Smoking reduction trajectories, and their association with smoking cessation: A secondary analysis of longitudinal RCT data

Short Title

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# ABSTRACT

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# INTRODUCTION

Smoking is the number one cause of premature and preventable illness worldwide (1). Smoking accounts for approximately 5.7% of total health expenditure worldwide and 6.5% in high income countries like the UK and USA (2), and 1 in two smokers will die unless they quit (3,4).

Smoking reduction to quit is often recommended to smokers who have found it difficult to quit using ‘abrupt quitting’ methods in the past. Though magnitude and duration vary, broadly, smoking reduction is defined as a decrease in the number of cigarettes smoked per day. In the UK and in some parts of Europe, smoking reduction is promoted as a second-line route to quitting smoking or as a harm reduction approach for smokers who cannot, or may not be ready, to stop smoking completely (5,6). In addition, the license for nicotine replacement therapy (NRT) explicitly states that it can be used for smoking reduction(7). In the USA smoking reduction is offered informally as part of smoking cessation treatment, and NRT is deemed appropriate for use as a reduction aid (8). There is limited evidence that reduction itself improves health (9), but clearer evidence that s smoking reduction is as effective as abrupt quitting in achieving complete cessation (10), which has well established health benefits.

Smokers report that they perceive smoking reduction as an acceptable way to stop smoking (11–15). Smokers reducing their daily number of cigarettes could use a range of different approaches to do so, including a combination of behavioral counselling and NRT (10). There is some evidence that providing behavioral support to reduce to quit helps more people to stop smoking than providing people with self‐help resources only. For example, setting a particular time period to reduce over before quitting completely, progressively reducing the time periods in the day when smoking occurs (i.e., timed reduction(16)), or gradually eliminating the easiest to the most difficult cigarettes to give up in a given day (i.e., hierarchical reduction(17)). Other approaches include simply advising smokers to reduce their smoking as much as possible without giving any specific guidance on how to do so (18–22). However, there is no clear evidence to support any particular behavioral reduction method over others (10,15).

A Cochrane Review has found that a number of trials have simply asked participants to reduce without giving them any specific instructions on how to do so (10). However, little is known about what the resulting, more unstructured, participant-led smoking reduction patterns look like. For example, after receiving a basic instruction to reduce their smoking do smokers cut down immediately, or later? Do they steadily reduce smoking until complete cessation? Do they reduce and then increase the amount smoked? Or are there other patterns of smoking reduction? Secondly, we do not know whether particular patterns of smoking reduction are associated with better smoking cessation outcomes, and if so, which ones? Third, we do not know if particular patterns of smoking reduction are determined by particular participant characteristics or dependency profiles. This information could be of importance when developing and tailoring smoking reduction interventions and could aid clinicians who recommend and offer smoking reduction treatment.

In this secondary analysis of five randomized placebo-controlled trials of NRT for smoking reduction we aim to:

* Use latent class analysis (LCA) to determine if there are trajectories in cigarettes per day (CPD) overtime in people who are asked to reduce their smoking before quitting, without specific instructions on how to do so.
* Determine which (if any) baseline participant characteristics predict latent class membership.
* Determine whether latent class membership is associated biochemically verified smoking cessation, while considering participant characteristics.

Although several studies have used LCA to explore heterogeneity in smoking behavior trajectories (e.g, 18–20), none to date have leveraged contemporary machine learning methods to determine characteristics associated with latent class membership. The present study uses regularized linear models to minimize noise associated with highly correlated predictors while emphasizing effects from relevant predictors of class membership and smoking cessation. These methods focus primarily on overall predictive performance rather than statistical significance.

# METHODS

This study was preregistered on OSF (https://osf.io/qh378/) and all code is available through GitHub <insert link>

## Study Design

This secondary analysis examined individual-level patient data from five randomized placebo-controlled trials of NRT for smoking reduction (18–22). The trials were carried out to a consistent protocol. Participants were provided with active NRT (inhaler, patches, or gum) in the intervention arm and a placebo form of the same NRT in the control arm. In both arms participants received the same minimal level of behavioral support for smoking reduction and were encouraged to reduce their smoking as much as possible with cessation as the end goal.

The trials were conducted and funded by McNeil AB (https://www.mcneilab.se/). The current authors were not involved with the original trials.

## Setting

The trials took place between 1997 and 2003 and were conducted in university and medical centers in Denmark, Switzerland, Australia, the USA and Germany.

## Study Size

There were 2066 participants enrolled in the trials.

## Participants

All participants were at least 18 years of age, reported smoking 15 or more cigarettes per day, and were selected because they wanted to reduce but not stop smoking, and had smoked regularly for at least 3 years. Participants were excluded if they were pregnant, breastfeeding, under psychiatric care, deemed to be unfit by a general practitioner, or part of a cessation program.

## Data Collection

At baseline, trial investigators gathered data on participants’ demographic details, age started smoking, cigarettes per day (CPD), nicotine dependence (Fagerström Test of Nicotine Dependence; FTND (26)), intention to reduce, intention to quit, smoking history (e.g., number of previous quit attempts, longest period without smoking), and self-rated effects from smoking, the Short Form Health Survey-36 (SF-36/RAND-36 (27–29)). To preserve anonymity, some demographic data were unavailable for this secondary analysis.

Participants were followed up with consistent measures at baseline, and at 2-, 10-, 18-, 26- and 52- weeks from baseline. On each occasion, investigators collected data on CPD and recorded an expired air carbon monoxide (CO) reading. Participants answered the following questions via self-report: “how many cigarettes do you smoke/day on average?”, “how many cigarettes do you smoke/week on average”, “how many cigarettes do you smoke/month on average?”.

## Variables

Latent trajectories were determined using percent change from baseline in average cigarettes per day (CPD) at weeks 2, 10, 18, and 26. When CPD was unavailable, participants self-reported cigarettes per week were divided by 7 and used instead. If a participant reported they had stopped smoking, CPD was set to 0. Abstinence was determined using CO values from week 52.

The baseline variables used to predict latent class were age at trial intake, age started smoking, longest period without smoking, number of times tried to quit smoking, FTND, intention to quit, length of time since last quit attempt, experience of anxiety in the last 24 hours, experience of depression in the last 24 hours, SF-36 subscales, carbon monoxide parts per million (CO ppm), relief from smoking, study site, and parent trial treatment group (22 variables in all).

## Bias

To address bias due to missing data, baseline predictors with greater than 25% missing observations were discarded. Additionally, subjects missing 7 or more baseline variables were excluded from analyses. Finally, missing observations for remaining baseline predictors were grouped by study site, sex, and age and imputed using average values within those groups.

## Statistical Methods

### Analysis 1: Trajectories in cigarettes per day over time

A latent class mixture model (30–32) was used to determine longitudinal trends in cigarettes per day from baseline assessed at trial weeks 2, 10, 18, and 26. The primary dependent variable was percent change average CPD (e.g., a participant smoking 90% of their baseline level at week 2 received a value of -10% for week 2).

Models ranging from 1 to 6 classes were estimated, and models for classes greater than 1 were initialized using parameters from the 1-class model. Grid search methods were performed for subsequent models, seeking to minimize information criteria at each step. The model that balanced fit and parsimony was selected as optimal.

Posterior classification was then used to assign subjects to each latent class using maximum likelihood estimation given the information (i.e., percent change in CPD at each week) collected in the longitudinal model.

### Analysis 2: Predicting longitudinal trajectories in CPD using baseline variables

Elastic net logistic regression (33,34) was used to build predictive models for each latent class using all baseline characteristics as features (i.e., independent variables), and class membership as the target (i.e., dependent variable). Class membership was treated as a binary outcome, with membership to each class predicted using a separate regression model.

Initially, the data were split into 80% training and 20% testing sets. The training data was then used to tune parameters for elastic net logistic regression models. Model selection and evaluation was performed using a nested cross-validation framework. Training was conducted using 5-fold cross validation, with 80% of the training set used for model training and 20% for evaluation. Model hyperparameter selection was conducted using a further divide of this training set using 5-fold cross-validation within each outer fold. Prediction accuracy was measured using receiver operator characteristic area-under-the-curve (ROC AUC). Parameters from the model whose ROC AUC results were within one standard error of the optimal cross-validated results were selected (35). For each model, AUC represents the accuracy of prediction of the internal validation set. Hyperparameters from the most successful of these models were used to fit a model to the initial training set to obtain coefficients. To confirm model generalizability, these hyperparameters were also used to fit a final model to the initial testing set. Null ROCs were computed for each predicted class, and overall statistical significance was assessed using to ROC AUC’s equivalence with the Mann-Whitney *U*-statistic (36). This procedure was repeated using each latent class as the target.

### Analysis 3: Which trajectories in CPD predict smoking cessation?

A linear elastic net regression model was used to predict smoking abstinence at 1-year follow-up using (1) all baseline characteristics from Analysis 2, and (2) Latent Class (from Analysis 1) in addition to those predictors, and (3) baseline predictors with only subjects in each Latent Class, respectively. The dependent variable was CO in parts per million. Predicted CO values <= 11 ppm were considered indicative of quitting smoking.

Each regression model was fit using the procedures outlined in Analysis 2, with model performance measured using the coefficient of determination, *R*2.

## Quantitative Variables

Ordinal predictors (i.e., longest period without smoking, number of times tried to quit smoking, intention to quit, length of time since last quit attempt, experience of anxiety in the last 24 hours, experience of depression in the last 24 hours, and relief from smoking) were treated as numeric variables. These plus additional numeric predictors (i.e., SF-36 scores, CO, age at intake) and outcomes (i.e., CO-confirmed abstinence at 1-year follow-up) in the training set were normalized and scaled to have a mean of 0 and standard deviation of 1. Numeric predictors in the testing set were normalized blindly using the same transformations as the training set.

# RESULTS

## Participants

Additionally, 101 subjects were missing 7 or more baseline measures and were not included in analyses. The783 remaining subjects had

Smoking trajectories were modeled using a total of 5,578 observations (Weeks 2, 10, 19, and 26 had 1764, 1148, 1384, 1282 observations respectively) from 1,783 participants.

## Descriptive data

Participants were from 5 countries (Australia, Denmark, Germany, Switzerland, and USA), were 44.8% male (798/1783), with a mean (SD) age of 44.10 (10.72) years and smoked a mean (SD) of 27.32 (9.73) CPD (see Table 1).

Two SF-36 sub score (General and Physical Functioning) values were 20.75% and 21.82% missing respectively and were discarded. Of the remaining missing values (i.e., RSQ pepping-up, calming effects, and overall last cigarette experience: 7.31%, 2.81%, and 0.05% missing respectively; intention to quit: 2.81%; SF-36 subscales: <1%), subjects’ ages were binned into 4 equally sized groups, and all remaining baseline variables were imputed within age-sex-site combinations, using the mean and mode of those combinations where appropriate.

## Analysis 1: Trajectories in cigarettes per day over time

Latent class model-fit information appears in Table 2, suggesting that models using 3-6 classes are optimal. The 3-class model was selected to balance minimal information criteria with parsimony; the 4, 5, and 6-class models did not reveal more information about smoking trajectories. Distributions of CPD changes for each follow-up point are available in the supplemental material.

Class 1 (n = 186, 10.43%) is characterized by an initial reduction in CPD of approximately 57% at week 2, followed by a trend toward 90% reduction by week 26. Participants in Class 2 (n = 803, 45.04%) initially reduced their smoking approximately 41% and remained consistent, for an average reduction of 46% from baseline at week 26. Class 3 participants (n = 794, 44.53%), in contrast, showed a modest (approximately 22%) reduction in smoking and a return to near-baseline levels (i.e., 6% reduction from baseline) by week 26. Average CPD trajectories for each of the selected 3 classes are shown in Figure 1.

Fixed effects maximum likelihood estimations show the initial smoking reduction (i.e., change from baseline smoking at week 2) for participants in Class 1 was significantly less than Class 3 (estimate (SE) = -1.31 (0.11), Wald = -12.32, p < .0001), but initial smoking reductions among Class 2 participants did not differ from those in Class 3 (estimate (SE) = 0.03 (0.08), Wald = 0.38, p = 0.7013). Within each trajectory, differences in CPD were observed for each week (p’s < .001).

## Predicting class membership using baseline characteristics

Regression models predicting membership to Classes 1 and 2 performed

All individual binary class prediction models were statistically significant, particularly for Class 1 (mean AUC [SE] = 0.626 [0.022]). Predictive performance within the model for Class 2 was close to chance (AUC = 0.501) and was only statistically significant due to the comparatively large sample size in Class 2 (n = 803, 45.0%). Contrasts, in which only subjects belonging to the listed classes were included in the binary prediction model, were statistically significant (*p’s* < 0.01) for all comparisons. Overall model results are shown in Table 2.

To determine the relative contributions of each baseline characteristic to the overall model’s predictive capacity, the average Beta value for each predictor was recorded across the 5 outer validation folds. These values are presented in Figure 4.

Participants assigned to Class 1 -- those who reduced smoking substantially -- tended to be older, have started smoking later in life, and have lower measures of anxiety and nicotine dependence. They were more likely to want to quit smoking at study baseline and to have slightly higher SF-36 social and physical sub scores, but below average pain sub scores.

Younger participants and those with high anxiety and moderate depression were less likely to be assigned to Class 1, as were participants with lower nicotine dependence scores, and those who had only ever stopped smoking for less than one week. Conversely, those who had attempted to quit recently, often, or who participated in a trial conducted outside the USA were more likely to be in Class 1, and less likely to be in Class 3. 10 subjects indicated they had never quit smoking, and none were in Class 1.

Intuitively, those in Class 1 – the group which reduced its smoking the most –were more likely to have been assigned to the active NRT condition, while those in Class 3 were more likely to have received placebo treatment. Finally, although it represents the largest group of smokers, the model predicting membership to Class 2 showed low overall performance, and therefore features tended toward 0.

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## Predicting smoking cessation at 1-year using latent class

Of the 1783 participants assigned to latent classes, 911 had CO values at the 1-year follow-up point (6 months following the conclusion of the trial). Using a quit threshold of CO <= 11ppm, 261 (28.6%) had quit smoking at this point. More specifically, 66.9% (n = 95) of subjects in Class 1 had quit, 24.3% (n = 120) in Class 2, and 16.7% (n = 46) in Class 3.

An elastic net linear regression model was used to predict 1-year CO values using baseline characteristics alone, achieving an average cross-validated (mean [SE]) R2 = 0.207 [0.005], with R2 = 0.162 on the testing set. Adding latent class as a predictor improved average cross-validated prediction performance by an average of 6.3% (CV R2 = 0.270 [0.003], test R2 = 0.238). Each showed greater performance than predicting 1-year CO values from predictors while limiting subjects to those within each class respectively. These results, plus predictions limited to subjects assigned to each latent class are seen in Table 4.

Using the initial 20% testing data set to make predictions of 1-year follow-up CO values, subjects whose predicted values were > 11ppm were labelled smokers, and those with values equal to or below 11ppm non-smokers. This was also done with the actual 1-year CO values to assess the linear model’s ability to predict those who quit smoking. 150/187 (80.2%) of participants were accurately identified according to whether they quit smoking (see Figure 4). Specifically, 62.9% of subjects in Class 1 were predicted to have CO values <11ppm, 2.9% in Class 2, and 6.0% in Class 3. Classification accuracy counts by latent class on unseen data are presented in Table 5.

Beta values from each cross-validation fold were averaged to assess feature importance for each regression model. These values are presented in Figure 6. The model using all baseline predictors and assigned latent class offers the strongest correlation with follow-up CO values. More specifically, assignment to Class 2 or Class 3 is the strongest predictor of a high CO value relative to Class 1, as is having a high baseline CO value, and having quit more than 10 times before the trial. Within this model, a site effect presents compared to the USA, with German and Danish sites predicting lower follow-up CO values and Switzerland slightly higher.

# DISCUSSION

The present study examined smoking patterns in a secondary analysis of five NRT trials and found three distinct repeated measures smoking trajectories. Specifically, some smokers initially reduced and nearly eliminated their smoking (Class 1), some reduced by approximately half and remained at that level throughout the trial (Class 2), and others reduced initially but reverted to cigarette use near their baseline levels (Class 3). Regularized predictive modelling showed relatively strong positive associations between Class 1 and affective disorders, nicotine dependence, and those whose previous periods of smoking cessation were shorter than one week.

Regularized regression models predicting CO values 6 months after the trial’s conclusion showed stronger performance with access to latent class as opposed to baseline characteristics alone, suggesting smoking trajectories may have implications for predicting smoking cessation. Those in Class 1 have lower 1-year CO values, while those in Classes 2 and 3 tended to have higher follow-up readings.

Most importantly, despite random assignment to active or placebo NRT and consistent instructions to reduce smoking, cigarette use trajectories are not homogenous. As expected, those who failed to reduce their smoking during the trial or who only cut out a small number of cigarettes were less likely to have quit smoking following the trial. Although reduction and cessation patterns aligned with treatment assignment, baseline reports of anxiety and depression were similarly important. Smoking trajectories were substantially more predictive of follow-up CO than assignment to either condition.

These results align with a previous LCA (24) which concluded that smokers who are not looking to quit are not homogenous. In the present study, the group most likely to have a low follow-up CO was Class 1, who reduced their smoking substantially by trial week 2, and continued to reduce throughout the trial’s duration. Participants who had quit before as well as those reporting anxiety and depression were less likely to follow this trajectory, consistent with known overrepresentation of those with affective disorders among smokers (37,38).

## Limitations

There are a range of unmeasured variables that might confound the association in question, and we will have no way of measuring the impact of residual confounding. There are also a range of variables that we predict are important, but were not measured, or not measured consistently across the trials, i.e., ethnicity, education, intention to reduce.

Additionally, we are unable to measure short term changes in CPD that occurred temporarily between measurements, which could affect outcomes (39). Latent classes were developed based on self-reported cigarettes per day (CPD). It is possible that participants inaccurately reported their CPD, however it is not possible to biochemically confirm CPD using the collected carbon monoxide readings (CO ppm). Although a person may reduce their CPD, they may also inhale their remaining cigarettes more deeply, which could mean that the CO reading does not decrease in-line with the reduction in CPD. Furthermore, CO has a half-life of around 4 hours meaning that the magnitude of the measurement is affected by the recency of smoking (40). Therefore, even if a person has reduced their daily CPD overall this would not be reflected in the CO measurement if they had smoked their remaining cigarettes just before the measure was taken. However, our smoking cessation outcome will be biochemically verified (CO ppm ≤11) (41).

The McNeil trials recruited participants because they wanted to reduce but not stop smoking and had smoked for at least 3 years. Therefore, our analyses may not generalize to participants who consciously seeking to reduce smoking to quit, although many participants in these trials did quit smoking as a result of smoking reduction intervention.

# CONCLUSIONS

Examining latent trajectories in smoking behavior among a sample of smokers not looking to quit reveals heterogeneity in smoking patterns. Identifying these subgroups may allow for targeted intervention with the goal of reducing cigarette use particularly among populations predisposed to tobacco use.

# Tables

Table Participant characteristics by latent class.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Overall | Class 1 | Class 2 | Class 3 |
| N (%) | 1783 (100) | 186 (10.4) | 803 (45.0) | 794 (44.5) |
| Study Site (%) |  |  |  |  |
| Australia | 360 (20.2) | 32 (17.2) | 159 (19.8) | 169 (21.3) |
| Denmark | 340 (19.1) | 35 (18.8) | 175 (21.8) | 130 (16.4) |
| Germany | 353 (19.8) | 60 (32.3) | 153 (19.1) | 140 (17.6) |
| Switzerland | 301 (16.9) | 29 (15.6) | 139 (17.3) | 133 (16.8) |
| USA | 429 (24.1) | 30 (16.1) | 177 (22.0) | 222 (28.0) |
| Study Treatment Group = active (%) | 900 (50.5) | 125 (67.2) | 413 (51.4) | 362 (45.6) |
| Sex = Male (%) | 798 (44.8) | 96 (51.6) | 357 (44.5) | 345 (43.5) |
| Age (mean (SD)) | 44.10 (10.72) | 45.79 (11.41) | 44.26 (10.52) | 43.53 (10.73) |
| Baseline FTND (mean (SD)) | 6.14 (2.00) | 5.60 (2.13) | 6.11 (2.01) | 6.30 (1.94) |
| Baseline CPD (mean (SD)) | 27.32 (9.73) | 25.65 (10.37) | 27.42 (9.78) | 27.62 (9.50) |

Table Latent class model fit comparison (n = 1783).

|  |  |  |  |
| --- | --- | --- | --- |
| Number of Classes | BIC | AIC | Maximum Log-Likelihood |
| 1 | 2102.42 | 2085.97 | -1039.98 |
| 2 | 577.95 | 545.04 | -266.52 |
| 3\* | 43.75 | -5.62 | 11.81 |
| 4 | -36.02 | -101.85 | 62.92 |
| 5 | -87.61 | -169.90 | 99.95 |
| 6 | -116.79 | -215.54 | 125.77 |

\*Selected model. BIC = Bayesian Information Criterion, AIC = Akaike Information Criterion.

Table 3 Elastic net logistic regression results predicting latent class from baseline characteristics.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Mean Cross-validated AUC | SE | Test Partition AUC | *p* |
| Class 1 Overall | 0.629 | 0.032 | 0.691 | <.001 |
| Class 2 Overall | 0.510 | 0.014 | 0.520 | <.001 |
| Class 3 Overall | 0.581 | 0.020 | 0.582 | <.001 |
| Class 1 vs. Class 2 | 0.594 | 0.028 | 0.646 | <.001 |
| Class 1 vs. Class 3 | 0.683 | 0.026 | 0.693 | <.001 |
| Class 2 vs. Class 3 | 0.527 | 0.014 | 0.553 | <.001 |

Table 4 Elastic net regression results predicting expired breath CO values at 1-year trial follow-up.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean Cross-validated *R*2 | SE | Test Partition *R*2 |
| Latent Class Alone | 0.108 | 0.006 | 0.216 |
| Baseline Predictors Alone | 0.245 | 0.006 | 0.214 |
| Baseline Predictors + Latent Class | 0.299 | 0.013 | 0.307 |

Table 5 Post-hoc quit smoking classification from 1-year follow-up CO prediction using elastic net regression model. CO values <= 11ppm were considered indicative of smoking cessation.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Class 1 | | Class 2 | | Class 3 | |
|  |  | *Actual* | | *Actual* | | *Actual* | |
|  |  | Not Quit | Quit | Not Quit | Quit | Not Quit | Quit |
| *Predicted* | Not Quit | 6 | 7 | 82 | 20 | 42 | 5 |
|  | Quit | 3 | 19 | 2 | 1 | 0 | 0 |
| **Accuracy** |  | 66.7% | 73.1% | 97.6% | 4.8% | 100% | 0% |

# FIGURES

Figure 1 Three-class smoking trajectories.

Chart, line chart

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Chart, line chart

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Figure Latent class mixture model goodness of fit.

Chart

Description automatically generated with medium confidence

Figure 4 Average cross-validated feature importance when predicting membership to latent class. Black square indicates reference class for ordinal variables. Largest group was used as the reference class.

Chart, scatter chart

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Figure 5 Predicting 1-year follow-up CO values using baseline predictors and latent class. 11ppm CO threshold is indicated with dashed lines.

A picture containing table

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Figure 6 Average cross-validated feature importance when predicting CO values at 1-year follow-up.

# Appendix

Figure Distributions of CPD values at each time point.

Timeline

Description automatically generated

# References

1. World Health Organization. WHO report on the global tobacco epidemic, 2011: warning about the dangers of tobacco. 2011 [cited 2023 Jan 20]; Available from: https://apps.who.int/iris/handle/10665/44616

2. Goodchild M, Nargis N, Tursan d’Espaignet E. Global economic cost of smoking-attributable diseases. Tob Control. 2018 Jan;27(1):58–64.

3. Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. The Lancet. 2013 Jan;381(9861):133–41.

4. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years’ observations on male British doctors. BMJ. 2004 Jun 26;328(7455):1519.

5. NICE. National Institute for Clinical Excellence (NICE). Smoking: Harm reduction Public health guideline [PH45] [Internet] [Internet]. 2013. Available from: https://www.nice.org.uk/guidance/ph45

6. European Network for Smoking and Tobacco Prevention. Guidelines for treating tobacco dependence. 2018.

7. Medicine and Healthcare Products Regulatory Agency Committee. Report of the Committee on Safety of Medicines Working Group on Nicotine Replacement Therapy. London; 2005.

8. Fucito LM, Bars MP, Forray A, Rojewski AM, Shiffman S, Selby P, et al. Addressing the Evidence for FDA Nicotine Replacement Therapy Label Changes: A Policy Statement of the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco. Nicotine Tob Res. 2014 Jul 1;16(7):909–14.

9. Pisinger C, Godtfredsen NS. Is there a health benefit of reduced tobacco consumption? A systematic review. Nicotine Tob Res. 2007 Jun;9(6):631–46.

10. Lindson N, Klemperer E, Hong B, Ordóñez-Mena JM, Aveyard P. Smoking reduction interventions for smoking cessation. Cochrane Tobacco Addiction Group, editor. Cochrane Database Syst Rev [Internet]. 2019 Sep 30 [cited 2022 Dec 7];2019(9). Available from: http://doi.wiley.com/10.1002/14651858.CD013183.pub2

11. Beard E, Vangeli E, Michie S, West R. The Use of Nicotine Replacement Therapy for Smoking Reduction and Temporary Abstinence: An Interview Study. Nicotine Tob Res. 2012 Jul;14(7):849–56.

12. Shiffman S, Hughes J, Ferguson S, Pillitteri J, Gitchell J, Burton S. Smokers’ interest in using nicotine replacement to aid smoking reduction. Nicotine Tob Res. 2007 Nov;9(11):1177–82.

13. Schmidt L, Reidmohr A, Harwell TS, Helgerson SD. Prevalence and Reasons for Initiating Use of Electronic Cigarettes Among Adults in Montana, 2013. Prev Chronic Dis. 2014 Nov 20;11:140283.

14. SMOKERS WHO CHOOSE TO QUIT GRADUALLY VERSUS ABRUPTLY. Addiction. 2007 Aug;102(8):1326–7.

15. Lindson N, Michie S, Aveyard P. Exploratory Analyses of the Popularity and Efficacy of Four Behavioral Methods of Gradual Smoking Cessation. Nicotine Tob Res. 2020 Dec 12;22(12):2257–61.

16. Cinciripini PM, Lapitsky L, Seay S, Wallfisch A, Kitchens K, Van Vunakis H. The effects of smoking schedules on cessation outcome: Can we improve on common methods of gradual and abrupt nicotine withdrawal? J Consult Clin Psychol. 1995;63(3):388–99.

17. Brockway BS, Kleinmann G, Edleson J, Gruenewald K. Non-aversive procedures and their effect on cigarette smoking. Addict Behav. 1977 Jan;2(2–3):121–8.

18. Haustein K. A double-blind, randomized, placebo-controlled multicentre trial of a nicotine chewing gum in smoking reduction. Study ID 980-CHC-9021-0013 Unpubl Data. 2001;

19. Batra A, Klingler K, Landfeldt B, Friederich H, Westin A, Danielsson T. Smoking reduction treatment with 4-mg nicotine gum: A double-blind, randomized, placebo-controlled study. Clin Pharmacol Ther. 2005 Dec;78(6):689–96.

20. Bolliger CT. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. BMJ. 2000 Aug 5;321(7257):329–33.

21. Rennard S, Glover E, Leischow S, Daughton D, Glover P, Muramoto M, et al. Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial. Nicotine Tob Res. 2006 Aug 1;8(4):555–64.

22. Wennike P, Danielsson T, Landfeldt B, Westin Å, Tønnesen P. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up: Smoking reduction with nicotine gum. Addiction. 2003 Oct;98(10):1395–402.

23. Evans-Polce R, Lanza S, Maggs J. Heterogeneity of alcohol, tobacco, and other substance use behaviors in U.S. college students: A latent class analysis. Addict Behav. 2016 Feb;53:80–5.

24. Borrelli B, Gaynor S, Tooley E, Armitage CJ, Wearden A, Bartlett YK. Identification of three different types of smokers who are not motivated to quit: Results from a latent class analysis. Health Psychol. 2018 Feb;37(2):179–87.

25. McCarthy DE, Ebssa L, Witkiewitz K, Shiffman S. Paths to tobacco abstinence: A repeated-measures latent class analysis. J Consult Clin Psychol. 2015 Aug;83(4):696–708.

26. Fagerstrom KO, Heatherton TF, Kozlowski LT. Nicotine addiction and its assessment. Ear Nose Throat J. 1990 Nov;69(11):763–5.

27. Hays RD, Sherbourne CD, Mazel RM. The rand 36-item health survey 1.0. Health Econ. 1993 Oct;2(3):217–27.

28. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001 Jan;33(5):350–7.

29. Hays RD, Prince-Embury S, Chen H. RAND-36 health status inventory. Psychological Corporation San Antonio, TX; 1998.

30. Proust-Lima C, Philipps V, Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The *R* Package **lcmm**. J Stat Softw [Internet]. 2017 [cited 2022 Nov 14];78(2). Available from: http://www.jstatsoft.org/v78/i02/

31. Hagenaars JA, McCutcheon AL, editors. Applied latent class analysis. Cambridge ; New York: Cambridge University Press; 2002. 454 p.

32. Proust-Lima C, Philipps V, Diakite A, Liquet B. lcmm: Extended Mixed Models Using Latent Classes and Latent Processes [Internet]. 2022. Available from: https://cran.r-project.org/package=lcmm

33. Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw. 2010;33(1):1–22.

34. Simon N, Friedman J, Hastie T, Tibshirani R. Regularization Paths for Cox’s Proportional Hazards Model via Coordinate Descent. J Stat Softw. 2011;39(5):1–13.

35. Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification And Regression Trees [Internet]. 1st ed. Routledge; 2017 [cited 2022 Nov 23]. Available from: https://www.taylorfrancis.com/books/9781351460491

36. Mason SJ, Graham NE. Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation. Q J R Meteorol Soc. 2002 Jul 15;128(584):2145–66.

37. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and Mental Illness: A Population-Based Prevalence Study. JAMA. 2000 Nov 22;284(20):2606.

38. Tidey JW, Miller ME. Smoking cessation and reduction in people with chronic mental illness. BMJ. 2015 Sep 21;h4065.

39. Klemperer EM, Hughes JR, Naud S. Distal Measurements Can Produce False Negative Results: A Prospective Secondary Analysis of a Natural History Study. Nicotine Tob Res. 2019 Nov 19;21(12):1727–30.

40. Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res. 2020 Jun 12;22(7):1086–97.

41. Piper ME, Bullen C, Krishnan-Sarin S, Rigotti NA, Steinberg ML, Streck JM, et al. Defining and Measuring Abstinence in Clinical Trials of Smoking Cessation Interventions: An Updated Review. Nicotine Tob Res. 2020 Jun 12;22(7):1098–106.