Table E1: Patient characteristics at entry date to the cohort in the propensity score matched samples

	NRT N=341	**vs.**	**Bupropion** N=341	**NRT** N=3,484	**vs.**	**Varenicline** N=3,484
Age, mean (SD)	52.19 (9.20)		52.18 (9.27)	52.30 (8.55)		52.04 (8.42)
Female sex	154 (45.16)		161 (47.21)	1,807 (51.86)		1,776 (50.97)
MRC‡ score, mean (SD)	2.17 (0.98)		2.21 (0.95)	2.19 (0.96)		2.20 (0.97)
Socio-economic status†, mean (SD)	3.10 (1.35)		3.13 (1.32)	3.23 (1.35)		3.19 (1.37)
Diabetes	16 (4.69)		14 (4.10)	323 (9.27)		299 (8.58)
Peptic ulcer disease	15 (4.39)		23 (6.74)	198 (5.68)		228 (6.54)
Renal disease	11 (3.22)		10 (2.93)	208 (5.97)		203 (5.82)
Rheumatological disease	10 (2.93)		12 (3.51)	189 (5.42)		189 (5.42)
Cancer	27 (7.91)		28 (8.21)	245 (7.03)		259 (7.43)
Alcohol misuse	22 (6.45)		20 (5.86)	263 (7.54)		276 (7.92)
Prior ischaemic heart disease	23 (6.74)		28 (8.21)	419 (12.02)		398 (11.42)
Prior stroke	21 (6.15)		20 (5.86)	180 (5.16)		205 (5.88)
Prior heart failure	1 (0.29)		4 (1.17)	39 (1.11)		55 (1.57)
Prior peripheral vascular disease	4 (1.17)		5 (1.46)	103 (2.95)		103 (2.95)
Prior arrhythmia	13 (3.81)		12 (3.51)	81 (2.32)		99 (2.84)
Prior depression	114 (33.43)		130 (38.12)	1,224 (35.13)		12,09 (34.70)
Prior self-harm	25 (7.33)		31 (9.09)	369 (10.59)		349 (10.01)

Data are presented as N (percentage within drug group) unless stated otherwise. NRT = nicotine replacement therapy. ‡Medical Research Council dyspnoea score: 1 (lowest) to 5 (highest level of dyspnoea). †Townsend Index: 1 (lowest) to 5 (highest level of deprivation).

Table E2: Hazard ratio (95%CI) for ischaemic heart disease during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	1.02 (0.83, 1.24)	1.22 (1, 1.49)	1.43 (1.16, 1.74)	1.63 (1.33, 1.98)	1.84 (1.49, 2.23)	2.04 (1.66, 2.48)	2.24 (1.83, 2.73)	2.45 (1.99, 2.98)	2.65 (2.16, 3.22)	2.86 (2.32, 3.47)	3.06 (2.49, 3.72)
0.1	0.85 (0.69, 1.03)	1.02 (0.83, 1.24)	1.19 (0.97, 1.45)	1.36 (1.11, 1.65)	1.53 (1.25, 1.86)	1.7 (1.38, 2.07)	1.87 (1.52, 2.27)	2.04 (1.66, 2.48)	2.21 (1.8, 2.69)	2.38 (1.94, 2.89)	2.55 (2.08, 3.1)
0.2	0.73 (0.59, 0.89)	0.87 (0.71, 1.06)	1.02 (0.83, 1.24)	1.17 (0.95, 1.42)	1.31 (1.07, 1.59)	1.46 (1.19, 1.77)	1.6 (1.3, 1.95)	1.75 (1.42, 2.13)	1.89 (1.54, 2.3)	2.04 (1.66, 2.48)	2.19 (1.78, 2.66)
0.3	0.64 (0.52, 0.78)	0.77 (0.62, 0.93)	0.89 (0.73, 1.09)	1.02 (0.83, 1.24)	1.15 (0.93, 1.4)	1.28 (1.04, 1.55)	1.4 (1.14, 1.71)	1.53 (1.25, 1.86)	1.66 (1.35, 2.02)	1.79 (1.45, 2.17)	1.91 (1.56, 2.33)
0.4	0.57 (0.46, 0.69)	0.68 (0.55, 0.83)	0.79 (0.65, 0.96)	0.91 (0.74, 1.1)	1.02 (0.83, 1.24)	1.13 (0.92, 1.38)	1.25 (1.01, 1.52)	1.36 (1.11, 1.65)	1.47 (1.2, 1.79)	1.59 (1.29, 1.93)	1.7 (1.38, 2.07)
0.5	0.51 (0.42, 0.62)	0.61 (0.5, 0.74)	0.71 (0.58, 0.87)	0.82 (0.66, 0.99)	0.92 (0.75, 1.12)	1.02 (0.83, 1.24)	1.12 (0.91, 1.36)	1.22 (1, 1.49)	1.33 (1.08, 1.61)	1.43 (1.16, 1.74)	1.53 (1.25, 1.86)
0.6	0.46 (0.38, 0.56)	0.56 (0.45, 0.68)	0.65 (0.53, 0.79)	0.74 (0.6, 0.9)	0.83 (0.68, 1.01)	0.93 (0.75, 1.13)	1.02 (0.83, 1.24)	1.11 (0.91, 1.35)	1.21 (0.98, 1.47)	1.3 (1.06, 1.58)	1.39 (1.13, 1.69)
0.7	0.43 (0.35, 0.52)	0.51 (0.42, 0.62)	0.6 (0.48, 0.72)	0.68 (0.55, 0.83)	0.77 (0.62, 0.93)	0.85 (0.69, 1.03)	0.94 (0.76, 1.14)	1.02 (0.83, 1.24)	1.11 (0.9, 1.34)	1.19 (0.97, 1.45)	1.28 (1.04, 1.55)
0.8	0.39 (0.32, 0.48)	0.47 (0.38, 0.57)	0.55 (0.45, 0.67)	0.63 (0.51, 0.76)	0.71 (0.57, 0.86)	0.78 (0.64, 0.95)	0.86 (0.7, 1.05)	0.94 (0.77, 1.14)	1.02 (0.83, 1.24)	1.1 (0.89, 1.34)	1.18 (0.96, 1.43)
0.9	0.36 (0.3, 0.44)	0.44 (0.36, 0.53)	0.51 (0.42, 0.62)	0.58 (0.47, 0.71)	0.66 (0.53, 0.8)	0.73 (0.59, 0.89)	0.8 (0.65, 0.97)	0.87 (0.71, 1.06)	0.95 (0.77, 1.15)	1.02 (0.83, 1.24)	1.09 (0.89, 1.33)
1.0	0.34 (0.28, 0.41)	0.41 (0.33, 0.5)	0.48 (0.39, 0.58)	0.54 (0.44, 0.66)	0.61 (0.5, 0.74)	0.68 (0.55, 0.83)	0.75 (0.61, 0.91)	0.82 (0.66, 0.99)	0.88 (0.72, 1.07)	0.95 (0.77, 1.16)	1.02 (0.83, 1.24)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E3: Hazard ratio (95%CI) for stroke during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0,0	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0
0,0	0,76 (0,52, 1,11)	0,91 (0,62, 1,33)	1,06 (0,73, 1,55)	1,22 (0,83, 1,78)	1,37 (0,94, 2)	1,52 (1,04, 2,22)	1,67 (1,14, 2,44)	1,82 (1,25, 2,66)	1,98 (1,35, 2,89)	2,13 (1,46, 3,11)	2,28 (1,56, 3,33)
0,1	0,63 (0,43, 0,93)	0,76 (0,52, 1,11)	0,89 (0,61, 1,3)	1,01 (0,69, 1,48)	1,14 (0,78, 1,67)	1,27 (0,87, 1,85)	1,39 (0,95, 2,04)	1,52 (1,04, 2,22)	1,65 (1,13, 2,41)	1,77 (1,21, 2,59)	1,9 (1,3, 2,78)
0,2	0,54 (0,37, 0,79)	0,65 (0,45, 0,95)	0,76 (0,52, 1,11)	0,87 (0,59, 1,27)	0,98 (0,67, 1,43)	1,09 (0,74, 1,59)	1,19 (0,82, 1,74)	1,3 (0,89, 1,9)	1,41 (0,97, 2,06)	1,52 (1,04, 2,22)	1,63 (1,11, 2,38)
0,3	0,48 (0,33, 0,69)	0,57 (0,39, 0,83)	0,67 (0,46, 0,97)	0,76 (0,52, 1,11)	0,86 (0,59, 1,25)	0,95 (0,65, 1,39)	1,05 (0,72, 1,53)	1,14 (0,78, 1,67)	1,24 (0,85, 1,8)	1,33 (0,91, 1,94)	1,43 (0,98, 2,08)
0,4	0,42 (0,29, 0,62)	0,51 (0,35, 0,74)	0,59 (0,4, 0,86)	0,68 (0,46, 0,99)	0,76 (0,52, 1,11)	0,84 (0,58, 1,23)	0,93 (0,64, 1,36)	1,01 (0,69, 1,48)	1,1 (0,75, 1,6)	1,18 (0,81, 1,73)	1,27 (0,87, 1,85)
0,5	0,38 (0,26, 0,56)	0,46 (0,31, 0,67)	0,53 (0,36, 0,78)	0,61 (0,42, 0,89)	0,68 (0,47, 1)	0,76 (0,52, 1,11)	0,84 (0,57, 1,22)	0,91 (0,62, 1,33)	0,99 (0,68, 1,44)	1,06 (0,73, 1,55)	1,14 (0,78, 1,67)
0,6	0,35 (0,24, 0,5)	0,41 (0,28, 0,61)	0,48 (0,33, 0,71)	0,55 (0,38, 0,81)	0,62 (0,43, 0,91)	0,69 (0,47, 1,01)	0,76 (0,52, 1,11)	0,83 (0,57, 1,21)	0,9 (0,61, 1,31)	0,97 (0,66, 1,41)	1,04 (0,71, 1,51)
0,7	0,32 (0,22, 0,46)	0,38 (0,26, 0,56)	0,44 (0,3, 0,65)	0,51 (0,35, 0,74)	0,57 (0,39, 0,83)	0,63 (0,43, 0,93)	0,7 (0,48, 1,02)	0,76 (0,52, 1,11)	0,82 (0,56, 1,2)	0,89 (0,61, 1,3)	0,95 (0,65, 1,39)
0,8	0,29 (0,2, 0,43)	0,35 (0,24, 0,51)	0,41 (0,28, 0,6)	0,47 (0,32, 0,68)	0,53 (0,36, 0,77)	0,58 (0,4, 0,85)	0,64 (0,44, 0,94)	0,7 (0,48, 1,02)	0,76 (0,52, 1,11)	0,82 (0,56, 1,2)	0,88 (0,6, 1,28)
0,9	0,27 (0,19, 0,4)	0,33 (0,22, 0,48)	0,38 (0,26, 0,56)	0,43 (0,3, 0,63)	0,49 (0,33, 0,71)	0,54 (0,37, 0,79)	0,6 (0,41, 0,87)	0,65 (0,45, 0,95)	0,71 (0,48, 1,03)	0,76 (0,52, 1,11)	0,81 (0,56, 1,19)
1,0	0,25 (0,17, 0,37)	0,3 (0,21, 0,44)	0,35 (0,24, 0,52)	0,41 (0,28, 0,59)	0,46 (0,31, 0,67)	0,51 (0,35, 0,74)	0,56 (0,38, 0,81)	0,61 (0,42, 0,89)	0,66 (0,45, 0,96)	0,71 (0,49, 1,04)	0,76 (0,52, 1,11)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E4: Hazard ratio (95%CI) for heart failure during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.56 (0.34, 0.92)	0.67 (0.41, 1.1)	0.78 (0.48, 1.29)	0.9 (0.54, 1.47)	1.01 (0.61, 1.66)	1.12 (0.68, 1.84)	1.23 (0.75, 2.02)	1.34 (0.82, 2.21)	1.46 (0.88, 2.39)	1.57 (0.95, 2.58)	1.68 (1.02, 2.76)
0.1	0.47 (0.28, 0.77)	0.56 (0.34, 0.92)	0.65 (0.4, 1.07)	0.75 (0.45, 1.23)	0.84 (0.51, 1.38)	0.93 (0.57, 1.53)	1.03 (0.62, 1.69)	1.12 (0.68, 1.84)	1.21 (0.74, 1.99)	1.31 (0.79, 2.15)	1.4 (0.85, 2.3)
0.2	0.4 (0.24, 0.66)	0.48 (0.29, 0.79)	0.56 (0.34, 0.92)	0.64 (0.39, 1.05)	0.72 (0.44, 1.18)	0.8 (0.49, 1.31)	0.88 (0.53, 1.45)	0.96 (0.58, 1.58)	1.04 (0.63, 1.71)	1.12 (0.68, 1.84)	1.2 (0.73, 1.97)
0.3	0.35 (0.21, 0.58)	0.42 (0.26, 0.69)	0.49 (0.3, 0.81)	0.56 (0.34, 0.92)	0.63 (0.38, 1.04)	0.7 (0.43, 1.15)	0.77 (0.47, 1.27)	0.84 (0.51, 1.38)	0.91 (0.55, 1.5)	0.98 (0.6, 1.61)	1.05 (0.64, 1.73)
0.4	0.31 (0.19, 0.51)	0.37 (0.23, 0.61)	0.44 (0.26, 0.72)	0.5 (0.3, 0.82)	0.56 (0.34, 0.92)	0.62 (0.38, 1.02)	0.68 (0.42, 1.12)	0.75 (0.45, 1.23)	0.81 (0.49, 1.33)	0.87 (0.53, 1.43)	0.93 (0.57, 1.53)
0.5	0.28 (0.17, 0.46)	0.34 (0.2, 0.55)	0.39 (0.24, 0.64)	0.45 (0.27, 0.74)	0.5 (0.31, 0.83)	0.56 (0.34, 0.92)	0.62 (0.37, 1.01)	0.67 (0.41, 1.1)	0.73 (0.44, 1.2)	0.78 (0.48, 1.29)	0.84 (0.51, 1.38)
0.6	0.25 (0.15, 0.42)	0.31 (0.19, 0.5)	0.36 (0.22, 0.59)	0.41 (0.25, 0.67)	0.46 (0.28, 0.75)	0.51 (0.31, 0.84)	0.56 (0.34, 0.92)	0.61 (0.37, 1)	0.66 (0.4, 1.09)	0.71 (0.43, 1.17)	0.76 (0.46, 1.25)
0.7	0.23 (0.14, 0.38)	0.28 (0.17, 0.46)	0.33 (0.2, 0.54)	0.37 (0.23, 0.61)	0.42 (0.26, 0.69)	0.47 (0.28, 0.77)	0.51 (0.31, 0.84)	0.56 (0.34, 0.92)	0.61 (0.37, 1)	0.65 (0.4, 1.07)	0.7 (0.43, 1.15)
0.8	0.22 (0.13, 0.35)	0.26 (0.16, 0.42)	0.3 (0.18, 0.5)	0.34 (0.21, 0.57)	0.39 (0.24, 0.64)	0.43 (0.26, 0.71)	0.47 (0.29, 0.78)	0.52 (0.31, 0.85)	0.56 (0.34, 0.92)	0.6 (0.37, 0.99)	0.65 (0.39, 1.06)
0.9	0.2 (0.12, 0.33)	0.24 (0.15, 0.39)	0.28 (0.17, 0.46)	0.32 (0.19, 0.53)	0.36 (0.22, 0.59)	0.4 (0.24, 0.66)	0.44 (0.27, 0.72)	0.48 (0.29, 0.79)	0.52 (0.32, 0.85)	0.56 (0.34, 0.92)	0.6 (0.36, 0.99)
1.0	0.19 (0.11, 0.31)	0.22 (0.14, 0.37)	0.26 (0.16, 0.43)	0.3 (0.18, 0.49)	0.34 (0.2, 0.55)	0.37 (0.23, 0.61)	0.41 (0.25, 0.67)	0.45 (0.27, 0.74)	0.49 (0.29, 0.8)	0.52 (0.32, 0.86)	0.56 (0.34, 0.92)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E5: Hazard ratio (95%CI) for peripheral vascular disease during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.62 (0.37, 1.05)	0.74 (0.44, 1.26)	0.87 (0.52, 1.47)	0.99 (0.59, 1.68)	1.12 (0.67, 1.89)	1.24 (0.74, 2.1)	1.36 (0.81, 2.31)	1.49 (0.89, 2.52)	1.61 (0.96, 2.73)	1.74 (1.04, 2.94)	1.86 (1.11, 3.15)
0.1	0.52 (0.31, 0.88)	0.62 (0.37, 1.05)	0.72 (0.43, 1.23)	0.83 (0.49, 1.4)	0.93 (0.56, 1.58)	1.03 (0.62, 1.75)	1.14 (0.68, 1.93)	1.24 (0.74, 2.1)	1.34 (0.8, 2.28)	1.45 (0.86, 2.45)	1.55 (0.93, 2.63)
0.2	0.44 (0.26, 0.75)	0.53 (0.32, 0.9)	0.62 (0.37, 1.05)	0.71 (0.42, 1.2)	0.8 (0.48, 1.35)	0.89 (0.53, 1.5)	0.97 (0.58, 1.65)	1.06 (0.63, 1.8)	1.15 (0.69, 1.95)	1.24 (0.74, 2.1)	1.33 (0.79, 2.25)
0.3	0.39 (0.23, 0.66)	0.47 (0.28, 0.79)	0.54 (0.32, 0.92)	0.62 (0.37, 1.05)	0.7 (0.42, 1.18)	0.78 (0.46, 1.31)	0.85 (0.51, 1.44)	0.93 (0.56, 1.58)	1.01 (0.6, 1.71)	1.09 (0.65, 1.84)	1.16 (0.69, 1.97)
0.4	0.34 (0.21, 0.58)	0.41 (0.25, 0.7)	0.48 (0.29, 0.82)	0.55 (0.33, 0.93)	0.62 (0.37, 1.05)	0.69 (0.41, 1.17)	0.76 (0.45, 1.28)	0.83 (0.49, 1.4)	0.9 (0.53, 1.52)	0.96 (0.58, 1.63)	1.03 (0.62, 1.75)
0.5	0.31 (0.19, 0.53)	0.37 (0.22, 0.63)	0.43 (0.26, 0.74)	0.5 (0.3, 0.84)	0.56 (0.33, 0.95)	0.62 (0.37, 1.05)	0.68 (0.41, 1.16)	0.74 (0.44, 1.26)	0.81 (0.48, 1.37)	0.87 (0.52, 1.47)	0.93 (0.56, 1.58)
0.6	0.28 (0.17, 0.48)	0.34 (0.2, 0.57)	0.39 (0.24, 0.67)	0.45 (0.27, 0.76)	0.51 (0.3, 0.86)	0.56 (0.34, 0.95)	0.62 (0.37, 1.05)	0.68 (0.4, 1.15)	0.73 (0.44, 1.24)	0.79 (0.47, 1.34)	0.85 (0.5, 1.43)
0.7	0.26 (0.15, 0.44)	0.31 (0.19, 0.53)	0.36 (0.22, 0.61)	0.41 (0.25, 0.7)	0.47 (0.28, 0.79)	0.52 (0.31, 0.88)	0.57 (0.34, 0.96)	0.62 (0.37, 1.05)	0.67 (0.4, 1.14)	0.72 (0.43, 1.23)	0.78 (0.46, 1.31)
0.8	0.24 (0.14, 0.4)	0.29 (0.17, 0.48)	0.33 (0.2, 0.57)	0.38 (0.23, 0.65)	0.43 (0.26, 0.73)	0.48 (0.28, 0.81)	0.52 (0.31, 0.89)	0.57 (0.34, 0.97)	0.62 (0.37, 1.05)	0.67 (0.4, 1.13)	0.72 (0.43, 1.21)
0.9	0.22 (0.13, 0.38)	0.27 (0.16, 0.45)	0.31 (0.19, 0.53)	0.35 (0.21, 0.6)	0.4 (0.24, 0.68)	0.44 (0.26, 0.75)	0.49 (0.29, 0.83)	0.53 (0.32, 0.9)	0.58 (0.34, 0.98)	0.62 (0.37, 1.05)	0.66 (0.4, 1.13)
1.0	0.21 (0.12, 0.35)	0.25 (0.15, 0.42)	0.29 (0.17, 0.49)	0.33 (0.2, 0.56)	0.37 (0.22, 0.63)	0.41 (0.25, 0.7)	0.45 (0.27, 0.77)	0.5 (0.3, 0.84)	0.54 (0.32, 0.91)	0.58 (0.35, 0.98)	0.62 (0.37, 1.05)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E6: Hazard ratio (95%CI) for arrhythmia during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.84 (0.59, 1.2)	1.01 (0.71, 1.44)	1.18 (0.83, 1.68)	1.34 (0.94, 1.92)	1.51 (1.06, 2.16)	1.68 (1.18, 2.4)	1.85 (1.3, 2.64)	2.02 (1.42, 2.88)	2.18 (1.53, 3.12)	2.35 (1.65, 3.36)	2.52 (1.77, 3.6)
0.1	0.7 (0.49, 1)	0.84 (0.59, 1.2)	0.98 (0.69, 1.4)	1.12 (0.79, 1.6)	1.26 (0.89, 1.8)	1.4 (0.98, 2)	1.54 (1.08, 2.2)	1.68 (1.18, 2.4)	1.82 (1.28, 2.6)	1.96 (1.38, 2.8)	2.1 (1.48, 3)
0.2	0.6 (0.42, 0.86)	0.72 (0.51, 1.03)	0.84 (0.59, 1.2)	0.96 (0.67, 1.37)	1.08 (0.76, 1.54)	1.2 (0.84, 1.71)	1.32 (0.93, 1.89)	1.44 (1.01, 2.06)	1.56 (1.1, 2.23)	1.68 (1.18, 2.4)	1.8 (1.26, 2.57)
0.3	0.53 (0.37, 0.75)	0.63 (0.44, 0.9)	0.74 (0.52, 1.05)	0.84 (0.59, 1.2)	0.95 (0.66, 1.35)	1.05 (0.74, 1.5)	1.16 (0.81, 1.65)	1.26 (0.89, 1.8)	1.37 (0.96, 1.95)	1.47 (1.03, 2.1)	1.58 (1.11, 2.25)
0.4	0.47 (0.33, 0.67)	0.56 (0.39, 0.8)	0.65 (0.46, 0.93)	0.75 (0.52, 1.07)	0.84 (0.59, 1.2)	0.93 (0.66, 1.33)	1.03 (0.72, 1.47)	1.12 (0.79, 1.6)	1.21 (0.85, 1.73)	1.31 (0.92, 1.87)	1.4 (0.98, 2)
0.5	0.42 (0.3, 0.6)	0.5 (0.35, 0.72)	0.59 (0.41, 0.84)	0.67 (0.47, 0.96)	0.76 (0.53, 1.08)	0.84 (0.59, 1.2)	0.92 (0.65, 1.32)	1.01 (0.71, 1.44)	1.09 (0.77, 1.56)	1.18 (0.83, 1.68)	1.26 (0.89, 1.8)
0.6	0.38 (0.27, 0.55)	0.46 (0.32, 0.65)	0.53 (0.38, 0.76)	0.61 (0.43, 0.87)	0.69 (0.48, 0.98)	0.76 (0.54, 1.09)	0.84 (0.59, 1.2)	0.92 (0.64, 1.31)	0.99 (0.7, 1.42)	1.07 (0.75, 1.53)	1.15 (0.8, 1.64)
0.7	0.35 (0.25, 0.5)	0.42 (0.3, 0.6)	0.49 (0.34, 0.7)	0.56 (0.39, 0.8)	0.63 (0.44, 0.9)	0.7 (0.49, 1)	0.77 (0.54, 1.1)	0.84 (0.59, 1.2)	0.91 (0.64, 1.3)	0.98 (0.69, 1.4)	1.05 (0.74, 1.5)
0.8	0.32 (0.23, 0.46)	0.39 (0.27, 0.55)	0.45 (0.32, 0.65)	0.52 (0.36, 0.74)	0.58 (0.41, 0.83)	0.65 (0.45, 0.92)	0.71 (0.5, 1.02)	0.78 (0.54, 1.11)	0.84 (0.59, 1.2)	0.9 (0.64, 1.29)	0.97 (0.68, 1.38)
0.9	0.3 (0.21, 0.43)	0.36 (0.25, 0.51)	0.42 (0.3, 0.6)	0.48 (0.34, 0.69)	0.54 (0.38, 0.77)	0.6 (0.42, 0.86)	0.66 (0.46, 0.94)	0.72 (0.51, 1.03)	0.78 (0.55, 1.11)	0.84 (0.59, 1.2)	0.9 (0.63, 1.29)
1.0	0.28 (0.2, 0.4)	0.34 (0.24, 0.48)	0.39 (0.28, 0.56)	0.45 (0.31, 0.64)	0.5 (0.35, 0.72)	0.56 (0.39, 0.8)	0.62 (0.43, 0.88)	0.67 (0.47, 0.96)	0.73 (0.51, 1.04)	0.78 (0.55, 1.12)	0.84 (0.59, 1.2)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E7: Hazard ratio (95%CI) for depression during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.73 (0.61, 0.86)	0.88 (0.73, 1.03)	1.02 (0.85, 1.2)	1.17 (0.98, 1.38)	1.31 (1.1, 1.55)	1.46 (1.22, 1.72)	1.61 (1.34, 1.89)	1.75 (1.46, 2.06)	1.9 (1.59, 2.24)	2.04 (1.71, 2.41)	2.19 (1.83, 2.58)
0.1	0.61 (0.51, 0.72)	0.73 (0.61, 0.86)	0.85 (0.71, 1)	0.97 (0.81, 1.15)	1.1 (0.92, 1.29)	1.22 (1.02, 1.43)	1.34 (1.12, 1.58)	1.46 (1.22, 1.72)	1.58 (1.32, 1.86)	1.7 (1.42, 2.01)	1.83 (1.53, 2.15)
0.2	0.52 (0.44, 0.61)	0.63 (0.52, 0.74)	0.73 (0.61, 0.86)	0.83 (0.7, 0.98)	0.94 (0.78, 1.11)	1.04 (0.87, 1.23)	1.15 (0.96, 1.35)	1.25 (1.05, 1.47)	1.36 (1.13, 1.6)	1.46 (1.22, 1.72)	1.56 (1.31, 1.84)
0.3	0.46 (0.38, 0.54)	0.55 (0.46, 0.65)	0.64 (0.53, 0.75)	0.73 (0.61, 0.86)	0.82 (0.69, 0.97)	0.91 (0.76, 1.08)	1 (0.84, 1.18)	1.1 (0.92, 1.29)	1.19 (0.99, 1.4)	1.28 (1.07, 1.51)	1.37 (1.14, 1.61)
0.4	0.41 (0.34, 0.48)	0.49 (0.41, 0.57)	0.57 (0.47, 0.67)	0.65 (0.54, 0.76)	0.73 (0.61, 0.86)	0.81 (0.68, 0.96)	0.89 (0.75, 1.05)	0.97 (0.81, 1.15)	1.05 (0.88, 1.24)	1.14 (0.95, 1.34)	1.22 (1.02, 1.43)
0.5	0.37 (0.31, 0.43)	0.44 (0.37, 0.52)	0.51 (0.43, 0.6)	0.58 (0.49, 0.69)	0.66 (0.55, 0.77)	0.73 (0.61, 0.86)	0.8 (0.67, 0.95)	0.88 (0.73, 1.03)	0.95 (0.79, 1.12)	1.02 (0.85, 1.2)	1.1 (0.92, 1.29)
0.6	0.33 (0.28, 0.39)	0.4 (0.33, 0.47)	0.46 (0.39, 0.55)	0.53 (0.44, 0.63)	0.6 (0.5, 0.7)	0.66 (0.55, 0.78)	0.73 (0.61, 0.86)	0.8 (0.67, 0.94)	0.86 (0.72, 1.02)	0.93 (0.78, 1.09)	1 (0.83, 1.17)
0.7	0.3 (0.25, 0.36)	0.37 (0.31, 0.43)	0.43 (0.36, 0.5)	0.49 (0.41, 0.57)	0.55 (0.46, 0.65)	0.61 (0.51, 0.72)	0.67 (0.56, 0.79)	0.73 (0.61, 0.86)	0.79 (0.66, 0.93)	0.85 (0.71, 1)	0.91 (0.76, 1.08)
0.8	0.28 (0.23, 0.33)	0.34 (0.28, 0.4)	0.39 (0.33, 0.46)	0.45 (0.38, 0.53)	0.51 (0.42, 0.6)	0.56 (0.47, 0.66)	0.62 (0.52, 0.73)	0.67 (0.56, 0.79)	0.73 (0.61, 0.86)	0.79 (0.66, 0.93)	0.84 (0.7, 0.99)
0.9	0.26 (0.22, 0.31)	0.31 (0.26, 0.37)	0.37 (0.31, 0.43)	0.42 (0.35, 0.49)	0.47 (0.39, 0.55)	0.52 (0.44, 0.61)	0.57 (0.48, 0.68)	0.63 (0.52, 0.74)	0.68 (0.57, 0.8)	0.73 (0.61, 0.86)	0.78 (0.65, 0.92)
1.0	0.24 (0.2, 0.29)	0.29 (0.24, 0.34)	0.34 (0.28, 0.4)	0.39 (0.33, 0.46)	0.44 (0.37, 0.52)	0.49 (0.41, 0.57)	0.54 (0.45, 0.63)	0.58 (0.49, 0.69)	0.63 (0.53, 0.75)	0.68 (0.57, 0.8)	0.73 (0.61, 0.86)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E8: Hazard ratio (95%CI) for self-harm during 6 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.78 (0.37, 1.63)	0.94 (0.44, 1.96)	1.09 (0.52, 2.28)	1.25 (0.59, 2.61)	1.4 (0.67, 2.93)	1.56 (0.74, 3.26)	1.72 (0.81, 3.59)	1.87 (0.89, 3.91)	2.03 (0.96, 4.24)	2.18 (1.04, 4.56)	2.34 (1.11, 4.89)
0.1	0.65 (0.31, 1.36)	0.78 (0.37, 1.63)	0.91 (0.43, 1.9)	1.04 (0.49, 2.17)	1.17 (0.56, 2.45)	1.3 (0.62, 2.72)	1.43 (0.68, 2.99)	1.56 (0.74, 3.26)	1.69 (0.8, 3.53)	1.82 (0.86, 3.8)	1.95 (0.93, 4.08)
0.2	0.56 (0.26, 1.16)	0.67 (0.32, 1.4)	0.78 (0.37, 1.63)	0.89 (0.42, 1.86)	1 (0.48, 2.1)	1.11 (0.53, 2.33)	1.23 (0.58, 2.56)	1.34 (0.63, 2.79)	1.45 (0.69, 3.03)	1.56 (0.74, 3.26)	1.67 (0.79, 3.49)
0.3	0.49 (0.23, 1.02)	0.59 (0.28, 1.22)	0.68 (0.32, 1.43)	0.78 (0.37, 1.63)	0.88 (0.42, 1.83)	0.98 (0.46, 2.04)	1.07 (0.51, 2.24)	1.17 (0.56, 2.45)	1.27 (0.6, 2.65)	1.37 (0.65, 2.85)	1.46 (0.69, 3.06)
0.4	0.43 (0.21, 0.91)	0.52 (0.25, 1.09)	0.61 (0.29, 1.27)	0.69 (0.33, 1.45)	0.78 (0.37, 1.63)	0.87 (0.41, 1.81)	0.95 (0.45, 1.99)	1.04 (0.49, 2.17)	1.13 (0.53, 2.35)	1.21 (0.58, 2.54)	1.3 (0.62, 2.72)
0.5	0.39 (0.19, 0.82)	0.47 (0.22, 0.98)	0.55 (0.26, 1.14)	0.62 (0.3, 1.3)	0.7 (0.33, 1.47)	0.78 (0.37, 1.63)	0.86 (0.41, 1.79)	0.94 (0.44, 1.96)	1.01 (0.48, 2.12)	1.09 (0.52, 2.28)	1.17 (0.56, 2.45)
0.6	0.35 (0.17, 0.74)	0.43 (0.2, 0.89)	0.5 (0.24, 1.04)	0.57 (0.27, 1.19)	0.64 (0.3, 1.33)	0.71 (0.34, 1.48)	0.78 (0.37, 1.63)	0.85 (0.4, 1.78)	0.92 (0.44, 1.93)	0.99 (0.47, 2.07)	1.06 (0.5, 2.22)
0.7	0.33 (0.15, 0.68)	0.39 (0.19, 0.82)	0.46 (0.22, 0.95)	0.52 (0.25, 1.09)	0.59 (0.28, 1.22)	0.65 (0.31, 1.36)	0.72 (0.34, 1.49)	0.78 (0.37, 1.63)	0.85 (0.4, 1.77)	0.91 (0.43, 1.9)	0.98 (0.46, 2.04)
0.8	0.3 (0.14, 0.63)	0.36 (0.17, 0.75)	0.42 (0.2, 0.88)	0.48 (0.23, 1)	0.54 (0.26, 1.13)	0.6 (0.28, 1.25)	0.66 (0.31, 1.38)	0.72 (0.34, 1.5)	0.78 (0.37, 1.63)	0.84 (0.4, 1.76)	0.9 (0.43, 1.88)
0.9	0.28 (0.13, 0.58)	0.33 (0.16, 0.7)	0.39 (0.19, 0.82)	0.45 (0.21, 0.93)	0.5 (0.24, 1.05)	0.56 (0.26, 1.16)	0.61 (0.29, 1.28)	0.67 (0.32, 1.4)	0.72 (0.34, 1.51)	0.78 (0.37, 1.63)	0.84 (0.4, 1.75)
1.0	0.26 (0.12, 0.54)	0.31 (0.15, 0.65)	0.36 (0.17, 0.76)	0.42 (0.2, 0.87)	0.47 (0.22, 0.98)	0.52 (0.25, 1.09)	0.57 (0.27, 1.2)	0.62 (0.3, 1.3)	0.68 (0.32, 1.41)	0.73 (0.35, 1.52)	0.78 (0.37, 1.63)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT Rx (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E9: Incidence Rates of Events and Hazard Ratios (95%CI) of Medication Groups for all Events During 3 Months Follow-up

Event	Patient-years	Number of events	Incidence of event per 1,000 patient-years	Hazard ratio (95% CI)	
				Crude	Adjusted*
Ischemic heart disease					
NRT	2,549	260	102.0	1	1
Bupropion	86	6	69.8	0.68 (0.30-1.53)	1.02 (0.45-2.30)
Varenicline	882	68	77.1	0.76 (0.58-0.99)	0.85 (0.65-1.12)
Stroke					
NRT	2,575	89	34.6	1	1
Bupropion	87	1	11.5	0.33 (0.05-2.39)	0.37 (0.05-2.64)
Varenicline	888	15	16.9	0.49 (0.28-0.85)	0.58 (0.33-1.01)
Heart failure					
NRT	2,577	77	29.9	1	1
Bupropion	87	1	11.5	0.38 (0.05-2.77)	0.59 (0.08-4.28)
Varenicline	889	10	11.2	0.38 (0.20-0.73)	0.47 (0.24-0.93)
Peripheral vascular disease					
NRT	2,580	57	22.1	1	1
Bupropion	87	1	11.5	0.52 (0.07-3.76)	0.97 (0.13-7.14)
Varenicline	889	10	11.2	0.51 (0.26-1.00)	0.63 (0.32-1.23)
Arrhythmia					
NRT	2,574	107	41.6	1	1
Bupropion	87	3	34.5	0.83 (0.26-2.62)	1.19 (0.37-3.77)
Varenicline	887	21	23.7	0.57 (0.36-0.91)	0.75 (0.47-1.21)
Depression					
NRT	2,531	394	156.9	1	1
Bupropion	87	5	57.5	0.37 (0.15-0.90)	0.36 (0.15-0.86)
Varenicline	880	82	93.2	0.60 (0.47-0.76)	0.61 (0.48-0.78)
Self-harm					
NRT	2,585	20	7.7	1	1
Bupropion	87	1	11.5	1.49 (0.20-11.06)	1.65 (0.22-12.49)
Varenicline	890	5	5.6	0.73 (0.27-1.94)	0.80 (0.30-2.15)

NRT = nicotine replacement therapy. *Adjusted for age, sex, socio-economic status, Strategic Health Authority of the general practice, comorbidities (i.e., prior recordings of COPD, diabetes, peptic ulcer disease, renal disease, rheumatological disease, or cancer), alcohol misuse, and any recordings of the neuropsychiatric and cardiovascular events of interest that occurred prior to the patient's entry date to the cohort.

Table E10: Hazard Ratios (95%CI) of Events during 3 Months Follow-up in the Propensity Score Matched Samples

Event	Hazard ratio (95% CI)	
	Bupropion vs. NRT (N=341)	**Varenicline vs. NRT** (N=3,484)
Ischemic heart disease	0.99 (0.32-3.06)	0.74 (0.53-1.02)
Stroke	0.25 (0.03-2.20)	0.93 (0.45-1.93)
Heart failure	0.99 (0.06-15.89)	0.64 (0.28-1.48)
Peripheral vascular disease	N/A	0.50 (0.22-1.11)
Arrhythmia	N/A	0.82 (0.45-1.51)
Depression	0.32 (0.12-0.89)	0.57 (0.43-0.75)
Self-harm	0.99 (0.06-15.85)	0.55 (0.19-1.65)

NRT = nicotine replacement therapy. N/A = sample size or event rate too low to calculate a hazard ratio.

Table E11: Hazard ratio (95%CI) for ischaemic heart disease during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.85 (0.65, 1.12)	1.02 (0.78, 1.34)	1.19 (0.91, 1.57)	1.36 (1.04, 1.79)	1.53 (1.17, 2.02)	1.7 (1.3, 2.24)	1.87 (1.43, 2.46)	2.04 (1.56, 2.69)	2.21 (1.69, 2.91)	2.38 (1.82, 3.14)	2.55 (1.95, 3.36)
0.1	0.71 (0.54, 0.93)	0.85 (0.65, 1.12)	0.99 (0.76, 1.31)	1.13 (0.87, 1.49)	1.28 (0.98, 1.68)	1.42 (1.08, 1.87)	1.56 (1.19, 2.05)	1.7 (1.3, 2.24)	1.84 (1.41, 2.43)	1.98 (1.52, 2.61)	2.13 (1.63, 2.8)
0.2	0.61 (0.46, 0.8)	0.73 (0.56, 0.96)	0.85 (0.65, 1.12)	0.97 (0.74, 1.28)	1.09 (0.84, 1.44)	1.21 (0.93, 1.6)	1.34 (1.02, 1.76)	1.46 (1.11, 1.92)	1.58 (1.21, 2.08)	1.7 (1.3, 2.24)	1.82 (1.39, 2.4)
0.3	0.53 (0.41, 0.7)	0.64 (0.49, 0.84)	0.74 (0.57, 0.98)	0.85 (0.65, 1.12)	0.96 (0.73, 1.26)	1.06 (0.81, 1.4)	1.17 (0.89, 1.54)	1.28 (0.98, 1.68)	1.38 (1.06, 1.82)	1.49 (1.14, 1.96)	1.59 (1.22, 2.1)
0.4	0.47 (0.36, 0.62)	0.57 (0.43, 0.75)	0.66 (0.51, 0.87)	0.76 (0.58, 1)	0.85 (0.65, 1.12)	0.94 (0.72, 1.24)	1.04 (0.79, 1.37)	1.13 (0.87, 1.49)	1.23 (0.94, 1.62)	1.32 (1.01, 1.74)	1.42 (1.08, 1.87)
0.5	0.43 (0.33, 0.56)	0.51 (0.39, 0.67)	0.6 (0.46, 0.78)	0.68 (0.52, 0.9)	0.77 (0.59, 1.01)	0.85 (0.65, 1.12)	0.94 (0.72, 1.23)	1.02 (0.78, 1.34)	1.11 (0.85, 1.46)	1.19 (0.91, 1.57)	1.28 (0.98, 1.68)
0.6	0.39 (0.3, 0.51)	0.46 (0.35, 0.61)	0.54 (0.41, 0.71)	0.62 (0.47, 0.81)	0.7 (0.53, 0.92)	0.77 (0.59, 1.02)	0.85 (0.65, 1.12)	0.93 (0.71, 1.22)	1 (0.77, 1.32)	1.08 (0.83, 1.43)	1.16 (0.89, 1.53)
0.7	0.35 (0.27, 0.47)	0.43 (0.33, 0.56)	0.5 (0.38, 0.65)	0.57 (0.43, 0.75)	0.64 (0.49, 0.84)	0.71 (0.54, 0.93)	0.78 (0.6, 1.03)	0.85 (0.65, 1.12)	0.92 (0.7, 1.21)	0.99 (0.76, 1.31)	1.06 (0.81, 1.4)
0.8	0.33 (0.25, 0.43)	0.39 (0.3, 0.52)	0.46 (0.35, 0.6)	0.52 (0.4, 0.69)	0.59 (0.45, 0.78)	0.65 (0.5, 0.86)	0.72 (0.55, 0.95)	0.78 (0.6, 1.03)	0.85 (0.65, 1.12)	0.92 (0.7, 1.21)	0.98 (0.75, 1.29)
0.9	0.3 (0.23, 0.4)	0.36 (0.28, 0.48)	0.43 (0.33, 0.56)	0.49 (0.37, 0.64)	0.55 (0.42, 0.72)	0.61 (0.46, 0.8)	0.67 (0.51, 0.88)	0.73 (0.56, 0.96)	0.79 (0.6, 1.04)	0.85 (0.65, 1.12)	0.91 (0.7, 1.2)
1.0	0.28 (0.22, 0.37)	0.34 (0.26, 0.45)	0.4 (0.3, 0.52)	0.45 (0.35, 0.6)	0.51 (0.39, 0.67)	0.57 (0.43, 0.75)	0.62 (0.48, 0.82)	0.68 (0.52, 0.9)	0.74 (0.56, 0.97)	0.79 (0.61, 1.05)	0.85 (0.65, 1.12)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E12: Hazard ratio (95%CI) for stroke during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0,0	0,1	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0
0,0	0,58 (0,33, 1,01)	0,7 (0,4, 1,21)	0,81 (0,46, 1,41)	0,93 (0,53, 1,62)	1,04 (0,59, 1,82)	1,16 (0,66, 2,02)	1,28 (0,73, 2,22)	1,39 (0,79, 2,42)	1,51 (0,86, 2,63)	1,62 (0,92, 2,83)	1,74 (0,99, 3,03)
0,1	0,48 (0,28, 0,84)	0,58 (0,33, 1,01)	0,68 (0,39, 1,18)	0,77 (0,44, 1,35)	0,87 (0,5, 1,52)	0,97 (0,55, 1,68)	1,06 (0,61, 1,85)	1,16 (0,66, 2,02)	1,26 (0,72, 2,19)	1,35 (0,77, 2,36)	1,45 (0,83, 2,53)
0,2	0,41 (0,24, 0,72)	0,5 (0,28, 0,87)	0,58 (0,33, 1,01)	0,66 (0,38, 1,15)	0,75 (0,42, 1,3)	0,83 (0,47, 1,44)	0,91 (0,52, 1,59)	0,99 (0,57, 1,73)	1,08 (0,61, 1,88)	1,16 (0,66, 2,02)	1,24 (0,71, 2,16)
0,3	0,36 (0,21, 0,63)	0,44 (0,25, 0,76)	0,51 (0,29, 0,88)	0,58 (0,33, 1,01)	0,65 (0,37, 1,14)	0,73 (0,41, 1,26)	0,8 (0,45, 1,39)	0,87 (0,5, 1,52)	0,94 (0,54, 1,64)	1,02 (0,58, 1,77)	1,09 (0,62, 1,89)
0,4	0,32 (0,18, 0,56)	0,39 (0,22, 0,67)	0,45 (0,26, 0,79)	0,52 (0,29, 0,9)	0,58 (0,33, 1,01)	0,64 (0,37, 1,12)	0,71 (0,4, 1,23)	0,77 (0,44, 1,35)	0,84 (0,48, 1,46)	0,9 (0,51, 1,57)	0,97 (0,55, 1,68)
0,5	0,29 (0,17, 0,51)	0,35 (0,2, 0,61)	0,41 (0,23, 0,71)	0,46 (0,26, 0,81)	0,52 (0,3, 0,91)	0,58 (0,33, 1,01)	0,64 (0,36, 1,11)	0,7 (0,4, 1,21)	0,75 (0,43, 1,31)	0,81 (0,46, 1,41)	0,87 (0,5, 1,52)
0,6	0,26 (0,15, 0,46)	0,32 (0,18, 0,55)	0,37 (0,21, 0,64)	0,42 (0,24, 0,73)	0,47 (0,27, 0,83)	0,53 (0,3, 0,92)	0,58 (0,33, 1,01)	0,63 (0,36, 1,1)	0,69 (0,39, 1,19)	0,74 (0,42, 1,29)	0,79 (0,45, 1,38)
0,7	0,24 (0,14, 0,42)	0,29 (0,17, 0,51)	0,34 (0,19, 0,59)	0,39 (0,22, 0,67)	0,44 (0,25, 0,76)	0,48 (0,28, 0,84)	0,53 (0,3, 0,93)	0,58 (0,33, 1,01)	0,63 (0,36, 1,09)	0,68 (0,39, 1,18)	0,73 (0,41, 1,26)
0,8	0,22 (0,13, 0,39)	0,27 (0,15, 0,47)	0,31 (0,18, 0,54)	0,36 (0,2, 0,62)	0,4 (0,23, 0,7)	0,45 (0,25, 0,78)	0,49 (0,28, 0,85)	0,54 (0,3, 0,93)	0,58 (0,33, 1,01)	0,62 (0,36, 1,09)	0,67 (0,38, 1,17)
0,9	0,21 (0,12, 0,36)	0,25 (0,14, 0,43)	0,29 (0,17, 0,51)	0,33 (0,19, 0,58)	0,37 (0,21, 0,65)	0,41 (0,24, 0,72)	0,46 (0,26, 0,79)	0,5 (0,28, 0,87)	0,54 (0,31, 0,94)	0,58 (0,33, 1,01)	0,62 (0,35, 1,08)
1,0	0,19 (0,11, 0,34)	0,23 (0,13, 0,4)	0,27 (0,15, 0,47)	0,31 (0,18, 0,54)	0,35 (0,2, 0,61)	0,39 (0,22, 0,67)	0,43 (0,24, 0,74)	0,46 (0,26, 0,81)	0,5 (0,29, 0,88)	0,54 (0,31, 0,94)	0,58 (0,33, 1,01)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E13: Hazard ratio (95%CI) for heart failure during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.47 (0.24, 0.93)	0.56 (0.29, 1.12)	0.66 (0.34, 1.3)	0.75 (0.38, 1.49)	0.85 (0.43, 1.67)	0.94 (0.48, 1.86)	1.03 (0.53, 2.05)	1.13 (0.58, 2.23)	1.22 (0.62, 2.42)	1.32 (0.67, 2.6)	1.41 (0.72, 2.79)
0.1	0.39 (0.2, 0.78)	0.47 (0.24, 0.93)	0.55 (0.28, 1.09)	0.63 (0.32, 1.24)	0.71 (0.36, 1.4)	0.78 (0.4, 1.55)	0.86 (0.44, 1.71)	0.94 (0.48, 1.86)	1.02 (0.52, 2.02)	1.1 (0.56, 2.17)	1.18 (0.6, 2.33)
0.2	0.34 (0.17, 0.66)	0.4 (0.21, 0.8)	0.47 (0.24, 0.93)	0.54 (0.27, 1.06)	0.6 (0.31, 1.2)	0.67 (0.34, 1.33)	0.74 (0.38, 1.46)	0.81 (0.41, 1.59)	0.87 (0.45, 1.73)	0.94 (0.48, 1.86)	1.01 (0.51, 1.99)
0.3	0.29 (0.15, 0.58)	0.35 (0.18, 0.7)	0.41 (0.21, 0.81)	0.47 (0.24, 0.93)	0.53 (0.27, 1.05)	0.59 (0.3, 1.16)	0.65 (0.33, 1.28)	0.71 (0.36, 1.4)	0.76 (0.39, 1.51)	0.82 (0.42, 1.63)	0.88 (0.45, 1.74)
0.4	0.26 (0.13, 0.52)	0.31 (0.16, 0.62)	0.37 (0.19, 0.72)	0.42 (0.21, 0.83)	0.47 (0.24, 0.93)	0.52 (0.27, 1.03)	0.57 (0.29, 1.14)	0.63 (0.32, 1.24)	0.68 (0.35, 1.34)	0.73 (0.37, 1.45)	0.78 (0.4, 1.55)
0.5	0.24 (0.12, 0.47)	0.28 (0.14, 0.56)	0.33 (0.17, 0.65)	0.38 (0.19, 0.74)	0.42 (0.22, 0.84)	0.47 (0.24, 0.93)	0.52 (0.26, 1.02)	0.56 (0.29, 1.12)	0.61 (0.31, 1.21)	0.66 (0.34, 1.3)	0.71 (0.36, 1.4)
0.6	0.21 (0.11, 0.42)	0.26 (0.13, 0.51)	0.3 (0.15, 0.59)	0.34 (0.17, 0.68)	0.38 (0.2, 0.76)	0.43 (0.22, 0.85)	0.47 (0.24, 0.93)	0.51 (0.26, 1.01)	0.56 (0.28, 1.1)	0.6 (0.31, 1.18)	0.64 (0.33, 1.27)
0.7	0.2 (0.1, 0.39)	0.24 (0.12, 0.47)	0.27 (0.14, 0.54)	0.31 (0.16, 0.62)	0.35 (0.18, 0.7)	0.39 (0.2, 0.78)	0.43 (0.22, 0.85)	0.47 (0.24, 0.93)	0.51 (0.26, 1.01)	0.55 (0.28, 1.09)	0.59 (0.3, 1.16)
0.8	0.18 (0.09, 0.36)	0.22 (0.11, 0.43)	0.25 (0.13, 0.5)	0.29 (0.15, 0.57)	0.33 (0.17, 0.64)	0.36 (0.18, 0.72)	0.4 (0.2, 0.79)	0.43 (0.22, 0.86)	0.47 (0.24, 0.93)	0.51 (0.26, 1)	0.54 (0.28, 1.07)
0.9	0.17 (0.09, 0.33)	0.2 (0.1, 0.4)	0.24 (0.12, 0.47)	0.27 (0.14, 0.53)	0.3 (0.15, 0.6)	0.34 (0.17, 0.66)	0.37 (0.19, 0.73)	0.4 (0.21, 0.8)	0.44 (0.22, 0.86)	0.47 (0.24, 0.93)	0.5 (0.26, 1)
1.0	0.16 (0.08, 0.31)	0.19 (0.1, 0.37)	0.22 (0.11, 0.43)	0.25 (0.13, 0.5)	0.28 (0.14, 0.56)	0.31 (0.16, 0.62)	0.34 (0.18, 0.68)	0.38 (0.19, 0.74)	0.41 (0.21, 0.81)	0.44 (0.22, 0.87)	0.47 (0.24, 0.93)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E14: Hazard ratio (95%CI) for peripheral vascular disease during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.63 (0.32, 1.23)	0.76 (0.38, 1.48)	0.88 (0.45, 1.72)	1.01 (0.51, 1.97)	1.13 (0.58, 2.21)	1.26 (0.64, 2.46)	1.39 (0.7, 2.71)	1.51 (0.77, 2.95)	1.64 (0.83, 3.2)	1.76 (0.9, 3.44)	1.89 (0.96, 3.69)
0.1	0.53 (0.27, 1.03)	0.63 (0.32, 1.23)	0.74 (0.37, 1.44)	0.84 (0.43, 1.64)	0.95 (0.48, 1.85)	1.05 (0.53, 2.05)	1.16 (0.59, 2.26)	1.26 (0.64, 2.46)	1.37 (0.69, 2.67)	1.47 (0.75, 2.87)	1.58 (0.8, 3.08)
0.2	0.45 (0.23, 0.88)	0.54 (0.27, 1.05)	0.63 (0.32, 1.23)	0.72 (0.37, 1.41)	0.81 (0.41, 1.58)	0.9 (0.46, 1.76)	0.99 (0.5, 1.93)	1.08 (0.55, 2.11)	1.17 (0.59, 2.28)	1.26 (0.64, 2.46)	1.35 (0.69, 2.64)
0.3	0.39 (0.2, 0.77)	0.47 (0.24, 0.92)	0.55 (0.28, 1.08)	0.63 (0.32, 1.23)	0.71 (0.36, 1.38)	0.79 (0.4, 1.54)	0.87 (0.44, 1.69)	0.95 (0.48, 1.85)	1.02 (0.52, 2)	1.1 (0.56, 2.15)	1.18 (0.6, 2.31)
0.4	0.35 (0.18, 0.68)	0.42 (0.21, 0.82)	0.49 (0.25, 0.96)	0.56 (0.28, 1.09)	0.63 (0.32, 1.23)	0.7 (0.36, 1.37)	0.77 (0.39, 1.5)	0.84 (0.43, 1.64)	0.91 (0.46, 1.78)	0.98 (0.5, 1.91)	1.05 (0.53, 2.05)
0.5	0.32 (0.16, 0.62)	0.38 (0.19, 0.74)	0.44 (0.22, 0.86)	0.5 (0.26, 0.98)	0.57 (0.29, 1.11)	0.63 (0.32, 1.23)	0.69 (0.35, 1.35)	0.76 (0.38, 1.48)	0.82 (0.42, 1.6)	0.88 (0.45, 1.72)	0.95 (0.48, 1.85)
0.6	0.29 (0.15, 0.56)	0.34 (0.17, 0.67)	0.4 (0.2, 0.78)	0.46 (0.23, 0.89)	0.52 (0.26, 1.01)	0.57 (0.29, 1.12)	0.63 (0.32, 1.23)	0.69 (0.35, 1.34)	0.74 (0.38, 1.45)	0.8 (0.41, 1.57)	0.86 (0.44, 1.68)
0.7	0.26 (0.13, 0.51)	0.32 (0.16, 0.62)	0.37 (0.19, 0.72)	0.42 (0.21, 0.82)	0.47 (0.24, 0.92)	0.53 (0.27, 1.03)	0.58 (0.29, 1.13)	0.63 (0.32, 1.23)	0.68 (0.35, 1.33)	0.74 (0.37, 1.44)	0.79 (0.4, 1.54)
0.8	0.24 (0.12, 0.47)	0.29 (0.15, 0.57)	0.34 (0.17, 0.66)	0.39 (0.2, 0.76)	0.44 (0.22, 0.85)	0.48 (0.25, 0.95)	0.53 (0.27, 1.04)	0.58 (0.3, 1.14)	0.63 (0.32, 1.23)	0.68 (0.34, 1.32)	0.73 (0.37, 1.42)
0.9	0.23 (0.11, 0.44)	0.27 (0.14, 0.53)	0.32 (0.16, 0.62)	0.36 (0.18, 0.7)	0.41 (0.21, 0.79)	0.45 (0.23, 0.88)	0.5 (0.25, 0.97)	0.54 (0.27, 1.05)	0.59 (0.3, 1.14)	0.63 (0.32, 1.23)	0.68 (0.34, 1.32)
1.0	0.21 (0.11, 0.41)	0.25 (0.13, 0.49)	0.29 (0.15, 0.57)	0.34 (0.17, 0.66)	0.38 (0.19, 0.74)	0.42 (0.21, 0.82)	0.46 (0.23, 0.9)	0.5 (0.26, 0.98)	0.55 (0.28, 1.07)	0.59 (0.3, 1.15)	0.63 (0.32, 1.23)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E15: Hazard ratio (95%CI) for arrhythmia during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.75 (0.47, 1.21)	0.9 (0.56, 1.45)	1.05 (0.66, 1.69)	1.2 (0.75, 1.94)	1.35 (0.85, 2.18)	1.5 (0.94, 2.42)	1.65 (1.03, 2.66)	1.8 (1.13, 2.9)	1.95 (1.22, 3.15)	2.1 (1.32, 3.39)	2.25 (1.41, 3.63)
0.1	0.63 (0.39, 1.01)	0.75 (0.47, 1.21)	0.88 (0.55, 1.41)	1 (0.63, 1.61)	1.13 (0.71, 1.82)	1.25 (0.78, 2.02)	1.38 (0.86, 2.22)	1.5 (0.94, 2.42)	1.63 (1.02, 2.62)	1.75 (1.1, 2.82)	1.88 (1.18, 3.03)
0.2	0.54 (0.34, 0.86)	0.64 (0.4, 1.04)	0.75 (0.47, 1.21)	0.86 (0.54, 1.38)	0.96 (0.6, 1.56)	1.07 (0.67, 1.73)	1.18 (0.74, 1.9)	1.29 (0.81, 2.07)	1.39 (0.87, 2.25)	1.5 (0.94, 2.42)	1.61 (1.01, 2.59)
0.3	0.47 (0.29, 0.76)	0.56 (0.35, 0.91)	0.66 (0.41, 1.06)	0.75 (0.47, 1.21)	0.84 (0.53, 1.36)	0.94 (0.59, 1.51)	1.03 (0.65, 1.66)	1.13 (0.71, 1.82)	1.22 (0.76, 1.97)	1.31 (0.82, 2.12)	1.41 (0.88, 2.27)
0.4	0.42 (0.26, 0.67)	0.5 (0.31, 0.81)	0.58 (0.37, 0.94)	0.67 (0.42, 1.08)	0.75 (0.47, 1.21)	0.83 (0.52, 1.34)	0.92 (0.57, 1.48)	1 (0.63, 1.61)	1.08 (0.68, 1.75)	1.17 (0.73, 1.88)	1.25 (0.78, 2.02)
0.5	0.38 (0.24, 0.61)	0.45 (0.28, 0.73)	0.53 (0.33, 0.85)	0.6 (0.38, 0.97)	0.68 (0.42, 1.09)	0.75 (0.47, 1.21)	0.83 (0.52, 1.33)	0.9 (0.56, 1.45)	0.98 (0.61, 1.57)	1.05 (0.66, 1.69)	1.13 (0.71, 1.82)
0.6	0.34 (0.21, 0.55)	0.41 (0.26, 0.66)	0.48 (0.3, 0.77)	0.55 (0.34, 0.88)	0.61 (0.38, 0.99)	0.68 (0.43, 1.1)	0.75 (0.47, 1.21)	0.82 (0.51, 1.32)	0.89 (0.56, 1.43)	0.95 (0.6, 1.54)	1.02 (0.64, 1.65)
0.7	0.31 (0.2, 0.5)	0.38 (0.24, 0.61)	0.44 (0.27, 0.71)	0.5 (0.31, 0.81)	0.56 (0.35, 0.91)	0.63 (0.39, 1.01)	0.69 (0.43, 1.11)	0.75 (0.47, 1.21)	0.81 (0.51, 1.31)	0.88 (0.55, 1.41)	0.94 (0.59, 1.51)
0.8	0.29 (0.18, 0.47)	0.35 (0.22, 0.56)	0.4 (0.25, 0.65)	0.46 (0.29, 0.74)	0.52 (0.33, 0.84)	0.58 (0.36, 0.93)	0.63 (0.4, 1.02)	0.69 (0.43, 1.12)	0.75 (0.47, 1.21)	0.81 (0.51, 1.3)	0.87 (0.54, 1.4)
0.9	0.27 (0.17, 0.43)	0.32 (0.2, 0.52)	0.38 (0.24, 0.61)	0.43 (0.27, 0.69)	0.48 (0.3, 0.78)	0.54 (0.34, 0.86)	0.59 (0.37, 0.95)	0.64 (0.4, 1.04)	0.7 (0.44, 1.12)	0.75 (0.47, 1.21)	0.8 (0.5, 1.3)
1.0	0.25 (0.16, 0.4)	0.3 (0.19, 0.48)	0.35 (0.22, 0.56)	0.4 (0.25, 0.65)	0.45 (0.28, 0.73)	0.5 (0.31, 0.81)	0.55 (0.34, 0.89)	0.6 (0.38, 0.97)	0.65 (0.41, 1.05)	0.7 (0.44, 1.13)	0.75 (0.47, 1.21)

This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

Table E16: Hazard ratio (95%CI) for depression during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.61 (0.48, 0.78)	0.73 (0.58, 0.94)	0.85 (0.67, 1.09)	0.98 (0.77, 1.25)	1.1 (0.86, 1.4)	1.22 (0.96, 1.56)	1.34 (1.06, 1.72)	1.46 (1.15, 1.87)	1.59 (1.25, 2.03)	1.71 (1.34, 2.18)	1.83 (1.44, 2.34)
0.1	0.51 (0.4, 0.65)	0.61 (0.48, 0.78)	0.71 (0.56, 0.91)	0.81 (0.64, 1.04)	0.92 (0.72, 1.17)	1.02 (0.8, 1.3)	1.12 (0.88, 1.43)	1.22 (0.96, 1.56)	1.32 (1.04, 1.69)	1.42 (1.12, 1.82)	1.53 (1.2, 1.95)
0.2	0.44 (0.34, 0.56)	0.52 (0.41, 0.67)	0.61 (0.48, 0.78)	0.7 (0.55, 0.89)	0.78 (0.62, 1)	0.87 (0.69, 1.11)	0.96 (0.75, 1.23)	1.05 (0.82, 1.34)	1.13 (0.89, 1.45)	1.22 (0.96, 1.56)	1.31 (1.03, 1.67)
0.3	0.38 (0.3, 0.49)	0.46 (0.36, 0.59)	0.53 (0.42, 0.68)	0.61 (0.48, 0.78)	0.69 (0.54, 0.88)	0.76 (0.6, 0.98)	0.84 (0.66, 1.07)	0.92 (0.72, 1.17)	0.99 (0.78, 1.27)	1.07 (0.84, 1.37)	1.14 (0.9, 1.46)
0.4	0.34 (0.27, 0.43)	0.41 (0.32, 0.52)	0.47 (0.37, 0.61)	0.54 (0.43, 0.69)	0.61 (0.48, 0.78)	0.68 (0.53, 0.87)	0.75 (0.59, 0.95)	0.81 (0.64, 1.04)	0.88 (0.69, 1.13)	0.95 (0.75, 1.21)	1.02 (0.8, 1.3)
0.5	0.31 (0.24, 0.39)	0.37 (0.29, 0.47)	0.43 (0.34, 0.55)	0.49 (0.38, 0.62)	0.55 (0.43, 0.7)	0.61 (0.48, 0.78)	0.67 (0.53, 0.86)	0.73 (0.58, 0.94)	0.79 (0.62, 1.01)	0.85 (0.67, 1.09)	0.92 (0.72, 1.17)
0.6	0.28 (0.22, 0.35)	0.33 (0.26, 0.43)	0.39 (0.31, 0.5)	0.44 (0.35, 0.57)	0.5 (0.39, 0.64)	0.55 (0.44, 0.71)	0.61 (0.48, 0.78)	0.67 (0.52, 0.85)	0.72 (0.57, 0.92)	0.78 (0.61, 0.99)	0.83 (0.65, 1.06)
0.7	0.25 (0.2, 0.33)	0.31 (0.24, 0.39)	0.36 (0.28, 0.46)	0.41 (0.32, 0.52)	0.46 (0.36, 0.59)	0.51 (0.4, 0.65)	0.56 (0.44, 0.72)	0.61 (0.48, 0.78)	0.66 (0.52, 0.85)	0.71 (0.56, 0.91)	0.76 (0.6, 0.98)
0.8	0.23 (0.18, 0.3)	0.28 (0.22, 0.36)	0.33 (0.26, 0.42)	0.38 (0.3, 0.48)	0.42 (0.33, 0.54)	0.47 (0.37, 0.6)	0.52 (0.41, 0.66)	0.56 (0.44, 0.72)	0.61 (0.48, 0.78)	0.66 (0.52, 0.84)	0.7 (0.55, 0.9)
0.9	0.22 (0.17, 0.28)	0.26 (0.21, 0.33)	0.31 (0.24, 0.39)	0.35 (0.27, 0.45)	0.39 (0.31, 0.5)	0.44 (0.34, 0.56)	0.48 (0.38, 0.61)	0.52 (0.41, 0.67)	0.57 (0.45, 0.72)	0.61 (0.48, 0.78)	0.65 (0.51, 0.84)
1.0	0.2 (0.16, 0.26)	0.24 (0.19, 0.31)	0.28 (0.22, 0.36)	0.33 (0.26, 0.42)	0.37 (0.29, 0.47)	0.41 (0.32, 0.52)	0.45 (0.35, 0.57)	0.49 (0.38, 0.62)	0.53 (0.42, 0.68)	0.57 (0.45, 0.73)	0.61 (0.48, 0.78)

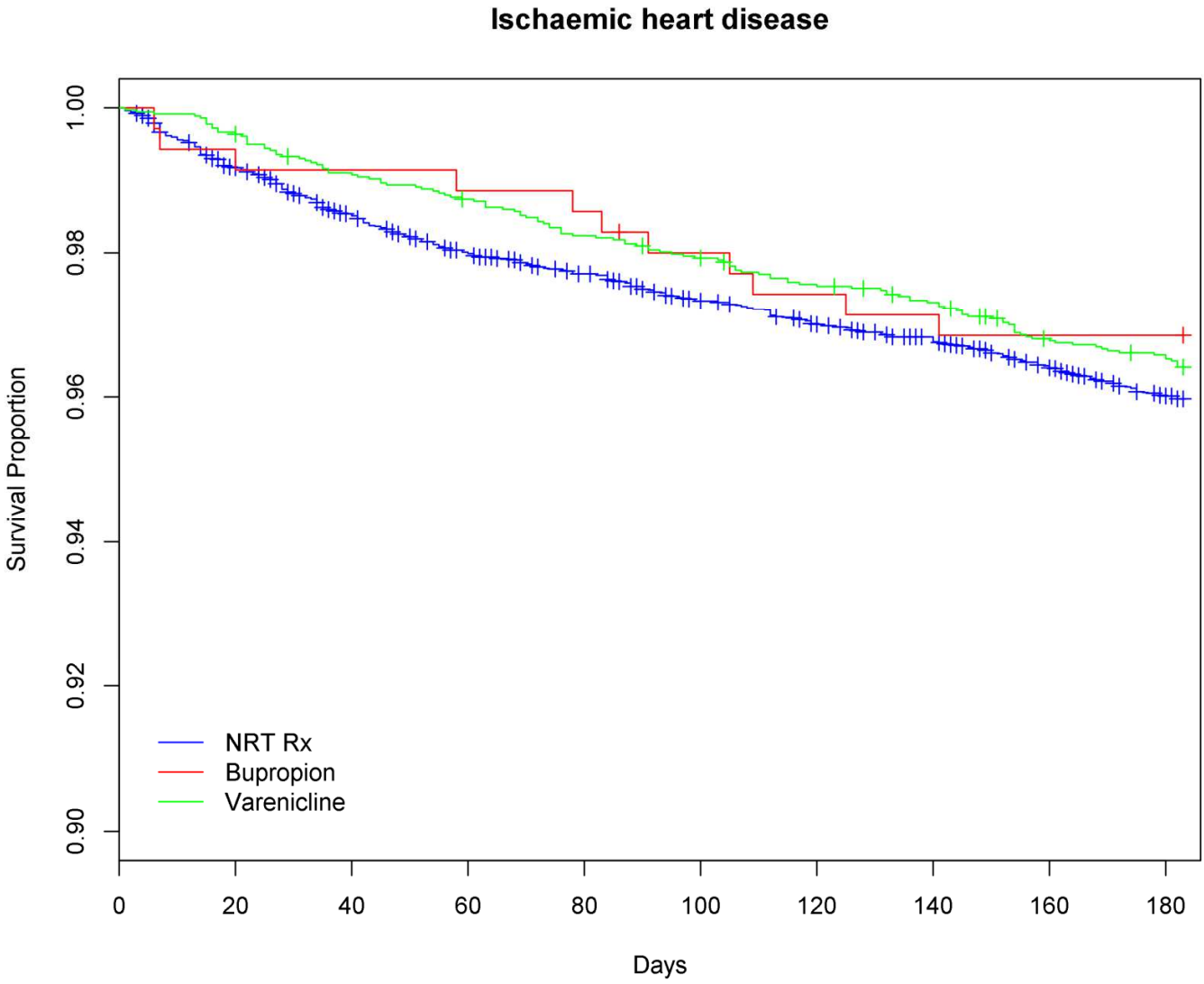
This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

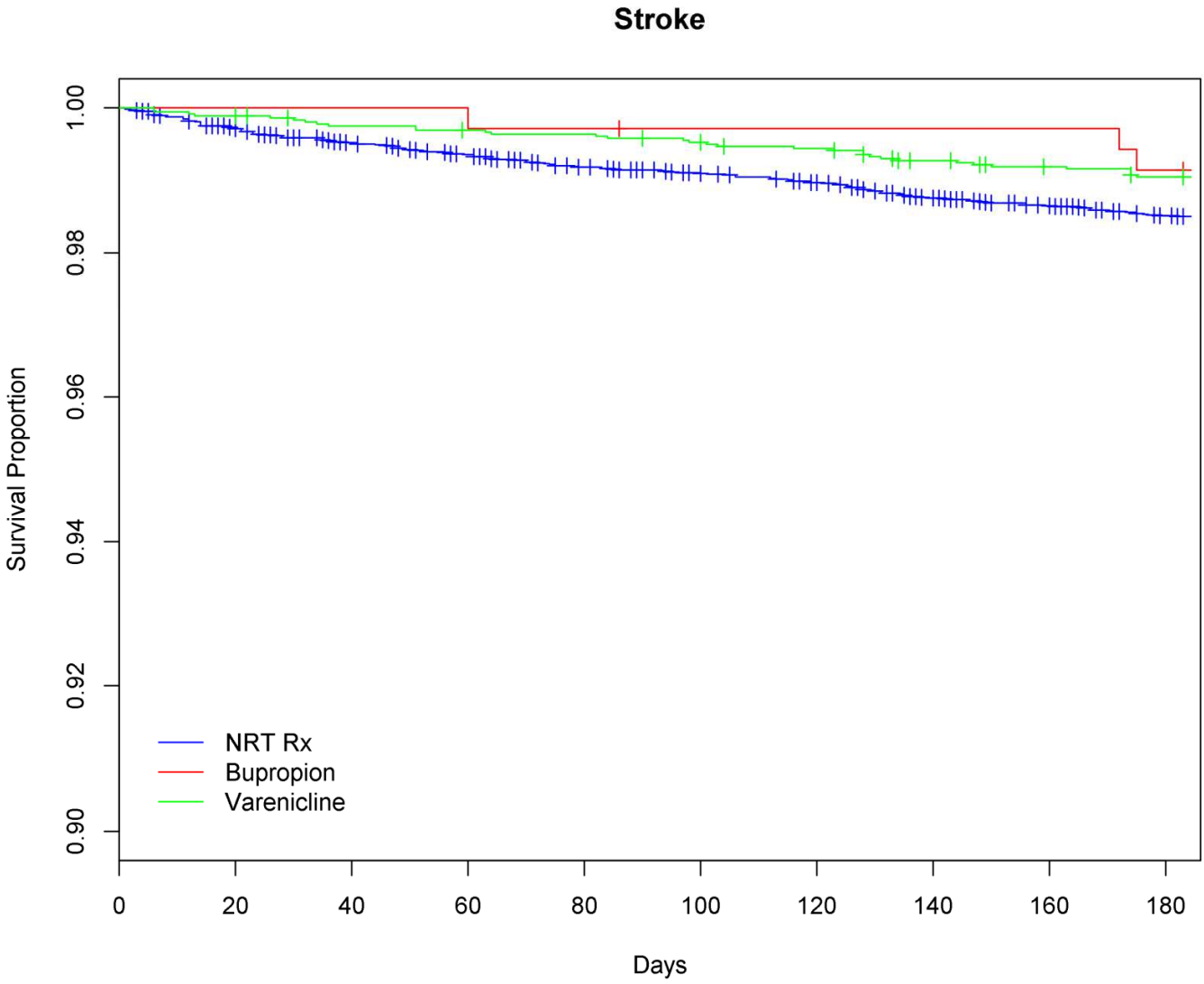
Table E17: Hazard ratio (95%CI) for self-harm during 3 months follow-up in users of varenicline vs. NRT, adjusted for an unmeasured binary confounder with a hazard ratio of 3

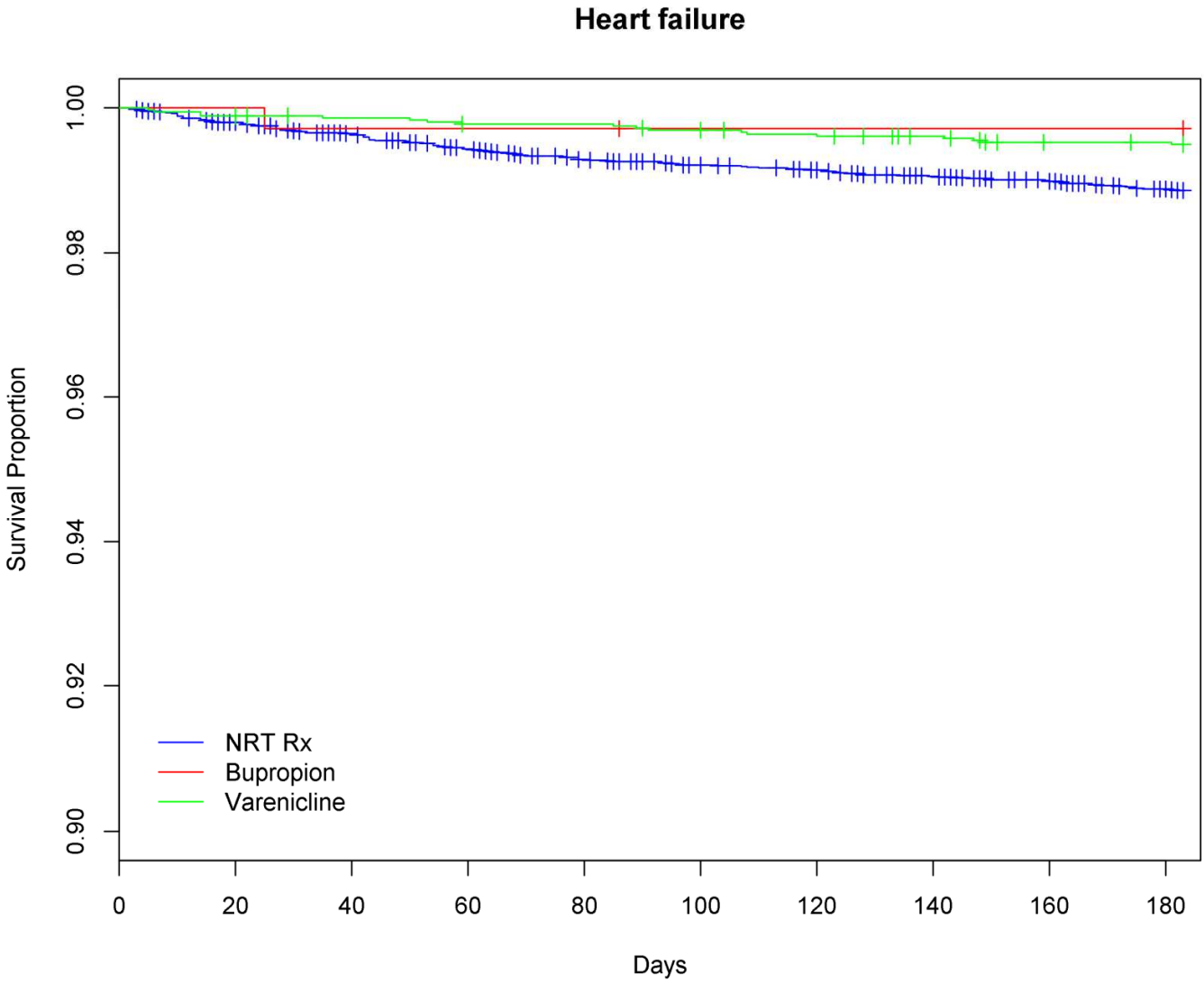
P1 / P0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
0.0	0.8 (0.3, 2.15)	0.96 (0.36, 2.58)	1.12 (0.42, 3.01)	1.28 (0.48, 3.44)	1.44 (0.54, 3.87)	1.6 (0.6, 4.3)	1.76 (0.66, 4.73)	1.92 (0.72, 5.16)	2.08 (0.78, 5.59)	2.24 (0.84, 6.02)	2.4 (0.9, 6.45)
0.1	0.67 (0.25, 1.79)	0.8 (0.3, 2.15)	0.93 (0.35, 2.51)	1.07 (0.4, 2.87)	1.2 (0.45, 3.23)	1.33 (0.5, 3.58)	1.47 (0.55, 3.94)	1.6 (0.6, 4.3)	1.73 (0.65, 4.66)	1.87 (0.7, 5.02)	2 (0.75, 5.38)
0.2	0.57 (0.21, 1.54)	0.69 (0.26, 1.84)	0.8 (0.3, 2.15)	0.91 (0.34, 2.46)	1.03 (0.39, 2.76)	1.14 (0.43, 3.07)	1.26 (0.47, 3.38)	1.37 (0.51, 3.69)	1.49 (0.56, 3.99)	1.6 (0.6, 4.3)	1.71 (0.64, 4.61)
0.3	0.5 (0.19, 1.34)	0.6 (0.23, 1.61)	0.7 (0.26, 1.88)	0.8 (0.3, 2.15)	0.9 (0.34, 2.42)	1 (0.38, 2.69)	1.1 (0.41, 2.96)	1.2 (0.45, 3.23)	1.3 (0.49, 3.49)	1.4 (0.53, 3.76)	1.5 (0.56, 4.03)
0.4	0.44 (0.17, 1.19)	0.53 (0.2, 1.43)	0.62 (0.23, 1.67)	0.71 (0.27, 1.91)	0.8 (0.3, 2.15)	0.89 (0.33, 2.39)	0.98 (0.37, 2.63)	1.07 (0.4, 2.87)	1.16 (0.43, 3.11)	1.24 (0.47, 3.34)	1.33 (0.5, 3.58)
0.5	0.4 (0.15, 1.08)	0.48 (0.18, 1.29)	0.56 (0.21, 1.51)	0.64 (0.24, 1.72)	0.72 (0.27, 1.94)	0.8 (0.3, 2.15)	0.88 (0.33, 2.37)	0.96 (0.36, 2.58)	1.04 (0.39, 2.8)	1.12 (0.42, 3.01)	1.2 (0.45, 3.23)
0.6	0.36 (0.14, 0.98)	0.44 (0.16, 1.17)	0.51 (0.19, 1.37)	0.58 (0.22, 1.56)	0.65 (0.25, 1.76)	0.73 (0.27, 1.95)	0.8 (0.3, 2.15)	0.87 (0.33, 2.35)	0.95 (0.35, 2.54)	1.02 (0.38, 2.74)	1.09 (0.41, 2.93)
0.7	0.33 (0.13, 0.9)	0.4 (0.15, 1.08)	0.47 (0.18, 1.25)	0.53 (0.2, 1.43)	0.6 (0.23, 1.61)	0.67 (0.25, 1.79)	0.73 (0.28, 1.97)	0.8 (0.3, 2.15)	0.87 (0.33, 2.33)	0.93 (0.35, 2.51)	1 (0.38, 2.69)
0.8	0.31 (0.12, 0.83)	0.37 (0.14, 0.99)	0.43 (0.16, 1.16)	0.49 (0.18, 1.32)	0.55 (0.21, 1.49)	0.62 (0.23, 1.65)	0.68 (0.25, 1.82)	0.74 (0.28, 1.98)	0.8 (0.3, 2.15)	0.86 (0.32, 2.32)	0.92 (0.35, 2.48)
0.9	0.29 (0.11, 0.77)	0.34 (0.13, 0.92)	0.4 (0.15, 1.08)	0.46 (0.17, 1.23)	0.51 (0.19, 1.38)	0.57 (0.21, 1.54)	0.63 (0.24, 1.69)	0.69 (0.26, 1.84)	0.74 (0.28, 2)	0.8 (0.3, 2.15)	0.86 (0.32, 2.3)
1.0	0.27 (0.1, 0.72)	0.32 (0.12, 0.86)	0.37 (0.14, 1)	0.43 (0.16, 1.15)	0.48 (0.18, 1.29)	0.53 (0.2, 1.43)	0.59 (0.22, 1.58)	0.64 (0.24, 1.72)	0.69 (0.26, 1.86)	0.75 (0.28, 2.01)	0.8 (0.3, 2.15)

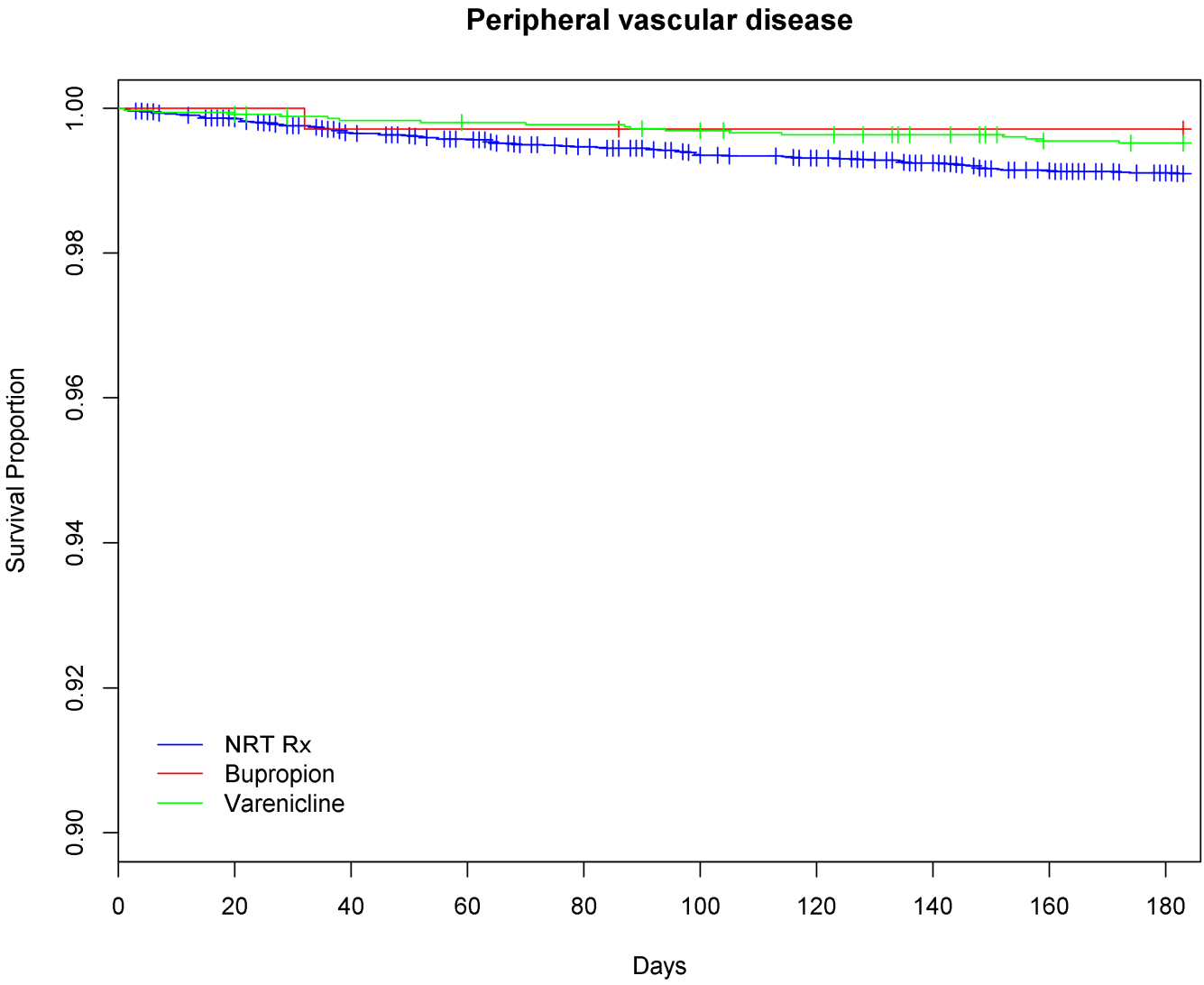
This tables shows how the observed hazard ratio (diagonal line of cells filled with light blue) would change in the presence of an unmeasured confounder with a hazard ratio of 3 and different combinations of prevalence rates among the user groups. P1/P0 = prevalence of the unmeasured confounder among users of varenicline (P1) and NRT Rx (P0). The cells filled with red mark the situations in which varenicline would be associated with a statistically significant increased hazard of the event. In addition, the cells filled with dark red mark the situations in which this hazard would also be clinically meaningful according to our study protocol (HR>=1.5). These calculations are based on: Lin et al. Biometrics 1998, 54(3), 948-963 (equation 2.9).

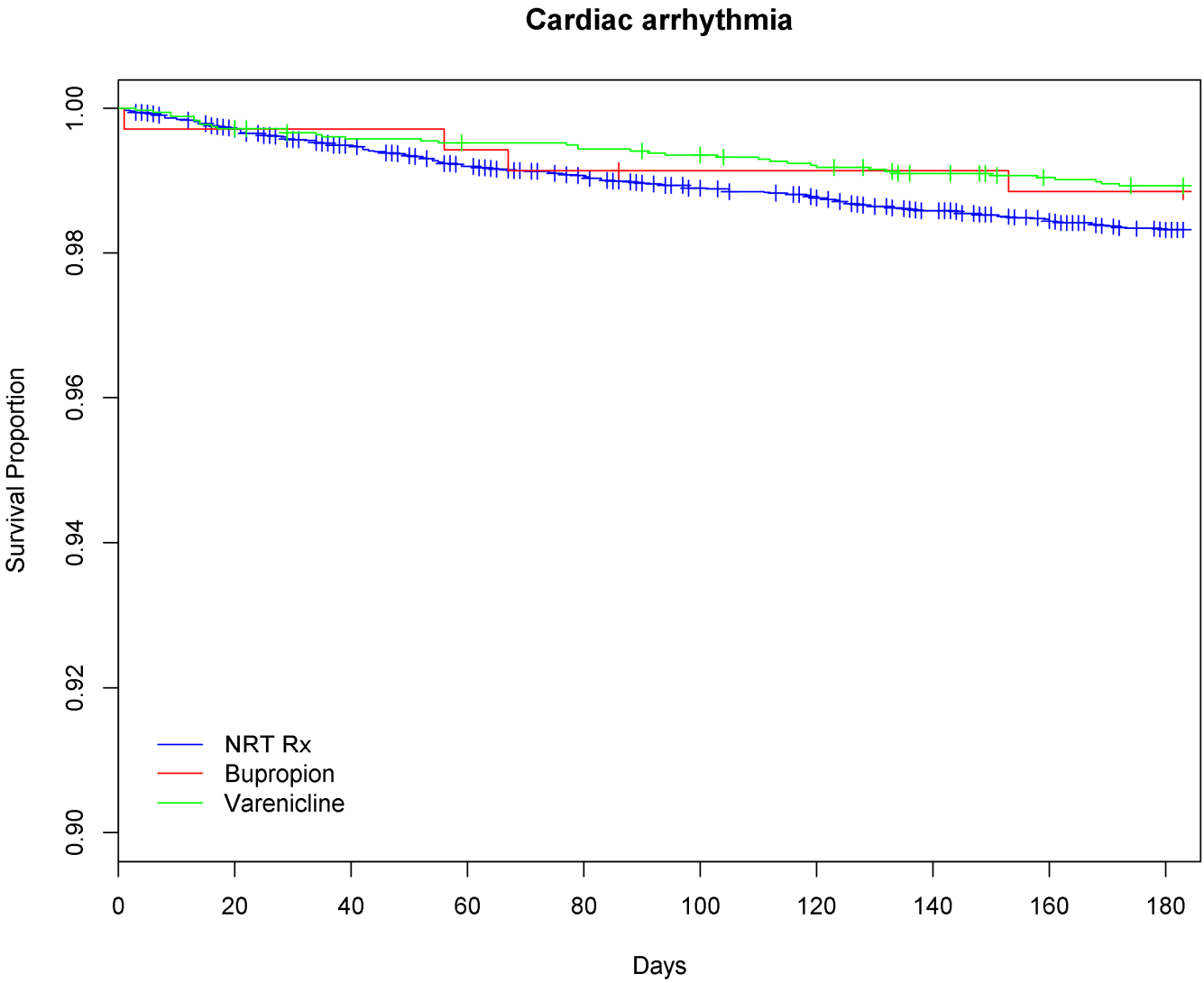
Figures E1-7: Kaplan-Meier survival curves for each neuropsychiatric/cardiovascular event during 6 months follow-up

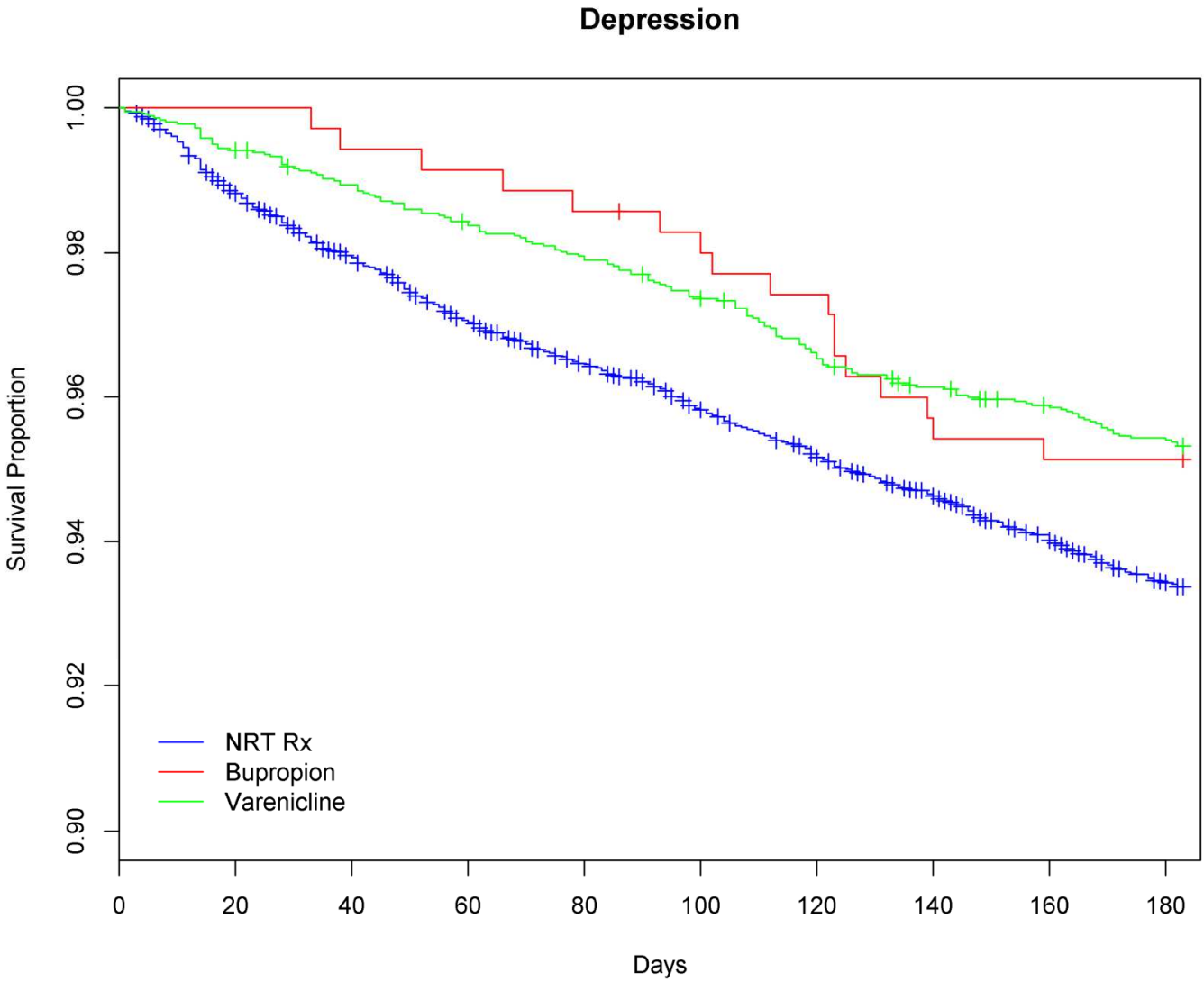

Ischaemic heart disease
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days

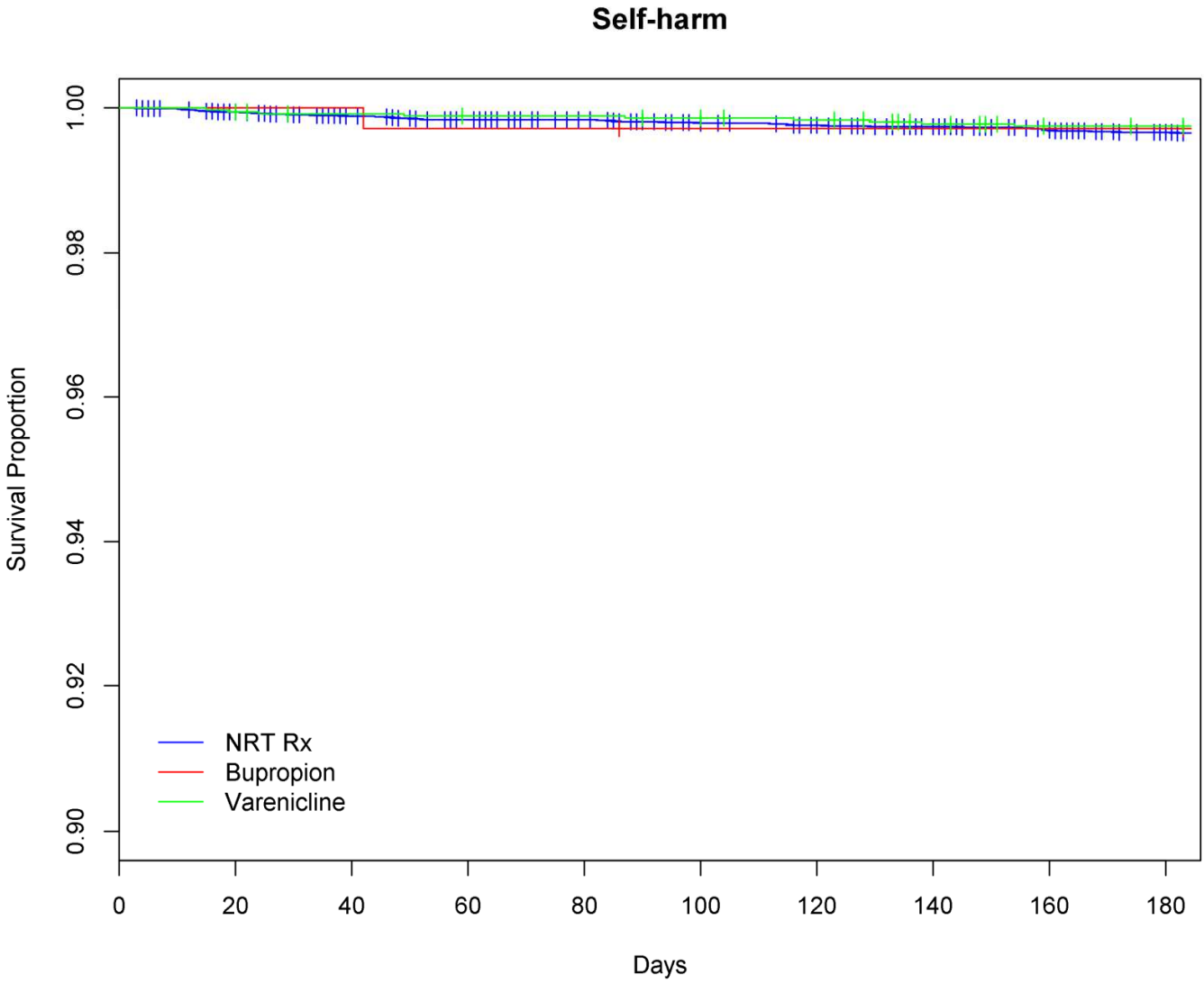

Stroke
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days


Heart failure
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days


Peripheral vascular disease
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days


Cardiac arrhythmia
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
0
20
40
60
80
100
120
140
160
180
Days
NRT Rx
Bupropion
Varenicline


Depression
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days


Self-harm
Survival Proportion
1.00
0.98
0.96
0.94
0.92
0.90
NRT Rx
Bupropion
Varenicline
0
20
40
60
80
100
120
140
160
180
Days

```
###START#########################################################################################

options(warn=1)

rm(list=ls()) #clear the workspace

### install packages, load libraries
#print(.packages()) #to list loaded packages
if(!require("ROCR"))
  install.packages("ROCR")
if(!require("MatchIt"))
  install.packages("MatchIt")
library(survival)
library(ROCR)
library(MatchIt)

#getwd() ### check working directory
setwd("C:/Users/Daniel Kotz/Documents/Data/stata12/csv") ### set working directory on Nottingham server
#setwd("D:/UM Network/WORK - UM/Funding/Q Award/Data-analyses") ### set working directory on D harddisk

### read in dat_final.csv
dat <- read.table("dat_final.csv", header=TRUE, sep=",", as.is=TRUE)

### read in dat_random1000.csv
#dat <- read.table("dat_random1000.csv", header=TRUE, sep=",", as.is=TRUE)

### coerce "med" into a factor with level N, B, and V (N is reference)
dat$med <- factor(dat$med, levels=c("N", "B", "V"))

### rename "sex1" variable to "sex"
names(dat)[which(names(dat) == "sex1")] <- "sex"

### coerce "sex" into a factor with level female and male (female is reference)
dat$sex <- factor(dat$sex, levels=c("female", "male"))

### create age deciles
dat$age.cat <- cut(dat$age, breaks=quantile(dat$age, prob=seq(0,1,.1)), include.lowest=TRUE)

### create age dummy
dat$age.cat <- ifelse(dat$age > median(dat$age), "older", "younger")

###Sample size#####################################################################################

### number of patients with missing data / definition complete case sample
head(dat,1)
sum(is.na(dat$age))
sum(is.na(dat$sex))
sum(is.na(dat$townsend_quintile))
sum(is.na(dat$sha1))

### show data for patients that have missing values on these variables
#dat[is.na(dat$age),]
#dat[is.na(dat$sex),]
```

```
#dat[is.na(dat$townsend_quintile),]
#dat[is.na(dat$sha1),]

### filter out patients that have missing values on these variables
dat <- dat[!is.na(dat$age),]
dat <- dat[!is.na(dat$sex),]
dat <- dat[!is.na(dat$townsend_quintile),]
dat <- dat[!is.na(dat$sha1),]

### create subset of COPD patients
dat <- subset(dat, copd==1)

### create dummies if abnormal spiro happened
head(dat,0)
dat$spiro.abnormal <- ifelse(is.na(dat$spiro.abnormal.day), 0, 1)

### number of patients with missing data / definition complete case sample
head(dat,1)
sum(is.na(dat$age))
sum(is.na(dat$sex))
sum(is.na(dat$townsend_quintile))
sum(is.na(dat$sha1))
sum(is.na(dat$mrc.score))
sum(is.na(dat$spiro.any.day))

### number of patients <35 years of age
length(dat$age[dat$age < 35])

### show data for patients that have missing values on these variables
dat[is.na(dat$age),]
dat[is.na(dat$sex),]
dat[is.na(dat$townsend_quintile),]
dat[is.na(dat$sha1),]
dat[is.na(dat$mrc.score),]
dat[is.na(dat$spiro.any.day),]

### show data for patients <35 years of age
dat[(dat$age < 35),]

### filter out patients that have missing values on these variables
dat <- dat[!is.na(dat$age),]
dat <- dat[!is.na(dat$sex),]
dat <- dat[!is.na(dat$townsend_quintile),]
dat <- dat[!is.na(dat$sha1),]
dat <- dat[!is.na(dat$mrc.score),] # thus only COPD patients with MRC score included!
dat <- dat[!is.na(dat$spiro.any.day),] # thus only COPD patients with any sprio (even if normal included!

### filter out patients <35 years of age
dat <- dat[!(dat$age < 35),]

### number of patients and patient-years per drug group
table(dat$med)
```

```
sum(dat$selfharm.day[dat$med == "N"])/365 #other way of coding: sum(dat[dat$med == "N","selfharm.day"])
sum(dat$selfharm.day[dat$med == "B"])/365
sum(dat$selfharm.day[dat$med == "V"])/365
sum(dat$depression.day[dat$med == "N"])/365
sum(dat$depression.day[dat$med == "B"])/365
sum(dat$depression.day[dat$med == "V"])/365
sum(dat$ihd.day[dat$med == "N"])/365
sum(dat$ihd.day[dat$med == "B"])/365
sum(dat$ihd.day[dat$med == "V"])/365
sum(dat$stroke.day[dat$med == "N"])/365
sum(dat$stroke.day[dat$med == "B"])/365
sum(dat$stroke.day[dat$med == "V"])/365
sum(dat$hf.day[dat$med == "N"])/365
sum(dat$hf.day[dat$med == "B"])/365
sum(dat$hf.day[dat$med == "V"])/365
sum(dat$pvd.day[dat$med == "N"])/365
sum(dat$pvd.day[dat$med == "B"])/365
sum(dat$pvd.day[dat$med == "V"])/365
sum(dat$arrhythmia.day[dat$med == "N"])/365
sum(dat$arrhythmia.day[dat$med == "B"])/365
sum(dat$arrhythmia.day[dat$med == "V"])/365

### baseline characteristics for categorical variables
table(dat$med, dat$sex)
prop.table(table(dat$med, dat$sex), margin=1)
table(dat$med, dat$sha1)
prop.table(table(dat$med, dat$sha1), margin=1)

table(dat$spiro.abnormal)
dat$mrc.score

table(dat$med, dat$diabetes.prior)
prop.table(table(dat$med, dat$diabetes.prior), margin=1)
table(dat$med, dat$ulcer.prior)
prop.table(table(dat$med, dat$ulcer.prior), margin=1)
table(dat$med, dat$renal.prior)
prop.table(table(dat$med, dat$renal.prior), margin=1)
table(dat$med, dat$rheuma.prior)
prop.table(table(dat$med, dat$rheuma.prior), margin=1)
table(dat$med, dat$cancer.prior)
prop.table(table(dat$med, dat$cancer.prior), margin=1)
table(dat$med, dat$alcohol.prior)
prop.table(table(dat$med, dat$alcohol.prior), margin=1)

table(dat$med, dat$selfharm.prior)
prop.table(table(dat$med, dat$selfharm.prior), margin=1)
table(dat$med, dat$depression.prior)
prop.table(table(dat$med, dat$depression.prior), margin=1)
table(dat$med, dat$ihd.prior)
prop.table(table(dat$med, dat$ihd.prior), margin=1)
table(dat$med, dat$stroke.prior)
prop.table(table(dat$med, dat$stroke.prior), margin=1)
table(dat$med, dat$hf.prior)
```

```
prop.table(table(dat$med, dat$hf.prior), margin=1)
table(dat$med, dat$pvd.prior)
prop.table(table(dat$med, dat$pvd.prior), margin=1)
table(dat$med, dat$arrhythmia.prior)
prop.table(table(dat$med, dat$arrhythmia.prior), margin=1)

### baseline characteristics for continuous variables
by(dat$age, dat$med, summary)
by(dat$age, dat$med, sd)
by(dat$townsend_quintile, dat$med, summary)
by(dat$townsend_quintile, dat$med, sd)
by(dat$mrc.score, dat$med, summary)
by(dat$mrc.score, dat$med, sd)

### testing baseline characteristics (all three groups) and pairwise comparisons for a dichotomous variable
res <- glm(sex ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(sex ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(diabetes.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(diabetes.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(ulcer.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(ulcer.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(renal.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(renal.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(rheuma.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(rheuma.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(cancer.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(cancer.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(alcohol.prior ~ med, family=binomial, data=dat)
summary(res)
```

```
anova(res, test="LRT")
res <- glm(alcohol.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(selfharm.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(selfharm.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(depression.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(depression.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(ihd.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(ihd.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(stroke.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(stroke.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(hf.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(hf.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(pvd.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(pvd.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

res <- glm(arrhythmia.prior ~ med, family=binomial, data=dat)
summary(res)
anova(res, test="LRT")
res <- glm(arrhythmia.prior ~ relevel(med, ref="B"), family=binomial, data=dat)
summary(res)

### testing baseline characteristics (all three groups) and pairwise comparisons for a continuous variable
res <- lm(age ~ med, data=dat)
summary(res)
anova(res)
res <- lm(age ~ relevel(med, ref="B"), data=dat)
summary(res)
```

```
res <- lm(townsend_quintile ~ med, data=dat)
summary(res)
anova(res)
res <- lm(townsend_quintile ~ relevel(med, ref="B"), data=dat)
summary(res)

res <- lm(mrc.score ~ med, data=dat)
summary(res)
anova(res)
res <- lm(mrc.score ~ relevel(med, ref="B"), data=dat)
summary(res)

### number and proportion of patients that experienced the specific event
table(dat$med, dat$selfharm)
prop.table(table(dat$med, dat$selfharm), margin=1)
#prop.test(x=sum(dat$med=="N" & dat$selfharm==1), n=sum(dat$med=="N")) #to calculate 95%CI
#binom.test(x=sum(dat$med=="N" & dat$selfharm==1), n=sum(dat$med=="N")) #same, but in case of low proportion
(more exact)
table(dat$med, dat$depression)
prop.table(table(dat$med, dat$depression), margin=1)
table(dat$med, dat$ihd)
prop.table(table(dat$med, dat$ihd), margin=1)
table(dat$med, dat$stroke)
prop.table(table(dat$med, dat$stroke), margin=1)
table(dat$med, dat$hf)
prop.table(table(dat$med, dat$hf), margin=1)
table(dat$med, dat$pvd)
prop.table(table(dat$med, dat$pvd), margin=1)
table(dat$med, dat$arrhythmia)
prop.table(table(dat$med, dat$arrhythmia), margin=1)

### chi^2 test of independence for the specific event # not for paper!
chisq.test(table(dat$med, dat$selfharm))
chisq.test(table(dat$med, dat$depression))
chisq.test(table(dat$med, dat$ihd))
chisq.test(table(dat$med, dat$stroke))
chisq.test(table(dat$med, dat$hf))
chisq.test(table(dat$med, dat$pvd))
chisq.test(table(dat$med, dat$arrhythmia))

###Survival analyses (COPD)#############################################################################

### survival analysis and Kaplan-Meier curves: selfharm

resp <- Surv(dat$selfharm.day, dat$selfharm)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_selfharm_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file
```

```
plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Self-harm")

dev.off()

### survival analysis and Kaplan-Meier curves: depression

resp <- Surv(dat$depression.day, dat$depression)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_depression_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Depression")

dev.off()

### survival analysis and Kaplan-Meier curves: ihd

resp <- Surv(dat$ihd.day, dat$ihd)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_ihd_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Ischaemic heart disease")

dev.off()

### survival analysis and Kaplan-Meier curves: stroke

resp <- Surv(dat$stroke.day, dat$stroke)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
```

```
print(res, print.rmean=TRUE)

png(filename="fig_KM_stroke_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Stroke")

dev.off()

### survival analysis and Kaplan-Meier curves: hf

resp <- Surv(dat$hf.day, dat$hf)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_hf_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Heart failure")

dev.off()

### survival analysis and Kaplan-Meier curves: pvd

resp <- Surv(dat$pvd.day, dat$pvd)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_pvd_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Peripheral vascular disease")

dev.off()

### survival analysis and Kaplan-Meier curves: arrhythmia

resp <- Surv(dat$arrhythmia.day, dat$arrhythmia)
```

```
ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_arrhythmia_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,180,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Cardiac arrhythmia")

dev.off()

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): selfharm

resp <- Surv(dat$selfharm.day, dat$selfharm)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res) #GLOBAL p should not be p<.05

#newdat <- data.frame(med=factor(rbind("N","B","V"))) #to plot crude Cox survival; not in paper!
#preds  <- survfit(res, newdata=newdat)
#plot(preds, col=c("blue", "red", "green"), xlab="days", ylab="Survival Proportion", xlim=c(0,186), ylim=c(ylow,1),
xaxt="n")
#axis(side=1, at=seq(0,180,20))
#legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
#title("Self-harm")

### examine residuals -- but figure out later exactly what the point of this is
#dfbs <- residuals(res, type="dfbeta")
#par(mfrow=c(2,1))
#plot(dfbs[,1], ylab=names(coef(res))[1], pch=19, cex=.5)
#plot(dfbs[,2], ylab=names(coef(res))[2], pch=19, cex=.5)
#abline(h=0, lty=2)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
```

```
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): depression

resp <- Surv(dat$depression.day, dat$depression)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): ihd

resp <- Surv(dat$ihd.day, dat$ihd)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
```

```
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): stroke

resp <- Surv(dat$stroke.day, dat$stroke)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): hf

resp <- Surv(dat$hf.day, dat$hf)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
```

```
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): pvd

resp <- Surv(dat$pvd.day, dat$pvd)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): arrhythmia

resp <- Surv(dat$arrhythmia.day, dat$arrhythmia)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
```

```
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

###Propensity scores (COPD)#############################################################################

### propensity score analysis for N vs. B - step 1: trim and match 1:1

datNB <- subset(dat, med == "N" | med == "B")
datNB$med <- factor(datNB$med, levels=c("N","B"))
str(datNB)
table(datNB$med)

datNB$medB <- ifelse(datNB$med == "B", 1, 0)
res <- glm(medB ~ age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior +
hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior +
cancer.prior + alcohol.prior, family=binomial, data=datNB)
preds <- predict(res, type="response") #preds = predicted probabilities = propensity scores
by(preds, datNB$med, summary)
nrow(datNB)
table(datNB$med)

### ROC cruve and AUC
pred <- prediction(preds, datNB$medB)
perf <- performance(pred, measure = "tpr", x.measure = "fpr")
plot(perf, lwd=2)
abline(a=0, b=1, lty="dotted")
performance(pred, measure="auc")@"y.values"[[1]]

### trim away the highest propensity scores of the N group and the lowest scores of the B group
sel1 <- datNB$med == "B" | (datNB$med == "N" & preds < quantile(preds[datNB$med == "N"], .975))
sel2 <- datNB$med == "N" | (datNB$med == "B" & preds > quantile(preds[datNB$med == "B"], .025))
datNB <- datNB[sel1 & sel2,]
preds <- preds[sel1 & sel2]

by(preds, datNB$med, summary)
nrow(datNB)

datNB$preds <- preds

dat.temp <- datNB[,c("medB","preds")]
res <- matchit(medB ~ preds, data=dat.temp)

datNB <- datNB[is.element(rownames(datNB), c(row.names(res$match.matrix), c(res$match.matrix))),]

table(datNB$med)
by(datNB$preds, datNB$med, summary)

### compare baseline characteristics of the two matched groups N vs. B

table(datNB$med, datNB$sex)
prop.table(table(datNB$med, datNB$sex), margin=1)
table(datNB$med, datNB$sha1)
```

```
prop.table(table(datNB$med, datNB$sha1), margin=1)
table(datNB$med, datNB$copd)
prop.table(table(datNB$med, datNB$copd), margin=1)
table(datNB$med, datNB$diabetes.prior)
prop.table(table(datNB$med, datNB$diabetes.prior), margin=1)
table(datNB$med, datNB$ulcer.prior)
prop.table(table(datNB$med, datNB$ulcer.prior), margin=1)
table(datNB$med, datNB$renal.prior)
prop.table(table(datNB$med, datNB$renal.prior), margin=1)
table(datNB$med, datNB$rheuma.prior)
prop.table(table(datNB$med, datNB$rheuma.prior), margin=1)
table(datNB$med, datNB$cancer.prior)
prop.table(table(datNB$med, datNB$cancer.prior), margin=1)
table(datNB$med, datNB$alcohol.prior)
prop.table(table(datNB$med, datNB$alcohol.prior), margin=1)
table(datNB$med, datNB$selfharm.prior)
prop.table(table(datNB$med, datNB$selfharm.prior), margin=1)
table(datNB$med, datNB$depression.prior)
prop.table(table(datNB$med, datNB$depression.prior), margin=1)
table(datNB$med, datNB$ihd.prior)
prop.table(table(datNB$med, datNB$ihd.prior), margin=1)
table(datNB$med, datNB$stroke.prior)
prop.table(table(datNB$med, datNB$stroke.prior), margin=1)
table(datNB$med, datNB$hf.prior)
prop.table(table(datNB$med, datNB$hf.prior), margin=1)
table(datNB$med, datNB$pvd.prior)
prop.table(table(datNB$med, datNB$pvd.prior), margin=1)
table(datNB$med, datNB$arrhythmia.prior)
prop.table(table(datNB$med, datNB$arrhythmia.prior), margin=1)
by(datNB$age, datNB$med, summary)
by(datNB$age, datNB$med, sd)
by(datNB$townsend_quintile, datNB$med, summary)
by(datNB$townsend_quintile, datNB$med, sd)
by(datNB$mrc.score, datNB$med, summary)
by(datNB$mrc.score, datNB$med, sd)

### propensity score analysis for N vs. B - step 2: Cox models for all 8 events

resp <- Surv(datNB$selfharm.day, datNB$selfharm)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$depression.day, datNB$depression)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$ihd.day, datNB$ihd)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)
```

```
resp <- Surv(datNB$stroke.day, datNB$stroke)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$hf.day, datNB$hf)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$pvd.day, datNB$pvd)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$arrhythmia.day, datNB$arrhythmia)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

### propensity score analysis for N vs. V - step 1: trim and match 1:1

datVB <- subset(dat, med == "N" | med == "V")
datVB$med <- factor(datVB$med, levels=c("N","V"))
str(datVB)
nrow(datVB)
table(datVB$med)

datVB$medV <- ifelse(datVB$med == "V", 1, 0)
res <- glm(medV ~ age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior +
hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior +
cancer.prior + alcohol.prior, family=binomial, data=datVB)
preds <- predict(res, type="response") #preds = predicted probabilities = propensity scores
by(preds, datVB$med, summary)

### ROC cruve and AUC
pred <- prediction(preds, datVB$medV)
perf <- performance(pred, measure = "tpr", x.measure = "fpr")
plot(perf, lwd=2)
abline(a=0, b=1, lty="dotted")
performance(pred, measure="auc")@"y.values"[[1]]

### trim away the highest propensity scores of the N group and the lowest scores of the B group
sel1 <- datVB$med == "V" | (datVB$med == "N" & preds < quantile(preds[datVB$med == "N"], .975))
sel2 <- datVB$med == "N" | (datVB$med == "V" & preds > quantile(preds[datVB$med == "V"], .025))
datVB <- datVB[sel1 & sel2,]
preds <- preds[sel1 & sel2]

by(preds, datVB$med, summary)
nrow(datVB)

datVB$preds <- preds
```

```
dat.temp <- datVB[,c("medV","preds")]
res <- matchit(medV ~ preds, data=dat.temp)

datVB <- datVB[is.element(rownames(datVB), c(row.names(res$match.matrix), c(res$match.matrix))),]

table(datVB$med)
by(datVB$preds, datVB$med, summary)

### compare baseline characteristics of the two matched groups N vs. V

table(datVB$med, datVB$sex)
prop.table(table(datVB$med, datVB$sex), margin=1)
table(datVB$med, datVB$sha1)
prop.table(table(datVB$med, datVB$sha1), margin=1)
table(datVB$med, datVB$copd)
prop.table(table(datVB$med, datVB$copd), margin=1)
table(datVB$med, datVB$diabetes.prior)
prop.table(table(datVB$med, datVB$diabetes.prior), margin=1)
table(datVB$med, datVB$ulcer.prior)
prop.table(table(datVB$med, datVB$ulcer.prior), margin=1)
table(datVB$med, datVB$renal.prior)
prop.table(table(datVB$med, datVB$renal.prior), margin=1)
table(datVB$med, datVB$rheuma.prior)
prop.table(table(datVB$med, datVB$rheuma.prior), margin=1)
table(datVB$med, datVB$cancer.prior)
prop.table(table(datVB$med, datVB$cancer.prior), margin=1)
table(datVB$med, datVB$alcohol.prior)
prop.table(table(datVB$med, datVB$alcohol.prior), margin=1)
table(datVB$med, datVB$selfharm.prior)
prop.table(table(datVB$med, datVB$selfharm.prior), margin=1)
table(datVB$med, datVB$depression.prior)
prop.table(table(datVB$med, datVB$depression.prior), margin=1)
table(datVB$med, datVB$ihd.prior)
prop.table(table(datVB$med, datVB$ihd.prior), margin=1)
table(datVB$med, datVB$stroke.prior)
prop.table(table(datVB$med, datVB$stroke.prior), margin=1)
table(datVB$med, datVB$hf.prior)
prop.table(table(datVB$med, datVB$hf.prior), margin=1)
table(datVB$med, datVB$pvd.prior)
prop.table(table(datVB$med, datVB$pvd.prior), margin=1)
table(datVB$med, datVB$arrhythmia.prior)
prop.table(table(datVB$med, datVB$arrhythmia.prior), margin=1)
by(datVB$age, datVB$med, summary)
by(datVB$age, datVB$med, sd)
by(datVB$townsend_quintile, datVB$med, summary)
by(datVB$townsend_quintile, datVB$med, sd)
by(datVB$mrc.score, datVB$med, summary)
by(datVB$mrc.score, datVB$med, sd)

### propensity score analysis for N vs. V - step 2: Cox models for all 8 events

resp <- Surv(datVB$selfharm.day, datVB$selfharm)
res <- coxph(resp ~ med, data=datVB)
```

```
summary(res)
cox.zph(res)

resp <- Surv(datVB$depression.day, datVB$depression)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$ihd.day, datVB$ihd)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$stroke.day, datVB$stroke)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$hf.day, datVB$hf)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$pvd.day, datVB$pvd)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$arrhythmia.day, datVB$arrhythmia)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

###3-months outcomes (COPD)#############################################################################
###3-months outcomes (COPD)#############################################################################
###3-months outcomes (COPD)#############################################################################

### number of patients and patient-years per drug group
table(dat$med)

sum(dat$selfharm.day.3m[dat$med == "N"])/365 #other way of coding: sum(dat[dat$med == "N","selfharm.day.3m"])
sum(dat$selfharm.day.3m[dat$med == "B"])/365
sum(dat$selfharm.day.3m[dat$med == "V"])/365
sum(dat$depression.day.3m[dat$med == "N"])/365
sum(dat$depression.day.3m[dat$med == "B"])/365
sum(dat$depression.day.3m[dat$med == "V"])/365
sum(dat$ihd.day.3m[dat$med == "N"])/365
sum(dat$ihd.day.3m[dat$med == "B"])/365
sum(dat$ihd.day.3m[dat$med == "V"])/365
sum(dat$stroke.day.3m[dat$med == "N"])/365
sum(dat$stroke.day.3m[dat$med == "B"])/365
sum(dat$stroke.day.3m[dat$med == "V"])/365
sum(dat$hf.day.3m[dat$med == "N"])/365
```

```
sum(dat$hf.day.3m[dat$med == "B"])/365
sum(dat$hf.day.3m[dat$med == "V"])/365
sum(dat$pvd.day.3m[dat$med == "N"])/365
sum(dat$pvd.day.3m[dat$med == "B"])/365
sum(dat$pvd.day.3m[dat$med == "V"])/365
sum(dat$arrhythmia.day.3m[dat$med == "N"])/365
sum(dat$arrhythmia.day.3m[dat$med == "B"])/365
sum(dat$arrhythmia.day.3m[dat$med == "V"])/365

### number and proportion of patients that experienced the specific event
table(dat$med, dat$selfharm.3m)
prop.table(table(dat$med, dat$selfharm.3m), margin=1)
table(dat$med, dat$depression.3m)
prop.table(table(dat$med, dat$depression.3m), margin=1)
table(dat$med, dat$ihd.3m)
prop.table(table(dat$med, dat$ihd.3m), margin=1)
table(dat$med, dat$stroke.3m)
prop.table(table(dat$med, dat$stroke.3m), margin=1)
table(dat$med, dat$hf.3m)
prop.table(table(dat$med, dat$hf.3m), margin=1)
table(dat$med, dat$pvd.3m)
prop.table(table(dat$med, dat$pvd.3m), margin=1)
table(dat$med, dat$arrhythmia.3m)
prop.table(table(dat$med, dat$arrhythmia.3m), margin=1)

### chi^2 test of independence for the specific event # not for paper!
chisq.test(table(dat$med, dat$selfharm.3m))
chisq.test(table(dat$med, dat$depression.3m))
chisq.test(table(dat$med, dat$ihd.3m))
chisq.test(table(dat$med, dat$stroke.3m))
chisq.test(table(dat$med, dat$hf.3m))
chisq.test(table(dat$med, dat$pvd.3m))
chisq.test(table(dat$med, dat$arrhythmia.3m))

###Survival analyses (COPD 3m)#############################################################################

### survival analysis and Kaplan-Meier curves: selfharm

resp <- Surv(dat$selfharm.day.3m, dat$selfharm.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_selfharm_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Self-harm during 3 months follow-up")
```

```
dev.off()

### survival analysis and Kaplan-Meier curves: depression

resp <- Surv(dat$depression.day.3m, dat$depression.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_depression_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0, bty="n")
title("Depression during 3 months follow-up")

dev.off()

### survival analysis and Kaplan-Meier curves: ihd

resp <- Surv(dat$ihd.day.3m, dat$ihd.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_ihd_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0, bty="n")
title("Ischaemic heart disease during 3 months follow-up")

dev.off()

### survival analysis and Kaplan-Meier curves: stroke

resp <- Surv(dat$stroke.day.3m, dat$stroke.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_stroke_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
```

```
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Stroke during 3 months follow-up")

dev.off()

### survival analysis and Kaplan-Meier curves: hf

resp <- Surv(dat$hf.day.3m, dat$hf.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_hf_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Heart failure during 3 months follow-up")

dev.off()

### survival analysis and Kaplan-Meier curves: pvd

resp <- Surv(dat$pvd.day.3m, dat$pvd.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)

png(filename="fig_KM_pvd_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0,
bty="n")
title("Peripheral vascular disease during 3 months follow-up")

dev.off()

### survival analysis and Kaplan-Meier curves: arrhythmia

resp <- Surv(dat$arrhythmia.day.3m, dat$arrhythmia.3m)

ylow <- .90 #lower y-axis limit for KM curve

res <- survfit(resp ~ med, data=dat)
print(res, print.rmean=TRUE)
```

```
png(filename="fig_KM_arrhythmia_3m_COPD.png", res=350, width=3000, height=2500, type="cairo") #to save as png file

plot(res, col=c("blue", "red", "green"), xlab="Days", ylab="Survival Proportion", xlim=c(0,93), ylim=c(ylow,1), xaxt="n")
axis(side=1, at=seq(0,90,20))
legend(x=3, y=ylow, legend=c("NRT Rx", "Bupropion", "Varenicline"), col=c("blue", "red", "green"), lty="solid", yjust=0, bty="n")
title("Cardiac arrhythmia during 3 months follow-up")

dev.off()

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): selfharm

resp <- Surv(dat$selfharm.day.3m, dat$selfharm.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): depression

resp <- Surv(dat$depression.day.3m, dat$depression.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
```

```
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): ihd

resp <- Surv(dat$ihd.day.3m, dat$ihd.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): stroke

resp <- Surv(dat$stroke.day.3m, dat$stroke.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
```

```
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): hf

resp <- Surv(dat$hf.day.3m, dat$hf.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior
+ ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior
+ rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior +
depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior +
ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): pvd

resp <- Surv(dat$pvd.day.3m, dat$pvd.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior +
stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior +
rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
```

```
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

### crude and adjusted Cox proportional hazard model, and test for interaction (med x sex): arrhythmia

resp <- Surv(dat$arrhythmia.day.3m, dat$arrhythmia.3m)

res <- coxph(resp ~ med, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B"), data=dat))
cox.zph(res)

res <- coxph(resp ~ med + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
summary(res)
summary(coxph(resp ~ relevel(med, ref="B") + age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

res1 <- coxph(resp ~ med*sex + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat)
anova(res1, res)
summary(res1)
summary(coxph(resp ~ med*relevel(sex, ref="male") + age + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, data=dat))

###Propensity scores (COPD 3m)#########################################################################

### propensity score analysis for N vs. B - step 1: trim and match 1:1

datNB <- subset(dat, med == "N" | med == "B")
datNB$med <- factor(datNB$med, levels=c("N","B"))
str(datNB)
table(datNB$med)

datNB$medB <- ifelse(datNB$med == "B", 1, 0)
res <- glm(medB ~ age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior + hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior + cancer.prior + alcohol.prior, family=binomial, data=datNB)
preds <- predict(res, type="response") #preds = predicted probabilities = propensity scores
```

```
by(preds, datNB$med, summary)
nrow(datNB)
table(datNB$med)

### ROC cruve and AUC
pred <- prediction(preds, datNB$medB)
perf <- performance(pred, measure = "tpr", x.measure = "fpr")
plot(perf, lwd=2)
abline(a=0, b=1, lty="dotted")
performance(pred, measure="auc")@"y.values"[[1]]

### trim away the highest propensity scores of the N group and the lowest scores of the B group
sel1 <- datNB$med == "B" | (datNB$med == "N" & preds < quantile(preds[datNB$med == "N"], .975))
sel2 <- datNB$med == "N" | (datNB$med == "B" & preds > quantile(preds[datNB$med == "B"], .025))
datNB <- datNB[sel1 & sel2,]
preds <- preds[sel1 & sel2]

by(preds, datNB$med, summary)
nrow(datNB)

datNB$preds <- preds

dat.temp <- datNB[,c("medB","preds")]
res <- matchit(medB ~ preds, data=dat.temp)

datNB <- datNB[is.element(rownames(datNB), c(row.names(res$match.matrix), c(res$match.matrix))),]

table(datNB$med)
by(datNB$preds, datNB$med, summary)

### compare baseline characteristics of the two matched groups N vs. B

table(datNB$med, datNB$sex)
prop.table(table(datNB$med, datNB$sex), margin=1)
table(datNB$med, datNB$sha1)
prop.table(table(datNB$med, datNB$sha1), margin=1)
table(datNB$med, datNB$copd)
prop.table(table(datNB$med, datNB$copd), margin=1)
table(datNB$med, datNB$diabetes.prior)
prop.table(table(datNB$med, datNB$diabetes.prior), margin=1)
table(datNB$med, datNB$ulcer.prior)
prop.table(table(datNB$med, datNB$ulcer.prior), margin=1)
table(datNB$med, datNB$renal.prior)
prop.table(table(datNB$med, datNB$renal.prior), margin=1)
table(datNB$med, datNB$rheuma.prior)
prop.table(table(datNB$med, datNB$rheuma.prior), margin=1)
table(datNB$med, datNB$cancer.prior)
prop.table(table(datNB$med, datNB$cancer.prior), margin=1)
table(datNB$med, datNB$alcohol.prior)
prop.table(table(datNB$med, datNB$alcohol.prior), margin=1)
table(datNB$med, datNB$selfharm.prior)
prop.table(table(datNB$med, datNB$selfharm.prior), margin=1)
table(datNB$med, datNB$depression.prior)
```

```
prop.table(table(datNB$med, datNB$depression.prior), margin=1)
table(datNB$med, datNB$ihd.prior)
prop.table(table(datNB$med, datNB$ihd.prior), margin=1)
table(datNB$med, datNB$stroke.prior)
prop.table(table(datNB$med, datNB$stroke.prior), margin=1)
table(datNB$med, datNB$hf.prior)
prop.table(table(datNB$med, datNB$hf.prior), margin=1)
table(datNB$med, datNB$pvd.prior)
prop.table(table(datNB$med, datNB$pvd.prior), margin=1)
table(datNB$med, datNB$arrhythmia.prior)
prop.table(table(datNB$med, datNB$arrhythmia.prior), margin=1)
by(datNB$age, datNB$med, summary)
by(datNB$age, datNB$med, sd)
by(datNB$townsend_quintile, datNB$med, summary)
by(datNB$townsend_quintile, datNB$med, sd)
by(datNB$mrc.score, datNB$med, summary)
by(datNB$mrc.score, datNB$med, sd)

### propensity score analysis for N vs. B - step 2: Cox models for all 8 events

resp <- Surv(datNB$selfharm.day.3m, datNB$selfharm.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$depression.day.3m, datNB$depression.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$ihd.day.3m, datNB$ihd.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$stroke.day.3m, datNB$stroke.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$hf.day.3m, datNB$hf.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$pvd.day.3m, datNB$pvd.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
cox.zph(res)

resp <- Surv(datNB$arrhythmia.day.3m, datNB$arrhythmia.3m)
res <- coxph(resp ~ med, data=datNB)
summary(res)
```

```
cox.zph(res)

### propensity score analysis for N vs. V - step 1: trim and match 1:1

datVB <- subset(dat, med == "N" | med == "V")
datVB$med <- factor(datVB$med, levels=c("N","V"))
str(datVB)
nrow(datVB)
table(datVB$med)

datVB$medV <- ifelse(datVB$med == "V", 1, 0)
res <- glm(medV ~ age + sex + townsend_quintile + sha1 + selfharm.prior + depression.prior + ihd.prior + stroke.prior +
hf.prior + pvd.prior + arrhythmia.prior + mrc.score + diabetes.prior + ulcer.prior + renal.prior + rheuma.prior +
cancer.prior + alcohol.prior, family=binomial, data=datVB)
preds <- predict(res, type="response") #preds = predicted probabilities = propensity scores
by(preds, datVB$med, summary)

### ROC cruve and AUC
pred <- prediction(preds, datVB$medV)
perf <- performance(pred, measure = "tpr", x.measure = "fpr")
plot(perf, lwd=2)
abline(a=0, b=1, lty="dotted")
performance(pred, measure="auc")@"y.values"[[1]]

### trim away the highest propensity scores of the N group and the lowest scores of the B group
sel1 <- datVB$med == "V" | (datVB$med == "N" & preds < quantile(preds[datVB$med == "N"], .975))
sel2 <- datVB$med == "N" | (datVB$med == "V" & preds > quantile(preds[datVB$med == "V"], .025))
datVB <- datVB[sel1 & sel2,]
preds <- preds[sel1 & sel2]

by(preds, datVB$med, summary)
nrow(datVB)

datVB$preds <- preds

dat.temp <- datVB[,c("medV","preds")]
res <- matchit(medV ~ preds, data=dat.temp)

datVB <- datVB[is.element(rownames(datVB), c(row.names(res$match.matrix), c(res$match.matrix))),]

table(datVB$med)
by(datVB$preds, datVB$med, summary)

### compare baseline characteristics of the two matched groups N vs. V

table(datVB$med, datVB$sex)
prop.table(table(datVB$med, datVB$sex), margin=1)
table(datVB$med, datVB$sha1)
prop.table(table(datVB$med, datVB$sha1), margin=1)
table(datVB$med, datVB$copd)
prop.table(table(datVB$med, datVB$copd), margin=1)
table(datVB$med, datVB$diabetes.prior)
prop.table(table(datVB$med, datVB$diabetes.prior), margin=1)
```

```
table(datVB$med, datVB$ulcer.prior)
prop.table(table(datVB$med, datVB$ulcer.prior), margin=1)
table(datVB$med, datVB$renal.prior)
prop.table(table(datVB$med, datVB$renal.prior), margin=1)
table(datVB$med, datVB$rheuma.prior)
prop.table(table(datVB$med, datVB$rheuma.prior), margin=1)
table(datVB$med, datVB$cancer.prior)
prop.table(table(datVB$med, datVB$cancer.prior), margin=1)
table(datVB$med, datVB$alcohol.prior)
prop.table(table(datVB$med, datVB$alcohol.prior), margin=1)
table(datVB$med, datVB$selfharm.prior)
prop.table(table(datVB$med, datVB$selfharm.prior), margin=1)
table(datVB$med, datVB$depression.prior)
prop.table(table(datVB$med, datVB$depression.prior), margin=1)
table(datVB$med, datVB$ihd.prior)
prop.table(table(datVB$med, datVB$ihd.prior), margin=1)
table(datVB$med, datVB$stroke.prior)
prop.table(table(datVB$med, datVB$stroke.prior), margin=1)
table(datVB$med, datVB$hf.prior)
prop.table(table(datVB$med, datVB$hf.prior), margin=1)
table(datVB$med, datVB$pvd.prior)
prop.table(table(datVB$med, datVB$pvd.prior), margin=1)
table(datVB$med, datVB$arrhythmia.prior)
prop.table(table(datVB$med, datVB$arrhythmia.prior), margin=1)
by(datVB$age, datVB$med, summary)
by(datVB$age, datVB$med, sd)
by(datVB$townsend_quintile, datVB$med, summary)
by(datVB$townsend_quintile, datVB$med, sd)
by(datVB$mrc.score, datVB$med, summary)
by(datVB$mrc.score, datVB$med, sd)

### propensity score analysis for N vs. V - step 2: Cox models for all 8 events

resp <- Surv(datVB$selfharm.day.3m, datVB$selfharm.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$depression.day.3m, datVB$depression.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$ihd.day.3m, datVB$ihd.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$stroke.day.3m, datVB$stroke.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)
```

```
resp <- Surv(datVB$hf.day.3m, datVB$hf.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$pvd.day.3m, datVB$pvd.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

resp <- Surv(datVB$arrhythmia.day.3m, datVB$arrhythmia.3m)
res <- coxph(resp ~ med, data=datVB)
summary(res)
cox.zph(res)

###THE END#############################################################################################
```