Role of Smoking and Cholesterol in CVD, CHD, and Stroke in the Framingham Heart Study

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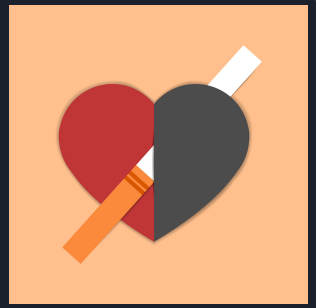
Introduction

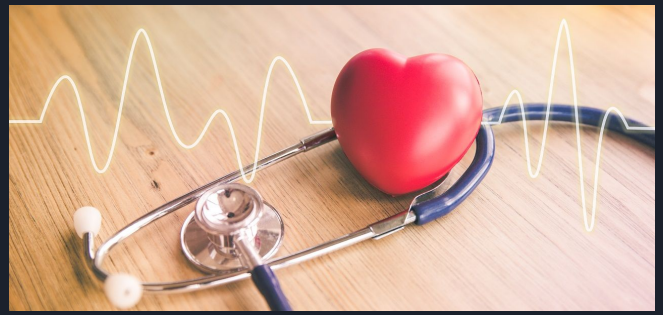
- Goal: study association between smoking, cholesterol, and heart disease

- Framingham Heart Study
  - longitudinal prospective cohort study on etiology of cardiovascular disease
  - free-living subjects in Framingham, MA
  - established in 1948
  - now contains data on 3 generations of participants

- Literature Review
  - CDC states smoking causes almost 1 in 4 deaths from cardiovascular disease
  - high cholesterol levels increases risk for heart disease
  - Age, sex, family history of heart disease, obesity, diabetes, unhealthy diet, clinical depression also contribute to heart disease



Dataset



- 4,434 unique participants between 32-70 years old

- 3 follow-up periods
  - only baseline data from first exam was used

- Outcomes of interest: Incidence and Time To
  - cardiovascular disease (CVD) (includes CHD & stroke)
  - coronary heart disease (CHD)
  - stroke

Explanatory Variables

- Quantitative Variables
  - age
  - systolic blood pressure (mmHg)
  - diastolic blood pressure (mmHg)
  - number of cigarettes smoked per day
  - serum total cholesterol (mg/dL)
  - high-density lipoprotein cholesterol (mg/dL),
  - low-density lipoprotein cholesterol (mg/dL)
  - BMI (kg/m^2)
  - serum glucose (mg/dL)
  - heart rate (beats per minute)
- Binary Yes/No Variables
  - use of antihypertensive medication
  - current smoker
  - diabetes (serum glucose of over 200 mg/dL)
- Categorical Variables
  - cigarette category
    - 0 cigarettes
    - 1-10 cigarettes
    - 11-20 cigarettes
    - 21+ cigarettes
  - sex
    - Male
    - Female
  - cholesterol category
    - <200 mg/dL
    - 200-219 mg/dL
    - 220-259 mg/dL
    - 260+ mg/dL

Descriptive Characteristics

Table 1: Baseline Characteristics of the Framingham Dataset

	Male n=1,944 43.84%	**Female** n=2,490 56.16%	**Total** (n=4,434)	**p-value**
Age (mean, SD)	49.79 (8.72)	50.03 (8.64)	49.93 (8.68)	0.3450
Systolic BP (mean, SD)	131.74 (19.44)	133.82 (24.46)	132.91 (22.42)	0.0016
Diastolic BP (mean, SD)	83.71 (11.44)	82.60 (12.50)	83.08 (12.06)	0.0020
Use of BP Meds (n,%)				
No BP Meds	1,880 (97.81%)	2,349 (95.84%)	4,229 (96.71%)	0.0003
BP Meds	42 (2.19%)	102 (4.16%)	144 (3.29%)	
Heart Rate (mean, SD)	74.40 (11.90)	77.06 (12.15)	75.89 (12.11)	<0.0001
Total Cholesterol (mean, SD)	233.58 (42.36)	239.68 (46.22)	236.98 (44.65)	<0.0001
Cholesterol Category (n,%)				
<200	392 (20.16%)	530 (21.29%)	922 (20.79%)	<0.001
200 - 219	364 (18.72%)	369 (14.82%)	733 (16.53%)	
220 - 259	710 (36.52%)	817 (32.81%)	1,527 (34.44%)	
260+	478 (24.59%)	774 (31.08%)	1,252 (28.24%)	

Descriptive Characteristics (cont.)

	Male n=1,944 43.84%	**Female** n=2,490 56.16%	**Total** (n=4,434)	**p-value**
Smoking Status (n,%)				
Not Smokers	769 (39.56%)	1483 (59.56%)	4,229 (96.71%)	<0.0001
Smokers	1,175 (60.44%)	1006 (40.40%)	144 (3.29%)	
Cigarettes Per Day (mean, SD)	13.23 (13.78)	5.65 (8.96)	8.97 (11.93)	<0.0001
Cigarette Category (n, %)				
0 Cigarettes	769 (39.89%)	1,484 (59.98%)	2,253 (51.18%)	<0.0001
1-10 Cigarettes	195 (10.11%)	460 (18.59%)	655 (14.88%)	
11-20 Cigarettes	583 (30.24%)	433 (17.50%)	1016 (23.08%)	
21+ Cigarettes	381 (19.76%)	97 (3.92%)	478 (10.86%)	
BMI (mean, SD)	26.17 (3.41)	25.59 (4.56)	25.85 (4.10)	<0.0001
Serum Glucose (mean, SD)	82.32 (24.72)	82.07 (24.14)	82.19 (24.40)	0.7468
Diabetes (n,%)				
No Diabetes	1,885 (96.97%)	2,428 (97.51%)	4,313 (97.27%)	0.269
Diabetes	59 (3.03%)	62 (2.49%)	121 (2.73%)	

Descriptive Characteristics (cont.)

	Male n=1,944 43.84%	**Female** n=2,490 56.16%	**Total** (n=4,434)	**p-value**
Cardiovascular Disease (n,%)				
No CVD	1,258 (64.71%)	2,019 (81.08%)	3,277 (73.91%)	<0.0001
CVD	686 (35.29%)	471 (18.92%)	1,157 (26.09%)	
Coronary Heart Disease (n,%)				
No CHD	1,234 (63.48%)	1,960 (78.71%)	3,194 (72.03%)	<0.0001
CHD	710 (36.52%)	530 (21.29%)	1,240 (27.97%)	
Stroke (n,%)				
No Stroke	1,751 (90.07%)	2,268 (91.08%)	4,019 (90.64%)	0.2508
Stroke	193 (9.93%)	222 (8.92%)	415 (9.36%)	
Days to CVD (mean, SD)	6,273.70 (3,015.18)	7242.86 (2,549.01)	6,817.95 (2,804.32)	<0.0001
Days to CHD (mean, SD)	6,155.88 (3,066.85)	7064.61 (2,656.32)	6,666.20 (2,878.82)	<0.0001
Days to Stroke (mean, SD)	7,003.43 (2,509.10)	7539.78 (2,262.43)	7,304.63 (2,388.34)	<0.0001

Methods

- Cox proportional hazards models used to model survival time to CVD, CHD, and stroke
- zph tests using Schoenfeld residuals used to check proportional hazards assumption
- model fit determined using Schwarz Information Criterion (SBC)

- Previous studies adjusted for
  1) age
  2) sex
  3) total cholesterol
  4) SBP
  5) BMI
  6) BP Meds
  7) smoking
  8) diabetes
  9) HDL
- LDL and HDL not provided in first exam, so the other 8 covariates were added to the model

Model Selection - Step 1

cholesterol and smoking as continuous or categorical variables

Model	Covariates	SBC Values		
		CVD	CHD	Stroke
A1	Cholesterol Category, Smoking Status, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17614.792	19070.508	6240.337
A2	Total Cholesterol, Smoking Status, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17395.850	18798.445	6171.734
A3	Cholesterol Category, Cigarettes, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17438.741	18884.722	6198.189
A4	Total Cholesterol, Cigarettes, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17218.240	18611.223	6129.658
A5	Cholesterol Category, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17432.678	18883.124	6196.626
A6	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17221.371	18623.770	6129.222

Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17221.371	18623.770	6129.222

Model Selection - Step 2

include all covariates SBP, BP meds, diabetes, BMI

Model	Covariates	SBC Values		
		CVD	CHD	Stroke
B1	Total Cholesterol, Cigarette Category, Sex, Age, SBP, Diabetes, BMI	17561.616	19022.870	6239.411
B2	Total Cholesterol, Cigarette Category, Sex, Age, BP_Meds, Diabetes, BMI	17323.587	18683.627	6189.006
B3	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, BMI	17248.935	18636.664	6138.645
B4	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes	17323.721	18720.604	6174.435
B5	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds	17354.297	18736.694	6184.307
B6	Total Cholesterol, Cigarette Category, Sex, Age, SBP	17692.309	19135.546	6292.885
B7	Total Cholesterol, Cigarette Category, Sex, Age, BP_Meds	17498.227	18832.719	6259.920
B8	Total Cholesterol, Cigarette Category, Sex, Age, Diabetes, BMI	17686.540	19099.878	6321.740
B9	Total Cholesterol, Cigarette Category, Sex, Age, Diabetes	17823.262	19230.967	6382.562
B10	Total Cholesterol, Cigarette Category, Sex, Age, BMI	17719.230	19117.457	6331.885
B11	Total Cholesterol, Cigarette Category, Sex, Age	17865.377	19256.106	6396.214

Model Selection - Step 3

logarithmically transformed continuous variables

Model	Covariates	SBC Values		
		CVD	CHD	Stroke
C	Log Total Cholesterol, Cigarette Category, Sex, Log Age, Log SBP, BP_Meds, Diabetes, Log BMI	17222.656	18624.123	6127.548

Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17221.371	18623.770	6129.222

Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17221.371	18623.770	6129.222

Model Selection - Step 4

interaction terms with age and sex

Model	Covariates	SBC Values		
		CVD	CHD	Stroke
D1	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, total_chol*age	17218.851	18623.479	6132.931
D2	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, total_chol*sex	17227.769	18630.692	6131.973
D3	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, cigarette_cat*age	17234.640	18641.426	6140.327
D4	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, cigarette_cat*sex	17239.428	18644.196	6145.981
D5	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, sbp*age	17227.997	18630.819	6134.558
D6	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, sbp*sex	17228.365	18630.168	6135.025
D7	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, diabetes*age	17225.991	18627.899	6132.961
D8	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, diabetes*sex	17227.538	18630.565	6134.421
D9	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, bmi*age	17227.970	18628.161	6135.194
D10	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, bmi*sex	17228.303	18630.830	6135.090
D11	Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI, total_chol*cigarette_cat	17240.466	18644.435	6150.721

Model Selection - Step 5

sex-stratified analysis

Variable	Males	Hazard Ratio	95% Confidence Interval	Females	Hazard Ratio	95% Confidence Interval
Total Cholesterol	CVD	1.003	1.002-1.005	CVD	1.002	1.000-1.005
1-10 Cigarettes		1.185	0.908-1.545		1.252	0.966-1.621
11-20 Cigarettes		1.375	1.137-1.663		1.833	1.422-2.363
21+ Cigarettes		1.361	1.090-1.698		1.386	0.789-2.436
Total Cholesterol	CHD	1.004	1.003-1.006	CHD	1.005	1.003-1.007
1-10 Cigarettes		1.105	0.849-1.438		1.049	0.818-1.344
11-20 Cigarettes		1.246	1.032-1.504		1.204	0.933-1.555
21+ Cigarettes		1.353	1.094-1.673		1.044	0.607-1.794
Total Cholesterol	Stroke	1.001	0.997-1.004	Stroke	0.996	0.996-1.000
1-10 Cigarettes		1.144	0.697-1.877		1.271	0.863-1.873
11-20 Cigarettes		1.725	1.226-2.426		2.104	1.463-3.024
21+ Cigarettes		1.150	0.728-1.815		1.202	0.488-2.962

Final Cox Proportional Hazards Model

- Total Cholesterol
- Cigarette Category — reference = 0 cigarettes
  - 0 cigarettes
  - 1-10 cigarettes
  - 11-20 cigarettes
  - 21+ cigarettes
- Sex — reference = females
- Age
- SBP
- BP Meds — reference = no BP Meds
- Diabetes — reference = no diabetes
- BMI

Covariates	SBC Values		
	CVD	CHD	Stroke
Total Cholesterol, Cigarette Category, Sex, Age, SBP, BP_Meds, Diabetes, BMI	17221.371	18623.770	6129.222

If statistical modeling is an art, then this is our masterpiece.

CVD Analysis

Proportional hazard regression coefficients for CVD

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	0.00306	1.003	1.002-1.004	0.0907	<0.0001
1-10 Cigarettes	0.19715	1.218	1.013-1.465	0.0737	0.0363
11-20 Cigarettes	0.41644	1.517	1.302-1.766	0.8954	<.0001
21+ Cigarettes	0.34842	1.417	1.159-1.728	0.4318	0.0007
Sex (Male)	0.88603	2.425	2.128-2.765	0.1703	<0.0001
Age	0.05847	1.060	1.052-1.069	0.0543	<0.0001
Systolic Blood Pressure	0.01533	1.015	1.013-1.018	0.5499	<0.0001
BP Meds	0.36172	1.436	1.103-1.868	0.1807	0.0071
Diabetes	0.82074	2.272	1.777-2.906	0.0513	<0.0001
BMI	0.02754	1.028	1.013-1.043	0.8981	0.0003

- For each 1 unit increase in mg/dL of total cholesterol, hazard of CVD increased 1.003 times
- Compared to nonsmokers, hazard of CVD increased
  - 1.218 times for 1-10 cigarettes
  - 1.517 times for 11-20 cigarettes
  - 1.417 times for 21+ cigarettes
- Males had 2.425 times the hazard of CVD compared to females
- For each additional year older a subject was, hazard of CVD increased 1.060 times
- For each 1 unit increase in mmHg of SBP, hazard of CVD increased 1.015 times
- People taking BP meds had 1.436 times the hazard of CVD compared to those not taking BP meds
- Subjects with diabetes had 2.272 times the hazard of CVD compared to those without diabetes
- For each 1 unit increase in kg/m^2 of BMI, hazard of CVD increased 1.028 times

CHD Analysis

Proportional hazard regression coefficients for CHD

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	0.00424	1.004	1.003-1.005	0.9061	<.0001
1-10 Cigarettes	0.07421	1.077	0.900-1.289	0.3348	0.4184
11-20 Cigarettes	0.20775	1.231	1.060-1.430	0.0772	0.0065
21+ Cigarettes	0.26895	1.309	1.081-1.584	0.1531	0.0058
Sex (Male)	0.77762	2.176	1.922-2.464	0.1452	<0.0001
Age	0.04513	1.046	1.038-1.054	<0.0001	<0.0001
Systolic Blood Pressure	0.01177	1.012	1.009-1.015	0.4850	<0.0001
BP Meds	0.35662	1.428	1.105-1.846	0.4430	0.0065
Diabetes	0.64325	1.903	1.469-2.464	0.0547	<0.0001
BMI	0.03603	1.037	1.022-1.052	0.7864	<0.0001

- For each 1 unit increase in mg/dL of total cholesterol, hazard of CHD increased 1.004 times
- Compared to nonsmokers, hazard of CHD increased
  - 1.077 times for 1-10 cigarettes
  - 1.231 times for 11-20 cigarettes
  - 1.309 times for 21+ cigarettes
- Males had 2.176 times the hazard of CHD compared to females
- For each additional year older a subject was, hazard of CHD increased 1.012 times
- For each 1 unit increase in mmHg of SBP, hazard of CHD increased 1.012 times
- People taking BP meds had 1.428 times the hazard of CHD compared to those not taking BP meds
- Subjects with diabetes had 1.903 times the hazard of CHD compared to those without diabetes
- For each 1 unit increase in kg/m^2 of BMI, hazard of CHD increased 1.037 times

Stroke Analysis

Proportional hazard regression coefficients for Stroke

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	-0.00213	0.998	0.996-1.000	0.5234	0.0764
1-10 Cigarettes	0.21597	1.241	0.915-1.683	0.2316	0.1646
11-20 Cigarettes	0.62455	1.867	1.456-2.396	0.7705	<0.0001
21+ Cigarettes	0.19017	1.209	0.812-1.800	0.5039	0.3489
Sex (Male)	0.37031	1.448	1.166-1.799	0.5493	0.0008
Age	0.08563	1.089	1.075-1.104	0.0202	<0.0001
Systolic Blood Pressure	0.01889	1.019	1.015-1.024	0.0870	<0.0001
BP Meds	0.72410	2.063	1.448-2.938	0.3536	<0.0001
Diabetes	0.88064	2.412	1.629-3.572	0.5560	<0.0001
BMI	0.01663	1.017	0.993-1.041	0.3227	0.1626

- For each 1 unit increase in mg/dL of total cholesterol, hazard of stroke decreased by a factor of 0.998
- Compared to nonsmokers, hazard of stroke increased
  - 1.241 times for 1-10 cigarettes
  - 1.867 times for 11-20 cigarettes
  - 1.209 times for 21+ cigarettes
- Males had 1.448 times the hazard of stroke compared to females
- For each additional year older a subject was, hazard of stroke increased 1.089 times
- For each 1 unit increase in mmHg of SBP, hazard of stroke increased 1.019 times
- People taking BP meds had 2.063 times the hazard of stroke compared to those not taking BP meds
- Subjects with diabetes had 2.412 times the hazard of stroke compared to those without diabetes
- For each 1 unit increase in kg/m^2 of BMI, hazard of stroke increased 1.017 times

Checking Collinearity

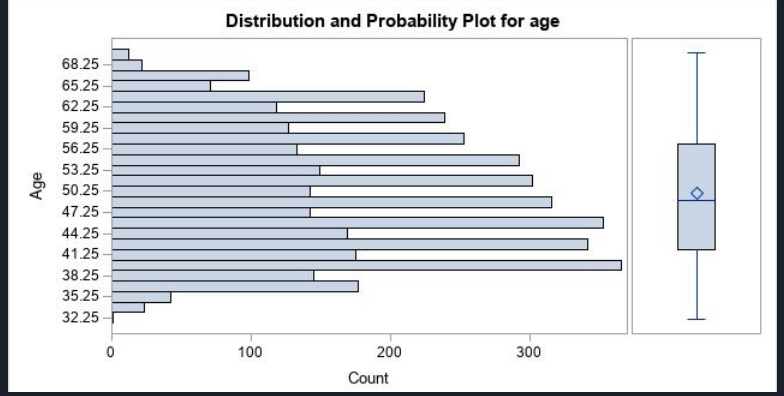
Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	total_chol	cigarette_cat	sex	age	sbp	bp_meds	diabetes	bmi
total_chol **Serum Total Cholesterol**	1.00000 4382	-0.03891 0.0103 4350	0.06787 <.0001 4382	0.24931 <.0001 4382	0.19996 <.0001 4382	0.08158 <.0001 4322	0.04165 0.0058 4382	0.12268 <.0001 4364
cigarette_cat **Cigarettes Per Day Category**	-0.03891 0.0103 4350	1.00000 4402	-0.29556 <.0001 4402	-0.20976 <.0001 4402	-0.11421 <.0001 4402	-0.05608 0.0002 4342	-0.04269 0.0046 4402	-0.13231 <.0001 4383
sex **Sex**	0.06787 <.0001 4382	-0.29556 <.0001 4402	1.00000 4434	0.01418 0.3450 4434	0.04615 0.0021 4434	0.05497 0.0003 4373	-0.01660 0.2691 4434	-0.06978 <.0001 4415
age **Age**	0.24931 <.0001 4382	-0.20976 <.0001 4402	0.01418 0.3450 4434	1.00000 4434	0.39849 <.0001 4434	0.13506 <.0001 4373	0.10626 <.0001 4434	0.13421 <.0001 4415
sbp **Systolic Blood Pressure**	0.19996 <.0001 4382	-0.11421 <.0001 4402	0.04615 0.0021 4434	0.39849 <.0001 4434	1.00000 4434	0.26607 <.0001 4373	0.11519 <.0001 4434	0.32809 <.0001 4415
bp_meds **Use of BP Meds**	0.08158 <.0001 4322	-0.05608 0.0002 4342	0.05497 0.0003 4373	0.13506 <.0001 4373	0.26607 <.0001 4373	1.00000 4373	0.04045 0.0075 4373	0.09848 <.0001 4354
diabetes **Diabetes**	0.04165 0.0058 4382	-0.04269 0.0046 4402	-0.01660 0.2691 4434	0.10626 <.0001 4434	0.11519 <.0001 4434	0.04045 0.0075 4373	1.00000 4434	0.08778 <.0001 4415
bmi **BMI**	0.12268 <.0001 4364	-0.13231 <.0001 4383	-0.06978 <.0001 4415	0.13421 <.0001 4415	0.32809 <.0001 4415	0.09848 <.0001 4354	0.08778 <.0001 4415	1.00000 4415

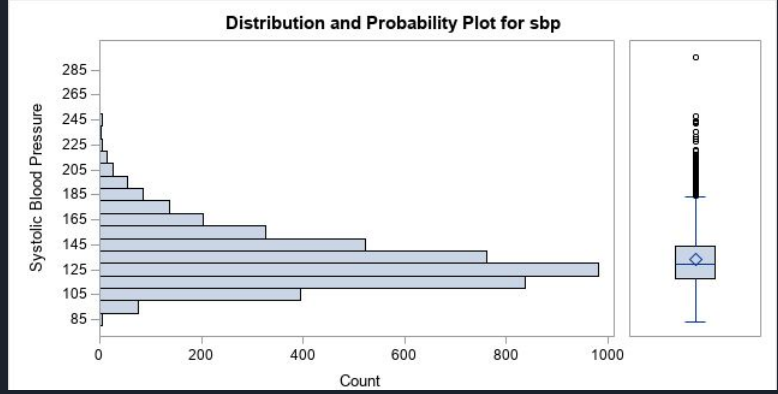
Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	total_chol	cigarette_cat	sex	age	sbp	bp_meds	diabetes	bmi
total_chol **Serum Total Cholesterol**	1.00000 4382	-0.04571 0.0026 4350	0.06327 <.0001 4382	0.27395 <.0001 4382	0.21732 <.0001 4382	0.07970 <.0001 4322	0.03208 0.0337 4382	0.15082 <.0001 4364
cigarette_cat **Cigarettes Per Day Category**	-0.04571 0.0026 4350	1.00000 4402	-0.27513 <.0001 4402	-0.21428 <.0001 4402	-0.11879 <.0001 4402	-0.05606 0.0002 4342	-0.04487 0.0029 4402	-0.14807 <.0001 4383
sex **Sex**	0.06327 <.0001 4382	-0.27513 <.0001 4402	1.00000 4434	0.01605 0.2852 4434	0.01195 0.4263 4434	0.05497 0.0003 4373	-0.01660 0.2691 4434	-0.13049 <.0001 4415
age **Age**	0.27395 <.0001 4382	-0.21428 <.0001 4402	0.01605 0.2852 4434	1.00000 4434	0.39597 <.0001 4434	0.13084 <.0001 4373	0.10594 <.0001 4434	0.14478 <.0001 4415
sbp **Systolic Blood Pressure**	0.21732 <.0001 4382	-0.11879 <.0001 4402	0.01195 0.4263 4434	0.39597 <.0001 4434	1.00000 4434	0.21180 <.0001 4373	0.09447 <.0001 4434	0.32403 <.0001 4415
bp_meds **Use of BP Meds**	0.07970 <.0001 4322	-0.05606 0.0002 4342	0.05497 0.0003 4373	0.13084 <.0001 4373	0.21180 <.0001 4373	1.00000 4373	0.04045 0.0075 4373	0.08660 <.0001 4354
diabetes **Diabetes**	0.03208 0.0337 4382	-0.04487 0.0029 4402	-0.01660 0.2691 4434	0.10594 <.0001 4434	0.09447 <.0001 4434	0.04045 0.0075 4373	1.00000 4434	0.07501 <.0001 4415
bmi **BMI**	0.15082 <.0001 4364	-0.14807 <.0001 4383	-0.13049 <.0001 4415	0.14478 <.0001 4415	0.32403 <.0001 4415	0.08660 <.0001 4354	0.07501 <.0001 4415	1.00000 4415

Outliers



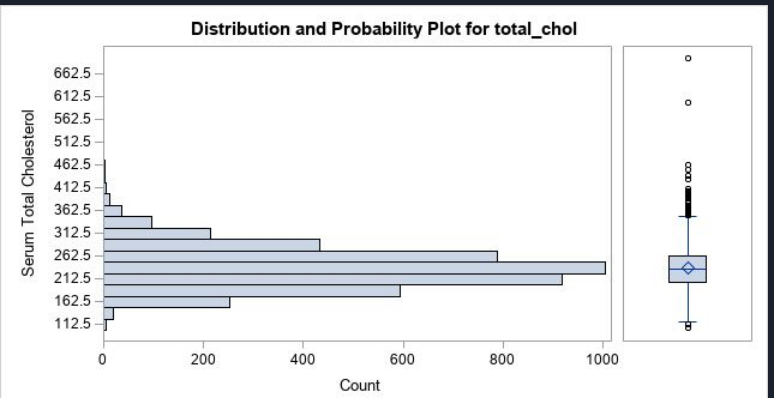
0 outliers



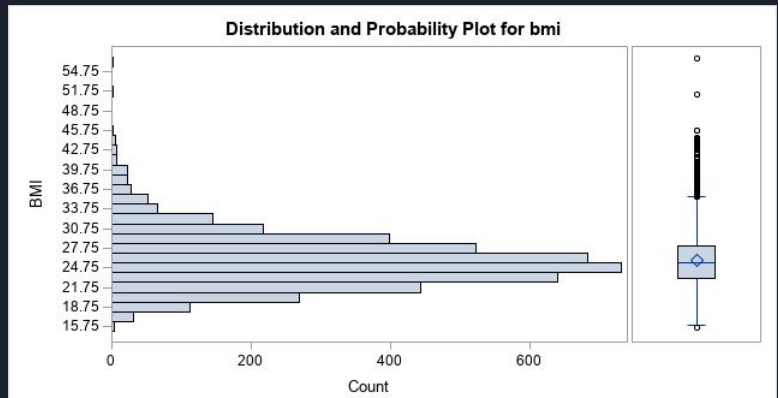
150 outliers
threshold of 183.75 mmHg

- large sample size of 4,434
- <3% observations being outliers won't impact distribution meaningfully

115 outliers
threshold of 331 mg/dL



1 outlier below threshold of 15.59 kg/m^2
103 outliers above threshold of 35.59 kg/m^2



CVD Discussion

Proportional hazard regression coefficients for CVD

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	0.00306	1.003	1.002-1.004	0.0907	<0.0001
1-10 Cigarettes	0.19715	1.218	1.013-1.465	0.0737	0.0363
11-20 Cigarettes	0.41644	1.517	1.302-1.766	0.8954	<.0001
21+ Cigarettes	0.34842	1.417	1.159-1.728	0.4318	0.0007
Sex (Male)	0.88603	2.425	2.128-2.765	0.1703	<0.0001
Age	0.05847	1.060	1.052-1.069	0.0543	<0.0001
Systolic Blood Pressure	0.01533	1.015	1.013-1.018	0.5499	<0.0001
BP Meds	0.36172	1.436	1.103-1.868	0.1807	0.0071
Diabetes	0.82074	2.272	1.777-2.906	0.0513	<0.0001
BMI	0.02754	1.028	1.013-1.043	0.8981	0.0003

- All variables significantly associated with time to CVD
- No violation of proportional hazards assumption
- Estimated hazard ratio for 21+ cigarettes smaller than for 11-20 cigarettes
- 95% confidence intervals overlap, so no significant difference for hazard of CHD

CHD Discussion

Proportional hazard regression coefficients for CHD

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	0.00424	1.004	1.003-1.005	0.9061	<.0001
1-10 Cigarettes	0.07421	1.077	0.900-1.289	0.3348	0.4184
11-20 Cigarettes	0.20775	1.231	1.060-1.430	0.0772	0.0065
21+ Cigarettes	0.26895	1.309	1.081-1.584	0.1531	0.0058
Sex (Male)	0.77762	2.176	1.922-2.464	0.1452	<0.0001
Age	0.04513	1.046	1.038-1.054	<0.0001	<0.0001
Systolic Blood Pressure	0.01177	1.012	1.009-1.015	0.4850	<0.0001
BP Meds	0.35662	1.428	1.105-1.846	0.4430	0.0065
Diabetes	0.64325	1.903	1.469-2.464	0.0547	<0.0001
BMI	0.03603	1.037	1.022-1.052	0.7864	<0.0001

- Smoking 1-10 cigarettes not associated with CHD
- Age violated proportional hazards assumption
- 95% confidence intervals overlap, so no significant difference for hazard of CHD

Stroke Discussion

Proportional hazard regression coefficients for Stroke

Variable	Parameter Estimate	Hazard Ratio	95% Hazard Ratio Confidence Interval	zph test p-value	p-value
Total Cholesterol	-0.00213	0.998	0.996-1.000	0.5234	0.0764
1-10 Cigarettes	0.21597	1.241	0.915-1.683	0.2316	0.1646
11-20 Cigarettes	0.62455	1.867	1.456-2.396	0.7705	<0.0001
21+ Cigarettes	0.19017	1.209	0.812-1.800	0.5039	0.3489
Sex (Male)	0.37031	1.448	1.166-1.799	0.5493	0.0008
Age	0.08563	1.089	1.075-1.104	0.0202	<0.0001
Systolic Blood Pressure	0.01889	1.019	1.015-1.024	0.0870	<0.0001
BP Meds	0.72410	2.063	1.448-2.938	0.3536	<0.0001
Diabetes	0.88064	2.412	1.629-3.572	0.5560	<0.0001
BMI	0.01663	1.017	0.993-1.041	0.3227	0.1626

- Total cholesterol and smoking 1-10 cigarettes and 21+ cigarettes were not associated with time to stroke
- Age violated proportional hazards assumption
- Estimated hazard ratio for 21+ cigarettes smaller than for 11-20 cigarettes
- 95% confidence intervals overlap, so no significant difference for hazard of CHD

Discussion

- age violated proportional hazards assumption in CHD and stroke model
  - violation most likely didn't make a large difference in main parameter estimates
    - large sample size of 4,273 observations
    - age wasn't explanatory variable of interest
  - stratifying age into categories still violated proportional hazards assumption
  - age range 32-70, so study population skewed towards older ages

- not having HDL data to adjust for may decrease accuracy of models
- including physical activity levels and eating habits may provide more information

Conclusion

- CVD
  - hazard increased 1.003 times for every increase in mg/dL
  - hazard increased 1.218 times for those who smoked 1-10 cigarettes a day
  - hazard increased 1.517 times for those who smoked 11-20 cigarettes a day
  - hazard increased 1.417 times for those who smoked 21+ cigarettes a day
- CHD
  - hazard increased 1.004 times for every increase in mg/dL
  - hazard increased 1.213 times for those who smoked 11-20 cigarettes a day
  - hazard increased 1.309 times for those who smoked 21+ cigarettes a day
- Stroke
  - hazard increased 1.867 times for those who smoked 11-20 cigarettes a day
- CVD, CHD, and stroke all significantly associated with **sex**, **age**, **SBP**, **BP meds**, and **diabetes**
  - males had >2x hazard for CVD and CHD, almost 50% increase in hazard for stroke
  - hazard increased for each year of age and mmHg of SBP
  - subjects taking BP meds had almost 50% in hazard for CVD and CHD, >2x hazard for stroke
  - diabetes had >2x hazard for CVD and stroke, almost 2x hazard for CHD
    - matches 2014 National Diabetes Statistics Report "Adults with diabetes are nearly twice as likely to die from heart disease or stroke as people without diabetes."

➢ A male who is a smoker with diabetes and high total cholesterol and taking blood pressure medications will have a much higher risk of heart disease.

Questions?