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REVIEW

ADDICTION SSA

Systematic review and meta-analysis investigating nicotine, cotinine and carbon monoxide exposures in people who both smoke and use nicotine replacement therapy

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Abstract

Aims: To determine effects of concurrent smoking and nicotine replacement therapy (NRT) use on reported heaviness of smoking, nicotine (cotinine) body fluid and exhaled air carbon monoxide (CO) concentrations.

Methods: Systematic review and meta-analysis of RCTs, which test interventions permitting concurrent NRT use and smoking and comparing, within participants, outcomes when smoking with those when smoking and using NRT concurrently. Measurements included reported number of cigarettes smoked per day (CPD), body fluid cotinine and expired air CO concentrations.

Results: Twenty-nine studies were included in the review. Meta-analysis of nine showed that, compared with when solely smoking, fewer cigarettes were smoked daily when NRT was used (mean difference during concurrent smoking and NRT use, −2.06 CPD [95% CI = −3.06 to −1.07, $P < 0.0001$]). Meta-analysis of seven studies revealed a non-significant reduction in exhaled CO during concurrent smoking and NRT use (mean difference, −0.58 ppm [95% CI = −2.18 to 1.03, $P = 0.48$]), but in the three studies that tested NRT used in the lead-up to quitting (i.e. as preloading), a similar reduction in exhaled CO was statistically significant (mean difference, −2.54 ppm CO [95% CI = −4.14 to −0.95, $P = 0.002$]). Eleven studies reported cotinine concentrations, but meta-analysis was not possible because of data reporting heterogeneity; of these, seven reported lower cotinine concentrations with concurrent NRT use and smoking, four reported no differences, and none reported higher concentrations.

Conclusions: People who smoke and also use nicotine replacement therapy report smoking less heavily than people who solely smoke. When nicotine replacement therapy is used in the lead-up to quitting (preloading), this reported smoking reduction has been biochemically confirmed. There is no evidence that concurrent smoking and nicotine replacement therapy use result in greater nicotine exposure than solely smoking.

Anna Podlasek and Ravinder Claire contributed equally.

KEYWORDS
carbon monoxide, cotinine, meta-analysis, nicotine, nicotine replacement therapy, preloading, reduction, smoking

BACKGROUND AND AIMS

Smoking is a major international public health problem. Unfortunately, tobacco use still leads to preventable morbidity and mortality worldwide [1]. In 2020, 22.3% of the global population used tobacco, causing smoking-related deaths in half of users, amounting to 8 million deaths per year, including 1.2 million non-smokers exposed to second-hand smoke. There is a male predominance in tobacco use; 36.7% of the world's men and 7.8% of women smoked in 2020 [2]. Additionally, of 1.3 billion tobacco users, 20% live in developed countries and the vast majority, ~80%, live in low- and middle-income countries [2]. The economic cost of the smoking epidemic is high, estimated as between 1% and 3.4% of gross domestic product in Canada, Australia and the United States (US) [3]. Clearly, given the harms outlined above, people who smoke have the greatest chance of preventing further harm and improving their health if they stop smoking completely. However, many people who smoke cannot quit, and for them, smoking fewer cigarettes could be better for their health than 'smoking as usual'. For example, there is a strong dose–response relationship between heaviness of smoking and death from cardiovascular disease [4], which is very likely causal [5].

As using nicotine replacement therapy (NRT) alongside smoking has been demonstrated to help achieve abstinence, smoking treatment guidelines such as those produced by the National Institute for Health and Care Excellence in England recommend this as a cessation strategy. NRT used to cut down smoking by people with no immediate plans to stop induces long-term abstinence measured at least 6 months later (RR = 1.87, 95% CI = 1.43–2.44) [6]. Similarly, people who are still smoking, but also use NRT 2 to 4 weeks before their quit dates ('nicotine preloading') are also more likely to stop smoking (RR = 1.25, 95% CI = 1.08–1.44) [7]. However, although NRT used like this helps smokers to quit, the effects of using NRT and smoking concurrently on short- to medium-term tobacco smoke exposure are unclear. It is possible that when people smoke fewer cigarettes, they take longer, deeper puffs, inhaling more tobacco smoke per cigarette, therefore, minimising potential benefits to their health [8].

This review aims to understand how concurrent use of NRT and smoking affects heaviness of smoking and nicotine and CO exposures. To achieve this, we searched for trials testing NRT used as preloading, or for smoking reduction, comparing measures of these three exposures at baseline (i.e. when smoking) and shortly after participants were offered trial interventions (i.e. when using NRT and smoking concurrently).

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods [9], and a protocol has been published [10]. We included RCTs, which tested interventions permitting concurrent NRT use and smoking in studies either aiming at smoking reduction or 'preloading' studies that report data on the initial period of concomitant period of smoking and NRT use before the quit date. Participants were adults who concurrently smoke and use NRT. There was no restriction on NRT type (inhalers, gums, patches). Studies had to report nicotine (cotinine) or exhaled carbon monoxide (CO) concentrations or reported numbers of cigarettes per day before and after intervention. A scoping review indicated there were likely to be sufficient RCTs to answer review research questions, so observational studies were excluded. However, where secondary analyses of RCT data presented relevant data, these were included.

Search strategy

We developed a draft MEDLINE search strategy and adapted this for EBSCO and Web of Science (see Appendix S1); the draft strategy was optimised against its ability to find three studies that we knew should be included in the final review. This final strategy was run in MEDLINE, Embase, PsycINFO, Maternity and Infant Care Database (MIDRIS), CINAHL and Social Sciences Citation Index (SSCI) databases. We also manually searched for studies in the US National Library of Medicine Clinical Trials database (www.ClinicalTrials.gov/), the World Health Organisation International Clinical Trials Registry Platform (www.who.int/trialsearch) and the ISRCTN Registry (http://www.isrctn.com/). Additionally, we searched relevant pharmaceutical company registries (e.g. https://www.gsk-clinicalstudyregister.com/) and the Cochrane database and reviewed studies cited in relevant Cochrane reports and in the reference lists of included studies. There were no language restrictions, and searches were conducted from 1980, after which the first RCTs testing NRT were reported and were concluded by December 2021.

Study selection and data extraction

We imported title and abstract records into Covidence review management software [11], and at least two of four co-authors (R.C., T.C., R.T. and K.C.) independently assessed each record whether corresponding full texts should be retrieved. Where an assessor was uncertain, they discussed this with another assessor to achieve consensus; if after discussion there was no consensus, a full text was sought. At least two of five co-authors (R.C., S.O., K.C., R.T. and T.C.) independently assessed each full text to decide on inclusion; where assessments diverged, they achieved consensus through discussion.

We designed a data extraction form within Covidence, and, for each included study, at least two of six co-authors (R.C., S.O, K.C.,

R.T., T.C. and A.P.) independently extracted general study data, in details setting and design, the number of follow-up points; participant numbers and their characteristics; dose(s) and type(s) of NRT issued any instructions on how NRT should be used.

Outcome data

From each study, we extracted data from two or more intervention groups (i.e. a control group that did not use NRT and at least one group that did). We used data from two or more time points: baseline, before intervention (i.e. when participants only smoked) and at least one after the intervention was offered (i.e. when participants smoked and used NRT). At all time points, we extracted the reported number of cigarettes smoked per day (CPD), concentrations of CO in expired air and the concentration of nicotine or cotinine (as nicotine's main metabolite) in bodily fluids, with the timing of smoking or NRT use relative to samples being taken. At follow-up time points, where possible, we noted the numbers of participants providing these data. These data were usually reported within trial groups, but if any longitudinal, 'within-person' data were available, we also extracted these.

Risk of bias assessment

Risk of bias was assessed by one co-author (A.P.) using RoB-2 tool [12] for RCTs and robvis tool [13] for visualisation.

Statistical analysis

Study characteristics and extracted variables were summarised using standard descriptive statistics. Continuous variables were expressed as means and SD, and categorical variables were expressed as frequencies or percentages. Meta-analyses of continuous variables were expressed as mean difference (MD) with a 95% CI. A random-effect model and the Mantel–Haenszel method were used.

Tests of heterogeneity were conducted with the Q statistic distributed as a χ^2 variate (assumption of homogeneity of effect sizes). The extent of between-study heterogeneity was assessed with the I^2 statistic. Funnel plots were used to assess publication bias for the primary outcome. *P*-values were two-tailed, with values <0.05 considered statistically significant.

All analyses were implemented using Excel and Review Manager 5.4.1 software.

Ethics

As no participants were recruited to this secondary analysis of published work, ethical approval was not required.

RESULTS

Searches identified 12 590 citations, and 5797 duplicates were removed. A total of 6793 titles and abstracts were screened, of which 6644 were considered irrelevant, leaving 149 records for which we sought complete manuscripts. Three could not be retrieved; therefore, 146 reports were assessed for eligibility, and 29 studies were included in the review. (Figure 1)

Included studies and participants

Tables 1 and 2 give full details of included studies that recruited participants in Taiwan [14], South Africa [15], Hong Kong [16], New Zealand [17, 18], Korea [19], the United States [20–31] and Europe (including the United Kingdom) [31–41]. Five studies recruited people who smoked with only particular characteristics, including serious mental health problems [14], cardiovascular [27] or chronic obstructive pulmonary disease [30], adolescents [24] and pregnancy [39, 40].

Interventions

Seven studies assessed the use of NRT gum or patches as preparation for stopping smoking in a period before quit dates (preloading) [15, 20–22, 32, 33, 42], and in 17 NRT use was aimed at achieving smoking reduction [14, 16, 17, 19, 24–29, 34–38, 43, 44]. 'Traditional' cessation studies in which NRT is only used from a quit date onward were generally excluded. However, we included five cessation-orientated RCTs, which reported findings from subgroups of participants who continued to smoke, as they contained variables of interest and did not fit our exclusion criteria [30, 39–41, 45]. Two of these papers were conducted among pregnant women [39, 40].

Risk of bias

Overall, we assessed 29 studies for risk of bias, which revealed 19 (65.5%) studies with low risk of bias, nine (31%) studies with some concerns and one study (3.5%) with high risk of bias. Of seven preloading studies, five (71.4%) studies had low risk of bias, and two (28.6%) has some concerns. Of five RCT secondary analyses, three (60%) studies had low risk of bias, one (20%) has some concerns and one (20%) has a high risk of bias. Of 17 reduction studies, 11 (64.7%) studies had low risk of bias and six (35.3%) had some concerns. One study had a high risk of bias in one domain; however, it was not included in the meta-analysis; therefore, no sensitivity analysis was required. Further details are presented in Figure S1.

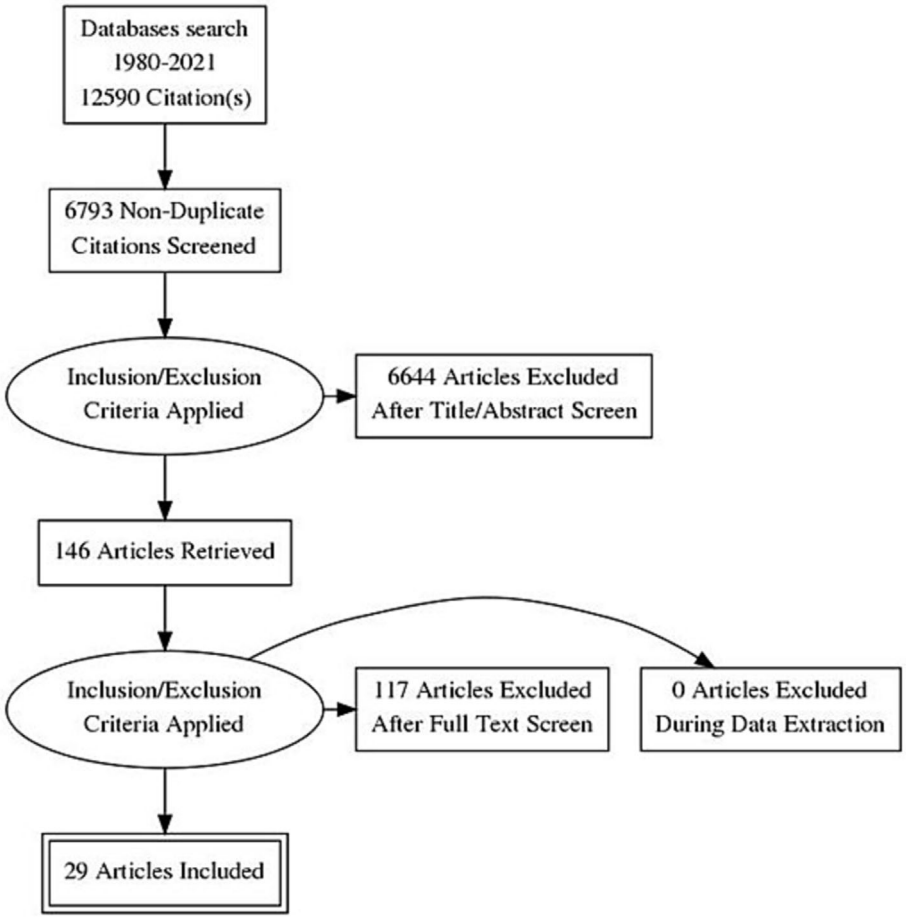

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart summarising study selection.

Outcomes

Among the seven preloading studies, the preloading period lasted for 2 to 8 weeks before quit dates, and follow-up data used collected at 1 to 3 weeks post-randomisation. All studies reported information about CPD and exhaled CO, but none presented data on cotinine concentrations (Table 1).

Among the 17 reduction studies, follow-up data used in the review were collected between 2 weeks and 12 months post-randomisation. Twelve studies reported exhaled CO concentrations, 16 CPD and eight cotinine concentrations (Table 2).

Among the five studies describing *post hoc* analyses of RCT data, follow-up data used in the review were collected between 2 weeks and 6 months post-randomisation. Three studies reported exhaled CO concentrations, five CPD and four cotinine concentrations (Table 2).

CPD

Nine studies reported CPD at baseline and at follow-up following the offer of intervention; these included six reduction studies [16, 24, 27, 29, 36, 40] and three preloading ones [22, 32, 42]. A total of 2649 of 4523 (58.6%) participants who completed follow-up received NRT, whereas the remaining participants received placebo or another non-NRT-based intervention.

Analysis of all studies (i.e. NRT for smoking reduction and preloading) revealed a MD of −2.06 CPD (95% CI = −3.06 to −1.07, $P < 0.0001$); for reduction studies, the MD was −1.77 CPD (95% CI = −3.29 to −0.25, $P = 0.02$), and for preloading studies, this was −2.58 CPD (95% CI = −3.81 to −1.35, $P < 0.001$) (Figure 2). Heterogeneity was moderate for reduction studies, $I^2 = 44\%$, and minimal for preloading ones, as a particularly large study drove preloading analyses findings ($n = 1792$, 46.1% of total participants in this analysis) [32]. The publication bias is represented graphically (Figure S2).

Among 20 studies not included in the meta-analysis, 12 reported CPD changes in varying detail; in 11, there was a reduction in CPD, and in one, there was no evidence of difference. (Tables 1 and 2).

CO

Seven studies reported CO concentrations at the baseline and following intervention, including four reduction studies [16, 24, 27, 40] and three preloading ones [22, 32, 42]. A total of 2207 of 3658 (60.3%) participants who completed follow-up in the relevant study arm received NRT, whereas the remaining participants received placebo or other non-NRT based intervention.

The publication bias is represented graphically (Figure S3).

Across all studies, there was a non-significant reduction in CO concentrations (MD = 0.58 ppm, 95% CI = −2.18 to 1.03 ppm). The

TABLE 1 Baseline characteristics of preloading studies.

Author, year, country	Inclusion criteria	Length of preloading	FU	Study groups	Number of participants (loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
Aveyard *et al.* [32], 2018, UK	Regular smokers ≥18 y, seeking support with stopping and willing to set QD for 4 w later	4 w	1 w after BL	A 21-mg nicotine patch daily used for ≤4 w before QD + behavioural intervention	899 (NA)	BL: 23.5 ± 12.3 FU: 20.41 ± 11.7	BL: 19.1 ± 11.41 D-7: 20.41 ± 11.7	NA
				Behavioural intervention	893 (NA)	BL: 23.8 ± 12.8 FU: 23.58 ± 12.8	BL: 23.8 ± 12.8 D-7: 23.58 ± 12.8	NA
Dedert *et al.* [42], 2018, USA	Smoking ≥10 CPD for 1 y; age 18–70, willing try quitting; PTSD diagnosis	3 w	2–3 w after BL	Before QD, 21-mg nicotine patch for 2 w and then for 1 w bupropion added. Told to smoke as normal	37 (NA)	BL: 16.16 ± 7.96 FU: 13.08 ± 6.29	BL: 18.91 ± 11.41 FU: 18.12 ± 10.25	NA
				Before QD, placebo patch for 2 w and then for 1 w bupropion added. Told to smoke as normal	44 (NA)	BL: 17.07 ± 10.72 FU: 14.38 ± 8.62	BL: 20.36 ± 10.71 FU: 18.76 ± 14.46	NA
Hughes *et al.* [20], 2010, USA	≥18 y; CPD ≥15; wants to quit within 30 days and prefers to try gradual quitting and willing to try nicotine lozenge	<4 w	1 w before QD	Gradual reduction with 2 or 4 mg NRT lozenge before QD over five support sessions (90% given 4 mg matched to smoking heaviness) (reduce lozenge then quit lozenge)	297 (NA)	FU: −21%	BL: 23 ± 9 FU: −54%	NA
				2 behavioural support sessions only before QD and quit lozenge	299 (NA)	FU: −0%	BL: 23 ± 8 FU: −1%	NA
				Minimal treatment + quit lozenge	150 (NA)	NA	BL: 24 ± 9 FU: −5%	NA
Lindson-Hawley *et al.* [33], 2016, UK	CPD ≥15; willing to stop smoking in 2 w; exhaled CO ≥15 ppm	2 w	2 w after BL, before QD	Abrupt cessation on QD and 21 mg or 14 mg nicotine patches before this	355 (NA)	FU: −18%	FU: −29%	NA
				Told to reduce before QD; nicotine patches as above plus fast-acting NRT	342 (NA)	FU: −46%	FU: −68%	NA
Schuurmans *et al.* [15], 2004, South Africa	≥18 y; CPD ≥15 for >3 y; exhaled CO > 10 ppm; ≥1 quit attempt(s) in past 12 months	2 w	2 w before and after QD	Before QD, 15 mg/16-hour nicotine patches for 2 w and told to smoke as normal	100 (4)	BL: 25.7 ± 9.7 FU: −0.81	BL: 23.1 ± 8 FU: −3.1	NA
				Before QD, placebo patches for 2 w and told to smoke as normal	100 (12)	BL: 25.2 ± 9.8 FU: −0.7	BL: 26.4 ± 11.4 FU: −0.8	NA
		<8 w	2 w after BL	NRT 2 mg gum	819 (NA)	FU: −25%	FU: −38%	NA

(Continues)

TABLE 1 (Continued)

Author, year, country	Inclusion criteria	Length of preloading	FU	Study groups	Number of participants (loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
Shiffman *et al.* [21], 2009, USA	≥18 y; interest in quitting smoking using gradual reduction in 30 days			NRT 4 mg gum	830 (NA)	FU: −21%	FU: −45%	NA
				Placebo 2 mg gum	817 (NA)	FU: −17%	FU: −35%	NA
				Placebo 4 mg gum	831 (NA)	FU: −4%	FU: −36%	NA
Smith *et al.* [22], 2019, USA	≥18 y; CPD ≥5; CO ≥10 ppm or urinary cotinine >2000 mg/mL; no intention to quit within 30 days; ≤3 days abstinence in previous 30	6 w	2 w after BL	21 mg or 14 mg NRT patch, matched to smoking heaviness	59 (NA)	BL: 23.2 ± 10.6 FU: 24.3 ± 12.2	BL: 19.65 ± 10.6 FU: 21.8 ± 13.18	NA
				Usual cigarettes	61 (NA)	BL: 23.9 ± 12.0 FU: 23.7 ± 11.7	BL: 17.94 ± 8.15 FU: 20.59 ± 10.23	NA

Abbreviations: BL, baseline; CO, carbon monoxide; CPD, cigarettes per day; FU, follow-up; NA, not available; NRT, nicotine replacement therapy; PTSD, post-traumatic stress disorder; QD, quit date; UK, United Kingdom; USA, United States of America; w, weeks; y, years.

analysis revealed a non-statistically significant MD of 0.14 ppm CO (95% CI = −1.21 to 1.49 ppm, $P = 0.84$) among reduction studies and significant MD of −2.54 ppm CO (95% CI = −4.14 to −0.95 ppm, $P = 0.002$) among preloading ones (Figure 3). There was minimal heterogeneity for both reduction and preloading studies.

Among the studies not included in the meta-analysis, 13 provided data on exhaled CO concentrations in varying detail. In 10 studies, compared to when solely smoking, CO concentrations were lower when smoking and using NRT, and in three, there was no evidence of difference (Tables 1 and 2).

Cotinine

The 11 studies that provided on cotinine concentration data reported this with varying detail and format, such as percentage changes or mead reductions, so studies' findings could not be aggregated in a meta-analysis. Seven reported reductions in cotinine concentrations during concurrent use, and in four, there was no evidence of difference in these compared with when only smoking. None of the studies reported increase in cotinine when using NRT concurrently with smoking (Table 2).

DISCUSSION

This review collates all trials reporting short-term effects of NRT used for preloading or smoking reduction on reported and validated levels of tobacco smoke exposure and cotinine concentrations. These treatment strategies both involve NRT use while still smoking and both resulted in lower reported heaviness of cigarette smoking, which, for NRT preloading, was validated by concurrent reductions in exhaled CO concentrations. It was not possible to meta-analyse studies reporting nicotine (cotinine) exposures before and after treatments, but there was no evidence of nicotine over-exposure from studies' findings considered narratively.

Studies were conducted in varied settings in different countries and comparators were diverse and included placebo, snus, very low nicotine content cigarettes and behavioural interventions. Nevertheless, our analyses of 29 studies including 13 807 participants produced consistent findings, suggesting an underlying phenomenon in which NRT use substitutes for smoking. We did not formally assess whether NRT side effects might contribute to treatment discontinuation or how these might be mitigated, as nicotine has already been shown to be a safe treatment for smoking cessation [7, 46].

A possible limitation of this review is that RCT data were treated as if collected for cohorts, and as review outcomes were not primary RCT outcomes, there was substantial loss to follow-up. Bias in outcome ascertainment might have affected study findings, but it is difficult to predict in what way. It is likely, however, that study participants retained in studies for follow-up would be those who were actively using trial interventions, and it is in this group of trial participants that determining intervention effects on relevant

TABLE 2 Baseline characteristics of reduction studies, data presented as mean SD unless specified otherwise.

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
Batra *et al.* [34], 2005, Germany and Switzerland	≥18 y; CPD ≥20 for >3 y; exhaled CO > 15 ppm; ≥1 quit attempt(s) in past 24 months. Attempts to exclude potential participants who wish to stop smoking. Participants told to use the gum whenever urges to smoke; chew 6–24 pieces daily for up to 12 months, and maximal smoking reduction was study aim	6 m for CPD and CO, 4 m for cotinine	4 mg nicotine gum	184 (45)	FU: −36.7 ± 27.4%	FU: −45.8 ± 25.3%	FU: −7.2 ± 37.8%
			Visually identical and similar tasting placebo	180 (61)	FU: −26.9 ± 26.8%	FU: −39.5 ± 19.7%	FU: −25.4 ± 26.3%
Bolliger *et al.* [35], 2000, Switzerland	≥18 y, ≥15 CPD, CO ≥10 ppm, smoking regularly ≥3 y, ≥1 quit attempt in the last year; wants to reduce	2 w	NRT inhaler	200 (32)	BL:27.1 ± 11.5 FU: −26.4 ± 31.4%	BL: 28.2 ± 11.4 FU: −51.5 ± 20%	NA
			Placebo	200 (36)	BL: 27.1 ± 11.1 FU:−18 ± 37.9%	BL: 30.3 ± 12.1 FU: −45.3 ± 18.9%	NA
Caldwell *et al.* [17], 2010, New Zealand	≥18 y; CPD ≥15, Fagerstrom Test for Nicotine Dependence ≥3	2 w	Snus	63 (13)	NA	FU: −37 ± 26%	NA
			NRT gum		NA	FU: −33 ± 26%	NA
			Zonnic		NA	FU: −42 ± 24%	NA
Carpenter *et al.* [23], 2003, USA	≥18 y; CPD ≥10; exhaled CO > 10 ppm, interested in quitting—but not within 30d, ≥1 quit attempt; no recent change in smoking behaviours (25% change in <2 months); no use of non-cigarette tobacco in <1 month, no contraindication for NRT	4 w	NRT gum patch or inhaler + behavioural reduction intervention with the goal of 50% reduction	32 (3)	BL: 27 FU: 19	BL: 25 FU: 14	NA
			NRT gum patch or inhaler for those who set QD + brief advice only	35 (0)	BL: 30 FU: 26	BL: 25 FU: 22	NA
Chan *et al.* [16], 2011, Hong Kong	≥18 y; CPD ≥2 for ≥2 y; initially - no intention to quit in the 'near future'—modified to, 'in the next 4 weeks' as many excluded because	6 m	NRT gum or patches (dose matched to CPD) plus reduction and adherence counselling	479 (52)	BL1: 16.4 ± 8.5 BL2: 18.2 ± 9.7 FU1 + 2: 7.6 ± 9.3	BL1: 19.8 ± 9.4 BL2: 20.1 ± 10.1 FU1 + 2: 9.5 ± 8.4	NA
			NRT gum or patches (dose matched to CPD)	449 (44)			

(Continues)

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
	of wanting to stop at some point in future; interested in reducing smoking Participants told to use prescribed dose of NRT for 4 w		Simple advice on cessation	226 (10)	BL: 16.7 ± 8.9 FU: 5.2 ± 10.7	BL: 19.2 ± 8.9 FU: 13.1 ± 9.3	
Chen *et al*. [14], 2013, Taiwan	Regular smokers with DSM-IV diagnosed schizophrenia/ shizoaffective disorder Tried to persuade patients to stop smoking if they could, but if this is too hard, encouraged participants reduce CPD. No QD set	5 w for CPD, 8 w for CO	Low-dose NRT (20.8 mg for 8 w)	92 (16)	BL: 9.2 ± 8 FU: 9.2 ± 8.3	BL: 13.7 ± 8 FU: 9.7 ± 5.7	NA
			31.2 mg for 4 w , followed by 4 w of 20.8 mg	92 (21)	BL: 11 ± 9.7 FU: 9.2 ± 8.4	BL: 12.7 ± 7.6 FU: 11 ± 7.7	
Etter *et al*. [36], 2002, Switzerland	18–60 y, CPD ≥20, no intention to quit in the next 6 m, non-pregnant	6 m	NRT: choice between patch, gum, inhaler or combination	265 (0)	NA	BL: 29.8 ± 10.3 FU: 19 ± 11.1	NA
			Placebo	269 (0)	NA	BL: 29.4 ± 9.4 FU: 20.6 ± 10	NA
Fagerstrom *et al*. [37], 2000, Sweden	20–65 y; CPD ≥5 Randomised crossover study. After BL, 2 fortnight-long periods on each treatment, followed by 2-w period of usual smoking afterward No counselling. Told to smoke as few cigarettes and to use as much of NRT as possible	2 + 4 w	'Eclipse', a heat-not-burn nicotine device	50 (40)	BL: 21, SE 1 FU: 33.0, SE 2,3	BL: 19.1, SE 1 FU 2,1, SE 0.5	BL: 330, SE 15 FU: 312, SE 19
			Nicotrol inhaler (NRT, delivering nicotine concentration of 3-6 mg/L)		BL: 21, SE 1 FU: 12.7, SE 1.5	BL: 19.1, SE 1 FU 4.8, SE 0.7	BL: 330, SE 15 FU: 259, SE 17
Hanson *et al*. [24], 2008, USA	13–19 y; CPD ≥5 for ≥6 months, wants to reduce smoking, no quit date within next 2 months Dose of gum or patch based on CPD at baseline. Participants told to	4 w	NRT patch	34 (NA)	BL: 7.1 ± 4.1 FU: 5.2 ± 4.0	BL: 11.1 ± 5.2 FU: 5.0 ± 4.5	BL: 3476.4 ± 2025.3 FU: 3464.4 ± 2763.1
			NRT gum	33 (NA)	BL: 6.9 ± 3.4 FU: 6.7 ± 3.9	BL: 12.7 ± 4.9 FU: 6.9 ± 3.4	BL: 3759.4 ± 2652.2

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
	reduce smoking when medication started, aiming for 25% less after Week 1 and 50% reduction by Week 3						FU: 3946.0 ± 2671.1
			Placebo	36 (NA)	BL: 5.7 ± 3.2 FU: 5.1 ± 3.6	BL: 11.6 ± 6.7 FU: 5.4 ± 2.3	BL: 3071.6 ± 2099.7 FU: 2505.0 ± 2486.8
Hatsukami *et al*. [25], 2013, USA	18–70 y, 10–40 CPD	6 w	NRT patch	80 (20)	NA	BL: 19.4 ± 6.2	Geometric mean (95% CI) out of 54 BL: 17.12 (14.44, 20.09) FU: 2.03 (1.20, 3.45)
			VLNC	79 (24)	NA	BL: 19.5 ± 8.6	Geometric mean (95% CI) out of 59 BL: 16.78 (14.30, 19.69) FU: 5.50 (3.31, 9.13)
			NRT patch + VLNC	76 (18)	NA	BL:17.7 ± 6.3	Geometric mean (95% CI) out of 58 BL: 17.99 (15.33, 21.12) FU: 7.65 (4.59, 12.76)
Hatsukami *et al*. [26], 2016, USA	≥18 ≤ 70 y; CPD ≥10 ≤ 40 for ≥1 y NRT group advised to us at least 6–8 pieces daily for ∼30 min each (ideally every 1–2 h) Participants advised to reduce consumption of intervention products on a sliding scale from Weeks 7 to 12 and encourage to report any smoking; analyses in	4 w	4 mg nicotine gum but if side effects, 2 mg substituted	195 (NA)	NA	NA	BL:3572 ± 2297 FU: 2838 ± 2229
			Snus	196 (NA)	NA	NA	NA

(Continues)

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
	those who used products and smoked. Study tested the extent to which those smoking could replace this with NRT/Snus (i.e. smoking reduction)						
Joseph *et al.* [27], 2008, USA	≥18 ≤ 80 y; CPD ≥15 and a diagnosis of cardiovascular disorder (from list of 11) Participants encouraged to substitute each piece of gum for a cigarette smoked or to aim for reduction, if using patch Study powered to detect smoking reduction at 6 months but acknowledges that not all participants used NRT: 'Among smoking reduction group subjects 57% used nicotine gum, 62% used nicotine patch and 88% used some form of NRT' Hence data at 1 months used, as use of NRT more likely at this time point	1 m	4 mg NRT gum, changed to patches if >6 pieces used daily	78 (NA)	BL: 24 ± 16 FU: 25 ± 12	BL: 27.7 ± 12.5 FU: 19.3 ± 13.1	BL: 4233 ± 2621 FU: 3870 ± 2647
			Usual care	74 (NA)	BL: 21 ± 12 FU: 21 ± 11	BL: 27 ± 11 FU: 21.6 ± 11	BL: 4499 ± 2359 FU: 3870 ± 2647
Klemperer *et al.* [28], 2019, USA	≥18 y; CPD ≥10 on each day Participants in group NRT1 encouraged to reduce the number of their usual cigarettes smoked daily after 1 w of smoking as normal	1 m	21 mg NRT patch	32 (NA)	BL: 22.5 ± 12.1 FU: 16.5 ± 11.9	BL: 21.1 ± 12.2 FU: 8.5 ± 6.9	BL: 1267 ± 1051–1483; 567 FU: 1542 ± 1308–1777; 658
			VLNC + 21 mg NRT patch	36 (NA)	NA	NA	NA
Kralikova *et al.* [43], 2009, Czech Republic	≥18 y; CPD ≥15 for ≥3 y; CO ≥10 ppm; want to reduce smoking and made one failed quit	2 w–12 m	NRT inhaler 10 mg or NRT gum 4 mg	209 (NA)	BL: 22.9 ± 10	BL: 25.7 ± 9.8	NA
			Placebo inhaler or placebo gum	105 (NA)	BL: 23.9 ± 9	BL: 252 ± 8.2	NA

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
	attempt. Do not currently wish to quit All participants asked to reduce smoking as much as possible. Cessation recommended, if possible.						
Lee *et al.* [19], 2019, Korea	≥18 y, CPD ≥10 for ≥3 y, motivated to stop or reduce	24 w	NRT	75 (14)	NA	BL: 19.27 ± 7.22 FU change: −25.3%, −6.55 ± 2.87	NA
			Electronic cigarettes	75 (4)	NA	BL: 20.95 ± 7.41 FU change: −41.3%, −6.55 ± 2.87	NA
Rennard *et al.* [29], 2006, USA	≥18 y; CPD ≥20 for ≥3 y; CO ≥10 ppm; one failed quit attempt in last 2 y; want to reduce smoking Advised to reduce smoking as much as possible. Little behavioural intervention. Cessation within 6 months recommended	2 w	NRT inhaler 10 mg	215 (15)	BL: 29.7 ± 10.7	BL: 29.3 ± 10.1 FU: 17.3 ± 8.1	NA
			Placebo inhaler	214 (29)	BL: 29.5 ± 9.0	BL: 30.4 ± 9.9 FU: 19.4 ± 7.7	NA
Wennike *et al.* [38], 2003, Denmark	≥18 y; CPD ≥15 for ≥3 y; CO ≥15 ppm; want to reduce smoking using nicotine gum	4 m	NRT gum 2 or 4 mg	205 (83–85)	FU -71 ± 39%	FU: −56 ± 31%	FU −98 ± 36%
			Placebo gum	206 (84–108)	FU: −84 ± 33%	FU: −67 ± 25%	FU: −86 ± 25%
RCT sub-analysis							
Bowker *et al.* [39], 2014, UK	Secondary analysis of RCT (SNAP trial) RCT enrolled pregnant women aged 16–45 y,12–24 w pregnant, ≥5 CPD and ≥10 CPD before pregnancy, CO ≥8 ppm	1 m	NRT patch	33 (NA)	NA	NA	BL median IQR: 98.5 (71.3–177.8) FU median IQR: 62.8 (33.3–82.7)
		2 w	NRT patch	146 (NA)	BL: 11.8 ± 6.7	BL: 12 ± 6	BL: 117.83

(Continues)

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
Claire *et al.* [40], 2019, France	Secondary analysis of 2014 multi-centre, double-blind, placebo-controlled RCT RCT enrolled pregnant women; ≥18 y; CPD ≥5; between 12 and 20 w gestation. This analysis on a subgroup Participants were using NRT in the run up to quitting and were told they could continue to use NRT in smoking lapses				FU: 8.7 ± 6.5	FU: 6 ± 5	FU: 111.14
			Placebo	122 (NA)	BL: 12.2 ± 7.3 FU: 10.2 ± 9.1	BL: 12 ± 6 FU: 6 ± 6	BL: 122.46 FU: 83.01
Ellerbeck *et al.* [30], 2018, USA	Outcomes from a cessation trial reported in the subgroup who was still smoking. RCT participants: ≥18 y; CPD ≥5 on 25/30 previous days; reported COPD diagnosis NRT used: 14–42 mg nicotine patches, based on heaviness of smoking, plus 2 mg of nicotine gum and/or lozenges Told to use complete course of NRT and not to stop even if continued smoking	3 m	Standard smoking cessation treatment, including NRT	198 (24)	BL: 22.9 ± 13.3 FU: 16.4 ± 12.6	BL: 22.1 ± 11.3 FU: 8.7 ± 8.8	NA
			Long-term NRT plus counselling after standard treatment ends	200 (27)	BL: 23.6 ± 15.1 FU: 18.8 ± 13.2	BL: 23.8 ± 12.2 FU: 11.4 ± 8.5	NA
Fornai *et al.* [41], 2001, Italy	Secondary analysis of smoking cessation RCT Instructions for using NRT not stated, but as a cessation trial likely to have been told to stop smoking	4 w	This analysis is of a subgroup within RCT participants allocated 15 mg/16 h or 25 mg/16-h NRT patch (n = 237) and who attended all 7 FU appointments (i.e. were 'compliant', n = 80)	80 (NA)	FU: −47%	FU: −80%	FU: −31%
		6 m		86/571	NA		NA

TABLE 2 (Continued)

Author, year, country	Inclusion criteria	FU	Study groups	Number of participants (not completed + loss to follow-up)	CO (ppm)	CPD (number)	Cotinine
O'Brien *et al.* [45], 2015, New Zealand	Secondary analysis of the ASCEND trial ≥18 y, motivated to quit		NRT patch (mental illness/no mental illness)			FU change: −5.7 ± 6.3/−7.4 ± 7	
			Electronic cigarette (mental illness/no mental illness)	35/260	NA	FU change: −9.9 ± 7/−9.4 ± 7.1	NA
			Placebo electronic cigarette (mental illness/no mental illness)	12/61	NA	FU change: −4.7 ± 3.5/−8.3 ± 5.9	NA

Abbreviations: BL, baseline; CO, carbon monoxide; CPD, cigarettes per day; COPD, chronic obstructive pulmonary disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; FU, follow-up; IQR, interquartile range; NA, not available; NRT, nicotine replacement therapy; QD, quit date; UK, United Kingdom; USA, United States of America; VLNC, very low nicotine content; w, weeks; y, years.

exposures is most relevant. Hence, review findings are likely generalizable to people who actually use NRT for preloading or smoking reduction after being offered these interventions. Funnel plots suggest that for CPD and exhaled CO outcomes, small studies with either positive or negative findings might be missing. However, in recent years, mandatory trial registration means that most started trials are published, negating the likelihood of any publication bias markedly affecting findings. Another criticism, which can be levelled both at included RCTs and analyses that aggregate their findings, is that of having limited external validity. However, as relatively consistent findings were reported across studies set in different health systems, generalisability may be reasonably robust. Finally, as included RCTs NRT only used patches and gum, findings cannot necessarily be extrapolated to other modes of NRT administration. As nicotine dosage varies with the mode of NRT administration, so other nicotine delivery systems, like NRT inhalators or e-cigarettes, might have different effects on exposure to tobacco smoke or nicotine [47].

Study strengths are that we used a systematic approach so that for the first time, short-term, but relevant impacts of NRT used for preloading and smoking reduction are summarised together. Cochrane reviews have evaluated the effectiveness of NRT preloading [7] and smoking reduction [46] on smoking abstinence, but this is the first review to systematically investigate effects of these cessation strategies on tobacco smoke and nicotine exposures. The Cochrane review, which investigated NRT preloading focussed primarily on abstinence outcomes and did not report any of the outcomes we sought [7]. The review of reduction-orientated studies did include CPD and CO outcomes, reporting that people using NRT for smoking reduction were more likely to report smoking 50% or 75% fewer cigarettes at follow-up (RR, [95% CI] = 1.75 [1.08–2.83]) [46]. However, this only included two studies reporting exhaled CO concentrations, and these could not be aggregated, so no validation of self-reported CPD data through meta-analysis of CO concentrations was possible. Neither previous review included body fluid concentration of either nicotine or cotinine as outcomes.

Our finding that reported lighter smoking with NRT was validated by lower CO concentrations for NRT used as preloading, but not for cutting down smoking is novel, as is our narratively reported observation that when NRT was used as preloading or for smoking reduction, there was no evidence of increased nicotine exposure. Studies generally offered NRT for smoking reduction to people who had previously failed to stop smoking, whereas preloading NRT was offered to people preparing to quit, so motivational differences in trial participants could explain the apparently greater impact of preloading NRT on heaviness of smoking. Another potential explanation for this is the different instructions about NRT use given in preloading and reduction studies. When preloading, people were mostly advised to use NRT instead of some cigarettes before a quit date, whereas in many 'reduction' studies, participants were told to 'smoke as normal'. A caveat is that, when NRT was used as preloading, although reported heaviness of smoking was reduced in all three meta-analysed studies, the reduction in exhaled air CO concentrations was observed in only one [32]. Although this study was large and well conducted, it remains

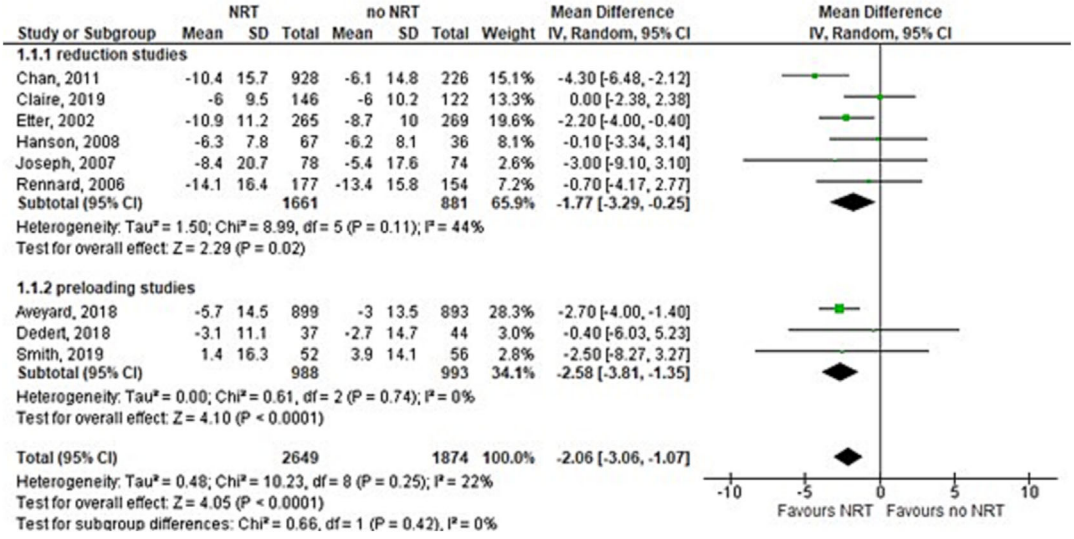

FIGURE 2 Forest plot of the mean difference between the baseline and follow-up in the number of cigarettes smoked per day.

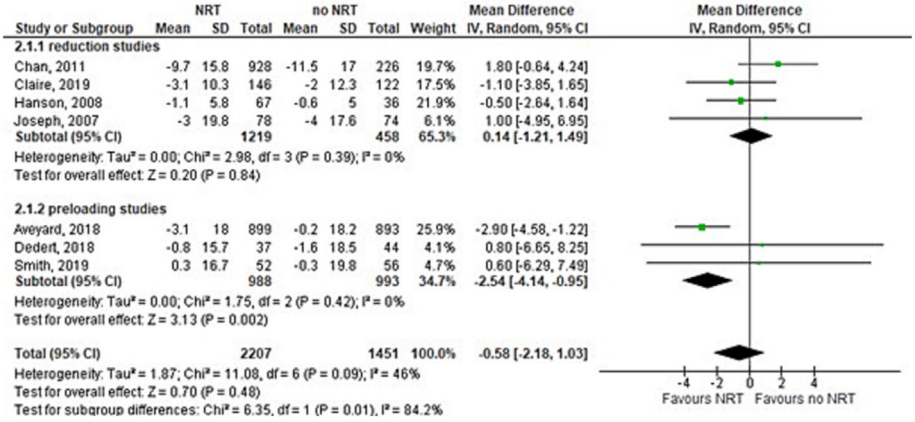

FIGURE 3 Forest plot of the mean difference between the baseline and follow-up in the exhaled carbon monoxide (CO) concentrations.

that biochemical validation of lighter smoking reported in the three studies is driven by this sole study. More data from future studies are required for greater certainty.

This review provides reassurance for using NRT alongside smoking as a means of smoking reduction or cessation; findings suggest that NRT administered in these ways is more likely to decrease than increase either tobacco smoke or nicotine exposures in the immediate period after use commences. Although it was not possible to meta-analyse cotinine data, and no studies reported increased concentrations following intervention, it seems highly unlikely that either use of NRT would lead to dangerous overexposure to nicotine. Most people who receive support to help them stop smoking are not successful; however, these data emphasise that clinician's fears about harming quitters who fail should not deter them from suggesting NRT as preloading or for smoking reduction to assist cessation, even for people whom they suspect have slim chances of becoming abstinent.

Study findings could help facilitate trials of either NRT preloading or NRT for smoking reduction in pregnancy. In pregnancy, heavier maternal smoking causes greater fetal harm; for example, there is growing evidence for a dose-dependent association between maternal smoking and fetal weight [48, 49]. Animal studies suggest nicotine exposure is harmful [50], although human studies have found no evidence that nicotine from NRT is more harmful to the foetus than smoking [51]. However, as neither tobacco smoke nor nicotine exposure was increased by either use of NRT, trials of both strategies to help pregnant smokers should be considered ethical.

CONCLUSIONS

People report smoking less when they use NRT, and this seems to occur without a concomitant increase in nicotine exposure. When people use NRT as 'preloading', to prepare for a quit date, reported lighter smoking is reflected in lower exhaled CO concentrations.

AUTHOR CONTRIBUTIONS

Anna Podlasek: Conceptualization (equal); data curation (equal); formal analysis (lead); project administration (equal); resources (equal);

software (equal); validation (equal); visualization (lead); writing—original draft (lead); writing—review and editing (supporting). **Ravinder Claire:** Conceptualization (lead); data curation (lead); funding acquisition (lead); methodology (equal); project administration (equal); resources (equal); software (equal); writing—review and editing (equal). **Katarzyna Anna Campbell:** Data curation (equal); methodology (equal); project administration (equal); resources (equal); writing—review and editing (equal). **Sophie Orton:** Data curation (equal); methodology (equal); project administration (equal); resources (equal); writing—review and editing (equal). **Ross Thomson:** Data curation (equal); methodology (equal); project administration (equal); resources (equal); writing—review and editing (equal). **Tim Coleman:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (lead); validation (equal); writing—original draft (lead); writing—review and editing (lead).

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DECLARATION OF INTERESTS

None.

PROSPERO REGISTRATION

CRD42020220687, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220687.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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