UNIVERSITÄT BERN

Personalized counselling on the use of e-cigarettes to achieve tobacco abstinence: secondary analysis of data from an RCT

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Study disclosure

No co-author has a relationship with the tobacco, vaping, or pharmaceutical industries that would create a conflict of interest in these analyses.

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Background

- E-cigarettes, also called Electronic Nicotine-Delivery Systems (ENDS) are used by some tobacco smokers to assist with quitting.
- E-cigarettes increase tobacco abstinence (**TA**), but not necessarily nicotine abstinence **(NA)**.
- Presentation of therapy options for smoking abstinence should incorporate patient's preferences and values regarding **TA** and **NA** to enable shared decision-making.*
  - For those motivated for **TA**, but not necessarily **NA**, E-cigarettes might be a viable option
  - For those motivated for **TA** and **NA**, cytisine or varenicline might be more suited.
- When counseling patients, we could inform them about the characteristics of ESTxENDS participants for whom the intervention had high or low effects on **TA**, while considering the effects of the intervention on **NA**

* Auer et al, JACC-Advances, 2025. DOI: 10.1016/j.jacadv.2025.102106

Aims

- ❑ To predict effects of ENDS for TA and NA at the individual level
- ❑ To validate our predictions
- ❑ To develop an online tool that can be used to implement our models

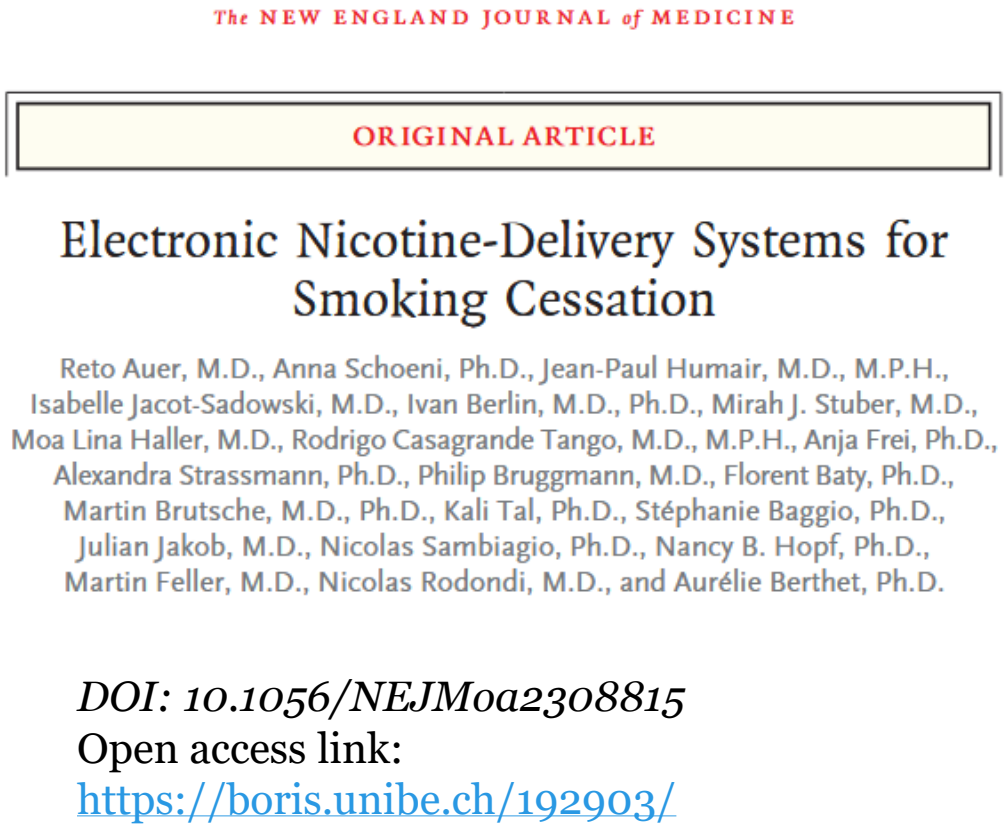
What we wanted to know is:

- For an individual with X characteristics, what outcomes on TA and NA do we expect based on ESTxENDS data? How to identify people who will have:
  - higher treatment effects ("high benefit") from vaping devices, i.e., ↑ **TA** without ↓ **NA**
  - lower treatment effects ("low benefit") from vaping devices, i.e., ↓ **TA** and ↓ **NA**

Data (1)

We used data from the ESTxENDS (*Efficacy, Safety and Toxicology of ENDS*) randomized trial

- Inclusion criteria: >18y, smoking 5 cigarettes/day, willing to set a quit date
- Control group: Standards-of-care smoking cessation counselling (SOC)
- 30 minutes of counseling at baseline visit, then 2 months of phone counseling
- Intervention group: SOC + free e-cigarettes and choice of e-liquids for 6 months, no specific advice on e-liquid use or duration
- 1246 participants randomized at a 1:1 ratio (July 2018 – June 2021); 5 study sites in Switzerland; follow-up at 6-months.



DOI: 10.1056/NEJMoa2308815
Open access link:
https://boris.unibe.ch/192903/

Data (2)

Outcomes

- continuous tobacco abstinence (**TA**), defined as self-reported TA for 6 months.
- 7-days **TA** (biochemically validated, last 7 days before the 6-month visit)
- 7-days nicotine abstinence **NA** (biochemically validated, last 7 days before the 6-month visit)

Predictors at baseline

- sex, age, PHQ9 score, time to first cigarette of the day (>60 minutes/31-60 minutes/6-30 min/< 5 min), # of previous smoking cessation attempts, cigarettes per day, years of smoking, tried to quit via e-cigarettes previously (Y/N), use of psychiatric medication (Y/N).
- This list was based on clinical experience but without checking the predictor-outcome relationship, to avoid overfitting

Overview of the baseline data

	N=1109	
	E-cigarettes 564 (50.9%)	**SOC 545 (49.1%)**
Predictors		
Male sex (N, %)	296 (52.5%)	288 (52.8%)
Age (mean, SD)	40.6 (13.6)	41.8 (13.2)
Smoking duration (mean, SD)	22.4 (12.7)	21.9 (13.0)
Time to first cigarette of the day (N, %)		
more than 60 min	96 (17.0%)	106 (19.4%)
31-60 minutes	125 (22.2%)	103 (18.9%)
6-30 minutes	243 (43.1%)	231 (42.4%)
<5 minutes	100 (17.7%)	105 (19.3%)
# previous smoking cessation attempts (median, IQR)	2 (1-3)	2 (1-3)
# cigarettes per day (median, IQR)	15 (10-20)	15 (10-20)
tried to quit via e-cigarettes previously (N, %)	98 (17.4%)	87 (16.0%)
PHQ9 (mean, SD)	4.5 (4.2)	4.4 (4.2)
Use of psychiatric medication (N, %)	103 (18.3%)	108 (19.8%)

Methods (1): prediction models

- We first estimated the average treatment effect for each outcome, as risk difference (RD), i.e. difference in probability of an event in e-cigarettes minus SOC.
- $RD > 0 \rightarrow$ e-cigarettes are better (increase abstinence)
- We fit statistical and machine learning models for each outcome separately (*logistic regression; logistic regression with treatment covariate interactions; LASSO & ridge regressions; gradient boosting machine; causal forest*), where:
  - ✓ **Input**: predictors.
  - ✓ **Output**: probability of an event for all 3 outcomes for both interventions (e-cigarettes, SOC), and from that patient-level treatment effects (RD)

Methods (2): assessing model performance

- We performed (a) an **internal** and (b) an **internal-external** cross-validation (CV)
- **Internal**: 10-fold cross-validation approach repeated 20 times
- **Internal-external**: similar to internal, but folds according to the sites where ESTxENDS was conducted
- We did not do an **external validation**, following recent guidelines*

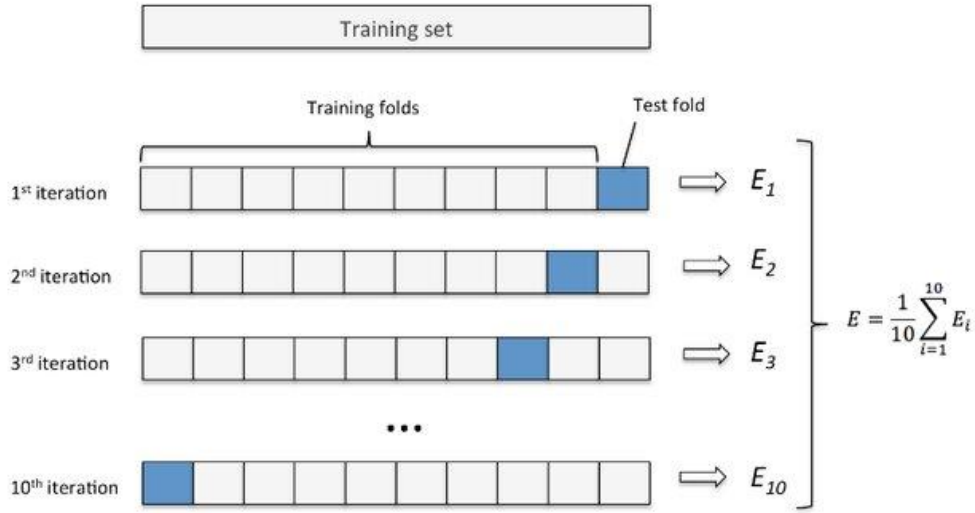


Image from DOI: 10.1007/978-3-030-01057-7_35

**Efthimiou O et al. Developing clinical prediction models: a step-by-step guide. BMJ. 2024*

Methods (3): assessing model performance

- To measure performance, we used absolute outcome predictions (risk) using calibration and discrimination measures (AUC, calibration slope)

*However, minimizing the error of outcome predictions, however, does not necessarily minimize the error of the treatment effect predictions **

- Thus, we assessed performance also discrimination for benefit and calibration for benefit

*Efthimiou O et al. Measuring the performance of prediction models to personalize treatment choice. Stat Med. 2023

Methods (4): Identifying subgroups

- After model selection, we used the predicted treatment effects for each participant to define two groups (based on the 33rd and 66th percentiles of predicted effects)
  - **High benefit**: participants in this group were predicted to have a high benefit from e-cigarettes with respect to TA, without a substantial deterioration in the probability of NA, i.e. ↑ **TA** without much ↓ **NA**
  - **Low benefit**: participants in this group are predicted to benefit less from e-cigarettes with respect to TA and may decrease their probability of NA even if they achieve TA, i.e. ↓ **TA and** ↓ **NA**
- We summarized and compared the characteristics and outcomes of these two groups (using again out-of-sample predictions)

Methods (5): missing data

- Very few missing data on covariates
- Missing data on the outcomes were more frequent (~10%), but we could not reliably impute them.
- We performed a complete case analysis, removing participants with missing outcomes or covariates
- In **sensitivity analysis** we assumed that all missing outcomes were negative (i.e. no tobacco/nicotine abstinence) and compared results with the primary analysis.

Results (1): Continuous tobacco abstinence

- Average treatment effect RD **+12.9% [7.9%; 17.9%]** favoring e-cigarettes.
- Best model: ridge regression.
- Modest discrimination (AUC=0.61[0.58; 0.65], and calibration (calibration slope 0.85 [0.55; 1.16]).
- Predicted treatment effects ranged from RD=-4% to +26%.
- Rather low discrimination for benefit (C-for-benefit=0.56 [0.51; 0.60])
- Good calibration for benefit (slope 0.99 [0.58; 1.41]).

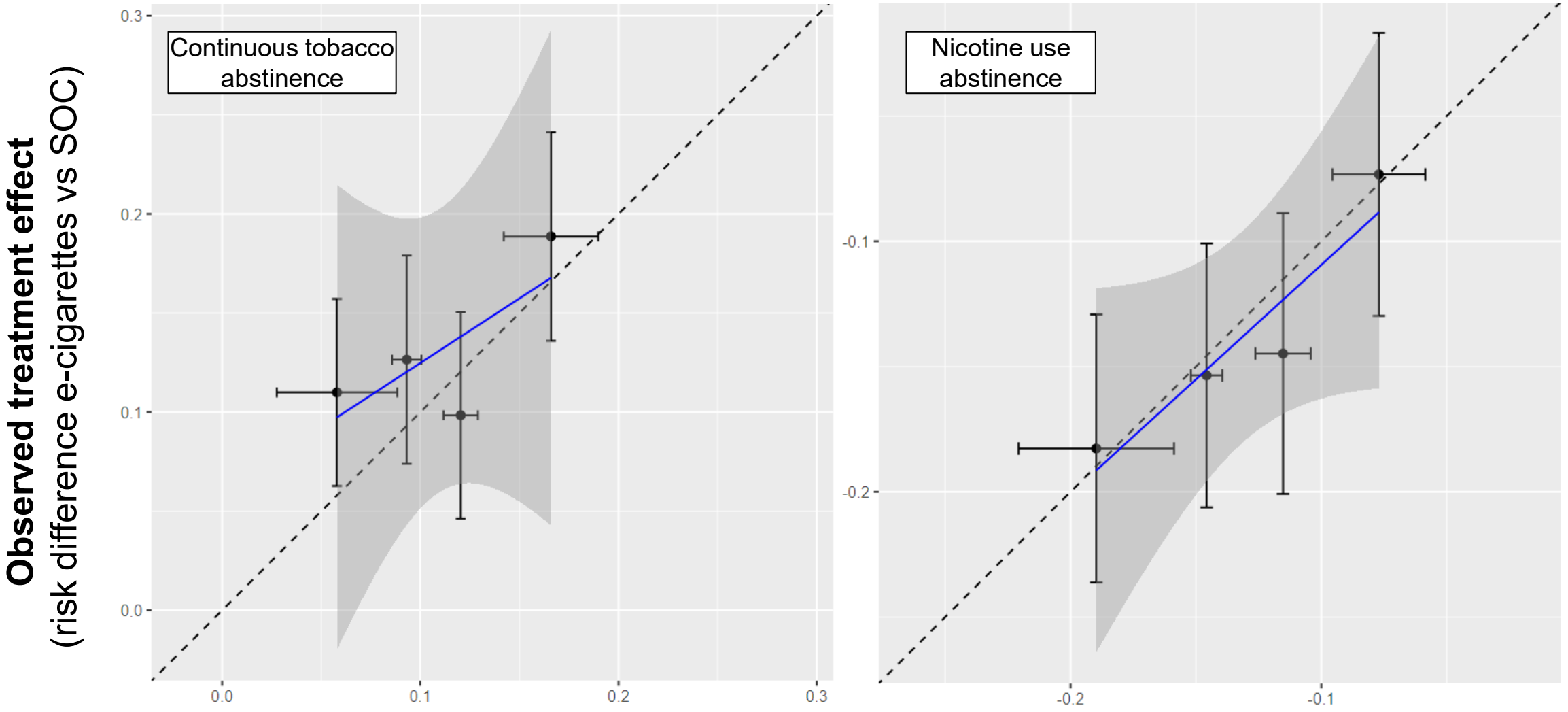
Results (2): Seven-days tobacco abstinence

- Average treatment effect RD **+20.6% [14.6%; 26.5%]** favoring e-cigarettes
- No model showed good performance in our cross-validation
- We were unable to develop a model to reliably predict effects at the individual level

Results (3): Seven-days nicotine abstinence

- Average treatment RD **-14.0% [-19.4%; -8.6%]** favoring SOC.
- Best model: ridge regression.
- Modest discrimination (AUC=0.64 [0.60; 0.68]) good calibration (slope 0.97 [0.70; 1.26]).
- Predicted treatment effects ranged from RD=-28% to -2%.
- Rather low discrimination for benefit (C-for-benefit=0.55 [0.50; 0.60]) but good calibration for benefit (slope 1.03 [0.67; 1.41])

Results (4): Calibration for benefit



Results (5): high vs low benefit groups*

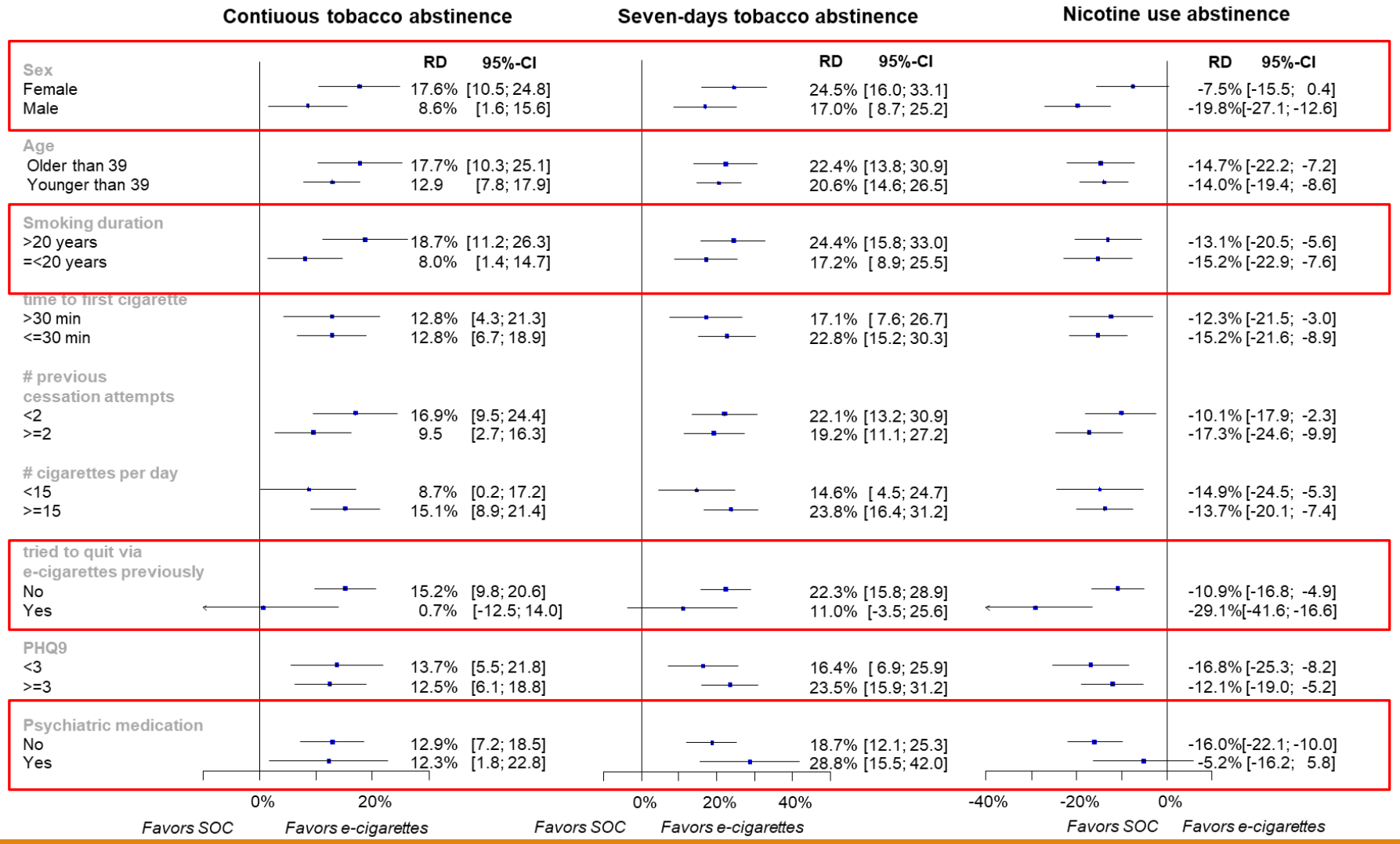
		High benefit	Low benefit
Number of participants	Total	117	146
	SOC	58	72
	e-cigarettes	59	74
Continuous smoking abstinence	SOC (events, %)	11 (19.0%)	20 (27.8%)
	e-cigarettes (events, %)	19 (32.2%)	22 (29.7%)
	Average treatment effect	**+13.2% [-2.3%; 28.9%]**	**+2.0% [-12.7%; 16.6%]**
Seven-day smoking abstinence	e-cigarettes (N, %)	18 (31.0%)	34 (47.2%)
	SOC (N, %)	36 (61.0%)	51 (68.9%)
	Average treatment effect	**+30.0% [12.8%; 47.2%]**	**+21.7% [6.1%; 37.3%]**
Nicotine use abstinence	e-cigarettes (N, %)	16 (27.6%)	28 (38.9%)
	SOC (N, %)	11 (18.6%)	12 (16.2%)
	Average treatment effect	**-8.9% [-24.1%; +6.3%]**	**-22.7% [-36.7%; -8.6%]**

**out of sample results*

Results (6): high vs low benefit groups

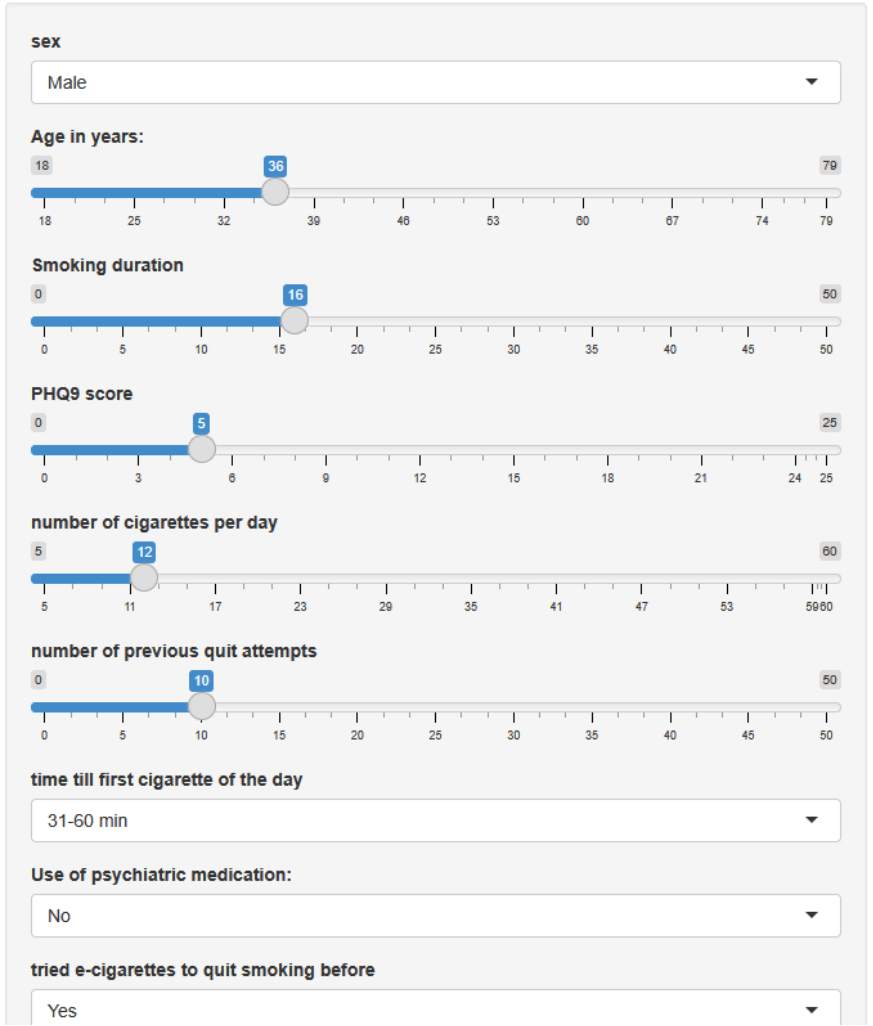
	High benefit (N=117)	Low benefit (N=146)
Women (N, %)	103 (88.0%)	29 (19.9%)
Age (mean, SD)	51.1 (11.0)	32.6 (8.5)
Smoking duration (mean, SD)	32.7 (11.1)	13.9 (7.7)
Time to first cigarette of the day (N, %)		
more than 60 min	20 (17.1%)	20 (13.7%)
31-60 minutes	26 (22.2%)	32 (21.9%)
6-30 minutes	60 (51.3%)	62 (42.5%)
<5 minutes	11 (9.4%)	32 (21.9%)
# previous smoking cessation attempts (median, IQR)	1 (1-2)	2 (1-4)
# cigarettes per day (median, IQR)	17 (10-20)	15 (10-20)
tried to quit via e-cigarettes previously (N, %)	0 (0%)	95 (65.1%)
PHQ9 (mean, SD)	4.2 (3.3)	4.6 (3.9)
Use of psychiatric medication (N, %)	42 (35.9%)	6 (4.1%)

Results (7): Effects by covariate subgroups



Results (8): Predicting individual effects

Personalised predictions for active intervention vs standard-of-care



Prediction of outcomes at 6 months

Probability of continuous smoking abstinence in control=31.8%
Probability of continuous smoking abstinence in intervention= 36.8%
Probability of nicotine abstinence in control= 51.6%
Probability of nicotine abstinence in interention= 21.5%

Treatment effects at 6 months

Treatment effect (active minus control) for continuous smoking absinence= 5%
Treatment effect (active minus control) for nicotine absinence= -30.1%

Outcome	Control	Intervention	Effect of intervention
Smoking Abstinence (continuous)	32 %	37 %	5 %
Nicotine abstinence	52 %	21 %	-30 %

https://oefthimiou.shinyapps.io/ecigarettes

Results (6): Sensitivity analysis on missing data

- Assuming all missing outcomes to be failures (no TA/NA) led to similar results

Summary (1): Limitations

- 6 months follow-up only, maybe effects are attenuated at later follow ups
- Data from only 1 RCT conducted in Switzerland. Results might not apply to other populations.
- Sample size limited for personalized effects. Study powered for average effects.
- Low predictive performance for 7-days TA, modest for continuous TA and 7-days NA
- We did not examine side effects – “high” and “low benefit” only apply for TA and NA

Summary (2): Strengths

- Largest (?) RCT in the field
- Use of cutting-edge statistical methodologies to model development, avoiding overfitting, assessing model performance
- Very few missing data on predictors. Relatively few (~10%) missing data on outcomes.
- Good calibration for benefit

Summary (3): Future research

- External validation(s) of our models are required before implementing them in clinical practice
- Re-calibration/model update may be needed for other populations
- Re-development of the model using more data (IPD meta-analysis) may increase discrimination

Summary (4): Conclusions

- We identified high and low benefit groups. Particularly:
  - *Older women who have not already tried e-cigarettes and are on psychiatric medications may increase their chances of TA from adding e-cigarettes to SOC compared to SOC alone, with weak evidence of a possible small negative effect on NA.*
  - *Younger men who have already tried e-cigarettes may not increase their chances of TA and may decrease their chances of NA.*
- Future research required to validate our tool and corroborate its usefulness in diverse settings
- If validated with further data, the online tool could be used to make personalized recommendations to facilitate shared decision making

Thank you for your attention!

Bern, Switzerland

Ioannina, Greece