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Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial

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ABSTRACT

Background Smoking cessation was examined among a subset of current smokers who were high-risk participants in the UK Lung Cancer Screening (UKLS) pilot trial of low-dose CT screening.

Methods High-risk individuals aged 50–75 years who completed baseline questionnaires were randomised to CT screening (intervention) or usual care (no screening control). Smoking habit was determined at baseline using self-report. Smokers were asked whether they had quit smoking since joining UKLS at short-term follow-up (2 weeks after baseline scan results or control assignment) and longer-term follow-up (up to 2 years after recruitment). Intention to treat (ITT) regression analyses were undertaken, adjusting for baseline lung cancer distress, trial site and sociodemographic variables.

Results Of a total of 4055 individuals randomised to CT screening or control, 1546 were baseline smokers (787 control, 759 intervention). Smoking cessation rates were 5% (control n=36/786) versus 10% (intervention n=75/758) at 2 weeks and 10% (control n=79/775) versus 15% (intervention n=115/749) at up to 2 years follow-up. ITT analyses indicated that the odds of quitting among screened participants were significantly higher in the short term (adjusted OR (aOR) 2.38, 95% CI 1.56 to 3.64, p<0.001) and longer term (aOR 1.60, 95% CI 1.17 to 2.18, p=0.003) compared with control. Intervention participants who needed additional clinical investigation were more likely to quit in the longer term than the control group (aOR 2.29, 95% CI 1.62 to 3.22, p=0.007) and those receiving a negative result (aOR 2.43, 95% CI 1.54 to 3.84, p<0.001).

Conclusion CT lung cancer screening for high-risk participants offers a teachable moment for smoking cessation, especially among those who receive a positive scan result. Further behavioural research is needed to evaluate optimal strategies for integrating smoking cessation intervention with stratified lung cancer screening.

INTRODUCTION

Smoking is the leading cause of preventable morbidity and premature mortality worldwide.¹ In the UK, an estimated 86% of lung cancer cases are attributable to smoking.² The prevalence of cigarette smoking in the UK remained relatively stable between 2006 and 2014 at approximately 10 million adults (~20%),³ and although these rates are much lower than those of the 1970s, this

Key messages

What is the key question?

What is the effect on smoking cessation of taking part in the UK randomised pilot trial of low dose CT lung screening?

What is the bottom line?

CT lung cancer screening does not appear to falsely reassure smokers or reduce their motivation to stop smoking.

Why read on?

For clinicians and policy makers who are considering implementation of risk-stratified lung cancer screening, this study adds to evidence suggesting that integrating CT screening with evidence-based smoking cessation interventions could prompt quitting in motivated high-risk smokers.

declining trend has begun to plateau.⁴ The association between cigarette smoking and socioeconomic group is well established, with higher smoking rates among people living in more deprived areas.⁵

Trials have been undertaken to ascertain the effectiveness of low-dose CT screening for the earlier detection of lung cancer in high-risk groups including smokers.^{6–9} The impact of CT lung screening on smoking cessation and abstinence has been examined in response to concerns that taking part in lung screening may offer a ‘license to smoke’, especially for smokers who receive favourable screening results.¹⁰ Evidence from controlled trials, however, suggests that participating in lung screening significantly increases smoking cessation rates overall compared with the general population, and that receiving a positive CT screening result may provide an additional cue to action in prompting cessation. The Danish Lung Cancer Screening Trial (DLCST) reported smoking cessation rates of almost 12% in both trial arms at 1 year follow-up, compared with the Danish population rate of 4%.¹¹ Quit rate was significantly higher in smokers who had a positive CT result that required repeat scans.¹¹ In the Dutch-Belgian NELSON trial, the overall quit rate at 2 years follow-up was 16.6% compared with a background population rate of 3–7%. Although a lower prolonged abstinence rate was observed in the screened arm (14.5%) versus



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control (19.1%), this effect disappeared following intention to treat analysis, suggesting an overall positive effect of trial participation.¹² A non-significant trend towards increased smoking cessation was seen in those with multiple indeterminate screening results.¹³ The US National Lung Screening Trial (NLST)¹⁴ found that, compared with normal lung screening results, receiving any screen-detected abnormality significantly reduced the probability of continued smoking.

In addition to the moderating effect of lung screening results, sociodemographic predictors of increased likelihood of smoking cessation have been observed in previous lung cancer screening studies. These have included older age,^{11 14 15} higher socioeconomic group,¹⁴ higher education,¹² being married¹⁴ and lower nicotine dependency.^{11 14} In addition, participants with higher levels of concern about lung cancer and greater perceived benefits of stopping smoking,¹⁰ and those who intend to stop smoking,^{11 12} are more likely to quit in the context of lung cancer screening.

The UK Lung Cancer Screening (UKLS) pilot trial is the first to assess the feasibility, cost-effectiveness and psychosocial impact of lung cancer screening using a single low-dose CT screen versus no screening in a UK high-risk population.^{9 16} The current study builds on previous UKLS reports by examining the behavioural effects of trial participation and modifying variables on smoking cessation at short-term and long-term follow-up. It was expected that screened participants, and in particular those receiving positive CT results, would be more likely to report quitting compared with control arm participants.

METHODS

Participants and procedures

A random sample of 247354 individuals aged 50–75 years residing in six recruitment areas in the UK (Liverpool, Knowsley and Sefton; Cambridgeshire, Peterborough and Bedfordshire) were sent trial information packs that included a self-report questionnaire regarding lung cancer risk factors. From the questionnaire responders, 8729 patients were identified as at high risk of lung cancer ($\geq 5\%$ over 5 years) using the Liverpool Lung Project (LLP_{v2}) risk prediction model which includes age, sex, family history of lung cancer, smoking duration, personal history of other cancers and non-malignant respiratory diseases, and exposure to asbestos.⁹ Characteristics of trial non-participants are reported elsewhere.^{17 18}

Following completion of a second questionnaire to identify trial eligibility, those meeting the criteria were invited to attend their local recruitment centre in Liverpool or Cambridge (trial sites). High-risk individuals who gave informed written consent were randomised on a 1:1 ratio to the intervention (screening) or control arms. Randomisation used unique random personal ID codes and computer-generated sequencing for allocation concealment.⁹ Participants who self-reported smoking in the first questionnaire were eligible for inclusion in the current analyses. Participants in both trial arms were offered standard smoking cessation advice leaflets and given a list of local NHS Stop Smoking services pre-randomisation.

Participants completed a touchscreen questionnaire that included baseline psychosocial measures (T_0). A second psychosocial questionnaire (T_1) was sent approximately 2 weeks after receiving either a letter of assignment to the control group or a baseline CT scan result letter (intervention arm). T_2 psychosocial questionnaires were sent in a single mailshot during January 2014.

Measures

Smoking status was calculated at T_0 based on self-report data within the first UKLS questionnaire. Participants were categorised into current smokers, ex-smokers and never smokers.

Smoking cessation was assessed using self-report at T_1 and T_2 . Participants were asked whether they had quit smoking since joining UKLS, with response options 'yes', 'no', 'no but I intend to quit smoking within the next 6 months', 'not applicable' (ie, not a smoker at baseline). Participants who responded 'no' or 'no, but intend to quit' were categorised as non-quitters. Those who responded 'not applicable' or who returned the questionnaire but missed out the smoking cessation question were categorised as non-completers.

Lung cancer distress was measured using six items adapted from Lerman *et al*¹⁹ and Watson *et al*²⁰ to assess the frequency of lung cancer-related thoughts and their impact on mood and daily functioning. Total score range was 6–24, with a score above 12.5 corresponding to a clinically significant threshold score on the General Health Questionnaire-28.²¹

Sociodemographic variables (age and gender) were obtained from medical records. Socioeconomic group was measured using Index of Multiple Deprivation (IMD) ranks calculated from postcodes and categorised into standard deprivation quintiles (quintile 1 = most deprived, quintile 5 = least deprived). Marital group and experience of lung cancer (self and/or close others) were included in the T_0 questionnaire.

Screening results

Baseline CT scan results in the intervention arm included negative (normal) results, those requiring a repeat scan in 3 or 12 months, those requiring referral to the multidisciplinary team due to a major lung abnormality and significant incidental findings (such as aortic aneurysms and pneumonia but with no findings suspicious for lung cancer).

Statistical analysis

Analyses were conducted using Stata V.14. Following descriptive analyses to examine baseline equivalence of trial arms, the baseline characteristics of smokers who did and did not complete follow-up questionnaires were compared using chi-squared and independent t-tests. Participants who did not answer the smoking cessation question at T_1 or T_2 were imputed as smokers and included in the primary analysis of intervention effect using the intention to treat (ITT) population, in accordance with the Russell Standard for reporting smoking cessation trials.²² Complete case analyses were also conducted using univariable logistic regression models fitted to the smoking cessation outcome data at T_1 and T_2 independently with an inverse probability weighting.²³ Additionally, as a secondary analysis to adjust for confounders, multivariable logistic regression models were fitted to evaluate the impact of trial allocation on smoking cessation at T_1 and T_2 adjusting for T_0 (baseline) lung cancer distress, sociodemographic factors (gender, age group, marital group, deprivation quintile, experience of lung cancer) and trial site.¹⁶ Odds ratios (ORs) and adjusted ORs (aORs) with 95% CIs and p values are presented. Due to multiple testing, $p < 0.01$ was used to denote statistical significance.

To investigate the effect of the baseline scan result on smoking cessation, we summarised intervention arm participants into those who had a scan leading to additional clinical investigation (including repeat scan, major abnormality and incidental findings) and those receiving a negative result (ie, not requiring further investigation). Participants randomised to the control

group were used as the reference category in order to reflect current practice. The impact of additional clinical investigation on smoking cessation at T_1 and T_2 was analysed using univariable and multivariable logistic regression in the ITT and complete case populations. Lung cancer distress, sociodemographic factors and trial site were included in multivariable analysis.

Further subgroup analyses were carried out within the intervention arm only, involving additional univariable regression analyses to examine T_1 and T_2 smoking cessation in those receiving additional clinical investigation compared with a negative result as the reference category. We carried out this analysis to reflect a potential national policy where participants receive routine lung screening.

RESULTS

Trial participation

In total, 4061 individuals (5% of 75 958 responders to the risk questionnaire; 47% of all high-risk positive responders) attended the recruitment clinic and consented to participate.²⁴ As shown in figure 1, 4055 trial participants were randomised (n=2028 CT intervention, n=2027 control). In the subset of smokers who were included in the study, 759 (49%) were in the intervention arm and 787 (51%) were in the control arm. Characteristics of the smokers split by trial arm are provided in table 1, and indicate equivalence of groups in baseline sociodemographic and psychological characteristics.

Among smokers who were sent questionnaires, the completion rate at T_1 (2 weeks follow-up) was n=527/758 (70%) for the intervention arm and n=479/786 (61%) for the control arm, giving a total T_1 sample of n=1006. The completion rate at T_2 (up to 2 years follow-up) was n=488/749 (65%) for the screening arm and n=377/775 (49%) for the control arm (total T_2 n=865) (see figure 1).

Factors associated with non-completion

Baseline smokers in the control arm and those with experience of lung cancer were significantly less likely than those in the intervention arm to complete T_1 questionnaires (see online Supplementary table 1). Trial site, age, gender, marital group, deprivation and T_0 lung cancer distress were not statistically significantly associated with T_1 completion.

T_2 questionnaire completion was significantly lower among baseline smokers in the control arm and those recruited at the Liverpool site, in the most deprived quintile and with experience of lung cancer. Age, marital group, gender and baseline distress were not statistically significantly associated with T_2 completion (see online Supplementary table 2).

Effect of trial allocation on T_1 and T_2 smoking cessation

Primary ITT and complete case analyses are summarised in table 2. After imputing missing data as smokers in the primary ITT analysis, within the screening arm 75/758 (10%) quit smoking at T_1 and there were 527 eligible responders. In the control arm, 36/786 (5%) participants quit smoking at T_1 and there were 479 eligible responders. T_1 smoking cessation was statistically significantly higher in screened individuals compared with controls (OR 2.29, 95% CI 1.52 to 3.45, $p<0.001$), and remained statistically significant after adjusting for T_0 distress and all other covariates (aOR 2.38, 95% CI 1.56 to 3.64, $p=0.001$). Complete case analysis confirmed that T_1 smoking cessation was statistically significantly higher in the intervention group (aOR 2.09, 95% CI 1.36 to 3.23, $p<0.001$). Effects of covariates on T_1

smoking cessation are included in online Supplementary table 3 (ITT analysis).

At T_2 , 115/749 (15%) participants quit smoking and 488 returned the questionnaire in the screening arm. There were 79/775 (10%) individuals who quit in the control arm and 377 eligible responses at T_2 (see table 2). The effect of trial arm on quitting smoking at T_2 was statistically significant in the crude ITT analysis (OR 1.60, 95% CI 1.18 to 2.17, $p=0.003$) and after adjusting for covariates (aOR 1.60, 95% CI 1.17 to 2.18, $p=0.003$). In complete case analysis, the difference in cessation rate between the intervention and control groups at T_2 was not statistically significant (aOR 1.16, 95% CI 0.65 to 1.33, $p=0.36$), therefore these findings should be interpreted with caution. The influence of covariates on longer term smoking outcomes in ITT analysis are included in online Supplementary table 4.

Impact of additional clinical investigation on smoking cessation

As shown in table 3, T_1 smoking cessation was reported by 16% (48/299) of participants who had additional clinical investigation following the baseline scan result and 11% (26/227) who received a negative result. These were both compared with 8% (36/479) who reported T_1 smoking cessation in the control group. Using the imputed population, the impact of needing additional clinical investigation on T_1 smoking cessation was statistically significant in univariable (OR 2.72, 95% CI 1.73 to 4.26, $p<0.001$) and multivariable (aOR 2.85, 95% CI 1.79 to 4.53, $p<0.001$) analysis. The effect of receiving a negative result on T_1 smoking cessation was not significant at the 1% significance level in the univariable (OR 1.73, 95% CI 1.02 to 2.91, $p=0.04$) and multivariable (aOR 1.78, 95% CI 1.04 to 3.05, $p=0.03$) analysis. Similar findings were observed in complete case analysis for both T_1 comparisons.

At T_2 , 30% (83/275) of participants who received additional clinical investigation following the baseline scan result and 15% (32/212) who had negative results reported cessation. These were compared with 21% (79/377) in the control group who reported quitting at T_2 . There was a statistically significant effect of additional clinical investigation on T_2 smoking cessation in univariable (OR 2.24, 95% CI 1.60 to 3.14, $p<0.001$) and multivariable (aOR 2.29, 95% CI 1.62 to 3.22, $p<0.001$) ITT analysis. The effect of a negative result on T_2 smoking cessation was not significant in univariable (OR 0.92, 95% CI 0.60 to 1.42, $p=0.71$) and multivariable (aOR 0.90, 95% CI 0.58 to 1.40, $p=0.64$) analysis; however, caution is needed when interpreting these findings. Similar results were observed in complete case analysis (see table 3).

Subgroup analyses in the intervention group only

At T_1 there was no statistically significant effect of needing additional clinical investigation on smoking cessation compared with receiving a negative result (aOR 1.60, 95% CI 0.96 to 2.67, $p=0.07$). At T_2 there was a clear effect on smoking cessation of additional clinical investigation compared with a negative result (aOR 2.57, 95% CI 1.64 to 4.03, $p<0.001$). Similar results were found in complete case analysis (results not shown).

DISCUSSION

Tobacco control is the major primary prevention option for lung cancer. The present study is the first to report the behavioural impact of CT screening in a UK high-risk population, and confirms the findings of previous trials that lung cancer screening does not falsely reassure smokers or reduce their motivation to

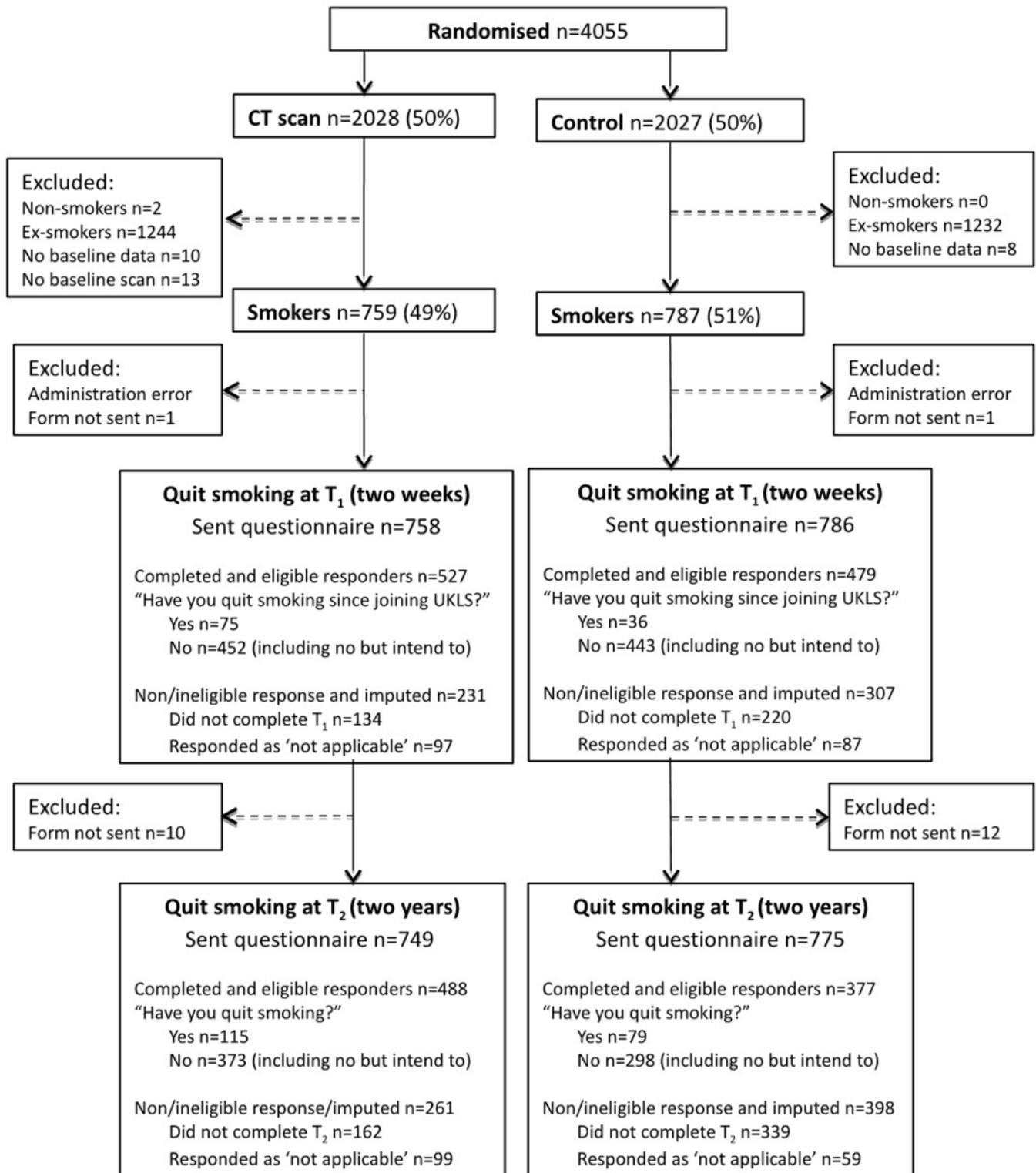


Figure 1 Trial CONSORT (Consolidated Standards of Reporting Trials) diagram.

stop smoking. Using the imputed population, the short-term quit rate of 10% among screened participants was higher than the background cessation rate in the general UK population (4%),^{25 26} with the longer term quit rate of 15% similar to that reported in the Dutch-Belgian NELSON trial¹² and higher than the DLCST trial.¹¹ Participating in the UKLS appeared to prompt smoking cessation overall, with a differential and positive effect of lung screening at short-term and longer-term follow-up.

While a degree of caution is needed due to imputation of missing responders as smokers,²² the present findings indicate that smoking cessation was higher in the intervention arm and that engaging in CT lung cancer screening increased the likelihood of stopping smoking in the longer term. Despite concerns about a negative lung screen offering a 'license to smoke',¹⁰ there was no evidence that UKLS screening participants who received an all-clear CT result were less likely to quit. Analysis indicated

Table 1 Sample characteristics

		Not recorded (missing)	CT Scan (n=759) n (%) or mean (SD)	Control (n=787) n (%) or mean (SD)
Site	Liverpool		425 (56%)	431 (55%)
	Cambridge		334 (44%)	356 (45%)
Age (years)			66.7 (4.10)	66.3 (4.3)
Gender	Male		532 (70%)	551 (70%)
	Female		227 (30%)	236 (30%)
Marital group	Married/cohabiting	3	502 (66%)	519 (66%)
	Not married/cohabiting		256 (34%)	266 (34%)
IMD	Quintile 1 (most deprived)		265 (35%)	265 (34%)
	Quintile 2		93 (12%)	97 (12%)
	Quintile 3		128 (17%)	125 (16%)
	Quintile 4		108 (14%)	136 (17%)
	Quintile 5 (least deprived)		165 (22%)	164 (21%)
Lung cancer experience	No	4	442 (58%)	433 (55%)
	Yes		315 (42%)	352 (45%)
Cancer distress (T ₀)*			2.23 (0.30)	2.24 (0.30)
			<i>9.86 (3.08)</i>	<i>9.72 (2.99)</i>

Percentages were calculated based on available data.

*Log_n scores in normal text, original scores in italics (analyses performed using log_n scores).

IMD, Index of Multiple Deprivation.

that a positive CT scan result prompted smoking cessation in the longer term compared with participants who were not screened and participants who received a negative scan, suggesting that a positive lung screening result may provide an additional stimulus for quitting over and above that of screening participation. This mirrors the findings of other controlled trials including the DLCST¹¹ and US NLST,¹⁴ where smokers with identified abnormalities were more likely to stop smoking than those with normal results.

The current evidence suggests that an integrated package of CT lung screening and smoking cessation support has the potential to expedite quitting in smokers who are motivated and receptive. The voluntary nature of the trial meant that smokers who took part were self-selected and may already have been contemplating quitting.²⁷ It is difficult, therefore, to directly attribute smoking cessation to UKLS participation, although Ostroff *et al*¹⁰ reported that smokers who quit after CT lung screening ascribed their decision to screening participation. In the current trial we observed a marginal trend towards higher baseline distress in those who reported quitting in the short term (see supplementary materials), which suggests that experiencing a degree of concern about lung cancer may be necessary to galvanise smoking cessation. However, we did not directly

assess baseline quit intentions, and future evaluations of CT lung screening would therefore benefit from examining the influence of both mood and smoking-related cognitions on behavioural outcomes.

The limitations of sample size and study design are acknowledged. The UKLS trial was not specifically designed to test the effects of lung screening combined with smoking cessation support, hence the types of stop-smoking interventions accepted by participants were not recorded, nor were comparative data available on cessation rates in the Liverpool and Papworth regions during the life of the trial. It was not possible to ascertain the moderating role of nicotine dependence or biochemically validate self-reported smoking behaviour, therefore the current findings should be interpreted cautiously due to the sole use of self-reported cessation. Nevertheless, the present study adds to growing evidence that integrating CT lung screening with evidence-based smoking cessation interventions could prompt quitting in motivated high-risk smokers. While our sample was not sufficiently large to examine continued smoking abstinence in those who reported quitting at short-term follow-up, the NELSON trial indicated that combining low-dose CT screening with smoking cessation advice led to sustained abstinence.¹² Most smokers enrolling in CT lung screening studies are motivated

Table 2 Effect of trial allocation on smoking cessation at T₁ (2 weeks) and T₂ (2 years) follow-up

Time point	Analysis population	Quit smoking/total		Univariable OR (95% CI)	Multivariable OR [‡] (95% CI)
		CT scan (n=759)	Control (n=787)		
T ₁ (2 weeks)	Primary ITT*	75/758 (10%)†	36/786 (5%)†	2.29 (1.52 to 3.45)	2.38 (1.56 to 3.64)
	complete case	75/527 (14%)	36/479 (8%)	2.04 (1.34 to 3.10)	2.09 (1.36 to 3.23)
T ₂ (2 years)	Primary ITT* complete case	115/749 (15%)†	79/775 (10%)†	1.60 (1.18 to 2.17)	1.60 (1.17 to 2.18)
		115/488 (24%)	79/377 (21%)	1.16 (0.84 to 1.61)	1.16 (0.65 to 1.33)

*Primary intention to treat (ITT) analysis using the imputed population. Where no data were available on smoking status at follow-up, the participant was assumed to be smoking.

†Participants were excluded due to administrative error: T₁ CT scan (n=1); T₁ control (n=1); T₂ CT scan (n=10); T₂ control (n=12).

‡Adjusted for T₀ cancer distress, recruitment site, gender, age, marital group, deprivation and experience of lung cancer.

Table 3 Impact of baseline scan result on smoking cessation at T₁ (2 weeks) and T₂ (2 years) follow-up

Baseline scan result		Quit smoking	Total	Univariable OR (95% CI)	Multivariable OR [†] (95% CI)
ITT analysis*					
T ₁	Control group	36	786	Reference	Reference
	Negative result‡	26	340	1.73 (1.02 to 2.91)	1.78 (1.04 to 3.05)
	Additional investigation‡	48	416	2.72 (1.73 to 4.26)	2.85 (1.79 to 4.53)
T ₂	Control group	79	775	Reference	Reference
	Negative result‡	32	338	0.92 (0.60 to 1.42)	0.90 (0.58 to 1.40)
	Additional investigation‡	83	409	2.24 (1.60 to 3.14)	2.29 (1.62 to 3.22)
Complete case analysis					
T ₁	Control group	36	479	Reference	Reference
	Negative result	26	227	1.59 (0.94 to 2.71)	1.61 (0.93 to 2.77)
	Additional investigation‡	48	299	2.35 (1.49 to 3.72)	2.46 (1.53 to 3.96)
T ₂	Control group	79	377	Reference	Reference
	Negative result	32	212	0.67 (0.43 to 1.05)	0.65 (0.41 to 1.04)
	Additional investigation‡	83	275	1.63 (1.14 to 2.33)	1.66 (1.15 to 2.39)

*Primary intention to treat (ITT) analysis using the imputed population.

†Adjusted for T₀ cancer distress, recruitment site, gender, age, marital group, deprivation and experience of lung cancer.

‡One participant removed due to protocol deviation.

to quit, therefore it will be critical to evaluate actual quit rates prompted by screening, and whether they are maintained over time in the context of a lung screening health service. We found that longer term study retention was less likely in smokers who were from socioeconomically deprived areas and who had experience of lung cancer. Evidence from other studies suggests that these high-risk groups may be deterred from lung screening due to fearful and fatalistic beliefs about lung cancer outcomes,^{28–30} stigma and scepticism about the benefits of screening.^{31–33} The consistent association between smoking, deprivation and lower screening uptake is a problem for public health that must be addressed in future lung screening.

Implementation of a UK national lung cancer screening programme for high-risk groups offers opportunities for smoking cessation at multiple points in the screening process, from the initial screening invitation to CT scanning and disclosure of results.¹⁰ Smoking cessation counselling combined with pharmacotherapy is effective,^{34–36} and could be successfully implemented in the lung screening setting.³⁷ However, further behavioural research is needed to identify ways of engaging harder to reach smokers, and to robustly test the optimal type and timing of strategies for delivering stop-smoking support to high-risk participants. Successful integration of evidence-based strategies for smoking cessation with stratified lung cancer screening could be a prudent use of limited healthcare resources, translating into major health benefits for all smoking-related diseases.

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Contributors KB: trial conception and design, data analysis, data interpretation, manuscript preparation; BC: trial statistician, statistical analysis, data interpretation, manuscript review; KJL: data collection, data analysis, data interpretation, manuscript review; OB: data analysis and interpretation, manuscript review; AD: radiological

review, data interpretation and manuscript review; DRB - trial design, UK Lung Cancer Screening (UKLS) care pathway, data interpretation, manuscript review; SD: trial design, data interpretation, manuscript review; JFK: trial conception and design, data interpretation, manuscript review.

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Competing interests None declared.

Ethics approval Ethical approval for the study was given by Liverpool Central Research Ethics Committee in December 2010 (reference number 10/H1005/74). All UKLS participants provided informed consent before taking part. The trial was registered with the International Standard Randomised Controlled Trial Register (ISRCTN) under the reference 78513845.

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