

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## **Abbreviations**

BMI: body mass index

CI: confidence interval

CVD: cardiovascular disease

IRD: incidence rate difference

SD: standard deviation

SI: international system of units

**eTable 1. Baseline Characteristics of Original Cohort by Smoking Status and Intensity**

Characteristic <sup>a</sup>	Never Smokers (Total N = 1631)		Former Smokers <20 Pack-Years (Total N = 164)		Former Smokers ≥20 Pack-Years (Total N = 104)		Current Smokers <20 Pack-Years (Total N = 893)		Current Smokers ≥20 Pack-Years (Total N = 1013)	
	N	Summary	N	Summary	N	Summary	N	Summary	N	Summary
Age, years	1631	52.0 ± 8.6	164	48.8 ± 8.5	104	52.3 ± 8.2	893	47.4 ± 8.0	1013	49.3 ± 7.8
Male Sex	1631	332 (20.4)	164	65 (39.6)	104	95 (91.4)	893	256 (28.7)	1013	780 (77.0)
Education	1610	--	163	--	97	--	886	--	1004	--
<i>Less than High School Graduate</i>	--	734 (45.6)	--	51 (31.3)	--	47 (48.5)	--	320 (36.1)	--	412 (41.0)
<i>High School Graduate</i>	--	437 (27.1)	--	56 (34.4)	--	20 (20.6)	--	308 (34.8)	--	323 (32.2)
<i>More than High School</i>	--	439 (27.3)	--	56 (34.4)	--	30 (30.9)	--	258 (29.1)	--	269 (26.8)
Systolic Blood Pressure, mmHg	1631	137.0 ± 24.6	164	131.0 ± 20.4	104	133.2 ± 19.2	893	127.8 ± 21.0	1013	130.9 ± 19.7
Diastolic Blood Pressure, mmHg	1631	84.9 ± 12.3	164	82.3 ± 11.3	104	84.6 ± 11.3	893	80.5 ± 11.8	1013	82.8 ± 11.4
Antihypertensive Medication	1624	76 (4.7)	164	1 (0.6)	104	4 (3.9)	892	19 (2.1)	1013	24 (2.4)
Hypertension	1629	714 (43.8)	164	57 (34.8)	104	42 (40.4)	893	244 (27.3)	1013	345 (34.1)
Body Mass Index, kg/m <sup>2</sup>	1626	26.5 ± 4.3	163	25.6 ± 3.9	104	26.7 ± 4.0	892	24.7 ± 4.0	1013	25.2 ± 3.5
Diabetes	1615	43 (2.7)	161	2 (1.2)	104	4 (3.9)	885	11 (1.2)	1006	15 (1.5)
Total Cholesterol, mg/dL	1612	241.9 ± 45.2	164	240.5 ± 45.5	104	233.5 ± 40.6	878	234.3 ± 43.9	1006	238.3 ± 42.3
Current Drinkers	1613	822 (51.0)	159	112 (70.4)	104	86 (82.7)	886	691 (78.0)	1002	855 (85.3)
Cigarettes per day	--	--	--	--	--	--	893	12.5 ± 7.7	1013	24.4 ± 9.4
Cumulative Pack-Years	--	--	164	6.1 ± 5.7	104	38.9 ± 21.7	893	9.9 ± 5.9	1013	36.2 ± 15.2
Years Since Quitting	--	--	164	4.8 ± 6.0	104	4.9 ± 4.3	--	--	--	--

SI conversion factors: To convert total cholesterol to mmol/L, multiply values by 0.0259.

a Summary statistics are displayed as Mean ± SD for continuous variables, and as N (%) for categorical variables.

**eTable 2. Baseline Characteristics of Offspring Cohort by Smoking Status and Intensity**

Characteristic <sup>a</sup>	Never Smokers (Total N = 1831)		Former Smokers <20 Pack-Years (Total N = 623)		Former Smokers ≥20 Pack-Years (Total N = 302)		Current Smokers <20 Pack-Years (Total N = 1257)		Current Smokers ≥20 Pack-Years (Total N = 952)	
	N	Summary	N	Summary	N	Summary	N	Summary	N	Summary
Age, years	1831	34.7 ± 11.2	623	36.4 ± 8.5	302	45.6 ± 7.4	1257	31.0 ± 8.4	952	42.4 ± 7.6
Male Sex	1831	760 (41.5)	623	309 (49.6)	302	239 (79.1)	1257	513 (40.8)	952	557 (58.5)
Education	1435	--	490	--	241	--	917	--	680	--
<i>Less than High School Graduate</i>	--	64 (4.5)	--	26 (5.3)	--	43 (17.8)	--	51 (5.6)	--	119 (17.5)
<i>High School Graduate</i>	--	449 (31.3)	--	146 (29.8)	--	89 (36.9)	--	334 (36.4)	--	273 (40.2)
<i>More than High School</i>	--	922 (64.3)	--	318 (64.9)	--	109 (45.2)	--	532 (58.0)	--	288 (42.4)
Systolic Blood Pressure, mmHg	1831	121.5 ± 16.1	623	121.9 ± 15.1	302	131.5 ± 19.5	1256	117.5 ± 13.9	952	125.2 ± 17.9
Diastolic Blood Pressure, mmHg	1831	78.5 ± 10.6	623	79.2 ± 10.4	302	84.6 ± 11.7	1256	75.2 ± 9.9	952	80.6 ± 11.4
Antihypertensive Medication	1829	55 (3.0)	623	15 (2.4)	300	28 (9.3)	1255	15 (1.2)	947	39 (4.1)
Hypertension	1830	339 (18.5)	623	122 (19.6)	302	122 (40.4)	1255	127 (10.1)	948	238 (25.1)
Body Mass Index, kg/m <sup>2</sup>	1829	25.0 ± 4.5	623	25.0 ± 4.2	302	27.1 ± 3.8	1256	24.3 ± 4.3	951	25.8 ± 4.1
Diabetes	1793	24 (1.3)	612	7 (1.1)	295	14 (4.8)	1240	12 (1.0)	934	31 (3.3)
Total Cholesterol, mg/dL	1817	193.6 ± 38.5	621	199.2 ± 38.1	302	218.7 ± 43.1	1247	190.4 ± 39.0	948	214.4 ± 40.3
Current Drinkers	1818	1415 (77.8)	617	558 (90.4)	301	267 (88.7)	1240	1095 (88.3)	944	843 (89.3)
Cigarettes per day	--	--	--	--	--	--	1257	15.0 ± 8.6	952	30.2 ± 10.8
Cumulative Pack-Years	--	--	623	7.9 ± 5.4	302	39.0 ± 20.3	1257	8.4 ± 5.6	952	36.5 ± 16.3
Years Since Quitting	--	--	623	8.4 ± 6.5	303	6.4 ± 4.6	--	--	--	--

SI conversion factors: To convert total cholesterol to mmol/L, multiply values by 0.0259.

a Summary statistics are displayed as Mean ± SD for continuous variables, and as N (%) for categorical variables.

**eTable 3. CVD Event Types by Cohort**

<b>Event Type</b>	<b>Original Cohort</b>	<b>Offspring Cohort</b>	<b>Total</b>
Myocardial Infarction	502	335	837
Cerebrovascular Event	450	222	672
CVD Death	254	60	314
Heart Failure	406	206	612
<i>Total</i>	<i>1,612</i>	<i>823</i>	<b><i>2,435</i></b>

**eTable 4. Adjusted Risk of Incident CVD in Heavy Former vs. Current Smokers – Additionally Adjusted for Cumulative Pack-Years<sup>a</sup>**

Years Since Quitting Category	Person-Exams	Incident CVDs	Person-Years (PY)	Incidence Rate per 1000 PY [95% CI]	Hazard Ratio [95% CI]	p-value
<b><i>Pooled Cohort</i></b>						
Current Smokers	13,885	558	41,725	11.28 [10.00, 12.74]	1.00	--
<5 years	2586	101	7851	6.81 [5.49, 8.45]	0.62 [0.50, 0.77]	<0.001
[5, 10) years	2088	99	6342	6.95 [5.58, 8.66]	0.63 [0.50, 0.79]	<0.001
[10, 15) years	1429	76	4455	6.28 [4.90, 8.06]	0.57 [0.44, 0.74]	<0.001
[15, 25) years	2123	145	6741	6.15 [5.05, 7.50]	0.59 [0.47, 0.73]	<0.001
25+ years	1326	116	4187	5.16 [4.10, 6.49]	0.50 [0.38, 0.66]	<0.001
<b><i>Original Cohort</i></b>						
Current Smokers	9727	363	20,450	12.89 [11.01, 15.08]	1.00	--
<5 years	1711	70	3613	8.53 [6.55, 11.12]	0.68 [0.52, 0.89]	0.005
[5, 10) years	1268	63	2623	8.32 [6.30, 11.00]	0.67 [0.50, 0.89]	0.007
[10, 15) years	850	44	1757	7.41 [5.35, 10.28]	0.60 [0.43, 0.86]	0.004
[15, 25) years	1128	63	2361	5.65 [4.24, 7.54]	0.51 [0.37, 0.70]	<0.001
25+ years	670	62	1378	5.99 [4.39, 8.17]	0.53 [0.36, 0.79]	0.002
<b><i>Offspring Cohort</i></b>						
Current Smokers	4158	195	21,275	7.51 [6.06, 9.32]	1.00	--
<5 years	875	31	4239	3.79 [2.56, 5.60]	0.52 [0.35, 0.76]	<0.001
[5, 10) years	820	36	3720	4.24 [2.94, 6.13]	0.60 [0.42, 0.85]	0.005
[10, 15) years	579	32	2698	3.85 [2.60, 5.70]	0.53 [0.35, 0.79]	0.002
[15, 25) years	995	82	4379	4.74 [3.54, 6.35]	0.67 [0.49, 0.92]	0.013
25+ years	656	54	2809	3.11 [2.17, 4.45]	0.47 [0.31, 0.70]	<0.001

<sup>a</sup> This analysis is limited to current and former smokers with at least 20 cumulative pack-years. Incidence rates and hazard ratios are adjusted for age, sex, education, examination decade, systolic blood pressure, antihypertensive medication, diabetes status, body mass index, total cholesterol, and alcohol consumption. Dynamic variables are time-updated.

**eTable 5. Comparison of Adjusted Risk of Incident CVD by Years Since Quitting: Polynomial Versus Linear Terms<sup>a</sup>**

Years Since Quitting Category	Model with Polynomials		Model with Linear Terms	
	Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
<b><i>Pooled Cohort – Former vs. Current</i></b>				
Current Smokers	1.00	---	1.00	---
<5 years	0.61 [0.49, 0.76]	<0.001	0.60 [0.49, 0.75]	<0.001
[5, 10) years	0.61 [0.49, 0.77]	<0.001	0.62 [0.49, 0.77]	<0.001
[10, 15) years	0.54 [0.42, 0.70]	<0.001	0.55 [0.43, 0.71]	<0.001
[15, 25) years	0.55 [0.45, 0.68]	<0.001	0.55 [0.45, 0.68]	<0.001
25+ years	0.45 [0.35, 0.58]	<0.001	0.45 [0.35, 0.58]	<0.001
<b><i>Pooled Cohort – Former vs. Never</i></b>				
<5 years	1.40 [1.12, 1.73]	0.002	1.38 [1.11, 1.71]	0.003
[5, 10) years	1.42 [1.15, 1.77]	0.001	1.43 [1.15, 1.77]	0.001
[10, 15) years	1.25 [0.98, 1.60]	0.08	1.26 [0.98, 1.61]	0.07
[15, 25) years	1.22 [1.00, 1.47]	0.045	1.23 [1.02, 1.48]	0.033
25+ years	0.98 [0.78, 1.22]	0.85	0.98 [0.78, 1.23]	0.85
Never Smokers	1.00	---	1.00	---

<sup>a</sup> Models are limited to never and heavy ( $\geq 20$  pack-years) ever smokers. Hazard Ratios are adjusted for age, sex, education, examination decade, hypertension, diabetes status, body mass index, total cholesterol, and alcohol consumption. Dynamic variables are time-updated.

**eTable 6. Comparison of CVD Incidence Rates by Cohort and Influence of Age<sup>a</sup>**

Years Since Quitting Category	Adjusted Incidence Rate [95% CI] <sup>b</sup>		
	Offspring Cohort	Offspring Cohort: Participants Aged $\geq 50$	Original Cohort
Current Smoker	7.71 [6.27, 9.48]	11.50 [8.94, 14.78]	13.04 [11.21, 15.18]
<5 years	3.83 [2.59, 5.65]	6.49 [4.26, 9.88]	8.62 [6.63, 11.20]
[5, 10) years	4.29 [2.97, 6.18]	7.49 [5.12, 10.96]	8.39 [6.35, 11.07]
[10, 15) years	3.86 [2.61, 5.72]	6.19 [4.11, 9.32]	7.45 [5.37, 10.32]
[15, 25) years	4.70 [3.52, 6.29]	8.01 [6.01, 10.66]	5.65 [4.24, 7.53]
25+ years	3.00 [2.10, 4.28]	5.14 [3.62, 7.31]	5.97 [4.39, 8.11]
Never Smoker	2.57 [2.07, 3.20]	4.35 [3.46, 5.46]	6.72 [5.77, 7.82]

a Results are limited to never smokers and heavy ever smokers ( $\geq 20$  pack years) since they are the focus of our primary analyses.

b Incidence rates are adjusted for age, sex, education, examination decade, systolic blood pressure, diabetes status, body mass index, total cholesterol, and alcohol consumption. Incidence rates were estimated from a Poisson regression model with an offset equal to the natural logarithm of follow-up time.



**eTable 7. Adjusted Risk of Incident CVD Among All Current and Former Smokers<sup>a</sup>**

Years Since Quitting Category	Person-Exams	Incident CVDs	Person-Years (PY)	Incidence Rate per 1000 PY [95% CI]	Hazard Ratio [95% CI]	p-value
<b><i>Pooled Cohort – Former vs. Current</i></b>						
Current Smokers	21,111	666	67,478	9.81 [8.83, 10.90]	1.00	---
<5 years	4743	138	15,004	5.89 [4.90, 7.09]	0.60 [0.50, 0.72]	<0.001
[5, 10) years	3947	132	12,765	5.62 [4.65, 6.79]	0.56 [0.46, 0.68]	<0.001
[10, 15) years	2916	106	9611	4.99 [4.04, 6.16]	0.49 [0.40, 0.61]	<0.001
[15, 25) years	4857	238	16,625	5.28 [4.50, 6.20]	0.53 [0.45, 0.63]	<0.001
25+ years	4191	260	14,916	4.64 [3.92, 5.49]	0.45 [0.37, 0.54]	<0.001
<b><i>Pooled Cohort – Former vs. Never</i></b>						
<5 years	4743	138	15,004	5.89 [4.90, 7.09]	1.27 [1.06, 1.53]	0.01
[5, 10) years	3947	132	12,765	5.62 [4.65, 6.79]	1.23 [1.02, 1.48]	0.03
[10, 15) years	2916	106	9610	4.99 [4.04, 6.16]	1.08 [0.88, 1.33]	0.48
[15, 25) years	4857	238	16,625	5.28 [4.50, 6.20]	1.15 [0.99, 1.34]	0.07
25+ years	4191	260	14,916	4.64 [3.92, 5.49]	0.98 [0.84, 1.15]	0.83
Never Smokers	29,089	895	91,227	4.72 [4.22, 5.28]	1.00	---

<sup>a</sup> Incidence rates and hazard ratios are adjusted for age, sex, education, examination decade, hypertension, diabetes status, body mass index, total cholesterol, and alcohol consumption. Dynamic variables are time-updated.

**eTable 8. Adjusted Risk of Incident CVD Among Heavy Ever and Never Smokers Using 6 Time Points<sup>a</sup>**

Years Since Quitting Category	Person-Exams	Incident CVDs	Person-Years (PY)	Incidence Rate per 1000 PY [95% CI]	Hazard Ratio [95% CI] <sup>b</sup>	p-value
<i>Pooled Cohort – Former vs. Current</i>						
Current Smokers	6917	778	53,222	8.79 [8.00, 9.66]	1.00	---
<5 years	1303	134	9815	4.96 [4.21, 5.85]	0.62 [0.51, 0.75]	<0.001
[5, 10) years	839	116	6616	5.14 [4.32, 6.11]	0.64 [0.52, 0.78]	<0.001
[10, 15) years	641	78	4878	5.21 [4.28, 6.34]	0.58 [0.45, 0.74]	<0.001
[15, 25) years	1065	180	7307	5.52 [4.81, 6.34]	0.63 [0.52, 0.75]	<0.001
25+ years	587	97	3694	4.18 [3.56, 4.90]	0.51 [0.39, 0.66]	<0.001
<i>Pooled Cohort – Former vs. Never</i>						
<5 years	1303	134	9815	4.96 [4.21, 5.85]	1.24 [1.03, 1.51]	0.027
[5, 10) years	839	116	6616	5.14 [4.32, 6.11]	1.24 [1.01, 1.52]	0.035
[10, 15) years	641	78	4878	5.21 [4.28, 6.34]	1.12 [0.86, 1.45]	0.40
[15, 25) years	1065	180	7307	5.52 [4.81, 6.34]	1.24 [1.04, 1.48]	0.014
25+ years	587	97	3694	4.18 [3.56, 4.90]	1.04 [0.82, 1.33]	0.73
Never Smokers	14,188	1180	110,709	4.69 [4.26, 5.16]	1.00	---

a This analysis is limited to never smokers and ever smokers with at least 20 cumulative pack-years.

b Incidence rates and hazard ratios are adjusted for age, sex, education, examination decade, systolic blood pressure, antihypertensive medication use, diabetes status, body mass index, total cholesterol, and alcohol consumption. Dynamic variables are time-updated.

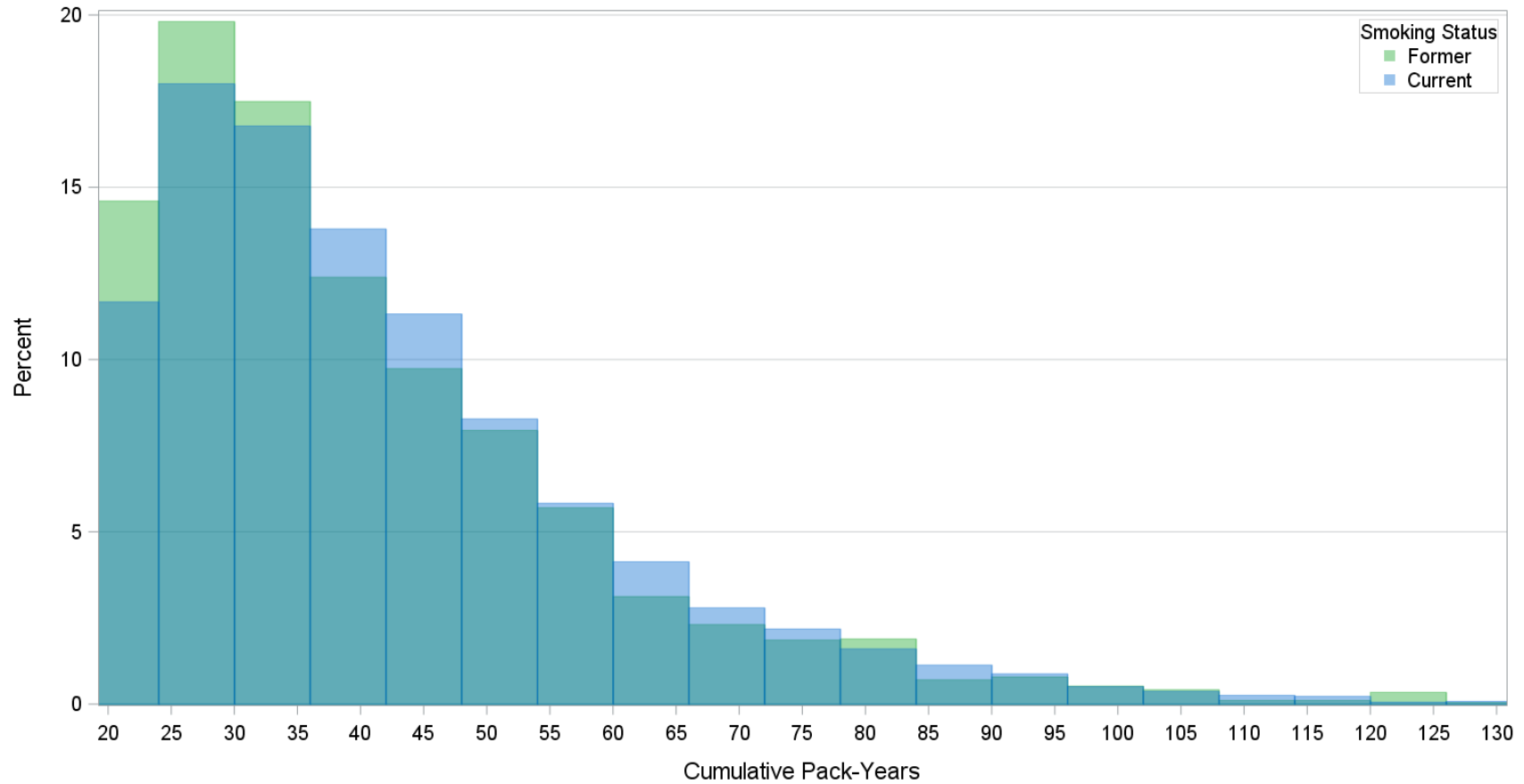
**eTable 9. Adjusted Risk of Incident CVD Among Heavy Ever and Never Smokers Using 2 Time Points<sup>a</sup>**

Years Since Quitting Category	Person-Exams	Incident CVDs	Person-Years (PY)	Incidence Rate per 1000 PY [95% CI]	Hazard Ratio [95% CI] <sup>b</sup>	p-value
<b><i>Pooled Cohort – Former vs. Current</i></b>						
Current Smokers	3416	895	56,012	8.04 [6.80, 9.49]	1.00	---
<5 years	198	30	2695	4.26 [2.62, 6.92]	0.68 [0.41, 1.13]	0.14
[5, 10) years	608	226	11,389	5.54 [3.71, 8.27]	0.63 [0.51, 0.77]	<0.001
[10, 15) years	128	40	2253	5.19 [3.28, 8.20]	0.51 [0.35, 0.76]	<0.001
[15, 25) years	203	66	3859	4.66 [3.43, 6.34]	0.58 [0.43, 0.80]	<0.001
25+ years	33	9	519	4.06 [2.77, 5.95]	0.38 [0.16, 0.91]	0.030
<b><i>Pooled Cohort – Former vs. Never</i></b>						
<5 years	198	30	2695	4.26 [2.62, 6.92]	1.63 [1.01, 2.63]	0.044
[5, 10) years	608	226	11,389	5.54 [3.71, 8.27]	1.21 [0.92, 1.59]	0.18
[10, 15) years	128	40	2253	5.19 [3.28, 8.20]	0.99 [0.62, 1.57]	0.96
[15, 25) years	203	66	3859	4.66 [3.43, 6.34]	1.13 [0.76, 1.67]	0.55
25+ years	33	9	519	4.06 [2.77, 5.95]	0.64 [0.26, 1.60]	0.34
Never Smokers	6072	1211	113,144	4.87 [3.26, 7.26]	1.00	---

a This analysis is limited to never smokers and ever smokers with at least 20 cumulative pack-years.

b Incidence rates and hazard ratios are adjusted for age, sex, education, examination decade, systolic blood pressure, antihypertensive medication use, diabetes status, body mass index, total cholesterol, and alcohol consumption. Dynamic variables are time-updated.

**eFigure. Cumulative Pack-Years Among Current and Former Smokers With  $\geq 20$  Pack-Years**



Overlaid histogram is limited to heavy ever smokers with at least 20 cumulative pack-years. The plot displays the distribution of cumulative pack-years among former smokers in green and among current smokers in blue. The intermediate color (which takes up the majority of the plot) displays the overlap in distribution of cumulative pack-years between these two groups of ever smokers.

## eAppendix. Supplemental Methods

### *Covariate Definitions*

This investigation included age, sex, education, decade of examination to account for temporal trends, hypertension status, diabetes mellitus, body mass index (BMI), total cholesterol, and alcohol consumption as covariates. Education was included as a categorical variable based on self-reported highest level of education completed; categories included: less than high school education, high school graduate or equivalent, or education beyond high school, with high school education or equivalent serving as the referent group. Systolic blood pressure was averaged based on two physician's readings. Receipt of an antihypertensive medication was self-reported. Participants were classified as having diabetes mellitus on the basis of any of the following: fasting blood glucose >126 mg/dL; non-fasting blood glucose > 200 mg/dL; or receipt of medication for the treatment of diabetes mellitus. At each examination, participants' weight was measured in kilograms and height in centimeters. From these values, BMI was calculated. Total cholesterol was directly measured using standardized assays.<sup>1</sup> Blood was drawn from participants at each examination cycle following an overnight fast of at least 10 hours. Biosamples were stored at -20 (pre-1990 exams) to -80 C (post-1990 exams) until they were assayed. Alcohol consumption was based on self-reported consumption of at least one alcoholic beverage per month and from their responses, participants were classified as current, former, or never drinkers.

### *Incidence Rate Estimation*

To estimate adjusted incidence rates, we used a Poisson regression model with an offset term equal to the natural-logarithm of follow-up time. Estimates were generated for the "average" characteristics among participants in each cohort. For continuous variables, the median value was used. For categorical variables, dummy variables were created and the proportion of individuals falling into each category (except the referent) was used to estimate incidence rates (similar to the calculation of least square means in linear regression). Since each row in our dataset corresponded to a single person-exam, we were able to account for changing covariate values over time, making these incidence rates "time-updated."

### *Incidence Rate Difference*

The primary models for statistical inference are the proportional hazards regression models. The Poisson regression models are used to provide descriptive statistics on an absolute scale. To maintain consistency with the primary analysis model, approximate adjusted incident rate differences (IRD) were anchored on the base rate for the reference group estimated by the Poisson regression and calculated using the respective hazard ratio from the primary analysis model, i.e. base rate  $\times$  (hazard ratio - 1). The 95% confidence bounds were derived from the bounds for the hazard ratio. These may be interpreted as an estimate of the incident rate difference that would be observed in a cohort consisting of patients with "average" characteristics, which were used in the calculation of the base rate.

### *Choice of Polynomial Terms on Continuous Variables*

Many of the continuous covariates in our models may not have a linear association with CVD risk and we sought to incorporate such non-linearity. We started with second-order polynomials on all continuous covariates and added up to 4th order terms so long as the higher order terms were statistically significant. We performed a sensitivity analysis with all covariates as linear and observed very similar results (eTable 5).

## eReference

1. Cobain MR, Pencina MJ, D'Agostino RB, Vasan RS. Lifetime risk for developing dyslipidemia: the Framingham Offspring Study. *Am J Med.* 2007;120(7):623-630.