

Table S1. Three-way interaction of sex, smoking status and sleep disordered breathing by clinical cutoffs for risk of incident cardiovascular disease.

<u>Main Effects</u>	Model 1 (n=3852)		Model 2 (n=3852)		Model 3 (n=4214)		Model 4 (n=3852)
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Adjusted [‡]
Sex	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Male Sex	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female Sex	0.55 (0.39-0.80)	0.49 (0.33-0.71)	0.55 (0.38-0.79)	0.45 (0.31-0.66)	0.56 (0.40-0.80)	0.49 (0.34-0.70)	0.46 (0.32-0.68)
Smoking Status							
Non-Smoker	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Former-Smoker	1.10 (0.74-1.63)	0.90 (0.60-1.36)	1.14 (0.77-1.69)	0.90 (0.61-1.34)	1.09 (0.75-1.58)	0.89 (0.60-1.32)	0.85 (0.57-1.28)
Current-Smoker	1.43 (0.86-2.38)	1.51 (0.87-2.60)	1.49 (0.90-2.46)	1.60 (0.97-2.66)	1.33 (0.81-2.20)	1.45 (0.85-2.48)	1.46 (0.85-2.49)
Sleep Disordered Breathing							
No SDB (AHI <5 events/hour)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Mild SDB (AHI 5 to <15 events/hour)	1.17 (0.78-1.75)	1.02 (0.67-1.56)	1.22 (0.81-1.82)	0.98 (0.65-1.47)	1.12 (0.76-1.66)	0.94 (0.63-1.43)	0.91 (0.60-1.38)
Mod-Sev SDB (AHI ≥15 events/hour)	1.35 (0.90-2.02)	0.88 (0.57-1.37)	1.45 (0.97-2.17)	0.91 (0.60-1.36)	1.32 (0.89-1.96)	0.86 (0.56-1.32)	0.79 (0.51-1.21)
Interactions							
Female Sex*Former-Smoker	1.18 (0.70-2.00)	1.45 (0.85-2.47)	1.16 (0.69-1.95)	1.52 (0.90-2.57)	1.16 (0.70-1.92)	1.40 (0.84-2.34)	1.43 (0.84-2.43)
Female Sex*Current-Smoker	0.94 (0.47-1.88)	0.95 (0.46-1.96)	0.93 (0.47-1.86)	0.98 (0.49-1.97)	0.99 (0.50-1.95)	1.06 (0.53-2.15)	1.00 (0.48-2.05)
Female Sex*Mild SDB	1.24 (0.73-2.10)	1.02 (0.60-1.74)	1.21 (0.71-2.06)	1.06 (0.62-1.80)	1.33 (0.80-2.22)	1.11 (0.66-1.87)	1.12 (0.66-1.91)
Female Sex*Mod-Sev SDB	1.03 (0.57-1.87)	0.84 (0.45-1.57)	0.99 (0.55-1.79)	0.84 (0.46-1.53)	1.06 (0.60-1.89)	0.86 (0.47-1.57)	0.94 (0.51-1.73)
Former-Smoker*Mild SDB	1.19 (0.70-2.02)	1.10 (0.64-1.9)	1.13 (0.67-1.91)	1.07 (0.63-1.82)	1.27 (0.76-2.12)	1.19 (0.70-2.02)	1.20 (0.70-2.06)
Former-Smoker*Mod-Sev SDB	1.08 (0.63-1.85)	1.30 (0.74-2.28)	1.03 (0.60-1.76)	1.26 (0.73-2.16)	1.09 (0.65-1.84)	1.33 (0.77-2.29)	1.34 (0.77-2.33)
Current-Smoker*Mild SDB	0.74 (0.32-1.67)	0.94 (0.40-2.20)	0.68 (0.30-1.54)	0.89 (0.39-2.04)	0.80 (0.36-1.79)	0.96 (0.41-2.22)	1.04 (0.44-2.45)
Current-Smoker*Mod-Sev SDB	0.60 (0.23-1.54)	0.71 (0.28-1.84)	0.57 (0.22-1.46)	0.70 (0.27-1.79)	0.71 (0.29-1.73)	0.90 (0.36-2.24)	0.86 (0.33-2.27)
Female Sex*Former-Smoker*Mild SDB	0.85 (0.40-1.82)	0.84 (0.39-1.80)	0.90 (0.42-1.92)	0.85 (0.40-1.82)	0.76 (0.36-1.57)	0.77 (0.37-1.6)	0.85 (0.39-1.82)
Female Sex*Former-Smoker*Mod-SDB	1.13 (0.47-2.74)	1.14 (0.47-2.76)	1.14 (0.48-2.74)	1.08 (0.45-2.60)	1.05 (0.45-2.46)	1.03 (0.44-2.43)	1.21 (0.50-2.94)
Female Sex*Current-Smoker*Mild SDB	1.96 (0.60-6.37)	1.56 (0.43-5.63)	2.20 (0.67-7.20)	2.01 (0.61-6.61)	1.85 (0.60-5.77)	1.45 (0.42-4.98)	1.31 (0.37-4.72)
Female Sex*Current-Smoker*Mod-Sev SDB	3.44 (0.86-13.74)	4.30 (1.08-17.18)	3.66 (0.92-14.49)	4.54 (1.14-18.14)	2.80 (0.77-10.21)	3.40 (0.92-12.52)	3.95 (1.01-15.55)

SDB-Sleep disordered breathing; AHI-Apnea Hypopnea Index; Mod-Sev-Moderate to Severe. HR-Hazard ratio. Significant hazard ratios in **bold**.

All models are three way interactions including main effects, two way, and three way interactions: *Sex + Smoking Status + Sleep Apnea Severity + Sex*Smoking Status + Sex*Sleep Apnea Severity + Smoking Status*Sleep Apnea Severity + Sex*Smoking Status*Sleep Apnea Severity*

Model 1: Primary analysis with Fine-Gray regression accounting for competing risk of death from any other cause with adjusted model adjusted for age, bmi, race, systolic blood pressure, diastolic blood pressure, presence of type 2 diabetes, total cholesterol and high density lipoprotein levels.

Model 2: Sensitivity analysis with Cox proportional hazard regression with adjusted model adjusted for age, bmi, race, systolic blood pressure, diastolic blood pressure, presence of type 2 diabetes, total cholesterol and high density lipoprotein levels.

Model 3: Sensitivity analysis with Fine-Gray regression accounting for competing risk of death from any other cause with adjusted model adjusted for age, bmi, race, systolic blood pressure, diastolic blood pressure, presence of type 2 diabetes, but not lipids. This model includes 362 individuals who were only missing lipid covariate data.

Model 4: Sensitivity analysis with Fine-Gray regression accounting for competing risk of death from any other cause with adjusted model adjusted for age, bmi, race, presence of hypertension defined as SBP ≥140 or DBP ≥90 or use of any antihypertensive, presence of type 2 diabetes, total cholesterol and high density lipoprotein levels.

[‡]Unadjusted model is the same as Model 1.

Table S1. (cont)

Main Effects	Model 5 (n=3851)		Model 6 (n=3,736)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Sex	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Male Sex	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female Sex	0.55 (0.39-0.79)	0.48 (0.33-0.70)	0.54 (0.37-0.78)	0.51 (0.34-0.76)
Smoking Status				
Non-Smoker	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Former-Smoker	1.10 (0.74-1.63)	0.90 (0.59-1.36)	1.1 (0.74-1.62)	0.88 (0.58-1.33)
Current-Smoker	1.43 (0.86-2.38)	1.53 (0.88-2.65)	1.42 (0.86-2.37)	1.41 (0.81-2.45)
Sleep Disordered Breathing				
No SDB (AHI <5 events/hour)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Mild SDB (AHI 5 to <15 events/hour)	1.17 (0.78-1.75)	1.04 (0.68-1.58)	1.19 (0.8-1.78)	1.04 (0.68-1.60)
Mod-Sev SDB (AHI ≥15 events/hour)	1.35 (0.90-2.02)	0.92 (0.59-1.44)	1.35 (0.9-2.03)	0.89 (0.57-1.39)
Interactions				
Female Sex*Former-Smoker	1.18 (0.70-1.99)	1.47 (0.86-2.50)	1.22 (0.72-2.06)	1.44 (0.84-2.47)
Female Sex*Current-Smoker	0.94 (0.47-1.88)	0.96 (0.46-1.98)	1.00 (0.50-2.00)	0.99 (0.47-2.06)
Female Sex*Mild SDB	1.24 (0.73-2.11)	1.03 (0.60-1.77)	1.21 (0.71-2.06)	1.01 (0.59-1.74)
Female Sex*Mod-Sev SDB	1.03 (0.57-1.87)	0.86 (0.46-1.60)	1.06 (0.58-1.93)	0.90 (0.48-1.67)
Former-Smoker*Mild SDB	1.19 (0.70-2.02)	1.11 (0.64-1.91)	1.14 (0.67-1.93)	1.06 (0.61-1.83)
Former-Smoker*Mod-Sev SDB	1.08 (0.63-1.85)	1.31 (0.74-2.30)	1.07 (0.62-1.84)	1.27 (0.72-2.25)
Current-Smoker*Mild SDB	0.74 (0.32-1.68)	0.94 (0.40-2.20)	0.78 (0.34-1.76)	0.99 (0.42-2.36)
Current-Smoker*Mod-Sev SDB	0.60 (0.23-1.55)	0.71 (0.27-1.81)	0.61 (0.24-1.56)	0.71 (0.27-1.83)
Female Sex*Former-Smoker*Mild SDB	0.85 (0.40-1.82)	0.83 (0.38-1.77)	0.89 (0.41-1.92)	0.89 (0.41-1.93)
Female Sex*Former-Smoker*Mod-SDB	1.13 (0.47-2.73)	1.13 (0.46-2.74)	1.03 (0.42-2.50)	1.11 (0.45-2.72)
Female Sex*Current-Smoker*Mild SDB	1.96 (0.60-6.36)	1.52 (0.42-5.50)	1.67 (0.48-5.81)	1.34 (0.34-5.19)
Female Sex*Current-Smoker*Mod-Sev SDB	3.44 (0.86-13.71)	4.17 (1.04-16.74)	3.14 (0.79-12.56)	4.07 (1.02-16.26)

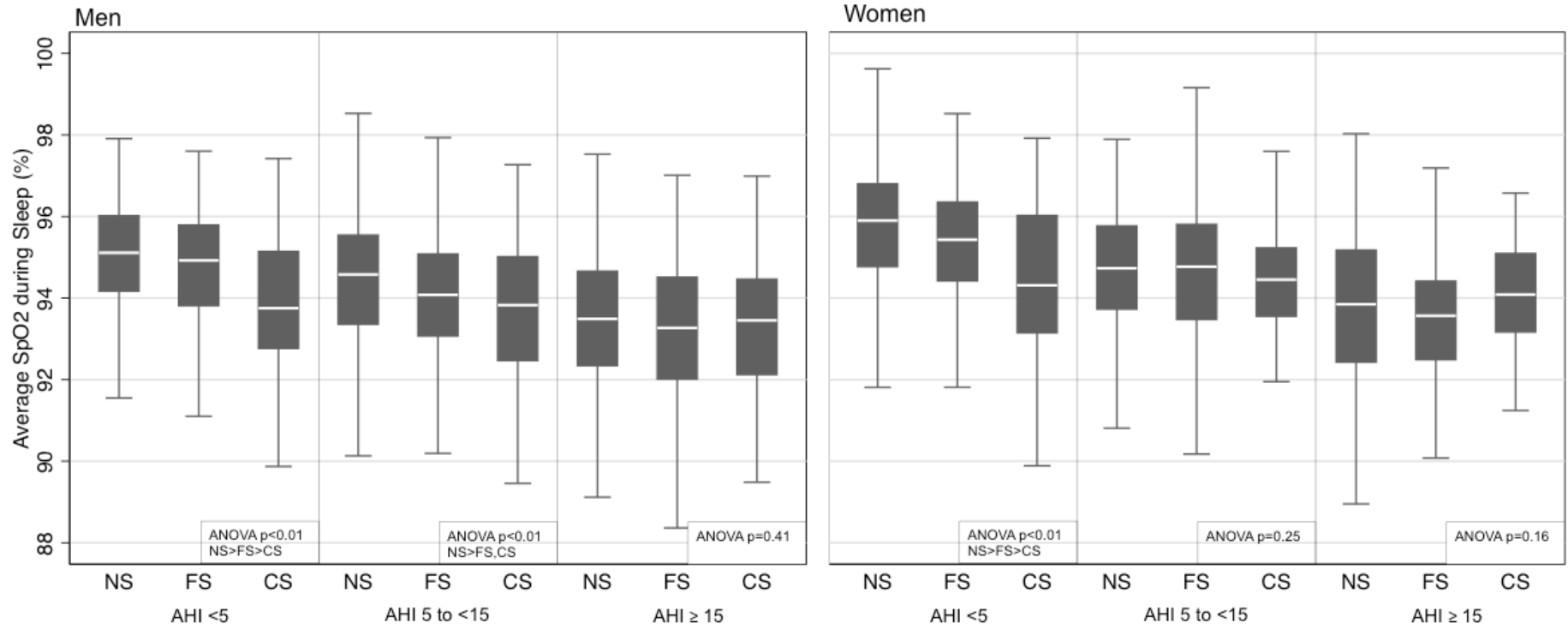
SDB-Sleep disordered breathing; AHI-Apnea Hypopnea Index; Mod-Sev-Moderate to Severe. HR-Hazard ratio. Significant hazard ratios in **bold**.

All models are three way interactions including main effects, two way, and three way interactions: *Sex + Smoking Status + Sleep Apnea Severity + Sex*Smoking Status + Sex*Sleep Apnea Severity + Smoking Status*Sleep Apnea Severity + Sex*Smoking Status*Sleep Apnea Severity*

Model 5: Sensitivity analysis with Fine-Gray regression accounting for competing risk of death from any other cause with adjusted model adjusted for age, bmi, race, systolic blood pressure, diastolic blood pressure, presence of type 2 diabetes, total cholesterol and high density lipoprotein levels, nadir (minimum) oxygen saturation during sleep, and average oxygen saturation during sleep. This model excludes one subject without data regarding minimum oxygen saturation.

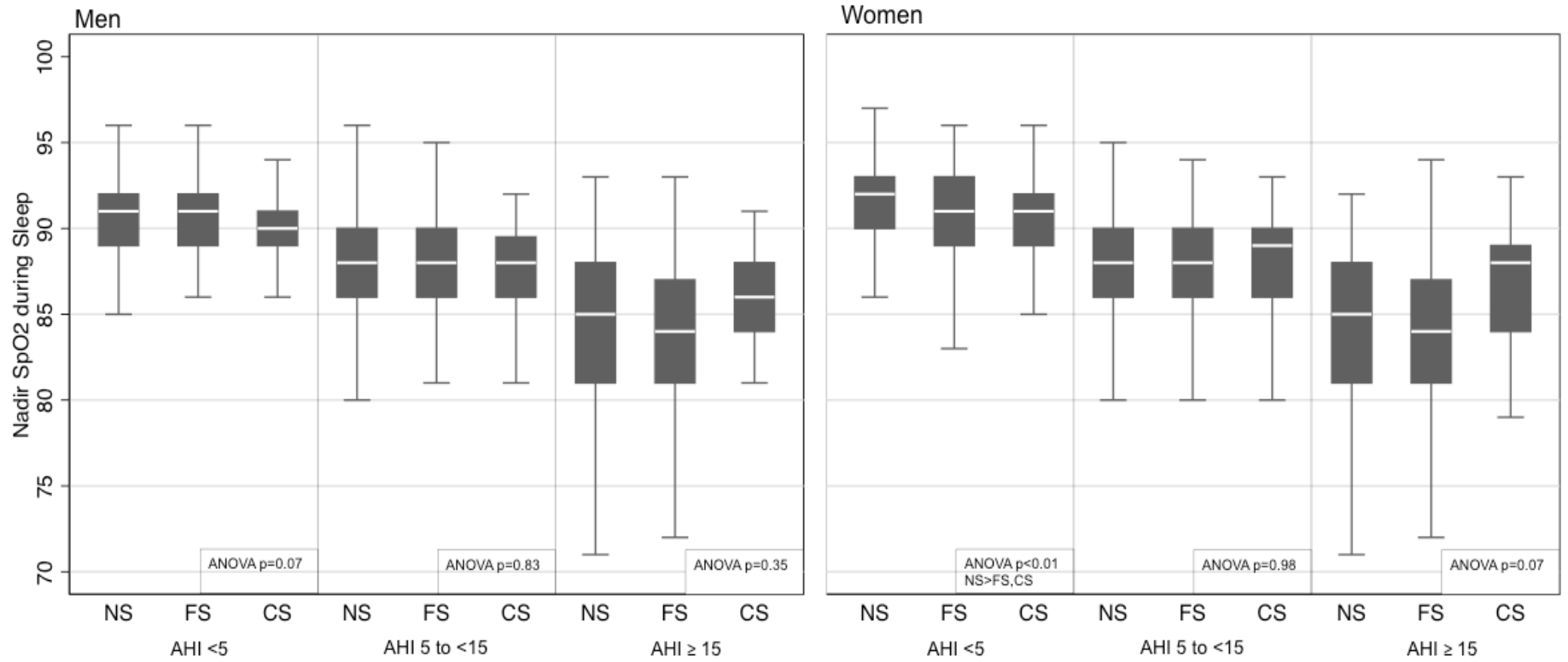
Model 6: Sensitivity analysis with Fine-Gray regression accounting for competing risk of death from any other cause with adjusted model adjusted for age, bmi, race, systolic blood pressure, diastolic blood pressure, presence of type 2 diabetes, total cholesterol and high density lipoprotein levels, and percent predicted forced expiratory volume in 1 second. This model only includes the subset of subjects with spirometry.

Figure S1. Average Oxygen Saturation During Sleep for Men and Women by SDB and Smoking Category



SDB-Sleep Disordered Breathing; SpO2-Oxygen Saturation; NS-Non-smoker; FS-Former Smoker, CS-Current Smoker; AHI-Apnea Hypopnea Index. Box and whisker plots for average oxygen saturation by group are each strata of AHI are presented. Differences between smoking categories compared by ANOVA with post-hoc pairwise t-tests if ANOVA $p < 0.05$.

Figure S2. Nadir Oxygen Saturation During Sleep for Men and Women by SDB and Smoking Category



SDB-Sleep Disordered Breathing; SpO2-Oxygen Saturation; NS-Non-smoker; FS-Former Smoker, CS-Current Smoker; AHI-Apnea Hypopnea Index. Box and whisker plots for nadir oxygen saturation by group are each strata of AHI are presented. Differences between smoking categories compared by ANOVA with post-hoc pairwise t-tests if ANOVA $p < 0.05$.