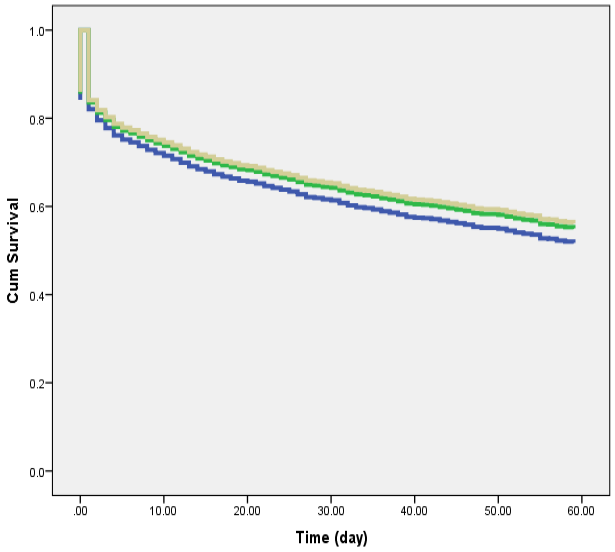
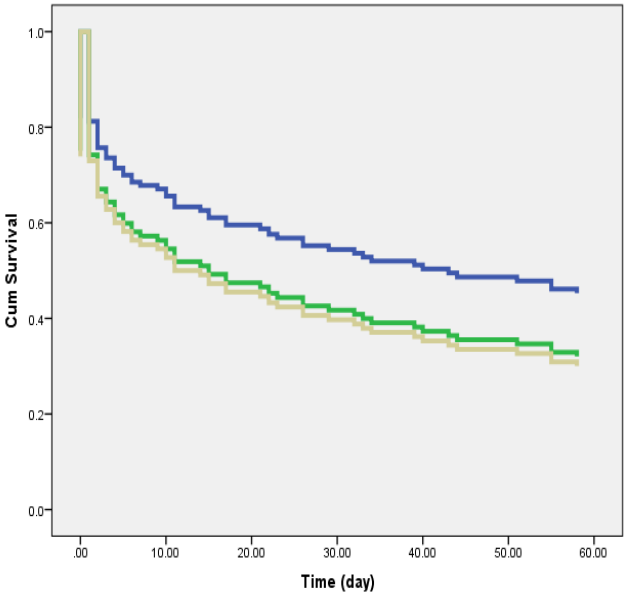
Figure S1. Interaction of Haplotypic Risk and Treatment Effect on Days to Relapse After Quitting

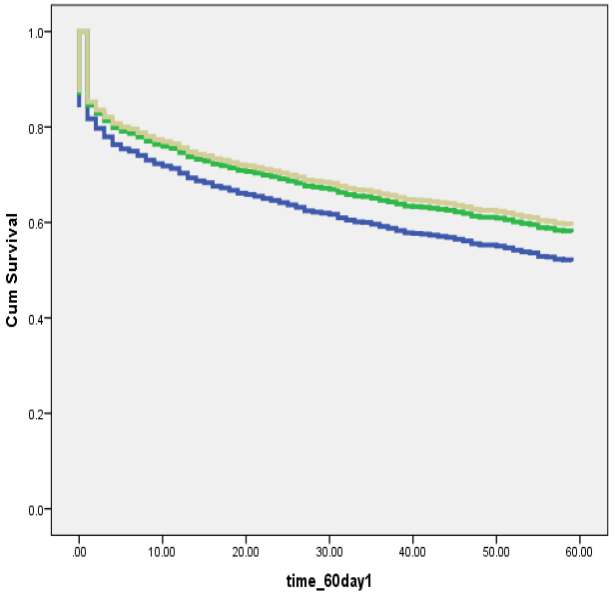
a. Entire Sample (N=1015)



b. Placebo group (N=117)



c. Treatment group (N=898)



The interaction of haplotypes and treatment is significant (wald= 6.46, df=2, p=0.040).

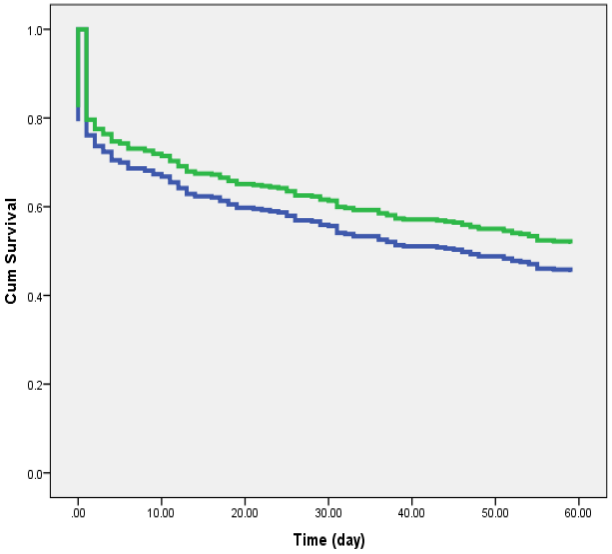
Modeling days to relapse over 60 days in UW-TTURC study.
Haplotypes based on 2 SNPs (rs16969968, rs680244)

H1=G_C	20.8%	
H2=G_T	43.7%	
H3=A_C	35.5%	

Figure S2. Treatment Effect Varies with Haplotypes on Ability to Quit Smoking (Time to Relapse)

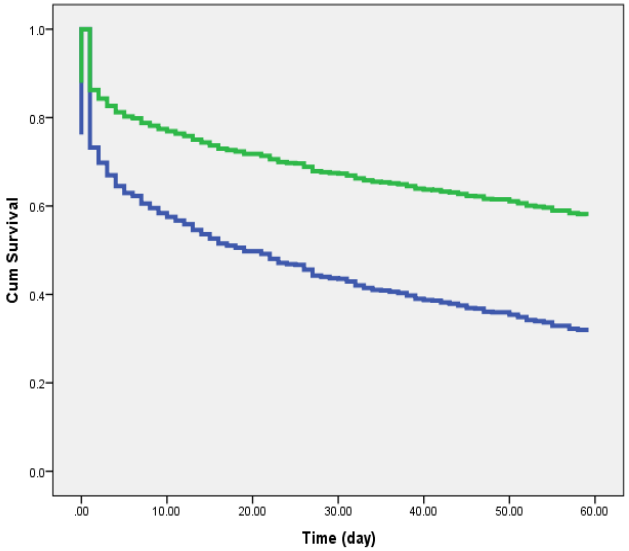
a. Haplotype H1 (G_C): N=422
(20.8%)
(54 placebo, 368 treatment)

RH=0.83, p=0.36



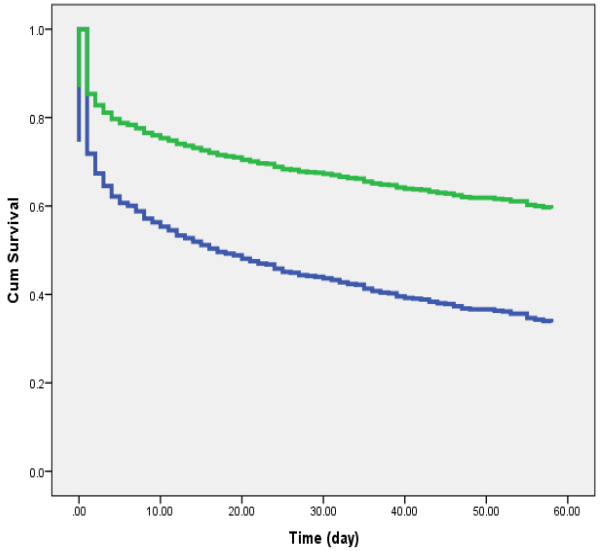
b. Haplotype H2 (G_T): N=889
(43.7%)
(100 placebo, 789 treatment)

RH=0.48, p=2.7*10^{-8}



c. Haplotype H3 (A_C): N=719
(35.5%)
(80 placebo, 639 treatment)

RH=0.48, p=9.7*10^{-7}

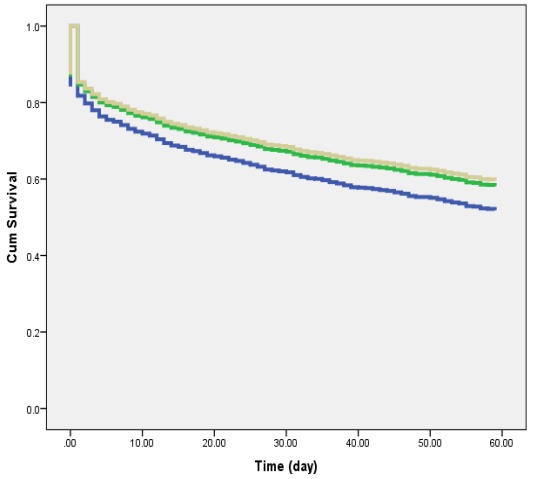


Placebo
Active Treatment

Modeling RH (relative hazard) for relapse to smoking over 60 days in UW-TTURC study (1015 subjects).
Haplotypes based on 2 SNPs (rs16969968, rs680244)
Note- the N based on haplotypes is 2 times the number of subjects.

Figure S3. Haplotypic Risk on Ability to Quit Smoking for Each Active Treatments (Bupropion, Nicotine Replacement Therapy (NRT), Combined Bupropion and NRT)

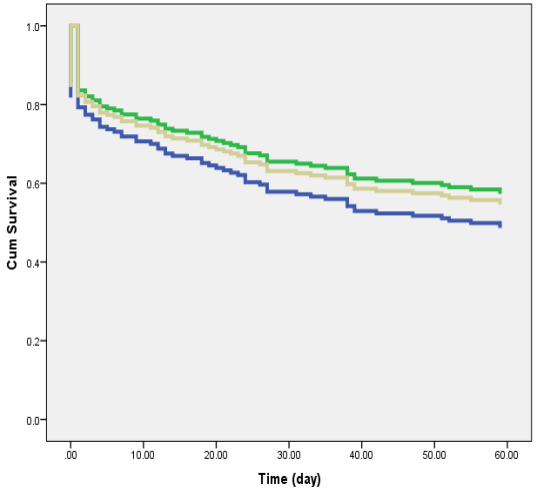
a. Active Treatment group (N=898)



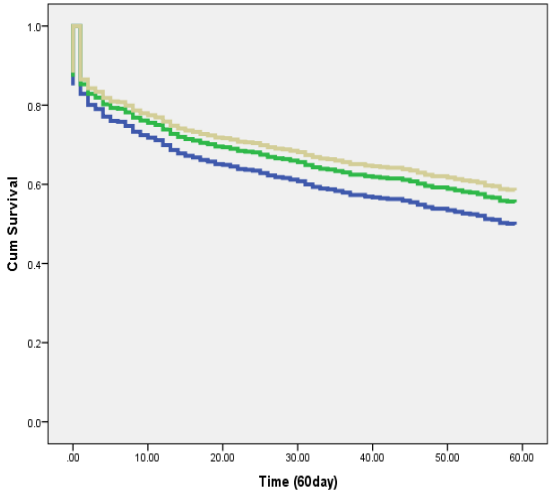
Haplotypes based on 2 SNPs (rs16969968, rs680244)

H1=G_C	20.8%
H2=G_T	43.7%
H3=A_C	35.5%

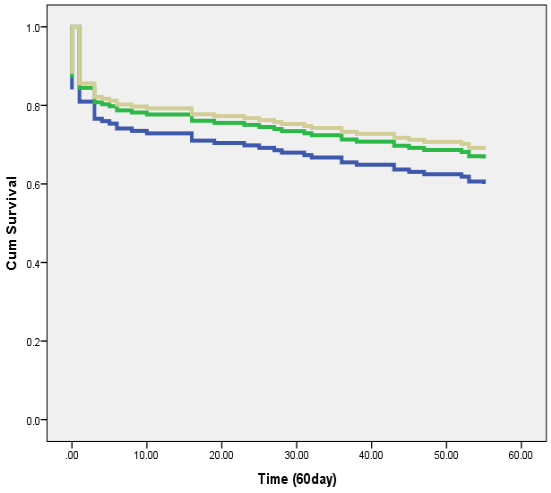
b. Bupropion group (N=179)



c. Nicotine Replacement group (NRT) (N=534)



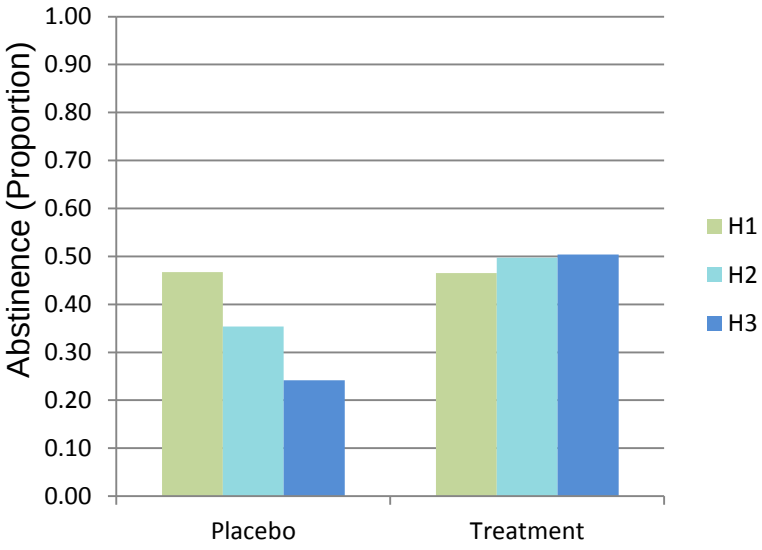
d. Combined Bupropion/NRT group (N=185)



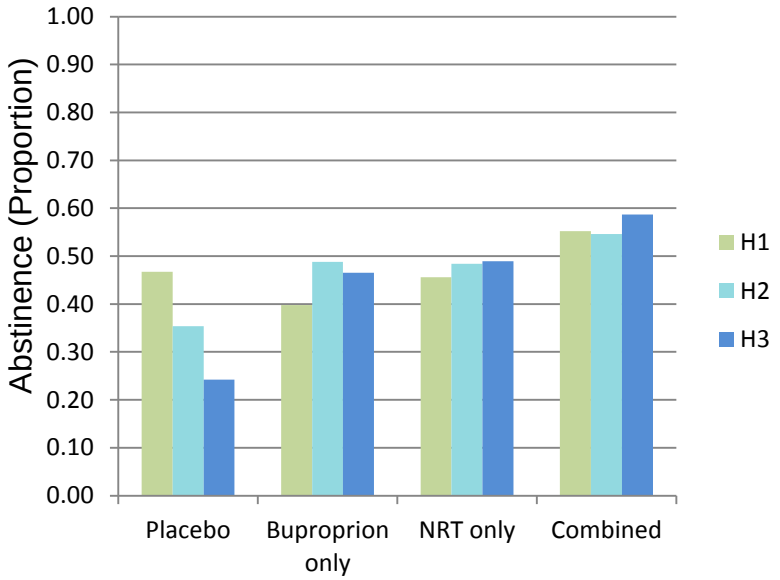
Haplotypic risk is not significant in predicting ability to quit (Wald=1.08, df=2, p=0.58).
No significant differences in haplotypic risks on ability to quit between groups (Wald=1.16, df=4, p=0.88).

Figure S4. Abstinence at End of Treatment Differs by Haplotypes in the Placebo Group, But Not in the Treatment Group

a. Abstinence in the Placebo and Treatment Groups, by Haplotype



b. Abstinence in the Placebo and 3 Treatment Groups (Buproprion only, NRT[a] only, and Combined) by Haplotype



The interaction of haplotypes and treatment on abstinence is significant (X^2=8.97, df=2, p=0.011).

[a]NRT: Nicotine Replacement Therapy
Abstinence is defined at end of 8 Week treatment. Odds ratios are adjusted for age and gender.
Haplotypes based on 2 SNPs (rs16969968, rs680244): H1=G_C(20.8%), H2=G_T(43.7%), H3=A_C(35.5%).
N=1073 (132 in the placebo group; 941 in the treatment group (188 with Buproprion only, 563 with NRT only, and 190 with the combined group).

Table S1. Characteristics of the ARIC and UW-TTURC Samples

	Study	
	ARIC N=5,216	**UW-TTURC** N=1073
Age, mean ± (sd)	54.3 (5.7)	44.6 (11.4)
Gender, N (%)		
Female	2285 (43.8)	623 (58.1)
Male	2931 (56.2)	450 (41.9)
Cigarettes per day, mean ± (sd)	23.6 (13.6)	21.8 (9.04)
Haplotypes (rs16969968-rs680244*), N (%)		
H1- G_C	2547 (24.4)	447 (20.8)
H2- G_T	4421 (42.4)	938 (43.7)
H3- A_C	3464 (33.2)	761 (35.5)
Intervention, N (%)		
Placebo	Not Applicable	132 (12.3)
Active Treatment	Not Applicable	941 (87.7)

* In the ARIC sample, rs951266 was used as a proxy for rs16969968 (r^2 = 0.97 in CEU in 1000 Genomes database); rs6495306 was used as a proxy for rs680244 (r^2=1 in CEU in 1000 Genomes database).

Table S2. Modeling Smoking Heaviness (Cigarettes per Day) in the ARIC and UW-TTURC Samples*

Predictors	Study					
	ARIC			UW-TTURC		
	β	95% C.I.	P	β	95% C.I.	P
Haplotypes (rs16969968-rs680244)**			(a)			(b)
H1- G_C	reference					
H2- G_T	.097	(.048, .15)	8.9×10^{-5}	0.029	(-0.055, .11)	.50
H3- A_C	.19	(.14, .24)	8.1×10^{-14}	0.11	(.019, .19)	.017

*All models were adjusted for age (quartiles) and gender.

**In the ARIC sample, rs951266 was used as a proxy for rs16969968 ($r^2 = 0.97$ in CEU in 1000 Genomes database); rs6495306 was used as a proxy for rs680244 ($r^2=1$ in CEU in 1000 Genomes database).

(a) Wald=56.4, df=2, omnibus $p=5.8 \times 10^{-13}$ for the overall haplotype effect.

(b) Wald=7.15, df=2, omnibus p=0.028 for the overall haplotype effect.

Table S3. Interaction of Haplotypes and Treatment Effect on Abstinence at End-of-Treatment, Adjusting for Smoking Heaviness (Cigarettes Smoked per Day) (N=1,073) *

	Abstinence at End of Treatment		
Predictors	**Odds Ratio**	**95% C.I.**	**P**
Haplotypes (rs16969968-rs680244*)			
H1- G_C	reference		
H2- G_T	0.62	(0.32, 1.19)	0.15
H3- A_C	0.39	(0.19, 0.80)	0.010
Cigarettes Per Day	0.67	(0.59, 0.75)	$3.6*10^{-11}$
Treatment			
Placebo	reference		
Active Treatment	0.99	(0.57, 1.73)	0.98
Interaction of Haplotypes and Intervention			(a)
H1* Active Treatment	reference		
H2* Active Treatment	1.84	(0.92, 3.68)	0.083
H3* Active Treatment	3.08	(1.45, 6.53)	0.0033

* All models were adjusted for age (quartiles) and gender.

(a) chi squared=8.61, df=2, omnibus p=0.013 for the overall interaction effect.

Table S4. Interaction of Hapltoypes and Treatment Effect on Time to Relapse over 60 Days Post-quit in the UW-TTURC Study* (N=1015)

Predictors	Relative Hazard	95% C.I.	P
Haplotypes (rs16969968-rs680244)**			
H1- G_C	reference		
H2- G_T	1.40	(0.91, 2.16)	0.13
H3- A_C	1.46	(0.93, 2.29)	0.10
Treatment			
Placebo	reference		
Active Treatment	0.84	(0.56, 1.24)	0.37
Interaction			(a)
H1* Active Treatment	reference		
H2* Active Treatment	0.60	(0.37, 0.95)	0.031
H3* Active Treatment	0.54	(0.33, 0.89)	0.015

*All models were adjusted for age (quartiles) and gender.

**Haplotypes were based on rs16969968-rs680244.

(a) chi squared=6.46, df=2, omnibus p=0.040 for the overall haplotype effect.

Table S5. Interaction of Haplotypes and Specific Treatment Effects on Abstinence at End-of-Treatment, Adjusting for Smoking Heaviness (Cigarettes Smoked per Day) (N=1,073) *

	Abstinence at End of Treatment		
Predictors	**Odds Ratio**	**95% C.I.**	**P**
Haplotypes (rs16969968-rs680244*)			
H1- G_C	reference		
H2- G_T	0.62	(0.33, 1.17)	0.14
H3- A_C	0.37	(0.18, 0.75)	0.0057
Treatment			
Placebo	reference		
Bupropion Only	0.74	(0.38,1.44)	0.37
NRT Only	0.95	(0.54,1.69)	0.87
Combined Bupropion/NRT	1.36	(0.70,2.64)	0.36
Interaction of Haplotypes and Bupropion			(a)
H1* Bupropion Only	reference		
H2* Bupropion Only	2.32	(1.01,5.35)	0.048
H3* Bupropion Only	3.59	(1.46,8.82)	0.0053
Interaction of Haplotypes and NRT			(b)
H1* NRT Only	reference		
H2* NRT Only	1.79	(0.88,3.66)	0.11
H3* NRT Only	2.99	(1.38,6.48)	0.0056
Interaction of Haplotypes and Combined Treatment			(c)
H1* Combined Bupropion/NRT	reference		
H2* Combined Bupropion/NRT	1.61	(0.71,3.69)	0.26
H3* Combined Bupropion/NRT	3.14	(1.29,7.61)	0.011

No significant differences in haplotypic risks on ability to quit betwee 3 active treatment groups (Wald=1.21, df=4, p=0.88).

* All models were adjusted for age (quartiles) and gender.
(a) chi squared=7.89, df=2, omnibus p=0.019 for the overall interaction effect.
(b) chi squared=7.68, df=2, omnibus p=0.021 for the overall interaction effect.
(c) chi squared=6.62, df=2, omnibus p=0.037 for the overall interaction effect.

Table S6. Genotypic Risk for Age of Smoking Cessation (N=5,216) in the ARIC Study

	Age of Smoking Cessation		
Predictors	**Relative Hazard**	**95% C.I.**	**P**
Genotype (rs16969968*)	0.92	(0.86,0.99)	0.018
Genotype (rs680244*)	0.99	0.93,1.05)	0.73

All models were adjusted for age (quartiles) and gender.
Genotypes were coded additively as covariates.

*In the ARIC sample, rs951266 was used as a proxy for rs16969968 (r^2 = 0.97 in CEU in 1000 Genomes database); rs6495306 was used as a proxy for rs680244 (r^2=1 in CEU in 1000 Genomes database).

Table S7. Interaction of Gentotypes (rs16969968, rs680244) and Treatment on Abstinence at End-of-Treatment, Adjusting for Smoking Heaviness (Cigarettes Smoked per Day) in the UW-TTURC Study (N=1,073) *

	Abstinence at End of Treatment		
Predictors	**Odds Ratio**	**95% C.I.**	**P**
Genotype (rs16969968)	0.37	(0.18,0.77)	0.0083
Genotype (rs680244)	0.64	(0.34,1.22)	0.17
Treatment			
Placebo	reference		
Active Treatment	0.59	(0.21,1.67)	0.32
Interaction of Genotype (rs16969968) and Active Treatment	3.24	(1.48,7.10)	0.0032
Interaction of Genotype (rs680244) and Active Treatment	1.78	(0.90,3.53)	0.099

* All models were adjusted for age (quartiles) and gender.
Genotypes were coded additively as covariates.