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1 **Prevalence and impact of long-term use of nicotine replacement therapy in UK Stop-**
2 **Smoking Services: findings from the ELONS study**

3
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22 ABSTRACT

23 **Background:** Nicotine Replacement Therapy (NRT) was licensed for harm reduction in the UK in 2005,
24 and guidance to UK Stop Smoking Services (SSS) to include long-term partial or complete substitution of
25 cigarettes with NRT was issued in 2013. Yet, NRT prevalence data and data on changes in biomarkers
26 associated with long-term NRT use among SSS clients are scarce.

27 **Methods:** SSS clients abstinent 4 weeks post-quit date were followed up at 12 months. At baseline standard
28 socio-demographic, smoking and SSS use characteristics were collected and of those eligible, 60.6%
29 (1,047/1,728) provided data on smoking status and NRT use at follow-up. A subsample also provided saliva
30 samples at baseline and of those eligible, 36.2% (258/712) provided follow-up samples. Saliva was analysed
31 for cotinine (a metabolite of nicotine) and alpha-amylase (a stress biomarker).

32 **Results:** Among those who had used NRT during their initial quit attempt (61.5%, 95%CI 58.4-64.6), 6.0%
33 (95%CI 4.3-8.3%) were still using NRT at one year, significantly more ex-smokers than relapsed smokers
34 (9.5% vs. 3.7%; $p=0.005$). In adjusted analysis, NRT use interacted with smoking status to determine change
35 in cotinine, but not alpha-amylase, levels (Wald χ^2 (1)=13.0, $p<0.001$): cotinine levels remained unchanged
36 in relapsed smokers and ex-smokers with long-term NRT use but decreased in ex-smokers without long-
37 term NRT use.

38 **Conclusions:** Long-term NRT use is uncommon in SSS clients, particularly among relapsed smokers. Its
39 use is associated with continued high intake of nicotine among ex-smokers but does not increase nicotine
40 intake in smokers. It does not appear to affect stress response.

41
42 **Key words:** Stop Smoking Services, Nicotine Replacement Therapy, Cotinine, Harm Reduction, Alpha-
43 amylase

44 **IMPLICATIONS**

45 Little is known about the long-term effects of Nicotine Replacement Therapy (NRT). Given an
46 increasing shift towards harm reduction in tobacco control, reducing the harm from combustible products by
47 complete or partial substitution with non-combustible products, more data on long-term use are needed. This
48 study shows that in the context of stop smoking services, clients rarely use products for up to a year and that
49 NRT use does not affect users' stress response. Ex-smokers using NRT long-term can completely replace
50 nicotine from cigarettes with nicotine from NRT; long-term NRT use by continuing smokers does not
51 increase nicotine intake. Long-term NRT appears to be a safe and effective way to reduce exposure to
52 combustible nicotine.

53 INTRODUCTION

54 The main aim of Stop Smoking Services (SSS) is to support smokers to quit tobacco use. However,
55 not all smokers either feel able to or want to stop smoking completely. For this reason, alternative
56 approaches have been explored to reduce harm from smoking in this population. Harm reduction refers to
57 the reduced psychological or physiological harm from substance use without complete cessation ¹. For
58 current smokers, harm reduction may refer to the partial substitution of cigarettes with non-combustible
59 forms of nicotine delivery such as nicotine replacement therapy (NRT) to reduce cigarette consumption or
60 for temporary abstinence. For ex-smokers, harm reduction constitutes the complete, long-term substitution
61 of combustible tobacco products (e.g. cigarettes) with less harmful non-combustible nicotine delivery
62 devices ². There is good evidence from both population studies and clinical trials that the provision of NRT
63 to smokers who cut down their cigarette consumption results in more sustained decreases in cigarette
64 consumption and improves their chances to stop smoking completely ^{3,4}. It increases motivation to stop and
65 improves quit rates ^{1,3} but does not increase overall nicotine intake ^{5,6}. Trials have also shown that extended
66 use of NRT by ex-smokers may result in better long-term abstinence rates by reducing relapse ^{7,8}. For these
67 reasons, NRT has been licensed for harm reduction in the UK since 2005 ^{9,10}. Based on a previous report ¹¹,
68 guidance was also issued to UK Stop Smoking Services (SSS) in 2013 to include partial or complete long-
69 term substitution of cigarettes with NRT in tailored quit plans for smokers who have difficulty to stop
70 smoking completely so as to help them reduce consumption with the eventual aim to stop smoking ¹².

71
72 The vast majority of the harm from smoking is caused by the burning of tobacco and not nicotine ¹³.
73 Thus NRT as a substitute for cigarettes is important to study. Although the importance of e-cigarettes for
74 harm reduction purposes cannot be doubted, NRT is likely to remain a major component of harm reduction
75 strategies, given its long history in tobacco control and continuing NRT product innovation ¹⁴ and on-going
76 resistance of some smokers to e-cigarettes ¹⁵. Despite being an established treatment, there is considerable
77 worry among potential users ¹⁶ and stop-smoking advisors ¹⁷ regarding the safety of long-term NRT use,
78 possibly due to misunderstandings about the role of nicotine separate from smoked tobacco ¹⁸. While studies

79 which have looked at this issue find that long-term NRT use is safe and any associated health risks small ¹⁹,
80 certainly compared with continued smoking ^{20,21}, most data come from clinical trials, which have samples
81 that tend to differ in important ways from general population samples, biasing outcomes ²². Given recent
82 calls for further research in the area of harm reduction ¹², more studies on real-world use are required.

84 A recent population-based study suggested that only a small percentage of ex-smokers continue to
85 use NRT beyond the standard length of three months and that long-term use is associated with lower
86 nicotine intake compared with smokers ⁶. However, in many industrialised countries most NRT is purchased
87 over the counter ²³, rather than coupled with specialist behavioural support, which is more effective ²⁴.
88 Therefore, existing findings may not generalise to smokers attending UK SSS, especially since in this
89 context the NRT provided is either free or heavily subsidised. In light of the recent broadening in the
90 provision of NRT in SSS, there remains a need to evaluate harm reduction with NRT in this context.

92 This study describes the impact of longer-term NRT use among smokers who made a quit attempt
93 with SSS support and agreed to take part in the ‘*Evaluating Long Term Outcomes of NHS Stop-Smoking*
94 *Services*’ (ELONS) study conducted 2012-2014 ²⁵. Participants were followed up for one year and provided
95 information on their NRT use. A subset also provided saliva samples which were analysed for two
96 biomarkers of interest: cotinine, the primary metabolite of nicotine as a biomarker of exposure; and alpha-
97 amylase, a digestive enzyme and indicator of autonomic nervous system activation which correlates with
98 acute and chronic stress, as a biomarker of risk/potential harm ²⁶. We included this biomarker as animal
99 research has shown that chronic nicotine self-administration can alter stress response in rodents ^{27,28}.

100 Specifically, this study aimed to answer the following research questions:

- 101
- 102 1) What is the prevalence of long-term NRT use among smokers and ex-smokers who had attempted
- 103 to stop smoking using SSS?
- 104 2) What is the impact of long-term NRT use on biomarkers of nicotine exposure and stress among
- 105 smokers and ex-smokers who had attempted to stop smoking using SSS?

METHODS

Study design and participants

Given the aims of this study, we report only on those with baseline and follow-up data. Full details of the study design and sampling are provided elsewhere²⁵. Briefly, as part of the ELONS study, clients participating in English SSS who set a quit date were asked if they were interested in taking part in a long-term (12 months) evaluation of the services by advisors and informed consent was obtained from all participants, resulting in a baseline sample of 3,045 clients. As per standard NHS SSS guidelines, smoking status was recorded at 4-week follow-up²⁹ and only those who were abstinent at 4 weeks (56.7%; 1,728/3,045) were eligible for long-term follow-up. Of all eligible participants for 12 month follow-up, 60.6% (1,047/1,728) could be contacted by telephone to assess smoking status and NRT use, thus providing complete baseline and follow-up questionnaire data (see Table 1 for participant details). Of those contactable, 53.3% (558/1,047) self-reported as abstinent and were eligible for a home visit to verify their smoking status, of whom 4.6% (26/558) failed CO-verification and were therefore reclassified as smokers for the purposes of this analysis. The 12-month follow-up started in April 2013 and finished in March 2014.

A subsample of participants also provided a saliva sample at baseline, before their target quit date (61.6%; 1,875/3,045). Of those who were eligible to provide a saliva sample at follow-up (i.e. successful quitters at four weeks with a baseline saliva sample who self-reported abstinence at 12-month follow-up and therefore had a home visit), 52.8% (169/320) provided a sample. Because relapsers did not have a home visit (and therefore were not asked to provide a saliva sample), an additional random selection of participants with baseline saliva samples who had relapsed at 4-week follow-up were contacted at 12 months (83.4%, 392/470) to obtain follow-up saliva samples from smokers. Participants were sent a saliva kit through the post and asked to return samples directly to UCL. The saliva kit contained two Sarstedt Salivettes®, a letter from the Principal Investigator asking for their help, detailed instructions on sample collection and a £10 shopping voucher. Of those approached, 22.6% (89/392) returned a saliva sample, resulting in an overall response rate from face-to-face or postal collection of 36.2% (258/712) with complete baseline and follow-up biomarker data (see Table 1 for participant details).

133

134 **Measures**

135 *Questionnaire items*

136 In addition to standard questions on smoking and socio-demographic characteristics, a number of
137 items were included in the baseline questionnaire to help evaluate UK SSS (see ²⁵. Advisors recorded the
138 types of pharmacotherapy and behavioural intervention used during the quit attempt. It should be noted that
139 at the time of the study, e-cigarettes (another harm reduction tool) were only just becoming popular and
140 client use was not routinely recorded by SSS. At 12-month follow-up, questions related to long-term NRT
141 use were also assessed retrospectively: participants were asked to indicate whether they had used NRT for
142 their initial quit attempt and, if so, how long they had used NRT for, and if they were still using NRT now.
143 As the use of other nicotine-containing products (including e-cigarettes) was not assessed at baseline, this
144 was assessed at follow-up only. In order to ascertain smoking status and use of NRT in those participants
145 who provided a saliva sample through the post and did not receive a home visit, these respondents were
146 asked to indicate on a tick box included on the salivettes whether they were currently smoking (yes/no) and
147 used NRT or e-cigarettes (yes/no).

148

149 *Biomarkers*

150 Saliva samples were collected with Sarstedt Salivettes® and stored in -20°C freezers, ready for
151 analysis. Saliva was analysed for cotinine by ABS laboratory using rapid liquid-gas chromatography ³⁰ and
152 for alpha-amylase activity by Salimetrics laboratory using an established enzyme-kinetic methodology ³¹.
153 Although alpha-amylase activity is largely independent of flow-rate ³², all participants were instructed to
154 keep the salivettes in the mouth for the same amount of time (1-2 minutes) without chewing as per
155 recommendation ³³. In addition, all participants were asked to abstain from drinking or eating immediately
156 before providing a sample. Whilst alpha-amylase exhibits a diurnal pattern, it remains relatively stable
157 throughout the day following a rise in the first hours after waking ³⁴. Participants were therefore instructed to
158 provide two samples during waking hours, approximately ten minutes apart to increase reliability of

159 measurement (the average coefficient of variation in alpha-amylase activity at baseline was 1.7% and at
160 follow-up 1.8%).

162 **Analysis**

163 Data were analysed with IBM SPSS Statistics 20.0.0. Comparisons were made between those who
164 did and did not have complete baseline and follow-up data for questionnaire items (to assess NRT
165 prevalence) and those who did or did not have complete baseline and follow-up biomarker data (to assess
166 impact). Differences were assessed with χ^2 -tests and independent t-tests for categorical and continuous
167 variables, respectively. In the prevalence analysis, descriptive statistics including 95% confidence intervals
168 (95%CI) were calculated and, where applicable, groups compared using logistic regression. To correct for
169 non-response all prevalence estimates are weighted (see ²⁵).

171 In the biomarker analysis, due to the typically positively skewed distribution of cotinine and alpha-
172 amylase values and relatively small sample size, geometric means and interquartile ranges were calculated.
173 The non-parametric Kruskal-Wallis and Wilcoxon tests were used to assess between-group differences and
174 within-group differences (to look at change across time), respectively. In sensitivity analysis, findings were
175 re-examined with generalized linear models for between- and within-group comparisons that used a gamma
176 distribution with a log link (all zero values were replaced with 0.001) to account for the non-normal
177 distribution and adjusted for potential confounders (age, sex, ethnicity, occupation, any medical condition
178 and nicotine dependence). Statistical significance was set at the standard level ($p < 0.05$), and the Bonferroni
179 correction was applied to account for multiple comparisons and Type I error rate. The study received ethical
180 approval from the South East Scotland Research Ethics Committee (11/AL/0256) and was carried out in
181 accordance with the ethical principles on human research, as set out in the Declaration of Helsinki.

183 RESULTS

184 Prevalence of long-term NRT use among current smokers and ex-smokers

185 Information on long-term NRT use was provided by 1,047 participants (34.4% of the total ELONS
186 sample) who constitute the analytic sample for the prevalence analysis. Those who were lost at follow-up
187 were younger, had smoked for a shorter period, were less likely to have a medical condition, to be white or
188 cohabiting (Table 1). All prevalence estimates in this section are weighted.

189
190 Of clients followed-up, 61.5% (95%CI 58.4-64.6, N=583) reported using NRT during their initial
191 quit attempt. This figure was somewhat higher than the recorded NRT use in SSS (around N=500 when
192 including the 'Other' category in Table 1), suggesting that some participants had obtained additional NRT
193 over the counter. Figure 1A provides a breakdown of clients in terms of the length of use of NRT and as a
194 function of smoking status at follow-up. As can be seen, most clients who started on NRT used it for at least
195 eight weeks and more than one in five (21.5%, 95%CI 18.3-25.0, N=137) for longer than the standard 12
196 weeks. However, long-term use was relatively rare with less than one in ten participants still using non-
197 combustible nicotine delivery devices at 12-month follow-up (8.4%, 95%CI 6.4-11.0, N=50), including both
198 NRT and e-cigarettes. In this sample, NRT use was twice as prevalent (6.0%, 95%CI 4.3-8.3%, N=35) as
199 use of e-cigarettes at 12 months (2.9%, 1.8-4.7%, N=18; some participants were dual product users).

200
201 Generally, the pattern of NRT use across the study period was relatively similar for those who had
202 remained abstinent and those who had relapsed by 12-month follow-up (Figure 1A). However, ex-smokers
203 had higher rates of NRT use compared with relapsers at all time-points. At 12-month follow-up, long-term
204 ex-smokers were over four-times more likely than relapsers to be still using non-combustible nicotine
205 delivery devices (OR 4.25, 95%CI 2.15-8.40, $p<0.001$): 14.0% (95%CI 10.3-18.7, N=38) of ex-smokers were
206 still using these compared with 3.7% (95%CI 2.0-6.5, N=12) of relapsers. This difference, while being
207 attenuated, remained significant when excluding those who used e-cigarettes only (OR 2.91, 95%CI 1.38-
208 6.11, $p=0.005$) with 9.5% (95%CI 6.4-13.8, N=25) of ex-smokers and 3.5% (95%CI 1.9-6.3, N=10) of
209 relapsers still using NRT, respectively. Comparing the quitters and relapsers who were or were not using

210 NRT at follow-up in terms of the characteristics presented in Table 1 showed that dependence was the only
211 variable (other than medication use, as would be expected) that differed between groups ($F(3, 1037)=5.52$,
212 $p<0.001$). Relapsers without NRT use had significantly higher dependence scores than quitters, irrespective
213 of their NRT use.

214
215 When looking at individual nicotine-delivery devices still used at 12-month follow-up, e-cigarettes
216 were the most popular, followed by the nicotine lozenge, patch and gum (Figure 1B). No-one used the nasal
217 spray, possibly due to the higher cost of the nasal spray compared with other NRT products, and 16.8% were
218 using multiple products. Due to the small numbers involved, there was insufficient power to detect
219 meaningful differences between those who had remained abstinent and those who had relapsed.

220 221 **Impact of long-term NRT use on biomarkers of nicotine exposure and stress among current smokers** 222 **and ex-smokers**

223 Baseline and follow-up saliva samples were provided by 258 participants (8.5% of the total sample)
224 who constitute the analytic sample for the biomarker analysis. Those lost to follow-up were younger, less
225 likely to be cohabiting and there were some differences in the treatments used; they were also more
226 dependent (Table 1).

227
228 There were no differences in baseline cotinine levels between any of the groups (Table 2). This was
229 confirmed in adjusted analysis controlling for potential confounders which showed that older age (Wald χ^2
230 (1)= 6.6, $p=0.011$) and greater dependence (Wald χ^2 (1)=26.7, $p<0.001$) were the only significant predictors
231 of baseline cotinine levels. Similarly, there were no group differences in baseline alpha-amylase levels,
232 again confirmed in adjusted analysis (Table 2). This showed that older age (Wald χ^2 (1)=10.6, $p=0.001$),
233 being non-white (Wald χ^2 (1)=5.3, $p=0.022$) and having any medical condition (Wald χ^2 (1)=9.8, $p=0.002$)
234 were associated with higher alpha-amylase activity at baseline.

236 At follow-up, there was a clear difference between groups in cotinine levels (Kruskal Wallis H
237 (3)=130.2, $p<0.001$). Ex-smokers using no NRT had significantly lower cotinine values at follow-up than all
238 other groups (Table 2). Adjusted analysis confirmed these group differences (Wald χ^2 (3)=78.9, $p<0.001$)
239 and showed baseline nicotine dependence as the only additional significant predictor of follow-up cotinine
240 levels (Wald χ^2 (1)=15.4, $p<0.001$). There were no group differences in follow-up alpha-amylase levels
241 which was confirmed in adjusted analysis (Table 2); only greater nicotine dependence at baseline was
242 positively associated with follow-up alpha-amylase activity (Wald χ^2 (1)=8.1, $p=0.004$).

243
244 In addition to the cross-sectional analyses for baseline and follow-up data reported above, we also
245 examined within-person changes from baseline to follow-up in longitudinal analysis (please note that this
246 group is slightly smaller as not all participants who provided both baseline and follow-up saliva samples had
247 provided either two samples at each time point or samples that were viable). As shown in Figure 2A,
248 cotinine levels significantly reduced from baseline to follow-up only in ex-smokers not using NRT at
249 follow-up (Standardized $Z=-9.9$, $p<0.001$) and not in other groups. Adjusted analysis confirmed the
250 significant NRT use by smoking status interaction for changes in cotinine levels (Wald χ^2 (1)=13.0,
251 $p<0.001$) and also showed that greater baseline age (Wald χ^2 (1)=4.3, $p=0.037$) and dependence (Wald χ^2
252 (1)=44.8, $p<0.001$) were associated with an increase in cotinine levels.

253
254 While unadjusted analysis indicated that there was an increase in alpha-amylase activity from
255 baseline to follow-up in ex-smokers not using NRT at follow-up (Standardized $Z=3.0$, $p=0.003$) and not in
256 other groups (Figure 2B), this was not confirmed in adjusted analysis. Neither the NRT use by smoking
257 status interaction for changes in alpha-amylase levels (Wald χ^2 (1)=2.1, $p=0.147$) nor main effects for NRT
258 use (Wald χ^2 (1)=0.9, $p=0.352$) or smoking status (Wald χ^2 (1)=0.8, $p=0.373$) were significant. However,
259 greater baseline age (Wald χ^2 (1)=4.4, $p<0.036$), dependence (Wald χ^2 (1)=6.0, $p=0.014$) and reporting any
260 medical condition at baseline (Wald χ^2 (1)=5.8, $p=0.016$) were independently associated with an increase in
261 alpha-amylase activity.

DISCUSSION

Extended use of NRT among SSS clients was relatively prevalent, with over one in five who achieve short-term abstinence continuing to use it beyond the standard treatment length of three months, but continued long-term use of NRT by those who achieve long-term abstinence at one year is less common at just below 10%. Nonetheless, given that one year usage rates were estimated at around 5% among ex-smokers who attend SSS in 2002³⁵, this suggests that recent policy and licensing changes in favour of harm reduction^{9,10,12} may have had some impact on long-term NRT use among services users. This contrasts with a lack of change in NRT usage pattern observed in the general population following an earlier relaxation of NRT licensing in 2005³⁶. However, the low 4% prevalence of concurrent long-term use of NRT among SSS clients who had relapsed is similar to figures from the general population suggesting that longer-term NRT use among smokers is rare³⁷. Indeed, concurrent NRT use among smokers, either for temporary abstinence or cutting down, has remained relatively stable since 2002³⁸, with most smokers using NRT for less than three months³⁷.

Interestingly, despite a steady increase in the prevalence of e-cigarette use among smokers and ex-smokers in the UK³⁹, the long-term use of e-cigarettes among past SSS clients in this study was surprisingly low at less than 3% compared with estimates of one in five smokers or recent ex-smokers using e-cigarettes in the general population⁴⁰. However, this may be due to the specificity of the sample selection and the timing of the study, being conducted around the time of increasing awareness of e-cigarettes in the UK but before use became widespread amongst smokers and recent quitters⁴¹.

This study provides some rare insights in the exposure to nicotine associated with long-term dual or single use of NRT as well as its impact on a biological index of stress, alpha-amylase. Clinical trials suggest that permanent replacement of cigarettes with NRT among ex-smokers can result in 40% of baseline levels of nicotine being substituted by nicotine replacement products long-term^{42,43}. Our findings not only confirm substantial substitution of nicotine from cigarettes with nicotine from NRT but, given the lack of changes in ex-smokers using NRT from baseline to follow-up, suggest that virtually all baseline nicotine may be

290 replaced by NRT among long-term ex-smokers. This increase in substitution levels compared with previous
291 work may reflect differences in our sample or changes in the NRT products available. It is unlikely to be the
292 result of other product use as all ex-smokers were CO verified and participants with concurrent use of other
293 nicotine delivery devices, i.e. e-cigarettes, were excluded.

294
295 Confirming previous research ^{5,44}, the concurrent use of NRT among smokers did not appear to
296 increase their nicotine intake. These findings are in agreement with the hypothesis that smokers are very
297 adept at titrating nicotine levels, with some nicotine otherwise obtained from cigarettes being replaced by
298 nicotine from NRT ⁴⁵. However, our results indicate this also applies to ex-smokers, which is consistent with
299 a strong genetic component in nicotine intake ⁴⁶ but at odds with clinical ⁴² and general population studies ⁶
300 showing that nicotine substitution from NRT tapers off over time. Behavioural support in SSS includes
301 detailed instructions on the correct use of NRT ⁴⁷ which is not available in other settings and may explain
302 the differential in both NRT effectiveness and associated nicotine intake when used with and without
303 behavioural support.

304
305 Although it is unlikely that a substantially increased nicotine intake from NRT would be harmful
306 ^{48,49}, it clearly is a concern for some people and a potential barrier to effective use of nicotine products ¹⁶.
307 Our results not only suggest that dual use with NRT does not increased nicotine intake compared with
308 continued smoking, they also indicate that use of NRT (either with or without concurrent smoking) is not
309 associated with an increase in a biomarker of stress response, alpha-amylase, used as a proxy here to signal
310 potential harm. Given observed reductions in stress levels in smokers following cessation ⁵⁰, it was
311 surprising not to see any reductions alpha-amylase levels in quitters. However, it should be noted that
312 tobacco smoke has been shown to acutely inhibit alpha amylase activity ³³, which means that the benefit of
313 smoking cessation may have been masked by the impact of baseline smoking. Moreover, spot sampling may
314 not be reliable enough to pick up true long-term changes. While there was an expected association of
315 increased biological stress with older age and having a medical condition, the association of increased alpha-
316 amylase activity with greater baseline nicotine dependence was not predicted and deserves further

317 investigation. Altogether, these findings are consistent with the view that long-term NRT use is safe and not
318 associated with increased health risks, certainly compared with continued smoking ²¹.

319
320 This study has a number of limitations. Despite an initial large sample size, drop out across the study
321 was inevitably substantial, resulting in relatively few clients with complete baseline and follow-up data on
322 biomarkers. In addition, the baseline sample differed from the sample followed up. However, differences
323 were relatively modest, and prevalence data were weighted to account for differential drop out. As clients
324 self-selected into groups rather than being experimentally assigned, we cannot exclude potential reverse
325 causation, e.g. particular individuals who happen to have a high sensitivity to nicotine intake may use NRT
326 for longer. Moreover, we were only able to assess current NRT use but not frequency of NRT use at follow-
327 up which means that it is difficult to ascertain how comparable NRT use was across relapsers and quitters.
328 However, this study reflects real-world use of NRT and the longitudinal within-group design reduced
329 confounding by allowed participants to be their own control. Lastly, different methodologies were used to
330 collect follow-up saliva samples which may have impacted results. However, the same clear instructions
331 were provided to participants and researchers who for postal and face-to-face collection, respectively. All
332 assessments were carried out with established, ecologically valid measures and smoking status verified, but
333 further research would benefit from measuring a wider array of biomarkers of smoking-related harm,
334 including different biomarkers of chronic stress such as cortisol.

335
336 In conclusion, among former SSS clients long-term NRT use by ex-smokers is relatively rare but
337 more common than use by smokers. Furthermore, long-term use seems to have increased since the
338 introduction of harm reduction guidance in the UK. Long-term use of NRT does not appear to have a
339 detrimental effect on chronic stress response among smokers or ex-smokers and does not increase overall
340 nicotine intake in smokers but is associated with continuing nicotine intake in ex-smokers, comparable to
341 when they were smoking.

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459 **ADDITIONAL INFORMATION**

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463 464 **Author contributions statement**

465 LS, AM & LB conceived the original idea for this study. LB obtained funding. LS, FD and RH managed the
466 day-to-day running of the study. LS undertook the data analyses and wrote the initial draft with further input
467 from FD, RH, AM and LB. LS is guarantor for this article. All authors read, reviewed and approved the final
468 version. All researchers listed as authors are independent from the funders and all final decisions about the
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480 481 **Conflict of Interest**

482 LS has received an honorarium for a talk, an unrestricted research grant and travel expenses to attend
483 meetings and workshops from Pfizer, a pharmaceutical company that makes smoking cessation products,
484 and has acted as paid reviewer for grant awarding bodies and as a paid consultant for health care companies.
485 The other authors have no conflicts of interest to declare.

487 Table 1: Baseline characteristics

	Questionnaire data		Biomarker data	
	Available (N=1,047)	Lost to follow-up (N=681)	Available (N=258)	Lost to follow-up (N=454)
<i>Socio-demographic/health characteristics</i>				
Mean (SD) Age	46.4 (14.0)	41.1 (13.7)‡	45.7 (13.4)	42.2 (14.6) †
% (N) Female	55.0 (576)	53.6 (365)	51.6 (133)	48.7 (221)
% (N) White	97.2 (1018)	94.7 (645)†	96.5 (249)	93.8 (426)
% (N) Cohabiting	53.4 (559)	47.3 (322)*	53.9 (139)	44.9 (204)*
% (N) Routine/manual occupation	30.9 (323)	34.5 (235)	25.2 (65)	30.6 (139)
% (N) Degree or equivalent	10.6 (111)	10.4 (71)	10.5 (27)	9.3 (42)
% (N) Medical condition	59.5 (622)	52.9 (360)†	57.4 (148)	58.4 (265)
<i>Smoking characteristics</i>				
Mean (SD) Heaviness of smoking index	3.28(1.45)	3.22 (1.46)	3.19 (1.54)	3.51 (1.41)†
% (N) Smoking length < 10 years	10.9 (114)	17.4 (118)‡	9.3 (24)	14.3 (65)
% (N) Quit attempt last 12 months	41.7 (434)	41.0 (275)	38.1 (98)	38.4 (172)
<i>NHS SSS treatment characteristics</i>				
% (N) Intervention type				*
Closed group	3.2 (34)	2.9 (20)	6.6 (17)	4.6 (21)
Open (rolling) group	20.8 (218)	17.6 (120)	21.3 (55)	13.9 (63)
Drop-in clinic	26.5 (277)	27.2 (185)	24.4 (63)	30.4 (138)
One to one support	49.2 (515)	51.9 (353)	47.7 (123)	50.7 (230)
Other	0.3 (3)	0.3 (2)	0 (0)	0.4 (2)
% (N) Medication				†
Single NRT	17.4 (182)	17.9 (122)	17.4 (45)	15.2 (69)
Combination NRT	12.2 (128)	15.1 (103)	16.3 (42)	27.3 (124)
Varenicline	50.2 (526)	48.5 (330)	48.4 (125)	37.4 (170)
Otherl	19.0 (199)	17.0 (116)	16.3 (42)	19.2 (87)
None	1.1 (12)	1.5 (10)	1.6 (4)	0.9 (4)

488 *p<0.05; †p<0.01; ‡<0.001; ||Bupropion and mixed medication (mainly NRT)

Table 2: Biomarker results by follow-up NRT use and follow-up smoking status

	Smokers (relapsers)		Ex-smokers (quitters)	
	NRT use (N=18)	No NRT use (N=73)	NRT use (N=14)	No NRT use (N=153)
<i>Baseline assessment</i>				
Geometric Mean (IQR/n) Cotinine in ng/mL	193.7 (323.1/17)	241.1 (238.8/68)	340.1 (163.9/13)	197.6 (174.6/146)
Geometric Mean (IQR/n) Alpha-amylase in U/mL	20.1 (59.1/12)	21.8 (27.2/45)	29.1 (14.2/11)	23.6 (30.5/109)
<i>Follow-up assessment</i>				
Geometric Mean (IQR/n) Cotinine in ng/ml	210.8 (240.0/16) ^a	244.7 (198.7/69) ^a	169.9 (449.6/10) ^a	1.2 (21.6/149) ^b
Geometric Mean (IQR/n) Alpha-amylase in U/mL	25.8 (69.6/13)	26.7 (32.2/43)	22.4 (49.7/10)	27.6 (37.7/111)

^{a,b}Different letters indicate significant differences between groups (p<0.05); IQR-Interquartile Range

492 **Figure legends**

493 Figure 1: (A) NRT use across follow-up period among those who had used NRT during initial quit attempt
494 (N=583)*; (B) Product type used among those with long-term NRT use at follow-up (N=50)

495 *Includes e-cigarettes (users of products at 12-month provide denominator for Figure 1B); †No use of
496 nicotine nasal spray reported at 12-month follow-up; users could indicate multiple products; Error bars are
497 95% confidence intervals

498

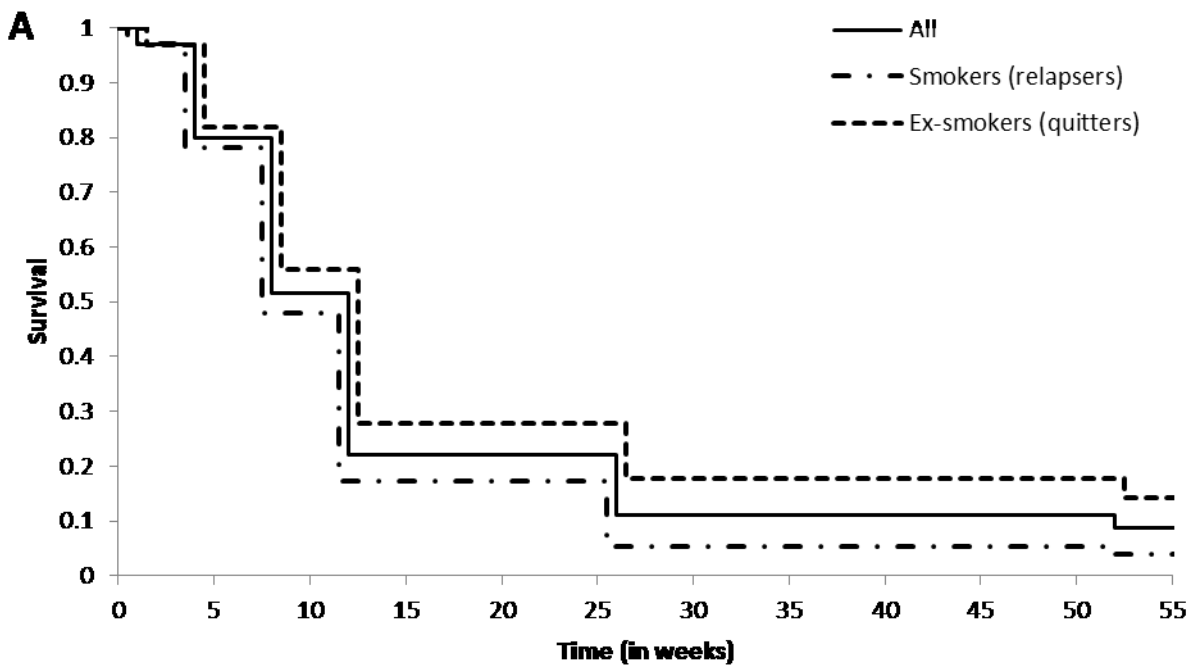
499 Figure 2: Change in (A) cotinine levels (N=232) and (B) alpha-amylase activity (N=166) from baseline to
500 follow-up as a function of NRT use and smoking status at follow-up

501 Data not available from N participants due to insufficient samples or contamination: *26 cases; †92 cases;

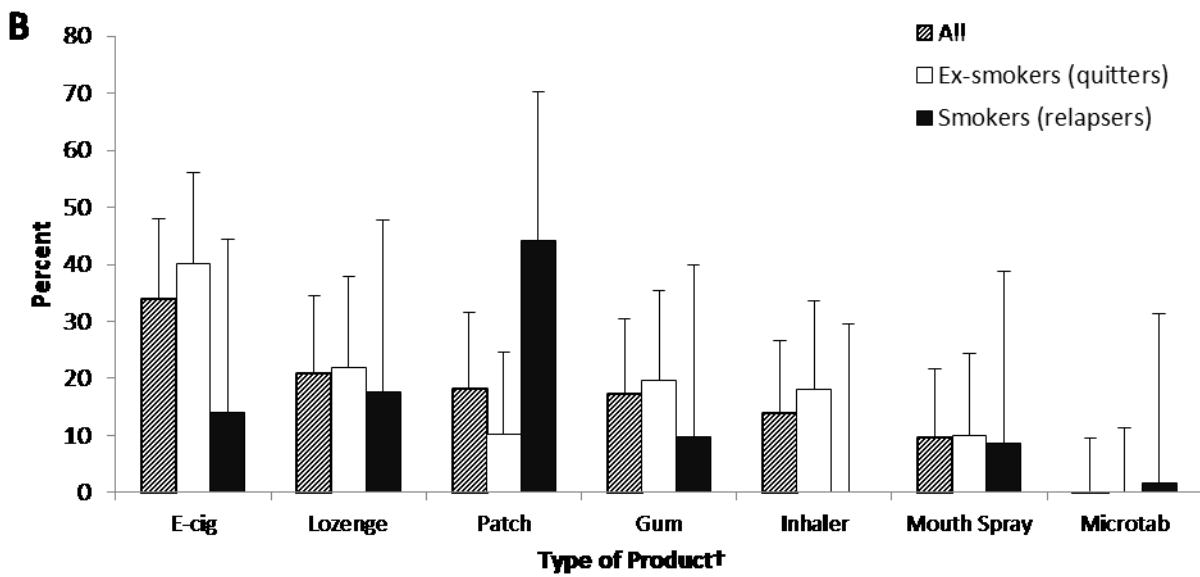
502 Error bars are interquartile range

503

504 Figure 1:



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