UK National Screening Committee

Screening for lung cancer in individuals at increased risk

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by the Office for Health Improvement and Disparities (OHID).

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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Plain English summary

Lung cancer is an important cause of death worldwide. In 2017 there were about 48,000 people who were diagnosed with lung cancer and about 35,000 people who died from the disease in the UK. Lung cancer is more common in older people over the age of 60. Lung cancer in men is decreasing whilst lung cancer in women is increasing. However currently there are still more men that develop lung cancer than women. People who smoke tobacco are more likely to develop lung cancer than those who do not smoke. People who have lung cancer are often diagnosed late when it is difficult to cure. This is because they may not have any symptoms that they are concerned about so do not visit their doctor.

The aim of a lung cancer screening programme is to find people with the disease early when they may not have any symptoms. People are more likely to be cured of lung cancer if the disease is found early before it has spread to other parts of the body.

The UK NSC last looked at screening for lung cancer in adults in 2006. The UK NSC decided not to recommend screening. There was little evidence that screening the general population would be beneficial.

This evidence summary looks at new evidence about lung cancer published up to June 2021. There are 5 questions; questions 1, 2 and 3 are contextual questions providing an overview for a lung cancer screening programme:

- question 1 is about the risk factors that make it more likely some people will develop lung cancer and the number of people diagnosed in the UK
- question 2 is about how to choose the right people to be screened and how well the lung cancer screening test works
- question 3 is about how much screening will cost compared to the health benefits of screening

Questions 4 and 5 are key review questions with systematic searches for evidence:

- question 4 is about whether lung cancer screening reduces the number of people who die from the disease and if we can diagnose it earlier. We also want to know what the harms are from lung cancer screening
- question 5 is about the views of health professionals and people who might be invited for screening

This evidence summary found that there was a lot of evidence about lung cancer screening for older people who had smoked for many years. In this group of people lung cancer screening reduced the number of people who died from the disease. If people did have

cancer when they were screened they were more likely to have it diagnosed early when it could be cured.

There was evidence that there are some people who will be harmed because of lung cancer screening. This includes people whose screen shows they have might have cancer but further tests show that they don't have it or that they have a different condition. Being screened and further tests may cause short term unnecessary anxiety and distress. Some further tests may also have side effects, cause further problems and be painful. It was difficult to understand how much harm was due to screening because the studies we looked at were carried out in different ways. It is not yet clear how best to set up a lung cancer screening programme which would save the most lives and do the least harm.

There was evidence that people thought lung cancer screening was a good idea. In studies that invited people to come for lung cancer screening about half the people attended. There were no studies about whether people who had a positive test result would be keen to have further tests and then treatment for lung cancer.

Some studies asked health professionals what they thought about lung cancer screening. Many thought it was a good idea but wanted evidence about how and why it worked. They also wanted to be sure they had enough guidance and funding to be able to make it work well.

This evidence summary showed that there are still some questions about lung cancer screening that need to be answered. Researchers are exploring the best way to screen for lung cancer. These plans should be tested with an implementation study with the aim of answering the remaining questions about lung cancer screening.

Executive summary

Purpose of the review

This document reviews the evidence about screening for lung cancer for adults at increased risk of developing the condition against the UK National Screening Committee (NSC) criteria about the harms, benefits and acceptability of a screening programme using rapid review methodology. The document also provides a narrative overview about the natural history of lung cancer, the accuracy of lung cancer screening tests and the cost effectiveness of a potential lung cancer screening programme.

Background

There is a high prevalence, morbidity and mortality of lung cancer in the UK. Around 35,000 people die and 48,000 people are diagnosed with lung cancer each year. It has one of the lowest survival rates of all cancers with 16.2% of people living beyond 5 years and 9.5% living beyond 10 years. These outcomes are largely attributed to lung cancer being diagnosed at a late stage when treatment is much less likely to be effective. Over recent years there has been considerable research in the form of cohort studies, randomised controlled trials and pilot studies to test whether screening for lung cancer is feasible. The role of lung cancer screening would be to detect the condition early with the use of low dose computed tomography (LDCT). Early detection and treatment of lung cancer is more likely to be effective than treating later once symptoms have developed.

Focus of the review

This evidence summary about lung cancer screening is organised around 3 contextual questions and 2 key questions. The contextual questions were addressed using a targeted search and narrative review methodology with no quality appraisal while the key questions were addressed using a systematic search and rapid review methodology.

1. Contextual question: What factors increase the risk of lung cancer? What is the incidence, prevalence and mortality of lung cancer by risk groups, and what are the trends in the risk factors over time? (UK NSC criterion 1)
2. Contextual question: What is the accuracy of risk assessment algorithms and/or low dose computed tomography (LDCT) to predict/detect lung cancer? (UK NSC criterion 4)
3. Contextual question: What is the cost effectiveness of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk, compared with no

screening? What is the cost effectiveness of different strategies using LDCT screening (e.g. different intervals, use of risk algorithm, etc.)? (UK NSC criterion 14)

4. Review question: What is the clinical effectiveness of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk, compared with no screening? (UK NSC criteria 11 and 13)
    - sub- question: What is the clinical effectiveness of different strategies using LDCT screening (e.g. different intervals, use of risk algorithm, etc.)?
5. Review question: What is the acceptability of screening programmes for lung cancer using LDCT in individuals at increased risk? (UK NSC criterion12).

The search for evidence for review questions 4 and 5 about the harms and benefits of screening and acceptability of a lung cancer screening programme included relevant studies to May 2021 and June 2021 respectively.

Recommendation under review

Systematic population screening for lung cancer is not currently recommended in the UK. The UK NSC last reviewed lung cancer screening in 2006, concluding that there was insufficient evidence, particularly as there were no completed randomised controlled trials (RCTs), that screening would be effective at improving outcomes for people with the condition. There was also limited evidence of an available test which would be suitable for use in a screening programme. With the increase in volume and quality of evidence from numerous RCTs with long term follow up, it is now important to consider the most recent evidence for a potential screening programme. The aim of this evidence summary is to update and summarise the evidence on key areas relating to screening for lung cancer.

Findings and gaps in the evidence

Contextual questions

Contextual question 1 concerns the epidemiology of lung cancer and drew heavily on the most recent data published from the UK cancer registries about the prevalence, incidence, mortality and risk factors associated with developing lung cancer.

The risk of developing lung cancer is largely attributable to age and smoking status with the incidence and mortality rates highest in older age groups of both men and women who are current or former smokers. Lung cancer rates are highest in men but are decreasing year on year whereas rates are increasing year on year in women but are still lower than in men. Across all age groups lung cancer incidence and mortality are a third higher in men than women. Smoking is estimated to cause 72% of lung cancer cases and 86% of lung cancer

deaths. Other factors such as air pollution, occupational exposure to inhaled carcinogens, and pre-existing lung conditions also increase the risk of developing lung cancer but not to the same degree. The increased risk associated with factors such as ethnicity, socioeconomic status, country of residence and gender may well be a proxy for the smoking behaviour within each of those populations. There is estimated to be an approximately thirty-year lag time between smoking prevalence and lung cancer rates, so current rates of lung cancer largely reflect patterns of cigarette smoking in the 1990's.

Contextual question 2 is about the accuracy of risk algorithms to identify people to be invited for lung cancer screening and the definition of a positive result following the screening test of a LDCT scan. There are a range of risk algorithms incorporating different factors predicting lung cancer risk from between a year to 9 years for smokers, former smokers and people who have never smoked and people in all age groups. The most accurate risk prediction algorithms can correctly predict the people who will develop lung cancer from those who will not, over 80% of the time. Only a few of the risk algorithms have been used in lung cancer screening RCTs. Therefore, risk algorithms have not yet been tested extensively in comparable groups who have and have not been invited for screening to evaluate outcomes. Rather than risk algorithms, most lung cancer screening RCTs have used a range of eligibility criteria based on smoking status and age to identify those who should be invited for screening. In addition to differences in eligibility criteria there are differences in the number of screening rounds, the intervals between rounds and the threshold for a positive test in RCTs that have published LDCT accuracy results. Despite this, most studies reported a sensitivity of over 80% and specificity over 75% with negative predictive values of over 95%. However, positive predictive value varied significantly (3.3% to 43.5%) across RCTs which may well be due to these differences in screening strategy.

Contextual question 3 focusses on the cost effectiveness of screening for lung cancer with LDCT. Overall, regardless of screening strategy LDCT was reported to be more effective but more costly than no screening. Some studies reported cost per Quality Adjusted Life Years (QALYs) for lung cancer screening with LDCT as between £10,000-20,000/QALY; the cost effectiveness threshold applied to UK interventions. For example, in the UK cost per QALY for annual screening of adults aged 55 to 74 years with a 6 year lung cancer risk of 1.15% was £10,069. However, there is such a wide variation in Incremental Cost Effectiveness Ratios (ICERs) (£2835 to £149,400) across strategies that without a better understanding of the sources of variation there could be little confidence that this level of cost effectiveness could be reliably demonstrated in further studies and in practice.

Key questions

Clinical effectiveness of lung cancer screening

Key question 4 concerns the clinical effectiveness of lung cancer screening programmes using LDCT in individuals at increased risk of developing the condition. Evidence from 9 RCTs with long term follow up, particularly 2 large, fair to good quality RCTs, suggest screening people at high risk of lung cancer with LDCT can reduce lung cancer mortality but it is less clear whether there is an improvement in all cause mortality. These results have been confirmed in meta-analyses. The RCTS also showed that screening identified people at an earlier stage of lung cancer when treatment is more effective, compared to people who had no screening and were diagnosed with lung cancer.

There are also harms associated with lung cancer screening including a substantial number of people who will receive a false positive result leading to unnecessary tests and invasive procedures which may lead to adverse events. Other harms include overdiagnosis, incidental findings and short term anxiety and distress. Across the studies there was a substantial heterogeneity of factors related to outcomes including lung screening eligibility criteria, threshold for a positive screen, round length, number of rounds of screening, follow up period and definition of significant incidental findings. This has led to some inconsistency in findings and leads to uncertainty about the approach which would be the most clinically effective to reduce mortality and morbidity from lung cancer screening whilst reducing possible harms to a minimum.

Acceptability of lung cancer screening

Key question 5 relates to the acceptability of a lung cancer screening programme to the public, patients and health professionals in the UK. On balance, the evidence base suggests that there is acceptance for the lung cancer screening test and that about half of people invited may take up the offer to participate. For example, 2 UK trials inviting people for a lung health check that incorporated an LDCT screen reported uptake of 46.5% and 52.5%. In qualitative studies reporting the response of people to hypothetical scenarios, a high proportion of people also expressed an intention to take up the offer of screening. Acceptance by professionals is predicated on reassurance about the evidence for the harms and benefits of lung cancer screening in tandem with the right resources and guidance. Larger good quality studies would improve the consistency of the evidence base for the UK population. Evidence about the acceptance of the full screening pathway including the diagnostic work up and treatment or management of lung cancer is also needed.

Evidence and uncertainties about lung cancer screening

The 9 RCTs identified that have examined the clinical effectiveness of lung cancer screening have been the predominate source of information for both review questions about lung cancer screening clinical effectiveness, the balance of harms and benefits of screening and the acceptability of lung cancer screening to public, patients and health professionals. All the RCTs focussed on the population with the factors that contribute the most risk in developing lung cancer; older people and current or former smokers.

The multiple articles published by the 9 RCTs has resulted in a high volume of generally fair to good quality evidence. However, due to differences in screening strategy including lung screening eligibility criteria, threshold for a positive screen, round length, number of rounds of screening, follow up period and definition of significant incidental findings, there is substantial heterogeneity of outcomes.

Review question 4 focusses on identifying evidence about 2 UK NSC criteria; 11 and 13. The volume, quality and direction of new evidence addressing criterion 11 concerning the effectiveness of lung cancer screening to reduce mortality and morbidity is sufficient to ensure that this criterion is met. The volume, quality and direction of evidence addressing criterion 13 concerning the harms and benefits of a lung cancer screening programme is sufficient to understand that there are clear harms of overdiagnosis, high false positive rates, and short term anxiety and distress experienced by people who participate in screening. However, the balance of these harms compared to benefits is uncertain due to the heterogeneity of screening strategies employed by RCTs. The evidence base addressing criterion 13 is therefore met for volume, applicability and quality of the evidence but unmet for consistency of findings.

Review question 5 focusses on identifying evidence about UK NSC criterion 12 concerning the acceptability of the full screening programme including the public, patients and health professionals. The volume, quality and applicability of the evidence is sufficient to understand that on balance people, patients and professionals are likely to consider lung cancer screening to be beneficial. However, there was limited evidence concerning the acceptability of the full screening pathway including diagnostic work up and treatment of lung cancer for those people who test positive. The evidence base addressing criterion 12 is therefore met for volume, applicability and quality of the evidence but unmet for consistency of findings.

Recommendations and implications for research

To address the uncertainty about the best approach to achieve maximum clinical effectiveness in reducing mortality and morbidity from lung cancer screening whilst reducing possible harms to a minimum, this review recommends further work incorporating the results of a modelling exercise which is currently underway. This modelling work will update the health economic analysis by Snowsill et al (2018)[1] and be used to estimate the clinical effectiveness and cost effectiveness of different lung cancer screening strategies including the population (age and smoking history), screening intervals, lung cancer risk thresholds and CT scanning schedules. Assuming screening is found to be cost effective, further studies would be helpful to understand shorter term outcomes, for example those relating to feasibility and acceptability. Studies with these aims might be considered as part of an implementation strategy, the prioritisation of research questions and the design of which should be discussed and planned with stakeholders in these areas.

Limitations

This rapid review process was conducted over a condensed period of time. Studies not available in the English language, abstracts and poster presentations, were not included.

Due to the fast moving pace of this field of research, evidence about lung cancer screening is published frequently. This has meant that articles published after the systematic search was carried out have not been included in review questions 4 and 5. Abstracts of 3 known and important articles were reviewed to rapidly assess if their conclusions varied from those of the studies included in this review. The abstracts reviewed were from:

- Field et al (2021)[2] – presenting the lung cancer mortality, and cancer stage distribution outcomes of the UKLS RCT at 7.3 years follow up. This showed a non significant reduction in lung cancer mortality. The same article reports a meta analysis of 9 RCTs with a 16% relative reduction in lung cancer mortality in the LDCT arm versus the non LDCT control arm (risk ratio 0.84; 95% CI 0.76 – 0.92).
- Hunger et al (2021)[3] – a meta analysis of 8 RCTs reporting a 12% relative reduction in lung cancer mortality in the LDCT arm compared to a non LDCT control arm (RR =0.88; 95% CI 0.79-0.97). Between 4% to 24% of scans were classified as positive with 84% to 96% false positive. Overdiagnosis rates were estimated as between 19% and 69% of diagnosed lung cancers.
- Passiglia et al (2021)[4] – a meta analysis of 9 RCTs reporting a 20% relative reduction in lung cancer mortality in the LDCT arm compared to a non LDCT control arm (RR 0.87 ;95% CI 0.78 – 0.98). There was a non significant reduction in all cause mortality. Significantly more cancers in the LDCT arm were diagnosed at an early stage compared to a non LDCT control arm (RR 2.84 95% CI 1.76 – 4.58) and

significantly fewer cancers were diagnosed in the LDCT arm compared to the non LDCT control arm at a late stage (RR0.75; 95% CI 0.68 – 0.83). There was a significant increase in overdiagnosis rates (38%; 95% CI 14 – 63).

The results of these particular article abstracts do not change the direction of the conclusions and recommendations of this review. In addition to these articles there may be others that have been published after the search date of this review which haven't come to the reviewers attention which could only be determined with a further systematic search of the literature.

Introduction and approach

Background

There is a high prevalence of, and morbidity and mortality from, lung cancer in the UK. Around 35,000 people die and 48,000 people are diagnosed with lung cancer each year (Cancer Research UK)[5]. Lung cancer has one of the lowest survival rate of all cancers with 16.2% of people living beyond 5 years and 9.5% living beyond 10 years (Office for National Statistics 2019)[6]. These outcomes are largely attributed to lung cancer being diagnosed at a late stage when treatment is much less likely to be effective[7]. Symptoms of lung cancer vary from person to person and include a persistent cough, breathlessness, fatigue and weight loss which may not concern patients until they become severe[7]. In 2016 around a quarter of all lung cancer diagnoses in England were made following emergency presentation to an accident and emergency department and a third overall were made following an emergency referral from a health service provider[5]. Of those presenting through an emergency route 72% were likely to be diagnosed with late stage lung cancer compared to 45% if diagnosed following GP referral[5]. Many people do not have any noticeable symptoms of lung cancer in the early stages of the condition and in recent years there has been considerable research in the form of cohort studies, RCTs and pilot studies and systematic reviews and meta-analyses of these, to test whether screening for lung cancer is effective and feasible (Jonas et al 2021)[8]. The role of lung cancer screening would be to detect the condition early when treatment is more likely to be effective.

Systematic population screening for lung cancer is not currently recommended in the UK. The UK NSC last reviewed lung cancer screening in 2006, concluding that there was insufficient evidence, particularly as there were no completed RCTs, that screening would be effective at improving outcomes for people with the condition. There was also limited evidence of an available test which would be suitable for use in a screening programme. With the increase in volume and quality of evidence from numerous RCTs with long term follow up reported it is now important to consider the most recent evidence for a potential screening programme. The aim of this evidence summary is to update and summarise the evidence on key areas relating to screening for lung cancer.

Focus of the review

This report is divided in 2 parts: a narrative review looking at 3 contextual questions using a targeted search and narrative review methodology with no quality appraisal, and an evidence summary looking at 2 key questions using a systematic search and rapid review methodology in accordance with the UK NSC evidence review process.

Contextual questions:

1. What factors increase the risk of lung cancer? What is the incidence, prevalence and mortality of lung cancer by risk groups, and what are the trends in the risk factors over time? (UK NSC criterion 1)
2. What is the accuracy of risk assessment algorithms and/or low dose computed tomography to predict/detect lung cancer? (UK NSC criterion 4)
3. What is the cost effectiveness of screening programmes for the detection of lung cancer using low dose computed tomography in individuals at increased risk, compared with no screening? What is the cost effectiveness of different strategies using low dose computed tomography screening (e.g. different intervals, use of risk algorithm, etc.)? (UK NSC criterion 14)

The evidence summary

4. Review question: What is the clinical effectiveness of screening programmes for the detection of lung cancer using low dose computed tomography in individuals at increased risk, compared with no screening? (UK NSC Criteria 11 and 13)
    a. Sub- question: What is the clinical effectiveness of different strategies using low dose computed tomography screening (e.g. different intervals, use of risk algorithm, etc.)?
5. Review question: What is the acceptability of screening programmes for lung cancer using low dose computed tomography in individuals at increased risk? (UK NSC criterion 12).

Evidence summary

Objectives

The current evidence summary aims to look at the clinical effectiveness and acceptability to professionals and the public of screening for lung cancer for individuals at increased risk.

Table 1. Key review questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key review questions	Studies Included
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.	What is the clinical effectiveness of screening programmes for the detection of lung cancer using low dose computed tomography in individuals at increased risk, compared with no screening?	3 systematic reviews and meta analyses plus 25 additional papers relating to RCTs reported in the 3 systematic reviews and meta-analyses
13	The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.	Sub- question: What is the clinical effectiveness of different strategies using low dose computed tomography screening (e.g. different intervals, use of risk algorithm, etc.)?	
12	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	What is the acceptability of screening programmes for lung cancer using low dose computed tomography in individuals at increased risk?	10

Methods

The current evidence summary was conducted by Solutions for Public Health (SPH), in keeping with the UK National Screening Committee evidence review process. To identify studies relevant to each of the key review questions detailed in Table 1, database searches were conducted on 7th May 2021 for question 4 and 7th June 2021 for question 5 (Appendix 1).

For question 4 about the clinical effectiveness of lung cancer screening and the balance of benefits and harms, the evidence for studies aimed at current and former smokers was considered separately from evidence about lung cancer screening for other risk factors.

For evidence about lung cancer screening for current and former smokers, systematic reviews and meta analyses of RCTs that included the NELSON trial were sought and the original peer reviewed publications from the RCTs considered. For other risk groups systematic reviews and meta-analyses of RCTs and RCTs alone were sought.

The results of the search for question 4 informed the search strategy for question 5. Prior to the search for evidence for question 4 it was clear the results would identify lung screening studies of current and former smokers but unclear if published evidence about groups with

other risk factors would be identified. The presence or absence of clinical effectiveness studies about lung cancer screening for people with risk factors other than smoking in the search for question 4 determined whether we specified those groups in the search for question 5 about acceptability.

Eligibility for inclusion in the evidence summary

The following review process was followed:

1. Each title and abstract was reviewed against the inclusion/exclusion criteria by 1 reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured
2. Full-text articles required for the full-text review stage were acquired
3. Each full-text article was reviewed against the inclusion/exclusion criteria by 1 reviewer, who determined whether the article was relevant to 1 or more of the review questions
4. Any queries at the abstract or full-text stage were resolved through discussion with a second reviewer
5. The review was quality assured by a second senior reviewer, not involved with the writing of the review in accordance with SPH's quality assurance process.

Eligibility criteria for each question are presented in Table 2 below.

A total of 987 unique references were identified and sifted for potential relevance to the review. Overall, 90 studies were identified as possibly relevant during title and abstract sifting and further assessed at full text. Appendix 2 contains a full PRISMA flow diagram (Figure 5), along with the tables of the included publications for each question (Table 43 and 44).

Table 2. Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria						Exclusion criteria
	Population	**Target condition**	**Intervention**	**Comparator**	**Outcome**	**Study type**	
What is the clinical effectiveness of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk, compared with no screening?	Adults (50 and over) without confirmed or suspected lung cancer but who are at increased risk of lung cancer, as defined by authors e.g. ever-smokers, occupational hazards, family history, etc. Studies from the UK and comparable countries. Report results overall and by important sub-groups e.g. ethnicity, socioeconomic status (SES),	Lung cancer	Screening programmes using low dose computed tomography (LDCT) (any type of LDCT) for the prevention of lung cancer in individuals at increased risk. Where algorithms were used please clarify whether they have been validated in the UK.	No screening Chest x-ray screening	• lung cancer mortality • all-cause mortality • incidence of lung cancer and other morbidity outcomes • cancer stage at diagnosis • quality of life • number of incidental findings and effectiveness of programme on their mortality, morbidity and quality of life • adverse side effects from a screening test, diagnostic test, and treatment, including overdiagnosis and false positive and negative results, false reassurance, anxiety	For smokers: Systematic reviews and meta-analyses of RCTs that include the NELSON trial. Please include the systematic reviews as well as all the original papers for the trials that were included in each systematic review. For other risk groups: systematic reviews and meta-analyses of RCTs and RCTs alone	For smokers: systematic reviews and meta analyses excluded if they did not include the NELSON trial and were published before 2020 For non smokers: systematic reviews, meta analyses and RCTs excluded if published before 2006

	sex, where possible				(including from uncertain findings) • number needed to screen • number needed to treat • smoking cessation		
What is the acceptability of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk?	Individuals who were or would be invited to screening, professionals including respiratory physicians and public health professionals, general population. Report results overall and by important sub-groups e.g. ethnicity, SES, sex, where possible. Studies from the UK, if no studies are found in the UK then include studies from comparable countries.	Lung cancer	Screening programmes for the prevention of lung cancer using LDCT. Results of question 4 determined that the patient group should only include current and former smokers.	Any or none, as reported by the authors	Acceptability of a lung cancer screening programme, including but not limited to: • uptake of screening, diagnosis, treatment • adherence to treatment • user experience (e.g. anxiety)	Any study design including: Qualitative studies (e.g. surveys, interviews) RCTs Systematic reviews of the above	N/A

Appraisal for quality/risk of bias tool

The critical appraisal tools published by the Joanna Briggs Institute (JBI)[9] were used to assess the quality and risk of bias for each study included in the review. These included:

- JBI for Systematic reviews
- JBI for RCTs
- JBI for Cross sectional studies
- JBI for Qualitative studies

Results of the quality assessments are presented in the summary and appraisal of individual studies in Appendix 3.

Databases/sources searched

Systematic searches of 4 databases were conducted to identify studies relevant to the review detailed in Table 2. The databases searched for both questions were, Medline, Embase and the Cochrane Library. For question 4, PubMed was also searched whilst for question 5 PsychINFO was also included.

The searches were conducted on 7th May 2021 for question 4 and June 7th for question 5 and the search strategies are presented in Appendix 1.

The contextual questions were addressed using a targeted search approach using key words in the Trip Medical database, google scholar and relevant publications from the searches for questions 4 and 5.

Contextual questions

Contextual question 1. What factors increase the risk of lung cancer? What is the incidence, prevalence and mortality of lung cancer by risk groups, and what are the trends in the risk factors over time (UK NSC criterion 1)?

Lung cancer screening was previously considered by the UK NSC in 2006 and the condition described as a major public health problem exacerbated by late presentation of symptoms to health services and short survival times.

Overview of lung cancer risk factors, incidence, prevalence and mortality

Routine registry data collected about cancers in the UK, reported by Cancer Research UK[5] and the Office for National Statistics (2019)[6] show lung cancer is the third most common cancer in the UK, with almost 48,000 new cases diagnosed in 2017. It is the leading cause of death due to cancer with 35,137 deaths in 2016-18. The estimated lifetime risk of being diagnosed with lung cancer is 1 in 13 (8%) for males, and 1 in 15 (7%) for females born after 1960 in the UK[5]. Late diagnosis of lung cancer increases mortality risk resulting in one of the worst 5 and 10 year survival rates for any cancer[6]. Data for 2013-2017 in England show 16.2% of people diagnosed with lung cancer survived for 5 years or more dropping to 9.5% surviving over 10 years[6].

An overview of the evidence by CRUK[5], the National Cancer Intelligence Network (2006)[10] and Turner et al (2020)[11] report the important risk factors in developing lung cancer. These are examined in turn below with data on the incidence, prevalence and mortality presented by risk groups with trends over time where available. These include:

- age and gender: the incidence of lung cancer is strongly related to age and is higher in males than females[5]
- UK country: the incidence and mortality of lung cancer varies between UK countries[5]
- socioeconomic status: increasing deprivation is strongly associated with increasing incidence and mortality of lung cancer[5]
- ethnicity: the incidence of lung cancer differs between ethnic groups in England[10]
- smoking: smoking is estimated to cause 72% of lung cancer cases[5]
- occupation: asbestos exposure is linked to an estimated 6%-8% of lung cancer deaths[5]
- air pollution: outdoor air pollution and particulate matter are recognised risk factors for lung cancer[11]

- family history and health status: a family history of lung cancer and certain diseases increase the risk of lung cancer[5].

Trends of incidence and mortality of lung cancer by age and gender

Lung cancer accounts for 13% of new cancer cases of cancer among both males and females, with 48% (23,087 cases) in females and 52% (24,881 cases) in males in 2017 in the UK[5]. The incidence of lung cancer rises steadily with age in both females and males (Figures 1 and 2). In the UK the highest incidence rates for females are those aged 80 to 84 years and for males, those aged 85 to 89 years[5]. In 2017 lung cancer incidence was 22% higher in males than females (89.1 vs 69.6 cases per 100,000)[5]. Overall, lung cancer incidence rates decreased by 8% in the UK between 1993-95 and 2015-17, but there were marked differences between males and females[5].

Rates in females increased by 31%, while rates in males decreased by 33%[5]. Incidence for older female age groups (from 50 years) increased by between 9% and 80% whilst in males, incidence for all age groups decreased by between 23% and 44% over the same 20 year period[5]. Cases in females aged over 80 years increased from 1993-95 (223.3 per 100,000) and were highest in 2012-2014 (328.4 per 100,000), then decreased with 2015-17 rates at 318.9 per 100,000[5].

Figure 1. European age-standardised incidence rates per 100,000 (females), by age, UK[5]

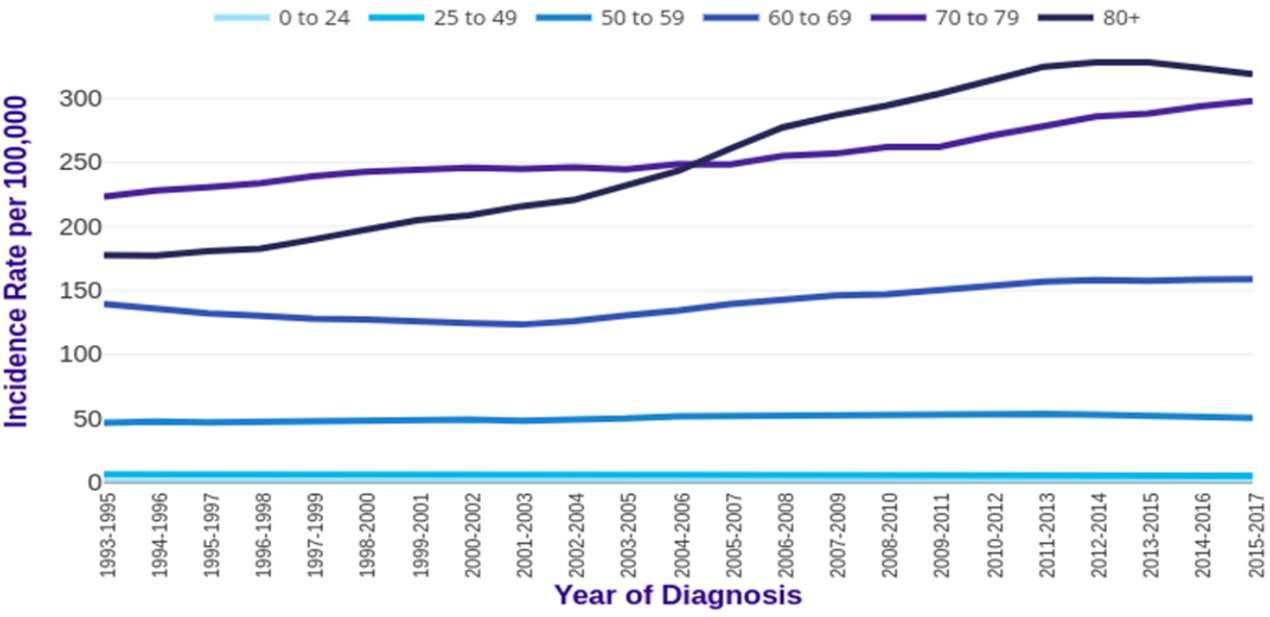
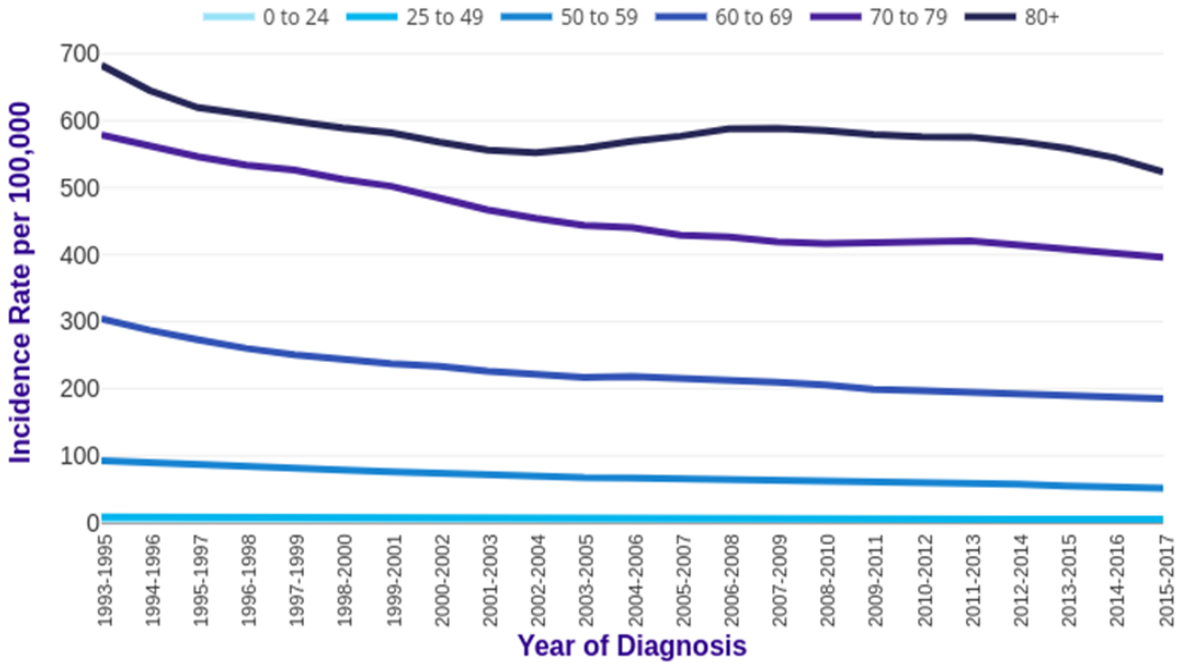
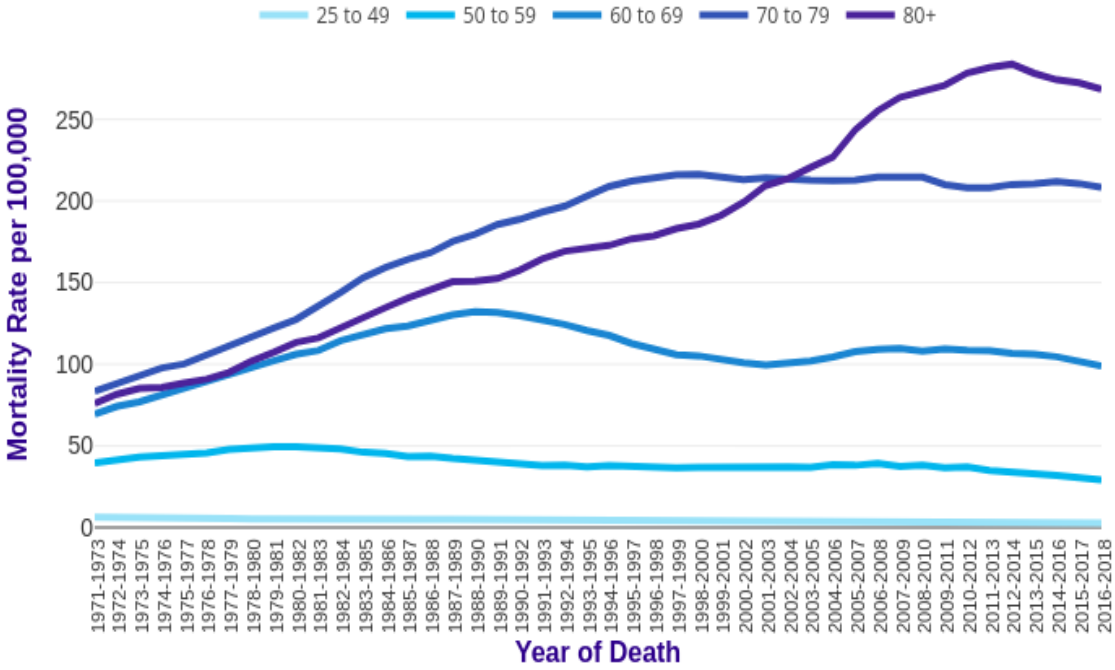


Figure 2. European age-standardised incidence per 100,000 (males) by age, UK[5]



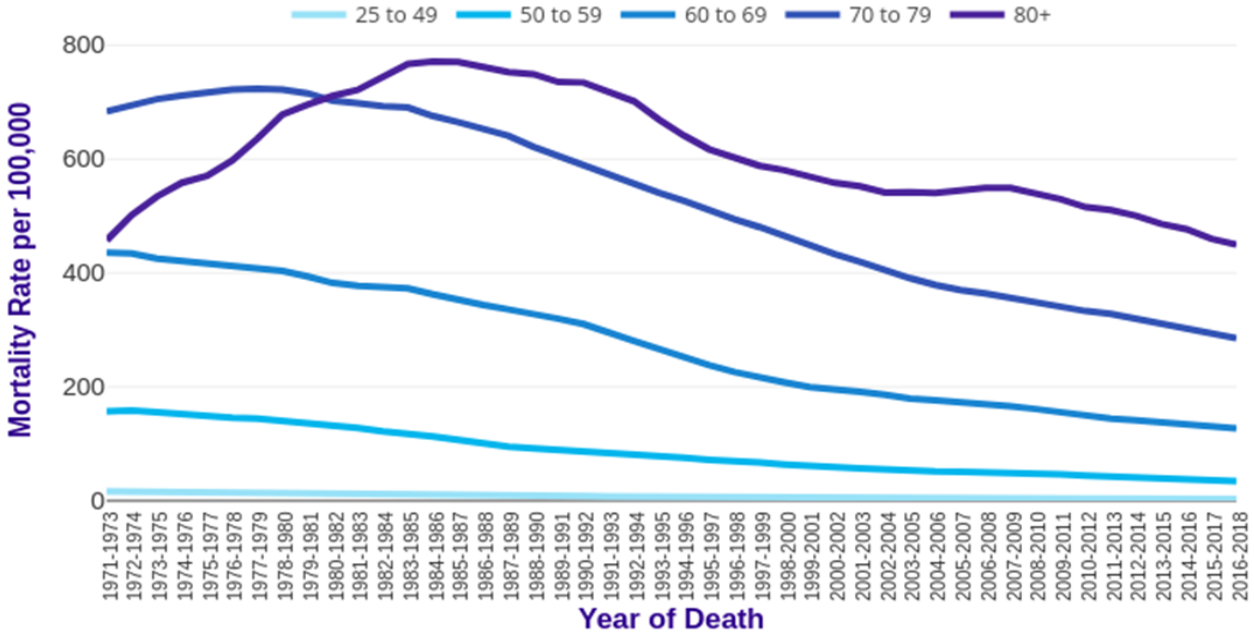
Lung cancer mortality rate shows a similar pattern to incidence when comparing males and females and the trend over time (Figures 3 and 4).

Figure 3. European age-standardised mortality per 100,000 (females), by age, UK[5]



Male cancer mortality is around a third higher than female cancer mortality but has consistently decreased by age group between 1993-1995 to 2016-18[5]. In females aged 70 to 79 years mortality rates were highest in 1998 to 2000 (216.1 per 100,000) then decreased gradually (208.2 per 100,000 in 2016-18) whilst rates in those aged over 80 years were highest in 2012-14 (283.8 per 100,000) followed by a decline (268.5 per 100,000 in 2016-18)[5].

Figure 4. European age-standardised mortality rates per 100,000 (males), by age, UK[5]



Lung cancer incidence and mortality by UK country

In 2017 the age-standardised incidence for females was lower in England and Wales than the UK average, and higher in Scotland than the UK average. For males, the rate was higher in both Scotland and Northern Ireland than the UK average (Table 3)[5]. The picture for mortality rates is similar with Scotland and Northern Ireland having the highest rates compared to the UK average for both males and females[5].

Table 3. Lung cancer incidence by gender and UK country[5]

	Lung cancer age-standardised incidence rate per 100,000 2017 (95%CI)		Lung cancer age-standardised mortality rate per 100,000 2018 (95%CI)	
	Female	Male	Female	Male
England	67.0(66.1-68.0)	86.9(85.7-88.1)	44.5(43.7-45.2)	63.6(62.5-64.6)
Scotland	95.7(92.1-99.3)	111.7(107.4-116.0)	68.2(65.2-71.2)	84.8(81.1-88.5)
Wales	67.1(63.2-70.9)	84.0(79.4-88.7)	49.2(45.9-52.4)	68.1(64.0-72.3)
Northern Ireland	69.2(63.7-74.8)	97.8(90.6-105.1)	53.8(49.0-58.6)	78.3(71.8-84.8)
UK	69.6(68.7-70.5)	89.1(88.0-90.2)	47.0(46.3-47.8)	65.9(65.0-66.9)

CI — Confidence intervals

Lung cancer incidence and mortality and socioeconomic status

Table 4 shows that incidence and mortality rates for both males and females are almost 3 times higher in the most deprived quintile of England compared with the least deprived quintile, with the largest increase between the fourth and fifth quintiles[5]. This translates to an estimated 6,571 excess cases of lung cancer in females and 7,760 excess cases in males per year in deprivation quintiles 2 to 5 compared with those in the least deprived quintile[5], which had an average number of 2,510 cases in females and 2,941 in males.

Table 4. Lung cancer incidence and mortality by gender and deprivation quintile, England[5]

	Lung cancer age-standardised incidence rate per 100,000, 2013-17 (average number of cases per year)		**Lung cancer average number excess cases per year**		**Lung cancer age-standardised mortality rate per 100,000, 2007-2011**	
Deprivation quintile*	Female	Male	Female excess cases	Male excess cases	Female	Male
1	41.8 (2510)	57.5 (2941)	0	0	18.6	29.6
2	50.9 (3159)	71.7 (3726)	555	754	22.9	36.1
3	62.3(3541)	87.5 (4082)	1137	1427	27.4	45.7
4	81.2(4007)	112.7 (4511)	1909	2250	36.3	59.1
5	114.6(4715)	153.9 (5202)	2970	3329	51.3	80.1

*1= least deprived

Lung cancer incidence and ethnicity

Registry data linked to hospital episode statistics in England was reported by the National Intelligence Cancer Network[10] and showed differences in the incidence of lung cancer between ethnic groups. The estimates in Table 5 are based on data from 2002-2006. The linkage between the 2 databases was not complete with 13% of patients unmatched between the databases and 11% of people with no recorded ethnicity. An upper and lower incidence range was calculated for each group by assigning people with unknown ethnicity in 3 different ways, first by assuming the missing cases were similarly distributed to the known cases, second by assuming all the missing cases were people of white ethnicity and thirdly assuming none of the missing cases were of white ethnicity. The age-standardised incidence rates in the white ethnic group ranged from 61.1 to 62.6 per 100,000 for males and 35.2 to 36.0 per 100,000 for females, and rates in all non-white ethnic groups were considerably lower than in the white ethnic group for both genders.

Table 5. Lung cancer incidence by gender and ethnic group, England[10]

	Lung cancer age-standardised incidence rate (range) per 100,000, 2002-06	
Ethnic group	Female	Male
White	35.2 to 36.0	61.1 to 62.6
Asian	6.9 to 12.4	23.1 to 37.2
Black	8.5 to 15.1	30.1 to 48.9
Chinese	10.7 to 25.5	22.4 to 48.6
Mixed	8.9 to 20.0	21.9 to 43.1

Smoking tobacco

It is estimated that 79% of lung cancer cases in the UK are preventable[5]. By far the biggest single cause of lung cancer is tobacco smoking, which is estimated to cause 72% of cases[5]. Other important risk factors and the proportions of cases they are estimated to cause are workplace exposures (13%), air pollution (8%) and ionising radiation (5%)[5].

Active tobacco smoking is estimated to cause 71% of cases leading to 86% of lung cancer deaths whilst 1% of cases are due to environmental tobacco smoke (also known as passive smoking and second-hand smoking)[5]. Parkin et al (2011)[12] modelled the likely attributable fraction of lung cancer deaths caused by smoking by comparing estimated rates in people who have never smoked with the number actually observed. In 2010, it was estimated that smoking caused around 19,000 cases of lung cancer in men and around 14,500 in women in the UK[12]. Lung cancer risk increased with both duration and amount of smoking, but duration had the larger impact and the risk was higher in those who started smoking at a younger age[12]. Risk of death due to lung cancer also increased with the number of cigarettes smoked per day; compared with people who have never smoked[12]. The risk increased from around 5 times higher in people who smoked 1–4 cigarettes a day to at least 24 times higher in people who smoked 25+ cigarettes per day and 39 times higher in people who smoked 42+ cigarettes a day[5].

There is estimated to be an approximately thirty-year lag time between smoking prevalence and lung cancer rates, the current epidemiology of lung cancer is largely dictated by historical patterns of cigarette smoking[13,14]. The Office for National Statistics (2021)[15] reported the trend analysis from the Annual Population Survey from 1974 to 2020. Figure 5 shows the male and female proportion of the population aged 16 and above who smoke from 1974 to 2020. Rates from 1974 to 1999 are unweighted and weighted from 2000 onwards.

Figure 5. Proportion of males and females in the population who smoke 1974 to 2020[15]

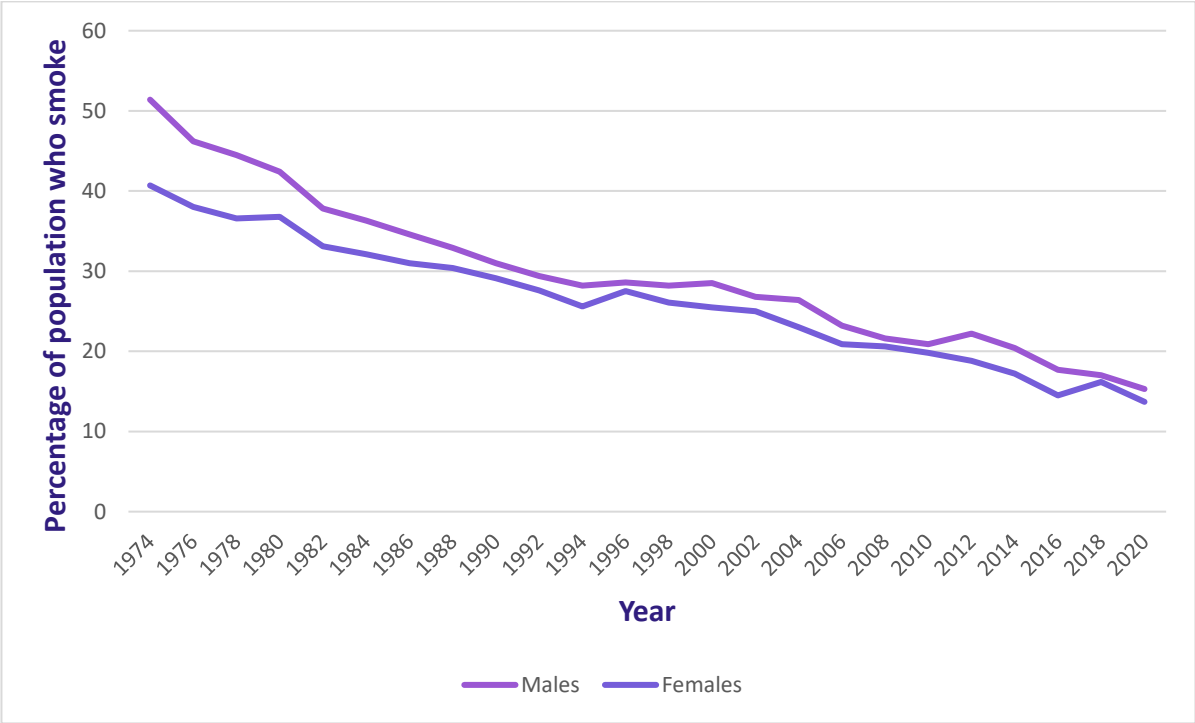


Table 6 shows that the proportion of smokers in the UK who were 16 and over halved from 30% in 1990 to 14.5% in 2020[15]. The proportion of males who smoked in 2020 was 15.3% and for females was 13.7%. Smoking prevalence is highest in those aged 25 to 34 years, at 18.1% (Table 6). The age group with the largest decline in smoking since 1990 are those aged over 60 for males (59%) and those aged 16 to 24 for females (60%) (Table 6).

Table 6. Smoking prevalence by age group and sex[15]

	All 1990	All 2020	Change	Female 1990	Female 2020	Females Change	Male 1990	Male 2020	Males Change
16-24	34.6	15.2	↓ 56%	35.7	14.4	↓ 60%	33.2	15.9	↓ 52%
25-34	35.2	18.1	↓ 49%	34.1	17.9	↓ 48%	36.3	18.4	↓ 49%
35-49	33.5	16.9	↓ 50%	32.8	15.1	↓ 54%	34.3	18.7	↓ 45%
50-59	28.5	16.3	↓ 43%	29.2	16.1	↓ 45%	27.8	16.4	↓ 41%
60 +	21.5	9.4	↓ 56%	19.5	9.1	↓ 53%	24.1	9.8	↓ 59%
All ≥16	30.0	14.5	↓ 47%	29.1	13.7	↓ 53%	31.0	15.3	↓51%

Other environmental risk factors for lung cancer

The single biggest occupational risk factor for lung cancer in the UK is asbestos exposure, which is linked to an estimated 6%-8% of lung cancer deaths each year and according to CRUK[5] increases lung cancer mortality by 77% compared with the general population.

There is also evidence of a synergistic effect between asbestos exposure and smoking; the combined effect of exposure to both increases the risk of lung cancer more than the sum of their individual effects[5]. Workplace asbestos exposure peaked in the early 1960s and has declined markedly since then partly due to the 1969 asbestos regulations that limited exposure to prevent the inhalation of asbestos fibres and banning the use of it in the late 1990s[5]. Other workplace exposures causing less than 1% of lung cancers combined include silica in glass manufacture, diesel engine exhaust and carcinogens handled by metal workers, printworkers, painters and those involved in pesticide production. Boffetta and Borron (2019)[16] also describe the evidence for a dose response association between arsenic exposure in drinking water and lung cancer.

Turner et al (2020)[11] described the wealth of evidence for the association of outdoor air pollution including nitrogen oxides, nitrogen dioxide, sulphur dioxide and particulate matter and lung cancer[11].The increase in lung cancer mortality with increasing concentrations of particulate matter has been found in both smokers and non-smokers[17], and is higher in people living near major roads[11].

It is estimated that 5% of lung cancer cases in the UK are caused by ionising radiation, including indoor exposure to radon[5]. Exposure to other forms of radiation such as treatment with radiotherapy also increases the risk of lung cancer, with approximately a 5-fold increase in the condition in patients treated for Hodgkin's lymphoma and a 23% increase in patients treated for breast cancer[8].

Family history and health status

A family history of lung cancer increases the risk of developing the condition, independent of smoking and other environmental risk factors, with an 82% higher risk in people whose sibling has had lung cancer, and 25%-37% higher risk in people whose parent has had the disease[5]. The increase in risk is greatest in those with first degree relatives (parents, siblings or children) affected, but there is still an increased risk in those with second or third degree relatives affected, although the risk is lower the more distant the relationship[18].

Lung cancer risk independent of smoking and other environmental factors is significantly increased in people with a history of pneumonia or tuberculosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, pulmonary fibrosis and emphysema[8,17,19,20,21,22].

Summary

The risk of developing lung cancer is largely attributable to age and smoking status. Other factors such as air pollution, occupational exposure to inhaled carcinogens, and pre-existing lung conditions also increase the risk of developing lung cancer but not to the same degree. The increased risk associated with factors such as ethnicity, socioeconomic status, country of residence and gender may well be a proxy for the smoking behaviour within each of those populations. There is estimated to be an approximately thirty-year lag time between smoking prevalence and lung cancer rates, so current rates of lung cancer largely reflect patterns of cigarette smoking in the 1990's.

Contextual question 2. What is the accuracy of risk assessment algorithms and/or low dose computed tomography to predict/detect lung cancer? (UK NSC criterion 4)

The UK NSC last considered evidence about a screening test for lung cancer in 2006, concluding that there was insufficient evidence that there was an available test which would be suitable for use in a screening programme.

Lung cancer screening RCTs have focussed on using the non-invasive medical imaging technique, LDCT, as the screening test for those at high risk of developing the condition. This involves a person lying still in a medical scanner and being exposed to low dose radiation to make detailed images of the lungs. The effective radiation dose of 1.5 millisieverts (mSv) per LDCT is estimated to be the equivalent to approximately 6 months natural background radiation[23] LDCT is a test accessible to most people however there will be a minority of those eligible for screening with some disabilities or claustrophobia who may find undertaking the test difficult.

This narrative summary explores the accuracy of lung cancer screening taking into account the eligible population, how they were recruited and how the results of the test are interpreted using different radiological image classification systems.

Overview of the accuracy of risk algorithms and low dose computed tomography (LDCT) for the detection of lung cancer

The effectiveness of a lung cancer screening strategy relies heavily on the factors that affect the accuracy of the screening programme to identify people at highest risk of developing lung cancer.

This question focuses on the accuracy of risk assessment algorithms to predict lung cancer, the inclusion of the factors that contribute most to the risk of developing lung cancer and the accuracy of LDCT in relation to the definition used to determine a positive test result.

The role of risk assessment algorithms in identifying the high risk population

Identifying the population at risk of developing lung cancer requires developing eligibility criteria in order to determine who would most benefit from being screened and having a method for inviting that group of people to participate in the screening programme.

The risk factors with the strongest association with lung cancer are older age and smoking status with other environmental and inheritable risk factors also contributing to the risk of developing the condition[17]. The most common approach used by RCTs and cohort studies

is to target people within a specified older age group, who are current or former smokers, with exposure to tobacco smoking defined as a minimum number of pack years or, if they are former smokers, abstinence for a maximum specified time period[8]. However, this approach of using only age and smoking status to select the lung screening eligible populations has led to some low risk people being screened and reductions in estimates of cost effectiveness[24]. In response, a range of risk prediction algorithms have been developed incorporating a wide range of other risk factors such as, gender, ethnicity, family history, body mass index, education, and other lung conditions to calculate the percentage risk of developing lung cancer over a particular time period[25]. These allow individual risk to be determined for each potentially eligible participant prior to a LDCT scan[25].

In practice, identifying the group of people who will be assessed for lung cancer risk by either eligibility criteria or a risk prediction algorithms has not been straightforward[26]. Age is likely to be the only lung cancer risk factor consistently recorded on population based datasets, although in the UK primary care practices also collect smoking status of patients. Lung cancer screening studies have used a staged approach to recruiting people; by inviting a broader population group to express an interest in screening followed by individual assessment of eligibility for the screening test of those who respond[26].

There are a range of ways that trials and pilot studies have recruited people for lung cancer screening. People have been invited to express an interest in screening by:

- mass media including posters, TV, newspaper and internet adverts and community outreach to churches, community groups and minority groups inviting people to contact the trial investigators[27]
- directly contacting people of a particular age using population based data with a questionnaire for people to complete[28]
- directly contacting people of a particular age and smoking status and inviting them for a scheduled lung health check appointment[29]

Once people have expressed an interest in screening, methods to further check eligibility include:

- self report questionnaire[28]
- telephone assessment[27]
- face to face assessment which may be a stand-alone appointment or as part of the lung health check[30]
- automatic scanning of questionnaire response to check against a risk prediction algorithm[29]

Table 7 outlines the methods of recruitment, eligibility criteria and invitation response in 9 lung cancer screening studies using LDCT, reported in a systematic review by Rankin et al (2020)[26].

Of the 9 trials reported by Rankin et al (2020)[26] 4 (ITALUNG, LUSI, NELSON, and UKLS) targeted specific age groups with direct mailing and reported a 24.9% to 39.9% response (Table 7). By contrast, the LSUT directly mailed current or recent former smokers in a specific age group with a pre-scheduled lung check appointment combined with prenotification reminders, resulting in a 52.6% response. A further 2 trials (DANTE and NLST) recruited participants by direct mail and mass media marketing but did not report the response rate whilst 2 other trials (DLCST and MILD) only used a mass media approach. Of the 4 trials targeting only particular age groups the proportion of people eligible for screening of those who responded, ranged from 4.9% to 20.5% which was in contrast to the 79.7% eligibility of those who responded to LSUT that targeted people of a particular age and smoking status with a pre-appointment letter[26].

Two UK studies (LSUT and UKLS) used risk prediction algorithms to determine who is eligible for LDCT whilst the other RCTs used age and smoking history as eligibility criteria[26]. The Liverpool Lung Project score (LLP) and the Prostate Lung Colorectal and Ovarian model (PLCO) was used by the LSUT) and the LLP version 2 (LLPv2) was used by the UK Lung Screening RCT (UKLS)[26].

Table 7. Lung screening trials recruitment method and response[26]

Trial Country	Method	LDCT eligibility criteria, pack years; years since quitting or lung cancer risk model	App	Resp	Eligible	Decl	Cons
DANTE Italy	Direct mail and mass media aimed at 60-74 yrs	≥20 pyrs; quit<10yrs	NR	2811	2532	0	2532
DLCST Denmark	Mass media aimed at people 50-70 yrs	≥20 pyrs;<10 yrs or quit after age 50yrs	N/A	5861	4443	339	4104
ITALUNG Italy	Direct mail aged 55-69yrs	≥20 pyrs in the last 10yrs; quit <10yrs	71,232	17,055	3206	0	3206
LSUT UK	Direct mail aged 60-75 yrs recorded as smoker from 2010	NLST criteria ≥ 30pyrs; quit ≤15 yrs or PLCO≥1.51% or LLPv2≥2.5%	2012	1058	844	74	770
LUSI Germany	Direct mail and mass media aimed at 50-69 yrs	≥25 yrs of 15 cigs/d or ≥30 pyrs of 10 cigs/d; quit <10yrs	292,440	95,797	4913	861	4052
MILD Italy	Mass media aimed at people 49-75yrs	≥20pyrs;quit<10yrs	N/A	5880	4099	0	4099
NELSON N'lands & Belgium	Direct mail aged 50-75 yrs	>15 cigs/d for >25 yrs or>10 cigs/d for>30 yrs; quit ≤10yrs	606,409	150,920	30,969	15,137	15,822

NLST US	Direct mail and Mass media aimed at people 55-74 yrs	≥30pyrs; quit ≤15yrs	N/A	53454	53439	953	52486
UKLS UK	Direct mail aged 50-75 yrs	Risk model; LLPv2≥2.5%	247,354	98,746	4868	807	4061

Abbreviations: App – Approached, cigs – Cigarettes, Cons – Consented, d – Day, Decl – Declined, LDCT – Low dose computed tomography, LLPv2 – Liverpool lung project version 2, N'lands – Netherlands, N – Number, N/A – Not applicable, NR – Not reported, pyrs – pack years, PLCO – Prostate Lung Colorectal and Ovarian model Resp – Response, US – United States, UK – United Kingdom, yrs – Years

Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LSUT – Lung Screening Uptake Trial, LUSI – Lung cancer Screening Intervention Trial, MILD - Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

The accuracy of risk prediction algorithms

Systematic reviews of lung cancer risk prediction algorithms by Tang et al (2019)[31] and Gray et al (2016)[25] have identified around 25 models developed since 2003. These have mostly been based on results of case control and cohort studies. Table 8 presents the information about 7 models or versions of models described by Gray et al (2016)[25] and developed in the UK or in other high income countries such as the US and the Netherlands. The models varied in whether they were applicable to all people or just older age groups, people of any smoking status or only with those who are former or current smokers[25]. Smoking history was considered by all the models. However, there was variation in whether pack years, smoking duration, smoking cessation age and duration, cigarettes smoked per day and exposure to environmental tobacco smoke, were taken into account[25]. Models also varied in whether they considered sex, family history of lung cancers, other lung cancer risk factors and personal characteristics such as BMI and ethnicity[25]. The models also varied in the timescale within which they predicted people would develop lung cancer ranging from 1 year to 10 years. The LLP, for example, predicts the percentage likelihood of developing lung cancer over a 5 year period whereas the PLCOM2012 uses a 6 year time horizon and Hoggart a year or less[25].

Gray et al (2016)[25] reported the area under the curve (AUC) of the lung cancer risk prediction models to distinguish between cases and controls. The AUC ranged from 0.59 to 0.86 indicating that different models correctly predicted the people who would develop lung cancer from those who will not between 59% and 86% of the time[25]. The PLCO, PLCOM2012, Hoggart and LLP models have reported the best AUC performance of over 0.80 (AUC of 0.86 and 0.81, 0.86 and 0.82 respectively)[25]. Extended versions of some models, for example the LLP and Spitz, have added genetic markers to the list of factors associated with an increased risk of lung cancer and it is hoped this change of focus may improve performance[25].

Table 8. Risk prediction models, variables included, applicability, length of time of predicted risk and performance[25]

	Applicability		Variables included						
Model	Applicable age yrs	Applicable smoking history	Sex	Smoking history	Family history	Exposure or lung condition	Other variables	Risk years	AUC
Bach	50-75	C, F Restricted to ≥30 py	Yes	Yes	No	Asbestos	None	1-10	0.66-0.72
Spitz	≥20	C, F, N	Yes	Yes	Yes	Asbestos, dust, hay fever, emphysema	None	≤1	0.59-0.67
LLP	40-80	C, F, N	Yes	Yes	Yes	Asbestos, pneumonia	PMT	5	0.67-0.82
LLPv2	40-80	C, F, N	Yes	Yes	Yes	Asbestos, pneumonia TB, COPD, emphysema	PMT	5	NR
PLCO	All	C, F, N	No	Yes	Yes	COPD	BMI	9	0.86
PLCO Ever	All	C, F	No	Yes	Yes	COPD	BMI, PMT ethnicity,	9	0.81
PLCOM 2012	All	C, F	No	Yes	Yes	COPD	BMI, PMT ethnicity Education	6	0.80
Hoggart	≥35	C, F	No	Yes	No	None	None	≤1	0.79-0.84

Abbreviations: AUC – Area under the curve, BMI – Body mass index, C – Current smokers, COPD – Chronic obstructive pulmonary disorder, F – Former smokers, LLP – Liverpool lung project model, LLPv2 – Liverpool lung project model version 2, N – Never smokers, PLCO – Prostate Lung colorectal and ovarian model, PLCOM2012 – Prostate Lung colorectal and ovarian model 2012 version, PMT – Previous malignant tumour, py – Pack years, TB – Tuberculosis, yrs – Years

In order to assess the benefit of using risk prediction models versus eligibility criteria, the systematic review by Jonas et al (2021)[8] reported studies that compared the application of different risk prediction models to baseline data from the large US National Lung Cancer Trial (NLST) with the original eligibility criteria. Typically, the results were similar between the models and the trial. The PLCOM2012 was applied to the NLST data, using 3 risk thresholds to estimate the 1.3%, 1.51% and 2.19% chance of developing lung cancer in the next 6 years. The number needed to screen to prevent 1 lung cancer death was 222, 207 and 169 respectively, in comparison with 203 reported by the NLST RCT[8]. Jonas et al (2021)[8] concluded that in general, the estimates of risks and benefits between the trial data and the models were consistent but imprecise mainly because of the lack of an established risk threshold to apply to the model.

Nodule classification and accuracy of LDCT screening

In addition to identifying the population considered at sufficient risk, the accuracy of LDCT as a lung cancer screening test is determined by the definition of a positive result. There are several nodule classification systems or frameworks used by studies to define the parameters of a positive LDCT screen[32]. These combine a range of features of lung nodules on the LDCT scan such as nodule composition, diameter and volume. The change in size of the nodule and volume doubling time (VDT), is also taken into account for those who have a repeat scan after 3 months[32].

Table 9 presents the criteria used to establish a positive LDCT screen in 9 RCTs reported in the systematic review by Jonas et al (2021)[8]. This shows the lung nodule frameworks used, threshold for a positive LDCT test result, number of screening rounds and overall sensitivity, specificity, positive predictive value and negative predictive value reported. The most used nodule framework was the International Early Lung Cancer Action Project (I-ELCAP) and its precursor the ELCAP. Other nodule frameworks are typically developed by individual trials such as the NLST framework or the NELSON framework which has been shared and modified by other trials[8].

Jonas et al (2021)[8] reported that sensitivity across the 9 RCTs ranged from 59% to 95% and specificity from 26.4% to 99.2%. The reference standard used to calculate screening performance metrics are the results of nodule biopsy and/or a confirmed diagnosis of lung cancer during follow up. The 2 RCTs, NELSON and NLST were considered to be adequately powered, and had sensitivities of 59.0% and 93.1% and specificities of 95.8% and 76.5% respectively (Table 9)[8]. Across all the RCTs positive predictive value ranged from 3.3% to 43.5% and negative predictive value from 97.7% to 99.9%[8]. For the NELSON and NLST RCTs positive predictive value was 43.5% and 3.3% and negative predictive value 97.7% and 99.9% respectively[8]. Jonas et al (2021)[8] has suggested the differences in the screening performance between the NELSON and NLST RCTs could be accounted for by the difference in screening protocols, as NELSON assessed the volume of nodules and introduced an indeterminate category whereas the NLST RCT used maximum diameter but did not have an indeterminate category. Alternatively, the differences in approach to screening has led to a trade off between sensitivity and specificity whereby a high sensitivity, correctly finding a high proportion of people with lung cancer, is off set by a low specificity leading to a high number of false positive test results[8].

Table 9. Nodule framework threshold for positive screens and screening performance[8]

Trial Country	LDCT Arm N	Nodule framework	Threshold for positive LDCT scan result	Number rounds	Sensitivity and specificity (%)	PPV and NPV (%)
DANTE Italy	2450	I-ELCAP	Diam≥5mm	5 annual	Sn 79.5 Sp 75.5	PPV 18.6 NPV 98.1
DLCST Denmark	4104	DLCST	Diam>15mm or 5-15mm with >25% V increase at 3 months	5 annual	Sn NR Sp NR	PPV 9.5 NPV NR
ITALUNG Italy	1406	I-ELCAP	Diam≥5mm	4 annual	Sn 95.0 Sp 26.4	PPV 3.6 NPV 99.4
LSS US	1610	NLST	Round 1>3mm Other rounds>4mm	2 annual	Sn NR Sp NR	PPV 7.0 NPV NR
LUSI Germany	2028	I-ELCAP	Diam≥5mm	5 annual	Sn 93.5 Sp 62.0	PPV 7.2 NPV 99.7
MILD Italy Annual	1152	Modified NELSON	V>250mm3 or 60-250mm3 with>25% V increase at 3 months	5 annual	Sn 68.5 Sp 99.2	PPV 40.6 NPV 99.8
MILD Italy Biennial	1151	Modified NELSON	V>250mm3 or 60-250mm3 with>25% V increase at 3 months	3 biennial	Sn 73.5 Sp 99.2	PPV 42.4 NPV 99.8
NELSON N'lands and Belgium	6583	NELSON	Diam>5mm or V>500mm3 & VDT 400-600 d at 3 months	4 rounds at: baseline, 1yr,3yrs 5.5yrs	Sn 59.0 Sp 95,8	PPV 43.5 NPV 97.7
NLST US	26,022	NLST	Diam>3mm round 1 Diam>4mm other rounds	3 annual	Sn 93.1 Sp 76.5	PPV 3.3 NPV 99.9
UKLS UK	1994	Modified NELSON	V>500mm3 or 50-500mm^3 & VDT<400 d at 3 months	1 screen	Sn 75 Sp NR	PPV 36.6 NPV NR

Abbreviations: Ann - Annual, Bien – Biennial , Cigs – Cigarettes, CXR – Chest x-ray, d – Day, Diam- Diameter, F/up – Follow-up, LDCT – Low dose computed tomography, mm – Millimetre, N – Number, N'lands – Netherlands, No Scr – No screening, NPV – Negative predictive value, NR – Not reported, PPV – Positive predictive value, Sn – Sensitivity, Sp – Specificity, US – United States, UK – United Kingdom, V – Volume, VDT – Volume doubling time, yrs – Years

Trials: DANTE -Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LSS – Lung screening Study, LUSI – Lung cancer Screening Intervention Trial, MILD – Multicentric Italian Lung Detection, NELSON - Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

Retrospective studies have evaluated what the change in screening performance would be for the NLST RCT if other nodule frameworks had been used[33],[34]. Pinsky et al (2015)[33] applied the Lung-RADS nodule classification framework to NLST data and found that using Lung-RADS would lead to an increase in specificity of LDCT from 73.4% to 87.2% in the incident screening round and 78.2% to 94.7% in subsequent rounds (both p<0.001). The

concomitant decrease in sensitivity was from 93.5% to 84.9% in the incident round and from 93.8% to 78.6% in subsequent rounds (both p<0.001)[33]. Yip et al (2014)[34] evaluated how I-ELCAP criteria compared to the NLST nodule framework alter the frequency of positive results and found that using a 5mm diameter nodule threshold (compared to 4mm) increases PPV from 4% to 5.7% and if a 7mm threshold is used PPV would be 12.2%. This would likely result in concomitant changes in other screening performance measures but these were not reported[34].

Jonas et al (2021)[8] reported that volumetric approaches to nodule classification seemed to result in higher PPVs than nonvolumetric approaches although no direct comparisons were made. In order to improve screening performance, studies are now considering the development of lung cancer pulmonary nodule risk models, combining population and individual risk prediction models such as the PLCOM2012 with nodule frameworks such as I-ELCAP for use in screening programmes[32]. In addition, automated or semiautomated nodule volume evaluations and calculation of volume doubling time are methods increasingly being used by screening trials to improve consistency of results[32].

Summary

There are a range of risk algorithms incorporating different factors predicting lung cancer risk from between a year to 9 years for smokers, former smokers and people who have never smoked and people in all age groups. Only a few of the risk algorithms have been used in lung cancer screening RCTs. The most accurate risk prediction algorithms can, correctly predict the people who will develop lung cancer from those who will not over 80% of the time. Rather than risk algorithms, most lung cancer screening RCTs have used a range of eligibility criteria based on smoking status and age to identify those who should be invited for screening. In addition to differences in eligibility criteria there are differences in the number of screening rounds, the intervals between rounds and the threshold for a positive test in RCTs that have published LDCT accuracy results. Despite this, most studies reported a sensitivity of over 80% and specificity over 75% with NPVs of over 95%. However, PPV varied significantly across RCTs which may well be due to these differences in screening strategy.

Contextual Question 3. What is the cost-effectiveness of screening programmes for the detection of lung cancer using Low Dose Computed Tomography (LDCT) in individuals at increased risk, compared with no screening? What is the cost-effectiveness of different strategies using LDCT screening (UK NSC criterion 14)?

The cost effectiveness of lung cancer screening was not addressed in the previous assessment of the evidence in 2006, the focus at that time was on identifying evidence of a suitable test and that a lung cancer screening programme was clinically effective. With the increase in volume and quality of evidence about clinical effectiveness and a suitable screening test it is now important to consider the cost effectiveness of a potential screening programme.

Recently, the Exeter Test Group updated a systematic review of the cost effectiveness of LDCT for lung cancer screening first published in 2018[1]. The findings of this update form the basis of the discussion of the findings for this contextual question.

Overview of the cost effectiveness of screening for lung cancer with LDCT

In 2018, Snowsill et al (2018)[1] published a systematic review of the clinical and cost effectiveness of the use of LDCT for lung cancer screening in high-risk populations. In total 19 studies were included. Using the same search strategy, the authors (Peters et al, in press)[35] updated the cost effectiveness analysis with a final search date of July 2020. This resulted in the inclusion of a total of 34 studies, including the 19 from Snowsill et al 2018[1].

Overall, 6 health economic modelling approaches were identified including; decision tree modelling, Markov model, cohort model, multistate model using individual participant data, a range of microsimulation models and discrete event simulation[35]. Most of the models used lung cancer diagnostic stage shift at diagnosis as the outcome of effectiveness. Other measures of screening effectiveness included use of participant level data, and reduced mortality for screen detected stage I and stage II cancers[35].

Studies used a similar definition of high-risk individuals eligible for screening although there were differences in the models about how often people were screened (a single screen, screening annually and biennially) the time horizon (from 5 years to lifetime) and price years (from1999 to 2016)[35].

Incremental Cost Effectiveness Ratios (ICERs) reported by Peters et al (2021)[35] were either calculated by Cost Utility Analysis (CUA) resulting in costs per Quality Adjusted Life Years (QALYs), (where 1 QALY is equal to 1 year of life in perfect health, and the ratio is calculated by dividing the incremental costs of an intervention by its incremental QALY gain

compared with standard treatment), or Cost Effectiveness Analysis (CEA) resulting in cost per Life Year gained (LYG); a modified measure of mortality where remaining life expectancy is taken into account.

ICERs were only reported when the therapeutic benefit of screening was cost effective when using an efficiency frontier approach (EFA)[35]. This approach plots different therapeutic values and costs of usual interventions to form a curve; when the new intervention is plotted and lies on or above the curve it is considered equally or more cost effective but if it is below the curve it is considered less cost effective[35].

Cost per QALY and cost per LYG are reported in the currency of the country of the setting of the study[35]. In order to show an approximate comparison between the highest and lowest cost per QALY and LYG, an online currency converter was used to convert currencies to GBP on 30th June 2021 (https://www.currency-convertor.uk/).

Strategy: Single LDCT screen

A total of 7 studies from, Israel (n=1), the UK (n=3) and the US (n=3), evaluated the cost effectiveness of a single LDCT screen for lung cancer compared to no screening (Table 10)[35]. Analysis using CUA were reported by 5 studies whilst 2 studies reported CEA. Cost per QALY varied from US$1,464 to US$207,000 (£1,054 to £149,400) whist cost per LYG varied from US$2,500 to US$5940 (£1,800 to £4,277)[35]. UK studies using decision tree models reported a cost per QALY for screening high risk men over the age of 61 years as £13,910 and £8,466 for all adults aged 50-75 years with a >5% risk of developing lung cancer[35]. The third UK study used a discrete event simulation model which had a higher cost per QALY (£28,169-£30,821) than the UK studies using the decision tree models[35].

Table 10. Cost effectiveness of single LDCT screening for high risk population vs no screening[35]

Country/ Price year	Eligible population	Model/time horizon	ICER
US, 1999	Very high risk smokers 60-74yrs	Decision tree, 5 years	US$5,940/LYG (£4277)
US, 2000	Adults ≥60 yrs ≥10 pack yr smoking history	Decision tree, unclear	US$ 2,500/LYG (£1,800)
UK, 2004	Men ≥61 yrs at high risk	Decision tree, 40 years	£13,910/QALY
US, 2006	Men 50-70 yrs ≥ 20 pack yr history	Microsimulation, Lifetime	US$144,000-$207,000/QALY (£1,054 to £149,400)
Israel, 2012	Adults ≥ 45 yrs ≥10 yr history	Decision tree, lifetime	US$1,464/QALY (£1,054)
UK, Field, 2016	Adults 50-75 yrs, ≥5% risk lung cancer with LLPRPM	Decision tree, Lifetime	£8,466/QALY
UK, Snowsill, 2016	Adults 55-80 yrs current/former smokers with 3%-5% risk of lung cancer with LLPRPM	Discrete event simulation model, Lifetime	£28,169-£30,821/QALY

ICER – Incremental cost-effectiveness ratio, LDCT – Low Dose Computed Tomography, LLPRPM – Liverpool Lung Project Risk Prediction Model, LYG – Life years gained, QALY – Quality adjusted life year, yr(s) – Year(s)

Strategy: Annual lung cancer screening with LDCT

The cost effectiveness of annual screens was evaluated in 26 studies with variation in the length of time that people were invited for an annual screen limited to 3 or 5 years or defined by the eligible age range[35].

A total of 6 studies from Australia (n=1), Canada (n=2), the UK (n=2) and the US (n=1), evaluated annual LDCT over 3 years compared to no screening (Table 11)[35]. Cost per QALY varied from £10,069 to Aus$233,000 (£125,820) whilst cost per LYG varied from US$52,000 to AUD$138,000 (£37,440 to £74,520). UK studies reported a cost per QALY for screening adults aged 55 to 74 years who had ever smoked as £10,069 when the 6 year lung cancer risk was estimated to be 1.15% and £40,034 in ever smokers aged 55-80 years where the lung cancer risk was estimated to be 3%-5%[35].

Table 11. Cost effectiveness of annual LDCT screening for 3 years vs no screening[35]

Country/ Price year	Eligible population	Model/time horizon	ICER
Canada, 2008	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Microsimulation	Can $74,000/QALY (£42,920)
US, 2009	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Decision tree, Lifetime	US$52,000/LYG (£37,440) US$81,000/QALY (£58,320)
UK, 2015	Adults 55-74 yrs ever smokers with 6 yr lung cancer risk of 1.51% (using data from PLCO)	Decision tree, Lifetime	£10,069/QALY
Canada 2015	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Markov, 30 years	Can $20,724/QALY (£12,020)
Australia, 2015	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Decision tree, 10 years	AUD $138,000/LYG £74,520 AUD $233,000/QALY (£125,820)
UK, 2016	Adults 55-80 yrs current/former smokers with 3%-5% risk of lung cancer with LLPRPM	Discrete event simulation model, Lifetime	£40,034/QALY

ICER – Incremental cost-effectiveness ratio, LDCT – Low Dose Computed Tomography, LLPRPM – Liverpool Lung Project Risk Prediction Model, LYG – Life years gained, NLST – National Lung Screening Trial, PLCO - Prostate, Lung, Colon, and Ovarian Cancer Screening trial, QALY – Quality adjusted life year, yr(s) – Year(s)

Studies from the US (n=2), Australia (n=1), Germany (n=1) and Italy (n=2) evaluated annual LDCT over 5 years compared to no screening (Table 12). Cost per QALY varied from €3297 to AUD$105,090 (£2,835 to £56,750) whist cost per LYG varied from €2,944 to US$90,022 (£2,531 to £64,615)[35].

Table 12. Cost effectiveness of annual LDCT screening for 5 years for high risk population vs no screening[35]

Country/ Price year	Eligible population	Model/time horizon	ICER
US 1999	'High risk' adults 60-74 yrs	Decision tree, 5 years	US$19,533/QALY (£14,064) US$18,968/LYG (£13,647)
US, 2000	Adult smokers 45-74yrs	Cohort model 15 yrs	US$33,557 – $90,022/LYG (£24161- £64,615)
Australia 2002	Male smokers 60-64 yrs	Markov 15 yrs	AUD $105,090/QALY (£56,750) AUD $57,325/LYG (£30,955)
Germany, 2016	Adults 50-55 to 75-80 yrs current/former smokers 15-40 pack yrs stopped 9-15 yrs	Microsimulation, Lifetime	€16,754-€20,870/LYG (£14,408 - £17,948)
Italy, 2018	Adults 55-79 current/former smokers≥30 pack yr history and stopped <15 yrs	Decision tree, 5 years	€3,297/QALY (£2,835) €2,944/LYG (£2,531)

ICER – Incremental cost-effectiveness ratio, LDCT – Low Dose Computed Tomography, LLPRPM – Liverpool Lung Project Risk Prediction Model, LY – Life years, NLST – National Lung Screening Trial, PLCO - Prostate, Lung, Colon, and Ovarian Cancer Screening trial, QALY – Quality adjusted life year, yr(s) – Year(s)

A total of 12 studies from Canada (n=2), Germany (n=1), Netherlands (n=1), Switzerland (n=1), the UK, US (n=6), evaluated annual LDCT over 5 years compared to no screening (Table 13)[35]. Cost per QALY varied from €19,302 to US$203,000 (£16,600 to £146,100) whist cost per LYG varied from US$18,862 to Can$64,000 (£13,580 to £37,120)[35]. The single UK study did not report a cost per QALY as none of the strategies evaluated were cost effective compared with the usual intervention based on whether they were on or above the efficiency frontier[35].

Table 13. Cost effectiveness of annual LDCT screening for an eligible age range vs no screening[35]

Country/ Price year	Eligible population	Model/time horizon	ICER
US 2001	Adults 60-80 yrs current/former smokers ≥20 pack yr history	Markov , 40 years	US$116,300/QALY (£83,736)
US 2006	Adults 50-74 yrs current/former smokers ≥20 pack yr history	Microsimulation, Lifetime	US$110,000/QALY - $203,000/QALY (£79,200 – 146,100)
Canada 2008	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Microsimulation, Lifetime	Can$52,000 -$56,000/QALY (£30,160 - £32,480)
US 2012	Adults 50-64 yrs current and former smokers ≥30 pack yr history	Cohort model, 15 yrs	US$18,862/LYG (£13,580) US$28.240/QALY (£20,332) based on ELCAP data US$47,115/QALY (£33,922) based on NLST data
US 2014	Adults 55-80yrs current/former smokers ≥30 pack yr history within past 15 yrs	Cohort model, 20 years	US$18,452/LYG (£13,285)
Canada 2015	Adults 10-40 pack yrs Current/former smokers with 10-20 yrs since smoking cessation	Microsimulation, Lifetime	Can$39,000-$64,000/LYG (£22,620 - £37,120)
Switzerland 2015	Adults 10-40 pack yrs Current and former smokers with 10-20 yrs since smoking cessation	Microsimulation, Lifetime	€30,500-€48,500/LYG (£26,230
Germany 2016	Adults 55-75 yrs current/former smokers ≥ 20 cigarettes/day	Markov models, 15 years	€31,291/QALY (£26,910)
Germany 2016	Adults 55-75 yrs current and former smokers ≥ 20 cigarettes/day	Markov models, 15 years	€19,302/QALY (£16,600)
UK 2016	Adults 55-80 yrs current/former smokers with 3%,4%,5% risk of lung cancer with LLPRPM	Discrete event simulation model	No cost effective strategies using EFA
US 2018	Adult 55 yrs upwards with ≥30 pack yr smoking history, screening stopped at age 74, 77, 80 y	Microsimulation, Lifetime	Screening stopped at: Age 74 -US$49,200/QALY (£35,424) Age77: US$68,000/QALY (£48,960) Age 80 -US$96,700/QALY (69,624)
US 2019	Adults with 20-40 pack years. Current/former smokers with 10-20 yrs since smoking cessation	Microsimulation, Lifetime	US$55,968-US$125,147/QALY (£40,296 - £90,105)
Netherlands 2020	Adult current smokers ≥20 cigarettes/day	Microsimulation, Lifetime	€24,922-€32,357/LYG (£21,432 - £27,827)

ICER – Incremental cost-effectiveness ratio, LDCT – Low Dose Computed Tomography, LLPRPM – Liverpool Lung Project Risk Prediction Model, LY – Life years, QALY – Quality adjusted life year, yr(s) – Year(s)

Strategy: Biennial LDCT screening

Biennial screening for lung cancer using LDCT was evaluated by 8 studies from Canada, Germany, Netherlands, New Zealand, Switzerland the UK and the US (Table 14)[35]. CUA only was reported by 4 studies, CEA only by 3 studies and a single study reported both analyses.

Compared to no screening cost per QALY varied from NZ$30,000 to US$76,909 (£15,300 to £55,377) whist cost per LYG varied from €17,672 to €31,000 (£15,197 to £26,660). The

single UK study did not report a cost per QALY as none of the strategies evaluated were cost effective compared with the usual intervention based on whether they were on or above the efficiency frontier[35].

One Canadian study compared 20 years of biennial screens with 20 years of annual screens and the cost per QALY varied between £31,320 and £2.78m depending on estimates of sensitivity and specificity of LDCT.

Table 14. Cost effectiveness of biennial LDCT screening for high risk population[35]

Country/ Price year	Eligible population	Model/time horizon	Comparison	ICER
Canada, 2008	NLST cohort (aged 55-74 years with ≥30 pack-year smoking history)	Microsimulation, Lifetime	Annual screen for 20 years	CAN$54,000/QALY to $4.8M/QALY (£31,320 to £2.78M) depending on estimates of sensitivity and specificity of LDCT
New Zealand 2011	NLST cohort adults 55-74 yrs and ≥30 pack yr smoking history	Markov model, Lifetime	No screening	NZ$30,000-NZ$89,000/QALY (£15,300 - £51,620)
Canada, 2015	Adults up to 40 pack yrs and up to 20 yrs smoking cessation	Microsimulation, Lifetime	No screening	No efficient strategies to model
Netherlands, 2015	Adult current smokers ≥20 cigarettes/day	Microsimulation, Lifetime	No screening	€17,672-€22,641/LYG (£15,198 - £19,471)
Switzerland, 2015	Adults 30-40 pack yrs of smoking history	Microsimulation, Lifetime	No screening	€25,500 - €31,000/LYG (£21,500 - £26,660)
Germany, 2016	Adults 55-75 yrs current/former smokers ≥20 cigarettes/day	Markov, 15 years	No screening	€38,694/QALY (£33,276) €24,594/LYG (£21,150)
UK, 2016	Adults 55-80 yrs current/former smokers with 3%,4%,5% risk of lung cancer with LLPRPM	Discrete event simulation model, Lifetime	No screening	No cost effective strategies using EFA
US 2019	Adults with 30-40 pack yrs, or 10-15 yrs smoking	Microsimulation, Lifetime	No screening	US$43,118-US$76,909/QALY (£31,045 - £55,374)

CEA – Cost effectiveness analysis, CUA - Cost utility analysis, ICER – Incremental cost-effectiveness ratio, LDCT – Low Dose Computed Tomography, LLPRPM – Liverpool Lung Project Risk Prediction Model, LY – Life years, QALY – Quality adjusted life year, yr(s) – Year(s)

Critical appraisal of the included studies by the systematic review authors found most studies were of sufficient quality as they met most appraisal criteria. However, only a few studies had appropriately valued outcomes, undertook sufficient sensitivity analysis and clarified that there were no conflicts of interest.

The heterogeneity between the included studies meant it was difficult to understand the sources of variation resulting in favourable or unfavourable ICERs. For example, the 4 UK studies included in the systematic review varied in whether they included only males or all

people, the target age range, the risk algorithm for identifying eligible people, whether they considered overdiagnosis, whether the model was based on RCT data and whether there was any external validation.

Summary

Overall, regardless of screening strategy, LDCT was reported to be more effective but more costly than no screening. There are marked differences in cost per QALY or LYG between studies and it is unclear what assumptions or aspects of the models are introducing this variation. The definition of the eligible high risk population used by the studies overlap or are similar, reducing the likelihood that this was an important source of the variation. Some studies reported cost per QALYs for lung cancer screening with LDCT as between £10,000 -20,000/QALY; the cost effectiveness threshold applied to UK interventions. UK studies of 2 strategies; a single one off LDCT screen and an annual screen for 3 years showed ICERs below the UK cost effectiveness threshold. However overall, there is such a wide variation in ICERs across strategies that without a better understanding of the sources of variation there could be little confidence that this level of cost effectiveness could be reliably demonstrated in a further study or in practice.

Synthesis of key review questions

Criteria 11, 13 — Clinical effectiveness of the screening programme

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

13. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

Review Question 4. What is the clinical effectiveness of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk, compared with no screening?

Sub- question: What is the clinical effectiveness of different strategies using LDCT screening (e.g. different intervals, use of risk algorithm, etc.)?

The UK NSC last looked at the evidence about screening for lung cancer in 2006, concluding that there was insufficient evidence, particularly as no RCTs had been completed, that screening would be effective at improving outcomes for people with a positive test result following screening. Since the last review, numerous RCTs have now been completed on screening for lung cancer using LDCT.

Eligibility for inclusion in the review

For this question peer-reviewed published studies reporting results from RCTs about the mortality, incidence, stage at diagnosis and harms reported for people screened with LDCT compared with chest x-ray or no screening were included. Where screening trials targeted smokers, systematic reviews and meta-analyses that included the latest published results of the NELSON lung cancer screening trial were sought. For other risk groups, systematic reviews and RCTs published since 2006 were sought. At full paper review, articles publishing the results of RCTs were excluded if they did not report on any of the outcomes listed in Table 2.

Description of the evidence

Database searches yielded 603 results, of which 22 systematic reviews and meta analyses were assessed at full text and 3 were included. All 3 included publications concerning lung cancer screening for people who were at high risk of developing lung cancer due to current or past smoking behaviour and older age. No eligible systematic reviews or individual RCTs that reported outcomes of lung cancer screening using LDCT in people who had never smoked were identified.

The 3 included systematic reviews and meta-analyses were Jonas et al (2021)[8], Brodersen et al (2020)[36] and Sadate et al (2020)[37]. In total 9 eligible RCTs were described by the systematic reviews and meta-analyses but no review included all 9 RCTs. Brodersen (2020)[36] identified an additional tenth RCT, a Chinese RCT (Yang et al 2018)[38] but it was excluded from the analysis as only baseline results were available. Jonas et al (2021)[8] also reported results from separate cohort studies but only results associated with the RCTs are reported in this evidence summary in line with the inclusion criteria for this key question.

The full texts of papers associated with the RCTs included in the systematic reviews and meta-analyses were also reviewed. Information from 25 additional studies associated with 7 of the 9 RCTs were included. For the remaining 2 RCTs all the relevant information was extracted from 1 or more of the systematic reviews and meta-analyses.

Of the 3 systematic reviews and meta-analyses eligible for inclusion, Jonas et al (2021)[8] reported multiple outcomes including mortality, harms and adverse outcomes, whilst Brodersen et al (2020)[36] examined overdiagnosis and Sadate et al (2020)[37] explored lung cancer mortality and all-cause mortality. Both Brodersen et al (2020)[36] and Sadate et al (2020)[37] carried out meta-analysis of their included RCTS whilst Jonas et al (2021)[8] did not conduct meta-analysis because of substantial clinical and methodological heterogeneity between the RCTs.

Table 15 shows the outcomes and included RCTs reported by each systematic review and meta-analysis.

Table 15. Systematic reviews and meta-analyses, with the RCT outcomes they reported

	Type of study	Eligible outcomes reported (number of RCTs included)	RCTs
Jonas et al (2021)[8]	Systematic review	Lung cancer mortality (7)	DANTE, DLCST, ITALUNG, LSS, LUSI, NELSON, NLST
		All-cause mortality (7)	DANTE, DLCST, ITALUNG, LSS, LUSI, NELSON, NLST
		Lung cancer incidence (7)	DANTE, DLCST, ITALUNG, LSS, LUSI, NELSON, NLST
		Stage at diagnosis (5)	DANTE, DLCST, ITALUNG, MELSON, NLST
		False positive results (5)	DLCST, LSS, LUSI, MILD, UKLS
		Overdiagnosis (7)	DANTE, DLCST, ITALUNG, LSS, MILD, NELSON, NLST
		Psychosocial harms (4)	DLCST, NELSON, NLST, UKLS
		Smoking cessation (5)	DLCST, NELSON, NLST, UKLS
		Incidental findings (3)	NELSON, NLST, UKLS
Brodersen et al (2020)[36]	Systematic review and meta-analysis	Overdiagnosis (5)	DLCST, ITALUNG, LUSI, MILD, NELSON,
Sadate et al (2020)[37]	Systematic review and meta-analysis	Lung cancer mortality (7) All-cause mortality (7)	DANTE, DLCST, ITALUNG, LUSI, MILD, NELSON, NLST

Abbreviations: RCT – Randomised controlled trial
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

Table 16 shows the characteristics of each of the eligible RCTs included by 1 or more of the systematic reviews or meta-analyses.

Table 16. Characteristics of RCTs identified as evaluating screening with LDCT compared with chest x-ray or no screening

Trial Country	N	Control	Age range	% Men	Eligibility criteria – pack years; years since quitting or lung cancer risk model	No. rounds	F/up yrs	Systematic review and meta-analysis where study reported
DANTE Italy	2472	No Scr	60-74	100	≥20 yrs;<10yrs	5	8.4	Jonas et al (2021)[8] Sadate et al (2020)[37]
DLCST Denmark	4104	No Scr	50-70	56	≥20 yrs;<10 yrs or quit after age 50yrs	5	9.8	Jonas et al (2021)[8] Brodersen et al (2020)[36] Sadate et al (2020)[37]
ITALUNG Italy	3206	No Scr	55-69	65	≥20 yrs in the last 10yrs; or quit within the last 10yrs	4	9.3	Jonas et al (2021)[8] Brodersen et al (2020)[36] Sadate et al (2020)[37]
LSS US	3318	CXR	55-74	59	≥30yrs;<10yrs	2	5.2	Jonas et al (2021)[8]
LUSI Germany	4052	No Scr	50-69	65	≥25 yrs of 15 cigs/d or ≥30 yrs of 10 cigs/d;<10yrs	5	8.8	Jonas et al (2021)[8] Brodersen et al (2020)[36] Sadate et al (2020)[37]
MILD Italy	4099	No Scr	49-75	68	≥20yrs;<10yrs	Ann 6 Bien 4	10	Brodersen et al (2020)[36] Sadate et al (2020)[37]
NELSON N'lands and Belgium	15,792	No Scr	50-74	84	>15 cigs/d for >25 yrs or>10 cigs/d for>30 yrs;≤10yrs	4	10	Jonas et al (2021)[8] Brodersen et al (2020)[36] Sadate et al (2020)[37]
NLST US	53,542	CXR	55-74	59	≥30yrs;≤15yrs	3	12.3	Jonas et al (2021)[8] Sadate et al (2020)[37]
UKLS UK	4055	No Scr	50-75	75	Risk model; LLPV2*	1	1	Jonas et al (2021)[8]

Abbreviations: Ann – Annual, Bien – Biennial, Cigs – Cigarettes, CXR – Chest x-ray, d – Day, F/up – Follow-up, N'lands – Netherlands, No. – Number, No Scr – No screening, US – United States, UK – United Kingdom, yrs – Years
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LSS – Lung screening Study, LUSI – Lung cancer Screening Intervention Trial, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial
*Variables included in LLPV2 risk model include age, sex, prior history of cancer, previous asbestos exposure, any first degree relative with lung cancer (and any under the age of 60), number of years smoked and previous history of one or more of the following: pneumonia, emphysema, bronchitis, tuberculosis and chronic obstructive pulmonary disease

Appendix 2 contains a full PRISMA flow diagram (Figure 6), along with a table of the included publications identified as being relevant to question 4 (Table 43).

Quality of the evidence base

There is a substantial volume of evidence from multiple RCTs in Europe, the UK and US examining the harms and benefits of screening for lung cancer with LDCT.

The 3 included systematic reviews and meta-analyses (Jonas et al 2021, Brodersen et al 2020 and Sadate et al 2020)[8,36,37] summarised the harms and benefits of 9 RCTs. Each of the 3 publications was critically appraised using the JBI critical appraisal checklist for systematic reviews. A summary of the quality appraisal by Jonas et al (2021)[8], Brodersen et al (2020)[36] and Sadate et al (2020)[37] of each of the RCTs is also reported below. Detailed results of the quality assessments are presented in the 'summary and appraisal of individual studies' in Appendix 3.

Critical appraisal of systematic reviews

The systematic review by Jonas et al (2021)[8] met all the JBI critical appraisal checklist questions concerning clarity of review questions, search strategies, the method for selecting, extracting, analysing, appraising and reporting information for each of the 8 key questions (Table 17).

Table 17. Summary critical appraisal of included systematic reviews and meta-analyses

JBI Critical Appraisal Checklist for systematic reviews	Jonas et al (2021)[8]	Brodersen et al (2020)[36]	Sadate et al (2020)[37]
Is the review question clearly and explicitly stated?	Yes	No	Yes
Were the inclusion criteria appropriate for the review question?	Yes	Yes	Yes
Was the search strategy appropriate?	Yes	Unclear	Yes
Were the sources and resources used to search for studies adequate?	Yes	No	Yes
Were the criteria for appraising studies appropriate?	Yes	Yes	No
Was critical appraisal conducted by two or more reviewers independently?	Yes	Yes	Yes
Were there methods to minimize errors in data extraction?	Yes	Yes	Yes
Were the methods used to combine studies appropriate?	N/A	Yes	Yes
Was the likelihood of publication bias assessed?	No	No	Yes
Were recommendations for policy and/or practice supported by the reported data?	Yes	Yes	N/A
Were the specific directives for new research appropriate?	Yes	Yes	N/A

Abbreviations: JBI – Joanna Briggs Institute, N/A – not applicable as areas not addressed

Brodersen et al (2020)[36] addressed 1 key question about overdiagnosis, although this was not explicitly stated at the beginning of the article. The search strategy used key words in Pubmed only, which risks missing important publications that may have been identified by a more comprehensive search approach. Brodersen et al (2020)[36] also did not assess the likelihood of publication bias. Sadate et al (2020)[37] addressed 2 key questions about lung cancer specific and all-cause mortality and met most of the JBI checklist criteria. However, the CONSORT checklist that they used for appraising their included studies is aimed at improving standards of reporting in journals and can aid critical appraisal but is not in itself a critical appraisal tool.

Critical appraisal of RCTs

Each of the 3 included systematic reviews and meta-analyses critically appraised the RCTs they summarised with different critical appraisal tools. Jonas et al (2021)[8] used a tool developed by the USPSTF, used for all their systematic reviews, Brodersen et al (2020)[36] used the Cochrane risk of bias tool version 2 and Sadate et al (2020)[37] used the CONSORT checklist. An overall rating was given for each RCT and also for each included paper published with RCT data. All 3 critical appraisal tools included an assessment of randomisation, inclusion criteria and measurement of outcomes. The USPSTF tool and Cochrane risk of bias tool version 2 also covered an assessment of contamination and concealment, adherence to the intervention and approach to missing data. In addition the USPSTF tool included detailed questions scrutinising the methodological approach and statistical analysis used by the RCTs such as differential attrition rates and the use of intention to screen analysis.

The overall outcome of the critical appraisal process for each of the trials by each of the 3 systematic reviews and meta-analyses is summarised in Table 18. Both Brodersen et al (2020)[36] and Sadate et al (2020)[37] used ‘high’, ‘low’ and ‘some’ to indicate the level of risk of bias (RoB) they attributed to an RCT whilst Jonas et al (2021)[8] used ‘good’, ‘fair’, and ‘poor’ to describe the quality of the RCTs and related studies.

Table 18. Overall risk of bias of RCTs in the systematic reviews and meta-analysis included in this review

	Jonas et al (2021)[8]	Brodersen et al (2020)[36]	Sadate et al (2020)[37]
Risk of bias tool	USPSTF critical appraisal tool	Cochrane risk of bias tool v2	CONSORT checklist for RCTs
Trial Country			
DANTE Italy	FAIR	NA	LOW
DLCST Denmark	FAIR/GOOD	LOW	LOW
ITALUNG Italy	FAIR	SOME	LOW
LSS US	FAIR	NA	NA
LUSI Germany	FAIR	LOW	LOW
MILD Italy	POOR	HIGH	SOME
NELSON N'lands and Belgium	FAIR	SOME	LOW
NLST US	GOOD	NA	LOW
UKLS UK	FAIR/POOR	NA	NA

Abbreviations: CONSORT – NA – Not applicable, N'lands – Netherlands, UK – United Kingdom, US – United States USPSTF – United States Preventative Services Task Force
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

Of the 9 studies considered by Jonas et al (2021)[8], 5 were considered 'fair' (DANTE, ITALUNG, LSS, LUSI, and NELSON), defined as RCTs with generally comparable groups but with some questions remaining about the methodology, although with no fatal flaws. There was variable concordance with Brodersen et al (2020)[36] who rated DLCST and LUSI as at 'low' RoB and NELSON and ITALUNG as having 'some' RoB concerns whilst Sadate et al (2020)[37] rated them all as 'low' RoB. Brodersen et al (2020)[36] was concerned that with the NELSON trial there was limited data about contamination in later rounds and a focus on men although the protocol suggested data about men and women would be reported together.

The NLST RCT was appraised as 'good' and DLCST was apprised as 'fair' with some publications rated as 'good' by Jonas et al (2021)[8]. The definition of 'good' (Jonas et al (2021)[8] is that the RCT meets all criteria;

- comparable groups are maintained throughout the study
- reliable and valid measurements are applied equally to both groups
- interventions are spelled out clearly

- all important outcomes are considered
- intention to treat analysis is used.

Sadate et al (2020)[37] rated the NLST RCT as 'low' RoB in concordance with Jonas et al (2021)[8]. The MILD RCT was rated as poor by Jonas et al (2021)[8], with high RoB by Brodersen et al (2020)[36] and as having 'some' concerns by Sadate et al (2020)[37]. The definition of 'poor' by Jonas et al (2021)[8] was that generally there were fatal flaws concerning randomisation, similarity of groups at baseline, and a lack of clarity about the reliability and validity of measures used and their application to groups equally. For the MILD RCT specifically, Jonas et al (2021)[8] was concerned about the high risk of selection bias, unclear methods of randomisation and allocation concealment, changing protocol and addition of a control arm later in the trial. There was also a lack of similar groups at baseline for important variables, differential follow up between groups and a high risk of measurement bias. For these reasons the findings of the MILD trial weren't included in systematic review by Jonas et al (2021)[8]. The UKLS RCT included by Jonas et al (2021)[8] was rated 'fair' but with 'poor' related studies. This was due to numerous unclear domains including allocation concealment and assessor and provider masking, differential attrition and methods to handle missing data. There was also no reporting on crossovers and contamination in the control group.

From the quality appraisal of the systematic reviews and meta-analyses and their assessment of the included RCTs, the evidence base is overall fair to good with a generally low RoB. However only 2 of the RCTs (NELSON and NLST) were considered adequately powered to evaluate the clinical effectiveness of lung cancer screening with LDCT.

Discussion of findings

A study-level summary of data extracted from each included publication is presented in the 'summary and appraisal of individual studies in Appendix 3. Publications in Appendix 3 are stratified by question.

Mortality

Jonas et a (2021)[8] included 7 RCTs reporting lung cancer mortality and all-cause mortality following screening with LDCT compared to no screening (DANTE, DLCST, ITALUNG, LUSI, NELSON) or chest x-ray (LSS, NLST). Sadate et al (2020)[37] included 7 RCTs in a meta-analysis of lung cancer mortality and all-cause mortality following screening with LDCT compared to no screening (DANTE, DLCST, ITALUNG, LUSI, MILD, NELSON) or chest x-ray (NLST).

Lung cancer specific mortality

Jonas et al (2021)[8] reported that 2 (NLST and NELSON) of the 7 RCTs reported a reduction in lung cancer mortality in the LDCT group compared to the control groups as a decrease in incidence rate ratio. Incidence rate ratio[39] compares the incidence rates of events occurring in the exposed and unexposed groups at any given point in time. These same 2 trials were also reported as the only trials to be adequately powered to assess lung cancer screening mortality benefit[8]. NLST (n=53,542) reported a reduction in lung cancer mortality (Incidence Rate Ratio (IRR) 0.85 (95% CI 0.75 – 0.96)) in 3 rounds of LDCT compared to chest x-ray, whilst the NELSON trial (n=15,792) had an IRR of 0.75 (95% CI 0.61 to 0.90) with 4 rounds of LDCT screening at increasing intervals compared with no screening[8]. The meta-analysis by Sadate et al (2020)[37] of 7 trials reported similar individual trial risk ratios (RR) to the IRR reported by Jonas et al (2021)[8]. The risk ratio is the ratio of the cumulative incidences in the exposed and unexposed groups giving a probability of an outcome in an exposed group compared to the probability of an outcome in an unexposed group[39]. Across all 7 trials Sadate et al (2020)[37] reported a significant relative reduction of lung specific mortality in the LDCT group of 17% (RR; 0.83 (0.76-0.91).

Table 19 shows the lung cancer mortality as IRR or RR for each individual RCT from Jonas et al (2021)[8] and Sadate et al (2020)[37].

Table 19. Lung cancer mortality with LDCT screening vs control

Trial	Number of events		Deaths per 100,000 persons		IRR (95% CI) or RR (95%CI)	Study
	LDCT	Control	LDCT	Control		
DANTE	59	55	543	544	IRR; 1.00 (0.69-1.44) RR; 1.01 (0.70-1.44)	Jonas et al (2021)[8] Sadate et al (2020)[37]
DLCST	39	38	201	194	IRR; 1.03 (0.66-1.61) RR; 1.03 (0.66-1.60)	Jonas et al (2021)[8] Sadate et al (2020)[37]
ITALUNG	43	60	293	421	IRR; 0.70 (0.47-1.03) RR; 0.71 (0.48-1.12)	Jonas et al (2021)[8] Sadate et al (2020)[37]
LSS	32	26	383	310	IRR; 1.24 (0.74-2.07)	Jonas et al (2021)[8]
LUSI	29	40	NR	NR	NR RR; 0.72 (0.45-1.16)	Jonas et al (2021)[8] Sadate et al (2020)[37]
MILD	40	40	173	247	RR; 0.73 (0.47-1.12)	Sadate et al (2020)
NELSON	181	242	241	324	IRR; 0.75 (0.61-0.90) RR; 077 (0.62-0.94)	Jonas et al (2021)[8] Sadate et al (2020)[37]
NLST	469	552	280	332	IRR - 0.85 (0.75-0.96) RR; 0.85 (0.75-0.96)	Jonas et al (2021)[8] Sadate et al (2020)[37]

Abbreviations: CI – Confidence intervals, IRR - Incidence rate ratio, LDCT – Low dose computed tomography, NR – Not reported, RR – Risk ratio

Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LSS – Lung screening Study, LUSI - Lung cancer Screening Intervention Trial, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial

Lung cancer mortality: sub-group analysis

Of the 7 RCTs, Jonas et al (2021)[8] observed that 4 (DLCST, LUSI, NELSON and NLST) reported sub-group analysis of at least 1 of the following factors; age, sex, smoking status, ethnicity, and pulmonary conditions. These were post hoc analyses, the results of which should be treated with caution. The results of subgroup analysis typically only become relevant if they can be replicated in a subsequent randomised clinical trial.

The NLST RCT carried out a sub-group analysis of lung cancer mortality at 12.3 years follow up by gender, age and smoking status in the LDCT group compared to chest x-ray[40]. There was no statistically significant difference in these factors between the trial arms. The NLST RCT also compared lung cancer mortality outcomes for white participants (n=47,902, 89%), black participants (n=2361, 4%) and a third group combining other (n=2969, 5%) and missing (n=220, 0.4%) ethnicity by screening arm, sex, age group and smoking status[41]. With a significance level of $p<0.5$ screening with LDCT compared to chest x-ray was more likely to be beneficial for white people (HR 0.86; 0.75-0.98, $p<0.5$) and those of other ethnicities (HR 0.72; 0.53-0.98, $p<0.05$) but not for black people (HR 0.61; 0.37-1.01).

The DLCST RCT compared mortality outcomes for people with and without COPD (n=856 vs n=1196) in those screened with LDCT and those not screened[42]. People with both COPD and more than 35 pack years of smoking had a 2 to 5 times risk of dying compared to other high risk groups. There was a nonsignificant lower HR in the screening group compared to the control in the group with this combination of risk factors (HRs 5.2 vs 6.8 $p<0.425$).

Number needed to screen to prevent 1 death from lung cancer

Jonas et al (2021)[8] reported that for the NLST RCT, in order to prevent 1 death from lung cancer 323 people need to be screened over a period of 6.5 years. For the NELSON trial this was 130 people over a period of 10 years.

All-cause mortality

Of the 8 RCTs reported by either Jonas et al (2021)[8] or Sadate et al (2020)[37] only the NLST RCT observed a reduction in all-cause mortality for LDCT compared to chest x-ray with 3 rounds of screening (IRR 0.93 (95% CI 0.88-0.99). NELSON was the only other trial that Jonas et al (2021)[8] judged to be adequately powered to evaluate all-cause mortality and observed an IRR of 1.01 (95%CI 0.92-1.11) for LDCT in comparison to no screening. Sadate et al (2020)[37] calculated an overall reduction in mortality of 6.7% in the NLST RCT with a rate ratio of 0.94 (95% CI 0.88-1.00). To prevent 1 death from all-cause mortality 219 people would need to be screened based on the NLST outcomes[37].

The meta analysis by Sadate et al (2020)[37] of the 7 RCTs included 84,558 participants and reported a relative reduction of overall mortality of 4% in the screening group compared to the control group (RR=0.96, 95% CI 0.92-1.00) with no heterogeneity in the data. The lack of a clear reduction in all-cause mortality for most of the RCTs is likely due to being both underpowered and subject to a dilution effect from higher rates of other causes of death besides lung cancer. The impact of a reduction in lung cancer deaths due to early detection by screening is therefore too small compared to other causes of death to make an overall difference in mortality rates.

Table 20 shows all-cause mortality for LDCT screening versus control in 8 RCTs.

Table 20. All-cause mortality for LDCT screening vs control

Trial	Number of events		Deaths per 100,000 persons		IRR (95% CI) or RR (95%CI)	Systematic review or meta-analysis
	LDCT	Control	LDCT	Control		
DANTE	180	176	1655	1742	IRR; 0.95 (0.77-1.17) RR; 0.96 (0.79-1.16)	Jonas et al (2021)[8] Sadate et al (2020)[37]
DLCST	165	163	849	834	IRR; 1.02 (0.82-1.26) RR; 1.01 (0.82-1.25)	Jonas et al (2021)[8] Sadate et al (2020)[37]
ITALUNG	154	181	1051	1270	IRR; 0.83 (0.67-1.03) RR; 0.84 (0.69-1.03)	Jonas et al (2021)[8] Sadate et al (2020)[37]
LSS	139	116	1667	1384	IRR; 1.20 (0.94-1.53)	Jonas et al (2021)[8]
LUSI	148	150	NR	NR	IRR; 0.98 (0.79-1.22) RR; 0.98 (0.79-1.22)	Jonas et al (2021)[8] Sadate et al (2020)[37]
MILD	137	106	594	654	RR; 0.94(0.73-1.20)	Sadate et al (2020)
NELSON	868	860	1393	1376	IRR; 1.01(0.92-1.11) RR; 1.01(0.93-1.11)	Jonas et al (2021)[8] Sadate et al (2020)[37]
NLST	1912	2039	1141	1225	IRR; 0.93(0.88-0.99) RR; 0.94(0.88-1.00)	Jonas et al (2021)[8] Sadate et al (2020)[37]

Abbreviations: CI – Confidence interval, IRR-Incidence rate ratio, LDCT – Low dose computed tomography, NR – Not reported, RR – Risk ratio
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial

The NLST RCT compared all-cause mortality outcomes for white participants (n=47,902, 89%), black participants (n=2361, 4%) and a third group combining other (n=2969, 5%) and missing (n=220, 0.4%) ethnicity by screening arm, sex, age group and smoking status[41]. Adjusting for sociodemographic and behavioural characteristics, people who were black overall experienced higher all-cause mortality than people who were white (HR 1.35;95% CI 1.22-1.49). However, black individuals screened with LDCT had a significant reduction in all-cause mortality compared to those screened with chest x-ray. This reduction was not observed in people who were white (Table 21).

Table 21. Adjusted hazard ratio (HR) for all-cause mortality by ethnicity (NLST RCT)[41] Error! Bookmark not defined.

	White people HR (95% CI)	Black people HR (95% CI)	Other/missing ethnicity HR (95% CI)
All-cause mortality	**Reference**	**1.35(1.22-1.49)***	**0.93(0.81-1.06)**
Screening: LDCT (versus CXR)	0.95(0.89-1.02)	0.81(0.65-1.00)^	0.78(0.62-0.99)^
Sex: Female (compared to male)	**0.56(0.52-0.60)***	**0.59(0.42-0.82)^**	**0.49(0.32-0.75)^**
Age group: age ≥70 yr (versus age < 70 yr)	1,07(0.97-1.18)	1.79(1.04-3.00)^	0.96(0.50-1.84)
Smoking status: Current smokers (compared to former smokers)	**1.82(1.70-1.95)***	**1.82(1.51-2.23)***	**1.76(1.47-2.11)***

Abbreviations: CI – Confidence interval, CXR – Chest x-ray, HR- Hazard ratio, LDCT – Low dose computed tomography, NLST – **National Lung Screening Trial,** yr – Year
*Significantly different to comparison p<0.001,
^ Significantly different to comparison p<0.05

Lung cancer incidence and stage

A higher cumulative incidence of lung cancer was reported in groups screened with LDCT compared to no screening in 5 RCTs (DANTE, DLCST, LUSI, MILD, NELSON,) and chest x-ray in 2 RCTs (LSS, NLST), but not in the remaining RCT (ITALUNG, LDCT vs no screening)[8,43,44]. Incidence in LDCT trial arms ranged from 2.4% to 8.2%[8]. In the control arms of 5 RCTs with no screening, incidence was 3.3% to 5.2% whilst the incidence in the chest x-ray control arm for LSS[43] was 1.5% and 6.3% for NLST[8] (Table 22). The difference in incidence between the LDCT and control arms was not always statistically significant. The NLST RCT at 11.3 years follow up showed no statistical difference in incidence between the LDCT and chest x-ray (RR 1.01; 95% CI 0.95-1.08) and similarly for NELSON at 10 years follow up comparing LDCT with no screening (RR 1.14,95% CI0.97-1.33)[8].

Table 22. Cumulative incidence of lung cancer

	Screened (n)	Control (n)	F/up (yrs)	Screened n(%)	Control n(%)	Rate ratio (95% CI)	Systematic review or study
DANTE	1276	1196	8.4	106(8.2)	73(5.2)	1.35(1.00-1.81)	Jonas et al (2021)[8]
DLCST	2052	2052	9.8	100(4.9)	53(2.6)	1.89(1.36-2.64)	Jonas et al (2021)[8]
ITALUNG	1613	1593	9.3	67(4.1)	71(4.5)	0.92(0.66-1.28)	Jonas et al(2021)[8]
LSS	1660	1658	2	40(2.4)	20(1.5)	NR	Doroudi (2018)[43]
LUSI	2029	2023	8.8	85(4.2)	67(3.3)	NR	Jonas et al (2021)[8]
MILD	2376	1723	10	98(4.1)	60(3.5)	NR	Pastorino et al (2019a)[44]
NELSON	6583	6612	10	344(5.2)	304(4.6)	1.14(0.97-1.33)	Jonas et al (2021)[8]
NLST	26,722	26,737	11.3	1701(6.4)	1681(6.3)	1.01 (0.95-1.08)	Jonas et al (2021)[8]

Abbreviations: CI – Confidence interval, F/up – Follow up, N – Number, yrs – Years
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS - Lung screening Study, MILD - Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

All RCTs reported more stage I cancers in LDCT groups than control groups[8,29,44,45,46,]. Table 23 and 24 show the differences in the proportions of early stage (I and II) and later stage (III and IV) cancers detected by the LDCT and control groups.

Table 23. Incidence of LDCT screening vs control for early stage (I-II) lung cancer

Trial	Number		Number early stage I-II cancers (% all cancers in each arm)		IRR (95% CI) HR (95% CI) or p value	Systematic review or study
Trial	Screened	Control	Screened	Control		
DANTE	1276	1196	54(56)	21(32)	IRR 2.38 (1.44-3.94)	Jonas et al (2021)[8]
DLST	2052	2052	54 (54)	10 (20)	IRR 5.42 (2.76-10.63)	Jonas et al (2021)[8]
ITALUNG	1613	1593	29 (47)	13 (23)	IRR 2.17(1.13-4.16)	Jonas et al (2021)[8]
LSS	1660	1658	24 (60)	11(55)	X^2 p=0.08	Gohagan et al (2005)[46]
LUSI	2029	2023	47 (76)	8(22)	HR 5.92(2.79-12.53)	Becker et al (2019)[45]
MILD	2376	1723	53 (54)	18 (33)	NR	Pastorino et al (2019a)[44]
NELSON	6583	6612	168(52)	71 (25)	IRR 2.39(1.81-3.16)	Jonas et al (2021)[8]
NLST	26,722	26,737	818 (52)	615 (40)	IRR 1.33(1.20-1.48)	Jonas et al (2021)[8]
UKLS	2028	2027	36 (86)	NR	NR	Field et al (2016)[29]

Abbreviations: CI – Confidence interval, HR – Hazard ratio, IRR – Incidence rate ratio, NR – Not reported, X^2 – Chi squared statistic

Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

In the LDCT arms, stage I and II cancers comprise between 47% and 86% of the cancers detected whereas in the control arms early stage cancers comprise 20% to 55% (Table 23). Jonas et al (2021)[8] reported the IRR of early stage cancers (I and II) for 5 RCTs (DANTE, DLCST, ITALUNG, NELSON and NLST) which showed a significantly higher incidence of people being diagnosed with early stage cancer in the LDCT arm than the control arm. For the LUSI RCT, the HR of being diagnosed with early stage lung cancer was reported to be significantly higher in the LDCT arm than control arm of the trial[45]. No statistical comparisons were reported for MILD[44] and UKLS whilst LSS[46] did not observe a statistical difference (Table 23).

Late stage cancers comprise 24% to 53% of diagnoses in the LDCT arms whereas the proportion in the control arms ranges from 45% to 80% (Table 24). This reflects a stage shift towards detecting early cancers, which are more likely to be successfully treated than later stage cancers. Of the 5 RCTs examined by Jonas et al (2021)[8], 2 (NELSON and NLST) had significantly lower incidence of people with late stage cancers (III and IV) diagnosed in the LDCT arm compared to the control arm (IRR 0.72 (0.58-0.88) and 0.84 (0.76-0.92 respectively). For the LUSI RCT the HR of being diagnosed with late stage lung

cancer was statistically significantly lower in the LDCT arm than control arm of the trial[Error! Bookmark not defined.]. The DANTE[8], DLCST[8], ITALUNG[8] and LUSI[45] RCTs did not show any statistical difference between trial arms although LDCT arms for these trials all had a lower proportion of late stage cancers detected than the in control arm. No statistical comparisons were reported for MILD[44] and UKLS[29] RCTs.

Table 24. Incidence of LDCT screening vs control for late stage (III-IV) lung cancer

Trial	Number		Number cancers (stage III-IV)		IRR (95% CI) or HR (95% CI)	Systematic review or study
	LDCT	Control	Screened	Control		
DANTE	1276	1196	43 (44)	45 (68)	IRR 0.89 (0.59-1.35)	Jonas et al (2021)[8]
DLST	2052	2052	46 (46)	41 (80)	IRR 1.13 (0.74-1.72)	Jonas et al (2021)[8]
ITALUNG	1613	1593	33(53)	43 (77)	IRR 0.75 (0.47-1.17)	Jonas et al (2021)[8]
LSS	1660	1658	16(40)	9(45)	X^2 p=0.09	Gohagan et al (2005)[46]
LUSI	2029	2023	15 (24)	28 (78)	HR 5.92 (2.79 - 12.53)	Becker et al (2019)[45]
MILD	2376	1723	45 (46)	42 (67)	NR	Pastorino et al (2019a)[44]
NELSON	6583	6612	153 (48)	216 (75)	IRR 0.72 (0.58-0.88)	Jonas et al (2021)[8]
NLST	26,722	26,737	766 (48)	918 (60)	IRR 0.84 (0.76-0.92)	Jonas et al (2021)[8]
UKLS	2028	2027	6 (14)	NR	NR	Field et al (2016)[29]

Abbreviations: CI – Confidence interval, HR – Hazard ratio, IRR – Incidence rate ratio, NR – Not reported, X^2 – Chi squared statistic.
Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS - UK Lung Cancer Pilot Screening Trial

Lung cancer screening intervals

Of the 9 RCTs considered by the Jonas et al (2021)[8] systematic review, 6 (DANTE, DLCST, ITALUNG, LSS, LUSI, NLST) implemented annual screening whilst UKLS carried out a single one off screen of the targeted cohort. The remaining 2 RCTs (NELSON and MILD) screened people with different intervals between LDCT scans allowing for comparison of outcomes between different lung cancer screening intervals[8].

The NELSON RCT invited all eligible people to be screened with LDCT at increasing intervals starting at baseline then 1 year, 2 years and 2.5 years[47,48]. People participating in the LDCT arm of the RCT will have therefore been screened 4 times over a period of 5.5 years. In a comparison of the outcomes of the different intervals of the NELSON trial, the 2.5 year screening interval culminating in round 4 compared to a 1 year interval (round 2) had a lower proportion of stage I cancers (60.9% vs 75.9%) and higher proportion of stage IIIb/IV cancers (17.3% vs 6.8%) (p=0.02)[48]. A similar trend was observed between the 2.5

year interval (round 4) and the 2 year interval (round 3) for cancer stage at diagnosis (stage I 60.9% vs 72.7% and stage IIIb/IV 17.3% vs 5.2% respectively) but did not reach significance (p=0.10)**.** No differences in lung cancer detection rate was observed between the 4 rounds and the different screening intervals (0.8 – 1.1%)[47].

The MILD trial directly compared annual screening with biennial screening and no screening[49]. There were no statistically significant differences between the LDCT biennial and annual screening groups at 10 year follow up for, lung cancer specific mortality (HR=1.10, 95%CI 0.59-2.05), all-cause mortality (HR=0.80, 95% CI 0.57-1.12), the occurrence of stage II-IV cancers (p=0.4110) and the rate of interval cancers (p=0.3625).

Harms and adverse events resulting from screening

The harms resulting from the lung screening programmes evaluated by the systematic reviews, meta-analyses and RCTs cover 3 broad areas; the proportion of false positive results; overdiagnosis and psychosocial harms of participating in the screening programme.

False positive results and the diagnostic pathway following LDCT
Identifying and tracking the outcomes of people with a false positive LDCT result is important to understand the proportion of people who have an abnormal result but do not have lung cancer and may experience harm due to unnecessary procedures the person would have avoided if there had been no screening. People may experience complications from the diagnostic procedures they undergo and psychosocial harms such as stress, anxiety and depression.

Jonas et al (2021)[8] reported false positive rates from 9 RCTs ranging from 7.9% to 26.9% for baseline prevalent screening rounds and 1.6% to 27.2% in subsequent incident screening rounds with rates generally declining with each round (Table 25). Of the 2 RCTs that reported to be adequately powered to evaluate lung cancer screening with LDCT, the NLST RCT reported false positive rates of 26.3%, 27.2% and 15.9% for baseline, round 1 and round 2 respectively whilst the NELSON RCT reported lower rates with baseline rates of 19.8%, followed by 7.1%, 9% and 3.9% in the 3 subsequent rounds[8]. The wide range of false positive rates between RCTs was attributed to the differences in eligibility criteria and radiological definition of nodule size and volume used as the threshold between a positive and negative screen. An analysis using NLST RCT data reported that the aggregate false-positive rate was higher in people aged ≥65 years compared to those aged <65 years (27.7% vs. 22.0%; p< 0.001)[33].

Table 25. False positive rates reported by 9 lung cancer screening RCTs[8]

	Screening years	Cut off for positive nodule	False positive rates by screening round
DANTE	0,1,2,3,4	≥10 mm diameter or smaller if showing spiculated margins	NR for whole screening pathway by round.17/90(18.8%) surgical procedures had benign nodule findings
DLCST	0,1,2,3,4	≥5mm	R0; 7.9%, R1; 1.7%,R2; 2.0%, R3; 1.6% R4; 1.9%
ITALUNG	0,1,2,3	≥5mm	NR for whole screening pathway by round. 4/38(10%) surgical procedures had benign nodule findings
LSS	0,1	Baseline>3mm Year 1 ≥4mm	R0; 18.6%, R1; 25.2%
LUSI	0,1,2,3,4,	≥5mm Incidence of nodules volume doubling time<600 of known nodule	R0; 21.1%, R1; 4.1%, R2; 3.5% R3; 5.2%, R4; 5.2%
MILD	Annual 0,1,2,3,4,5,6 Biennial 0, 2, 4, 6	>60mm^3 Incidence nodules: volume increases>25%	Annual R0;13.9%, R1;2.8%, R2;4.4%, R3;2.4%, R4;1.8%, R 5;0.6%, R6;2.6% Biennial R013.2%, R1;2.2%, R2;2.6%, R3;4.4%
NELSON	0,1,3,5.5	Volume>50mm^3 (>9.8mm diameter) Incidence of nodules: Volume doubling time<400 days	R0; 19.8%, R1; 7.1% R2; 9.0% (males only) R3; 3.9% (males only)
NLST	0,1,2	≥4mm	R0; 26.3%, R1;27.2%, R2; 15.9%
UKLS	Baseline	>50mm3	R0; 26.9%

Abbreviations: mm – Millimetre, NR – Not reported, R – Round

Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, LSS – Lung screening Study, MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST - National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

All people with a positive test result are evaluated to decide what follow up procedures should be used to determine a definitive diagnosis. A proportion of these follow up tests will result in complications some of which will be experienced by people who are ultimately found to not have lung cancer and had a false positive LDCT screening result. Jonas et al (2021)[8] reported the complication rates observed by 6 RCTs of those people with a false positive test result (Table 26). The corresponding figures reporting people who had an adverse event from a procedure for suspected cancer that subsequently wasn't found to be cancer in the control arms of the RCTs was not reported by Jonas et al, (2021)[8].

Table 26. Complication rates from invasive follow up diagnostic procedures in people with a false positive LDCT screen[8]

	LDCT n	Needle biopsy n (%)	Bronchoscopy/EBUS n (%)	Surgical procedures n (%)
DANTE	1276	NR	NR	17(1.33)
ITALUNG	1406	1 (0.07)	NR	4(0.28)
LUSI	2029	9 (0.44)	NR	NR
NELSON	7915	NR	121(1.53)	NR
NLST	26,722	66 (0.25)	227 (0.85) Severe 2 (0.007) Intermediate 9 (0.034) Minor 0 (0) Death within 60 days 4 (0.015)	164 (0.61) Severe: 9 (0.034) Intermediate: 13 (0.049) Minor: 4 (0.015) Death within 60 days: 2 (0.007)
UKLS	1994	7(0.35)	1(0.05)	NR

Abbreviations: EBUS – Endobronchial ultrasound, LDCT Low dose computed tomography, n – Number, NR – Not reported

Trials: DANTE – Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, , NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek, NLST – National Lung Screening Trial, UKLS – UK Lung Cancer Pilot Screening Trial

Jonas et al (2021)[8] observed that for every 1000 people screened in the NLST RCT, 0.9 to 5.6 needle biopsies resulted in benign findings and 0.3 to 0.7 complications whilst 5 to 13 surgical procedures resulted in benign findings and <1 major complication. An analysis using NLST RCT data reported that invasive diagnostic procedures in those with a false-positive screening result were more frequent in the older cohort (3.3% vs. 2.7%; p= 0.039)[33].

True positives and overdiagnosis

Overdiagnosis is the detection of cancer in a patient that would not have become clinically important in the patient's lifetime. This can happen for example when a cancer is slow to develop to a point where it is symptomatic and screening is carried out in older age groups. If there had been no screening in this cohort of people the slow growing cancers may not have become symptomatic before the end of their lifetime. Identifying and tracking the outcomes of this subset of people with a true positive LDCT result who would have never become symptomatic is important to understand the proportion of people who may experience harm due to unnecessary procedures and treatment that could be avoided if there had been no screening.

In order to determine the size of this subset of over diagnosed cancers, cumulative lung cancer incidence with LDCT is compared to no screening or chest x-ray over an extended follow up period. Excess incidence is usually due to detecting lung cancers earlier during the lead time it usually takes for a cancer to develop and become symptomatic. If there is no overdiagnosis, the increase in diagnoses during the screening period in the LDCT group should be offset by diagnoses made in the control group during the follow up period. When

overdiagnosis is present the control group does not 'catch up' in terms of cumulative lung cancer incidence during the extended follow up period.

Brodersen et al (2020)[36] pooled overdiagnosis rates across 5 RCTs (DLCST, ITALUNG, LUSI, MILD, NELSON) summarising results with a random effects meta-analysis. The NLST RCT was excluded from the meta-analysis as the comparator was chest x-ray rather than no screening. The follow up periods ranged from 3 to 5 years for DLCST, ITALUNG, LUSI and NELSON but was unclear for the MILD RCT.

Table 27 shows the RR of cumulative incidence of lung cancer estimates for the individual RCTs. In the meta-analysis, LDCT increased the cumulative incidence of lung cancer (RR 1.22 95% CI 1.02-1.47) with a high unexplained heterogeneity across the trials (I^2=55%)[36]. A similar result was reported when the 2 RCTs with the least risk of bias were pooled (DLCST and LUSI) (RR 1.51 95% CI 1.06-2.14 I^2=58%) (Table 26)[36].

Table 27. Cumulative incidence and overdiagnosis of lung cancer reported by individual RCTs[36]

Trial	F/U (yrs)	LDCT		No screening		Ovediag %	RR (95% CI)
		Events	Total	Events	Total		
DLCST	5	96	2052	53	2052	67.2%	1.81 (1.30-2.52)
ITALUNG	5	67	1613	71	1593	-13%	0.93 (0.67-1.29)
LUSI	3	85	2029	67	2023	28%	1.26 (0.92-1.73)
MILD	Unclear	98	2376	60	1723	62%	1.18 (0.86-1.62)
NELSON	4.5	344	6583	304	6612	20%	1.14 (0.98-1.32)

Abbreviations: CI – Confidence interval, F/U – Follow up period LDCT – Low dose computed tomography, Overdiag – Overdiagnosis, RR – Risk ratio, yrs – Years
Trials: DLCST – Danish Lung Cancer Screening Trial, ITALUNG – Italian Lung Cancer Screening Trial, LUSI – Lung cancer Screening Intervention Trial, , MILD – Multicentric Italian Lung Detection, NELSON – Nederlands-Leuvens Longkanker Screenings Onderzoek,

Brodersen et al (2020)[36] calculated the overall fraction of screen detected lung cancers that represent overdiagnosis and estimated that 38% (95% CI 14-63, I^2=65%) were over diagnosed. Restricting the analysis to the 2 RCTs of lowest risk of bias (DLCST, LUSI) showed 49% (95% CI 11-84 I^2=58%) of screen detected cancers were over diagnosed[36].There is uncertainty about this high level of overdiagnosis due to the substantial unexplained heterogeneity across the trials[36].

Jonas et al (2021)[8] reported that for the NLST RCT with a follow up of 6.5 years there were 4 cases of overdiagnosis and 3 lung cancer deaths prevented per 1000 people screened in the same period. A further study of NLST RCT data estimated a rate of 1.38 cases of cancers were over diagnosed for every 320 patients needed to screen to prevent 1 death from lung cancer.

Both Broderdsen et al (2020)[36] and Jonas et al (2021)[8] observed that determining the rate of overdiagnosis in any trial can be challenging because the number of excess cancers are influenced by the target population risk, length of follow up period, whether the data in the follow up period is accurate and complete and whether people had undergone subsequent screening. Comparing trials is also challenging as there are differences in the criteria used to determine a positive screening result, the length of screening intervals, number of screening rounds and the methodology for collecting follow up data. These differences will all contribute towards the observed heterogeneity of the meta-analysis carried out by Brodersen et al (2020)[36] and limits the certainty of the results.

Two studies examining LUSI RCT data[50] and NLST RCT data[51] both looked at overdiagnosis by type of lung cancer with similar follow up periods of 5 years. The 2 estimates they made were:

- the percentage of all lung cancer cases diagnosed by LDCT that would not have become clinically apparent (PA)
- the likelihood (%) that a participant's cancer would not have become clinically apparent if there had been no screening or chest x-ray only (PS)

The overdiagnosis incidence in the LDCT RCT screening arm of the LUSI RCT appeared to be largely due to adenocarcinomas (50%, 95% CI 14-88.4) especially bronchioalveolar carcinoma (112.5% 95% CI 68.2 to 113.1). This pattern was also reported for the NLST RCT, although the overdiagnosis rates were much lower (Table 28).

Table 28. Overdiagnosis rates by lung cancer type for NLST[51] and LUSI RCTs[50]

Study (follow up)	Measure	All lung cancers	All NSCLC	Non-BAC	BAC only
NLST (3 yrs of annual screens with 4.5 yrs f/up)*	PA % (95% CI)	11.0 (3.2-18.2)	14.4 (6.1-21.8)	7.1 (-2.3 to15.6)	67.6 (53.5 to 78.5)
NLST (3 yrs of annual screens with 4.5 yrs f/up)*	PS-CXR% (95% CI)	18.5 (5.4-30.6)	22.5 (9.7-34.3)	11.7 (-3.7 to 25.6)	78.9 (62.2 to 93.5)
LUSI (5 yrs of annual screens plus 5 yrs f/up)~	PA% (95% CI)	25.4 (-11.4 to 64.3)	50.0 (14.0 to 88.4)	36.1 (-8.4 to 84.8)	112.5 (68.2 to 113.1)
LUSI (5 yrs of annual screens plus 5yrs f/up)~	PS-NS% (95% CI)	17.8 (-7.4 to 44.7)	37.3 (11.5 to 65.4)	26.5 (-5.3 to 61.8)	90.0 (54.3 to 164.4)

Abbreviations: BAC – bronchioalveolar cell carcinoma, CXR – Chest x-ray, incl – including, LDCT – Low dose computed tomography, NOS – not otherwise specified, NSCLC – non-small cell lung cancer PA= % of all lung cancer cases diagnosed by LDCT that would not have become clinically apparent, PS-CXR = % likelihood that a participant's cancer would not have become clinically apparent if CXR screening only (PS-CXR), PS-NS= % likelihood that a participants cancer would not have become clinically apparent if there had been no screening

*NLST, Patz et al (2014)[51], ~ LUSI, Maldondo et al (2021)[50]

The follow up times for both the LUSI and NLST RCTs may not have been long enough to account for the lead time of all LDCT detected cancers particularly because tumour growth rates are variable and are not consistent. This is illustrated by the extended analysis at a median of 11.3 years follow up in the NLST RCT reporting an overall reduction of overdiagnosis from 18.5% to 3.1%. However overdiagnosis of bronchioalveolar cell carcinoma remained the same at 79% for both follow up periods.

Estimates based on LUSI RCT data were that 47.5% (95% CI 43.2-50.7) of tumours had a lead time of ≥4 years, 32.8% (95%CI 28.4-36.1) ≥6 years and 22.6% (95%CI 18.6-25.7) ≥8 years[50]. About 43% of screen detected tumours would have remained preclinical over 4 years and 11% over 12 years if screening had not been performed[50]. Given that people were eligible for screening as part of the LUSI RCT until age 69 and 74 for the NLST RCT it is possible that screening will detect a proportion of cancers that would not have become clinically apparent until age 81 or 86. In Germany where the LUSI RCT was undertaken the average life expectancy in 2016 at birth was 83 and 78 years for women and men respectively and 81 and 76 years in the US where the NLST RCT was carried out[52].

Psychosocial outcomes

Jonas et al (2021)[8] found 4 RCTs (DLCST, NESON, NLST and UKLS) which included evaluations of possible psychosocial outcomes of undergoing LDCT screening for lung cancer. The studies examined general health related quality of life (HRQoL), (NELSON, NLST) anxiety, (NLST, DLCST, UKLS) depression (UKLS) and distress (NELSON, UKLS). Jonas et al (2021)[8] concluded there was moderate evidence to suggest that compared with no screening, individuals who receive LDCT screening do not have worse HRQoL, anxiety depression, or distress over 2 years of follow up. There was evidence that in the short term, around the time of screening, that HRQoL and anxiety were worse for individuals who received true positive results compared with other screening results. Distress was worse for people receiving an indeterminate result compared with other results[8].

Health related quality of life

There were 2 RCTs that assessed HRQoL over different time periods and found different results. Jonas et al (2021)[8] observed that the NELSON RCT reported no statistically significant differences over 2 years of follow up between people who had LDCT screening for lung cancer and those in the control group for measures from the Short Form12-item HRQoL questionnaire (SF12) physical component score (PCS), mental component score (MCS) and the EurQoL (EQ 5D) visual analogue scale. None of the parameters for time or trial arm or the interaction between time and trial arm was significant for any of the HRQoL outcome measures[8]. Using the Short Form 36-item HRQoL questionnaire (SF36), the NLST RCT evaluated PCS and MCS from baseline to 6 month follow up between individuals with true positive, false positive and negative screening results in addition to those with

significant incidental findings[53]. Table 29 shows that the only group where there is a significant worsening of HRQoL from baseline to 1 and 6 months is the true positive cohort.

Table 29. HRQoL as change in SF36 physical component score (PCS) and mental component score (MCS) at 1 month and 6 months compared to baseline by screening test result (NLST RCT)[53Error! Bookmark not defined.]

	SF 36 PCS change from baseline		SF 36 MCS change from baseline	
	1 month (95% CI)	6 months (95% CI)	1 Month (95% CI)	6 months (95% CI)
True +ve	-1.18 (-2.81, 0.45)	-7.02 (-8.80, 5.24)***	-3.95 (-5.87,-2.04)***	-4.15 (-6.27, 2.03)***
False +ve	0.46 (-0.04, 0.97)	0.30 (-27,0.87)	-0.22 (-82,0.37)	0.03 (-0.65,0.70)
SIF	0.13 (-0.62, 0.88)	-0.16 (-1.01,0.69)	-0.04(-0.93,0.84)	0.29 (-0.72,1.31)
-ve	0	0	0	0

Abbreviations: +ve – positive, -ve – negative, CI – Confidence interval, HRQoL – health related quality of life, MCS – mental component score, PCS – physical component score, SIF – significant incidental findings, SF – Short from *p<0.05 **p<0.01 ***p<0.001

Jonas et al (2021)[8] points out that in the NLST RCT, participants received extensive counselling as part of the consent process about the high risk of a false positive screen and related follow up, something which may not be implemented as part of a full screening programme.

Anxiety, depression and distress

Three RCTs (DLCST, NLST and UKLS)[54,53,55] explored anxiety and depression in screening and control groups and in the screened group comparing people with different test results for up to 2 years following screening. The measures used by the RCTs varied with NLST using the State Trait Anxiety Inventory (STAI), DLCST using the consequences of screening in lung cancer questionnaire with 15 measures (COS-LC) and UKLS using the Hospital Anxiety and Depression Scale (HADS). Overall negative psychosocial impacts including anxiety and depression were reported for people with true positive and sometimes for people with false positive results no later than 6 months after screening.

DLCST[54] reported that false positive results were associated with more negative short-term psychosocial consequences compared to the control and true negative groups. There was no significant difference in COS-LC scores for any interaction at 6 and 18 months.

In contrast NLST[53] found a significant difference in the ratio of STAI anxiety scores between LDCT and the control (chest x ray) only for those with a true positive result at 1 month and 6 months respectively compared to those with a true negative result. They did not report any worsening in anxiety for those with a false positive outcome.

In the longer term, up to 2 years, the UKLS RCT[55] found people who had been screened did not show any greater anxiety or depression compared to the controls.

Two RCTs (NELSON and UKLS)[56,55] examined the impact of screening on levels of distress in participants. Overall, both studies found that whilst there were some differences in distress levels around the time of screening, by 2 years after screening there were no differences in measures of distress between screening and control groups and those who were screened who received different results.

Incidental findings

Incidental findings unrelated to the target condition are a common element of a screening programme. The use of LDCT as the screening tool, resulting in a cross sectional image from the lower neck to the upper abdomen, means it is inevitable that other clinically significant findings such as cancers of the thyroid, kidney and liver and not so significant findings such as minor coronary artery calcification and small lymph nodes are likely to be detected during screening.

Jonas et al (2021)[8] reported the screen detected incidental findings from 3 RCTs (NELSON, NLST, UKLS). Rates of incidental findings varied substantially between the 3 RCTs reporting them as there is no standard definition to determine which incidental findings were considered significant enough to require further evaluation. For example some findings reported by the NELSON RCT were considered not clinically significant but these were reported as significant by the UKLS such as bronchiectasis, emphysema and pulmonary fibrosis[8].

In a sample of participants from the NELSON RCT(n=1929) 7% of people (n=129) and in the UKLS RCT 5% (n=100) of 1994 people screened had clinically significant incidental findings. In contrast the NLST RCT reported that 58.7% 95% CI 58.0-59.5%) had an extrapulmonary incidental finding with 19.6% (n=3398) being clinically significant from a sample of 17,309 people screened. Common incidental findings were pneumonia, coronary artery calcification, aortic aneurysms, emphysema infections, masses and cysts[8].

The NELSON RCT[57] reported the rate of incidental findings that were both clinically significant and not significant. Of 1929 screened participants, 1409 (73%) had at least 1 incidental finding that was not significant at a rate of 1.34 per participant. There were 144 significant incidental findings requiring further evaluation reported for 129 (7%) people. Of these, 76 (53%) were abnormalities of the liver, 53 (37%) of the kidney, 9 (6%) of the thyroid, 2 (1%) cardiovascular conditions, and 1 abnormality each for the adrenal gland, breast, colon and spine. Overall, 135 additional imaging studies were carried out in 118 participants to obtain a diagnosis. All additional imaging for all participants also revealed new abnormalities not previously seen with the screening LDCT. These included 3

abdominal aortic aneurysms, 2 renal cysts, 1 renal lesion, 1 gall bladder polyp and a metastised carcinoma of the pancreas[57].

The NLST RCT[58] reported a retrospective analysis of clinically significant incidental findings unrelated to the lungs (extrapulmonary findings). In a subset of all those screened with LDCT (n=17,309), 3398 (19.6%, 95% CI 19.0-20.2) were found to have significant extrapulmonary findings. Overall, 1447 (8%) significant incidental findings were cardiovascular, 407(2.4%) renal, 369 (2.1%) hepatobiliary, 207(1.2%) adrenal and 100(0.6%) were thyroid related. There were 67 cancers diagnosed during screening and additional evaluation of 17,309 participants (0.39% 95% CI 0.3%-0.5%), comprised of 45 (0.26%) kidney, 14 (0.08%) thyroid and 8 (0.05%) liver cancers. None of the patients diagnosed with liver cancer had potentially significant liver abnormalities reported on screening CT although they were all diagnosed during the screening period following the first screening CT and within a year of the last screening CT. Similarly, 2 renal malignancies and 1 thyroid malignancy were present in participants findings but not considered potentially significant[58].

A further study from the NLST RCT[59] reported that the LDCT scan was associated with a non-significant increase in thyroid cancer risk (HR = 1.61; 95% CI: 0.96-2.71) which was stronger during the first 3 years when participants were actively screened (HR = 2.19; 95% CI: 1.07-4.47), but not subsequently (HR = 1.08; 95% CI: 0.49-2.37).

For the 1994 people screened by the UKLS[29], 128 significant incidental findings were detected in about 5% (n=100) of people. A significant incidental finding was defined as when a supplementary report needed to be sent to the GP or other referral pathway following standard radiology guidance. Pneumonia accounted for 43% (55) of these findings, other lung conditions 29% (37), cardiovascular conditions 15% (19), masses in other parts of the body 7% (9) and other organ abnormalities 6% (7).

Smoking cessation

Overall, Jonas et al (2021)[8] identified 5 RCTs comparing smoking outcomes between the screening and control arm (DLCST, ITALUNG, NELSON, NLST, UKLS). Of the 5 studies 3 (NELSON, NLST and UKLS) showed that screening compared to no screening may increase smoking cessation especially in people with a true positive or intermediate screening test result.

In the DLCST RCT no differences between the LDCT and control group were found 1 year after randomisation (11.9% vs 11.8%, p=0.95) and similarly for ITALUNG at 4 years post randomisation (16.04% vs 14.64% p=0.059)**Error! Bookmark not defined.**. The NELSON RCT r

eported that the control group had a somewhat higher abstinence rate than the LDCT group (15.1% vs 19.8%, p=0.04)[8]. In contrast, UKLS smoking cessation rates were found to be higher in the LDCT group compared to no screening at 2 years after screening (24% vs 21%, p=0.003)**Error! Bookmark not defined.**. Intention to treat analysis indicated the odds of quitting a mong screened participants in the UKLS RCT was significantly higher at 2 weeks after baseline scan results were received (adjusted OR 2.38 95% CI1.56-3.64 p<0.001) and up to 2 years after recruitment (adjusted OR 1.60 95% CI 1.17-2.18 p=0.003) compared with control[60]. People who needed additional clinical evaluation following screening were also more likely to quit in the longer term compared with the control group (aOR 2.29, 95% CI1.62-3.22, p=0.007) and those receiving a negative result (aOR 2.43, 95% CI 1.54-3.84, p<0.001).

Analysis of DLCST[61] and NLST RCT[62] data also showed some evidence that screening results (true positive or intermediate vs negative) may increase smoking cessation and decrease relapse. Of the 16,964 NLST RCT screened participants, any false positive result was associated with a greater likelihood of a report of quitting (HR 1.23, 95% CI 1.13-1.35) and sustained abstinence for 6 months (HR 1.28, 95% CI 1.15-1.43) among smokers. Among 3745 DLCST participants with smoking behaviour data, smokers receiving positive results following LDCT screening were more likely to quit than those with negative results (17.7% vs 11.4%, p=0.04) and ex smokers with positive results were less likely to relapse than those with negative results (4.7% vs 10.6% p<0.01)[60].

Conclusion

From the quality appraisal of the 3 included systematic reviews and meta-analyses and their assessment of the included RCTs, the evidence base about the clinical effectiveness of screening for lung cancer is overall fair to good with a generally low RoB. All 9 RCTs included by the systematic reviews and meta analyses evaluated some of the harms emerging from lung cancer screening with LDCT; these included false positive scan results, incidental findings, overdiagnosis, adverse events resulting from unnecessary procedures, tests, surgery and concomitant psychosocial outcomes.

It is difficult to assess the balance of harms and benefits of lung cancer screening with LDCT as the outcomes of possible harms are inconsistent across the studies. For example, false positive scan results vary between RCTs from 1.6% to 27.2 %, whilst over diagnosis rates vary from -13% to 67.2%. There was no consistent reporting of incidental findings or adverse outcomes from invasive follow up procedures. Studies examining psychosocial outcomes were somewhat consistent in showing that the screening process may induce negative psychosocial outcomes in the short term but these were persistent only in the medium term for those with a true positive scan result.

At least some of the inconsistency in reported outcomes across RCTs is attributable to substantial methodological heterogeneity such as differences in lung cancer screening eligibility criteria, threshold for a positive screen, round length, number of rounds of screening, follow up period and definition of significant incidental findings. The inconsistency of the findings will affect the certainty with which a lung cancer screening approach can be implemented that both maximises the reduction in lung cancer mortality and morbidity whilst reducing possible screening harms to a minimum.

Summary of Findings Relevant to Criterion 11 (met) and criterion13 (uncertain)[1]

The 3 included systematic reviews and meta-analyses included in this review summarised the harms and benefits of lung cancer screening with LDCT reported from 9 RCTS. Results from the RCTs, particularly 2 large, fair to good quality and adequately powered RCTs, suggest screening people at high risk of lung cancer with LDCT can reduce lung cancer mortality. A meta-analysis across 7 RCTS reported a significant relative reduction of lung specific mortality in the LDCT group of 17% (RR; 0.83 (0.76-0.91). There were different results from 2 adequately powered RCTs concerning all-cause mortality, with 1 showing an overall reduction of 6.7% and the other finding no difference between the LDCT and control arms of the trial. A meta-analysis of the 7 RCTs reported a non-significant relative reduction of overall mortality of 4% in the screening group compared to the control group (RR=0.96, 95% CI 0.92-1.00).

In terms of morbidity, the 2 adequately powered large trials reported a significantly lower incidence of people with late stage cancers diagnosed in the LDCT arm compared to the control arms (IRR 0.72 (95% CI 0.58-0.88) and 0.84 (95% CI 0.76-0.92). Criteria 11 is therefore met.

The RCTS explored harms associated with lung cancer screening and reported a substantial number of people who received a false positive result leading to unnecessary tests and invasive procedures which may lead to adverse events. Other harms included overdiagnosis, incidental findings and short term anxiety and distress.

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[1] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Across the studies there was a substantial heterogeneity of factors related to outcomes including lung screening eligibility criteria, threshold for a positive screen, round length, number of rounds of screening, follow up period and definition of significant incidental findings. This has led to some inconsistency in findings and leads to uncertainty about the approach which would be the most clinically effective to reduce mortality and morbidity from lung cancer screening whilst reducing possible harms to a minimum. Therefore, evidence addressing criterion 13 is met for volume, applicability and quality of evidence but unmet for consistency of findings. Further testing of implementation strategies is therefore necessary to evaluate the most clinically effective screening approach.

Criterion 12 — Acceptability of screening for lung cancer with LDCT

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

Review Question 5. What is the acceptability of screening programmes for lung cancer using LDCT in individuals at increased risk?

Lung cancer screening was previously considered by the UK NSC in 2006, when the strength of evidence about the clinical effectiveness of a screening programme, and the availability of an accurate test was assessed. With the increase in volume and quality of evidence about clinical effectiveness and a suitable screening test since 2006 it is now important to consider the acceptability of a potential screening programme to health professionals and the adult population, especially those likely to be eligible for lung cancer screening. It is essential to understand whether people who are invited for screening are likely to take up the offer and whether those who are diagnosed with screen detected lung cancer are likely to accept treatment. If people do not want to take up the offer of screening or treatment, there will be minimal benefit in the programme being implemented.

Eligibility for inclusion in the review

This review prioritised studies from the UK, reporting lung cancer screening uptake and adherence to treatment, the views and experiences of adults who were or would be invited for screening, and the opinions of lung cancer screening held by professionals.

Description of the evidence

Database searches yielded 384 results, of which 108 were judged to be relevant to this question. 0contains a full PRISMA flow diagram (Appendix 2; Figure 6), along with a table of the included publications were identified as being relevant to question 5 (Table 44). After review of the full texts, 10 UK studies met the inclusion criteria for this question and were prioritised. These consisted of:

- 2 studies as part of RCTs assessing barriers to the uptake of lung cancer screening in those that declined (Ali et al 2015)[63] and whether different types of information about screening made a difference (Quaife et al 2020)[30]
- 2 papers from 1 cohort study about lung cancer screening uptake (Crosbie et al 2019a, Crosbie et al 2019b)[64,65]

- 4 qualitative studies compiling views about lung cancer screening from professionals and groups of people at high risk of developing lung cancer (Kummer et al 2020a, Margariti et al 2020, Ruparel et al 2019, Quaife et al 2016)[66,67,68,69]
- 1 cohort study about the psychological impact of an invitation for lung cancer screening compared to people unaware of screening (Kummer er al 2020b)[70]
- 1 national survey in England of the views of people aged 50-70 about lung cancer screening, (Quaife et al 2018)[71].

No studies were identified that explored the acceptability of treatment following the diagnosis of lung cancer via the lung cancer screening pathway.

Critical appraisal

A range of different types of studies from the UK exploring the acceptance of lung cancer screening across different population groups were identified. These included RCTs, cohort studies and qualitative studies. The RCTs and cohort studies reported screening uptake whilst the qualitative studies used semi structured interviews, focus groups and surveys to understand the enablers, barriers and beliefs of people in the context of lung cancer screening.

Concerns about the studies largely involved population sampling, such as too few current smokers being included, high attrition rates, bias in the characteristics of the group responding to the questionnaires, and unbalanced groups for comparison.

There were few areas of concern about the UKLS RCT[63] when appraised against the JBI RCT checklist. Response bias was observed in the group who completed the non participation questionnaire as younger people and those from lower socioeconomic groups were less likely to respond, thus the self reported barriers from these groups were underrepresented. There were no concerns identified for the LSUT trial and the primary results reported by Quaife et al (2020)[30], but there were concerns about the associated cohort study Kummer et al (2020b)[70] comparing depression, anxiety and cancer worry in people invited for the LSUT RCT and a group of people unaware of lung screening identified from the community. The 2 groups were significantly different with the screening group being more ethnically diverse ($p<0.01$), having lower educational attainment ($p<0.01$), having more retirees ($p<0.01$), more commonly cohabiting ($p<0.01$) and a smaller proportion were current smokers ($p<0.001$). It was not clear if the differences between the groups concerning anxiety, depression and cancer worry were pre-existing differences between the groups or whether they were due to the screening group being targeted for screening. There was a high level of attrition in the screening group between T0 (82.5%),

T1 (51.5%) and T2 (43.1%) and no strategies were described that addressed the loss to follow up.

The Lung Health Check pilot cohort study was reported by Crosbie et al (2019a)[64] and Crosbie et al (2019b)[65] as a pragmatic evaluation of an NHS commissioned pilot lung health check programme. It was a single arm study with follow up of the same participants over 2 annual screening rounds. This study was assessed using the JBI Cohort study checklist. A potential risk of bias was that differences in the demography of people attending and not attending the second year screening test were described but no strategies were used to deal with the potential confounding factors.

The 2 studies by Quaife et al (2018 and 2016)[71,69] were assessed with the JBI cross sectional study checklist. The national survey (Quaife et al 2018)[71] asked people to agree/disagree with statements and comparisons were made between different groups such as between current and former smokers. There were few concerns about the study methodology which aimed to explore views from a representative sample of the older general population, although this group would not necessarily reflect the characteristics of the cohort who would be invited for lung cancer screening. The qualitative study by Quaife et al (2016)[69] used both a survey and semi structured interviews to explore beliefs and attitudes about lung cancer and lung cancer screening in people in lower socioeconomic groups. There were few concerns about this study although people were sampled from a particular urban area of London likely to be part of lower socioeconomic groups with a target age outside of the likely eligible age range for a screening programme. The study found differences in the beliefs between current smokers and former smokers a result not observed in Quaife et al (2018)[71] who sampled people in the general population aged 50-70. The lack of consistency was attributed to small numbers of current heavy smokers in the survey population in the latter study.

A further 3 studies (Kummer 2020a, Margaritii 2020 and Ruparel 2019)[66,67,68] used semi structured interviews and focus groups to explore people's views about specific aspects of lung cancer and screening. These were assessed using the JBI qualitative study checklist. There were few concerns about these studies against the checklist, although there was discussion about the possible reluctance of people to voice views that were perceived as less acceptable. Inevitably the studies only present the voices of those who were prepared to take part in the research, and this may not be representative of the wider population of health professionals in the UK or people eligible for lung cancer screening.

Discussion of findings

A study-level summary of data extracted from each included publication is presented in the 'summary and appraisal of individual studies' in Appendix 3. In Appendix 3 publications are stratified by question.

Lung cancer screening uptake

The acceptance of an invitation to participate in a screening programme (screening uptake) is typically a reflection of people's views about the programme and the ease with which they can attend a screening appointment. However inviting people for lung cancer screening is complex with typically 3 stages:

- inviting a large group of people to express an interest in screening
- using a set of criteria assess who is eligible and book them for a lung health check (LHC),
- prior or during the LHC ask detailed questions to evaluate their eligibility for LDCT

This staged approach means uptake of the LHC or LDCT is unlikely to be representative of the views of all those who could be eligible to be screened in the population.

Uptake of lung cancer screening in the UK was reported in 4 articles from 2 RCTs and 1 cohort study[30,64,65,66] and they reported that between 46.5% and 92.4% who were eligible for a LHC attended their appointment and of those who were evaluated as eligible for LDCT >90% attended.

In order to recruit participants GP lists were searched for people within a target age range of between 50 to 75 years and in the case of Quaife et al (2020)[30] those who were recorded as smokers since 2010. People were contacted and those who responded positively were assessed for eligibility for a lung health check (LHC) comprising a range of tests such as spirometry and carbon monoxide testing. In 2 of the 3 studies[30,] those who attended the LHC were then assessed for eligibility for lung cancer screening with LDCT, using one of 3 risk prediction models; the Liverpool Lung project model (LLP); the Prostate, Lung, Ovarian model and identifying people who had smoked for ≥30 pack years and/or quit ≤15 years. The assessment process differed in the third study of people who agreed to participate in the UKLS RCT, where the LLP version 2 was used to check for eligibility for lung cancer screening with LDCT prior to an LHC appointment being made.

Table 30 shows the trial recruitment method risk model uptake of the lung health check and of the LDCT screen.

Table 30. outlines the recruitment method, risk model used and uptake reported from each of the studies.

Trial (study)	Trial recruitment method	Year recruited	Risk model	LHC uptake* (%)	LDCT uptake^ (%)
UKLS (Ali et al 2015)[63]	Search of GP list: people invited aged 50-75 yrs (n=247,354), 8729 appts booked for LHC	2011	LLPLv2≥5%	4061/8729 (46.5%)	1994/2028 (98.3%)
LSUT (Quaife et al 2020)[30]	Search of GP list for people aged 60-75 yrs, smokers since 2010 (n=147,015), 2012 appts booked for LHC and LDCT eligibility	2015 to 2017	≥30 pack years or quit ≤15 yrs or PLCOM score ≥1.5% or LLP≥2.5%	1058/2012 (52.5%)	770/844 (91.2%)
Manchester's LHC year 1 (Crosbie et al 2019a)[64]	Search of GP list: people invited aged 55-74 yrs (n=16,402), 2827 appts booked for LHC and LDCT eligibility	2016	PLCOM2012 ≥1.5%	2613/2827 (92.4%)	1384/1394 (99.3%)
Manchester's LHC year 2 (Crosbie et al 2019b[65]	1337 people from previous round of which, 1323 invited for LDCT	2016	PLCOM2012 ≥1.5%	1194/1323 (90.2%)	1194/1323 (90.2%)

*LHC uptake – proportion of all those booked for an appointment who attended
^LDCT uptake – all those who had LDCT of those who were eligible following LHC
Abbreviations: Appts – Appointments, GP – General practitioner, LDCT – Low dose computed tomography, LHC – Lung health check LLPLv2 – Liverpool Lung Project model version 2, PLCOM2012 – Prostate, Lung, Colorectal and Ovarian 2012 risk prediction model, Yrs – Years. **Trials**: LSUT – Lung screening uptake trial, UKLS – UK lung screening

Ali et al (2015)[63] reported the uptake from the UKLS RCT and evaluated the demographic factors and self reported barriers of those who declined the invitation to be screened. Recruitment to the trial involved inviting 247,354 people from 2 sites in the Liverpool and Cambridgeshire areas of the country to express an interest in participating, of which 75,958 (30.7%) responded positively. Of this group, 8729 were classified as high risk of developing lung cancer using the LLPv2 and were invited to the trial recruitment centre; 4061 (46.5%) took attended the appointment and were eligible for screening and 2756 (31.6%) actively declined to participate. A further 1906 (21.9%) people did not participate for other reasons such as they changed their mind or on further assessment at the recruitment centre were not eligible for LDCT[63].

Of the 2756 people who declined to participate, 748 (27.1%) completed a non-participation questionnaire**Error! Bookmark not defined.**. Age, gender, smoking status and socioeconomic group, w ere significantly associated with lung cancer screening uptake. Older people were less

likely to attend than those ≤65 years (OR 0.73, p<0.001); women were less likely to take part compared to men (OR 0.64, p<0.001); current smokers were less likely to attend than former smokers (OR 0.70, p<0.001); and people in highest socioeconomic quintile (5) were more likely to attend than those in the lowest quintile (1) (OR 0.56, p<0.001). There were 6 overarching themes mentioned by people returning the questionnaire as important in declining to participate in screening[Error! Bookmark not defined.]. These were:

- practical barriers (n=350, 46.8%) for example; distance to travel, lack of public transport, cost of journey, hospital parking, comorbidities and related treatments, carer responsibilities, already receiving screening and not being in the area at the time of screening
- emotional barriers (n=138, 18.4%) for example, avoidance of lung cancer information and fear
- trial acceptability (18, 2.4%) for example, duration, frequency, and concern of randomisation to a group that would not receive an LDCT scan
- age (n=16, 2.1%) for example, some people felt too old to be screened
- dislikes (n=13, 1.7%) for example, dislike of the hospital system, of health care, of scans and tests
- low perceived risk (n=12, 1.6%) for example, no longer smoking or smoking too few cigarettes to warrant screening.

The associations between the demographic risk factors and self reported barriers to attendance included[Error! Bookmark not defined.]:

- people in socioeconomic status quintiles 3-5 more likely to cite travel as a barrier than those in quintile 1 (Q3 =OR 2.37, p=0.005, Q4 =OR 2.91, p<0.001, Q5 =OR 2.25, p=0.009)
- people more concerned about the risk of lung cancer were more likely to cite comorbidities as a barrier to participation (OR 1.84, p=0.005)
- current smokers vs former smokers were more likely to cite emotional barriers for non participation (OR 2.02, p=0.013)[63].

The Lung Screen Uptake Trial (LSUT)[30] invited people aged 60-75 years with a history of smoking since 2010, from 3 CCG areas in London for a LHC involving a spirometry test, carbon monoxide reading, and for current smokers, smoking cessation advice. At the same appointment people were assessed for LDCT scan eligibility[30]. On invitation people were randomised into 2 groups with each group receiving either a leaflet called ‘MOT for your lungs’ (intervention group) or information similar in presentation to ‘the facts’ booklets distributed with other UK cancer screening programmes (control group)[30]. Uptake of the offer of the LHC appointment was similar in both groups (52.3% vs 52.9%) as was the uptake by eligible participants of LDCT (92.8% vs 89.7%)[30]. In contrast to the UKLS RCT[Error! Bookmark not defined.], neither age, nor gender was associated with LHC or LDCT u

ptake in either group[30]. Similar to the UKLS RCT findings, across both groups current smokers were less likely than former smokers to attend the LHC (OR 0.7; 95% CI 0.56-0.86) and the odds of uptake of those in the least deprived socioeconomic status quintile was nearly twice as high as those in the most deprived quintile (OR1.93; 95% CI 1.28-2.93[30]. Ethnicity was associated with uptake in the intervention group only; there was lower uptake of those with no stated ethnicity compared to other groups (OR 0.15; 95% CI 0.06-0.35)[30].

Most participants reported awareness of the value and benefits of screening, felt supported and were clear about their choice (>89% across both groups)[30]. Risks were well understood although fewer control participants reported that they knew what the risks were compared to the intervention group (76.2% vs 83.2%, p<0.05). Overall, both groups were satisfied with the decision they had made to be screened (>97.3% across both groups)[30].

Crosbie et al (2019a)[64]**Error! Bookmark not defined.** and Crosbie et al (2019b)[65] reported screening u ptake from Manchester's lung health check pilot based in deprived areas of the city. People aged 55-74 were contacted and asked if they had an interest in screening. Of those who responded, current or former smokers were invited to attend an LHC in a venue next to local shopping centres. There was immediate access to LDCT for those eligible at highest risk, according to the risk prediction model PLCOM2012**Error! Bookmark not defined.**. Demand was h igh and all appointments were booked within a few days (n=2827) of which 214 (7.6%) were subsequently unattended**Error! Bookmark not defined.**. Overall, 1394 people were eligible for L DCT screening and of those 1384 (99.3%) had an LDCT scan**Error! Bookmark not defined.**. The following year those people who had tested negative and were eligible were invited for a further LDCT scan (n=1323) of which 1255 (94.9%) made an appointment and 1194 (90.2%) scans were carried out**Error! Bookmark not defined.**. Of those across both screening r ounds who had a positive screening test result (n=111) 1 person declined to accept further diagnostic work up. Non attendees in the second screening round were significantly more likely to be current smokers (63.6% vs 50.6%, p=0.005) but there was no difference in deprivation, gender, age group or lung cancer risk.

User experience: perceptions, attitudes and responses of those involved in lung cancer screening studies

Two studies from the LSUT RCT[66,70] reported the factors influencing people to participate in screening when they receive an invitation and the concerns of people who have been screened. Both positive and negative view points were voiced with the overall balance being that people supported lung cancer screening.

The LSUT RCT compared uptake of LDCT screening from 2 different types of invitation. As part of the LSUT trial, Kummer (2020a)[66]**Error! Bookmark not defined.** and Kummer (2020b)[70]**Error! Bookmark not defined.** mapped the psychological and behavioural responses to LDCT, of people invited for LDCT lung cancer screening with either method. They also compared the psychological outcomes of LDCT screening with current and former smokers who were unaware of lung cancer screening who were recruited via a national survey about smoking behaviour.

Kummer et al (2020a)[66] interviewed 28 people to identify the key factors influencing their psychological and behavioural responses to be being invited for LDCT screening, these included:

- existing concerns; about lung health and smoking history
- social support; some people shared the invitation with spouses or other people to ask their opinion about attending whilst others did not share the information
- stigma and self blame; some people felt guilty for smoking and worry about future cancer risk
- negativity and fatalism; current smokers especially held negative views about their respiratory health and perception of irreversible damage, also the perception of lung cancer as a 'death sentence', and hesitancy in seeking social support for a follow up appointment
- competing priorities; some people with existing medical conditions considered their results unimportant and others found external circumstances were 'more pressing' so the lung health check was of less concern.

People had a range of responses to the lung health check itself and the information they received at different points along the screening pathway. This included:

- welcoming the offer of a lung health check
- anxiety about being targeted for an invitation
- apprehension about being scanned
- concern about abnormal spirometry results and how this would play out with the LDCT results
- relief at having an incidental finding as it meant they did not have lung cancer
- concern that indeterminant results were cancer
- positive intention to take part in any future lung screening programmes
- more attentive of possible lung cancer symptoms and intention to seek help early if symptoms arose
- motivation to quit smoking
- not motivated to stop smoking because they had not been explicitly told to stop
- increasing smoking while waiting for the LDCT result
- intending to go to the GP for regular spirometry readings

- positive engagement in other cancer prevention behaviours such as increasing exercising, changing diet or avoiding air pollution.

As part of the LSUT RCT, Kummer et al (2020b)[70]**Error! Bookmark not defined.** asked those who w ere invited for LDCT screening (n=787) to complete 2 questionnaires; a 7 point cancer worry scale and a Hospital Anxiety and Depression scale (HADS). At the LDCT appointment and 3 months after the appointment people were asked to complete both questionnaires, whilst the day after the appointment people were asked to complete only the cancer worry scale. A similarly high risk group (n=383) of people unaware of screening, recruited from people completing the national survey 'Smoking Study toolkit' were asked to complete both measures once**Error! Bookmark not defined.**. Table 32 shows the comparison of g roups using multivariable analysis adjusting for socio-demographic characteristics and smoking status. The cancer worry score was significantly worse for people on the day of LDCT (p<0.001) and 3 months later (p<0.001) but not the day after the LDCT appointment (p=0.56) compared to those unaware of screening. Similarly, the HADS results were significantly worse for both anxiety and depression on the day of LDCT (p<0.001 and p=0.04 respectively) and 3 months later (p<0.001 for both anxiety and depression) for the LDCT group compared to the those unaware of screening**Error! Bookmark not defined.**.

Table 32. Multivariable analysis of cancer worry and Hospital Anxiety and Depression Score (HADS) results for an LDCT screened group vs a group unaware of screening (Kummer et al 2020b)[70]

	Community group UE Mean (95% CI)	LDCT group Mean (95% CI)	p value	Estimate adjusted Beta (95% CI)	p value
Cancer worry T0	9.32 (8.96-9.69)	11.34 (11.09-11.59)	p<0.001	1.99 (1.51-2.64)	p<0.001
Cancer worry T1		10.97 (10.66-11.28	p<0.001	0.08 (-0.19 to 0.34)	p=0.56
Cancer worry T2		11.88 (11.49-12.27)	p<0.001	0.87 (0.49-1.25)	p<0.001
Anxiety T0	3.32 (2.94-3.70)	4.73 (4.42-5.04)	p<0.001	1.38 (0.85-1.92)	p<0.001
Anxiety T2		5.78 (5.33-6.23)	p<0.001	1.33 (0.99-1.68)	p<0.001
Depression T0	3.85 (3.44-4.27)	3.32 (3.06-3.57)	p=0.02	-0.51 (-0.99 to -0.03)	p=0.04
Depression T2		4.15 (3.76-4.55)	p=0.30	0.64 (-0.32 to 0.95)	p<0.001

CI – confidence interval, UE – Unadjusted estimate, LDCT - low dose computed tomography, T0 – Day of LDCT screening or single set of results for HADS and Cancer Worry scores for screening unaware group, T1 – Day after LDCT scan , T2 – 3 months after LDCT scan.

Public perceptions and opinions about lung cancer

Three studies[Error! Bookmark not defined.Error! Bookmark not defined.] explored perceptions of lung ca ncer screening by different groups of the public, a high proportion of whom may be eligible for future lung cancer screening. The studies reported that most people thought lung cancer screening was a good idea and would participate if invited (>90%) but had conflicting views about lung cancer treatment,

Ruparel et al (2019)[68][Error! Bookmark not defined.] held 7 focus groups each with people likely to b e eligible for screening. Groups of 5 people who were either smokers or former smokers aged 60 to 75 and with higher or lower educational backgrounds were asked about their beliefs about lung cancer screening, what information would be helpful and views about the harms of screening[Error! Bookmark not defined.].

People's responses to a potential lung cancer screening programme and information about screening included[Error! Bookmark not defined.]:

- relating negative experiences and fatalism about lung cancer, wariness of screening when there was likely to be a poor prognosis
- positive views about the benefits of early detection, an opportunity to be checked and a precautionary measure
- scepticism about statistics
- too much information and 'information overload' and the subsequent difficulty in making a decision
- the importance of being informed and making an informed choice but feeling that people did not often read the leaflets

People's responses about the harms of screening included:

- anxiety about indeterminate results
- acknowledgement that false negative and false positive results would be difficult to cope with
- a lack of understanding about overdiagnosis
- little concern about exposure to radiation

A further study by Quiafe et al (2016)[69][Error! Bookmark not defined.] explored cancer beliefs from c ommunities in London in people who smoked, were former smokers, or who had never smoked, who were aged over 40, with a low socioeconomic status,. Researchers combined a survey of 175 people and 21 semi structured interviews to provide insights into effective engagement strategies[Error! Bookmark not defined.]. The survey asked people whether they agreed w ith different statements.

Current smokers were more likely to believe they had smoked too long to benefit from screening compared to former smokers ($p<0.05$) and that if the LDCT was negative they

could continue smoking (p<0.001)[Error! Bookmark not defined.]. Current smokers were also more l ikely to believe that cancer was a ‘death sentence’ compared to former or never smokers (p<0.005) and that they were at high risk of developing lung cancer in the next few years (p<0.001). However, overall 64.8% (n=105) of survey respondents agreed that LDCT could improve the chances of surviving lung cancer, but 17.9% (n=29) thought screening was only necessary if you had symptoms whilst 22% (n=35) thought lung cancer treatment would be worse than lung cancer itself[Error! Bookmark not defined.].

The findings of the semi structured interviews suggested that although most people were supportive of lung cancer screening this conflicted with negative views about survival and treatment. People were concerned there was little they could do to reduce their risk of lung cancer irrespective of smoking status because of the presence of other lung cancer risk factors, such as air pollution, that they felt they could do little about. Some older participants voiced a fear of diagnosis, lung cancer screening avoidance, fatalism and perceived stigma around screening (because smoking is considered a negative behaviour), which could deter participation. Targeting individuals based on highly stigmatised behaviour which they may feel guilty about appeared to complicate people’s decision making.

The Attitudes Behaviour and Cancer UK survey (ABACUS), asked for people’s views about lung cancer screening in England. Quaife et al (2018)[7171] analysed 1464 people aged 50 to 70 who completed the survey. People were asked about lung cancer and lung cancer screening and to rate their intention to participate in screening if invited in 3 different ways; by GP recommendation; NHS screening programme or pre-scheduled appointment.

Quaife et al (2018)[7171] reported that of the 1445 people responding to the question ‘is lung cancer a death sentence‘ 47.6% (582) agreed it was; a higher proportion (35%) than those asked the same question by Quaife et al (2016)[69Error! Bookmark not defined.]. There were no d ifferences in the response to the question between current smokers and former smokers but in Quaife et al (2016)[69Error! Bookmark not defined.] smokers with a lower socioeconomic status w ere much more likely than former and never smokers to believe the statement (47.7% vs 13.0% vs 10.9% respectively, p<0.001). Quaife et al (2018)[7171] found half of people (50.8%, n=689) thought detecting cancer early meant there was a good chance of them surviving, whilst 91.5% said they would opt for surgery if it was offered. Current smokers were less likely to agree with these views compared to former smokers (OR 0.64; 95% CI 0.46 to 0.88, p=0.01 and OR 0.38; 95%CI 0.21 to 0.68, p<0.001 respectively)[71]. A total of 1354 (91.7%) thought lung cancer screening was a good idea and of those who were current or former smokers (n=642), 91.6% (n=588) indicated they would participate in screening if they received an NHS invitation, 95.8% (n=615) if they received a GP invitation and 91.9% (n=590) if a pre-scheduled appointment was made for the following month[71].

Professional perceptions and opinions about lung cancer

Overall, 2 small studies explored the views about lung cancer screening held by health professionals[Error! Bookmark not defined.Error! Bookmark not defined.]. The studies reported cautious ac ceptance of lung cancer screening with some concerns relating to evidence for the harms and benefits of lung cancer screening and access to the right resources and guidance.

Margariti et al (2020)[67Error! Bookmark not defined.] and Ruparel et al (2019)[68Error! Bookmark not defined.] bo th explored the views about lung cancer screening held by health professionals (n=16, n=18 respectively) including GPs, staff from smoking cessation services and respiratory clinics and pharmacists. Thematic analysis of the transcripts of semi structured interviews identified the following key themes:

- lack of awareness and understanding of lung cancer screening; generally health professionals did not feel confident about their knowledge and understanding, of the subject and were unaware of UK pilot trials
- perception of a lack of awareness by the public of curative treatments
- perception that sometimes patients were more worried than they need to be about diagnostic findings
- ambivalence about screening; whilst acknowledging the possible benefits to their patients, health professionals were concerned about the harms of screening
- concern that overdiagnosis would be difficult to explain to patients and people would find it difficult to choose not to be treated in those situations
- radiation exposure was a concern for some
- the time and resources needed to support the programme; for example, the extra education and training for professionals, additional reassurance and time spent with patients to help them decide whether to be screened or not
- implications for guidelines, risk modelling, organisational resources; health professionals emphasised the need for clear guidance about implementing the programme and the evidence behind the choice of risk model to determine eligibility for screening.

Summary of Findings Relevant to Criterion 12: Criterion met for volume, applicability and quality of evidence, unmet for consistency. [2]

A range of different types of studies from the UK exploring the acceptance of lung cancer screening across different population groups were identified. All the included studies primarily targeted those who would be eligible for lung cancer screening or health professionals who would be involved in implementing a screening programme.

Studies reporting uptake focussed on people expressing an interest in screening, taking up the offer of a lung health check and consenting to the actual screening test comprising LDCT. No studies reporting the acceptance rate of lung cancer treatment or management. Data reported from the UKLS (n=8729)**Error! Bookmark not defined.** , LSUT (n=2012) RCTs and the LHC cohort study reported uptake of a lung health check of 46.5%. 52.5% and 92.4% respectively. Of those who attended the lung health check, ≥90% of those eligible for an LDCT took up the offer of a scan. However, current smokers in both studies were less likely to take up the offer of a scan which reflects a lower acceptability of lung cancer screening by this group. A single study reported the number of people refusing further diagnostic workup following a positive (n=1/111) screening test result**Error! Bookmark not defined.**.

Although the qualitative studies are all applicable to the UK it is less clear whether they entirely reflect the balance of beliefs and viewpoints likely to be encountered when implementing a screening programme. Both positive and negative view points were voiced with the overall balance being that people supported lung cancer screening. In 1 study (n=1445)[71] over 90% of people thought lung cancer screening was a good idea and a high proportion (≥ 90%) intended to participate if offered a screening appointment. Health professionals were more ambivalent about screening and the balance of harms and benefits of a programme, also flagging the need for adequate evidence based guidance, resources and training to ensure screening was effective.

Concerns about the qualitative studies largely involve population sampling, such as too few current smokers being included, high attrition rates, bias in the characteristics of the group responding to the questionnaires, and unbalanced groups for comparison.

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[2] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

On balance, the evidence base suggests that there is acceptance for the lung cancer screening test and that about half of people invited may take up the offer to participate. In hypothetical scenarios a high proportion of people also intend to take up the offer of screening. Acceptance by professionals is predicated on reassurance about the evidence for the harms and benefits of lung cancer screening in tandem with the right resources and guidance.

Larger good quality studies would improve the consistency of the evidence base for the UK population. Evidence about the acceptance of the full screening pathway including the diagnostic work up and treatment or management of lung cancer is also needed. Currently the evidence for the acceptability of the screening test is met but the lack of evidence about acceptability of the diagnostic and treatment elements of the pathway are unclear. The evidence base addressing criterion 12 is therefore met for volume, applicability and quality of evidence, but unmet for consistency of findings.

Review summary

Overall conclusions and implications for policy

This review focussed on systematically identifying evidence about the clinical effectiveness, balance of harms and benefits (review question 4) and acceptability of lung cancer screening for individuals at high risk of developing the condition (review question 5).

The 9 RCTs that have tested the clinical effectiveness of lung cancer screening, identified and reported by 3 systematic reviews and meta analyses, have been the predominate source of information for both review questions. All the RCTs focussed on the main factors that contribute the most risk in developing lung cancer including older people and exposure to tobacco by current or former smokers.

Key questions

Clinical effectiveness of lung cancer screening
Key question 4, which links to UK NSC criteria 11 and 13, concerns the clinical effectiveness of lung cancer screening programmes using LDCT in individuals at increased risk of developing the condition. Evidence from 9 RCTs with long term follow up, particularly 2 large fair to good quality RCTs, suggest screening people at high risk of lung cancer with LDCT can reduce lung cancer mortality and may reduce all-cause mortality. These results have been confirmed in meta-analyses. The RCTS also showed that screening identified people at an earlier stage of lung cancer when treatment is more effective, compared to people who had no screening and were diagnosed with lung cancer. Therefore, the volume, quality and direction of new evidence addressing criterion 11 concerning the effectiveness of lung cancer screening to reduce mortality and morbidity is sufficient to ensure that this criterion is met.

There are also harms associated with lung cancer screening. The volume, quality and direction of evidence about criterion 13 concerning the harms and benefits of a lung cancer screening programme is sufficient to understand that there are clear harms including a substantial number of people who will receive a false positive result leading to unnecessary tests and invasive procedures which may lead to adverse events. Other harms include overdiagnosis, incidental findings and short term anxiety and distress. However, across the studies there was a substantial heterogeneity of factors related to outcomes including lung screening eligibility criteria, threshold for a positive screen, round length, number of rounds of screening, follow up period and definition of significant incidental findings. This heterogeneity in approach means that there is inconsistency in the evidence, and that the

balance between the benefits and harms for specific screening strategies is not clear. This element of UK NSC criterion 13 is therefore unmet. The impact of the variation in screening strategies might be addressed in updated cost effectiveness evaluations in which quality of life is factored into the life years gained through screening. The systematic review on the cost-effectiveness of lung cancer screening reported here showed a broad range of ICERs reported from evaluations undertaken internationally and new evidence from the 9 RCTs is frequently published, therefore a UK model incorporating this evidence would be helpful.

Acceptability of lung cancer screening

Key question 5 relates to UK NSC criterion 12 about acceptability of the lung cancer screening programme to the public, patients and health professionals in the UK. The volume, quality and applicability of the evidence is sufficient to understand that on balance people, patients and professionals are likely to consider lung cancer screening to be beneficial. The evidence base suggests that there is acceptance for the lung cancer screening test and that about half of people invited may take up the offer to participate. For example, 2 UK trials inviting people for a lung health check that incorporated an LDCT screen reported uptake of 46.5% and 52.5%. In qualitative studies reporting the response of people to hypothetical scenarios, a high proportion of people also expressed an intention to take up the offer of screening. Acceptance by professionals is predicated on reassurance about the evidence for the harms and benefits of lung cancer screening in tandem with the right resources and guidance. There was limited evidence concerning the acceptability of the full screening pathway including diagnostic work up and treatment of lung cancer for those people who test positive. The evidence base addressing criterion 12 is therefore met for volume, applicability and quality of the evidence but unmet for consistency of findings.

Contextual questions

In addition to the key review questions, contextual questions 1 to 3 give a narrative overview of the epidemiology of lung cancer, the accuracy of the LDCT screening test and of algorithms to identify people at highest risk of developing the condition and the cost effectiveness of lung cancer screening. This overview suggests that the epidemiology of lung cancer is well understood and criteria for identifying people at most risk of developing lung cancer who would benefit from screening have been tested on a large scale by RCTs and observational studies. However, the more complex algorithms developed by researchers have largely been tested in smaller scale observational studies. There is a lack of consistency in the outcomes of studies exploring cost effectiveness of lung cancer screening. Overall, lung cancer screening is likely to be more expensive than treating people through the current symptomatic pathway of diagnostic testing. Some scenarios, including 2 reported by UK studies, indicate a lung cancer screening programme would

meet the cost effectiveness threshold (£10,000-20,000 per QALY) applied to UK interventions. However, overall there is such a wide variation in ICERs across strategies that without a better understanding of the sources of variation there could be little confidence that this level of cost effectiveness could be reliably demonstrated in a further study or in practice.

Recommendations and research implications

To address the uncertainty about the best approach to achieve maximum clinical effectiveness in reducing mortality and morbidity from lung cancer screening whilst reducing possible harms to a minimum, this review recommends further work incorporating the results of a modelling exercise which is currently underway. This modelling work will update the health economic analysis by Snowsill et al (2018)[1] and be used to estimate the clinical effectiveness and cost effectiveness of different lung cancer screening strategies including the population (age and smoking history), screening intervals, lung cancer risk thresholds and CT scanning schedules. Assuming screening is found to be cost effective, further studies would be helpful to understand shorter term outcomes, for example those relating to feasibility and acceptability. Studies with these aims might be considered as part of an implementation strategy, the prioritisation of research questions and the design of which should be discussed and planned with stakeholders in these areas.

Limitations

This rapid review process was conducted over a condensed period of time. Studies not available in the English language, abstracts and poster presentations, were not included.

Due to the fast moving pace of this field of research, evidence about lung cancer screening is published frequently. This has meant some known important articles published after the systematic search was carried out have been excluded from review questions 4 and 5. Abstracts of 3 articles were reviewed to rapidly assess if their conclusions varied substantially from those of the studies included in this review. The abstracts reviewed were from:

- Field et al (2021)[2] – presenting the lung cancer mortality, and cancer stage distribution outcomes of the UKLS RCT at 7.3 years follow up. This showed a non significant reduction in lung cancer mortality. The same article reports a meta analysis of 9 RCTs estimating a 16% relative reduction in lung cancer mortality in the LDCT arm compared to the non LDCT control arm (risk ratio (RR) 0.84; 95% CI 0.76 – 0.92)

- Hunger et al (2021)[3] – a meta analysis of 8 RCTs reporting a 12% relative reduction in lung cancer mortality in the LDCT arm compared to a non LDCT control arm (RR =0.88; 95% CI 0.79-0.97). Between 4% to 24% of scans were classified as positive with 84% to 96% false positive. Overdiagnosis rates were estimated as between 19% and 69% of diagnosed lung cancers.
- Passiglia et al (2021)[4] – a meta analysis of 9 RCTs reporting a 20% relative reduction in lung cancer mortality in the LDCT arm compared to a non LDCT control arm (RR 0.87 ;95% CI 0.78 – 0.98). There was a non significant reduction in all cause mortality. Significantly more cancers in the LDCT arm were diagnosed at an early stage compared to a non- LDCT control arm (RR 2.84 95% CI 1.76 – 4.58) and significantly fewer cancers were diagnosed in the LDCT arm compared to the non LDCT control arm at a late stage (RR0.75; 95% CI 0.68 – 0.83). There was a significant increase in overdiagnosis rates (38%; 95% CI 14 – 63).

Based on these particular article abstracts the results do not change the direction of the conclusions and recommendations of this review. In addition to these articles there may be others that have been published after the search date of this review which haven't come to the reviewers attention which could only be determined with a further systematic search of the literature.

Appendix 1 — Search strategy

Electronic databases

The search strategy for question 4 included searches of the databases shown in Table 31 and Table 32 shows the databases searched for question 5.

Table 31. Summary of electronic database searches and dates for question 4

Database	Platform	Searched on date	Date range of search
MEDLINE,	Ovid SP	07/05/2021	2020 to Present for smokers 2006 to present for risk factors other than smoking
Embase	Ovid SP	07/05/2021	2020 to Present for smokers 2006 to present for risk factors other than smokers
PubMed	https://pubmed.ncbi.nlm.nih.gov/	07/05/2021	
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	07/05/2021	Issue 5 of 12, May 2021

Table 32. Summary of electronic database searches and dates for question 5

Database	Platform	Searched on date	Date range of search
MEDLINE,	Ovid SP	07/06/2021	2006 to Present
Embase	Ovid SP	07/06/2021	2006 to Present
PsychINFO	Ovid SP	07/06/2021	2006 to Present
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	07/06/2021	Issue 6 of 12, June 2021

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase). For question 4 separate searches were undertaken for studies concerning smokers and those concerning other risk

factors in Medline and Embase. The PubMed search for question 4 used "lung cancer" screening[title] and was limited to systematic reviews, English and 2006 onwards.

Tables 33 to 34 show the search terms for question 4 for all databases. Tables 35 to 41 show the question 5 search terms for all databases.

Table 33. Medline search strategy for question 4 (smokers)

#	Searches	Results
1	exp Lung Neoplasms/	241912
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	222762
3	1 or 2	320158
4	mass screening/	107191
5	exp early diagnosis/	55529
6	(screen* or diagnos* or detect*).ti.	1165641
7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	890134
8	4 or 5 or 6 or 7	1881168
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	4766
10	Tomography, X-Ray Computed/	391667
11	9 or 10	393664
12	3 and 8 and 11	5945
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	2239
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	2421
15	12 or 13 or 14	6434
16	ex-smokers/ or smokers/	2643
17	exp smoking/	151434
18	Tobacco Smoke Pollution/	13599
19	(smoker? or exsmoker? or smoking or "tobacco use").ti,ab,kw.	273870
20	16 or 17 or 18 or 19	321310
21	15 and 20	1359
22	randomized controlled trial.pt.	529265
23	controlled clinical trial.pt.	94146
24	randomized.ab.	519008
25	placebo.ab.	217708
26	clinical trials as topic.sh.	195713
27	randomly.ab.	356818

28	trial.ti.	239484
29	22 or 23 or 24 or 25 or 26 or 27 or 28	1364659
30	exp animals/ not humans/	4822137
31	29 not 30	1256357
32	21 and 31	312
33	limit 21 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	53
34	32 or 33	338
35	limit 34 to yr="2020 -Current"	49
36	limit 35 to english language	47

Table 34. Embase search strategy for question 4 (smokers)

#	Searches	Results
1	exp lung cancer/	347069
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	335091
3	1 or 2	463937
4	mass screening/ or cancer screening/ or screening test/ or screening/	381743
5	early diagnosis/ or early cancer diagnosis/	122215
6	(screen* or diagnos* or detect*).ti.	1384761
7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	1300781
8	4 or 5 or 6 or 7	2471602
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	8708
10	computer assisted tomography/ or exp x-ray computer tomography/	777437
11	9 or 10	781887
12	3 and 8 and 11	11181
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	3899
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	4205
15	12 or 13 or 14	12119
16	exp smoking/ or "tobacco use"/	417977
17	(smoker? or exsmoker? or smoking or "tobacco use").ti,ab,kw.	413078
18	16 or 17	526807
19	15 and 18	3376
20	(randomised controlled trial/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or (random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin	2149337

	square or assign* or allocat* or volunteer*).ti,ab.) not ((exp animals/ or nonhuman/) not human/)	
21	19 and 20	613
22	limit 19 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	103
23	21 or 22	669
24	limit 23 to yr="2020 -Current"	78
25	limit 24 to english language	77

Table 35. Medline search strategy for question 4 (other risk factors)

#	Searches	Results
1	exp Lung Neoplasms/	241912
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	222762
3	1 or 2	320158
4	mass screening/	107191
5	exp early diagnosis/	55529
6	(screen* or diagnos* or detect*).ti.	1165641
7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	890134
8	4 or 5 or 6 or 7	1881168
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	4766
10	Tomography, X-Ray Computed/	391667
11	9 or 10	393664
12	3 and 8 and 11	5945
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	2239
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	2421
15	12 or 13 or 14	6434
16	exp Lung Neoplasms/ci, ge	38900
17	Occupational Exposure/ or Occupational Diseases/	128747
18	Asbestos/ae or Chromium/ae or Arsenic/ae or Radon/ae or Coal Tar/ae or Coal/ae or exp Air Pollutants/ae	21911
19	exp Pulmonary Disease, Chronic Obstructive/	58133
20	exp Idiopathic Pulmonary Fibrosis/	5777
21	*Risk Factors/	1176

22	((work place or workplace or occupational) adj5 (exposure? or hazard? or risk? or disease?)).ti,ab,kw.	49342
23	(asbsetos or chromium or arsenic or radon or coal or pollutant?).ti,ab,kw.	144405
24	((chronic adj2 (lung or pulmonary or bronchitis)) or copd or emphysema).ti,ab,kw.	118759
25	idiopathic pulmonary fibrosis.ti,ab,kw.	9439
26	((family or genetic) adj2 history).ti,ab,kw.	64831
27	(((high* or increas* or cancer or predict*) adj3 risk*) or (risk? adj5 (based or eligib))).ti,ab,kw.	949076
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	1427484
29	15 and 28	1562
30	randomized controlled trial.pt.	529265
31	controlled clinical trial.pt.	94146
32	randomized.ab.	519008
33	placebo.ab.	217708
34	clinical trials as topic.sh.	195713
35	randomly.ab.	356818
36	trial.ti.	239484
37	30 or 31 or 32 or 33 or 34 or 35 or 36	1364659
38	exp animals/ not humans/	4822137
39	37 not 38	1256357
40	29 and 39	294
41	limit 29 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	50
42	40 or 41	321
43	limit 42 to yr="2006 -Current"	293
44	limit 43 to english language	279

Table 36. Embase search strategy for question 4 (other risk factors)

#	Searches	Results
1	exp lung cancer/	347069
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	335091
3	1 or 2	463937
4	mass screening/ or cancer screening/ or screening test/ or screening/	381743
5	early diagnosis/ or early cancer diagnosis/	122215
6	(screen* or diagnos* or detect*).ti.	1384761

7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	1300781
8	4 or 5 or 6 or 7	2471602
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	8708
10	computer assisted tomography/ or exp x-ray computer tomography/	777437
11	9 or 10	781887
12	3 and 8 and 11	11181
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	3899
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	4205
15	12 or 13 or 14	12119
16	occupational exposure/ or occupational disease/ or occupational cancer/ or exp occupational lung disease/ or coal worker/	143004
17	carcinogen/ or asbestos/ae, to or arsenic/ae, to or radon/ae, to or coal/ae or coal tar/ae, to or air pollutant/ae, to	52151
18	chronic obstructive lung disease/	143885
19	fibrosing alveolitis/	26810
20	*risk factor/	92124
21	high risk patient/	142099
22	((work place or workplace or occupational) adj5 (exposure? or hazard? or risk? or disease?)).ti,ab,kw.	66084
23	(asbsetos or chromium or arsenic or radon or coal or pollutant?).ti,ab,kw.	185829
24	((chronic adj2 (lung or pulmonary or bronchitis)) or copd or emphysema).ti,ab,kw.	187594
25	idiopathic pulmonary fibrosis.ti,ab,kw.	16747
26	((family or genetic) adj2 history).ti,ab,kw.	115375
27	(((high* or increas* or cancer or predict*) adj3 risk*) or (risk? adj5 (based or eligib))).ti,ab,kw.	1442902
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	2201684
29	15 and 28	3529
30	(randomised controlled trial/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or (random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.) not ((exp animals/ or nonhuman/) not human/)	2149337
31	29 and 30	615

32	limit 29 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	108
33	31 or 32	676
34	limit 33 to yr="2006 -Current"	640
35	limit 34 to english language	623

Table 37. Cochrane library search strategy for question 4

#	Search
1	MeSH descriptor: [Lung Neoplasms] explode all trees
2	(((lung or pulmonary) NEAR/3 (cancer* or neoplas* or carcinoma* or tumor* or tumour*))):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Mass Screening] this term only
5	MeSH descriptor: [Early Detection of Cancer] explode all trees
6	(screen* or diagnos* or detect*):ti,ab,kw
7	((screen* or (early NEAR/2 (diagnos* or detect*)))):ti,ab,kw
8	#4 or #5 or #6 or #7
9	MeSH descriptor: [Tomography Scanners, X-Ray Computed] explode all trees
10	((("low dose" NEAR/5 ("computed tomogra*" or ct)) or ldct)):ti,ab,kw
11	#9 or #10
12	#3 and #8 and #11
13	((("computed tomogra*" or ct) NEAR/5 screen*) and ((lung or pulmonary) NEAR/3 (cancer* or neoplas* or carcinoma* or tumor* or tumour*))):ti,ab,kw
14	((("lung cancer" NEAR/3 screen*) and ("computed tomogra*" or ct))):ti,ab,kw
15	#12 or #13 or #14

Table 38. Medline search strategy for question 5

#	Searches	Results
1	exp Lung Neoplasms/	243519
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	224151
3	1 or 2	321916
4	mass screening/	107774
5	exp early diagnosis/	56256
6	(screen* or diagnos* or detect*).ti.	1171044
7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	896806
8	4 or 5 or 6 or 7	1891884
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	4815
10	Tomography, X-Ray Computed/	393261

11	9 or 10	395263
12	3 and 8 and 11	5993
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	2264
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	2443
15	12 or 13 or 14	6489
16	exp Lung Neoplasms/ci	5370
17	(((high* or increas* or cancer or predict*) adj3 risk*) or (risk? adj5 (based or eligib))).ti,ab,kw.	956566
18	ex-smokers/ or smokers/	2789
19	exp smoking/	152194
20	Tobacco Smoke Pollution/	13661
21	(smoker? or exsmoker? or smoking or "tobacco use").ti,ab,kw.	275327
22	16 or 17 or 18 or 19 or 20 or 21	1221530
23	attitude to health/ or health knowledge, attitudes, practice/ or exp "treatment adherence and compliance"/	425762
24	(acceptab* or acceptance or attitude? or perception? or perspective? or view* or opinion? or experience? or satisf*).ti,ab,kw.	2483828
25	(attendan* or nonattendan* or adheren* or nonadheren* or comply or complian* or noncomplian* or concordan* or uptake or utili?ation or dropout? or drop out?).ti,ab,kw.	1008456
26	mental fatigue/ or stress, psychological/ or anxiety/	202754
27	(anxious or anxiety or psycholog* or stress).ti,ab,kw.	1203240
28	(barrier? or obstacle? or challenge? or facilitat* or enabl* or opportunit*).ti,ab,kw.	2183963
29	23 or 24 or 25 or 26 or 27 or 28	6135226
30	15 and 22 and 29	703
31	randomized controlled trial.pt.	532823
32	controlled clinical trial.pt.	94194
33	randomized.ab.	522387
34	placebo.ab.	218585
35	clinical trials as topic.sh.	196141
36	randomly.ab.	358907
37	trial.ti.	241291
38	31 or 32 or 33 or 34 or 35 or 36 or 37	1371445
39	exp animals/ not humans/	4838132
40	38 not 39	1262435
41	30 and 40	160

42	limit 30 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	20
43	grounded theory/ or exp qualitative research/	64478
44	focus groups/ or interviews as topic/ or "surveys and questionnaires"/	571631
45	(qualitative research or interview* or focus group* or questionnaire* or survey* or grounded theory or hermeneutics or ethnograph* or thematic or mixed method*).ti,ab,kw.	1449570
46	(qualitative or synthesis or metareview or meta-review or metaethnograph*).ti.	368914
47	43 or 44 or 45 or 46	1933811
48	30 and 47	156
49	41 or 42 or 48	287
50	limit 49 to yr="2006 -Current"	275
51	limit 50 to english language	261

Table 39. Embase search strategy for question 5

#	Searches	Results
1	exp lung cancer/	346446
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab,kw.	334606
3	1 or 2	462868
4	mass screening/ or cancer screening/ or screening test/ or screening/	378488
5	early diagnosis/ or early cancer diagnosis/	121083
6	(screen* or diagnos* or detect*).ti.	1376174
7	(screen* or (early adj2 (diagnos* or detect*))).ab,kw.	1297738
8	4 or 5 or 6 or 7	2459436
9	((low dose adj5 (computed tomogra* or ct)) or ldct).ti,ab,kw.	8755
10	computer assisted tomography/ or exp x-ray computer tomography/	772854
11	9 or 10	777361
12	3 and 8 and 11	11199
13	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab,kw.	3927
14	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab,kw.	4238
15	12 or 13 or 14	12140
16	(((high* or increas* or cancer or predict*) adj3 risk*) or (risk? adj5 (based or eligib))).ti,ab,kw.	1442416

17	exp smoking/ or "tobacco use"/	415705
18	(smoker? or exsmoker? or smoking or "tobacco use").ti,ab,kw.	411452
19	16 or 17 or 18	1860946
20	exp patient attitude/	428792
21	program acceptability/	2317
22	(acceptab* or acceptance or attitude? or perception? or perspective? or view* or opinion? or experience? or satisf*).ti,ab,kw.	3560447
23	(attendan* or nonattendan* or adheren* or nonadheren* or comply or complian* or noncomplian* or concordan* or uptake or utili?ation or dropout? or drop out?).ti,ab,kw.	1392144
24	mental stress/	87078
25	anxiety/ or anticipatory anxiety/	224075
26	(anxious or anxiety or psycholog* or stress).ti,ab,kw.	1599564
27	(barrier? or obstacle? or challenge? or facilitat* or enabl* or opportunit*).ti,ab,kw.	2708109
28	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	8047393
29	15 and 19 and 28	1583
30	limit 29 to (meta-analysis or "systematic review" or "reviews (maximizes specificity)")	54
31	(randomised controlled trial/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or (random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.) not ((exp animals/ or nonhuman/) not human/)	2138092
32	29 and 31	339
33	exp qualitative research/	88632
34	grounded theory/ or exp interview/ or exp observational method/ or exp questionnaire/	1034426
35	(qualitative research or interview* or focus group* or questionnaire* or survey* or grounded theory or hermeneutics or ethnograph* or thematic or mixed method*).ti,ab,kw.	1922995
36	(qualitative or synthesis or metareview or meta-review or metaethnograph*).ti.	462038
37	33 or 34 or 35 or 36	2529532
38	29 and 37	300
39	30 or 32 or 38	588
40	conference*.pt.	4873906
41	39 not 40	301
42	limit 41 to (english language and yr="2006 -Current")	277

Table 40. PsychINFO search strategy for question 5

#	Searches	Results
1	exp Lung/ and exp Neoplasms/	724
2	((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?)).ti,ab.	3335
3	1 or 2	3382
4	health screening/ or screening/ or cancer screening/ or disease screening/ or screening tests/	25129
5	(screen* or diagnos* or detect*).ti.	84614
6	(screen* or (early adj2 (diagnos* or detect*))).ab.	110728
7	4 or 5 or 6	173935
8	((low dose adj5 (computed tomogra* or ct)) or ldct).mp.	60
9	3 and 7 and 8	50
10	(((computed tomogra* or ct) adj5 screen*) and ((lung or pulmonary) adj3 (cancer? or neoplas* or carcinoma? or tumor? or tumour?))).ti,ab.	47
11	((lung cancer adj3 screen*) and (computed tomogra* or ct)).ti,ab.	55
12	9 or 10 or 11	62
13	(((high* or increas* or cancer or predict*) adj3 risk*) or (risk? adj5 (based or eligib))).ti,ab.	131891
14	exp tobacco smoking/	34423
15	(smoker? or exsmoker? or smoking or "tobacco use").ti,ab.	56901
16	13 or 14 or 15	185073
17	treatment compliance/ or exp client attitudes/ or treatment barriers/ or treatment refusal/	43827
18	(acceptab* or acceptance or attitude? or perception? or perspective? or view* or opinion? or experience? or satisf*).ti,ab.	1595175
19	(attendan* or nonattendan* or adheren* or nonadheren* or comply or complian* or noncomplian* or concordan* or uptake or utili?ation or dropout? or drop out?).ti,ab.	155489
20	psychological stress/	9101
21	Anxiety/ or Health Anxiety/	66017
22	(anxious or anxiety or psycholog* or stress).ti,ab.	889481
23	(barrier? or obstacle? or challenge? or facilitat* or enabl* or opportunit*).ti,ab.	622628
24	17 or 18 or 19 or 20 or 21 or 22 or 23	2515842
25	12 and 16 and 24	37
26	limit 25 to (english language and yr="2006 -Current")	35

Table 41. Cochrane library search strategy for question 5

ID	Search
1	MeSH descriptor: [Lung Neoplasms] explode all trees
2	(((lung or pulmonary) NEAR/3 (cancer* or neoplas* or carcinoma* or tumor* or tumour*))):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Mass Screening] this term only
5	MeSH descriptor: [Early Detection of Cancer] explode all trees
6	(screen* or diagnos* or detect*):ti,ab,kw
7	((screen* or (early NEAR/2 (diagnos* or detect*)))):ti,ab,kw
8	#4 or #5 or #6 or #7
9	MeSH descriptor: [Tomography Scanners, X-Ray Computed] explode all trees
10	((("low dose" NEAR/5 ("computed tomogra*" or ct)) or ldct)):ti,ab,kw
11	#9 or #10
12	#3 and #8 and #11
13	((("computed tomogra*" or ct) NEAR/5 screen*) and ((lung or pulmonary) NEAR/3 (cancer* or neoplas* or carcinoma* or tumor* or tumour*))):ti,ab,kw
14	((("lung cancer" NEAR/3 screen*) and ("computed tomogra*" or ct))):ti,ab,kw
15	#12 or #13 or #14
16	MeSH descriptor: [Attitude to Health] explode all trees
17	MeSH descriptor: [Anxiety] this term only
18	MeSH descriptor: [Mental Fatigue] this term only
19	MeSH descriptor: [Stress, Psychological] explode all trees
20	(acceptab* or acceptance or attitude* or perception* or perspective* or view* or opinion* or experience* or satisf*):ti,ab,kw OR (attendan* or nonattendan* or adheren* or nonadheren* or comply or complian* or noncomplian* or concordan* or uptake or utilisation or utilization or dropout* or "drop out?*"):ti,ab,kw OR (anxious or anxiety or psycholog* or stress):ti,ab,kw OR (barrier* or obstacle* or challenge* or facilitat* or enabl* or opportunit*):ti,ab,kw
21	#16 or #17 or #18 or #19 or #20
22	#15 and #21

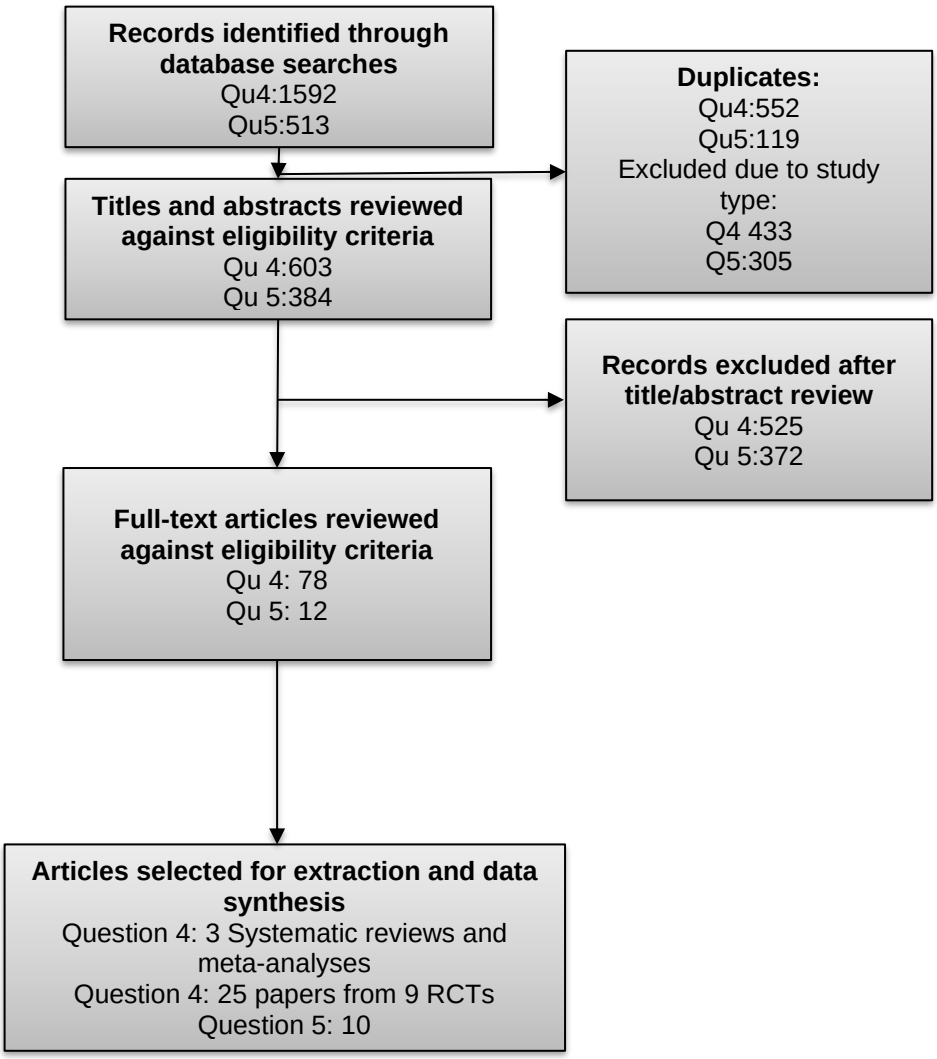
Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 6 summarises the volume of publications included and excluded at each stage of the review. A total of 90 publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 6. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction.

For question 4 about the clinical effectiveness of lung cancer screening and the balance of benefits and harms, the evidence for studies aimed at current and former smokers was considered separately from evidence about lung cancer screening for other risk factors.

For evidence about lung cancer screening for current and former smokers, systematic reviews and meta analyses of RCTs that included the NELSON trial were sought and the original peer reviewed publications from the RCTs considered. For other risk groups systematic reviews and meta-analyses of RCTs and RCTs alone were sought.

A total of 3 systematic reviews and meta-analyses about lung cancer screening for current and former smokers met the criteria for inclusion for question 4. A further 24 original peer reviewed publications associated with 9 RCTs reported in the 3 systematic reviews and meta analyses were also included. There were no systematic reviews or RCTs that met the criteria for inclusion examining lung cancer screening for risk factors other than smoking.

Studies for question 5 were prioritised *a priori* with the following approach:

1. Studies from the UK
    a. Systematic reviews and meta-analyses from the UK
    b. RCTs from the UK
    c. Cohort and qualitative studies from the UK
2. In the absence of studies from the UK, studies from countries with populations analogous to the UK
    a. Systematic reviews and meta-analyses
    b. RCTs
    c. Cohort and qualitative studies

Publications selected for inclusion are presented in Tables 42 (question 4) and 43 (Question 5).

Publications not selected for extraction and data synthesis are clearly detailed in Tables 44, 45 and 46 below.

Table 42. Summary of systematic reviews and meta analyses included after review of full-text articles and RCTs and additional studies within those articles relevant to key question 4 about the clinical effectiveness and balance of harms and benefits of lung cancer screening

	RCT	Additional studies assessed from RCTs included in systematic review and meta-analysis	Jonas et al (2021)[8] Systematic review	Brodersen et al (2020)[36] Meta-analysis	Sadate et al (2020)[37] Systematic review and meta-analysis
1	**DANTE**	No additional studies	x		x
2	**DLCST**	Willi et al (2016)[42]	x		x
3	**DLCST**	Ramussen et al (2020)[54]	x		
4	**DLCST**	Ashraf et al (2009)[61]	x		
5	**ITALUNG**	No additional studies	x	x	x
6	**LUSI**	Maldonado et al (2020)[50]	x		
7	**LUSI**	Becker et al (2019)[45]	x	x	x
8	**LSS**	Doroudi et al (2018)[43]	x		
9	**LSS**	Gohagan et al (2005)[46]			
10	**MILD**	Pastorino et al (2019a)[44]**Error! Bookmark not defined.**	x	x	x
11	**MILD**	Pastorino et al (2019b)[49]	x		
12	**NELSON**	de Koning et al (2020)[47]**Error! Bookmark not defined.**	x	x	x
13	**NELSON**	Yousauf Khan et al (2017)[48]	x		
14	**NELSON**	Van den Bergh et al (2011)[56]	x		
15	**NELSON**	Van de Wiel et al (2007)[57]	x		
16	**NLST**	Iaccarino et al (2019, 72)[72]	x		
17	**NLST**	Aberle et al et al (2019)[40]	x		
18	**NLST**	Nguyen et al (2017)[58]	x		
19	**NLST**	Clark et al (2016)[60]	x		
20	**NLST**	Tanner et al (2015)[41]	x		
21	**NLST**	Gareen et al (2014)[53]	x		
22	**NLST**	O'Grady et al (2014)[59]	x		
23	**NLST**	Patz et al (2014)[51]	x		
24	**NLST**	Pinsky et al (2014)[33]	x		
25	**UKLS**	Brain et al (2017)[60]	x		

26	**UKLS**	Brain et al (2016)[55] **Error! Bookmark not defined.**	x		
27	**UKLS**	Field et al (2016)[29]	x		

Table 43. Publications included after review of full-text articles, for key question 5 about the acceptability of a lung cancer screening programme

Study	Objective
Kummer et al (2020a)[66] Qualitative study	To report outcomes of psychological impact of invitation to lung cancer screening compared with 'screening unaware' individuals
Kummer et al (2020b)[70] LSUT cohort study	To explore the range of psychological and behavioural responses to LDCT screening offered as part of a lung health check including LDCT, risk assessment, spirometry testing, carbon monoxide reading and smoking cessation advice
Margariti et al (2020)[67] Qualitative study	To explore healthcare professionals' views about lung cancer screening and willingness to be involved in implementation
Quaife et al (2020)[30] UKLS RCT	To compare the effect of a targeted low-burden stepped invitation strategy versus control on uptake of hospital based Lung Health Check Appointments
Crosbie et al (2019a)[64] Cohort study	To report results of screening adherence from baseline screen and second annual screening round of Manchester's' Lung Health Check pilot of community based lung screening in deprived areas year 1
Crosbie et al (2019b)[65] Cohort study	To report results of screening adherence from baseline screen and second annual screening round of Manchester's' Lung Health Check pilot of community based lung screening in deprived areas year 2
Ruparel et al (2019)[68] Qualitative study	To explore knowledge and perceptions around lung cancer screening by people eligible to be screened with a focus on harms
Quaife et al (2018)[71] Survey	To examine interest in a national lung cancer screening programme and modifiable attitudinal factors that may affect participation by smokers in England
Quaife (2016)[69] Qualitative study	To compare smokers' beliefs about lung cancer screening with those of former or never smokers within a low socioeconomic status (SES) sample, and to provide insights into effective engagement strategies
Ali et al (2015)[63] Survey	To identify barriers to participation among high risk individuals who declined an invitation for screening in the UK lung cancer Screening (UKLS) pilot randomised controlled trial

Publications excluded after review of full-text articles

Of the 90 publications remaining after the review of titles and abstracts, 56 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 58, 59 and 60.

Table 44. Publications excluded after review of full-text articles: Q4: Systematic reviews of clinical effectiveness of lung cancer screening in high risk populations

Smoking or other risk factor	Study	Exclusion reason
Smoking	Tringali G, Milanese G, Ledda RE, Pastorino U, Sverzellati N, Silva M. Lung Cancer Screening: Evidence, Risks, and Opportunities for Implementation. RoFo Fortschritte auf dem Gebiet der Rontgenstrahlen und der Bildgebenden Verfahren. 2021	Not a systematic review/RCT
Smoking	Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. Nature Reviews Clinical Oncology. 2021;18(3):135-51.	Not a systematic review/RCT
Smoking	Moldovanu D, de Koning HJ, van der Aalst CM. Lung cancer screening and smoking cessation efforts. Translational Lung Cancer Research. 2021;10(2):1099-109.	Not a systematic review/RCT
Smoking	Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-86.	Systematic review of cohort/population based studies not RCTs
Smoking	Huang J, Yue N, Wu J, Shi N, Wang Q, Cui T, et al. Screening rate and influential factors of lung cancer with low-dose computed tomography in Asian population: a systematic review and meta-analysis. Journal of Public Health. 2020;22:22	Systematic review of cohort/population based studies not RCTs
Smoking	Ebell MH, Bentivegna M, Hulme C. Cancer-Specific Mortality, All-Cause Mortality, and Overdiagnosis in Lung Cancer Screening Trials: A Meta-Analysis. Annals of Family Medicine. 2020;18(6):545-52.	Did not include NELSON trial
Smoking	Dezube AR, Jaklitsch MT. New evidence supporting lung cancer screening with low dose CT & surgical implications. European Journal of Surgical Oncology. 2020;46(6):982-90	Not a systematic review
Smoking	Yang H, Varley-Campbell J, Coelho H, Long L, Robinson S, Snowsill T, et al. Do we know enough about the effect of low-dose computed tomography screening for lung cancer on survival to act? A systematic review, meta-analysis and network meta-analysis of randomised controlled trials. Diagnostic and Prognostic Research. 2019;3:23.	Prior to 2020 search cut off.
Other	Tang X, Qu G, Wang L, Wu W, Sun Y. Low-dose CT screening can reduce cancer mortality: A meta-analysis. Revista da Associacao Medica Brasileira. 2019;65(12):1508-14.	No non smoking trials included
Other	Huang KL, Wang SY, Lu WC, Chang YH, Su J, Lu YT. Effects of low-dose computed tomography on lung cancer screening: a	No non smoking trials included

	systematic review, meta-analysis, and trial sequential analysis. BMC Pulmonary Medicine. 2019;19(1):126.	
Other	Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England). 2018;22(69):1-276.	No non smoking trials included
Other	Usman Ali M, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, et al. Screening for lung cancer: A systematic review and meta-analysis. Preventive Medicine. 2016;89:301-14.	2 RCTs within meta-analysis included non/never smokers but did not use LDCT
Other	Falaschi F, Romei C, Fiorini S, Lucchi M. Imaging of malignant pleural mesothelioma: It is possible a screening or early diagnosis program? - A systematic review about the use of screening programs in a population of asbestos exposed workers. Journal of Thoracic Disease. 2018;10(Supplement2):S262-S8	Not a systematic review
Other	Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, et al. Screening high-risk populations for lung cancer: guideline recommendations. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2013;8(10):1232-7	No non smoking trials included
Other	Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, et al. Screening for lung cancer. Cochrane Database of Systematic Reviews. 2013(6):CD001991.	Chest X-ray not LDCT
Other	Fu C, Liu Z, Zhu F, Li S, Jiang L. A meta-analysis: is low-dose computed tomography a superior method for risky lung cancers screening population? The clinical respiratory journal. 2016;10(3):333-41.	No non smoking trials included
Other	Ollier M, Chamoux A, Naughton G, Pereira B, Dutheil F. Chest CT scan screening for lung cancer in asbestos occupational exposure: a systematic review and meta-analysis. Chest. 2014;145(6):1339-46.	No RCTs included only cohort studies
Other	Boiselle PM. Computed tomography screening for lung cancer. JAMA. 2013;309(11):1163-70.	No non smoking trials included
Other	Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418-29.	No non smoking trials included
Other	Gopal M, Abdullah SE, Grady JJ, Goodwin JS. Screening for lung cancer with low-dose computed tomography: a systematic review and meta-analysis of the baseline findings of randomized controlled trials. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2010;5(8):1233-9	No non smoking trials included
Other	Black C, De Verteuil R, Walker S, Ayres J, Boland A, Bagust A, et al. Population screening for lung cancer using computed tomography, is there evidence of clinical effectiveness? A systematic review of the literature. Thorax. 2007;62(2):131-8.	1 study with some non- smokers included but before 2006 search date cut off
Other	McCunney RJ. Should we screen for occupational lung cancer with low-dose computed tomography? Journal of Occupational & Environmental Medicine. 2006;48(12):1328-33.	No non smoking trials included

Table 45. Publications excluded after review of full-text articles: Question 4 - RCT associated publications of clinical effectiveness of lung cancer screening in high risk populations with history of smoking

Trial	Study	Exclusion reason
DANTE	Infante M, Chiesa G, Solomon D, Morenghi E, Passera E, Lutman FR, et al. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. Journal of thoracic oncology. 2011;6(2):327-35.Infante 2011	No PICO outcomes reported
DANTE	Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. American journal of respiratory and critical care medicine. 2009;180(5):445-53	More recent results reported with longer follow up
DANTE	Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer. 2008;59(3):355-63.	More recent results reported with longer follow up
DLCST	Kaerlev L, Iachina M, Pedersen JH, Green A, Norgard BM. CT-Screening for lung cancer does not increase the use of anxiolytic or antidepressant medication. BMC Cancer. 2012;12:188Mental health issues from screening	No PICO outcomes reported
DLCST	Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax. 2012;67(4):296-301	More recent results reported with longer follow up
DLCST	Saghir Z, Ashraf H, Dirksen A, Brodersen J, Pedersen JH. Contamination during 4 years of annual CT screening in the Danish Lung Cancer Screening Trial (DLCST). Lung cancer (Amsterdam, Netherlands). 2011;71(3):323-7.Contamination rates of control participants receiving lung CT.CXR	No PICO outcomes reported
DLCST	Pedersen JH Ashraf H, Dirksen A, Bach, K, Hansen H, Toennesen P, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. Journal of thoracic oncology. 2009;4(5):608-14.	More recent results reported with longer follow up
DLCST	Rasmussen JF, Siersma V, Pedersen JH, Brodersen J. Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST). Lung cancer (Amsterdam, Netherlands). 2015;87(1):65-72	More recent results reported
DLCST	Malmqvist J, Siersma V, Thorsen H, Heleno B, Rasmussen JF, Brodersen J. Did psychosocial status, sociodemographics and smoking status affect non-attendance in control participants in the Danish Lung Cancer Screening Trial? A nested observational study. BMJ Open. 2020;10(2):e030871.	No PICO outcomes reported
ITALUNG	Mascalchi M, Comin C, Bertelli E, Sali L, Maddau C, Zuccharelli eta l Screen-detected multiple primary lung cancers in the ITALUNG trial. Journal of thoracic disease. 2018;10(2):1058-66.	No PICO outcomes reported
NELSON	Walter JE, Heuvelmans MA, de Bock GH, Yousaf-Khan U, Groen HJM, van der Aalst CM, et al. Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening: The NELSON study. Lung Cancer. 2018;125:103-8	No PICO outcomes reported
NELSON	Heuvelmans MA, Walter JE, Peters RB, Bock GH, Yousaf-Khan U, Aalst CMV, et al. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: the	No PICO outcomes reported

	NELSON study. Lung cancer (Amsterdam, Netherlands). 2017;113:45-50	
NELSON	Walter JE, Heuvelmans MA, de Jong PA, Vliegenthart R, van Ooijen PMA, Peters RB, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. Lancet Oncology. 2016;17(7):907-16	No PICO outcomes reported
NELSON	Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. The lancet Oncology. 2014;15(12):1332-41	No PICO outcomes reported
NELSON	Yousaf-Khan U, Horeweg N, van der Aalst C, Ten Haaf K, Oudkerk M, de Koning H. Baseline Characteristics and Mortality Outcomes of Control Group Participants and Eligible Non-Responders in the NELSON Lung Cancer Screening Study. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2015;10(5):747-53	No PICO outcomes reported
NELSON	van der Aalst CM, van Iersel CA, van Klaveren RJ, Frenken FJM, Fracheboud J, Otto SJ, et al. Generalisability of the results of the Dutch-Belgian randomised controlled lung cancer CT screening trial (NELSON): does self-selection play a role? Lung cancer (Amsterdam, Netherlands). 2012;77(1):51-7	No PICO outcomes reported
NELSON	Ying Ru Zhao,a Xueqian Xie,a Harry J de Koning,b Willem P Mali,c Rozemarijn Vliegenthart,a and Matthijs Oudkerkcorresponding authora NELSON lung cancer screening study Cancer Imaging	Set up of trial and early results. More recent results are available.
NELSON	Baecke E, de Koning HJ, Otto SJ, van Iersel CA, van Klaveren RJ. Limited contamination in the Dutch-Belgian randomized lung cancer screening trial (NELSON). Lung Cancer. 2010;69(1):66-70	No PICO outcomes reported
NELSON	van Iersel CA, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). International Journal of Cancer. 2007;120(4):868-74	No PICO outcomes reported
NLST	Henderson LM, Durham DD, Tammemagi MC, Benefield T, Marsh MW, Rivera MP. Lung Cancer Screening With Low Dose Computed Tomography in Patients With and Without Prior History of Cancer in the National Lung Screening Trial. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2021;10:10	No PICO outcomes reported
NLST	Caverly TJ, Cao P, Hayward RA, Meza R. Identifying Patients for Whom Lung Cancer Screening Is Preference-Sensitive: A Microsimulation Study. Annals of Internal Medicine. 2018;169(1):1-9	No PICO outcomes reported
NLST	Yip R, Yankelevitz DF, Hu M, Li K, Xu DM, Jirapatnakul A, et al. Lung Cancer Deaths in the National Lung Screening Trial Attributed to Nonsolid Nodules. Radiology. 2016;281(2):589-96	No PICO outcomes reported
NLST	Stang A, Schuler M, Kowall B, Darwiche K, Kühl H, Jöckel KH. Lung Cancer Screening Using Low Dose CT Scanning in Germany. Extrapolation of results from the National Lung Screening Trial. Deutsches Arzteblatt international. 2015;112(38):637-44	No PICO outcomes reported
NLST	Yip R, Henschke CI, Yankelevitz DF, Smith JP. CT screening for lung cancer: alternative definitions of positive test result based on the national lung screening trial and international early lung cancer action program databases. Radiology. 2014;273(2):591-6	No PICO outcomes reported

NLST	Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, et al. Results of initial low-dose computed tomographic screening for lung cancer. New England journal of medicine. 2013;368(21):1980-91.	More recent results reported with longer follow up
NLST	Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. New England Journal of Medicine. 2013;369(3):245-54.	More recent results reported with longer follow up
NLST	National Lung screening trial research team Computed tomography screening for lung cancer: has it finally arrived? implications of the national lung screening trial. Journal of clinical oncology. 2013;31(8):1002-8	More recent results reported with longer follow up
NLST	National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. New England Journal of Medicine. 2011;365(5):395-409. Aberle 2011	More recent results reported with longer follow up

Table 46. Publications excluded after review of full-text articles: Question 5 – Studies about acceptability of screening programmes for lung cancer using LDCT in individuals at increased risk

Study	**Exclusion reason**
Lam ACL, Aggarwal R, Cheung S, Stewart EL, Darling G, Lam S, et al. Predictors of participant nonadherence in lung cancer screening programs: a systematic review and meta-analysis. Lung Cancer. 2020;146:134-44	Only one study was included from the UK and that study is included in this review (Crosbie 2019)
Dunn CE, Edwards A, Carter B, Field JK, Brain K, Lifford KJ. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. Patient Education & Counseling. 2017;100(8):1572-9	The study is about the congruence of people's expectations of screening and the outcome – not acceptability of screening

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Question 4: What is the clinical effectiveness of screening programmes for the detection of lung cancer using LDCT in individuals at increased risk, compared with no screening?

Systematic reviews

Table 47. Jonas et al (2021)[8]

Publication	Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. 2021:03.
Study details	Systematic review
Study objectives	To review the evidence of screening for lung cancer with low-dose computed tomography to inform the US Preventative Services Task Force (USPSTF)
Inclusions	English language studies of: • screening for lung cancer with LDCT • accuracy of LDCT • externally validated risk prediction model including demographic and clinical variables or biomarkers intended for identifying persons at increased risk who are likely to benefit from screenings • treatment for early stage lung cancer
Exclusions	Children, people with symptoms, people with prior diagnosis of lung cancer, risk prediction models including a single variable or biomarker, models not considering smoking and age, studies without a comparison group
Population	Asymptomatic adults ≥18 years
Comparisons	Chest X-ray, no screening, or usual care
Outcomes	7 RCTs described in 26 publications including: NLST, DANTE, DLCST, ITALUNG, LSS, LUSI, and NELSON trials Two trials – NLST and the NELSON trial were adequately powered to assess mortality benefit. One further trial was considered (MILD) but excluded because of poor quality. Trial characteristics

Trial	Sample size; country	Age range in years	% Male	Eligibility criteria – pack years; years since quitting	Screening rounds	F/up in years
DANTE	2472; Italy	60-74	100	≥20;<10	5	8.4
DLCST	4104; Denmark	50-70	56	≥20;<10 or quit after age 50	5	9.8
ITALUNG	3206; Italy	55-69	65	≥20 in the last 10y or quit within the last 10y	4	9.3
LSS	3318; US	55-74	59	≥30;<10	2	5.2
LUSI	4052; Germany	50-69	65	≥25 y of 15 cigarettes/d or ≥30 y of 10 cigarettes/d; <10	5	8.8

NELSON	15,792; Netherlands and Belgium	50-74	84	>15 cigarettes/d for >25 y or>10 cigarettes/d for>30 y;≤10	4	10
NLST	53,542; US	55-74	59	≥30;≤15	3	12.3

d – Day, F/up – Follow-up, y – Years

Comparison of incidence between LDCT screening group and control for early stage (I-II) lung cancer

Trial	Number		Number early cancers (stage I-II)		IRR (95% CI)
	Screened	Control	Screened	Control	
DANTE	1276	1196	54	21	2.38(1.44-3.94)
DLST	2052	2052	54	10	5.42(2.76-10.63)
ITALUNG	1613	1593	29	13	2.17(1.13-4.16)
NELSON	6583	6612	168	71	2.39(1.81-3.16)
NLST	26,722	26,737	818	615	1.33(1.20-1.48)

CI – Confidence intervals, IRR - Incidence rate ratio

Comparison of incidence between LDCT screening group and control for late stage (III-IV) lung cancer

Trial	Number		Number cancers (stage III-IV)		IRR (95% CI)
	Screened	Control	Screened	Control	
DANTE	1276	1196	43	45	0.89(0.59-1.35)
DLST	2052	2052	46	41	1.13(0.74-1.72)
ITALUNG	1613	1593	33	43	0.75(0.47-1.17)
NELSON	6583	6612	153	216	0.72(0.58-0.88)
NLST	26,722	26,737	766	918	0.84(0.76-0.92)

CI – Confidence intervals, IRR - Incidence rate ratio

Comparison of lung cancer mortality between LDCT screening group and control

Trial	Number of events		Deaths per 100,000 persons		IRR (95% CI)
	Screened	Control	Screened	Control	
DANTE	59	55	543	544	1.00(0.69-1.44)
DLST	39	38	201	194	1.03(0.66-1.61)
ITALUNG	43	60	293	421	0.70(0.47-1.03)
LSS	32	26	383	310	1.24(0.74-2.07)
NELSON	181	242	241	324	0.75(-.61-0.90)
NLST	469	552	280	332	0.85(0.75-0.96)

CI – Confidence intervals, IRR - Incidence rate ratio

For NLST the number needed to screen to prevent 1 lung cancer death was 323 over 6.5 years follow up and for NELSON it was 130 over a 10 year follow up.

Comparison of all-cause mortality between LDCT screening and control

Trial	Number of events		Deaths per 100,000 persons		IRR (95% CI)
	Screened	Control	Screened	Control	
DANTE	180	176	1655	1742	0.95(0.77-1.17)
DLST	165	163	849	834	1.02(0.82-1.26)
ITALUNG	154	181	1051	1270	0.83(0.67-1.03)
LSS	139	116	1667	1384	1.20(0.94-1.53)
NELSON	868	860	1393	1376	1.01(0.92-1.11)
NLST	1912	2039	1141	1225	0.93(0.88-0.99)

CI – Confidence intervals, IRR - Incidence rate ratio

Risk prediction models
Studies of 3 models (PCLOm2012, LCDRAT, and Kovalchik model) reported increased screen-preventable deaths (based on number needed to screen) compared with risk factor based criteria (21,682,066 participants from 4 cohorts).

Studies of all models reported similar numbers of false positive selections for screening (i.e. the model selected people to be screened who did not have or develop lung cancer or die from lung cancer) and mixed findings for rates of false positive selections or false positive selections for prevented death, when comparing risk prediction models with risk factor based criteria.

Harms

Radiation exposure

- two included studies estimated cumulative radiation exposure for participants undergoing screening and this data was used by the SR authors to estimate cumulative radiation exposure for 25 years of annual screening (from age 55-80) which yielded 20.8millsieverts (mSv) to 35.5mSv.
- one study calculated that the lifetime risk of fatal cancer after 4 screening rounds of medium dose CT was 0.11 per 1000 participants
- one study estimated that there would be one major radiation-induced cancer for every 100 lung cancers detected by screening during the 10 years of the study

False positive results and consequent evaluations

- false positive results ranged from 7.9% to 49.3% depending on differences in definitions of positive results such as cut off, use of volume doubling time and nodule characteristics considered
- among all patients screened the percentage who had a needle biopsy for a false positive result ranged from 0.09% to 0.56%
- complication rates for needle biopsy for false positives ranged from 0.03% to 0.07% of all those screened
- in the NLST trial, false positive results led to invasive procedures (needle biopsy, thoracotomy, thoracoscopy mediantinoscopy and bronchoscopy) in 1.7% of those screened. Complications occurred in 0.1% of all those screened with major intermediate and minor complications occurring in 0.03%, 0.05% and 0.01% respectively of those screened. Death in the 60 days following the most invasive procedure performed occurred in 0.007% (n=1) of those screened.

Overdiagnosis
Overall 5 studies specifically examined overdiagnosis and 7 additional studies also examined differences in cancer incidence between LDCT and comparison groups. Estimates of overdiagnosis ranged from 0% to 67.2% that a screen detected lung cancer is over diagnosed

Incidental findings

- there was no consistent definition of what constitutes an incidental finding, nor which findings were actionable or clinically significant
- screening related incidental findings were reported at between 4.4% to 40.7% across the 7 RCTs included.
- in the SR, older age was associated with a greater likelihood of incidental findings
- incidental findings included coronary artery calcification, aortic aneurysms, emphysema, infectious and inflammatory processes, masses, nodules or cysts of kidney, breast, adrenal glands, liver, thyroid, pancreas, spine and lymph nodes

	Smoking behaviour 7 studies (4 RCTs and 3 cohort studies) reported outcomes of lung cancer screening on smoking behaviour either cessation or relapse. Studies comparing LDCT vs controls did not indicate that screening leads to false reassurance. Abnormal or indeterminate screening tests may increase cessation or abstinence, but normal screening tests had no influence. **Psychosocial harms** • 5 studies (4 RCTs and one cohort study) evaluated potential psychosocial consequences of LDCT screening • studies examined general health related quality of life, anxiety, depression, distress and other psychosocial harms • overall there was moderate evidence that compared to no screening people who receive LDCT screening do not have a worse general health related quality of life, anxiety or distress over 2 years follow up • there was some evidence of the differential consequences of different screening results, with HRQOL and anxiety being worse in the short term for individuals who received true positive results compared to other results • distress was worse for people receiving indeterminate results, compared to other results
Quality appraisal criteria of included studies	Quality appraisal criteria applied to each study was developed by the USPSTF and is used for all their systematic reviews. The overall quality ratings included assessment of: • adequate randomisation • adequate concealment of allocation • similarity of groups at baseline • eligibility criteria specified • outcome measures – are they equal, valid and reliable • outcome assessors masked • care providers masked • patients masked • adherence to the intervention • crossovers and contamination • overall attrition rates • differential attrition and attrition bias • method used to handle missing data • was intention to screen analysis used • ascertainment of outcomes adequately described • ascertainment techniques are they equal, valid and reliable

Quality appraisal	**JBI Critical Appraisal Checklist for systematic reviews**	**Y/N/U /NA**	**Comments**	Not applicable
	Is the review question clearly and explicitly stated?	Yes	All 8 key questions and sub questions are explicitly stated and formulated around a PICO	□
	Were the inclusion criteria appropriate for the review question?	Yes	Asymptomatic adults, screening with LDCT, comparison with no screening or chest Xray	□
	Was the search strategy appropriate?	Yes	Clear search strategy identifying all elements of the PICO	□
	Were the sources and resources used to search for studies adequate?	Yes	Pubmed, Cochrane Library, ClinicalTrials.gov	□
	Were the criteria for appraising studies appropriate?	Yes	Predefined criteria developed by USPSTF and adapted for the topic were used. Studies were rated good or fair or poor	□
	Was critical appraisal conducted by two or more reviewers independently?	Yes	2 reviewers independently assessed quality of studies and resolved disagreements by discussion	□
	Were there methods to minimize errors in data extraction?	Yes	1 person extracted data and a second person reviewed information for completeness and accuracy	□
	Were the methods used to combine studies appropriate?	N/A	Heterogeneity of studies was assessed and meta-analysis was not conducted because of substantial clinical and methodological issues	□
	Was the likelihood of publication bias assessed?	No	Although a comprehensive search strategy was used reducing the likelihood of publication bias it is unclear whether it was assessed.	□
	Were recommendations for policy and/or practice supported by the reported data?	Yes	With moderate strength evidence a recommendation was made for annual screening using LDCT in adults aged 50 to 80 who have a 20 pack year smoking history and currently smoke or who quit within the past 15 years	□
	Were the specific directives for new research appropriate?	Yes	The low volume of evidence and uncertainty around the current nodule management protocols and use of risk prediction models which may improve the balance of benefits and harms were highlighted	□

Table 48. Brodersen et al (2020)[36]

Publication	**Brodersen J, Voss T, Martiny F, Siersma V, Barratt A, Heleno B. Overdiagnosis of lung cancer with low-dose computed tomography screening: Meta-analysis of the randomised clinical trials. Breathe. 2020;16(1).**
Study details	Meta-analysis
Study objectives	To estimate the degree of overdiagnosis of LDCT screening for lung cancer compared to no screening
Inclusions	RCTs included if they reported incidence of lung cancer for people screened with LDCT compared to people who were not screened (usual care)
Exclusions	If study did not include long term follow up after active phase of trial or if the control group was offered any other form of screening
Population	9 trials were identified 5 of which were included and 4 were excluded

Included trials (n=28,656) were NELSON, DLCST, ITALUNG, LUSI, MILD
Excluded trials and reason

Excluded Trials	Exclusion reason
NLST	Used an active comparator: chest X-ray
DANTE	Offered single baseline chest X-ray to control group
UKLS	No data on incidence at the end of the trial
Chinese Yang	No data on incidence at the end of the trial

Comparison No screening

Outcomes LDCT screening for lung cancer of former or current smokers increased the cumulative incidence of lung cancer with a relative risk (RR) of 1.22 (95% CI 1.02-1.47) and a heterogeneity (I^2) of 55%

Of the screen detected cancers it was estimated that 38% (95%CI 14-63%) may be over diagnosed with a heterogeneity (I^2) of 65%

Sensitivity analysis of 2 trials with low risk of bias (DLCST and LUSI) showed a RR of 1.51 (95% CI 1.06-2.14) and heterogeneity ($I^{2)}$) of 58% The probability that screen detected cancers were over diagnosed was 49% (95% CI 11-87%)

Quality appraisal criteria used by study Cochrane risk of bias tool v2.0. Areas of bias assessed includes:

- randomisation process
- contamination- deviation from intended intervention
- missing outcome data
- measurement of outcome including lead time bias
- selection of reported result
- overall risk of bias

Quality appraisal of study

JBI Critical Appraisal Checklist for systematic reviews	**Y/N/U /NA**	**Comments**	Not applicable
Is the review question clearly and explicitly stated?	No	The review question was not explicitly stated	□
Were the inclusion criteria appropriate for the review question?	Yes	RCTs reporting incidence of lung cancer for people screened with LDCT compared to no screening plus: • included long term follow up after the end of the active phase of the trial • the control group was not offered any type of lung cancer screening	□
Was the search strategy appropriate?	Unclear	Use of key words 'screening', 'low-dose computed tomography' and 'lung cancer' plus the names of all the known trials. This search strategy is limited, and risks missing important publications that may have been identified by a more comprehensive search strategy.	□
Were the sources and resources used to search for studies adequate?	No	Search of Pubmed only	□
Were the criteria for appraising studies appropriate?	Yes	Cochrane risk of bias v 2	□
Was critical appraisal conducted by two or more reviewers independently?	Yes		□

	Were there methods to minimize errors in data extraction?	Yes	Data was extracted independently by 2 authors	□
	Were the methods used to combine studies appropriate?	Yes	Results summarised with a random effects meta-analysis of lung cancer incidence and overdiagnosis and included an assessment of heterogeneity A secondary analysis restricted to trials of low risk of bias was also carried out	□
	Was the likelihood of publication bias assessed?	No		□
	Were recommendations for policy and/or practice supported by the reported data?	Yes	Recognised that the significant overdiagnosis reported would make it a difficult decision to implement lung cancer screening	□
	Were the specific directives for new research appropriate?	Yes	Discussed benefits and harms of lung cancer screening in the light of the combined results and the significant variation in overdiagnosis between studies and suggested the research focus that might reduce this	□

Table 49. Sadate et al (2020)[37]

Publication	**Sadate A, Occean BV, Beregi JP, Hamard A, Addala T, de Forges H, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. European Journal of Cancer. 2020;134:107-14.**
Study details	Systematic review and meta-analysis
Study objectives	To evaluate the efficacy of screening with LDCT to any other comparator in populations who reported smoking for more than 15 years for lung cancer mortality and all-cause mortality
Inclusions	RCT design, with any comparator, in people with an average smoking history of over 15 pack years
Exclusions	
Population	7 RCTs were included n=84,558 DANTE, DLCST, ITALUNG, MILD, LUSI, NLST, NELSON
Comparison	No screening, chest X-ray
Outcomes	The relative reduction of all-cause mortality was 4% in the screening group compared to control (RR 0.96, 95% CI 0.92-1.00) For lung cancer specific mortality a relative reduction of 17% in the screening group compared to the control group was reported (RR 0.83, 95% CI 0.76 – 0.91) To prevent 1 lung cancer related death 294 patients need to be screened .
Quality appraisal criteria used by study	The CONSORT checklist for RCTs was used covering the areas of: • randomisation • planned complete diagnostic workup • inclusion criteria described • valid measurement of mortality – all-cause and lung cancer specific • blinded outcomes assessment • follow up

Quality appraisal of study	JBI Critical Appraisal Checklist for systematic reviews	Y/N/U /NA	Comments	Not applicable
	Is the review question clearly and explicitly stated?	Yes	What is the efficacy of lung cancer screening by LDCT in populations highly exposed to tobacco on cancer specific and overall mortality?	□
	Were the inclusion criteria appropriate for the review question?	Yes	RCT design with LDCT compared to any other intervention or no screening, in populations reporting an average smoking history of 15 pack years, that reported data on lung cancer specific or all-cause mortality	□
	Was the search strategy appropriate?	Yes	A detailed search strategy was reported	□
	Were the sources and resources used to search for studies adequate?	Yes	Two databases were searched (Medline and Cochrane Library databases) and other internet searches were carried out	□
	Were the criteria for appraising studies appropriate?	No	The CONSORT checklist is aimed at improving standards of reporting in journals and can aid critical appraisal but is not in itself a critical appraisal tool	□
	Was critical appraisal conducted by two or more reviewers independently?	Yes	Two reviewers undertook critical appraisal independently	□
	Were there methods to minimize errors in data extraction?	Yes	Two reviewers independently extracted the data which were collected and managed using REDCap electronic data capture tools	□
	Were the methods used to combine studies appropriate?	Yes	Results summarised with a random effects meta-analysis of lung cancer mortality and all-cause mortality and included an assessment of heterogeneity	□
	Was the likelihood of publication bias assessed?	Yes	By visual analysis of funnel plots confirming the studies included did not present major biases	□
	Were recommendations for policy and/or practice supported by the reported data?	N/A	No recommendations made	□
	Were the specific directives for new research appropriate?	N/A	No specific directives made	□

Randomised Controlled Trials

Table 50 presents the details, results and quality appraisal of the DANTE RCT which were reported in one study publication.

Table 50. Detection and Screening of Early Lung cancer by Novel Imaging and Molecular Essays (DANTE); Country; Italy

<table>
<tr><td>Trial objectives</td><td>To compare clinical review with chest x-ray vs spiral CT at annual intervals for 4 years</td></tr>
<tr><td>Study</td><td>Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. American journal of respiratory and critical care medicine. 2015;191(10):1166-75[73]</td></tr>
<tr><td>Inclusions</td><td>Males aged 60 to 74 exposed to at least 20 pack years of tobacco smoking and were current smokers or former smokers who quit <10 years ago</td></tr>
<tr><td>Exclusions</td><td>Severe comorbidity, life expectancy <5 years, severe heart failure, inability to comply with follow up protocol, drug or alcohol addiction</td></tr>
<tr><td>Population</td><td>N=2472</td></tr>
<tr><td>Intervention</td><td>Baseline chest x-ray, baseline spiral CT scan, and annual spiral CT for 4 years</td></tr>
<tr><td>Comparator</td><td>Control group received baseline chest x-ray only</td></tr>
<tr><td>Outcomes</td><td>Mortality

There was no difference in male lung cancer mortality or all-cause mortality between LDCT and the control arms of the trial at follow up.

Male lung cancer specific and all-cause mortality per 100,000 person years

<table>
<tr><td></td><td>LDCT</td><td>Control</td><td>All</td></tr>
<tr><td>Subjects n (%)</td><td>1,264(51.59%)</td><td>1,186(49.41%)</td><td>2450(100%)</td></tr>
<tr><td>Lung cancer mortality per 100,000 PY(95% CI)</td><td>543 (413-700)</td><td>544 (410-709)</td><td>543 (448-653)</td></tr>
<tr><td>All-cause mortality per 100,000 PY (95% CI)</td><td>1,655 (1,422-1,916)</td><td>1,742 (1,494-2,019)</td><td>1,697 (1,525-1,883)</td></tr>
</table>
CI – Confidence intervals, LDCT - Low dose computed tomography, PY- Pack years

Lung cancer stage

There was a significantly higher proportion of males diagnosed with stage IA lung cancers in the LDCT arm compared to the control arm (p<0.0001) but there was no statistically significant difference in the proportions of males with stage IV diagnoses between the trial arms.

Of the 104 males who developed 118 lung cancers 66(63%) were diagnosed following LDCT, 1 following sputum cytology, 13(12.5%) due to symptoms developing between screening rounds and 4(3.8%) males were diagnosed through different routes</td></tr>
</table>

Male lung cancer stage at diagnosis

Stage n(%)	LDCT	Control	All	p value
IA	31(30.99)	6(8.33)	37(21.02)	p<0.0001
IB	16(15.38)	10(13.89)	26(14.72)	
II	7(6.73)	5(6.94)	12(6.81)	
IIIA	9(8.65)	6(8.33)	15(8.52)	
IIIB	8(7.69)	6(8.33)	14(7.95)	
IV	26(26.00)	33(27.8)	63(35.79)	p=0.2915
Missing	7(6.73)	6(8.33)	13(7.38)	
Total	104	72	176	

LDCT - Low dose computed tomography, N - number

Diagnostic investigations

- Of 96 surgical procedures in 90 patients 17 (17.7% procedures and 18.9% of patients) did not reveal any lung cancer
- In the LDCT arm 3 patients (3.3%) and in the control group 1 patient (3.2%) died post operatively. None of those who died following surgical procedures had benign lesions

Quality appraisal

The tables below outline the critical appraisal of the DANTE trial carried out by Jonas 2021, and Sadate 2020 (DANTE was not included in the Brodersen 2020 meta-analysis).

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB:** DANTE RCT assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	Yes
	Was allocation concealment adequate?	Yes
	Were groups similar at baseline?	Yes
	Were eligibility criteria specified?	Yes
	Wre patients masked?	No – patients knew they were being screened or not
	Were care providers masked	Unclear

	Were outcomes assessors masked?	Unclear
	Were outcome measures equal reliable and valid?	The trial was underpowered
	Adherence to the intervention	High adherence rates >90%
	Did the study have crossovers and contamination	Low <10%
	Overall attrition rates	Low <10%
	Differential attrition and attrition bias	Low
	Method used to handle missing data	Unclear
	Was intention to screen analysis used	Yes
	Ascertainment of outcomes adequately described	No
	Ascertainment techniques are they equal, valid and reliable	Unclear
Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
	CONSORT Checklist for RCTs	Comment
	Recruitment strategies well defined	Yes
	Random assignment	Yes
	Complete diagnostic workup planned	Yes
	Inclusion criteria described and respected	Yes
	Valid measurement of all-cause mortality	Yes
	Valid measurement of lung cancer specific mortality	Yes
	Blinded outcomes assessment	Yes
	Long enough follow up	Yes

Table 51 presents the details and quality appraisal of the DLCST RCT

Table 51. Danish Lung Cancer Screening Trial (DLCST) RCT (Country; Denmark)

<table>
<tr><td>Trial objectives</td><td colspan="3">To evaluate if annual low dose CT screening can reduce lung cancer mortality by more than 25%</td></tr>
<tr><td>Inclusions</td><td colspan="3">People aged 50 to 70 years without lung cancer related symptoms exposed to at least 20 pack years of tobacco smoking and were either current smokers or former smokers who quit <10 years ago. People had to be able to climb 2 flights of stairs (36 steps) without pausing. Annual spirometry should indicate forced expiratory volume in 1 second of at least 30% of predicted normal at baseline</td></tr>
<tr><td>Exclusions</td><td colspan="3">People with body weight >130kg, previous treatment for lung cancer, breast cancer, malignant melanoma and hypernephroma, a history of any other cancer within 5 years, tuberculosis within 2 years or any serious illness that would shorten life expectancy to less than 10 years, previous CT scan of the chest within 1 year</td></tr>
<tr><td>Population</td><td colspan="3">N=4104</td></tr>
<tr><td>Intervention</td><td colspan="3">LDCT scan annually for 5 years</td></tr>
<tr><td>Comparator</td><td colspan="3">No screening</td></tr>
<tr><td>Quality appraisal</td><td colspan="3">
<table>
<tr><th>Systematic review/meta-analysis</th><th colspan="2">Quality appraisal</th></tr>
<tr><td>Jonas et al (2021)[8]</td><td colspan="2">Overall ROB: DLCST RCT assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist.
One of the 3 included papers for this RCT (Willi et al 2016) was rated GOOD (Meets all criteria; comparable groups are assembled initially and maintained throughout the study, reliable and valid measurements are applied equally to both groups, interventions are spelled out clearly; all important outcomes are considered, intention to treat analysis is used)</td></tr>
<tr><td></td><td>USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR</td><td>Comment</td></tr>
<tr><td></td><td>Was randomisation adequate?</td><td>Yes</td></tr>
<tr><td></td><td>Was allocation concealment adequate?</td><td>Yes</td></tr>
<tr><td></td><td>Were groups similar at baseline?</td><td>Yes</td></tr>
<tr><td></td><td>Were eligibility criteria specified?</td><td>Yes</td></tr>
<tr><td></td><td>Were patients masked?</td><td>No – patients knew they were being screened or not</td></tr>
<tr><td></td><td>Were care providers masked</td><td>No</td></tr>
<tr><td></td><td>Were outcomes assessors masked?</td><td>Yes</td></tr>
</table>
</td></tr>
</table>

		Were outcome measures equal reliable and valid?	The trial was underpowered
		Adherence to the intervention	High adherence rates >90%
		Did the study have crossovers and contamination	Low <10%
		Overall attrition rates	Low <10%
		Differential attrition and attrition bias	Low
		Method used to handle missing data	Unclear
		Was intention to screen analysis used	Yes
		Ascertainment of outcomes adequately described	No
		Ascertainment techniques are they equal, valid and reliable	Unclear
	Brodersen et al (2020)[36]	**Overall ROB:** DLCST RCT assessed as LOW ROB	
		Cochrane risk of bias tool v2 (assessed as low, unclear or high risk of bias)	Comment
		Randomisation process	Low
		Contamination- deviation from intended intervention	Low
		Missing outcome data	Low
		Measurement of outcome including lead time bias	Low
		Selection of reported result	Low
	Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
		CONSORT Checklist for RCTs	Comment
		Recruitment strategies well defined	Yes
		Random assignment	Yes
		Complete diagnostic workup planned	Yes
		Inclusion criteria described and respected	Yes
		Valid measurement of all-cause mortality	Yes
		Valid measurement of lung cancer specific mortality	Yes
		Blinded outcomes assessment	Unclear
		Long enough follow up	Yes

Table 52. Results of the DLCST RCT

	Objective	Outcome measures	Outcomes
Rasmussen et al (2020)[54]	To analyse the psychosocial consequences of false-positive lung cancer CT screening using the lung cancer screening-specific questionnaire	Study approach: True positives and false-positive groups were matched with 1. the control group and 2. true negatives (by sex, age time of screening or clinic visit). Outcomes: psychosocial consequences measured at 5 time points	• people with a false positive result experienced significantly more negative psychosocial consequences in 7 outcomes at 1 week (anxiety, behaviour, dejection, self blame, focus on airway symptoms, introversion, harm of smoking) and in 3 outcomes at 1 month (self blame, focus on airway symptoms, and harm of smoking) compared with the control group and the true-negative group (p<0.001) • people with a true positive result experienced significantly more negative psychosocial consequences in one outcome at 1 week (dejection; p=0.0024) and in 3 outcomes at 1 month (behaviour, dejection, focus on airway symptoms p<0.004) compared with the true-negative group and the control group • no long-term psychosocial consequences were identified either in false positives or true positives
Willi et al (2016)[42]	Report of mortality, causes of death and lung cancer findings of screening	lung cancer mortality all-cause mortality screening uptake and false positive rates diagnosis by stage	Lung cancer mortality (9.8 yrs follow up) There was no difference in lung cancer mortality between the LDCT and control trial arms. LDCT screening group: 39/2052 participants died of lung cancer (2.0 per 1000PY) Control group: 38/2052 participants died of lung cancer (1.9 per 1000 PY) Hazard ratio 1.03 (95% CI 0.66-1.6; p=0.888) All-cause mortality There was no difference in the all-cause mortality between the LDCT and control trial arms. Hazard ratio 1.02 (95% CI 0.82-1.27; p=0.867) Screening uptake and outcomes LDCT screening group uptake 95.5% Control group uptake 93.0% False positive rates were 7.9% in baseline round and 1.7%, 2.0%, 1.6 % and 1.9% in the 4 subsequent rounds. Cancer stage at diagnosis

At 5 years follow up significantly more stage I cancers had been diagnosed in the LDCT screening arm than the control arm of the trial. There was no difference in the proportion of stage III and IV cancers diagnosed between the 2 arms of the trial.

Using the TNM- system where T1N0MO indicates a small tumour that has not metastasized to regional lymph nodes and other organs there was a significantly higher proportion in the LDCT trial arm than the control arm (p<0.001). For T4N3M1 where the patient has a fairly large tumour that has metastasized to many lymph nodes and spread to 1 or more organs there was a significantly lower proportion in the LDCT trial arm than the control arm (p=0.025).

Stage at diagnosis

Stage at diagnosis n (%)	LDCT	Control	All	p value
T1N0M0	41%	6%	47%	p<0.001
T4N3M1	8%	21%	29%	p=0.025
Stage I	50 (50.00)	8 (15.09)	58 (37.90)	p<0.001
Stage II	4 (4.00)	2 (3.77)	6 (3.92)	p=0.687
Stage IIIa	15 (15.00)	3 (5.66)	18 (11.76)	p=0.009
Stage IIIb	8 (8.00)	6 (11.32)	14 (9.15)	p=0.789
Stage IV	23 (23.00)	32 (60.37)	55 (35.94)	p=0.278
Unknown	0 (0.00)	2 (3.77)	2 (1.30)	p=0.500
Total	100	53	153	p<0.001

LDCT - Low dose computed tomography, N - Number

Ashraf et al (2009)[61]

Evaluate changes in smoking behaviour at baseline and 1 year follow up

Throughout 1 year follow up equal number of smokers quit in the 2 groups:

- LDCT arm 174(11.9%) and control arm 165(11.8%) p=0.95
- missing values were 5.3% in LDCT and 11.6% in the control group (p<0.01)
- baseline predictors for smoking abstinence at 1 year in the LDCT group were
  - lower FEV1/FEC ratio
  - lower number of cigarettes smoked on average per day since smoking started
  - lower number of pack years exposure
  - lower Fagerstrom questionnaire Q1 score
  - higher motivation to quit
- 129 smokers received a positive test result and were re-scanned 3 months later. The quit rate was 17.7% compared with the smoking group with no significant screening findings (11.4%) p<0.04
- in the smoking relapse group the rate was 4.7% in the LDCT with positive test results and 10.6% in the LDCT group with negative test results (p<0.01)

Table 53 presents the details, results and quality appraisal of the ITALUNG RCT which were reported in one study publication.

Table 53. Italian Lung Cancer Screening Trial (ITALUNG) RCT (Country; Italy)

<table>
<tr><td>Trial objectives</td><td>To evaluate the efficacy of chest LDCT as a screening test in reducing lung cancer mortality</td></tr>
<tr><td></td><td>Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax. 2017;72(9):825-31[74]</td></tr>
<tr><td>Inclusions</td><td>Asymptomatic smokers and former smokers aged 55-69 years with an exposure of 20 pack years smoking tobacco in the last 10 years.</td></tr>
<tr><td>Exclusions</td><td>History of cancer, or general conditions precluding thoracic surgery</td></tr>
<tr><td>Population</td><td>N=3206</td></tr>
<tr><td>Intervention</td><td>Smoking cessation programme offered to active smokers, plus 4 rounds of annual screening with LDCT</td></tr>
<tr><td>Comparator</td><td>Smoking cessation programme offered to active smokers</td></tr>
<tr><td>Outcomes</td><td>Lung cancer mortality and all-cause mortality at 9.3 years follow up
Overall mortality during the screening phase of the trial was similar in both the LDCT and the control trial arms (RR=0.97, p=0.86). A significant reduction of 23% was observed after the screening phase had finished (RR=0.77, p=0.045).

<table>
<tr><td></td><td colspan="2">Mortality per 1000 person years (n)</td><td></td><td></td></tr>
<tr><td></td><td>LDCT group</td><td>Control group</td><td>Rate ratio (95% CI)</td><td>p value</td></tr>
<tr><td>Lung cancer</td><td>29.3 (43)</td><td>127(181)</td><td>0.70(0.47-1.03)</td><td>p=0.07</td></tr>
<tr><td>All-cause</td><td>105.1(154)</td><td>42.1(60)</td><td>0.83(0.67-1,03)</td><td>p=0.08</td></tr>
<tr><td>All except lung cancer</td><td>75.7(111)</td><td>84.9(121)</td><td>0.89(0.69-1.15)</td><td>p=0.38</td></tr>
<tr><td>Cardiovascular disease</td><td>15.0(22)</td><td>29.5(42)</td><td>0.51(0.30-0.85)</td><td>p=0.009</td></tr>
<tr><td>Other causes</td><td>60.7(89)</td><td>55.5(79)</td><td>1.10(0.81-1.48)</td><td>p=0.56</td></tr>
</table>
CI – Confidence intervals, LDCT - Low dose computed tomography, py – Pack years

Lung cancer incidence at 8.5 yrs follow up
LDCT group: 67 cancers (49.9 per 10,000 PY) of which 38(57%) were screen detected, 25(37%) symptomatic detection, 4(6%) clinically detected but did not follow screening protocol
Control group 71 cancers (53.7 per 10,000 PY)
Rate ratio 0.93(95% CI 0.67 -1.30)

Cancer stage at diagnosis

A higher proportion of cancers were diagnosed at stage I in the LDCT group than the control group (p<0.001)</td></tr>
</table>

Stage at diagnosis

Stage	LDCT group (n=67)	Control group (n=71)	p value
I	24(36%)	8(11%)	p<0.001
II	5(7%)	5(7%)	NR
III	9(13%)	8(11%)	NR
IV	24(36%)	35(49%)	NR
Unknown	5(7%)	15(21%)	p=0.005

LDCT - Low dose computed tomography, NR – Not reported

Adverse events
Death rates within 60 days of surgical treatment were 1.2 per 1000 (2/1613) vs1.3 per 1000(2/1593) in the LDCT and control group respectively
Deaths within 60 days of an invasive diagnostic procedure were 3.7 per 1000(6/1613) vs 3.8(6/1593 per 1000, (p=0.98) in the LDCT and control group respectively

Quality appraisal

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB: ITALUNG** RCT assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	Yes
	Was allocation concealment adequate?	Yes
	Were groups similar at baseline?	Yes
	Were eligibility criteria specified?	Yes
	Were patients masked?	No
	Were care providers masked	No
	Were outcomes assessors masked?	Yes
	Were outcome measures equal reliable and valid?	The trial was underpowered
	Adherence to the intervention	Across 4 rounds 81%
	Did the study have crossovers and contamination	Yes (but minimal)

		Overall attrition rates	Low <10%
		Differential attrition and attrition bias	Low <10%
		Method used to handle missing data	N/A
		Was intention to screen analysis used	Yes
		Ascertainment of outcomes adequately described	Yes
		Ascertainment techniques are they equal, valid and reliable	Unclear
	Brodersen et al (2020)[36]	**Overall ROB: ITALUNG** RCT assessed as having SOME ROB	
		Cochrane risk of bias tool v2 (assessed as low, unclear or high risk of bias)	Comment
		Randomisation process	Low
		Contamination- deviation from intended intervention	Some
		Missing outcome data	Low
		Measurement of outcome including lead time bias	Low
		Selection of reported result	Low
	Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
		CONSORT Checklist for RCTs	Comment
		Recruitment strategies well defined	Yes
		Random assignment	Yes
		Complete diagnostic workup planned	Yes
		Inclusion criteria described and respected	Yes
		Valid measurement of all-cause mortality	Yes
		Valid measurement of lung cancer specific mortality	Yes
		Blinded outcomes assessment	Yes
		Long enough follow up	Yes

Table 54 presents the details and quality appraisal of the LUSI RCT

Table 54. Lung cancer Screening Intervention Trial (LUSI) RCT (Country; Germany)

<table>
<tr><td>Trial objectives</td><td colspan="2">To compare incidence, mortality and adverse outcomes of 5 annual rounds of LDCT lung cancer screening vs no screening</td></tr>
<tr><td>Inclusions</td><td colspan="2">People aged 50-69 with exposure to tobacco smoking of >15 cigarettes a day for 25 years or
>10 cigarettes a day for >30 years who are current or former smokers who quit smoking <10 years ago</td></tr>
<tr><td>Exclusions</td><td colspan="2">Not reported</td></tr>
<tr><td>Population</td><td colspan="2">N=4052</td></tr>
<tr><td>Intervention</td><td colspan="2">Baseline (prevalence round) followed by 4 annual rounds of multi-slice CT</td></tr>
<tr><td>Comparator</td><td colspan="2">No screening</td></tr>
<tr><td>Quality appraisal</td><td colspan="2">
<table>
<tr><th>Systematic review/meta-analysis</th><th colspan="2">Quality appraisal</th></tr>
<tr><td>Jonas et al (2021)[8]</td><td colspan="2">Overall ROB: LUSI RCT assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist.</td></tr>
<tr><td></td><td>USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR</td><td>Comment</td></tr>
<tr><td></td><td>Was randomisation adequate?</td><td>Yes</td></tr>
<tr><td></td><td>Was allocation concealment adequate?</td><td>Unclear</td></tr>
<tr><td></td><td>Were groups similar at baseline?</td><td>Yes</td></tr>
<tr><td></td><td>Were eligibility criteria specified?</td><td>Yes</td></tr>
<tr><td></td><td>Wre patients masked?</td><td>No</td></tr>
<tr><td></td><td>Were care providers masked</td><td>No</td></tr>
<tr><td></td><td>Were outcomes assessors masked?</td><td>Unclear</td></tr>
<tr><td></td><td>Were outcome measures equal reliable and valid?</td><td>Yes</td></tr>
<tr><td></td><td>Adherence to the intervention</td><td>High adherence rates >90%</td></tr>
<tr><td></td><td>Did the study have crossovers and contamination</td><td>Unclear</td></tr>
<tr><td></td><td>Overall attrition rates</td><td>Low <10%</td></tr>
<tr><td></td><td>Differential attrition and attrition bias</td><td>Low <10%</td></tr>
<tr><td></td><td>Method used to handle missing data</td><td>Unclear</td></tr>
</table>
</td></tr>
</table>

	Was intention to screen analysis used	Yes
	Ascertainment of outcomes adequately described	Yes
	Ascertainment techniques are they equal, valid and reliable	Yes
Brodersen et al (2020)[36]	**Overall ROB: LUSI** RCT assessed as LOW ROB	
	Cochrane risk of bias tool v2 (assessed as low, unclear or high risk of bias)	Comment
	Randomisation process	Low
	Contamination- deviation from intended intervention	Low
	Missing outcome data	Low
	Measurement of outcome including lead time bias	Low
	Selection of reported result	Low
Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
	CONSORT Checklist for RCTs	Comment
	Recruitment strategies well defined	Yes
	Random assignment	Yes
	Complete diagnostic workup planned	Yes
	Inclusion criteria described and respected	Yes
	Valid measurement of all-cause mortality	Yes
	Valid measurement of lung cancer specific mortality	No
	Blinded outcomes assessment	Yes
	Long enough follow up	Yes

Table 55. Results of the LUSI RCT

<table>
<tr><th></th><th>Objective</th><th>Outcome measures</th><th>Outcomes</th></tr>
<tr><td>Maldonado et al (2021)[50]</td><td>To report lung cancer incidence and screen test sensitivity</td><td>Lung cancer overdiagnosis at median 9.77 years follow up and 5.73 years since last screening</td><td>Lung cancer excess cumulative incidence (overdiagnosis)

A high proportion of excess lung cancer incidence is from bronchiolo-alveolar carcinoma (BAC)

Lung cancer overdiagnosis rates
<table>
<tr><th>Lung cancer type</th><th>% (95% CI) of all lung cancer cases diagnosed by LDCT that would not have become clinically apparent</th><th>% likelihood (95% CI) that a participant’s cancer would not have become clinically apparent if no screening</th></tr>
<tr><td>All lung cancers</td><td>25.4(-11.4 to 64.3)</td><td>17.8(-7.4 to 44.7)</td></tr>
<tr><td>All adenocarcinomas including BAC</td><td>50.0(14.0 to 88.4)</td><td>37.3(11.5 to 65.4)</td></tr>
<tr><td>BAC</td><td>112.5(68.2 to 113.1)</td><td>90.0(54.3 to 164.4)</td></tr>
<tr><td>Non- BAC</td><td>36.1(-8.4 to 84.8)</td><td>26.5(-5.3 to 61.8)</td></tr>
<tr><td>Other (non adenocarcinomas)</td><td>-31.6 (-130.8 to 83.0 to 83.0)</td><td>-19.4(-76.8 to 45.6)</td></tr>
</table>
BAC - Bronchiolo-alveolar carcinoma, CI – Confidence intervals, LDCT - Low dose computed tomography</td></tr>
<tr><td>Becker et al (2019)[45]</td><td>To report results of lung cancer screening outcomes including uptake and mortality</td><td>Outcomes:
lung cancer mortality
all-cause mortality lung cancer incidence
lung cancer diagnosis by stage</td><td>Lung cancer and all-cause mortality at 8.8 yrs follow up
There was no significant difference in lung cancer mortality or all-cause mortality between the LDCT and control arms of the trial. There was a significant reduction in lung cancer mortality in females compared to males.

Overall cumulative lung cancer mortality
HR =0.74 (95% CI 0.46-1.19;0=0.21)

Males HR =0.94 (95%CI 0.54 – 1.61; p=0.81)
Females HR = 0.31 (95% CI 0.10-0.96; p=0.04)

All-cause mortality
HR=0.99 (95% CI 0.79-1.25, p=0.95)</td></tr>
</table>

Lung cancer incidence (stage I)
At the end of the active screening phase (5 annual screening rounds) there was a higher proportion of early stage lung cancers in the LDCT group (n=32) vs the control group (n=1)
HR=14.1(96% CI 4.37-45.5; p<0.0001)

Lung cancer incidence (Stage I and II combined)
At the end of the active screening phase there was a higher proportion of stage I/II lung cancers in the LDCT group (n=47) vs the control group (n=8)
HR= 5.92(95%CI 2.79 - 12.53; p<0.0001)

Lung cancer incidence (stage II +)
At the end of the active screening phase there were fewer lung cancers at stage II and above in the LDCT group (n=20) vs the control group (n=33), but this difference was not statistically significant.
HR=0.61(96% CI 0.35-1.07; p=0.083)

Over the full follow up period (> 5 years post randomisation) there were fewer lung cancers diagnosed at stage II or above in the LDCT group (n=16) vs the control group (n=27)
HR=0.61(95% CI 0.40-0.92; p=0.02)

Lung cancer incidence (stage III and IV combined)
At the end of the active screening phase there were fewer lung cancers diagnosed at stage III/IV in the LDCT group (n=15) vs the control group (n=28), but this difference was not statistically significant
HR=0.54(95%CI 0.29 - 1.01; p=0.06).

Over the full follow up period (> 5 years post randomisation) there were fewer lung cancers diagnosed at stage III/IV in the LDCT group (n=14) vs the control group (n=21)
HR=0.58(95%CI 0.37 - 0.91; p=0.02)

Cancer at stage of diagnosis

Incidence by years since randomization, gender and tumour stage

		LDCT (n=2029)	Control (n=2023)	

Years after randomization		Male(n)	Female(n)	Male(n)	Female(n)	Total (n)
0-5 years (active screening)	IA	19	13	1		33
	IB	7	3	1	1	12
	IIA	2		2	1	5
	IIB	2	1	1	1	5
	IIIA	6	1	5	5	17
	IIIB	1		2	1	4
	IV	5	2	11	4	22
	not available	1				1
	Subtotal	43	20	23	13	99
>5 years (screening rounds completed)	IA	3	1	1		5
	IA1	1				1
	IB	1		2		3
	IIA	1		2		3
	IIB	1		1	1	3
	IIIA	1	2	3	3	9
	IIIB		1	2		3
	IV	8	2	10	3	23
	IVA			1		1
	IVB				1	1
	not available			1		1
	Subtotal	16	6	23	8	53
8.8 years	Total	59	26	46	21	152

LDCT - Low dose computed tomography

Table 56 presents the details and quality appraisal of the LSS RCT

Table 56. Lung screening Study (LSS) RCT (Country; USA)

<table>
<tr><td>Trial objectives</td><td colspan="2">Pilot RCT to assess the feasibility of conducting a large scale RCT of LDCT vs Chest X-ray (prior to launch of NLST) over 2 screening rounds</td></tr>
<tr><td>Inclusions</td><td colspan="2">People aged 55 to 74 exposed to 30 pack years tobacco smoking and either current smoker or former smoker who quit <10 years</td></tr>
<tr><td>Exclusions</td><td colspan="2">Chest X-ray or CT of thorax in previous 24 months, history of lung cancer, current treatment for any cancer, removal of part or entire lung, participation in another cancer screening or cancer primary prevention trial other than a smoking cessation study</td></tr>
<tr><td>Population</td><td colspan="2">N=3318</td></tr>
<tr><td>Intervention</td><td colspan="2">2 annual rounds of LDCT (n=1660)</td></tr>
<tr><td>Comparator</td><td colspan="2">2 annual rounds of chest x-ray (1658)</td></tr>
<tr><td>Quality appraisal</td><td colspan="2">The table below outline the critical appraisal of the LSS trial carried out by Jonas 2021. The LSS was not included in the Brodersen 2020 or Sadate 2020 systematic reviews and meta-analyses
<table>
<tr><td>Systematic review/meta-analysis</td><td colspan="2">Quality appraisal</td></tr>
<tr><td>Jonas et al (2021)[8]</td><td colspan="2">Overall ROB: LSS RCT assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist</td></tr>
<tr><td></td><td>USPSTF risk of bias tool is based on the findings of the questions below.
Overall ROB is assessed as GOOD, FAIR or POOR</td><td>Comment</td></tr>
<tr><td></td><td>Was randomisation adequate?</td><td>Yes</td></tr>
<tr><td></td><td>Was allocation concealment adequate?</td><td>Yes</td></tr>
<tr><td></td><td>Were groups similar at baseline?</td><td>Yes</td></tr>
<tr><td></td><td>Were eligibility criteria specified?</td><td>Yes</td></tr>
<tr><td></td><td>Wre patients masked?</td><td>No</td></tr>
<tr><td></td><td>Were care providers masked</td><td>No</td></tr>
<tr><td></td><td>Were outcomes assessors masked?</td><td>No</td></tr>
<tr><td></td><td>Were outcome measures equal reliable and valid?</td><td>The trial was underpowered</td></tr>
<tr><td></td><td>Adherence to the intervention</td><td>High adherence to the intervention >85%</td></tr>
</table></td></tr>
</table>

	Did the study have crossovers and contamination	Unclear
	Overall attrition rates	High >10%
	Differential attrition and attrition bias	High >10%
	Method used to handle missing data	Unclear
	Was intention to screen analysis used	Unclear
	Ascertainment of outcomes adequately described	Unclear
	Ascertainment techniques are they equal, valid and reliable	Unclear

Table 57. Results of the LSS RCT

<table>
<tr><th></th><th>Objective</th><th>Outcome measures</th><th>Outcomes</th></tr>
<tr><td>Doroudi et al (2018)[43]</td><td>To report lung cancer mortality after long term follow up of 5 years</td><td>Outcomes:
lung cancer mortality
all-cause mortality</td><td>Lung cancer specific and all-cause mortality

At median follow up of 5.2 years there were no differences between the LDCT and chest x-ray (CXR) arms of the trial

Mortality rates for LDCT and CXR trial arms
<table>
<tr><th></th><th>Deaths (n)</th><th>Mortality rate (per 1000 PY)</th><th>Mortality Rate Ratio (95% CI)</th></tr>
<tr><td colspan="4">Lung cancer specific mortality</td></tr>
<tr><td>LDCT</td><td>32</td><td>3.84</td><td>1.24-2.08)</td></tr>
<tr><td>CXR</td><td>26</td><td>3.10</td><td></td></tr>
<tr><td colspan="3">Causes other than lung cancer mortality</td><td></td></tr>
<tr><td>LDCT</td><td>107</td><td>12.83</td><td>1.20(0.90 – 1.58)</td></tr>
<tr><td>CXR</td><td>90</td><td>10.74</td><td></td></tr>
<tr><td colspan="3">All-cause mortality</td><td></td></tr>
<tr><td>LDCT</td><td>139</td><td>16.67</td><td>1.20(0.94-1.54)</td></tr>
<tr><td>CXR</td><td>116</td><td>13.84</td><td></td></tr>
</table>
CI – Confidence intervals, CXR – Chest x-ray, LDCT - Low dose computed tomography, N – Number, PY – Pack years</td></tr>
</table>

Gohagan et al (2005)[46]

Report mortality. incidence and stage lung screening RCT at end of active screening period

Adherence, screening outcome, mortality, incidence, stage at diagnosis

Lung cancer incidence after 2 screening rounds at the end of the active screening period

	LDCT			Control		
	Baseline	Year 1	Total	Baseline	Year 1	Total
Stage I	16+1*	2	19(48%)	6	2	8(40%)
Stage II	3	0	3(8%)	0	1	1(5%)
Stage III	6	5	11(28%)	0+1*	4	5(25%)
Stage IV	3+1	1	5(13%)	0+3*	1	4(20%)
Unknown	2	0	2(5%)	1	1	2(10%)
Total	30+2	8	40	7+4	9	20

*Where there is +n this refers to additional interval cancers diagnosed

Table 58 presents the details and quality appraisal of the MILD RCT

Table 58. Multicentric Italian Lung Detection (MILD) RCT (Country; Italy)

Trial objectives	**Investigate the efficacy of LDCT screening beyond 4 years with 10 year follow up after randomisation**
Inclusions	People aged 49 to 75 years exposed to at least 20 pack years of tobacco smoking
Exclusions	History of cancer within 5 years of trial commencement
Population	N=4099
Intervention	LDCT every 12 months (n=1190), LDCT every 24 months (n=1186) for 5 years
Comparator	No screening (n=1723) over a 10 year follow up
Quality appraisal	The tables below outline the critical appraisal of the MILD trial carried out by Jonas 2021, Brodersen 2020 and Sadate 2020. The Jonas 2021 article critically appraises each individual study.

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB: MILD** RCT assessed as POOR - Generally there were fatal flaws concerning randomisation, similarity of groups at baseline, and a lack of clarity about the reliability and validity of measures used and their application to groups equally. Specifically there was high risk of selection bias, unclear methods of randomisation and allocation concealment, changing protocol and addition of a control arm later in the trial, lack of similar groups at baseline for important variables, differential follow up between groups and a high risk of measurement bias	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	No
	Was allocation concealment adequate?	Unclear
	Were groups similar at baseline?	No
	Were eligibility criteria specified?	Yes
	Were patients masked?	No
	Were care providers masked	No
	Were outcomes assessors masked?	No

	Were outcome measures equal reliable and valid?	Unclear
	Adherence to the intervention	High adherence rates >95%
	Did the study have crossovers and contamination	Unclear for 5 year follow up. For 10 year follow up 1.2% of control group had LDCT
	Overall attrition rates	Low <10%
	Differential attrition and attrition bias	Unclear for loss to follow up overall but differential follow up as 35.2% fewer people from control group had 10 year follow up than LDCT group
	Method used to handle missing data	Unclear
	Was intention to screen analysis used	Yes
	Ascertainment of outcomes adequately described	No
	Ascertainment techniques are they equal, valid and reliable	Unclear
Brodersen et al (2020)[36]	**Overall ROB:** assessed the MILD RCT as HIGH ROB	
	Cochrane risk of bias tool v2 (assessed as low, unclear or high risk of bias)	Comment
	Randomisation process	High
	Contamination- deviation from intended intervention	Low
	Missing outcome data	Low
	Measurement of outcome including lead time bias	Some
	Selection of reported result	Some
Sadate et al (2020)[37]	**Overall quality appraisal** – there were SOME CONCERNS about the MILD RCT methodology. All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
	CONSORT Checklist for RCTs	Comment
	Recruitment strategies well defined	Yes
	Random assignment	Yes
	Complete diagnostic workup planned	Yes
	Inclusion criteria described and respected	Yes
	Valid measurement of all-cause mortality	Yes

		Valid measurement of lung cancer specific mortality	Yes
		Blinded outcomes assessment	Yes
		Long enough follow up	No

Table 59. Results of the MILD RCT

	Objective	Outcome measures	Outcomes
Pastorino et al (2019a)[44]	To report the 10 year follow up lung cancer incidence and mortality of LDCT vs control	Outcomes: • lung cancer mortality • all-cause mortality • lung cancer incidence • stage at diagnosis	Lung cancer mortality at 10 year follow up Analysis beyond 5 years showed that for lung cancer specific mortality there was a 0.7% cumulative risk in the LDCT group vs 1.5% in the control group corresponding to a 58% risk reduction for LDCT HR=0.42 (95% CI 0.22-0.79; p=0.0037) All-cause mortality at 10 year follow up There was 3.4% cumulative risk of all-cause mortality in the LDCT group and 4.5% in the control group with a 32% risk reduction for LDCT HR=0.68 (95% CI 0.49-0.94; p=0.01)

Lung cancer and all-cause mortality at 10 year follow up

	LDCT (n=2376)	Control (n=1723)	p value
Lung cancer deaths	40(1.7%)	40(2.3%)	p=0.14
Lung cancer mortality rate per 100,000PY	173.3	246.8	p=0.12
All deaths	137(5.8%)	106(6.2%)	p=0.61
All-cause mortality per 100,000 PY	593.5	653.9	p=0.45

LDCT - Low dose computed tomography, N – Number, PY – Pack years

Lung cancer incidence at 10 year follow up

	LDCT	Control	p value
Lung cancer incidence	98(4.1%)	60(3.5%)	p=0.29
Lung cancer incidence per 100,000PY	431.5	372.6	p=0.37

LDCT - Low dose computed tomography, PY – Pack years

			Of the lung cancers observed in the LDCT group 27.6% (n=27) were not screen detected. Cancer stage at diagnosis at 10 year follow up LDCT was significantly more likely to result in lung cancer diagnosed at stage I as a proportion of all lung cancers diagnosed compared to the control (49/98 vs 13/60, p=0.0004) Stage / LDCT / Control I: 49(50.0%) / 13(21.7%) II: 4(4.1%) / 5(8.3%) III: 16(16.3%) / 10(16.7%) IV: 29(29.6%) / 32(53.3%) LDCT - Low dose computed tomography 154 LDCTs and 1.4 Positron Emission Tomography (PET) scans were needed to diagnose 1 lung cancer.
Pastorino et al (2019b)[49]	To report lung cancer incidence and mortality of the 2 screening arms of the trial (biennial screening vs annual screening) over 10 years follow up	Outcomes • lung cancer mortality • all-cause mortality • lung cancer incidence • stage at diagnosis	There were no significant differences between the LDCT biennial and annual screening groups at 10 year follow up for: • all-cause mortality (HR=0.80, 95% CI 0.57-1.12) • lung cancer specific mortality (HR=1.10, 95%CI 0.59-2.05) • the occurrence of stage II-IV cancers (p=0.4110) • interval cancers (p=0.3625)

Table 60 presents the details and quality appraisal of the NELSON RCT

Table 60. Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON); Country: Netherlands/Belgium

Trial objectives	**To evaluate if screening using low dose CT can reduce lung cancer mortality by at least 25% at 10 years follow up**
Inclusions	Men born between January 1st 1928 and January 1953 from population registries in 7 districts of the Netherlands and men and women born within the same dates from population registries of 14 municipalities in Belgium. Of the people completing the NELSON

	trial questionnaire after being approached for recruitment those eligible for inclusion were age 50-75 had smoked 15 cigarettes a day for 25 years or >10 cigarettes a day for >30 years and were current smokers or former smokers who quit smoking <10 years ago
Exclusions	People with moderate or bad self reported health who were unable to climb 2 flights of stairs; people with a body weight of ≥140kg; people with current or past renal cancer, melanoma or breast cancer, lung cancer diagnosed less than 5 years ago and those diagnosed over 5 years ago and still receiving treatment and people who had received a chest x-ray less than a year before they filled in the NELSON trial questionnaire after being approached
Population	15,792 people were recruited between December 2003 and July 2006
Intervention	Screening group (n=7900) were screened by 16 detector multi-slice computerised tomography at baseline(round 1), 1 year(round 2), 2 years(round 3) and 2.5 years(round 4)
Comparator	No screening (n=7892)
Quality appraisal	The tables below outline the critical appraisal of the NELSON trial carried out by Jonas 2021, Brodersen 2020 and Sadate 2020. The Jonas 2021 article critically appraises each individual study. Where individual studies vary in risk of bias these are mentioned in the comments column.

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB: NELSON** RCT was assessed as FAIR - Generally comparable groups assembled but some questions remain although no fatal flaws exist	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	Yes
	Was allocation concealment adequate?	Yes
	Were groups similar at baseline?	Yes
	Were eligibility criteria specified?	Yes
	Were patients masked?	No
	Were care providers masked	No
	Were outcomes assessors masked?	Yes
	Were outcome measures equal reliable and valid?	Yes
	Adherence to the intervention	High adherence rates
	Did the study have crossovers and contamination	There was limited reporting of crossovers and contamination

		Overall attrition rates	Low <10% for the overall trial but for Van den Bergh et al 2011 there was high attrition of people completing HRQoL questionnaires
		Differential attrition and attrition bias	Low <10% for the overall trial but for Van den Bergh et al 2011 there was high >10% attrition of people completing HRQoL questionnaires
		Method used to handle missing data	Unclear
		Was intention to screen analysis used	Yes
		Ascertainment of outcomes adequately described	No
		Ascertainment techniques are they equal, valid and reliable	Unclear
	Brodersen et al (2020)[36]	**Overall ROB: NELSON** RCT assessed as having SOME CONCERNS of ROB	
		Cochrane risk of bias tool v2 (assessed as low, unclear or high risk of bias)	Comment
		Randomisation process	Low
		Contamination- deviation from intended intervention	Some concerns as data about contamination restricted to the baseline round
		Missing outcome data	Low
		Measurement of outcome including lead time bias	Low
		Selection of reported result	Some concerns as focus on men although protocol; suggest data about men and women would be reported in the same analysis
	Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
		CONSORT Checklist for RCTs	Comment
		Recruitment strategies well defined	Yes
		Random assignment	Yes
		Complete diagnostic workup planned	Yes
		Inclusion criteria described and respected	Yes
		Valid measurement of all-cause mortality	Yes
		Valid measurement of lung cancer specific mortality	Yes
		Blinded outcomes assessment	Yes
		Long enough follow up	Yes

Table 61. Results of the NELSON RCT

<table>
<tr><th></th><th>Objective</th><th>Study approach and/or outcome measures</th><th>Outcomes</th></tr>
<tr><td>de Koning et al (2020)[47] Error! Bookmark not defined.</td><td>To report long term follow up of the NELSON trial reporting uptake, lung cancer detection, incidence and mortality</td><td>Outcomes:
screening uptake
• results of screening rounds
• lung cancer mortality
• all-cause mortality
• cumulative incidence of lung cancer
• main analysis males with sub group analysis of females
• proportion of cancers detected in screening group
• cancer stage at diagnosis</td><td>Screening uptake in male participants
Screening group uptake was on average 90% (95%CI 76.9 to 95.8)

Lung cancer detection

Results of screening rounds in male participants
<table>
<tr><td></td><td>Positive n (%)</td><td>Lung cancer detection n (%)</td><td>Indeterminate n (%)</td></tr>
<tr><td>Round 1
Baseline (n=6309)</td><td>147(2.3)</td><td>56(0.9)</td><td>1241(19.7)</td></tr>
<tr><td>Round 2
1 year (n=6086)</td><td>95(1.6)</td><td>45(0.7)</td><td>357(5.9)</td></tr>
<tr><td>Round 3
2 years (n=5768)</td><td>136(2.4)</td><td>65(1.1)</td><td>385(6.7)</td></tr>
<tr><td>Round 4
2.5 years (n=4437)</td><td>89(2.0)</td><td>37(0.8)</td><td>86(1.9)</td></tr>
</table>
N - Number

Lung cancer mortality
At 10 year follow up male lung cancer mortality:
Screening: 2.50 per 1000 PY
Control: 3.30 per 1000 PY
Rate ratio 0.76 (95% CI 0.61 - 0.94, p=0.01)

Lung cancer as cause of death as proportion of all deaths
Screening group: 18.4% (160/868)
Control: 24.4% (210/860)</td></tr>
</table>

At 11 year follow up male lung cancer mortality:
Rate ratio 0.78 (95% CI 0.63 to 0.95)

Female 10 year follow up lung cancer mortality
Rate ratio 0.46 (95% CI 0.21 to 0.96)

All-cause mortality
Male all-cause mortality at 10 year follow up:
Screening: 13.93 per 1000 PY
Control: 13.76 per 1000 PY
Rate ratio 1.01 (95% CI 0.92 - 1.11)

Lung cancer incidence
Male cumulative incidence of lung cancer:
Screening: 5.58 per 1000 PY
Control: 4.91 per 1000 PY
Rate ratio 1.14 (95%CI 0.97 - 1.33)

Screening group - lung cancers in males detected:
From active screening: 59% (203/344)
Interval cancers: 12.8% (44/344)
Follow up period: 28.2% (97/344)

Cancer stage at diagnosis

Stage at diagnosis	Screening group Screen detected n (%)	Screening group Interval and follow up n (%)	Control n (%)
IA	95(46.8)	10(7.1)	21(6.9)
IB	24(11.8)	10(7.1)	20(6.6)
IIA	8(3.9)	4(2.8)	13(4.3)
IIB	11(5.4)	6(4.3)	17(5.6)
IIIA	20(9.9)	14(9.9)	43(14.1)
IIIB	13(6.4)	14(9.9)	34(11.2)
IV	19(9.4)	73(51.8)	139(45.7)
Unknown	13(6.4)	10(7.1)	17(5.6)
Total	203	141	304

N - Number

Yousaf-Khan et al (2017)[48]

To report results of the fourth screening round of 2.5 years compared to intervals of 1 and 2 years

Outcomes by screening round:

- lung cancer detection rate
- positive predictive value
- false positive rate
- number needed to screen to detect 1 lung cancer

Comparison of different screening intervals

The 2.5 year screening interval (round 4) compared to 1 year (round 2) had a lower proportion of stage I cancers (60.9% vs 75.9%) and higher proportion of stage IIIb/IV cancers (17.3% vs 6.8%) (p=0.02)

There was no difference in the 2.5 year (round 4) screening interval compared to 2 year (round 3) although a lower proportion of cancers were diagnosed at stage I (60.9% vs 72.7%) and a higher proportion of stage IIIb/IV (17.3% vs 5.2%). This did not reach significance (p=0.10)

No differences in lung cancer detection rate was observed between the 4 rounds and different screening intervals

The ratio of true positives (TP) to false positives (FP) improved to round 3 with the 2 year screening interval (0.83) and then drops for round 4 with the 2.5yr interval (0.69)

Outcomes of LDCT screening by screening round

	Round 1- Baseline (95% CI)	Round 2- 1 yr (95% CI)	Round 3 -2 yrs (95% CI)	Round 4 -2.5 yrs (95% CI)
LC Detection Rate %	0.9 (0.7-1.2)	0.8 (0.6-1.0)	1.1 (0.8-1.3)	0.8 (0.6-1.1)
PPV%	35.5 (28.4-42.1)	42.0 (34.4-49.6)	45.5 (37.6-53.5)	41.0 (31.6-50.5)
FP%	64.5 (57.9-71.6)	58.0 (50.4-65.6)	54.5 46.7-62.4	59.0 49.5-68.4
TP/FP	0.69	0.72	0.83	0.69
Overall FP rate*				1.2*
NNS	108	133	92	123

*overall FP rate across all 4 screening rounds

			CI – Confidence intervals, FP – False positive, LC – Lung cancer, NNS – Number needed to screen to detect 1 lung cancer, PPV- Positive predictive value, TP – True positive, Y - Year **Quality appraisal (Jonas et al 2021**Error! Bookmark not defined.**)** USPTF appraised this paper as a non randomised study and rated it as POOR due to the high risk of self selection bias for the 4th round of screening. Enrolment of 78% of eligible patients from the 3rd round of study (about 70% of initial sample) and observation that the 4th round differed significantly from the initial sample in several ways (eg more current smokers in the 4th round).
Van den Bergh et al (2011)[56]	To examine HRQoL of LDCT screening for lung cancer on screening and control groups of the NELSON RCT	Study approach: Health related quality of life questionnaires were completed by participants at : 1. Baseline in screening (n=658) and control groups (n=630) 2. 2 months after baseline screen in screening group (n=600) 3. 6 months after second screening round (2 years from baseline) in screening (n=609) and control groups (n=322) Outcomes were : • generic HRQoL (using SF 12 and EQ-5D scales) • generic anxiety (using STAI6 scales) • lung cancer specific distress (using IES)	**Health related quality of life (HRQoL) outcomes** No statistically significant differences were found in HRQoL over time between the screening and control groups for any outcome measure. None of the parameters for time or trial arm or the interaction between time x trial arm was significant for any of the HRQoL outcome measures. HRQoL scores were worse for: • females than males (p<0.05) Self reported and physical health was worse for: • people with more pack years vs fewer pack years (p<0.05) • smokers vs former smokers (p<0.05) Current smoking was negatively associated with Impact of Event Scales (IES) (p<0.01) In the screening group differences in the IES for total, intrusive and avoidance scores were statistically significant better for those with a negative result compared to an indeterminate result were (p<0.01) for the 2nd questionnaire (2 months after the baseline screen). These differences were not seen prior to baseline screening (1st questionnaire) or 2 years later after the second screen (3rd questionnaire).
Van de Wiel et al (2007)[57]	To examine the benefit of searching for incidental findings in the Dutch-Belgian lung	Study approach: All people who had a baseline scan from April 2004 to January 2006 at one centre were reviewed (n=1929) Outcomes measures were number of:	Non clinically relevant incidental findings (1 or more) were found in 1409 (73%) of participants. Non clinically relevant incidental finding: Number (%)

cancer screening trial (NELSON) using low-dose multidetector CT	• non clinically and possibly clinically relevant incidental findings at baseline scan	<table><tr><td>Coronary artery calcification</td><td>1306(93)</td></tr><tr><td>Emphysema</td><td>321(23)</td></tr><tr><td>Pulmonary fibrosis</td><td>117(8)</td></tr><tr><td>Pleural plaques</td><td>66(5)</td></tr><tr><td>Pleural calcifications</td><td>51(4)</td></tr><tr><td>Adrenal lesions</td><td>13(0.9)</td></tr><tr><td>Small lymph nodes</td><td>5(0.4)</td></tr><tr><td>Bronchiectasis</td><td>3(0.2)</td></tr></table> Possibly clinically relevant findings (1 or more) were found in 163 (8%) of participants. All apart from one incidental finding were benign. <table><tr><td>Site of possible clinically relevant incidental findings</td><td>Number (%)</td></tr><tr><td>Liver lesions</td><td>76(53)</td></tr><tr><td>Kidney lesions</td><td>53(37)</td></tr><tr><td>Thyroid gland</td><td>9(6)</td></tr><tr><td>Mediastinum</td><td>2(1)</td></tr><tr><td>Breast</td><td>1(1)</td></tr><tr><td>Colon</td><td>1(1)</td></tr><tr><td>Spine</td><td>1(1)</td></tr></table>

Table 62 presents the details and quality appraisal of the NLST RCT

Table 62. National Lung Screening Trial (NLST); Country; USA.

Trial objectives	**To determine whether screening with low dose CT could reduce mortality from lung cancer**
Inclusions	People aged 55-75 who had been exposed to at least 30 pack years of tobacco smoking and were either current smokers or former smokers who quit <15 years ago
Exclusions	People who had previously received a diagnosis of lung cancer, had undergone chest CT in the previous 18 months before enrolment, had haemoptysis or unexplained weight loss of more than 6.8kg in the previous year
Population	N=53,454
Intervention	3 annual screenings of LDCT
Comparator	3 annual screenings single view posteroanterior chest radiography
Quality appraisal	The tables below outlines the critical appraisal of the NLST trial carried out by Jonas 2021, and Sadate 2020 (NLST was not included in the Brodersen 2020 meta-analysis). The Jonas 2021 article critically appraises each individual study. Where individual studies vary in risk of bias these are mentioned in the comments column. Some papers of

trial results were critically appraised as non randomised trials by Jonas 2021 and in these cases comments on critical appraisal are found within the individual study tables.

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB: NLST**RCT was assessed as GOOD. Meets all criteria; comparable groups are assembled initially and maintained throughout the study, reliable and valid measurements are applied equally to both groups, interventions are spelled out clearly; all important outcomes are considered, intention to treat analysis is used.	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	Yes
	Was allocation concealment adequate?	Yes
	Were groups similar at baseline?	Yes
	Were eligibility criteria specified?	Yes
	Were patients masked?	Yes
	Were care providers masked	No
	Were outcomes assessors masked?	Yes
	Were outcome measures equal reliable and valid?	For all but 1 study when different methods were used for different rounds **Error! Bookmark not defined.**
	Adherence to the intervention	High adherence rates
	Did the study have crossovers and contamination	Low <10%
	Overall attrition rates	Low <10%
	Differential attrition and attrition bias	Low
	Method used to handle missing data	Unclear in all apart from O'Grady et al (2014) who did report the method
	Was intention to screen analysis used	Yes
	Ascertainment of outcomes adequately described	Yes
	Ascertainment techniques are they equal, valid and reliable	Yes

Sadate et al (2020)[37]	**Overall quality appraisal** – All studies presented a complete diagnostic work up planned in the protocol with well described and respected inclusion criteria. Validity of mortality measurement was checked	
	CONSORT Checklist for RCTs	Comment
	Recruitment strategies well defined	Yes
	Random assignment	Yes
	Complete diagnostic workup planned	Yes
	Inclusion criteria described and respected	Yes
	Valid measurement of all-cause mortality	Yes
	Valid measurement of lung cancer specific mortality	Yes
	Blinded outcomes assessment	Yes
	Long enough follow up	Yes

Table 63. Results of the NLST RCT

	Objective	Study approach and/or outcome measure	Outcomes
Iaccarino et al (2019)[72]	Secondary analysis of patient level and LDCT level adverse outcomes of screening for lung cancer	Study approach: Patient level outcomes of 26,453 people undergoing LDCT screening and subset of 4632 with self reported COPD Outcomes were numbers of subjects: • participating in screening • receiving diagnostic evaluation	Adverse outcomes of LDCT screening Overall patient level outcomes through 3 years of annual screening

	All subjects n(%)	Subjects without COPD n(%)	Subjects with COPD n(%)	Adjusted OR with and without COPD (95% CI)
LDCT screening (n)	26,453	21,821	4632	
Diagnostic evaluation	8073(30.5)	6396(29.3)	1677(36.2)	1.29*(1.20-1.38)
Invasive procedure	1,106 (4.2)	830(3.8)	276(6.0)	1.41(1.22-1.63)
• No LC	454 (41.0)	NR	NR	
Complication	230(0.9)	159(0.7)	71(1.5)	1.83*(1.37-2.44)
• No LC	44(19.1)	NR	NR	
Serious complication	88(0.3)	59(0.3)	29(0.6)	1.78*(1.13-2.83)

		• undergoing invasive procedures • who had complications	• No LC	11(12.5)	NR	NR	
			Lung cancer diagnosed	1076(4.1%)	793(3.6)	283(6.1)	1.43*(1.24-1.66)

*p<0.01

CI- Confidence interval, COPD – Chronic obstructive pulmonary disease, LDCT – Low dose computed tomography, LC – Lung cancer, n- Number, OR- Odds ratio

Aberle et al (2019)[40]

Explore if with extended follow up originally reported reduction in lung cancer mortality was maintained

Outcomes:
- lung cancer mortality
- all-cause mortality
- cumulative incidence of lung cancer
- stage at diagnosis
- overdiagnosis

Lung cancer mortality over 12.3 years including dilution adjusted rate ratio (adjusting for the proportion of people developing lung cancer after the end of the active screening period who could not have benefitted from screening). The overdiagnosis rate at 11.3 years follow up was 3.1% overall and 79% for Bronchioalveolar cell carcinoma (BAC).

Lung cancer deaths	LDCT n (n per 1000 subjects)		CXR n (n per 1000 subjects)		Rate ratio (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
All subjects	1147(42.9)	578(21.6)	1236(46.2)	646(24.2)	0.93 (0.85-1.00)	0.89 (0.80-0.97)
Men	733(46.5)	373(23.7)	755(47.9)	390(24.7)	0.97 (0.87-1.07)	0.95 (0.83-1.10)
Women	414(37.8)	205(18.7)	481(43.9)	256(23.3)	0.86 (0.75-0.98)	0.80 (0.66-0.96)
Current smoker	724(56.3)	356(27.7)	818(63.4)	423(32.8)	0.88 (0.80-0.97)	0.84 (0.73-0.97)
Former smoker	423(30.5)	222(16.0)	418(30.2)	223(16.1)	1.01 (0.88-1.15)	0.99 (0.82-1.19)
Age 55-64 at start of trial	641(32.7)	310(15.8)	739(37.7)	362(18.4)	0.86 (0.75-0.98)	0.85 (0.75-0.99)
Age 65-74 at start of trial	506(71.2)	268(37.7)	497(69.9)	284(40.0)	1.01 (0.90-1.15)	0.94 (0.80-1.11)

CI – Confidence intervals, CXR – Chest x-ray, LDCT - Low dose computed tomography, N - Number

There was no significant difference in rate ratios (RR) between men and women, smokers and former smokers or age at start of the trial

Overall mortality (unadjusted) excluding lung cancer deaths 12.3 years follow up
LDCT screening n= 4106 (153.7 per 1000 subjects)
CXR screening n=4130 (154.5 per 1000 subjects)
RR 0.99 (95% CI 0.95 -1.03)

Cumulative incidence of lung cancer at 11.3 years follow up
LDCT screening n= 1701 (6.4 per 1000 PY)
CXR n=1681 (6.3 per 1000 PY)
RR 1.01 (95% CI 0.95 - 1.09)

Lung cancer stage at diagnosis

Stage	LDCT screening n (%)	CXR screening n(%)	p value of difference in proportion of cases
I	673(39.6)	462(27.5)	<0.0001
II	145(8.5)	153(9.1)	0.65
III	298(17.5)	321(35.5)	0.36
IV	468(27.5)	597(35.5)	<0.001
Occult	5(0.0)	4(0.0)	
Unknown	112(16.6)	143(8.5)	

CXR – Chest x-ray, LDCT - Low dose computed tomography, N - Number

Overdiagnosis
Overall overdiagnosis rate was 3.1% of positive screens (20/649)
Most over diagnosed cases were identifiable by histology. Bronchioalveolar carcinoma was the most commonly over diagnosed finding in 79% of cases (75/95).

Nguyen et al (2017)[58]Error! Bookmark not defined.	To determine extrapulmonary findings from LDCT lung screening	Study approach: A subset (65% n=17,309) of records of people screened with LDCT were searched for extrapulmonary findings Outcomes:	Extrapulmonary findings Extrapulmonary findings (incidental findings of the pleura, chest wall, hilar and mediastinal lymph nodes and lungs eg pneumonia were excluded)

Site of incidental finding	All (out of 17,309 (%)	Possibly clinically significant
Cardiovascular	2625(15.2)	1477(8.5)
Thyroid	221(1.3)	100(0.6)

- prevalence of extrapulmonary findings
- extrapulmonary malignancy rate

Adrenal	419(2.4)	207(1.2)
Renal	780(4.5)	407(2.4)
Hepatobiliary	1064(6.1)	369(2.1)
Total	4428(25.6)	2376(13.7)

Malignancy rate of extrapulmonary findings

Possibly clinically significant extrapulmonary findings diagnosis of malignancies

	Thyroid	Adrenal	Kidney	Liver
Total malignancies diagnosed during the screening period (n)	14	0	45	8
Possible clinically significant findings (n)	100	207	407	369
Malignancy diagnosed from possible clinically significant findings (n)	7	0	11	0

N - Number

Quality appraisal (Jonas 2021)
There is a medium risk of selection bias due to possible health volunteer bias and potential outcome measurement bias because definition of potentially significant extrapulmonary findings was left to radiologists interpreting CT scans to decide.

Clarke et al (2016)[62]

To evaluate smoking cessation and relapse by LDCT result

Point prevalent quit rates and abstinence rates and hazard ratio

- during 5 years of follow up annual point prevalence quit rates ranged from 11.6% to 13.4%
- 48% of current smokers attempted to quit and 7% of long term smokers relapsed
- any false positive screening result was associated with subsequent increased quitting and sustained abstinence among smokers (multivariable hazard ratio (HR) quitting = 1.23, 95% CI 1.13 -1.35) (sustained abstinence HR = 1.28, 95% CI 1.15 - 1.43)
- recent quitters with ≥1 false positive screen were less likely to relapse (HR = 0.72, 95% CI 0.54 - 0.96)
- screening result was not associated with relapse among long term, former smokers or baseline smokers who quit during follow up

Annual rates for smoking behaviours by year

	Year Point (7-day) abstinence among smokers, n = 8358	Sustained (6-months) abstinence among	Relapse among recently quit former	Relapse among long-term former smokers, n = 7820	Relapse among baseline smokers who quit during

		smokers, n = 8358	smokers, n = 786		follow-up, n = 2549
Year 1	11.6%	4.1%	50.9%	4.2%	30.9%
Year 2	13.4%	8.8%	23.4%	1.7%	7.9%
Year 3	11.7%	8.2%	4.1%	0.8%	2.7%
Year 4	12.6%	8.3%	2.1%	0.5%	3.9%
Year 5	11.9%	10.1%	2.3%	0.3%	0.9%

N - Number

Tanner et al (2015)[41]

To report mortality by ethnicity

Outcomes: comparison of African American black individuals and white Americans for;

- lung cancer specific mortality
- all-cause mortality by ethnicity

Lung cancer mortality by ethnicity

Of 53,452 people n=47,902 were American white individuals and n=2361 were African American black individuals with n=3,189 described as 'other'. Mortality rates were adjusted for socioeconomic status, lung cancer risk factors and residential region

Adjusted hazard ratios (HR) for lung cancer mortality by ethnicity

	White individuals HR (95% CI)	Black individuals HR (95% CI)	Other/missing ethnicity HR (95% CI)
Screening: LDCT (compared to CXR)	0.86(0.75-0.98)^	0.61(0.37-1.01)	0.72 (0.53-0.98)^
Sex: Female (compared to male)	0.84(0.74-0.96)^	0.91(0.60-1.39)	1.06(0.66-1.70)
Age group: age ≥70 yr (compared to age < 70 yr)	0.93(0.74-1.17)	1.03(0.40-2.67)	1.73(0.49-6.14)
Smoking status: Current smokers (compared to former smokers)	2.25(2.00-2.54)*	4.10(2.05-8.20)*	2.48(1.47-4.17)^

*Significantly different to comparison p<0.001
^ Significantly different to comparison p<0.05
CI – Confidence interval, CXR – Chest x-ray, HR - Hazard ratio, LDCT- Low dose computed tomography, yr - Year

All-cause mortality by ethnicity

Adjusted hazard ratio (HR) for all-cause mortality by ethnicity

	White individuals	Black individuals HR (95% CI)	Other/missing ethnicity

				HR (95% CI)		HR (95% CI)
			Screening: LDCT (compared to CXR)	0.95(0.89-1.02)	0.81(0.65-1.00)^	0.78(0.62-0.99)^
			Sex: Female (compared to male)	0.56(0.52-0.60)*	0.59(0.42-0.82)^	0.49(0.32-0.75)^
			Age group: age ≥70 yr (compared to age < 70 yr)	1,07(0.97-1.18)	1.79(1.04-3.00)^	0.96(0.50-1.84)
			Smoking status: Current smokers (compared to former smokers)	1.82(1.70-1.95)*	1.82(1.51-2.23)*	1.76(1.47-2.11)*
			*Significantly different to comparison p<0.001 ^ Significantly different to comparison p<0.05 CI – Confidence interval, CXR – Chest x-ray, HR - Hazard ratio, LDCT- Low dose computed tomography, yr - Year			
Gareen et al (2014)[53]	Assess the impact of abnormal findings on HRQoL and anxiety	Study approach: 2812 participants (of which 1947 had LDCT and 865 had CXR) who had baseline HRQoL assessments were asked to complete SF-36 and STAI questionnaires at baseline, 1 month and 6 months Outcomes were: • SF 36 physical component score (PCS) by screening result • SF 36 Mental component score (MCS) by screening result • STAI score (for anxiety) by screening result	Health related quality of life (HRQoL) by screening test result • at baseline there were no differences in the groups of patients who subsequently screened positive, negative, false positive, and those with significant incidental findings (SIF) for any measure • for true positives at 1 month and 6 months there was a significant worsening of HRQoL in the SF 36 PCS and MCS and STAI compared to people with those with different screening results • for true positives at 1 month and 6 months there was a significant worsening in both the SF 36 PCS and MCS scores and an increase in STAI anxiety scores compared to baseline • there were no differences between the LDCT and CXR arms of the trial HRQoL as change in SF36 PCS and MCS and STAI ratio at 1 month and 6 months compared to baseline by screening test result					
				SF 36 PCS change from baseline		SF 36 MCS change from baseline		STAI Ratio	
				1 month (95% CI)	6 months (95% CI)	1 month (95% CI)	6 months (95% CI)	1 month (95% CI)	6 months (95% CI)
			True +ve	-1.18 (-2.81, 0.45)	-7.02 (-8.80, 5.24)***	-3.95 (-5.87,-2.04)***	-4.15 (-6.27, 2.03)***	1.47 (1.16,1.88)**	1.38 (1.05,1.82)*

False +ve	0.46 (-0.04, 0.97)	0.30 (-27,0.87)	-0.22 (-82,0.37)	0.03 (-0.65,0.70)	1.06 (0.98, 1.15)	1.00 (0.92,1.10)
SIF	0.13 (-0.62, 0.88)	-0.16 (-1.01,0.69)	-0.04 (-0.93,0.84)	0.29 (-0.72,1.31)	1.06 (0.94, 1.20)	1.05 (0.91,1.21)
-ve	0	0	0	0	1.0	1.0

*p<0.05 **p<0.01 ***p<0.001
+ve – Positive, -ve – Negative, CI – Confidence interval, HRQoL – Health related quality of life, MCS- Mental component score, PCS - Physical component score, SIF – Significant incidental findings, SF- Short from, STAI- State Trait Anxiety Inventory

Quality appraisal, (Jonas 2021)
There is risk of selection bias because selection was related to outcome but with adjustment. Potential for selective reporting bias in that results are inconsistent with *a priori* plan.

O'Grady et al (2014)[59]	Assess the detection of thyroid cancer as an incidental finding of LDCT for lung cancer screening	Outcomes: 6 year follow up of incident thyroid cancer cases as thyroid cancer specific hazard ratio	LDCT scan was associated with a non-significant increase in thyroid cancer risk (HR = 1.61; 95% CI 0.96-2.71) which was stronger during the first 3 years of follow-up, during which participants were actively screened (HR = 2.19; 95% CI 1.07-4.47), but not subsequently (HR = 1.08; 95% CI 0.49-2.37)
Patz et al (2014)[51]	To estimate over diagnosis in LDCT screening	Outcomes of overdiagnosis: • probability that a lung cancer detected by screening is an overdiagnosis • Proportion of cases considered to be over diagnosed relative to	Overdiagnosis during active screening phase of lung screening programme Overdiagnosis rates by lung cancer type during the screening intervention period of 3 annual screens

Lung cancer type	% of all lung cancer cases diagnosed by LDCT that would not have become clinically apparent (95% CI)	% likelihood that a participant's cancer would not have become clinically apparent if no screening (95% CI)
All lung cancers	11.0(3.2-18.2)	18.5(5.4-30.6)
All NSCLC including BAC and NOS	14.4(6.1-21.8)	22.5(9.7-34.3)

		number of people needed to be screened to prevent 1 cancer	All NSCLC excluding BAC and including NOS: 7.1(-2.3 - 15.6); 11.7(-3.7 - 25.6) BAC only: 67.6(53.5 - 78.5); 78.9(62.2 - 93.5) BAC – Bronchioalveolar cell carcinoma, CI – Confidence intervals, CXR – Chest x-ray, LDCT – Low dose computed tomography, NOS- Not otherwise specified, NSCLC – Non-small cell lung cancer Estimate of overdiagnosis at follow up and lifetime time horizon Overdiagnosis rates by lung cancer type with a screening intervention of 3 annual screens and follow up of 7 years or lifetime

Lung cancer type	Likelihood a cancer would not become clinically apparent with 3 annual screens and 7 year follow up % (95% CI)	Likelihood a cancer would not become clinically apparent with 3 annual screens and lifetime follow up % (95%CI)
All NSCLC including BAC vs no screening	31(27-34)	11(7-15)
All NSCLC including BAC vs CXR	19(16-230)	9(5-15)
NSCLC excluding BAC vs no screening	21(16-25)	2.6(2.0-3.3)
NSCLC excluding BAC vs CXR	9(6-12)	1.2(0.7-1.7)
BAC only vs no screening	85(69-93)	49(34-71)
BAC only vs CXR	71(52-83)	41(28-62)

BAC – Bronchioalveolar cell carcinoma, CI – Confidence intervals, CXR – Chest x-ray, LDCT – Low dose computed tomography, NOS- Not otherwise specified, NSCLC – Non-small cell lung cancer

The number of cases of overdiagnosis found in the number needed to screen (320 people) to prevent 1 cancer death is 1.38

Pinsky et al (2014)[33]	To examine the results of the NLST LDCT group by age (Medicare-	Outcome measures: Demographics, smoking and medical history, screening examination adherence and results, diagnostic follow-up procedures	• the aggregate false-positive rate was higher in the 65+ cohort than in the under-65 cohort (27.7% vs. 22.0%; $p < 0.001$) • invasive diagnostic procedures after false-positive screening results were more frequent in the older cohort (3.3% vs. 2.7%; $p = 0.039$) • complications from invasive procedures were low in both groups (9.8% in the under-65 cohort vs. 8.5% in the 65+ cohort)

	eligible >65 vs <65 years	and complications, lung cancer diagnoses, treatment, survival, and mortality.	• prevalence and positive predictive value (PPV) were higher in the 65+ cohort than the under-65 cohort (PPV, 4.9% vs. 3.0%; p<0.001) • resection rates for screen-detected cancer were similar (75.6% in the under-65 cohort vs. 73.2% in the 65+ cohort) • five-year all-cause survival was lower in the 65+ cohort than the under-65 cohort (55.1% vs. 64.1%; p = 0.018) Quality appraisal (Jonas et al 2021)**Error! Bookmark not defined.** This study overall had a low risk of bias apart from being a post hoc analysis and not *a priori* planned analysis

Table 64 presents the details and quality appraisal of the UKLS RCT.

Table 64. UK Lung Cancer Pilot Screening Trial (UKLS) RCT (Country; UK)

Trial objectives	**Pilot trial to assess the feasibility, cost effectiveness and psychosocial impact of lung cancer screening using LDCT vs no screening in a high risk UK population**
Inclusions	People aged between 50 and 70 years with a 5 year lung cancer risk ≥5% based on LLPv2 risk prediction model
Exclusions	Inability to give consent, comorbidity which would unequivocally contraindicate screening or treatment if lung cancer were detected, thoracic CT performed within 1 year preceding invitation to be screened, inability to lie flat
Population	N=4055
Intervention	LDCT scan (n=2028)
Comparator	No screening (n=2027)
Quality appraisal	The table below outlines the critical appraisal of the UKLS trial carried out by Jonas 2021. Neither Brodersen 2020 nor Sadate (year) included the UKLS in their systematic reviews or meta analyses. The Jonas 2021 article critically appraised each individual study. Where individual studies vary in risk of bias these are mentioned in the comments column.

Systematic review/meta-analysis	**Quality appraisal**	
Jonas et al (2021)[8]	**Overall ROB:** UKLS RCT assessed as FAIR Generally comparable groups assembled but some questions remain although no fatal flaws exist Brain 2016 and Brain 2017 and Field 2016 were considered POOR quality studies due to numerous unclear domains including allocation concealment and assessor and provider masking, differential attrition and methods to handle missing data. There was no reporting on crossovers and contamination in the control group.	
	USPSTF risk of bias tool is based on the findings of the questions below. Overall ROB is assessed as GOOD, FAIR or POOR	Comment
	Was randomisation adequate?	Yes
	Was allocation concealment adequate?	Yes
	Were groups similar at baseline?	Yes
	Were eligibility criteria specified?	Yes
	Were patients masked?	No
	Were care providers masked	No
	Were outcomes assessors masked?	Unclear
	Were outcome measures equal reliable and valid?	This varied by study Brain et al 2017 - Unclear Brain et al 2016 - Yes

		Field et al 2016 - No
	Adherence to the intervention	The trial overall had high adherence (Field et al 2016) but associated studies exploring psychosocial outcomes and smoking cessation had low adherence in completing questionnaires.
	Did the study have crossovers and contamination	Unclear
	Overall attrition rates	Low attrition rate of the trial overall <10%
	Differential attrition and attrition bias	Overall the attrition bias was low for the trial but was >10% for Brain et al (2017) and Brain et al (2016)
	Method used to handle missing data	Method of mean replacement imputation was described in Brain et al (2016) and Brain et al (2017)
	Was intention to screen analysis used	Varied by study - Field et al (2016) – No Brain et al (2017) -Yes Brain et al (2016)- Yes
	Ascertainment of outcomes adequately described	Varied by study - Field et al (2016) – No Brain et al (2017) Yes Brain et al (2016)- Yes
	Ascertainment techniques are they equal, valid and reliable	Varied by study - Field et al (2016) – No Brain et al (2017) Yes Brain et al (2016)- Yes

Table 65. Results of UKLS RCT

	Objective	Approach and/or outcome measures	Outcomes
Brain et al (2017)[60]	To report change in smoking habit among participants of the trial	Approach: Current smokers eligible for inclusion in the trial from either LDCT or control groups completed a baseline psychosocial questionnaire (T0) and were offered standard smoking cessation advice and details of local NHS Stop Smoking Services. The psychosocial	Completion of questionnaires Smokers in the control arm vs those in LDCT were less likely to complete the questionnaires Baseline (T0) LDCT n=527 (52%) Control n=429 (48%) p<0.001 Repeat (T1) LDCT n= 488 (56%)

		questionnaire was repeated (T1) in the intervention arm with the baseline CT scan result letter and in the control group at the point of assignment to the group. The questionnaires covered smoking status and smoking cessation. Outcomes: • completion of questionnaires • effect of trial allocation on smoking cessation rates • effect of additional clinical investigation on smoking cessation rates	Control n=377 (44%) p<0.001 Effect of trial allocation on smoking cessation rates A multivariable logistic regression model to adjust for confounders evaluated the impact of trial allocation on smoking cessation. Participants who did not answer the smoking cessation question at T0 or T1 were imputed using the intention to treat population. **T0 (n=111/1544)** / **Yes quit** / **Multivariable odds ratio (95% CI, p value)** LDCT / 75(68%) / 2.38 (aOR1.56-3.64; p=0.001) Control / 36(32%) **T1 (n=194/1524)** LDCT / 115(59%) / 1.60 (aOR1.17-2.18; p=0.003) Control / 79(41%) aOR – adjusted odds ratio, CI – Confidence intervals, LDCT – Low dose computed tomography, N - Number Effect of additional clinical investigation on smoking cessation rates Smoking cessation was reported by 16% (48/299) participants who had additional clinical investigations following the baseline scan result and 11% (26/227) who received a negative result Sub group analysis of the T1 responses of those with screen negative vs screen positive results (requiring additional investigations) showed a clear effect on smoking cessation (OR 2.43,95% CI 1.54-3.84, p<0.001). This association between these sub groups was not observed from the T0 responses (OR 1.48 95% CI 0.89-2.47, p=0.09)
Brain et al (2016)[55]	To report on the long term psychosocial outcomes of being invited for lung cancer screening	Approach: Current smokers eligible for inclusion in the trial from either LDCT or control groups completed a baseline psychosocial questionnaire (T0). The psychosocial questionnaire was repeated in the intervention arm (T1) on	Anxiety T2 anxiety (p≤0.001) was higher in the control arm but absolute differences were small and not clinically relevant Anxiety / LDCT (95%CI) / Control (95%CI) T1(n=3232, LDCT n=1653, Control n=1579) / 1.54(1.51-1.57) / 1.56(1.53-1.59)

receipt of the CT scan result letter and in the control group at the point of assignment to the group. A third questionnaire (T2) was completed up to 2 years later for long term follow up.
The questionnaires were the 6 item Cancer worry scale and the Hospital Anxiety and Depression Score (HADS).
Outcomes:

- anxiety
- depression
- cancer distress

T2 (n=2855, LDCT n=1553, Control n=1302)	1.54(1.51-1.57)	1.61(1.36-1.42)**

**p<0.001
CI - Confidence intervals, LDCT – Low dose computed tomography, N - Number

Depression
T1 (p≤0.001) and T2 (p≤0.01) depression was higher in the control arm but absolute differences were small and not clinically relevant

Depression	LDCT (95%CI)	Control (95%CI)
T1(n=3232, LDCT n=1653, Control n=1579)	1.26(1.23-1.29)	1.34(1.31-1.37)**
T2(n=2855, LDCT n=1553, Control n=1302)	1.33(1.30-1.36)	1.39(1.36-1.42)*

*p<0.01 **p<0.001
CI - Confidence intervals, LDCT – Low dose computed tomography, N - Number

Cancer distress
Cancer distress was higher in T1 LDCT group (p≤0.001) for those who received a positive screening test result compared to the control group but not at T2 (p=0.04)

Multivariable analysis adjusting for covariates found the impact of trial allocation on cancer distress was not significant but sex (p≤0.01), smoking status (p≤0.001), age (p≤0.001), lung cancer experience (p≤0.001) and recruitment site (p≤0.001) did show differences in cancer distress

Lung cancer distress scores for T1 and T2 questionnaire

	Adjusted estimate (95%CI), p value
LDCT vs Control	0.03(-020 to 0.26) p=0.39
Female vs Male	0.02(0.03 to 0.07) p≤0.01
Ex smoker vs Current smoker	-0.06(-0.05 to-0.08) p≤0.001

			Age (≤65 years vs >70 years) 0.05(0.03 to 0.07) p≤0.001 Lung cancer experience Yes vs no 0.03(0.02 to 0.05) p≤0.001 Recruitment site Liverpool vs Cambridge 0.06(0.04 to 0.07) p≤0.001 CI - Confidence intervals, LDCT – Low dose computed tomography, N - Number
Field et al (2016)[29]	To report the findings of the screening arm of the UKLS	Outcomes: • stage of lung cancer in those diagnosed from single screen •	A total of 1994 participants were screened with LDCT: • Overall 951/1994 (47.7%) underwent at least one further follow up CT scan • A total of 64(3.2%) were immediately referred to the Multidisciplinary Team (MDT) for diagnostic work up and of those 32(2.6%) had confirmed cancer • 50(2.5%) people were referred for repeat scans and to MDT and of those 10(0.5%) had confirmed lung cancer • A total of 72(3.6%) participants were referred either immediately or after a follow up scan to the MDT but were not diagnosed with lung cancer (false positives) Stage at diagnosis

Stage	N	Early stage I-II
IA	26 (62.0%)	36 (85.8%)
IB	2 (4.7%)	
IIA	7 (16.7%)	
IIB	1 (2.4%)	
IIIA	3 (7.1%)	Late stage III-IV
IIIB	0	6 (14.2%)
IV	3 (7.1%)	
Total	42 (100)	

Question 5: What is the acceptability of screening programmes for lung cancer using LDCT in individuals at increased risk?

Table 66. Kummer et al (2020a)[66]

Publication	Kummer S, Waller J, Ruparel M, Cass J, Janes SM, Quaife SL. Mapping the spectrum of psychological and behavioural responses to low-dose CT lung cancer screening offered within a Lung Health Check. Health Expectations. 2020;23(2):433-41.
Study details	Qualitative study as part of LSUT RCT
Study objectives	To explore the range of psychological and behavioural responses to LDCT screening offered as part of a lung health check including LDCT, risk assessment, spirometry testing, carbon monoxide reading and smoking cessation advice
Inclusions	Purposive sampling of people who had received the lung health check (people aged 60 to 75 years recorded as smokers since 2010) comprising people who varied in: • smoking status • socioeconomic status • LDCT results – had either indeterminate or incidental findings To participate, people had to be approached and consent to face to face or telephone semi structured interviews
Exclusions	People with active lung cancer or metastatic lung cancer, were on the palliative care register or had undergone CT of the thorax in the previous 12 months
Population	129 people were approached, 55 agreed to participate and 28 were selected for interview
Comparisons	N/A
Outcomes	Thematic analysis of the semi structured interviews revealed the factors influencing psychological and behavioural responses: • existing concerns about lung health and smoking history eg: anxiety, apprehension if worried about effect of smoking or lack of concern if asymptomatic • social support – some people shared the invitation with spouses or other people to ask their opinion about attending whilst others did not share the information • stigma and self blame – guilt for smoking, and worry about future cancer • negativity and fatalism – current smokers especially held negative views about their respiratory health and perception of irreversible damage, also the perception of lung cancer as a 'death sentence', and hesitancy in seeking social support for a follow up appointment • competing priorities – some people with existing medical conditions considered their results unimportant and others found external circumstances were more pressing so the lung health check was of less concern People had a range of responses to the lung health check and the information they received at different points along the screening pathway. This included • welcoming and feeling glad of the offer of a lung health check, anxiety about being targeted for an invitation • apprehension about being scanned • concern about abnormal spirometry results and how this would play out with the LDCT results • relief at having an incidental finding as it meant they did not have lung cancer • concern that indeterminant results were cancer

- intention to take part in any future lung screening programmes
- more attentive of possible lung cancer symptoms and intention to seek help seeking if symptoms arose
- motivation to quit smoking
- not motivated to stop smoking because they had not been explicitly told to stop
- increasing smoking while waiting for the LDCT result
- intending to go to the GP for regular spirometry readings
- engaging in other cancer prevention behaviours such as exercising more, changing diet or avoiding air pollution

Quality appraisal

JBI checklist for qualitative research	Y/N/U/NA	Comment
1.Congruity between the stated philosophical perspective and the research methodology	Y	The study aimed to understand the attitudes, views and beliefs of a group of patients who have experienced being invited for lung cancer screening so their views are important.
2. Congruity between the research methodology and the research question or objectives	Y	The study aimed to identify attitudes beliefs and perspectives and used an appropriate method (semi structured interviews) to elicit the information
3. Congruity between the research methodology and the methods used to collect data	Y	The researcher guided the interviewee through topic areas during the semi structured interviews with an opportunity for all issues to be discussed
4. Congruity between the research methodology and the representation and analysis of data	Y	Key emerging themes were identified from a transcript of the interviews to understand peoples beliefs, attitudes and views
5. There is congruence between the research methodology and the interpretation of results	Y	Yes the researchers describe the limitations of the inferences that can be drawn as the group interviewed were self selecting and may not represent the views of the whole target group. There was also a focus on those with indeterminate and incidental findings which does not cover all the different types of results people may receive.
6. Locating the researcher culturally or theoretically	N	This is not explicitly stated
7. Influence of the researcher on the research, and vice-versa, is addressed	N	This is not addressed
8.Representation of participants and their voices	Y	Relevant quotes from transcripts of the interviews were included in the article

	9. Appropriate ethical approval obtained	Y	Yes, this was reported
	10. Relationship of conclusions to analysis, or interpretation of the data	Y	The conclusions drawn by the researcher appear to be based on the text generated through the interviews

Table 67. Kummer et al (2020b)[70]

Publication	**Kummer S, Waller J, Ruparel M, Duffy SW, Janes SM, Quaife SL. Psychological outcomes of low-dose CT lung cancer screening in a multisite demonstration screening pilot: the Lung Screen Uptake Trial (LSUT). Thorax. 2020;75(12):1065-73.**
Study details	Cohort study within LSUT RCT
Study objectives	To report outcomes of psychological impact of invitation to lung cancer screening compared with 'screening unaware' individuals
Inclusions	People aged 60 to 75 years recorded as smokers since 2010 (within 7 years of invitation)
Exclusions	People with active lung cancer or metastatic lung cancer, were on the palliative care register or had undergone CT of the thorax in the previous 12 months
Population	Current and former smokers at high risk of lung cancer (n=787) aged 60-75 invited for screening and similarly high risk people (n=400 who are 'screening unaware' in the community
Intervention	Current and former smokers at high risk of lung cancer (n=787) aged 60-75 invited for screening with LDCT
Comparisons	400 people not invited for screening aged 60-75 years current or former smokers (quit within 7 years of study invitation) recruited via the Smoking Study Toolkit (a nationally representative random location sampling design that Ipsos MORI use to collect smoking behaviour of current and former smokers in England)
Outcomes	Psychological impact was measured using the Hospital Anxiety and Depression Scores (HADS) and a 7 point Cancer Worry Scale. The Cancer Worry scale was completed at: T0 – appointment for LDCT group T1 – next day after appointment T2 – 3 months after The HADS was completed at T0 and T2. The 'screening unaware' community sample completed both measures once -T0 In unadjusted analysis the LDCT group had significantly higher mean cancer worry scores at all time points. In multivariable analysis adjusting for socio-demographic characteristics, smoking status and baseline (T0) worry score this difference for cancer worry continued to be significant at T0 and T2 but not T1. For anxiety, adjusted estimates showed significantly worse anxiety scores in the LDCT group compared to the community groups at T0 and T2. This was similarly observed with depression scores although T0 scores were not significantly different as the difference did not reach p<0.01 as pre-specified in the methodology (p=0.04). The absolute differences in scores for all measures were quite small (between 0.3 and 2) and all were within in the normal clinical range Psychological outcomes applying multivariable linear regression for LDCT vs community group

	Community group unadjusted estimate	LDCT group mean (95% CI)	p value	Estimate adjusted Beta (95% CI)	p value

	mean (95% CI)				
Cancer worry T0	9.32 (8.96-9.69)	11.34 (11.09-11.59)	p<0.001	1.99 (1.51-2.64)	p<0.001
Cancer worry T1		10.97 (10.66-11.28	p<0.001	0.08 (-0.19 to 0.34)	p=0.56
Cancer worry T2		11.88 (11.49-12.27)	p<0.001	0.87 (0.49-1.25)	p<0.001
Anxiety T0	3.32 (2.94-3.70)	4.73 (4.42-5.04)	p<0.001	1.38 (0.85-1.92)	p<0.001
Anxiety T2		5.78 (5.33-6.23)	p<0.001	1.33 (0.99-1.68)	p<0.001
Depression T0	3.85 (3.44-4.27)	3.32 (3.06-3.57)	p=0.02	-0.51 (-0.99 to -0.03)	p=0.04
Depression T2		4.15 (3.76-4.55)	p=0.30	0.64 (-0.32 to 0.95)	p<0.001

CI - Confidence intervals, LDCT – Low dose computed tomography

Quality appraisal	JBI Checklist for cohort studies	Y/N/ U/NA	Comment
	Were the two groups similar and recruited from the same population?	N	The screening group was recruited using the LSUT trial protocol in London whilst the community group was recruited from the Smoking Toolkit Study from across England. Relative to the community sample the screening group was more ethnically diverse (p<0.01), more frequently retirees (p<0.01), more commonly married /cohabiting (p<0.01) and reported lower education (p<0.01). A smaller proportion of the screening sample were smokers (p<0.001)
	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	N	The LSUT group were known to have received an invitation for screening as set out in the trial protocol. It is not clear how it was confirmed that the participants from the community group had not ever had a lung cancer screening invitation from another trial
	Was the exposure measured in a valid and reliable way?	N	There was evidence from the trial that the LSUT participants received an invitation for screening. It is not clear whether individuals in the community group were asked to self report whether they had been invited for screening elsewhere or if there was another method used confirming they had not ever been invited or if there was just the assumption that they had not ever had a lung cancer screening invitation from another trial
	Were confounding factors identified?	Y	Differences between the two groups were identified (ethnicity, smoking status, education level, working status and marital status)
	Were strategies to deal with confounding factors stated?	Y	Differences were adjusted for by multivariable analysis

	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	N	There was a difference in baseline cancer worry, anxiety and depression between the groups
	Were the outcomes measured in a valid and reliable way?	Y	The HADS tool and cancer worry tool have both been used in other studies
	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Y	Short term follow up of 3 months but enough time for increasing levels of cancer worry, anxiety or depression to develop. Longer follow up would be helpful to confirm persistent/transient differences between groups
	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	N	A description of the differences between groups completing the HADS and Cancer worry tools was included but no exploration of loss to follow up. Eg for the LDCT group 82.5% completed the tools at T0, 51.5% at T1 and 43.1% at T2. Response rates were unknown for the community sample
	Were strategies to address incomplete follow up utilized?	N	No
	Was appropriate statistical analysis used?	Y	Multivariable linear regression was used to take account of baseline differences in groups

Table 68. Margariti et al (2020)[67]

Publication	**Margariti C, Kordowicz M, Selman G, Nair A, Akande Y, Saleem A, et al. Healthcare professionals' perspectives on lung cancer screening in the UK: a qualitative study. British Journal of General Practice. 2020;70(suppl 1).**
Study details	Qualitative observational study
Study objectives	To explore healthcare professional's views about lung cancer screening and willingness to be involved in implementation
Inclusions	People invited to participate in a High-Risk Lung Health Study and were any of the following: • GPs within Southwark and Lambeth CCG • community pharmacists within Southwark and Lambeth CCG • members of staff in smoking cessation clinics within Southwark and Lambeth CCG • staff of the respiratory clinic at Guys and St Thomas' NHS Foundation Trust
Exclusions	None reported
Population	N=16
Approach	Semi-structured interviews carried out by a single researcher
Outcomes	Three key themes were identified: • **awareness and understanding of lung cancer screening** – generally people did not feel confident about knowledge and understanding and were not aware of UK pilots and thought most research was in the US • **lung cancer screening; optimism vs scepticism** – participants were ambivalent about screening – whilst acknowledging the possible benefits to their patients they were concerned about the harms screening can bring and

the extra education and training for professionals and additional reassurance required for patients

- **implications for guidelines, risk modelling, organisational resources** - participants emphasised the need for clear guidance about implementing the programme and the evidence behind the choice of risk model to determine eligibility for screening

Quality appraisal

JBI checklist for qualitative research	Y/N/U/NA	Comment
1.Congruity between the stated philosophical perspective and the research methodology	Y	The study aimed to understand the attitudes, views and beliefs of a group of health professionals who would be important in implementing a potential lung screening programme
2. Congruity between the research methodology and the research question or objectives	Y	The study aimed to identify attitudes beliefs and perspectives and used an appropriate method (semi structured interviews) to elicit the information
3. Congruity between the research methodology and the methods used to collect data	Y	The researcher guided the interviewee through topic areas during the semi structured interviews with an opportunity for all issues to be discussed
4. Congruity between the research methodology and the representation and analysis of data	Y	Key emerging themes were identified from a transcript of the interviews to understand peoples beliefs, attitudes and views
5. There is congruence between the research methodology and the interpretation of results	Y	The authors accept that this small study is unlikely to identify and be completely representative of all the attitudes, beliefs and views of professionals who would be involved in a potential UK lung screening programme. They also acknowledge that in their sampling of participants they were likely to have a higher understanding about lung screening than other professionals as they had been invited to participate in the High-Risk Lung Health Study. Additionally 10 of the 16 participants were GPs so other professions (such as pharmacists and respiratory Drs) are underrepresented
6. Locating the researcher culturally or theoretically	N	This is not explicitly stated
7. Influence of the researcher on the research, and vice-versa, is addressed	N	This is not addressed

8.Representation of participants and their voices	Y	Relevant quotes from transcripts of the interviews were included in the article
9. Appropriate ethical approval obtained	Y	Yes, this was reported
10. Relationship of conclusions to analysis, or interpretation of the data	Y	The conclusions drawn by the researcher appear to be based on the text generated through the interviews

Table 69. Quaife et al (2020)[30]

Publication	Quaife SL, Ruparel M, Dickson JL, Beeken RJ, McEwen A, Baldwin DR, et al. Lung Screen Uptake Trial (LSUT): Randomized Controlled Clinical Trial Testing Targeted Invitation Materials. American Journal of Respiratory & Critical Care Medicine. 2020;201(8):965-75.
Study details	Randomised controlled trial
Study objectives	To compare the effect of a targeted low-burden stepped invitation strategy versus control on uptake of hospital based Lung Health Check Appointments
Inclusions	People aged 60 to 75 years recorded as smokers since 2010 (within 7 years of invitation)
Exclusions	People with active lung cancer or metastatic lung cancer, were on the palliative care register or had undergone CT of the thorax in the previous 12 months
Population	2012 people were invited for screening
Intervention	2012 people were invited for a lung health check appointment and LDCT of which 1006 people in the intervention group received a leaflet called 'MOT for your lungs'
Comparisons	The control group of 1006 received information similar in presentation to 'the facts' booklets distributed with other cancer screening programmes
Outcomes	Primary outcome – attendance at lung health check appointment spirometry test, carbon monoxide reading, smoking cessation advice (for current smokers), and for those eligible, a LDCT scan People were invited to a health check appointment and at that appointment were assessed as eligible or not and consented or not for LDCT

	Intervention group 'MOT for your lungs leaflet N=1006	Control group 'The facts' leaflet N=1006
Attended lung health check and agreed to the study	526(52.3%)	532(52.9%)
Participated in study	494	511
Ineligible for LDCT	70	83
Eligible and took up offer of LDCT	386(92.8%)	384(89.7%)
Eligible and did not take up offer of screen	30	44

LDCT – Low dose computed tomography, N - Number

Secondary outcomes

Attendance of lung health check:

- neither age nor sex were associated with attendance
- ethnicity was associated with attendance across groups. Compared with those of a White ethnic background individuals of other ethnic backgrounds were more likely to attend (OR 2.34;95% CI 1,30-4.20) and those with no recorded ethnic group were less likely to attend (OR 0.09;95% CI0.04-0.19)

- higher deprivation was associated with lower attendance across IMD quintiles (p<0.01). People in the 3 least deprived quintiles had higher odds of attendance compared to those in the most deprived quintile (OR 1.62;95% CI 1.21-2.15 intervention and OR 1.68;95%CI 1.26-2.25 in control respectively)
- current smokers were less likely to attend than former smokers (OR 0.7;95% CI 0.56-0.86)

Uptake of offer of LDCT screen

- most people attending the lung health check and eligible to be screened chose to have the LDCT scan (91.2%)

Results of satisfactory decision making scale

- there was no difference in mean scores of conceptual and numerical knowledge by invitation group
- most participants reported awareness of the benefits and valued screening, felt supported and were clear about their choice (all >89%)
- risks were well understood although fewer control participants reported that they knew what the risks were compared to the intervention group (76.2% vs 83.2%, p<0.05)
- decisional satisfaction was >97.3% across both groups for both nurse and self reported satisfaction

Quality appraisal

JBI Checklist for RCTs	Y/N/U/NA	Comment
Was true randomization used for assignment of participants to treatment groups?	Y	A web based programme individually randomised participants
Was allocation to treatment groups concealed?	Y	Individual details were concealed from researchers performing the allocation
Were treatment groups similar at the baseline?	Y	There were no differences in sex, age ethnicity
Were participants blind to treatment assignment?	Y	Participants were blind to the nature of the research at invitation
Were those delivering treatment blind to treatment assignment?	N/A	Delivery of the treatment was posting the leaflets to individuals
Were outcomes assessors blind to treatment assignment?	N/A	The outcome was people's response to the invitation. Once at the lung health check it is unclear if staff knew who had received each leaflet and if that was likely to have a bearing on consenting to have an LDCT scan
Were treatment groups treated identically other than the intervention of interest?	Y	Both were invited on the same screening pathway
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	N/A	For this part of the screening pathway (concerning uptake of invitation to screen) further follow up was not required
Were participants analysed in the groups to which they were randomized?	Y	Participants were analysed both in randomised groups and as a complete population cohort
Were outcomes measured in the same way for treatment groups?	Y	Outcome measures were the same for each group
Were outcomes measured in a reliable way	Y	Yes by attendance and consent to undergo LDCT
Was appropriate statistical analysis used?	Y	Analysis was carried out using a prospectively registered statistical analysis plan with an intention to treat

		approach. Attendance was compared by invitation group using logistic regression and a deviance chi squared test for statistical significance
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Standard RCT design

Table 70. Crosbie et al (2019a)[64] and Crosbie et al (2019b)[65]

Publication	Crosbie P, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D et al. Implementing lung cancer screening: baseline results from a community based 'lung health check' pilot deprived areas of Manchester. Thorax 2019;74; 405-409. Crosbie P, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D et al. Second round results from the Manchester 'Lung Health Check' community-based targeted lung cancer screening pilot Thorax 2019;74:700-704.
Study details	Cohort study
Study objectives	To report results of screening adherence from baseline screen and second annual screening round of Manchester's' Lung Health Check pilot of community based lung screening in deprived areas
Inclusions	Ever smokers aged 55-74 at participating general practices (n=14) who were high risk of lung cancer following risk assessment, had received a first LDCT screen and were eligible to be reinvited for a second annual screen
Exclusions	People who were diagnosed with other cancers, those who had a CT thorax in the past 3 months, those who were uncontactable and those who had died
Population	LDCT screening n=1429 at baseline screen and n=1323 second annual screen
Comparisons	Comparisons were made between the baseline and second round of screening
Outcomes	People were invited to participate in the lung health check within a community setting with immediate access to mobile CT scanners on site. Respiratory symptoms and spirometry were assessed followed by a 6 year lung cancer risk assessment (PLCOM2012) and smoking cessation advice. If people were eligible for LDCT based on their risk assessment score of a ≥1.5% risk of developing lung cancer in the next 6 years they were offered an immediate LDCT. People who received a scan at baseline and had a negative result or who were discharged after a diagnostic follow up of a positive scan were invited for a repeat scan a year later

	Baseline screen (%)	**Second round screen (%)**
Invited for LDCT	1429	1,323
People who underwent LDCT	1,384(96.8%)	1194(90.2%)
• positive result	65(4.7%)	24(2%)
• indeterminate result	176(12.7%)	71(6%)
• positive result 3 months after indeterminate result	16(1.2%)	6(8.7%)
• negative result	1,143(82.6%)	1,099(92%)
Total positive screens	81(5.9%)	30(2.5%)
• diagnosed with lung cancer	42 patients(3.0%) 46 cancers(3.3%)	19(1.6%)
○ stage I	29(63%)	15(79%)
○ stage II	8(17.4%)	0
○ stage III	4(8.7%)	2(10.5%)
○ stage IV	4(10.9%)	2(10.5%)
• refused diagnostic pathway	0	1

• referred to next screening round, discharge or surveillance	21(1.5%)	10(0.8%)

The data collected at the second round screen showed:

- non attendees were significantly more likely to be current smokers (63.6% vs 50.6%, p=0.005) than attendees
- there was no difference in proportion of attenders by deprivation (median indices of multiple deprivation rank measured by interquartile range)
- of the 19 people with lung cancer 13 had had a negative first scan the year before. A retrospective review showed 5 were visible at the first scan as <5mm nodules that were subsequently diagnosed as stage I cancer in the second round

Quality appraisal

JBI Checklist for cohort studies	Y/N/ U/NA	Comment
Were the two groups similar and recruited from the same population?	NA	Single arm study with follow up of same eligible group
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Y	Following invitation (exposure) the response to the exposure, attendance, was the same measure across the baseline and second screening round
Was the exposure measured in a valid and reliable way?	Y	Invitation and attendance of lung cancer screening
Were confounding factors identified?	Y	The article describes factors that may affect attendance and aimed to find those factors that would affect adherence
Were strategies to deal with confounding factors stated?	N	Differences in demography of people attending and not attending were described
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Y	The outcome (attending) was the response to the exposure (invitation)
Were the outcomes measured in a valid and reliable way?	Y	Attendance was measured for all participants
Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Y	Response to exposure is attendance of an appointment no further follow up after appointment date was required
Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Y	
Were strategies to address incomplete follow up utilized?	NA	
Was appropriate statistical analysis used?	Y	Differences in characteristics of proportions of attendees and non attendees responding to the intervention were compared

Table 71. Ruparel et al (2019)[68]

Publication	**Ruparel M, Quaife S, Baldwin D, Waller J, Janes S. Defining the information needs of lung cancer screening participants: a qualitative study. BMJ open respiratory research. 2019;6(1):e000448**
Study details	Qualitative study
Study objectives	To explore knowledge and perceptions around lung cancer screening with a focus on harms
Inclusions	• screening eligible individuals aged 60-75 recorded as smokers in the past 15 years from 3 GP surgeries • health professionals including GPs, respiratory physicians, lung cancer nurse specialists and public health consultants
Exclusions	Not reported
Population	7 focus groups (n=35) with screening eligible individuals divided into current vs former smokers and shorter vs longer time spent in education. 16 interviews (n=18) with health professionals including GPs, respiratory physicians, lung cancer nurse specialists and public health consultants
Outcomes	Themes were coded by researchers and collated into 2 groups: 1. Views about lung cancer screening in the context of what would be helpful information for people to receive about lung cancer screening 2. Views and opinions about the possible harms associated with lung cancer screening Views about lung cancer screening • fatalism about a lung cancer diagnosis and poor prognosis • lack of awareness of curative treatment options • where treatment had been encountered with a good outcome this was considered unusual • wariness about screening given poor prognosis of lung cancer • screening could be preventative and there were benefits to early detection of cancer • screening considered worthwhile, precautionary and an opportunity to be checked • reluctance to acknowledge harms • important to be informed and make an individual choice • balancing harms and benefits could be challenging for health professionals for the group where it was less clear about the benefits • most commonly current smokers observed that too much information made it difficult to make any decision • people with more time in education were more likely to express scepticism about the statistics that could be manipulated • providing information with too many statistics could be off putting and 'information overload' • people often did not read the leaflets Views about harms of screening • anxiety about indeterminate results • how you tell people those results was important especially the low risk of an indeterminant result turning out to be positive at a later scan to help people worry less • false positives and false negatives were acknowledged as difficult outcomes to cope with • overdiagnosis was not clearly understood and even following detailed explanation didn't impact on intention to attend for screening given the opportunity

- health professionals observed some patients did not want to know the harms of overdiagnosis whilst one thought it was a fallacy
- radiation exposure was not a big concern especially as the size of the risk was not easily quantified as it is cumulative and very personal to an individual's circumstances
- there were some concerns about radiation but only from the perspective that people wanted to be informed about it but it did not impact on their intention to attend screening

Quality appraisal

JBI checklist for qualitative research	Y/N/U/NA	Comment
1.Congruity between the stated philosophical perspective and the research methodology	Y	The study aimed to understand the attitudes, views and beliefs about lung cancer screening of a group of screening eligible individuals and health professionals by the use of qualitative methods
2. Congruity between the research methodology and the research question or objectives	Y	The study aimed to identify attitudes beliefs and perspectives and used an appropriate method (focus groups and semi structured interviews) to elicit the information
3. Congruity between the research methodology and the methods used to collect data	Y	Researchers ran the focus groups and undertook the semi structured interviews with 2 areas of interest linked to the research questions. There was opportunity for all issues to be discussed and any themes to emerge
4. Congruity between the research methodology and the representation and analysis of data	Y	Key emerging themes were identified from a transcript of the focus groups/ interviews to understand people's beliefs, attitudes and views
5. There is congruence between the research methodology and the interpretation of results	Y	Results were interpreted as indicators of the views of some parts of the population eligible for lung cancer screening. It was acknowledged that some viewpoints may have been missed due to the sample of people selected, and that although people's intentions around screening were expressed this may differ to actual screening behaviour
6. Locating the researcher culturally or theoretically	N	This is not explicitly stated
7. Influence of the researcher on the research, and vice-versa, is addressed	N	This is not addressed

	8.Representation of participants and their voices	Y	Relevant quotes from transcripts of the focus groups/interviews were included in the article
	9. Appropriate ethical approval obtained	Y	This was reported
	10. Relationship of conclusions to analysis, or interpretation of the data	Y	The conclusions drawn by the research are based on the text generated through the interviews

Table 72. Quaife et al (2018)[71]

Publication	Quaife S, Vrinten C, Ruparel M, Janes S, Beeken R, Waller J, McEwan A. Smokers' interest in a lung cancer screening programme: a national survey in England BMC Cancer 2018;18:497
Study details	Population based survey
Study objectives	To examine interest in a national lung cancer screening programme and modifiable attitudinal factors that may affect participation by smokers
Inclusions	People aged 50-70 who took part in the Attitudes Behaviour and Cancer UK survey (ABACUS)
Exclusions	People who did not report smoking status, or people who had been diagnosed with lung cancer
Population	N=1464 participants completed the survey
Comparisons	Smoking history, age, gender, social group, lung cancer beliefs, lung cancer screening attitudes
Outcomes	• intention to be screened was high for current (≥89%) and former (≥94%) smokers • smoking status was associated with screening intention if GPs were sending out invitations to attend for a screen (93% current smokers vs 98% former smokers p<0.01;OR 0.24, 95% CI 0.09-0.65). There was no association with smoking status if the invitation came from a national NHS programme, or as a pre-scheduled appointment • smokers were less likely to agree that early stage survival of lung cancer is good (43% vs 53% OR;0.64, 95% CI 0.46-0.88) or be willing to have surgery for an early screening detected cancer (84% vs 94%, OR;0.38, 95% CI 0.21-0.68) compared with former smokers. Using NHS money to screen smokers was thought to be a wate of time by 21% of people • gender, age, ethnicity. Level of education, marital status and cancer experience were not associated with screening intentions

Quality appraisal	JBI check list for cross sectional studies	Y/N/U/ NA	Comment	
	Were the criteria for inclusion in the sample clearly defined?	Y	People aged 50 to 70 who took part in the Attitudes, behaviour and cancer UK survey (ABACUS)	
	Were the study subjects and the setting described in detail?	Y	Demographic information about participants was collected	

Was the exposure measured in a valid and reliable way?	N	Self report of smoking status but no detail gathered of number of pack years so could not determine likely eligibility for screening	
Were objective, standard criteria used for measurement of the condition?	U	People were only asked how high their chances of giving up smoking for good was (Motivation to Stop Scale)	
Were confounding factors identified?	N	No confounding factors were identified	
Were strategies to deal with confounding factors stated?	Y	It is assumed that the sampling strategy via the ABACUS survey would reduce possible selection bias that would confound the results	
Were the outcomes measured in a valid and reliable way?	Y	People's intentions to be screened were gathered in a valid way. However limited conclusions can be drawn from asking about intentions as the screening offer was hypothetical and social desirability bias may have inflated the results	
Was appropriate statistical analysis used?	Y	Chi squared and logistic regression to test for associations	

Table 73. Quaife et al (2016)[69]

Publication	Quaife S, Marlow L, Janes S, McEwan A, Wardle J. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities; informing screening communication Health Expectation 2016;1-11
Study details	Survey and semi structured interviews of a sample of survey participants
Study objectives	To compare smokers' beliefs (n=45) about lung cancer screening with those of former(n=71) or never smokers(n=47) within a low socioeconomic status (SES) sample, and to provide insights into effective engagement strategies
Inclusions	People aged ≥40 recruited from lower SES communities in Central and South East London
Exclusions	None reported
Population	N=175 survey participants, 21 semi-structured interviews with a sample of survey participants
Comparisons	Smoking status
Outcomes	Main findings - survey: • 64.8%(n=105) survey respondents said they agreed that a CT scan could improve the chances of surviving lung cancer • 23.1% (n=37) said they had other priorities which were more important than getting a lung cancer test • 32.7% (n=51) thought people with lung cancer would have pain or another symptom before being diagnosed and 17.9% (n=29) thought screening would only be necessary if you had symptoms • current smokers were more likely to believe they had smoked too long to benefit from screening vs former smokers (20%, (n=9) vs 4% (n=3), p<0.05) • current smokers were more likely to agree that 'if the CT scan is negative you can continue to smoke without worrying about lung cancer' (30% (n=13) vs 6% (n=4) former smokers vs 4% (n=2) never smokers p<0.001)

- fewer than half of survey respondents (n=71) agreed 'people with lung cancer can expect to continue with normal activities'
- 22% (n=35) of respondents thought treatment was worse than the lung cancer itself
- nearly half of smokers considered cancer a death sentence (48% (n=21) smokers, vs 13% (n=9) former smokers vs 11%(n=5) never smokers; p<0.005)

	All % (n=163)	Smoker % (n=45)	Ex % (n=71)	Never %(n=47)	p value
People doing lung cancer screening could be rude to smokers	13.1 (21)	20.5(9)	8.7(6)	12.8 (6)	0.489
There is no point going for LC screening while you are still smoking	10.7 (17)	2.3(1)	14.5(10)	13.0(6)	0.046
If the CT scan is negative you can continue to smoke without worrying about LC	12.0 (19)	29.5(13)	5.8(4)	4.4(2)	<0.001
I have smoked too long to benefit from LC screening	10.3 (12)	20.0(9)	4.3(3)	-	0.020
My personal risk of getting LC in my lifetime is higher than other smokers	-	35.6(16)	-	-	-
I would have got LC by now if I was going to	8.4 (13)	9.1(4)	5.9(4)	11.9(5)	0.505
I think I have a high chance of getting LC in the next few years	19.5 (31)	47.7(21)	10.1(7)	6.5(3)	<0.001
I think I already have lung cancer	8.2(13)	17.8(8)	4.3(3)	4.5(2)	0.53
There's no risk of getting lung cancer if you only smoke for a few years	5.0 (8)	4.4(2)	7.2(5)	2.2(1)	0.534
I feel I will get lung cancer during my life	21.7 (35)	44.4(20)	19.1(7)	17.0(8)	<0.001
Once you stop smoking you are no longer at risk of lung cancer	8.8(14)	8.9(4)	11.6(8)	4.4(2)	0.264
A clear CT scan would stop me worrying about LC	69.7 (108)	54.5(24)	80.6(54)	68.2(30)	0.023
I often worry about my chance of getting LC	38.0 (62)	75.0(33)	24.6(17)	26.7(12)	<0.001
I'd be too worried about LC to have a screening test	11.0(19)	13.3(6)	11.3(8)	8.5(4)	0.095
I'm very scared of getting lung cancer	57.8 (93)	60.0(27)	54.3(38)	60.9(28)	0.426
If I ever get lung cancer I could be cured	38.8(47)	28.0(7)	36.8(21)	48.7(19)	0.125

A diagnosis of lung cancer is a death sentence	22.0 (35)	47.7(21)	13.0(9)	10.9(5)	<0.001
Lung cancer can often be cured	46.3(74)	40.9(18)	50.7(35)	44.7(21)	0.498
These days many people with LC can expect to continue with their normal activities and responsibilities	44.9 (71)	39.5(17)	54.3(38)	35.6(16)	0.085
Most lung cancer treatment is worse than lung cancer itself	21.6 (35)	20.5(9)	19.7(14)	25.5(12)	0.713

Main findings semi structured interviews:

- majority of people were superficially supportive of screening but these conflicted with negative views of treatment and survival
- many participants were concerned there was little they could do to reduce their risk of lung cancer irrespective of smoking status and other risk factors such as genetics, pollution, asbestos, poor housing, work place exposures, stress and 'cancer grown foods' meant that they did not consider stopping smoking to be protective and their risk was attributed to chance
- fear of the diagnosis, avoidance, fear, fatalism and stigma surrounding screening was particularly voiced by older current smokers which could deter participation
- addiction, difficult life circumstances and negative perceptions of treatment seemed to exacerbate pessimism and lack of control
- the targeting of individuals based on a highly stigmatised behaviour and the expectation of a diagnosis among smokers appears to complicate decision making

Quality appraisal

JBI check list for cross sectional studies	Y/N/U/ NA	Comment
Were the criteria for inclusion in the sample clearly defined?	Y	People aged ≥40 in London from lower SES group
Were the study subjects and the setting described in detail?	Y	Demographic information about participants was collected
Was the exposure measured in a valid and reliable way?	Y	Self report of smoking status and SES was determined either by IMD score of residence or educational background
Were objective, standard criteria used for measurement of the condition?	N	A series of statements were presented and people asked if they agreed or disagreed with them. A sample of people were asked in more depth about the reasoning behind their responses
Were confounding factors identified?	N	No confounding factors were identified

Were strategies to deal with confounding factors stated?	N	None described
Were the outcomes measured in a valid and reliable way?	Y	The responses to the statements were either to agree or disagree with them. Themes were derived from the semi structured interviews
Was appropriate statistical analysis used?	Y	Chi squared univariate and Fishers exact test for associations was used. There were too few

Table 74. Ali et al (2015)[63]

Publication	Ali N, Lifford KJ, Carter B, McRonald F, Yadegarfar G, Baldwin DR, et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: a mixed methods analysis of the UK Lung Cancer Screening (UKLS) trial. BMJ Open. 2015;5(7):e008254
Study details	Survey within an RCT
Study objectives	To identify barriers to participation among high risk individuals who declined an invitation for screening in the UK lung cancer Screening (UKLS) pilot randomised controlled trial
Inclusions	High risk individuals aged 50-75 who declined to participate in the UKLS pilot trial
Exclusions	None reported
Population	N=748 (27.1%) returned the survey of the 2756 who declined to participate in the trial
Comparisons	Age, gender, socioeconomic group, smoking status and affective risk perception.
Outcomes	Recruitment to the trial: • 247,354 individuals approached from the population of which 148,608 (60.1%) did not respond, 22,788 (9.2%) responded negatively and 75,958 (30.7%) responded positively • of the positive responders 8729 were classified at high risk of developing lung cancer and were invited to the trial recruitment centre • 4061 (46.5%) were eligible and provided informed consent • 2762 (32%) declined to participate Factors influencing uptake of the offer of screening (n=4061): • age – older people less likely to attend vs those ≤65 years (OR 0.73, p<0.001) • gender – women less likely to attend vs men (OR 0.64 p<0.001) • smoking status - current smokers less likely to attend vs former smokers OR 0.70, p<0.001) • socioeconomic group – people in highest socioeconomic quintile (5) more likely to attend than those in the lowest quintile (1) (OR 0.56, p<0.001) Non-participation questionnaire: • of 2756 people sent a non-participant questionnaire 748 were completed. People more likely to complete the questionnaire were: o older people vs younger (OR 2.15 p<0.001) o former vs current smokers (OR1.49, p<0.001) o people in the lowest SES quintile (Q1) vs highest (Q5) (OR 0.65, p=0.001) There were 6 overarching themes: • **practical barriers (n=350, 46.8%)** included; distance to travel, lack of public transport, cost of journey, hospital parking, comorbidities and

related treatments, carer responsibilities, already receiving screening and not being in the area
- **emotional barriers (n=138, 18.4%)** included; avoidance of lung cancer information and fear
- **trial acceptability (18, 2.4%)** included; duration, frequency, may be randomised to a group that does not receive an LDCT scan
- **age (n=16, 2.1%)–** felt too old
- **dislikes (n=13 1.7%)** included**;** of the hospital system, health care scans and tests
- **low perceived risk (n=12 1.6%)** included: no longer smoking or smoking too few cigarettes to warrant screening
- **other (n=30, 40%) –** included; no reason stated, already have/had lung cancer, thought request was for partner, would like to take part

Association between risk factor and barrier to attendance:
- people in SES quintiles 3-5 more likely to cite travel as a barrier than those in Quintile 1 (Q3 =OR 2.37 p=0.005, Q4 OR2.91,p<0.001) Q5 =OR 2.25, p=0.009)
- people more concerned about the risk of lung cancer were more likely to cite comorbidities as a barrier to participation (OR 1.84, p=0.005)
- smokers vs former smokers were more likely to cite emotional barriers for non participation (OR 2.02, p=0.013)

Quality appraisal

JBI check list for cross sectional studies	Y/N/U/ NA	Comment
Were the criteria for inclusion in the sample clearly defined?	Y	People eligible to be invited for screening who declined
Were the study subjects and the setting described in detail?	Y	Demographic information about participants was collected
Was the exposure measured in a valid and reliable way?	Y	Receipt of and decline of invitation to participate in lung cancer screening
Were objective, standard criteria used for measurement of the condition?	Y	A non participant questionnaire was developed to capture reasons for declining to participate in the screening trial
Were confounding factors identified?	N	Not described
Were strategies to deal with confounding factors stated?	Y	The RCT was set up to remove confounding factors prior to this study taking place
Were the outcomes measured in a valid and reliable way?	Y	Standard options to respond to questions were developed. Themes were derived from the text boxes and responses to questions
Was appropriate statistical analysis used?	Y	Themes were coded by one researcher with repeat coding of 25% of questionnaires. Exploratory regression analysis was undertaken

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 76.

Table 75. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	4
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6
2.	INTRODUCTION AND APPROACH1212		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	13
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	17
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	19
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	20
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.	88

		Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	16
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	109
4.2	Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer.	N/A
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	44, 70
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	45, 70
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	51, 73
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	84
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	86

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