



VENERDI' 1 MARZO

LA SIGARETTA ELETTRONICA

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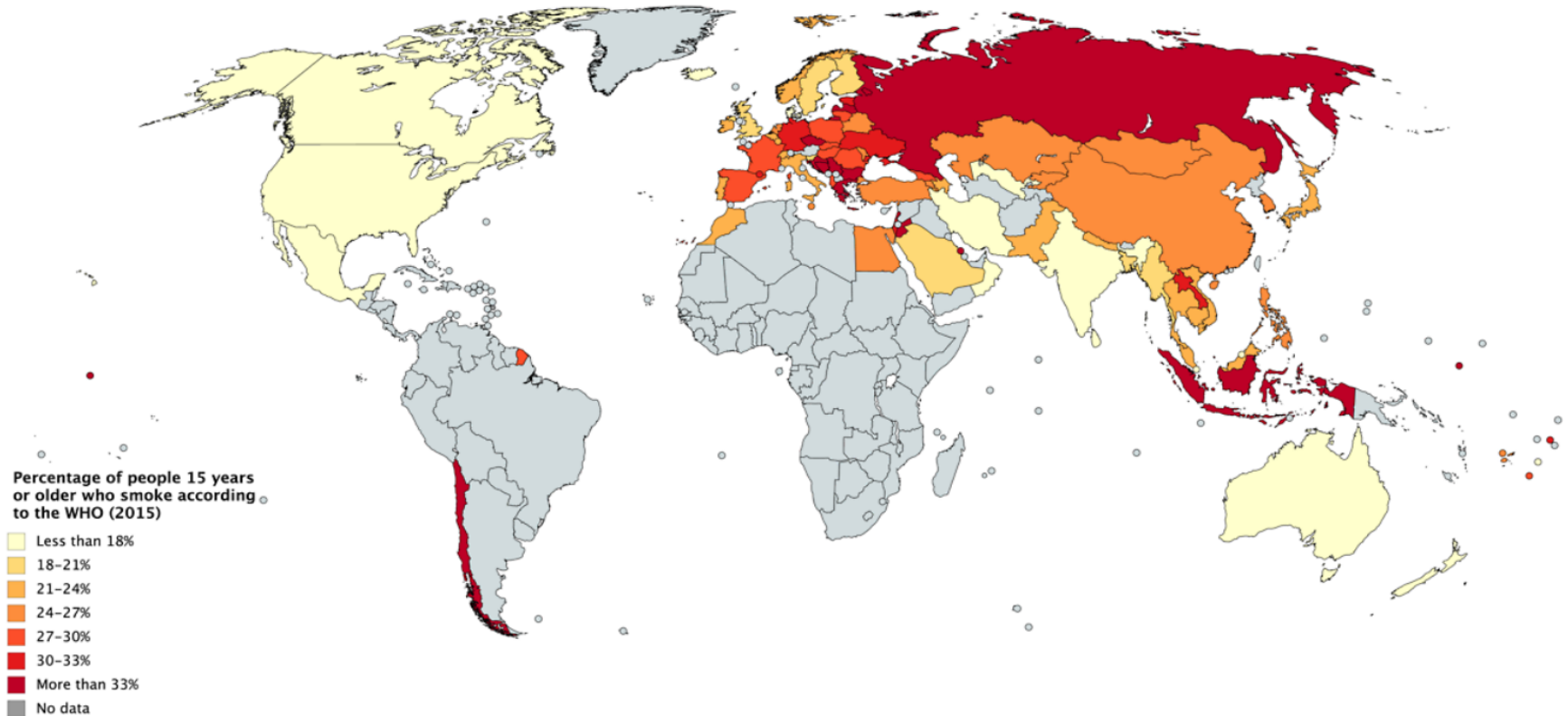
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Disclosure

- I have consulted for Abbott Vascular and Bayer.

The smoking epidemic



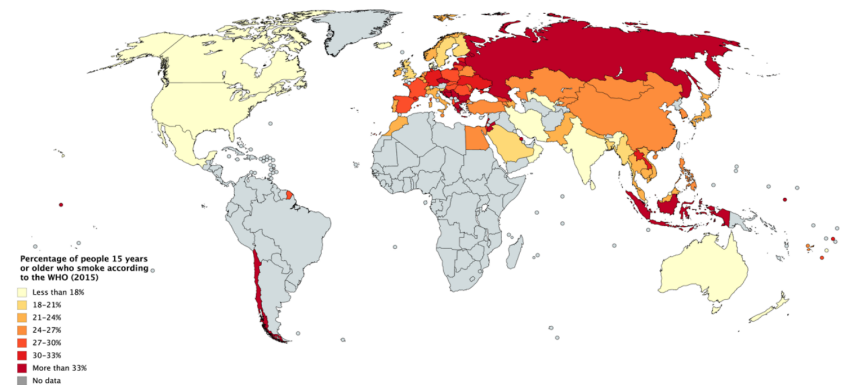
The smoking epidemic

- 1 billion smokers
- 5 million deaths every year due to smoking
- These figures will double by 2030

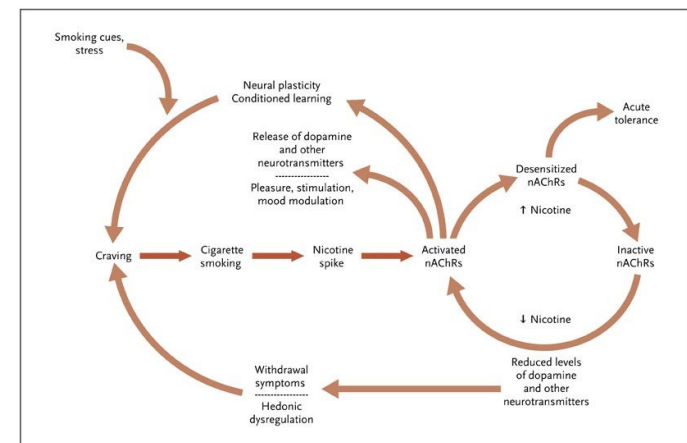
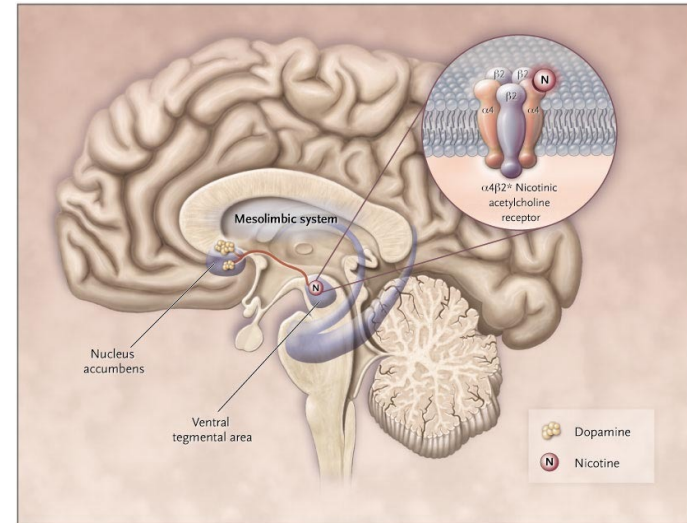
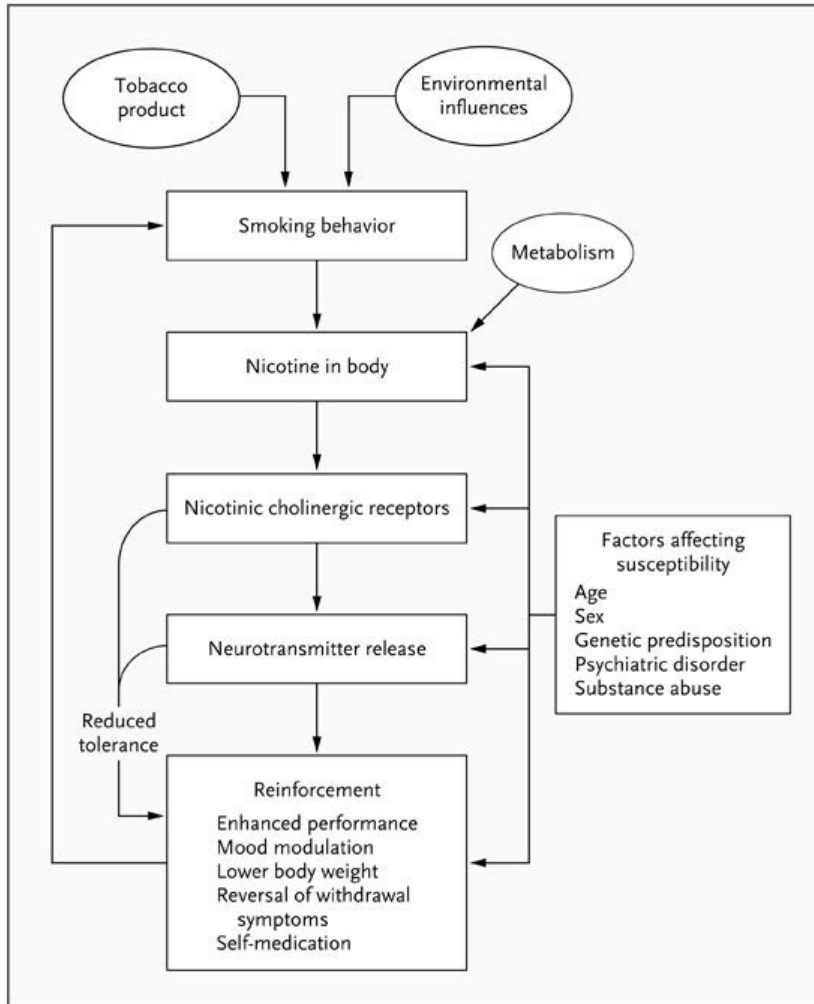


75% want to quit

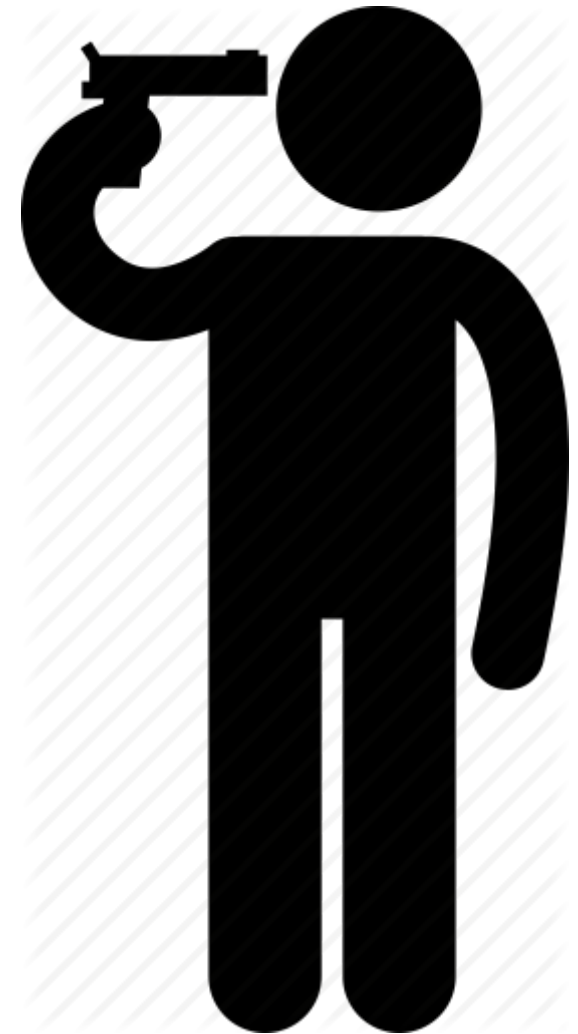
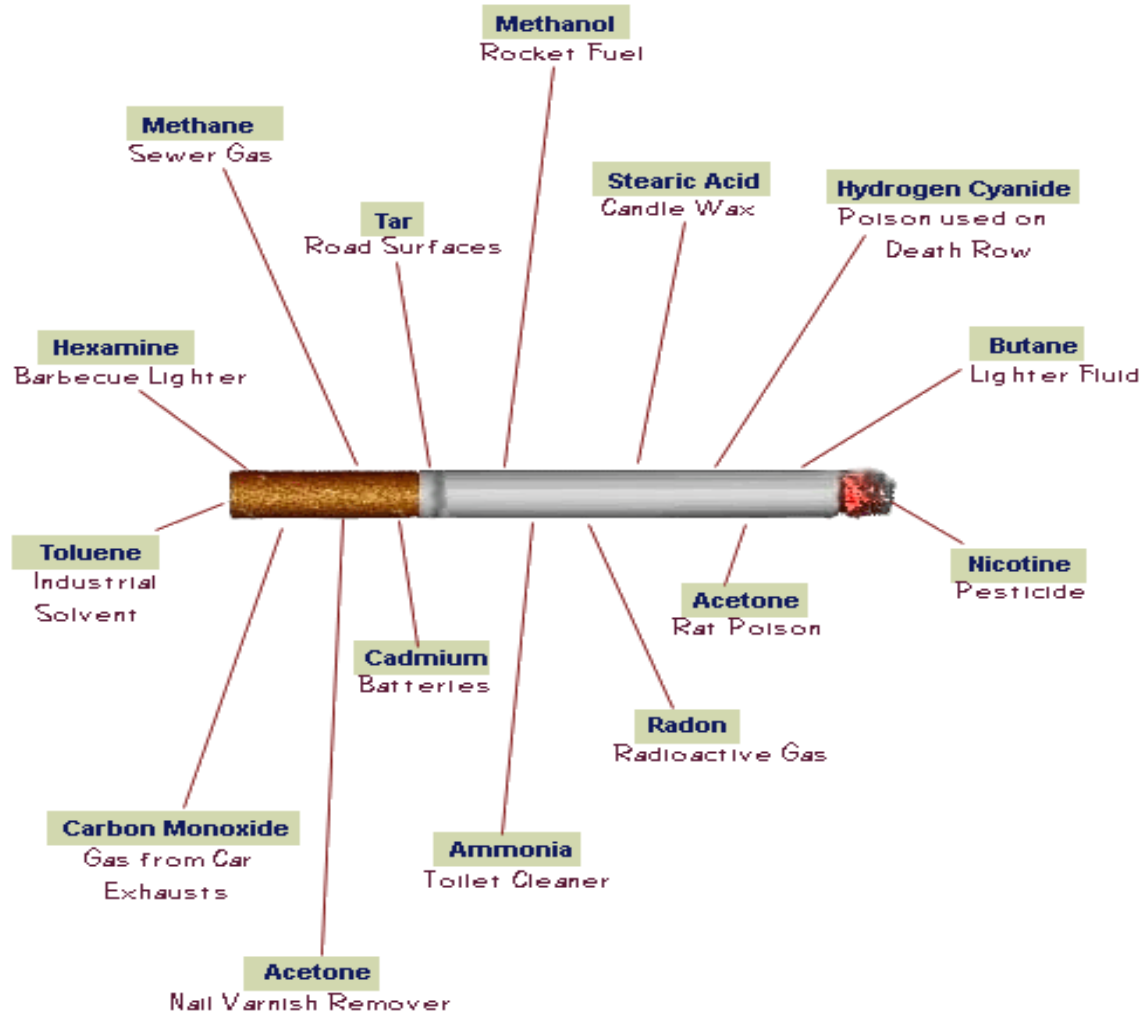
<2% succeed



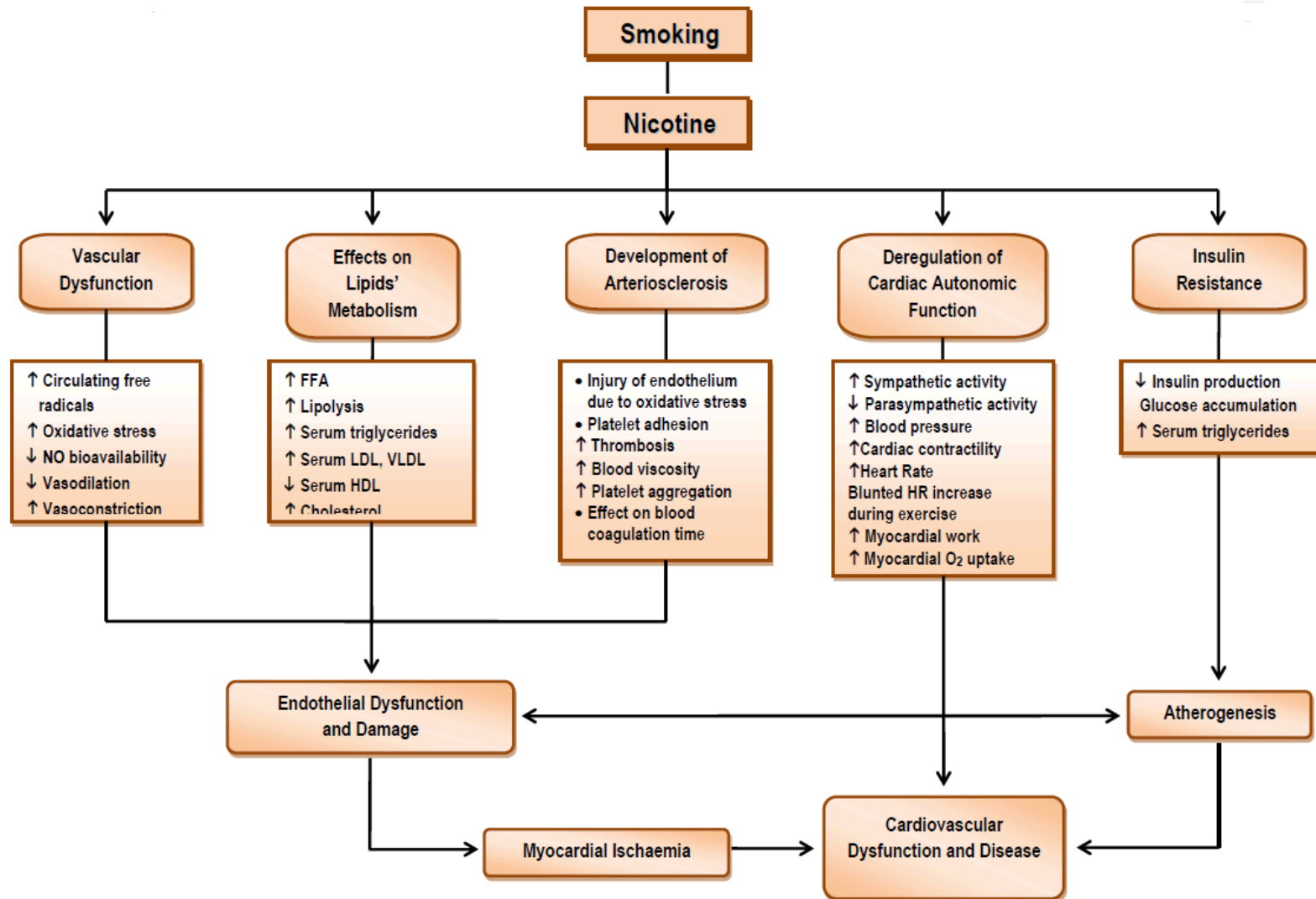
Pathophysiology of addiction



Cigarettes as suicide weapons



Cardiovascular effects of smoking



Quitting is best



Potential scenarios

Cigarette



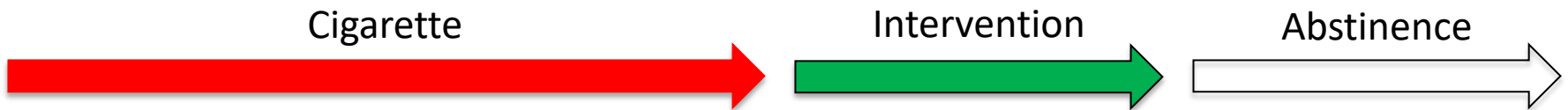
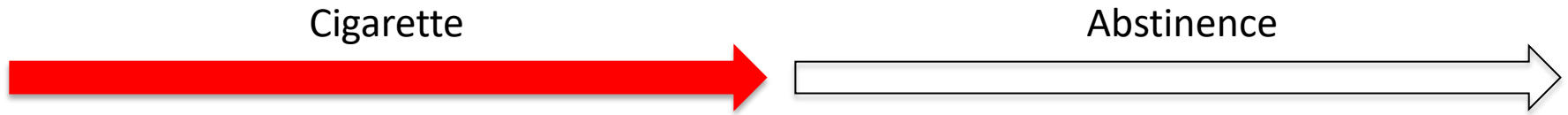
Abstinence



Cigarette



Potential scenarios

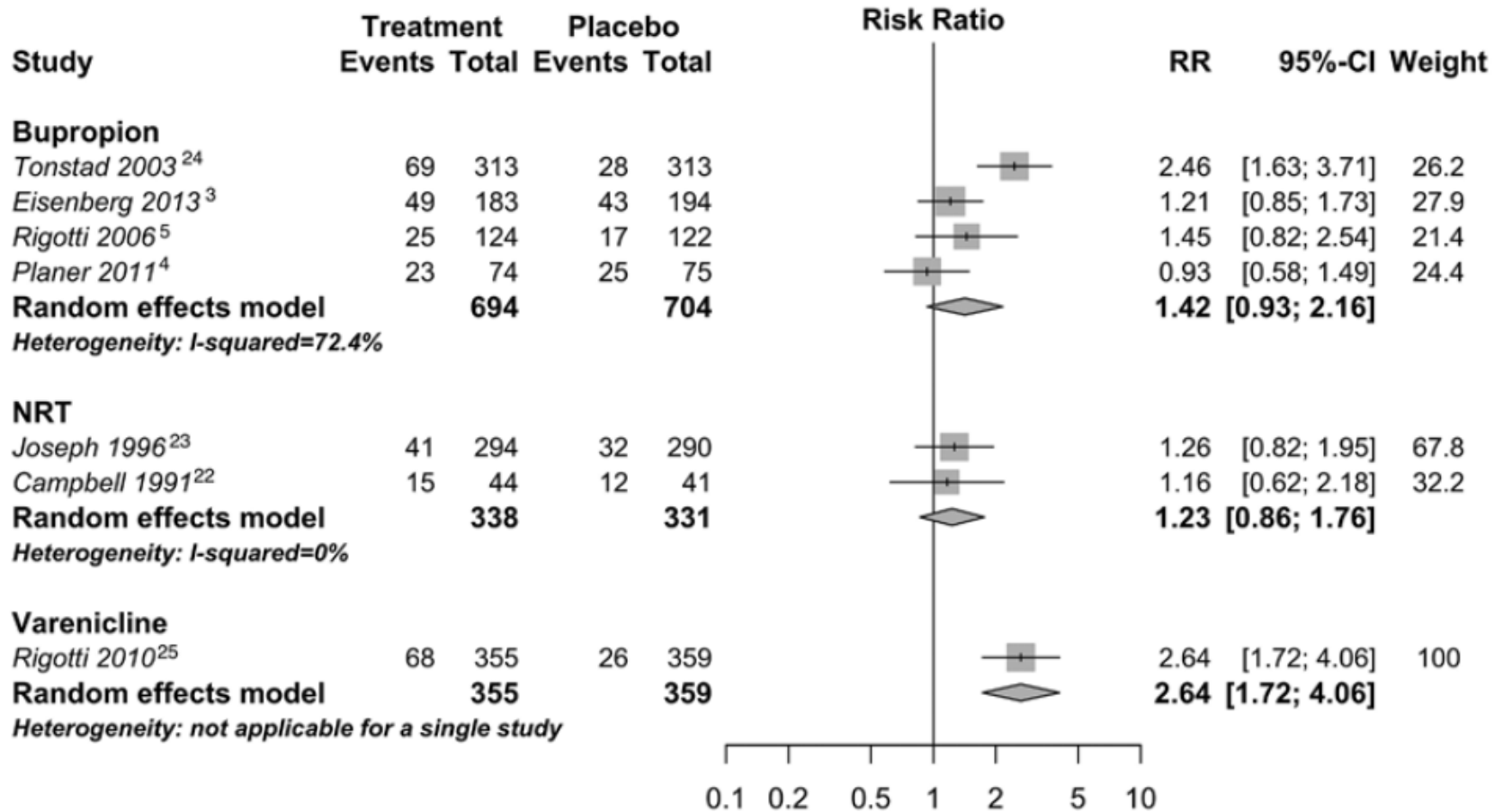


Pharmacotherapy

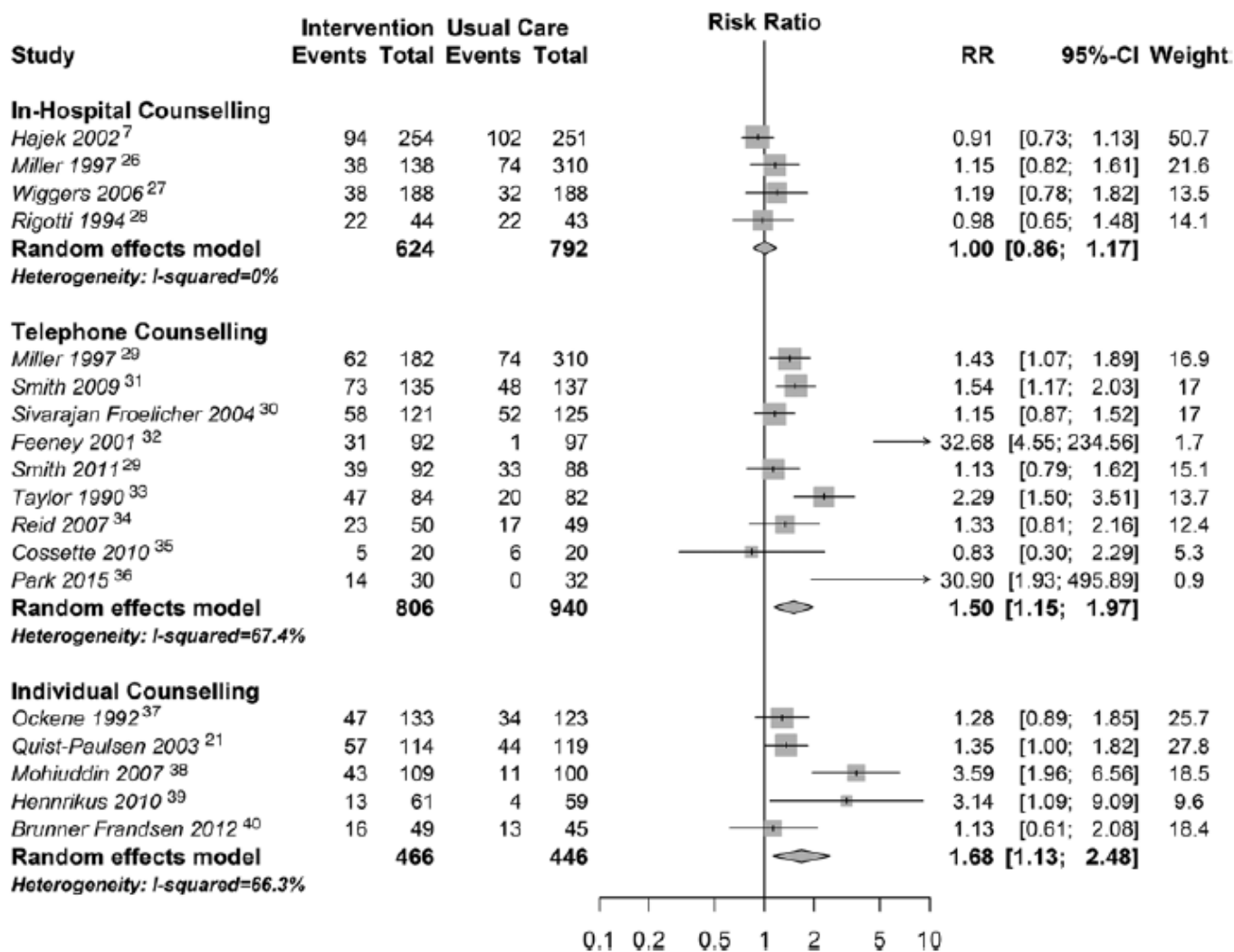
■ Most favorable (green) ► Moderately favorable (yellow) ● Least favorable (red)				
Considerations	NRT (monotherapy)	Bupropion SR	Varenicline	NRT combination therapy: Patch + PRN short-acting NRT
Efficacy	■	■	■ (Highest)	■ (Highest)
Route of administration	■ Patch: Transdermal ● Gum/Lozenge: Requires "parking" ► Nasal spray ► Inhaler	■ Oral	■ Oral	►
Cost	■ Nicotine gum/lozenge/patch ► Nicotine Inhaler ► Nicotine Nasal spray	■	►	►
Availability	■ OTC: Gum, lozenge, patch ► Rx: Inhaler, nasal spray	► Rx	► Rx	■ OTC: Patch + PRN gum/lozenge ► Rx: PRN inhaler or nasal spray
Frequency	■ Patch: Once daily ● Gum/lozenge/inhaler/nasal spray: Multiple/day	■ Twice daily	■ Twice daily	► Multiple, depending on agent in combination
Cardiovascular considerations	► Avoid if recent MI (2 weeks), angina arrhythmia, or uncontrolled HTN	■ Avoid in uncontrolled HTN	► Precautions exist, benefits outweigh risk	► Avoid in uncontrolled HTN, recent MI (2 weeks), angina, or arrhythmia
Psychiatric disorders (use caution with all products)	■	► Avoid if Hx of suicide ideation, attempt, or major depressive disorder (can help with minor depressive symptoms)	► Avoid if Hx of suicide ideation or attempt	■
Renal impairment	■	► Use caution, consider dose reduction	► Dose reduction	■
Hepatic impairment	■	► Severe impairment: Dose reduction	■	■
Pregnancy	●	►	►	●
Additional precautions	Precaution in Hx of ulcers, diabetes, sodium restriction Patch: Avoid in Hx of dermatologic conditions Gum: Avoid if extensive dental work or jaw problems Nasal spray: Highest dependence potential Gum/Lozenge/Inhaler: Do not eat 15 min prior or during use	Precaution: seizures, conditions that lower seizure threshold, narrow angle glaucoma, insomnia	Caution in patients with pre-existing nausea	

Key: NRT, Nicotine replacement therapy; OTC, over-the-counter; Rx, prescription; PRN, as needed use; MI, myocardial infarction; HTN, hypertension; Hx, History

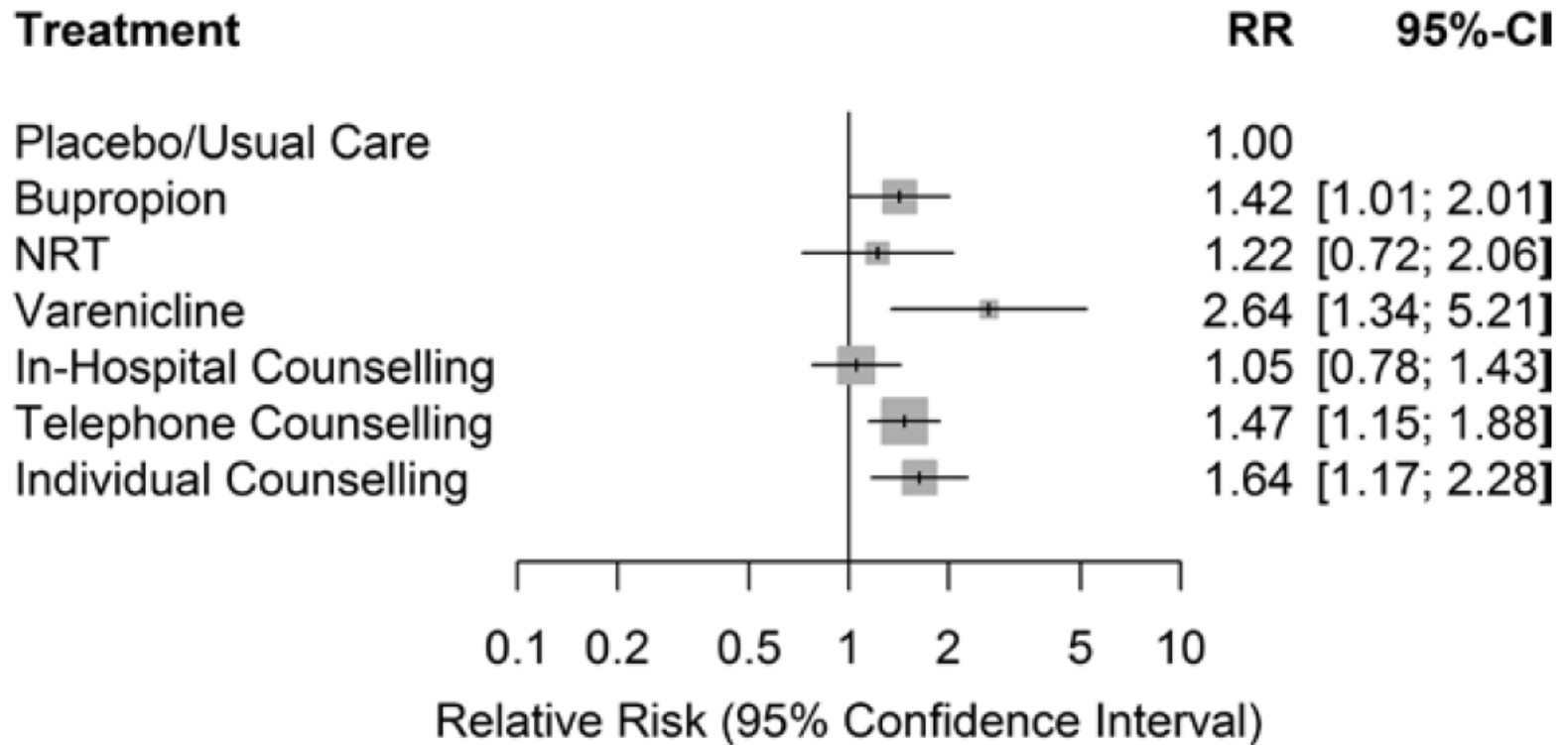
Pharmacotherapy



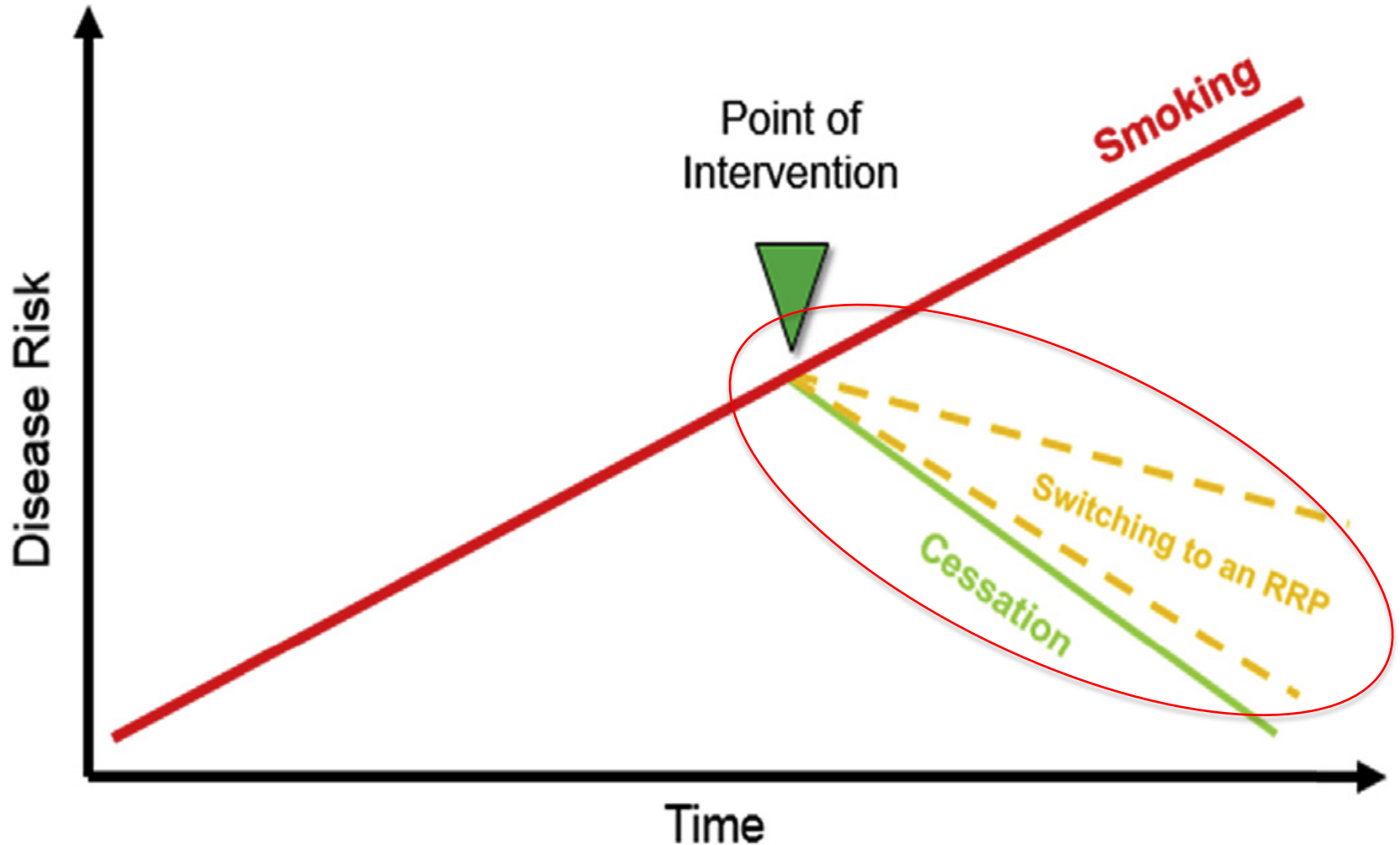
Behavioral therapy



Network meta-analysis



Alternative to quitting

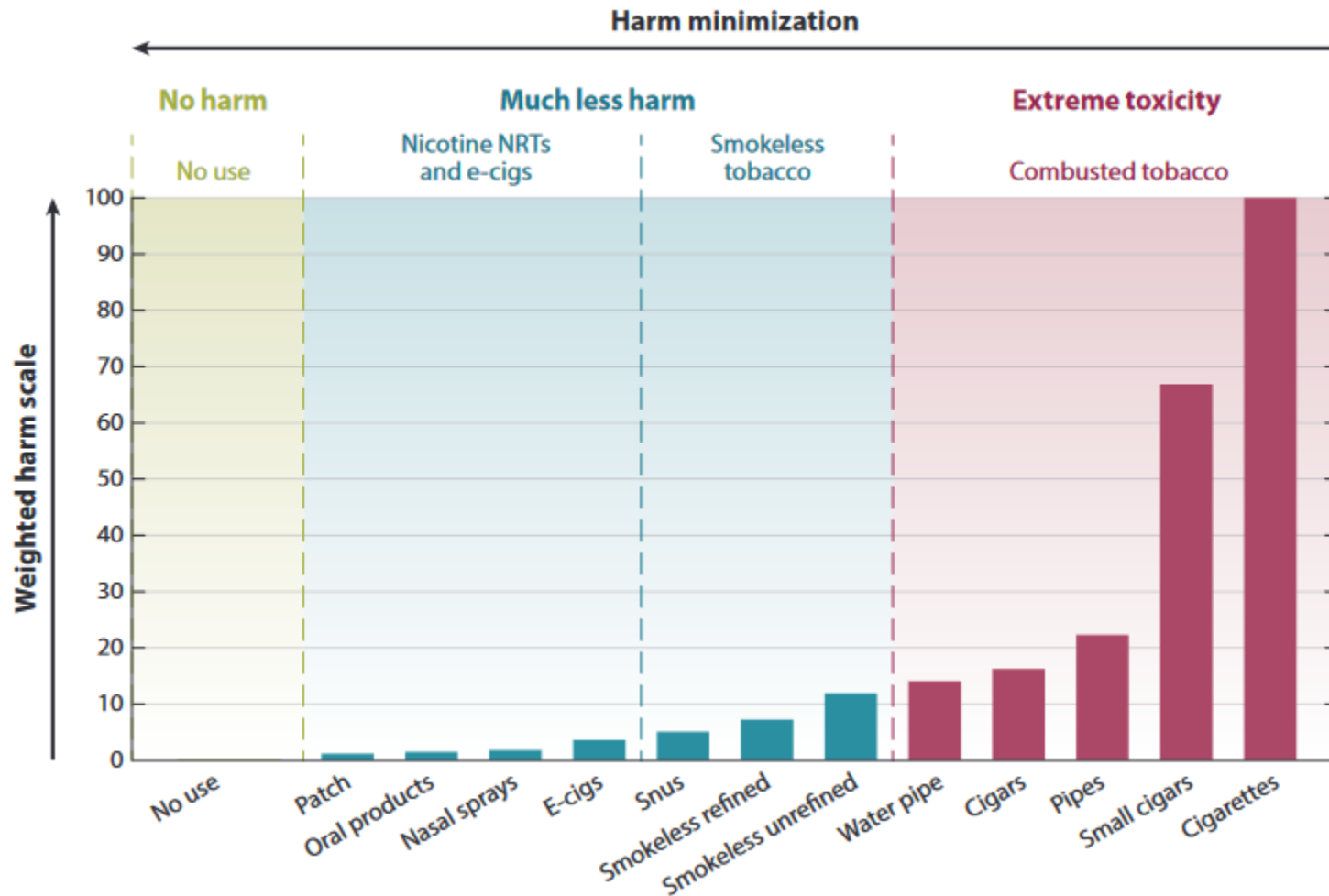


RRP=reduced risk product

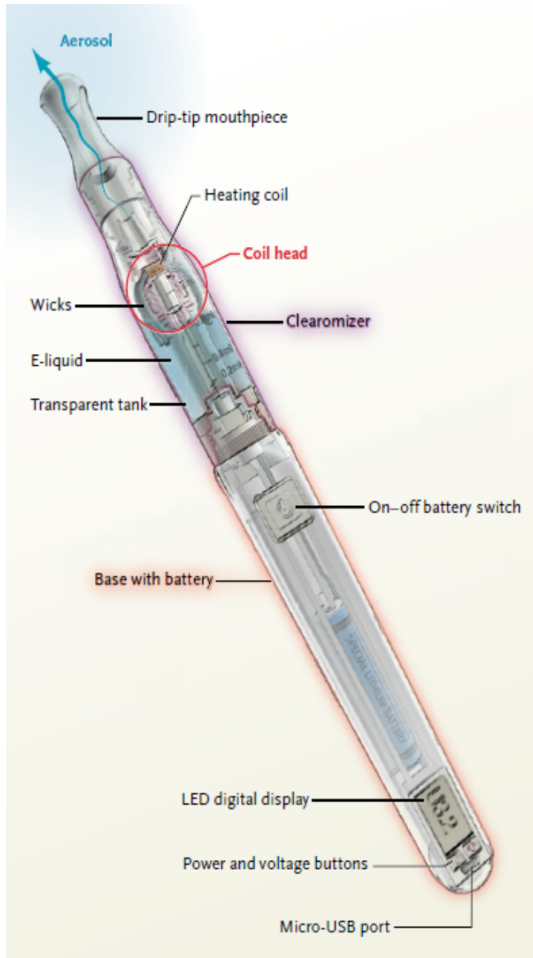
Modified risk product

- A modified risk product (MRP) is a tobacco or tobacco-like product which can modify (hopefully reduce) the global burden of disease associated with smoking
- An MRP claim is a complex one and not synonym of a reduced risk product (RRP) claim
- Typical MRPs are electronic vaping cigarettes (EVC) such as JUUL, and heat not burn cigarettes (HNBC) such as IQOS or GLO

Harm minimization

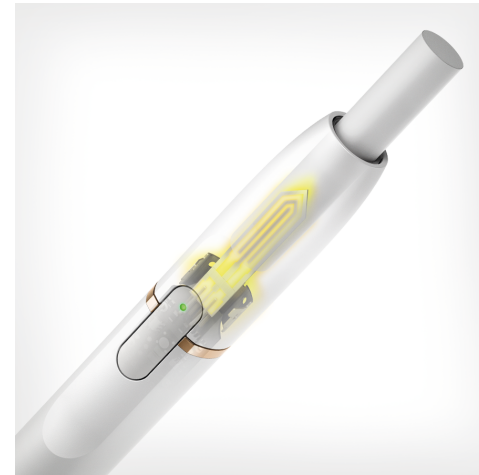


Electronic vaping cigarette

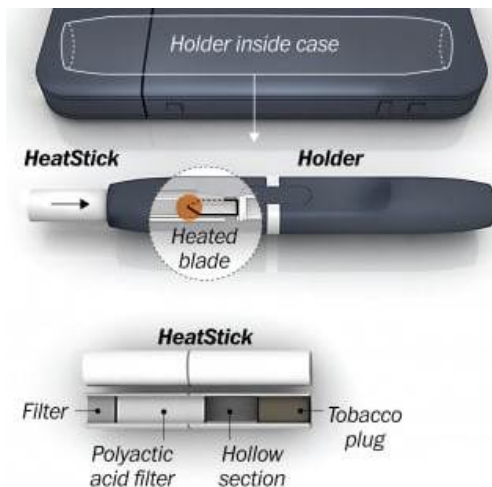


Key mechanism: heating (not combustion) up to 250° of nicotine-filled liquid

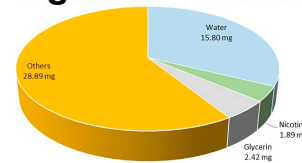
Heat not burn cigarette



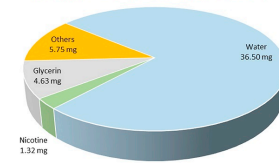
Key mechanism: heating (not combustion) up to 350° of processed tobacco leaves



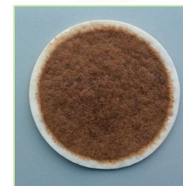
Cigarette Smoke



IQOS Aerosol



Smoke

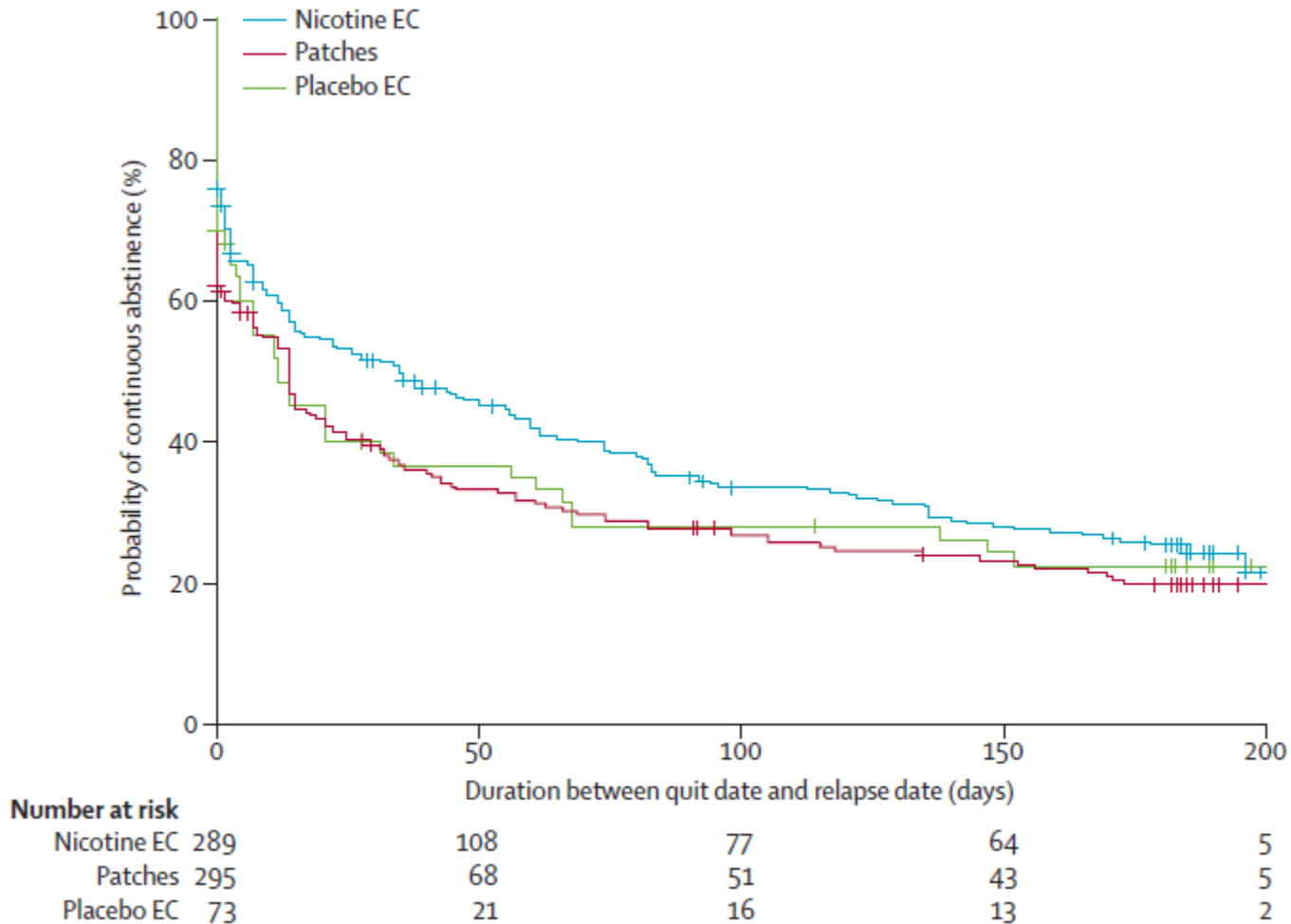


Aerosol

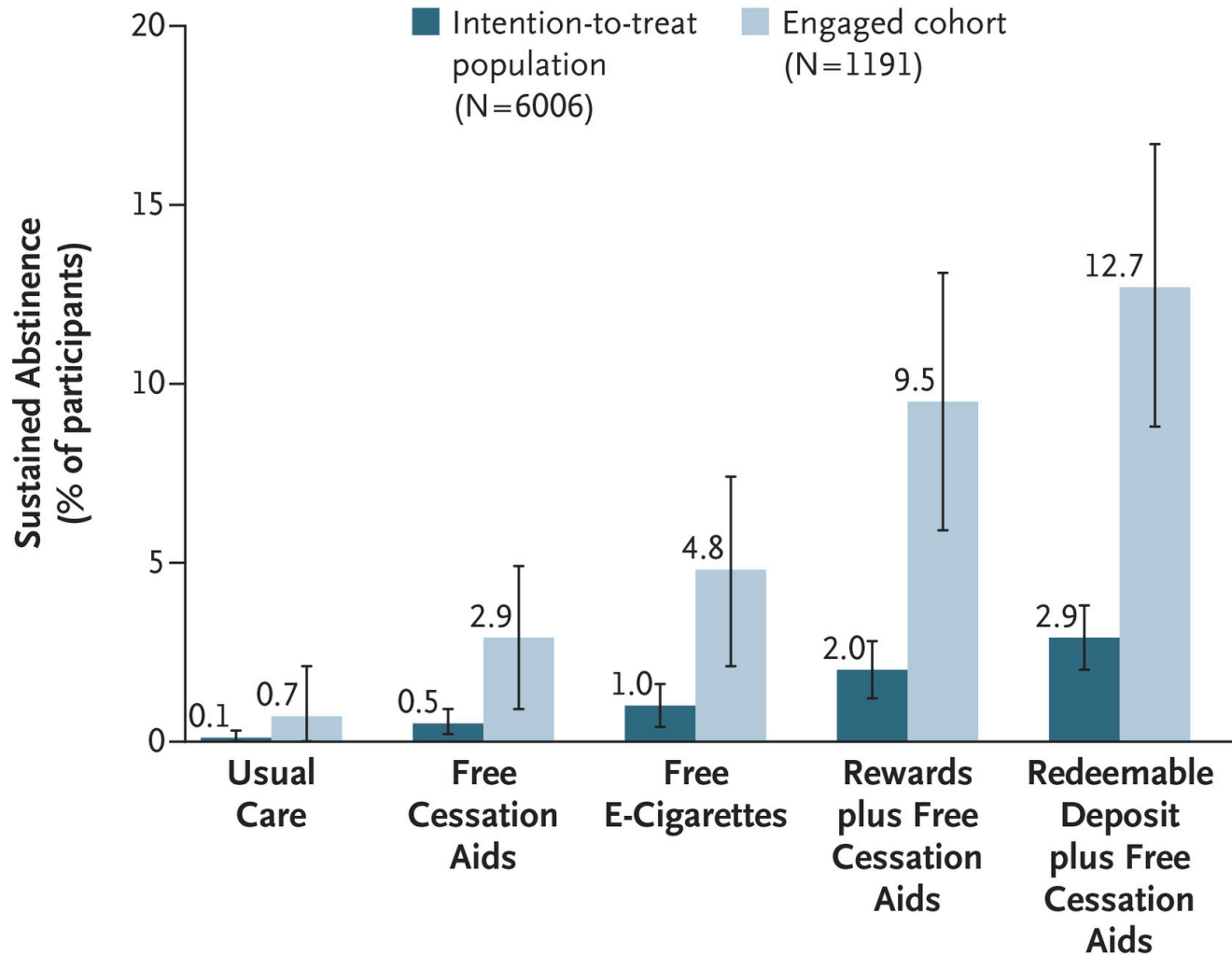


Particulate Matter

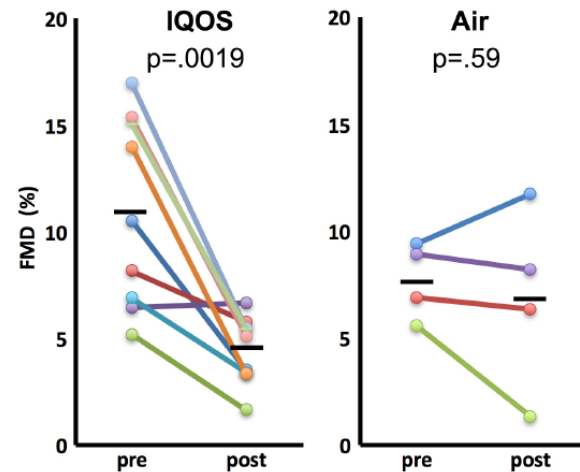
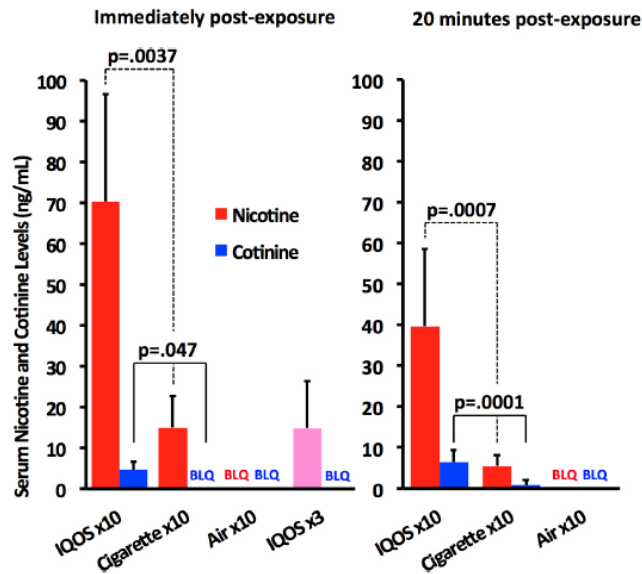
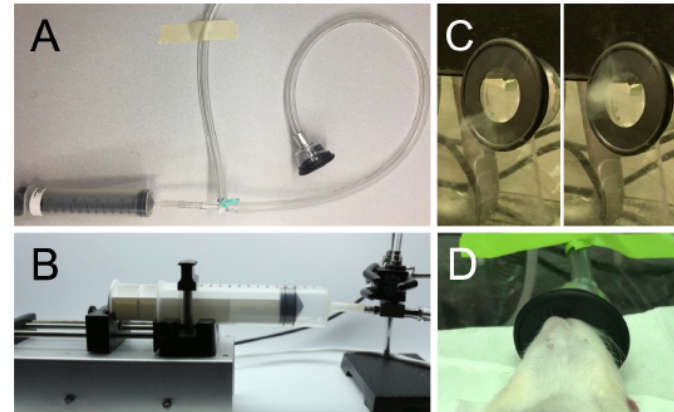
RCT of EVC for smoking cessation



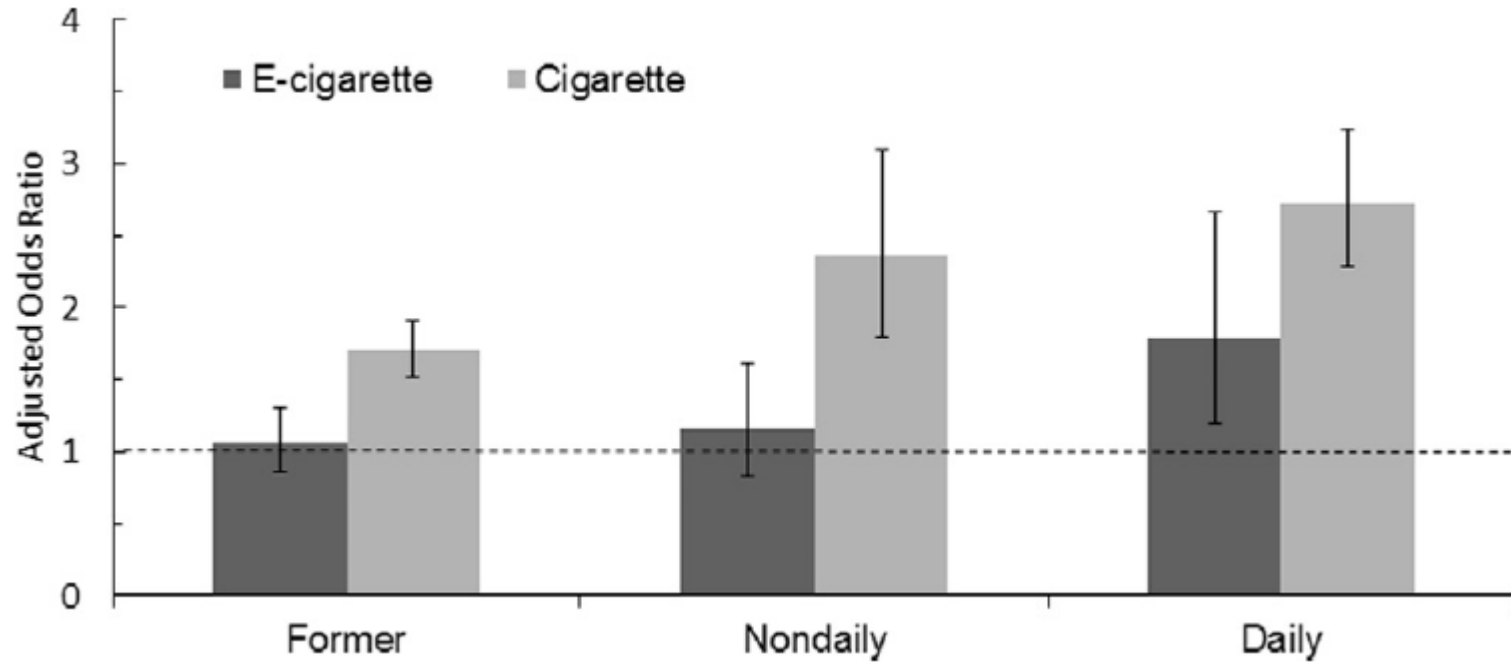
RCT of rewards for smoking cessation



HNBC and endothelial dysfunction



Risk of AMI in EVC users



Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) Study Program



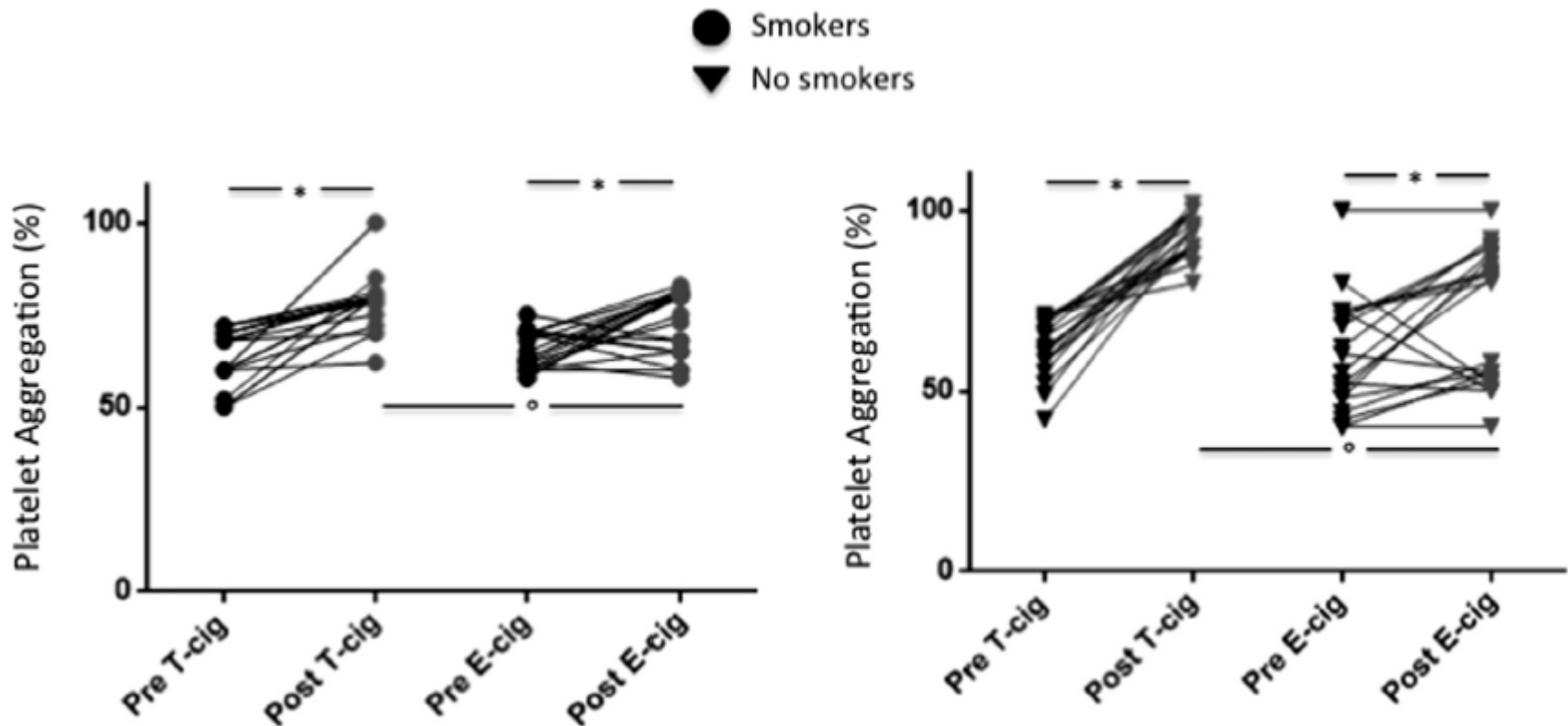
Effects of EVC on oxidative stress and endothelial dysfunction: SUR-VAPES 1

Variable	Time	Descriptive Analysis			Exploratory Inferential Analysis ²		
		Overall (N = 40)	Nonsmokers Only (n = 20)	Smokers Only (n = 20)	Overall (N = 40)	Nonsmokers Only (n = 20)	Smokers Only (n = 20)
sNOX2-dp, pg/mL	Before tobacco cigarette	23.6 ± 7.8	19.4 ± 7.6	27.8 ± 5.3	< .001	< .001	< .001
	After tobacco cigarette	38.2 ± 9.9	32.4 ± 7.4	44.1 ± 8.7			
	Before e-Cigarette	21.6 ± 6.8	17.6 ± 4.9	25.6 ± 6.1	< .001	< .001	< .001
	After e-Cigarette	30.2 ± 6.2	26.4 ± 3.18	34.1 ± 6.1			
8-iso-PGF2 α , pmol/L	Before tobacco cigarette	134.5 ± 55.8	84.9 ± 18.2	183.6 ± 31.2	< .001	< .001	< .001
	After tobacco cigarette	203.3 ± 80.6	129.7 ± 12.6	277.0 ± 41.9			
	Before e-Cigarette	133.1 ± 54.2	84.9 ± 18.2	181.3 ± 28.6	< .001	< .001	< .001
	After e-Cigarette	186.6 ± 61.9	136.4 ± 35.2	236.9 ± 36.4			
NO bioavailability, μ M	Before tobacco cigarette	35.3 ± 12.0	44.0 ± 10.3	26.5 ± 5.0	< .001	< .001	< .001
	After tobacco cigarette	19.5 ± 9.9	28.6 ± 4.5	10.5 ± 3.0			
	Before e-Cigarette	35.5 ± 12.5	44.9 ± 9.4	26.1 ± 6.9	< .001	.004	< .001
	After e-Cigarette	25.9 ± 12.1	35.9 ± 7.3	16.0 ± 6.0			
Vitamin E, μ mol/mmol	Before tobacco cigarette	4.58 ± 1.81	5.08 ± 1.55	4.08 ± 1.95	< .001	.002	.001
	After tobacco cigarette	3.13 ± 1.93	3.64 ± 2.23	2.63 ± 1.49			
	Before e-Cigarette	3.83 ± 1.62	4.25 ± 1.71	3.41 ± 1.44	< .001	.037	.002
	After e-Cigarette	2.76 ± 1.15	3.21 ± 1.35	2.31 ± 0.71			
FMD, %	Before tobacco cigarette	6.73 ± 4.34	7.83 ± 5.22	5.62 ± 2.96	< .001	< .001	.002
	After tobacco cigarette	3.39 ± 3.85	3.96 ± 4.09	2.82 ± 3.59			
	Before e-Cigarette	6.68 ± 3.62	7.48 ± 3.89	5.88 ± 3.23	.001	.026	.017
	After e-Cigarette	4.27 ± 2.22	4.56 ± 2.42	3.99 ± 2.02			

8-iso-PGF2 α = 8-iso-prostaglandin F2 α ; FMD = flow-mediated dilation; sNOX2-dp = soluble NOX2-derived peptide.

²With paired Student t test.

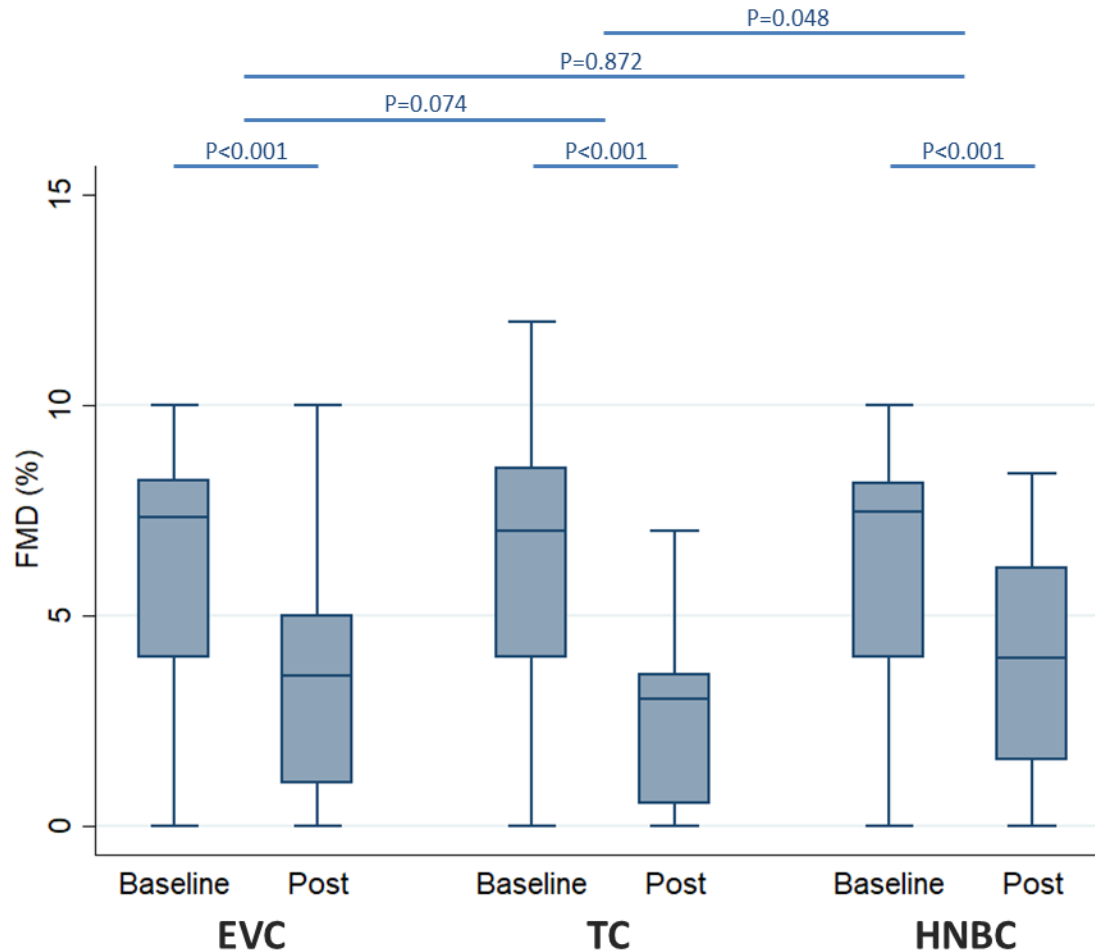
Effects of EVC on platelet function: SUR-VAPES 1 substudy



Predictors of EVC effects: SUR-VAPES 1 substudy

Feature	Soluble NOX2-derived peptide	Nitric oxide production	8-iso-prostaglandin F2a	Vitamin E	Flow-mediated dilation
Systolic pressure	0.01 (-0.07; 0.09) p=0.816	-0.06 (-0.15; 0.04) p=0.589	0.16 (-0.29; 0.62) p=0.481	-0.01 (-0.03; 0.02) p=0.626	0.02 (-0.04; 0.07) p=0.562
Diastolic pressure	0.02 (-0.10; 0.14) p=0.764	-0.04 (-0.18; 0.10) p=0.589	-0.07 (-0.73; 0.60) p=0.836	0.01 (-0.02; 0.039) p=0.545	0.00 (-0.08; 0.08) p=0.985
Cholesterol	0.03 (-0.06; 0.12) p=0.497	0.01 (-0.09; 0.11) p=0.854	-0.14 (-0.63; 0.34) p=0.558	0.00 (-0.02; 0.03) p=0.694	0.00 (-0.06; 0.06) p=0.975
Smoking history	9.29 (5.88; 12.70) p<0.001	-17.34 (-21.10; -13.57) p<0.001	109.54 (93.05; 126.02) p<0.001	-0.99 (-1.85; -0.13) p=0.021	-2.20 (-4.15; -0.26) p=0.020
Smoking since	0.20 (-0.29; 0.68) p=0.428	0.02 (-0.57; 0.60) p=0.955	0.70 (-2.04; 3.44) p=0.618	-0.07 (-0.19; 0.05) p=0.247	0.09 (-0.23; 0.41) p=0.575
Cigarettes per day	-0.11 (-0.39; 0.17) p=0.431	0.15 (-0.18; 0.48) p=0.382	0.35 (-1.22; 1.93) p=0.661	-0.05 (-0.11; 0.02) p=0.198	-0.01 (-0.19; 0.18) p=0.952
Drug therapy					
Fluvoxamine	2.64 -2.60; 7.88) p=0.323	-4.86 (-11.00; 1.27) p=0.120	7.18 (-22.49; 6.85) p=0.635	-0.47 (-1.79; 0.85) p=0.487	1.34 (-2.10; 4.77) p=0.446
Levetiracetam	0.20 (-0.29; 0.68) p=0.958	-6.67 (-15.11; 1.77) p=0.121	44.95 (6.44; 83.46) p=0.022	-0.34 (-2.16; 1.49) p=0.719	-0.05 (-4.80; 4.72) p=0.984
Oral contraceptive	-2.18 (-6.42; 2.05) p=0.313	-2.79 (-7.83; 2.24) p=0.277	-1.10 (-25.16; 22.97) p=0.929	1.55 (0.59; 2.51) p=0.002	3.47 (0.89; 6.05) p=0.008

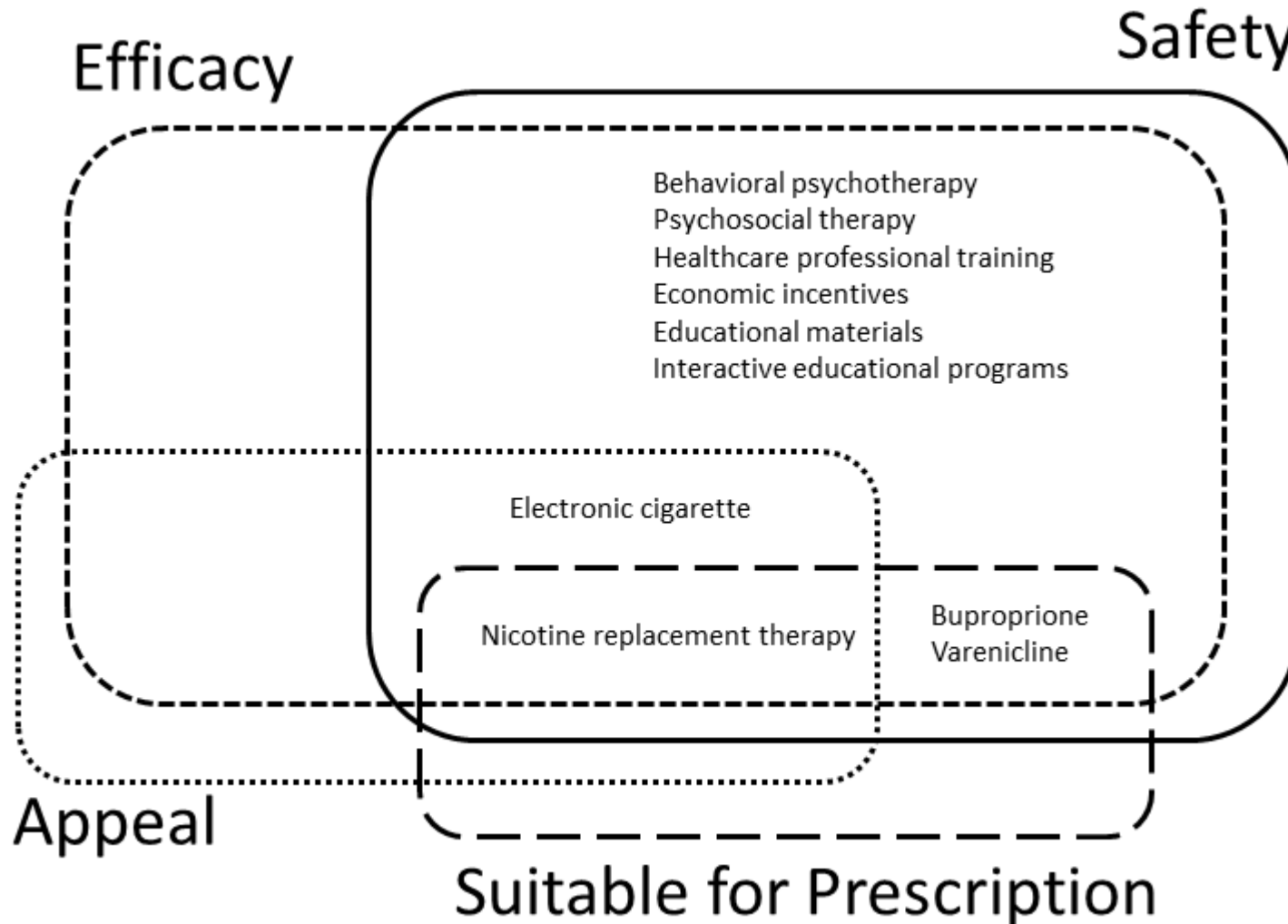
SUR-VAPES 2: RCT of IQOS vs EVC



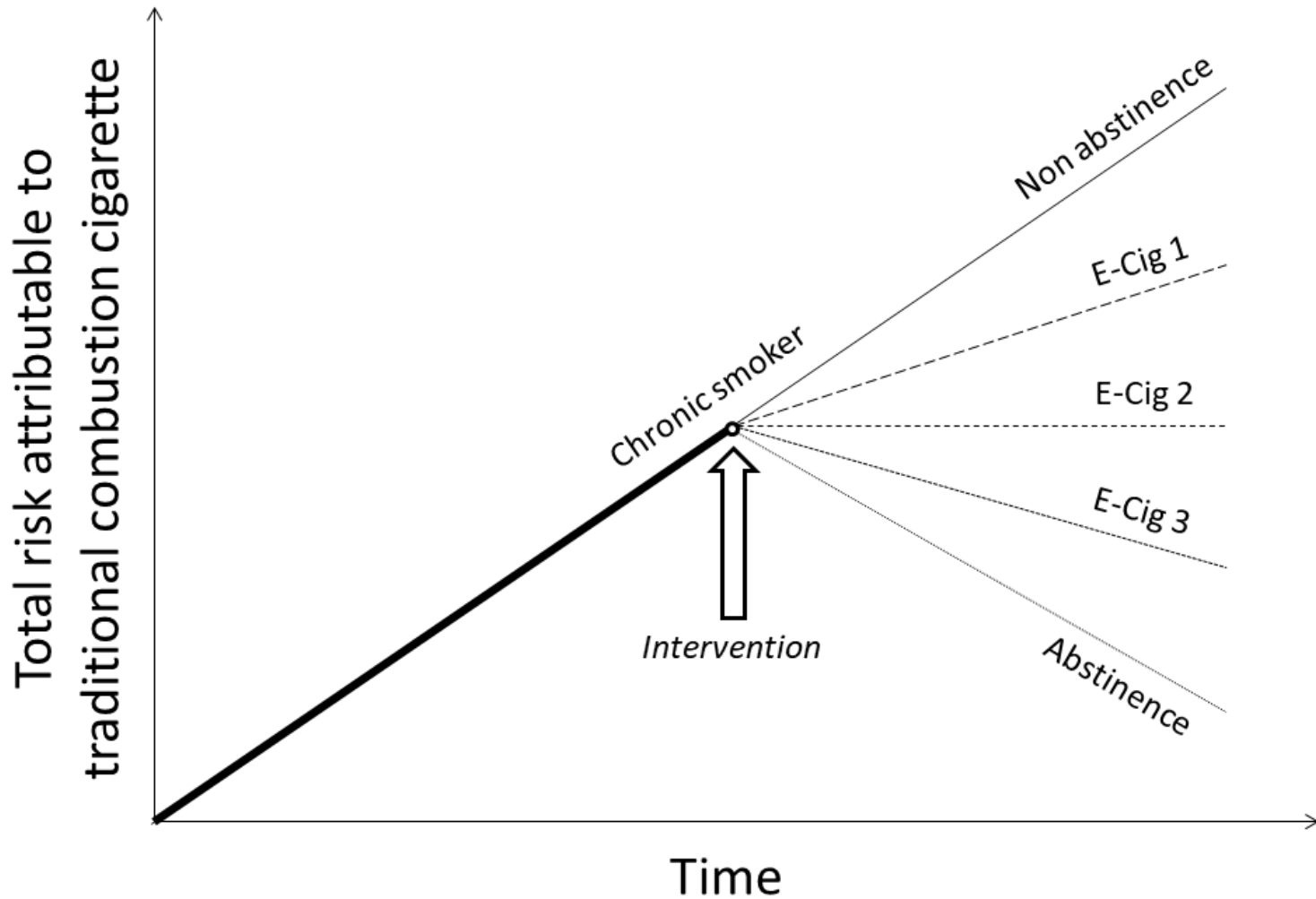
Upcoming studies

- SUR-VAPES 3: RCT of mentoring to EVC and HNBC in primary prevention (primary endpoint: abstinence)
- SUR-VAPES 4: RCT of EVC vs HNBC in the catheterization laboratory (primary endpoint: coronary flow reserve)
- SUR-VAPES 5: RCT of EVC vs HNBC in secondary prevention (primary endpoint: major adverse cardiac events)

Pros and cons of different strategies



Time and interventions



Conclusions

- Smoking represents the most impactful yet actionable risk factor for cardiovascular disease and cancer
- Whenever abstinence is not immediately achievable, pharmacologic and behavioral therapy may provide useful incremental support
- Modified risk products may prove beneficial in selected subjects, but caution is paramount given the limited data on safety and the risk of eventually discouraging abstinence

Many thanks for your attention

For any query:

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Quitting TC vs EVC

Prevalence of withdrawal symptoms on most recent quit attempt.

	EC only users who stopped ECs	TC only users who stopped TCs	Dual users who stopped ECs, but not TCs	Dual users who stopped TCs, but not ECs	Within-Ss comparison of dual users who stopped both ECs and TCs	
					ECs	TCs
N	25	2528	60	355	242	
Weighted N	105,331	12,047,992	260,107	1,589,342	1,103,762	
% any Sx	40	71**	30	80***	50	74***
% 4+ Sx	25	33	12	45***	23	43***
Mean (SD) # Sx	1.7 (2.3)	2.5 (2.3)*	0.9 (1.9)	3.1 (2.4)***	1.8 (2.2)	3.0 (2.4)***
Individual Sx (%)						
Angry	30	49	21	62	34	61
Anxious	23	45	14	48	35	52
Depressed	22	19	11	24	10	19
Difficulty concentrating	12	25	10	36	21	35
Eat more	40	43	12	49	28	49
Insomnia	13	26	10	33	18	35
Restless	25	43	16	51	30	53

EC = electronic cigarette, N = sample size, TC = tobacco cigarette, Ss = subjects, Sx = symptoms.

* p < 0.05.

** p < 0.01.

*** p < 0.001.

Mean, standard deviation, and (sample size) for number of symptoms by outcome.

	EC-only users who stopped ECs	TC-only users who stopped TCs	Dual users who stopped ECs, but not TCs	Dual users who stopped TCs, but not ECs	Within-Ss comparison of dual users who stopped:	
					ECs	TCs
Quit successfully	2.5 (2.9) (10)	1.4 (1.9) (270)	0.6 (1.6) (41)	2.4 (2.6)*** (70)	1.4 (2.2) (20)	3.3 (2.3)*** (20)
Failed to quit	1.2 (1.6) (9)	2.9 (2.3)*** (1558)	1.6 (2.1) (14)	3.5 (2.3)*** (214)	2.6 (2.4) (41)	3.4 (2.7)*** (41)
Reduced only	0.9 (1.4) (6)	2.1 (2.2)** (700)	2.3 (2.4) (5)	2.5 (2.3) (71)	1.1 (1.7) (15)	2.0 (2.3) (15)

EC = Electronic cigarette, Ss = subjects, TC = tobacco cigarette.

** p < 0.01 in comparison to preceding column.

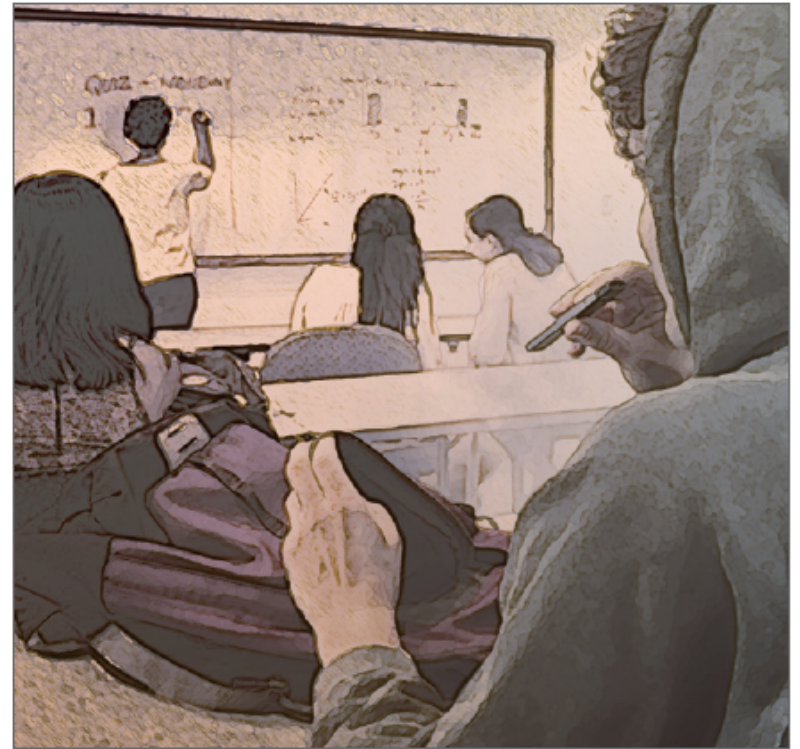
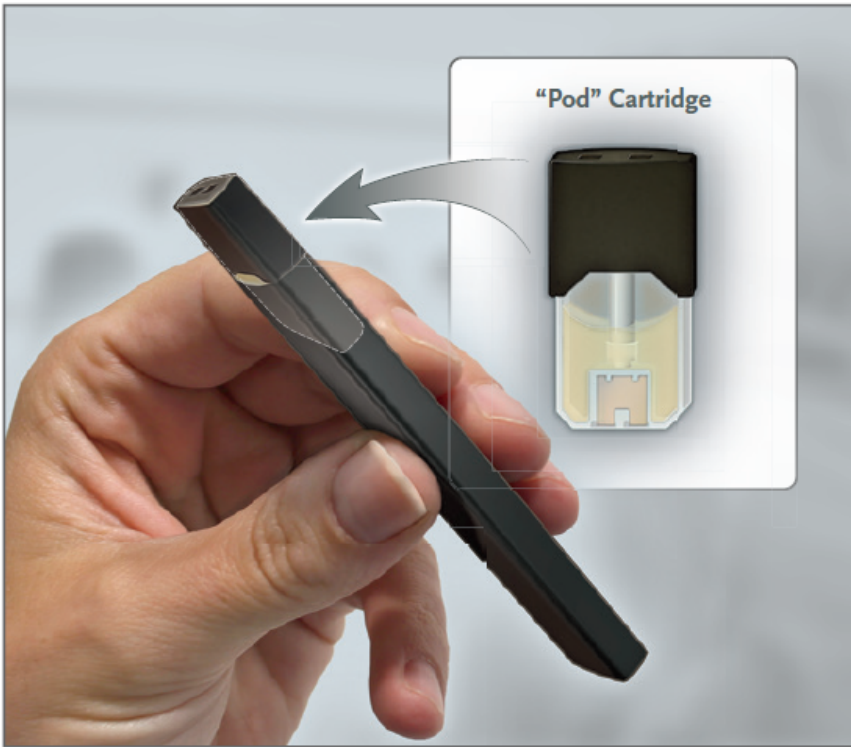
*** p < 0.001 in comparison to preceding column.

EVC and cannabis

Table. Prevalence and Correlates of Cannabis Use in e-Cigarettes Among US Middle and High School Students

Characteristic	Any Cannabis Use ^a			Participants Who Ever Used e-Cigarette Devices (n = 5217) ^b		
	All Participants (N = 20 675)		P Value ^c	Unweighted No.	Weighted % (95% CI)	P Value ^c
	Unweighted No.	Weighted % (95% CI)				
Overall	1783	8.9 (8.1-9.9)	NA	1621	30.6 (28.3-33.1)	NA
Sex						
Male	1087	10.6 (9.7-11.6)	<.001	997	33.3 (30.7-36.0)	.005
Female (reference)	682	7.2 (6.1-8.6)	NA	612	27.2 (23.6-31.3)	NA
Race/ethnicity						
White non-Hispanic (reference)	769	8.5 (7.5-9.6)	NA	697	29.1 (26.4-31.9)	NA
Other non-Hispanic	112	7.2 (5.6-9.3)	.20	99	32.9 (26.0-40.7)	.31
Black non-Hispanic	250	8.4 (7.2-9.7)	.91	217	32.8 (28.3-37.6)	.19
Hispanic	588	10.8 (9.0-12.9)	.04	551	32.4 (28.4-36.6)	.16
School level						
Middle school (reference)	446	4.5 (4.0-5.0)	NA	380	23.1 (20.5-25.9)	NA
High school	1327	12.4 (10.9-14.2)	<.001	1232	33.3 (30.1-36.6)	<.001
Current (past 30 d) e-cigarette use						
No (reference)	1166	6.1 (5.5-6.9)	NA	1008	26.3 (23.6-29.2)	NA
Yes	582	39.5 (35.7-43.5)	<.001	579	40.3 (36.4-44.3)	<.001
No. of days e-cigarettes used in the past 30 d ^d						
1-5 (reference)	NA	NA	NA	308	33.5 (28.8-38.6)	NA
6-19	NA	NA	NA	121	39.8 (33.3-46.5)	.14
20-30	NA	NA	NA	166	63.7 (55.4-71.2)	<.001
Current (past 30 d) use of any non-e-cigarette tobacco products ^e						
No (reference)	981	5.3 (4.7-6.0)	NA	834	22.6 (20.4-24.9)	NA
Yes	799	38.5 (33.9-43.2)	<.001	785	46.9 (42.3-51.6)	<.001
Live with a tobacco user						
No (reference) ^f	726	6.0 (5.3-6.8)	NA	633	27.8 (25.0-30.7)	NA
Yes	905	13.0 (11.5-14.8)	<.001	848	31.7 (29.0-34.7)	.008

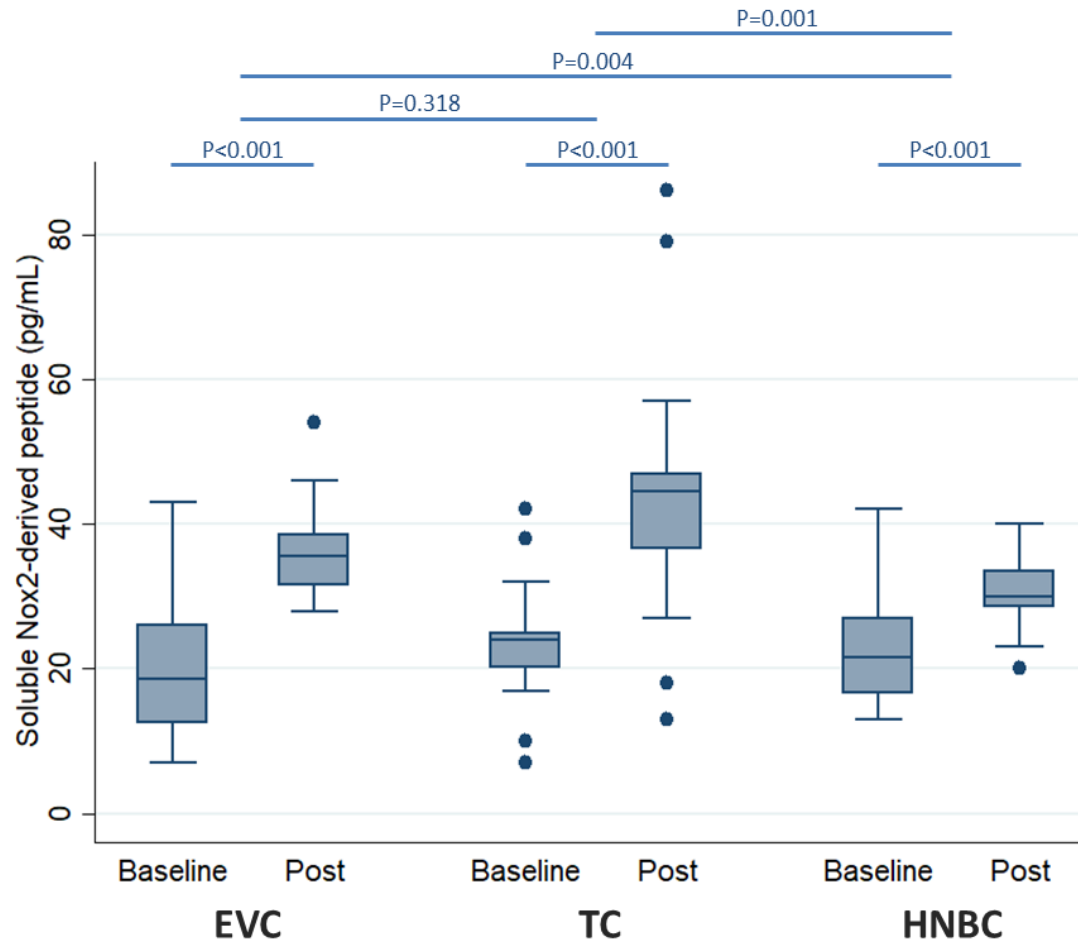
Misuse of pod mod EVC



SUR-VAPES 2: RCT of HNBC vs EVC

- **Methods:** Independent cross-over randomized trial in 20 TC smokers, to HNBC, EVC, and TC. Endpoints were oxidative stress, antioxidant reserve, PLT activation, flow-mediated dilation (FMD), blood pressure (BP), and satisfaction scores.
- **Results:** Any product led to an adverse impact on oxidative stress, antioxidant reserve, PLT function, FMD, and blood pressure.
 - HNBC had less impact than EVC and TC on soluble Nox2-derived peptide (respectively $p=0.004$, $p=0.001$), 8-iso-prostaglandin F2 α -III ($p=0.004$, $p<0.001$), and vitamin E ($p=0.018$, $p=0.044$).
 - HNBC and EVC were equally less impactful than TC on FMD ($p=0.872$ for HNBC vs EVC), hydrogen peroxide ($p=0.522$), H₂O₂ breakdown activity ($p=0.091$), soluble CD40 ligand ($p=0.849$), and soluble P-selectin ($p=0.821$).
 - The effect of HNBC and, to a lesser extent EVC, on BP was less evident than that of TC, whereas HNBC appeared more satisfying than EVC (all $p<0.05$).
- **Trial registration:** <https://clinicaltrials.gov/ct2/show/NCT03301129>.

SUR-VAPES 2: RCT of IQOS vs EVC



Pragmatism taking into account appeal

