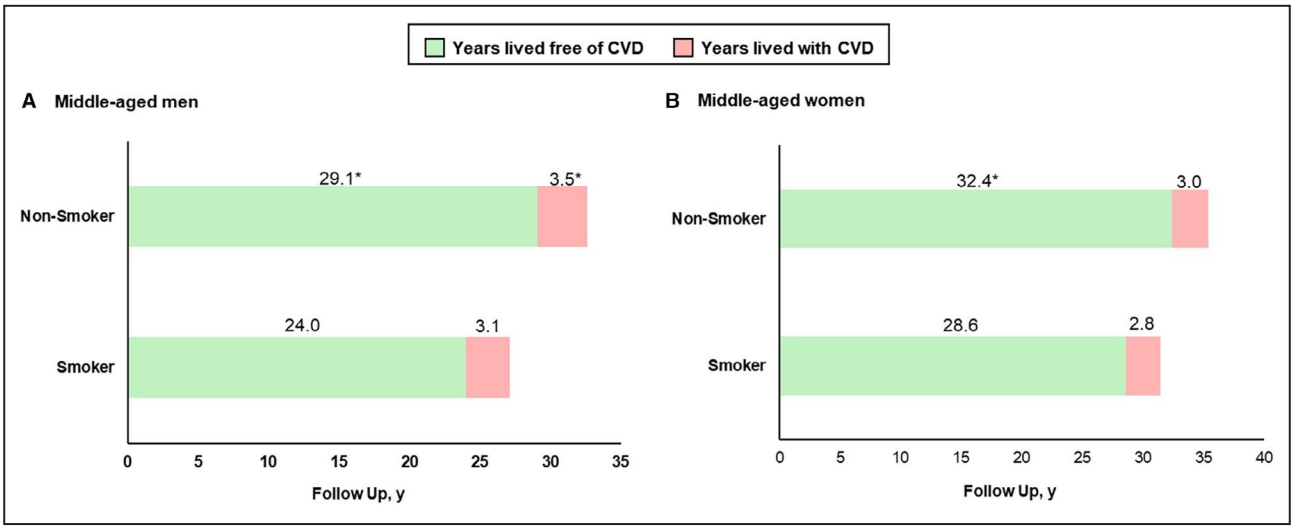

Figure 2. Years lived (cumulative years lived under observation to date) free of and with cardiovascular disease (CVD) among middle-aged adults.
Years lived free of and with CVD in middle-aged (index age 40–59 years) (**A**) men and (**B**) women. Adults who do not smoke lived more years free of CVD compared with those who did smoke. Years lived with CVD were similar in those who did and did not smoke. Compared with those who do not smoke, men and women with current cigarette smoking had an earlier onset of CVD by 5.1 and 3.8 years, respectively, and had reduced overall survival by 5.5 and 4.0 years, respectively. *P<0.05 compared with those who smoke.

HF prevention strategies. These findings suggest that smoking contributes substantially to the long-term risk of HF across sex and age groups.

We also quantified CVD morbidity as proportion of life lived without and with CVD. Those who did not report smoking at baseline had a later age of onset of CVD by about 5 years than those who reported smoking. This greater number of years lived without CVD was seen across all age and sex groups in those who did not smoke. After developing incident CVD, the years lived with CVD were overall similar among those who smoked and those who did not smoke in men and women across all age groups. This highlights relative compression of morbidity with postponement of onset of CVD and longer overall lifespan in those who do not smoke.

Prior studies of long-term CVD risk have focused primarily on middle-aged and older adults.[6,24,25] There

Table 4. Cumulative Incidences for First Event (CVD Event or Non-CVD Death) Among Young (Index Age 20–39 Years), Middle-Aged (Index Age 40–59 Years), and Older Adults (60–79 Years) According to Sex and Smoking Status*

	Young adults, aged 20–39 y		Middle-aged adults, aged 40–59 y		Older adults, aged 60–79 y	
	Smoking	Nonsmoking	Smoking	Nonsmoking	Smoking	Nonsmoking
Men						
Non-CVD death, %	22.3	12.6	36.5	28.6	43.5	36.7
CVD event, %	24.6	19.9	52.1	49.5	54.7	59.2
Fatal and nonfatal MI, %	15.6	11.7	28.3	23.8	24.7	27.1
Fatal and nonfatal stroke, %	5.0	4.4	9.9	10.9	10.5	11.3
CHF, %	2.3	2.8	9.1	10.4	12.8	15.6
CVD death, %	1.7	1.0	4.8	4.4	6.7	5.2
Women						
Non-CVD death, %	16.5	11.0	33.9	27.9	47.2	41.9
CVD event, %	15.3	11.4	44.1	41.2	52.1	57.5
Fatal and nonfatal MI, %	6.5	4.1	17.2	13.9	18.0	20.0
Fatal and nonfatal stroke, %	5.1	4.4	11.2	13.4	13.3	14.6
CHF, %	2.1	2.3	11.1	10.3	15.8	17.5
CVD death, %	1.6	0.6	4.5	3.6	4.9	5.4

CHF indicates congestive heart failure; CVD, cardiovascular disease; and MI, myocardial infarction.
*Lunn and McNeil method.

Table 5. Adjusted* Competing HRs for First Presentation of CVD as a Fatal or Nonfatal Event Across the Life Course in Young, Middle-Aged, and Older Adults Stratified by Sex in Individuals who Reported Smoking Compared with Not Smoking Confirmed

	Young adults, aged 20–39 y	Middle-aged adults, aged 40–59 y	Older adults, aged 60–79 y
Men			
Nonfatal CVD event	1.64 (1.41–1.90)	1.29 (1.21–1.38)	1.17 (1.06–1.28)
Fatal CVD event	2.38 (2.05–2.75)	1.79 (1.68–1.92)	1.38 (1.27–1.51)
Women			
Nonfatal CVD event	1.58 (1.33–1.88)	1.46 (1.35–1.57)	1.35 (1.23–1.48)
Fatal CVD event	2.01 (1.62–2.49)	1.82 (1.68–1.98)	1.30 (1.17–1.43)

Data are presented as adjusted HR (95% CI). CVD indicates cardiovascular disease; and HR, hazard ratio.
*Adjusted for age, race and ethnicity, education, body mass index, hypertension, hyperlipidemia, and diabetes. The Fine and Gray method was used with nonsmokers as the reference.

are limited data on smoking-related CVD risk in young adults in general. Therefore, our data build on available evidence with long-term CVD risk estimates of young adults from the index ages 20 to 39 years. In young men, the risk for CVD started to increase significantly in those who smoked near the 10-year follow-up mark, whereas in young women the increased risk for CVD in those who smoked became more evident near the 20-year follow-up mark. With respect to CVD subtypes, young men had the highest long-term risk for MI (24.0%), whereas young women had the highest long-term risk for other CVD death (11.3%). In general, the results suggest that young adults who smoke have an equal if not greater burden of non-CVD mortality compared with morbidity and mortality from CVD. In both young men and women, the absolute difference in long-term risks between those who smoked and did not smoke was greater for non-CVD death than overall CVD. These data may inform policy and population-level approaches to target the epidemic expansion of nicotine exposure in youth and young adults using electronic nicotine delivery systems.

Strengths and Limitations

Key limitations of our study include the lack of data on smoking intensity given the known graded association between number of cigarettes per day and CVD. However, there is a sharp increase in CVD risk even with low levels of cigarette exposure that we were able to quantify for baseline smoking status. There is the potential to bias our results toward the null by classifying those who smoked but quit >1 year ago as not smoking at baseline, which may be underestimating the true risk of CVD morbidity and mortality related to prior cigarette smoking exposure. Another limitation is the use of baseline risk factor levels, which does not incorporate change over time. Lastly, the long-term data required for lifetime risk estimates lead to the inclusion of relatively older data and the potential for results to be biased by changes in secular trends, such as declines in smoking prevalence over time. However, our sensitivity analysis in recent years were consistent, and prior analyses in the LRPP have also examined differences across birth cohorts with similar findings for the relationships of each risk factor with CVD.[20] However, our study has many strengths including a large sample size of adults with a representative sample of women and Black participants who were free of CVD at baseline with adjudicated CVD events by type and non-CVD death in follow-up. Our inclusion of young adults and extended follow-up allows us to quantify the effects of smoking at the beginning and end of adulthood.

CONCLUSIONS

In summary, we demonstrate an increased risk of CVD across all subtypes, in particular on the occurrence of a fatal CVD event as first presentation of CVD, in those who reported smoking compared with those who did not. Those who reported smoking had, on average, earlier onset of CVD and shorter overall survival across the life course.

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Supplementary Material

Tables S1–S2
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Adjusted[*] Competing Hazard Ratios for First Event[†] (Cardiovascular disease event or Non-Cardiovascular death) Stratified by Sex and Smoking Status.

		Adjusted HR (95% CI) Young Adults (20-39 years)	Adjusted HR (95% CI) Middle-Aged Adults (40-59 years)	Adjusted HR (95% CI) Older Adults (60-79 years)
Men				
Non-CVD death		2.28 (2.04-2.54)	1.92 (1.81-2.05)	1.58 (1.46-1.70)
CVD event		2.05 (1.85-2.28)	1.61 (1.54, 1.69)	1.33 (1.25-1.42)
	Fatal and nonfatal MI	2.23 (1.95-2.56)	1.62 (1.52-1.73)	1.20 (1.10-1.32)
	Fatal and nonfatal stroke	1.67 (1.32-2.12)	1.39 (1.24-1.55)	1.17 (1.01-1.35)
	CHF	1.54 (1.14-2.09)	1.31 (1.17-1.46)	1.27 (1.11-1.44)
	CVD death	1.69 (1.24-2.31)	1.53 (1.30-1.79)	1.69 (1.38, 2.08)
Women				
Non-CVD death		1.82 (1.62-2.05)	1.73 (1.62-1.85)	1.64 (1.52, 1.78)
CVD event		1.76 (1.54, 2.01)	1.69 (1.60-1.79)	1.38 (1.29-1.48)
	Fatal and nonfatal MI	2.01 (1.61-2.52)	1.80 (1.65-1.96)	1.25 (1.11-1.39)
	Fatal and nonfatal stroke	1.75 (1.38-2.20)	1.20 (1.08-1.34)	1.24 (1.08-1.41)
	CHF	1.19 (0.89-1.59)	1.59 (1.43-1.77)	1.40 (1.24-1.58)
	CVD death	2.12 (1.30-3.47)	1.81 (1.53-2.16)	1.33 (1.06-1.67)

[*]Adjusted for age, race/ethnicity, education, body mass index, hypertension, hyperlipidemia, and diabetes;
[†]Fine and Gray Method with those who do not smoke as reference.
CVD = Cardiovascular disease; MI = myocardial infarction; CHF = congestive heart failure

Table S2. Adjusted[*] Competing Hazard Ratios for First Presentation of Cardiovascular Disease Across the Life Course in Middle-Aged Adults Stratified by Sex and Year of Baseline Exam (before or after 1985)[†]

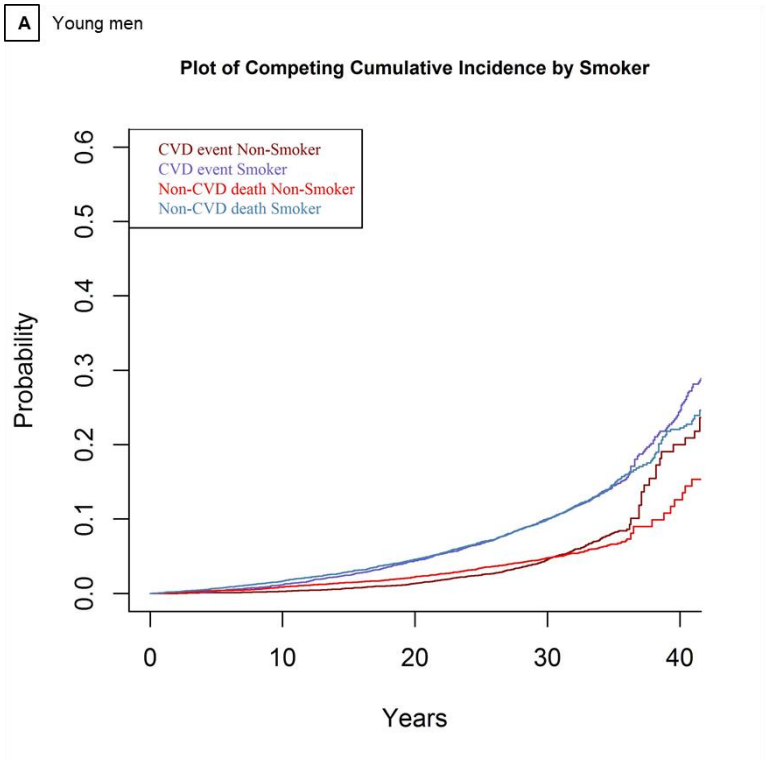
	Adjusted HR (95% CI) Exam year before 1985	Adjusted HR (95% CI) Exam year after 1985
Male		
Nonfatal CVD Event	1.32 (1.14-1.52)	1.83 (1.60 - 2.08)
Fatal CVD Event	1.88 (1.70-2.07)	2.10 (1.65 – 2.67)
Female		
Nonfatal CVD Event	1.16 (0.98 - 1.38)	2.21 (1.92 - 2.55)
Fatal CVD Event	2.25 (1.95- 2.59)	2.96 (2.19 - 3.98)

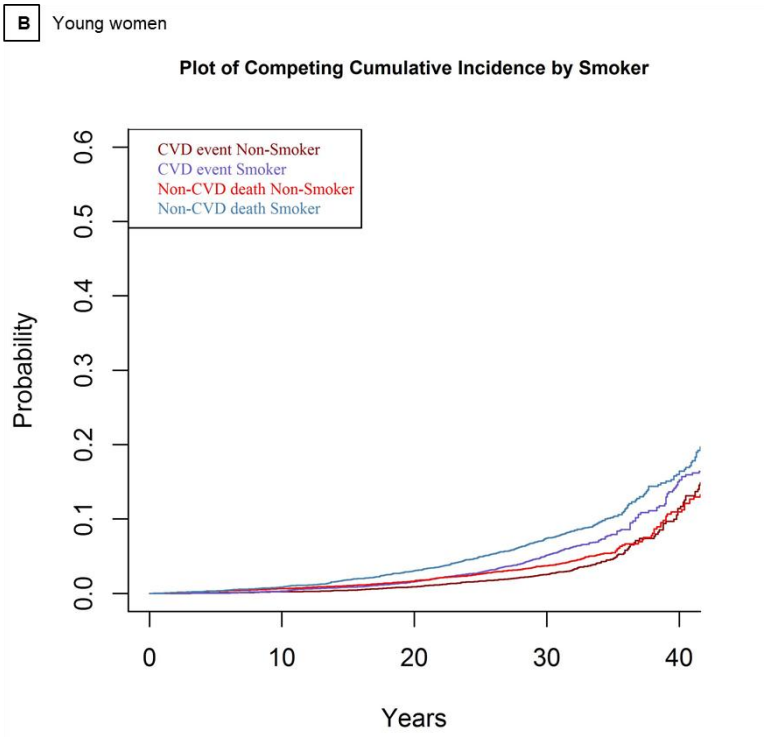
[*]Adjusted for age, race/ethnicity, education, BMI, HTN, HLD, and diabetes;

[†]Fine and Gray Method with those who do not smoke as reference.

CVD = Cardiovascular disease; MI = myocardial infarction; CHF = congestive heart failure

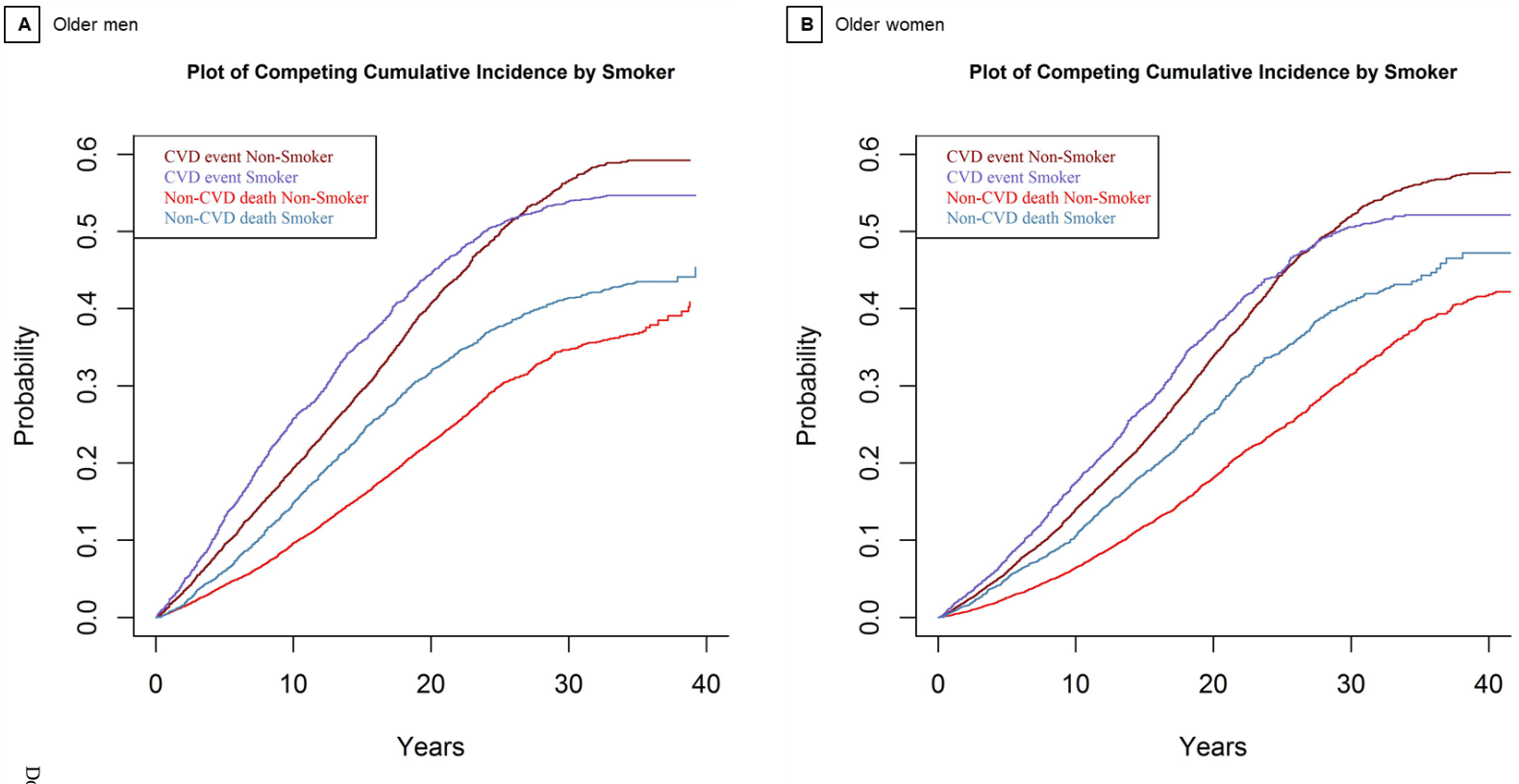
Figure S1. Cumulative Incidence of Cardiovascular Disease Morbidity and Mortality Among Young Adults.





Men (A) and Women (B) (Index Age 20-39 years) Stratified by Baseline Smoking Status and Adjusted for Competing Risks of Non-Cardiovascular Death

Figure S2. Cumulative Incidence of Cardiovascular Disease Morbidity and Mortality Among Older Adults.



Men (A) and Women (B) (Index Age 60-79 years) Based on Smoking Status and Adjusted for Competing Risks of Non-Cardiovascular Death

Figure S3. Years Lived[#] Free of and With Cardiovascular Disease (CVD) Among Young Adults.

Years lived free of and with CVD in young (index age 20-39 years) men (A) and women (B). Adults who did not smoke lived more years free of CVD compared with those who reported smoking at baseline. Years lived with CVD was similar in both groups. Compared with those who did not smoke, men and women who reported cigarette smoking had an earlier onset of CVD by 4.2 and 2.0 years, respectively, and had reduced overall survival by 3.6 and 2.2 years, respectively.

[#]Cumulative years lived under observation-to-date

*$p<0.05$ compared to smokers

Figure S4. Years Lived[#] Free of and With Cardiovascular Disease (CVD) Among Old Adults.

Years lived free of and with CVD in old (index age 60-79 years) men (A) and women (B). Adults who did not smoke lived more years free of CVD compared with those who reported smoking at baseline. Years lived with CVD was similar in smokers and non-smokers. Compared to non-smokers, men and women with current cigarette smoking had an earlier onset of CVD by 2.9 and 2.8 years, respectively, and had reduced overall survival by 3.1 and 3.1 years, respectively.

[#]Cumulative years lived under observation-to-date; *p<0.05 compared to smokers