The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial

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ABSTRACT

Aim   To determine the combined effect of very low nicotine content (VLNC) cigarettes and usual Quitline care [nicotine replacement therapy (NRT) and behavioural support] on smoking abstinence, in smokers motivated to quit. **Design**   Single-blind, parallel randomized trial. **Setting**   New Zealand. **Participants**   Smokers who called the Quitline for quitting support were randomized to either VLNC cigarettes to use whenever they had an urge to smoke for up to 6 weeks after their quit date, in combination with usual Quitline care (8 weeks of NRT patches and/or gum or lozenges, plus behavioural support) or to usual Quitline care alone. **Measurements**   The primary outcome was 7-day point-prevalence smoking abstinence 6 months after quit day. Secondary outcomes included continuous abstinence, cigarette consumption, withdrawal, self-efficacy, alcohol use, serious adverse events and views on the use of the VLNC cigarettes at 3 and 6 weeks and 3 and 6 months. **Findings**   A total of 1410 participants were randomized (705 in each arm), with a 24% loss to follow-up at 6 months. Participants in the intervention group were more likely to have quit smoking at 6 months compared to the usual care group [7-day point-prevalence abstinence 33 versus 28%, relative risk (RR) = 1.18, 95% confidence interval (CI): 1.01, 1.39, $P = 0.037$; continuous abstinence 23 versus 15%, RR = 1.50, 95% CI: 1.20, 1.87, $P = 0.0003$]. The median time to relapse in the intervention group was 2 months compared to 2 weeks in the usual care group ($P < 0.0001$). **Conclusions**   Addition of very low nicotine content cigarettes to standard Quitline smoking cessation support may help some smokers to become abstinent.

Keywords   Cessation, clinical trial, nicotine replacement therapy, Quest 3, randomized, reduced nicotine cigarettes, smoking.

INTRODUCTION

Smoking cessation treatments are part of a comprehensive package of strategies aimed at helping people to quit. However, most people who achieve short-term abstinence relapse within a year. Current cessation strategies tend to focus on alleviating nicotine withdrawal symptoms and

craving or helping people to cope with such symptoms. Although pharmacological treatments such as nicotine replacement therapy (NRT), bupropion and varenicline are of proven effectiveness, none address the non-nicotine aspects of tobacco smoking, such as the tactile action of puffing on a cigarette, the sensation of smoke in the mouth and throat [1], the smell and taste and the

activity of other psychoactive substances in tobacco smoke that may strengthen nicotine dependence (such as acetaldehyde [2] or monoamine oxidase inhibitors [3]).

Reduced nicotine cigarettes (RNCs) offer the closest replacement to regular cigarettes. A number of different RNC brands have been marketed by tobacco companies, but the majority of research has been undertaken using the 'Quest' brand, produced and marketed by Vector Tobacco, Inc. (Miami, FL, USA). Three 'strengths' (1, 2 and 3) of Quest RNCs were produced with nicotine yields of 0.6 mg, 0.3 mg and ≤0.05 mg per cigarette, respectively, a nicotine content of 8.9 mg, 5.1 mg and 0.5 mg per cigarette, respectively, and a tar content of between 8 and 9 mg per cigarette (similar to the level in regular cigarettes) [4]. Quest RNCs were marketed to smokers as a way of reducing their nicotine consumption over time, but never as a way of achieving complete abstinence, despite evidence from five small trials ($n = 35–346$) [4–7] that suggested the use of RNCs alone [7,8] or in combination with NRT [4–6] may help smokers to address both the nicotine and non-nicotine aspects of smoking, with a positive impact on withdrawal, craving and quitting success [9]. Based on this evidence [9], we designed a large, community-based, parallel group, randomized controlled trial to determine the combined effect of using RNCs and usual Quitline care (NRT and behaviour support) on long-term quit rates in smokers motivated to quit. We selected the lowest nicotine-content cigarettes (Quest 3) to minimize the issue of compensatory smoking [4], and refer to these cigarettes hereafter as very low nicotine content (VLNC) cigarettes. We hypothesized that quit rates would be increased by offering smokers who wanted to quit VLNC cigarettes together with usual Quitline care.

METHODS

Setting and participants

The rationale and methodology for this trial have been reported previously [10]. Between April 2009 and October 2010 all eligible callers to New Zealand's Quitline were invited to participate. Participants were eligible if they were aged ≥18 years, smoked their first cigarette within 30 minutes of waking, were interested in trying to quit smoking now, were not pregnant/breastfeeding, were not currently using NRT or non-cigarette tobacco products, had not experienced a stroke or angina in the last 2 weeks, were not using bupropion, clonidine, nortriptyline or varenicline, were not enrolled in alternative Quitline support programmes and could provide verbal consent. Ethics approval for the trial was obtained from the NZ Multi-region Ethics Committee (MEC/08/10/

117). The trial is registered with the Australasian Clinical Trials Network: ACTRN12608000410358.

Randomization, allocation concealment and blinding

Participants were allocated randomly in a 1 : 1 ratio by computer, with stratified minimization by sex, ethnicity [Māori (the indigenous people of New Zealand) versus non-Māori] and level of nicotine dependence (>5 points or ≤5 points on the Fagerström Test of Nicotine Dependence [11]). Participants were not blinded to treatment allocation, but research staff undertaking outcome assessment were blinded.

Intervention

Participants were randomized to VLNC cigarettes plus usual Quitline care (NRT and behavioural support) or usual Quitline care alone.

Intervention group participants were delivered a carton of 200 VLNC cigarettes (Quest 3 brand; Vector Tobacco Inc.) by courier, at no cost. Participants were instructed to stop smoking their regular cigarettes on their designated quit day (QD) and to smoke the VLNC cigarettes *ad libitum* whenever they had an urge to smoke during the subsequent 6 weeks. In addition, participants received standard smoking cessation support through Quitline (as described below). No additional instructions were given about the combined use of the VLNC cigarettes and NRT, and no restrictions were placed on the number of VLNC cigarettes smoked per day. Participants could request a second carton of the cigarettes at a 3-week follow-up call. Independent verification of nicotine and tar content by Labstat Canada found the VLNC cigarettes had a nicotine content of 1.5 mg per cigarette, a nicotine yield of ≤0.05 mg per cigarette and a tar content of 4 mg per cigarette (not 8–9 mg as in previously tested Quest 3 cigarettes). The cigarettes used in the trial were not available for general sale in New Zealand.

Participants randomized to the usual Quitline care group received an 8-week supply of NRT (7, 14 or 21 mg patch, and/or 2 or 4 mg gum or 2 mg lozenge) issued by post via a voucher. Participants were instructed to redeem the voucher at a pharmacist for subsidized NRT (NZ$3 per item per 4 weeks' supply, equivalent to approximately €2 or US$2.5). The strength and type of NRT was determined by the Quitline adviser, based on each person's level of nicotine dependency and Quitline guidelines. Usual Quitline care also included an average of three behavioural support calls from trained Quitline advisers over 8 weeks, each call lasting 10–15 minutes. QD in this study referred to the day each participant stopped smoking regular cigarettes (containing nicotine).

Outcome measures

All data were collected by telephone. Baseline data included socio-demographic characteristics, smoking history and quitting self-efficacy [belief in their ability to quit measured on a scale of 1 (very low) to 5 (very high)]. Tobacco withdrawal symptoms were measured using the Mood and Physical Symptoms Scale (MPSS) [12], with additional questions on disturbed sleep, anxiety, mouth ulcers, cough, impatience, dizziness and increased dreaming [13]. Alcohol use and misuse was measured using the Alcohol Use Disorders Identification Test (AUDIT-C) [14].

Outcome data were collected at 3 and 6 weeks and 3 and 6 months after QD. The primary outcome was self-reported 7-day point-prevalence of smoking abstinence 6 months after QD (defined as no regular cigarettes, not a single puff, in the previous 7 days [15]). Biochemical verification of abstinence was not undertaken. Details on secondary outcomes are reported in another publication [10]; they included continuous abstinence (self-report of smoking not more than five regular cigarettes since QD [15]), use of NRT (type, dose and quantity per day), other cessation treatments used during the study period, concomitant medication and cost-related outcomes. Intervention group participants were also asked at 3 and 6 weeks about the number of VLNC cigarettes smoked per day, whether they would recommend them to friends and family who smoked and wanted to quit, if they had concerns about the use of VLNC cigarettes and the extent to which they experienced any rewarding effects from smoking VLNC cigarettes [assessed using the modified Cigarette Evaluation Questionnaire (mCEQ), which measures smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations and craving reduction [16]]. At 6 weeks participants in the intervention group were also asked if they felt that 6 weeks was a long enough period to use the VLNC cigarettes.

Sample size

The sample size of 1410 people (705 in each group) assumed a quit rate in the usual care group of 15%, loss to follow-up of 20%, and conferred 90% power at $P = 0.05$ to detect a difference in point-prevalence abstinence of 7.5%. A fixed proportion of at least 25% Māori was sought by adjusting the sampling ratio according to self-reported ethnicity [17]. Māori, who comprise 15% of the NZ population, have a high smoking prevalence (46% in 2008 [18]) and appear to metabolize nicotine more slowly than non-Māori [19,20]. This recruitment strategy for Māori ensures that they are not under-represented in research of relevance to them [21,22].

Analyses

Analyses were undertaken on an intention-to-treat basis, and per-protocol analysis was performed to check for robustness of results. Participants with missing smoking status data, withdrawals or lost to follow-up were considered to be still smoking [15]. We used χ^2 analysis to compare the proportion quit by treatment group. Pre-specified subgroup analyses were undertaken for ethnicity (Māori, non-Māori), age (<40 years, ≥40 years), sex and socio-economic status (dichotomized as those who left school below year 12 or with no school qualification, and those who completed year 12 and above). Repeated-measures analyses were also undertaken using generalized estimating equation (GEE) models to assess the treatment effect over time, and to mitigate the effect of missing data (when missing at random). The analyses included an interaction between treatment group and time, and adjustment for gender, ethnicity and nicotine dependence. Change in number of cigarettes per day and withdrawal symptoms (in abstainers only) over time were analysed using repeated-measures mixed models and adjusted for baseline value. Time-to-first-lapse was analysed by Kaplan–Meier analysis. Serious adverse events were defined as per the International Conference on Harmonisation Guideline for Clinical Safety Data Management [23], and coded using ICD-10AM. Three *post-hoc* analyses were undertaken to assess the heterogeneity of the primary outcome according to type of cigarettes smoked (factory-made only, roll-your-own only or both), baseline alcohol use (AUDIT-C: female: <3, ≥3, and male: <4, ≥4) and if at least one quit attempt or not had been made in the last 12 months.

RESULTS

Figure 1 shows participant flow throughout the trial and Table 1 shows participant baseline characteristics. Final loss to follow-up for the trial was 24%. The number of requested withdrawals from the trial was significantly higher in the usual care group compared with the intervention group (32 people versus 11 at 6 months, $P = 0.001$). No difference was seen in baseline variables between those in the usual care group who withdrew compared to those who did not withdraw.

Cessation rates

Seven-day point-prevalence 6-month abstinence rates were significantly greater in the intervention group (231, 33%) compared to the usual care group (195, 28%) [crude relative risk (RR) 1.18, 95% confidence interval (CI): 1.01, 1.39, $P = 0.037$; absolute risk difference 0.051, 95% CI: 0.003, 0.099; number needed to treat
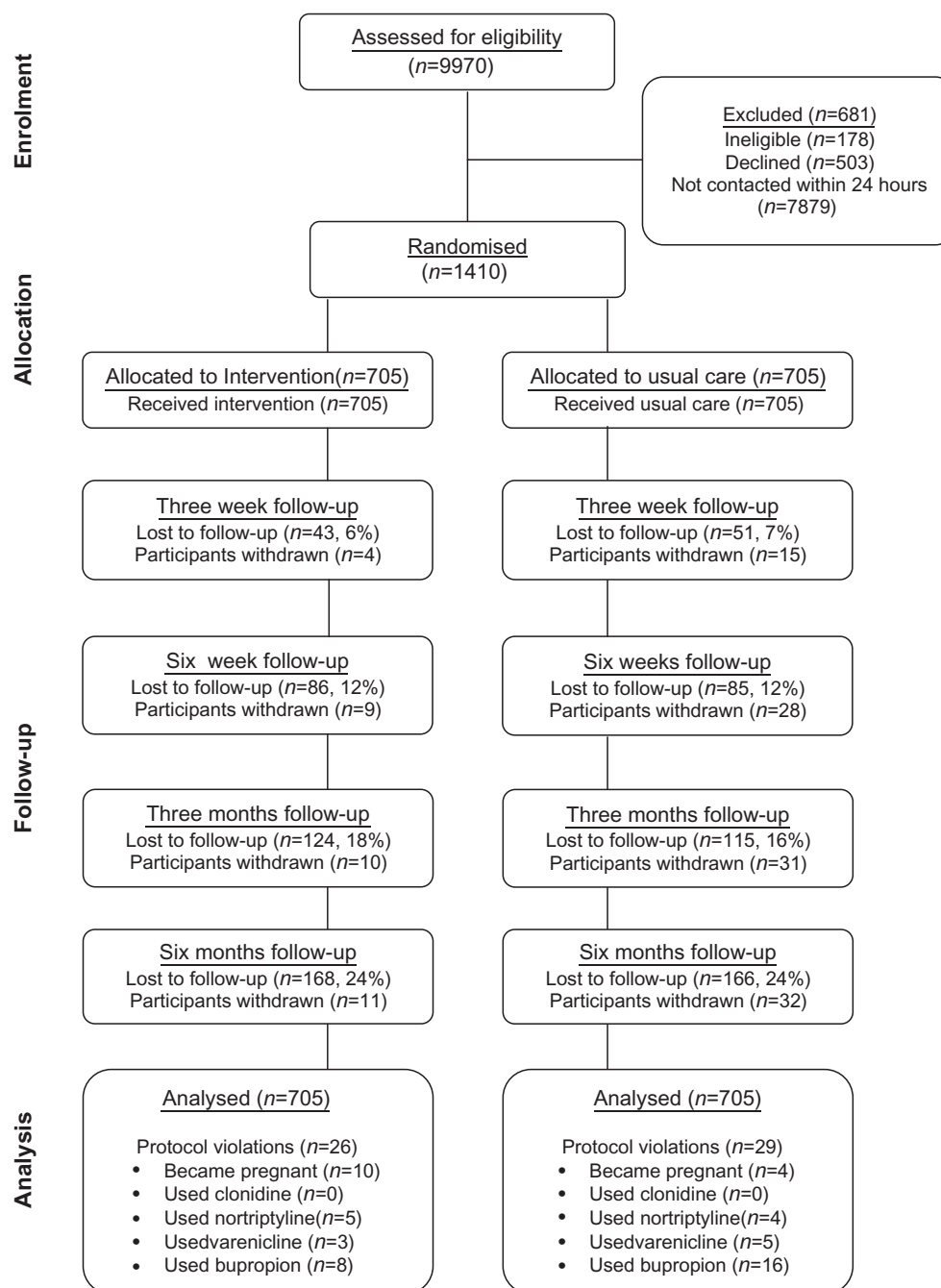
Figure 1 Flow-chart of recruitment and retention of participants throughout the trial

(NNT) = 19.6] (Table 2). Results were similar when only participants with complete smoking data were included and with per protocol analyses. Subgroup analyses showed no difference in the primary outcome according to age, sex, ethnicity, socio-economic status, type of cigarettes smoked, alcohol use at baseline, level of nicotine dependence or whether at least one quit attempt had been made in the last 12 months. Use of GEE repeated-measures analysis showed a highly significant time and

treatment effect, with the treatment effect strongest earlier in the intervention period (Table 2).

Using continuous abstinence as the measure of outcome showed that 160 (23%) participants from the intervention group and 107 (15%) in the usual care group were abstinent at 6 months. This result gave a crude RR of 1.50 (95% CI: 1.20, 1.87) with a *P*-value of 0.0003, an absolute risk difference of 0.08 (95% CI: 0.03, 0.12) and NNT of 13 (Table 2).

Table 1 Baseline characteristics of participants.

Variables	Intervention group n = 705 (%)	Usual care group n = 705 (%)
Sex		
Female	413 (59)	413 (59)
Male	292 (41)	292 (41)
Age (years)		
Mean	41.1	42.4
SD	12.4	12.7
Ethnicity		
Māori	171 (24)	170 (24)
Non-Māori	534 (76)	535 (76)
Education		
Below year 12/no qualification	363 (51)	371 (53)
Year 12 and above	342 (49)	330 (47)
Refused to answer	0	4
Cigarettes smoked per day		
Mean	21.8	21.4
SD	9.8	9.4
Fagerström Test of Nicotine Dependence (1–10)[a]		
Mean	6.2	6.2
SD	1.7	1.7
Type of cigarettes smoked		
Factory-made only	263 (37)	301 (43)
Roll-your-own only	375 (53)	346 (49)
Both	67 (10)	58 (8)
'Roll-your-own' smokers		
Grams smoked per week (mean, SD)	52.2 (23.9)	54.0 (27.2)
Pouch size in grams (mean, SD)	39.5 (9.9)	39.4 (9.9)
Days taken to smoke contents (mean, SD)	5.9 (2.2)	5.8 (1.9)
Lives with other smokers		
Yes	342 (49)	324 (46)
No	363 (52)	377 (54)
Missing	0	4 (1)
At least one quit attempt in last 12 months	217 (31)	198 (28)
Last method used to quit		
NRT patch	37 (17)	32 (16)
NRT gum	10 (5)	8 (4)
NRT lozenge	0	4 (2)
Zyban	2 (1)	3 (2)
Other	17 (8)	15 (8)
Nothing	151 (70)	136 (69)
Alcohol use (AUDIT-C: 0–12)[b]		
Female (mean, SD)	4.2 (3.1)	4.1 (3.2)
Male (mean, SD)	5.6 (3.5)	5.5 (3.6)
Self-efficacy[c]		
Mean	4.2	4.2
SD	0.8	0.8

SD: standard deviation; NRT: nicotine replacement therapy; AUDIT: Alcohol Use Disorders Identification Test. [a]A higher level of dependence was noted in Māori (n = 341, mean score = 6.4, SD = 1.4) compared to non-Māori (n = 1069, mean score = 6.1, SD = 1.7; P = 0.008) participants. [b]For men, a score ≥4 indicates an increased risk of hazardous drinking or alcohol dependence, while in women it is a score of ≥3. The higher the score, the greater the risk of alcohol dependence. [c]Belief in their ability to quit this time, measured on a scale of 1–5, where 1 was 'very low' and 5 was 'very high'.

Time to first lapse

Results of the time-to-first-lapse Kaplan–Meier analysis showed a significant difference between groups in favour of the intervention group, with 391 versus 465 participants relapsing within 6 months [median days to relapse: 61 in the intervention compared to 13 days for the usual care group, *P*-value for log-rank test

Table 2 Point-prevalence and continuous abstinence rates, by treatment group (intention-to-treat analysis).

	Intervention n = 705 (%)	Usual care n = 705 (%)	Relative risk (95% CI)	P-value
Seven-day point-prevalence abstinence				
Three-week quit rate[a]	378 (54)	256 (36)	1.48 (1.31–1.66)	<0.0001
Six-week quit rate[a]	333 (47)	232 (33)	1.44 (1.26–1.64)	<0.0001
Three-month quit rate[a]	280 (40)	211 (30)	1.33 (1.15–1.53)	0.0001
Six-month quit rate (primary outcome)[a]	231 (33)	195 (28)	1.18 (1.01–1.39)	0.037
Sensitivity analyses for 6-month quit data				
Complete cases only[b]	231/537 (43)	195/539 (36)	1.19 (1.03–1.38)	0.022
Per protocol[c]	224/512 (44)	186/513 (36)	1.21 (1.04–1.40)	0.014
Repeated-measures analyses[d]				
Overall treatment effect	–	–	1.67 (1.39–2.00)	<0.0001
Three-week effect	–	–	2.06 (1.66–2.56)	<0.0001
Six-week effect	–	–	1.86 (1.49–2.31)	<0.0001
Three-month effect	–	–	1.56 (1.25–1.95)	<0.0001
Six-month effect			1.29 (1.02–1.62)	0.03
Continuous abstinence				
Three-week quit rate[a]	393 (56)	275 (39)	1.43 (1.28–1.60)	<0.0001
Six-week quit rate[a]	293 (42)	203 (29)	1.44 (1.25–1.67)	<0.0001
Three-month quit rate[a]	227 (32)	148 (21)	1.53 (1.28–1.83)	<0.0001
Six-month quit rate[a]	160 (23)	107 (15)	1.50 (1.20–1.87)	0.0003

Six-month 7-day point-prevalence abstinence is the primary outcome. All other variables presented are secondary outcomes. CI: confidence interval. [a]Assumes all participants with missing smoking status were smoking (including those who withdrew). [b]Only includes participants for whom data on smoking status was complete at 6 months (withdrawn participants excluded). [c]Excludes participants with missing 6-month data and protocol violations. [d]Adjusted for gender, ethnicity and level of nicotine dependence.

<0.0001, hazard ratio (HR) = 0.70, 95% CI: 0.61, 0.80] (Fig. 2).

Use of the VLNC cigarettes

Overall, 94% (583) of the 619 participants in the intervention group who could be contacted at 6 weeks had smoked the VLNC cigarettes given to them, with 21% (n = 132) asking for a second carton. The average number of VLNC cigarettes smoked weekly decreased during the 6-week intervention period (Table 3). Table 3 also summarizes whether participants smoked the VLNC cigarettes with or without the use of NRT and/or whether or not they also smoked their regular cigarettes.

At 6 weeks, 90% (560) of the remaining 619 participants in the intervention arm said they would recommend the VLNC cigarettes to friends and family who smoked and wanted to quit. The main reasons given by the 10% of participants not recommending the cigarettes were: they would encourage them to start smoking 'normal cigarettes' again (29%); the cigarettes were habit-forming (19%); and they gave no relief from cravings (17%). In addition, 11% (65) of the 619 had concerns about using the VLNC cigarettes—these were that the cigarettes were still bad for your health (31%); that they would encourage them to start smoking 'normal cigarettes' again (12%); and the cigarettes were habit-forming (6%). Seventy per cent (435) felt that 6 weeks

was a long enough period to use the cigarettes, with 19% (119) preferring a longer period (mean suggested period: 76 days, SD = 45 days, median 90 days), 2% (12) a shorter period (mean suggested period: 24 days, SD = 22 days, median 18 days) and 9% (53) unsure.

The mean mCEQ subscale scores for participants in the intervention group (302 answered the mCEQ at both 3 and 6 weeks) were not statistically different between weeks 3 and 6, or according to NRT use or non-use. Participants reported 'a little' to a 'moderate' level of smoking satisfaction and psychological reward from using the VLNC cigarettes (Table 4). There was 'very little' to 'a little' aversion and enjoyment of the respiratory tract sensations associated with use of the VLNC cigarettes, but craving reduction was 'moderate' to 'a lot' (Table 4).

Other outcomes

There was no significant difference between the intervention group and the usual care group in the average amount of NRT used in abstainers at any time point (Table 5) or in the proportion of participants who had reduced their daily consumption of regular cigarettes by at least 25% at 6 months (n = 467, 66% intervention versus n = 445, 63% usual care, RR = 1.05, 95% CI: 0.97, 1·13, P = 0.2). For abstainers only, symptoms associated with nicotine withdrawal and urges to smoke did
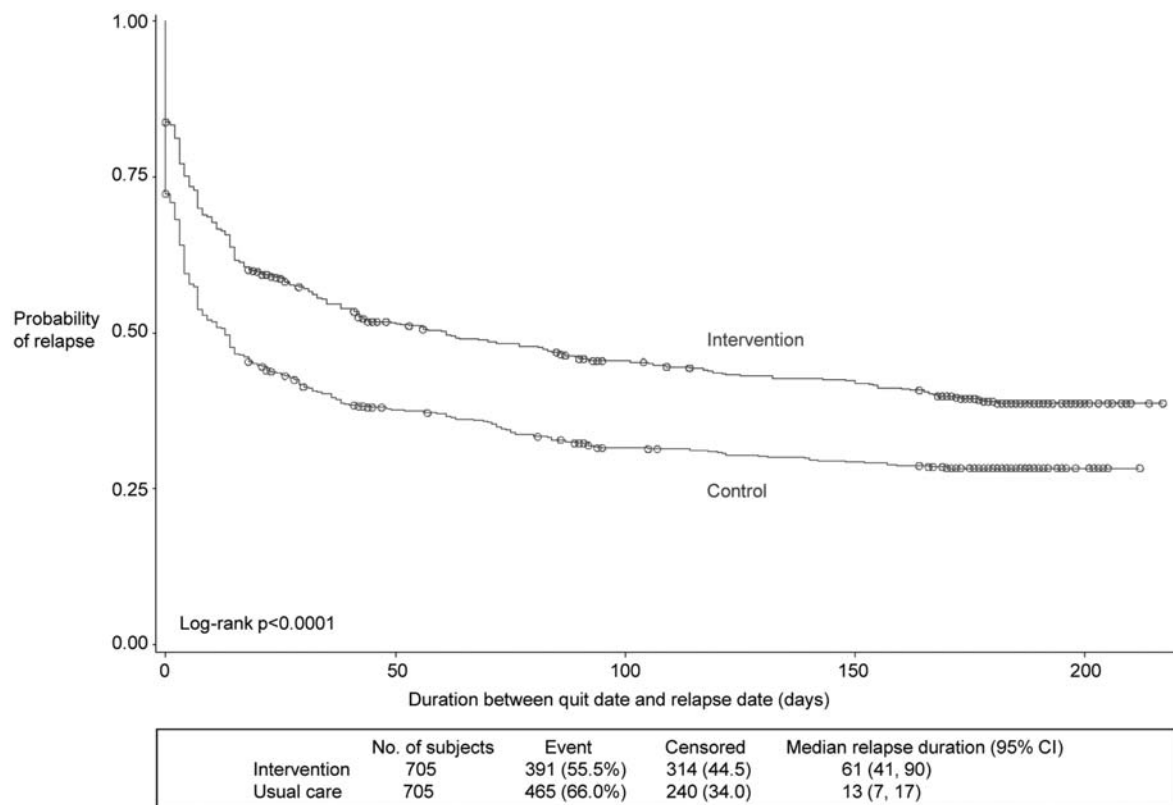
Figure 2 Kaplan–Meier curve for time to first relapse (days)

Table 3 Very low nicotine content (VLNC) cigarettes smoked, during the 6-week intervention period.

Number of VLNC cigarettes smoked each week

	Mean (SD)	*Median, range*
Week 1 (*n* = 662)	26 (31)	20, 0–200
Week 2 (*n* = 662)	20 (26)	10, 0–120
Week 3 (*n* = 662)	13 (21)	3, 0–140
Week 4 (*n* = 619)	10 (19)	0, 0–200
Week 5 (*n* = 618)	8 (16)	0, 0–100
Week 6 (*n* = 618)	6 (13)	0, 0–80

Use of the VLNC cigarettes, with NRT and regular cigarettes

	Intervention n = 619 (%)	*Usual care n = 617 (%)*
Smoked VLNC cigarettes and regular cigarettes, and used NRT	235 (38%)	–
Smoked VLNC cigarettes and used NRT	149 (24%)	–
Smoked VLNC cigarettes and regular cigarettes	135 (22%)	–
Smoked VLNC cigarettes only	64 (10%)	–
Used NRT only	13 (2%)	106 (17%)
Smoked regular cigarettes only	13 (2%)	187 (30%)
Used nothing	8 (1%)	33 (5%)
Smoked regular cigarettes and used NRT	2 (0.3%)	291 (47%)

SD: standard deviation; NRT: nicotine replacement therapy. No definition of 'smoked VLNC cigarettes' was provided, thus users may have had only a few puffs or more than one cigarette. 'Smoked regular cigarettes' was defined as having smoked more than one nicotine-containing cigarette. No ethnic differences in the data were observed.

Table 4 Views on the use of the very low nicotine content (VLNC) cigarettes, as measured using the modified cigarette evaluation questionnaire (intervention group only).

	Three weeks	Six weeks
	Mean (SD) (n = 302)[a]	Mean (SD) (n = 302)[a]
Smoking satisfaction		
Did you find the cigarettes satisfying?	3.8 (2.0)	3.9 (2.1)
Did the cigarettes taste good?	2.9 (1.9)	3.1 (1.9)
Did you enjoy smoking the cigarettes?	3.9 (2.2)	3.7 (2.1)
Average score	3.5 (1.7)	3.5 (1.7)
Psychological reward		
Did smoking the cigarettes calm you down?	4.2 (2.0)	4.2 (1.9)
Did smoking the cigarettes make you feel more awake?	2.4 (1.9)	2.5 (1.9)
Did smoking the cigarettes make you feel more irritable?	4.0 (2.0)	3.9 (2.0)
Did smoking the cigarettes help you concentrate?	3.3 (2.1)	3.1 (2.1)
Did smoking the cigarettes reduce your hunger for food?	2.6 (2.0)	2.5 (2.0)
Average score	3.3 (1.5)	3.2 (1.5)
Aversion		
Did smoking the cigarettes make you less dizzy?	2.5 (2.0)	2.5 (2.0)
Did smoking the cigarettes make you nauseous?	1.5 (1.2)	1.5 (1.3)
Average score	2.0 (1.2)	2.0 (1.3)
Enjoyment of respiratory tract sensations		
Did you enjoy the sensation in your throat and chest?	2.9 (2.0)	3.0 (2.0)
Craving reduction		
Did smoking the cigarettes immediately relieve your craving for a cigarette?	4.8 (2.0)	4.7 (2.1)

SD: standard deviation. [a]Those participants in the intervention group who were using the VLNC cigarettes ± nicotine replacement therapy (NRT) during the 6-week study period, and answered the modified Cigarette Evaluation Questionnaire (mCEQ) at both 3 and 6 weeks. Each scale is 1–7, where: 1 is 'not at all', 2 is 'very little', 3 is 'a little', 4 is 'moderately', 5 is 'a lot', 6 is 'quite a lot' and 7 is 'extremely'.

Table 5 Mean amount of nicotine replacement therapy (NRT) used over time in abstainers.

Time-period	Mean NRT used in mg/day (SD)	Median	P-value[a]
Three weeks			
Intervention (n = 231)	15.3 (12.2)	21	0.89
Usual care (n = 195)	15.6 (12.5)	21	
Six weeks			
Intervention (n = 231)	11.7 (11.9)	11	0.87
Usual care (n = 195)	11.7 (13.1)	6	
Three months			
Intervention (n = 231)	3.2 (7.5)	0	0.15
Usual care (n = 195)	4.4 (8.3)	0	
Six months			
Intervention (n = 231)	2.1 (5.9)	0	0.83
Usual care (n = 195)	1.6 (5.0)	0	

SD: standard deviation. [a]From Wilcoxon's Mann–Whitney U-test.

not differ significantly between each group from baseline to 6 weeks. Participants who were abstinent at 6 months were asked about their use of non-NRT methods of cessation during the trial—four participants in the intervention arm had used another pharmaceutical intervention (namely bupropion, nortriptyline or varenicline) compared to nine in the usual care arm. A further 11 participants in the intervention arm compared to nine in the usual care arm had used a non-pharmaceutical cessation intervention; namely, Allan Carr, hypnosis, exercise, alternative medicine, sweets, 'cold turkey', psychological support or nicotine-free e-cigarettes.

There was no significant difference in the occurrence of serious adverse events between the intervention group (36 events in 36 participants, 5·1%) and usual care group (35 events in 35 participants, 5.0%, incidence rate ratio = 1.04, 95% CI: 0.65, 1·65, P = 0.9). Injuries to the body (eight versus four events) and mental and behavioural disorders (two versus no events) were more common in the intervention group than the usual care group, while in the usual care group more gastrointestinal events (four versus seven events) and symptoms and signs (one versus six events) occurred. All other events were similar in both groups. There were two deaths, one in each group, both due to cancer.

Data on concomitant medication and cost-related outcomes will be presented in subsequent publications.

DISCUSSION

This is the largest trial conducted to date that explores the combined effect of VLNC cigarettes and usual Quitline care (NRT and behavioural support) on short- and

long-term abstinence rates in people motivated to quit. A clear increase in quit rates over usual Quitline care was found, with a positive impact on time to relapse and high participant acceptability. In abstainers, NRT use was similar in both groups and very few participants used non-trial cessation interventions during the study period, adding weight to the strong effect of the VLNC cigarettes, particularly within the first 3 weeks of quitting. This finding suggests that VLNC cigarettes may be associated not only with extinction, but may provide a coping mechanism to get through the initial stages of abstinence by replacing some of the conditioned rituals associated with smoking, such as the hand-to-mouth action, the tactile action of puffing on a cigarette and the sensation of smoke in the mouth and throat [1]. Although not tested directly in the present study, the activity of other psychoactive substances in tobacco smoke that may strengthen nicotine dependence (such as acetaldehyde [2] or monoamine oxidase inhibitors [3]) may also play a role. There was no evidence of any excess adverse events in the intervention group.

One of the strengths of this study is that it was conducted in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, was well-powered and outcome assessments were undertaken by researchers blind to treatment allocation. The study population was similar to Quitline callers and NZ smokers as a whole [24,25]. The trial had broad entry criteria, helping to ensure the generalizability of the findings. This generalizability is supported by the fact that the primary outcome was consistent, irrespective of the subgroups investigated. A number of limitations should be acknowledged. First, we did not verify self-reported abstinence biochemically, due to limited success with our previous cessation trials [17,26], and that attempts to validate quit status in population studies may introduce a selection bias unrelated to participants' smoking status [27]. Secondly, the study population drew upon a population that underrepresents Asian, Pacific Island, male, older and more dependent smokers [28], and Quitline callers may be more ready to quit than smokers identified from other sources [29]. Thirdly, the results of the *post-hoc* analyses should be interpreted with caution due to the potential for bias [30,31]. Fourthly, no definition of having 'smoked VLNC cigarettes' was provided to participants, thus we were unable to differentiate between participants who had had a few puffs, smoked only one to two cigarettes or smoked a larger number of the study cigarettes. Finally, some may question whether people increased puff frequency and intensity when smoking the VLNC cigarettes in an effort to maintain the desired level of nicotine [32]. Although compensatory smoking was not measured we feel it was unlikely, given the extremely low level of nicotine present in the study cigarettes and the

concomitant provision of NRT. Becker *et al.* reported no compensatory smoking in the treatment group in their trial who received combination Quest 3 and NRT [4].

This trial provides strong evidence for the combined use of VLNC cigarettes, NRT and behavioural support as an effective smoking cessation strategy, and supports previous findings from the three smaller trials that investigated the use of RNCs in combination with NRT [4–6]. We observed no difference in the effect of the intervention according to specific subgroups, despite Becker *et al.* reporting that tapered use of Quest cigarettes and NRT had a greater effect on continuous abstinence at 4 weeks for women than for men [4]. Previous research has also shown that RNCs can suppress the signs and symptoms of nicotine withdrawal [7,27,33–37] and craving [7,33–37], due possibly to the automatic and non-automatic processes of drug-seeking behaviour and the non-nicotine components of tobacco smoke. We found no such effect in this trial when withdrawal and craving were measured using the MPSS, possibly because the time-points at which we measured these symptoms may have been too far into the period of abstinence. However, the use of the VLNC cigarettes resulted in a moderate effect on calming people and reducing irritability and craving when measured using the mCEQ, due possibly to the behavioural components of smoking cigarettes or to nicotine effects. When smoking a VLNC cigarette there is still sufficient nicotine to occupy, on average, 26% of the main nicotine acetylcholine receptors in the brain 3.1 hours after smoking, with occupancy likely to be higher immediately after smoking [38]. However, the low level of nicotine is insufficient to release dopamine, and thus there is little effect on smoking satisfaction [39]. The mCEQ was not asked at baseline, and thus we are unable to say how participants in the intervention group rated their level of satisfaction and craving reduction with the VLNC cigarettes compared to their regular brand. The lack of any significant difference in adverse events between the two groups in this trial has also been noted in earlier trials of RNCs [9], and contrasts with *in-vivo* research which postulated that RNCs may increase the risk of harm as 'cigarette nicotine modulates platelet activation *in vivo* in smokers' and therefore may 'moderate the risk of cardiovascular disease caused by non-nicotine smoke components' [40].

Complete cessation of all tobacco products confers the greatest health benefit to the individual. However, among smokers for whom safer smoking cessation interventions are contraindicated or have been tried unsuccessfully, our findings indicate that the use of a short course of VLNC cigarettes combined with NRT and behavioural support may be an option worth pursuing. Furthermore, the trial findings add weight to the idea of a stepped reduction in the nicotine content of cigarettes [41,42], or to an

immediate and significant reduction of nicotine to a level where no compensation occurs [42], as a means to end smoking at a population level.

Clinical trial registration

This trial is registered with the Australasian Clinical Trials Network: number ACTRN12608000410358.

Declarations of interest

All authors declare that: (i) no authors have received support from any companies for the submitted work; (ii) C.B. and H.M. have previously undertaken research on behalf of NicoNovum, but prior to the purchase of the company by R. J. Reynolds. H.M. has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. N.W. has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications. M.G. has provided consultancy to the manufacturers of smoking cessation medications; (iii) their spouses, partners or children have no financial relationships that may be relevant to the submitted work; and (iv) all authors have no non-financial interests that may be relevant to the submitted work. The VLNC cigarettes used in the trial were purchased from Vector Group Ltd, Miami, FL, USA. The tobacco company had no role in development of the study design, data collection, data analysis, data interpretation or writing of the publication.

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